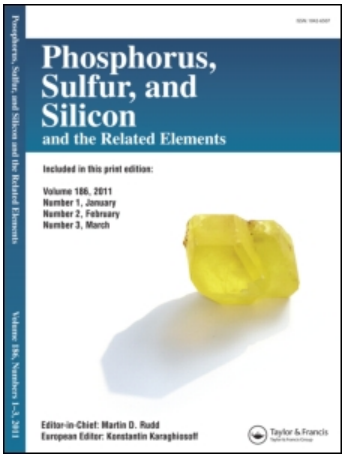

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STUDIES WITH ALKYLHETEROCYCLIC CARBONITRILES: A NOVEL SYNTHETIC ROUTE TO SEVERAL NEW ANNELATED PYRAZOLO[5,1-*C*]-1,2,4-TRIAZINE DERIVATIVES

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STUDIES WITH ALKYLHETEROCYCLIC CARBONITRILES: A NOVEL SYNTHETIC ROUTE TO SEVERAL NEW ANNELATED PYRAZOLO[5,1-*C*]-1,2,4-TRIAZINE DERIVATIVES

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3-Phenylpyrazol-5-yl diazonium chloride (***1a***) was coupled with 2-aminocrotonitrile (***4***) to afford 4-phenyl-6-methylpyrazolo[5,1-*c*]-1,2,4-triazine-7-carbonitrile (***5***). Upon reaction with sulfur, compound ***5*** was transformed into 8-amino-4-phenylthieno[4,3-*e*]pyrazolo[5′,1′-*c*′]-1,2,4-triazine. Compound ***6*** underwent 4 + 2 cycloaddition with several dipolarophiles such as maleic anhydride, N-phenylmaleimide and acrylonitrile to afford a variety of new annelated pyrazolo[5,1-*c*]-1,2,4-triazine derivatives via hydrogen sulfide elimination. The structures of the newly synthesized compounds were determined by elemental analyses and spectral data. A sequence leading to the formation of these compounds and their reactions is described.

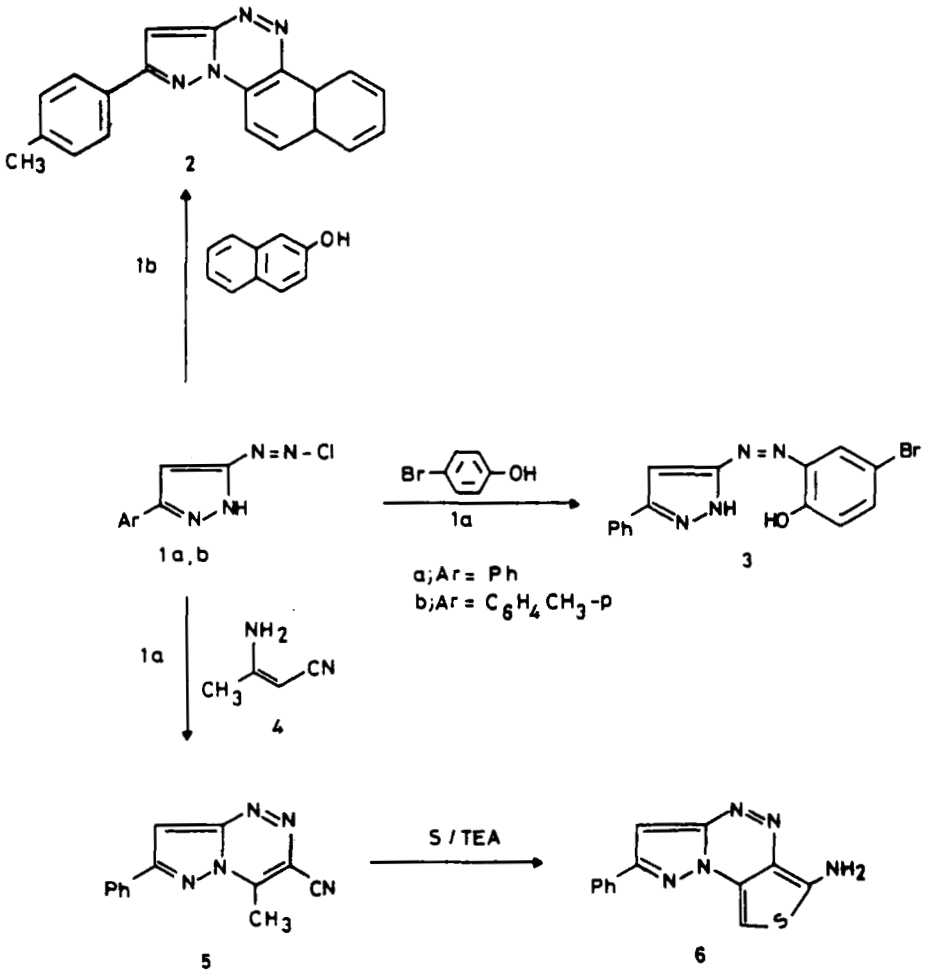
Key words: 4 + 2 Cycloaddition; thieno[4,3-*e*]pyrazolo-triazines; annelated pyrolotriazines.

INTRODUCTION

The chemistry of condensed pyrazole derivatives has received considerable interest due to their biological importance.[1–3] In continuation to our interest in the synthesis of fused pyrazole derivatives as a potential antischistozomal agent,[4] we report herein the synthesis of thieno[4,3-*e*]pyrazolo[5′,1′-*c*′]-1,2,4-triazine and pyrazolo[5,1-*c*]benzo[*e*]-1,2,4-triazine derivatives required for a medicinal chemistry program. Literature survey revealed that derivatives of such ring systems have not been synthesized.

It has been thought that such ring systems could be synthesized via a route similar to that reported for the naphthoanalogues[5] (***2***). These compounds are easily obtained by coupling diazotized aminopyrazoles with 2-naphthol via dehydrocyclization which readily takes place under the reaction conditions. On the other hand, the reaction of diazotized aminopyrazole (***1a***) with substituted phenol led only to the formation of the coupling products (***3***). Attempts to cyclize ***3*** into derivatives of ***2*** have failed which indicates that the formation of ***2*** from diazotized aminopyrazole and 2-naphthol does not involve an azo-derivative intermediate. It has been suggested[6] that these reactions proceed via 4 + 2 cycloaddition mechanism.

Thus, an alternate route to the required derivatives of ***2*** was investigated. It has been found that, diazotized amino-pyrazole (***1a***) coupled readily with 2-aminocrotonitrile (***4***) to afford 4-aryl-6-methylpyrazolo[5,1-*c*]-1,2,4-triazine-7-carbonitrile (***5***). Structure ***5*** was established on the basis of elemental analyses and spectral data (ir



Scheme 1

and ^{1}H nmr, cf. Tables I and II). Compound ***5*** reacted readily with sulfur in ethanol containing catalytic amount of triethyl amine to yield 8-amino-4-phenylthieno[4,3-*e*]pyrazolo[5′,1′-*c*′]-1,2,4-triazine (***6***). Structure ***6*** was also established on the basis of elemental analyses and spectral data (ir and ^{1}H nmr, cf. Tables I and II).

Compound ***6*** is very versatile, and therefore can be utilized for further chemical transformations. Thus, the reaction of ***6*** with maleic anhydride and N-phenylmaleimide afforded addition products via hydrogen sulfide elimination. These products were formulated as ***8a,b*** respectively, and are considered to be formed via the 4 + 2 cycloadduct intermediate ***7***. Acetylation of ***6*** afforded the N-acetyl derivative ***9***, which upon bromination in glacial acetic acid affected hydrolysis of the acetyl group to yield the dibromo-derivative ***10***. Compound ***10*** was also obtained by bromination of ***6*** in glacial acetic acid. Unlike compound ***6***, compound ***9*** did not add electron poor olefines while its bromoderivative ***10*** added maleic anhydride to yield ***12*** which was also obtained by bromination of ***8a*** in glacial acetic acid.

TABLE I

Characterization of the newly synthesized compounds

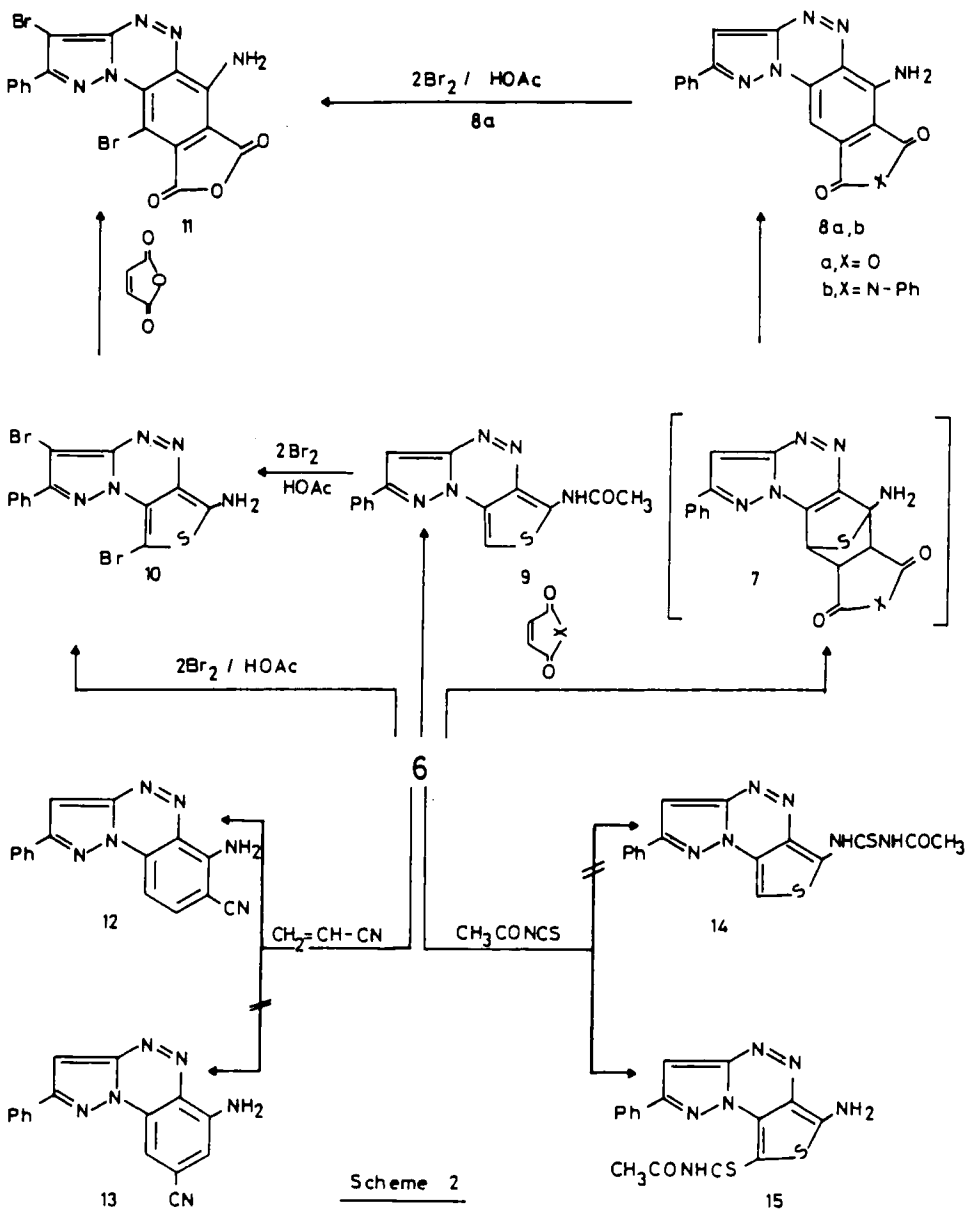
Compd.	Solvent of Cryst.	m.p(C)	Yield (%)	Mol. Formula (M.Wt.)	Found / Calcd (%) C	H	N	S
2	EtOH/Dioxan	238	71	$C_{20}H_{14}N_4$	77.7	4.3	18.2	
				(310.360)	77.4	4.6	18.1	
3	EtOH/DMF	>300	67	$C_{15}H_{11}BrN_4O$	52.3	3.4	16.0	
				(343.189)	52.5	3.2	16.3	
5	EtOH	180	78	$C_{13}H_9N_5$	66.8	3.6	30.0	
				(235.250)	66.4	3.9	29.8	
6	EtOH/DMF	>300	81	$C_{13}H_9N_5S$	58.0	3.6	26.6	12.4
				(267.314)	58.4	3.4	26.2	12.0
8a	EtOH/DMF	290	66	$C_{17}H_9N_5O_3$	61.8	2.4	21.4	
				(331.291)	61.6	2.5	21.1	
8b	EtOH/DMF	>300	59	$C_{23}H_{14}N_6O_2$	67.6	3.7	20.0	
				(406.405)	68.0	3.5	20.1	
9	EtOH/DMF	>300	56	$C_{15}H_{11}N_5OS$	58.0	3.7	22.8	10.5
				(309.351)	58.2	3.6	22.6	10.4
10	EtOH/DMF	>300	83	$C_{13}H_7Br_2N_5S$	37.0	1.9	16.8	7.8
				(425.116)	36.7	1.7	16.5	7.5
11	EtOH/DMF	>300	69	$C_{17}H_7Br_2N_5O_3$	41.7	1.8	14.5	
				(489.093)	41.8	1.5	14.3	
12	EtOH/DMF	285	64	$C_{12}H_{10}N_6$	66.9	3.6	29.1	
				(286.298)	67.1	3.5	29.4	
15	EtOH/DMF	>300	52	$C_{16}H_{12}N_6OS_2$	52.5	3.3	23.0	
				(368.441)	52.2	3.3	28.8	

The difference in reactivity between *6* and *9* can be rationalized in terms of the electronic effect of the acetyl group. Compound *6* is a strained electron rich thiophene derivative; these derivatives have recently been shown to add readily to electron poor olefines.[7] On the other hand, acylation of this derivative to *9* reduces the electron donating effect of the amino group, which in turn lowers the electron demand required to affect the cycloaddition reaction.

TABLE II
Spectroscopic data for the compounds listed in Table I

Compd.	IR (cm^{-1}) (Selected bands)	^1H NMR (δ ppm)
2	1610 (C=C)	6.3(s, 1H, pyrazole 4-H); 7.2-8.1(m, 11H, aromatic protons).
3	3560 (OH); 3240 (NH)	
5	2220 (CN); 1600 (C=C)	2.1(s, 3H, CH_3); 6.4(s, 1H, pyrazole 4-H); 7.3-7.9(m, 5H, C_6H_5).
6	3250-3050 (NH_2); 1600 (C=C).	6.4(s, 1H pyrazole 4-H); 7.0-8.3(m, 8H aromatics and NH_2).
8a	3250-3080 (NH_2); 1700 (CO); 1600 (C=C).	
8b	3300-3050 (NH_2); 1680 (CO); 1590 (C=C).	
9	3150 (NH); 1650 (CO); 1600 (C=C).	1.9(s, 3H, acetyl); 6.4(s, 1H, pyrazole 4-H); 7.3-8.1(m, 7H, aromatics and NH).
10	3250-3050 (NH_2); 1590	7.9-7.2(m, 5H, C_6H_5); 9.1(s, 2H, NH_2).
11	3320-3100 (NH_2); 1710 (CO); 1600 (C=C).	7.8-7.2(m, 5H, C_6H_5); 9.6(s, 2H, NH_2).
12	3250-3150 (NH_2); 2210 (CN); 1600 (C=C).	3.4(s, 2H, NH_2); 6.3(s, 1H, pyrazole 4-H); 7.1 (d, *J*9 Hz, 2H, aromatic protons); 7.6(m, 5H, C_6H_5).
15	3170 (NH); 1660 (CO); 1590 (C=C).	2.0(s, 3H, acetyl); 6.3(s, 1H, pyrazole 4-H); 6.9-7.4(m, 6H, C_6H_5 and NH); 8.7(s, 2H, NH_2).

The reaction of *6* with acrylonitrile in pyridine afforded a product which could be formulated as *12* or the isomeric structure *13*. Structure *12* is preferred based on its ^1H nmr spectrum, since the ring protons appeared as a doublet at δ7.1 ppm with J = 9 Hz, for *o*-coupling. If the product had the isomeric structure *13*, one would expect a lower J value for *m*-coupling. Compound *6* also reacted with ace-



tylisothiocyanate to yield a product which can be formulated as either the thiourea or the thiocarboxamide derivatives (*14* and *15*), respectively. Structure *14* was ruled out based on the ^1H nmr spectrum. Proton nmr spectrum of *15* showed a two protons singlet at $\delta 8.7$ due to the presence of NH_2 group.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded (KBr) using a Perkin-Elmer model 1430 ratio recording spectrometer. ^1H nmr spectra were measured on a Varian EM 390-90 NHz in $CDCl_3$

using TMS as internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the Microanalytical Center at Cairo University. Compounds ***1a,b*** were prepared as reported.[8,9]

Coupling reactions of 4-arylazo-3,5-diamino(1H)pyrazoles (***1a,b***). *General procedure:* A suspension of the aminopyrazole derivative (0.01 mol) was gradually added to a cold solution of 0.01 mol of each of 2-naphthol, 4-bromophenol or 2-aminocrotonitrile in 20 ml ethanol containing 0.02 mol sodium acetate with continuous stirring; to give ***2***, ***3*** and ***5*** respectively. The products were collected by filtration, washed with water and crystallized from the proper solvent.

8-Amino-4-phenylthieno[4,3-e]pyrazolo[5',1'-c']-1,2,4-triazine (***6***). To a solution of ***5*** (0.01 mol) in 25 ml absolute ethanol, sulfur (0.01 mol) and triethylamine (0.5 ml) were added. The resulting solution was refluxed for 3 h, cooled, poured into ice-cold water and then neutralized with conc. HCl. The solid so formed was collected by filtration, washed with water and crystallized from EtOH/DMF.

4 - Phenylpyrazolo[5,1 - c]benz[c]furo - and 10 - amino - 4,8 - diphenyl[5,1 - c]benz[c]pyrrolo - 1,2,4 - triazine-7,9-diones (***8a,b***). A mixture of ***6*** (0.01 mol) and each of maleic anhydride or N-phenylmaleimide (0.01 mol) in 30 ml pyridine was refluxed for 3 h, cooled to room temperature, poured into ice-cold water and acidified with conc. HCl. The resulting solid product was collected by filtration washed with water and crystallized from EtOH/DMF.

8-N-Acetylamino-4-phenylthieno[4,3-e]pyrzazolo[5',1'-c']-1,2,4-triazine (***9***). A mixture of ***6*** (0.01 mol), 20 ml glacial acetic acid and 10 ml acetic anhydride was refluxed for 2 h, cooled and poured into ice-cold water. The precipitated solid product was filtered off, washed with water and crystallized from EtOH/DMF.

8-Amino-3,6-dibromo-4-phenylthieno[4,3-e]pyrzolo[5',1'-c']-1,2,4-triazine (***10***). Method a: To a solution of ***6*** (0.01 mol) in 20 ml glacial acetic acid, bromine (0.02 mol) was gradually added at room temperature. The reaction mixture was stirred for further 3 h, then diluted with water (80 ml). The resulting solid product was collected by filtration and crystallized from EtOH/DMF.
Method b: The same procedure as described in "method a" was followed, starting with compound ***9*** to give compound ***10***.

10-Amino-3,6-dibromo-4-phenylpyrazolo[5,1-c]benz[c]furo-1,2,4-triazine-7,9-dione (***11***). Method a: A mixture of ***10*** (0.01 mol) and maleic anhydride (0.01 mol) in 30 ml pyridine was heated under reflux for 3 h, cooled, poured into ice-cold water and acidified with conc. HCl. The precipitated solid was collected by filtration and crystallized from EtOH/DMF.

Method b: To a solution of ***8a*** (0.01 mol) in 20 ml glacial acetic acid, bromine (0.02 mol) was gradually added with stirring at room temperature. The reaction mixture was further stirred for 3 h, diluted with water (80 ml); the so formed solid product was collected by filtration and crystallized from EtOH/DMF.

8-Amino-4-phenylpyrazolo[5,1-c]benz[e]triazine-7-carbonitrile (***12***). A mixture of ***6*** (0.01 mol) and acrylonitrile (0.01 mol) in 30 ml pyridine was refluxed for 3 h, cooled to room temperature, poured into ice-cold water and acidified with conc. HCl. The resulting solid was filtered off, washed with water and crystallized from EtOH/DMF.

6-Acetylthiocarboxamido-8-amino-4-phenylthieno[4,3-e]pyrazolo[5',1'-c']-1,2,4-triazine (***15***). To a solution of ***6*** (0.01 mol) in 20 ml dry acetone, acetylisocyanate (0.01 mol) was added. The reaction mixture was heated under reflux for 2 h, cooled to room temperature and poured into ice-cold water. The precipitated solid was collected by filtraton and crystallized from EtOH/DMF.

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