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Synthesis of C-(2-Furyl)-N-(4-nitrophenyl)methanohydrazonyl Bromide. Reactions with Nucleophiles and Active Methylene Compounds

Hamdi M. Hassaneen*, Ahmad S. Shawali, Nehal M. Elwan and Al Hossien A. Ibrahim

Department of Chemistry, Faculty of Science, University of Cairo Giza, Egypt

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Abstract □ Synthesis of C-(2-furyl)-N-(4-nitrophenyl)methanohydrazonyl bromide **2** is described. Treatment of **2** with nucleophiles affords the corresponding substitution products **3-7**. Also, compound **2** reacts with selenocyanate anion and thiocyanate anion and give the corresponding selenadiazoline and thiadiazoline **8** and **9**, respectively. Moreover, reaction of **2** with enolates of various active methylene compounds afforded the pyrazole derivatives **17-20**.

Keywords □ Hydrazonyl bromide, pyrazoles, selenadiazolines, thiadiazolines

Hydrazonyl halides proved to be biologically active and their properties depend on the nature of the groups on the carbon and nitrogen atoms. For example, C-alkylhydrazonyl halides possess miticidic, insecticidic and herbicidic properties[1], whereas their C-aryl-and C-aroyl analogues exhibit antiviral and antimicrobial[2] properties. C-Acetyl- and C-ethoxycarbonyl-methanohydrazonyl halides were reported to be active against red spiders on beans and apple trees[3].

Recently, we have been involved in the program directed for utility of heterocyclic hydrazonyl halides[4-7] in the synthesis of heterocyclic compounds. In continuation of this work, our objectives here are on one hand to prepare compounds that might have biological activity and on the other hand to study the reactivity of C-(2-furyl)-N-(4-nitrophenyl) methanohydrazonyl bromide **2** towards some nucleophiles and active methylene compounds.

RESULTS AND DISCUSSION

1-(4-Nitrophenyl)-2-(2-furoyl)hydrazine was converted to C-(2-furyl)-N-(4-nitrophenyl)methanohydrazonyl bromide **2** according to method of Wolkoff[8]. Thus, addition of carbon tetrabromide to a suspension of **1** and triphenylphosphine in dry acetonitrile afforded the bromide **2** in 75% yield. The structure of the product **2** was established on the basis of its spectra, elemental analyses and its substitution reaction (Scheme 1) (Table I-III).

Treatment of **2** with morpholine in ethanol afforded the amidrazone **7** in quantitative yield. Similar treatment of **2** with various nucleophiles (cyanide, phenoxide, thiophenoxide and azide) in ethanol resulted in the displacement of the bromine atom and afforded the corresponding substitution products **3-6**, respectively (Scheme 2). The structures of the products follow their preparation and their physical data (Table I-III).

The reaction of **2** with selenourea or potassium selenocyanate in ethanol at room temperature yielded product identified as 2-(2-furyl)-5-imino-4-(4-nitrophenyl)-Δ^2-1,3,4-selenadiazoline **8** (Scheme 3). Also, compound **2** reacts with thiourea or potassium thiocyanate and gave 2 (2-furyl)-5-imino-4-(4-nitrophenyl)-Δ^2-1,3,4-thiadiazoline **9**. The probable reaction sequence leading to **8** and **9** is summerized in Scheme 3. The structures of the products **8, 9** were confirmed by their microanalyses and spectral data together with their chemical behaviour summerized in Scheme 3. In the IR spectra, compounds **8, 9** had band due to imino NH at 3300 cm^{-1}. Nitrosation of **8** and **9** with sodium nitrite in acetic

Table I. Melting points and analytical data of compounds 2-22

Compound no.	mp. (a)	Molecular formula	Anal. Calcd. (Found) C%	H%	N%
2	185 (A)	$C_{11}H_{18}N_3O_3Br$	42.6 (42.8)	2.6 (2.4)	13.6 (13.3)
3	179 (E)	$C_{12}H_8N_4O_3$	56.1 (56.1)	3.2 (3.0)	21.9 (22.1)
4	123 (E)	$C_{17}H_{13}N_3O_4$	63.2 (63.6)	4.3 (4.3)	13.0 (12.8)
5	123 (E)	$C_{17}H_{13}N_3O_3S$	60.2 (60.5)	3.9 (4.2)	12.4 (12.1)
6	122 (E)	$C_{11}H_8N_6O_3$	48.7 (48.7)	3.0 (3.2)	30.5 (30.5)
7	150 (E)	$C_{15}H_{16}N_4O_4$	56.8 (56.8)	5.1 (5.3)	17.7 (17.6)
8	183 (E)	$C_{12}H_8N_4O_3Se$	43.0 (43.3)	2.4 (2.7)	16.6 (16.5)
9	188 (E)	$C_{12}H_8N_4O_3S$	50.0 (49.8)	2.8 (3.1)	19.4 (19.6)
10	150 (A)	$C_{12}H_7N_5O_4Se$	39.6 (39.2)	1.9 (2.1)	19.2 (19.4)
11	138 (A)	$C_{12}H_7N_5O_4S$	45.4 (45.2)	2.2 (2.5)	22.1 (21.9)
12	258 (A)	$C_{14}H_{10}N_4O_4Se$	49.8 (49.5)	2.4 (2.6)	14.5 (14.2)
13	219 (A)	$C_{14}H_{10}N_4O_4S$	44.8 (45.0)	2.7 (2.7)	14.9 (14.6)
14	208 (A)	$Cl_{14}H_{10}N_4O_4S$	50.9 (50.4)	3.1 (3.1)	17.0 (17.3)
15	256 (A)	$C_{19}H_{12}N_4O_4Se$	52.0 (52.2)	2.8 (3.0)	12.8 (13.0)
16	228 (A)	$C_{19}H_{12}N_4O_4S$	58.2 (58.6)	3.1 (3.3)	14.3 (13.9)
17	130 (E)	$C_{16}H_{13}N_3O_4$	61.7 (61.3)	4.2 (4.1)	13.5 (14.6)
18	173 (E)	$C_{26}H_{17}N_3O_4$	71.7 (72.0)	4.0 (4.5)	10.0 (9.6)
19	130 (E)	$C_{22}H_{17}N_3O_5$	65.5 (65.2)	4.4 (4.4)	10.5 (10.5)
20	216 (E)	$C_{21a1H16}N_4O_4$	64.9 (64.8)	4.2 (4.5)	14.4 (14.6)
21	248 (E)	$C_{14}H_9N_3O_3$	57.0 (57.3)	3.0 (3.0)	23.7 (23.5)
22	231 (E)	$C_{14}H_{11}N_5O_4$	53.7 (53.9)	4.0 (4.0)	22.4 (22.5)

(a) Solvent of crystallization: A, Acetic acid; E, Ethanol.

acid yielded the N-nitroso derivatives **10** and **11**, thermolysis of **11** in xylene gave thiadiazolone derivative **12**. Acetylation of **8, 9** with acetic anhydride yielded the N-acetyl derivatives **13, 14**. Also, compounds **8, 9** undergo benzoylation with benzoyl chloride in pyridine to give the N-benzoyl derivatives **15, 16**, respectively. The spectral data and the satisfactory elemental analyses of the products **10-17** were consistant with their assigned structures (Tables I-III).

Addition of **2** to an ethanolic solution enolate of 2,4-pentane-dione yielded **4**-acetyl-3-(2-furyl)5-methyl-1-(4-nitrophenyl)pyrazole **17** in 80% yield. Reaction of **2** with sodium enolates of other methylene compounds under similare conditions gave the corresponding pyrazole derivatives. The structures of the products were consistant with their spectral data (Sheme 4) (Table I-III).

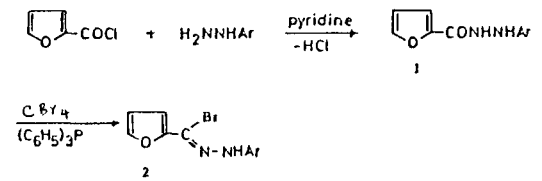
Treatment of **2** with malononitrile and cyanoacetamide in ethanol in the presence of sodium ethoxide affords the 5-aminopyrazole derivatives **21** and **22**. The structures of the latter products were established from their elemental and spectral analyses. Moreover, the structure of the 4-aminocarbonyl-5-aminopyrazole **22** was supported by alternate synthesis from hydrolysis of 4-cyano-5-aminopyrazole **21** by concentrated sulfuric acid.

EXPERIMENTAL

All melting points were measured on Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide on Pye Unicam SP3-300 infrared spectrophotometer. The ^{1}H-NMR sepectra were recorded in deuterated chloroform and DMSO on Varian T-60A NMR spectrometer using tetramethylsilane as internal reference. Elemental analyses were carried out at microanalytical laboratory of university of Cairo, Giza, Egypt.

Preparation of N-(4-nitrophenyl)-C-(2-furyl)methanohydrazonyl bromide 2

Carbon tetrabromide (6.6 gm, 20 mmoles) was ad-



Scheme 1

ded to a stirred suspension of 1-(4-nitrophenyl)-2-(furoyl)hydrazine **1** (4.9 gm, 20 mmoles) and triphenylphosphine (6.6 gm, 20 mmoles) in dry acetonitrile (40 m*l*). The mixture was stirred for 1 h. During this period, the hydrazide **1** dissolved and a yellow solid precipitated. This was collected and crystallized from acetic acid to give **2** in 80% yield (Table I).

Reaction of hydrazonyl bromide 2 with nucleophiles

Equimolecular amounts of **2** and the appropriate nucleophile (NaCN, NaOPh, NaSPh, NaN_3, morpholine) were stirred in ethanol (40 m*l*) for 24 h at room temperature. The crude substitution products, that precipitated were collected, washed with water and recrystallized from ethanol to give compounds **3-7**, respectively (Table I).

Preparation of 2-(2-furyl)-5-imino-4-(4-nitrophenyl)-Δ^2-1,3,4-selenadiazoline 8

A solution of selenourea or potassium selenocyanate (5 mmoles) in ethanol (5 m*l*) was added to a solution of hydrazonyl bromide (1.6 gm, 5 mmoles) in ethanol (20 m*l*) at room temperature. The reaction mixture was stirred for 2 h and the crude product was collected, washed with water, dried and finally crystallized from ethanol to give **8** in 85% yield (Table II).

Preparation of 2-(2-furyl)-5-imino-4-(4-nitrophenyl)-Δ^2-1,3,4-thiadiazoline 9

This compound was prepared by the same method described for the preparation of **8** using thiourea (or potassium thiocyanate) in place of selenourea (or potassium selenocyanate). Compound **8** was obtained in 70% yield. (Table I).

Preparation of 5-N-nitrosoiminoselenadiazoline 10 and 5-N-nitrosoiminothiadiazoline 11

To a suspension of **8** *and* **9** (5 mmoles) in acetic acid (15 m*l*) a saturated solution of sodium nitrite was added dropwise while stirring. The reddish products were collected and crystallized from acetic acid to give the corresponding nitrosoimino compounds **10** and **11**, respectively (Table I).

Table II. Infrared spectra of compounds 2-22

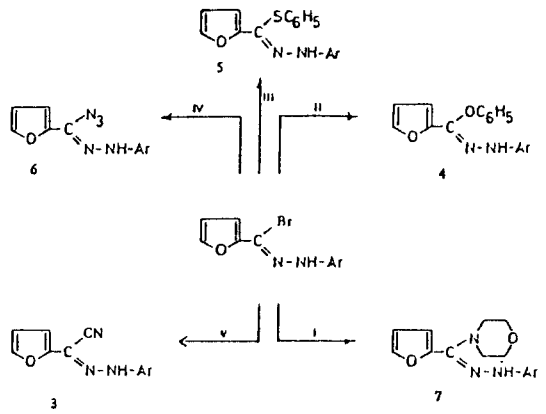
Compound no.	cm^{-1}
2	3300 (NH), 1600 (C=N)
3	3200 (NH), 2210 (C=N), 1600 (C=N)
4	3288 (NH), 1595 (C=N)
5	3284 (NH), 1600 (C=N)
6	3224 (NH), 2105 (N_3), 1600 (C=N)
7	3305 (NH), 1600 (C=N)
8	3450 (NH), 1600 (C=N)
9	3315 (NH), 1600 (C=N)
10	1580 (C=N)
11	1600 (C=N)
12	1690 (C=O), 1600 (C=N)
13	1620 (C=O), 1596 (CN)
14	1640 (C=O), 1595 (C=N)
15	1690 (C=N), 1595 (C=N)
16	1700 (C=O), 1600 (C=N)
17	1660 (C=O), 1600 (C=N)
18	1665 (C=O), 1595 (C=N)
19	1700 (C=O), 1590 (C=N)
20	1660 (C=O), 1600 (C=N)
21	3418, 3300 (NH_2), 2200 (C=N), 1595 (C=N)
22	3450, 3220 (NH), 1640 (C=O), 1590 (C=N)

Thermolysis of 5-N-nitrosoiminothiadiazoline 11

The compound **11** (0.2 gm) was refluxed in xylene (20 m*l*) untill no more nitrogen was evolved. The solvent was evaporated and the residue was triturated with petroleum ether 40/60℃. The solid formed was collected and cystallized from acetic acid to give 2-(2-furyl)-4-(4-nitrophenyl)-Δ^2-1,3,4-thiadiazoline-5-one (**12**); 75% yield (Table I).

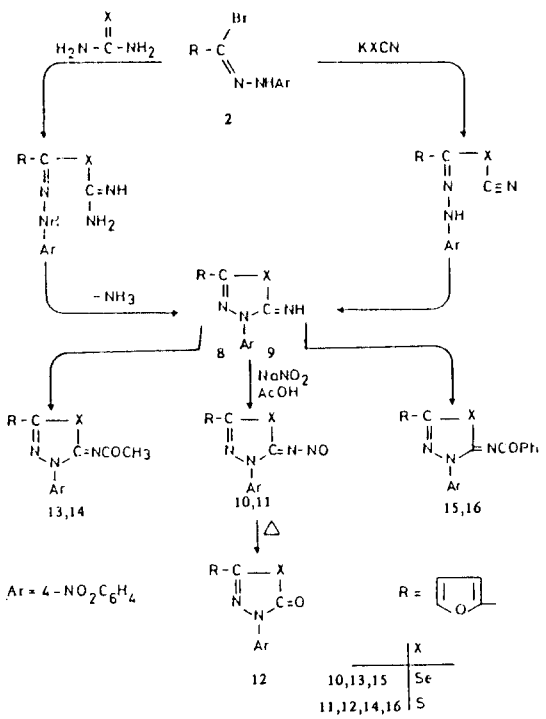
Acetylation of selenadiazoline 8 and thiadiazoline 9

Compounds **8** and **9** (3 mmoles) were refluxed in acetic anhydride (20 m*l*) for 30 min and the mixture was cooled and diluted with water. The crude products were collected and crystallized from acetic to give compounds **13** and **14**, respectively (Table I).



I, morpholine; II, phenol; III, thiophenol; IV, sodium azide; V, sodium cyanide

Scheme 2

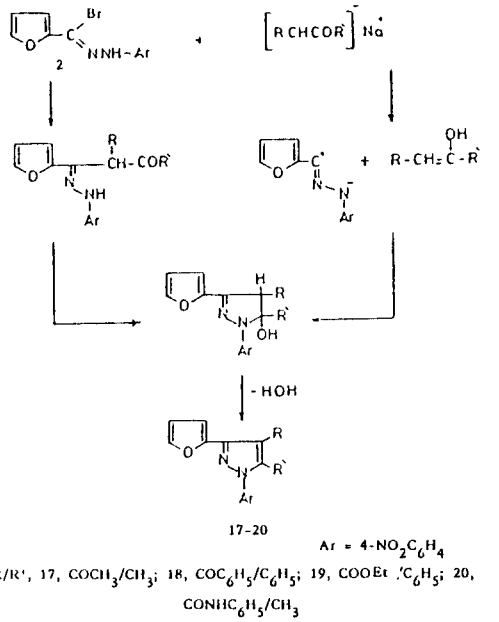


Ar = 4-$NO_2C_6H_4$

Scheme 3

Benzoylation of selenadiazoline 8 and thiadiazoline 9

Compounds **8** and **9** (3 mmoles) were refluxed with benzoyl chloride (0.4 gm, 3 mmoles) in pyridine (20 ml) for 30 min. The reaction was left to cool and treated with hydrochloric acid (50 ml, 10%). The crude products were collected and crystallized from

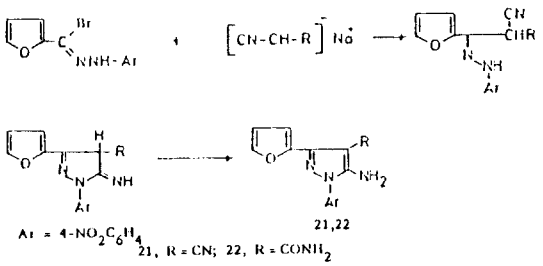


17-20

Ar = 4-$NO_2C_6H_4$

R/R', 17, $COCH_3/CH_3$; 18, COC_6H_5/C_6H_5; 19, $COOEt/C_6H_5$; 20, $CONHC_6H_5/CH_3$

Scheme 4



Ar = 4-$NO_2C_6H_4$

21, R = CN; 22, R = $CONH_2$

Scheme 5

acetic acid to give the corresponding N-benzoyl-imino derivatives **15** and **16**, respectively (Table I).

1-(4-Nitrophenyl)-3-(2-furyl)pyrazole derivatives 17-20

To an ethanolic sodium ethoxide solution [prepared from sodium (0.1 gm 0.005 gm atom) and absolute ethanol (20 ml)] was added the appropriate active methylene compound (5 mmoles) with stirring. To the resulting solution. The hydrazonyl bromide **2** (1.6 gm, 5 mmoles) was added at room temperature. The mixture was stirred for 4 h during which the bromide **2** dissolved and the crude pyrazole precipitated. The latter was collected, washed with water, dried and crystallized from ethanol. The compounds prepared with their physical data are listed in Table I.

Table III. ^{1}H-NMR spectral data of compounds 4-22

Compound no.	ppm
4	6.2-8.0 (m, 12H), 11 (s, 1H)
5	6.3-8.2 (m, 12H), 11.2 (s, 1H)
7	3.2 (dd, 2H), 3.8 (dd, 2H), 6.5-8.3 (m, 6H), 8.4 (s, 1H)
8	6.5-7.6 (m, 7H), 8.2 (s, 1H)
9	6.4-8.1 (m, 7H), 8.3 (s, 1H)
13	2.4 (s, 3H), 6.5-8.4 (m, 7H)
14	2.3 (s, 3H), 2.6 (s, 3H), 6.4-8.0 (m, 7H) 6.3-8.3 (m, Ar-H).
19	1.0 (t, J=7 Hz, 3H), 4.1 (q, J=7 Hz, 2H), 6.4-8.3 (m, 12H)
20	2.7 (s, 3H), 6.5-8.2 (m, 12H), 8.4 (s, 1H)

1-(4-Nitrophenyl)3-(2-furyl)-5-aminopyrazole derivatives 21 and 22

These compounds were prepared by the same general procedure described for the preparation of **17-20** using equimolecular amounts of the hydrazonyl bromide **2** and the appropriate active methylene nitrile (5 mmoles each) in ethanol in the presence of sodium ethoxide (5 mmoles). The crude product was crystallized from acetic acid. The compounds prepared with their physical data are listed in Table I.

Alternative method for synthesis of 22

Concentrated sulfuric acid (3 m*l*) was cooled to 20℃ and finally powdered 5-amino-4-cyanopyrazole **21** (5 mmoles) was added with stirring, the addition took about 10 min. The sulfuric acid solution was then poured with stirring into a cold water (15 m*l*) and the solution set aside overnight in the refrigerator. The solution was then filtered and the product was washed to be free of excess sulfuric acid. Recrystallization from acetic acid gave a product identical in all respects (mp. mixed mp. and IR) with compound **22**.

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