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Reactions with Halogenated Compound: Synthesis of Several New Pyrazolo[3,2-c] triazine and 2-Benzenesulfonylglyoxal arylhydrazone Derivatives

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Abstract □ Diazotized primary artomatic amines **4** coupled with the ketosulfones **1-3** in ethanol in the presence of sodium acetate at 0℃ to afford the corresponding hydrazones 5-7. Also diazotized 3-aminopyrazoles **14** coupled with **1-3** in ethanolic sodium acetate to give the pyrazolotriazines **18-20** in good yields. Compounds **5-7** and **18** can also be obtained from the reaction of hydrazidoyl halides **8-10** and **21** with sodium benzenesulfinate. The hydrazones **11-13** can easy be oxidized to the hydrazones **5-7**, using hydrogen peroxide in acetic acid.

Keywords □ Hydrazones, pyrazolotriazines, hydrazidoyl halides, aminopyrazoles, ketosulfones.

The reaction of aromatic diazonium salts with active methylene compound were reported previouly to give the corresponding hydrazone derivatives[1-4]. Diazotized 3-aminopyrazole derivatives are versatile reagents[5,6], which couple with active methylene compound to form hydrazones that may be cyclized readily to yield pyrazolo[3,2-c]-1,2,4-triazine derivatives[7]. We have previouly reported on the synthesis of fused triazines, pyridazino[3,2-b] quinazolones and triazino[4,3-b] indazoles[8]. This communication describes the synthesis of several hydrazones and pyrazolo[3,2-c〉 triazine derivatives which are required for a medicinal chemistry program as well as for other chemical transformations.

RESULT AND DISCUSSION

Thus, it has been found that the ketosulfones **1-3** coupled with diazotized aromatic amines **4a-e** in sodium acetate buffered solution in ethanol at 0℃ to afford single products **5-7**, respectively in each case in 85-90% yields. (scheme. 1). On the basis of their spectroscopic data and elemental analyses, the products were assigned to the structure of 2-benzensulfonyl substituted glyoxal-2-arylhydrazones **5-7**. The ^{1}H-NMR (δppm) spectrum of **6b** showed signals at 2.2 (s, 3H, CH_3-Ar-p), 6.9-7.8(m, 12H, ArH's and furan) and 8.4(s, br, 1H, NH). IR (cm^{-1}) spectra of **5-7** revealed an absorption band at 1660 due to CO group. The structure of **4-7** was further evidenced by the alternate synthesis from the reaction of hydrazidoyl halides **8-10** with sodium thiophenolate in ethanol to give the sulfides **11-13**, respectively which were oxidized using hydrogen peroxide in acetic acid solution[9] to give the final isolable **5-7**, respectively (cf scheme. 1). Similar treatment of diazotized aminopyrazoles[10] **14** with **1-3** in ethanolic solution contaning sodium acetate gave **18-20** in 70-75% yields, respectively (scheme 2). The products gave analytical and spectral data in accord with formulation as 3-benzenesulfonyl-4-substituted-

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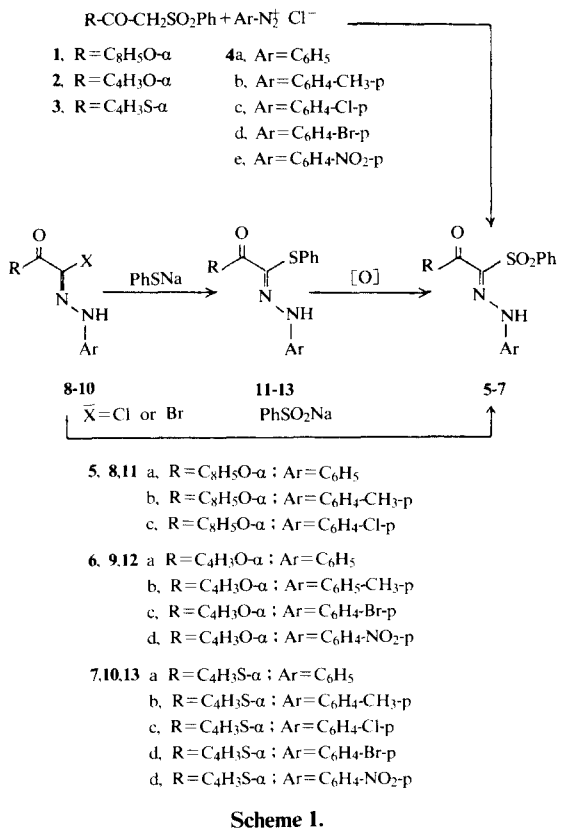
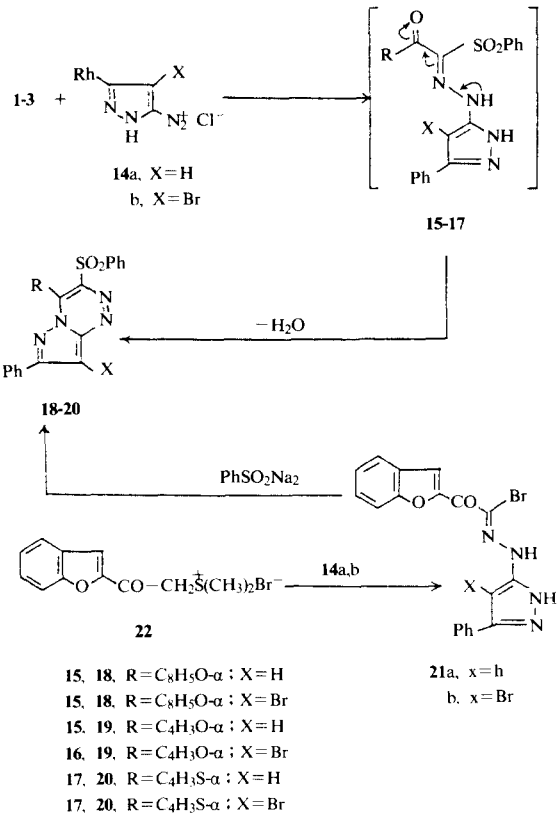


Scheme 1.



Scheme 2.

7-phenylazo[3,2-c]-1,2,4-triazines **18-20**. For example, IR spectra revealed the absence of bands due to CO and NH groups. The reaction of hydrazidoyl bromide **21a** (prepared from coupling of **14a** with 1-(2′-benzofuroyl)-ethan-1-one-2-dimethylsulfonium bromide 22[11], with benzene sulfinate afforded 3-benzenesulfonyl-4-benzofuryl-7-phenylazo[3,2-c]-1,2,4-triazine **18a**, follows from its spectral and elemental analysis(see Experimental). These results indicate that the intermediate hydrazones **15-17** undergo cyclization as soon as they are formed to afford the corresponding pyrazolo[3,2-c]-1,2,4-triazine derivatives **18-20**. The results of the present work indicate that the coupling of diazotized primary aromatic amines and diazotized 3-aminopyrazoles with ketosulfones provided a convenient procedure for the synthesis of several (otherwise difficult obtainable) hydrazones and fused pyrazolo[3,2-c]triazine derivatives.

EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallenkamp melting point apparatus. The IR spectra were recorded on a Pye-Unicam sp_3-300 spectrophotometer. The ^{1}H-NMR spectra were obtained in $CDCL_3$ or $(CD_3)_2SO$ on a Varian EM-390 spectrometer (90 MHz), with TMS as internal reference. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Egypt.

Ketosulfones 1-3[4,12], 2-bromothienylglyoxalarylhydrazones[13], 2-chlorofurylglyoxalarylhydrazones[14] and 2-bromo-(2′-benzofuryl)-glyoxal-2-arylhydrazones[15] were prepared as previouly described.

1-(2′-Benzofuroyl)-1-benzenesulfonyl-methane, 1

A solution of 2-bromoacetylbenzofuran[16] (2.47g,

Table I. Characterization data of the newly synthesized compounds

Comp.	Mp. ℃	Mol. Formula	% Analysis Calcd. Found C	H	N	S
5a	188-9	$C_{22}H_{16}N_2SO_4$	65.33	3.98	6.92	7.92
			65.20	4.10	7.00	7.80
5b	175-7	$C_{23}H_{18}N_2SO_4$	66.01	4.33	6.69	7.65
			65.90	4.10	6.80	7.40
5c	166-8	$C_{22}H_{15}ClN_2SO_4$	60.20	3.44	6.38	7.30
			60.30	3.50	6.60	7.10
6a	192-3	$C_{18}H_{14}N_2SO_4$	61.00	3.98	7.90	9.04
			61.20	4.10	7.70	8.80
6b	201-2	$C_{19}H_{16}N_2SO_4$	61.94	4.37	7.60	8.69
			61.80	4.20	7.80	8.80
6c	223	$C_{18}H_{13}BrN_2SO_4$	49.89	3.02	6.46	7.39
			49.70	3.10	6.60	7.20
6d	231-2	$C_{18}H_{13}N_3SO_6$	54.13	3.28	10.52	8.02
			54.00	3.30	10.70	8.20
7a	210-11	$C_{18}H_{14}N_2S_2O_3$	58.36	3.80	7.56	17.30
			58.50	3.90	7.70	17.10
7b	205-6	$C_{19}H_{16}N_2S_2O_3$	59.26	4.19	7.28	16.67
			59.20	4.00	7.40	16.80
7d	230	$C_{18}H_{13}BrN_2S_2O_3$	48.11	2.91	6.23	14.26
			48.20	2.80	6.40	14.40
7e	252-3	$C_{18}H_{13}N_3S_2O_5$	52.04	3.15	10.11	15.42
			52.10	3.30	10.30	15.20
11a	158-9	$C_{22}H_{16}N_2SO_2$	70.95	4.33	7.52	8.60
			71.10	4.50	7.70	8.50
11b	120-1	$C_{23}H_{18}N_2SO_2$	71.48	4.69	7.24	8.29
			71.60	4.50	7.40	8.10
11c	130-1	$C_{22}H_{15}ClN_2SO_2$	64.94	3.71	6.88	7.87
			65.10	3.60	7.00	7.70
12b	155	$C_{19}H_{16}N_2SO_2$	67.83	4.79	8.32	9.52
			67.90	4.90	8.40	9.40
12c	163	$C_{18}H_{13}BrN_2SO_2$	53.87	3.26	6.98	7.98
			53.60	3.40	6.70	7.70
12d	182	$C_{18}H_{13}N_3SO_4$	58.85	3.56	11.43	8.72
			58.70	3.70	11.20	8.90
13a	124	$C_{18}H_{14}N_2S_2O$	63.88	4.17	8.27	18.93
			63.70	3.90	8.40	19.10
18a	267	$C_{25}H_{16}N_4SO_3$	66.36	3.56	12.38	7.08
			66.40	3.70	12.20	6.80
18b	197	$C_{25}H_{15}BrN_4SO_3$	56.50	2.84	10.54	6.03
			56.30	2.60	10.70	5.80
19a	264-5	$C_{21}H_{14}N_4SO_3$	62.67	3.50	13.92	7.96
			62.70	3.60	13.70	8.30
19b	195	$C_{21}H_{13}BrN_4SO_3$	52.24	2.72	11.64	6.65
			52.40	2.60	11.40	6.50
20a	264-5	$C_{21}H_{14}N_4S_2O_2$	60.27	3.37	13.38	15.31
			60.40	3.10	13.10	15.50
20b	192-3	$C_{21}H_{13}BrN_4S_2O_2$	50.71	2.63	11.26	12.88
			50.60	2.50	11.40	13.00
21a	160-1	$C_{19}H_{13}BrN_4O_2$	55.76	3.20	13.69	19.52
			55.90	3.10	13.50	19.70
21b	170-1	$C_{19}H_{12}Br_2N_4O_2$	46.74	2.47	11.47	32.74
			46.60	2.60	11.20	32.80

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

Compd.	IR (cm^{-1})	^{1}H-NMR (δppm)
5a	3400(NH); 3060(C-H aromatic); 1665(C=O) and 1350, 1320(SO_2).	7.0-78(m, 15H, aromatic and benzofuryl) and 8.5(s, br, 1H, NH).
5b	3400(NH); 3070(C-H aromatic); 2900-2850(C-H aliphatic); 1660(C=O) and 1350, 1330(SO_2).	2.2(S, 3H, CH_3-Ar-p); 6.9-7.8(m, 14H aromatic and benzofuryl) and 8.4(s, br, 1H, NH).
5c	3390(NH), 3060(C-H aromatic); 1670(C=O) and 1355, 1330(SO_2).	7.0-7.8(m, 14H, aromatic and benzofuryl) and 8.6 (s, br, 1H, NH).
6a	3400(NH); 3060(C-H aromatic); 1670(C=O) and 1350, 1320(SO_2).	7.0-7.5(m, 13H, aromatic and furyl) and 8.4(s, br, 1H, NH).
6b	3400(NH); 3060(C-H aromatic); 2950, 2900(C-H aliphatic); 1660(C=O) and 1350, 1330(SO_2).	2.2(s, 3H, CH_3-Ar-p); 6.9-7.8(m, 12H aromatic and furyl) and 8.4(s, br, 1H, NH).
6c	3400(NH); 3060(C-H aromatic); 1670(C=O) and 1350, 1320(SO_2).	7.0-7.9(m, 12H, aromatic and furyl) and 8.5(s, br, 1H NH).
6d	3400(NH); 3060(C-H aromatic); 1670(C=O); 1500, 1360(NO_2) and 1350, 1320(SO_2).	7.1-8.0(m, 12H, aromatic and furyl) and 8.7(s, br, 1H, NH).
7a	3400(NH); 3060(C-H aromatic); 1670(C=O) and 1350, 1325(SO_2).	7.0-7.8(m, 13H, aromatic and thienyl) and 8.5(s, br, 1H, NH).
7b	3400(NH); 3060(C-H aromatic); 2900-2850(C-H aliphatic); 1665(C=O) and 1350, 1325(SO_2).	2.4(s, 3H, CH_3-Ar-p); 7.0-7.8(m, 12H, aromatic and thienyl) and 8.5(s, br, 1H, NH).
7d	3400(NH); 3060(C-H aromatic); 2950, 2870(C-H aliphatic); 1665(C=O) and 1350, 1330(SO_2).	7.0-7.8(m, 12H, aromatic and thienyl) and 8.6(s, br, 1H, NH).
7e	3400(NH); 3070(C-H aromatic); 2950, 2900(C-H aliphatic); 1670(C=O) 1500, 1400(NO_2) and 1350, 1330 (SO_2).	7.0-8.0(m, 12H, aromatic and thienyl) and 8.7(s, br, 1H, NH).
11a	3400(NH); 3070(C-H aromatic) and 1660(C=O).	6.9-7.8(m, 15H, aromatic and benzofuryl) and 8.6 (s, br, 1H, NH).
11b	3400(NH); 3060(C-H aromatic); 2930, 2870(C-H aliphatic) and 1665(C=O).	2.3(s, 3H, CH_3-Ar-p); 6.8-7.6(m, 14H, aromatic and benzofuryl) and 8.5(s, br, 1H, NH).
11c	3400(NH); 3065(C-H aromatic) and 1660(C=O).	6.9-7.8(m, 14H, aromatic and benzofuryl) and 8.6 (s, br, 1H, NH).
12a	3400(NH); 3060(C-H aromatic) and 1660(C=O).	6.8-7.7(m, 13H, aromatic and 8.6(s, br, 1H, NH).
12b	3400(NH); 3070(C-H aromatic); 2900, 2850(C-H aliphatic and 1670(C=O).	2.4(s, 3H, CH_3-Ar-p); 6.8-7.9(m, 12H, aromatic and furyl) and 8.7(s, br, 1H, NH).
12c	3390(NH); 3060(C-H aromatic); and 1660(C=O).	6.7-7.8(m, 12H, aromatic and furyl) and 8.6(s, br, 1H, NH).
12d	3400(NH); 3070(C-H aromatic); 1670(C=O) and 1500, 1350(NO_2).	6.9-7.9(m, 12H, aromatic and furyl) and 8.7(s, br, 1H, NH).
13a	3400(NH); 3060(C-H aromatic) and 1660(C=O).	6.8-7.7(m, 13H, aromatic and thienyl) and 8.6(s, br, 1H, NH).
13d	3400(NH); 3060(C-H aromatic) and 1670(C=O).	6.7-7.8(m, 12H, aromatic and thienyl) and 8.7(s, br, 1H, NH).
13e	3400(NH); 3070(C-H aromatic) 1670(C=O) and 1500, 1350(NO_2).	6.7-7.9(m, 12H, aromatic and thienyl and 8.9(s, br, 1H, NH).
18a	3060(C-H aromatic) and 1350, 1300(SO_2).	6.8-8.0(m, aromatic, benzofuryl and pyrazole H-4).
18b	3060(C-H aromatic) and 1350, 1300(SO_2).	6.9-8.0(m, aromatic and benzofuryl protons).
19a	3060(C-H aromatic) and 1350, 1300(SO_2).	6.9-7.9(m, aromatic, pyrazole H-4) and furyl protons).
19b	3070(C-H aromatic) and 1350, 1320(SO_2).	7.0-8.0(m, aromatic and furyl protons).
20a	3070(C-H aromatic) and 1355, 1325(SO_2).	6.8-8.2(m, aromatic, thienyl and pyrazole H-4).
20b	3070(C-H aromatic) and 1350, 1320(SO_2).	6.9-7.8(m, aromatic and thienyl protons).
21a	3400(NH); 3070(C-H aromatic) and 1670(C=O).	6.2(s, 1H, pyrazole H-4); 7.0-7.9(m, 10H, aromatic and benzofuryl) and 8.6(s, br, 2H, two NH).
21b	3400(NH); 3060(C-H aromatic) and 1660(C=O).	7.0-7.8(m, 10H, aromatic and benzofuryl) and 8.5 (s, br, 2H, two NH).

0.01 mol) and sodium thiophenolate (1.64g, 0.01 mol) in ethanol (100 m*l*) was stirred for 2 h. The reaction mixture was left overnight. The crude solid was collected, washed with water and crystallized from ethanol to give pale yellow needles with m.p. 145-6℃ (cf. Table I).

Synthesis of 2-benzenesulfonylsubistitutedglyoxal-2-arylhydrazones, 5-7 and pyrazolo[3,2-c]-1,2,4-triazines, 18-20

Method (A) : To a cold appropriate solution of **1-3**(0.01 mol) and sodium acetate (1.3 g) in ethanol(50 m*l*) was added dropwise a solution of the appropriate diazotized primary aromatic amine **4** (0.01 min.), with stirring. After the addition was completed (30 min.), the reaction mixture was left for overnight in a refrigerator. The yellow solid that precipitated was collected and crystallized from ethanol (except **18-20** from acetic acid) to give **5-7** and **18-20**, respectively (cf. Table I).

Method (B) : To a suspension of the appropriate **8-10** or **21a,b** (0.005 mol) in ethanol (30 m*l*) a solution of benzenesulfinate(0.82g, 0.005 mol) in water (5 m*l*) was added. The reaction mixture was refluxed for 2 h., then cooled, the crude products were collected, washed with water and crystallized from ethanol. The products obtained were found to be identical in all respects (m.p., mixed m.p. and spectra) with that obtained above by coupling of **4** or **14** with **1-3**.

Method (C) :To a suspension of the appropriate **11-13**(1g) in acetic acid (25 m*l*), a solution of hydrogen peroxide (10 m*l*, 30%) was added. the reaction mixture was stirred for 24 h., and then allowed to stand for 2 days at room temperature. The solid so formed was collected and crystallized from ethanol. The products obtained were found to be identical in all respects (m.p., mixed m.p. and spectra) with that obtained from methods (A) and (B) above.

Synthesis of 2-benzsulfoxysubstituted glyoxal-2-arylhdrazones, 11-13

To an ethanolic solution (25 m*l*) containing sodium metal (0.11g, 0.005 g-atom) and thiophenol (0.55 g, 0.005 mol), the appropriate hydrazidoyl halides, **8-10** (0.005 mol) were added. the reaction mixture was stirred for 3 h. The crude solids were collected, washed with water and recrystallized from ethanol to give **11-13**, respectively (cf. Table I).

Synthesis of 2-bromo-2-benzofuroylglyoxal-2-(3′-pyrazolyl-5′-substituted) hydrazone, 21a,b

To a suspension of the sulfonium bromide **23** (1.5 g, 0.01 mol) and sodium acetate (1.3g) in ethanol (50 m*l*), a solution of each of diazotized **14a,b** (0.01 mol) was added. The reaction mixture was stirred for 4 h at room temperature. The yellow solid, so formed, was collected, washed with water and crystallized from acetic acid to give **21a,b**, respectively (cf. Table I).

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