

CYCLIZATIONS OF 1,2,4-TRIAZINIUM SALTS WITH BIFUNCTIONAL  
NUCLEOPHILES - A NEW ROUTE TO CONDENSED 1,2,4-TRIAZINES <sup>1</sup>

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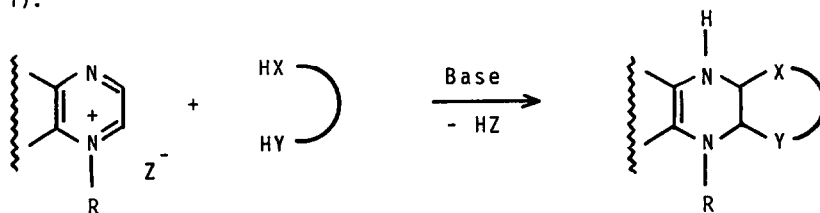
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**Summary:** The reaction of 1,2,4-triazinium salts with amides of acetoacetic acid yielding 1,4,4a,5,7,7a-hexahydro-6H-pyrrolo[3,2-e]-1,2,4-triazin-6-ones exemplifies the first direct annelation to the 1,2,4-triazine ring based on the diaddition of bifunctional nucleophiles at C-5 and C-6.

In previous papers of this series we reported that cyclizations of N-alkyl substituted pyrazinium, quinoxalinium, pyrido[2,3-b]pyrazinium and pteridinium salts with 1,3- and 1,4-bifunctional nucleophiles enabled us to obtain a large variety of novel heterocyclic compounds in which the tetrahydropyrazine ring is fused with a five- or six-membered heterocycle (Scheme 1).<sup>2</sup>

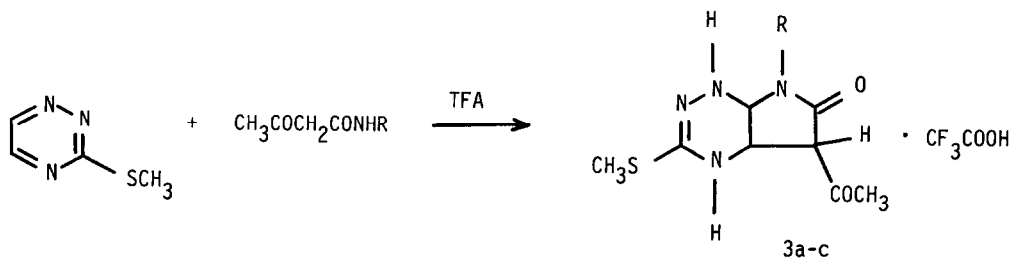
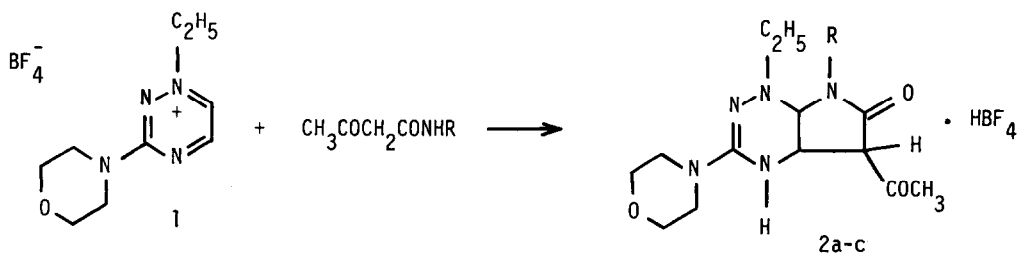


Scheme 1

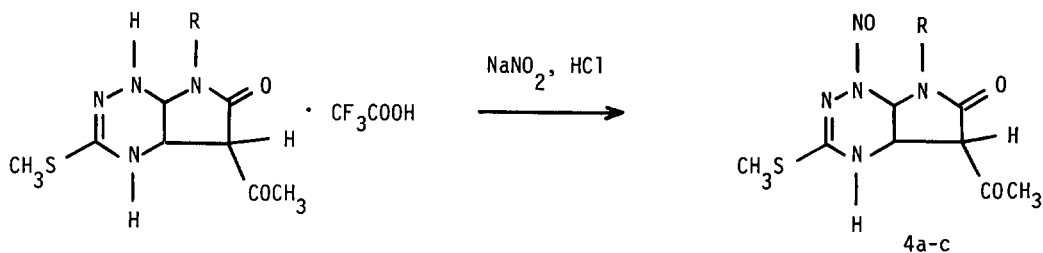
1,2,4-Triazines can be regarded as 2-aza analogues of 1,4-diazines. However, no examples of cyclizations based on the diaddition of bifunctional nucleophiles at C-5 and C-6 of the 1,2,4-triazine ring have so far been reported in the literature.<sup>3</sup> In this communication we show that reactions of 1,2,4-triazinium cations with bifunctional nucleophilic reagents can be successfully applied to the synthesis of condensed 1,2,4-triazines.

It has been found that 1,4,4a,5,7,7a-hexahydro-6H-pyrrolo[3,2-e]-1,2,4-triazin-6-ones 2a-c are formed when 3-morpholino-1-ethyl-1,2,4-triazinium borofluoride (1) reacts with N-substituted amides of acetoacetic acid in ethanolic solution (Scheme 2, Table 1).

Activation of 3-methylthio-1,2,4-triazine by protonation with trifluoroacetic acid (TFA) also makes it capable of reacting with amides of acetoacetic acid in a chloroform solution to produce cycloadducts 3a-c analogous to those obtained from the 1-ethyl-1,2,4-triazinium salt 1 (Scheme 3, Table 1).



Condensed triazines 2 and 3 are quite stable in acidic solutions and are isolated as crystalline hydroborofluorides 2 and trifluoroacetates 3 (Table 1), but all attempts to obtain these compounds as free bases have failed. However, when treated with sodium nitrite in dilute hydrochloric acid pyrrolo[3,2-e]-1,2,4-triazines 3 are smoothly converted into their 1-nitroso derivatives 4 which are stable as neutral species (Scheme 4, Table 1).



Evidence for the structures 2-4 is provided by the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy data (Tables 1 and 2). Regio-orientation of the pyrrole ring in 1-alkyl substituted pyrrolo[3,2-e]-1,2,4-triazines 2a-c is apparent from chemical shifts and splitting patterns of the H-4a and H-7a in the proton NMR spectra (Table 1). The doublet of H-7a is at a lower field than that of H-4a which appears as a multiplet due to spin-spin couplings with H-5, H-7a and H-4 (NH) protons (Table 1). A similar picture is observed for pyrrolo-triazines 3a-c (Table 1). Nitrosation of compounds 3a-c causes the signal of H-7a to shift approximately 1.3 ppm downfield for the N-nitroso derivatives 4a-c indicating that N-1 is the site of nitrosation (Table 1). Indeed, the x-ray diffraction study performed on 5-acetyl-3-methylthio-1-nitroso-7-(p-tolyl)-1,4,4a,5,7,7a-hexahydro-6H-pyrrolo[3,2-e]-1,2,4-triazin-6-one (4b)<sup>4</sup> provides

TABLE 1 Melting points, yields and  $^1\text{H}$  NMR data for compounds 2-4

Compound*	R	M.p., °C (decomp.)	Yield, %	$^1\text{H}$ NMR data in DMSO- $d_6$				
				$\delta$ , ppm			$^3\text{J}$ (H,H), Hz	
				H-5	H-4a	H-7a	J(5,4a)	J(4a,7a)
2a	$\text{C}_6\text{H}_5$	181-185	64	4.26	4.75	5.80	2.9	8.3
2b	$\text{C}_6\text{H}_4\text{-CH}_3$ (p)	189-190	95	4.27	4.72	5.72	2.9	7.9
2c	$\text{C}_6\text{H}_5\text{-CH}_2$	198-202	72	4.10	4.76	4.53	2.9	7.6
3a	$\text{C}_6\text{H}_5$	132-135	68	4.15	4.57	5.48	4.4	5.9
3b	$\text{C}_6\text{H}_4\text{-CH}_3$ (p)	132-135	57	4.12	4.55	5.41	4.4	5.7
3c	$\text{C}_6\text{H}_4\text{-OH}$ (o)	122-124	33	4.05	4.56	5.35	2.6	5.9
4a	$\text{C}_6\text{H}_5$	159-162	85	3.99	4.82	6.80	-	5.4
4b	$\text{C}_6\text{H}_4\text{-CH}_3$ (p)	154-157	93	3.99	4.80	6.77	-	5.4
4c	$\text{C}_6\text{H}_4\text{-OH}$ (o)	152-154	75	3.93	4.82	-**	-	5.8

\* All new compounds gave satisfactory elemental analyses.

\*\* The signal is overlapped by the multiplet of aromatic protons.

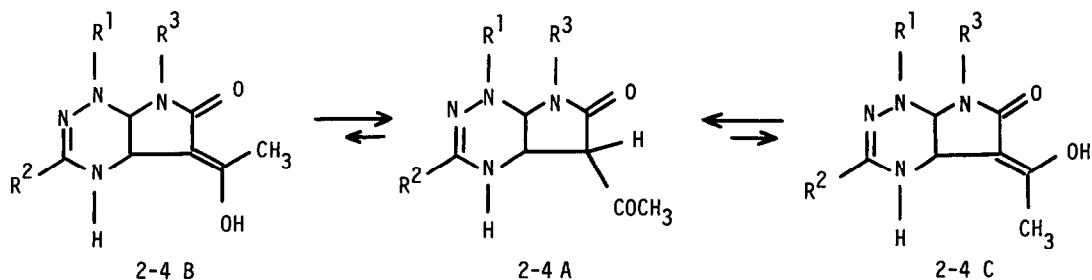
TABLE 2 The  $^{13}\text{C}$  NMR data for pyrrolo[3,2-e]-1,2,4-triazines 2-4 in DMSO- $d_6$ 

Compound	$\delta$ , ppm			One-bond coupling constants, $^1\text{J}(\text{C,H})$ , Hz		
	C-5	C-4a	C-7a	$^1\text{J}(\text{C-5, H-5})$	$^1\text{J}(\text{C-4a, H-4a})$	$^1\text{J}(\text{C-7a, H-7a})$
2a	63.7	45.0	76.1	138	-*	155
2c	63.5	42.7	73.8	140	-*	159
3a	62.3	49.4	67.9	140	159	165
3b	62.3	49.8	68.4	139	158	165
4a	63.3	50.3	70.6	142	161	169
4b	63.6	50.6	71.1	142	163	168

\* The coupling constant can not be measured because of absorption of the solvent.

convincing arguments for the structure 4, thus fully supporting conclusions made on the basis of the proton and carbon-13 NMR data (Tables 1 and 2).

Compounds 2-4 exhibit tautomeric equilibria. A detailed analysis of the proton NMR spectra of pyrrolo-triazines 2-4 in DMF at temperatures from  $-50$  to  $40^\circ\text{C}$  has shown that two enolic forms, B and C, coexist as minor tautomers together with the dominant keto form A (Scheme 5). Spectral features of minor tautomers B and C will be discussed in a subsequent paper. As far as the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral parameters for the keto forms A of compounds 2-4



Scheme 5

are concerned (Tables 1 and 2) they are very similar to those of hexahydropyrrolo[2,3-b]pyrazin-2-ones and other related heterocyclic systems.<sup>5</sup>

The reaction discovered is the first example of the ortho-cyclization on the 1,2,4-triazine ring based on the diaddition of dinucleophiles. It can apparently be applied to the synthesis of new types of condensed 1,2,4-triazines by using bifunctional nucleophilic reagents of different nature.<sup>6</sup> Investigation of the scope of this reaction is in progress now.

#### REFERENCES AND NOTES

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- a) V.N. Charushin, A.I. Chernyshev, N.N. Sorokin and O.N. Chupakhin, *Org. Magn. Reson.*, 22, 775 (1984). b) V.N. Charushin, N.N. Sorokin, A.I. Chernyshev, V.G. Baklykov, M.G. Ponyzovskii and O.N. Chupakhin, *Magn. Reson. Chem.*, 24, 777 (1986).
- Typical experimental procedures. 1-Ethyl-3-morpholino-1,2,4-triazinium borofluoride (1, 500 mg, 1.77 mmol) and the appropriate amide of acetoacetic acid (1.77 mmol) were dissolved under heating in 3 ml of ethanol, and the reaction mixture was kept at room temperature for 50 hours. A precipitate of 2 was obtained which was filtered off and recrystallized from the mixture of ethanol and water 3:1 (Tables 1 and 2).  
The same procedure was used to convert 3-methylthio-1,2,4-triazine into pyrrolo-triazines 3a-c, however in this case the reaction was carried out in a chloroform solution in the presence of TFA (1 eqv.).  
Nitrosation. Compound 3 (2.4 mmol) was dissolved in 5 ml of 2N HCl, cooled to 5 °C and treated with a solution of sodium nitrite (0.33 g, 4.78 mmol) in water (2.4 ml). The mixture was stirred for 15 min at 5 °C, the solid was collected and recrystallized from ethanol (Tables 1 and 2).  
For numerous examples of reactions between 1,4-diazinium cations and dinucleophiles see reviews.<sup>2</sup>

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