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Reactions with Heterocyclic Amidines (V). Synthesis of some new imidazo[1, 2-b] pyrazole, pyrazolo[5, 1-c]-1, 2, 4-triazine and pyrazolo[5, 1-c]-1, 2, 4-triazole derivatives

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Abstract □ Several new imidazo [1, 2-b] pyrazole, pyrazolo [5, 1-c]-1, 2, 4-triazine and pyrazolo [5, 1-c] triazole derivatives were prepared from the reaction of 3-antipyrinyl-5-aminopyrazole or its diazonium salt with α-chloroacetyl derivatives.

Keywords □ Imidazo [1, 2-b] pyrazole, pyrazolo [5, 1-c]-1, 2, 4-triazine, Pyrazolo [5, 1-c]-1, 2, 4-triazole

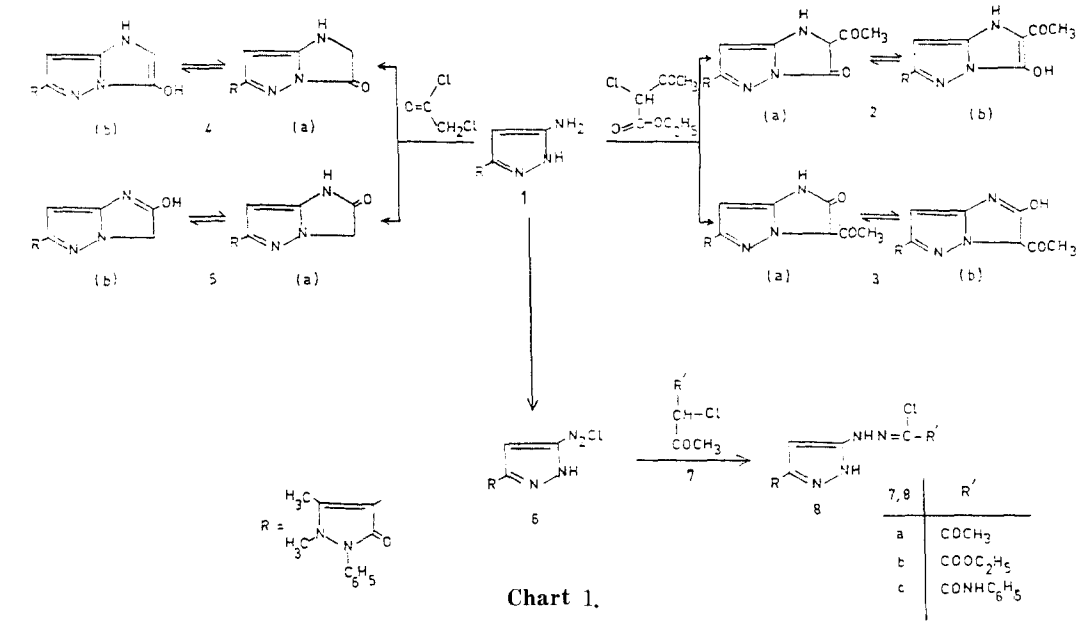
Interest in the synthesis of fused pyrazoles has recently been revived[1,2]. The reported antipyretic[3], analgesic[4], *c*AMP phosphodiesterase inhibitory action[5,6] and CNS activity[7,8] of certain pyrazolo [1, 5-a] pyrimidines as well as its azo analogues have promoted this interest. These considerable biological activities have stimulated interest in the synthesis and chemistry of a new class of fused pyrazole compounds carrying antipyrinyl moiety at C-2.

In spite of enormous literatures reported for the synthesis of fused pyrazole derivatives, relatively few successful synthesis of imidazo [1, 2-b] pyrazoles has been reported[9,10]. Thus, 3-antipyrinyl-5-aminopyrazole[11] (**1**) reacts with ethyl α-chloroacetoacetate to yield a product with molecular formula $C_{18}H_{17}N_5O_3$. From several possible isomeric structures, structure **3b** was established based on ^{1}H-NMR spectrum which revealed the absence of NH proton and the presence of H-6 proton in the aromatic region. Also, **1** reacts with chloroacetyl chloride to give a product for which isomeric structures **4** and **5** were considered (Chart 1). Structures **4a, 4b** and **5a** were ruled out based on ^{1}H-NMR spectrum which revealed the presence of OH and CH_2 signals at $\delta = 10.85$ and 4.20. Other isomeric structures were not detected with the reaction product **5a**. The IR spectra of structures **3b** and **5b** revealed a broad band extending from 2500-3300 cm^{-1} for chelated OH[10,12]. It is interesting to note that the C-6 proton in compound **3b** is deshielded down field as compared with **5b** due to the anisotropy of exocyclic CO group.

Diazotized cyclic amidines have been shown to couple with active hydrogen reagents to yield hydrazones which cyclized readily into azolotriazines[13-15]. It occurred to us that if diazotized aminopyrazole **6** could be coupled with α-chloro derivatives, the resulting hydrazones may serve as excellent starting material for preparation of fused pyrazoles. Thus it has been found that **6** couples with α-chloroacetylacetone, ethyl α-chloroacetoacetate and α-chloroacetoacetanilide to yield the corresponding hydrazonyl halides **8a-c**, respectively (Chart 1). **8** could be readily cyclized into pyrazolo-[5, 1-c]-1, 2, 4-triazines and pyrazolo [5, 1-c]-1, 2, 4-triazole. Compound **8a** was cyclized into the pyrazolo [5, 1-c] triazines **9** and **10** on treatment with phenylhydrazine and aniline, respectively. Compound **8b** reacts with malononitrile and ethyl cyanoacetate in ethanolic sodium ethoxide solution to yield **11a,b.** Structure **11** was established based on elemental analysis, IR and ^{1}H-NMR spectra. Alkaline elimination of methyl group in position-3 of antipyrine ring was previously reported[16]. **8c** converted to pyrazolo [5, 1-c]-1, 2, 4-triazole **12** in boiling pyridine (Chart 2).

EXPERIMENTAL METHODS

Melting points are uncorrected. Infrared spectra were recorded using a Pye Unicam SP-1000



7,8	R′
a	$COCH_3$
b	$COOC_2H_5$
c	$CONHC_6H_5$

Chart 1.

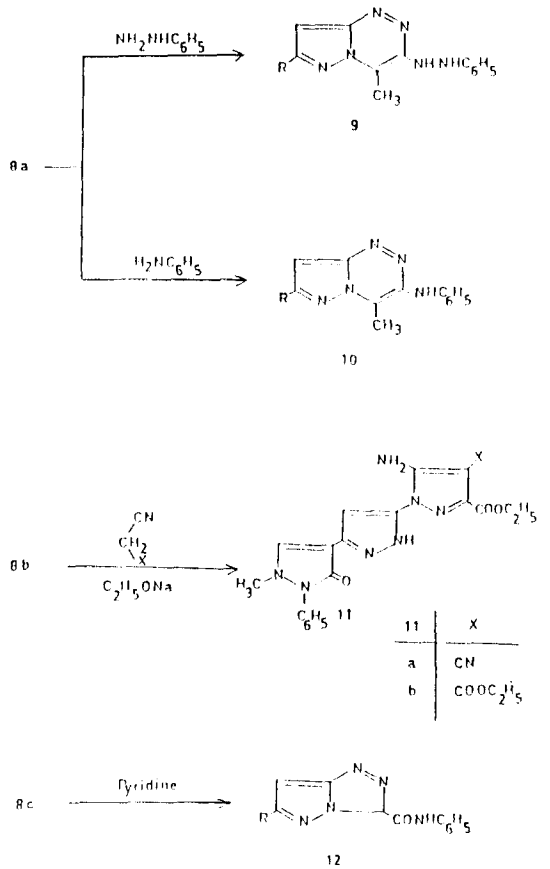


Chart 2.

spectrophotometer. The ^1H NMR spectra were measured on a Varian EM-390 90 MHz using TMS as an internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the analytical Data Unit at Cairo University.

2-Antipyrinyl-5-hydroxyimidazo [1, 2-b] pyrazoles (3b, 5b)

1 (0.01 mol) and ethyl α-chloroacetoacetate (0.01 mol) or chloroacetyl chloride (0.01 mol) in dry benzene was refluxed for 2 h. The solvent was removed in vacuo, the product was heated with (5%) Na_2CO_3 solution, and then crystallized to give **3b** and **5b**(Table I and II).

Arylhydrazone derivatives of 1

A cold solution of **6** (prepared from 0.01 mol of **1** and the appropriate quantities of HCl and $NaNO_2$ as previously[17] described) was added to a solution of **7** (0.01 mol) in ethanol (30 ml) and sodium acetate (3g). The reaction mixture was stirred for 2 h, the solid product was crystallized and identified as **8a-c**(Table I and II).

2-Antipyrinyl-6-substituted amino-7-methyl pyrazolo [5, 1-c]-1, 2, 4-triazine (9 and 10)

A suspension of **8a** (0.01 mol) in ethanol (30 ml) was refluxed with phenylhydrazine and/or aniline (0.012 mol) for 4 h. The solvent was evaporated in vacuo and the remaining product was washed several times with water then crystallized and identified as **9** and **10**(Table I and II).

Table I. Spectroscopic data of new compounds.

Compound	IR (cm^{-1})	^{1}H-NMR (δ ppm)
3 b	3300 – 2500 (OH dimer); 1680 (CO acetyl); 1640 (CO antipyrinyl).	2.3 (s, 3H, CH_3); 2.6 (s, 3H, CH_3); 3.3 (s, 3H, N-CH_3); 6.2 (s, 1H, pyrazole H-4); 7.33 (m, 6H, C_6H_5 +1CH); 10.9 (s, 1H, OH).
5 b	3300 – 2500 (OH); 1640 (CO antipyrinyl).	2.3 (s, 3H, CH_3); 3.2 (s, 3H, N-CH_3); 4.2 (s, 2H, CH_2); 6.66 (s, 1H, pyrazole H-4); 7.45 (m, 5H, C_6H_5); 10.85 (s, 1H, OH).
8 a	3500 – 3350 (NH); 1680 (CO acetyl); 1640 (CO antipyrinyl).	
8 b	3550 – 3200 (NH); 3000, 2995 (CH_3); 1740 (ester CO); 1650 (antipyrinyl CO).	1.3 (t, 3H, CH_3); 2.45 (s, 3H, ester CH_3); 3.2 (s, 3H, N-CH_3); 4.2 (q, 2H, CH_2 ester); 6.2 (s, 1H, pyrazole H-4); 7.4 (m, 6H, C_6H_5 +1NH); 10.6 (s, 1H, NH).
8 c	3600 – 3150 (NH); 3010, 2995 (CH_3); 1690 (amide CO); 1650 (antipyrinyl CO).	2.58 (s, 3H, CH_3); 3.2 (s, 3H, N-CH_3); 6.4 (s, 1H, pyrazole H-4); 7.6 (m, 11H, $2C_6H_5$ +1NH); 10.0 (s, 1H, NH); 10.66 (s, 1H, NH).
9	3500 – 3150 (NH); 3000, 2990 (CH_3); 1640 (antipyrinyl CO).	2.3 (s, 3H, CH_3); 2.9 (s, 3H, CH_3); 3.2 (s, 3H, N-CH_3); 4.3 (s, 1H, NH); 6.4 (s, 1H, pyrazole H-4); 7.6 (m, 10H, $2C_6H_5$); 9.8 (s, 1H, NH).
10	3450 (NH); 3010, 2995 (CH_3); 1640 (antipyrinyl CO).	
11 a	3600 – 3350 (NH, NH_2); 3010, 2995 (CH_3); 2220 (CN); 1760 (CO ester); 1660 (antipyrinyl CO).	1.1 (t, 3H, CH_3); 2.8 (s, 3H, N-CH_3); 3.9 (q, 2H, CH_2 ester); 4.6 (s, 1H, pyrazolone H-3); 6.3 (s, 1H, pyrazole H-4); 7.6 (m, 8H, C_6H_5 +NH +NH_2).
11 b	3550 – 3300 (NH); 3000, 2990 (CH_3); 1750 (CO ester); 1660 (antipyrinyl CO).	
12	3320 (NH); 3000, 2990 (CH_3); 1680 (CO amide); 1640 (antipyrinyl CO).	2.4 (s, 3H, CH_3); 3.1 (s, 3H, N-CH_3); 6.1 (s, 1H, pyrazole H-4); 7.2 (m, 7H, C_6H_5, NH, H-7).

Reaction of 8 b with malononitrile and ethyl cyanoacetate

To an ethanolic sodium ethoxide solution (5%) (50 m*l*) was added 0.01 mol of **8b** and 0.01 mol of malononitrile and/or ethyl cyanoacetate. The reaction mixture was then stirred at room temperature for 10 h, then poured into ice cold water (100 m*l*) and acidified with c-HCl. The solid product was collected by filtration and identified as **11a, b**(Table I and II).

2-Antipyrinyl-6-carbanilidepyrazolo [5, 1-c] -1, 2, 4-triazole (12)

A solution of **8c** (2.0g) in dry pyridine (30 m*l*) was refluxed for 2 h. The solvent was removed *in vacuo* and the remaining solid product was triturated with H_2O and collected by filtration(Table I and II).

Table II.

Compd. (colour)	Cryst. solvent	M. P. (℃)	Yield (%)	Mol. Form. (Mol. Mass)	Analysis % C	Calc. H	Found N
3b	DMF	> 300	79	$C_{18}H_{17}N_5O_3$	61.5	4.88	19.9
(yellow)				(351.37)	61.4	4.72	19.8
5b	Dioxane	265	85	$C_{16}H_{15}N_5O_2$	62.1	4.89	22.6
(yellow)				(309.33)	62.3	4.77	22.4
8a	EtOH	> 300	72	$C_{17}H_{17}N_6O_2Cl$	54.8	4.60	22.5
(yellow)				(372.82)	55.0	4.81	22.4
8b	EtOH	209	75	$C_{18}H_{19}N_6O_3Cl$	54.9	4.86	21.3
(yellow)				(393.85)	54.8	4.76	21.2
8c	EtOH	221	61	$C_{22}H_{20}N_7O_2Cl$	58.7	4.48	21.8
(yellow)				(449.90)	58.6	4.71	21.6
9	EtOH	189	55	$C_{23}H_{22}N_8O$	64.8	5.20	26.3
(red)				(426.49)	64.8	5.26	26.2
10	Dioxane	> 300	42	$C_{23}H_{21}N_7O$	67.1	5.40	23.8
(yellow)				(411.47)	67.3	5.30	23.6
11a	DMF	275	55	$C_{20}H_{18}N_8O_3$	57.4	4.34	26.8
(brown)				(418.42)	57.2	4.32	26.5
11b	DMF	262	50	$C_{22}H_{24}N_7O_5$	56.7	5.19	21.0
(brown)				(466.48)	56.6	5.11	20.8
12	DMF	> 300	85	$C_{22}H_{19}N_7O_2$	63.9	4.63	23.7
(red)				(413.44)	63.2	4.39	23.6

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