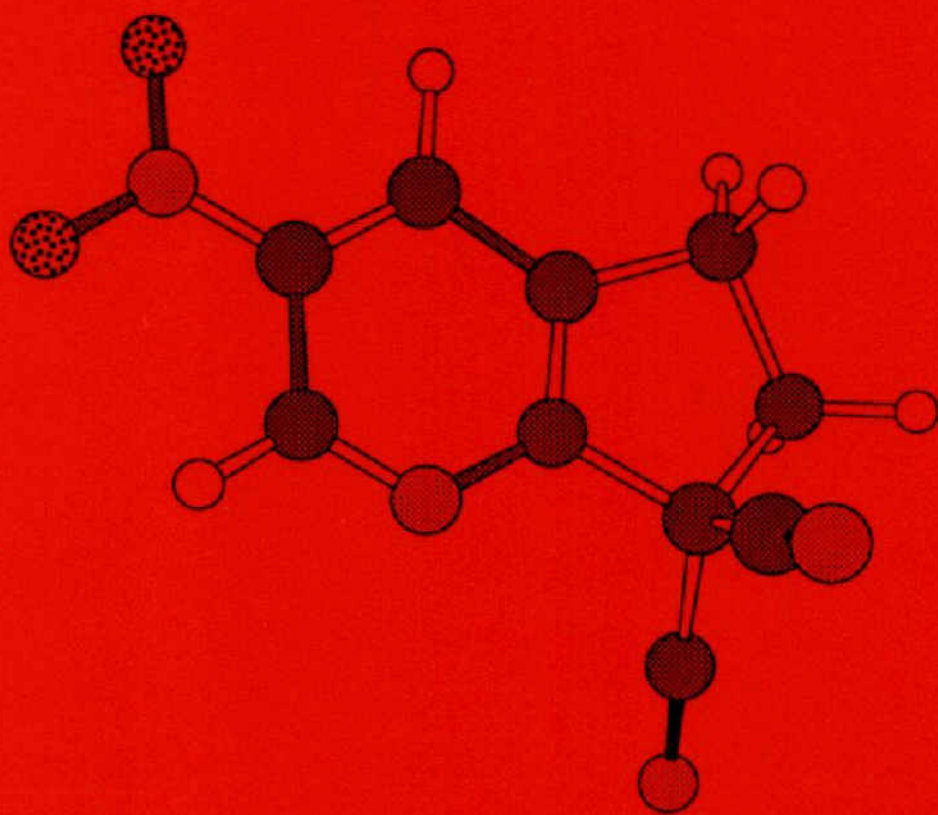# INTRAMOLECULAR INVERSE ELECTRON DEMAND
DIELS-ALDER REACTIONS OF PYRIMIDINES

A.E. Frissen

INTRAMOLECULAR INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF PYRIMIDINES

ter nagedachtenis aan Lei
aan mijn ouders

A.E. Frissen

INTRAMOLECULAR INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF PYRIMIDINES

Proefschrift

ter verkrijging van de graad van

doctor in de landbouw- en milieuwetenschappen,

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op donderdag 18 oktober 1990

des namiddags te vier uur in de aula

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CONTENTS

CHAPTER 1

INTRODUCTION

1.1   GENERAL

The thermal 1,4-cycloaddition of a double (or triple) bond ($_\pi2_s$ component) to a conjugated diene ($_\pi4_s$ component) is known as the Diels-Alder reaction. Although not discovered by Diels and Alder[1] their names have been inevitably connected with this type of reaction due to their systematic and extensive work on this reaction in the 1920's[2]. As a result of their studies Diels and Alder were able to determine the fundamental stereochemical and regiochemical principles of this reaction. Since these initial investigations numerous papers have been published concerning the synthetic applicability[3], mechanistic aspects[4], stereochemistry[5], reaction kinetics[6] and the influence of high pressure[7].

The FMO-theory[8] ascribes the reactivity of dienes and dienophiles in [4+2]-cycloadditions to the interaction of the frontier orbitals, i.e. the Highest Occupied Molecular Orbitals (HOMO's) and the Lowest Unoccupied Molecular Orbitals (LUMO's) of the reaction partners (Figure 1.1). Activation

Figure 1.1

Diene   Dienophile   Diene   Dienophile   Diene   Dienophile

Normal: $\Delta E''>\Delta E'$ Neutral: $\Delta E''\approx\Delta E'$ Inverse: $\Delta E''<\Delta E'$
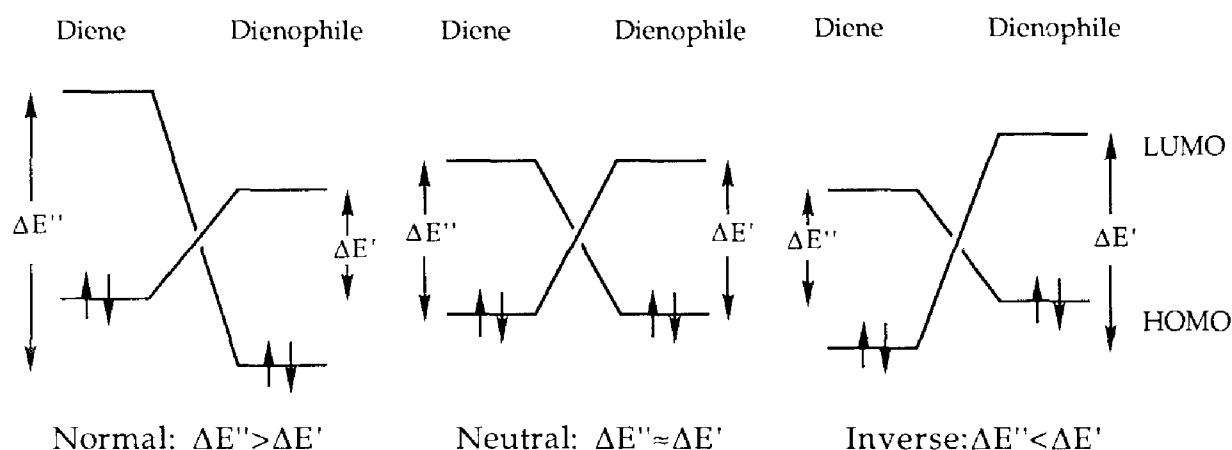
of the diene and the dienophile by introduction of electron-donating or electron-withdrawing substituents influences the HOMO and LUMO energy levels of the reaction partners and consequently the reactivity of the Diels-Alder reaction. For these activated compounds the interaction of the pair of frontier orbitals which are nearest in energy offers a good approximation of the total stabilization energy ΔE resulting from the interaction, since ΔE is inversely proportional to the HOMO-LUMO energy separation. Thus, the FMO-theory provides the basis for further classification of these [4+2]-cycloadditions into one of three processes (Figure 1.1):

(i) Normal Diels-Alder reactions, defined as reactions between electron-rich dienes (increased HOMO and LUMO) and electron-deficient dienophiles (decreased HOMO and LUMO):

$\Delta E'$ (HOMO$_{diene}$ - LUMO$_{dienophile}$) < $\Delta E''$ (HOMO$_{dienophile}$ - LUMO$_{diene}$).

(ii) Neutral Diels-Alder reactions taking place between dienes and dienophiles having intermediate electronic character: $\Delta E' \approx \Delta E''$.

(iii) Inverse electron demand Diels-Alder reactions, defined as reactions between electron-deficient dienes (decreased HOMO and LUMO) and electron-rich dienophiles (increased HOMO and LUMO):

$\Delta E''$ (HOMO$_{dienophile}$ - LUMO$_{diene}$) < $\Delta E'$ (HOMO$_{diene}$ - LUMO$_{dienophile}$).

1.2 THE INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF HETEROAROMATIC AZADIENES

Heteroaromatic systems which possess a 4π electron-deficient azadiene moiety are ideally suited for participation in inverse electron demand (LUMO$_{diene}$-controlled) Diels-Alder reactions[9]. The first experimental demonstration of this type of Diels-Alder reaction was performed by Carboni et al.[10] who found that the highly electron-deficient perfluoroalkyl-1,2,4,5-tetrazine 1 reacts with styrene 2 with the evolution of 1 equivalent of nitrogen to yield the perfluoroalkylphenyldihydropyrazine 4 (Scheme 1.1). The reaction apparently proceeds by 1,4-addition of the -C=N-N=C- diene system to the olefinic dienophile. These early results stimulated others to full investigations of this inverse electron demand Diels-Alder reaction[11-14].

2

Scheme 1.1
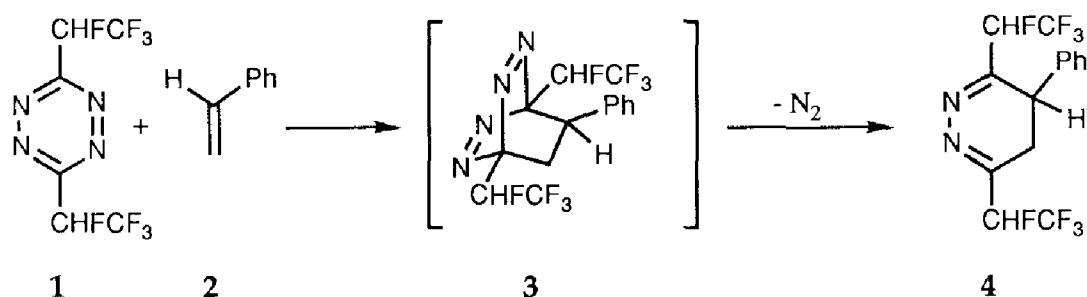
1,2,3-Triazines[15], 1,3,5-triazines[16] and 1,2,4-triazines[17] are also suf-
ficiently electron-deficient to participate in an inverse electron demand
Diels-Alder reaction with electron-rich dienophiles. Among these, 1,2,4-
triazines constitute one of the most thoroughly investigated heterocyclic
azadiene systems capable of 4π diene participation[17,18] . In the case of the
parent 1,2,4-triazine, cycloaddition can occur across C-3/C-6 or C-5/N-2 of
the 1,2,4-triazine nucleus. Electron-rich olefins (e.g. enamines **6**) add across
1,2,4-triazine C-3/C-6 and the nucleophilic carbon of the electron-rich
olefin attaches to C-3 (Scheme 1.2). The presence of electron-withdrawing
groups on the 1,2,4-triazine nucleus as well as the nature of substituents on
the dienophile influence the rate of cycloaddition and control the observed
regioselectivity. On the other hand, ynamines (e.g. **10**) add across C-3/C-6 to
give **11** and/or add across C-5/N-2 to give **13** depending on the substitution
pattern of the 1,2,4-triazine nucleus (Scheme 1.3). The initial cycloadducts
11 lose nitrogen resulting in pyridine derivatives **12**, whereas R^3CN is
eliminated from cycloadducts **13** affording pyrimidine derivatives **14**.

Scheme 1.2
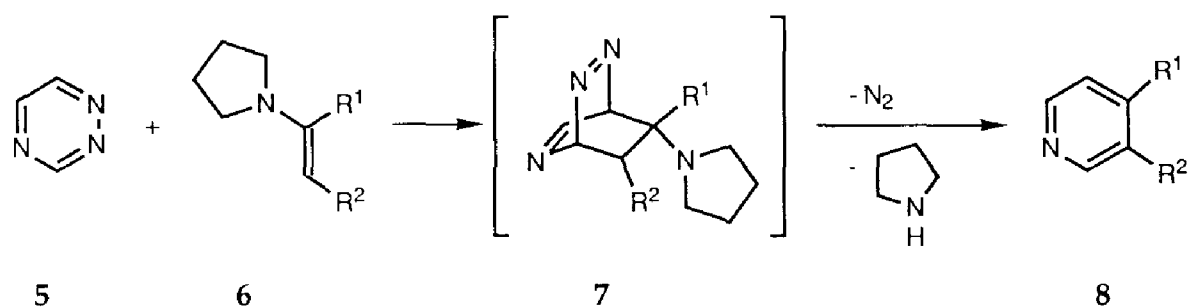
Scheme 1.3
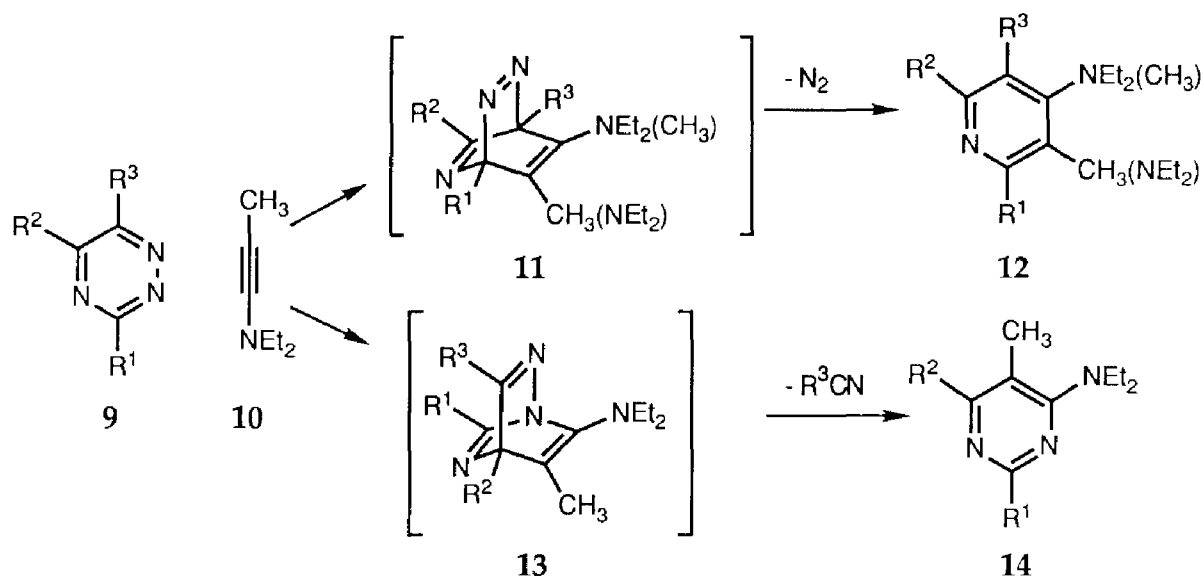
Even the less electron-deficient pyrimidines have been found to undergo the intermolecular inverse electron demand Diels-Alder reaction with electron-rich dienophiles, provided that they are substituted at position 5 with an electron-withdrawing group (SO_2Me, CO_2Me, CO_2Et, NO_2). The reaction of pyrimidines **15** with ynamine **16** gives rise to cycloadducts **17** resulting from addition across the C-2 and C-5 positions of the pyrimidines, which by subsequent loss of hydrogen cyanide give the 3,4,5-trisubstituted pyridines **18**[19] (Scheme 1.4).

Scheme 1.4

$R^1 = CO_2Et, CO_2Me, SO_2Me$

4
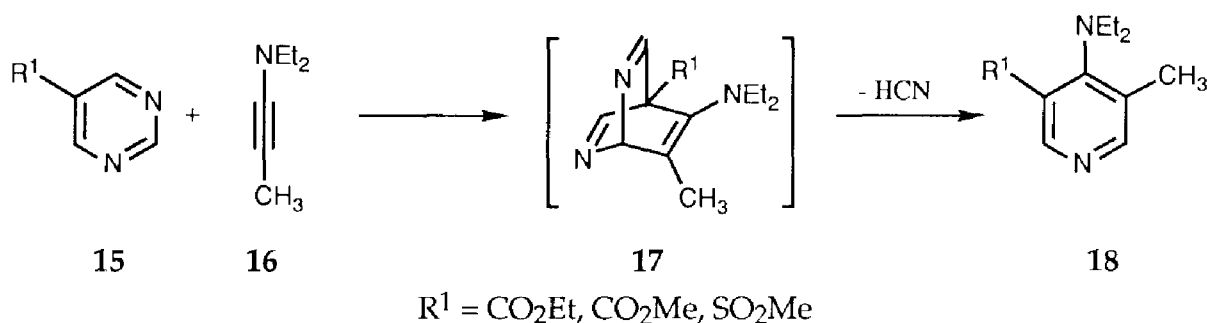
On the other hand, reaction of 5-nitropyrimidine **19** with enamines **20** results in regioselective addition across N-1 and C-4, affording the pyridine derivatives **22**[20,21] (Scheme 1.5). This preference of enamines for regioselective cycloaddition across N-1 and C-4 of 5-nitropyrimidine was correctly predicted by FMO perturbation theory[21]. This study has recently been extended to cyclic enamines which give rise to the regioselective formation of [b]-annelated pyridines[22]. For example, five to eight membered cyclic enamines **23** and 5-nitropyrimidine **19** afford the [b]-annelated pyridines **24** in 60-80% yield upon refluxing in ethanol for 2h.

Scheme 1.5

NR$_2$ = morpholine, piperidine

n = 1, 2, 3, 4
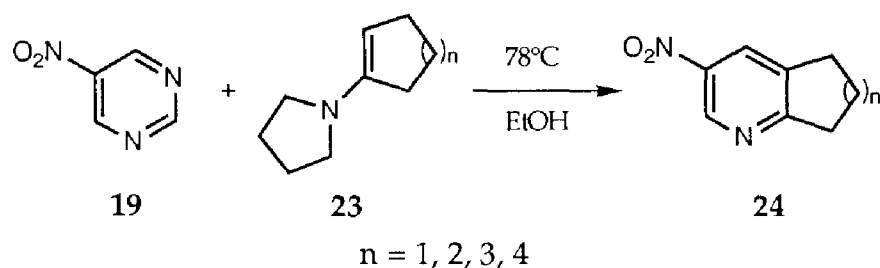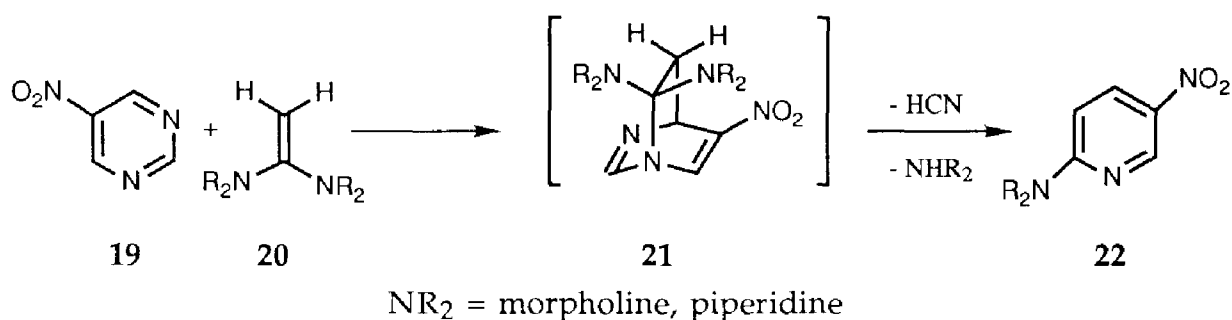
Pyridazines (1,4-diazines) and pyrazines (1,2-diazines) substituted with additional electron-withdrawing substituents also participate in inverse electron demand [4+2]-cycloaddition reactions with electron-rich dienophiles[23,24]. The rate and regioselectivity of the reaction are dependent upon the number and position of the electron-withdrawing substituents present on the diazine nucleus.

In conclusion, the inverse electron demand Diels-Alder reaction of heterocyclic azadienes offers a useful tool for the synthesis of a wide range of new heterocyclic compounds. This concept has also been applied to provide the key intermediates in the total syntheses of several natural products, like

octamethylporphyrin[25], prodigiosin[26], streptonigrin[27], lavendamycin[28], fa-
bianine[15b,c], guaiapyridine[15d] and onychine[15e]. As an example the key steps
in the total synthesis of streptonigrin are depicted in Scheme 1.6.

Scheme 1.6

Streptonigrin

6
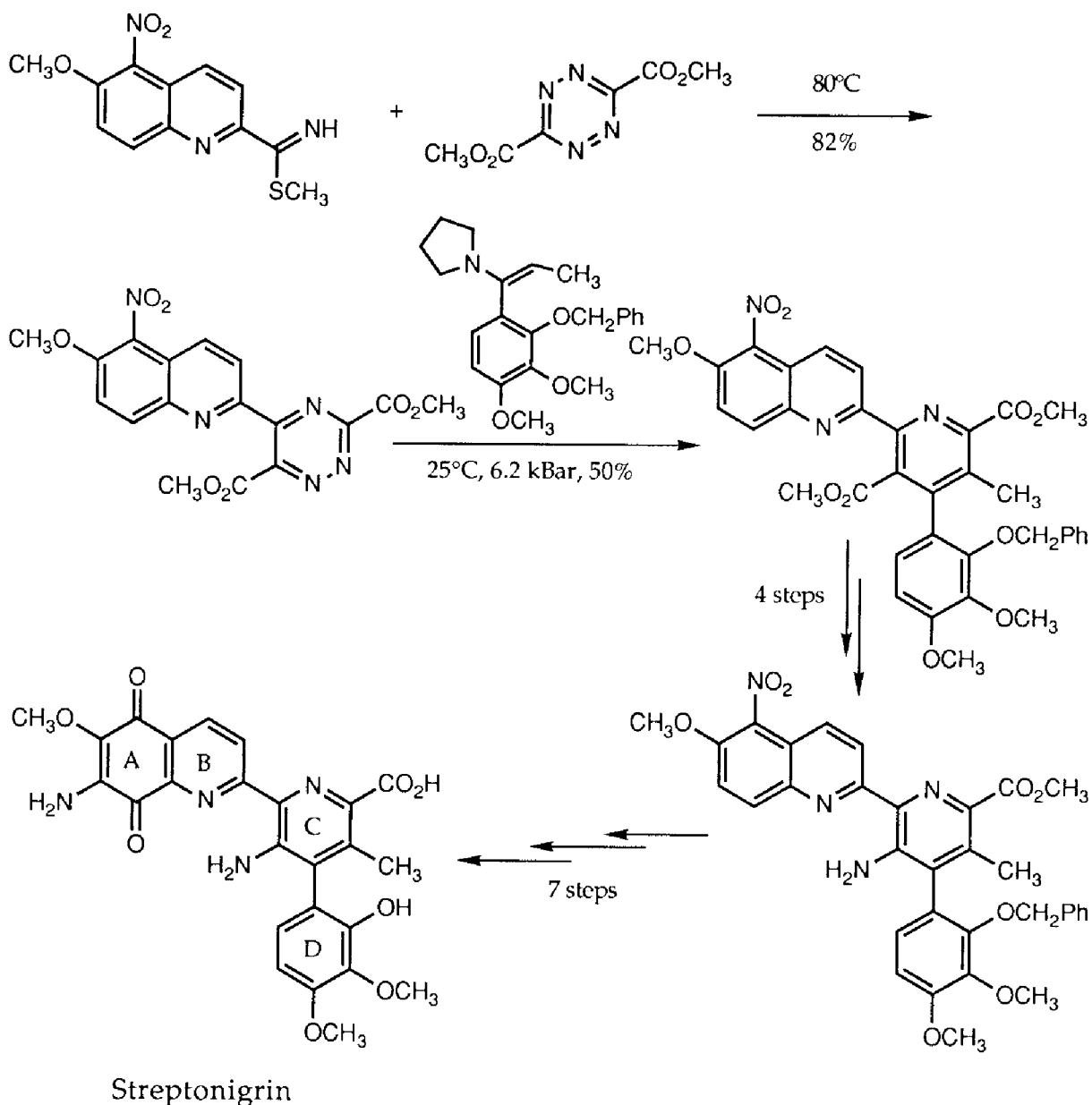
1.3 INTRAMOLECULAR DIELS-ALDER REACTIONS OF HETEROAROMATIC AZADIENES.

The Diels-Alder reaction proceeds through a highly ordered transition state that is reflected in large negative activation entropies. In the intramolecular version, some ordering can be accomplished in advance by making the two reacting functionalities part of the same molecule. This results in less negative activation entropies and increased reaction rates under often surprisingly mild conditions. Thus, the entropic assistance provided by the intramolecular Diels-Alder reaction offers a useful tool to promote the Diels-Alder reactivity. Although the first examples of the intramolecular Diels-Alder reaction of heteroaromatic azadienes have been presented in the early 1970's, more extensive studies of this intramolecular cycloaddition reaction, especially those with inverse electron demand, have still been limited to a few examples. Recently, exhaustive reviews have appeared dealing with, among others, the Diels-Alder reaction of heteroaromatic azadienes[29]. In this paragraph some examples of the intramolecular hetero Diels-Alder methodology are presented. It is not the intention to cover the very extense of literature about this subject, but some examples are selected to show the scope of this methodology and its limitations.

1.3.1 1,2,4,5-Tetrazines

Seitz *et al.*[30] recently described the intramolecular inverse electron demand Diels-Alder reaction of 1,2,4,5-tetrazines **25** carrying an ω-alkynyl-amino or ω-alkynyloxy side-chain attached to C-3 of the tetrazine nucleus (Scheme 1.7). The initial cycloadducts **26** lose nitrogen to afford the five to seven membered heterocyclic annelated pyridazines **27**. The Diels-Alder reactivity of these 1,2,4,5-tetrazines was found to depend upon the nature of the heteroatom in the dienophilic side-chain (O > NH) and especially on the length of the alkynyl side-chain (n = 1 > n = 2 > n = 3).

Scheme 1.7
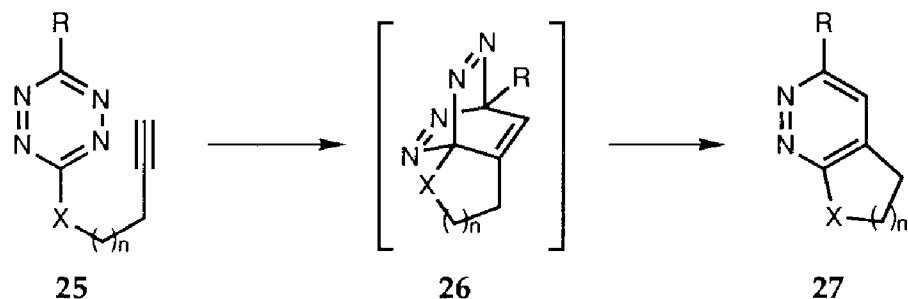
$$R = Ph, SMe, SOMe, SO_2Me; X = NH, n = 1, 2, 3; X = O, n = 1, 2$$

1.3.2 1,2,4-Triazines

Recent studies have explored and confirmed the utility of the intramolecular inverse electron demand Diels-Alder reaction of 1,2,4-triazines. 1,2,4-Triazines having the dienophilic side-chain attached to C-3 (e.g. compounds **28**) or C-6 (i.e. **31**) cycloadd across C-3/C-6 of the 1,2,4-triazine nucleus (Scheme 1.8). The initial tricyclic products **29** and **32** lose nitrogen to afford [b]- and [c]-annelated pyridine derivatives **30** and **33**, respectively[30b,c,31,32]. Whilst the regioselectivity of cycloaddition in most intermolecular reactions of 1,2,4-triazines is under strict electronic control, the analogous intramolecular reactions are sterically constrained. This concept has been applied to the intramolecular Diels-Alder reaction of 1,2,4-triazines **34** bearing the dienophilic tether at C-5: the cycloaddition must occur across C-5/N-2 of the 1,2,4-triazine nucleus (Scheme 1.9). The resulting cycloadducts **35** lead exclusively to condensed pyrimidines **36** by loss of R^2CN (and not to condensed pyridazines by loss of R^1CN) as a consequence of the fragility of the bridgehead N-N bond[33]. The reactivity of these intramolecular cycloaddition reactions has been shown to be dependent on the steric and electronic disposition of the dienophilic side-chain, the length of the tether between azadiene and dienophile and the point of attachment of the dienophilic side-chain to the 1,2,4-triazine nucleus. Incorporation of a phenyl group into the dienophilic side-chain leads to substantially milder

Scheme 1.8

X = O, S, SO, SO$_2$, NH, C(CN)$_2$, C(CN)CO$_2$Et, n = 1,2; X=O, S, NH, n = 3
X = CONH, n = 0

X = S, SO, SO$_2$, n = 1,2
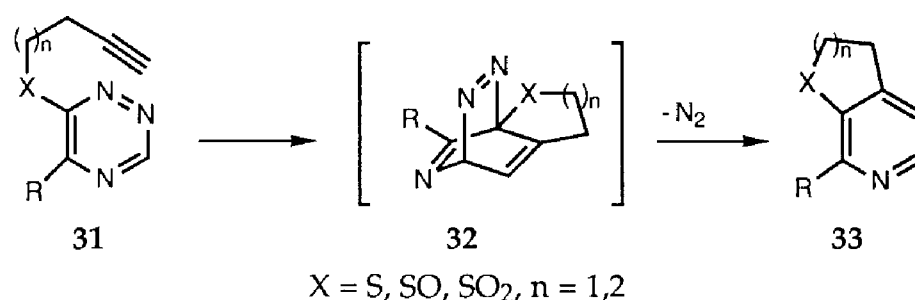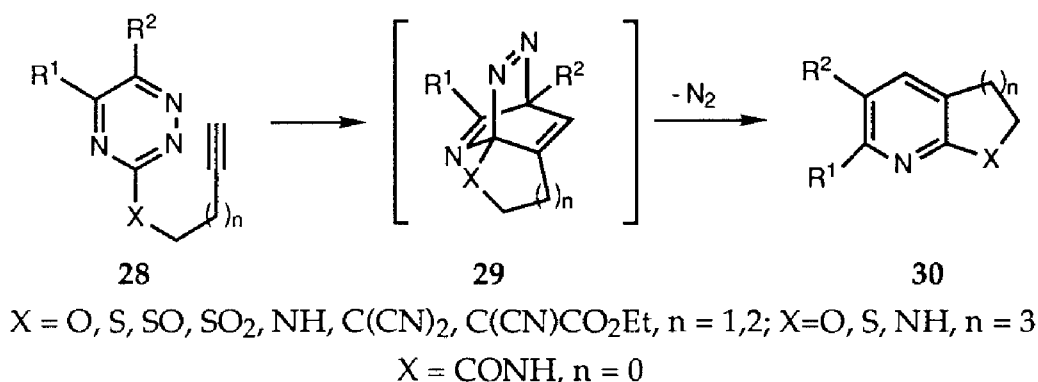
reaction conditions due to the presence of conformationally restrictive planar aromatic rings in the chain tethering the diene and dienophile[34]. These reactions were successfully extended to the use of electron-deficient nitrile dienophiles which result in the formation of novel tricyclic[34] and tetracyclic[35b] condensed pyrazines. Further extensions of these studies have led to the intramolecular Diels-Alder reaction of 6- and 7-azalumazines and 6-azapterins[35]. These reactions provide novel 6,7-annelated lumazines and 8-deazalumazines and 6,7-annelated 5-deazapteridines.

Scheme 1.9

X = S, O, C(CN)$_2$, R^1 = p-CH$_3$C$_6$H$_4$, CH$_3$, R^2 = C$_6$H$_5$, CH$_3$

9
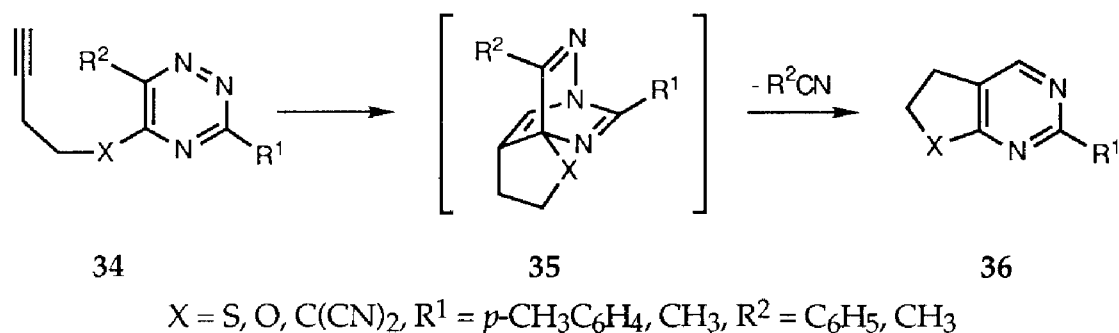
1.3.3 Pyridazines

The first reported intramolecular inverse electron demand Diels-Alder reactions of pyridazines involve ethers of type **36** (Scheme 1.10). The initial adducts **37** lose nitrogen to give dihydroxanthenes **38**. When R = H and R^1 = Cl, xanthene **39** is formed from the corresponding dihydroxanthene **38**[36].

Scheme 1.10

36   **37**   **38**   **39**

$R = CH_3, H; R^1 = Ph, Cl.$

Scheme 1.11

40   **41**

X = NCO_2CH_3	n = 1 (72-92%)
	n = 2, 3 (0%)
X = O	n = 1, 2, 3 (0%)

$R^1 = H, Cl; R^2 = H, CH_3, CH_2OTBMS.$
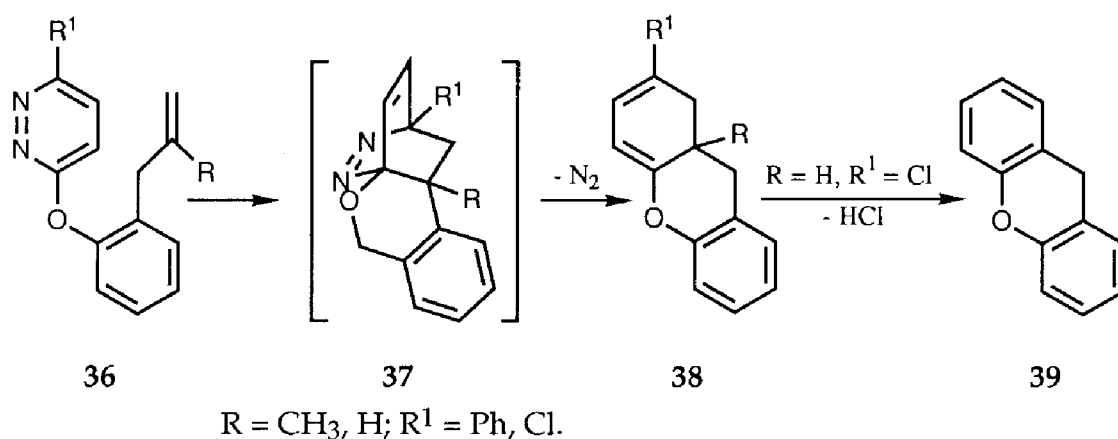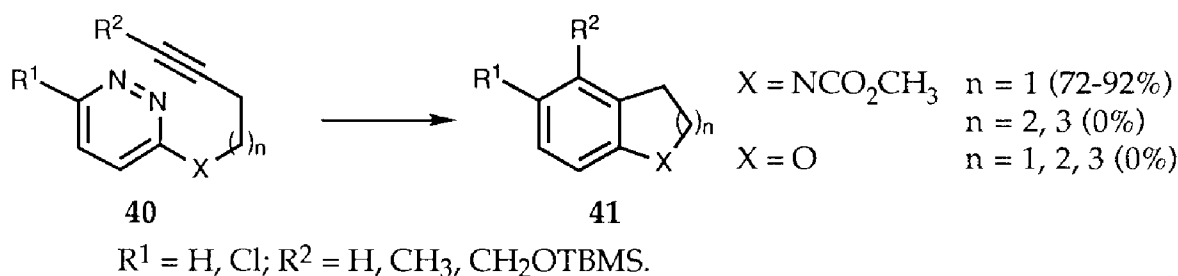
Recently, Boger and Coleman have explored the scope of the intramolecular Diels-Alder reaction of alkynylpyridazines **40** (Scheme 1.11)[37]. Their study suggests that the appropriate choice of the length of the alkyne side-chain (n = 1) and the heteroatom (X = NCO_2CH_3) primarily determines the success of the intramolecular Diels-Alder reaction of the alkynyl-pyridazines. This concept has found application in the total synthesis of the potent 3',5'-c-AMP phosphodiesterase inhibitors PDE-I (**44**, R = $CONH_2$)[38]

and PDE-II (**44**, R = $COCH_3$)[39] (Scheme 1.12), the antitumor antibiotic CC-1065[40] and related agents[41].

Scheme 1.12

42 230°C 82% 17h **43** **44**

Scheme 1.13

45 - N$_2$ **46**

47 - N$_2$ **48** - CH_3SO_2H **49**
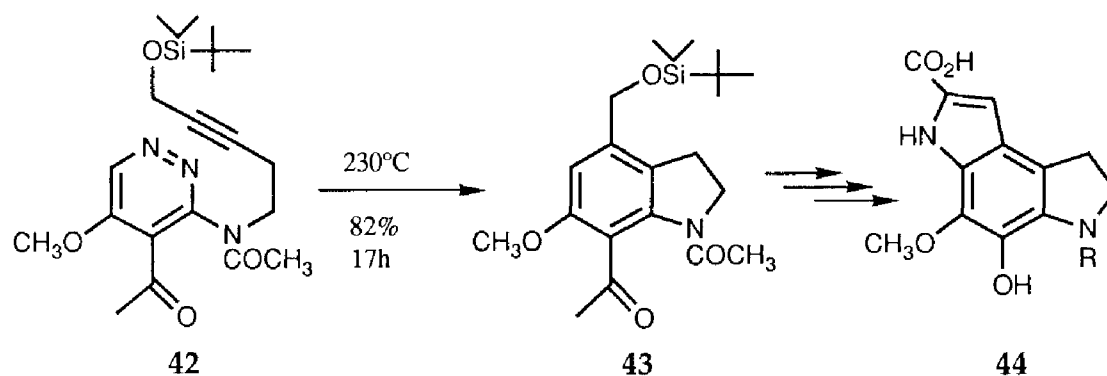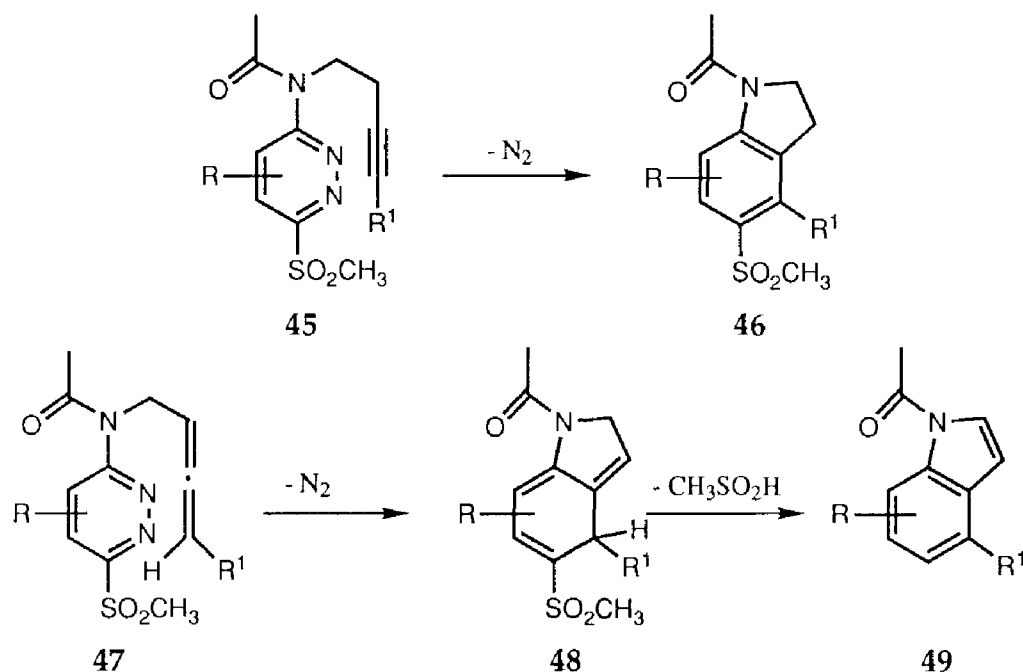
The intramolecular Diels-Alder reaction of alkynylpyridazines **45** and allenylpyridazines **47** permits the preparation of indolines **46** and indoles **49**, respectively (Scheme 1.13)[42]. The allenylpyridazines were found to undergo the intramolecular Diels-Alder reaction under substantially milder reaction conditions (120-160°C, 27h) than the corresponding alkynyl-

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pyridazines (235°C, 22h) due to the increased reactivity of the dienophile and entropically favoured potential for achieving the productive conformation necessary for participation in the intramolecular Diels-Alder reaction.

1.3.4 Pyrazines

The intramolecular inverse electron demand Diels-Alder reaction of pyrazines carrying an ω-alkyne side-chain -XCH$_2$CH$_2$C≡CH (X = NAc, O, S, SO, SO$_2$, C(CN)$_2$) has been described recently by de Bie et al. (Scheme 1.14)[43]. Pyrazines **50** with an electron-donating group (X = NAc, O, S) as link between diene and dienophile afford [c]-fused pyridines **53** as the main products, together with the [b]-fused products **52**, whereas pyrazines **50** carrying an electron-withdrawing group (X = SO, SO$_2$) are exclusively converted into [b]-fused pyridines **52**. The [b]-fused pyridine **52** (X = C(CN)$_2$, R = C(CN)$_2$(CH$_2$)$_2$C≡CH) is also the major product in the reaction of 2,5-bis-(1,1-dicyano-4-pentynyl)pyrazine, when heated at 120°C. The product distribution can be explained by the formation of intermediate **51**. In this unsymmetrical intermediate the loss of hydrogen cyanide can occur according

Scheme 1.14

50	51	52	53
X = NAc; R =H		17%	83%
X = O; R = H		12%	44%
X = S, R = H		24%	68%
X = SO, R = H		57%	
X = SO$_2$, R = H		88%	
X = C(CN)$_2$, R = C(CN)$_2$(CH$_2$)$_2$C≡CH		53%	35%
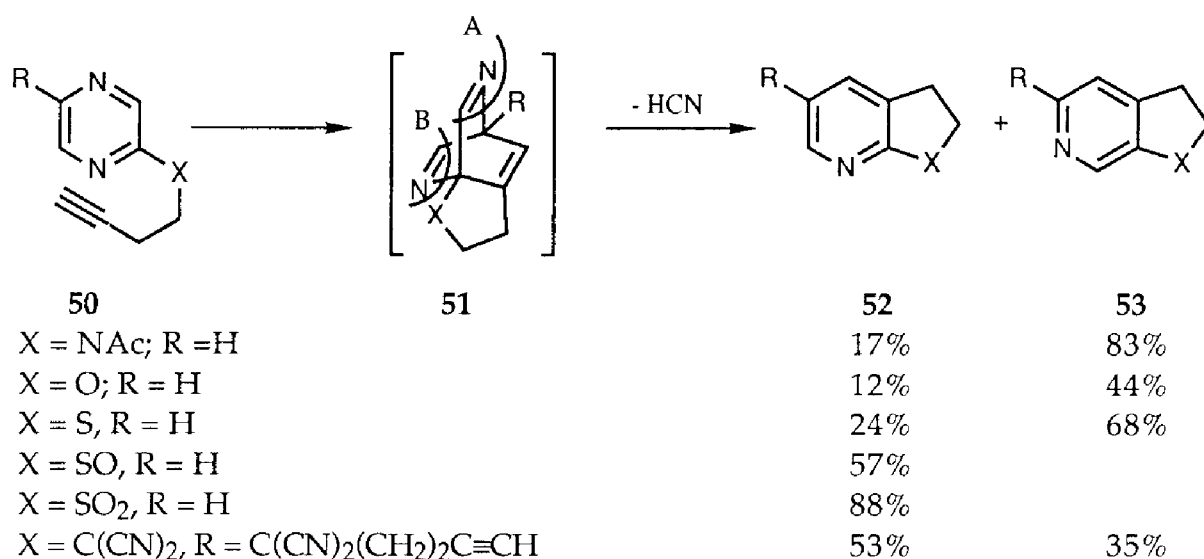
to route A and route B (see **51**) leading to **52** and **53**, respectively. It is shown that the electronic effect of the atom X attached directly to the pyrazine ring influences the course of the intramolecular cycloaddition reaction as a consequence of a transition state with some ionic character in going from **51** to **52** and **53**. Interestingly, compounds **52** and **53** (X = $C(CN)_2$, R = $C(CN)_2(CH_2)_2C\equiv CH$) undergo a second intramolecular Diels-Alder reaction on heating at 210°C. In both cases the resulting product is 1,1,5,5-tetracyano-1,2,3,5,6,7-hexahydro-s-indacene.

When the heteroatom between diene and dienophile is placed in the β-position of the side-chain (cf **54**; n = 1) the reaction occurs under mild conditions[44]. However, elongation of the tether between diene and dienophile results in more strenuous reaction conditions due to loss of entropic assistance (Scheme 1.15; n = 2)[45]. On the other hand, N-alkylation or N-protonation of these ω-alkynyloxymethylpyrazines and other ω-alkynylpyrazines results in considerably milder reaction conditions for the intramolecular Diels-Alder reaction due to a reduced HOMO/LUMO energy separation[44].

Scheme 1.15

54   55   56
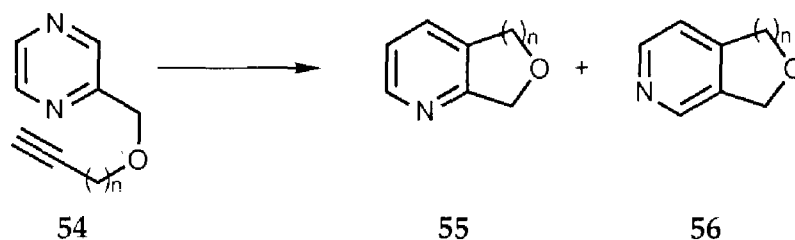
1.3.5 Pyrimidines

Intramolecular Diels-Alder reactions of simple pyrimidones **57** and **60** bearing olefinic, acetylenic or C≡N dienophiles at position 2 or 5 have been investigated thoroughly (Scheme 1.16)[46]. Apparently, these compounds give Diels-Alder reactions with normal electron demand. The observations have subsequently been applied to the total synthesis of (±)-actinidine **66** (Scheme 1.17)[47].

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Scheme 1.16

n = 1, 2; R = CH₃, OH; X = CH₂ (double bond), CH, N (triple bond)

R = H, CH₂Ph

Scheme 1.17

(±)-actinidine
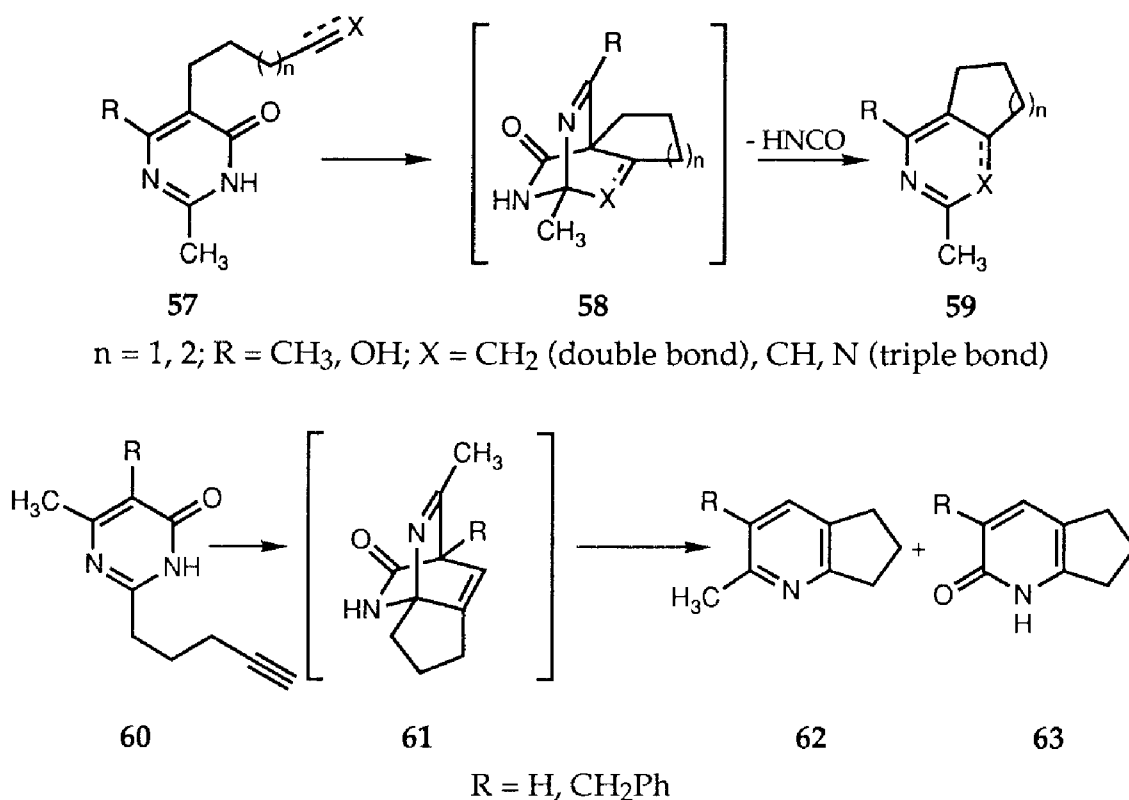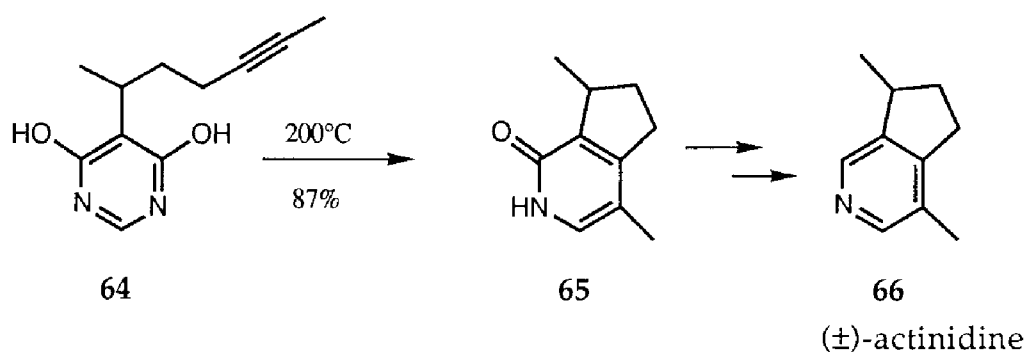
Until recently, the only clear examples of intramolecular inverse electron demand Diels-Alder reactions of pyrimidines have been described by Jojima *et al.*, who employed 2-(2-allylphenoxy)pyrimidines **67** as substrates (Scheme 1.18)[48]. However, the yields of adducts **68** were generally poor. Recently, a more detailed investigation on the intramolecular inverse

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electron demand Diels-Alder reaction of pyrimidines has been started at our laboratory[49]. The results of these studies are described in this thesis.

Scheme 1.18

67   68   69

R^1 = H, CH_3; R^2 = Cl, Br, H, CH_3
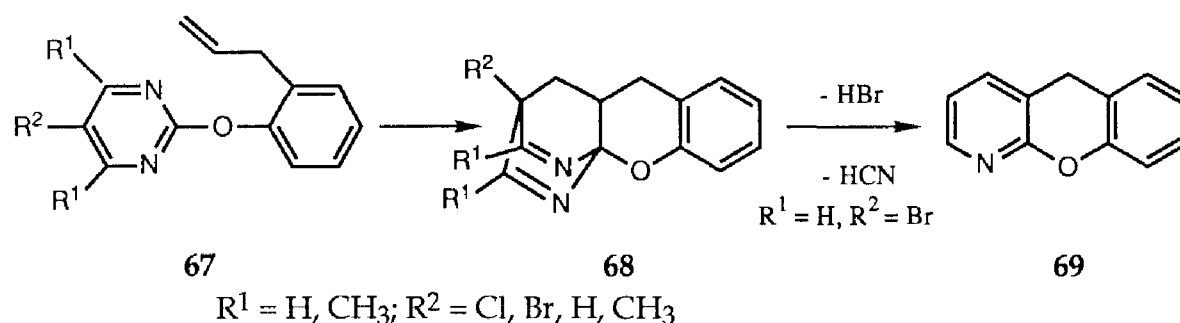
1.4   SCOPE OF THE PRESENT STUDY

Until recently, most investigations dealing with the intramolecular inverse electron demand Diels-Alder reaction of heterocyclic azadienes have been concentrated on the highly electron-deficient 1,2,4,5-tetrazines and 1,2,4-triazines.

Up to now there are only a few examples of intramolecular Diels-Alder reactions of pyrimidines, most of them employing pyrimidones and probably reacting with normal electron demand. The purpose of the investigations presented in this thesis was to extend the concept of the intramolecular inverse electron demand Diels-Alder reaction of heteroaromatic azadienes to the less electron-deficient pyrimidine system.

The first objective of our study was to investigate the synthetic applicability of pyrimidines carrying an appropriate dienophilic side-chain for the synthesis of new annelated pyridines. Furthermore, an important objective was to get more insight in the electronic and steric factors which determine the reactivity of compounds that undergo this intramolecular cycloaddition reaction.

As a first orientation the intramolecular inverse electron demand Diels-Alder reaction of pyrimidines carrying an ω-alkyne side-chain $XCH_2CH_2C\equiv CH$ at the 2-position (X = O, NH, NAc, S, SO, SO_2) or at the 5-position (X = S) is described in Chapter 2. In this way new syntheses of 2,3-dihydrofuro[2,3-b]-

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pyridines, 2,3-dihydropyrrolo[2,3-<u>b</u>]pyridines, 2,3-dihydrothieno[2,3-<u>b</u>]pyridines and 2,3-dihydrothieno[2,3-<u>c</u>]pyridines have become available. The electronic influence of the heteroatom (X) in the dienophilic side-chain as well as the electronic and steric influence of substituents in the pyrimidine ring on the reactivity is discussed.

In Chapter 3 the intramolecular Diels-Alder reaction of 2-(4-pentynyl)-pyrimidines and 2-(1,1-dicyano-4-pentynyl)pyridines to the corresponding 6,7-dihydro-5H-1-pyrindines is described. The influence of electronic and steric effects, especially the effect of gem-disubstitution on the chain connecting the reaction centers, on the rate of cycloaddition is discussed. Furthermore, the influence of the length of the tether between azadiene and dienophile on the reactivity of 2-(1,1-dicyano-ω-alkynyl)pyrimidines has been established.

In Chapter 4 the synthesis of several 2- and 5-propynyloxymethylpyrimidines and their subsequent intramolecular Diels-Alder reaction to 5,7-dihydrofuro[3,4-<u>b</u>]pyridines and 1,3-dihydrofuro[3,4-<u>c</u>]pyridines, respectively, is described. The effect of introducing one or two alkyl (aryl) groups at the α- or γ-position of the side-chain of the 5-propynyloxymethylpyrimidines on the reaction rate will be discussed in terms of relative rotamer population.

Chapter 5 describes some kinetic investigations on the intramolecular Diels-Alder reaction of 2-(1,1-dicyanopent-4-yn-1-yl)-5-(p-substituted phenyl)pyrimidines. From a Hammett plot of rate constants against σ-constants the type of Diels-Alder reaction and the influence of electronic factors on the reactivity have been studied. The influence of solvent effects on the reactivity has been determined for a series of solvents with different polarity.

In Chapter 6 the effect of N-alkylation and N-protonation of several ω-alkynylpyrimidines on their Diels-Alder reactivity is described and explained in terms of HOMO/LUMO energy separation.

A general discussion on the contents of this thesis and some miscellaneous results are given in Chapter 7.

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CHAPTER 2

RINGTRANSFORMATIONS OF PYRIMIDINES BY INTRAMOLECULAR DIELS-ALDER REACTIONS. SYNTHESIS OF ANNELATED PYRIDINES.

2.1   INTRODUCTION

In the last two decades inverse electron demand Diels-Alder reactions of heterocyclic azadienes with electron-rich dienophiles have recieved considerable attention[1]. Especially the intermolecular versions of these cycloaddition reactions are well documented. Among these, 1,2,4,5-tetrazines and 1,2,4-triazines constitute the most thoroughly investigated azadiene systems capable of 4π-diene participation[2]. In case of less reactive pyrimidines and pyrazines, reactivity can be enhanced by introducing electron-withdrawing substituents in the azadiene[3,4]. The entropic advantage inherent in intramolecular Diels-Alder reactions has allowed extensions of such cyclizations to exploit less reactive dienophiles such as terminal alkynes and alkenes. Successful applications of this strategy are described for 1,2,4,5-tetrazines[5], 1,2,4-triazines[5,6], pyridazines[7], pyrazines[8], pyrimidines[9] and pyridines[10]. Recently, intramolecular inverse electron demand cycloaddition reactions of pyrimidines[11] and nitro-pyridines[11b] carrying an appropriate dienophilic side-chain at the 2- or 5-position were observed at our laboratory. In this paper we describe detailed results of our research on intramolecular Diels-Alder reactions of pyrimidines carrying an appropriate dienophilic side-chain, connected through a heteroatom (oxygen, sulfur or nitrogen) to the pyrimidine ring.

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2.1 RESULTS AND DISCUSSION

First, the cycloaddition reaction of 2-(3-butynyloxy)pyrimidines **1a-d** and 2-(3-pentynyloxy)pyrimidines **1e-f** was investigated. These compounds were prepared from the corresponding 2-chloropyrimidines and the sodium salt of 3-butyn-1-ol or 3-pentyn-1-ol, respectively, in good yields. Heating of compounds **1** in refluxing nitrobenzene under nitrogen led to the formation of 2,3-dihydrofuro[2,3-b]pyridines **3** in reasonable yields (Scheme 2.1). Their formation is supposed to occur via the intermediacy of tricyclic adducts **2** resulting from an intramolecular cycloaddition across the C-2 and C-5 position and subsequent elimination of hydrogen cyanide or acetonitrile. The supposed intermediate cycloaddition products **2** could not be isolated or identified by NMR spectroscopy.

The reaction conditions necessary for the complete disappearance of **1a** and **1b** (see Table 2.1) are comparable. This means that the activating effect of the strong electron-withdrawing nitro group at the 5-position of the pyrimidine does not lead to an increased rate of cycloaddition. This may be due to steric effects.

Scheme 2.1

1	**2**	**3**

a; $R^1, R^2, R^3, R^4 = H$ b; $R^1, R^3, R^4 = H; R^2 = NO_2$

c; $R^2, R^4 = H; R^1, R^3 = CH_3$ d; $R^2, R^3, R^4 = H; R^1 = CH_3$

e; $R^1, R^2, R^3 = H; R^4 = CH_3$ f; $R^1, R^3 = H; R^2 = NO_2; R^4 = CH_3$
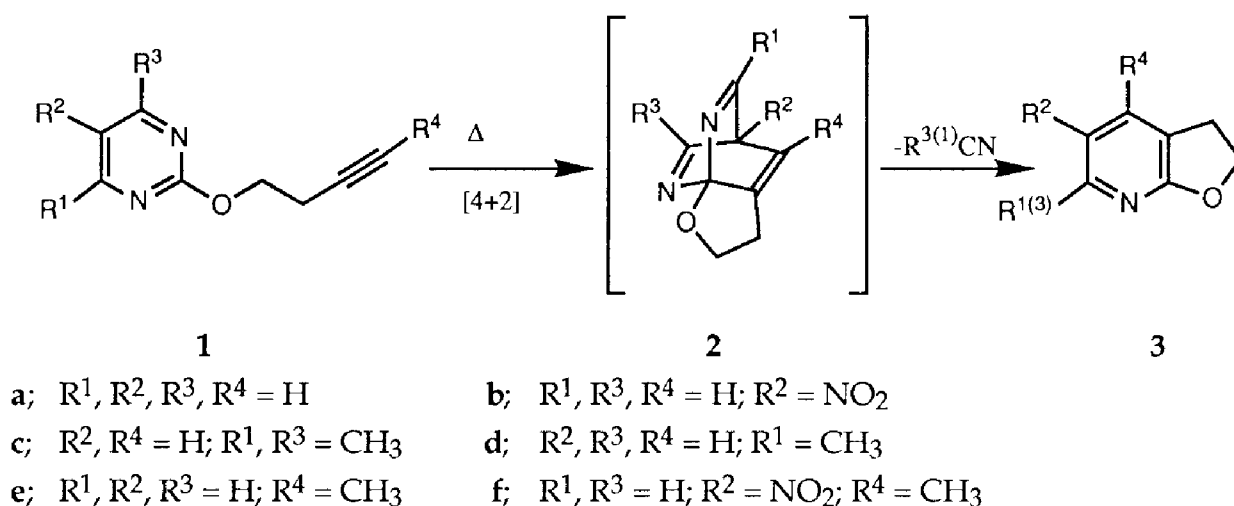
Introduction of one weak electron donating methylgroup at C-4 (C-6), i.e. compound **1d**, does not lead to a considerable decrease of cycloaddition rate. Interestingly, a mixture of 2,3-dihydrofuro[2,3-b]pyridine **3a** and 2,3-

dihydro-6-methylfuro[2,3-b]pyridine **3c** is obtained in a ratio of approximately 1:1.8. These cyclization products arise from intermediate cycloadduct **2d** by loss of acetonitrile or hydrogen cyanide, respectively. In this case the loss of hydrogen cyanide is favoured more than the loss of acetonitrile[12]. It is interesting that introduction of methyl groups at both C-4 and C-6, i.e. **1c**, results in a considerable decreased rate of cycloaddition. Taking into account that introduction of one methyl group hardly influences the rate of cycloaddition it is reasonable to suggest that in the conversion of **1c** into **3c** not only the electron donating character of the methyl groups must be taken into account, but also that the combined steric effects of both methyl groups at C-4 and C-6 disfavour the cycloaddition.

Comparison of the reaction conditions for complete disappearance of **1a** and **1e** shows that introduction of a methyl group at the triple bond of the dienophilic side-chain decreases reactivity. We have to conclude that in this reaction the activating electronic effect of the methyl group is exceeded by steric hindrance of this group exerted by approach of the dienophile to C-5. The higher reactivity of 5-nitro-2-(3-pentynyloxy)pyrimidine **1f** towards cycloaddition as compared to that of 2-(3-pentynyloxy)pyrimidine **1e** reflects the activating effect of the nitro group on the pyrimidine towards cycloaddition.

In order to investigate the influence of different heteroatoms in α-position of the dienophilic side-chain we also studied the intramolecular Diels-Alder reactions of 2-(3-butynylamino)pyrimidines **4** and 2-(3-butynylthio)pyrimidines **7**. Heating of **4a** and **4b**, prepared in good yields from the corresponding 2-chloropyrimidines and 4-amino-1-butyne, in refluxing nitrobenzene under nitrogen for 36 hours only led to decomposition and no indication for the formation of 1H-2,3-dihydropyrrolo[2,3-b]-pyridines **6a** and **6b** could be found. However, when the NH group was acetylated, the resulting 2-(N-acetyl-3-butynylamino)pyrimidines **4c** and **4d**, in which the pyrimidine rings are less electron-rich than in case of **4a**, **4b**, smoothly underwent the intramolecular Diels-Alder reaction in high yield at 180°C, affording the 1-acetyl-2,3-dihydropyrrolo[2,3-b]pyridines **6c** and **6d**.

With exception of **7b** the 2-(3-butynylthio)pyrimidines **7** were prepared in good yields from the corresponding 2-mercaptopyrimidines and 4-iodo-1-butyne in the presence of triethylamine. Compound **7b** was obtained from sodium nitromalonaldehyde and S-3-butynylthiourea hydroiodide in low

Scheme 2.2

4

a; R, R^1 = H
c; R^1 = H; R = C(O)CH$_3$

5

b; R = H; R^1 = NO$_2$
d; R^1 = NO$_2$; R = C(O)CH$_3$

6
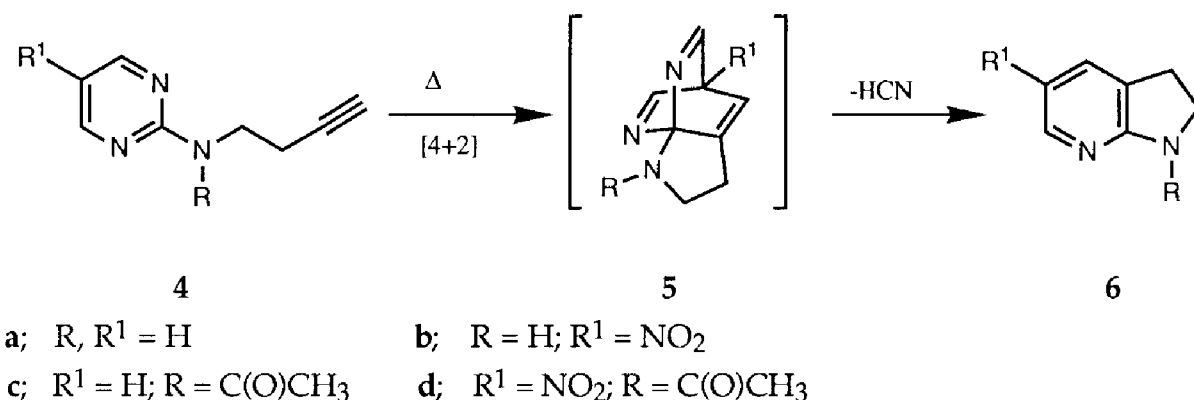
yield. On heating in refluxing nitrobenzene the compounds **7** cyclized to the corresponding 2,3-dihydrothieno[2,3-b]pyridines **9**. In analogy with **1d**, 2-(3-butynylthio)-4-methylpyrimidine **7d** cyclized to a mixture of thieno[2,3-b]pyridines **9a** and **9c** in a ratio of approximately 1:2.2 by loss of either acetonitrile or hydrogen cyanide from intermediate cycloadduct **8d**.

Scheme 2.3

7

a; R^1, R^2, R^3 = H
c; R^2 = H; R^1, R^3 = CH$_3$
d; R^1, R^3 = H; R^2 = Ph

8

b; R^1, R^2 = H; R^3 = NO$_2$
d; R^2, R^3 = H; R^1 = CH$_3$

9
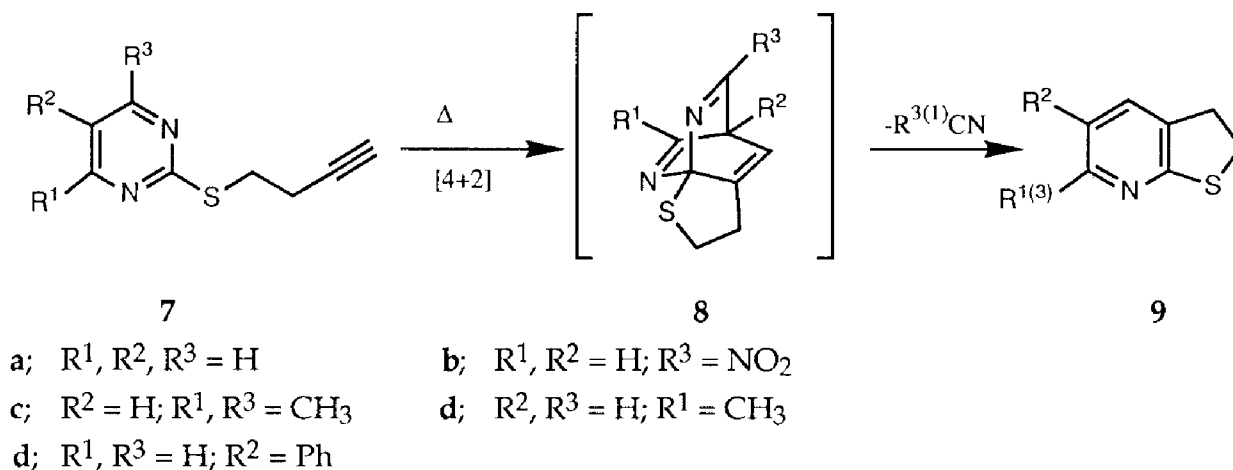
Comparison of the temperature and the reaction time for complete conversion of the compounds **4c** and **4d** as well as **7a** and **7b** confirm that the presence of the nitrogroup at C-5 does not considerably influence the rate of the reaction (see Table 2.1). We obtained the same result with the compounds **1a** and **1b**.

TABLE 2.1   Intramolecular Diels-Alder reactions of pyrimidines **1, 4, 7, 10b** and **12**. Reaction conditions, products and yields.

Pyrimidines Starting Compounds	Reaction Conditions Temp. (°C)	Time (h)	Reaction Compounds	Yield (%)
1a	210	24	**3a**	52
1b	210	24	**3b**	55
1c	210	60	**3c**	68
1d	210	26	**3a + 3c**	60
1e	210	96	**3e**	40
1f	210	28	**3f**	83
4c	180	12	**6c**	85
4d	180	12	**6d**	87
7a	210	18	**9a**	57
7b	210	18	**9b**	75
7c	210	26	**9c**	51
7d	210	18	**9a + 9c**	69
7e	210	21	**9e**	75
10b	180	16	**11b**	63
12a	180	12	**14a**	85
12c	180	46	**14c**	64
12d	180	34	**14c**	60

However, it is clear that the nature of the heteroatom in the dienophilic side-chain influences the reactivity. The reactivity increases in the order NH < O < S < NC(O)CH$_3$. This order of reactivity reflects the decrease of the electron donation into the π-system of the pyrimidine ring[13] and is similar to those found in the 1,2,4-triazine and pyrazine series[6b, 8].

From the observations described above it may be inferred that the reactivity towards intramolecular inverse electron demand Diels-Alder reactions may be enhanced by increasing the electron-deficiency of the pyrimidine ring. Therefore, the highly electron-deficient sulfoxide **10a** (X = SO) and sulfone **10b** (X = SO$_2$) were also studied. These compounds were easily prepared from the sulfide **7a** by oxidation with one or two equivalents of m-chloroperbenzoic acid, respectively. Indeed, 2-(3-butynylsulfonyl)-pyrimidine **10b** (X = SO$_2$) already cyclized to 1,1-dioxo-2,3-dihydrothieno-[2,3-b]pyridine **11b** when heated at 180°C for 16 hours, conditions being

less strenuous than those for the sulfide **7a**. Unfortunately, 2-(3-butynyl-sulfinyl)pyrimidine **10a** (X = SO) decomposes when heated above 100°C. No product formation could be detected. However, **10a** underwent cyclo-addition when heated at 55°C in CDCl$_3$ under a pressure of 15 kBar, yielding **11a**. In order to compare the reactivities of **7a**, **10a** and **10b** we also reacted **7a** and **10b** under the same high pressure conditions as **10a**. ^{1}H NMR spectroscopy showed that after one night **10a** was converted into **11a** for more than 90%, whereas **10b** was only converted into **11b** for approximately 25%. Under these conditions **7a** did not give the cycloadduct **9a** at all. This violation of the "normal" order of reactivity (sulfoxide > sulfone > sulfide) agrees with observations of Taylor and Macor in the 1,2,4-triazine series[6a]. It can be explained if one considers that in intramolecular cycloaddition reactions the reactivity is not only determined by electronic effects, but that

Scheme 2.4

7a $\xrightarrow{\text{mcpba}}$ 10 $\xrightarrow[\substack{55^0\text{C, 5 kbar,}\\ X = \text{SO, SO}_2}]{180^0\text{C, X = SO}_2}$ 11

a; X = SO   b; X = SO$_2$
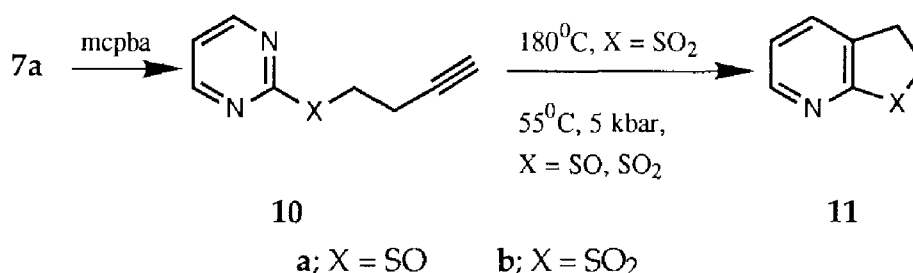
also the possibility for a good overlap between the HOMO$_{dienophile}$ and LUMO$_{azadiene}$ is essential. This is influenced by the nature of the tether between diene and dienophile. The smaller the C-S-C bond angle in the dienophilic side-chain, the closer the dienophile can approach the heterocyclic diene. Thus, the sulfoxide **10a**, having the smallest C-S-C bond angle[6a] has the fastest rate of intramolecular cyclization. The higher degree of electron deficiency in the ring in sulfone **10b** is partly negated by its larger C-S-C bond angle.

We also included in our investigations some pyrimidine derivatives with a dienophilic side-chain in the 5-position, i.e. the 5-(3-butynylthio)pyrimidines **12a-d**. The compounds **12a** and **12b** were prepared in good yield by treatment of the appropriate substituted bis-[pyrimidinyl-(5)]-disulfide with triethylamine and sodium dithionite followed by reaction with 4-iodo-1-

butyne. On heating at 180°C **12a** cyclized to 2,3-dihydro-5-phenylthieno-[2,3-c]pyridine **14a** in high yield. Under the same conditions **12c** and **12d** both reacted to 5-(acetylamino)-2,3-dihydrothieno[2,3-c]pyridine **14c**. The amino compound **12b** was found not to cyclize into **14b**.

Scheme 2.5

| 12 | 13 | 14 |

a; R = Ph   b; R = NH$_2$ c; R = NHC(O)CH$_3$ d; R = N(C(O)CH$_3$)$_2$
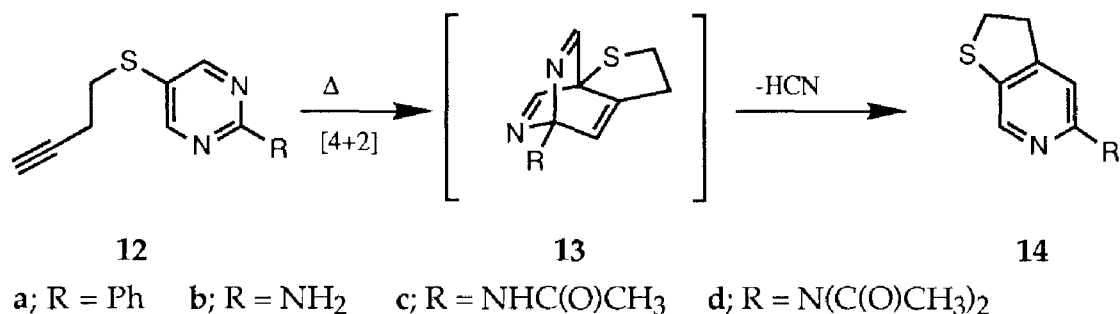
In order to compare the reactivities of pyrimidines with a dienophilic side-chain attached to the 2- and 5-position, respectively, we heated 2-(3-butynylthio)-5-phenylpyrimidine **7e** and 5-(3-butynylthio)-2-phenylpyrimidine **12a** at 190°C in nitrobenzene in a NMR tube. The rate of product formation and the rate of decrease of starting material was monitored by means of NMR spectroscopy. It was found that **12a** cyclizes 18.4 times faster than **7e**. This difference in reactivity is probably caused by a different resonance donation of the 3-butynylthio group to the pyrimidine ring being larger in 2-(3-butynylthio)-5-phenylpyrimidine **7e** than in 5-(3-butynylthio)-2-phenylpyrimidine **12a**. This greater resonance contribution in **7e** hampers rotation about the S-pyrimidine bond and consequently the dienophilic side-chain can more easily approach the azadiene in compound **12a** than in compound **7e**, resulting in a larger rate of cycloaddition of compound **12a**.

2.3   EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer. Chemical shifts are determined in ppm downfield from TMS. ^{13}C NMR spectra were recorded at 75.46 MHz on a Bruker CXP-300 spectrometer. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed on Merck silica gel 60 (70-230 mesh ASTM).

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<u>General procedure for the synthesis of 2-(3-alkynyloxy)pyrimidines (1).</u>

The appropriate chloropyrimidine (4.4 mmol, 1 eq) was added, with the exception of 2-chloro-5-nitropyrimidine, at room temperature to a solution of sodium (0.1 g, 4.4 mmol) in 3-butyn-1-ol (3 ml) or 3-pentyn-1-ol (3 ml, entries **1e** and **1f**). 2-Chloro-5-nitropyrimidine (entries **1b** and **1f**) was added at 0°C and the resulting mixture stirred first at room temperature for one hour. The mixture was then stirred at 80°C for the time given and after cooling ether (10 ml) was added. Sodium chloride was filtered off and the solvent evaporated under reduced pressure to afford the crude 2-(3-alkynyloxy)pyrimidine (1) which was purified by bulb-to-bulb destillation to remove any remaining alkynol, followed by column chromatography eluting with the given solvent.

<u>2-(3-Butynyloxy)pyrimidine (1a).</u> From 2-chloropyrimidine. Reaction time 2 h. Eluent ether. Obtained as a pale yellow oil (75%) which slowly solidifies upon standing: m.p. 39-41°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 8.50 (d, J = 5.0 Hz, 2H), 6.93 (t, J = 5.0 Hz, 1H), 4.45 (t, J = 7.2 Hz, 2H), 2.71 (dt, J$_1$ = 7.3 Hz, J$_2$ = 2.9 Hz, 2H), 2.03 (t, J = 2.8 Hz, 1H).
HRMS Calcd. for C$_8$H$_8$N$_2$O (M$^+$): 148.0637. Found: 148.0640.
Anal. Calcd. for C$_8$H$_8$N$_2$O (148.16): C, 64.84; H, 5.44; N, 18.90. Found: C, 64.58; H, 5.46; N, 19.21.

<u>2-(3-Butynyloxy)-5-nitropyrimidine (1b).</u> From 2-chloro-5-nitropyrimidine[14]. Reaction time 1 h. Eluent ether. Obtained as a yellow solid (70%): m.p. 61-63°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.32 (s, 2H), 4.62 (t, J = 6.9 Hz, 2H), 2.75 (dt, J$_1$ = 7.1 Hz, J$_2$ = 2.7 Hz, 2H), 2.10 (t, J = 2.7 Hz, 1H).
^{13}C NMR (CDCl$_3$) δ 166.7, 156.0, 138.5, 79.2, 70.5, 67.2, 19.0.
HRMS Calcd. for C$_8$H$_7$N$_3$O$_3$ (M$^+$): 193.0487. Found: 193.0486.
Anal. Calcd. for C$_8$H$_7$N$_3$O$_3$(193.16): C, 49.75; H, 3.65; N, 21.75. Found: C, 49.53; H, 3.73; N, 22.06.

<u>2-(3-Butynyloxy)-4,6-dimethylpyrimidine (1c).</u> From 2-chloro-4,6-dimethyl-pyrimidine[15]. Reaction time 3 h. Eluent: ether/petroleum ether 40-60 (1:1). Obtained as a pale yellow solid (72%): m.p. 39-41°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 6.75 (s, 1H), 4.51 (t, J = 7.2 Hz, 2H), 2.73 (dt, J$_1$ = 7.5 Hz, J$_2$ = 2.7 Hz, 2H), 2.44 (s, 6H), 2.05 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{10}$H$_{12}$N$_2$O (176.21): C, 68.16; H, 6.86; N, 15.90. Found: C, 67.94; H, 7.01; N, 15.99.

<u>2-(3-Butynyloxy)-4-methylpyrimidine (1d).</u> From 2-chloro-4-methyl-pyrimidine[16]. Reaction time 2.5 h. Eluent dichloromethane/ether (3:1). Obtained as a pale yellow oil (73%); ^{1}H NMR (CDCl$_3$) δ 8.34 (d, J = 4.8 Hz, 1H), 6.82 (d, J = 5.1 Hz, 1H), 4.47 (t, J = 7.2 Hz, 2H), 2.70 (dt, J$_1$ = 7.4 Hz, J$_2$ = 2.7 Hz), 2.45 (s, 3H), 2.03 (t, J = 2.7 Hz, 1H).
HRMS Calcd. for C$_9$H$_{10}$N$_2$O (M$^+$): 162.0793. Found: 162.0787.

2-(3-Pentynyloxy)pyrimidine (1e). From 2-chloropyrimidine. Reaction time 2 h. Eluent ether. Obtained as a pale yellow oil (65%); ^{1}H NMR (CDCl$_3$) δ 8.53 (d, J = 4.5 Hz, 2H), 6.95 (t, J = 4.9 Hz, 1H), 4.44 (t, J = 7.2 Hz, 2H), 2.65 (qt, J$_1$ = 7.2 Hz, J$_2$ = 2.7 Hz, 2H), 1.75 (t, J = 2.6 Hz, 3H). HRMS Calcd. for C$_9$H$_{10}$N$_2$O (M$^+$): 162.0793. Found: 162.0787.

2-(3-Pentynyloxy)-5-nitropyrimidine (1f). From 2-chloro-5-nitropyrimidine. Reaction time 2 h. Eluent dichloromethane. Obtained as a yellow solid (52%): m.p. 74-75°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.30 (s, 2H), 4.57 (t, J = 7.2 Hz, 2H), 2.68 (dt, J$_1$ = 7.3 Hz, J$_2$ = 2.5 Hz), 1.77 (t, J = 2.4 Hz, 3H).
Anal. Calcd. for C$_9$H$_9$N$_3$O$_3$ (207.19): C, 52.16; H, 4.37; N, 20.28. Found: C, 52.16; H, 4.39; N, 20.36.

General procedure for the synthesis of the 2-(3-butynylamino)pyrimidines 4a and 4b and 2-(N-acetyl-3-butynylamino)pyrimidines 4c and 4d.
A mixture of the appropriate chloropyrimidine (4.4 mmol) and 4-amino-1-butyne[17] (0.61 g; 8.8 mmol) in ethanol was refluxed for the time given. After cooling the solvent was evaporated from the reaction mixture and the residue purified by column chromatography (eluting with ether) to yield the corresponding 2-(3-butynylamino)pyrimidine (4a or 4b). The latter compound (4a or 4b; 2 mmol) was heated for 4 hours at 90°C in acetic anhydride (3 ml) containing two drops of concentrated sulfuric acid. After cooling the excess of acetic anhydride was removed under reduced pressure. The residue was treated with water (10 ml), neutralized with sodium bicarbonate and extracted with dichloromethane. The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (ether as eluent) to give the corresponding 2-(N-acetyl-3-butynylamino)pyrimidine (4c or 4d).

2-(3-Butynylamino)pyrimidine (4a). From 2-chloropyrimidine. Reflux time 24 h. Obtained as a colourless solid (76%): m.p. 60-61°C (hexanes/toluene): ^{1}H NMR (CDCl$_3$) δ 8.29 (d, J = 4.9 Hz, 2H), 6.6 (br, 1H), 6.51 (t, J = 4.8 Hz, 1H), 3.58 (q, J$_{CH_2-CH_2}$ = J$_{CH_2-NH}$ = 6.6 Hz, 2H), 2.51 (dt, J$_1$ = 6.6 Hz, J$_2$ = 2.7 Hz, 2H), 2.02 (t, J = 2.5 Hz, 1H). MS: m/e 147 (M$^+$).
Anal. Calcd. for C$_8$H$_9$N$_3$ (147.18): C, 65.28; H, 6.16; N, 28.55. Found: C, 65.21; H, 6.18; N, 28.13.

2-(N-acetyl-3-butynylamino)pyrimidine (4c). Obtained as a yellow oil (65%) which slowly crystalizes: m.p. 68-69°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.68 (d, J = 5.0 Hz, 2H), 7.09 (t, J = 5.0 Hz, 1H), 4.28 (t, J = 7.5 Hz, 2H), 2.56 (dt, J$_1$ = 7.6 Hz, J$_2$ = 2.5 Hz, 2H), 2.45 (s, 3H), 1.88 (t, J = 2.7 Hz, 1H). MS: m/e 189 (M$^+$).
Anal. Calcd. for C$_{10}$H$_{11}$N$_3$O (189.21): C, 63.47; H, 5.86; N, 22.21. Found: C, 63.62; H, 5.91; N, 22.55.

<u>2-(3-Butynylamino)-5-nitropyrimidine (4b).</u> From 2-chloro-5-nitropyrimidine. Reflux time 3 h. Obtained as a pale yellow solid (65%): m.p. 124-126°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.09 (s, 2H), 6.5 (br, 1H), 3.72 (q, $J_{CH_2-CH_2}$ = J_{CH_2-NH} = 6.4 Hz, 2H), 2.52 (dt, J_1 = 6.5 Hz, J_2 = 2.7 Hz, 2H), 2.03 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_8$H$_7$N$_4$O$_2$ (192.18): C, 49.99; H, 4.19; N, 29.15. Found: C, 49.72; H, 4.16; N, 29.45.

<u>2-(N-acetyl-3-butynylamino)-5-nitropyrimidine (4d).</u> Obtained as a yellow oil (60%) which slowly solidifies upon standing in a refrigarator: m.p. 66-68°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.33 (s, 2H), 4.46 (t, J = 7.2 Hz, 2H), 2.60 (dt, J_1 = 7.2 Hz, J_2 = 2.7 Hz, 2H), 2.60 (s, 3H), 1.87 (t, J = 2,4 Hz, 1H).
Anal. Calcd. for C$_{10}$H$_{10}$N$_4$O$_3$ (234.21): C, 51.27; H, 4.30; N, 23.92. Found: C, 51.16; H, 4.31; N, 24.07.

<u>2-(3-Butynylthio)pyrimidine (7a).</u> To a stirred suspension of 2-mercapto-pyrimidine (1.12 g; 10 mmol) in water (20 ml) was added 3 g of triethylamine (30 mmol). When all 2-mercaptopyrimidine was dissolved 4-iodo-1-butyne[18] (1.8 g; 10 mmol) was added. The mixture was heated at 70°C for two hours, then cooled and extracted with ether. The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure to afford an oil which was purified by column chromatography (ether as eluent) to yield 0.93 g (57%) of **7a** as a pale brown oil; ^{1}H NMR (CDCl$_3$) δ 8.52 (d, J = 4.8 Hz, 2H), 6.98 (t, J = 4.9 Hz, 1H), 3.41 (t, J = 7.5 Hz, 2H), 2.65 (dt, J_1 = 7.5 Hz, J_2 = 2.7 Hz, 2H), 2.06 (t, J = 2.6 Hz, 1H). MS: m/e 164 (M$^+$).
Anal. Calcd. for C$_{14}$H$_{11}$N$_5$O$_7$S (393.33; picrate: m.p. 87-89°C): C, 42.75; H, 2.82; N, 17.81. Found: C, 43.08; H, 2.90; N, 18.16.

<u>S-3-butynylthiourea hydroiodide.</u> This compound was prepared quantitatively from 4-iodo-1-butyne and thiourea according to a known literature method[19]. It was obtained as a white solid; m.p. 92-94°C; ^{1}H NMR (acetone-d$_6$) δ 8.98 (brs, 4H), 3.60 (t, J = 6.8 Hz, 2H), 2.75 (dt, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 2H), 2.60 (t, J = 2.5 Hz, 1H).
Anal. Calcd. for C$_5$H$_9$IN$_2$S (256.10): C, 23.44; H, 3.54; N, 10.93. Found: C, 23.43; H, 3.57; N, 11.23.

<u>2-(3-Butynylthio)-5-nitropyrimidine (7b).</u> A mixture of sodium nitromalon-aldehyde[20] (2.56g; 18.4 mmol), S-3-butynylthiourea hydroiodide (4.21 g; 16.4 mmol) and ethylpiperidine (1.90 g; 16.8 mmol) in 40 ml of water was kept at 60°C for 15 minutes and then for 2 days at room temperature. The mixture was then extracted with dichloromethane. The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure to afford the crude product which was purified by column chromatography (dichloromethane as eluent) to give **7b** as a yellow solid (0.45 g; 13%): m.p. 74-75°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 9.24 (s, 2H), 3.36 (t, J = 7.2 Hz, 2H), 2.67 (dt, J_1 = 7.2

Hz, J_2 = 2.7 Hz, 2H), 2.06 (t, J = 2.7 Hz, 1H). MS: m/e 209 (M+).
Anal. Calcd. for $C_8H_7N_3O_2S$ (209.23): C, 45.92; H, 3.37; N, 20.09. Found: C, 45.87; H, 3.27; N, 19.89.

2-(3-Butynylthio)-4,6-dimethylpyrimidine (7c). 4,6-Dimethyl-2-mercapto-pyrimidine hydrochloride[21] (0.53 g; 3 mmol) in 10 ml of water was neutralized with sodium hydroxide (0.12 g; 3 mmol). Then 0.90 g (9 mmol) of triethylamine and 0.54 g (3 mmol) of 4-iodo-1-butyne were added and the mixture heated at 70°C for two hours. After cooling the mixture was extracted with ether. The organic layer was dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography (ether as eluent) to afford **7c** (0.38 g; 66%) as a pale yellow oil; ^{1}H NMR (CDCl$_3$) δ 6.72 (s, 1H), 3.31 (t, J = 7.2 Hz, 2H), 2.66 (dt, J_1 = 7.5 Hz, J_2 = 2.7 Hz, 2H), 2.39 (s, 1H), 2.03 (t, J = 2.6 Hz, 1H).
HRMS Calcd. for $C_{10}H_{12}N_2S$ (M+): 192.0721. Found: 192.0713.

2-(3-Butynylthio)-4-methylpyrimidine (7d). This compound was prepared according to the same procedure as described above for **7c** using 2-mercapto-4-methylpyrimidine hydrochloride[22] (0.49 g; 3 mmol). It was obtained as a yellow oil (0.34 g; 64%) after purification by column chromatography (ether as eluent); ^{1}H NMR (CDCl$_3$) δ 8.39 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 5.2 Hz, 1H), 3.30 (t, J = 7.5 Hz, 2H), 2.64 (dt, J_1 = 7.7 Hz, J_2 = 2.6 Hz, 2H), 2.43 (s, 3H), 2.05 (t, J = 2.7 Hz, 1H).
HRMS Calcd. for $C_9H_{10}N_2S$ (M+): 178.0565. Found: 178.0560.

2-(3-Butynylthio)-5-phenylpyrimidine (7e). 2-Mercapto-5-phenylpyrimidine[23] (1.00 g; 5.3 mmol) and triethylamine (1.6 g; 15.9 mmol) in 20 ml of water were stirred until all of the pyrimidine was dissolved. Then 4-iodo-1-butyne (0.96 g; 5.3 mmol) was added and the reaction mixture heated at 70°C for one hour. After cooling the mixture was extracted with dichloromethane. The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure to afford **7e** as a pale yellow solid (1.07 g; 84%) : m.p. 75.5-77.5°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 8.74 (s, 2H), 7.63-7.37 (m, 5H), 3.35 (t, J = 7.2 Hz, 2H), 2.70 (dt, J_1 = 7.2 Hz, J_2 = 2.7 Hz, 2H), 2.06 (t, J = 2.5 Hz, 1H).
^{13}C NMR (CDCl$_3$) δ 170.4, 155.4, 134.4, 129.8, 129.4, 128.6, 126.6, 82.5, 69.6, 30.0, 19.5.
Anal. Calcd. for $C_{14}H_{12}N_2S$ (240.32): C, 70.17; H, 5.08; N, 11.69. Found: C, 69.96; H, 5.03; N, 11.65.

2-(3-Butynylsulfinyl)pyrimidine (10a). To a stirred solution of 2-(3-butynyl-thio)pyrimidine (**7a**; 0.16 g; 1 mmol) in anhydrous chloroform (3 ml) at 0°C m-chloroperbenzoic acid (85% techn. solid, 0.20 g; 1 mmol) was added. The mixture was stirred at room temperature for 20 hours and then washed with a 2N solution of sodium carbonate. The organic layer was dried (MgSO$_4$) and evaporated to afford a clear, colourless oil which was purified

by column chromatography (dichloromethane/methanol 9:1 as eluent) to yield **10a** (0.15 g; 86%) as a clear, colourless oil; ^{1}H NMR (CDCl$_3$) δ 8.93 (d, J = 4.9 Hz, 2H), 7.48 (t, J = 4.9 Hz, 1H), 3.65-3.05 (mc, 2H), 3.05-2.35 (mc, 2H), 1.94 (t, J = 2.7 Hz, 1H).
HRMS Calcd. for C$_8$H$_8$N$_2$OS (M$^+$): 180.0358. Found: 180.0359.

2-(3-Butynylsulfonyl)pyrimidine (10b). To a stirred solution of 2-(3-butynyl-thio)pyrimidine (7a; 0.82 g; 5 mmol) in anhydrous chloroform (10 ml) at 0°C m-chloroperbenzoic acid (85% techn. solid, 2.50 g; 12.3 mmol) in chloroform (25 ml) was added in small portions over the course of a few minutes. The mixture was stirred at room temperature for 20 hours and then washed with a saturated solution of sodium hydrogen sulfite (2 x 15 ml) and subsequently with a 2N solution of sodium carbonate (2 x 25 ml). The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure to give **10b** as a colourless solid (0.95 g; 97%): m.p. 68-69°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.00 (d, J = 4.8 Hz, 2H), 7.70 (t, J = 4.9 Hz, 1H), 3.77 (t, J =7.5 Hz, 2H), 2.79 (dt, J$_1$ = 7.5 Hz, J$_2$ = 2.7 Hz, 2H), 2.00 (t, J = 2.7 Hz, 1H).
^{13}C NMR (CDCl$_3$) δ 165.5, 158.7, 123.9, 79.3, 70.6, 49.9, 13.1.
Anal. Calcd. for C$_8$H$_8$N$_2$O$_2$S (196.23): C, 48.96; H, 4.10; N, 14.27. Found: C, 48.84; H, 4.10; N, 14.12.

5-(3-Butynylthio)-2-phenylpyrimidine (12a). Bis-[2-phenylpyrimidinyl-(5)]-disulfide[24] (0.75 g; 2 mmol), triethylamine (0.61 g; 6 mmol), and sodium dithionite (0.82 g; 4.7 mmol) in water (5 ml) were stirred at 60°C until complete dissolution. After a further 3 hours at 60°C 4-iodo-1-butyne (0.72 g; 4 mmol) was added and the reaction mixture stirred for one hour at 60°C. After cooling the product was collected by filtration and washed with cold methanol to afford **12** (0.92 g; 95%) as a colourless solid: m.p. 72-73°C (methanol); ^{1}H NMR (CDCl$_3$) δ 8.79 (s, 1H), 8.55-8.27 (m, 2H), 7.59-7.37 (m, 3H), 3.07 (t, J = 7.5 Hz, 2H), 2.50 (dt, J$_1$ = 7.5 Hz, J$_2$ = 2.7 Hz, 2H), 2.03 (t, J = 2.7 Hz, 1H).
^{13}C NMR (CDCl$_3$) δ 163.0, 158.9, 136.9, 130.9, 128.6, 128.2, 81.3, 70.5, 33.5, 19.6.
HRMS Calcd. for C$_{14}$H$_{12}$N$_2$S (M$^+$): 240.0721. Found: 240.0721.
Anal. Calcd. for C$_{14}$H$_{12}$N$_2$S (240.32): C, 69.97; H, 5.03; N, 11.66. Found: C, 69.61; H, 5.06; N, 11.54.

2-Amino-5-(3-butynylthio)pyrimidine (12b). This compound was prepared in the same way as described above for **12a** using bis-[2-aminopyrimidinyl-(5)]-disulfide[24] (300 mg; 1.2 mmol). It was obtained as a colourless solid (290 mg; 68%): m.p. 137-139°C (ethanol); ^{1}H NMR (CDCl$_3$) δ 8.36 (s, 2H), 5.55 (brs, 2H), 2.82 (t, J = 7.1 Hz, 2H), 2.40 (dt, J$_1$ = 7.2 Hz, J$_2$ = 2.5 Hz, 2H), 2.01 (t, J = 2.6 Hz, 1H).
Anal. Calcd. for C$_8$H$_9$N$_3$S (179.24); C, 53.61; H, 5.06; N, 23.44. Found: C, 53.41; H, 4.99; N, 23.61.

2-(Acetylamino)-5-(3-butynylthio)pyrimidine (12c) and 5-(3-butynylthio)-2-(diacetylamino)pyrimidine (12d). Compound 12a (110 mg; 0.62 mmol) was heated for 4 hours at 90°C in acetic anhydride (2 ml) containing one drop of concentrated sulfuric acid. After cooling the excess of acetic anhydride was removed under reduced pressure. The residue was treated with water (10 ml), neutralized with sodium bicarbonate and extracted with dichloromethane. The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure to afford a mixture of 12c and 12d. Column chromatography (eluting with dichloromethane/methanol 9:1) of the latter mixture yielded 12c (68 mg; 50%) as a yellow solid and 12d (65 mg; 40%) as a pale yellow oil. Analytical and spectroscopic data of 12c and 12d:

12c: m.p. 136-138°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.57 (brs, 1H), 8.63 (s, 2H), 2.94 (t, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.60-2.30 (m, 2H), 2.01 (t, J = 2.6 Hz).
Anal. Calcd. for C$_{10}$H$_{11}$N$_3$OS (221.28); C, 54.28; H, 5.01; N, 18.99. Found: C, 53.99; H, 5.01; N, 19.06.

12d: ^{1}H NMR (CDCl$_3$) δ 8.76 (s, 2H), 3.17 (t, J = 7.1 Hz, 2H), 2.58 (dt, J$_1$ = 7.1 Hz, J$_2$ = 2.7 Hz, 2H), 2.28 (s, 6H), 2.07 (t, J = 2.6 Hz, 2H).
HRMS Calcd. for C$_{12}$H$_{13}$N$_3$O$_2$S (M$^+$): 263.0727. Found: 263.0728.

General procedure for the intramolecular Diels-Alder reactions of pyrimidines 1, 4, 7, 10b, and 12.

A stirred solution of the appropriate pyrimidine derivative in nitrobenzene (100 mg solute/1 ml solvent) under nitrogen was heated under conditions mentioned in Table 2.1. The resultant solution was chromatographed over silica gel; elution with the appropriate solvent system yielded the reaction products 3, 6, 9, 11b, and 14.

Cyclization of 2-(3-butynyloxy)pyrimidine (1a) to 2,3-dihydrofuro[2,3-b]-pyridine (3a). Column chromatography (eluting first with dichloromethane to remove nitrobenzene, followed by ether) of the reaction mixture obtained from 1a (1.4 mmol) yielded 2,3-dihydrofuro[2,3-b]pyridine (3a, 52%) as an oil; ^{1}H NMR (CDCl$_3$) spectrum was identical with that reported in literature[25].

Cyclization of 2-(3-butynyloxy)-5-nitropyrimidine (1b) to 2,3-dihydro-5-nitrofuro[2,3-b]pyridine (3b). Purification of the reaction mixture obtained from 1b (1.2 mmol) by column chromatography (eluting first with dichloromethane, then ether) afforded 3b (55%): m.p. 161-163°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.97 (d, J = 2.4 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H), 4.82 (t, J = 8.3 Hz, 2H), 3.36 (t, J = 8.6 Hz, 2H).
^{13}C NMR (CDCl$_3$) δ 172.4, 145.6, 140.0, 128.9, 121.2, 71.1, 27.4.
HRMS Calcd. for C$_7$H$_6$N$_2$O$_3$ (M$^+$): 166.0378. Found: 166.0378.
Anal. Calcd. for C$_7$H$_6$N$_2$O$_3$ (166.13): C, 50.60; H, 3.64; N, 16.86. Found: C, 50.68; H, 3.67; N, 17.31.

Cyclization of 2-(3-butynyloxy)-4,6-dimethylpyrimidine (1c) to 2,3-dihydro-6-methylfuro[2,3-b]pyridine (3c). Column chromatography (eluting first with dichloromethane, then dichloromethane/ether 1:1) of the reaction mixture resulting from 1c (2.0 mmol) gave 3c (68%): m.p. 39-41°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 7.36 (d, J = 7.5 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 4.60 (t, J = 8.7 Hz, 2H), 3.20 (t, J = 8.4 Hz, 2H), 2.38 (s, 3H).
HRMS Calcd. for C$_8$H$_9$NO (M$^+$): 135.0684. Found: 135.0672.
Anal. Calcd. for C$_8$H$_9$NO (135.16): C, 71.08; H, 6.71; N, 10.36. Found: C, 70.71; H, 6.84; N, 10.50.

Cyclization of 2-(3-butynyloxy)-4-methylpyrimidine (1d) to 3a and 3c. Column chromatography (eluting first with dichloromethane, then ether) of the reaction mixture obtained from 1d (1.3 mmol) gave a mixture of 3a and 3c (60%) in the ratio of approximately 1:1.8 as judged by ^{1}H NMR.

Cyclization of 2-(3-pentynyloxy)pyrimidine (1e) to 2,3-dihydro-4-methylfuro[2,3-b]pyridine (3e). Column chromatography (eluting first with dichloromethane, then dichloromethane/ether 4:1) of the reaction mixture obtained from 1e (0.7 mmol) gave crude 3e. Further purification by column chromatography on Merck silica gel 60 (230-400 mesh ASTM) eluting with dichloromethane/ether 3:1 afforded pure 3e (35%): m.p. 52-53°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 7.83 (d, J = 5.1 Hz, 1H), 6.57 (d, J = 5.4 Hz, 1H), 4.57 (t, J = 8.6 Hz, 2H), 3.14 (t, 8.7 Hz, 2H), 2.23 (s, 3H).
Anal. Calcd. for C$_8$H$_9$NO (135.16): C, 71.08; H, 6.71; N, 10.36. Found: C, 71.31; H, 6.63; N, 10.22.

Cyclization of 5-nitro-2-(3-pentynyloxy)pyrimidine (1f) to 2,3-dihydro-4-methyl-5-nitrofuro[2,3-b]pyridine (3f). Column chromatography (eluting first with dichloromethane, then ether) of the crude reaction mixture obtained from 1f (0.4 mmol) gave 3f (83%): m.p. 101-102°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.80 (s, 1H), 4.80 (t, J = 8.7 Hz, 2H), 3.30 (qt, J$_1$ = 8.7 Hz, J$_2$ ≈ 0.7 Hz, 2H), 2.53 (t, J ≈ 0.7 Hz, 3H).
Anal. Calcd. for C$_8$H$_8$N$_2$O$_3$ (180.16): C, 53.41; H, 4.50; N, 15.59. Found: C, 53.33; H, 4.47; N, 15.55.

Cyclization of 2-(N-acetyl-3-butynylamino)pyrimidine (4c) to 1-acetyl-2,3-dihydropyrrolo[2,3-b]pyridine (6c). Column chromatography (eluting first with dichloromethane, then ether) of the reaction mixture obtained from 4c (0.6 mmol) yielded 6c (85%): m.p. 123-124°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.12 (d, J = 4.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 6.86 (dd, J$_1$ = 7.2 Hz, J$_2$ = 4.8 Hz, 1H), 4.10 (t, J = 8.7 Hz, 2H), 3.04 (t, J = 8.4 Hz, 2H), 2.67 (s, 3H). MS: m/e 162 (M$^+$).
Anal. Calcd. for C$_9$H$_{10}$N$_2$O (162.19): C, 66.65; H, 6.22; N, 17.27. Found: C, 66.79; H, 6.41; N, 17.41.

Cyclization of 2-(N-acetyl-3-butynylamino)-5-nitropyrimidine (4d) to 1-acetyl-2,3-dihydro-5-nitropyrrolo[2,3-b]pyridine (6d). Column chromatography (eluting first with dichloromethane, then dichloromethane/ether 9:1) of the reaction mixture obtained from 4d (0.4 mmol) yielded 6d (87%): m.p. 186°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.03 (d, J = 2.4 Hz, 1H), 8.20 (dt, J$_1$ = 2.4 Hz, J$_2$ ≈ 1.5 Hz, 1H), 4.22 (t, J = 8.6 Hz, 2H), 3.17 (t, J = 8.7 Hz, 2H), 2.69 (s, 3H). MS: m/e 207 (M$^+$).
Anal. Calcd. for C$_9$H$_9$N$_3$O$_3$ (207.19): C, 52.17; H, 4.38; N, 20.28. Found: C, 52.20; H, 4.35; N, 20.49.

Cyclization of 2-(3-butynylthio)pyrimidine (7a) to 2,3-dihydrothieno[2,3-b]pyridine (9a). Column chromatography (eluting first with dichloromethane, then dichloromethane/ether 9:1) of the reaction mixture obtained from 7a (1.2 mmol) yielded 9a (57%) as a pale brown oil, ^{1}H NMR (CDCl$_3$) spectrum identical with that reported in the literature[5a]. MS: m/e 137 (M$^+$).
Anal. Calcd. for C$_{13}$H$_{10}$N$_4$O$_7$S (366.31; picrate: m.p. 103-105°C): C, 42.62; H, 2.75; N, 15.30. Found: C, 42.66; H, 2.73; N, 15.39.

Cyclization of 2-(3-butynylthio)-5-nitropyrimidine (7b) to 2,3-dihydro-5-nitrothieno[2,3-b]pyridine (9b). Column chromatography (eluting first with dichloromethane, then ether) of the reaction mixture obtained from 7b (1.2 mmol) yielded 9b (75%): mp 131-132°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.02 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 2.1 Hz, 1H), 3.69-3.25 (mc, 4H). MS: m/e 182 (M$^+$).
Anal. Calcd. for C$_7$H$_6$N$_2$O$_2$S (182.20): C, 46.14; H, 3.32; N, 15.38. Found: C, 46.29; H, 3.28: N, 15.27.

Cyclization of 2-(3-butynylthio)-4,6-dimethylpyrimidine (7c) to 2,3-dihydro-6-methylthieno[2,3-b]pyridine (9c). Column chromatography (eluting first with dichloromethane, then ether) of the reaction mixture obtained from 7c (0.7 mmol) yielded 9c (51%) as a pale brown oil; ^{1}H NMR (CDCl$_3$) δ 7.27 (d, J = 7.5 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 3.40-3.07 (mc, 4H), 2.42 (s, 3H).
HRMS Calcd. for C$_8$H$_9$NS (M$^+$): 151.0456. Found 151.0450.

Cyclization of 2-(3-butynylthio)-4-methylpyrimidine (7d) to 9a and 9c. Column chromatography (eluting first with dichloromethane, then ether) of the reaction mixture obtained from 7d (0.8 mmol) gave a mixture of 9a and 9b (69%) in the ratio of approximately 1:2.2 as established by ^{1}H NMR.

Cyclization of 2-(3-butynylthio)-5-phenylpyrimidine (7e) to 2,3-dihydro-5-phenylthieno[2,3-b]pyridine (9e). The reaction mixture obtained from 7e (0.8 mmol) was chromatographed twice using silica gel (first time eluting with dichloromethane, followed by dichloromethane/ether 2:1, second time eluting with dichloromethane/ether 9:1) to give 9e (75%): m.p. 101-102°C

(hexanes); ^{1}H NMR (CDCl3) δ 8.41 (d, J = 2.1 Hz, 1H), 7.67-7.29 (m, 6H), 3.62-3.29 (mc, 4H).
^{13}C NMR (CDCl3) δ 165.2, 146.8, 137.9, 134.0, 132.4, 129.8, 129.0, 127.7, 126.8, 33.6, 31.3.
Anal. Calcd. for C13H11NS (213.29): C, 73.31; H, 5.30; N, 6.52. Found: C, 73.20; H, 5.19; N, 6.56.

Cyclization of 2-(3-butynylsulfonyl)pyrimidine (10b) to 1,1-dioxo-2,3-dihydrothieno[2,3-b]pyridine (11b). Column chromatography (eluting first with dichloromethane, then dichloromethane/methanol 9:1) of the reaction mixture obtained from 10b (1.1 mmol) yielded 11b (63%): m.p. 109°C (hexanes/chloroform) (lit.[8]: 109-111°C); ^{1}H NMR spectrum (CDCl3) identical with the reported spectrum[8].
^{13}C NMR (CDCl3) δ 156.3, 150.8, 136.3, 131.3, 127.1, 48.5, 22.3.

Cyclization of 5-(3-butynylthio)-2-phenylpyrimidine (12a) to 2,3-dihydro-5-phenylthieno[2,3-c]pyridine (14a). Column chromatography (dichloromethane as eluent) of the reaction mixture obtained from 12 (0.6 mmol) gave 14 (85%): m.p. 82-83°C (hexanes/toluene); ^{1}H NMR (CDCl3) δ 8.51 (s, 1H), 8.03-7.80 (m, 2H), 7.50 (s, 1H), 7.48-7.29 (m, 3H), 3.50-3.12 (mc, 4H).
^{13}C NMR (CDCl3) δ 153.7, 150.2, 142.5, 139.3, 137.8, 128.7, 128.5, 126.6, 116.4, 35.9, 33.2. MS: m/e 213 (M+).
Anal. Calcd. for C13H11NS (213.29): C, 73.20; H, 5.20; N, 6.57. Found: C, 73.36; H, 5.32; N, 6.59.

Cyclization of 2-(acetylamino)-5-(3-butynylthio)pyrimidine (12c) to 5-(acetylamino)-2,3-dihydrothieno[2,3-c]pyridine (14c). Column chromatography (eluting first with dichloromethane, then dichloromethane/ether 1:1) of the reaction mixture obtained from 12c (0.2 mmol) gave 14c (64%) as a pale yellow solid: m.p. 155-157°C (hexanes/toluene); ^{1}H NMR (CDCl3) δ 8.90 (brs, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 3.33 (mc, 4H), 2.16 (s, 3H).
Anal. Calcd. for C9H10N2OS (194.26): C, 55.65; H, 5.19; N, 14.42. Found: C, 55.61; H, 5.05; N, 14.51.

Cyclization of 5-(3-butynylthio)-2-(diacetylamino)pyrimidine (12d) to 5-(acetylamino)-2,3-dihydrothieno[2,3-c]pyridine (14c). Work up of the reaction mixture obtained from 12d (0.2 mmol) as described above gave 14c (60%), m.p. and ^{1}H NMR (CDCl3) identical with those reported above.

High pressure promoted cyclization of compounds 7a, 10a, and 10b into the 2,3-dihydrothieno[2,3-b]pyridines 9a, 11a, and 11b, respectively. These experiments were run in a high pressure apparatus equipped with a one wall piston-cylinder for pressures up to 15 kbar[26]. The reactions were performed on a 1 mmole scale in sealed teflon tubes of 0.8 ml. After one night at 55°C and 15 kbar pressure the degree of conversion of 7a, 10a, and

10b was determined by ^{1}H NMR (see results and discussion). Detailed ^{1}H NMR spectra of the cyclization products **9a**[5a], **11a**[6a], and **11b**[8] have been published before.

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CHAPTER 3

INTRAMOLECULAR DIELS-ALDER REACTIONS OF 2-(ALKYNYL)PYRIMIDINES AND 2-(ALKYNYL)PYRIDINES

3.1 INTRODUCTION

Reports on inverse electron demand Diels-Alder reactions of diazines have until recently been limited to examples[1], which usually require strong electron-withdrawing groups on the diazine and electron-rich dienophiles[2,3]. However, with the use of the intramolecular version of this reaction the scope has been expanded considerably[4-6]. Recently, we have described some intramolecular Diels-Alder reactions of pyrimidines carrying a dienophilic side-chain attached to the 2- or the 5-position of the pyrimidine via a heteroatom (oxygen, sulfur or nitrogen)[7]. These reactions have led to new syntheses of dihydrofuro[2,3-b]-, dihydrothieno[2,3-b]-, dihydropyrrolo[2,3-b]- and dihydrothieno[2,3-c]pyridines. Due to the electron donating effect of the heteroatom in the dienophilic side-chain the reactivity is low, resulting in a rather high reaction temperature (180-210°C) required to achieve cycloaddition. In order to eliminate this rate-retarding effect of the heteroatom, we also studied intramolecular cyclizations of 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines having on position 2 a dienophilic side-chain linked to the heterocycle through an aliphatic $C(CN)_2$ group[8]. Due to the relatively low temperatures required to achieve reaction (130°C), we extended this study by investigating the cycloaddition reactions of some 2-(1,1-dicyanohex-5-yn-1-yl)pyrimidines which have an extra CH_2 group in the side-chain and the Diels-Alder reactions of some 2-(1,1-dicyanopent-4-yn-1-yl)pyridines. To assess the influence of the cyano groups we included in our study the cycloaddition of some 2-(pent-4-yn-1-yl)-pyrimidines, which have no α-CN groups.

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3.2 RESULTS AND DISCUSSION

The 2-[1,1-dicyanopent-4-yn-1-yl]pyrimidines **3** and the 2-[1,1-dicyano-hex-5-yn-1-yl]pyrimidines **7** were prepared in good yields from the corresponding 2-chloro- or 2-methylsulfonylpyrimidines **1** and the sodium salt of 5,5-dicyanopent-1-yne (**2**) and 6,6-dicyanohex-1-yne (**6**), respectively. By heating of compounds **3** in nitrobenzene at 130°C (140°C for **3d**) under nitrogen an intramolecular cycloaddition took place yielding the corresponding 7,7-dicyano-6,7-dihydro-5H-1-pyrindines **5** in excellent yields (Scheme 3.1; Table 3.1). The dicyanohexynylpyrimidines **7** were also found to undergo a Diels-Alder reaction in nitrobenzene, but only at considerably higher temperatures (210°C). Despite the more strenuous conditions the resulting 5,6,7,8-tetrahydroquinolines **15** were obtained in excellent yields. Until now there was only one precedent of an intramolecular inverse electron demand Diels-Alder reaction of a pyrimidine leading to a six-ring annelated pyridine; the reaction occurs in low yield[6a]. Previously, at our laborato-

Scheme 3.1

$$1 \quad + \quad 2\,(n = 1) \quad \xrightarrow[\text{THF}]{\text{NaH}} \quad 3\,(n = 1)$$

1
X = Cl, SO$_2$CH$_3$

2 (n = 1)
6 (n = 2)

3 (n = 1)
7 (n = 2)

5 (n = 1)
9 (n = 2)

4 (n = 1)
8 (n = 2)

−HCN

a R$_1$, R$_2$ = H   b R$_1$ = NO$_2$; R$_2$ = H
c R$_1$ = H; R$_2$ = CN   d R$_1$ = Ph; R$_2$ = H
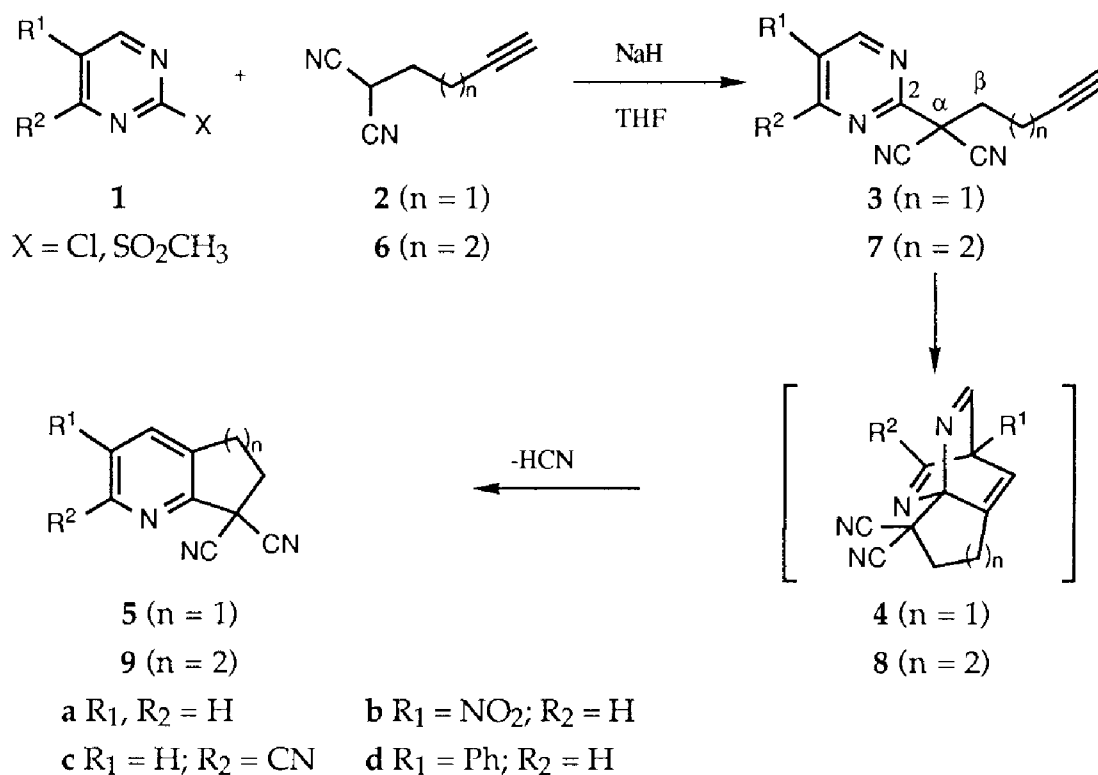
ry the 3-nitro derivatives of 6,7-dihydro-5H-1-pyrindine and 5,6,7,8-tetra-hydroquinoline have been prepared by intermolecular inverse electron demand Diels-Alder reactions of 5-nitropyrimidine with five- or six-membered cyclic enamines[3]. The formation of compounds **5** and **9** probably occurs through the intermediacy of cycloadducts **4** and **8**, respectively, which are formed by addition of the acetylene group across the C-2 and C-5 positions of the pyrimidine ring. These cycloaddition products could not be isolated or identified by NMR-spectroscopy due to their fast conversion into **5** and **9**, respectively, by expulsion of hydrogen cyanide.

As can be seen from Table 3.1 introduction of an electron-withdrawing cyano or nitro group in the pyrimidine results in an enhancement of the rate of cycloaddition. This result is in agreement with the inverse electron demand character of the cycloaddition reaction. The presence of the phenyl group at C-5 in **3** is found to lower slightly the reaction rate, probably due to steric hindrance which the dienophilic side-chain experiences in the approach of the pyrimidine ring. The higher temperature required for reaction of the hexynylpyrimidines **7** is due to a decreased entropic assistance caused by the additional methylene group. This phenomenon is general for intramolecular reactions and has for example also been found for cycloaddition reactions of triazines and tetrazines[9].

From all these results it can be concluded that in the compounds **3**, where the dienophile is linked to the pyrimidine via an aliphatic carbon atom (C(CN)$_2$), reactions occur at much lower temperature (about 130°C) than in compounds where the side-chain is linked to the azadiene via an oxygen, sulfur or nitrogen atom (about 210°C)[7].

In order to get insight in the contribution of the α-CN substituents to this increased reactivity we also examined the reactivity of pyrimidines **13** (Scheme 3.2) featuring the absence of CN groups on the carbon atom α to the pyrimidine ring. Compounds **13a-d** were prepared from the appropriate 1-dimethylamino-3-dimethylimonioprop-1-ene salt **10** and hex-5-yn-1-ylamidine hydrochloride (**11**) in good yield. Compound **13e** was prepared from 5-nitropyrimidine (**12**) and the amidine **11** by a ring degenerate transformation reaction developed at our laboratory[10]. The intramolecular cycloaddition of compounds **13** could only be achieved when heated at 210°C in nitrobenzene under an atmosphere of nitrogen (Scheme 3.2). The

resulting 6,7-dihydro-5*H*-1-pyrindines **15** were obtained in good yield (Table 3.1).

Scheme 3.2

a R = H   b R = Cl   c R = Ph
d R = *p*-NO₂Ph   e R = NO₂
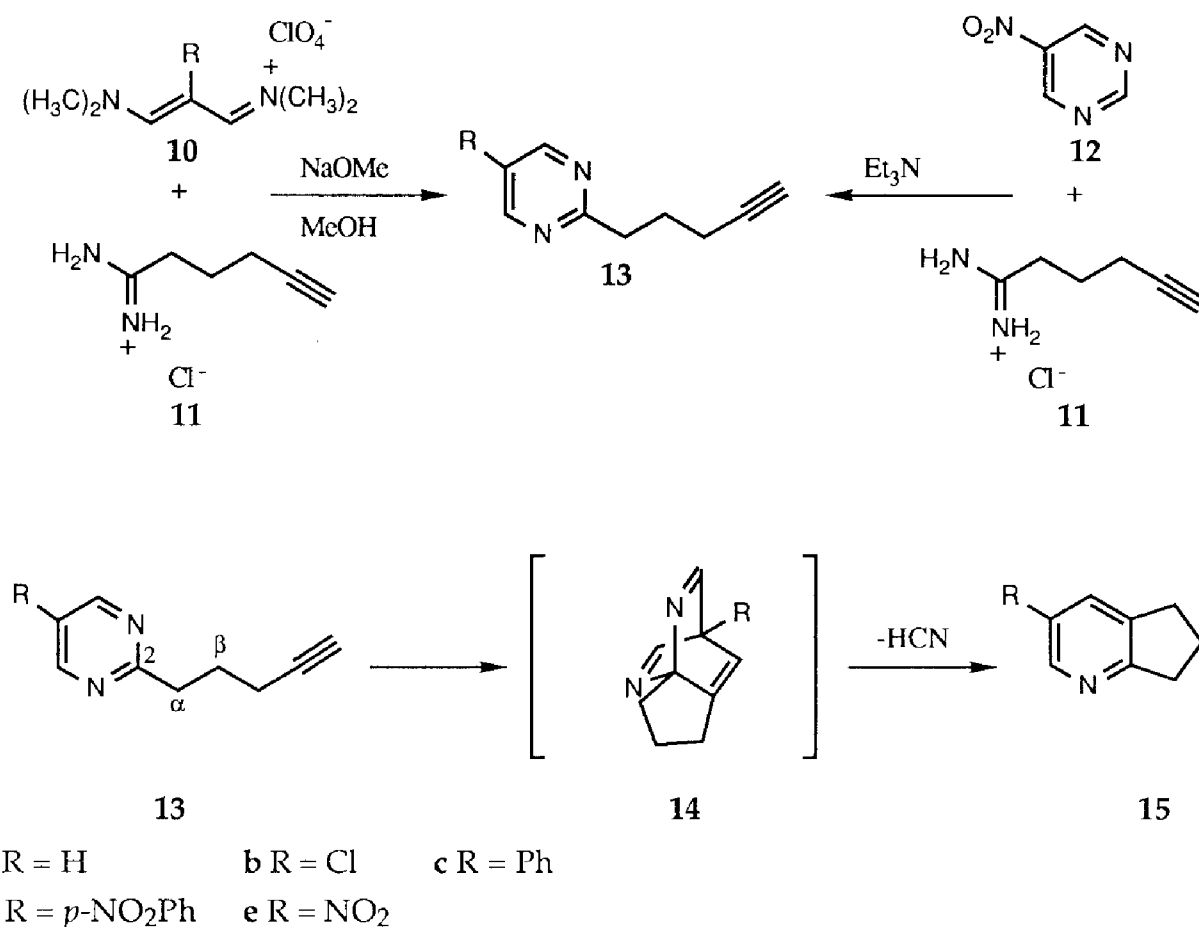
Only a slight influence on the reaction rate is observed for the substituents on C-5 of the pyrimidines. The electron-withdrawing nitro and chloro substituents increase the reaction rate, whereas the phenyl and *p*-nitrophenyl substituents decrease the reaction rate due to steric hindrance.

The temperature required for reaction of compounds **13** is comparable to the temperature required for compounds where the dienophile is linked to the azadiene through an ether, thioether or amine bond[7]. Therefore, the conclusion seems justified that the much higher reactivity of the α,α-dicyanoalkynylpyrimidines **3** cannot solely be explained by an electronic effect. We ascribe the remarkable difference in cycloaddition rate between

TABLE 3.1   Intramolecular Diels-Alder reactions of pyrimidines **3, 7, 13** and pyridines **16**. Reaction products and yields.

Pyrimidine/Pyridine Starting Compounds	Reaction Conditions Temp. (°C)	Time (h)	Reaction Product	Yield (%)
3a	130	24	**5a**	92
3b	130	6	**5b**	96
3c	130	4	**5c**	94
3d	140	15	**5d**	100
7a	210	96	**9a**	72
7b	210	21	**9b**	93
7c	210	21	**9c**	94
13a	210	2	**15a**	63
13b	210	1.5	**15b**	84
13c	210	3	**15c**	65
13d	210	3	**15d**	81
13e	210	0.5	**15e**	58
16a	180	10	**18a**	82
16b	210	3	**18b**	72
16c	210	12	**18c**	75

compounds **3** and **13** to the so-called "*gem*-dimethyl" effect[11], in this case due to the two cyano substituents. This acceleration may be due to reduction of the internal C_2-C_α-C_β angle in **3** as compared to the same bond angle in compounds **13** (the so-called "Thorpe-Ingold" effect[12]). Thus, in compounds **3** the reacting centers are forced in closer proximity, resulting in added entropic assistence and, consequently, rate enhancement in the cyclo-addition reaction. More recently, however, evidence has been presented that the rate increase on substitution can also be explained by a higher population of reactive *syn* rotamers due to substituents on the chain connecting the reaction centers[13]. This has recently been demonstrated for intramolecular Diels-Alder reactions of α,α-disubstituted furfuryl methyl fumarates[14]. Examination of the Newman projections about the carbon atoms α and β to the pyrimidine ring (Scheme 3.3) shows that the presence of the geminal substituents in **3** (R = CN) will affect the population distribution of the four presented rotational conformations when compared to **13** (R = H). Certainly, for both R = H and R = CN rotamer (A) is the most

Scheme 3.3

(A)   (B)   (C)   (D)

3 R = CN;   **13** R = H.

P = pyrimidine.
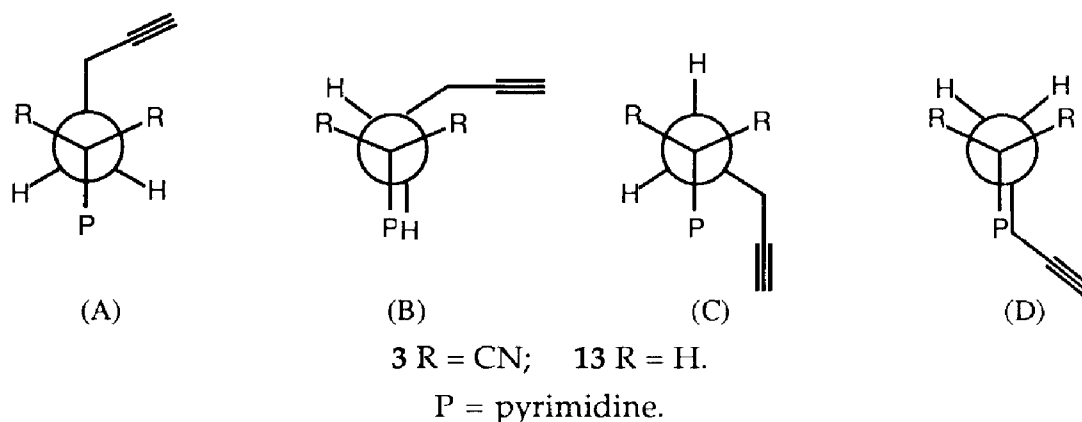
highly populated. However, due to the geminal CN substituents, rotamers (C) and especially (D) will have a much higher relative population in **3** than in **13**. The result is that on the average in time the dienophile is more in the vicinity of the azadiene in **3** than in **13** and hence a higher reactivity for the intramolecular Diels-Alder reaction of **3** versus **13** is observed.

Support for the correctness of our explanation in which a great deal of the rate enhancement of the intramolecular cycloaddition reaction is ascribed to the accessibility of the reactive *syn* conformations may be obtained from crystal structure analyses. For this purpose crystallographic studies of compounds **3b** and **13d** have been performed which allowed examination of their molecular structure in the solid state. 5-*p*-Nitrophenyl-2-(pent-4-yn-1-yl)pyrimidine (**13d**) was found to have the *anti*-periplanar conformation around the C_α-C_β bond as depicted in Figure 3.1. The internal bond angle C_2-C_α-C_β was 115.5°. On the other hand, 2-(1,1-dicyanopent-4-yn-1-yl)-5-nitropyrimidine (**3b**), featuring the presence of two cyano groups at the carbon atom α to the pyrimidine ring was found to have the *syn*-clinal conformation around the C_α-C_β bond (Figure 3.2), the internal bond angle C_2-$C\alpha$-C_β being 110.2°/111.0° (two independent structures in the unit cell). From these results it can be seen that *gem*-disubstitution indeed causes a reduction of the internal C_2-C_α-C_β bond angle in **3b** of about 5° as compared to the same bond angle in **13d**. Thus, it can be concluded that the Thorpe-Ingold effect may not be excluded in explaining the rate enhancement upon *gem*-disubstitution. However, the preference of compound **3b** to crystallize in the *syn*-clinal conformation, a conformation from which cycloaddition

takes place more easily than from the *anti*-periplanar conformation, indicates that conformational effects may be even more important than the Thorpe-Ingold effect in explaining the observed rate enhancement.

FIGURE 3.1:   Molecular structure of 5-*p*-nitrophenyl-2-(pent-4-yn-1-yl)pyrimidine (13d).
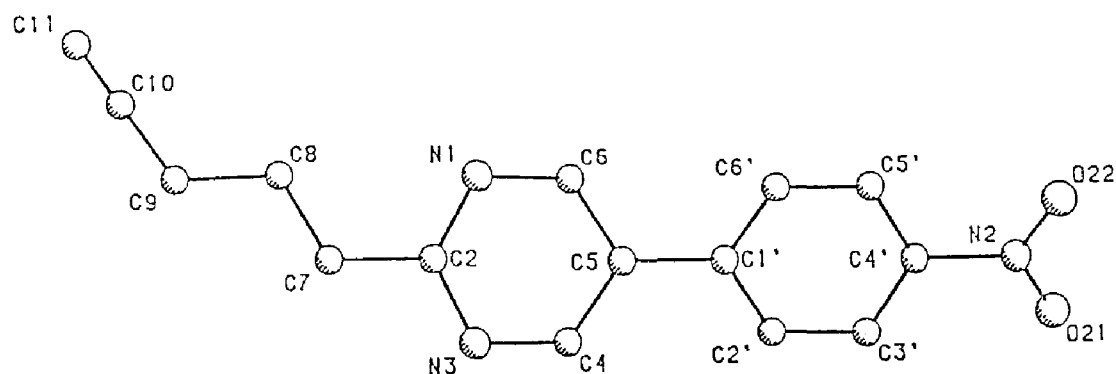
FIGURE 3.2:   Molecular structure of 2-(1,1-dicyanopent-4-yn-1-yl)-5-nitropyrimidine (3b).
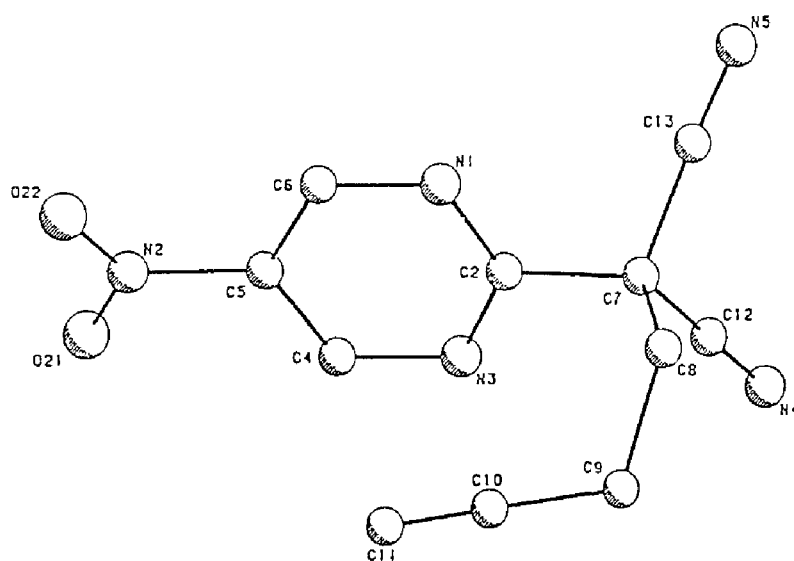
The ease of inverse electron demand Diels-Alder reactions of pyrimidines **3** (and **7**) with a 1,1-dicyanoalkynyl side-chain induced us to study the cycloaddition reaction of the less electron-deficient pyridines **16** (Scheme 3.4). These compounds were prepared in good yield from the corresponding 2-chloropyridines and the sodium salt of 5,5-dicyanopent-1-yne. We found that by heating of 2-(1,1-dicyanopent-4-yn-1-yl)-3,5-dinitropyridine (**16a**) for ten hours in nitrobenzene at 180°C under nitrogen 1,1-dicyano-2,3-dihydro-5,7-dinitro-1H-indene (**18a**) was obtained in good yield. The formation of this compound probably also occurs through the intermediacy of a cycloaddition product, i.e. **17a**, which can easily aromatize after expulsion of hydrogen cyanide.

Scheme 3.4

16

a R_1, R_2 = NO$_2$ b R_1 = NO$_2$, R_2 = H

c R_1 = H, R_2 = NO$_2$

17

18
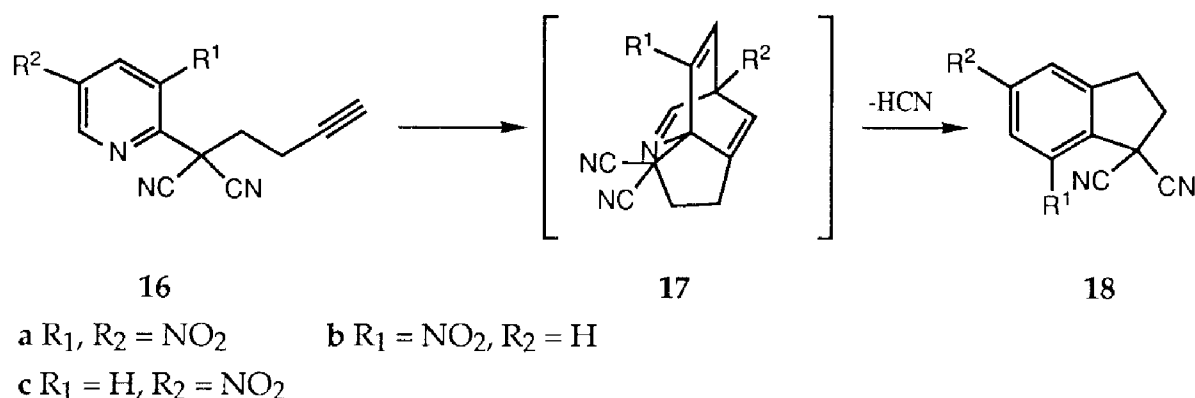
The presence of two electron-withdrawing nitro groups in the pyridine ring is not a structural requirement for the occurrence of the cycloaddition. When the *mono* nitro compounds **16b** and **16c** were heated at 210°C in nitrobenzene, in good yields 1,1-dicyano-2,3-dihydro-7-nitro-1H-indene (**18b**) and 1,1-dicyano-2,3-dihydro-5-nitro-1H-indene (**18c**), respectively, are obtained (see Table 3.1).

The cycloaddition reactions of **16b** and **16c** require a higher temperature (210°C) than **16a** (180°C). This result is certainly due to the lower π-electron-deficiency of the pyridine ring in **16b,c**. Furthermore, the fact that the reaction of **16b** to **18b** was complete in about 3 hours, whereas the reaction of **16c** to **18c** took about 12 hours, indicates that the formation of cycloadduct **17c** is hindered by the presence of the nitro group at the C-5

position of the pyridine. All these findings clearly indicate the inverse electron demand nature of the cycloaddition reaction. Recently, another example of an intramolecular Diels-Alder reaction of a pyridine derivative has been published[15].

In conclusion, intramolecular inverse electron demand Diels-Alder reactions of appropriately substituted pyrimidines lead to 6,7-dihydro-5H-1-pyrindines and 5,6,7,8-tetrahydroquinolines. Similarly, appropriately substituted nitropyridines lead to 2,3-dihydronitro-1H-indenes. Our studies indicate that steric effects play a more important role in governing the rate of cycloaddition than electronic effects.

3.3 EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer. Chemical shifts are determined in ppm downfield from TMS. Mass spectral data were obtained from a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed on Merck silica gel 60 (70-230 mesh ASTM).

General procedure for the synthesis of 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines (3) and 2-(1,1-dicyanohex-5-yn-1-yl)pyrimidines (7).
To a stirred suspension of sodium hydride (2.20 mmol [1.1 eq], 80% oil dispersion) in anhydrous tetrahydrofuran (10 ml) at room temperature was added 5,5-dicyanopent-1-yne[16] (2; 2.20 mmol; 1.1 eq; for compounds 3) or 6,6-dicyanohex-1-yne[16] (6; 2.20 mmol; 1.1 eq; for compounds 7). After the initial effervescence had subsided, the appropriate 2-chloro- or 2-methyl-sulfonylpyrimidine 1 (2.00 mmole) was added as a solid in one portion at room temperature and the reaction mixture was stirred at room temperature or under reflux for the appropriate time. Water was then added and the aqueous layer was extracted twice with dichloromethane. The organic layers were washed with water, dried (MgSO₄) and the solvent evaporated under reduced pressure. Column chromatography (eluting with dichloromethane) of the residue afforded the desired products.

2-(1,1-Dicyanopent-4-yn-1-yl)pyrimidine (3a). From 2-chloropyrimidine and 5,5-dicyanopent-1-yne[16]. Reflux time: 4 hours. Obtained as a colourless oil (64%). ^{1}H NMR (CDCl₃) δ 8.89 (d, J = 5.3 Hz, 2H), 7.50 (t, J = 5.3 Hz, 1H), 2.6 (mc, 4H), 1.98 (t, J = 2.5 Hz, 1H).
HRMS Calcd. for C₁₁H₈N₄ : 196.0749. Found: 196.0745.

<u>2-(1,1-Dicyanopent-4-yn-1-yl)-5-nitropyrimidine</u> **(3b).** From 2-chloro-5-nitropyrimidine[17] and 5,5-dicyanopent-1-yne. Reaction time: 0.5 hour at room temperature. Obtained as a pale yellow solid (88%): m.p. 99-100.5°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.62 (s, 2H), 2.9-2.5 (mc, 4H), 1.93 (t, J = 2.4 Hz, 1H). MS: m/e 241 (M+).
Anal. Calcd. for C$_{11}$H$_7$N$_5$O$_2$ (241.21): C, 54.77; H, 2.93; N, 29.04. Found: C, 54.64; H, 2.92; N, 29.34.

<u>4-Cyano-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidine</u> **(3c).** From 2-chloro-4-cyanopyrimidine[18] and 5,5-dicyanopent-1-yne. Reaction time: 1 hour at room temperature. Obtained as a colourless solid (91%): m.p. 90-91°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.17 (d, J = 5.4 Hz, 1H), 7.86 (d, J = 5.4 Hz, 1H), 2.7 (mc, 4H), 1.93 (t, J = 2.4 Hz, 1H). MS: m/e 221 (M+).
Anal. Calcd. for C$_{12}$H$_7$N$_5$ (221.22): C, 65.15; H, 3.19; N, 31.66. Found: C, 64.80; H, 3.04; N, 31.93.

<u>2-(1,1-Dicyanopent-4-yn-1-yl)-5-phenylpyrimidine</u> **(3d).** From 2-methyl-sulfonyl-5-phenylpyrimidine[19] and 5,5-dicyanopent-1-yne. Reflux time: 2 hours. Column chromatography (eluting with dichloromethane/petroleum ether 5:1) gave **3d** (91%) as a colourless solid: m.p. 97-98°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.00 (s, 2H), 7.55 (mc, 5H), 2.7 (mc, 4H), 1.97 (t, J = 2.4 Hz, 1H). MS: m/e 272 (M+).
Anal. Calcd. for C$_{17}$H$_{12}$N$_4$ (272.30): C, 74.97; H, 4.44; N, 20.57. Found: C, 74.93; H, 4.44; N, 20.64.

<u>2-(1,1-Dicyanohex-5-yn-1-yl)pyrimidine</u> **(7a).** From 2-chloropyrimidine and 6,6-dicyanohex-1-yne[16]. Reflux time: 5 hours. Obtained as a colourless solid (60%): m.p. 83.5-84.5°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 8.90 (d, J = 4.8 Hz, 2H), 7.47 (t, J = 5.1 Hz, 1H), 2.60 (mc, 2H), 2.34 (dt, J$_1$ = 6.9 Hz, J$_2$ = 2.4 Hz, 2H), 2.02 (t, J = 2.4 Hz, 1H), 1.95 (mc, 2H). MS: m/e 210 (M+).
Anal. Calcd. for C$_{12}$H$_{10}$N$_4$ (210.23): C, 68.55; H, 4.79; N, 26.65. Found: C, 68.41; H, 4.77; N, 26.53.

<u>2-(1,1-Dicyanohex-5-yn-1-yl)-5-nitropyrimidine</u> **(7b).** From 2-chloro-5-nitropyrimidine[17] and 6,6-dicyanohex-1-yne. Reaction time: 0.5 hour at room temperature. Obtained as a pale yellow solid (87%): m.p. 102-103°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.62 (s, 2H), 2.60 (mc, 2H), 2.33 (dt, J$_1$ = 6.3 Hz, J$_2$ = 2.4 Hz, 2H), 2.03 (t, J = 2.4 Hz, 1H), 1.85 (mc, 2H). MS: m/e 255 (M+).
Anal. Calcd. for C$_{12}$H$_9$N$_5$O$_2$ (255.23): C, 56.47; H, 3.55; N, 27.44. Found: C, 56.47; H, 3.55; N, 27.71.

<u>4-Cyano-2-(1,1-dicyanohex-5-yn-1-yl)pyrimidine (7c).</u> From 2-chloro-4-cyanopyrimidine[18] and 6,6-dicyanohex-1-yne. Reaction time: 0.5 hour at room temperature. Obtained as a colourless solid (90%): m.p. 94-95°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.18 (d, J = 5.1 Hz, 1H), 7.85 (d, J = 5.1 Hz, 1H), 2.62 (mc, 2H), 2.37 (dt, J$_1$ = 6.3 Hz, J$_2$ = 2.7 Hz, 2H), 2.03 (t, J = 2.4 Hz, 1H), 1.9 (mc, 2H). MS: m/e 235 (M$^+$).
Anal. Calcd. for C$_{13}$H$_9$N$_5$ (235.24): C, 66.37; H, 3.86; N, 29.77. Found: C, 66.07; H, 3.79; N, 29.93.

<u>2-(Pent-4-yn-1-yl)pyrimidine (13a).</u> To a stirred suspension of 1-dimethylamino-3-dimethylimonioprop-1-ene perchlorate[20] (10a; 521 mg, 2.3 mmol) and hex-5-yn-1-ylamidine hydrochloride[21] (11; 505 mg, 1.5 eq) in methanol (10 ml) 2M methanolic sodium methoxide (1.8 ml, 1.5 eq) was added dropwise at room temperature. After 0.5 hour another 1.2 ml (1 eq) of sodium methoxide solution was added and the reaction mixture refluxed for two hours. After cooling methanol was evaporated and the residue treated with water (20 ml) and extracted with dichloromethane (2 x 20 ml). The combined organic layers were dried (MgSO$_4$) and evaporated under reduced pressure to afford crude 13a which was purified by column chromatography (eluting with ether). It was obtained as a clear colourless oil (233 mg, 69%); ^{1}H NMR (CDCl$_3$) δ 8.64 (d, J = 4.8 Hz, 2H), 7.10 (t, J = 4.9 Hz, 1H), 3.08 (t, J = 7.1 Hz, 2H), 2.5-2.0 (mc, 4H), 1.95 (t, J = 2.7 Hz, 1H).
HRMS Calcd. for C$_9$H$_{10}$N$_2$ (M$^+$): 146.0844. Found: 146.0830.

<u>5-Chloro-2-(pent-4-yn-1-yl)pyrimidine (13b).</u> This compound was prepared from 2-chloro-1-dimethylamino-3-dimethylimonioprop-1-ene perchlorate[20] (10b; 600 mg, 2.3 mmol) and hex-5-yn-1-ylamidine hydrochloride (11; 505 mg, 1.5 eq) in the same way as described for 13a. It was obtained as a clear colourless oil (259 mg, 67%) after column chromatography (eluting with ether); ^{1}H NMR (CDCl$_3$) δ 8.60 (s, 2H), 3.07 (t, J = 7.2 Hz, 2H), 2.5-2.0 (mc, 4H), 1.96 (t, J = 2.6 Hz, 1H).
HRMS Calcd. for C$_9$H$_9$ClN$_2$ (M$^+$): 180.0454. Found: 180.0449.

<u>2-(Pent-4-yn-1-yl)-5-phenylpyrimidine (13c).</u> This compound was prepared from 1-dimethylamino-3-dimethylimonio-2-phenylprop-1-ene perchlorate[20] (10c; 696 mg, 2.3 mmol) and hex-5-yn-1-ylamidine hydrochloride (11, 505 mg, 1.5 eq) as described for 13a. It was obtained as a colourless solid (485 mg, 95%) after column chromatography (eluting with ether): m.p. 41-43°C; ^{1}H NMR (CDCl$_3$) δ 8.86 (s, 2H), 7.49 (mc, 5H), 3.13 (t, J = 7.2 Hz, 2H), 2.5-2.0 (mc, 4H), 1.97 (t, J = 2.4 Hz, 1H). MS: m/e 222 (M$^+$).
Anal. Calcd. for C$_{15}$H$_{14}$N$_2$ (222.28): C, 81.04; H, 6.34; N, 12.60. Found: C, 81.26; H, 6.57; N, 12.70.

5-*p*-Nitrophenyl-2-(pent-4-yn-1-yl)pyrimidine (**13d**). This compound was prepared from 1-dimethylamino-3-dimethylimonio-2-*p*-nitrophenylprop-1-ene perchlorate[20] (**10d**; 799 mg; 2.3 mmol) and hex-5-yn-1-ylamidine hydrochloride (**11**; 505 mg; 1.5 eq) as described for **13a**. It was obtained as a pale yellow solid (510 mg; 83%) after column chromatography (eluting with dichloromethane/ether 9:1): m.p. 129-130°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.92 (s, 2H), 8.36 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.9 Hz, 2H), 3.19 (t, J = 7.1 Hz, 2H), 2.5-2.0 (mc, 4H), 1.99 (t, J = 2.4 Hz, 1H). MS: m/e 267 (M$^+$).
Anal. Calcd. for C$_{15}$H$_{13}$N$_3$O$_2$ (267.29): C, 67.41; H, 4.90; N, 15.72. Found: C, 67.57 ; H, 4.99 ; N, 16.04.

5-Nitro-2-(pent-4-yn-1-yl)pyrimidine (**13e**). To a stirred mixture of 5-nitropyrimidine[22] (**12**; 500 mg, 4.0 mmol) and hex-5-yn-1-ylamidine hydrochloride (**11**; 590 mg, 4.0 mmol) in absolute ethanol (5 ml) was added triethylamine (1.2 ml). The resulting solution was heated under reflux for 2.5 hour. After this time the solvent was removed under reduced pressure. The residue was treated with water (20 ml) and extracted with dichloromethane (2 x 20 ml). The combined organic layers were dried (MgSO$_4$) and evaporated under reduced pressure to afford crude **13e** which was purified by column chromatography (eluting with dichloromethane). It was obtained as a yellow oil (480 mg; 63%); ^{1}H NMR (CDCl$_3$) δ 9.40 (s, 2H), 3.24 (t, J = 7.1 Hz, 2H), 2.5 - 2.0 (mc, 4H), 1.98 (t, J = 2.6 Hz, 1H) HRMS Calcd. for C$_9$H$_9$N$_3$O$_2$: 191.0695. Found: 191.0694.

General procedure for the synthesis of 2-(1,1-dicyanopent-4-yn-1-yl)nitropyridines **16**.
To a stirred suspension of sodium hydride (5.5 mmol, 80% oil dispersion) in anhydrous tetrahydrofuran (10 ml) at room temperature was added 5,5-dicyanopent-1-yne[16] (**2**, 5.5 mmol). After the initial effervescence had subsided, a solution of the appropriate 2-chloronitropyridine (5.0 mmol) in anhydrous tetrahydrofuran (10 ml) was added in one portion at room temperature and the reaction mixture stirred for the time given. Water was then added and the aqueous layer extracted twice with dichloromethane. The organic layers were washed with water, dried (MgSO$_4$) and the solvent evaporated under reduced pressure. Column chromatography (eluting with the appropriate solvent system) of the residue afforded the desired products **16**.

2-(1,1-Dicyanopent-4-yn-1-yl)-3,5-dinitropyridine (**16a**). From 2-chloro-3,5-dinitropyridine[23]. Reaction time: 0.5 hour. After column chromatography (eluting with petroleum ether 40-60/ether 2:1) **16a** was obtained as a yellow solid (58%): m.p. 109-110°C (chloroform/hexanes); ^{1}H NMR (CDCl$_3$) δ 9.72 (d, J = 2.4 Hz, 1H), 9.23 (d, J = 2.4 Hz, 1H), 3.1-2.5 (mc, 4H), 2.02 (t, J = 2.5 Hz, 1H). MS: m/e 285 (M$^+$).

Anal. Calcd. for $C_{12}H_7N_5O_4$ (285.22): C, 50.53; H, 2.47; N, 24.56. Found: C, 50.25; H, 2.41; N, 24.61.

2-(1,1-Dicyanopent-4-yn-1-yl)-3-nitropyridine (16b). From 2-chloro-3-nitropyridine[23,24]. Reaction time: 2 hours. After column chromatography (eluting with petroleum ether 40-60/ether 1:1) 16b was obtained as a yellow oil (48%); ^{1}H NMR (CDCl$_3$) δ 8.96 (dd, J_1 = 4.5 Hz, J_2 = 1.5 Hz, 1H), 8.53 (dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1H), 7.79 (dd, J_1 = 4.5 Hz, J_2 = 8.4 Hz, 1H), 3.1-2.8 (mc, 2H), 2.8-2.5 (mc, 2H), 2.03 (t, J = 2.4 Hz, 1H). HRMS Calcd. for $C_{12}H_8N_4O_2$: 240.0656. Found: 240.0647.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-nitropyridine (16c). From 2-chloro-5-nitropyridine[23,24]. Reaction time: 2 hours. After column chromatography (eluting with petroleum ether 40-60/ether 2:1) 16c was obtained as a yellow solid (69%): m.p. 71-72°C (chloroform/hexanes); ^{1}H NMR (CDCl$_3$) δ 9.52 (d, J = 2.4 Hz, 1H), 8.70 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 2.9-2.4 (mc, 4H), 2.03 (t, J = 2.4 Hz, 1H). MS: m/e 240 (M$^+$). Anal. Calcd. for $C_{12}H_8N_4O_2$ (240.22): C, 60.00; H, 3.36; N, 23.33. Found: C, 59.72; H, 3.31; N, 23.67.

General procedure for the intramolecular Diels-Alder reaction of compounds 3, 7, 13, and 16.

A stirred solution of the appropriate pyrimidine (or pyridine) derivative in nitrobenzene (100 mg solute/1 ml solvent) under nitrogen was heated under conditions mentioned in Table 3.1. The temperature was kept constant within 1°C. The disappearance of starting material was followed by thin layer chromatography and/or ^{1}H NMR spectroscopy. The resultant solution was chromatographed over silica gel; elution with the appropriate solvent system yielded the reaction products 5, 9, 15, and 18.

7,7-Dicyano-6,7-dihydro-5H-1-pyrindine (5a). Column chromatography (eluting first with dichloromethane, then dichloromethane/ether 5:1) of the reaction mixture obtained from 3a (0.6 mmol) afforded 5a (92%) as a colourless solid: m.p. 108-110°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.60 (d, J = 4.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.38 (dd, J_1 = 7.8 Hz, J_2 = 4.8 Hz, 1H), 3.24 (mc, 2H), 2.96 (mc, 2H). MS: m/e 169 (M$^+$).
Anal. Calcd. for $C_{10}H_7N_3$ (169.18): C, 70.99; H, 4.17; N, 24.84. Found: C, 70.67; H, 4.09; N, 25.10.

7,7-Dicyano-6,7-dihydro-3-nitro-5H-1-pyrindine (5b). Column chromatography (eluting with dichloromethane) of the reaction mixture obtained from 3b (0.7 mmol) afforded 5b (96%) as a pale yellow solid: m.p. 106.5-107.5°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.42 (d, J = 2.4 Hz, 1H), 8.53 (td, J_1 = 2.4 Hz, J_2 = 1.1 Hz, 1H), 3.35 (t, J = 6.4 Hz, 2H), 3.10 (mc, 2H). MS: m/e 214 (M$^+$).

Anal. Calcd. for $C_{10}H_6N_4O_2$ (214.18): C, 56.07; H, 2.82; N, 26.16. Found: C, 55.84; H, 2.75; N, 26.33.

2,7,7-Tricyano-6,7-dihydro-5H-1-pyrindine (5c). Column chromatography (first eluting with dichloromethane to remove nitrobenzene, then dichloromethane/ether 1:1) of the reaction mixture obtained from 3c (0.7 mmol) gave 5c (94%) as a slightly brownish solid: m.p. 152-153°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 7.97 (td, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 3.34 (mc, 2H), 3.04 (mc, 2H). MS: m/e 194 (M$^+$). Anal. Calcd. for $C_{11}H_6N_4$ (194.19): C, 68.03; H, 3.11; N, 28.85. Found: C, 68.23; H, 3.04; N, 29.05.

7,7-Dicyano-6,7-dihydro-3-phenyl-5H-1-pyrindine (5d). Column chromatography (eluting with dichloromethane/ether 9:1) of the reaction mixture obtained from 3d (1.0 mmol) gave 5d (100%) as a colourless solid: m.p. 134-135°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.74 (brs, 1H), 7.84 (t, J = 1.0 Hz, 1H), 7.50 (mc, 5H), 3.27 (brt, J = 6.1 Hz, 2H), 3.00 (mc, 2H). MS: m/e 245 (M$^+$).
Anal. Calcd. for $C_{16}H_{11}N_3$ (245.27): C, 78.34; H, 4.52; N, 17.13. Found: C, 78.10; H, 4.43; N, 17.01.

8,8-Dicyano-5,6,7,8-tetrahydroquinoline (9a). Column chromatography (eluting with dichloromethane/ether 19:1) of the reaction mixture obtained from 7a (0.7 mmol) gave 9a (72%) as a colourless solid: m.p. 98-99°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.59 (dd, J_1 = 4.5 Hz, J_2 = 1.5 Hz, 1H), 7.61 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.33 (dd, J_1 = 7.8 Hz, J_2 = 4.5 Hz, 1H), 2.93 (brt, J = 6.2 Hz, 2H), 2.64 (mc, 2H), 2.15 (mc, 2H). MS: m/e 183 (M$^+$).
Anal. Calcd. for $C_{11}H_9N_3$ (183.21): C, 72.11; H, 4.95; N, 22.94. Found: C, 72.28; H, 4.93; N, 23.01.

8,8-Dicyano-5,6,7,8-tetrahydro-3-nitroquinoline (9b). Column chromatography (eluting with dichloromethane) of the reaction mixture obtained from 7b (0.6 mmol) afforded 9b (93%) as a pale yellow solid: m.p. 120-121°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.35 (d, J = 2.4 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 3.10 (t, J = 6.8 Hz, 2H), 2.72 (mc, 2H), 2.22 (mc, 2H). MS: m/e 228 (M$^+$).
Anal. Calcd. for $C_{11}H_8N_4O_2$ (228.21): C, 57.89; H, 3.53; N, 24.55. Found: C, 57.96; H, 3.45; N, 24.66.

2,8,8-Tricyano-5,6,7,8-tetrahydroquinoline (9c). Column chromatography (eluting first with dichloromethane, then dichloromethane/ether 5:1) of the reaction mixture obtained from 7c (0.6 mmol) afforded 9c (94%) as a colourless solid: m.p. 153-155°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 7.76 (mc, 2H), 3.04 (t, J = 6.3 Hz, 2H), 2.69 (mc, 2H), 2.20 (mc, 2H). MS: m/e 208 (M$^+$).

Anal. Calcd. for $C_{12}H_8N_4$ (208.22): C, 69.22; H, 3.87; N, 26.91. Found: C, 68.97; H, 3.79; N, 27.03.

6,7-Dihydro-5H-1-pyrindine (15a). Column chromatography (eluting first with dichloromethane, then ether) of the reaction mixture obtained from 13a (1.5 mmol) gave 15a (63%) as a pale brown oil; ^{1}H NMR (CDCl$_3$) identical with that reported in literature[25]: δ 8.30 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 6.95 (dd, J_1 = 4.8 Hz, J_2 = 7.5 Hz, 1H), 2.95 (2 overlapping t, J = 7.6 Hz, 2H), 2.11 (m, 2H).

3-Chloro-6,7-dihydro-5H-1-pyrindine (15b). Column chromatography (first eluting with dichloromethane, then ether) of the reaction mixture obtained from 13b (1.2 mmol) gave 15b (84%) as an off-white solid: m.p. 58-59°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 8.25 (d, J = 2.1 Hz, 1H), 7.41 (d, J = 2.1 Hz, 1H), 2.95 (t, J = 7.5 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 2.12 (m, 2H). MS: m/e 153/155 (M$^+$).
Anal. Calcd. for C_8H_8ClN (153.61): C, 62.55; H, 5.25; N, 9.12. Found: C, 62.21; H, 5.37; N, 9.01.

6,7-Dihydro-3-phenyl-5H-1-pyrindine (15c). Column chromatography (eluting with dichloromethane, then dichloromethane/ether 1:1) of the reaction mixture obtained from 13c (0.7 mmol) afforded crude 15c, which was dissolved in dichloromethane and treated with active charcoal. After filtration of the charcoal the organic layer was evaporated to yield 15c (65%) as a white solid: m.p. 92-93°C (hexanes; lit.[26]: 94-95°C). ^{1}H NMR (CDCl$_3$) identical with that reported in literature[26]: δ 8.55 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.6-7.2 (m, 5H), 3.02 (2 overlapping t, J = 7.2 Hz, 4H), 2.16 (m, 2H).
Anal. Calcd. for $C_{14}H_{13}N$ (195.25): C, 86.11; H, 6.71; N, 7.17. Found: C, 86.22; H, 6.79; N, 7.08.

6,7-Dihydro-3-p-nitrophenyl-5H-1-pyrindine (15d). Column chromatography (eluting with dichloromethane/ether 9:1) of the reaction mixture obtained from 13d (0.8 mmol) gave crude 15d, which was dissolved in dichloromethane and treated with active charcoal. After filtration of the charcoal the filtrate was evaporated to afford 15d (81%) as a pale yellow solid: m.p. 171-173°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.59 (brs, 1H), 8.28 (d, J = 9.0 Hz, 2H), 7.70 (mc, 1H), 7.68 (d, J = 9.0 Hz, 2H), 3.07 (t, J = 7.5 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.19 (m, 2H). MS: m/e 240 (M$^+$).
Anal. Calcd. for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66. Found: C, 69.92; H, 5.01; N, 11.54.

6,7-Dihydro-3-nitro-5H-1-pyrindine (15e). Column chromatography (eluting first with dichloromethane, then ether) of the reaction mixture obtained from 13e (1.5 mmol) afforded 15e (58%) as a pale yellow solid: m.p. 94-

95°C (hexanes; lit.[3]: 94-95°C). ^{1}H NMR (CDCl$_3$) identical with that reported in literature[3]: δ 9.17 (brs, 1H), 8.21 (brs, 1H), 3.10 (m, 4H), 2.30 (m, 2H).

1,1-Dicyano-2,3-dihydro-5,7-dinitro-1H-indene (18a). Column chromatography (eluting with dichloromethane) of the reaction mixture obtained from 16a (1.4 mmol) afforded 18a (82%) as a colourless solid: m.p. 148-149°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.03 (d, J = 2.1 Hz, 1H), 8.55 (td, J$_1$ = 2.1 Hz, J$_2$ = 1.1 Hz, 1H), 3.50 (t, J = 6.6 Hz, 2H), 3.10 (mc, 2H). MS: m/e 258 (M$^+$).
Anal. Calcd. for C$_{11}$H$_6$N$_4$O$_4$ (258.19): C, 51.17; H, 2.34; N, 21.70. Found: C, 50.90; H, 2.26; N, 21.92.

1,1-Dicyano-2,3-dihydro-7-nitro-1H-indene (18b). Column chromatography (eluting with dichloromethane) of the reaction mixture obtained from 16b (0.6 mmol) gave 18b (72%) as a colourless solid: m.p. 118-119°C (hexanes/ chloroform); ^{1}H NMR (CDCl$_3$) δ 8.24 (dd, J$_1$ = 6.3 Hz, J$_2$ = 3.0 Hz, 1H), 7.76 (mc, 2H), 3.37 (mc, 2H), 3.12 (mc, 2H). MS: m/e 213 (M$^+$).
Anal. Calcd. for C$_{11}$H$_7$N$_3$O$_2$ (213.19): C, 61.97; H, 3.31, N, 19.71. Found: C, 61.82; H, 3.25; N, 19.88.

1,1-Dicyano-2,3-dihydro-5-nitro-1H-indene (18c). Column chromatography (eluting with dichloromethane) of the reaction mixture obtained from 16c (1.0 mmol) gave 18c (75%) as a colourless solid: m.p. 92-93°C (hexanes/ chloroform); ^{1}H NMR (CDCl$_3$) δ 8.29 (mc, 2H), 7.83 (dd, J$_1$ = 7.8 Hz, J$_2$ = 0.7 Hz, 1H), 3.36 (brt, J = 6.8 Hz, 2H), 3.03 (mc, 2H). MS: m/e 213 (M$^+$).
Anal. Calcd. for C$_{11}$H$_7$N$_3$O$_2$ (213.19): C, 61.97; H, 3.31; N, 19.71. Found: C, 61.88; H, 3.29; N, 19.86.

Cryctal structure analysis.
The X-ray analyses were performed on a NONIUS CAD-4 diffractometer. The non-hydrogen atoms were found by means of the symbolic addition program set SIMPEL[27]. The hydrogen atoms were found in a difference Fourier (ΔF) synthesis. The calculations were carried out with XRAY76[28]. The scattering factors were taken from Cromer and Mann[29].

2-(1,1-Dicyanopent-4-yn-1-yl)-5-nitropyrimidine (3b). The crystals of this compound belong to the monoclinic space group P2$_1$/n, with 8 molecules in a unit cell of dimensions: a = 22.604(2) Å, b = 10.271(2) Å, c = 10.146(2) Å, β = 98.75(2)°, V = 2328.1(7) Å^3; μ(Mo Kα) = 0.73 cm^{-1}; d$_{calcd.}$ = 1.32 g cm^{-3} (there are two independent structures in a unit cell). Crystal dimensions: 0.15 x 0.25 x 0.30 mm. 4051 Intensities were measured using graphite monochromated Mo Kα (λ = 0.71069 Å) radiation (1.1 ≤ ϑ ≤ 25°; h -26 to 26, k 0 to 12. 1 0 to 12). 2286 Reflections were below the 2.5 σ(I) level and were treated as unobserved. Block-diagonal least-square refinement, anisotropic for C, O and N atoms, isotropic for H atoms, gave a final R-value

of 0.054 (R_w = 0.094). A weighting scheme of w = (3.98 + F_{obs} + $0.0216F_{obs}^2)^{-1}$ was employed.

5-p-Nitrophenyl-2-(pent-4-yn-1-yl)pyrimidine (13d). The crystals of this compound belong to the orthorhombic space group Pbca, with 8 molecules in a unit cell of dimensions a = 10.066(2) Å; b = 34.428(6) Å; c = 7.647(3) Å, V = 2650(1) $Å^3$; μ(Mo Kα) = 0.86 cm^{-1}; $d_{calcd.}$ = 1.34 g cm^{-3}. Crystal dimensions: 0.18 x 0.20 x 0.50 mm. 2437 Intensities were measured using graphite monochromated Mo Kα (λ = 0.71069 Å) radiation (1.1 $\leq \vartheta \leq$ 25°; h 0 to 11, k 0 to 39, l 0 to 8). 1466 Reflections were below the 2.5 σ(I) level and were treated as unobserved. Block-diagonal least-square refinement, anisotropic for C, O and N atoms, isotropic for H atoms, converged to R = 0.052 (R_w = 0.062). A weighting scheme w = (85 + F_{obs} + $0.003F_{obs}^2)^{-1}$ was applied.

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SYNTHESIS OF 1,3-DIHYDROFURO[3,4-c]PYRIDINES AND 5,7-DIHYDROFURO[3,4-b]PYRIDINES BY INTRAMOLECULAR DIELS-ALDER REACTIONS OF PYRIMIDINES. INVESTIGATION OF THE EFFECT OF STERIC INTERACTIONS ON THE REACTION RATE.

4.1 INTRODUCTION

Recently, there has been a growing interest in inverse electron demand Diels-Alder reactions of six-membered heterocycles like tetrazines and triazines with appropriately substituted alkenes or alkynes[1]. Several less π-electron-deficient diazines[1-4] and even pyridines[4,5] have also been shown to undergo this type of reaction, especially when the intramolecular version of this reaction is employed. In previous studies we observed that pyrimidines containing a $-X-CH_2-CH_2-C\equiv CH$ (X = O, S, NAc, CH_2) group at position 2

$X = O, S, NAc, C(CN)_2, CH_2$
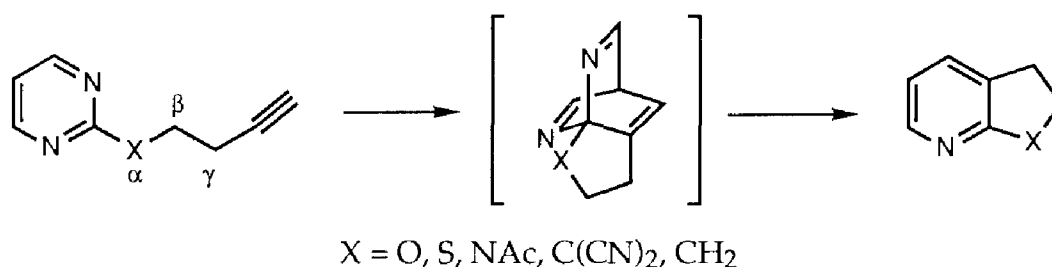
(or 5) required reaction temperatures of 180 - 210°C to give these intramolecular Diels-Alder reactions[3,4]. Surprisingly, when X = $C(CN)_2$ the cycloadditions could be performed at much lower temperatures (about 130°C)[4]. This rate enhancement is not uncommon in intramolecular reactions and can be ascribed to two factors[6]. First, the so-called "Thorpe-Ingold" ("scissoring") effect, caused by the two cyano groups, decreases the angle at Cα between diene and dienophile, thus enabling a closer approach between the diene and dienophile and thereby increasing the reaction rate[7]. Secondly, it has been recently recognized that steric interactions by the cyano groups

would relatively enhance the population of the reactive *syn* rotamers around $C\alpha$ - $C\beta$, thereby favouring the cycloaddition reaction[8].

To investigate whether the cycloaddition can also occur when the heteroatom is not present in the α-, but in the β-position, we decided to synthesize several 2- and 5-propynyloxymethylpyrimidines, **4** and **7** respectively, and to study the course and rate of cycloaddition. To obtain further insight in the relative importance of sterically hindering substituents in the α-position of the side-chain in **4** on the intramolecular Diels-Alder reactions of pyrimidines we prepared some 5-propynyloxymethyl-pyrimidines that contain in the α-position no substituents (**4a**), one methyl group (**4b**), one phenyl group (**4c**), two methyl groups (**4d**), or a cyclopentyl group (**4e**). In addition we studied the influence of two methyl groups in the γ-position of the propynyloxymethyl side-chain (**4f**) and of a *t*-butyl group in position 2 of the pyrimidine ring (**4g**) on the rate of cycloaddition. To gain insight in the influence of sterically hindering substituents at the alkyne group or in the pyrimidine ring we synthesized some 2-propynyloxymethyl-pyrimidines which contain no substituents (**7a**), a phenyl group at C-5 of the pyrimidine (**7b**), methyl substituents at C-4 and C-6 of the pyrimidine (**7c**), and a compound with a trimethylsilyl group at the alkyne and methyl groups at C-4 and C-6 of the pyrimidine (**7d**).

4.2 RESULTS AND DISCUSSION

It was found that the 5-propynyloxymethylpyrimidines **4a-g** are easily accessable by the methods outlined in Scheme 4.1. Treatment of 5-bromo-pyrimidine **1** at -100°C with n-butyllithium resulting in halogen-lithium exchange[9] and subsequent reaction with benzaldehyde, acetone or cyclo-pentanone gave the 5-hydroxymethylpyrimidines **2a-c**. These compounds were converted into the propynyloxymethylpyrimidines **4c-e** by reaction with propargyl bromide. The compounds **4a,b,f,g** were prepared by reaction of the sodium salt of the appropriate propargyl alcohol with 5-bromomethyl-pyrimidines **3a**[10] and **3b**[11], which have been described in the literature, and with 5-bromomethyl-2-*t*-butylpyrimidine **3c**, which was synthesized from 5-bromo-2-*t*-butylpyrimidine[12]. The 2-propynyloxymethylpyrimidines **7a** and **7c** were prepared from the corresponding 2-chloromethylpyrimidines **5a**[13]

and **5b**[14] by reaction with the sodium salt of prop-2-yn-1-ol; **7b** was conveniently prepared from 2-hydroxymethyl-5-phenylpyrimidine (**6**) and propargyl bromide. The trimethylsilylated **7d** was obtained in good yield from **7c** by reaction with n-butyllithium in THF at -70 °C, followed by treatment with trimethylsilylchloride.

Scheme 4.1

1

2a; $R^1 = H$, $R^2 = Ph$
b; $R^1 = R^2 = Me$
c; R^1,$R^2 = -(CH_2)_4-$

3a; $R^1 = R^2 = R^3 = H$
b; $R^1 = Me$, $R^2 = R^3 = H$
c; $R^1 = R^2 = H$, $R^3 = t$-Bu

4a; $R^1 = R^2 = R^3 = R^4 = H$
c; $R^1 = Ph$, $R^2 = R^3 = R^4 = H$
e; R^1,$R^2 = -(CH_2)_4-$, $R^3 = R^4 = H$
g; $R^1 = R^2 = R^3 = H$, $R^4 = t$-Bu

b; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
d; $R^1 = R^2 = Me$, $R^3 = R^4 = H$
f; $R^1 = R^2 = R^4 = H$, $R^3 = Me$

5a; $R^1 = R^2 = H$
b; $R^1 = Me$, $R^2 = H$

6

7a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^3 = H$, $R^2 = Ph$
**c**; $R^1 = Me$, $R^2 = R^3 = H$
d; $R^1 = Me$, $R^2 = H$, $R^3 = SiMe_3$

61
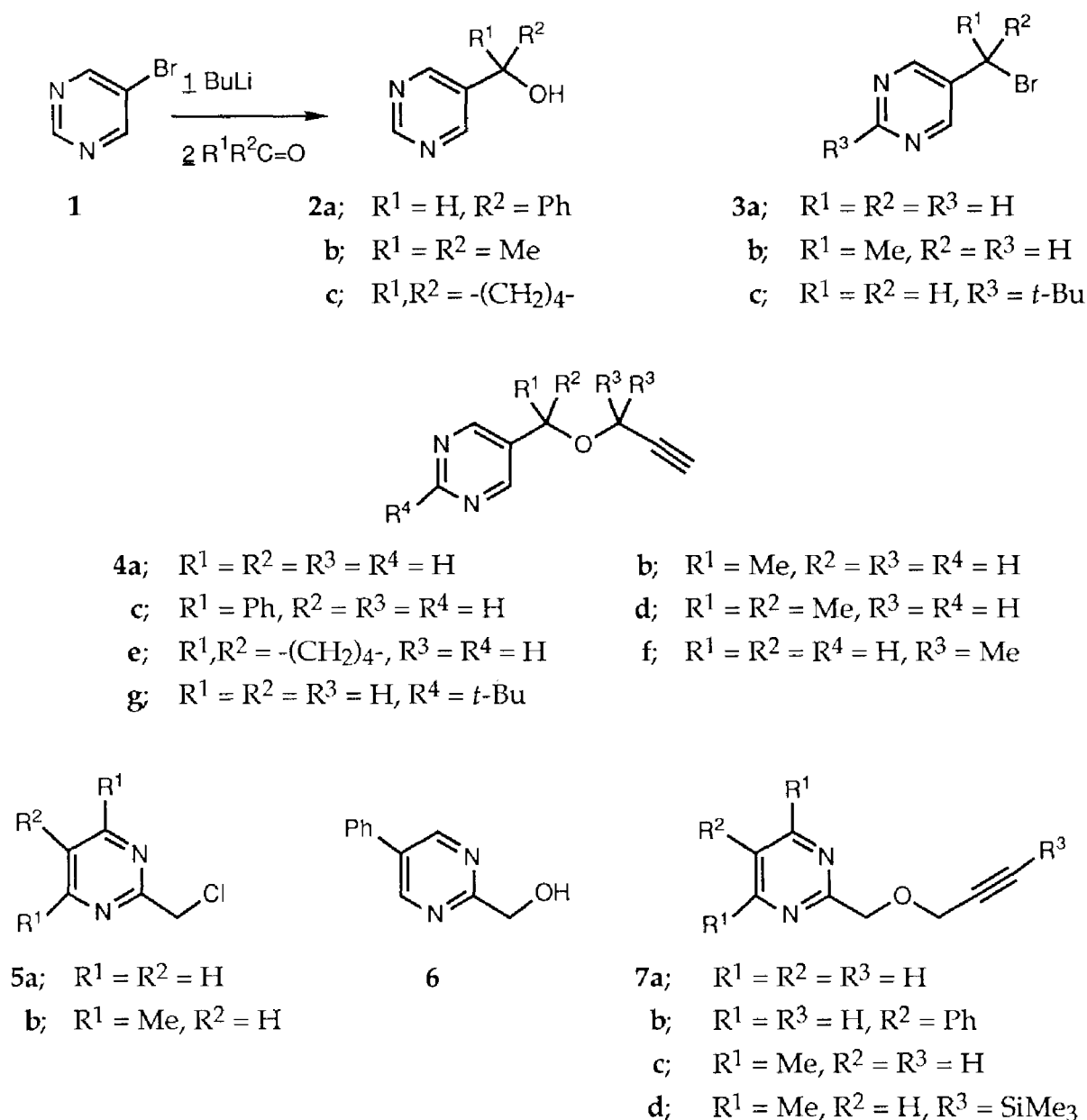
All propynyloxymethylpyrimidines **4** and **7** except **4g**, underwent cycloaddition at 140°C in nitrobenzene into the corresponding 1,3-dihydrofuro-[3,4-c]pyridines **8a-f** and 5,7-dihydrofuro[3,4-b]pyridines **9a-d** in good yields; **4g** reacted very slowly at 140°C and was reacted at 160°C to give **8g** (see Table 4.1). The structures of the cycloaddition products were established by their ^{1}H NMR spectra and confirmed by mass spectroscopy and/or elemental analyses. This new method to obtain 1,3-dihydrofuro[3,4-c]pyridines is of interest since they can easily be converted into analogs of pyridoxine (vitamin B6)[15].
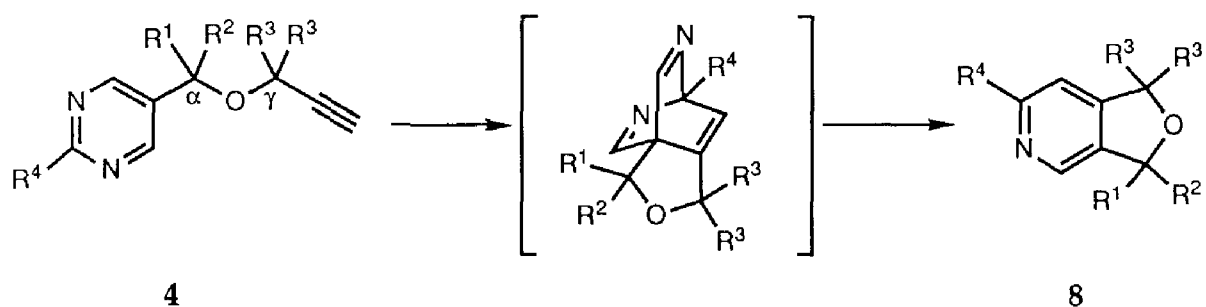
The 1,3-dihydrofuro[3,4-c]pyridines are readily oxidized when kept in contact with air. For example, **8d** appeared to be completely converted into 3,3-dimethylfuro[3,4-c]pyridin-1(3H)-one (**10a**) when kept for two months and 1,3-dihydrofuro[3,4-c]pyridine (**8a**) oxidized rapidly to a mixture of the known furo[3,4-c]pyridin-1(3H)-one (**10b**) and furo[3,4-c]pyridin-3(1H)-one (**10c**)[16] (Figure 4.1). The other compounds **8** also showed a tendency to oxidize rapidly, analogous to the behaviour of 1,3-dihydroisobenzofuran[17]. Therefore, the compounds **8** should be stored under nitrogen.

Figure 4.1

10a   10b   10c
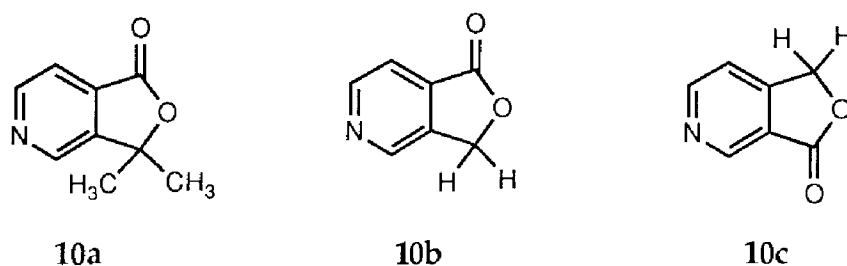
The rate of the cycloaddition reaction was monitored by ^{1}H NMR spectroscopy. A solution of 20 - 50 mg of the pyrimidine was dissolved in 0.5 ml of nitrobenzene, flushed with nitrogen, stoppered and heated at 140°C in an oil bath. The temperature was kept constant within 1°C and after several time intervals a spectrum was measured and the high-field signals were integrated. A plot of $-\ln(C_t/C_0)$ against t revealed that the reaction obeys simple first order kinetics and thus the reaction constant k and the half-life time $(t_{1/2})$ could be calculated. Addition of p-nitrotoluene as internal reference revealed that after heating the mixture for at least six half-life

TABLE 4.1 Reaction rates, products and yields of the intramolecular Diels-Alder reaction of **4a-g** and **7a-d** in nitrobenzene at 140 ± 1°C.

	R^1	R^2	R^3	R^4	rate constant x 10^3 (s^{-1})	t$_{1/2}$ (h)	product	yield (%)
4a	H	H	H	H	0.069	2.80	**8a**	90
4b	Me	H	H	H	0.128	1.50	**8b**	84
4c	Ph	H	H	H	0.108	1.75	**8c**	81
4d	Me	Me	H	H	0.667	0.28	**8d**	68
4e	-(CH$_2$)$_4$-		H	H	1.194	0.16	**8e**	81
4f	H	H	Me	H	0.231	0.83	**8f**	70
4g	H	H	H	t-Bu	a)	a)	**8g**	59

a) This compound was reacted at 160°C. Rate constant = 0.055 x 10^{-3} s^{-1}; t$_{1/2}$ = 3.4 h.
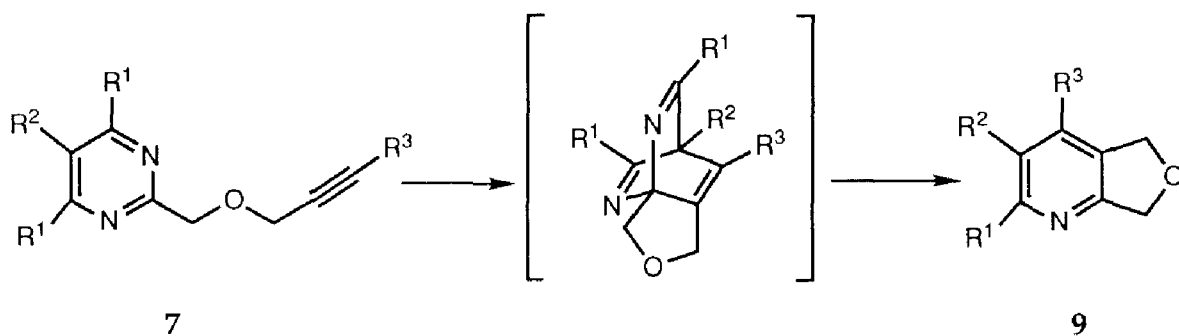
	R^1	R^2	R^3	rate constant x 10^3 (s^{-1})	t$_{1/2}$ (h)	product	yield (%)
7a	H	H	H	0.169	1.13	**9a**	63
7b	H	Ph	H	0.128	1.50	**9b**	87
7c	Me	H	H	0.139	1.39	**9c**	92
7d	Me	H	SiMe$_3$	0.081	2.40	**9d**	53

times ($t_{1/2}$) the signals of the product accounted for at least 90% of the starting material. Therefore, decomposition hardly occurs. In the spectra of the reaction mixture formed after partial reaction of the starting material an extra signal at $\delta = \pm 5$ ppm was observed, which disappeared after prolonged heating. In the reaction mixture obtained from the compounds **7c** and **7d** a larger signal appeared at ± 2 ppm accounting for about 3H as compared to product formed. These signals are ascribed to hydrogen cyanide or acetonitrile, respectively. No trace of a tricyclic intermediate is observed in the ^{1}H NMR spectra, indicating that the cycloreversion reaction to the pyridine compounds is fast and the rate determining step is the addition of the acetylene group to C-2 and C-5 of the pyrimidine.

From the rate of cycloaddition of compounds **4a-e** (see Table 4.1) it is clearly seen that the reaction rate increases when substituents are introduced at the α-position. The presence of one methyl or phenyl group only has a small enhancing effect on the reaction rate (± 1.8), but two *geminal* substituents increase the reaction rate significantly (± 10). This increase of reaction rate is satisfactorally explained by a relative increase of the population of the reactive *syn* rotamers about the Cα - O bond (Figure 4.2). In compound **4e** ($R^1, R^2 = -(CH_2)_4-$) the cyclopentyl group sterically hinders the unreactive *anti* rotamers and consequently the highest reaction rate is found for this compound.

Figure 4.2

anti-periplanar   *anti*-clinal   *syn*-clinal   *syn*-periplanar

P = pyrimidine
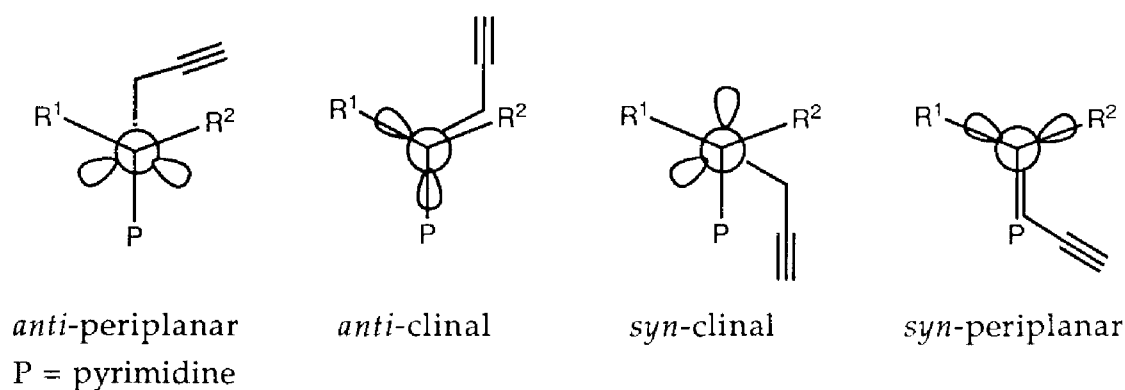
For compound **4f**, which contains two methyl groups at the γ-position, there is also a significant rate enhancement. Again, this can be explained by a more easily attainable reactive *syn* rotamer about the O - Cγ bond, although the rate enhancing effect is smaller then for substituents on Cα. For compound **4g** a strong decrease of reaction rate as compared to **4a** is observed. Due to steric hindrance by the *t*-butyl group approach of the alkyne group to the pyrimidine ring will be hindered. This same effect is also found for the 2-propargyloxymethylpyrimidines **7b-d**, which all react slower than the unsubstituted **7a**. Introduction of substituents on the diene or on the dienophilic acetylene causes a decrease of the cycloaddition rate. Substituents on the acetylene or on C-5 of the pyrimidine give more rate decrease than substituents on C-4 (C-6), which are not attached to reacting atoms.

It is interesting to note that 2-propynyloxymethylpyrimidine **(7a)** reacts much faster than 2-(pent-4-yn-1-yl)pyrimidine[4b]. It is possible that repulsion between the lone pairs on the β-oxygen and on the pyrimidine nitrogen atoms favours a perpendicular conformation between the Cα - O group and the aromatic ring[18] in which the repulsion is minimized. The molecule must adopt such a conformation before cycloaddition can occur. This phenomenon also explains the higher reactivity of **7a** as compared to **4a**. It is possible that other factors that influence the rotational barrier about the aromatic-alkyl (C-2/5 - Cα) bond also have an effect on the observed reaction rates[19].

4.3   EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer. Chemical shifts are determined in ppm downfield from Me_4Si. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed with Merck silica gel 60 (70 - 230 mesh ASTM).

Synthesis of 5-hydroxymethylpyrimidines **2a-c**.
A solution of 5-bromopyrimidine **1** (4.0 g; 25 mmol) in a 1:1 mixture of dry THF and diethyl ether (60 ml) was cooled under a nitrogen atmosphere to -100 to -110°C. Under vigorous stirring a solution of n-butyllithium in hexane (16 ml; 1.6 M) was introduced while keeping the temperature below

-100°C. After 0.25 h a solution of the appropriate carbonyl compound (35 mmol) in THF (10 ml) was added. The mixture was allowed to warm to room temperature. Then water (40 ml) was added and the mixture was extracted with ether (3 x 75 ml). The organic layers were combined, dried (MgSO$_4$) and concentrated by evaporation of the solvent. The residue was purified by column chromatography using ether/ethyl acetate as eluent.

Phenyl(pyrimidin-5-yl)methanol (2a). Carbonyl compound: benzaldehyde. Yield 80%; oil; ^{1}H NMR (CDCl$_3$) δ 8.88 (s, 1H, H-2), 8.62 (s, 2H, H-4 and H-6), 7.30 (s, 5H), 5.80 (s, 1H), 4.8 (br, 1H). HRMS Calcd. for C$_{11}$H$_{10}$N$_2$O (M$^+$): 186.0793. Found: 186.0796.

Dimethyl(pyrimidin-5-yl)methanol (2b). Carbonyl compound: acetone. Yield 55%; oil; ^{1}H NMR (CDCl$_3$) δ 9.06 (s, 1H, H-2), 8.85 (s, 2H, H-4 and H-6), 3.9 (br, 1H), 1.63 (s, 6H). HRMS Calcd. for C$_7$H$_{10}$N$_2$O (M$^+$): 138.0793. Found: 138.0785.

1-Hydroxy-1-(pyrimidin-5-yl)cyclopentane (2c). Carbonyl compound: cyclopentanone. Yield 33%; m.p. 77-78°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.00 (s, 1H, H-2), 8.82 (s, 2H, H-4 and H-6), 3.64 (s, 1H), 2.0 (br, 8H). HRMS Calcd. for C$_9$H$_{12}$N$_2$O (M$^+$): 164.0950. Found: 164.0950.
Anal. Calcd. for C$_9$H$_{12}$N$_2$O (M = 164.20): C, 65.82; H, 7.36; N, 17.06. Found: C, 65.91, H, 7.42; N, 17.14.

5-Bromomethyl-2-t-butylpyrimidine (3c).
2-t-Butyl-5-cyanopyrimidine. A mixture of 5-bromo-2-t-butylpyrimidine[12] (10.75 g; 50 mmol) and CuCN (5.4 g) in freshly distilled dry quinoline (35 ml) was refluxed for 2 h. After cooling the reaction mixture was distilled under vacuo. A solution of the destillate in ether was washed with a 1N HCl solution. The organic layer was dried (MgSO$_4$) and concentrated by evaporation of the solvent and the residue was recrystallized from hexane to give 2-t-butyl-5-cyanopyrimidine. Yield: 75%; m.p. 82-84°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 8.91 (s, 2H, H-4 and H-6), 1.39 (s, 9H); IR (KBr) 2225 cm^{-1} (C≡N stretch). HRMS Calcd. for C$_9$H$_{11}$N$_3$ (M$^+$): 161.0953. Found: 161.0952. Anal. Calcd. for C$_9$H$_{11}$N$_3$ (M = 161.20): C, 67.05; H, 6.88; N, 26.07. Found: C, 67.01; H, 7.09; N, 26.46.
2-t-Butylpyrimidine-5-carboxylic acid. A solution of 2-t-butyl-5-cyanopyrimidine (5.5 g; 34 mmol) in a mixture of water (50 ml), sulfuric acid (50 ml) and acetic acid (50 ml) was refluxed for 1 h. After removal of the acetic acid by repeated coevaporation with water the mixture was diluted with water and continuously extracted with ether to give 2-t-butyl-pyrimidine-5-carboxylic acid. Yield: 75%; m.p. 170-171°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 9.30 (s, 2H, H-4 and H-6), 1.41 (s, 9H). HRMS Calcd. for C$_9$H$_{12}$N$_2$O$_2$ (M$^+$): 180.0899. Found: 180.0898.
Anal. Calcd. for C$_9$H$_{12}$N$_2$O$_2$ (M = 180.20): C, 59.98; H, 6.71; N, 15.55. Found: C, 60.09; H, 6.64; N, 15.49.

2-*t*-Butyl-5-hydroxymethylpyrimidine. A mixture of 2-*t*-butyl-5-pyrimidine-carboxylic acid (1.44 g; 8 mmol) and LiAlH$_4$ (570 mg) in dry THF (50 ml) was stirred for 6 h at room temperature under a nitrogen atmosphere. After hydrolysis with a few drops of ethyl acetate followed by a few drops of a 0.01N H$_2$SO$_4$ solution, the mixture was filtered and the filtrate was concentrated. Water (20 ml) was added to the residue and the aqueous layer was extracted with chloroform (3 x 20 ml). After drying (MgSO$_4$) and concentration of the organic layer the residue was subjected to column chromatography using chloroform/methanol 19:1 as eluent. After a first fraction, which was identified as 2-*t*-butyl-5-pyrimidine carboxaldehyde a second fraction containing 2-*t*-butyl-5-hydroxymethylpyrimidine was isolated as a colourless oil. Yield 11%; ^{1}H NMR (CDCl$_3$) δ 8.62 (s, 2H, H-4 and H-6), 4.63 (s, 2H), 1.32 (s, 9H). HRMS Calcd. for C$_9$H$_{14}$N$_2$O (M$^+$): 166.1106. Found: 166.1107.

A mixture of 2-*t*-butyl-5-hydroxymethylpyrimidine (150 mg; 0.9 mmol) and POBr$_3$ (1 ml) was heated at 120°C for 4h. After cooling the mixture was poured on ice and neutralized with K$_2$CO$_3$. Extraction with chloroform, drying (MgSO$_4$) of the organic layer and concentration gave 5-bromomethyl-2-*t*-butylpyrimidine (3c). Yield 95%; m.p. 31-32°C; ^{1}H NMR (CDCl$_3$) δ 8.75 (s, 2H, H-4 and H-6), 4.40 (s, 2H), 1.40 (s, 9H). HRMS Calcd. for C$_9$H$_{13}$BrN$_2$ (M$^+$): 228.0263. Found: 228.0271.

Synthesis of the 5-(2-propynyloxymethyl)pyrimidines **4a,b,f,g** from 5-bromo-methylpyrimidines **3a-c**.

The bromide (1 mmol) was added to a solution of sodium propynolate (prepared by the addition of 1.5 mmol of 80% sodium hydride to 2 mmol of propynol in dry THF (15 ml)). The mixture was refluxed for 3 h. Water (30 ml) was added and the aqueous layer was extracted with ether (3 x 50 ml). The organic layers were combined, dried (MgSO$_4$) and concentrated by evaporation of the solvent. The residue was purified by column chromatography with ether as eluent.

5-(2-Propynyloxymethyl)pyrimidine (4a). This compound was prepared from the hydrobromide salt of **3a**[10] and sodium propynolate. Yield 34% (based on the pyrimidine hydrobromide salt, which was neutralized with one extra equivalent of sodium propynolate); m.p. 30-31°C (hexanes at -20°C); ^{1}H NMR (CDCl$_3$) δ 9.20 (s, 1H, H-2), 8.78 (s, 2H, H-4 and H-6), 4.66 (s, 2H), 4.28 (d, J = 2.4 Hz, 2H), 2.61 (t, J = 2.4 Hz, 1H).
Anal. Calcd. for C$_8$H$_8$N$_2$O (M = 148.16): C, 64.84; H, 5.44; N, 18.90. Found: C, 64.56; H, 5.47; N, 19.22.

5-(1-(2-Propynyloxy)ethyl)pyrimidine (4b). This compound was prepared from **3b** (synthesized from 5-ethylpyrimidine and N-bromosuccinimide without isolation of **3b**[11]) and sodium propynolate. Yield 44% (based on 5-ethylpyrimidine); m.p. 70-71°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 9.21 (s, 1H,

H-2), 8.78 (s, 2H, H-4 and H-6), 4.80 (q, J = 7.0 Hz, 1H), 4.13 (m, 2H), 2.50 (t, J = 2.4 Hz, 1H), 1.55 (d, J = 7.0 Hz, 3H).
Anal. Calcd. for $C_9H_{10}N_2O$ (M = 162.19): C, 66.64; H, 6.21; N, 17.27. Found: C, 66.52; H, 6.29; N, 17.39.

5-(2-Methyl-3-butyn-2-yloxymethyl)pyrimidine (4f). This compound was prepared from the hydrobromide salt of **3a**[10] and the sodium salt of 1,1-dimethylpropynol. Yield 4% (based on the pyrimidine hydrobromide salt, which was neutralized with one extra equivalent of sodium 1,1-dimethylpropynolate); oil; ^{1}H NMR (CDCl3) δ 9.16 (s, 1H, H-2), 8.72 (s, 2H, H-4 and H-6), 4.66 (s, 2H), 2.52 (s, 1H), 1.56 (s, 6H). HRMS Calcd. for $C_{10}H_{12}N_2O$ (M+): 176.0950. Found: 176.0949.

2-t-Butyl-5-(2-propynyloxymethyl)pyrimidine (4g). This compound was prepared from **3c** and sodium propynolate. Yield 89%; oil; ^{1}H NMR (CDCl3) δ 8.67 (s, H-4 and H-6, 2H), 4.57 (s, 2H), 4.22 (d, J = 2.7 Hz, 2H), 2.47 (t, J = 2.7 Hz, 1H), 1.39 (s, 9H). HRMS Calcd. for $C_{12}H_{16}N_2O$ (M+): 204.1263. Found: 204.1260.

Synthesis of the 5-(2-propynyloxymethyl)pyrimidines **4c-e** from the 5-hydroxymethylpyrimidines **2a-c**.
The appropriate alcohol (1 mmol) was added to a suspension of 1.1 mmol of sodium hydride in THF (25 ml). The mixture was stirred until the evolution of hydrogen had ceased. Then propargyl bromide (2 mmol) was added and the mixture was refluxed for 3 h. Water (50 ml) was added and the mixture was extracted with ether (3 x 50 ml). The organic layers were dried (MgSO4) and concentrated by evaporation of the solvent and the residue was purified by column chromatography using ether as eluent.

5-(Phenyl-2-propynyloxymethyl)pyrimidine (4c). This compound was prepared from **2a**. Yield 60%; oil; ^{1}H NMR (CDCl3) δ 9.13 (s, 1H, H-2), 8.71 (s, 2H, H-4 and H-6), 7.37 (s, 5H), 5.73 (s, 1H), 4.18 (m, 2H), 2.53 (t, J = 2.4 Hz, 1H). HRMS Calcd. for $C_{14}H_{12}N_2O$ (M+): 224.0950. Found: 224.0940.

5-(1-Methyl-1-(2-propynyloxy)ethyl)pyrimidine (4d). This compound was prepared from **2b**. Yield 45%; m.p. 48-49°C (hexanes); ^{1}H NMR (CDCl3) δ 9.12 (s, 1H, H-2), 8.80 (s, 2H, H-4 and H-6), 4.00 (d, J = 2.4 Hz, 2H), 2.48 (t, J = 2.4 Hz, 1H), 1.63 (s, 6H). HRMS Calcd. for $C_{10}H_{12}N_2O$ (M+): 176.0950. Found: 176.0945.
Anal. Calcd. for $C_{10}H_{12}N_2O$ (M = 176.21): C, 68.15; H, 6.86; N, 15.89. Found: C, 68.27; H, 6.99; N, 15.99.

1-(2-Propynyloxy)-1-(pyrimidin-5-yl)cyclopentane (4e). This compound was prepared from **2c**. Yield 32 %; oil; ^{1}H NMR (CDCl3) δ 9.12 (s, 1H, H-2), 8.78 (s, 2H, H-4 and H-6), 3.82 (d, J = 2.4 Hz, 2H), 2.34 (t, J = 2.4 Hz, 1H),

2.5-1.7 (br, 8H). HRMS Calcd. for $C_{12}H_{14}N_2O$ (M+): 202.1106. Found: 202.1108.

2-Hydroxymethyl-5-phenylpyrimidine (6). A 2 M methanolic solution of sodium methoxide (5.3 ml) was added dropwise at room temperature to a stirred mixture of hydroxyacetamidine hydrochloride[20] (500 mg) and 1-dimethylamino-3-dimethylimonio-2-phenylprop-1-ene tetrafluoroborate[21] (908 mg) in methanol (10 ml). The mixture was refluxed for 2 h, neutralized with acetic acid and concentrated. Water (25 ml) was added to the residue and the aqueous layer was extracted with ether (2 x 50 ml). After drying ($MgSO_4$) and concentration by evaporation of the solvent 2-hydroxymethyl-5-phenylpyrimidine (6) was obtained as pale yellow crystals. Yield 80%; m.p. 109 -111°C (hexanes/toluene); ^1H NMR ($CDCl_3$) δ 8.90 (s, H-4 and H-6, 2H), 7.50 (br, 5H), 4.92 (s, 2H).
Anal. Calcd. for $C_{11}H_{10}N_2O$ (M = 186.21): C, 70.95; H, 5.41; N, 15.05. Found: C, 70.87; H, 5.38; N, 15.09.

2-(2-Propynyloxymethyl)pyrimidine (7a). A solution of 2-chloromethyl-pyrimidine (5a)[13] (1 mmol) in THF (5 ml) was added to a solution of sodium propynolate (1.5 mmol) in THF (10 ml). The mixture was refluxed for 3 h. After cooling, water (30 ml) was added and the mixture was extracted with ether (3 x 50 ml). The ethereal extracts were dried ($MgSO_4$) and concentrated by evaporation of the solvent. Column chromatography of the residue with ether as eluent gave 7a. Yield 51%; oil; ^1H NMR ($CDCl_3$) δ 8.75 (d, J = 5.0 Hz, 2H, H-4 and H-6), 7.22 (t, J = 5.0 Hz, 1H, H-5), 4.90 (s, 2H), 4.42 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H). HRMS Calcd. for $C_8H_7N_2O$ (M+-1): 147.0556. Found: 147.0558.

5-Phenyl-2-(2-propynyloxymethyl)pyrimidine (7b). A solution of 2-hydroxy-methyl-5-phenylpyrimidine (6) (150 mg) in THF (5 ml) was added to a stirred suspension of sodium hydride (27 mg; 80% suspension in oil) in dry THF (10 ml). After the initial effervescence had subsided propargyl bromide (1 ml) was added and the reaction mixture was refluxed for 3 h. After addition of water (25 ml) the aqueous layer was extracted with ether (2 x 50 ml). The ethereal extracts were dried ($MgSO_4$) and concentrated by evaporation of the solvent. Column chromatography of the residue with ether as eluent gave 7b. Yield 40%; oil; ^1H NMR ($CDCl_3$) δ 8.93 (s, 2H, H-4 and H-6), 7.49 (m, 5H), 4.90 (s, 2H), 4.41 (d, J = 2.4 Hz, 2H), 2.47 (t, J = 2.4 Hz, 1H). HRMS Calcd. for $C_{14}H_{12}N_2O$ (M+): 224.0941. Found: 224.0950.

4,6-Dimethyl-2-(2-propynyloxymethyl)pyrimidine (7c). A solution of 2-chloromethyl-4,6-dimethylpyrimidine (5b)[14] (4.70 g; 30 mmol) in dry THF (15 ml) was added to a solution of sodium propynolate (50 mmol) in THF (50 ml). The mixture was refluxed for 3 h. After cooling water (40 ml) was added and the mixture was extracted with ether (3 x 75 ml). The organic layers were dried ($MgSO_4$) and concentrated by evaporation of the solvent.

The residue was purified by column chromatography using ether as eluent. Yield 4.35 g (82%); oil; ^{1}H NMR (CDCl$_3$) δ 6.94 (s, 1H, H-5), 4.74 (s, 2H), 4.35 (d, J = 2.4 Hz, 2H), 2.45 (7H, 2 CH$_3$ and C≡CH). HRMS Calcd. for C$_{10}$H$_{11}$N$_2$O (M$^+$-1): 175.0872. Found: 175.0872. Picrate; m.p. 100-102°C. Anal. Calcd. for C$_{16}$H$_{15}$N$_5$O$_8$ (picrate; M = 405.32): C, 47.41; H, 3.73; N, 17.28. Found: C, 47.17; H, 3.61; N, 17.34.

4,6-Dimethyl-2-(3-trimethylsilyl-2-propynyloxymethyl)pyrimidine (7d). A solution of n-butyllithium in hexane (1.3 ml; 1.6 M) was added to a solution of **7c** (352 mg; 2 mmol) in dry THF (15 ml) at -70°C under a nitrogen atmosphere. Then a solution of trimethylsilyl chloride (250 mg) in dry THF (10 ml) was added. After stirring for 1 h at -15°C a 1N HCl solution (30 ml) was added and the mixture was extracted with ether (3 x 75 ml). After drying (MgSO$_4$) of the organic layers and concentration compound **7d** was obtained. Yield 350 mg (71%); oil; ^{1}H NMR (CDCl$_3$) δ 6.98 (s, 1H, H-5), 4.80 (s, 2H), 4.41 (s, 2H), 2.50 (s, 6H, 2 CH$_3$), 0.17 (s, 9H). HRMS Calcd. for C$_{13}$H$_{20}$N$_2$OSi (M$^+$): 247.1267. Found: 247.1280.

Cycloaddition reaction of the 5-(2-propynyloxymethyl)pyrimidines 4a-g to the corresponding 1,3-dihydrofuro[3,4-c]pyridines 8a-g and of the 2-(2-propynyloxymethyl)pyrimidines 7a-d to the corresponding 5,7-dihydrofuro[3,4-b]pyridines 9a-d.
A solution of the appropriate 5-(2-propynyloxymethyl)pyrimidine **4a-g** or 2-(2-propynyloxymethyl)pyrimidine **7a-d** (1 mmol) in nitrobenzene (2 ml) was heated at 140 ± 1°C under a nitrogen atmosphere. After heating the mixture for 6 times t$_{1/2}$ the product was isolated by column chromatography using ether/ethyl acetate 1:1 as eluent.

1,3-Dihydrofuro[3,4-c]pyridine (8a). Yield 90%; oil; ^{1}H NMR (CDCl$_3$) δ 8.53 (s, 1H, H-4), 8.50 (d, J = 5.1 Hz, 1H, H-6), 7.20 (d, J = 5.1 Hz, 1H, H-7), 5.09 (br, 4H). HRMS Calcd. for C$_7$H$_7$NO (M$^+$): 121.0528. Found: 121.0531.

1,3-Dihydro-3-methylfuro[3,4-c]pyridine (8b). Yield 84%; oil; ^{1}H NMR (CDCl$_3$) δ 8.51 (d, J = 5.1 Hz, 1H, H-6), 8.47 (s, 1H, H-4), 7.2 (d, 1H, J = 5.1 Hz, H-7), 5.38 (m, 1H, H-3), 5.05 (m, 2H), 1.53 (d, J = 7.0 Hz, 3H). HRMS Calcd. for C$_8$H$_9$NO (M$^+$): 135.0684. Found: 135.0685.

1,3-Dihydro-3-phenylfuro[3,4-c]pyridine (8c). Yield 81%; m.p. 60-61°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 8.48 (d, J = 5.0 Hz, 1H, H-6), 8.33 (s, 1H, H-4), 7.30 (s, 5H), 7.17 (d, 1H, J = 5.0 Hz, H-7), 6.18 (br, 1H, H-3), 5.17 (m, 2H). HRMS Calcd. for C$_{13}$H$_{11}$NO (M$^+$): 197.0841. Found: 197.0834;
Anal. Calcd. for C$_{13}$H$_{11}$NO (M = 197.23): C, 79.16; H, 5.62; N, 7.10. Found: C, 78.84; H, 5.62; N, 7.03.

1,3-Dihydro-3,3-dimethylfuro[3,4-c]pyridine (**8d**). Yield 68%; oil; ^{1}H NMR (CDCl$_3$) δ 8.52 (d, J = 5.1 Hz, 1H, H-6), 8.47 (s, 1H, H-4), 7.19 (d, 1H, J = 5.1 Hz, H-7), 5.05 (s, 2H), 1.52 (s, 6H). HRMS Calcd. for C$_9$H$_{10}$NO (M$^+$-1): 148.0762. Found: 148.0762.

1,3-Dihydro-3-spirocyclopentylfuro[3,4-c]pyridine (**8e**). Yield 81%; m.p. 59-61°C (hexanes -20°C); ^{1}H NMR (CDCl$_3$) δ 8.48 (d, J = 5.1 Hz, 1H, H-6), 8.43 (s, 1H, H-4), 7.16 (d, J = 5.1 Hz, 1H, H-7), 5.00 (s, 2H), 2.2-1.8 (br, 8H).
Anal. Calcd. for C$_{11}$H$_{13}$NO (M = 175.22): C, 75.39; H, 7.47; N, 7.99. Found: C, 75.42; H, 7.62; N, 7.88.

1,3-Dihydro-1,1-dimethylfuro[3,4-c]pyridine (**8f**). Yield 70%; oil; ^{1}H NMR (CDCl$_3$) δ 8.50 (d, J = 5.1 Hz, 1H, H-6), 8.49 (s, 1H, H-4), 7.08 (d, J = 5.1 Hz, 1H, H-7), 5.10 (s, 2H), 1.47 (s, 6H). HRMS Calcd. for C$_9$H$_{11}$NO (M$^+$): 149.0841. Found: 149.0840.

6-*t*-Butyl-1,3-dihydrofuro[3,4-c]pyridine (**8g**). This compound was obtained upon heating of a solution of **4g** in nitrobenzene at 160°C for 24 h. Yield 59%; oil; ^{1}H NMR (CDCl$_3$) δ 8.48 (s, 1H, H-4), 7.26 (s, 1H, H-7), 5.09 (s, 4H), 1.37 (s, 9H). HRMS Calcd. for C$_{11}$H$_{15}$NO (M$^+$): 177.1154. Found: 177.1149.

5,7-Dihydrofuro[3,4-b]pyridine (**9a**). Yield 63%; oil; ^{1}H NMR (CDCl$_3$) δ 8.48 (d, J = 4.8 Hz, 1H, H-2), 7.54 (d, J = 7.5 Hz, 1H, H-4), 7.15 (dd, J$_1$ = 4.9 Hz, J$_2$ = 7.6 Hz, 1H, H-3), 5.15 (brs, 2H), 5.07 (brs, 2H). HRMS Calcd. for C$_7$H$_7$NO (M$^+$): 121.0528. Found: 121.0526.

5,7-Dihydro-3-phenylfuro[3,4-b]pyridine (**9b**). Yield 87%; m.p. 126-128°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 8.70 (s, 1H, H-2), 7.70 (s, 1H, H-4), 7.50 (mc, 5H), 5.21 (brs, 2H), 5.12 (t, J = 1.8 Hz, 2H).
Anal. Calcd. for C$_{13}$H$_{11}$NO (M = 197.23): C, 79.16; H, 5.62; N, 7.10. Found: C, 79.04; H, 5.56; N, 6.80.

5,7-Dihydro-2-methylfuro[3,4-b]pyridine (**9c**). Yield 92%; m.p. 92-93°C (hexanes); ^{1}H NMR (CDCl$_3$) δ 7.47 (d, J = 7.5 Hz, 1H, H-4), 7.06 (d, J = 7.5 Hz, 1H, H-3), 5.13 (br, 2H), 5.04 (br, 2H), 2.57 (s, 3H).
Anal. Calcd. for C$_8$H$_9$NO (M = 135.16): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.25; H, 6.87; N, 10.36.

5,7-Dihydro-2-methyl-4-trimethylsilylfuro[3,4-b]pyridine (**9d**). Yield 53%; oil; ^{1}H NMR (CDCl$_3$) δ 7.16 (s, 1H, H-3), 5.22 (br, 2H), 5.07 (br, 2H), 2.60 (s, 3H), 0.30 (s, 9H). HRMS Calcd. for C$_{11}$H$_{17}$NOSi (M$^+$): 207.1079. Found: 207.1073.

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<u>3,3-Dimethylfuro[3,4-c]pyridin-1(3H)-one</u> **(10a).** This compound was obtained in good yield by air oxidation of compound **8a**. M.p. 97-98°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.83 (s, 1H, H-4), 8.79 (d, J = 5.0 Hz, 1H, H-6), 7.70 (d, J = 5.0 Hz, 1H, H-7), 1.74 (s, 6H). HRMS Calcd. for C$_9$H$_9$NO$_2$ (M$^+$): 163.0633. Found: 163.0632.

Anal. Calcd. for C$_9$H$_9$NO$_2$ (M = 163.17): C, 66.24; H, 5.56; N, 8.58. Found: C, 66.54; H, 5.76; N, 8.64.

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CHAPTER 5

SUBSTITUENT EFFECTS IN THE INTRAMOLECULAR INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF 5-(P-SUBSTITUTED PHENYL)-2-(1,1-DICYANOPENT-4-YN-1-YL)PYRIMIDINES.

5.1   INTRODUCTION

Recently we have described intramolecular inverse electron demand Diels-Alder reactions of pyrimidines carrying an appropriate dienophilic side-chain attached to the 2- or the 5-position of the pyrimidine ring[1]. These reactions offer a useful tool to obtain several new annelated pyridines. In this way we have prepared dihydrofuro[2,3-b]-, dihydrothieno[2,3-b]-, dihydrothieno[2,3-c]- and dihydropyrrolo[2,3-b]pyridines[1a,b], 6,7-dihydro-5H-1-pyrindines[1c,d], 5,6,7,8-tetrahydroquinolines[1d] and also dihydrofuro-[3,4-b]- and dihydrofuro[3,4-c]pyridines[1e]. We have shown that the rate of cycloaddition depends largely upon the nature of the tether between azadiene and dienophile and upon the nature of substituents attached to the pyrimidine or the dienophilic acetylene group. Both electronic and steric effects have been found to influence the reactivity. Our studies thus far have indicated that steric (structural) effects are more important than electronic effects in governing the reactivity towards cycloaddition. Especially, reduction of the degrees of freedom in the chain connecting the dienophilic acetylene group and the azadiene, either by the introduction of bulky substituents at the carbon atom α (and to a lesser degree γ) to the pyrimidine ring[1c-e] or by creating repulsion between lone pairs on the pyrimidine nitrogen atoms and on a β-oxygen atom in the connecting chain[1e], greatly enhances the rate of cycloaddition.

In order to gain further insight into the electronic factors that govern the mechanism of this type of cycloaddition reactions of pyrimidines we looked for a quantitative relationship between the rate of reaction and the electronic influence of substituents on the 5-position of the azaheterocycle in 2-

(1,1-dicyanopent-4-yn-1-yl)pyrimidines. For this reason we prepared the 5-phenyl and a series of 5-(para-substituted phenyl) derivatives of 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidine and studied their cycloaddition reaction.

5.2   RESULTS AND DISCUSSION

5-Aryl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines **6** were synthesized by the methods outlined in Scheme 5.1. 5-Aryl-2-methylsulfonylpyrimidines **4** were obtained by condensation of the appropriate 2-aryl-1-dimethylamino-3-dimethylimonioprop-1-ene perchlorate **1**[2] with S-methylthiourea sulfate (**2**)[3] and subsequent oxydation of the resulting 5-aryl-2-methylthio-pyrimidines **3** with m-chloroperoxybenzoic acid. Nucleophilic substitution of the methylsulfonyl group with the sodium salt of 5,5-dicyanopent-1-yne **5**[4] then gave the desired starting materials **6**.

Scheme 5.1

a   R = H   b   R = Br   c   R = Cl
d   R = Me   e   R = MeO   f   R = NO2
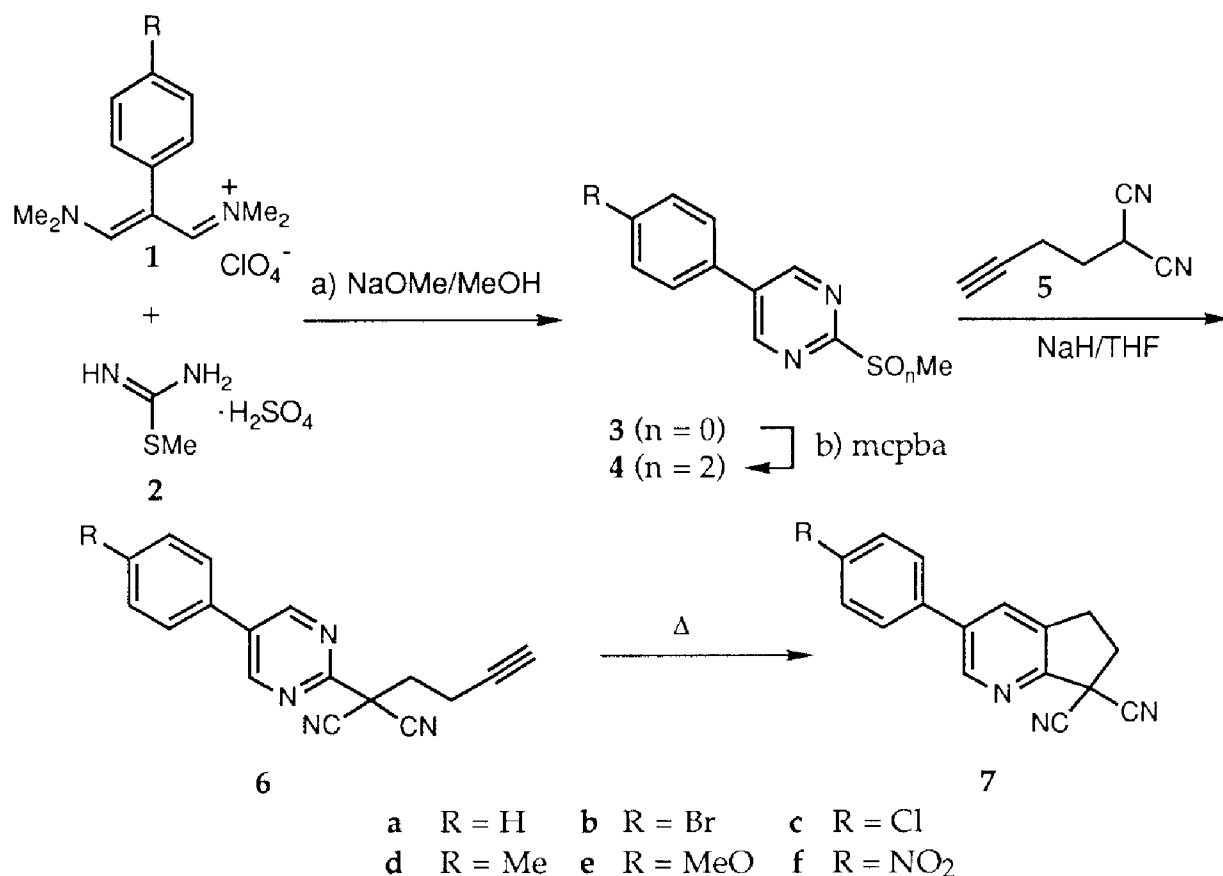
The intramolecular Diels-Alder reaction of compounds **6** was performed in nitrobenzene at 180°C under an atmosphere of nitrogen. Under these conditions the cycloaddition into the corresponding 3-aryl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindines **7** was complete within 1 hour; the yields were almost quantitative. The structures of all new compounds were established by their ^{1}H NMR spectra and confirmed by elemental analyses and/or mass spectroscopy.

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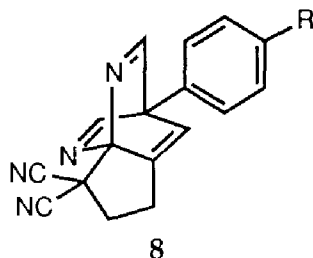
As stated before[1], a tricyclic intermediate cycloadduct **8** is formed by addition of the acetylene group accross the C-2 and C-5 positions of the pyrimidine ring. Such a cycloaddition product could, however, not be isolated or identified by NMR spectroscopy due to the spontaneous cycloreversion into **7** by expulsion of hydrogen cyanide. This indicates that the cycloreversion reaction to the pyrindines is fast and that the rate determining step is the addition of the acetylene group to C-2 and C-5 of the pyrimidine. In order to get more information about the electronic character of the transition state leading to this intermediate cycloadduct we investigated whether a quantitative relationship exists between the rate of cycloaddition and substituents on the C-5 position of the pyrimidine ring. We decided to study the cycloaddition reaction of the afore-mentioned 2-(1,1-dicyanopent-4-yn-1-yl)-5-(*para*-substituted phenyl)pyrimidines **6**, in which the electronic effect of each *para*-substituent is transmitted to the reaction site situated in a constant steric environment. Thus, we should be able to determine a correlation, i.e. a Hammett plot, between the rates of cycloaddition and known[5] σ values for *para*-substituents on the 5-phenyl group.

For these quantitative analyses we used HPLC liquid chromatography with Spherisorb S5 ODS as stationary phase. A mixture of acetonitrile, tetrahydrofuran and water (4 : 1 : 5; v/v) was found to be convenient to get good

separations between the solvent (nitrobenzene), the starting materials (the pyrimidines **6**) and the products (the pyrindines **7**). The retention time of the reaction products **7** was found to be intermediate between that of the solvent peak (t_r = 3.5 min) and the corresponding starting material **6** (see Table 5.1).

TABLE 5.1   Retention times of compounds **6** and **7** under the chromatographic conditions used in this study.

Compound	t_r (min)	Compound	t_r (min)
6a	9.2	7a	6.5
6b	16.6	7b	11.8
6c	14.9	7c	10.3
6d	13.7	7d	9.3
6e	9.4	7e	6.3
6f	8.3	7f	5.9

Our preliminary experiments (see above) revealed that the reactions take place in almost quantitative yield. Therefore, decomposition hardly occurs and the reaction rate can be calculated from the decrease of starting material and/or the increase of reaction product. The reactions for quantitative analyses were carried out at 140 ± 1°C in nitrobenzene.

First, we monitored the decrease of 2-(1,1-dicyanopent-4-yn-1-yl)-5-(p-methoxyphenyl)pyrimidine (**6e**), using 3-p-bromophenyl-7,7-dicyano-6,7-dihydro-5H-1-pyrindine (**7b**) as internal standard. As was found earlier for 2- and 5-propynyloxymethylpyrimidines[1e], a plot of $-\ln(C_t/C_0)$ against t revealed that the reaction obeys simple first order kinetics. Thus, the reaction constant (k_{MeO}) for the cycloaddition reaction of **6e** into **7e** could be determined and from this the half-life time ($t_{1/2}$) could be calculated (k_{MeO} = 0.63 x 10^{-4} s^{-1}; $t_{1/2}$ = 3.06 h). Since cycloreversion from the intermediate tricyclic cycloadduct is fast, these values reflect the rate determining addition of the acetylene group to C-2 and C-5 of the pyrimidine.

For reasons of accuracy, the reaction constants (k_R) and the half-life times ($t_{1/2}$) of each of the other cycloaddition reactions of 2-(1,1-dicyanopent-4-

yn-1-yl)-5-(*para*-substituted phenyl)pyrimidines **6** into their corresponding pyrindine derivatives **7** were determined using the cyclization of the 5-(p-bromophenyl) derivative **6b** into its pyrindine derivative **7b** as reference reaction[6]. Thus, we were able to calculate the reaction constant (k_R) for each cycloaddition reaction of **6** into **7** relative to that of **6b** into **7b** (R = Br), thereby eliminating the effect of small fluctuations in reaction temperature on the reaction rate. From the decrease of starting material **6** (entries **a**, **e**, and **f**) or the increase of reaction product **7** (entries **c** and **d**) at several time intervals we determined the relative reaction constants k_R/k_{Br} (R = H, Cl, Me, MeO, NO_2) and also k_R/k_H (Table 5.2). From these data and the indepen-dently determined reaction constant (k_{MeO}) for the cyclization of **6e** into **7e** (see above) the reaction constants (k_R) and half-life times ($t_{1/2}$) for the cycloaddition of the other compounds **6** were determined (see Table 5.2). A Hammett plot of log k_R/k_H against σ values for the *para*-substituents showed a rectilinear relationship (correlation coëfficient 0.993) with a positive slope $\rho = 0.061 \pm 0.003$ (Figure 5.1).

TABLE 5.2   Relative rates, rate constants and half-life times for the cycloaddition reaction of compounds **6** in nitrobenzene at 140°C.

Compound	R	k_R/k_{Br}	k_R/k_H	$k_R \times 10^{-4} s^{-1}$	$t_{1/2}$ (h)
6a	H	0.953	1.000	0.65	2.96
6b	Br	1.000	1.049	0.68	2.83
6c	Cl	0.998	1.047	0.68	2.83
6d	Me	0.938	0.984	0.64	3.01
6e	MeO	0.925	0.970	0.63	3.06
6f	NO_2	1.070	1.122	0.73	2.64

The positive sign for ρ is in agreement with the inverse electron demand character of this intramolecular Diels-Alder reaction[7,8]. The low value for ρ indicates that in the rate determining transition state leading from **6** to cycloadduct **8** there is hardly any charge separation and thus a two-step reaction via a zwitterionic intermediate can be excluded. This result is generally found for intermolecular Diels-Alder reactions[7] and has now also been found to hold for the intramolecular version.

Figure 5.1
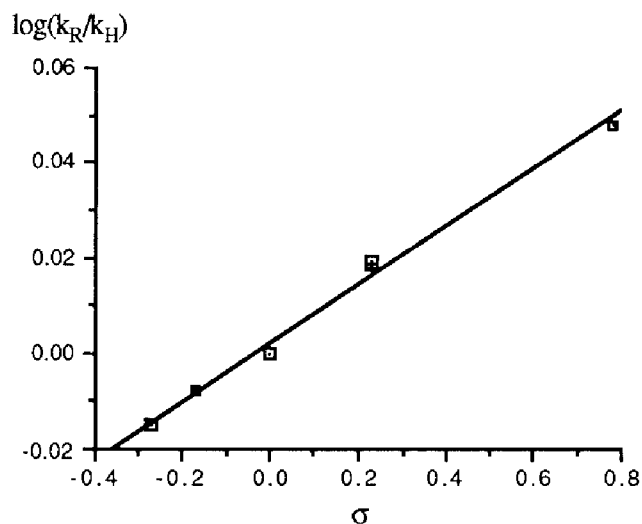
The magnitude of ρ for the intramolecular Diels-Alder reactions of compounds **6** into **7** (ρ = +0.061) is significantly lower than that for the comparable intermolecular Diels-Alder reaction of *para*-substituted phenyl-tetrazines (ρ = 1.25)[7]. This low value (ρ = 0.061) indicates that the reaction is less susceptible to polar effects. In terms of frontier molecular orbitals[8,9], the low magnitude of ρ indicates that the mean energy gap between LUMO$_{diene}$ and HOMO$_{dienophile}$ is large as compared to the differences in energy between the successive LUMO's of the diene resulting from changing the *para*-substituent.

TABLE 5.3   Rate constant and half-life time for the cycloaddition reaction of **6e** into **7e** in different solvents at 140°C.

Solvent	k x 10^{-4} s^{-1}	t$_{1/2}$ (h)
nitrobenzene	0.63	3.06
p-bromotoluene	0.45	4.31
mesitylene	0.28	6.97

We also studied the cyclization reaction of **6e** in solvents less polar than nitrobenzene. It was found (see Table 5.3) that **6e** cyclizes in nitrobenzene, *p*-bromotoluene and mesitylene with relative rates of 2.3, 1.6 and 1,

respectively. The effects of the solvent are small, indicating that the transition state has little or no ionic character. This result lends support to our previous conclusion (see above). Recently, similar solvent effects were found at our laboratory for the intramolecular Diels-Alder reaction of (3-butynylthio)pyrazine[10] and by others for the intermolecular Diels-Alder reaction of 3,6-diphenyl-1,2,4,5-tetrazine with styrene[7]. These differences in reactivity are, however, smaller than in the intermolecular Diels-Alder reaction of 5-nitropyrimidine with electron-rich dienophiles, in which case a zwitterionic intermediate has been postulated[11].

From the present investigations it can be concluded that the intra-molecular Diels-Alder reaction of the 2-alkynylpyrimidines used in our studies indeed have an inverse electron demand character[7]. Furthermore, the electronic influence on the reaction rate is small. This result lends support to our previous conclusions that the observed differences in reac-tion rate have to be attributed mainly to steric or conformational effects[1d,e].

5.3 EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer. Chemical shifts are determined in ppm downfield from Me_4Si. Mass spectral data were obtained on a AEI MS 902 spectro-meter equipped with a VG ZAB console. Column chromatography was performed with Merck silica gel 60 (70 - 230 mesh ASTM).
A Kratos Spectroflow 400 solvent delivery system and a Must Single Valco Injector equipped with a 10 µl sampling loop were used for the HPLC analyses. The detector was a Kratos Spectroflow 773 variable wavelenght spectrophotometer connected to a Hewlett Packard HP3396A Integrator which served also as recorder. The analytical separations were accom-plished using a column, 20.0 cm x 4.6 mm, filled with 5 µm Spherisorb S5 ODS. The mobile phase consisted of a mixture of acetonitrile, tetra-hydrofuran and water (double distilled) in a ratio of 4 : 1 : 5 (v/v). The flow rate was 1.6 ml/min. The UV detector was operated at 280 nm and the separations were carried out at room temperature.

Starting materials.
2-Aryl-1-dimethylamino-3-dimethylimonioprop-1-ene perchlorates 1 were synthesized as described in the literature[2]. 5-Aryl-2-methylthiopyrimidines 3 were prepared in excellent yields (see Table 5.4) from the appropriate trimethinium salt 1 and S-methylthiourea sulphate[3] (2) by the method described by Wagner and Jutz for 2-methylthio-5-phenylpyrimidine (3a)[12].

TABLE 5.4   Synthesis of 5-aryl-2-methylthiopyrimidines 3.

Compound	R	% yield
3a	H	81
3b	Br	96
3c	Cl	93
3d	Me	95
3e	MeO	90
3f	NO2	65

Melting points and ^{1}H NMR spectra of compounds **3a-e** were all in agreement with those reported in the literature[13]. In the same way compound **3f** was obtained from 1-dimethylamino-3-dimethylimonio-2-(p-nitrophenyl)prop-1-ene perchlorate[2a] (**1f**).

2-Methylthio-5-(p-nitrophenyl)pyrimidine (3f). Obtained as a pale yellow solid. Yield: 65%; m.p. 211-214°C (hexanes/chloroform); ^{1}H NMR (CDCl₃) δ 8.77 (s, 2H), 8.35 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 2.61 (s, 3H). Anal. Calcd. for $C_{11}H_9N_3O_2S$ (247.28): C, 53.42; H, 3.66; N, 16.99. Found: C, 53.14; H, 3.56; N, 17.00.

Oxidation of compounds **3** to the analogous 5-aryl-2-methylsulfonylpyrimidines **4** with m-chloroperoxybenzoic acid was performed according to the procedure described in literature[13].

General procedure for the synthesis of 5-aryl-2-(1,1-dicyanopent-4-yn-1-yl)-pyrimidines 6.

To a stirred suspension of sodium hydride (84 mg; 2.8 mmol, 80% oil dispersion) in anhydrous tetrahydrofuran (5 ml) 5,5-dicyanopent-4-yne[4] (330 mg; 2.8 mmol) was added at room temperature. After the initial effervescence had subsided, the appropriate 5-aryl-2-methylsulfonylpyrimidine (2.5 mmol) was added in one portion and the reaction mixture was refluxed for two hours. After cooling water was added and the aqueous layer extracted twice with dichloromethane. The combined organic layers were washed with water, dried (MgSO₄) and the solvent evaporated under reduced pressure. Column chromatography (eluting with dichloromethane/petroleum ether 40/60 5:1) of the residue afforded the desired products.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-phenylpyrimidine (6a). From 2-methylsulfonyl-5-phenylpyrimidine. Obtained as a colourless solid (91%): m.p. 97-98°C (hexanes/toluene); ^{1}H NMR (CDCl₃) δ 9.00 (s, 2H), 7.55 (s, 5H), 2.9-2.4 (mc, 4H), 1.97 (t, J = 2.4 Hz, 1H). MS: m/e 272 (M⁺).
Anal. Calcd. for $C_{17}H_{12}N_4$ (272.30): C, 74.97; H, 4.44; N, 20.57. Found: C, 74.93; H, 4.44; N, 20.64.

5-*p*-Bromophenyl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidine **(6b)**. From 5-*p*-bromophenyl-2-methylsulfonylpyrimidine. Obtained as a colourless solid (97%): m.p. 128-129°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.00 (s, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 2.9-2.4 (mc, 4H), 1.98 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{17}$H$_{11}$BrN$_4$ (351.21): C, 58.13; H, 3.15; N, 15.95. Found: C, 58.28; H, 3.11; N, 15.82.

5-*p*-Chlorophenyl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidine **(6c)**. From 5-*p*-chlorophenyl-2-methylsulfonylpyrimidine. Obtained as a colourless solid (88%): m.p. 134-135°C (hexanes/toluene; ^{1}H NMR (CDCl$_3$) δ 8.98 (s, 2H), 7.52 (s, 4H), 2.9-2.4 (mc, 4H), 1.96 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{17}$H$_{11}$ClN$_4$ (306.75): C, 66.55; H, 3.61; N, 18.26. Found: C, 66.38; H, 3.58; N, 18.53.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-*p*-methylphenylpyrimidine **(6d)**. From 5-*p*-methylphenyl-2-methylsulfonylpyrimidine. Obtained as a colourless solid (79%): m.p. 78-79°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.98 (s, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 2.9-2.4 (mc, 4H), 2.42 (s, 3H), 1.97 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{18}$H$_{14}$N$_4$ (286.32): C, 75.50; H, 4.92; N, 19.56. Found: C, 75.56; H, 4.83; N, 19.33.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-*p*-methoxyphenylpyrimidine **(6e)**. From 5-*p*-methoxyphenyl-2-methylsulfonylpyrimidine. Obtained as a colourless solid (77%): m.p. 111-112°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.97 (s,2H), 7.52 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.9-2.4 (mc, 4H), 1.97 (t , J = 2.4 Hz, 1H).
Anal. Calcd. for C$_{18}$H$_{14}$N$_4$O (302.32): C, 71.50; H, 4.66; N, 18.53. Found: C, 71.53; H, 4.64; N, 18.61.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-*p*-nitrophenylpyrimidine **(6f)**. From 2-methylsulfonyl-5-*p*-nitrophenylpyrimidine. Obtained as a yellow solid (87%): m.p. 169-174°C (with decomposition; hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 9.08 (s, 2H), 8.44 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 2.9-2.4 (mc, 4H), 1.97 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{17}$H$_{11}$N$_5$O$_2$ (317.30): C, 64.34; H, 3.49; N, 22.07. Found: C, 64.34; H, 3.44; N, 22.05.

General procedure for the intramolecular Diels-Alder reaction of 5-aryl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines **6** to 3-aryl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindines **7**.
The appropriate pyrimidine derivative was dissolved in nitrobenzene (100 mg/1 ml solvent) and heated at 180°C under nitrogen for one hour. After cooling the reaction mixture was chromatographed over silica gel. Eluting

first with dichloromethane to remove nitrobenzene, then dichloromethane/ether 4:1 gave the reaction products.

7,7-Dicyano-6,7-dihydro-3-phenyl-5H-1-pyrindine (7a). From 6a. 7a Was

obtained as a colourless solid (100%): m.p. 134-135°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.74 (brs, 1H), 7.84 (t, J = 1.0 Hz, 1H), 7.50 (mc, 5H), 3.27 (brt, J = 6.1 Hz, 2H), 3.00 (mc, 2H). MS: m/e 245 (M$^+$).
Anal. Calcd. for C$_{16}$H$_{11}$N$_3$ (245.27): C, 78.34; H, 4.52; N, 17.13. Found: C, 78.10; H, 4.43; N, 17.01.

3-p-Bromophenyl-7,7-dicyano-6,7-dihydro-5H-1-pyrindine (7b). From 6b.

7b Was obtained as a colourless solid (99%): m.p. 151-152°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.72 (brs, 1H), 7.83 (t, J = 1.0 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 3.29 (brt, J = 6.2 Hz, 2H), 3.01 (mc, 2H).
Anal. Calcd. for C$_{16}$H$_{10}$BrN$_3$ (324.18): C, 59.27; H, 3.10; N, 12.96. Found: C, 59.06; H, 3.11; N, 12.89.

3-p-Chlorophenyl-7,7-dicyano-6,7-dihydro-5H-1-pyrindine (7c). From 6c.

7c Was obtained as a colourless solid (97%): m.p. 147-148°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.73 (brs, 1H), 7.84 (brs, 1H), 7.49 (s, 4H), 3.29 (mc, 2H), 3.01 (mc, 2H).
Anal. Calcd. for C$_{16}$H$_{10}$ClN$_3$ (279.72): C, 68.69; H, 3.60; N, 15.02. Found: C, 68.47; H, 3.55; N, 15.00.

7,7-Dicyano-6,7-dihydro-3-p-methylphenyl-5H-1-pyrindine (7d). From 6d.

7d Was obtained as a colourless solid (100%): m.p. 119-121°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.75 (brs, 1H), 7.84 (brs, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 3.27 (mc, 2H), 2.99 (mc, 2H), 2.41 (s, 3H).
Anal. Calcd. for C$_{17}$H$_{13}$N$_3$ (259.30): C, 78.73; H, 5.05; N, 16.20. Found: C, 78.58; H, 5.03; N, 16.11.

7,7-Dicyano-6,7-dihydro-3-p-methoxyphenyl-5H-1-pyrindine (7e). From 6e.

7e Was obtained as a colourless solid (98%): m.p. 144-146°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.73 (brs, 1H), 7.81 (t, J = 1.0 Hz, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.26 (mc, 2H), 2.99 (mc, 2H).
Anal. Calcd. for C$_{17}$H$_{13}$N$_3$O (275.30): C, 74.16; H, 4.75; N, 15.26. Found: C, 74.13; H, 4.69; N, 14.96.

7,7-Dicyano-6,7-dihydro-3-p-nitrophenyl-5H-1-pyrindine (7f). From 6f. 7f

Was obtained as a pale yellow solid (100%): m.p. 205-208°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.83 (brs, 1H), 8.38 (d, J = 9.0 Hz, 2H), 7.94 (brs, 1H), 7.75 (d, J = 9.0 Hz, 2H), 3.34 (mc, 2H), 3.06 (mc, 2H).

Anal. Calcd. for $C_{16}H_{10}N_4O_2$ (290.27): C, 66.20; H, 3.47; N, 19.30. Found: C, 65.80; H, 3.40; N, 19.33.

Kinetic measurements.

a. Solvent effects. Weighed amounts of the pyrimidine **6e** and pyrindine **7e** (± 15 mg for each) were dissolved in the appropriate solvent (0.6 ml). This reaction mixture was heated at 140 ± 1°C in a stoppered flask on an oil bath and after several time intervals a sample was taken for quantitative analysis. For this purpose the sample was diluted with acetonitrile (± 5 ml) and the decrease of starting material was determined by HPLC analysis using compound **7e** as internal standard[14]. From a plot of $-\ln(C_t/C_0)$ against time the reaction constant (k_{MeO}) and the half-life time were calculated (see Table 5.3).

b. Substituent effect. Weighed amounts (± 15 mg for each) of a pyrimidine **6** (R = H, Cl, Me, MeO, NO_2), pyrimidine **6b** and 3-phenyl-5H-[1]benzopyrano-[4,3-b]pyridine[15], which served as internal standard in the HPLC analysis, were dissolved in 0.6 ml of nitrobenzene. The reaction mixture was heated at 140°C and after several time intervals a sample was taken, diluted with acetonitrile (± 5 ml) and subjected to quantitative analysis by means of HPLC. The decrease of starting material **6** (entries **a, e,** and **f**) relative to **6b** or the increase of reaction product **7** (entries **c** and **d**) relative to **7b** was determined. These data were used to calculate the relative reaction constants k_R/k_{Br} and k_R/k_H (see Table 5.2).

5.4   REFERENCES AND NOTES

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6. The conversion of **6b** into **7b** was chosen as reference reaction because good separations were obtained between these 2 compounds and all other compounds **6** and **7** (see Table 5.1).
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14. The retention times (t_r) for the solvents nitrobenzene, p-bromotoluene, and mesitylene on the HPLC column used are 3.5 min., 11.9 min., and 15.8 min., respectively.
15. This compound was prepared at our laboratory by an intramolecular Diels-Alder reaction of 5-phenyl-2-(2-prop-2-ynyloxyphenyl)pyrimidine. The retention time (t_r) of this compound on the HPLC column used was 17.8 min.

CHAPTER 6

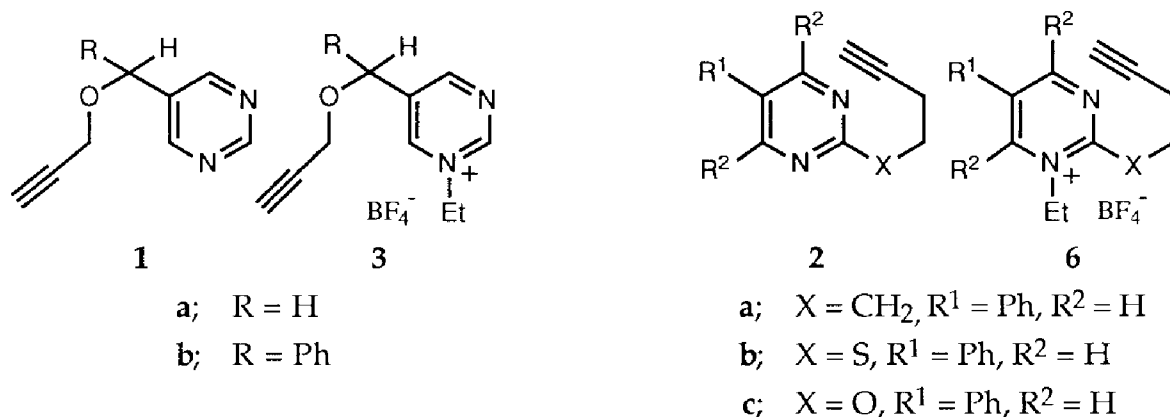# INTRAMOLECULAR CYCLIZATION REACTIONS OF PYRIMIDINIUM CATIONS.

6.1   INTRODUCTION

Intramolecular inverse electron demand Diels-Alder reactions of aromatic diazines carrying an appropriate dienophilic side-chain offer useful synthetic routes to new heterocyclic compounds[1-6]. It has been shown that rigidizing the chain between azadiene and dienophile in a conformation from which cycloaddition is more likely to take place leads to a considerable rate enhancement[4d,e,5], due to added entropic assistance. Introduction of electron-withdrawing substituents into the azaaromatic ring or electron-donating substituents at the acetylene group also enhances the reactivity as a result of a lower $HOMO_{dienophile}/LUMO_{diene}$ energy separation[4]. Another strategy to reduce the HOMO/LUMO energy separation is quaternization of the azaaromatic ring as has recently been shown in the pyrazine[7] and 1,2,4-triazine[8] series. In this paper we describe the quaternization of some pyrimidines carrying a dienophilic side-chain attached to the 2- or 5-position, and the subsequent intramolecular cycloaddition reaction of these pyrimidinium salts with the aim to compare their reactivity with that of the neutral compounds. Furthermore, the thermal reactivity of some N-protonated pyrimidines having a dienophilic side-chain at position 2 is investigated.

6.2   RESULTS AND DISCUSSION

Quaternization of 5-(2-propynyloxymethyl)pyrimidine (**1a**) and 5-(phenyl-2-propynyloxymethyl)pyrimidine (**1b**) as well as 2-(4-pentynyl)-5-phenyl-pyrimidine (**2a**), 2-(3-butynylthio)-5-phenylpyrimidine (**2b**) and 2-(3-butyn-yloxy)-5-phenylpyrimidine (**2c**) was easily achieved by treatment of a solu-
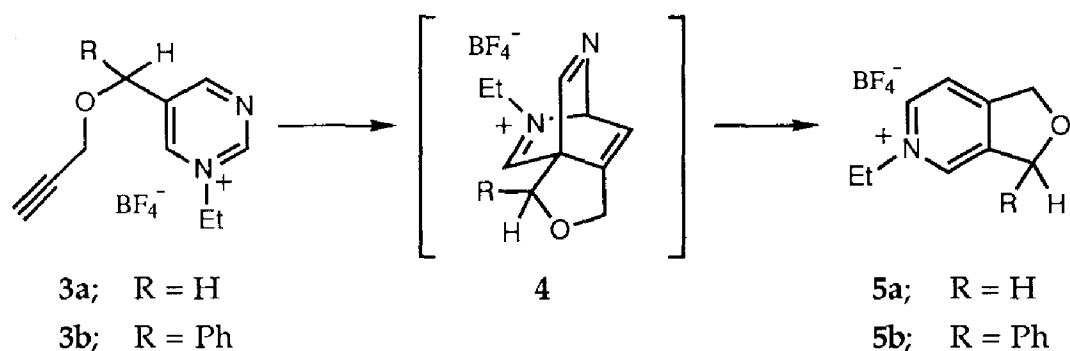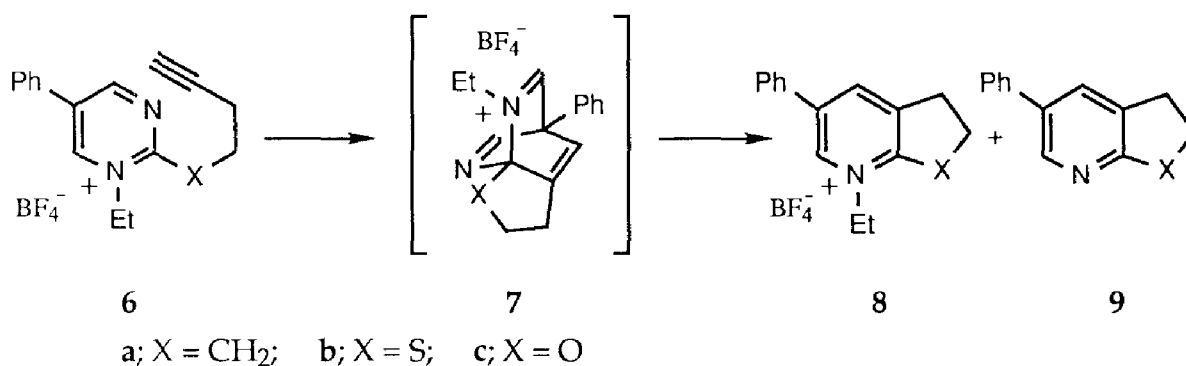
Scheme 6.1

R1   1   3   2   6

a;   R = H   a;   X = CH_2, R^1 = Ph, R^2 = H
b;   R = Ph   b;   X = S, R^1 = Ph, R^2 = H
                         c;   X = O, R^1 = Ph, R^2 = H

tion of these compounds in dry dichloromethane with one equivalent of triethyloxonium tetrafluoroborate (Meerwein reagent)[9] at room temperature. The resulting N-ethylpyrimidinium tetrafluoroborates **3a,b** and **6a-c**, respectively, were obtained in high yields. Attempts to quaternize 5-(3-butynylthio)-2-phenylpyrimidine, 2-(3-butynylsulfinyl)-5-phenylpyrimidine, 2-(3-butynylsulfonyl)-5-phenylpyrimidine and 4,6-dimethyl-2-(2-propynyloxymethyl)pyrimidine with one equivalent of the Meerwein reagent in a similar manner failed, probably due to the steric hindrance which the alkylating reagent experiences, when approaching a nitrogen atom of the pyrimidine ring.

Heating of a solution of **3a** (Scheme 6.2) in nitrobenzene at 110°C for 2 hours gave 5-ethyl-1,3-dihydrofuro[3,4-c]pyridinium tetrafluoroborate **(5a)** in 93% yield. A similar cyclization was observed upon heating a solution of **3b** in nitrobenzene at 110°C for 1.5 hours, yielding 5-ethyl-1,3-dihydro-3-phenylfuro[3,4-c]pyridinium tetrafluoroborate **(5b)** in high yield. The structure of **5b** was elucidated by comparison of its FD mass spectrum and ¹H NMR spectrum with those of the compound obtained by alkylation of 1,3-dihydro-3-phenylfuro[3,4-c]pyridine with the Meerwein reagent as described in the experimental part. The reaction conditions are considerably milder than those required for the intramolecular Diels-Alder reaction of the neutral pyrimidines **1a** and **1b** which require heating in nitrobenzene at 140°C for 17 and 11 hours, respectively[4e].

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Scheme 6.2

3a; R = H
3b; R = Ph

4

5a; R = H
5b; R = Ph

Scheme 6.3

6

7

8

9

a; X = CH₂; b; X = S; c; X = O

As examples of pyrimidines containing a dienophilic side-chain at the 2-position we examined the cycloaddition reaction of the pyrimidinium salts **6** (Scheme 6.3). The salts **6a** and **6b** undergo cyclization upon heating at 180°C for 15 minutes and 3 hours, respectively, whereas both corresponding pyrimidines (**2a** and **2b**) require heating at 210°C for a more extended period[4b,d]. Cyclization of **6a** yields 1-ethyl-6,7-dihydro-3-phenyl-5*H*-1-pyrindinium tetrafluoroborate (**8a**) as the product. However, salt **6b** gave in excellent yield a mixture of 7-ethyl-2,3-dihydro-5-phenylthieno[2,3-b]-pyridinium tetrafluoroborate (**8b**) and 2,3-dihydro-5-phenylthieno[2,3-b]-pyridine (**9b**) in a ratio of approximately 1 : 1.5. We suppose that in the reaction of the pyrimidinium salts **3** and **6** a cycloadduct (i.e. **4** and **7**, respectively) is the intermediate being formed by addition of the triple bond across C-2 and C-5 of the pyrimidine ring. Loss of hydrogen cyanide from the intermediate cycloadduct by a retro-Diels-Alder reaction leads to the N-

ethylpyridinium salts **5** and **8**, whereas loss of protonated ethyl isocyanide from cycloadduct **7b** gives the pyridine derivative **9b**. The exclusive formation of quaternary pyridinium salts **5** and **8a** indicates that loss of hydrogen cyanide from the intermediate cycloadduct is more facile than loss of protonated ethyl isocyanide. This result was also found in the pyrazine series[7]. In order to explain the formation of **9b** from **6b** we assume that the electron donating character of the sulfur atom plays a decisive role in the ring transformation of cycloadduct **7b**. Breaking of the C-N$^+$ bond in **7b** is promoted due to the electron donating effect of sulfur. Subsequently, protonated ethyl isocyanide is split off as indicated in Scheme 6.4 to give the neutral pyridine derivative **9b**. The possibility that first cycloaddition of **7b** to the quaternary pyridinium salt **8b** occurs followed by dealkylation to yield **9b** can be excluded since heating of an analytically pure sample of **8b** at 180°C in nitrobenzene for 3 hours did not result in any dealkylation. Furthermore, the presence of a quartet at $\delta = 3 - 3.3$ ppm and a triplet at about 1.2 ppm in the ^{1}H NMR spectrum of the reaction mixture obtained from **7b** after 1 and 3 hours of heating at 180°C in nitrobenzene may be due to the ethyl group of the protonated ethyl isocyanide or a product resulting from it. Breaking of the C-N$^+$ bond in the cycloadducts **4** and **7a** does not occur due to the absence of an electron donating atom at the α-position to the pyrimidine ring in these cases. With the aim to test this hypothesis we also subjected 2-(3-butynyloxy)-5-phenylpyrimidinium tetrafluoroborate (**6c**) to conditions suitable for cycloaddition (i.e. 180°C). Unfortunately, during heating cleavage of the alkynyloxy side-chain occurs.

Scheme 6.4
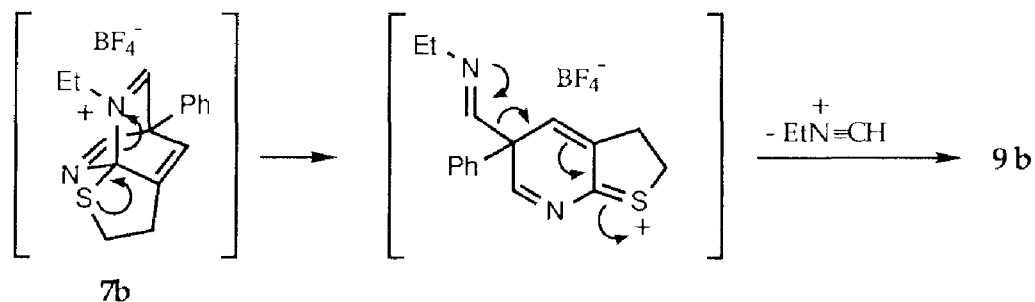
N-alkylation of pyrimidines **1** and **2** with triethyloxonium tetrafluoroborate is limited to examples in which the ring nitrogens are not sterically hindered for approach of the alkylating reagent. An alternative strategy to facilitate the intramolecular Diels-Alder reaction was thought to be protonation of the ring nitrogens of the pyrimidines. Trifluoroacetic acid was chosen as the protonating solvent.

Scheme 6.5
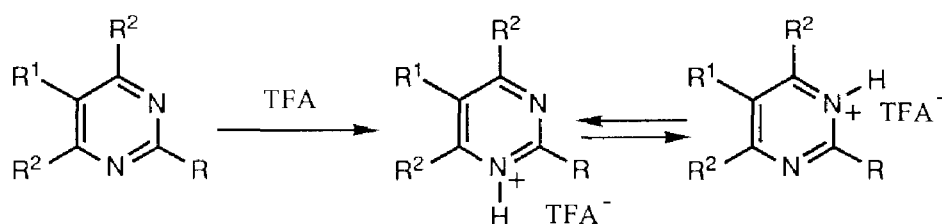
2

a; R = $(CH_2)_3C\equiv CH$, R^1 = Ph, R^2 = H   f; R = $CH_2OCH_2C\equiv CH$, R^1 = H, R^2 = Me

b; R = $S(CH_2)_2C\equiv CH$, R^1 = Ph, R^2 = H   g; R = $S(CH_2)_2C\equiv CH$, R^1 = H, R^2 =Me

c; R = $O(CH_2)_2C\equiv CH$, R^1 = Ph, R^2 = H   h; R = $SO(CH_2)_2C\equiv CH$, R^1 = H, R^2 = Me

d; R = $SO(CH_2)_2C\equiv CH$, R^1 = Ph, R^2 = H   i; R = $O(CH_2)_2C\equiv CH$, R^1 = H, R^2 = H

e; R = $SO_2(CH_2)_2C\equiv CH$, R^1 = Ph, R^2 = H

Comparison of the ^{1}H NMR spectra of compounds **2a-i** (Scheme 6.5) in trifluoroacetic acid (see Table 6.2) with those of the neutral species (recorded in $CDCl_3$; Table 6.1) shows one signal for the protons attached to C-4 and C-6 of the pyrimidine which is shifted downfield by 0.50 - 0.64 ppm as compared to the signal of the same protons in the neutral compound. Somewhat larger downfield shifts ($\Delta\delta$ = 0.64 - 0.85 ppm) are observed for the proton attached to C-5 of the pyrimidine ring. In acid solution the coupling constant $J_{4,5}$ = $J_{5,6}$ for compound **2i** was found to be 5.6 Hz. As might be expected[10,11], this coupling constant is somewhat larger than in the neutral pyrimidine ($J_{4,5}$ = $J_{5,6}$ = 5.0 Hz). From these results it can be concluded that pyrimidines **2** are monoprotonated[11] and that there is a fast proton exchange between N-1 and N-3 (Scheme 6.5).

Heating of 2-(3-butynylsulfinyl)pyrimidines **2d** and **2h** in trifluoroacetic acid at reflux temperature yielded the 1-oxothieno[2,3-b]pyridinium cations **10d** and **10h**, respectively, which after work up of the reaction mixtures

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TABLE 6.1   ¹H NMR spectral data for pyrimidines **2** in $CDCl_3$.

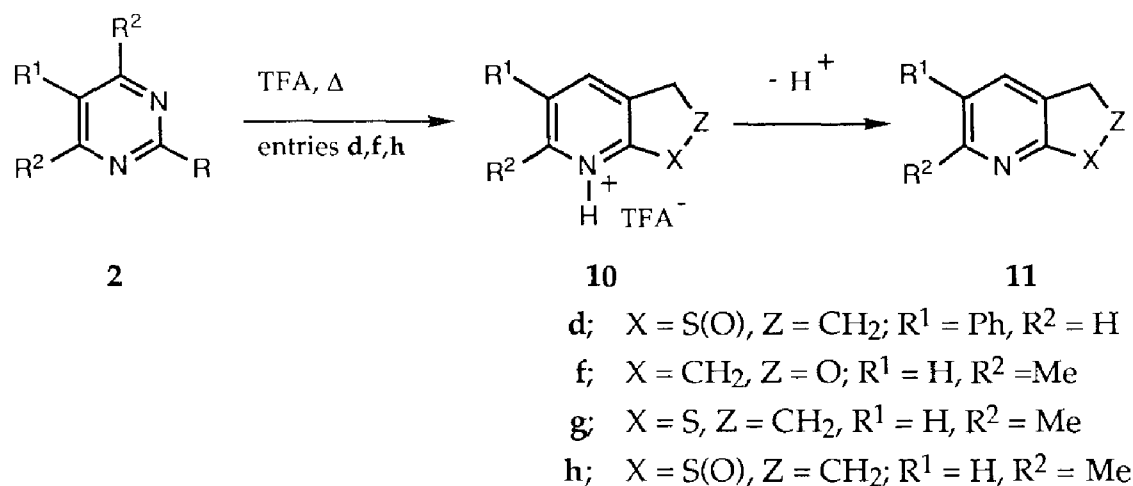| ¹H NMR shifts (ppm) and coupling constants (Hz) for the pyrimidine protons.		
Compound	H-5	H-4 and H-6
2a		8.86 (s, 2H)
2b		8.74 (s, 2H)
2c		8.67 (s, 2H)
2d		9.03 (s, 2H)
2e		9.07 (s, 2H)
2f	6.94 (s, 1H)	
2g	6.69 (s, 1H)	
2h	7.15 (s, 1H).	
2i	6.93 (t, J = 5.0, 1H)	8.50 (d, J = 5.0, 2H)

TABLE 6.2   ¹H NMR spectral data for pyrimidines **2** in trifluoroacetic acid.

¹H NMR shifts (ppm) and coupling constants (Hz)				
Compound	H-5	H-4 and H-6	Ph/CH₃	R
2a		9.50 (s, 2H)	7.66 (m, 5H)	1.98 (t, J = 2.5, 1H), 2.36 (m, 4H), 3.53 (t, J = 7.5 , 2H).
2b		9.24 (s, 2H)	7.68 (m, 5H)	2.06 (t, J = 2.6, 1H), 2.81 (dt, J₁ = 7.5, J₂ = 2.6, 2H), 3.75 (t, J = 7.5, 2H).
2c		9.25 (s, 2H)	7.65 (m, 5H)	2.03 (t, J = 2.6, 1H), 2.83 (dt, J₁ = 2.6, J₂ = 7.5, 2H), 4.95 (t, J = 7.5, 2H)
2d		9.53 (s, 2H)	7.68 (m, 5H) 3.79 (m, 2H).	1.94 (t, J = 2.6, 1H), 2.94 (m, 2H),
2e		9.65 (s, 2H)	7.66 (m, 5H)	1.85 (t, J = 2.5, 1H), 2.88 (dt, J₁ = 7.5, J₂ = 2.5, 2H), 3.91 (t, J = 7.5, 2H).
2f	7.66 (s, 1H)		2.85 (s, 6H)	2.56 (t, J = 2.5, 1H), 4.47 (d, J = 2.5, 2H), 5.06 (s, 2H).
2g	7.33 (s, 1H)			2.06 (t, 2.5, 1H), 2.69 (m, 8H), 3.56 (t, 7.5, 2H).
2h	8.00 (s, 1H)		3.85 (m, 2H).	1.81 (t, J = 2.5, 1H), 2.94 (m, 8H),
2i	7.66 (t, J = 5.6, 1H)	9.06 (d, J = 5.6, 2H)		2.09 (t, J = 2.5, 1H), 2.82 (dt, J₁ = 7.5, J₂ = 2.5, 2H), 4.85 (t, J =7.5, 2H).

Scheme 6.6

d; X = S(O), Z = CH$_2$; R^1 = Ph, R^2 = H
f; X = CH$_2$, Z = O; R^1 = H, R^2 =Me
g; X = S, Z = CH$_2$, R^1 = H, R^2 = Me
h; X = S(O), Z = CH$_2$; R^1 = H, R^2 = Me

afforded the corresponding neutral [2,3-b]-annelated pyridine derivatives **11d** and **11h** in moderate yield (Scheme 6.6). In case of cyclization of **2h** also a small amount (11%) of 2,3-dihydro-6-methylthieno[2,3-b]pyridine (**11g**) was isolated. The progress of the cyclization reaction could be monitored by ^{1}H NMR spectroscopy. Cycloaddition of the neutral pyrimidines **2d** and **2h** in nitrobenzene could not be established due to decomposition of starting material when heated above 100°C[4b]; only a small amount of bis-[4,6-dimethylpyrimidinyl-(2)]-disulfide was isolated after work up of the reaction mixture obtained from **2h**. The fact, however, that **2d** and **2h** easily undergo a Diels-Alder reaction in trifluoroacetic acid clearly demonstrates the usefulness of this method. Heating of **2f** in refluxing trifluoroacetic acid for 24 hours gave the cycloaddition product 5,7-dihydro-2-methylfuro[3,4-b]pyridine (**11f**) in 65% yield after work up of the reaction mixture. The reaction conditions are also with this compound considerably milder than those required for cyclization of the neutral species (9 h in nitrobenzene at 140°C)[4e]. Thus, protonation seems to be a very useful method to promote the inverse electron demand Diels-Alder reaction.

Attempts to cyclize 2-(3-butynylsulfonyl)-5-phenylpyrimidine (**2e**), which required reaction temperatures up to 180°C in nitrobenzene (see experimental), met with little success when heated at reflux temperature in trifluoroacetic acid; this is due to decomposition of the starting material under the reaction conditions employed.

2-(3-Butynylthio)-5-phenylpyrimidine (2b), when heated in trifluoroacetic acid also did not give the Diels-Alder product, but instead a product was isolated which after treatment with perchloric acid was identified as 3,4-dihydro-4-methylene-7-phenyl-2H-pyrimido[2,1-b][1,3]thiazin-5-ium perchlorate (13b) (Scheme 6.7). The structure of this compound was based on the presence of two doublets at 6.21 and 5.81 ppm (J = 3.0 Hz) for the protons of the exocyclic methylene group in the ^{1}H NMR spectrum (DMSO-d_6) and a triplet for the exocyclic methylene carbon at 116.8 ppm (J_{C-H} = 164 Hz) in the ^{13}C NMR spectrum (DMSO-d_6). The formation of 13b can be assumed to have as precursor 12b that is formed by an intramolecular coplanar cycloamination reaction[12-14]. This reaction is supposed to proceed via protonation of the terminal acetylenic carbon, followed by attack of the unprotonated nitrogen upon the internal acetylenic carbon and subsequent loss of a proton; this process is described recently for the same reaction in the pyrazine series[7]. To our knowledge, the above-mentioned reactions represent the first examples of an intramolecular coplanar cycloamination of

Scheme 6.7

2a-c   12a-c   13b

a;   X = CH$_2$ b;   X = S   c;   X = O
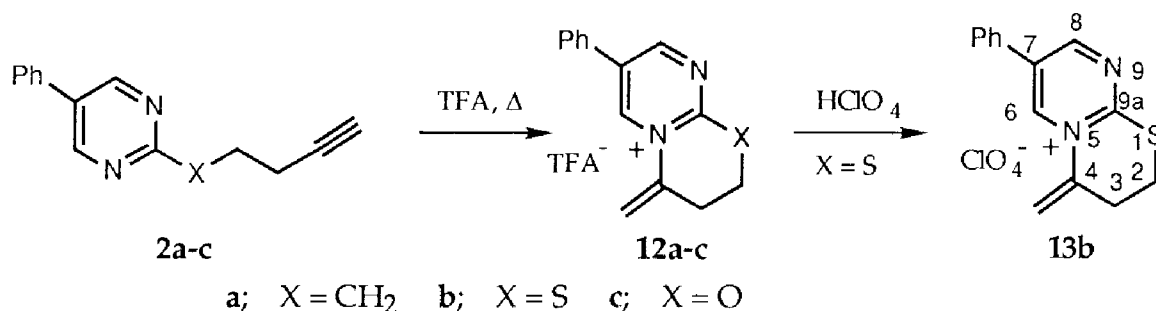
heterocyclic azadienes which are performed under acid conditions. Previously, pyrimidin-4-ones with an appropriate alkynyl side-chain attached to C-2 of the pyrimidine[12,13] and 3-(3-butynylthio)-1,2,4-triazin-5-ones[12,14] have been found to undergo the intramolecular coplanar cycloamination reaction under neutral or basic conditions. Intramolecular coplanar cycloamination was also observed when heating 2a and 2c in trifluoroacetic acid as judged by the presence of two doublets (J = 3.0 Hz) at about 6.0 and 5.7 ppm for the protons of the exocyclic methylene group in the ^{1}H NMR (TFA) spectrum and a triplet at about 115 ppm (J = 164 Hz) for the methylene

carbon in the ^{13}C NMR (TFA) spectrum. Thus, 6-methylene-3-phenyl-piperidino[1,2-a]pyrimidin-5-ium trifluoroacetate (12a) and 3,4-dihydro-4-methylene-7-phenyl-2H-pyrimido[2,1-b][1,3]oxazin-5-ium trifluoroacetate (12c), respectively, were obtained in moderate yield as oils. However, treatment of these trifluoroacetate salts (12a and 12c) with perchloric acid did not give analytically pure samples.

In conclusion, the reaction conditions for the intramolecular inverse electron demand Diels-Alder reactions of the N-alkylated pyrimidinium salts described in this paper are considerably milder than those required for the corresponding neutral species. In addition, N-protonation also facilitates the intramolecular Diels-Alder reaction. However, in case of less reactive pyrimidines (like 2a-c) no cycloaddition reaction takes place, but an intramolecular coplanar cycloamination.

6.3   EXPERIMENTAL SECTION

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Varian (90 MHz) EM 390 spectrometer with Me$_4$Si as internal standard (δ = 0 ppm). The ^{13}C NMR spectra were recorded at 75.46 MHz on a Bruker CXP-300 spectrometer. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed on Merck silica gel 60 (230-400 mesh ASTM).

Starting materials
5-(2-propynyloxymethyl)pyrimidine (1a)[4e], 5-(phenyl-2-propynyloxymethyl)-pyrimidine (1b)[4e], 5-(3-butynylthio)-2-phenylpyrimidine[4b], 2-(pent-4-yn-1-yl)-5-phenylpyrimidine (2a)[4d], 2-(3-butynylthio)-5-phenylpyrimidine (2b)[4b], 4,6-dimethyl-2-(2-propynyloxymethyl)pyrimidine (2f)[4e], 2-(3-butynylthio)-4,6-dimethylpyrimidine (2g)[4b] and 2-(3-butynyloxymethyl)pyrimidine (2i)[4b] as well as the Meerwein reagent (triethyloxonium tetrafluoroborate: TOF)[9b] were synthesized as described in the literature.

2-(3-butynyloxy)-5-phenylpyrimidine (2c). To a stirred suspension of 90 mg (3 mmol) of sodium hydride (80% oil dispersion) in dry tetrahydrofuran (5 ml) was added 280 mg (4 mmol) of 3-butyn-1-ol in tetrahydrofuran (2 ml). After the initial effervescence had subsided, 2-methylsulfonyl-5-phenyl-pyrimidine[4f] (468 mg; 2 mmol) was added all at once and the resulting reaction mixture stirred for another hour. Water (30 ml) was then added and the aqueous layer extracted with ether (3 x 50 ml). The organic layers were combined, dried (MgSO$_4$) and concentrated by evaporation of the

solvent. Column chromatography (eluting with dichloromethane/ether 9:1) of the residue afforded **2c** (421 mg; 94%): m.p. 93-95°C (hexanes/toluene); ^{1}H NMR (CDCl$_3$) δ 8.67 (s, 2H), 7.45 (s, 5H), 4.52 (t, J = 7.2 Hz, 2H), 2.74 (dt, J$_1$ = 7.2 Hz, J$_2$ = 2.7 Hz, 2H), 2.01 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{14}$H$_{12}$N$_2$O (224.25): C, 74.98; H, 5.39; N, 12.49. Found: C, 75.04; H, 5.44; N, 12.61.

2-(3-butynylsulfinyl)-5-phenylpyrimidine **(2d)**. To a stirred solution of 2-(3-butynylthio)-5-phenylpyrimidine **(2b**, 2.16 g, 9.0 mmol) in dry chloroform (100 ml) at 0°C was added *m*-chloroperbenzoic acid (85% techn. solid; 1.83 g, 9.0 mmol). This mixture was stirred at room temperature for 20 h and then washed with a 2N solution of sodium carbonate. The organic layer was dried (MgSO$_4$) and the solvent removed at reduced pressure. The residue was purified by column chromatography (eluting with ether) to afford 2.07 g (90%) of **2c**: m.p. 120-121°C (petroleum ether 40-60/ether); ^{1}H NMR (CDCl$_3$) δ 9.09 (s, 2H), 7.61 (m, 5H), 3.33 (m, 2H), 2.69 (m, 2H), 1.84 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{14}$H$_{12}$N$_2$OS (256.32): C, 65.59; H, 4.71; N, 10.93. Found: C, 65.34; H, 4.66; N, 11.04.

2-(3-butynylsulfonyl)-5-phenylpyrimidine **(2e)**. To a stirred solution of 2-(3-butynylthio)-5-phenylpyrimidine **(2b**, 0.30 g, 1.25 mmol) in anhydrous chloroform (10 ml) at 0°C *m*-chloroperbenzoic acid (85% techn. solid; 0.61 g, 3.0 mmol) in chloroform (25 ml) was added in small portions over the course of a few minutes. The mixture was stirred at room temperature for 20 hours and then washed with a saturated solution of sodium hydrogen sulfite (2 x 15 ml) and subsequently with a 2N solution of sodium carbonate (2 x 25 ml). The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure to give **2e** (0.34 g, 100%) as a colourless solid: m.p. 175-177°C (hexanes/chloroform); ^{1}H NMR (CDCl$_3$) δ 9.07 (s, 2H), 7.56 (s, 5H), 3.76 (t, J = 7.5 Hz, 2H), 2.81 (dt, J$_1$ = 7.5 Hz, J$_2$ = 2.7 Hz, 2H), 1.93 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for C$_{14}$H$_{12}$N$_2$O$_2$S (272.33): C, 61.74; H, 4.44; N, 10.29. Found: C, 61.44; H, 4.36; N, 10.30.

2-(3-butynylsulfinyl)-4,6-dimethylpyrimidine **(2 h)**. To a stirred solution of **2g** (1.21 g, 6.3 mmol) in dry chloroform at 0°C was added *m*-chloroperbenzoic acid (85%; 1.27g, 6.3 mmol). This mixture was stirred for 1 h at room temperature and then washed with a 2N solution of sodium carbonate. The organic layer was dried (MgSO$_4$) and the solvent removed under reduced pressure. The solid residue was purified by column chromatography (eluting with ether/methanol 5:1) to yield 1.2 g (92%) of **2h**: m.p. 61-62°C (petroleum ether 40-60); ^{1}H NMR (CDCl$_3$) δ 7.15 (s, 1H), 3.27 (m, 2H), 2.69 (m, 2H), 2.50 (s, 6H), 1.98 (t, J = 2.7 Hz).
Anal. Calcd. for C$_{10}$H$_{12}$N$_2$OS (208.28): C, 57.66; H, 5.80; N, 13.45. Found: C, 57.48; H, 5.76; N, 13.32.

Cyclization of 2-(3-butynylsulfonyl)-5-phenylpyrimidine (2e) to 2,3-dihydro-1,1-dioxo-5-phenylthieno[2,3-b]pyridine (11e) in nitrobenzene. Heating of 2e (326 mg; 1.2 mmol) in nitrobenzene (3 ml) under nitrogen for 18 h at 180°C yielded after column chromatography (eluting first with dichloromethane, then dichloromethane/ether 2:1) of the cooled reaction mixture 265 mg (90%) of 2,3-dihydro-1,1-dioxo-5-phenylthieno[2,3-b]pyridine (11e; X = SO_2, R^1 = Ph, R^2 = H) as a pale yellow solid: m.p. 205-206°C (hexanes/chloroform); ^{1}H NMR ($CDCl_3$) δ 8.83 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.51 (m, 5H), 3.67-3.30 (m, 4H).
Anal. Calcd. for $C_{13}H_{11}NO_2S$ (245.30): C, 63.65; H, 4.52; N, 5.71. Found: C, 63.49; H, 4.50; N, 5.82.

Reaction of 2-(3-butynylsulfinyl)-4,6-dimethylpyrimidine (2h) in nitrobenzene. Heating of 2h (104 mg, 0.5 mmol) in nitrobenzene (1.5 ml) under nitrogen for 4 h at 100°C yielded after column chromatography (eluting first with dichloromethane, then ether/methanol 9:1) of the cooled reaction mixture 20 mg (15%) of bis-[4,6-dimethylpyrimidinyl-(2)]-disulfide as an oil; ^{1}H NMR ($CDCl_3$) δ 6.75 (s, 1H), 2.39 (s, 6H). HRMS Calcd. for $C_{12}H_{14}N_4S_2$ (M^+): 278.0660. Found: 278.0654.

1-Ethyl-5-(2-propynyloxymethyl)pyrimidinium tetrafluoroborate (3a). To a stirred solution of 5-(2-propynyloxymethyl)pyrimidine (1a; 237 mg; 1.6 mmol) in 5 ml of dry dichloromethane was added at room temperature a solution of TOF (304 mg; 1 eq) in dry dichloromethane (4 ml) all at once. The mixture was then stirred for 1.5 h. After this time the solvent was evaporated under reduced pressure to afford 3a (422 mg; 100%) as a thick yellow oil; ^{1}H NMR (acetone-d_6) δ 9.76 (brs, 1H), 9.47 (d, J = 2.1 Hz, 1H), 9.39 (br, 1H), 4.95 (s, 2H), 4.84 (q, J = 7.4 Hz, 2H), 4.38 (d, J = 2.5 Hz, 2H), 3.06 (t, J = 2.5 Hz, 1H), 1.73 (t, J = 7.4 Hz, 3H). MS (FD): m/e 177 (M^+ - BF_4). This compound was used without further purification for the subsequent cyclization into 5a (see below).

1-Ethyl-5-(phenyl-2-propynyloxymethyl)pyrimidinium tetrafluoroborate (3b). To a stirred solution of 1b (515 mg; 2.3 mmol) in 5 ml of dry dichloromethane was added at room temperature all at once a solution of TOF (437 mg; 1 eq) in dry dichloromethane (4 ml). The mixture was then stirred for 1 h. After this time the solvent was evaporated to afford 3b (781 mg; 100 %) as a thick colourless oil: ^{1}H NMR (acetone-d_6) δ 9.67 (brs, 1H), 9.44 (t, J = 1.8 Hz, 1H), 9.32 (d, J = 2.1 Hz, 1H), 7.40 (mc, 5H), 6.10 (s, 1H), 4.80 (q, J = 7.3 Hz, 2H), 4.23 (m, 2H), 2.97 (t, J = 2.7 Hz, 1H), 1.67 (t, J = 7.5 Hz, 3H). MS (FD): m/e 253 (M^+ - BF_4). This compound was used without further purification for the subsequent cyclization into 5b (see below).

1-Ethyl-2-(pent-4-yn-1-yl)-5-phenylpyrimidinium tetrafluoroborate (6a). To a stirred solution of 2-(pent-4-yn-1-yl)-5-phenylpyrimidine (2a; 533 mg; 2.4 mmol) in 5 ml of dry dichloromethane was added at room temperature a solution of TOF (457 mg; 1 eq) in dichloromethane all at once. After stirring for 1 h the solvent was evaporated. The solid residue was then recrystallized from ethanol to afford 6a (617 mg; 76%) as colourless needles: m.p. 140-142°C; ^{1}H NMR (acetone-d$_6$) δ 9.64 (d, J = 2.4 Hz, 1H), 9.55 (d, J = 2.4 Hz, 1H), 7.91 (mc, 2H), 7.57 (mc, 3H), 4.87 (q, J = 7.5 Hz, 2H), 3.54 (t, J = 6.8 Hz, 2H), 2.5-2.0 (mc, 5H), 1.75 (t, J = 7.5 Hz, 3H).
Anal. Calcd. for C$_{17}$H$_{19}$BF$_4$N$_2$ (338.16): C, 60.38; H, 5.66; N, 8.28. Found: C, 60.23; H, 5.74; N, 8.42.

2-(3-Butynylthio)-1-ethyl-5-phenylpyrimidinium tetrafluoroborate (6b). To a stirred solution of 2-(3-butynylthio)-5-phenylpyrimidine (2b; 168 mg; 0.7 mmol) in dry dichloromethane (4 ml) was added at room temperature a solution of 133 mg (1 eq) of TOF in dry dichloromethane (3 ml). The resulting solution was stirred for another 2 h. After this time the solvent was evaporated to afford crude 6b which was recrystallized from ethanol to afford colourless needles. Yield: 187 mg (75%). M.p. 141.5-143.5°C. ^{1}H NMR (acetone-d$_6$) δ 9.56 (s, 2H), 7.92 (mc, 2H), 7.56 (mc, 3H), 4.72 (q, J = 7.4 Hz, 2H), 3.73 (t, J = 6.9 Hz, 2H), 2.79 (dt, J$_1$ = 7.0 Hz, J$_2$ = 2.7 Hz, 2H), 2.56 (t, J = 2.7 Hz, 1H), 1.68 (t, J = 7.4 Hz, 3H).
Anal. Calcd. for C$_{16}$H$_{17}$BF$_4$N$_2$S (356.20): C, 53.94; H, 4.81; N, 7.86. Found: C, 53.74; H, 4.80; N, 7.68.

2-(3-Butynyloxy)-1-ethyl-5-phenylpyrimidinium tetrafluoroborate (6c). To a stirred solution of 2-(3-butynyloxy)-5-phenylpyrimidine (2c; 180 mg; 0.8 mmol) in 3 ml of dry dichloromethane was added at room temperature 153 mg (1 eq) of TOF in 3 ml of dry dichloromethane. Stirring was continued and after about 0.3 h a solid began to deposit. After 1 h the solvent was removed in vacuo to give 6c (270 mg; 99%) as a colourless solid: m.p. 157-167°C (ethanol; with decomposition); ^{1}H NMR (acetone d$_6$) δ 9.51 (d, J = 2.7 Hz, 1H), 9.42 (d, J = 2.7 Hz, 1H), 7.86 (mc, 2H), 7.53 (mc, 3H), 4.96 (t, J = 6.2 Hz, 2H), 4.69 (q, J = 7.2 Hz, 2H), 2.94 (dt, J$_1$ = 6.3 Hz, J$_2$ = 2.7 Hz, 2H), 2.56 (t, J = 2.7 Hz, 1H), 1.66 (t, J = 7.2 Hz, 3H).
Anal. Calcd. for C$_{16}$H$_{17}$BF$_4$N$_2$O (340.13): C, 56.50; H, 5.04; N, 8.24. Found: C, 56.53; H, 5.13; N, 8.42.

General procedure for the intramolecular Diels-Alder reactions of compounds 3 and 6.
A stirred solution of the appropriate pyrimidinium salt 3 or 6 in nitrobenzene (100 mg solute/1 ml solvent) under nitrogen was heated under conditions mentioned. The resultant mixture was treated with water and extracted with ether. Evaporation of water from the water layer afforded the pyridinium salts 5 and 8, respectively. Work up of the organic layer

(obtained from the reaction mixture of **6b**) gave in addition to **8a** 2,3-dihydro-5-phenylthieno[2,3-b]pyridine (**9b**).

5-Ethyl-1,3-dihydrofuro[3,4-c]pyridinium tetrafluoroborate (**5a**). From **3a** (211 mg; 0.8 mmol). Reaction conditions: 110°C/2 h. Yield: 176 mg (93%); oil. It was further purified by washing with dry distilled ether. ^{1}H NMR (acetone-d$_6$) δ 9.03 (s, 1H), 8.99 (d, J = 6.0 Hz, 1H), 8.15 (d, J = 6.0 Hz, 1H), 5.30 (brs, 4H), 4.81 (q, J = 7.3 Hz, 2H), 1.69 (t, J = 7.3 Hz, 3H). Anal. Calcd. for C$_9$H$_{12}$BF$_4$NO (237.01): C, 45.60; H, 5.10; N, 5.91. Found: C, 45.36; H, 5.31; N, 6.06.

5-Ethyl-1,3-dihydro-3-phenylfuro[3,4-c]pyridinium tetrafluoroborate (**5b**). From **3b** (272 mg; 0.8 mmol). Reaction conditions: 110°C/1.5 h. Yield: 215 mg (86%); oil. ^{1}H NMR (acetone-d$_6$) δ 9.16 (d, J = 6.3 Hz, 1H), 8.83 (s, 1H), 8.20 (d, J = 6.3 Hz, 1H), 7.41 (mc, 5H), 6.47 (brs, 1H), 5.53 (m, 2H), 4.75 (q, J = 7.5 Hz, 2H), 1.62 (t, J = 7.4 Hz, 2H). MS (FD): m/e 226 (M$^+$ - BF$_4$).
This compound was identical with the one obtained by ethylation of 1,3-dihydro-3-phenylfuro[3,4-c]pyridine[4e]. Thus, to a stirred solution of the latter compound (71 mg) in dry dichloromethane (2 ml) was added at room temperature a solution of TOF (69 mg; 1 eq) in dichloromethane (2 ml). After one hour the solvent was evaporated to afford a colourless oil. Its mass spectrum (FD) and ^{1}H NMR spectrum (acetone-d$_6$) were in all detail identical with those of **5b** obtained by the intramolecular Diels-Alder reaction of **3b** (see above).

1-Ethyl-6,7-dihydro-3-phenyl-5*H*-1-pyrindinium tetrafluoroborate (**8a**). From **6a** (406 mg; 1.2 mmol). Reaction conditions: 180°C/0.25 h. Yield: 355 mg (95%). M.p. 201-203°C (ethanol). ^{1}H NMR (acetone-d$_6$) δ 9.07 (brs, 1H), 8.67 (brs, 1H), 7.85 (mc, 2H), 7.53 (mc, 3H), 4.79 (q, J = 7.3 Hz, 2H), 3.57 (t, J = 7.7 Hz, 2H), 3.30 (t, J = 7.7 Hz, 2H), 2.41 (qui, J = 7.5 Hz, 2H), 1.70 (t, J = 7.4 Hz, 3H). Anal. Calcd. for C$_{16}$H$_{18}$BF$_4$N (311.13): C, 61.76; H, 5.83; N, 4.50. Found: C, 62.06; H, 6.00; N, 4.48.

7-Ethyl-2,3-dihydro-5-phenylthieno[2,3-b]pyridinium tetrafluoroborate (**8b**) and 2,3-dihydro-5-phenylthieno[2,3-b]pyridine(**9b**). From **6b** (178 mg; 0.5 mmol). Reaction conditions: 180°C/3 h. **8b** Was obtained from the water layer. Yield: 56 mg (34%; isolated yield after recrystallization). M.p. 185.5-187.5°C (ethanol); ^{1}H NMR (acetone-d$_6$) δ 8.93 (brs, 1H), 8.51 (brs, 1H), 7.80 (mc, 2H), 7.50 (mc, 3H), 4.65 (q, J = 7.3 Hz, 2H), 3.90 (mc, 4H), 1.67 (t, J = 7.4 Hz, 3H). Anal. Calcd. for C$_{15}$H$_{16}$BF$_4$NS (329.17): C, 54.72; H, 4.25; N, 4.89. Found: C, 54.57; H, 4.27; N, 4.88.
The organic layer was dried (MgSO$_4$) and evaporated. Column chromatography of the residue (eluting first with dichloromethane, then dichloro-

methane/ether 2:1) gave **9b** (53 mg; 50%) as a colourless solid: m.p. 101-102°C (hexanes; lit.[4b] m.p. 101-102°C). ^{1}H NMR (CDCl$_3$) identical with that reported in literature[4b].

General procedure for the intramolecular Diels-Alder reaction of pyrimidines **2d**, **f**, and **h** in trifluoroacetic acid.

A stirred solution of the pyrimidine **2d**, **f**, or **h** in trifluoroacetic acid (100 mg/1 ml) was heated at reflux temperature (72°C). The reaction was monitored by ^{1}H NMR spectroscopy. After all the starting material had disappeared the reaction mixture was cooled, poured into water (25 ml/1 ml trifluoroacetic acid) and made slightly alkaline with 25% aqueous sodium hydroxide solution. This solution was extracted with dichloromethane, the organic layers were dried over MgSO$_4$ and the solvent removed in vacuo. The residue was worked up as described below.

Cyclization of 2-(3-butynylsulfinyl)-5-phenylpyrimidine (2d) to 2,3-dihydro-5-phenyl-1-oxothieno[2,3-b]pyridine (11d).

Reaction time: 1 h. Column chromatography (eluting with ether/methanol 5:1) of the reaction mixture obtained from **2d** (256 mg; 1 mmol) yielded **11d** (82 mg; 36%): m.p. 155-156°C (methanol/ether); ^{1}H NMR (CDCl$_3$) δ 8.81 (s, 1H), 8.00 (s, 1H), 7.53 (m, 5H), 3.66 (m, 2H), 3.39 (m, 2H).
Anal. Calcd. for C$_{13}$H$_{11}$NOS (229.29): C, 68.09; H, 4.83; N, 6.10. Found: C, 67.75; H, 4.72; N, 5.97.

Cyclization of 2-(3-butynylsulfinyl)-4,6-dimethylpyrimidine (2h) to 2,3-dihydro-6-methyl-1-oxothieno[2,3-b]pyridine (11h) and 2,3-dihydro-6-methyl-thieno[2,3-b]-pyridine (11g).

Reaction time: 0.5 h. Column chromatography (eluting first with ether, then ether/methanol 5:1) of the reaction mixture obtained from **2h** (416 mg; 2 mmol) yielded **11g** (33 mg; 11%) and **11h** (184 mg; 55%). **11h** Was obtained as a solid: m.p. 97-98°C (petroleum ether 40-60); ^{1}H NMR (CDCl$_3$) δ 7.75 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 4.00-3.15 (m, 4H), 2.66 (s, 3H).
Anal. Calcd. for C$_8$H$_9$NOS (167.23): C, 57.45; H, 5.42; N, 8.37. Found: C, 57.32; H, 5.39; N, 8.30.
Compound **11g** was identical with an authentic sample[4b].

Cyclization of 2-(2-propynyloxymeythyl)-4,6-dimethylpyrimidine (2f) to 5,7-dihydro-2-methylfuro[3,4-b]pyridine (11f).

Reaction time: 24 h. Column chromatography (eluting with ether) of the reaction mixture obtained from **2f** (352 mg; 2 mmol) afforded **11f** (176 mg; 65%). This compound was identical with an authentic sample[4e].

<u>Cyclization of 2-(3-butynylthio)-5-phenylpyrimidine (2b) to 3,4-dihydro-4-methylene-7-phenyl-2H-pyrimidino[2,1-b][1,3]thiazin-5-ium perchlorate (13b).</u> A solution of **2b** (1.10 g, 4.6 mmol) in trifluoroacetic acid (10 ml) was heated for 14 h at reflux temperature. The trifluoroacetic acid was then removed under reduced pressure and the residue was dissolved in a mixture of water (15 ml) and ethanol (15 ml). To this solution was added an excess of a 70% $HClO_4$ solution in water. The solid was collected and recrystallized from a mixture of acetone-methanol-water to yield pure **13b** (0.99 g, 63%): m.p. 234-236°C; ^{1}H NMR (DMSO-d_6) δ 9.69 (d, J = 2.4 Hz, 1H), 9.48 (d, J = 2.4 Hz, 1H), 7.94 (m, 2H), 7.30 (m, 3H), 6.21 (d, J = 3.0 Hz, 1H), 5.81 (d, J = 3.0 Hz, 1H), 3.59 (t, J = 6.2 Hz, 2H), 3.15 (t, J = 6.2 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 163.7 (s, C-9a), 161.8 (d, J_{C-H} = 196 Hz, C-8), 147.7 (d, J_{C-H} = 195 Hz, C-6), 142.2, 130.3, 127.7 (3 x s, Ph, C-4 and C-7), 130.2 (d, J_{C-H} = 159 Hz, Ph), 129.4 (d, J_{C-H} = 162 Hz, Ph), 127.5 (d, J_{C-H} = 165 Hz, Ph), 116.8 (t, J_{C-H} = 164 Hz, =CH_2), 28.5 (t, J_{C-H} = 146 Hz, C-2), 25.6 (t, J_{C-H} = 136 Hz, C-3).
Anal. Calcd. for $C_{14}H_{13}ClN_2O_4S$ (340.78): C, 49.33; H, 3.84; N, 8.22. Found: C, 49.15; H, 3.73; N, 8.24.

6.4   REFERENCES AND NOTES

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CHAPTER 7

GENERAL DISCUSSION

Since the early systematic research by Diels and Alder the thermal [4+2]-cycloaddition has grown into one of the most valuable tools in synthetic organic chemistry. The product of the intermolecular Diels-Alder reaction is always a six-membered ring. In case of the intramolecular version the product is a bicyclic annelated ring system. Application of the FMO-theory offers the basis for classification of the Diels-Alder reaction into one of three classes (Chapter 1):

(i)   Reactions between electron-rich dienes and electron-poor dienophiles.
(ii) Reactions between moderately activated (neutral) compounds.
(iii) Reactions between electron-poor dienes and electron-rich dienophiles.

Research at our laboratory[1] and others[2] revealed that the azadiene moiety of pyrimidines substituted at position 5 with an electron-withdrawing group (SO_2Me, CO_2Me, CO_2Et, NO_2) is sufficiently electron-deficient to participate in inverse electron demand intermolecular Diels-Alder reactions with electron-rich dienophiles. The entropic advantage inherent in intramolecular Diels-Alder reactions allows extensions of such cyclizations to exploit less activated pyrimidines and less reactive dienophiles such as terminal alkynes. The results of our research in this field are presented in this thesis.

7.1   SCOPE OF THE REACTION

The inverse electron demand intramolecular Diels-Alder reaction of pyrimidines opens the possibility to synthesize a variety of new annelated pyridines in a single ringtransformation reaction. These products are formed from the initial tricyclic adducts by a spontaneous cycloreversion reaction with the loss of hydrogen (or alkyl) cyanide. The nature of the condensed pyridines depends on the character of the tether between
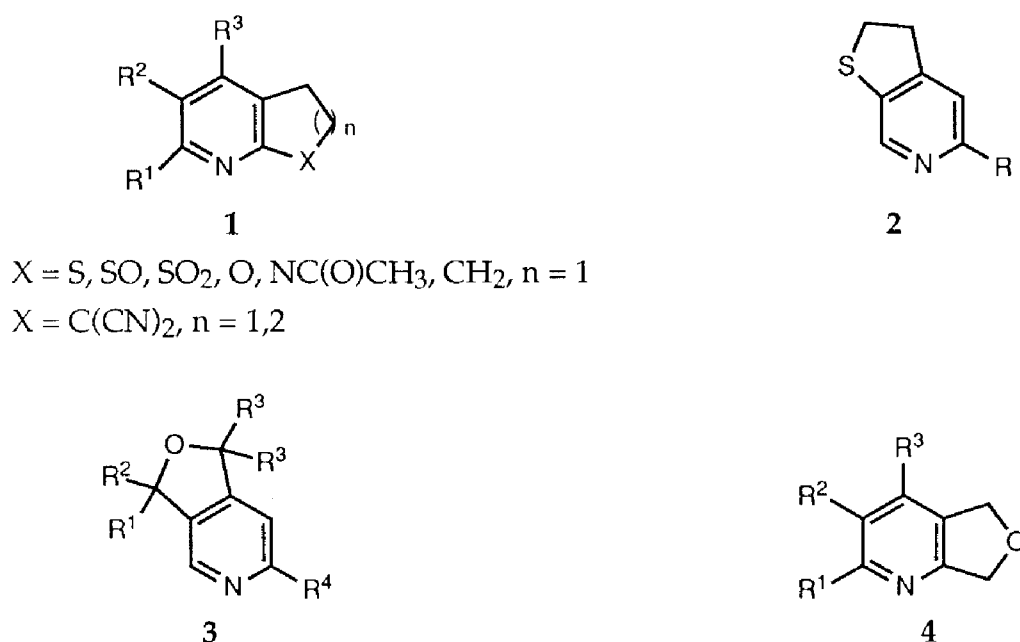
103

Scheme 7.1

X = S, SO, SO$_2$, O, NC(O)CH$_3$, CH$_2$, n = 1
X = C(CN)$_2$, n = 1,2

azadiene and dienophile and the point of attachment of the dienophilic side-chain to the pyrimidine nucleus.

Pyrimidines containing a dienophilic side-chain X(CH$_2$)$_n$CH$_2$C≡CH (X = S, SO, SO$_2$, O, NCOCH$_3$, CH$_2$, n = 1; X = C(CN)$_2$, n = 1, 2) at the 2-position are easily accessible through a nucleophilic displacement reaction or a condensation reaction (X = CH$_2$) (Chapter 2, 3, 5). The products of the intramolecular Diels-Alder reactions of the resulting compounds are [2,3-b]-annelated pyridines 1 (Scheme 7.1), i.e., thieno[2,3-b]-, furo[2,3-b]- and pyrrolo[2,3-b]pyridines (Chapter 2), cyclopenta[2,3-b]pyridines (5H-1-pyrindines) (Chapter 3, 5), and cyclohexa[2,3-b]pyridines (quinolines) (Chapter 3).

Pyrimidines having a dienophilic side-chain attached to the 5-position are less easily accessible. 5-(4-Butynylthio)pyrimidines are prepared from the appropriate substituted bis-[pyrimidinyl-(5)]-disulfide (Chapter 2). The intramolecular Diels-Alder reaction of these compounds leads to the formation of thieno[2,3-c]pyridines 2 (Scheme 7.1).

The synthesis of 5-propynyloxymethylpyrimidines and also 2-propynyloxymethylpyrimidines is described in Chapter 4. The intramolecular Diels-Alder reaction of these pyrimidines leads to 1,3-dihydrofuro[3,4-c]pyridines 3 and 5,7-dihydrofuro[3,4-b]pyridines 4, respectively (Scheme 7.1).

A third approach towards new annelated pyridines, applying the intra-molecular Diels-Alder reaction of pyrimidines containing the dienophilic side-chain at the 4-position appears to be unsuccesful. 4-(4-Butynylthio)-pyrimidine and 5-cyano-4-(1,1-dicyanopent-4-yn-1-yl)pyrimidine, being prepared by a nucleophilic substitution reaction from the corresponding 4-chloropyrimidine derivatives, show no Diels-Alder reactivity upon pro-longed heating in refluxing nitrobenzene[3].

In conclusion, pyrimidines carrying an appropriate dienophilic side-chain at the 2- or 5-position are ideally suited for participation in inverse electron demand intramolecular Diels-Alder reactions. In this way a variety of [b]- and [c]-annelated pyridines have become accessible, which are further functionalized through substituents at the pyrimidine nucleus and/or the terminal acetylene group in the starting compounds.

7.2   REACTIVITY

Introduction of electron-donating or electron-withdrawing substituents at the pyrimidine nucleus or the terminal acetylene group influences the HOMO/LUMO energy separation and consequently the reactivity of the intramolecular Diels-Alder reaction. It is found that electron-withdrawing substituents (NO_2, CN and also CF_3[4]) at the pyrimidine ring enhance the reactivity. This activating effect is partly undone when a nitro group is present at the 5-position, especially when there is a dienophilic side-chain at position 2 containing a heteroatom in the α-position. Another way to enhance the reactivity is N-alkylation or N-protonation of a pyrimidine nitrogen atom (Chapter 6). N-protonation of less activated pyrimidines does, however, not lead to products resulting from an intramolecular Diels-Alder reaction, but instead products are isolated wich result from a competitive intramolecular coplanar cycloamination reaction.

Weakly donating groups (CH_3, Ph) deactivate the Diels-Alder reactivity more by their steric effect than by their electronic effect (Chapter 2, 4). Steric effects also predominate when introducing a methyl or trimethylsilyl group at the terminal acetylene group. These compounds exhibit a lower Diels-Alder reactivity despite the activating electron-donating substituents at the dienophile.

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The inverse electron demand character of the reaction is established from a Hammett plot for the intramolecular Diels-Alder reaction of 5-(para-substituted phenyl)-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines, in which the electronic effect is transmitted to the reaction site situated in a constant steric environment (Chapter 5). A linear relationship is found with a positive slope $\rho = 0.061$.

The nature of the tether between azadiene and dienophile also influences the reactivity. Pyrimidines carrying an ω-alkyne side-chain $XCH_2CH_2C{\equiv}CH$ at the 2-position show an increased reactivity in the order $X = NH < O < S < CH_2 < NC(O)CH_3 \sim SO_2 < SO \sim C(CN)_2$. With the exception of $X = SO_2$ and $X = C(CN)_2$ this order reflects the decrease of electron donation into the π-electron system of the pyrimidine ring.

The violation of the "normal" order of reactivity in the sulfoxide > sulfone > sulfide series is explained by a smaller C-S-C bond angle in the sulfoxide as compared to the same bond angle in the sulfone. (Chapter 2).

The dicyano compounds $(X = C(CN)_2)$, featuring gem-disubstitution in the chain connecting diene and dienophile, react much faster than the compounds in which $X = CH_2$ (Chapter 3). This rate enhancement is ascribed to added entropic assistance resulting from a combination of the so-called "Thorpe-Ingold" ("scissoring") effect and an increase of reactive syn rotamers. Support for the correctness of this explanation is obtained from crystal structure analyses of 2-(1,1-dicyanopent-4-yn-1-yl)-5-nitro-pyrimidine and 5-p-nitrophenyl-2-(pent-4-yn-1-yl)pyrimidine.

Rate enhancement due to gem-disubstitution is also observed in a series of α,α- or γ,γ-substituted 5-(propynyloxymethyl)pyrimidines (Chapter 4).

The rate enhancing effect of the α-C(CN)$_2$ linkage is employed in the intramolecular Diels-Alder reaction of the less electron-deficient pyridine ring system. Whereas 2-(3-butynyloxy)-3,5-dinitropyridine and 2-(N-acetyl-3-butynylamino)-3,5-dinitropyridine do not exhibit any Diels-Alder reactivity, 2-(1,1-dicyanopent-4-yn-1-yl)pyridines containing one or two additional nitro groups in the pyridine ring undergo the Diels-Alder reaction upon heating at 180/210°C to yield the corresponding 1,1-dicyano-2,3-dihydro-1H-indenes 5 (Scheme 7.2).

From these results it is inferred that steric effects play a more important role in governing the reactivity than electronic effects. In this respect it is interesting to note that pyrimidines carrying a dienophilic side-chain

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Scheme 7.2

5
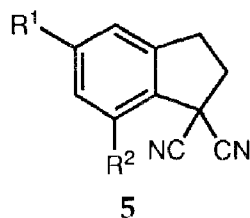
$CO_2CH_2C\equiv CH$ do not show any Diels-Alder reactivity despite the electron-withdrawing character of the ester linkage. This observation can be explained by the conjugation between the carbonyl group of the ester and the π-electron system of the pyrimidine ring[5]. The result is an unreactive conformation in which the azadiene and the dienophilic alkyne group are far apart from each other.

The intramolecular Diels-Alder reactivity is also influenced by the length of the dienophilic side-chain. Pyrimidines leading to five-membered ring annelated pyridines exhibit the largest reactivity. 2-(1,1-Dicyanohex-5-yn-1-yl)pyrimidines undergo the Diels-Alder reaction to the corresponding six-membered ring annelated pyridines (tetrahydroquinolines) upon heating at 210°C. These reaction conditions are more strenuous than for the Diels-Alder reaction of the analogous 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines due to the loss of added entropic assistance (Chapter 3). In addition, 2-(4-pentynyloxy)pyrimidines and 2-(4-pentynylthio)pyrimidines exhibit no Diels-Alder reactivity upon heating at 210°C, whereas the corresponding 2-(3-butynyloxy)pyrimidines and 2-(3-butynylthio)pyrimidines do.

5-(3-butynylthio)pyrimidines react much faster than the corresponding 2-(3-butynylthio)pyrimidines. The greater resonance donation of the 3-butynylthio group in the latter compound hampers rotation about the S-pyrimidine bond and consequently approach of the dienophile to the azadiene is more difficult. On the other hand, 2-(propynyloxymethyl)-pyrimidines react somewhat faster than 5-(propynyloxymethyl)pyrimidines. The reactivity of the 2-(propynyloxymethyl)pyrimidines is comparable to that of 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines and is ascribed to repulsion between the lone pairs on the β-oxygen and the pyrimidine nitrogen atoms, which favours a perpendicular conformation between the Cα-O group and the aromatic ring. The molecule must adopt such a conformation before

cycloaddition can occur.

The lack of Diels-Alder reactivity of pyrimidines having a dienophilic side-chain $XCH_2CH_2C\equiv CH$ (X = S, $C(CN)_2$) at the 4-position results from the sterical constraint inherent for intramolecular Diels-Alder reactions[3]. In this case the cycloaddition must take place across C-4 and N-1. This mode of cycloaddition is unfavourable. In the intermolecular version the only reaction taking place across C-4 and N-1 involves enamines as dienophiles[1a,b,e,6].

In summary, the reactivity of the intramolecular inverse electron demand Diels-Alder reaction of pyrimidines is affected by:

(i)   Electronic effects.

(ii)   Steric effects.

(iii)   The length of the dienophilic side-chain.

(iv)   The point of attachment of the dienophilic side-chain to the pyrimidine ring.

7.3   SUGGESTIONS FOR FUTURE RESEARCH

Further investigations of interest in the field of intramolecular Diels-Alder reactions of pyrimidines involve:

(i)   Studies towards the application of the intramolecular Diels-Alder reaction of pyrimidines in the synthesis of natural products such as alkaloids.

(ii)   Synthesis and Diels-Alder reactivity of 2-(2-propynyloxyphenyl)-pyrimidines. The expected products are 5H-[1]benzopyrano[4,3-b]-pyridines. The starting compounds feature the presence of a phenyl group in the αβ-position of the dienophilic side-chain.

(iii)   Synthesis of 2-(2-trimethylsilylethynylphenyl-X)pyrimidines (X = O, S, NH, NC(O)CH_3, CH_2, C=O) having a phenyl group in the βγ-position of the dienophilic side-chain and their Diels-Alder reaction into the corresponding tricyclic annelated pyridines.

(iv)   Molecular Mechanics and MNDO calculations in order to gain more insight into and predict observed differences in reactivity.

Studies concerning the above-mentioned aspects have already been initiated at our laboratory.

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SUMMARY

This thesis deals with the intramolecular inverse electron demand Diels-Alder reaction of pyrimidines. The main objective of the study was to investigate the synthetic applicability of this reaction and to get more insight in the electronic and steric effects which determine the reactivity of compounds that undergo this intramolecular cycloaddition reaction.

After a general introduction about the Diels-Alder reaction, in Chapter 1 a global historical overview is given of the inverse electron demand Diels-Alder reaction of heteroaromatic azadienes with emphasis on the intramolecular version, which has been developed in the recent past.

Pyrimidines carrying an ω-alkyne side-chain $-XCH_2CH_2C{\equiv}CH$ (X = O, N, S, SO, SO_2) at the 2- or 5-position undergo intramolecular inverse electron demand Diels-Alder reactions across the C-2 and C-5 positions; elimination of hydrogen (or alkyl) cyanide from the intermediate adducts leads to fused pyridines (Chapter 2). The influence of the heteroatom (X) in the dienophilic side-chain on the reactivity is discussed. It is found that the reactivity increases in the order NH < O < S < $NC(O)CH_3$, reflecting the decrease of electron-donation into the π-electron system of the pyrimidine ring. Substituents on the pyrimidine ring also influence the reactivity due to a combination of electronic and steric factors. In general electron-withdrawing groups increase the rate of reaction although this effect may be partly negated by steric hindrance.

Pyrimidines carrying an ω-alkynyl side-chain $-CR_2(CH_2)_nCH_2C{\equiv}CH$ (R = H, CN; n = 1, 2) at the 2-position also undergo intramolecular inverse electron demand Diels-Alder reactions across the C-2 and C-5 positions (Chapter 3). Loss of hydrogen cyanide, caused by a retro-Diels-Alder reaction, from the intermediate cycloadducts leads to 6,7-dihydropyrindines (n = 1) and 5,6,7,8-tetrahydroquinolines (n = 2), respectively. The dicyano compounds (R = CN) are found to be more reactive than the compounds in which R = H. This rate enhancement is ascribed to a combination of the so-called "Thorpe-Ingold" ("scissoring") effect and an increase in the relative population of reactive *syn* rotamers.

2-(1,1-Dicyanohex-5-yn-1-yl)pyrimidines, having an extra methylene group in the tether between diene and dienophile, react much slower than the corresponding 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines due to decreased entropic assistance.

Even 2-(1,1-dicyanopent-4-yn-1-yl)nitropyridines are found to undergo intramolecular Diels-Alder reactions into the corresponding 2,3-dihydro-nitro-1H-indenes.

In Chapter 4, the synthesis of 2- and 5-propynyloxymethylpyrimidines and their intramolecular Diels-Alder reaction is studied. The products of the reaction are 5,7-dihydrofuro[3,4-b]pyridines and 1,3-dihydrofuro[3,4-c]-pyridines, respectively. Introduction of one or two alkyl (aryl) groups at the α- or γ-position of the side-chain of the 5-propynyloxymethylpyrimidines results in an increased reaction rate. This phenomenon is discussed in terms of relative rotamer population.

A Hammett plot for the intramolecular Diels-Alder reaction of some p-substituted 5-phenyl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines into the corresponding 3-aryl-7,7-dicyano-6,7-dihydro-5H-1-pyrindines reveals a linear relationship with a positive slope $\rho = 0.061$ (Chapter 5), which is in agreement with the inverse electron demand character of this reaction. The low value of ρ and the small effect of solvent polarity indicates that there is little or no charge separation in the rate determining transition state.

N-Alkylpyrimidinium cations carrying a dienophilic side-chain at the 2- or 5-position undergo intramolecular inverse electron demand Diels-Alder reactions into the corresponding annelated pyridine derivatives under considerably milder conditions than the corresponding neutral pyrimidines as a result of a lower $HOMO_{dienophile}/LUMO_{diene}$ energy separation (Chapter 6). Protonation of the pyrimidine ring also facilitates the intramolecular Diels-Alder reaction. Protonation of less activated pyrimidines leads, however, to annelated pyrimidinium cations posessing an exocyclic methylene group in the annelated ring at the carbon atom α to the quaternary nitrogen atom. These products result from an intramolecular coplanar cycloamination reaction.

SAMENVATTING

In dit proefschrift wordt de intramoleculaire Diels-Alder reactie met omgekeerde electronenbehoefte van pyrimidines beschreven. Het belangrijkste doel van de studie was het onderzoeken van de synthetische toepasbaarheid van deze reactie en om meer inzicht te verkrijgen in de electronische en sterische factoren die de reactiviteit bepalen van verbindingen die deze intramoleculaire cycloadditie reactie geven.

Na een algemene inleiding over de Diels-Alder reactie, wordt in Hoofdstuk 1 een globaal historisch overzicht gegeven van de Diels-Alder reactie met inverse electronenbehoefte van heteroaromatische azadiënen, waarbij de nadruk ligt op de intramoleculaire versie die in het recente verleden is ontwikkeld.

Pyrimidines, die een ω-alkyn zijketen -$XCH_2CH_2C{\equiv}CH$ (X = O, N, S, SO, SO_2) bevatten op de 2- of de 5-plaats, ondergaan een intramoleculaire Diels-Alder reactie met omgekeerde electronenbehoefte over de C-2 en C-5 posities. Eliminatie van waterstof (of alkyl) cyanide uit de intermediaire adducten leidt tot nieuwe geanneleerde pyridines (Hoofdstuk 2). De invloed van het heteroatoom (X) in de diënofiele zijketen op de reactiviteit wordt besproken. Het blijkt dat de reactiviteit toeneemt in de volgorde NH < O < S < $NC(O)CH_3$; deze reeks weerspiegelt de afname van de electronen donatie aan het π-electronen systeem van de pyrimidine ring. Ook substituenten aan de pyrimidine ring beïnvloeden de reactiviteit ten gevolge van een combinatie van electronische en sterische factoren. In het algemeen verhogen electronenzuigende groepen de reactiviteit. Dit effect kan echter gedeeltelijk teniet gedaan worden door sterische invloeden.

Pyrimidines met een ω-alkynyl zijketen -$CR_2(CH_2)_nCH_2C{\equiv}CH$ (R = H, CN; n = 1, 2) op de 2-plaats ondergaan ook intramoleculaire Diels-Alder reacties met omgekeerde electronenbehoefte over C-2 en C-5 van het pyrimidine (Hoofdstuk 3). Afsplitsing van blauwzuur (HCN), veroorzaakt door een retro-Diels-Alder reactie, uit de intermediaire cycloadducten levert respectievelijk 6,7-dihydro-1H-pyrindines (n = 1) en 5,6,7,8-tetrahydroquinolines (n = 2). De dicyanoverbindingen (R = CN) blijken reactiever te zijn dan de verbindingen met R = H. Deze verhoogde reactiviteit wordt toegeschreven

aan een combinatie van het zgn. "Thorpe-Ingold" ("scissoring") effect en een toename van de relatieve populatie van reactieve *syn* rotameren.

2-(1,1-Dicyanohex-5-yn-1-yl)-pyrimidines, die een extra methyleen groep bezitten in de keten tussen het diëen en het diënofiel, reageren veel langzamer dan de overeenkomstige 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines ten gevolge van afgenomen entropische assistentie.

Zelfs 2-(1,1-dicyanopent-4-yn-1-yl)nitropyridines blijken intramoleculaire Diels-Alder reacties met omgekeerde electronenbehoefte te ondergaan. De produkten zijn de overeenkomstige 2,3-dihydronitro-1*H*-indenen.

In Hoofdstuk 4 wordt de synthese van 2- en 5-propynyloxymethyl-pyrimidines en hun intramoleculaire Diels-Alder reactie beschreven. De produkten van de Diels-Alder reactie zijn respectievelijk 5,7-dihydro-furo[3,4-b]pyridines en 1,3-dihydrofuro[3,4-c]pyridines. Introductie van één of twee alkyl (aryl) groepen op de α- of γ-plaats van de diënofiele zijketen van de 5-propynyloxymethylpyrimidines resulteert in een hogere reactie-snelheid. Dit fenomeen wordt besproken in termen van relatieve rotameer populatie.

Voor de intramoleculaire Diels-Alder reactie van enkele *p*-gesubstitueer-de 5-phenyl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines wordt een lineaire Hammett relatie gevonden met een positieve helling ρ = 0.061 (Hoofdstuk 5). Dit is in overeenstemming met de omgekeerde electronenbehoefte van deze reactie. De lage waarde van ρ en het kleine oplosmiddeleffect geven aan dat er weinig of geen ladingsscheiding is in de snelheidsbepalende overgangstoestand.

De intramoleculaire Diels-Alder reactie met omgekeerde electronenbe-hoefte van N-alkylpyrimidinium kationen naar de overeenkomstige geanne-leerde pyridinium kationen vindt onder aanzienlijk mildere reactie-omstandigheden plaats dan de intramoleculaire Diels-Alder reactie van de vergelijkbare neutrale pyrimidines. Dit is een gevolg van het lagere energie-verschil tussen HOMO$_{\text{dienofiel}}$ en LUMO$_{\text{dieen}}$ (Hoofdstuk 6). Ook protonering van de pyrimidine ring bevordert de intramoleculaire Diels-Alder reactie. Protonering van minder geactiveerde pyrimidines geeft echter gean-neleerde pyrimidinium kationen als produkten. Deze hebben een exocy-clische methyleen groep in de geanneleerde ring aan het koolstof atoom α ten opzichte van het quaternaire stikstof atoom. Deze produkten zijn het gevolg van een intramoleculaire coplanaire cycloaminering.

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CURRICULUM VITAE

Augustinus Emmanuel Frissen, roepnaam Guus, werd geboren op 4 december 1955 te Hoensbroek. Hij doorliep de lagere school te Hulsberg, waarna hij het St.-Janscollege te Hoensbroek bezocht. Het diploma Gymnasium-β werd in 1974 behaald. In datzelfde jaar werd begonnen met de studie Scheikunde aan de Katholieke Universitiet te Nijmegen. Het kandidaatsexamen Scheikunde (S_2) werd afgelegd in mei 1978. Het doctoraalexamen, met als hoofdvak Organische Chemie (prof. dr. R.J.F. Nivard) en als bijvakken Exobiologie (prof. dr. A.W. Schwarz) en Algemeen Gedeelte (bestaande uit de capita Instrumentele Methoden I, Quantum Chemie, Moleculaire Symmetrie en Chemische Technologie) werd afgelegd in juni 1984. De doctoraalfase werd in de periode 1982-1983 onderbroken voor het vervullen van de militaire dienst.

In de periode van februari 1985 tot april 1989 werd het in dit proefschrift beschreven onderzoek uitgevoerd onder leiding van prof. dr. H.C. van der Plas. Hij was eerst tot februari 1989 als onderzoekmedewerker in dienst bij de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO, voorheen ZWO), sectie Scheikundig Onderzoek in Nederland (SON) en vervolgens als toegevoegd onderzoeker bij de vakgroep Organische Chemie van de Landbouwuniversiteit Wageningen.

In de periode van april 1990 tot augustus 1990 was hij in tijdelijke dienst van het Rijks-Kwaliteitsinstituut voor Land- en Tuinbouwprodukten (RIKILT).