

Reactions with Hydrazidoyl Halides (V)¹⁾: Synthesis of Some Amidrazones, Hydrazides, Pyrazoles and Pyrazolo[3,4-d]pyridazine Derivatives

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Abstract □ 2-Bromo (2'-benzofuryl)glyoxal-2-arylhydrazones **I** reacted with nucleophiles displacing the bromide. Treatment of **I** with active methylene compounds yield the pyrazole derivatives **VIII-XI**. Compounds **XII-XIV** reacted with hydrazine to give pyrazolo[3,4-d]pyridazine derivative **XIV-XVI**. The structures of the products were assigned and confirmed on the basis of their elemental analysis and spectral data.

Keywords □ Amidrazones, hydrazidoyl halides, hydrazides, pyrazoles, pyrazolopyridazines.

Hydrazidoyl halides have been largely employed as an exceedingly successful tool for the synthesis of heterocyclic compounds, both through condensation reactions and as precursors of nitrile imines, which can undergo cycloaddition with several dipolarophiles²⁻¹⁰.

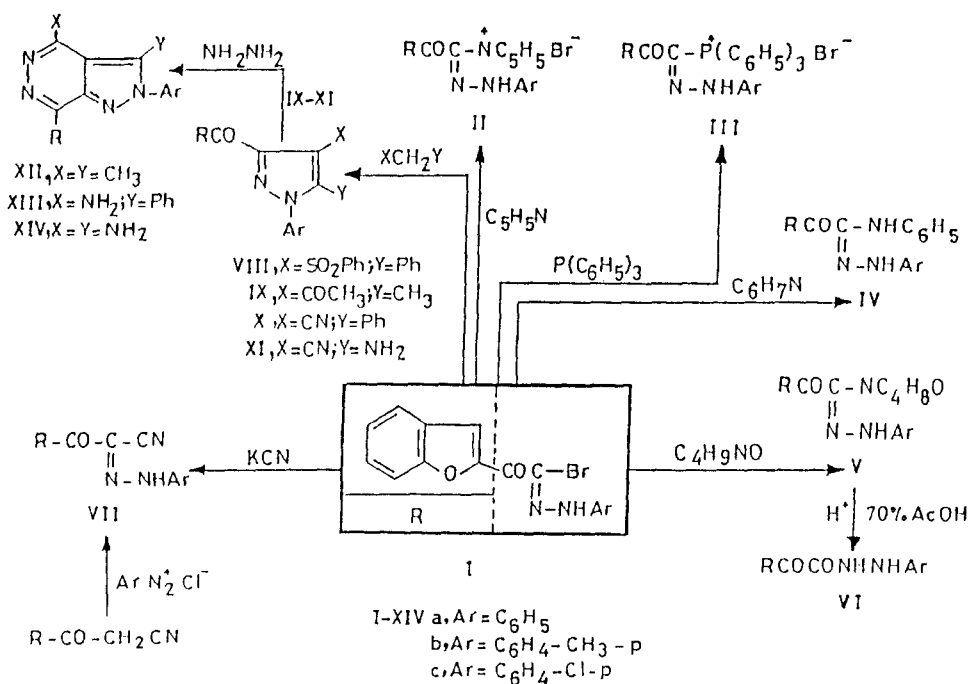
In this work, we reported the behaviour of 2-bromobenzofuryl glyoxal-2-arylhydrazone **I** towards some of nucleophilic reagents and active methylene compounds to yield amidrazones and substituted pyrazoles, respectively.

It has been found that reaction of **I** with pyridine or triphenylphosphine in refluxing ethanol to afford pyridinium bromides **II** and phosphonium bromides **III**, respectively. The structures **II** and **III** were confirmed, based on elemental analyses and spectral data. IR of **II** revealed a band at 1660 cm⁻¹ due to the CO group in addition to bands at 3330 and 1610 cm⁻¹ due to NH and C=N groups respectively. Compound **I** reacted with aniline, morpholine or potassium cyanide in ethanol to give compounds **IV**, **V** and **VII** respectively. The structures of compounds **IV-VII** were elucidated based on elemental analyses and spectral data. ¹H-NMR spectrum of **Va** showed signals at δ 7.2-8.2 (m, 11H, ArH's and NH proton), two quartets centered at δ 3.2 4.9 signals are assignable to the methylene group of morpholine moiety. The UV spectra was similar to N³-N³-disubstituted amidrazones¹¹. The IR (KBr) spectrum of **Va** showed bands at 3340

(NH), 2960, 2840, 2800, 2640 (CH₂), 1650 (α, β-unsaturated CO) and 1110 cm⁻¹ (ether linkage). Compound **V** was converted to **VI** by refluxing in acetic acid (70%). The structure of **VI** was confirmed by elemental analysis and spectral data. IR spectrum of **VIa** showed bands at 3278, 3225 (NH), 1650 (α, β-unsaturated CO), 1670 (hydrazide CO), 1600 (C=C) and 1538 (amide II band). Also the ¹H-NMR spectra of **VI** showed no signals due to (CH₂) resonance other than those of ArH's and benzofuran at δ 7.0-7.8 ppm. A key factor in our knowledge of the structure of **VI** is cleavage of linkage of morpholino group, cleavages to other tertiary amines group also occurred¹¹. Compound **VII** which was obtained through the reaction of **I** with potassium cyanide was elucidated based on elemental analyses, and spectral data. Compound **VII** could be synthesized by coupling of diazotized aromatic amines with (2'-benzofuroyl)-acetonitrile in ethanolic sodium acetate solution at 0°C.

When **I** was treated with each ω-benzenesulfonylacetophenone, acetylacetone, ω-cyanoacetophenone and malononitrile in ethanolic sodium ethoxide solution, it afforded the pyrazole derivatives **VIII-XI**, respectively. The structure of pyrazole derivatives was assigned based on spectral data and elemental analyses together with chemical reactions. ¹H-NMR spectra of **IXa** revealed signals (δ ppm) at 2.3 (s, 3H, CH₃), 2.4 (s, 3H, CH₃CO) and 6.9-7.8 (m, 10H, ArH's and furan H-3). IR spectrum of **IXa** showed peaks at 1690 and 1660 cm⁻¹ due to two carbonyl groups. ¹H-NMR spectrum of **XIa** revealed signals at 5.6 (s, br., 2H, NH₂) and 6.9-8.0 (m,

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10H, ArH's and furan H-3), upon shaking with D_2O the signals at 5.6 disappeared and a new signal appeared at 4.7 ppm for H_2O . IR spectrum of **IXa** showed peaks at 3420, 3320, 3220 (NH_2), 2220 (CN) and 1650 (CO).

Compounds **IX-XI** reacted with hydrazine hydrate in ethanol under reflux to give **XII-XIV** respectively. The structure of the pyrazolo[3,4-d]pyridazine derivatives **XII-XIV**. The structure of **XII-XIV** was elucidated by spectral and elemental analyses (See Experimental).

EXPERIMENTAL

Melting points are uncorrected. $^1\text{H-NMR}$ spectra of the compounds in CDCl_3 or $(\text{CD}_3)_2\text{SO}$ were recorded on a Varian T-60 A spectrometer using $(\text{CH}_3)_4\text{Si}$ as internal reference. IR (KBr) spectra were taken on a Pye-Unicam SP 1100 spectrophotometer. Elemental analyses were performed at the Microanalytical Centre at Cairo University, Giza, Egypt. 2-Bromo-2'-benzofuryl glyoxal-2-arylhyazone **I** were prepared according to literature procedure¹²⁾.

Synthesis of **II** and **III**

A mixture of the appropriate **I** (0.005 mol) and pyridine (0.5g, 0.006 mol) or triphenylphosphine (1.3g, 0.005 mol) was heated under reflux for 2 h. The reaction mixture was cooled and diluted with ether.

The crude solid was collected and crystallized from ethanol-ether to give yellow crystals of pyridinium bromide **II** and triphenylphosphonium bromide **III**, respectively (cf. Table I).

2-Anilino-2-benzofuryl glyoxal-2-arylhyazone **IV** and 2-morpholine-2'-benzofuryl glyoxal-2-arylhyazone **V**

A mixture of the appropriate hydrazidoyl bromide **I** (0.005 mol) and aniline (0.92g, 0.01 mol) or morpholine (0.5g, 0.006 mol) in ethanol (20 ml) was refluxed for 30 min. The solvent was evaporated under vacuum to its half. The solid so formed was collected and washed with water, then crystallized from acetic acid or ethanol to afford **IV** (as yellow crystals) and **V** as orange crystals respectively (cf. Table I).

Acid hydrolysis of amidrazone **V**

The solution of amidrazone **V** (0.005 mol) in acetic acid (70%) was refluxed gently for 30 min, left to cool and diluted with water. The solid precipitated was collected and crystallized twice from dilute acetic acid to give corresponding arylhydrazide **VI** as pale yellow crystals in 70-75% yield (cf. Table I).

Reaction of **I** with potassium cyanide

Equimolecular quantities of **I** and potassium cyanide in ethanol (20 ml), were stirred for 1 h and left overnight at room temperature. The product was

Table I. Characterization data of the newly synthesised compounds

Comp. No.	M.p. °C	Yield (%)	Molecular Formula	Analysis %			
				C	H	N	S
IIa	214	95	C ₂₁ H ₁₆ BrN ₃ O ₂	59.72	3.81	9.95	—
				59.80	3.70	10.10	—
IIb	185	92	C ₂₂ H ₁₈ BrN ₃ O ₂	60.56	4.15	9.63	—
				60.60	4.20	9.30	—
IIc	263-5	86	C ₂₁ H ₁₅ BrClN ₃ O ₂	55.22	3.31	9.20	—
				55.40	3.10	9.40	—
IIIa	213-4	91	C ₃₄ H ₂₆ BrN ₂ O ₂ P	67.44	4.32	4.62	—
				67.20	4.20	4.40	—
IIIb	159-60	87	C ₃₅ H ₂₈ BrN ₂ O ₂ P	67.85	4.55	4.52	—
				68.00	4.40	4.70	—
IIIc	171-3	95	C ₃₄ H ₂₅ BrClN ₂ O ₂ P	63.81	3.93	4.37	—
				63.90	4.10	4.40	—
IVa	200	62	C ₂₂ H ₁₇ N ₃ O ₂	74.35	4.82	11.82	—
				74.40	4.90	11.90	—
IVb	176-8	65	C ₂₃ H ₁₉ N ₃ O ₂	74.77	5.18	11.37	—
				74.90	5.00	11.50	—
IVc	181	66	C ₂₂ H ₁₆ ClN ₃ O ₂	67.78	4.13	10.77	—
				67.60	4.30	10.50	—
Va	151	71	C ₂₀ H ₁₉ N ₃ O ₃	68.75	5.48	12.02	—
				68.90	5.70	12.00	—
Vb	130-2	68	C ₂₁ H ₂₁ N ₃ O ₃	69.40	5.82	11.56	—
				69.20	5.60	11.50	—
Vc	129-31	63	C ₂₀ H ₁₈ ClN ₃ O ₃	62.58	4.72	10.94	—
				62.70	4.80	11.00	—
VIa	181-3	56	C ₁₆ H ₁₂ N ₂ O ₃	68.56	4.31	9.99	—
				68.70	4.10	10.10	—
VIb	158-9	49	C ₁₇ H ₁₄ N ₂ O ₃	69.37	4.79	9.51	—
				69.50	4.60	9.70	—
VIc	193-5	53	C ₁₆ H ₁₁ ClN ₂ O ₃	61.06	3.52	8.90	—
				61.20	3.10	9.10	—
VIIa	197-9	75	C ₁₇ H ₁₁ N ₃ O ₂	70.58	3.83	14.52	—
				70.70	3.90	14.40	—
VIIb	228-30	79	C ₁₈ H ₁₃ N ₃ O ₂	71.27	4.32	13.85	—
				71.30	4.30	13.90	—
VIIc	> 300	82	C ₁₇ H ₁₀ ClN ₃ O ₂	63.07	3.11	12.97	—
				63.20	3.00	13.10	—
VIIIa	215	80	C ₃₀ H ₂₀ N ₂ SO ₄	71.41	3.99	5.55	6.35
				71.60	4.00	5.70	6.50
VIIIb	216-18	91	C ₃₁ H ₂₂ N ₂ SO ₄	71.80	4.27	5.40	6.17
				71.90	4.30	5.50	6.20
VIIIc	212-13	88	C ₃₀ H ₁₉ ClN ₂ SO ₄	66.85	3.55	5.19	5.94
				66.90	3.40	5.00	6.10
IXa	135-5	82	C ₂₁ H ₁₆ N ₂ O ₃	73.24	4.68	8.13	—
				73.40	4.70	8.00	—
IXb	150-1	84	C ₂₂ H ₁₈ N ₂ O ₃	73.72	5.06	7.81	—
				73.90	5.10	7.90	—
IXc	160	79	C ₂₁ H ₁₅ ClN ₂ O ₃	66.58	3.99	7.39	—
				66.70	4.10	7.50	—
Xa	246	83	C ₂₅ H ₁₅ N ₃ O ₂	77.10	3.88	10.79	—
				77.20	3.90	10.60	—
Xb	281	79	C ₂₆ H ₁₇ N ₃ O ₂	77.40	4.24	10.41	—
				77.40	4.10	10.54	—

Table I. Continued

Comp. No.	MP. °C	Yield (%)	Molecular Formula	Analysis %			
				C	H	N	S
Xc	270	81	C ₂₅ H ₁₄ ClN ₃ O ₂	70.84	3.32	9.91	—
				70.90	3.20	9.80	—
XIa	284-5	87	C ₁₉ H ₁₂ N ₄ O ₂	69.50	3.68	17.06	—
				69.70	3.70	16.90	—
XIb	286	78	C ₂₀ H ₁₄ N ₄ O ₂	70.16	4.12	16.36	—
				70.30	4.00	16.40	—
XIc	295-7	76	C ₁₉ H ₁₁ ClN ₄ O ₂	62.90	3.05	15.44	—
				62.80	3.10	15.60	—
XIIa	290-2	62	C ₂₁ H ₁₆ N ₄ O	74.10	4.73	16.46	—
				74.00	4.90	16.60	—
XIIb	304-5	66	C ₂₂ H ₁₈ N ₄ O	74.55	5.11	15.80	—
				74.60	5.20	15.90	—
XIIc	> 305	63	C ₂₁ H ₁₅ ClN ₄ O	67.29	4.03	14.94	—
				67.30	4.10	14.80	—
XIIIa	290-2	70	C ₂₅ H ₁₇ N ₅ O	74.42	4.24	17.35	—
				74.30	4.20	17.10	—
XIIIb	269-71	71	C ₂₆ H ₁₉ N ₅ O	74.80	4.58	16.77	—
				74.70	4.60	16.50	—
XIIIc	> 300	65	C ₂₅ H ₁₆ ClN ₅ O	68.57	3.68	15.99	—
				68.70	3.60	16.10	—
XIVa	> 310	67	C ₁₉ H ₁₄ N ₆ O	66.55	4.12	24.54	—
				66.60	4.00	24.40	—
XIVb	> 310	80	C ₂₀ H ₁₆ N ₆ O	67.40	4.52	23.58	—
				67.20	4.40	23.60	—
XIVc	> 310	82	C ₁₉ H ₁₃ ClN ₆ O	60.56	3.47	22.30	—
				60.40	3.50	22.10	—

Table II. ¹H-NMR data of selected compounds

Comp.	¹ H-NMR (δ ppm)
IIb	2.3 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 6.9-7.8 (m, 14H, aromatic protons and furan H-3) and 8.5 (s, br, 1H, NH)
IIIb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 6.9-7.8 (m, 24H, aromatic protons and furan H-3) and 9.1 (s, br., 1H, NH)
IVb	2.3 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 6.9-8.3 (m, 16H, aromatic protons and furan H-3 and two NH)
Vb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 3.2 (q, 4H, CH ₂ -N-CH ₂); 4.9 (q, 4H, CH ₂ -O-CH ₂) and 7.2-8.2 (m, 10H, aromatic protons, furan H-3 and NH)
VIb	2.3 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 7.0-7.8 (m, 9H, aromatic protons and furan H-3) and 8.2 (s, br., 2H, two NH)
VIIb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 7.1-7.9 (m, 10H, aromatic protons, furan H-3 and NH)
VIIIb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 7.1-7.6 (m, 19H, aromatic protons and furan H-3)
IXb	2.3 (s, 3H, CH ₃); 2.4 (s, 3H, CH ₃ CO); 2.5 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p) and 7.0-7.5 (m, 9H, aromatic protons and furan H-3)
Xb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p) and 7.0-7.6 (m, 14H, aromatic protons and furan H-3)
XIb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 5.6 (s, br., 2H, NH ₂) and 6.9-7.8 (m, 9H, aromatic protons and furan H-3)
XIIb	2.1 (s, 3H, CH ₃); 2.2 (s, 3H, CH ₃); 2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p) and 7.0-7.8 (m, 9H, aromatic protons and furan H-3)
XIIIb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 6.2 (s, br., 2H, NH ₂) and 6.9-7.8 (m, 14H, aromatic protons and furan H-3)
XIVb	2.4 (s, 3H, <u>CH</u> ₃ -C ₆ H ₄ -p); 6.5 (s, br., 4H, 2 NH ₂) and 7.0-7.8 (m, 9H, aromatic protons and furan H-3)

collected, washed with water and recrystallized from ethanol to give yellow crystals of **VII**.

Synthesis of 2-benzofuroylacetonitrile

A mixture of 2-bromoacetylbenzofuran (8g, 0.05 mol) in ethanol (50 ml) and potassium cyanide (6.5g, 0.1 mol) in water (20 ml) were stirred for 2 h while the reaction mixture temperature kept at 40-50°C. The reaction was diluted with water and acidified with hydrochloric acid. The solid formed was collected and crystallized from dilute ethanol to give 2-benzofuroylacetonitrile as pale yellow crystals with mp. 136°C, Calc. for C₁₁H₇NO₂: C, 71.34; H, 3.81; N, 7.56; Found: C, 71.50; H, 3.70; N, 7.80%.

Synthesis of VII

A mixture of 2-benzofuroylacetonitrile and sodium acetate (2g) in ethanol (100 ml) were stirred at 0-5°C. A solution of diazotized primary aromatic amine (0.005 mol) was added dropwise while stirring for 3 h. The solid so formed, was collected and crystallized from ethanol to give **VII** identical with **VII** prepared from as above in all respects (cf. Table I).

Synthesis of 1-aryl-3-benzofuroyl-4,5-disubstituted pyrazoles VIII-XI

To an ethanolic solution of sodium ethoxide (prepared sodium metal (0.11g) in absolute ethanol (20 ml) was added to (0.005 mol) of each of (ω -benzenesulfonylacetophenone, acetylacetone, benzoylacetonitrile or malononitrile. After stirring for 10 min. at room temperature the appropriate **Ia-c** (0.005 mol) was added and stirring was continued for 30 min. The solid so formed was collected and crystallized from acetic acid or ethanol to give **VIII-XI** as almost colourless crystals (cf. Table I).

Synthesis of pyrazole[3,4-d]pyridazine derivatives XII-XIV

A mixture of the appropriate **IX-XI** (0.005 mol) in ethanol and hydrazine hydrate (5 ml) were heated under reflux for 4 h. The reaction mixture was cooled and collected the solid which precipitated was recrystallized from dil. dimethylformamide to give **XII-XIV**, respectively as colourless crystals (cf. Table I).

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