Facile Synthesis of Fused Heterocycles through 2-Bromobenzofurylglyoxal-2-arylhydrazones

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Several new imidazo[1,2-*a*]pyridine, pyrazolo[5,1-*a*]imidazole, quinazolinone, 1,4-benzothiazine, and pyrazole derivatives were synthesized by the reaction of 2-bromobenz-2-furylglyoxal-2-arylhydrazones with different reagents. The structures of the new heterocycles were based on elemental analysis and spectral data.

Synthese kondensierter Heterocyclen aus 2-Brombenzofurylglyoxal-2-arylhydrazonen

Einige neue Imidazo[1,2-*a*]pyridin-, Pyrazolo[5,1-*a*]imidazol-, Quinazolinon-, 1,4-Benzothiazine- und Pyrazol-Derivate wurden synthetisiert durch die Reaktionen von 2-Brombenzofurylglyoxal-2-arylhydrazonen mit verschiedenen Reagenzien. Die Strukturen der neu synthetisierten Derivate wurden mittels Elementaranalyse und spektroskopischer Daten geklärt.

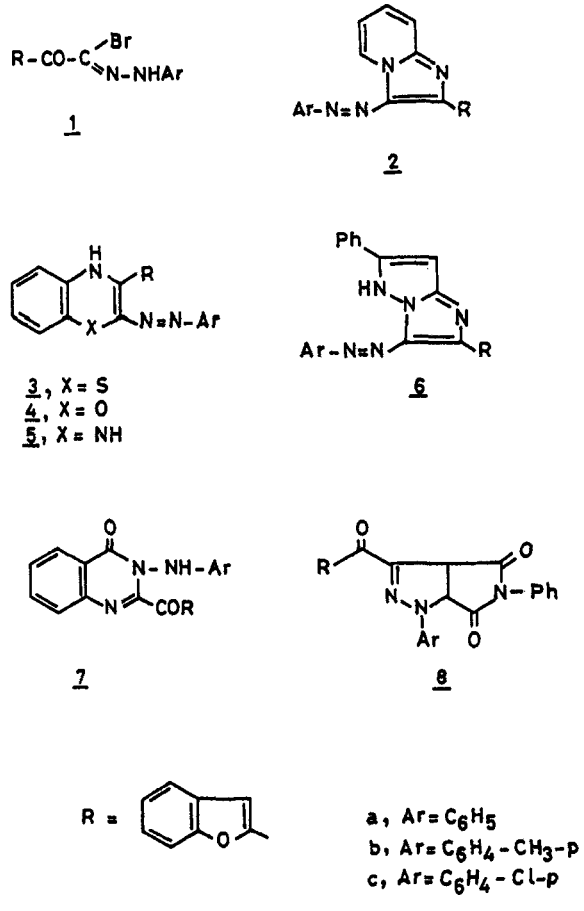
α-Ketohydrazidoyl halides have been widely employed as exceedingly useful tools for the synthesis of fused heterocyclic compounds[2-7]. The reactions take place through neucleophilic substitution or 1,3-dipolar cycloaddition[8-10].

We now report on the use of 2-bromobenzofurylglyoxal-2-arylhydrazones (**1**) in the synthesis of derivatives of five types of bicyclic systems (Scheme 1). Many derivatives of imidazo[1,2-*a*]pyridine[11-13], pyrazolo[5,1-*a*]imidazoles[6], quinazolinones[14-16], 1,4-benzothiazine, and pyrazole[17-18] have been previously prepared, because of their pharmaceutical and microbiological efficacies.

Results and Discussion

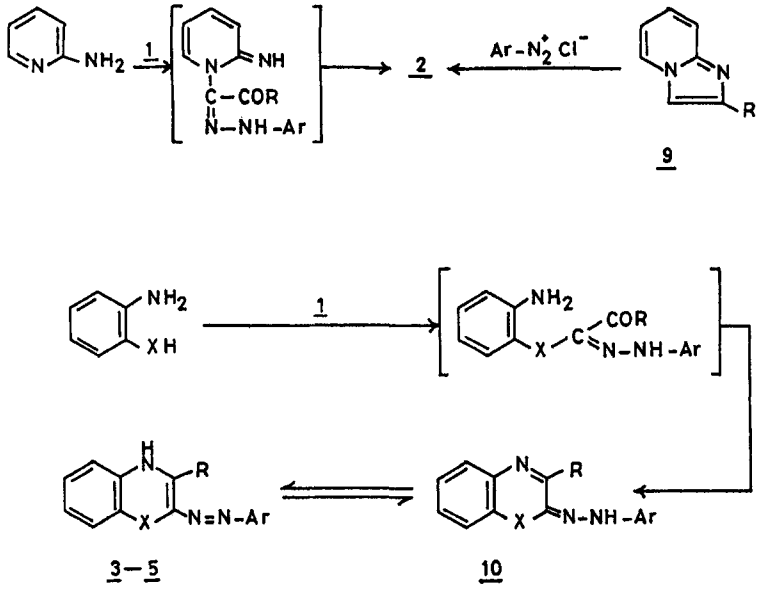
Treatment of **1a-c** with 1-2 equivalents of 2-aminopyridine in ethanol at reflux temp. yielded a single product (tlc) in each case. On the basis of spectroscopic data and elemental analyses, the products were assigned to be 2-benzofuryl-3-arylazoimidazo[1,2-*a*]pyridines **2** (Table 1). The absence of carbonyl and imino absorption bands in the IR-spectra indicated cyclization of **1** into **2**. This was supported by the absence of the NH signal in the ^{1}H-NMR spectra of **2**. Furthermore, coupling of 2-benzofurylimidazo[1,2-*a*]pyridine[19] **9** with diazotized anilines (Scheme 2) gave products identical in all respects with 2 (Scheme 1).

o-Aminothiophenol condensed easily with **1** in the presence of triethylamine as a HBr acceptor, to afford a single product (tlc). The Ir-spectrum showed a band at 3310 cm^{-1} (NH group), the ^{1}H-NMR spectra revealed NH signals at 9.5-11.2 ppm. The UV-vis spectra indicate λ max = 426 nm (log ε > 4). Therefore, the products were assigned the

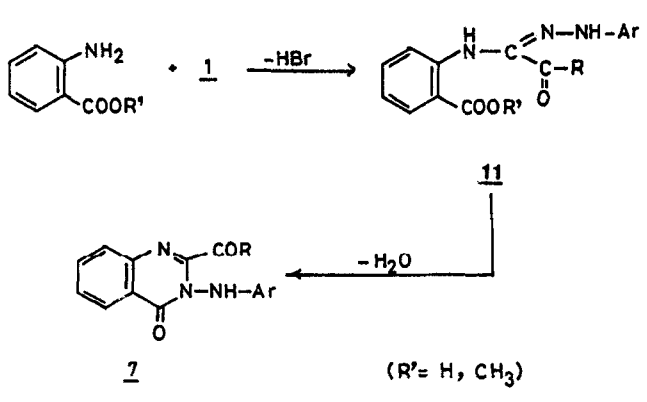


Scheme 1

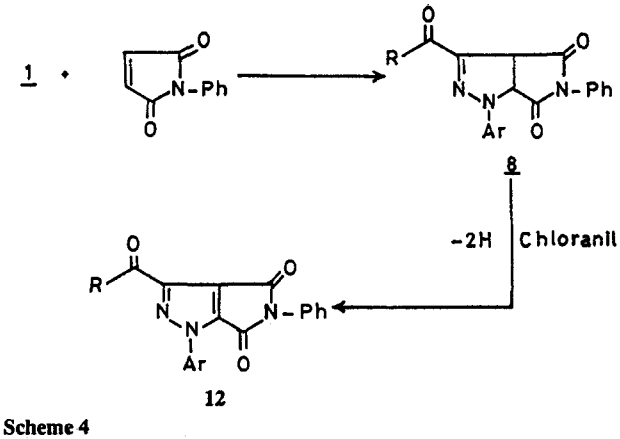
  0365-6233/92/0404-0205 $ 3.50 + .25/0



Scheme 2



Scheme 3



Scheme 4

2-arylazo-3-benzofuryl-4(*H*)-1,4-benzothiazine structure **3**. The tautomeric structure **10** was readily ruled out on the basis of UV-spectral data[5].

Compound **1** behaved similarly towards *o*-aminophenol to give the corresponding 2-arylazo-3-benzofuryl-1,4-benzoxazine derivatives **4** (Table 1) in almost quantitative yields.

Reaction of **1** with *o*-phenylenediamine yielded the corresponding 2-arylazo-3-benzofuryl-4(*H*)-1,4-benzopyrazine derivatives **5** in good yields. IR-spectra of **5** revealed no C=O-absorption but a week NH band near 3280 cm^{-1}.

Treatment of **1** with 3-amino-5-phenylpyrazole in ethanol afforded 1-phenyl-5-benzofuryl-4-arylazo-1*H*-pyrazolo[5,1-*a*]imidazoles **6** (Table 1). The infrared spectra of **6** exhibited a weak band around 3100 (NH), a broad band at 1620 cm^{-1} (C=N), but no C=O-band. On the other hand, appearance of a broad singlet at δ = 11.0-11.2 ppm (NH) and a characteristic singlet at δ = 6.5 (pyrazole H-4) in the ^{1}H-NMR spectra established further the structure of **6**. The hydrazone structure was ruled out due to the fact that the electron excitation spectra of **6** show a maximum in the 400-500 nm region. Molecular ion (M^+) peaks at m/z = 403 (**6a**), 417 (**6b**), and 437 (**6c**) corresponded to their molecular weights.

Reaction of **1** with anthranilic acid in ethanol in the presence of triethylamine readily afforded 3-arylamino-2-benzofuryl-4-(3*H*)quinazolinones **7**. The reaction takes place through elimination of HBr to form the amidrazone **11** which readily cyclized by loss of H_2O (Scheme 3). Treatment of **1** with methyl anthranilate in ethanol with triethylamine resulted in the formation of **11** (R' = Me). The ^{1}H-NMR spectrum of **11c** (R' = CH_3) revealed a singlet near δ = 3.6 ppm assignable to OCH_3. The infrared spectra of **11** (R' = CH_3) showed two carbonyl absorption bands near 1690 and 1640 cm^{-1} and NH absorption band in the 3100-3300 cm^{-1} region. The electron excitation spectra were found to be typical of amidrazones[20,21], exhibiting three intense maxima (log ε > 4) near 350-420, 310-340, and 240-275 nm. Saponification of **11** (R' = CH_3) followed by acidification resulted in the formation of products which were found to be identical with **7** in all respects.

Reaction of **1** with *N*-phenylmaleimide in presence of triethylamine yielded the pyrrolidino[3,4-*c*]pyrazole deriva-

Table 1: Characterization data of the newly synthesized derivatives.

Comp.	Colour	Solvent	Mp. °C	Yield %	Mol. Formula	Analysis % C	H	N	Calcd. Found S
2a	deep orange	EtOH	184-5	79	$C_{21}H_{14}N_4O$	74.55 74.7	4.14 4.00	16.56 16.4	- -
2b	orange	EtOH	183-4	83	$C_{22}H_{16}N_4O$	75.00 75.2	4.54 4.30	15.90 15.8	- -
2c	reddish brown	AcOH	223-5	80	$C_{21}H_{13}ClN_4O$	67.65 67.7	3.48 3.60	15.03 15.2	- -
3a	golden yellow	EtOH	174-5	93	$C_{22}H_{15}N_3SO$	71.54 71.6	4.06 4.20	11.38 11.5	8.67 8.8
3b	yellowish orange	EtOH	168-9	80	$C_{23}H_{17}N_3SO$	72.06 72.2	4.43 4.60	11.96 12.1	8.35 8.5
3c	orange	EtOH	295-7	82	$C_{22}H_{14}ClN_3SO$	65.42 65.0	3.46 3.70	10.40 10.6	7.93 7.8
4a	orange	AcOH	231-2	86	$C_{22}H_{15}N_3SO_2$	74.78 74.9	4.26 4.40	11.89 12.0	- -
4b	orange	AcOH	225-6	86	$C_{23}H_{17}N_3O_2$	75.20 75.3	4.63 4.70	11.44 11.6	- -
4c	brownish orange	DMF	211-3	84	$C_{22}H_{14}ClN_3O_2$	68.12 68.0	3.61 3.50	10.83 10.7	- -
5a	yellowish brown	EtOH	150	70	$C_{22}H_{16}N_4O$	75.00 75.2	4.54 4.60	15.90 15.8	- -
5b	golden brown	EtOH	171-2	90	$C_{23}H_{18}N_4O$	75.40 75.3	4.91 4.80	15.30 15.1	- -
5c	yellow	AcOH	199	92	$C_{22}H_{15}ClN_4O$	68.30 68.4	3.87 3.70	14.48 14.1	- -
6a	reddish brown	DMF	255-7	78	$C_{25}H_{17}N_5O$	74.42 74.5	4.24 4.30	17.35 17.4	- -
6b	reddish brown	DMF	257-8	80	$C_{26}H_{19}N_5O$	74.80 74.7	4.58 4.60	16.77 16.8	- -
6c	scarlet red	dioxan	256-7	62	$C_{25}H_{16}ClN_5O$	68.57 68.4	3.68 3.70	15.99 16.0	- -
7a	orange	EtOH	215-7	70	$C_{23}H_{15}N_3O_3$	72.43 72.5	3.96 4.10	11.01 11.0	- -
7b	brown	AcOH	199	64	$C_{24}H_{17}N_3O_3$	72.90 73.0	4.33 4.40	10.62 10.8	- -
7c	olive green	EtOH	202-4	74	$C_{23}H_{14}ClN_3O_3$	66.37 66.2	3.39 3.50	10.10 10.2	- -
8a	yellow	AcOH	253-9	72	$C_{26}H_{17}N_3O_4$	71.72 71.8	3.90 4.10	9.65 9.8	- -
8b	yellowish orange	DMF	250-2	78	$C_{27}H_{19}N_3O_4$	72.16 72.2	4.23 4.40	9.35 9.5	- -
8c	faint brown	DMF	253-5	61	$C_{26}H_{16}ClN_3O_4$	66.45 66.6	3.40 3.60	8.94 9.1	- -
11a	light orange	EtOH	204	80	$C_{24}H_{19}N_3O_4$	69.72 69.8	4.63 4.50	10.16 10.2	- -
11b	light orange	EtOH	180-1	72	$C_{25}H_{21}N_3O_4$	70.24 70.4	4.95 5.00	9.83 9.9	- -
11c	light orange	EtOH	171-2	70	$C_{24}H_{18}ClN_3O_4$	64.36 64.4	4.05 4.20	9.38 9.5	- -
12a	pale yellow	EtOH DMF	248-9	72	$C_{26}H_{15}N_3O_4$	72.05 72.1	3.46 3.50	9.69 9.5	- -
12b	pale yellow	EtOH	226-8	70	$C_{27}H_{17}N_3O_4$	72.48 72.5	3.80 3.70	9.39 9.4	- -
12c	colourless	DMF	>300	88	$C_{26}H_{14}ClN_3O_4$	66.73 66.9	2.99 3.10	8.98 9.1	- -

tives **8** (Scheme 4). The IR-spectra of **8** revealed bands at 1790-1720 and 1710-1690 cm^{-1} attributed to (-CO-NR-CO-) and CO groups. Compounds **8** were converted into **12** on prolonged heating with equimolar amounts of chloranil. The ^{1}H-NMR spectrum of **12b** revealed signals (δ ppm) at 2.3 (CH_3Ar) and 6.8-8.2 (m, 14H, ArH's and furan H-3). Signals which may be assignable to pyrazoline H-4 and H-5 were absent.

Table 2: ^{1}H-NMR data of some newly synthesized derivatives

Compd. No.	^{1}H NMR (δ ppm)
2b	2.2 (s, 3H, CH_3Ar-p) and 6.8-8.1 (m, 13H, furan H-3, ArH's and pyridines protons).
3b	2.3 (s, 3H, CH_3Ar-p), 6.8-7.9 (m, 13H, furan H-3, and ArH's) and 10.1 (s, br, 1H, NH).
4b	2.3 (s, 3H, CH_3Ar-p), 6.8-7.8 (m, 13H, furan H-3, and ArH's) and 9.7 (s, br, 1H, NH).
5b	2.3 (s, 3H, CH_3Ar-p), 6.8-7.8 (m, 13H, furan H-3, and ArH's) and 9.3 (s, br, 2H, two NH).
6b	2.2 (s, 3H, CH_3'Ar-p), 6.5 (s, 1H, pyrazole H-4) 6.8-7.7 (m, 14H, furan H-3 and ArH's) and 11.2 (s, br, 1H, NH).
7b	2.3 (s, 3H, CH_3Ar-p) and 6.9-8.3 (m, 14H, furan H-3, ArH's and NH).
8b	2.3 (s, 3H, CH_3Ar-p), 5.2 (d, J=10 Hz, 1H, pyrazoline H-4), 5.4 (d, J=10 Hz, 1H, pyrazoline H-5) and 6.8-8.2 (m, 14H, furan H-3 and ArH's).
11b	3.6 (s, 3H, OCH_3), 2.3 (s, 3H, CH_3Ar-p), 6.9-8.4 (m, 15H, ArH's, furan H-3 and two NH).
12b	2.3 (s, 3H, CH_3Ar-p) and 6.9-7.8 (m, 14H, furan H-3 and ArH's).

Experimental Part

Mp. uncorr.- IR spectra (KBr): SP-1100 spectrophotometer.- ^{1}H-NMR spectra: Varian EM 390 90 MHz. TMS int. stand., $CDCl_3$ or $(CD_3)_2SO$; Chemical shifts in δ ppm.- Electronic excitation spectra: Cary 118 Spectrophotometer.- Mass spectra: Kratos 30 and 50 spectrometers.- Microanalyses: Microanalytical Center at Cairo University.- 2-Bromo-benzofurylglyoxal-2-arylhydrazone (**1**) were prepared following Lit.[22].

2-Benzofuryl-3-arylazoimidazo[1,2-a]pyridines **2a-c**

Method A

A mixture of the appropriate hydrazidoyl bromide **1** (0.005 mole) and 2-aminopyridine (0.006 mole) in ethanol (50 ml) was refluxed for 3-4 h and then cooled. The precipitated solid was washed with water and crystallized from ethanol to give **2** in 65-75% yield (Table 1).

Method B

To a cooled solution of 2-benzofurylimidazo[1,2-a]pyridine (2.33 g, 0.01 mole) and 1.3 g sodium acetate in ethanol (30 ml) at 0°C was added the appropriate diazotized primary aromatic amines. The mixture was stirred at 0-5°C for 3 h. The precipitated products were crystallized from ethanol. The products obtained were identical with the corresponding products prepared by *Method A*.

Preparation of **3-5**

Equivalent amounts of a hydrazidoyl halide (0.005 mole), an appropriate amine (0.005 mole) and triethylamine (0.005 mole) in ethanol (50 ml) were refluxed for 3-4 h and then cooled. The precipitated solid was washed with water. Products **3-5** were obtained in almost quantitative yields (Table 1).

1H-Pyrazolo[1,5-b]imidazoles **6**

Equivalent amounts of 3-phenyl-5-aminopyrazole and the appropriate hydrazidoyl bromide **1** were refluxed in ethanol for 3 h and then cooled. The crude product, usually colored, was crystallized from ethanol to give **6** in almost quantitative yield (Table 1).

3-Arylamino-2-benzofuroyl-4-(3H)quinazolinones **7**

Anthranilic acid (1.37 g, 0.01 mole) was dissolved in ethanol (50 ml) together with the appropriate hydrazidoyl bromide **1** (0.01 mole) and triethylamine (1 g, 0.01 mole) was then added. The mixture was refluxed for 3-4 h and cooled. The crude product was crystallized from ethanol to give **7** in 75-83% yield (Table 1).

2-Anilino-(2'-methylcarboxylate)benzofurylglyoxal-2-arylhydrazones **11**

A suspension of **1** (0.005 mole) and methyl anthranilate (0.005 mole) in ethanol (50 ml) was refluxed for 2 h and the cooled. The solid formed was washed with water and crystallized from ethanol to give **11** in 70-72% yield (Table 1).

Conversion of **11** *into 3-arylamino-2-benzofuroyl-4(3H)quinazolinones* **7**

KOH (0.5 g) was dissolved in ethanol (10 ml), **11** (0.5 g) was added, and the mixture was stirred for 1 h. The mixture was diluted with water (10 ml), acidified with conc. HCl, heated on a water bath for 1 h, and cooled. The crude materials were crystallized from ethanol. The obtained products were identical with **7**.

Synthesis of Pyrrolidino[3,4-c]pyrazoles **8**

A solution of **1**, *N*-phenylmaleimide (0.005 mole), and triethylamine (0.5 g, 0.005 mole) in benzene (50 ml) was refluxed for 2 h. The mixture

was filtered while hot. The filtrate was evaporated in vacuo and the solid so formed was crystallized from acetic acid to give **8** in 80-85% yield (Table 1).

Dehydrogenation of **8** *to* **12**

A solution of **8** (0.005 mole) in xylene (30 ml) and chloranil (1.36 g, 0.005 mole) was heated under reflux for48 h. The mixture was cooled, washed with N NaOH three times (100 ml), then with water and dried (Na_2SO_4). The solvent was removed *in vacuo*. The crude solid was crystallized from DMF to give **12** in 72-88% yields (Table 1).

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