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The 1,3-Dipolar Cycloaddition Reaction of 5-Nitro-2-furyldiazomethane

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The 1,3-dipolar cycloaddition reaction of 5-nitro-2-furyldiazomethane (**1**) with acrylonitrile, acrylamide, methyl acrylate, diethyl fumarate, methyl methacrylate and methyl cinnamate afforded the corresponding 3-substituted pyrazolines (**2a-f**). Similarly the pyrazoles (**3b-d**) were prepared by addition of **1** to acetylenic compounds such as diethyl acetylenedicarboxylate, methyl phenylpropiolate and cyanoacetylene. Reaction of **1** with fumaronitrile and ω -nitrostyrene gave also the corresponding pyrazoles (**3a** and **3e**) instead of the pyrazolines. 3-(5'-Nitro-2'-furyl)-4-phenyl-5-carbomethoxypyrazoline (**2f**) was oxidized with lead tetraacetate to the corresponding pyrazole (**3f**), which was different from **3c**, an addition product of **1** with methyl phenylpropiolate. 3-(5'-Nitro-2'-furyl)-5-carbamidopyrazoline (**2b**) was pyrolyzed to the corresponding cyclopropane derivative **4** in low yield.

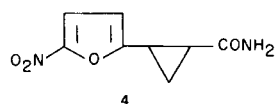
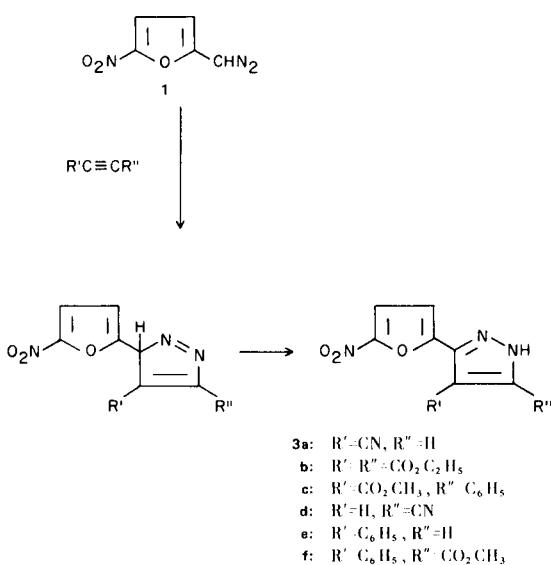
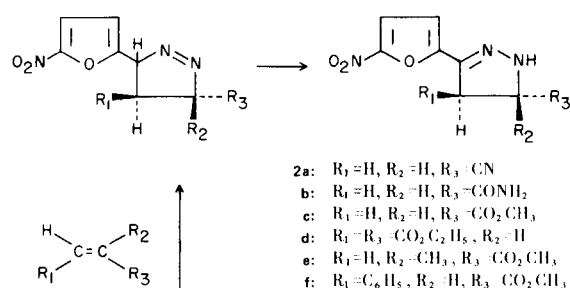
In the previous paper we have reported on the chemistry of 5-nitro-2-furyl diazo compounds (**2**). In this paper, we deal with the 1,3-dipolar cycloaddition reaction of 5-nitro-2-furyldiazomethane (**2**) with several unsaturated systems in an effort to obtain nitrofurylpyrazolines and -pyrazoles. The concerted cycloaddition mechanism has been generally accepted (3,4) and diazoacetophenone and the corresponding *p*-nitrophenyl compound are known to have the same order of addition rate constants to diethyl 2,3-diazabicyclo-(2,2,1) hept-5-ene-2,3-dicarboxylate (**3**). Therefore, **1** was expected to be an excellent starting material for 1,3-dipolar cycloaddition irrespective of the presence of a nitro group in the furan ring which strengthens the resonance stabilization and results in a poor reactivity in the carbenoid reaction as nucleophilic and electrophilic reagent (**2**).

In fact, the addition product (**2a**) was obtained by the reaction of **1** with acrylonitrile in quantitative yield as shown in Table I. The structure of **2a** was confirmed from analytical and spectral data and the direction of the cycloaddition was determined by nmr data in DMSO-D₆, which showed signals at 5.02 τ (1 H, doublet, $J = 8.9$ and 1.5 cps; the latter small coupling disappeared on deuteration) and 6.61 τ (2 H, d, $J = 8.9$ cps). The former signal was assignable to a proton at position-5 and the latter to a methylene proton at position-4 of a pyrazoline ring, which supports the structure 3-(5'-nitro-2'-furyl)-5-cyanopyrazoline.

In order to further examine the preparative utility of this cycloaddition, **1** was treated with acrylamide, methyl acrylate, diethyl fumarate, methyl methacrylate and methyl cinnamate to give the corresponding pyrazolines (**2b-f**), respectively. Similarly the pyrazoles (**3a-e**) were prepared by addition of **1** with fumaronitrile, diethyl acetylenedicarboxylate, methyl phenylpropiolate, cyanoacetylene and ω -nitrostyrene. Direct formation of the pyrazoles by the reaction of **1** with such olefinic compounds as fumaronitrile and ω -nitrostyrene instead of the expected pyrazoline derivatives can be explained by a simultaneous elimination of hydrogen cyanide and nitrous acid respectively from the corresponding pyrazoline derivatives produced as the primary adducts as illustrated in Scheme 2.

All results of the 1,3-dipolar cycloaddition reaction of **1** are summarized in Table I. The cycloaddition reaction of **1** with unsaturated systems having weakly electrophilic or nucleophilic substituents such as cyclohexene, styrene, vinyl ethers, crotonic acid, its ester, its amide, vinylchloride, vinylidenechloride, methyl sorbate, 2,6-dimethoxy-*p*-quinone, 5-nitro-2-furylacrylate, phenylacetylene, propargyl bromide, propargyl alcohol, propargyl aldehyde diethylacetal, acetonitrile, malonitrile, phenylisocyanate, phenylisothiocyanate, *N*-sulfinyltosylamide and dicyclohexylcarbodiimide were all unsuccessful. This trend of the reactivity is rather common in diazoalkanes (**4a**). The fact that **1** has lower reactivity than diazo-

Scheme 1

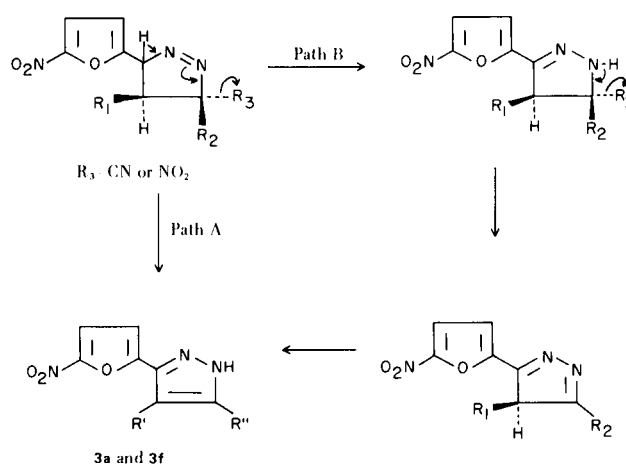


methane (5) will be explained in terms of the resonance stabilization of the ground state of **1** and of the steric hindrance as seen in some aromatic diazo compounds (6).

The infrared and the ultraviolet spectral data of these pyrazolines and pyrazoles are shown in Table II, from which it is clear that the pyrazolines as well as the pyrazoles all had characteristic NH bands at around 3300 cm^{-1} in their infrared spectra; the ultraviolet absorption maxima in ethanol were located at $373\text{--}383\text{ m}\mu$ for the pyrazolines and $337\text{--}358\text{ m}\mu$ for the pyrazoles, although simple pyrazoles show an absorption maximum at a longer wavelength than the corresponding pyrazolines.

The nmr signals of **2b** appeared at $5.64\ \tau$ (1 H, t, $J = 10.4$

Scheme 2



cps) and at $6.81\ \tau$ (2 H, q, $J = 10.4$ and 2.8 cps) as shown in Table III; these two signals are assignable as shown in this table, indicating 1,3-dipolar cycloaddition had occurred in the same direction as in the case of **2a**. Similarly the structures of the cycloaddition products (**2c-f**) were determined by their nmr spectra, among which, **2e** showed methylene proton signals at $6.30\ \tau$ and $7.06\ \tau$ in an AB-quartet with $J/\Delta\tau = 0.375$ and **2f** had signals at $5.20\ \tau$ (1 H, d, $J = 4.0$ cps) and at $5.60\ \tau$ (1 H, d, $J = 4.0$ cps); the former signal was sharpened slightly on deuteration and was assignable to a proton at position-5 and therefore, the latter to a proton at position-4 of a pyrazoline ring. The chemical shift of a proton at position-5 for **2f** was nearly the same as that of **2d** which had the signals of an AB-quartet at $5.42\ \tau$ (C-4-H) and $5.11\ \tau$ (C-5-H) with $J/\Delta\tau = 0.682$, supporting the above assignment for **2f**. The *trans*-configuration of the substituents at position-4 and -5 in **2d** and **2f** was confirmed from the coupling constants between C-4-H and C-5-H being 4.5 and 4.0 cps for **2d** and **2f** respectively, both in the range postulated for the *trans*-configuration (7). The somewhat lower yield of **2f** compared with the other compounds might be explained by the steric hindrance of a bulky phenyl group to a nitrofurane ring and this steric factor is known to be a more important factor in 1,3-dipolar cycloaddition than the electronic factor (**4a,8**). In fact, it was found that the direction of cycloaddition of methyl phenylpropionate was reversed from the expected direction based on the electronic factor, which was demonstrated by a comparison of **3c** with **3f** obtained directly by oxidation of **2f** with lead tetraacetate. As seen in Tables I and II, **3c** and **3f** had different melting points and spectra. By a comparison of **3a** with **3d**, **3a** had a nmr signal at $1.22\ \tau$ (1 H, s) assignable to a proton at position-5 of a pyrazole

TABLE I
1,3-Dipolar Cycloaddition Products

1,3-Dipolarophiles	Reaction Time, days	Product	Yield %	M.p., °C	Formula	Found, %(Calcd, %)		
						C	H	N
Acrylonitrile	3	2a	97	135-136.5 (r. (a) CHCl ₃)	C ₈ H ₆ O ₃ N ₄	47.03 (46.60)	3.02 (2.93)	27.34 (27.28)
Acrylamide	2	2b	94	188-191 (r. CH ₃ OH)	C ₈ H ₈ O ₄ N ₄	43.00 (42.86)	3.62 (3.60)	24.66 (24.99)
Methyl acrylate	1	2c	88	104-105 (c. r. (a) C ₂ H ₅ OH)	C ₉ H ₉ O ₅ N ₃	45.12 (45.19)	3.74 (3.79)	17.08 (17.57)
Diethyl fumarate	3	2d	58	liquid (c)	C ₁₃ H ₁₅ O ₇ N ₃	47.69 (48.00)	4.53 (4.65)	12.61 (12.92)
Methyl methacrylate	2	2e	47	88-89 (c. r. CHCl ₃)	C ₁₀ H ₁₁ O ₅ N ₃	47.42 (47.43)	4.36 (4.38)	15.91 (16.60)
Methyl cinnamate	5	2f	40	118-119 (c, r. C ₂ H ₅ OH)	C ₁₅ H ₁₃ O ₅ N ₃	56.76 (57.14)	4.22 (4.16)	13.48 (13.33)
Fumaronitrile	4	3a	85	240-241 (r. CH ₃ OH)	C ₈ H ₄ O ₃ N ₄	47.27 (47.07)	2.12 (1.98)	27.38 (27.45)
Diethyl acetylene-Dicarboxylate	53	3b	21	53-55 (c, r. CH ₃ OH)	C ₁₃ H ₁₃ O ₇ N ₃	48.58 (48.30)	4.06 (4.05)	12.54 (13.00)
Methyl phenyl-Propiolate	11	3c	36	161-163 (r. CHCl ₃)	C ₁₅ H ₁₁ O ₅ N ₃	57.28 (57.51)	3.38 (3.54)	13.01 (13.42)
Cyanoacetylene	1	3d	90	162-163 (r. CHCl ₃)	C ₈ H ₄ O ₃ N ₄	46.81 (47.07)	1.55 (1.98)	27.45 (27.45)
ω-Nitrostyrene	7	3e	26	161-162 (r. C ₆ H ₆)	C ₁₃ H ₉ O ₃ N ₃	60.52 (61.17)	2.98 (3.55)	16.22 (16.47)
		3f		196-198				

(a) γ. CHCl₃ = recrystallized from chloroform., c, r. CHCl₃ = chromatographed on a silica-gel column and recrystallized from chloroform.

ring, while **3b** showed a signal at 2.48 τ (1 H, s) assignable to a proton at position-4, indicating that elimination of hydrogen cyanide from the primary adduct of **1** with fumaronitrile had occurred via path A or B as shown in scheme 2.

Similarly nitrous acid elimination from the primary

adduct of **1** with ω-nitrostyrene gave a pyrazole derivative **3e** which had a signal at 1.86 τ (1 H, s), indicating the presence of a proton at position-5 of a pyrazole ring. This difference in the direction of the addition between **3c** and **2f** is quite interesting in explaining the mechanism of 1,3-dipolar cycloaddition, for which further investigation

TABLE II
IR and UV Spectral Data of 5-Nitro-2-furyl-pyrazolines (**2a-f**) and -pyrazoles (**3a-f**)

Compound	Infrared NH band (KBr) cm^{-1}	UV data (EtOH) $m\mu$ ($\epsilon \times 10^{-4}$)
2a	3380	373 (1.11), 268 (0.66)
2b	3290	380 (1.38), 272 (1.03)
2c	3310	384 (1.21), 274 (0.776)
2d	3370 (a)	383 (1.31), 272 (0.728)
2e	3360	385 (1.20), 275 (0.859)
2f	3360	380 (1.14), 275 (1.12)
3a	3380	337 (1.51), 225 (1.13)
3b	3640, 3380 and 3170	342 (1.55), 222 (1.98)
3c	3590, 3350 and 3250	345 (1.48), 225 (1.92)
3d	3540, 3380 and 3220	341 (1.45), 208 (2.02)
3e	3150	352 (1.50), 217 (2.42)
3f	3510, 3440 and 3230	358 (1.31), 222 (2.28)
3-(5'-nitro-2'- furyl)pyrazole (2)	3165	354 (1.53), 230 (1.15)

(a) In CCl_4

has been carried out.

Compound **1** was treated with cyanoacetylene to give the corresponding pyrazole derivative **3d**. These facts explain why all the pyrazolines obtained by the above-mentioned 1,3-dipolar cycloaddition of **1** were not Δ^1 - but Δ^2 -pyrazolines. Also the easy formation of **3a** and **3e** from the reactions with fumaronitrile and ω -nitrostyrene is explained by the strong acidity of a hydrogen at a carbon atom *alpha* to a furan ring and by the higher aromatic stability of the pyrazoles compared with the pyrazolines.

The 5-nitro-2-furylcyclopropane derivatives could not be prepared by the carbenoid reaction with some carbenophiles using **1** as a carbene precursor (**2**). Therefore, the above-mentioned 5-nitro-2-furylpyrazolines were tested for

that purpose and **2b** was pyrolyzed under high vacuum in a sublimation flask to afford a cyclopropane derivative **4**. The structure of this derivative was confirmed by the analytical and spectral data; the ultraviolet spectrum had an absorption maximum at $331 m\mu$ (ϵ 9740) which was located between $300 m\mu$ for 5-nitro-2-furylmethyl compounds and $350 m\mu$ for nitrofurylvinyl compounds. When **2b** was refluxed in toluene for several hours, only a trace amount of **4** was obtained, while 4-(5'-nitro-2'-furyl)-5-carbomethoxy-pyrazoline is known to give the corresponding cyclopropane derivative in 75% yield under similar reaction conditions (**5**). This different thermal behavior might come from the facile conversion of 4-(5'-nitro-2'-furyl)-5-carbomethoxy-pyrazoline to its Δ^1 -compound compared with **2b**.

TABLE III
NMR Data of 5-Nitro-2-furylpyrazolines and -pyrazoles (a).

	Nitro-furan-ring protons (b)	at 4-position	at 5-position	at 1-position (c)	Others
2a (d)	2.22, 2.90	6.61(2 H, d, J:8.9)	5.02(1 H, t, J:8.9 and d, J:1.5) (e)	1.32(1 H, d, J:1.5)	
2b (d)	2.25, 3.03	6.81(2 H, q, J:10.4 and 2.8)	5.64(1 H, t, (f) J:10.4)	1.81(1 H, broad s)	2.66(2 H, d, J:12.9, CONH ₂)
2d (g)	2.59, 3.05	5.42(1 H, d, J:4.5)	5.11(1 H, d, J:4.5)	3.0-3.25(1 H, broad s)	5.89 and 5.63 (h) (each 2H, q, J:7.0) 8.75 and 8.69 (h) (each 3 H, t, J:7.0)
2e (g)	2.64, 3.20	6.30 and 7.06 (each 1 H, d, J:17.1)		3.0-3.82(1 H, broad s)	6.22(3 H, s, CO ₂ CH ₃) 8.40(3 H, s, CH ₃)
2f (g)	2.78, 3.41	5.60(1 H, d, J:4.0)	5.20(1 H, d, J:4.0)	3.24(1 H, s)	2.69(5 H, broad s, C ₆ H ₅), 6.18(3 H, s, CO ₂ CH ₃)
3a (d)	2.16, 2.75		1.22(1 H, s)		
3c (d)	2.21, 2.68				2.46(5 H, broad s, C ₆ H ₅), 6.31(3 H, s, CO ₂ CH ₃)
3d (d)	2.17, 2.72	2.48(1 H, s)			
3e (g)	2.70, 3.53		1.86(1 H, s)	-1.00- -0.500 (1 H, very broad s)	2.55(5 H, s, C ₆ H ₅)

(a) Chemical shift in τ value and coupling constant, J in cps. (b) Each signal was for 1 H and doublet with J = 3.8-4.0 cps. (c) Signal was disappeared on deuteration with deuterium oxide and NH proton signal of pyrazole derivatives in DMSO-d₆ could not be observed. (d) In DMSO-d₆. (e) Doublet with J = 1.5 cps disappeared on deuteration. (f) Signal was sharpened on deuteration. (g) In deuteriochloroform. (h) Signals due to two ethyl groups at position-4 and -5.

EXPERIMENTAL (9)

Materials.

Cyanoacetylene (10) and ω -nitrostyrene (11) were prepared by the known methods; other reagents were all commercially available.

1,3-Dipolar Cycloaddition Reaction of 1.

A mixture of **1** (2), a small excess amount of olefinic or acetylenic compound and a few drops of triethylamine in ether was kept standing in a dark place at room temperature for a few days. After removing the ether and triethylamine, the crude product was purified either by recrystallization or by chromatography on a silica-gel column followed by recrystallization. Melting points, yields and analytical data are summarized in Table I, infrared and ultraviolet spectral data in Table II and nmr data in Table III.

graph on a silica-gel column followed by recrystallization. Melting points, yields and analytical data are summarized in Table I, infrared and ultraviolet spectral data in Table II and nmr data in Table III.

Oxidation of **2f** with Lead Tetraacetate.

A mixture of 1.02 g. (0.003 mole) of **2f** and 2.3 g. (0.005 mole) of lead tetraacetate in 50 ml. of dry ether was stirred at 0° for 9 hours and the crude products were purified by silica-gel chromatography. The fractions eluted with chloroform afforded 83 mg. (8.3%) of yellow crystals of **3f**, m.p. 196-198° (from chloroform).

Anal. Calcd. for C₁₅H₁₁O₅N₃: C, 57.51; H, 3.54; N, 13.42. Found: C, 57.62; H, 3.29; N, 13.67.

1-(5'-Nitro-2'-furyl)-2-carbamoylcyclopropane (4).

In a sublimation apparatus, 0.22 g. of **2b** was pyrolyzed at about 190° at a pressure of 10^{-3} mm. of Hg and the sublimed yellow solids were collected and recrystallized from ethanol to give 0.01 g. (10%) of **4** as yellow crystals, m.p. 194-195°: λ max (EtOH) 210 (ϵ , 8,180) and 331 m μ (ϵ , 9,740); ν (potassium bromide), 3390 and 3185 (NH), 1600 (CONH₂), 1528 and 1356 (NO₂), 1592, 1508, 1388, 1014 and 810 (furan) cm⁻¹; nmr (DMSO-D₆) τ , 2.18 and 2.89 (2 H, each very broad s, CONH₂), 2.38 and 3.31 (each 1 H, d, J = 3.8 cps, nitrofuran ring protons) 7.5-8.0 (2 H, complex m. C-1-H, C-2-H), 8.58 (2 H, broad unsymmetrical t, J = 7.5 cps, C-3-H).

Anal. Calcd. for C₈H₈O₄N₂: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.77; H, 4.10; N, 14.17.

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