Reactions with Heterocyclic Diazonium Salts: New Routes for the Synthesis of Pyrazolo[1,5-c]-1,2,4-triazoles and Pyrazolo[1,5-c]-*as*-triazines

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3-Phenylpyrazole-5-diazonium chloride (1) couples with α-chloro derivatives of acetylacetone, ethyl acetoacetate and aceto-*o*-anisidine to yield the corresponding pyrazole-5-yl hydrazonyl chloride derivatives **2a-c**. Compounds **2a,b** were cyclised to yield either the pyrazolo[1,5-c]-1,2,4-triazole derivatives **3a,b** or the pyrazolo[1,5-c]-*as*-triazines **4a,b** depending on the applied reaction conditions. Compound **2c** cyclised only into **3c** under different cyclization conditions. The pyrazolo[1,5-c]-*as*-triazine derivatives **4c-e** could be prepared *via* condensation of **2a** with potassium cyanide. Compound **2d** reacted with aromatic thioles and with sodium benzenesulphonate to yield the pyrazolo[1,5-c]-*as*-triazine derivatives **6a-d**. Compound **1** reacted with activated double bond systems to yield pyrazolo[1,5-c]-*as*-triazines **8a,b** and **9**.

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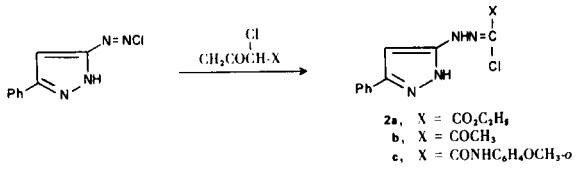
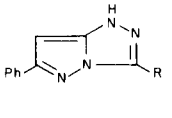
Heterocyclic diazonium salts represent an interesting class of reactive substrates and their synthetic potentialities have received recent attention (1-3). As a part of our program (4-7) directed for the development of new procedures for synthesis of fused pyrazoles of interest as potential anti-inflammatory (8) and antitumor (9) agents we have recently described the synthesis of differently substituted pyrazolo[1,5-c]-*as*-triazines based on the coupling reaction of 3-phenylpyrazole-5-diazonium chloride with active methylene compounds (10). In continuation of this work we report here a novel synthesis of some new pyrazolo[1,5-c]-*as*-triazoles and pyrazolo[1,5-c]-*as*-triazines from 3-phenylpyrazole 5-diazonium chloride. Thus, coupling 3-phenylpyrazole-5-diazonium chloride (1) with the α-chloro derivatives of acetylacetone, ethyl acetoacetate and of aceto-*o*-anisidine in ethanolic solution has afforded the corresponding hydrazonyl chloride derivatives **2a-c** in good yields. The formation of **2a-c** from this reaction is assumed to proceed *via* coupling with the methylene active hydrogen followed by acyl group cleavage. Attempts to isolate intermediates for this reaction were unsuccessful. The mechanism of the reaction of active methylene compounds with heterocyclic diazonium salts of similar structure has recently been discussed (3). The reaction of **1** with α-chloroketones is similar to the reaction of the latter compounds with aryldiazonium salts (11). The hydrazone structure 2 was assumed for compounds **2a-c** based on its spectroscopic properties which exludes the possible presence of azo or azine toutomer.



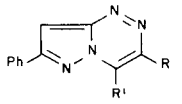
2a, X = $CO_2C_2H_5$
b, X = $COCH_3$
c, X = $CONHC_6H_4OCH_3$-*o*

Compounds **2a-c** cyclised into the pyrazolo[1,5-c]-*as*-triazole derivatives **3a-c** upon treatment with triethylamine in benzene solution. On the other hand, attempted cyclization of **2a,b** with methylamine or with hydrazine hydrate in protic media has afforded pyrazolo[1,5-c]-*as*-triazine derivatives **4a,b** whereas **2c** has afforded compounds **3c**. The possibility that cyclization of **2a-c** has involved pyrazole ring CH at position 4 was eliminated on the basis of ^1H nmr data which revealed signal for pyrazole CH proton. The structure assigned for **3a-c** and **2a,b** was inferred from their analytical and ir data. Thus, whereas **3a,c** revealed absorption bands for acetyl, ester and anilide carbonyl groups the ir of compounds **4a,b** revealed the absence of the former two functional groups and the appearance of bands for OH group.

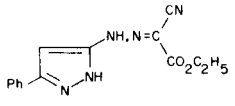
In order to explore the synthetic potentialities of compounds **2** as intermediates for the preparation of pyrazolo-[1,5-c]-*as*-triazines, the reactions of **2a-c** with a variety of reagents were performed. Thus, treatment of **2a-c** with



3a, R = $CO_2C_2H_5$
b, R = $COCH_3$
c, R = $CONHC_6H_4OCH_3$-*o*



4a, R = R' = CH
b, R = OH; R' = CH_3
c, R = $CO_2C_2H_5$; R' = NH_2
d, R = CN; R' = CH_3
e, R = $CONHC_6H_4OCH_3$-*o*; R' = NH_2
f, R = CN; R' = OH



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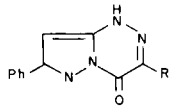
potassium cyanide in ethanolic aqueous media has afforded the pyrazolo[1,5-*c*]-*as*-triazines derivatives **4c-e**. Compound **4d** was found identical with an authentic specimen (10). Compound **4c** could be synthesised *via* coupling **1** with ethyl cyanoacetate under basic conditions or by cyclization of ethyl (3-phenylpyrazole-5-yl)hydrazonocyanoglyoxalate (5) with ethanolic sodium carbonate. It is interesting to report here that we have previously obtained **5** *via* coupling of **1** with ethyl cyanoacetate under different experimental conditions (10). It has been also shown that cyclization of **5** with concentrated sulphuric acid affords 2-phenyl-6-cyano-7-hydroxypyrazolo[1,5-*c*]-*as*-triazine (**3f**). The present result demonstrates the dependence of the nature of the product of cyclization of **5** on the applied cyclization conditions.

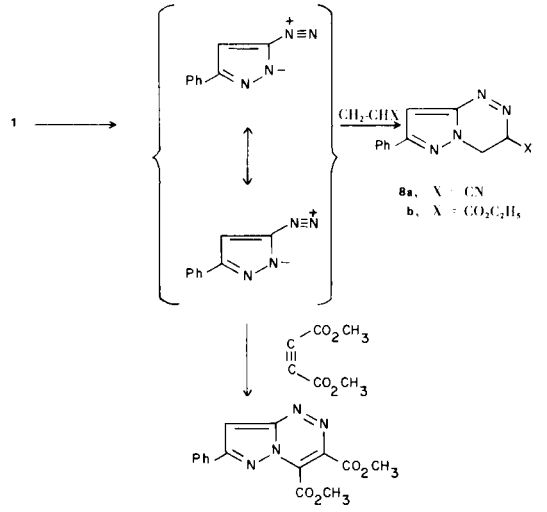
Compound **2a** reacted with aromatic thiols and with sodium benzenesulphenate in ehtanolic sodium ethoxide to yeild the pyrazolo[1,5-*c*]-*as*-triazin-7-one derivatives **6a-d**. Structure **6** was prefered over possible tautomeric **4**; R' = OH; R = SR based on ir data which showed a conjugated ring CO group at ~ 1680 cm^{-1} and revealed the absence of absorption corresponding for OH group.



6a, R = SC_6H_5
b, R = $SC_6H_4CH_3$-*p*
c, R = SC_6H_4Cl-*p*
d, R = $SO_2C_6H_5$

Compounds **2a-c** did not react with potassium thiocyanate in refluxing acetone using the experimental procedure previously reported to effect condensation of this reagent with arylhydrazonyl chloride (11). Cyclization (catalysed by the basicity of the reaction media) rather than condensation occurred and compounds **4a,b** and **3c** were the only isolable reaction products.

The observation that pyrazole-3-diazonium salts react with phenols to form pyrazolotriazines *via* a 1,4-dipolar cyclo-addition reaction (12) prompted us to investigate the behaviour of **1** in similar reactions. Thus, compound **1** was converted into the diazonium betaines **7a** or **7b** by action of sodium acetate. The latter reacted with a variety of activated double bond systems to yield pyrazolo[1,5-*a*]-*as*-triazine derivatives. Thus, treatment with acrylonitrile and with ethyl acrylate has afforded the pyrazolo[1,5-*c*]-*as*-triazine derivatives **8a,b**. Similarly treatment of **1** with acetylene dicarboxylic acid dimethyl



8a, X = CN
b, X = $CO_2C_2H_5$

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ester has resulte in the formation of the corresponding pyrazolotriazine derivative **9**.

The procedures described here for synthesis of pyrazolo[1,5-*c*]-1,2,4-triazoles and pyrazolo[1,5-*c*]-*as*-triazines are satisfactory, thus making it possible to obtain compounds with interesting synthetic and biological potentialities.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded (potassium bromide) on a Perkin-Elmer Model 337 Spectrophotometer. Proton magnetic resonance spectra were obtained with a variant A-60 spectrophotometer using TMS as internal standard.

3-Phenylpyrazole-5-ylhydrazonyl Chlorides (**2a-c**).

A solution of the appropriate α-chloroketone (0.1 mole) in ethanol (100 ml.) was treated with a solution of anhydrous sodium acetate (3.3 g.) in 10 ml. of water. To this solution was added a solution of 3-phenylpyrazole-5-diazonium chloride (0.1 mole; prepared as previously descrided (10)) in water (50 ml.). The reaction mixture was stirred at room temperature for 3 hours and the solid product, so formed, was collected by filtration and crystallised from the proper solvent.

Compound **2a** was brown crystals, yield 85%, m.p. 187° (benzene); ir 1605 (C=N), 1650 cm^{-1} (conjugated CO) and 3150 ~ 3380 cm^{-1} (NH group).

Anal. Calcd. for $C_{13}H_{13}ClO_2N_4$: C, 49.16; H, 4.87; N, 20.85; Cl, 13.22. Found: C, 48.97; H, 4.56; N, 20.87; Cl, 13.22.

Table I

Pyrazolo[1,5-*c*]-*as*-triazine Derivatives **4a-e**, **6a-d**, **8a,b** and **9**.

Compound	Crystallization Solvent	Yield %	M.p. °	Molecular Formula	Analysis Found Calcd. C	H	N	S
4a	Ethanol	80	188	$C_{11}H_8O_2N_4$	57.70 57.89	3.33 3.53	24.30 24.55	-- --
4b	Ethanol	85	149	$C_{12}H_{10}ON_4$	63.90 63.70	4.44 4.46	24.70 24.77	-- --
4c	Ethanol	90	211	$C_{13}H_9N_5$	66.56 66.37	4.00 3.86	30.00 29.77	-- --
4d	Ethanol	80	242	$C_{14}H_{13}O_2N_5$	59.35 59.35	4.63 4.63	24.72 24.72	-- --
4e	Methanol	85	218	$C_{19}H_{16}O_2N_6$	63.46 63.32	4.20 4.48	23.00 23.32	-- --
6a	Acetic acid	70	260	$C_{17}H_{12}ON_4S$	63.75 63.74	3.67 3.78	17.65 17.49	10.10 9.99
6b	Acetic acid	75	270	$C_{18}H_{14}ON_4S$	64.86 64.66	4.00 4.22	16.80 16.76	9.25 9.56
6c	Acetic acid	78	300	$C_{17}H_{11}ClON_4S$ (a)	57.20 57.54	3.10 8.01	15.17 15.36	9.00 8.77
6d	Ethanol	72	280	$C_{17}H_{12}O_3N_4S$	57.80 57.95	3.45 3.43	16.00 15.90	8.88 9.08
8a	Methanol	60	215	$C_{12}H_9N_5$	64.23 64.56	4.11 4.06	31.30 31.38	-- --
8b	Methanol	58	188	$C_{14}H_{14}O_2N_4$	62.00 62.21	5.00 5.22	20.49 20.73	-- --
9	Methanol-water	55	118	$C_{15}H_{12}O_4N_4$	57.31 57.69	4.00 3.87	17.67 17.94	-- --

(a) *Anal.* Calcd: 10.07. Found: 9.90.

Table II

Ir Spectral Data of the Pyrazolo[1,5-*c*]-*as*-triazines in Table I

Compound	N=N cm^{-1}	NH_2 cm^{-1}	CO cm^{-1}	CN		OH cm^{-1}
4a	1620	--	1680	--	3200	3450
4b	1620	--	--	--	--	3450
4c	1625	--	--	2260	--	--
4d	1620	1650	1730	--	3360 and 3420	--
4e	1615	1630	1690	--	3150, 3360 and 3420	--
6a	--	--	1690	--	3420	--
6b	--	--	1700	--	3350	--
6c	--	--	1695	--	3350	--
6d	--	--	1700	--	3350	--
8a	--	--	--	2240	3380	--
8b	--	--	1725	--	3400	--
9	1620	--	1690, 1710	--	--	--

Compound **2b** was yellowish-brown crystals, yield 85%, m.p. 137° (ethanol); ir: 1620 (conjugated CO); broad band at 3100 ~ 3450 (NH groups).

Anal. Calcd. for $C_{12}H_{11}ClON_4$: C, 54.85; H, 4.19; N, 21.71; Cl, 13.52. Found: C, 55.00; H, 4.12; N, 21.75; Cl, 13.63.

Compound **2c** was yellow crystals, yield 85%, m.p. 205° (benzene): ir: 1605 (C=N), 1640 cm^{-1} (amide CO) and 3150 ~ 3350 cm^{-1} (NH groups).

Anal. Calcd. for $C_{18}H_{16}ClO_2N_5$: C, 58.48; H, 4.38; N, 18.94; Cl, 9.61. Found: C, 58.69; H, 4.70; N, 19.00; Cl, 9.67.

3-Substituted-6-phenylpyrazolo[1,5-*c*]-1,2,4-triazoles (**3a-c**).

A suspension of each of **2a-c** (2.0 g.) in benzene (50 ml.) was treated with triethylamine (1.0 ml.). The reaction mixture was refluxed for 3 hours. The solvent was then removed *in vacuo*. The remaining solid product was triturated with ethanol and collected by filtration.

Compound **3a** was pale yellow crystals, yield 83%, m.p. 208° (ethanol); ir: 1615 cm^{-1} (C=N), 1700 cm^{-1} (ester CO) and 3410 (NH).

Anal. Calcd. for $C_{13}H_{12}O_2N_4$: C, 60.93; H, 4.72; N, 21.87. Found: C, 61.11; H, 4.63; N, 22.00.

Compound **3b** was pale yellow crystals, yield 80%, m.p. 152° (ethanol); ir: 1610 cm^{-1} (C=N), 1690 cm^{-1} (acyl C=O) and 3330 cm^{-1} (NH).

Anal. Calcd. for $C_{12}H_{10}ON_4$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.49; H, 4.22; N, 24.76.

Compound **3c** was yellow crystals, yield 85%, mp. 225° (methanol); ir: 1610 cm^{-1} (C=N), 1680 cm^{-1} (amide CO) and 3180-3350 cm^{-1} (NH groups).

Anal. Calcd. for $C_{18}H_{15}O_2N_5$: C, 64.85; H, 4.54; N, 21.01. Found: C, 64.76; H, 4.35; N, 20.85.

Reaction of **2a-c** with:

a) Methylamine.

A solution of each of **2a-c** (2.0 g.) in ethanol (100 ml.) was treated with aqueous methylamine solution (1.5 ml., 85%(. The reaction mixture was refluxed for two hours and the solvent was then removed *in vacuo*. The remaining product was then triturated with water and the resulting solid product was collected by filtration and crystallised from the proper solvent. The reaction of **2a,b** with methylamine has aggorded the pyrazolo[1,5-*c*]-*as*-triazine derivatives **4a,b** which are listed in Table I. with **2c** compound **3c** was formed in 80% yield. Ir spectral data for **4a,b** are compiled in Table II.

b) Hydrazine Hydrate.

A suspension of each of **2a-c** (2.0 g.) in ethanol (30 ml.) was treated with hydrazine hydrate (1.0 ml., 98%). The reaction mixture was refluxed for 3 hours and then evaporated *in vacuo*. The remaining product was triturated with water, collected by filtration and crystallized from ethanol. The reaction product in case of **2a,b** was identified (m.p. and mixed m.p.) as the pyrazolotriazines **4a,b**. In the case of **2c** the reaction product was identified (m.p. and mixed m.p.) as **3c**.

c) Potassium Cyanide.

A solution of each of **2a-c** (0.005 mole) in ethanol (30 ml.) was treated with a solution of potassium cyanide (0.003 mole) in 5 ml. of water. The reaction mixture was heated under reflux for two hours. The solvent was then removed *in vacuo*. The remaining product was triturated with water and acidified with acetic acid. The solid products, so formed, were collected by filtration and crystallized from the proper solvent. The resulting pyrazolo[1,5-*c*]-*as*-triazines **4c-e** are listed in Table I. Ir data for these products are compiled in Table II.

Compound **4c** was found to be identical with an authentic specimen.

Compound **4d** was also obtained by adding **1** (0.1 mole) to ethyl cyanoacetate (0.1 mole dissolved in 50 ml. of ethanol to which was added 5.0 g. of sodium acetate dissolved in 15 ml. of water) and chilling the reaction mixture for 24 hours.

Compound **4d** was also obtained by cyclization of **5a** with sodium carbonate.

Reaction of compounds **2** with Aromatic Thiols and with Sodium Benzenesulphonate.

To a sodium ethoxide solution (prepared from 0.5 g. of sodium metal and 50 ml. of ethanol) was added 2.0 g. of **2b** and 0.05 mole of the appropriate reagent. The reaction mixture was allowed to stand at room temperature for 24 hours then diluted with water and neutralised. The solid products, so formed, were collected by filtration and crystallized. The pyrazolo[1,5-*c*]-*as*-triazine derivatives (4) are listed in Table I.

Compound **6d** was also obtained in 75% yield *via* coupling of **1** with ω-benzenesulphonylacetophenone using experimental procedure previously utilised for coupling **1** with active methylene compounds.

Reaction of **1** with Activated Double Bond Systems.

A suspension of **1** (0.01 mole) in water was added to a saturated sodium acetate solution (10 ml.). After being allowed to stand for two hours at room temperature the reaction product was treated with an ethanolic solution of the appropriate unsaturated reagent (0.01 mole of reagent in 30 ml. of ethanol). The reaction mixture was left in the refrigator for 24 hours and the resulting solid product was then collected by filtration and crystallised from the proper solvents. The pyrazolo[1,5-*c*]-*as*-triazine derivatives thus prepare are listed in Table I.

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