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Activated Nitriles in Heterocyclic Synthesis. Synthesis of Pyrimidine Derivatives

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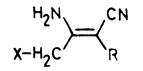
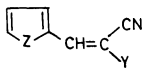
Synthesis of polyfunctional pyrimidine derivatives via the reaction of acrylonitrile derivatives **1a** and **b** with α,β-unsaturated nitriles **2a—f** has been reported.

Studies on α,β-unsaturated nitriles have revealed that these easily obtained reagents are excellent starting materials for the synthesis of polyfunctionally substituted heterocycles.[1-3] Previously our group reported the use of compounds **1a**, **b**, and **2a—f** for the

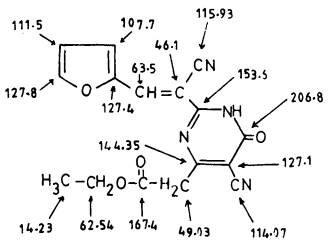


1a. R=X=$CO_2C_2H_5$
b. R=CN; X=$CO_2C_2H_5$
c. R=X=CN



2a. Z=O; Y=CN
b. Z=O; Y=$CO_2C_2H_5$
c. Z=O; Y=COPh
d. Z=S; Y=CN
e. Z=S; Y=$CO_2C_2H_5$
f. Z=S; Y=COPh

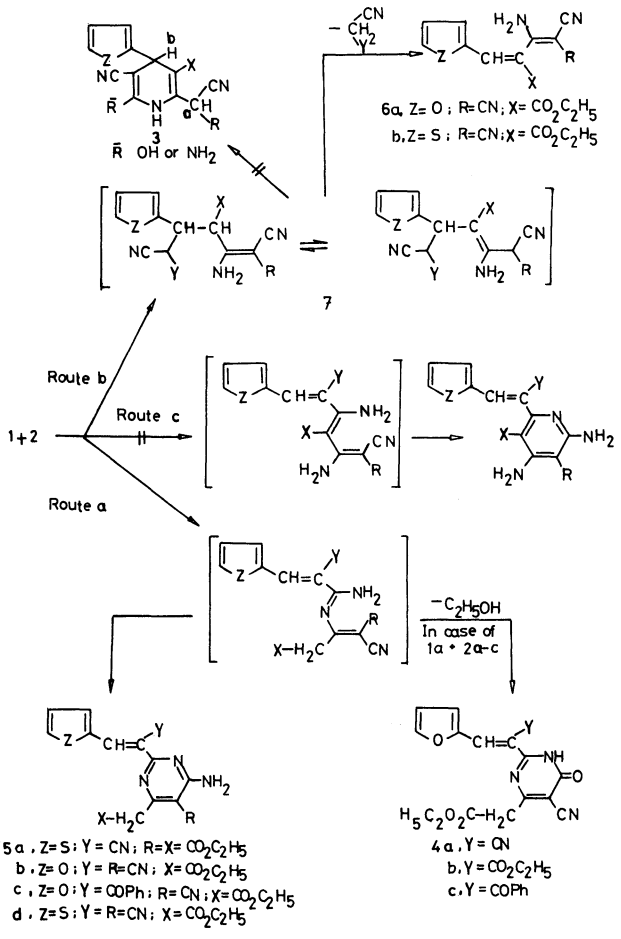
synthesis of pyrazoles,[4] pyranopyrazoles,[5] isoxazoles,[6] fused isoxazoles, pyridazines, and pyridine derivatives.[4] In continuation of this work, we report here the results of our investigations on the reactions of **1a** and **b** with **2a—f**. We found that **1a** reacts with **2a** to yield a product of molecular formula $C_{16}H_{12}N_4O_4$ (M^+=324, *m/z*). The ^{1}H NMR spectrum revealed that the reaction product cannot be the dihydropyridine **3**, which would be expected to be formed via a sequence similar to that suggested recently in literature.[7] High resolution ^{1}H NMR spectroscopy revealed signals for an ester function at δ 1.21 (t, 3H, CH_3) and at δ 4.33 (q, 2H, CH_2), as well as signals for furyl protons at δ 8.29, 7.82, and 6.46. In addition, a two-proton signals at δ 4.1 and a one-proton signal at δ 6.17 were observed. The signal at 4.1, overlapping in the 90 MHz ^{1}H NMR spectrum with the methylene signal, was shown to be due to two noncoupled magnetically equivalent protons and did not disappear on D_2O exchange. Hence, it cannot be assigned to the protons a and b in the dihydropyridine form **3**. The ^{13}C NMR spectrum confirms that the product has the pyrimidinone structure **4a** as it revealed C-4 at δ 206. If the product was the dihydropyridine **3**, extra sp^3 carbons should have been observed.



4a

Similarly, compound **1a** reacted with **2b** and **c** to yield the pyrimidinone derivatives **4b** and **c**. The formation of compounds **4a—c** in this reaction is assumed to proceed via addition of the amino function of **1a** to the cyano group in **2a—c** with elimination of ethanol (see Scheme 1). The structure of **4b** and **c** were well-documented by IR and ^{1}H NMR spectroscopy.

In contrast, compound **2d** reacted with **1a** to yield 1:1 adduct. The pyrimidine structure **5a** was formulated for the reaction product based on IR and ^{1}H NMR. Attempts at addition of **2e** and **f** to **1a** under



Scheme 1.

the same experimental conditions were unsuccessful. The reactants were recovered almost unchanged after reflux in ethanolic piperidine solution.

Compound **1b** reacted with **2a**, **c**, and **d** to yield 1 : 1 adducts which can be formulated as either the dihydropyridine **3** or as the pyrimidines **5b—d**. The establishment of a pyrimidine structure for the reaction products was based on spectral data which, in each case, revealed the presence of a signal for a CH_2 group. Such a signal cannot be assigned to alternative structures. On the other hand, attempted addition of **1b** to **2b** gave the furfurylidene derivative **6a** which could also be obtained from the reaction of **1b** with furfural. The formation of **6a** is assumed to proceed via the intermediacy of the Michael adduct **7**, which then loses ethyl cyanoacetate to yield the final isolated product. Similar ylidene formation on addition of α,β-unsaturated nitriles to active methylene reagents has been observed by us in several reactions.[8,9] In the same way, compound **1b** reacted with **2f** to yield the thenylidene derivative **6b**. The possible formation of **6** via a retro-aldol reaction of **2** affording an aldehyde which condenses with **1** cannot be completely excluded. In contrast to the observed formation of **6a** and **b** compound **1d** did not react with **2e**. The formation of pyrimidines from the reaction of **1a** and **b** with **2a—f** finds a parallel with the Frankland and Kolbe synthesis of pyrimidines.[10]

The results obtained in our investigation clearly reveal that the reaction of **1** with **2** proceeds via three different routes: i) Addition of the amino function to the cyano group and cyclization to yield pyrimidines

Table 1. Products from the Reactions of Compounds **1a** and **b** with the Nitriles **2a—f**

Compd	Crystallization solvent	Mp θ_m/°C	Yield/%	Mol form (Mol wt)	Analysis/% Found (Calcd)			
					C	H	N	S
4a	Ethanol-water	205	80	$C_{16}H_{12}N_4O_4$ (324)	59.2 (58.7	3.7 4.0	17.3 17.0)	
4b	Methanol-water	112	82	$C_{18}H_{17}N_3O_6$ (371)	58.2 (58.2	4.6 5.0	11.3 11.3)	
4c	Ethanol-water	110	77	$C_{22}H_{17}N_3O_5$ (403)	65.5 (65.8	4.2 4.3	10.4 10.2)	
5a	Ethanol	204	78	$C_{18}H_{18}N_4O_4S$ (386)	56.0 (56.0	4.7 5.0	14.5 14.3	8.2 8.5)
5b	Ethanol-water	230	70	$C_{16}H_{13}N_5O_3$ (323)	59.4 (59.4	4.0 4.0	21.7 21.8)	
5c	Ethanol-water	185	83	$C_{22}H_{18}N_4O_4$ (402)	65.7 (65.8	4.5 4.7	13.9 13.6)	
5d	Ethanol-water	>250	72	$C_{16}H_{13}N_5O_2S$ (339)	56.6 (56.7	3.8 3.5	20.6 20.5	9.4 9.3)
6a	Ethanol-water	90	75	$C_{13}H_{11}N_3O_3$ (257)	60.7 (61.0	4.3 4.5	16.3 16.2)	
6b	Ethanol	>250	76	$C_{13}H_{11}N_3O_2S$ (273)	57.1 (57.0	4.0 4.0	15.4 15.4	11.7 11.8)

Table 2. Selected IR and Complete ^{1}H NMR Data for the Compounds Listed in Table 1

Compd	ν_{max}/cm^{-1}	δ_H
4a	2900, 2970 (CH and CH_3); 2180, 2200 (CN groups); 1715 (CO)	1.2 (t, 3H, CH_3); 3.1 (OH and DOH); 4.1—4.4 (m, 4H, $2CH_2$); 6.7 (s, 1H, ylidene CH); 7.4—8.3 (m, $3H_{furan}$)
4b	2950 (CH and CH_3); 2200 (CN); 1730 (br., CO groups)	1.2, 1.22 (two triplets, 6H, $2CH_3$); 3.3 (OH and DOH); 4.18 (m, 6H, $3CH_2$); 6.3 (s, 1H, ylidene CH); 7.3—8.2 (m, $3H_{furan}$)
4c	2900, 2960 (CH and CH_3); 2200 (CN); 1675, 1730 (CO groups)	1.2 (t, 3H, CH_3); 3.3 (OH and DOH); 4.16 (q, 2H, CH_2); 4.2 (s, 2H, CH_2); 7.0—8.2 (m, 9H, aromatic and ylidene protons)
5a	3200, 3300 (NH_2); 2900 (CH_3); 2200 (CN) and 1630 (CO)	Insoluble in available ^{1}H NMR solvents
5b	3200, 3300 (NH_2); 2900 (CH_3); 2180, 2200 (CN groups) and 1640 (CO)	1.2 (t, 3H, CH_3); 3.3 (br., 2H, NH_2); 4.1 (br, 4H, $2CH_2$); 6.8 (s, 1H, ylidene CH); 7.2—8.2 (m, $3H_{furan}$)
5c	3200, 3350 (NH_2); 2900 (CH_3); 2200 (CN)	Insoluble in available ^{1}H NMR solvents
5d	3050, 3200, 3300 (NH_2); 2150, 2200 (CN groups) and 1640 (CO)	1.3 (t, 3H, CH_3); 3.7 (br., 2H, NH_2); 4.2 (m, 4H, $2CH_2$); 6.7 (s, 1H, ylidene CH); 7.2—8.3 (m, $3H_{furan}$)
6a	3200, 3350 (NH_2); 2900, 2950 (CH and CH_3); 2190, 2200 (CN groups); 1715 (CO)	1.3 (t, 3H, CH_3); 3.6 (br., 2H, NH_2); 4.3 (q, 2H, CH_2); 6.65 (s, 1H, ylidene CH); 7.3—8.2 (m, $3H_{furan}$)
6b	3350, 3450 (NH_2); 2900 (CH); 2180, 2200 (CN groups); 1630 (CO)	Insoluble in available ^{1}H NMR solvents

(route a), ii) Michael addition to the activated double bond of **2** to afford the Michael adducts **7** (route b) (in our hands these adducts usually lose active methylene moiety affording the corresponding ylidene derivatives; cyclization of the Michael adducts into dihydropyridines followed by oxidation into pyridines, as has been reported in the literature,[7] could not be observed), or iii) addition of active methylene to the cyano group and cyclization which may afford the pyridine derivative **8** (route c). This route, which has been recently reported[11] for the reaction of **1a** and **b** with trichloroacetonitrile, did not also take place. The predominance of any of these routes is determined by relative activities of the ylidenic bond, the cyano group and also by the energy of the transition states leading to the end products. In complex systems like those we are dealing with it is very difficult to predect the predominant reaction path. The predominance of route a in our case can be attributed to a decrease in the reactivity of the double bond in **2** being counterbalanced by the effect of the electron-rich heterocycles.

This work shows again that the reaction of α,β-unsaturated nitriles with active methylene reagents do not necessarily follow the simple pattern of Michael addition and cyclization. Alternative structures should always be considered and strong arguments should be introduced when assigning structures to the products of these reactions.

Experimental

All melting points are uncorrected. IR spectrum were recorded (potassium bromide) on a Shimadzu-408 spectrophotometer. ^{1}H NMR were measured in a mixture of chloroform-*d* and methanol-d_4 on a Varian EM-390 spectrophotometer at 90 MHz with TMS as internal reference and chemical shifts are expressed as δ. Microanalytical data (C,H,N,S) were obtained from the Microanalytical Data Unit at Cairo University.

Condensation of Compounds 1a and b with Nitriles 2a—f. General Procedure: A suspension of compound **1a** or **b** (0.01 mol) and the appropriate nitrile **2a—f** (0.01 mol) in ethanol (50 ml) was treated with piperidine (1.0 ml). The reaction mixture was heated under reflux for four hours and then the mixture was evaporated in vacuo. The solid product, so formed, was collected by filtration and recrystallized from the appropriate solvent (see Table 1).

Condensation of 1b with Furfural: Furfural (0.01 mol) was added to a solution of compound **1b** (0.01 mol) in ethanol (50 ml) in the presence of piperidine (1.0 ml). The reaction mixture was heated under reflux for 4h and then evaporated in vacuo. The solid product, so formed, was collected by filtration and recrystallized from an ethanol-water mixture. The product was identical with compound **6a**.

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