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BEHAVIOR OF HYDRAZONOYL CHLORIDES TOWARDS THE C=N DOUBLE BOND OF Δ^2-PYRAZOLINES. A STUDY ON 2-(4-NITRO-PHENYL)-2,3,3a,4,5,6-HEXAHYDRO-6-OXOFURO[3,4-*c*]PYRAZOLE

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Abstract- The reaction between title compound (**3**) and hydrazonoyl chlorides (**4**) was performed in the presence of triethylamine or silver salts. The product output was quite different depending upon the basic agent and, besides the formation of the novel pyrazolo[4,5-*b*]furo[3,4-*c*]pyrazole skeleton, a new degradative behavior of the pyrazoline ring has been observed.

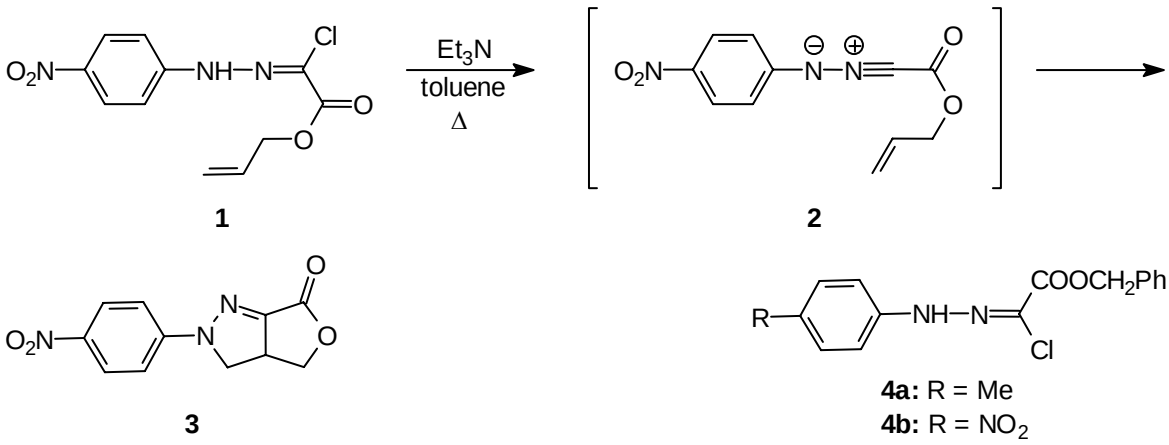
Dipolar cycloadditions[1] to heteroaromatic rings[2,3] is a well-documented matter. Our recent contributions to this subject is concerned with intramolecular nitrile imine cycloadditions to the furan[4] and the thiophene[5] rings. As a corollary of our research in this field, we realised that partially unsaturated furo[3,4-*c*]thieno[2,3-*d*]pyrazoles was capable of further cycloaddition on both C=C and C=N double bonds.[6] However, the competitive formation of products involving nitrile imine cycloaddition onto the above mentioned dipolarophiles was not readily rationalisable in the light of the FMO theory. Our somewhat unexpected findings led us to re-examine the subject of nitrile imine cycloadditions onto the C=N double bond of 3,4-disubstituted Δ^2-pyrazolines.

RESULTS AND DISCUSSION

First of all, we chose the new 2-(4-nitrophenyl)-2,3,3a,4,5,6-hexahydro-6-oxofuro[3,4-*c*]pyrazole (**3**) as the suitable reference substrate, which was synthesized *via* intramolecular cycloaddition of the nitrile imine intermediate (**2**). The latter was generated by base treatment of the corresponding hydrazonoyl chloride (**1**) following a well-established procedure elaborated by us[7] (Scheme 1). Owing to the electron-withdrawing or –donating character of the substituent R, hydrazonoyl chlorides (**4**) were chosen as the appropriate reaction counterparts (Scheme 1).

An equimolecular mixture of **3** and **4a** or **4b** was treated with the appropriate basic agent in dry dioxane. Reaction times and temperatures, products, isolated yields and eluents are collected in Table 1.

Scheme 1



Scheme 2

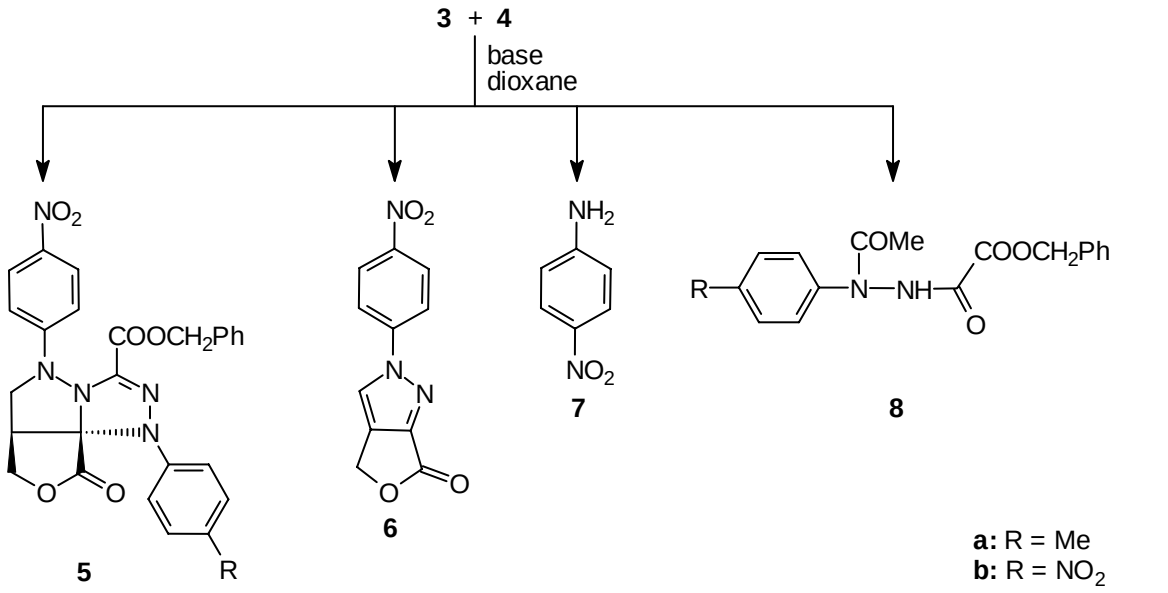


Table 1. Reaction between furopyrazoline (**3**) and hydrazonoyl chlorides (**4**) in dry dioxane.

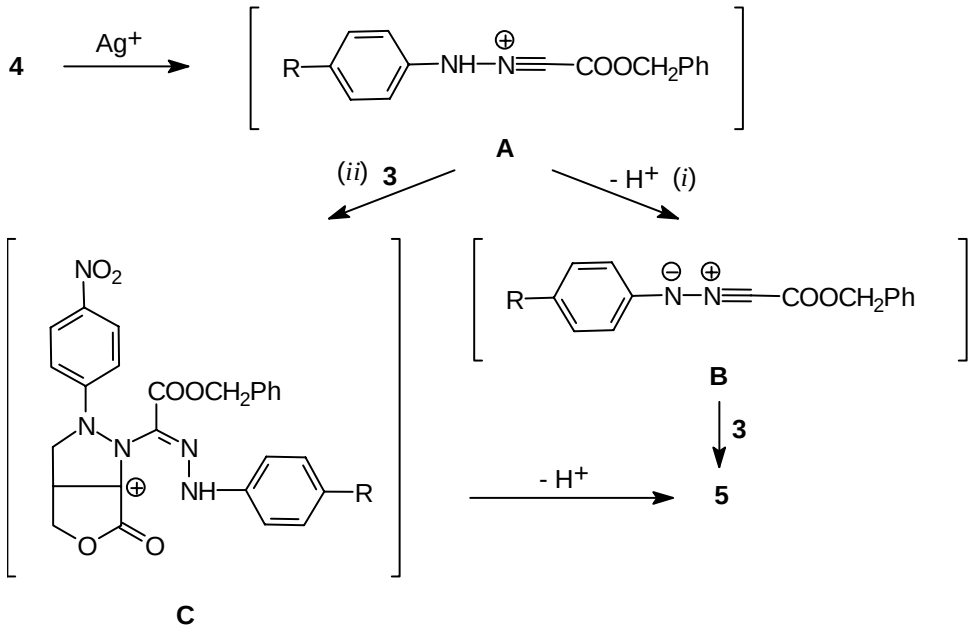
Entry	R	Base (Equivalents)	Time (h)	Products and Yields (%)[d]					Eluent[e]
				3	**5**	**6**	**7**	**8**	
1	Me	Et_3N (5)	15[a]	95	—	—	—	—	AcOEt–Et_2O 1:2
2	Me	Ag_2CO_3 (2)	7[b]	43	14	27	—	—	Et_2O
3	Me	AcOAg (1)	18[c]	16	13	—	30	24	AcOEt–LP 1:1
4	NO_2	Et_3N (5)	15[a]	94	—	—	—	—	AcOEt-Et_2O 1:2
5	NO_2	Ag_2CO_3 (2)	10[b]	48	2	21	—	—	AcOEt–LP 1:1
6	NO_2	AcOAg (1)	36[c]	20	32	—	19	31	AcOEt–LP 2:1

[a]Reflux. [b]At 75°C. [c]At room temperature. [d]Isolated yields. [e]LP = light petroleum, bp 40-60°C.

Structures (**5**-**8**) were firmly established on the basis of analytical and spectral data. In particular, ^{1}H NMR spectrum of **5** is in good agreement with those recently reported by us for similar tricyclic pyrazolines.[6] By performing the above reactions in the presence of triethylamine in boiling dioxane, according to the classic method for the *in situ* generation of nitrile imines from hydrazonoyl chlorides,[8] no noticeable reaction occurred onto the C=N double bond of **3**. In fact, unreacted **3** and some materials coming from the thermal decomposition of **4** were recovered. By replacing triethylamine with silver carbonate or silver acetate, it was possible to isolate the new pyrazolo[4,5-*b*]furo[3,4-*c*]pyrazoles (**5**) and by-products (**6**-**8**). The formation of the furo[3,4-*c*]pyrazole (**6**) is not surprising owing to the known oxidizing ability of silver carbonate,[9] while the *N*-oxalylhydrazides (**8**) is formed by the nucleophilic attack of the acetoxy anion to hydrazonoyl chlorides (**4**) followed by acetyl migration of the resulting acetoxylated intermediates.[10]

As can be inferred from Table 1, in the presence of silver carbonate or silver acetate the substituent R placed on the phenyl ring of hydrazonoyl chlorides (**4**) somewhat dictates the reaction outcome. In the former case better results were obtained with the electron-donating methyl group of **4a**, but in the presence of silver acetate this preference was just reversed and the electron-withdrawing nitro group of **4b** was found to be more effective. In order to rationalise the observed results, we propose the mechanistic picture outlined in the Scheme 3.

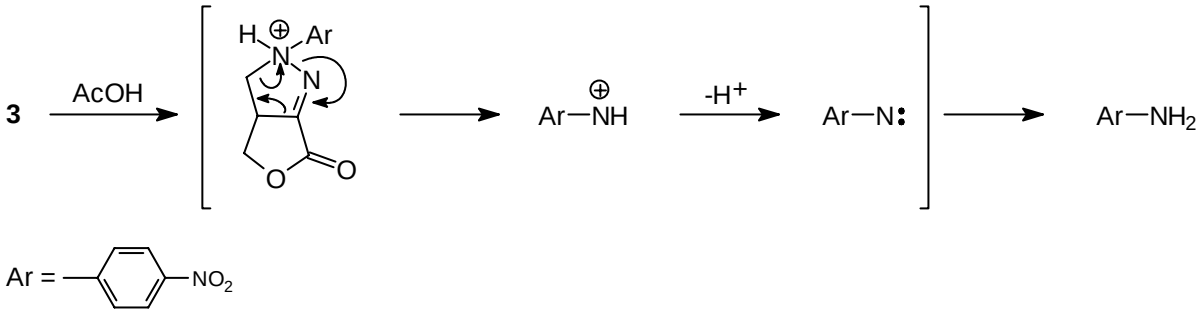
Scheme 3



Due to the well-known ability of the silver ion to facilitate the heterolysis of the carbon-halogen bond,[11] it is reasonable to admit the initial formation of the nitrilium-like carbocation (**A**).[12] This intermediate would then following two alternative pathways: (*i*) proton elimination to generate the nitrile imine species (**B**); (*ii*) electrophilic attack to the C=N π bond of **3** to form the new carbocation (**C**). Ring closure of the

latter would just produce tricyclic compounds (**5**). It can be argued that, according to pathway (*i*), the slow generation of nitrile imines (**B**) can only occur due to the base-like nature of silver carbonate, while the less basic silver acetate can drive the process through pathway (*ii*). This explanation is consistent with the results obtained in the presence of silver carbonate, which can be accounted by assuming that the preferential formation of **5a** (R = Me) arises from the HOMO-dipole controlled cycloaddition of nitrile imine intermediates (**B**) onto the C=N double bond of **3**.[13,14] It should be added that the disappointing results observed in the reaction using triethylamine as the base can be ascribed to the fast generation of nitrile imines (**B**), which can force intermolecular processes leading exclusively to resinous materials.[15] To this point, the degradation of **3** to give 4-nitroaniline deserves some comments. When silver acetate is used to promote the reaction between **3** and **4** acetic acid is formed, and early studies by Michelson describe the acid-induced ring opening for some Δ^2-pyrazolines.[16,17] Starting from this findings, which parallels the first step of Scheme 4, the formation of 4-nitroaniline could be tentatively justified, although we have not any evidence that nitrenes are really involved. As a control experiment, 4-nitroaniline was also obtained by refluxing a solution of **3** in 75% aqueous acetic acid (see EXPERIMENTAL).

Scheme 4



From the above results it can be concluded that the C=N double bond of furo[3,4-*c*]pyrazoline (**3**) show modest reactivity towards hydrazonoyl chlorides. However, a sharp dependence upon the basic agent was found, which implies two different reaction pathways. Finally, the formation of the pyrazolo[4,5-*b*]furo-[3,4-*c*]pyrazole skeleton is worth noting because of its novelty.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded on an FT IR Perkin Elmer 1725 X spectrophotometer. MS spectra were determined with a VG-70EQ apparatus. ^{1}H-NMR spectra were taken with a Bruker AC 300 or AMX 300 instrument in $CDCl_3$ solutions; chemical shifts are given as δ ppm from Me_4Si and *J* values are given in Hz. Hydrazonoyl chlorides (**4**) were prepared according to literature procedures.[6]

Preparation of hydrazonoyl chloride (1). A cold aqueous (50 mL of H_2O) solution of 4-nitrobenzene diazonium chloride (2.25 g, 15.0 mmol) was added dropwise to a solution of allyl 2-chloro-3-oxobutanoate[7] (2.64 g, 15.0 mmol) and sodium acetate (2.46 g, 30 mmol) in 80% aqueous methanol (60 mL) under vigorous stirring and ice cooling. The mixture was stirred overnight at rt. Water (80 mL) was added, the solid material was collected by filtration, washed with water and recrystallised with ethanol-acetone to give pure **1** (3.82 g, 90%) as yellow prisms having mp 165°C; IR (nujol): 3270, 1730 (cm^{-1}); ^{1}H-NMR: 4.83 (1H, dd, *J*=12.0, 5.6), 4.89 (1H, dd, *J*=12.0, 6.1), 5.30 (1H, dd, *J*=10.8, 2.5), 5.80 (1H, dd, *J*=17.1, 2.5), 6.09-6.96 (1H, m), 7.40-8.30 (4H, m), 8.60 (1H, br s); MS: *m/z* 283 (M^+). *Anal*. Calcd for $C_{11}H_{10}N_3O_4Cl$: C, 46.58; H, 3.55; N, 14.81. Found: C, 46.65; H, 3.61; N, 14.93.

Intramolecular cycloaddition of hydrazonoyl chloride (1). A solution of **1** (2.83 g, 10.0 mmol) in dry toluene (500 mL) was treated with triethylamine (5.05 g, 50.0 mmol) and refluxed for 14 h. The mixture was washed with water (3×75 mL). The organic layer was dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was recrystallised from acetone to give pure **3** (2.22 g, 90%) as dark yellow needles having mp 219°C; IR (nujol): 1770 (cm^{-1}); ^{1}H-NMR: 3.92 (1H, dd, *J*=12.5, 10.3), 4.14-4.29 (1H, m), 4.33 (1H, dd, *J*=8.8, 8.6), 4.60 (1H, dd, *J*=12.5, 10.5), 4.89 (1H, dd, *J*=8.8, 8.4), 7.17-8.31 (4H, m); MS: *m/z* 247 (M^+). *Anal*. Calcd for $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67; N, 17.00. Found: C, 53.52; H, 3.63; N, 16.90.

Treatment of furo[3,4-*c*]pyrazoline (3) with hydrazonoyl chlorides (4a,b) and triethylamine; General Procedure. To a solution of **3** (0.74 g, 3.0 mmol) and hydrazonoyl chloride (**4a**) or (**4b**) (3.0 mmol) in dry dioxane (150 mL) was added triethylamine (1.52 g, 15.0 mmol) and the mixture was refluxed for the time indicated in Table 1. The solvent was removed under reduced pressure and the residue was taken up with ethyl acetate (70 mL). The organic layer was washed with water (3×25 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with the eluent given in Table 1. First fractions contained unreacted **3** (yields are given in Table 1), further elution gave uncharacterisable material due to the decomposition of starting **4a** or **4b**.

Reaction of furo[3,4-*c*]pyrazoline (3) with hydrazonoyl chlorides (4a,b) in the presence of silver carbonate; General Procedure. To a solution of **3** (0.74 g, 3.0 mmol) and hydrazonoyl chloride (**4a**) or (**4b**) (3.0 mmol) in dry dioxane (150 mL) was added silver carbonate (1.66 g, 6.0 mmol) and the mixture was heated to 75°C in the dark for the time indicated in Table 1. The undissolved material was filtered off, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with the eluent given in Table 1. First fractions contained tricyclic pyrazolines (**5**).

Compound (**5a**) (0.22 g, 14%) as colorless needles having mp 156°C (from diisopropyl ether); IR (nujol): 1780, 1735 (cm^{-1}); ^{1}H-NMR: 2.35 (3H, s), 3.58 (1H, dd, *J*=12.1, 9.8), 3.83 (1H, dd, *J*=12.1, 9.3), 3.96-4.01 (1H, m), 4.18 (1H, dd, *J*=8.9, 8.4), 4.71 (1H, dd, *J*=8.9, 8.6), 5.40 (2H, s), 6.70-8.20 (13H, m); MS: *m/z* 513 (M^+). *Anal*. Calcd for $C_{27}H_{23}N_5O_6$: C, 63.15; H, 4.51; N, 13.64. Found: C, 63.23; H, 4.55; N, 13.76.

Compound (**5b**) (32 mg, 2%) as light yellow needles having mp 168°C (from chloroform-benzene); IR (nujol): 1790, 1740 (cm^{-1}); ^{1}H-NMR: 3.64 (1H, dd, *J*=12.6, 9.5), 3.88-4.05 (2H, m), 4.12 (1H, dd, *J*=9.1, 8.3), 4.59 (1H, dd, *J*=9.1, 8.6), 5.38 (2H, s), 7.40-8.30 (13H, m); MS: *m/z* 544 (M^+). *Anal*. Calcd for $C_{26}H_{20}N_6O_8$: C, 57.35; H, 3.70; N, 15.43. Found: C, 57.27; H, 3.73; N, 15.52.

Subsequent fractions contained compound (**6**) (yields are given in Table 1) as pale yellow needles having mp 290°C (decomp) (from acetone); IR (nujol): 1760 (cm^{-1}); ^{1}H-NMR: 5.40 (2H, d, *J*=1.3), 7.60-7.80 (2H, m), 7.88 (1H, t, *J*=1.3), 8.00-8.30 (2H, m); MS: *m/z* 245 (M^+). *Anal*. Calcd for $C_{11}H_7N_3O_4$: C, 53.88; H, 2.88; N, 17.14. Found: C, 53.98; H, 2.93; N, 17.10.

Further elution gave unreacted **3** (yields are given in Table 1).

Reaction of furo[3,4-*c*]pyrazoline (3) with hydrazonoyl chlorides (4a,b) in the presence of silver acetate; General Procedure. To a solution of **3** (0.74 g, 3.0 mmol) and hydrazonoyl chloride (**4a**) or(**4b**) (3.0 mmol) in dry dioxane (150 mL) was added silver acetate (0.50 g, 3.0 mmol) and the mixture was stirred at rt in the dark for the time indicated in Table 1. The undissolved material was filtered off, the solvent was removed under reduced pressure and the residue was taken up with ethyl acetate (80 mL). The organic layer was washed firstly with 5% aqueous sodium hydrogencarbonate (30 mL), then with water (50 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with the eluent given in Table 1.

First fractions contained compounds (**8**).

Compound (**8a**) (0.30 g, 31%) as colorless needles having mp 108°C (from hexane-benzene); IR (nujol): 3240, 1720, 1660, 1640 (cm^{-1}); ^{1}H-NMR: 2.03 (3H, s), 2.36 (3H, s), 5.31 (2H, s), 7.10-7.50 (9H, m), 9.36 (1H, br s); MS: *m/z* 326 (M^+). *Anal*. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.33; H, 5.60; N, 8.65.

Compound (**8b**) (0.26 g, 24%) as colorless needles having mp 76°C (from diisopropyl ether); IR (nujol): 3250, 1720, 1650 (cm^{-1}); ^{1}H-NMR: 2.08 (3H, s), 5.33 (2H, s), 7.37-8.25 (9H, m), 9.40 (1H, br s); MS: *m/z* 357 (M^+). *Anal*. Calcd for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76. Found: C, 57.23; H, 4.29; N, 11.84.

In order of elution, subsequent fractions contained: tricyclic pyrazolines (**5**), 4-nitroaniline and unreacted **3** (yields are given in Table 1).

Reaction of furo[3,4-*c*]pyrazoline (3) in acetic acid. A solution of **3** (0.50 g, 2.0 mmol) in 75% aqueous acetic acid (25 mL) was refluxed for 4 h. 2 M sodium hydroxide was added to pH 12 and the solution was extracted with ethyl acetate (2×50 mL). The organic layer was dried over sodium sulfate, evaporated under reduced pressure and the residue was chromatographed on a silica gel column with ethyl acetate-hexane 2:1 giving 4-nitroaniline (0.19 g, 68%).

ACKNOWLEDGEMENTS

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