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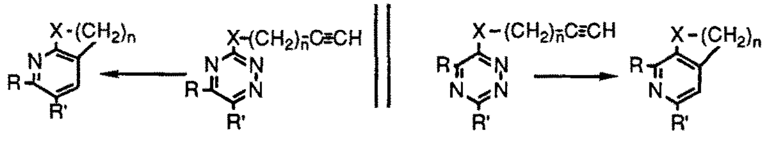
FURTHER INTRAMOLECULAR REACTIONS OF 1,2,4-TRIAZINES. SYNTHESIS OF FURO[2,3-b]PYRIDINES AND DIHYDROPYRANO[2,3-b]PYRIDINES

Edward C. Taylor* and John E. Macor
Department of Chemistry, Princeton University, Princeton, N.J. 08544

Summary: 3-(3-Butynyloxy)- and 3-(4-pentnyloxy)-1,2,4-triazines undergo facile intramolecular Diels-Alder reactions to yield 2,3-dihydrofuro(2,3-b)pyridines and dihydropyrano(2,3-b)-pyridines respectively. The former are readily dehydrogenated with DDQ to furo(2,3-b)pyridines.

Inverse electron demand Diels-Alder reactions of heterocyclic azadienes with electron-rich dienophiles have received considerable recent attention as flexible synthetic approaches to a variety of heterocyclic systems.[1] Intramolecular versions of these reactions, although much less intensively investigated until recently, sometimes proceed with exceptional ease. Recent publications from our laboratory have described facile syntheses of thieno[2,3-c]pyridines and thieno[2,3-b]pyridines from 6-(3-butynylthio)- and 3-(3-butynylthio)-1,2,4-triazines respectively (Scheme 1, X = S, n = 2).[2] A recent paper by Seitz and co-workers dealing with an extension of this methodology to the preparation of dihydrofuro[2,3-b]pyridines[3] prompts us to further describe our preliminary results in this area.[4]



Scheme 1

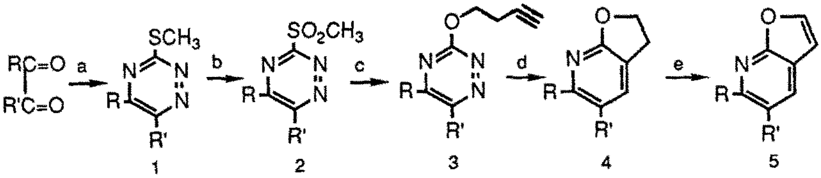
The 3-methylthio-1,2,4-triazines 1, conveniently prepared from 1,2-dicarbonyl compounds and S-methylthiosemicarbazide,[5] were efficiently oxidized with mcpba to the methylsulfones 2. Condensation of these extremely reactive intermediates with the sodium salt of 4-hydroxy-1-butyne at r.t. in anhydrous THF or CH_2Cl_2 led smoothly to the 3-(3-butynyloxy)-1,2,4-triazines 3. These compounds underwent intramolecular cycloaddition in refluxing chlorobenzene overnight to give a series of 2,3-dihydrofuro[2,3-b]pyridines (4). Of particular interest is the conversion of the 5,6-fused phenanthrene derivative 3e to 4e, since the cycloaddition reaction involves disruption of a fused benzene ring, and is the first example to our knowledge of the involvement of a 5,6-fused 1,2,4-triazine in an intramolecular Diels-Alder reaction.

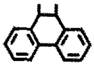
With the exception of the parent member of the series 4a, all of these dihydro compounds were smoothly dehydrogenated to the fully aromatic furo[2,3-b]pyridines 5 with excess DDQ in refluxing dioxane.

Nucleophilic displacement of methylsulfinate from 2a,c-e with the sodium salt of 5-hydroxy-1-pentyne, again at r.t. in anhydrous THF, afforded the homologous 3-(4-pentynyloxy)-1,2,4-triazines 6, which cyclized to the dihydropyrano[2,3-b]pyridines 7 in refluxing bromobenzene over a period of 2-3 days, or in triisopropylbenzene at 200°C in approximately 5 hours. Reduced "entropic assistance" in this intramolecular cycloaddition reaction, a consequence of the greater flexibility of the extended dienophilic sidechain, is probably responsible for the need for more drastic cyclization conditions.[6] Tables 1 and 2 summarize our results in the above series of condensed pyridines.

It is clear from our studies thus far that intramolecular Diels-Alder reactions of 1,2,4-triazines substituted with an appropriate dienophilic sidechain should provide ready access to a broad variety of condensed pyridine systems. We are currently exploring further synthetic applications of this intriguing concept (Scheme 1).

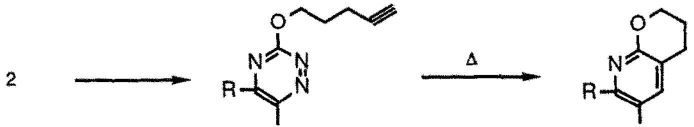
Table 1. Synthesis of Furo[2,3-b]pyridines



#	R	R'	Yield, %				
a	H	H	89	90	86	96	0
b	CH_3	CH_3	86	98	45	100	49
c	C_6H_5	H	81	71	67	95	63
d	$4\text{-}ClC_6H_4$	H	93	85	78	90	72
e			84	95	89	69	67

a) $H_2NNHC(SCH_3)=NH_2{}^+I^-$ b) mcpba c) $Na^+{}^-OCH_2CH_2C{\equiv}CH$ d) 132°, 12-50 hr e) DDQ, 2 eq

Table 2. Synthesis of Dihydropyrano[2,3-b]pyridines



Cmpd.	Yield, %		Time (hr), Temp.
	6	7	
a	41	61	5, 200°C
c	52	80	5, 210°C
d	78	68	48, 156°C
e	79	20	22, 200°C

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