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FURTHER INTRAMOLECULAR DIELS-ALDER REACTIONS OF 1,2,4-TRIAZINES. SYNTHESIS OF DIHYDROPYRROLO[2,3-b]PYRIDINES

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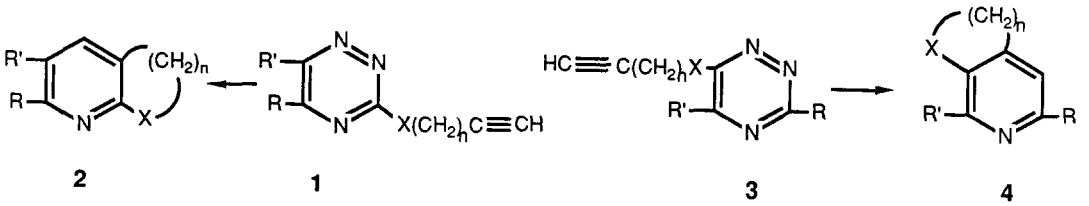
Summary: *3-(3-Butynylamino)-1,2,4-triazines undergo intramolecular Diels-Alder reactions to yield 2,3-dihydropyrrolo[2,3-b]pyridines.*

Inverse electron-demand Diels-Alder reactions of 1,2,4-triazines, where the dienophile is present in a sidechain tethered to the azadiene, can proceed with remarkable facility, leading to a variety of condensed pyridines (Scheme 1). Several recent publications from our laboratory have served to illustrate this concept.



Scheme 1

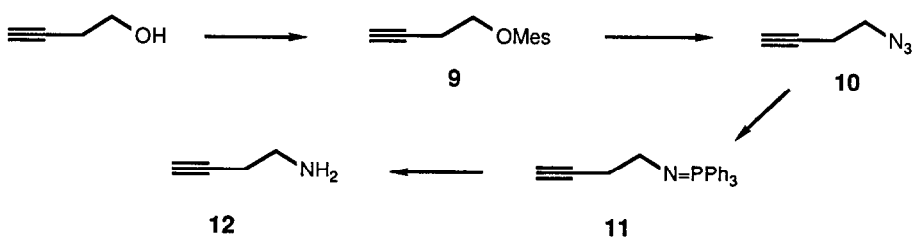
Thus, thieno[2,3-b]pyridines (**2**, X = S, n = 2) and thieno[2,3-c]pyridines (**4**, X = S, n = 2) are easily obtained from 3-(3-butynylthio)- and 6-(3-butynylthio)-1,2,4-triazines respectively (**1**, **3**, X = S, n = 2).[1] Dihydrofuro[2,3-b]pyridines (**2**, X = O, n = 2) are obtained from 3-(3-butynyloxy)-1,2,4-triazines (**1**, X = O, n = 2), and dihydropyrano[2,3-b]pyridines (**2**, X = O, n = 3) are readily obtained from the corresponding monocyclic homologs (**2**, X = O, n = 3).[2] 5,6,7,8-Tetrahydroquinolines (**2**, X = CR_2, n = 3), 2,3-cyclopentenopyridines (**2**, X = CR_2, n = 2), and a number of tricyclic condensed pyridines and pyrazines, have also been prepared utilizing this methodology.[3,4] An analogous intramolecular cycloaddition reaction has been

exploited by Boger for a synthesis of indolines from 3-[N-carbomethoxy-N-(3-pentynyl)amino]pyridazines.[5] We now describe a further exploitation of this concept for the preparation of 2,3-dihydropyrrolo[2,3-b]pyridines (**2**, X = NH, n = 2).

Condensation of 1,2-dicarbonyl compounds with S-methylthiosemicarbazide smoothly provided the 3-methylthio-1,2,4-triazines **5**, which were subsequently oxidized with mcpba to the methylsulfones **6**.[2] Nucleophilic displacement of methylsulfinate with 4-amino-1-butyne (**12**) in methylene chloride or DMF afforded the 3-(3-butynylamino)-1,2,4-triazines **7 a-e** (see Table 1). This displacement failed for **6f** (R,R' = CH_3); an analysis of the ^1H NMR (90 MHz) spectrum of the reaction mixture indicated deprotonation of the acidic 5-methyl substituent by the amine **12**, resulting in eventual degradation of the triazine ring. This is not a surprising observation in view of the known susceptibility of 5-methyl-1,2,4-triazines to rapid H-D exchange in basic D_2O.[6]

The aminotriazines **7 a-e** underwent intramolecular cycloaddition in refluxing bromobenzene over a 24-50 hr period to yield the 2,3-dihydropyrrolo[2,3-b]pyridines **8 a-e**. Yields were significantly lower when a substituent was present in the 6-position of the triazine ring. Since cycloaddition occurs across the 3 and 6 positions, this deleterious effect is presumably steric in nature. Only a trace of the 5,6-fused phenanthrene derivative **8e** was obtained, presumably because of further electronic constraints arising from the greater aromatic stability of the precursor triazine **7e**.

4-Amino-1-butyne (**12**) was obtained (see Scheme 2) from 3-butyn-1-ol by conversion to the



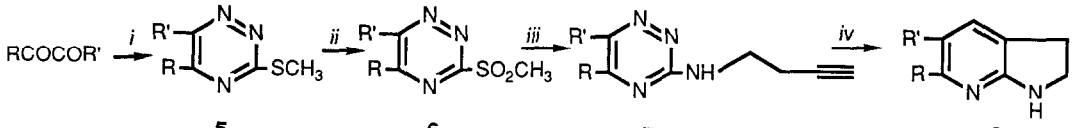
Scheme 2

mesylate **9** with methanesulfonyl chloride/Et_3N, reaction of **9** with NaN_3 in DMF at 60° C to give the azide **10**, and reaction of **10** with triphenylphosphine followed by hydrolysis of the resulting phosphinimine **11** (27% yield

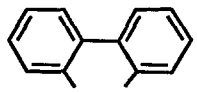
from **9**). In our hands, this method for the preparation of **12** proved to be preferable to an earlier method involving alkylation of sodium acetylide with 1-amino-2-bromoethane.[7]

Aminotriazines are generally poor dienes in inverse electron-demand Diels-Alder reactions because the electron donating amino substituent raises the triazine LUMO in energy relative to the dienophile HOMO, resulting in diminished frontier orbital overlap and a higher barrier of activation. That the described cycloadditions leading to **8 a-e** proceed at all can be attributed to the "entropic assistance" inherent in the intramolecularity of the reaction. The demonstrable versatility of these intramolecular Diels-Alder reactions of 1,2,4-triazines for the preparation of fused pyridines is a powerful stimulus to our continuing synthetic efforts in this area.

TABLE 1. SYNTHESIS OF DIHYDROPYRROLO[2,3-b]PYRIDINES



5 **6** **7** **8**

Cmpd #	R	R'	Yield, %	
a	H	H	64	51,73[v]
b	C_6H_5	H	80	44
c	4-ClC_6H_4	H (see ref. 2)	69	61
d	C_6H_5	C_6H_5	97	20
e			81	trace
f	CH_3	CH_3	0	-

i) $H_2NNHC(SCH_3)=NH_2^+ I^-$ *ii*) mcpba *iii*) $H_2NCH_2CH_2C\equiv CH$ *iv*) 156 °C, 24-50 hr *v*) 132 °C, 6 days

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