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by

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REACTION OF ARYL CARBAMOYL ARYL HYDRAZIDOYL CHLORIDES WITH ACTIVATED NITRILE

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ABSTRACT

The carbanions of ethylcyanoacetate, cyanoacetamide, malononitrile and cyanoacetamide react with Aryl carbamoyl aryl hydrazidoyl chlorides (1 a-f) in ethanol at room temperature to give the corresponding substituted pyrazoles (3a-f, 6a-c, 7a-e and 8a). The structural assignments have been made on the basis of elemental analysis, spectral data and the chemical evidence for the resulting pyrazoles. On the other hand, aminoacetonitrile was reacted with (1b) and 9 to give the corresponding substituted triazines (13b) and quinolino [1, 2-f] triazone derivative (12). The mechanism of the different reactions were discussed.

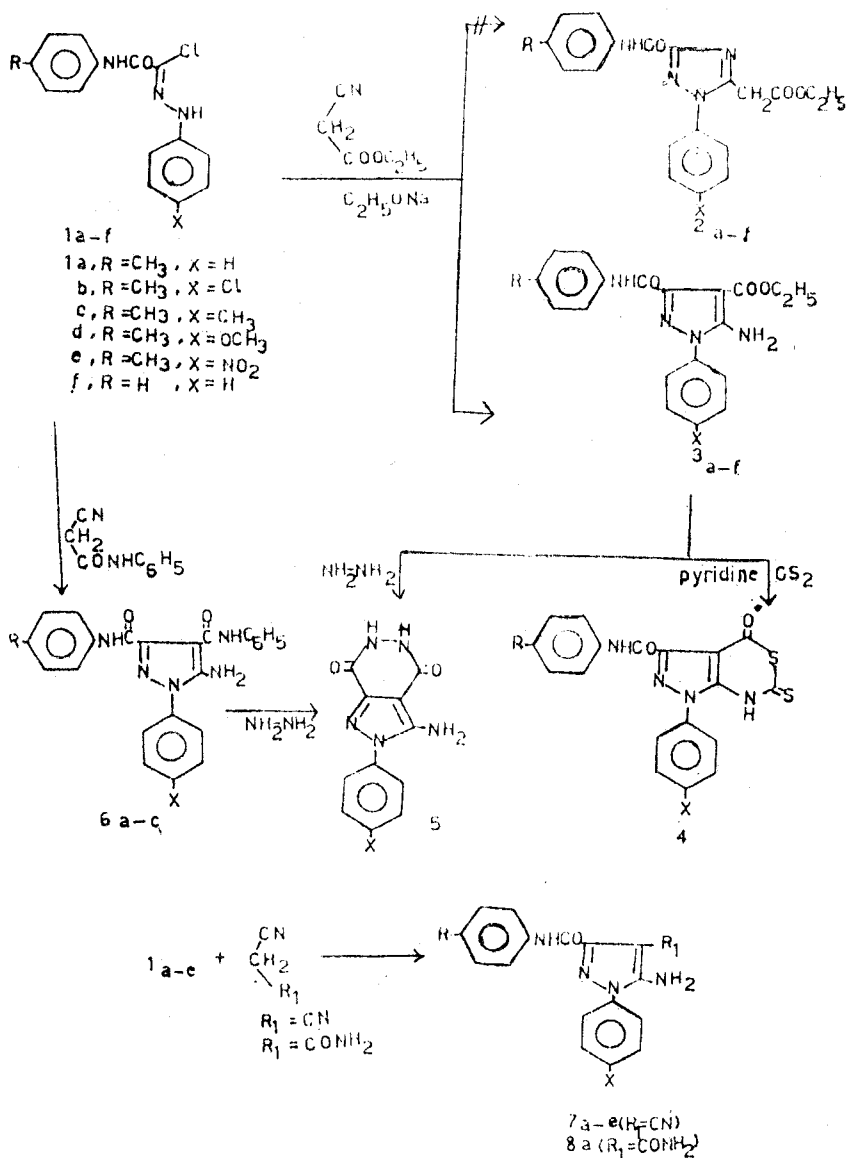
Hydrazidoyl halides are reactive intermediates and their utility in heterocyclic synthesis has considerable attention.¹⁻⁴ In previous work³⁻⁶ it has been reported that hydrazidoyl halides react with B-diketones to yield products which were formulated as pyrazole derivatives.

In continuation of this work we reported here the results of our further investigation on the reaction of hydrazidoyl halides. Thus, aryl carbamoyl aryl hydrazidoyl chlorides (1a-f) were reacted with ethylcyanoacetate in sodium ethoxide solution to produce either triazole derivatives (2a-f) or pyrazole derivatives (3-af). The first product (2a-f) was resulted via 1,3-dipolar cycloaddition reaction of nitrile imine generated via base catalyzed elimination of hydrogen chloride and cyano group. The second product (3-af) was resulted via nucleophilic substitution reaction of hydrazidoyl chloride (1a-f) and carbanion of ethylcyanoacetate followed by cyclization reaction on cyano group. The elemental analysis and IR data can't differentiate between the two possible structures 2a-f and 3a-f, but the ¹HNMR data excluded the structure 2a-f due to a singlet band for NH₂- group at 5.4 ppm which disappear by deuteration. The structure of 3a-f was supported by chemical evidence. It has been

found that, the product (3a) reacted with carbon disulphide in pyridine solution to give a pyrazolo [4,5-d] thiazine derivative (4). Also, equimolecular amounts of (3b) and hydrazine hydrate yielded product which was formulated as pyrazolo [3,4-d] pyridazine derivative (5). The structures of (4 and 5) were confirmed by elemental analysis and IR data. On the other hand, compound (1a-c) was reacted with cyanoacetanilide to give pyrazole derivatives (6a-c), the pyrazole products (6b) were reacted with hydrazine hydrate to yield the same product of reaction of compound (3b) with hydrazine hydrate to add another evidence for the structure (3b and 6b). If the reaction product of (1a-f) with ethylcyanoacetate was triazole (2a-f), it would be completely impossible to rationalize to formation of compounds (4 and 5), though we excluded triazole structure (2a-f). Compound (1a-f) also reacted with other activated nitrile reagents, such as, malononitrile and cyanoacetamide to yield the corresponding pyrazole derivatives (7a-f and 8a) respectively. Compound (7a-f) can't react with carbon disulphide or isothiocyanate derivative and we rationalize the deactivation of the amino group, for the formation of the Zwitter ion on the amino group generated from the adjacent cyano group. This is in contrast with compound (3a) which reacted smoothly with carbon disulphide to yield the pyrazolo [4,5-d] thiazine derivative (4), (cf. scheme I).

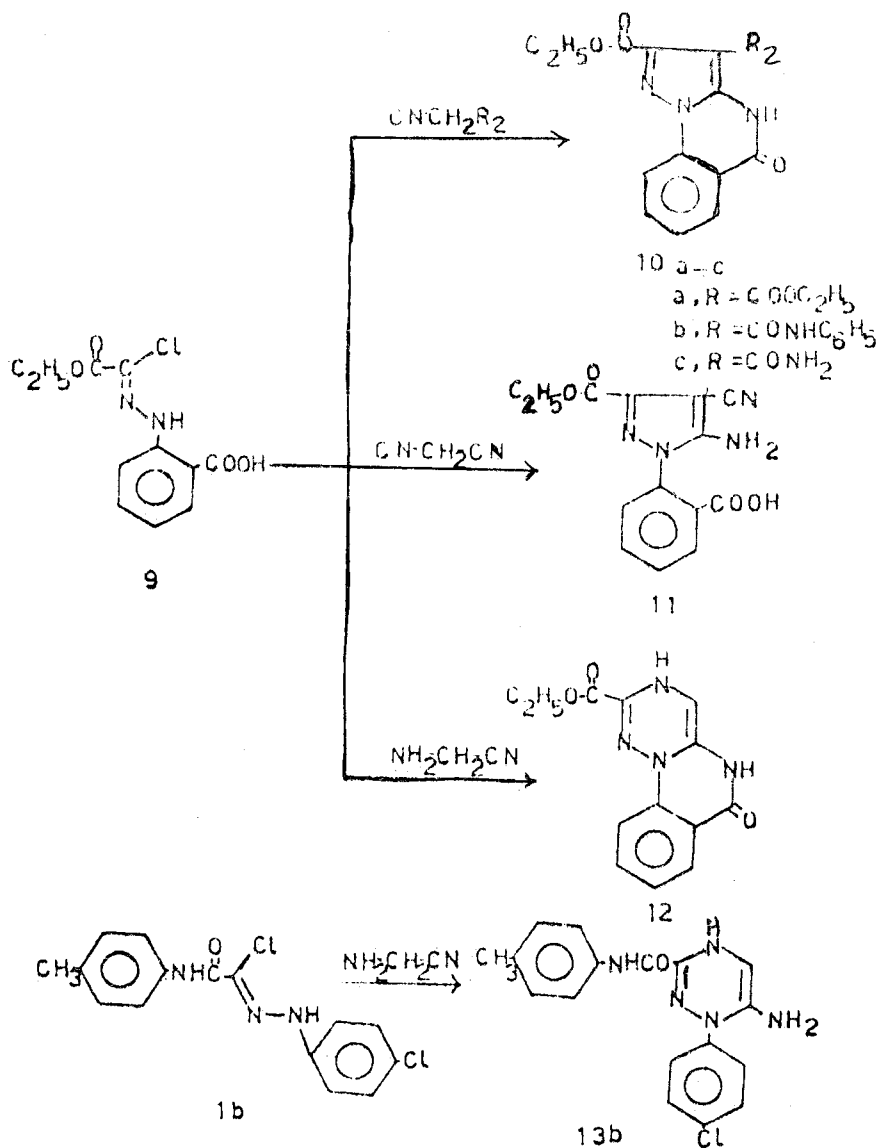
In the same way, hydrazidoyl chloride (9) was reacted with ethylcyanoacetate, cyanoacetanilide and cyanoacetamide to yield products, which were formulated as pyrazolo 1,5-b quinoline-6- one derivatives (10a-c). The formation of compounds (10a-c) would be rationalized through the pyrazole formation, followed by cyclization due to loss of water. In contrast, hydrazidoyl chloride (9) was reacted with malononitrile to yield the corresponding pyrazole derivative (11). The Zwitter ion on the amino group prevented cyclization retaining the pyrazole derivative (11). The structure of compounds (10a-c and 11) were confirmed by elemental analysis and spectral data.

On the other hand, hydrazidoyl chloride (9) reacted with aminoacetonitrile to yield a product which was formulated as quinoline [1,2-f] triazine derivative (12). The structure suggested for (12) was based on the elemental analysis and IR data. Also hydrazidoyl chloride (1b) was reacted with aminoacetonitrile to yield the triazine derivative (13b). The mechanistic pathway for formation of the compound (12) was described as, in first, the nucleophilic substitution reaction of compound (9) with amino group takes place followed by cyclization reaction with



cyano group to produce triazine derivative as intermediate product, which consequently cyclizes through loss of water to give quinoline [1,2-f] triazine derivative (12). Thus, we excluded the reaction of methylene group or the 1,3-dipolar cycloaddition reaction of aminoacetonit-

riple with hydrazidoyl chlorides (1b and 9) due to the chemical behaviour of the product and due to the fact that we can't rationalize the formation of quinoline [1,2-f] triazine derivative (12), (cf. scheme II).



EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr on a Pye Unicam SP. 1100 spectrophotometer. ^1H NMR were recorded on a Varian A-60 spectrometer and chemical shifts are expressed in δ units ppm down field from TMS as the internal standard. Analytical data were obtained from the Micro-Analytical Center at Cairo University.

General method to prepare pyrazole derivatives 3a-f, 6a-c, 7a-f and 8a:

To an ethanolic sodium ethoxide solution prepared by dissolving metallic sodium (0.11 g, 0.005 mole) in ethanol (20 ml) ethyl (0.005 mole) cyanoacetate or cyanoacetanilide or malononitrile and cyanoacetamide were added with stirring. To the resulting solution, the hydrazidoyl chlorides (1a-f) (0.005 mole) were added and stirring were continued for 2 hrs. The reaction was left overnight at room temperature. The solid precipitate was collected and recrystallized from suitable solvent to give pyrazole derivatives 3a-f, 6a-c, 7a-f and 8a respectively. (cf. table I).

Table: 1



List of new Aminopyrazole derivatives 3a-f, 6a-c, 7a-f, 8a and 11.

Compd. No.	R_1	R	X	m.p. C.	Molecular formula	Crystal solvent	Mol. wt.	Analysis %	
								Calcd.	Found
3a	COOC_2H_5	CH_3	H	80	$\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_3$	EtOH	364	65.9/65.7	5.5/5.4
3b	"	"	Cl	167	$\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_3\text{Cl}$	"	398.5	60.2/60.1	4.8/4.8
3c	"	"	CH_3	153	$\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_3$	"	378	66.7/66.5	5.8/5.6
3d	"	"	CH_3O	140	$\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_4$	"	394	63.9/63.8	5.6/5.5
3e	"	"	NO_2	193	$\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_5$	"	409	58.7/58.6	4.6/4.4
3f	"	H	H	115	$\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_3$	"	350	65.1/64.8	5.1/4.9
6a	$\text{C}_6\text{H}_5\text{NH-}$	CH_3	H	243	$\text{C}_{22}\text{H}_{21}\text{N}_5\text{O}_2$	AcOH	411	70.1/69.8	5.1/5.0
6b	"	"	Cl	275	$\text{C}_{24}\text{H}_{20}\text{N}_5\text{O}_2\text{Cl}$	"	445.5	64.6/64.7	4.5/4.4
6c	"	H	H	220	$\text{C}_{22}\text{H}_{19}\text{N}_5\text{O}_2$	"	397	69.5/69.3	4.8/4.9
7a	CN	CH_3	H	208	$\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}$	EtOH	317	68.1/68.0	4.7/4.5
7b	"	"	Cl	235	$\text{C}_{18}\text{H}_{14}\text{N}_5\text{OCl}$	"	351.5	61.4/61.2	4.0/3.8
7c	"	"	CH_3	200	$\text{C}_{19}\text{H}_{17}\text{N}_5\text{O}$	"	331	68.9/68.6	5.1/5.0
7d	"	"	CH_3O	205	$\text{C}_{19}\text{H}_{17}\text{N}_5\text{O}_2$	"	347	65.7/65.5	4.9/4.9
7e	"	"	NO_2	282	$\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}$	AcOH	362	59.7/59.6	3.9/3.7
7f	"	H	H	206	$\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}$	EtOH	303	67.3/67.1	4.3/4.1
8a	CONH_2	CH_3	H	164	$\text{C}_{18}\text{H}_{17}\text{N}_5\text{O}_2$	"	335	64.5/64.4	4.1/4.9
11				25	$\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_4$	AcOH	300	56.0/55.8	4.0/3.9

IR of these compounds were made and are in good agreement with structures proposed.

Table 2. List of ^1H NMR data

Compd. No.	^1H NMR beak ppm
3b	1.3 (t, 3H, CH_3), 1.7 (s, 3H, CH_3), 4.25 (q, 2H, CH_2) 5.4 (s, 2H, NH_2), 7.1-7.8 (m, 8H, Aromatic protons).
3e	1.28 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.3 (q, 2H, CH_2) 6.6 (s, 2H, NH_2), 7.2-7.45 (8, 8H Aromatic protons) 10.5 (s, 1H, NH).
3f	1.3 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 5.6 (s, 2H, NH) 7.1-7.9 (m, 10H, Aromatic protons), 11.6 (s, 1H, NH).
7c	2.4 (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 6.8 (s, 2H, NH_2) 7.1-7.8 (m, 8H, Aromatic protons), 10.0 (s, 1H, NH).
7d	2.5 (s, 3H, CH_3), 3.9 (s, 3H, -o- CH_3), 6.9 (s, 1H, NH) 7.0-7.9 (m, 8H, Aromatic protons), 10.4 (s, 1H, NH) 10.6 (s, 1H, NH).
7e	2.4 (s, 3H, CH_3), 6.98 (s, 1H, NH), 8.1-8.3 (m, 8H, Aromatic protons), 10.2 (s, 1H, NH), 10.9 (s, 1H, NH).
7f	6.2 (s, 2H, NH_2), 7.1-7.8 (m, 10H, Aromatic protons), 9.3 (s, 1H, NH).

Pyrazole [3,4-c] mercaptothiazin-6-one derivative (4):

A suspension of pyrazole (3a) (0.01 mole) was refluxed 6hrs in (50 ml) pyridine containing (0.01 mole) of carbon disulphide. The reaction mixture was poured into ice-water, then acidified by dilute hydrochloric acid, the product formed was crystallized from acetic acid to give compound 4 in 62 % yield.

compound 4 formed yellow powder m.p. 212 °C, Calcd. for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}_2\text{S}_2$ (380), C, 60.0; H, 3.7; N, 11.0; S, 16.8 %.

Found: C, 60.1; H, 3.5; N, 10.8; S, 16.5 %.

Pyrazolo [3,4-d] pyridazine derivative (5):

A mixture of pyrazole (3b) or (6b) was refluxed for 3hrs with hydrazine hydrate, then the reaction mixture was poured into ice-water, the solid precipitate was collected and recrystallized from ethanol to give pyrazolo, 3,4-d pyridazine derivative (5). Compound 5 formed white powder m.p. 260 °C in 50 % yield.

Calcd. for $\text{C}_{11}\text{H}_8\text{N}_5\text{O}_2\text{Cl}$ (277.5) C, 47.6; H, 2.9; N, 25.2 %.

Found. C, 47.4; H, 2.6; N, 25.1 %.

Pyrazolo 1,5-b quinoline derivative (10a-c):

To an ethanolic sodium ethoxide solution prepared by dissolving metallic sodium (0.11 g) in ethanol (20 ml) ethyl cyanoacetate, cyanoac-

tanilide and cyanoacetamide (0.005 mole) were added with stirring. To the resulting mixture, the hydrazidoyl chloride (9) (0.005 mole) was added and stirring continued for 2hrs. The reaction was left overnight at room temperature. the solid precipitate was collected and recrystallized from suitable solvent to give pyrazolo [1,5-b] quinoline derivative (10a-c) respectively.

compound 10a, m.p 232 °C in 65 % yield.

Calcd. for $C_{16}H_{15}N_3O_5$ (329) C, 58.3; H, 4.5; N, 12.8 %.

Found: C, 58.2; H, 4.3; N, 12.5 %.

compound 10b, m.p. 250 °C in 68 % yield.

Calcd. for $C_{20}H_{16}N_4O_4$ (376) C, 63.8; H, 4.2; N, 14.9 %.

Found: C, 63.7; H, 4.0; N, 14.7 %.

compound 10c, m.p. 197 °C in 53 % yield.

Calcd. for $C_{14}H_{12}N_4O_4$ (300) C, 56.0; H, 4.0; N, 18.7 %.

Found: C, 55.9; H, 3.8; N, 18.6 %.

Quinolino [1,2-d] triazine(12) and 6-Aminotriazine (13b)

A mixture of hydrazidoyl chlorides 9 or 1b and aminoacetonitrile was refluxed for 6hrs in ethanolic triethylamine, then the reaction mixture was poured into ice-water, the solid precipitate was collected and recrystallized from ethanol to give compounds (12) and (13) respectively.

compound (12), m.p. 215 °C in 55 % yield.

Calcd. for $C_{13}H_{12}N_4O_2$ (272) C, 57.3; H, 4.4; N, 20.6 %.

Found: C, 57.1; H, 4.3; N, 20.4 %.

compound (13b), m.p. 183 °C in 46 % yield.

Calcd. for $C_{17}H_{16}N_5OCl$ (341.5) C, 59.7; H, 4.7; N, 20.5 %.

Found: C, 59.6; H, 4.5; N, 20.2 %.

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