Nitriles in Heterocyclic Synthesis. A Novel Synthesis of 4-Phenacylpyrazole and Pyrrolo[2,3-*c*]pyrazole Derivatives

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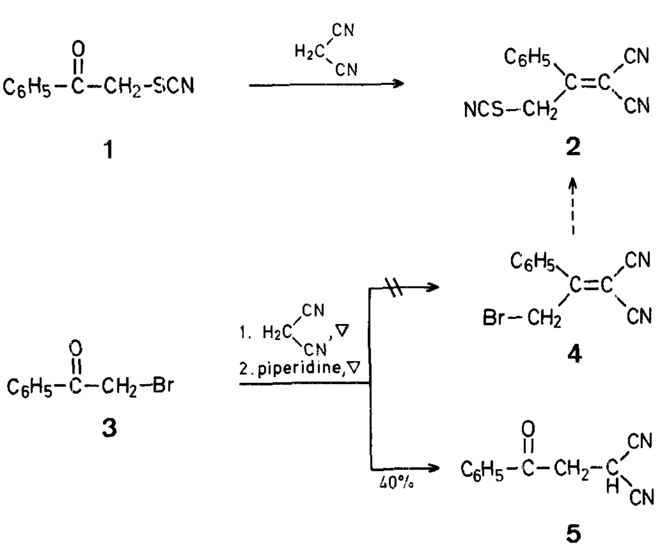
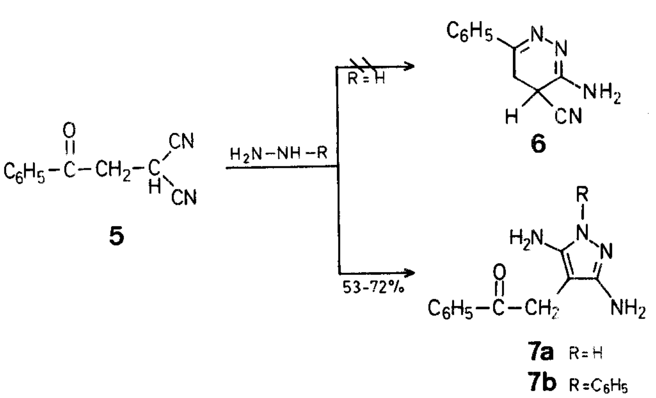
3,5-Diamino-4-phenacyclpyrazoles are prepared by reaction of phenacylmalononitrile with hydrazine or phenylhydrazine. Further reaction of the 3,5-diamino-4-phenacylpyrazoles with trichloroacetonitrile provides a novel synthesis of 1,6-dihydropyrrolo[2,3-*c*]pyrazoles.

In context with our search for new simple synthesis of azoles, azines, and their ring-fused derivatives$^{1-5}$ utilizing readily available starting materials, we have already reported^{5} that phenacyl thiocyanate (**1**) reacts with malononitrile to afford the Knoevenagel condensation product **2**. In an attempt to improve the yield, we tried to prepare the alkylidenemalonitrile **4** from ω-bromoacetophenone (**3**) and malononitrile and to then subject **4** to the reaction with potassium thiocyanate. This was not possible, however, the reaction of ω-bromoacetophenone (**3**) with malononitrile in the presence of piperidine leading to the formation of phenacylmalononitrile (**5**). Compound **5** was identified by microanalysis and spectral data. This behavior of malononitrile toward ω-bromoacetophenone (**3**) is in contrast to the behavior of ethyl cyanoacetate toward compound **3**^{6}.

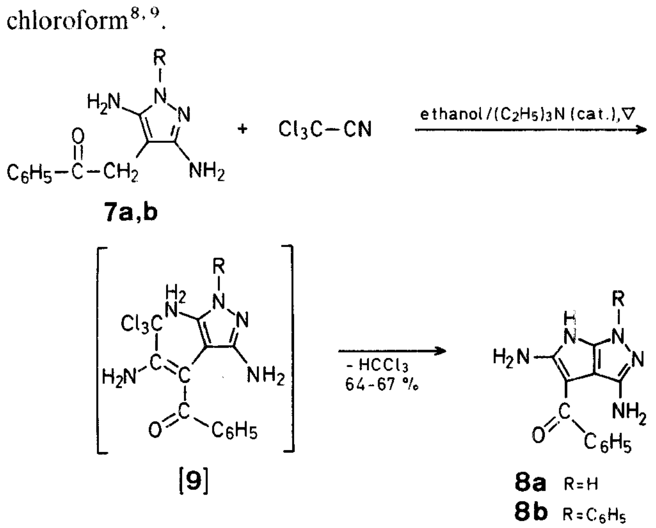


Compound **5** reacts vigorously with hydrazine hydrate to give a product for which the structures **6** and **7a** might be assumed. However, the dihydropyridazine structure **6** can be ruled out on the basis of the I.R. spectrum which does not show a $C\equiv N$ absorption band in the region $\nu = 2000-2270\ cm^{-1}$ and which shows a carbonyl absorption at $\nu = 1700\ cm^{-1}$. Element analysis and ^{1}H-N.M.R. data are in agreement with structure **7a**.

The analogous reaction of compound **5** with phenylhydrazine affords a product for which the pyrazole structure **7b** was established on the basis of analytical and spectral data^{7}.



The reactions of compounds **7a** and **7b** with trichloroacetonitrile in boiling ethanol afford brownish-yellow products for which structures **8a** and **8b** are suggested. Analytical and spectral data are in good agreement with these structures. The formation of compounds **8a, b** is assumed to proceed via Michael addition of the active methylene protons of **7a, b** to the activated cyano group of trichloroacetonitrile[2,8] and cyclization of the intermediate **9** with elimination of chloroform[8,9].



Thus, 4-phenacylpyrazoles can now be prepared from readily available starting materials under mild reaction conditions and using simple isolation procedures. The pyrrole[2,3-*c*]pyrazole derivatives **8** seem to be interesting compounds for biological studies, and the substituted pyrazoles **7** may be useful intermediates for further syntheses.

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

Phenacylmalononitrile (5):

A mixture of ω-bromoacetophenone (**3**; 19.9 g, 0.1 mol) and malononitrile (6.6 g, 0.1 mol) is warmed under dry conditions on a water bath until a homogeneous solution is obtained, and then allowed to cool to room temperature. To this, piperidine (~ 7 ml) is added portionwise with shaking, each portion being added after the vigorous reaction and evolution of fumes have ceased. After complete addition, the mixture is refluxed on a water bath for 1 h, then allowed to stand overnight. The white crystalline product is isolated by suction and recrystallized from ethanol; yield: 7.36 g (40%); m.p. 149–150°C.

$C_{11}H_8N_2O$	calc.	C 71.74	H 4.35	N 15.22
(184.2)	found	71.45	4.40	15.00

I.R. (KBr): ν = 2260 (CN); 1680 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 3.65 (d, 2H, CH$_2$); 4.34 (t, 1H, CH); 7.5–8.1 ppm (m, 5H$_{arom}$).

3,5-Diamino-4-phenacylpyrazole (7a):

Hydrazine hydrate (1 ml, 0.02 mol) is added to phenacylmalononitrile (**5**; 3.68 g, 0.02 mol). After the vigorous reaction which ensues, the mixture is allowed to cool to room temperature. The solid mass thus obtained is triturated with ethanol (~ 5 ml). The solid product is isolated by suction and recrystallized from ethanol; yield: 3.1 g (72%); m.p. 218–220°C.

$C_{11}H_{12}N_4O$	calc.	C 61.11	H 5.56	N 25.93
(216.2)	found	61.50	5.35	26.10

I.R. (KBr): ν = 3370–3100 (NH$_2$, NH); 1700 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 3.5 (s, 2H, CH$_2$); 7.45–7.65 (m, 5H$_{arom}$); 7.8 (s, 4H, 2NH$_2$); 8.28 (s, 1H, NH).

3,5-Diamino-4-phenacyl-1-phenylpyrazole (7b):

Phenylhydrazine (2.16 ml, 0.02 mol) and triethylamine (1 drop) are added to a solution of phenacylmaolononitrile (**5**; 3.68 g, 0.02 mol) in ethanol (30 ml). The mixture is heated to boiling for 2 h and then allowed to stand overnight. The solid product is isolated by suction and recrystallized from ethanol; yield: 3.1 g (53%); m.p. 200°C.

$C_{17}H_{16}N_4O$	calc.	C 69.86	H 5.48	N 19.18
(292.3)	found	70.15	4.95	18.84

I.R. (KBr): ν = 3300–3120 (NH$_2$); 1680 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 3.6 (s, 2H, CH$_2$); 6.75 (s, 2H, 3—NH$_2$); 7.2–7.6 ppm (m, 10H$_{arom}$ + 5—NH$_2$).

3,5-Diamino-4-benzoyl-1,6-dihydropyrrolo[2,3-*c*]pyrazoles 8a and 8b:

To a solution of compound **7a** or **7b** (0.01 mol) in ethanol (~ 30 ml) are added trichloroacetonitrile (1 ml, 0.01 mol) and triethylamine (3 drops). The mixture is refluxed for 30 min, then allowed to cool overnight. The solid product is isolated by suction and recrystallized from ethanol.

3,5-Diamino-4-benzoyl-1,6-dihydropyrrolo[2,3-c]pyrazole (**8a**); yield: 1.6 g (67%); m.p. > 270°C.

$C_{12}H_{11}N_5O$	calc.	C 59.75	H 4.65	N 29.05
(241.25)	found	60.25	4.10	28.80

I.R. (KBr): ν = 3300–3100 (NH$_2$, NH); 1670 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 7.4–7.65 (m, 5H$_{arom}$); 7.8–8.1 (br.s, 4H, 2NH$_2$); 8.8 ppm (s, 2H, 2NH).

3,5-Diamino-4-benzoyl-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazole (**8b**); yield: 2 g (64%); m.p. 255°C.

$C_{18}H_{17}N_5O$	calc.	C 67.71	H 5.33	N 21.94
(319.4)	found	67.35	5.00	21.60

I.R. (KBr): ν = 3320–3140 (NH$_2$, NH); 1680 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 7.38–7.75 (m, 10H$_{arom}$); 7.83–8.15 (br. s, 4H, 2NH$_2$), 8.82 ppm (s, 1H, NH).

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