Activated Nitriles in Heterocyclic Synthesis. A Novel Synthesis of Pyrazolo[1,5-*a*]pyrimidines and Pyrano[2,3-*c*]pyrazoles

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Several new pyrazolo[1,5-*a*]pyrimidines and pyrano[2,3-*c*]pyrazoles were synthesised *via* the reaction of the cinnamonitrile derivatives **1a-c** with 5-amino-3-phenylpyrazole (**1**), 3-amino-2-pyrazolin-5-one (**2**) and 3-amino-1-phenyl-2-pyrazolin-5-one (**22**).

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Pyrazolo[1,5-*a*]pyrimidines are purine analogues and as such have useful properties as antimetabolites in purine biochemical reaction (1-4). Robins *et al.* (5,6) have recently shown that derivatives of this ring system inhibits CAMP-Phosphodiesterase. As this enzyme activity has been proved by Bear *et al.* (7) to be responsible for anxiety, it was anticipated that these compounds would also exhibit anti-anxiety activity. Five years ago Robins and his group have shown that certain derivatives really have antianxiety activity comparable to benzodiazipam. These interesting biological activities have attracted the attention of many chemists to develop new effecient general procedures for the synthesis of pyrazolo[1,5-*a*]pyrimidines. Our group has participated in this effort during the last decade on the synthesis of pyrazolo[1,5-*a*]pyrimidines and pyrazolo-[1,5-*a*]-*as*-triazines. A recent observation by Robins and Coworkers (6) that pyrazolo[1,5-*a*]pyrimidines are potential drugs for schistosomiasis was of interest to us. Schistosomiasis is one of the most difficult diseases to treat and is a national problem in our country (Egypt). Thus, pyrazolo-[1,5-*a*]pyrimidines have again attracted our attention.

In the present work we report the synthesis of several new pyrazolo[1,5-*a*]pyrimidines *via* the reaction of cinnamonitrile derivatives with 5-amino-3-phenylpyrazole (**1**) and 3-amino-2-pyrazolin-5-one (**2**). Thus, it has been found that **1** reacts with ethyl benzylidenecyanoacetate (**3a**) to yield a product of molecular formula $C_{19}H_{14}ON_4$. Four theoretically possible isomeric structures were considered (*cf.* structures **4-7** Chart 1). Structures **4** and **5** were readily eliminated based on ^1H nmr spectra which revealed a pyrazole CH at δ 6.2 ppm. Structure **6** could also be eliminated based on the ir spectrum which revealed CO absorption at 1650 cm^{-1}. If this compound were **6**, CO absorption

Chart 1

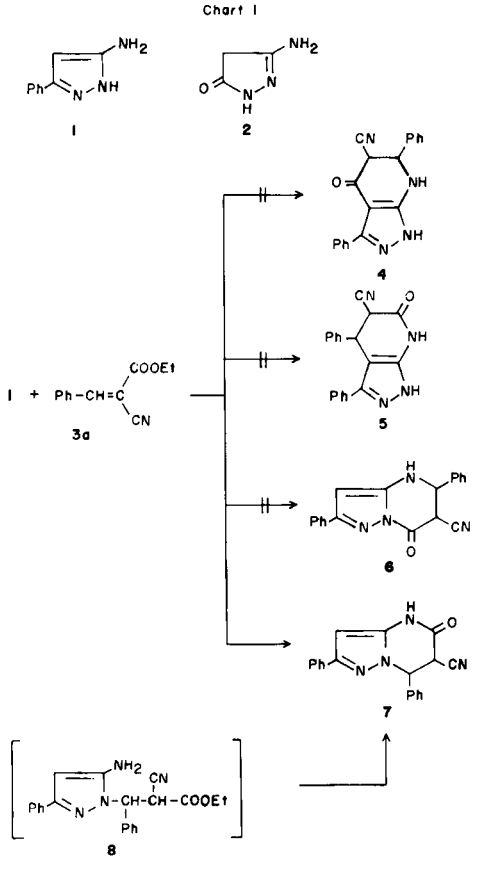

Chart 2

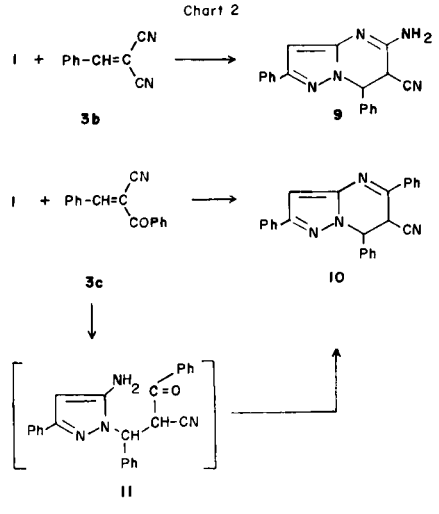

Chart 3

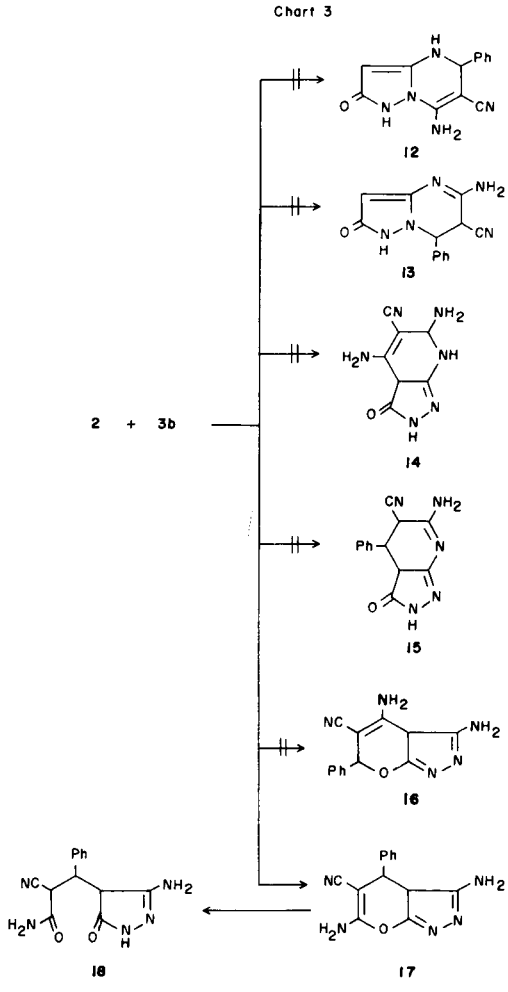

Chart 4

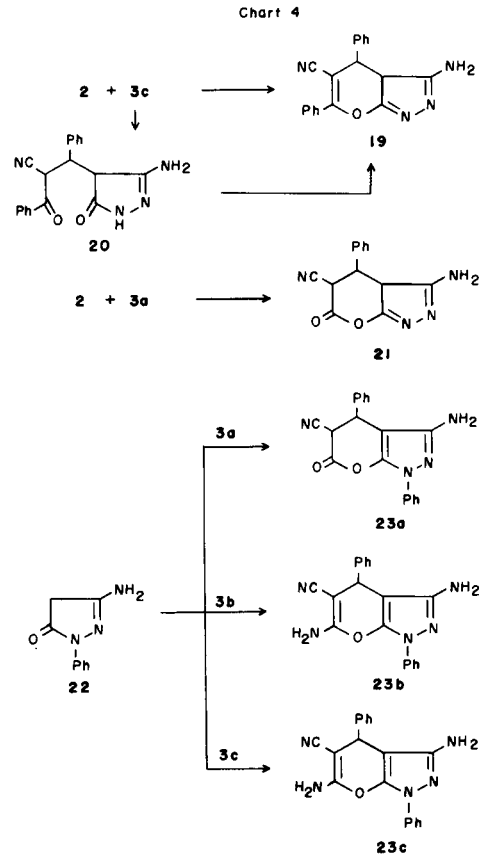

Table I

Products **7**, **9**, **10**, **17-21** and **23a-c**

Compound (Colour)	Time of reaction, hours	Solvent of crystallisation	Yield (%)	Mp (°C)	Molecular formula (Molecular weight)	Analyses Found/Required C	H	N
7 (Colourless)	11	Ethanol	75	284	$C_{19}H_{14}N_4O$ (314)	72.6 72.6	4.7 4.5	17.3 17.8
9 (Colourless)	14	Ethanol	65	103	$C_{19}H_{15}N_5$ (313)	72.4 72.8	5.2 4.8	22.0 22.4
10 (Colourless)	27	Ethanol	55	271	$C_{25}H_{18}N_4$ (374)	80.5 80.2	4.5 4.8	14.7 15.0
17 (Buff)	3	Ethanol	75	210	$C_{13}H_{11}N_5O$ (253)	61.2 61.6	4.8 4.3	27.5 27.7
18 (Yellow)	20	Ethanol	75	300	$C_{13}H_{13}N_5O_2$ (271)	57.2 57.6	5.1 4.8	26.2 25.8
19 (Brown)	17	DMF	65	267	$C_{19}H_{14}N_4O$ (314)	72.2 72.6	4.7 4.5	17.6 17.8
20 (Yellow)	3	Ethanol	55	203	$C_{19}H_{16}N_4O_2$ (332)	68.6 68.7	4.8 4.8	16.6 16.9
21 (Yellow)	5	Ethanol	65	279	$C_{13}H_{10}N_4O_2$ (254)	61.3 61.4	3.7 3.9	21.6 22.0
23a (Yellow)	10	Ethanol	75	225	$C_{19}H_{14}N_4O_2$ (330)	68.8 69.3	4.3 4.2	16.7 16.9
23b (Brown)	5	Ethanol	70	234	$C_{19}H_{15}N_5O$ (329)	68.9 69.3	4.5 4.6	20.9 21.3
23c (Colourless)	27	Ethanol	55	280	$C_{25}H_{18}N_4O$ (390)	76.5 76.9	4.5 4.6	14.0 14.4

at a higher frequency (*ca.* 1700 cm^{-1}) would have been observed.

The formation of **7** from the reaction of **1** and **3a** is assumed to proceed *via* initial addition of the ring nitrogen atom in **1** to the activated double bond followed by cyclisation into **7**. However, the possibility of the initial formation of the acylamino derivative **8** as an intermediate in this reaction can not be ruled out. Attempts to isolate the acyclic intermediate for the reaction in order to provide evidence were unsuccessful. However, the addition elimination sequence appears more likely since there is a parallel to the well documented mechanism of the reaction of acrylonitrile or ethyl acrylate with **1** (8).

Similar to the behaviour of **1** with **3a**, compound **1** reacted with benzylidinemalononitrile (**3b**) to yield the pyrazolo[1,5-*a*]pyrimidine derivative **9**. The formation of **9** in this reaction is assumed to proceed *via* a sequence similar to that discussed above for the reaction of **1** and **3a**. Compound **1** reacted also with the α-cyanochalcone **3c** to yield the pyrazolo[1,5-*a*]pyrimidine derivative **10**. The formation of **10** is assumed to proceed *via* an initial formation of the Michael adduct **11** which then undergoes intramolecular cyclocondensation, through elimination of water to yield the final isolable **10**.

Table II

IR and ^1H NMR Data for Compounds in Table I

Compound	IR cm^{-1} (selected bands)	^1H NMR (δ ppm)
7	3500-3200 (NH), 2220 (CN) and 1660 (ring CO)	2.9 (m, br, 2H, 2CH), 6.2 (s, 1H, C-4 pyrazole) and 6.8 (m, 10H, $2C_6H_5$)
9	3500-3300 (NH_2), 2220 (CN) and 1630 (C=N)	Insoluble in commonly used nmr solvents.
10	2220 (CN) and 1590 (C=N and C=C)	3.1 (s, br, 2H, 2CH), 6.4 (s, 1H, C-4 pyrazole) and 7.2-8.1 (m, 15H, $3C_6H_5$)
17	3400, 3350, 3150 (NH_2), 2220 (CN) and 1620 (C=N)	Insoluble in commonly used nmr solvents.
18	3500-3000 (NH and NH_2), 2220 (CN), 1660 (CO) and 1620 (C=N)	3.3 (m, br, 2H, 2CH), 6.5 (s, 1H, C-4 pyrazole) and 6.9 (m, 5H, C_6H_5)
19	3500-3000 (NH_2) and 2220 (CN)	Insoluble in commonly used nmr solvents.
20	3300-3100 (NH_2), 2210 (CN), 1720 (CO), and 1620 (C=N)	Insoluble in commonly used nmr solvents.
21	3550, 3250 (NH_2), 2220 (CN), 1690 (CO) and 1650 (C=N)	4.1 (m, br, 2H, 2CH), 6.4 (s, 1H, C-4 pyrazole) and 6.9-7.1 (m, 5H, C_6H_5)
23a	3500, 3200-3000 (NH_2), 2220 (CN), 1640 (CO) and 1620 (C=N)	Insoluble in commonly used nmr solvents.
23b	3500-3000 (NH_2), 2220 (CN) and 1640-1560 (C=N, C=C)	Insoluble in commonly used nmr solvents.
23c	3500-2900 (NH_2) and 2220 (CN)	Insoluble in commonly used nmr solvents.

Similar to the behaviour of **1**, compound **2** reacted with **3b** to yield a cyclocondensation product of molecular formula $C_{13}H_{11}ON_5$. Six isomeric structures were considered (*cf.* **12-17**). Although structures **12-15** seemed at first glance unlikely, based on analogy to the behaviour of **1** toward **3a** the activating effect of the carbonyl function in **2** to the methylene at C-4 made such arguments unconvincing and an independent structure proof seemed necessary. Structures **12-14** could be readily eliminated based on the isolation of the amide **18** on prolonged refluxing of the reaction product or the reaction of **1** and **3b** in ethanolic piperidine solution. This compound can only result from hydrolysis of the pyrano[2,3-*c*]pyrazole derivative **17**, thus, establishing this structure for the reaction product.

Similarly the reaction of **2** with **3c** afforded the cyclocondensation product **19** upon long reflux in ethanolic piperidine solution. The acyclic intermediate **20** could be isolated on treatment of **2** with **3c** in an ethanolic piperidine mixture for a shorter period.

Compound **2** reacted with **3a** to yield the pyrano[2,3-*c*]-pyrazole derivative **21**. The structure of **21** was suggested based on analogy to the behaviour of **2** toward **3b,c** and finds further support form ^1H nmr data.

The behaviour of 3-amino-1-phenyl-2-pyrazolin-5-one (**22**) toward **3a-c** was also investigated. It has been found that **22** reacts with **3a-c** to yield adducts which in the case of **3a,c** underwent cyclization *via* elimination of ethanol and water respectively. Structure **23a,c** was suggested for these products based on the ir spectra which revealed only the CO absorption in case of reaction of **22** and **3a**, and the absence of a CO band in the product of the reaction of **22** with **3c**. Similarly structure **23a** was suggested for the product of the reaction of **22** and **3b**.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) on a Shimadzo 200-91506 spectrophotometer. The ^1H nmr spectra were recorded on a Varian A-60 spectrometer and chemical shifts are expressed in δ ppm using TMS as the internal indicator. Analytical data were obtained from the Microanalytical Data Unit at Cairo University.

Reaction of **3a-c** With **1**, **2** or **22**.

General Procedure.

A suspension of an equimolecular amount (0.01 mole) of **3a-c** and the appropriate amount of **1**, **2** or **22** in ethanol (30 ml) was refluxed with piperidine (1 ml) until the reaction was complete (tlc control) (time ranges from 3 hours to 27 hours *cf.* Table I). The solvent was then evaporated *in vacuo* and the remaining product was triturated with a little water and then acidified with concentrated hydrochloric acid. The resulting solid products, listed in Table I, were collected by filtration and crystallized from the proper solvent (*cf.* Table I and II).

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