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Note

Nitriles in heterocyclic synthesis: Synthesis of new ethyl substituted polyfunctional hetero-aromatics

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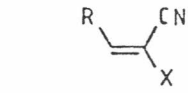
Several new pyran, pyridine, quinoline and isoquinoline derivatives have been prepared by treatment of aldehydes with compounds having active methylene or active hydrogen functions in basic media. The synthetic potential of the method has been investigated.

α, β-Unsaturated nitriles have been extensively utilized in the synthesis of heterocyclic compounds[1]. We have been extensively investigating the synthetic potentialities of α-functionally substituted cinnamonitriles **1a-c**[2-4] to produce a variety of new heterocyclic compounds. Although compounds **1d,e** are expected to react similarly, but some difficulties are encountered in attempted preparations of such compounds. Recently, Elnagdi *et al.*[5] have reported that a mixture of acetaldehyde and formaldehyde both containing an active methylene function can act as synthetic equivalents for methylidenemalononitrile and ethylidenemalononitrile. In the present note we report results of our investigation with a view to extending this approach for the *in situ* synthesis of **1d,e**. Equimolecular amounts of propionaldehtyde **2** and malononitrile **3** reacted readily with cyanothioacetamide **4** to yield the pyridinethione **5** in a good yield. Compound **5** is assumed to be formed through the addition of **3** to the *in situ* formed **1e** to yield Michael adduct which then cyclizes and aromatizes to **5** (Scheme I).

Similarly, ethyl acetoacetate reacted with a mixture of compounds **2** and **3**, for 3 hr to yield the Michael adduct which spontaneously cyclized to yield the pyran derivative **6**, the structure of which was established on the basis of ^{1}H NMR spectrum exhibiting, besides the usual signals, two singlets at δ5.95 and 6.04. The former was a deuterium oxide exchangeable signal due to the amino group protons, while the latter was due to the pyran 4-H proton. On the other hand, carrying



1a, R = C_6H_5 ; X = CN
b, R = C_6H_4-Cl-p ; X = CN
c, R = C_6H_4-CH_3O-p ; X = CN
d, R = CH_3CH_2 ; X = CN
e, R = CH_3CH_2 ; X = C(=S)-NH_2

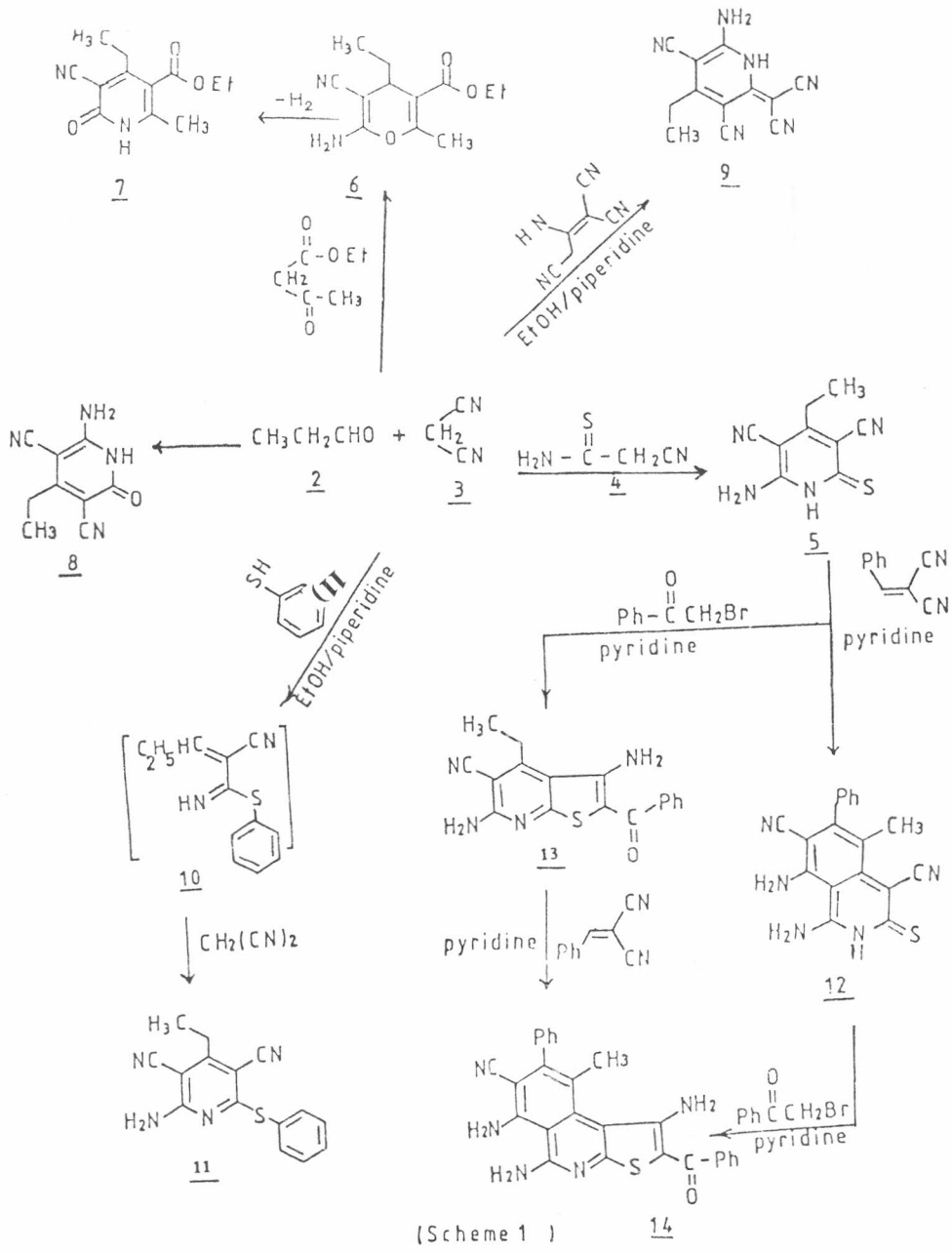
out the above reaction for 8 hr afforded the compound **7** as the only product, as evidenced by TLC. The pyridine structure **7** was established on the basis of ^{1}H NMR spectrum which did not reveal the presence of any signals due to the amino or the pyran 4-H protons (which appeared as a triplet due to CH_2 group). The formation of compound **7** is assumed to proceed via the formation of **6** which underwent rearrangement to the thermodynamically more stable pyridine derivative **7**. Compound **7** could also be obtained by refluxing compound **6** in pyridine for 6 hr.

A mixture of one mole of **2** with two moles of **3** reacted in refluxing aqueous pyridine to yield **8** via the formation of Michael adduct followed by its hydrolysis, aromatization and cyclization to **8**. Although arylidenemalononitrile has been reported to react with malononitrile in the presence of alkoxide ions[8], to yield 2-alkoxypyridines, the formation of pyrimidones in a way similar to that observed by us has not been reported earlier. The IR spectrum of **8** revealed that it exists in the keto-form (ν_{max} at 1660 cm^{-1} for C=O) rather than a potential hydroxy-form (enol-form).

The reaction of **2** and **3** with 2-amino-1-propane-1, 1, 3-tricarbonitrile gave **9**. Structure **9** was derived from ^{1}H NMR spectrum which exhibited a singlet at δ2.6 and a broad singlet at 7.2-8.0 for the imino and amino protons, respectively.

A mixture of **2, 3** and thiophenol reacted in ethanol in presence of few drops of piperidine to yield **11**, which is assumed to be formed via the initial addition of thiophenol to the cyano group in **1d** to yield the intermediate adduct **10**. Compound **10** then adds one molecule of malononitrile to yield the final product **11**[9].

Recently Elnagdi *et al.*[10-12] have shown that me-



(Scheme 1)

thyl azinyl carbonitriles are excellent precursors for the preparation of benzoarines. It appeared of interest to find out whether compound **5** with an ethyl group would behave similarly. It has been found that **5** reacts with benzylidene-malononitrile to yield **12**, the structure of which was established by treatment with phenacyl bromide giving **14**. Compound **14** could also be obtained by reacting **5** with phenacyl bromide to afford the compound **13** which on treatment with benzylidenemalononitrile afforded **14**.

Experimental Section

All melting points are uncorrected. IR spectra were recorded in KBr using a PYE-UNICAM SP 1100 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded in DMSO-d_6 on a Varian A-90 spectrometer (chemical shifts in δ, ppm downfield from TMS as internal standard). Elemental analyses were obtained from the Micro-Analytical Center, and Faculty of Pharmacy at Cairo University. Characterization data of various compounds prepared are recorded in Table 1.

2-Amino-4-ethyl-1, 6-dihydro-6-substituted-pyridine-3, 5-di-carbonitriles (5, 8, 9 and 11 and ethyl 2-amino-3-cyano-4-ethyl-6-methyl-4*H*-

Table 1—Characterization of various compounds synthesized

Compd	m.p. °C	Solvent (Yield, %)	Mol. formula	Found (Calc.) (%) C	H	N	S	^{1}H NMR (δ, ppm)
5	> 300	EtOH/DMF (70)	$C_9H_8N_4S$	53.1 (52.9	3.7 3.9	27.7 27.5	15.6 15.7)	1.20(t, 3H, CH_3), 2.72(q, 2H, CH_2), 5.3(s, 2H, NH_2), 7.25(s, 1H, NH)
6	182	Methanol (70)	$C_{12}H_{16}N_2O_3$	61.3 (61.0	6.5 6.7	11.5 11.8	— –)	1.2(m, 6H, $2CH_3$), 1.5(s, 3H, CH_3), 4.2(m, 4H, $2CH_2$), 5.9(s, 2H, NH_2), 6.0(t, 1H, pyran 4-H)
7	> 300	EtOH/DMF (80)	$C_{12}H_{14}N_2O_3$	61.2 (61.53	5.8 6.0	11.7 12.0	— –)	1.1(m, 6H, $2CH_3$); 1.5(s, 3H, CH_3), 3.9(q, 2H, CH_2); 4.1(q, 2H, NH_2); 7.3(s, br, 1H, NH)
8	112	MeOH (75)	$C_9H_8N_4O$	57.0 (57.4	4.4 4.2	30.0 29.9	— –)	1.15(t, 3H, CH_3), 2.7(q, 2H, CH_2), 5.0(s, 2H, NH_2), 7.2(s, 1H, NH)
9	> 300	EtOH/DMF (80)	$C_{12}H_8N_6$	60.7 (60.9	3.5 3.4	35.8 35.6	— –)	1.25(t, 3H, CH_3), 2.65(q, 2H, CH_2), 7.22-8.0(s, br, 3H, NH and NH_2)
11	120	MeOH (75)	$C_{15}H_{12}N_4S$	64.5 (64.2	4.1 4.3	20.3 20.1	11.3 11.4)	1.3(t, 3H, CH_3), 2.82(q, 2H, CH_2), 5.6(s, 2H, NH_2), 7.36-8.0(m, 5H, aromatic protons)
12	220	EtOH/DMF (70)	$C_{18}H_{13}N_5S$	65.3 (65.2	3.8 3.9	21.5 21.2	9.9 9.7)	2.4(s, 3H, CH_3), 3.4(s, 2H, NH_2), 4.8(s, 2H, NH_2) 7.2-7.9(m, 6H, aromatic protons & NH)
13	230	EtOH/DMF (75)	$C_{17}H_{14}N_4OS$	63.1 (63.3	4.5 4.3	17.4 17.4	10.1 9.9)	—
14	190	EtOH/DMF (70)	$C_{26}H_{19}N_5OS$	70.3 (70.1	4.2 4.1	15.1 15.3	6.8 7.0)	1.2(t, 3H, CH_3), 2.70(q, 2H, CH_2), 4.88(s, 2H, NH_2), 7.4-8.1(m, 7H, aromatic protons and NH_2)

pyran-5-carboxylate (6): General procedure. A mixture of malononitrile (0.66 g, 0.01 mole) and propionaldehyde (0.72 g, 0.01 mole) and the appropriate active methylene compound (0.01 mole) in ethanol (50 mL), and few drops of piperidine was refluxed for 3 hr, except for compound **8** which was refluxed in pyridine (30 mL). The reaction mixture was poured into cold water and neutralized with hydrochloric acid. The solid products so formed were filtered and crystallized from appropriate solvents.

Synthesis of compound ethyl 3-cyano-4-ethyl-6-methyl-2-oxo-pyridine-5-carboxylate 7. Method-A. The same procedure as described above was carried out except the reaction period was 8 hr. The product was crystallized from ethanol.

Method-B. Compound **6** (0.01 mole) in 20 mL pyridine was heated under reflux for 6 hr. The mixture was cooled and worked up as described above.

1, 8-Diamino-2, 3-dihydro-5-methyl-6-phenyl-3-thioxo-isoquinoline-4, 7-dicarbonitrile (12). A suspension of benzylidenemalononitrile (1.5 g, 0.01 mole) and **5** (0.01 mole) in pyridine (30 mL) was refluxed for 7 hr. The reaction mixture was poured into cold water and neutralized with hydrochloric acid. The solid product so formed was collected by filtration and crystallized from a proper solvent.

3, 6-Diamino-2-benzoyl-4-ethylthieno[2, 3-*b*]-pyridine-5-carbonitrile (13). As described above for the preparation of **12**, compound **13** could be prepared from the reaction of phenacyl bromide with **5**.

3, 7, 8-Triamino-2-benzoyl-4-methyl-5-phenylthieno[2, 3-*b*]isoquinolin-6-carbonitrile (14). As described above for the preparation of **12**, compound **14** was prepared by the reaction of phenacyl bromide with **12** and also by an alternate route involving the reaction of benzylidenemalononitrile with **13**. Samples of **14**, obtained from

both routes, had the same melting points, elemental analyses and spectral data, (Table I).

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