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Reactions of 3-Aminopyrazole Derivatives with Cyanothioacetamide and Its Derivatives: Synthesis and Reactions of Several New Pyrazole and Pyrazole[3,2-*b*]pyrimidine Derivatives

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Thiocarboxamidocinnamonitrile derivatives **2a-f** reacted with 3-aminopyrazole derivatives **3a-c** to give the pyrazole[3,2-*b*]pyrimidine derivatives **6a-p**. Compounds **6a-p** were used as starting material for syntheses of several heterocylic coompounds. Dehydrogenation of **6** gave pyrazole[3,2-*b*]pyrimidines **10a-d** while its reaction with diethyl oxalate gave **11**. Reactions of **6** with formic acid gave pyrazolopyrimidines **17a-j**, and pyrazolopyrimidopyrimidinoes **18a-j**.

Key words : 3-Aminopyrazole, Cyanothioacetamide, Pyrazole, Pyrazole[3,2-b] pyrimidine

INTRODUCTION

During the last few years, our research group has been interested in the chemistry of thiocyanoacetamide and its derivatives (Attaby *et al.*, 1990; Attaby *et al.*, 1992; Attaby *et al.*, 1995; Ismail *et al.*, 1992; Ismail *et al.*, 1992; Riad *et al.*, 1987) with objective of finding new routes for the synthesis of heterocyclic derivatives of expected biological activities.

The isolation of the pyrazolopyrimidine derivatives **6a-p**, **10a-d**, **11**, **17a-j** and **18a-j** and their reported biological activities as metabolites in purine metabolism (Alexander *et al.*, 1966; Elion *et al.*, 1963; Hildick *et al.*, 1971, Earl *et al.*, 1975), as inhibitors of CAMP-phosphodiesterase (Skipper *et al.*, 1957), as potential drugs for schistosomiasis (Skipper *et al.*, 1955) and as antiviral agent (Saxena *et al.*, 1990) stimulated our interest in the synthesis of additional new derivatives of the ring system.

RESULTS AND DISCUSSION

Reaction of α-thiocarboxamidocinnamonitrile **2a** with 3-aminopyrazole derivative **3a** in absolute ethanol in the presence of triethylamine afforded a sulfur free reaction product. Spectral data as well as elemental analyses confirm the given structure (cf. Table I and II). Based on the above data, this reaction product was formulated as either the dihydropyrazolo[3,2-*b*]pyrimidine derivatives **5a** or **6a**. However, the structure **6a** was supported by the ^{1}H-NMR spectral data where the doublets for pyrimidine H-5 and H-6 protons are not detected and only singlet for pyrimidine H-6 was detected (cf. Table II). Moreover, its mass spectrum gave m/z=313 (98.8%) which corresponded to the exact molecular weight of a molecular formula $C_{19}H_{15}N_5$. The formation of **6a** in this reaction was most probably proceeded via initial addition of the proton from NH in **3a** to the activated double bond in **2a** to give the non-isolable intermediate Michael addition product **4a**. Compound **4a** then cyclised via loss of hydrogen sulfied to yield the dihydropyrazole[3,2-*b*]pyrimidine derivative **5a** which tautomerizes into the final isolable dihydropyrazole[3,2-*b*]pyimidine derivative **6a** (cf. Chart 1).

An evidence for structure **6a** was obtained by its dehydrogenation into the corresponded **10a** by either prolonged boiling in ethanol containing catalytic amounts of triethylamine or ethanolic-HCl solutions (cf. Chart 2).

A further confirmation of structure **6a** was achieved through the reaction with diethyl oxalate in ethanolic sodium ethoxide to yield the imidazo[1,2:3',4']pyrazole[3,2-*b*]pyrimidindion **11** whose structure was in turn, established based on both elemental analyses and spectral data. The IR and ^{1}H-NMR data of **11** were in a good agreement with the assigned structure (cf. Tables I and II). If the reaction product from **2a** and **3a** is **8a** or **9a** the reaction with diethyl oxalate

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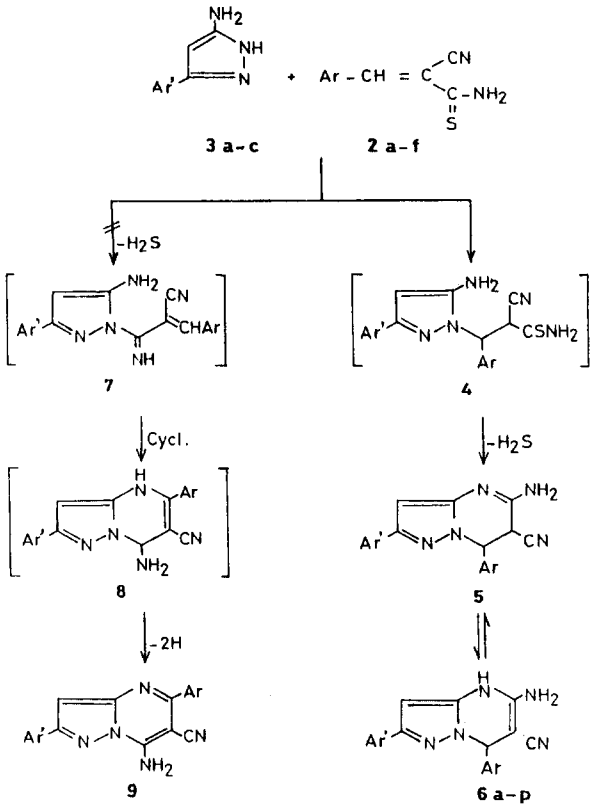
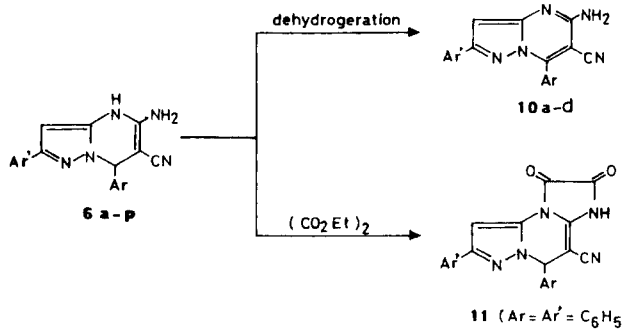


Chart 1.



6	Ar	Ar'
a	C_6H_5	C_6H_5
b	C_6H_4-Cl-*p*	C_6H_5
c	C_6H_4-OCH_3-*p*	C_6H_5
d	C_6H_4-NO_2-*p*	C_6H_5
e	C_4H_3O-α	C_6H_5
f	C_4H_3S-α	C_6H_5
g	C_6H_5	C_6H_4-CH_3-*p*
h	C_6H_4-Cl-*p*	C_6H_4-CH_3-*p*
i	C_6H_4-OCH_3-*p*	C_6H_4-CH_3-*p*
j	C_6H_4-NO_2-*p*	C_6H_4-CH_3-*p*
k	C_4H_3O-α	C_6H_4-CH_3-*p*
l	C_4H_3S-α	C_6H_4-CH_3-*p*
m	C_6H_5	C_6H_4-Br-*p*
n	C_6H_4-Cl-*p*	C_6H_4-Br-*p*
o	C_6H_4-OCH_3-*p*	C_6H_4-Br-*p*
p	C_4H_3O-α	C_6H_4-Br-*p*

Chart 2.

would have not occurred due to the non-adjacent of the pyrimidine ring-NH and C-NH_2 group necessary for completion of the reaction (cf. Charts 1 and 2).

The other analogs **2b-f** also, reacted with **3a** to yield products corresponded to the addition of one molecule of **3a** to one molecule of each of **2b-f** with the loss of H_2S molecule. The reaction products were formulated as the dihydropyrazole[3,2-*b*]pyrimidine derivatives **6b-f** respectively. The IR of each **6b-f** showed the presence of NH_2, NH, CN and C=N groups in each case (co. Table II). The mass spectra of each of **6b, d, e** as typical examples of the series gave m/z= 347, 358 and 303 respectively which corresponded to the exact molecular weight of the molecular formulae $C_{19}H_{14}N_5Cl$, $C_{19}H_{14}N_6O_2$ and $C_{17}H_{13}N_5O$ respectively (cf. Table II).

In a similar behaviour, compounds **2a-f** reacted with 3-amino-5-(4'-methylphenyl) pyrazole (**3b**) to give products which could also be formulated as the dihydropyrazolo[3,2-*b*]pyrimidine derivatives **6g-l** respectively. Structure of **6g-l** was based on both elemental analyses and spectral data studies. The IR spectra of the new series showed the absorption bands of NH_2, NH, CN, and C=N group in each case and their ^{1}H-NMR spectra were characterized by the presence of the signals corresponding to pyrazole H-4, pyrimiding H-6, aromatic protons, NH, NH_2 protons in each case. Moreover, the mass spectrum of **6l** as a typical example gave m/z=333 which corresponded to the exact molecular weight of a molecular formula $C_{18}H_{15}N_5S$ of the assigned structure (cf. Chart 1).

Compounds **2a-c,e** behaved similary towards 3-amino-5-(4'-bromophenyl)pyrazole (**3c**). Thus, the reaction between **3c** and each of **2a-c,e** resulted in the formation of the dihydro[3,2-*b*]pyrimidine derivatives **6m-p** respectively. Compounds **6m-p** were most likely formed via the intermediacy of the Michael addition products **4** which were cyclized by the loss of hydrogen sulfide to give **6m-p** via **5**. Elemental analyses and spectral data were the backgrounds for elucidation of the structure of **6m-p** as previously reported for **6a-l**.

Work was also, extended to study of the behavior of **3a** towards the action of other cinnamonitrile derivatives. Thus, **3a** reacted with α-carbox- amidocinnamonitrile (**2i**) to give a product with molecular formula $C_{19}H_{16}N_5OCl$. This formula corresponded to the addition of one molecule of **3a** to one molecule of **2i** (cf. Chart 3). The IR (cm^{-1}) spectrum of the reaction product showed the presence of two NH_2 (3470, 3360, 3300); CN (2225); CO (1670) and C=N (1620) groups. This reaction product was thus formulated as the Michael addition product **12a** and not **14a** based on similarity with the above finding for compounds **6a-g**. Compound **12a** was cyclised with treatment of ethanolic hydrochloric acid to yield 5-

Table I. Characterization data of the newly synthesized compounds

Comp.*	color	M.P. °C	Yield %	Molecular Formula	% Analysis, Calculated/Found					
					C	H	N	S	Cl	Br
6a	pale	275	78	$C_{19}H_{15}N_5$	72.84	4.79	22.36	----	----	
	Yellow				72.5	4.8	22.5	----	----	----
6b	White	285-6	68	$C_{19}H_{14}N_5Cl$	65.61	4.02	20.14	----	10.21	----
					65.6	4.1	20.2	----	10.3	----
6c	Pale	280-1	70	$C_{20}H_{17}N_5O$	69.97	4.95	20.40	----	----	----
	Yellow				69.9	5.0	20.5	----	----	----
6d	Yellow	316-8	65	$C_{19}H_{14}N_6O_2$	63.68	3.91	23.40	----	----	----
					63.7	4.0	23.4	----	----	----
6e	Brown	279	73	$C_{17}H_{13}N_5O$	67.32	4.29	23.10	10.03	----	----
					67.4	4.2	23.0	10.0	----	----
6f	Buff	293-4	75	$C_{17}H_{13}N_5S$	63.94	4.07	21.94	----	----	----
					64.0	4.1	22.0	----	----	----
6g	White	305-6	72	$C_{20}H_{17}N_5$	73.39	5.19	21.40	----	----	----
					74.0	5.2	21.3	----	----	----
6h	Pale	300-1	79	$C_{20}H_{16}N_5Cl$	66.39	4.42	19.36	----	9.82	----
	Yellow				66.4	4.5	19.4	----	9.9	----
6i	Yellow	270-1	71	$C_{21}H_{19}N_5O$	70.58	5.32	19.60	9.60	----	----
					70.6	5.4	19.7	9.6	----	----
6j	Yellow	310-2	60	$C_{20}H_{16}N_6O_2$	64.51	4.30	22.58	9.60	----	----
					64.5	4.3	22.6	9.7	----	----
6k	Brown	291-3	64	$C_{18}H_{15}N_5S$	68.13	4.50	21.02	----	----	----
					68.2	4.5	21.1	----	----	----
6l	Buff	285-6	62	$C_{18}H_{15}N_5S$	64.86	4.50	21.02	----	----	----
					65.0	4.5	21.1	----	----	----
6m	White	>300	58	$C_{19}H_{14}N_5Br$	58.16	3.57	17.85	----	----	20.40
					58.2	3.6	18.0	----	----	20.4
6n	Yellow	300-1	58	$C_{19}H_{14}N_5BrCl$	53.45	3.04	16.41	----	8.32	18.75
					53.5	3.1	16.5	----	8.3	18.8
6o	Yellow	295-6	74	$C_{20}H_{16}N_5Obr$	56.87	3.79	16.58	----	18.95	18.95
					56.9	3.8	16.9	----	19.0	19.0
6p	White	300-1	59	$C_{17}H_{12}N_5Obr$	53.40	3.14	18.32	----	----	20.94
					53.4	3.2	18.3	----	----	21.0
10a	Pale	225	60	$C_{19}H_{13}N_5$	73.31	4.18	22.50	----	----	----
	Yellow				73.3	4.2	22.5	----	----	----
10b	Yellow	>300	82	$C_{19}H_{12}N_5Cl$	65.99	3.47	20.26	----	10.27	----
					66.0	3.5	20.3	----	10.3	----
10c	Pale	245-6	74	$C_{20}H_{15}N_5$	73.84	4.61	21.53	----	----	----
	Yellow				73.9	4.6	21.6	----	----	----
10d	White	>300	62	$C_{20}H_{14}N_5Cl$	66.75	3.89	19.47	----	9.87	----
					66.8	3.9	19.5	----	9.9	----
11	White	245-6	65	$C_{21}H_{13}N_5O_2$	68.66	3.54	19.07	----	----	----
					68.7	3.6	19.1	----	----	----
12a	Yellow	285-6	55	$C_{19}H_{16}N_5OCl$	62.38	4.37	19.15	----	9.71	----
					62.4	4.4	19.2	----	9.7	----

Table I. Continued

Comp.*	color	M.P. °C	Yield %	Molecular Formula	% Analysis, Calculated/Found				
					C	H	N	S	Cl
15a	White	>300	68	$C_{19}H_{14}N_5OCl$	62.72	3.86	19.52	----	9.76
					62.8	3.9	19.5	----	10.0
15b	White	245-7	70	$C_{17}H_{13}N_5OS+H_2O$	57.79	4.24	19.83	9.06	----
					57.8	4.3	20.0	9.1	----
17a	White	265-7	65	$C_{20}H_{17}N_5O_2$	66.85	4.73	19.49	----	----
					66.9	4.8	19.5	----	----
17b	White	240-2	73	$C_{20}H_{16}N_5O_2Cl$	60.99	4.06	17.78	----	9.02
					61.0	4.1	17.8	----	9.0
17c	White	26302	78	$C_{21}H_{19}N_5O_3$	64.78	4.88	17.99	----	----
					64.9	4.9	18.0	----	----
17d	White	290-2	72	$C_{18}H_{15}N_5O^3$	61.89	4.29	20.05	----	----
					61.9	4.3	20.1	----	----
17e	Pale	280	60	$C_{18}H_{15}N_5O_2S$	59.17	4.10	19.17	8.76	----
	Yellow				59.2	4.1	19.2	8.8	----
17f	Yellow	240	74	$C_{21}H_{19}N_5O_2$	67.56	5.09	18.76	----	----
					67.6	5.1	18.8	----	----
17g	Pale	275	79	$C_{21}H_{18}N_5O_2Cl$	61.84	4.41	17.17	----	8.71
	Yellow				61.9	4.4	17.2	----	8.7
17h	Yellow	257-8	63	$C_{22}H_{21}N_5O_3$	65.50	5.21	17.36	----	----
					65.5	5.2	17.4	----	----
17i	Brown	275	71	$C_{19}H_{17}N_5O_3$	62.80	4.68	19.28	----	----
					62.8	4.7	19.3	----	----
17j	White	283-4	68	$C_{19}H_{17}N_5O$	60.15	4.48	18.46	8.44	----
					60.2	4.5	18.5	8.5	----
18a	White	180-1	74	$C_{19}H_{17}N_5O_2S$	70.38	4.39	20.52	----	----
					70.4	4.4	20.6	----	----
18b	Pale	225	59	$C_{20}H_{15}N_5O$	63.91	3.72	18.64	----	9.45
	Yellow				64.0	3.7	18.7	----	9.4
18c	Yellow	190-2	73	$C_{20}H_{14}N_5OCl$	67.92	4.58	18.86	----	----
					68.0	4.6	18.9	----	----
18d	Brown	230-2	57	$C_{18}H_{13}N_5O_2$	65.25	3.92	21.14	----	----
					65.3	4.0	21.1	----	----
18e	White	200-2	67	$C_{19}H_{13}N_5OS$	62.24	3.74	20.17	9.22	----
					62.3	3.8	20.2	9.3	----
18f	Yellow	220-2	59	$C_{21}H_{17}N_5O$	70.98	4.78	19.71	----	----
					70.9	4.8	19.7	----	----
18g	Pale	190-2	70	$C_{21}H_{16}N_5OCl$	64.69	4.10	17.19	----	9.11
	Yellow				64.7	4.1	17.2	----	9.1
18h	Yellow	162	74	$C_{22}H_{19}N_5O_2$	68.57	4.93	18.18	----	----
					68.6	4.9	18.2	----	----
18i	Buff	220	65	$C_{19}H_{15}N_5O_2$	66.08	4.34	20.28	----	----
					66.1	4.4	20.3	----	----
18j	White	213-2	64	$C_{19}H_{15}N_5OS$	63.15	4.15	19.39	8.86	----
					63.2	4.2	19.4	8.9	----

Table II. IR and ^{1}H-NMR spectral data

Comp.	IR (KBr, Cm^{-1})	^{1}H-NMR (DMSO-d_6)
6a	3450, 3360 (NH_2); 3240 (NH); 2200 (CN) and 1630 (C=N)	4.98 (s, 1H, pyrazole H-4); 5.52 (s, 1H, pyrimidine H-4); 6.9-7.6 (m, 10H, Ar. Protons) and 9.4 (s, br., 3H, NH_2 and NH)
6c	3450, 3380 (NH_2); 3250 (NH); 2200 (CN) and 1620 (C=N).	3.9 (s, 3H, OCH_3); 5.2 (s, 1H, pyrazole H-4); 5.7 (s, 1H, pyrimidine H-4); 6.9-7.6 (m, 9H, ArH, s) and 9.2 (s, br., 3H, NH_2 and NH).
6e	3420, 3320 (NH_2); 3150 *NH); 2200 (CN) and 1630 (C=N).	5.3 (s, 1H, pyrazole H-4); 5.6 (s, 1H, pyrimidine H-4); 6.8-7.5 (m, 8H, furyl and ArH, s) and 8.9 (s, br., 3H, NH_2 and NH).
6g	3450, 3350 (NH_2); 3200 (NH); 2200 (CN) and 1620 (C=N).	2.1 (s, 3H, CH_3); 5.3 (s, 1H, pyrazole H-4(; 5.8 (s, 1H, pyrimidine H-4); 6.9-7.6 (m, 9, Ar. protons); 9.3 (s, br, 2H, NH_2) and 9.7 (s, br., 1H NH).
6l	3420, 3350 (NH_2); 3200 (NH); 2220 (CN) and 1620 (C=N).	2.1 (s, 3H, CH_3); 3.95 (s, 3H OCH_3); 5.1 (s, 1H, pyrazole H-4); 5.9 (s, 1H, pyrimidine H-4); 7-7.5 (m, 8H ArH, s) and 9.7 (s, br., 3H, NH_2 and NH).
6k	3400, 3350 (NH_2); 3200 (NH); 2220 (CN) and 1620 (C=N).	2.0 (s, 3H, CH_3); 5.1 (s, 1H, pyrazole H-4); 5.8 (s, 1H, pyrimidine H-4); 6.9-7.4 (m, 7H, furyl and ArH, s) 9.3 (s, br., 2H, NH_2) and 9.6 (s, br., 1H NH).
6m	3420, 3350 (NH_2); 3210 (NH); 2220 (CN) and 1620 (C=N)	5.15 (s, 1H, pyrazole H-4); 6.0 (s, 1H, pyrimidine H-4); 6.7-7.4 (m, 9H, Ar.protons); 9.4 (s, br, 2H, NH_2) and 9.7 (s, br., 1H NH).
6o	3400, 3350 (NH_2); 3200 (NH); 2200 (CN) and 1630 (C=N).	4.1 (s, 3H, OCH_3); 5.3 (s, 1H, pyrazole H-4); 6.0 (s, 1H, pyrimidine H-4); 6.8-7.6 (m, 8H, Ar. protons) and 9.7 (s, br., 3H, NH_2 and NH).
6p	3450, 3350 (NH_2); 3250 (NH); 2220 (CN) and 1620 (C=N).	5.2 (s, 1H, pyrazole H-4); 6.1 (s, 1H, pyrimidine H-4); 6.8-7.7 (m, 7H, furyl and ArH, s) 9.7 (s, br., 3H, NH_2 and NH).
10a	3440, 3320 (NH_2); 2200 (CN) and 1630 (C=N)	5.3 (s, 1H, pyrazole H-4); 6.8-7.6 (m, 10H, ArHs) and 9.9 (s, br., 2H, NH_2, lost after D_2O exchange)
10c	3420, 3370 (NH_2); 2220 (CN) and 1620 (C=N).	2.1 (s, 3H, CH_3); 6.9-7.6 (m, 9H, ArH's) and 9.5 (s, br., 2H, NH_2, lost after D_2O exchange)
11	3200 (NH); 2220 (CN); 1700 (CO); 1680 (CO); and 1620 (C=N).	5.25 (s, 1H, pyrazole H-4); 5.75 (s, 1H, pyrimidine H-4); 6.7-7.6 (m, 10H, ArH's) and 9.8 (s, br., 1H NH).
12a	3470, 3420, 3360, 3300 (two NH_2); 2225 (CN); 1670 (CO) and 1620 (C=N).	4.1 (m, br., 2H, two CH); 5.4 (s, 1H, pyrazole (H-4); 6.7-7.4 (m, 9H, ArH's) and 9.7 (s, br., 4H, two NH_2)
15a	3450, 3400, 3360, 3300 (two NH_2); 2225 (CN); 1710 (CO) and 1620 (C=N).	5.4 (s, 1H, pyrazole H-4); 8-7.3 (m, 9H, ArH's) and 9.6 (s, br., 4H, two NH_2).
15b	3450, 3400, 3360, 3300 (two NH_2); 1710 (CO) and 1620 (C=N).	5.15 (s, 1H, pyrazole H-4); 5.8 (s, 1H, pyrimidine H-4); 6.9-7.4 (m, 11H, formamide-CH and ArH's); 9.8 (s, br., 3H NH_2 and NH) and 10.8 (s, br., 1H, OH).
17c	3500 (OH); 3450, 3400, (NH_2); 3250 (NH); 2780 (sat. CH); 1690 (CO) and 1625 (C= N)	3.9 (s, 3H, 3H, OCH_3); 5.3 (s, 1H, pyrazole H-4); 5.9 (s,d 1H, pyrimidine H-4); 6.8-7.3 (m, 10H, fomamide-CH and ArH's); 9.7 (s, br., 3H NH_2 and NH) and 10.8 (s, br., 1H, OH)
17f	3500 (OH); 3450, 3400, (NH_2); 3250 (NH); 2985 (sat. CH); 1700 (CO) and 1620 (C=N).	2.15 (s, 3H, CH_3); 5.1 (s, 1H, pyrazole H-4); 5.7 (s, 1H, pyrimidine H-4); 6.9-7.4 (m, 10H, fomamide-CH and ArH's); 9.5 (s, br., 3H NH_2 and NH) and 10.9 (s, br., 1H, OH)
17h	3490 (OH); 3440, 3350, (NH_2); 3250 (NH); 2980 (sat. CH); 1700 (CO) and 1620 (C=N).	2.2 (s, 3H, CH_3); 5.2 (s, 1H, pyrazole H-4); 6.0 (s, 1H, pyrimindine H-4); 6.8-7.3 (m, 9H, fomamide-CH and ArH's); 9.2 (s, br., 2H NH_2); 9.7 (s, br., 1H, NH) and 10.6 (s, br., 1H, OH)
18a	3300, 3250 (two NH); 1680 (CO) and 1625 (C=N).	5.4 (s, 1H, pyrazole H-4); 5.8 (s, 1H, pyrimidine H-4); 6.1 (s, 1H, pyrimidine H-2); 6.9-7.6 (m, 10H, ArH's); 9.4 (s, br., 1H, NH); and 9.7 (s, br., 1H, NH).
18b	3250, 3150, (two NH); 1690 (CO) and 1620 (C=N).	5.1 (s, 1H, pyrazole H-4); 5.6 (s, 1H, pyrimidine H-4); 5.8 (s, 1H, pyrimidine H-4); 6.8-7.3 (m, 9H, furyl and ArH's); 9.9 (s, br., 2H, two NH).

Table II. Continued.

Comp.	IR (KBr, Cm^{-1})	^{1}H-NMR (DMSO-d_6)
18d	3250, 3200, (two NH); 1690 (CO) and 1630 (C=N).	5.3 (s, 1H, pyrazole H-4); 5.6 (s, 1H, pyrimidine H-4); 5.9 (s, 1H, pyrimidine H-4); 6.7-7.4 (m, 8H, furyl and ArH's); .85 (s, br., 2H, two NH).
18f	3300, 3250 (two NH); 1690 (CO) and 1625 (C=N).	2.0 (s, 3H, CH_3); 5.3 (s, 1H, pyrazole H-4); 5.7 (s, 1H, pyrimidine H-4); 6.0 (s, 1H, pyrimidine H-2); 6.8-7.5 (m, 9H, ArH's); 9.7 (s, br., 1H, NH) and 9.9 (s, br., 1H, NH).
18g	3300, 3250, (two NH); 1685 (CO) and 1625 (C=N).	2.1 (s, 3H, CH_3); 5.4 (s, 1H, pyrazole H-4); 5.9 (s, 1H, pyrimidine H-4); 6.3 (s, 1H, pyrimidine H-2); 6.8-7.3 (m, 8H, ArH's); and 9.98 (s, br., 2H, two NH).
18i	3250, 3150, (two NH); 1695 (CO) and 1630 (C=N).	2.2 (s, 3H, CH_3); 5.3 (s, 1H, pyrazole H-4); 5.8 (s, 1H, pyrimidine H-4); 6.1 (s, 1H, pyrimidine H-2); 6.9-7.5 (m, 7H, furyl and ArH's); 9.85 (s, br., 2H two NH).

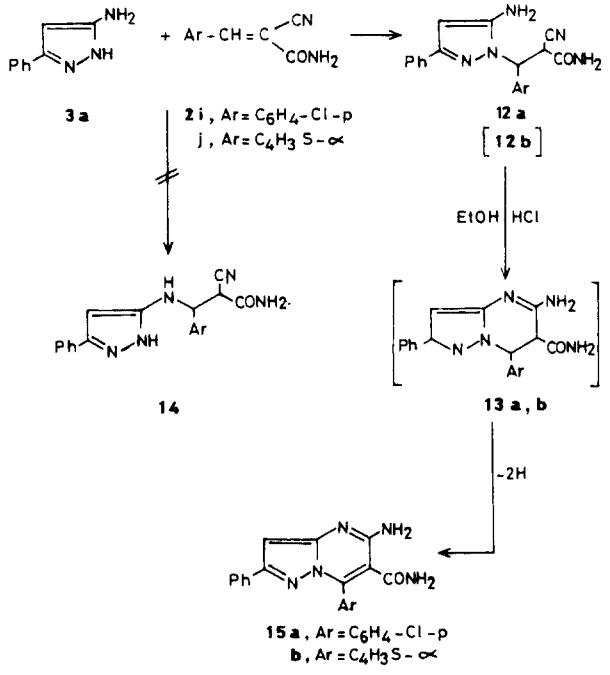


Chart 3.

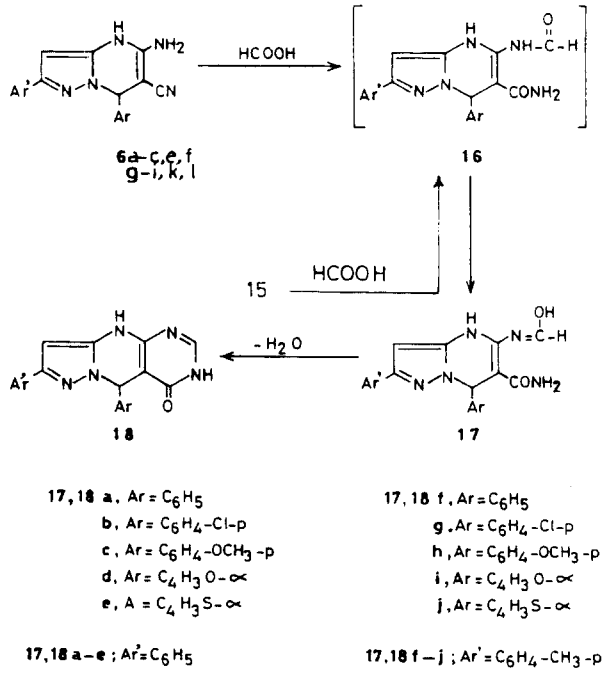


Chart 4.

amino-7-(4-chlorophenyl)-2-phenylpyrazolo[3,2-*b*] pyrimidine-6-carboxamide **15a** most likely formed via the intermediacy of the dihydropyrazolo[3,2-*b*]pyrimidine derivative **13a**. The IR spectrum of **15a** showed the absence of the CN group and this indicating that this group involved in the cyclization step (cf. Chart 3).

In contrast to the behavior of **2i** with **3a**, the α-carboxamidocinnamonitrile derivative **2j** also, reacted with **3a** to give a product with molecular formula $C_{17}H_{13}N_5OS$. The IR spectrum of this reaction product showed the absence of the nitrile function while its ^{1}H-NMR spectrum did not revelaed any pyrimidine protons. This reaction product was formulated as 5-amino-7-(2'thienyl)-2-phenylpyrazole[3,2-*b*] pyrimidine-6-carboxamide (**15b**). Compound **15b** was most likely formed via the intermediacy of the Michael addition product **12b** and the corresponding intermediate dihydropyrimidine derivative **13b** which underwent dehydrogenation into **15b** under the applied reaction conditions (cf. Chart 3.)

The enaminonitrile moiety in compounds **6** was utilised for builiding an additional fused heterocycle. Thus, compounds **6a-c,e,f** and **6g-i,k,l** reacted with anhydrous formic acid to yield products with molecular formulae corresponded to the addition of one molecule of formic acid to one molecule of each of **6**. The IR spectra of these reaction products showed the disappearance of the CN group and instead one carbonyl and a strong OH band were observed in each case. The reaction products were formulated as 5-formamido-6-carboxamidopyrazolo[3,2-*b*]pyrimidine

derivatives **17a-j** most likely formed via the intermediate of **16** respectively (cf. Chart 4). The isolation and characterization of **17a-j** have not been reported in literature. Compounds **17a-j** could, in turn, be cyclised by the action of a mixture of acetic acid-acetic anhydride, via the loss of water to yield the corresponding pyrazolo[1,2;4',5']pyrimido[4,5-*d*]pyrimidinone derivatives **18a-j** in good yields (cf. Chart 4). The IR spectra of **18a-j** showed the presence of bands related to NH, ring CO and C=N group in each case (cf. Table II); Singlets of pyrazole H-4, pyrimidinone H-2 and pyrimidine H-4 were also detected in the ^{1}H-NMR spectra of these derivatives.

Compounds **17** (and hence **18**) could also be obtained via another route by the action of formic acid on the corresponding **15**. Compounds **17** and **18** formed via this route were found completely identical in all respects as **17** **18** formed via the reaction of the corresponding **6** with formic acid followed by cyclization (cf. Chart 4).

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr discs) were recorded on a Pye-Unicame sp-1100 spectrophotometer. ^{1}H-NMR spectra in DMSO-d_6 or $CDCl_3$ were recorded on a Varian EM 390-90 MHz and Gemini 200 MHz spectrometers using TMS as an internal standard and chemical shifts are expressed as (δppm) units. Microanalyses were performed at the Microanalytical Center of Cairo University using Perkin-Elmer 2400 CHN Elemental Analyzer. The mass spectra were recorded at 15 eV using Hewlett-Packard (GC-MS) Model 5988 A spectrometer.

Synthesis of 6a-p, 10a-d, 12a and 15a,b (General procedure)

A solution of each of **3a-c** (0.01 mole) in absolute ethanol (30 ml) containing triethylamine (0.5 ml) was treated with each of **2a-j** (0.01 mole) and the reaction mixture was heated under reflux for 2~3 hours. The solid products separated either while the solution was still boiling or after cooling were filtered off and then recrystallized from the ethanol the give **6a-p**, **10a-d** and **15a,b** (cf. Tables I and II).

Cyclisation of 12a into 15a

A solution of **12a** (1 g) in absoluted ethanol (30 ml) was treated with concentrated hydrochloric acid and the reaction mixture was heated under reflux for 5 hours. Addition of cold water gave a solid product which was filtered off, washed with water then crystallized from ethanol to give **15a** (cf. Tables I and II).

Synthesis of 10a-d (General procedure)

A solution of each of **6a,b,g,h** (1 g) in absolute ethanol (30 ml) was treated with concentrated hydrochloric acid (5 ml) and the reaction mixture was then treated under reflux for 3 hours. The solid products obtained after cooling were filtered off, washed with water then recrystallized from the ethanol to give **10a-d** respectively (cf. Tables I, II).

Synthesis of 11

A solution of **6a** (0.01 mole) in sodium ethoxide (prepared from 0.01 atom of sodium metal in 30 ml of absolute ethanol) was treated with (0.01 mole) diethyl oxalate. The reaction mixture was heated under reflux for 6 hours and then cooled and poured onto ice-cold water, the solid product were filtered off, washed with water then recrystallized from the proper solvent to afford compound **11** (cf. Tables I and II).

Synthesis of 18

A mixture of the appropriate **17** and acetic anhydride/acetic acid (20 ml 1:1) was heated under reflux for 5 hours. The reaction mixture was cooled and poured onto ice-cold water. The solid produced were filtered off and then recrystallized for ethanol to afford **18** (cf. Tables I and II).

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