Substituted Acrylonitriles in Heterocyclic Synthesis. The Reaction of α-Substituted β-(2-Furyl)-acrylonitriles with Some Active-Methylene Heterocycles

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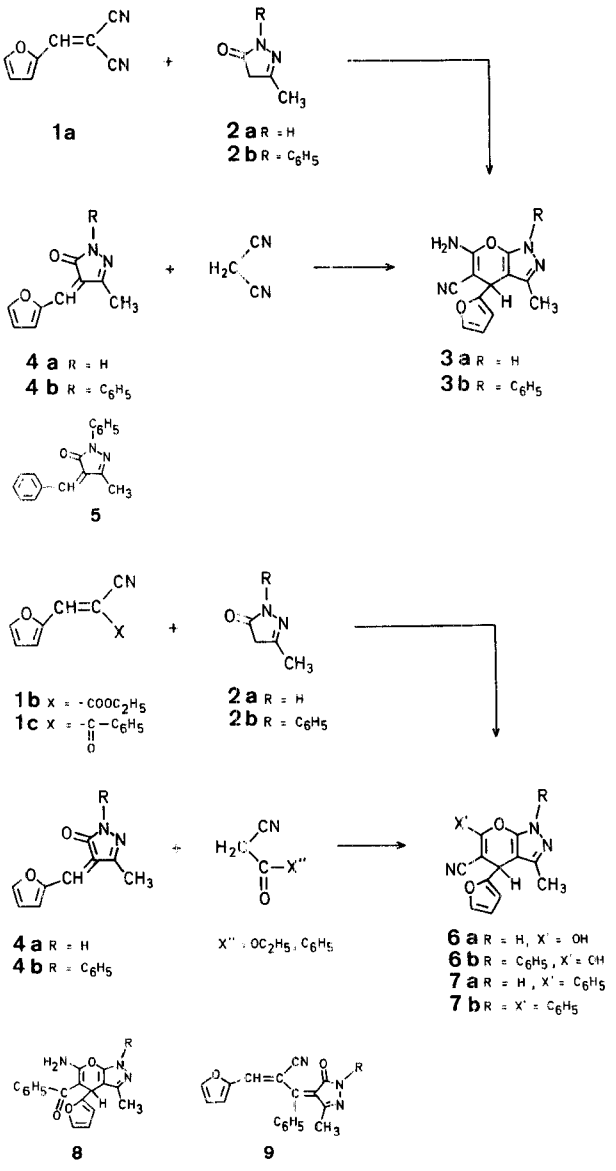
The biological activity of fused azoles has led to intensive research on methods for their syntheses[1-5]. Our group has previously reported several approaches to the synthesis of such compounds utilizing laboratory available materials[6-12]. In continuation of this work, we report here the synthesis of pyrano[2,3-*c*]pyrazole and pyrano[2,3-*d*]thiazole derivatives via reaction of β-(2-furyl)-acrylonitrile derivatives (**1a, b, c**) with 5-oxo-4,5-dihydropyrazoles (**2a, b**), 2,4-dioxotetrahydro-1,3-thiazole (**9a**), and 2-oxo-4-thioxotetrahydro-1,3-thiazole (**9b**).

2-Furylmethylenemalononitrile (**1a**) reacts with 3-methyl-2-pyrazolin-5-one (**2a**) to give a cycloadduct to which we assigned the structure **3a** on the basis of analytical and spectral data. The structure **3a** was corroborated by an independent synthesis from 4-furfurylidene-3-methyl-5-oxo-4,5-dihydropyrazole (**4a**) and malononitrile; this latter reaction is analogous to the reported reaction of the benzylidene derivative **5** with malonitrile[13,14]. In a similar manner, compound **1a** reacts with the 1-phenyl derivative **2b** to afford the cycloaddition product **3b**. The I.R. spectra of compounds **3a** and **3b** show NH_2 absorption bands at $\nu = 3350$ and 3310 cm^{-1} and a CN absorption band at $\nu = 2200$ cm^{-1}.

α-Ethoxycarbonyl-β-(2-furyl)-acrylonitrile (**1b**) reacts with compounds **2a, b** to give the pyrano[2,3-*c*]pyrazole derivatives **6a** and **6b**, respectively. Compound **6a** was also obtained from the reaction of **4a** with ethyl cyanoacetate. The



I. R. spectra of compounds **6a, b** showed an OH absorption band at $\nu = 3200-3050\ cm^{-1}$ and a CN absorption band near $\nu = 2195\ cm^{-1}$ but no C=O absorption (in the region of $1700\ cm^{-1}$).

The formation of compounds **3a, b** and **6a, b** may be assumed to proceed via an initial Michael addition to yield an acyclic adduct which then cyclizes via attack of the ring carbonyl on the cyano or ethoxycarbonyl group, respectively.

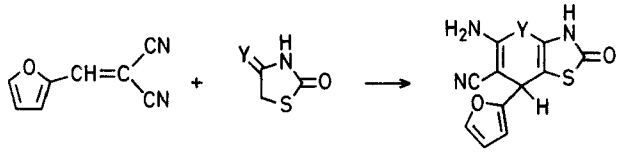
The formation of compound **3b** via Michael addition is in contrast to the reported reaction of **2b** with benzylidenemalononitrile which has been assumed to proceed via addition of **2b** to the cyano group of the latter[11].

α-Benzoyl-β-(2-furyl)-acrylonitrile (**1c**) reacts with compound **2a** to give a 1:1 adduct to which the three theoretically possible structures **7a**, **8** (R = H), and **9** (R = H) might be assigned. However, structures **8** and **9** can be ruled out because of the absence of a carbonyl absorption in the I. R. spectrum and the presence of a CN absorption band at $\nu = 2190\ cm^{-1}$. Similarly, compound **1c** reacts with **2b** to yield a product to which the structure **7b** can be assigned rather than structures **8** or **9**.

Compounds **7a** and **7b** are assumed to be formed via Michael addition of **2a** or **2b**, respectively, to acrylonitrile derivative **1c** followed by cyclization with elimination of water. This behaviour of **1c** toward **2a** and **2b** is in contrast to the reported reaction of the phenyl analog of **1c**, 2-benzoyl-3-phenylacrylonitrile, with **2b** which was assumed to afford an acyclic condensation product[11]. Compounds **7a** and **7b** were also obtained from the reaction of the pyrazole derivatives **4a** or **4b** with benzoylacetonitrile.

The different behaviour of the furyl compounds **1a, b, c** and the phenyl analogs toward the pyrazole derivatives **2a, b** may be attributed to the presence of the hetero atom in the furan ring. Further investigations on this subject are in progress.

Compounds **1a, b, c** were also subjected to the reaction with 2,4-dioxo- and 2-oxo-4-thioxotetrahydro-1,3-thiazole (**10a** and **10b**, respectively). It was found that compound **1a** reacts with compounds **10a, b** to give products to which the structures **11a** and **11b** were assigned on the basis of analytical and spectral data.



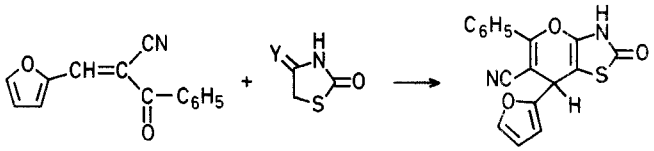
1a **10a** Y = O, **10b** Y = S **11a** Y = O, **11b** Y = S

Compound **1b** reacts with **10a** to give the cyclization product **12** whereas the reaction of **1b** with **10b** affords product **13**.

Whereas the formation of compounds **11a**, **11b** and **12** is assumed to proceed via Michael addition followed by attack of the ring carbonyl or thiocarbonyl group on the cyano group, the formation of compound **13** probably proceeds via attack of the ring thiocarbonyl group on the ester carbonyl group with elimination of hydrogen sulfide.

The I. R. spectrum of compound **12** shows an NH_2 absorption band at $\nu = 3350-3310\ cm^{-1}$ and compound **13** shows a cyano absorption at $\nu \approx 2195\ cm^{-1}$. The ^{1}H-N.M.R. spectrum of compound **12** shows a broad singlet at $\delta = 3.4-4.0$ ppm (2 H) corresponding to the NH_2 group while compound **13** does not show such a signal.

Compound **1c** reacts with both **10a** and **10b** to give the same product to which the structure **14** was assigned. Compound **14** may be assumed to be formed via a Michael addition followed by cyclization with elimination of water or hydrogen sulfide, respectively.



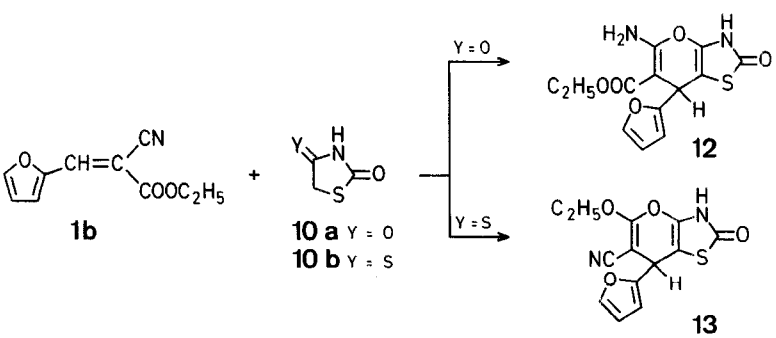
1c **10a** Y = O, **10b** Y = S **14**

All melting points are uncorrected. The microanalyses were performed by the microanalytical unit at Cairo University. I. R. spectra were recorded using a Pye-Unicam SP-1100 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a Varian A-60 spectrometer.

6-Substituted 5-Cyano-4-(2-furyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazoles (3, 6, 7) from Compounds 1 and 2; General Procedure:
The 3-(2-furyl)-acrylonitrile derivative **1** (0.01 mol) is added to a solution of the 3-methyl-5-oxo-4,5-dihydropyrazole **2** (0.01 mol) in absolute ethanol (75 ml). Then, piperidine (1 ml) is added and the mixture is refluxed on a water bath for 0.5–2.0 h (T.L.C. control). The mixture is then allowed to cool to room temperature, poured onto crushed ice (~ 25 g), and neutralized with cold hydrochloric acid. The precipitated dark solid product is isolated by suction and recrystallized from a suitable solvent (Table 1).

Compound 3a from Compound 4a and Malononitrile:
To a solution of 4-furfurylidene-3-methyl-5-oxo-4,5-dihydropyrazole (**4a**; 1.762 g, 0.01 mol) in ethanol (75 ml) are added malononitrile (0.661 g, 0.01 mol) and piperidine (1 ml) and the mixture is refluxed for 1 h. It is then cooled to room temperature and neutralized with dilute hydrochloric acid. The solid product is isolated by suction, washed with water, and recrystallized from acetic acid; yield: 1.7 g (70%). The product is identical with compound **3a** prepared by the general procedure.

Compounds 7a and 7b from Compounds 4a, b and Benzoylacetonitrile:
The 4-furfurylidene-3-methyl-5-oxo-4,5-dihydropyrazole **4a** or **4b** (0.01 mol) and benzoylacetonitrile (1.452 g, 0.01 mol) are dissolved in ethanol (75 ml), piperidine (1 ml) is added, and the mixture is refluxed for ~ 1 h. It is then cooled and neutralized with cold dilute



1b **10a** Y = O, **10b** Y = S **12** **13**

hydrochloric acid. The precipitated product is isolated by suction, washed with water, and recrystallized from methanol. The products thus obtained are identical with compounds **7a** or **7b**, respectively, obtained by the general procedure.

Table 1. Pyrano[2,3-*c*]pyrazole and pyrano[2,3-*d*]thiazole Derivatives prepared

Compound	Reaction Time [min]	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]
3a	30	90	>270 (AcOH)	$C_{12}H_{10}N_4O_2$ (242.2)
3b	30	93	233–235° (AcOH)	$C_{18}H_{14}N_4O_2$ (318.3)
6a	90	85	289–290° (AcOH)	$C_{12}H_9N_3O_3$ (243.2)
6b	60	95	190–191° (CH_3OH)	$C_{18}H_{13}N_3O_3$ (319.3)
7a	180	72	198–200° (CH_3OH)	$C_{18}H_{13}N_3O_2$ (303.3)
7b	90	76	184–185° (CH_3OH)	$C_{24}H_{17}N_3O_2$ (379.4)
11a	45	80	>290° (AcOH)	$C_{11}H_7N_3O_3S$ (261.2)
11b	46	85	189–190° (CH_3OH)	$C_{11}H_7N_3O_2S_2$ (277.2)
12	90	95	251–253° (AcOH)	$C_{13}H_{12}N_2O_5S$ (308.25)
13	60	91	124–125° (C_2H_5OH)	$C_{13}H_{10}N_2O_4S$ (290.25)
14	60	92	178–180° (C_2H_5OH)	$C_{17}H_{10}N_2O_3S$ (322.3)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.30; H, ±0.25; N, ±0.35; S, ±0.43.

Table 2. I.R. and ^{1}H-N.M.R. Data of Some New Compounds; Selected Bands/Signals

Compound	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$) δ [ppm]
3a	3350, 3310 (NH_2); 2210 (CN)	4.5–5.0 (br. s, 2H, NH_2); 8–8.2 (s, 1H, NH); 1.5 (s, 3H, CH_3); 6.2–6.7 (m, 3H$_{furan}$)
3b	3350, 3310 (NH_2); 2200 (CN)	–
6a	2195 (CN); 3200–3050 (OH); 3450–3110 (NH)	–
6b	2195 (CN); 3200–3050 (OH)	1.5 (s, 3H, CH_3); 8–8.3 (br. s, 1H, OH); 6.2–6.7 (m, 3H, furan Hs); 7.2–8.0 (m, 5H$_{arom}$)
7a	2190 (CN); 3350–3100 (NH)	1.7 (s, 3H, CH_3); 7.8–8.1 (br. s, 1H, NH); 6.5–8.0 (m, 8H$_{furan+arom}$)
7b	2190 (CN)	1.7 (s, 3H, CH_3); 6.3–8.1 (m, 13H$_{furan+arom}$)
11a	2210 (CN); 1695 (ring C=O); 3340, 3300 (NH_2)	8.1–8.3 (br. s, 1H, NH); 6.2–6.9 (m, 5H$_{furan}$ + NH_2)
12	3350, 3310 (NH_2); 1740–1720 (C=O groups)	3.7–4.3 (br. s, 2H, NH_2); 1.7–1.9 (t, 3H, CH_3); 2.5–2.8 (q, 2H, CH_2); 8.1–8.3 (br. s, 1H, NH); 6.3–6.9 (m, 3H$_{furan}$)
14	2210 (CN); 3450, 3210 (NH); 1730 (ring C=O)	–

4,5-Disubstituted 4-(2-Furyl)-2-oxo-1,2-dihydro-4*H*-pyrano[2,3-*d*][1,3]thiazoles (12, 13, 14) from Compounds 1 and 10; General Procedure:

The 3-(2-furyl)-acrylonitrile derivative **1** (0.01 mol) is added to a solution of the 1,3-thiazolidine derivative **10** (0.01 mol) in ethanol (75 ml), piperidine (1 ml) is added, and the mixture is refluxed for the time given in Table 1. The mixuture is then cooled, poured onto ice (~ 25 g), and neutralized with acetic acid. The precipitated dark solid product is isolated by suction and recrystallized from a suitable solvent (Table 1).

In the reactions of **1b** and **1c** with **10b**, evolution of hydrogen sulfide was observed; in these cases, the mixture was refluxed until H_2S evolution had ceased.

Received: June 13, 1984

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