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NOVEL INTRAMOLECULAR DIELS-ALDER REACTIONS OF PYRIMIDINES. SYNTHESIS OF HETEROCYCLIC ANNELATED PYRIDINES

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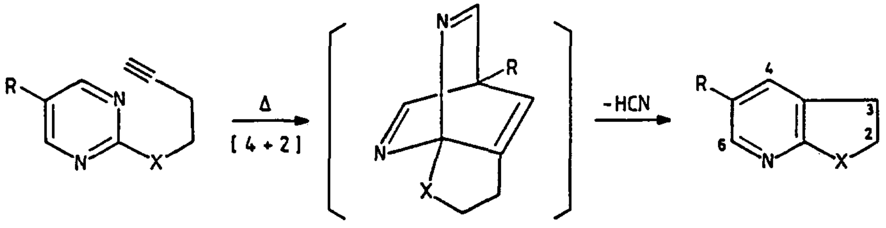
Abstract Pyrimidines carrying a dienophilic side-chain at the 2 or 5 position undergo intramolecular Diels-Alder reactions to give heterocyclic annelated pyridines.

Inverse electron demand Diels-Alder reactions of heterocyclic azadienes with electron-rich dienophiles are well documented[1]. Recently, the intramolecular version of these reactions with 1,2,4,5-tetrazines and 1,2,4-triazines has received considerable attention[2]. However, intramolecular Diels-Alder cyclizations with pyrimidines have less intensively been investigated[3].

Because of our interest in cycloaddition reactions of pyrimidines[4] we carried out research on intramolecular inverse electron demand Diels-Alder reactions of pyrimidines with side-chain dienophiles linked to the pyrimidine via a hetero-atom next to the aromatic ring.

Condensation of 2-chloropyrimidine with the sodium salt of 3-butyn-1-ol smoothly led to the 2-(3-butynyloxy)pyrimidine **1a**. In a similar way the 5-nitro derivative **1b** has been prepared. Heating of **1a** and **1b** for 24 hours in refluxing nitrobenzene (210°C) under nitrogen gave the 2,3-dihydrofuro[2,3-b]pyridines **3a** and **3b**. Their formation probably occurs via the intermediacy of the cycloaddition products **2** which, however, could not be isolated or identified by NMR-spectroscopy.

Similarly 2-(3-butynylthio)pyrimidine **1c**, prepared from 2-mercaptopyrimidine and 4-iodobutyne in moderate yield, and 2-(3-butynylthio)-5-nitropyrimidine **1d**, prepared from S-3-butynylthiourea hydroiodide and sodium nitromalonaldehyde in low yield, gave the corresponding 2,3-dihydrothieno [2,3-b]pyridines **3c** and **3d** by heating them in refluxing nitrobenzene for 18 hours.



1 2 3

a. R = H ; X = O
b. R = NO_2 ; X = O
c. R = H ; X = S
d. R = NO_2 ; X = S
e. R = H ; X = NC(O)CH_3
f. R = NO_2 ; X = NC(O)CH_3

Heating of the 2-(3-butynylamino)pyrimidines **1** (X=NH, R=H and R=NO_2) prepared in good yields from the corresponding 2-chloropyrimidines and 4-aminobutyne, in refluxing nitrobenzene for 36 hours only led to decomposition and no indication for the formation of 1H-2,3-dihydropyrrolo[2,3-b]pyridines **3** (X=NH) could be detected. However, interestingly when the NH group was acetylated the 2-(N-acetyl-3-butynylamino)pyrimidines **1e** and **1f** underwent an intramolecular Diels-Alder reaction in high yield within 12 hours at 180°C resulting in the 1-acetyl-2,3-dihydropyrrolo[2,3-b]pyridines **3e** and **3f**.

Our experiments indicate that increase of the electron deficiency of the pyrimidine by introduction of the strong electron withdrawing nitrogroup at the 5 position has little or no effect on the rate of the cycloaddition. Possibly, due to steric hindrance, this activating effect of the nitrogroup is counterbalanced. However, the rate of reaction is strongly influenced when changing the heteroatom in the dienophilic side-chain. Our preliminary experiments indicate that the reactivity is increased in the series X=NH < X=O < X=S < X=NC(O)CH_3.

Some characteristic analytical and spectroscopic data for the compounds **3** are listed in the Table. The structure of all new compounds was confirmed by their ^{1}H-NMR spectra and by microanalytical data.

We also investigated one pyrimidine derivative with a dienophilic side-chain in the 5 position. Thus, treating bis-(2-phenylpyrimidyl-5)disulfide[6] with triethylamine and sodiumdithionite followed by reaction with 4-iodobutyne gave 5-(3-butynylthio)-2-phenylpyrimidine **4** in excellent yield. Heating of **4** for 12 hours at 180°C in nitrobenzene gave 2,3-dihydro-5-phenylthieno[2,3-c]pyridine **5** in 85% yield (mp.: 82-83°C; ^{1}H NMR [$CDCl_3$]: *δ 3.30, H-4 and H-5; 7.49, H-5; 8.48, H-7*).

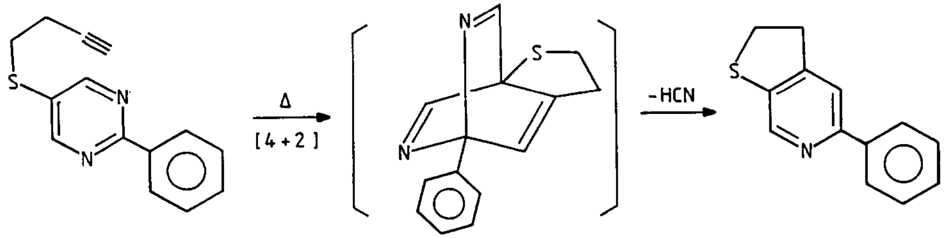
Table

Compound	mp(°C)[a]	yield(%)	^{1}H-NMR-data (90 MHz); δ (ppm)/TMS; $CDCl_3$[b] H-2	H-3	H-4	H-5	H-6	CH_3
3a[5]	oil	52	4.60	3.23	7.47	6.76	7.96	
3b	161-3	55	4.82	3.36	8.25	-	8.97	
3c[2d]	oil	57	3.32		7.33	6.87	8.18	
3d	131-2	75	3.49		8.07	-	9.02	
3e	123-4	85	4.10	3.04	7.45	6.86	8.12	2.67
3f	186	87	4.22	3.17	8.20	-	9.03	2.69

(a) All solids were recrystalized from hexane/toluene.

(b) J_{4-5} = 7.2-7.8 Hz; J_{5-6} = 4.5-5.0 Hz.

Further studies on the intramolecular Diels-Alder reactions of pyrimidines with a dienophilic side-chain are currently being conducted. Results will be reported independently.



4 **5**

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