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INTRAMOLECULAR CYCLIZATION REACTIONS OF PYRIMIDINIUM CATIONS.

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Abstract: 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. Protonation of the pyrimidine ring also facilitates the intramolecular Diels-Alder reaction. Protonation of less activated pyrimidines leads, however, to products resulting from an intramolecular coplanar cycloamination reaction.

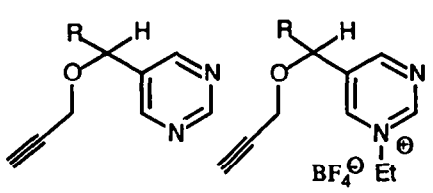
INTRODUCTION

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.

RESULTS AND DISCUSSION

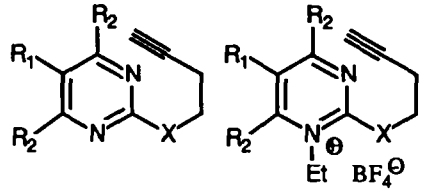
Quaternization of 5-(2-propynyloxymethyl)pyrimidine (**1a**) and 5-(phenyl-2-propynyloxymethyl)pyrimidine (**1b**) as well as 2-(4-pentynyl)-5-phenylpyrimidine (**2a**), 2-(3-butynylthio)-5-phenylpyrimidine (**2b**) and 2-(3-butynyloxy)-5-phenylpyrimidine (**2c**) was easily achieved by treatment of a solution of these compounds in dry dichloromethane with one equivalent of triethyloxonium tetrafluoroborate (Meerwein reagent)[9] at room temperature. The resulting N-

Scheme 1



1 3

a; R = H
b; R = Ph

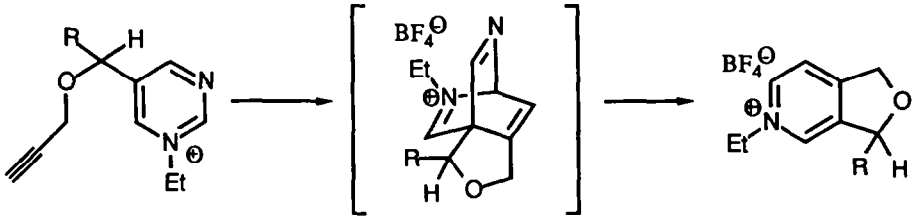


2 6

a; X = CH_2, R_1 = Ph, R_2 = H
b; X = S, R_1 = Ph, R_2 = H
c; X = O, R_1 = Ph, R_2 = H

ethylpyrimidinium tetrafluoroborates **3a,b** and **6a-c**, respectivily, 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.

Scheme 2



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

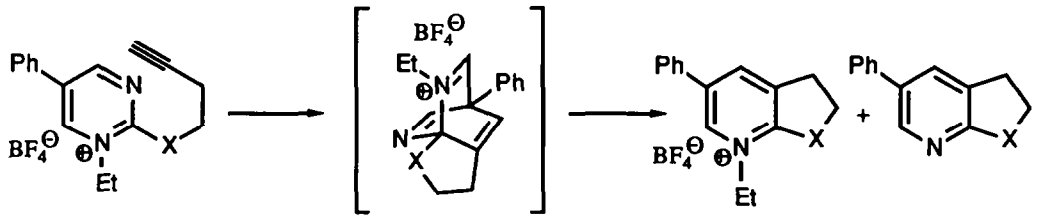
4

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

Heating of a solution of **3a** (Scheme 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 ^{1}H 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].

As examples of pyrimidines containing a dienophilic side-chain at the 2-position we examined the cycloaddition reaction of the pyrimidinium salts **6** (Scheme 3). The salts **6a** and **6b**

Scheme 3

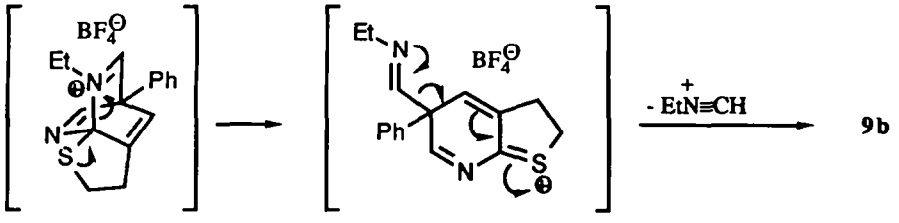


6 **7** **8** **9**

a; X = CH_2; **b**; X = S; **c**; X = O

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,

Scheme 4



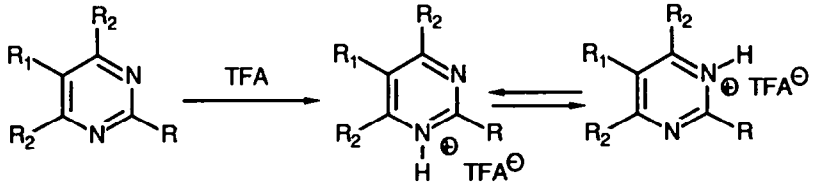
7b **9b**

protonated ethyl isocyanide is split off as indicated in Scheme 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 δ = 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.

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.

Comparison of the ^{1}H NMR spectra of compounds **2a-i** (Scheme 5) in trifluoroacetic acid (see Table 1) with those of the neutral species (recorded in $CDCl_3$; Table 3) 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 5).

Scheme 5



2

a; R = $(CH_2)_3C{\equiv}CH$, R_1 = Ph, R_2 = H
b; R = $S(CH_2)_2C{\equiv}CH$, R_1 = Ph, R_2 = H
c; R = $O(CH_2)_2C{\equiv}CH$, R_1 = Ph, R_2 = H
d; R = $SO(CH_2)_2C{\equiv}CH$, R_1 = Ph, R_2 = H
e; R = $SO_2(CH_2)_2C{\equiv}CH$, R_1 = Ph, R_2 = H
f; R = $CH_2OCH_2C{\equiv}CH$, R_1 = H, R_2 = Me
g; R = $S(CH_2)_2C{\equiv}CH$, R_1 = H, R_2 =Me
h; R = $SO(CH_2)_2C{\equiv}CH$, R_1 = H, R_2 = Me
i; R = $O(CH_2)_2C{\equiv}CH$, R_1 = H, R_2 = H

TABLE 1: ^{1}H NMR spectral data for pyrimidines **2** in trifluoroacetic acid.

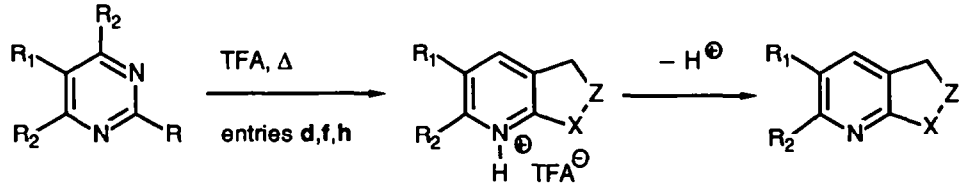
Compound	^{1}H NMR shifts (ppm) and coupling constants (Hz) H-5	H-4 and H-6	Ph/CH_3	R
2a		9.50 (s, 2H)	7.66 (m, 5H)	1.98 (t, J = 2.5, 1H), 2.36 (m, 4H), 3.53 (t, J = 7.5 , 2H).
2b		9.24 (s, 2H)	7.68 (m, 5H)	2.06 (t, J = 2.6, 1H), 2.81 (dt, J_1 = 7.5, J_2 = 2.6, 2H), 3.75 (t, J = 7.5, 2H).
2c		9.25 (s, 2H)	7.65 (m, 5H)	2.03 (t, J = 2.6, 1H), 2.83 (dt, J_1 = 2.6, J_2 = 7.5, 2H), 4.95 (t, J = 7.5, 2H)
2d		9.53 (s, 2H)	7.68 (m, 5H)	1.94 (t, J = 2.6, 1H), 2.94 (m, 2H), 3.79 (m, 2H).
2e		9.65 (s, 2H)	7.66 (m, 5H)	1.85 (t, J = 2.5, 1H), 2.88 (dt, J_1 = 7.5, J_2 = 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)			1.81 (t, J = 2.5, 1H), 2.94 (m, 8H), 3.85 (m, 2H).
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, J_1 = 7.5, J_2 = 2.5, 2H), 4.85 (t, J =7.5, 2H).

TABLE 2: ^{1}H NMR spectral data for pyrimidines **2** in $CDCl_3$.

Compound	^{1}H NMR shifts (ppm) and coupling constants (Hz) for pyrimidine protons. 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)

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 afforded the corresponding neutral [2,3-b]-annelated pyridine derivatives **11d** and **11h** in moderate yield (Scheme 6). In case of cyclization of **2i** 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.

Scheme 6



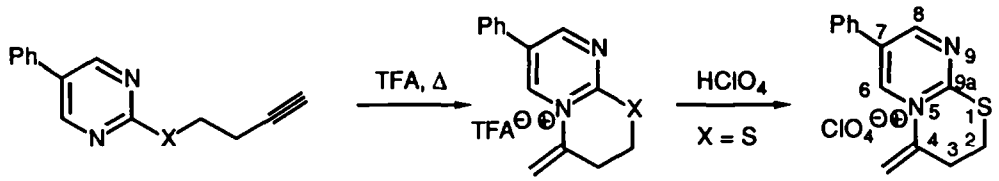
2 **10** **11**

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

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-2*H*-pyrimido[2,1-b][1,3]-thiazin-5-ium perchlorate (**13b**) (Scheme 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

Scheme 7



2a-c **12a-c** **13b**

a; X = CH_2 b; X = S c; X = O

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 proces 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 heterocyclic azadienes which are performed under acidic conditions. Previously, pyrimidin-4-ones with an appropriate alkynyl side-chain attached to the 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 ^1H 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-phenylpiperidino[1,2-a]pyrimidin-5-ium trifluoroacetate (**12a**) and 3,4-dihydro-4-methylene-7-phenyl-2*H*-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.

EXPERIMENTAL

Melting points are uncorrected. The ^1H NMR spectra were recorded on a Varian (90 MHz) EM 390 spectrometer with Me_4Si 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-(4-pentynyl)-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 mmole) of sodium hydride (80% oil dispersion) in dry tetrahydrofuran (5 ml) was added 280 mg (4 mmole) of 3-butyn-1-ol in tetrahydrofuran (2 ml). After the initial effervescence had subsided, 2-methylsulfonyl-5-phenylpyrimidine[4f] (468 mg; 2 mmole) 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 (hexane/toluene); ^1H 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 $C_{14}H_{12}N_2O$ (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 mmole) in dry chloroform (100 ml) at 0°C was added *m*-chloroperbenzoic acid (85% techn. solid; 1.83 g, 9.0 mmole). 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); ^1H 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 $C_{14}H_{12}N_2OS$ (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 mmole) in anhydrous chloroform (10 ml) at 0°C *m*-chloroperbenzoic acid (85% techn. solid; 0.61 g, 3.0 mmole) 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 (hexane/chloroform); ^1H 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 $C_{14}H_{12}N_2O_2S$ (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 mmole) in dry chloroform at 0°C was added *m*-chloroperbenzoic acid (85%; 1.27g, 6.3 mmole). This

mixture was stirred for 1h 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 using ether/methanol 5:1 as eluent to yield 1.2 g (92%) of **2h**: m.p. 61-62°C (petroleum ether 40-60); ^1H 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 $C_{10}H_{12}N_2OS$ (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 mmole) 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 (hexane/chloroform); ^1H 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 mmole) in nitrobenzene (1.5 ml) under nitrogen for 4h 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; ^1H 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 mmole) 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; ^1H NMR (acetone-d6) δ 9.76 (br s, 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 mmole) 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: ^1H NMR (acetone-d6) δ 9.67 (br s, 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-(4-pentynyl)-5-phenylpyrimidinium tetrafluoroborate(**6a**). To a stirred solution of 2-(pent-4-yn-1-yl)-5-phenylpyrimidine (**2a**; 533 mg; 2.4 mmole) 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; ^1H NMR (acetone-d6) 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 $C_{17}H_{19}BF_4N_2$ (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 mmole) 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-d6) 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 $C_{16}H_{17}BF_4N_2S$ (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 mmole) 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 d6) 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 $C_{16}H_{17}BF_4N_2O$ (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 mmole). 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-d6) δ 9.03 (s, 1H), 8.99 (d, J = 6.0 Hz, 1H), 8.15 (d, J = 6.0 Hz, 1H), 5.30 (br s, 4H), 4.81 (q, J = 7.3 Hz, 2H), 1.69 (t, J = 7.3 Hz, 3H).
Anal. Calcd. for $C_9H_{12}BF_4NO$ (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 mmole). Reaction conditions: 110°C/1.5 h. Yield: 215 mg (86%); oil. ^{1}H NMR (acetone-d6) δ 9.16 (d, J = 6.3 Hz, 1H), 8.83 (s, 1H), 8.20 (d, J = 6.3 Hz, 1H), 7.41 (mc, 7.5 Hz, 2H), 6.47 (br s, 1H), 4.75 (q, J = 7.5 Hz, 2H), 4.53 (m, 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 mmole). Reaction conditions: 180°C/0.25 h. Yield: 355 mg (95%). M.p. 201-203°C (ethanol). ^{1}H NMR (acetone-d6) δ 9.07 (br s, 1H), 8.67 (br s, 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 $C_{16}H_{18}BF_4N$ (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]pyrimidinium tetrafluoroborate (8b) and 2,3-dihydro-5-phenylthieno[2,3-b]pyrimidine(9b). From **6b** (178 mg; 0.5 mmole). 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-d6) δ 8.93 (br s, 1H), 8.51 (br s, 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 $C_{15}H_{16}BF_4NS$ (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 dichloromethane/ether 2:1) gave **9b** (53 mg; 50%) as a colourless solid: m.p. 101-102°C (hexane; lit.[4b] m.p. 101-102°C). ^1H 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 ^1H 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 mmole) yielded **11d** (82 mg; 36%): m.p. 155-156°C (methanol/ether); ^1H 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-methylthieno[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 mmole) 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); ^1H 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_8H_9NOS (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 mmole) afforded **11f** (176 mg; 65%). This compound was identical with an authentic sample[4e].

Cyclization of 2-(3-butynylthio)-5-phenylpyrimidine (**2b**) to 3,4-dihydro-4-methylene-7-phenyl-2*H*-pyrimidino[2,1-b][1,3]thiazinium perchlorate (**13b**). A solution of **2b** (1.10 g, 4.6 mmole) 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; ^1H 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 (d, J = 6.2 Hz, 2H), 3.15 (d, 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.

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