Pyrazoles. XVIII (1). Synthesis of a Novel Tripyrazolyl by Two Consecutive Cine Substitution Reactions

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Preparation of the C-N coupled tripyrazolyl VII, by two consecutive cine substitution reactions starting from 1,4-dinitropyrazole and using pyrazole as a nucleophile, is described. Solvent dependent nitrations of 4-nitro-3(5)-(1'-pyrazolyl)pyrazole I are reported.

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Recently we reported on the cine substitution reaction of 1,4-dinitropyrazoles (1,2). In this reaction, a nucleophilic aromatic substitution of the 1,2-addition elimination type, the entering group comes in *ortho* to the leaving group resulting in the formation of a 3*H*-pyrazole. The ultimate product is then formed in a subsequent fast 1,5-hydrogen shift. In the case of pyrazoles as nucleophiles (1) this cine substitution reaction affords bipyrazolyls. In

Chart 1

view of the excellent yields generally obtained in this reaction we expected that N-nitration of 4-nitro-3(5)-(1'-pyrazolyl)pyrazole I followed by a second cine substitution reaction with a pyrazole would provide a convenient method for the synthesis of twice C-N coupled tripyrazolyls of the general structure II. The feasibility of

III
$$R^1 = H$$
 II $R^1 = H = 4-NO_2$ VII $R^1 = 4-NO_2$ Chart 2

performing this cine substitution reaction on a 1,4-dinitropyrazole containing a large bulky group in the 3-position was demonstrated recently by J. Grant Buchanan, et al., in their elegant new synthesis of formycin (3).

Nitration of I in acetic acid with nitric acid followed by addition of acetic anhydride according to the procedure described previously (4) was unsuccessful. Only starting material I was recovered from the reaction mixture. However, treatment with acetyl nitrate, i.e., a freshly prepared mixture of nitric acid and acetic anhydride, gave instead of the wanted dinitro bipyrazolyl III the trinitro derivative IV contaminated with the N-acetyldinitrobipyrazolyl V. The structure assignments of IV and V were

primarily based on their proton nmr data. Acid hydrolysis of a sample of this reaction product followed by recrystal-lization gave 4-nitro-3(5)-(4'-nitro-1'-pyrazolyl)pyrazole VI. This dinitro bipyrazolyl VI was shown to be identical with an authentic sample obtained from the nitration of I with nitric acid in sulfuric acid.

The crude compound IV reacted readily with pyrazole at room temperature in acetonitrile solution. From the

reaction mixture the expected product, the dinitro-tripyrazolyl VII, was obtained in good yield thus demonstrating that a tripyrazolyl can be synthesized from 1,4-dinitropyrazole in three steps including two cine substitution reactions with pyrazole as nucleophile.

Finally, it is of interest to note that the nitration of I shows an interesting dependence on the reagent used (5). I might be viewed as a N-substituted pyrazole Ia as well as a 3(5)-substituted-4-nitropyrazole Ib. Like its Ia-type analogues, the N-(nitrophenyl)pyrazoles in mixed acid I are readily nitrated in the 4-position. On the other hand, under those nitration conditions that its Ib-type analogue 3(5)-phenyl-4-nitropyrazole VIII affords 1,4-dinitro-3-phenylpyrazole in high yield (4), I is recovered unchanged. However, as we report here, treatment of I with acetyl nitrate results in nitration both on the nitrogen as well as in the free 4-position giving IV.

Chart 4

EXPERIMENTAL

Nmr spectra were recorded on a Jeol Minimar 60 MHz or on a Jeol PS-100. Ir spectra (potassium bromide) were recorded on a Beckman IR-10 instrument. Elemental analyses were performed by Mr. W. J. Buis (TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands). Spraying with Rhodamine B solution (0.05% in ethanol) was used for detection of nitro pyrazoles on tlc; chromatograms were developed in chloroform-ethyl acetate 9:1. The melting points are uncorrected. The nitrobipyrazolyl I was synthesized as described previously (1).

Caution. Although we have never experienced detonations when working with 1,4-dinitropyrazole, the starting material for the synthesis of I, investigations by J. Verhoeff, J. H. M. van Liempt and J. Rooseboom (Prins Maurits Laboratory, TNO, Delft) showed that it is an explosive substance which can deflagrate and probably detonate. The sensitivity for explosion, however, is much lower than for primary explosives. 4-Nitro-3(5)-(4'-nitro-1'-pyrazolyl)pyrazole (VI).

To a solution of 1.22 g. of 4-nitro-3(5)-(1'-pyrazoly!)pyrazole I (1) in 5 ml. of sulfuric acid placed in a round bottom flask provided with a reflux condenser and drying tube was added 0.6 ml. of nitric acid. After heating for 9 hours on a boiling water bath the reaction mixture was poured on ice. The crystalline precipitate was collected, washed with water and air dried giving 0.74 g., yield 48%. Recrystallization twice from ethanol-

water 1:1 afforded light yellow colored crystals of which no melting point could be obtained; ir: 3140 cm⁻¹ (N-H), 1510-1580 and 1365 cm⁻¹ (NO₂); nmr (DMSO-d₆): δ 8.4, 8.9 and 9.2 (each a singlet).

Anal. Calcd. for $C_6H_4N_6O_4$: C, 32.14; H, 1.80; N, 37.50. Found: C, 32.31; H, 1.69; N, 37.15.

Nitration of I with Acetyl Nitrate.

Acetyl nitrate was freshly prepared by slow addition of 4 ml. of nitric acid (d 1.5) to 9.9 ml. of acetic anhydride under external cooling to maintain the temperature between 15° and 25°. The thus prepared acetyl nitrate, cooled to -20° , was then slowly added to a well stirred suspension of 1.5 g. of I in 10 ml. of acetic acid, while cooling to maintain the internal temperature at 0°. After allowing to warm to room temperature the reaction mixture was poured on 50 g. of ice. The light brown crystals were collected and dried giving 1.77 g. of product. Tlc analysis showed that the found N-nitrobipyrazolyl was contaminated with a small amount of an N-acetyl derivative. From the ir [1660 cm⁻¹ (C=0), 1575 and 1275 cm⁻¹ (N-NO₂), 1510 and 1350 (C-NO₂) (see reference 6)] and the nmr [(DMSO-d₆) δ 8.6, 9.6 and 10.3 besides δ 1.9, all singlets], it was inferred that the dinitration product IV was contaminated (10%) with the N-acetyl mononitration product V. Hydrolysis of 0.25 g. by refluxing in ethanol/hydrochloric acid (2:1) for 2.25 hours gave the N-unsubstituted 4,4'-dinitrobipyrazolyl VI.

4-Nitro-3(5)-(4'-nitro-1'-pyrazolyl)-5(3)-(1"-pyrazolyl)pyrazole (VII).

A solution of 1 g. of IV in 15 ml. of acetonitrile was dropped slowly to a solution of 0.51 g. of pyrazole in 8 ml. of acetonitrile. After 5 minutes of stirring a solid started to precipitate. After 3.5 hours tlc analysis showed that all IV had reacted. Sulfamic acid (0.4 g.) was added to the reaction mixture to destroy the nitrous acid present. The precipitate was collected, washed with a small amount of acetonitrile and dried giving 0.70 g. of product (72%). Recrystallization from ethanol gave pure VII, m.p. 246-248°; nmr (acetone-d₆): δ 6.7 (1H, m, 4"-proton), 7.9 (1H, d, 3"-proton), 8.5 (1H, s, 3'-proton), 8.6 (1H, d, 5"-proton) and 9.1 (1H, s, 5'-proton); ir: 3140 cm⁻¹ (N-H); 1610 and 1360 cm⁻¹ (NO₂).

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REFERENCES AND NOTES

- (1) Pyrazoles, Part XVII: P. Cohen-Fernandes, C. Erkelens, C. G. M. van Eendenburg, J. J. Verhoeven and C. L. Habraken, J. Org. Chem., 44, 4156 (1979).
 - (2) C. L. Habraken and E. K. Poels, ibid., 42, 2893 (1977).
- (3) J. Grant Buchanan, A. R. Edgar, R. J. Hutchison, A. Stobie and R. H. Wightman, J. Chem. Soc., Chem. Commun., 237 (1980).
- (4) J. W. A. M. Janssen and C. L. Habraken, J. Org. Chem., 38, 3081 (1971).
- (5) See also: K. Schofield, M. R. Grimmett and B. R. T. Keene, "The Azoles", Cambridge University Press, London, 1979, p. 60.
- (6) J. W. A. M. Janssen, H. J. Koeners, C. G. Kruse and C. L. Habraken, J. Org. Chem., 38, 1777 (1973).