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Synthesis and Cycloaddition Reactions of N-Aryl-2-furohydrazonyl Chlorides

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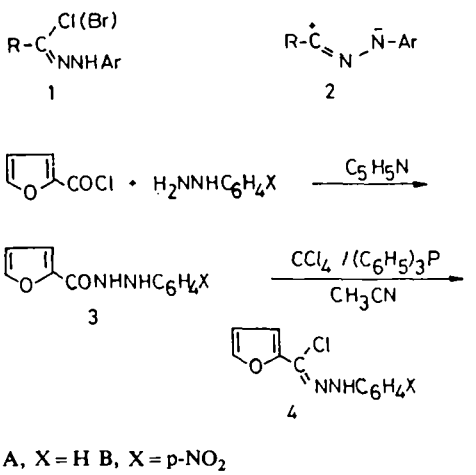
Abstract□The novel N-phenyl-2-furohydrazonyl chloride **4A** and its p-nitro analog **4B** have been prepared and identified. The cycloaddition reactions of nitrilimines **5A** and **5B**, derived by base catalyzed dehydrochlorination of **4A** and **4B** respectively, to a variety of dipolarophiles were investigated. The results showed that **4A** and **4B** are useful precursors for synthesis of differently substituted 3-(2-furyl)-2-pyrazoline derivatives and their pyrazoles and analogs.

Keywords□N-Aryl-2-furohydrazonyl chlorides, 2-pyrazolines, pyrazoles, pyrrolo [3,4-c] pyrazoles.

Hydrazonyl halides **1** are a long known and throughly investigated class of nitrilimines precursors[1]. Recently some series of **1** were reported to have efficacy against a variety of helminths of domestic animals[2]. Although numerous halides of type **1** have widely been investigated and the 1,3-dipolar cycloaddition reaction of nitrilimines **2**, generated in situ by base catalyzed dehydrohalogenation of **1**, have led to synthesis of a variety of interesting heterocyclic compounds[3, 4], N-aryl-2-furohydrazonyl halides **4** have not yet been reported. In this communication we wish to report the synthesis of **4** and the cycloaddition reactions of the corresponding N-aryl-2-furonitrilimines **5** to a variety of unsaturated compounds (Schemes 1-3).



A, X = H B, X = p-NO_2

Scheme 1

RESULTS AND DISCUSSION

The synthesis of N-aryl-2-furohydrazonyl chlorides **4A** and **4B** was accomplished by reacting the corresponding N-(furoyl)-N'-arylhydrazines **3A** and **3B** respectively with triphenylphosphine and carbon tetrachloride in acetonitrile at room temperature following the procedure of Wolkoff[5] in transforming 1-aryl-2-benzoylhydrazine into N-arylbenzohydrazonyl chlorides. The structures of the previously unreported hydrazonyl chlorides **4A** and **4B** were confirmed by their spectra and elemental analyses. For example, the infrared spectra of both **4A** and **4B** revealed the absence of the amino CO band and showed band at 3265 and 1610 cm^{-1} assignable to NH and C = N group, respectively. In addition the chemical reactions of **4** outlined below are also in support of their assigned structures.

N-Phenyl-2-furonitrilimine **5A**, generated in situ from **4A** and triethylamine in dry chloroform, reacts with acrylamide and gives the cycloadduct **8A** (Scheme 2). Both its spectra and elemental analysis are consistent with its assigned structure. Similary N-(4-nitrophenyl)-2-furonitrilimine **5B** reacts with acrylamide,

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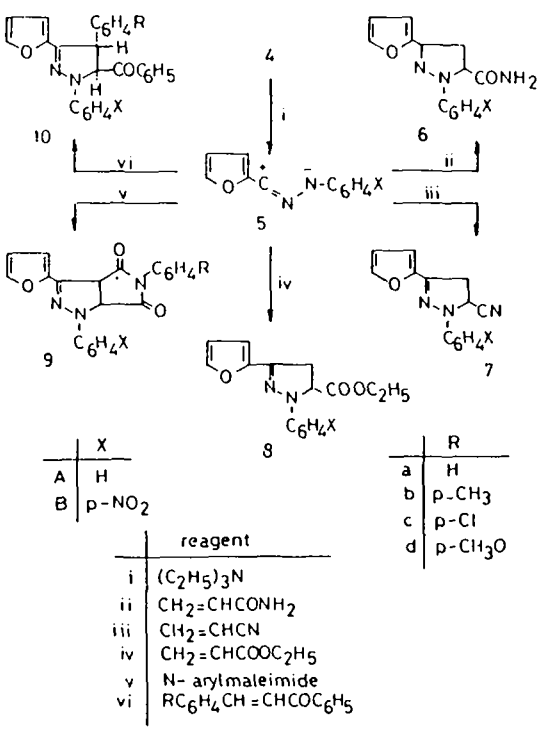
acrylonitrile and ethyl acrylate and afforded exculsively 3-(2-furyl)-1-(4-nitrophenyl)-5-substituted 2-pyrazolines **6B-8B** respectively in good yields (Scheme 2). The assigned structures of the latter products **6B-8B** were supported by analytical and spectral data (Tables I and II). The chemical shifts of the methine and methylene protons of **6A** and **6B-8B** compare favourably with those reported for 1,3-diphenyl-5-R substituted 2-pyrazolines[6]. Such a similarity, while confirming the assigned structures, indicates that both substituents, the 2-furyl and phenyl groups, have similar effects on chemcial shifts of the methylene protons at C-4 of substituted 2-pyrazoline derivatives. Also, the structure of **7B** was further confirmed by the absence of the nitrile absorption in its infrared spectrum as it is the case of aliphatic nitriles activated by a nitrogen or an oxygen atom in the alpha position[7].

Treatment of **4A** with-N-phenylmaleimide in refluxing benzene or chloroform in the presence of triethylamine afforded one product identified as **9Aa** (Scheme 2). The structure of the latter was assigned on the basis of its elemental analysis and spectral data (Table I). The infrared spectrum of **9Aa** showed an intense absorption band at 1710 cm^{-1} corresponding to C=O group. Its ^{1}H-NMR spectrum showed two doublets at δ 4.77 (J = 12 Hz) and 5.25 (J = 12 Hz) ppm.

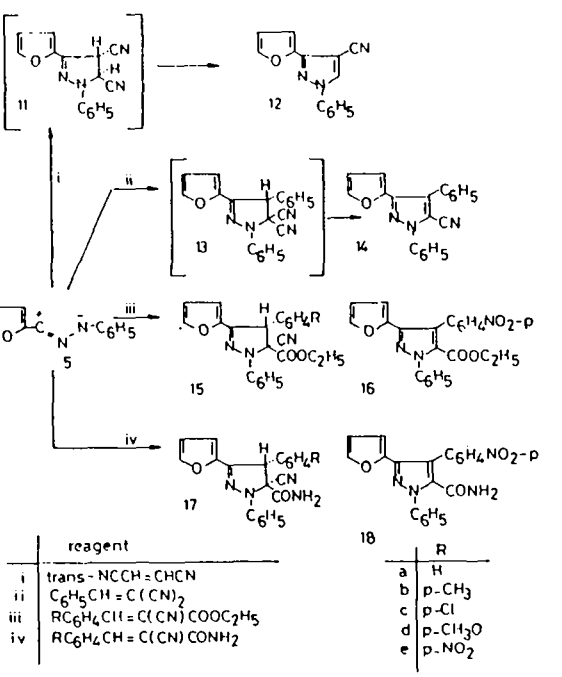
The chloride **4B** reacts similarly with N-phenylmaleimide and its substituted derivatives and gives the corresponding cycloadducts **9Ba-d** (Scheme 2). The structures of the latter products followed their elemental analyses and spectra (Tables I and II).

Benzalacetophenone reacts readily with **4A** and **4B** in refluxing chloroform and in the presence of triethylamine. ^{1}H-NMR spectral analysis of the crude reaction product showed in each case one regioisomer. The products isolated were shown to be **10Aa** and **10Ba** respectively (Scheme 3). The reaction of the hydrazonyl chloride **4A** with other substituted benzalacetophenones under similar conditions yielded the corresponding cycloadducts **10Ab-e** in good yields (Scheme 3). Both IR and ^{1}H-NMR spectra of **10A** and **10B** were compatible with assigned stereo- and regio-chemical structures (Table II). For example, the ^{1}H-NMR spectrum of **10A** showed two doublets at δ 4.56 (J = 6 Hz) and 5.58 (J = 6 Hz) assignable to 4-CHPh and 5-CHCOPh methine protons respectively. The coupling constant ($J_{4,5}$ = 6 Hz) substantiates the trans configuration indicated for the products **10.** This is because in 2-pyrazoline derivatives the coupling constants between cis and trans-4- and 5- protons are 12 and 6 Hz respectively[8].

The product from the reaction of trans-1,2-dicyanoethylene with **4A** in refluxing benzene in the pre-



Scheme 2



Scheme 3

Table I. Melting points and analytical data of compounds 3-18

Compound No.	M.p., (a)	Molecular formula	Anal. Calcd. (Found) C,%	H,%	N,%
3A	143 (A)	$C_{11}H_{10}N_2O_2$	65.3 (65.1)	4.9 (4.7)	13.8 (13.7)
3B	149 (A)	$C_{11}H_9N_3O_4$	53.4 (53.1)	3.7 (3.5)	17.0 (17.2)
4A	140 (M)	$C_{11}H_9ClN_2O$	59.9 (60.0)	4.1 (4.3)	12.7 (12.5)
4B	179 (E)	$C_{11}H_8ClN_3O_3$	49.7 (49.8)	3.0 (3.2)	15.8 (15.6)
6A	224 (A)	$C_{14}H_{13}N_3O_2$	65.9 (66.1)	5.1 (5.2)	16.4 (16.4)
6B	276 (A)	$C_{14}H_{12}N_4O_4$	56.0 (56.1)	4.0 (4.0)	18.6 (18.6)
7B	168 (A)	$C_{14}H_{10}N_4O_3$	59.6 (59.4)	3.6 (3.5)	19.8 (20.0)
8B	119 (A)	$C_{16}H_{15}N_3O_5$	58.4 (58.3)	4.6 (4.8)	12.7 (12.5)
9Aa	196 (A)	$C_{21}H_{15}N_3O_3$	70.5 (70.3)	4.2 (4.4)	11.7 (11.8)
9Ba	265 (A)	$C_{21}H_{14}N_4O_5$	62.7 (62.5)	3.5 (3.4)	13.9 (14.0)
9Bb	241 (A)	$C_{22}H_{16}N_4O_5$	63.5 (63.3)	3.9 (4.1)	13.5 (13.3)
9Bc	257 (A)	$C_{21}H_{13}ClN_4O_5$	57.6 (57.4)	2.9 (3.0)	12.8 (12.6)
9Bd	245 (A)	$C_{22}H_{16}N_4O_6$	61.1 (61.0)	3.7 (3.8)	12.9 (13.0)
10Aa	159 (A)	$C_{26}H_{20}N_2O_2$	79.6 (79.5)	5.1 (5.0)	7.1 (7.1)
10Ab	142 (A)	$C_{27}H_{22}N_2O_2$	79.8 (79.6)	5.5 (5.5)	6.9 (6.8)
10Ac	155 (A)	$C_{26}H_{19}ClN_2O_2$	73.2 (73.1)	4.5 (4.7)	6.6 (6.4)
10Ad	206 (A)	$C_{27}H_{22}N_2O_3$	76.8 (76.5)	5.3 (5.2)	6.6 (6.5)
10Ae	131 (A)	$C_{26}H_{19}N_3O_4$	71.4 (71.2)	4.4 (4.3)	9.7 (9.7)
10Ba	171 (A)	$C_{26}H_{19}N_3O_4$	71.4 (71.6)	4.4 (4.3)	9.7 (9.6)
12	150 (A)	$C_{14}H_9N_3O$	71.5 (71.6)	3.9 (4.0)	17.9 (17.7)
14	182 (A)	$C_{20}H_{13}N_3O$	77.6 (77.7)	4.2 (4.6)	13.5 (13.8)
15Aa	112 (M)	$C_{23}H_{19}N_3O_3$	71.7 (71.2)	5.0 (4.8)	10.9 (10.8)
15Ab	86 (M)	$C_{24}H_{21}N_3O_3$	72.2 (72.3)	5.3 (5.5)	10.5 (10.4)
15Ac	93 (M)	$C_{23}H_{18}ClN_3O_3$	65.8 (65.6)	4.3 (4.8)	10.0 (10.0)
15Ad	80 (M)	$C_{24}H_{21}N_3O_4$	69.4 (69.6)	5.1 (5.1)	10.1 (9.9)
16Ae	177 (A)	$C_{22}H_{17}N_3O_5$	65.5 (66.3)	4.3 (4.4)	10.4 (10.3)

Table I. Cont.

Compound no.	M.p., (a)	Molecular formula	Anal. Calcd. (Found) C,%	H,%	N,%
17Aa	216 (A)	$C_{21}H_{16}N_4O_2$	70.8 (70.9)	4.5 (4.5)	15.7 (15.6)
17Ab	194 (A)	$C_{22}H_{18}N_4O_2$	71.3 (71.4)	4.9 (4.7)	15.1 (15.3)
17Ac	188 (A)	$C_{21}H_{15}ClN_4O_2$	64.5 (64.3)	3.9 (4.0)	14.3 (14.1)
18Ae	284 (A)	$C_{20}H_{14}N_4O_4$	64.2 (64.1)	3.8 (4.0)	14.9 (14.8)

(a) Solvent of crystallization: A, acetic acid, E, ethanol, M, methanol.

Table II. Infrared spectra of compounds 3-18

Compound No.	ν, cm⁻¹ NH	ν, cm⁻¹ CO (C = N)	Compound no.	ν, cm⁻¹ CO (C = N)	ν, cm⁻¹ C = N [NH_2]
3A	3335,3280	1660	**10Ab**	1698 (1959)	
3B	3340,3280	1660	**10Ac**	1680 (1600)	
4A	3260	(1610)	**10Ad**	1685 (1595)	
4B	3265	(1610)	**10Ae**	1690 (1600)	
6A	3360,3200	1650 (1595)	**12**	(1595)	2218
6B	3435,3310	1683 (1595)	**14A**	(1590)	2220
7B		(1600)	**15Aa**	1745 (1593)	
8B		1738 (1600)	**15Ab**	1725 (1600)	
9Aa		1710 (1590)	**15Ac**	1720 (1605)	
9Ba		1715 (1600)	**15Ad**	1710 (1585)	
9Bb		1715 (1590)	**16Ae**	1710 (1590)	
9Bc		1718 (1590)	**17Aa**	1670 (1600)	[3440,3300]
9Bd		1718 (1590)	**17Ab**	1710 (1595)	[3480,3200]
10Aa		1690 (1590)	**18Ae**	1650 (1585)	[3328,3160]

sence of triethylamine was shown to be 1-phenyl-3-(2-furyl)4-cyanopyrazole **12A** (Scheme 3). The structure of the latter was derived on the basis of analytical and spectral data. Its IR spectrum showed two bands at 2218 and 1595 cm^{-1} corresponding to C≡N and C = N groups respectively. The ^{1}H-NMR spectrum of **12A** revealed the absence of the two doubles characteristics of 4,5-disubstituted 2-pyrazoline derivatives **11**, but instead it showed a singlet near 8.25 ppm assignable to the 4-CH proton of **12A**. The latter product seems to be formed via thermal elimination of hydrogen cyanide from the cycloadduct **11**.

Following our previous experiments the reaction of the hydrazonyl chloride **4A** with α-cyanocinnamonitrile was studied in benzene in the presence of triethylamine in order to explore the ease of aromatization of 2-pyrazoline derivatives via elimination of hydrogen cyanide. The product obtained from this reaction was identified as 1,3,5-trisubstituted 4-cyanopyrazole **14** (Scheme 3). The ^{1}H-NMR spectrum of the latter product showed a characteristics singlet near δ 8.1 ppm assignable to the 5-CH of the pyrazole ring residue. The spectrum of **14** showed a nitrile absorption near 2220 cm^{-1}. This finding suggests that 5,5-dicyano-2-pyrazoline cycloadduct **13** is easily aromatized by thermal elimination of hydrogen cyanide.

In the light of the foregoing results we investigated the reactions of **4A** and **4B** with ethyl α-cyanocinnamate and α-cyanocinnamamide and their ring substituted derivatives. The results showed that the type of the end product obtained depends on the elec-

Table III. ^{1}H-NMR spectral data of compounds 6-16

Compound no.	δ, ppm
6A	3.47 (dd, 1H), 3.73 (dd, 1H), 4.52 (dd, 1H), 6.1-7.58 (m, 8H)
7B	3.74 (d, J = 9 Hz, 2H), 5.3 (t, J = 9 Hz, 1H), 6.45-8.3 (m, 7H)
8B	1.24 (t, J = 7 Hz, 3H), 3.58 (dd, 2H), 4.21 (q, J = 7 Hz, 2H), 4.88 (dd, 1H), 6.4-8.22 (m, 7H).
9Aa	4.77 (d, J = 10 Hz, 1H), 5.25 (d, J = 10 Hz, 1H), 6.4-7.7 (m, 13H)
10Aa	4.56 (d, J = 6 Hz, 1H), 5.58 (d, J = 6 Hz, 1H), 6.7-8.1 (m, 18H)
10Ab	2.38 (s, 3H), 4.55 (d, J = 6 Hz, 1H), 5.59 (d, J = 6 Hz, 1H), 6.7-8.1 (m, 17H)
10Ac	4.51 (d, J = 6 Hz, 1H), 5.51 (d, J = 6 Hz, 1H), 6.75-8.0 (m, 17H)
10Ad	3.79 (s, 3H), 4.49 (d, J = 6 Hz, 1H), 5.51 (d, J = 6 Hz, 1H), 6.8-8.1 (m, 17H)
10Ae	4.69 (d, J = 6 Hz, 1H), 5.6 (d, J = 6 Hz, 1H) 6.75-8.34 (m, 17H)
10Ba	4.55 (d, J = 6 Hz, 1H), 5.68 (d, J = 6 Hz, 1H), 6.2-8.2 (m, 17H)
12	6.48-7.82 (m, 8H), 8.1 (s, 1H)
14	6.3-8.0 (m, ArH)
15Aa	1.2 (t, J = 7 Hz, 3H), 4.28 (q, J = 7 Hz, 2H), 5.13 (s, 1H), 6.2-7.45 (m, 13H)
15Ab	1.2 (t, J = 7 Hz, 3H), 2.38 (s, 3H), 4.28 (q, J = 7 Hz, 2H), 5.1 (s, 1H), 6.3-7.5 (m, 12H)
15Ac	1.2 (t, J = 7 Hz, 3H), 4.3 (q, J = 7 Hz, 2H), 5.12 (s, 1H), 6.2-7.6 (m, 12H)
15Ad	1.2 (t, J = 7 Hz, 3H), 3.8 (s, 3H), 4.3 (q, J = 7 Hz, 2H), 5.13 (s, 1H), 6.3-7.7 (m, 12H)
16Ae	1.0 (t, J = 7 Hz, 3H), 4.04 (q, J = 7 Hz, 2H), 6.15-8.35 (m, 12H)

tronic nature of the substituent. Thus, reactions of **4A** with both ethyl α-cyanocinnamate and its 4-CH_3, 4-Cl and 4-CH_3O substituted derivatives in refluxing chloroform in the presence of triethylamine yielded the cycloadducts **15Aa-d** in good yields. However, reaction of **4A** with ethyl α-cyano-4-nitrocinnamate gave, when carried out under similar conditions, the pyrazole derivative **16Ae** (Scheme 5). The IR spectra of **15Aa-d** revealed the nitrile absorption, thus confirming their regiochemical assignment[7]. Their ^{1}H-NMR spectra showed, in each case, a characteristics singlet near δ 5.13 ppm assignable to the 4-CH of the 2-pyrazoline ring residue. The IR spectrum of **16Ae** showed a strong absorption at 1710 cm^{-1} due to an α, β-unsaturated ester carbonyl group. The ester carbonyl absorption band of **16Aa-d** appeared at higher frequency (1750 cm^{-1}).

Reactions of **4A** with α-cyanocinnamamides in refluxing chloroform in the presence of triethylamine gave similar results. Thus, the products obtained from the reactions of **4A** with α-cyanocinnamamide and its 4-CH_3- and 4-Cl- derivatives proved to be the 2-pyrazoline derivatives **17Aa-d** respectively (Schem 3). However, reaction of **4A** and α-cyano-nitrocinnamamide afforded the pyrazole derivative **18Ae** (Scheme 3). The observed elimination of hydrogen cyanide from the cycloadducts of type **11, 13, 15Ae** and **17Ae** is similar to thermal elimination of hydrazoic acid from 5-azido-5-benzoyl-1,3,4-triphenyl-2-pyrazoline[9]. Furthermore, the observation that such elimination occurs easily from **15Ae** and **17Ae** and not from **15Ae-d** and **17Aa-d** seems to be due to the higher acidity of the 4-H in **15Ae** and **17Ae.**

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 spectra 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.

Synthesis of 2-aryl-1-(2-furoyl) hydrazines, 3A,B

To a cold solution of the appropriate arylhydrazine (0.1 mol) in pyridine (50 ml) was added dropwise over a period of 30 min while stirring 2-furoyl chloride (13.0g, 0.1 mol). After the addition was completed, the reaction mixture was stirred for further 1 h, after

which it was poured onto ice-cooled solution of hydrochloric acid (25%, 200 ml). The precipitated hydrazide was collected, washed with cold dilute hydrochloric acid and water. The crude product was dried and crystallized from acetic acid. The physical constants of the compounds prepared are given in Table I.

Synthesis of N-aryl-2-furohydrazonyl chlorides, 4A,B

Carbon tetrachloride (2 ml, 0.02 mol) was added to a stirred stirred suspension of the appropriate 2-aryl-1-(2-furoyl)-hydrazine **3** (0.02 mol) and triphenylphosphine (6.6g, 0.022 mol) in dry acetonitrile (40 ml). The mixture was stirred for 24 h. During this period the hydrazine derivative dissolved. The reaction mixture wa poured onto water while stirring and the crude product that precipitated was collected, dried and crystallized from the suitable solvent (Table I).

Synthesis of 2-pyrazoline and pyrazole derivatives, 6-18

General Procedure-To a solution of the hydrazonly chloride **4** (0.005 mol) and the appropriate dipolarophile (0.005 mol) in chloroform or benzene (40 ml) was added triethylamine (0.7 ml, 0.005 mol) at room temperature. The mixture was refluxed for 4-6 h and then cooled. The mixture was then extracted with water and the organic layer was collected, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the residue was triturated with methanol where it solidified. The solid was collected and crystallized from acetic acid to give the corresponding cycloadduct in 70-85% yield. The products **6-18** obtained together with their physical constants are listed in Tables I-IV.

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