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Cine-Substitution of 2-Methyl-1,4-dinitroimidazole in Dimethylsulfoxide Solution. Synthesis of 4(5)-(Azol-1′-yl)-2-methyl-5(4)-nitroimidazoles

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4(5)-(Azol-1-yl)-5(4)-nitroimidazoles were obtained in moderate yields by nucleophilic *cine*-substitution of 2-methyl-1,4-dinitroimidazole. Nucleophilic azole anions were generated from salts of parent heterocycles with 1,8-diazabicyclo[5.4.0]-undec-7-ene.

Key words: 1,4-dinitroimidazoles, *cine* substitution, DBU salts of azoles

Azole derivatives containing electron-withdrawing substituents and a nucleophugal group at the "pyrrole type" nitrogen atom can undergo nucleophilic *cine*-substitution. Thus, 1,4-dinitropyrazoles react with several (*N-, O-, S-, C-* and *P*-centered) nucleophiles to give respective *cine*-substitution products [1]. Such reactions have found some useful applications, *e.g.*, in syntheses of *C*-nucleosides [2–4]. Usually a nucleophile enters the position 5 of a pyrazole derivative. When the latter position is occupied, position 3 can be attacked instead [5]. The *cine*-substitution reactions of that type occur under very mild conditions. *N*-Denitration commonly accompanies the reactions. 3,4-Benzodinitropyrazoles, usually called 2,5- and 2,6-dinitroindazoles, react with secondary cyclic amines to give 1*H*-3-amino-5(or 6 respectively)-nitroindazoles [6–7].

Also 1,4-dinitroimidazoles undergo nucleophilic *cine*-substitution very easily though a scope of its known applications is much narrower. *Cine*-substitution of benzimidazole derivatives is not known. Till now only reactions of 1,4-dinitroimidazole and its 2-methyl derivative with some alcohols [8], 1*H*-azoles [9] and cyanide anions [10] have found synthetic applications. In all the investigated cases a new substituent entered the position 5. The reactions occurred in aqueous solutions in the presence of sodium bicarbonate or in buffers of pH 7–8.5. It is worth of mentioning, that 1,4-dinitroimidazoles also react very easily in aqueous solutions with several compounds containing primary amino group to give high yields of respectively 1-substituted 4-nitroimidazoles (so called *ANRORC* or a degenerated ring transformation reaction) [11]. Under similar conditions 1,4-dinitroimidazoles with some sec-

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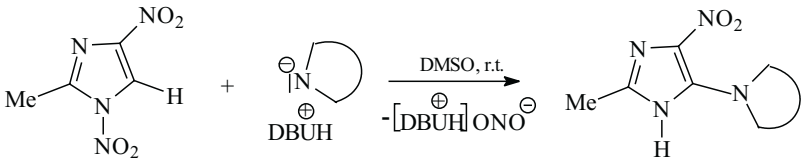
ondary amines afford 5(4)-amino-4(5)-nitroimidazoles [9] but with primary amines no traces of *cine*-substitution products were observed. Besides water and water-alcohol only dimethylsulfoxide was suitable as a solvent for the *ANRORC* reaction [11]. This paper presents first attempts to perform *cine*-substitution of 1,4-dinitroimidazoles in dimethylsulfoxide solution. In contrast to the well-proved mechanism of the *ANRORC* reaction [11], a mechanism of 1,4-dinitroimidazole *cine*-substitution is not clear yet. Nevertheless the first step of both the reactions probably involves the formation of respective σ^H complexes; therefore, the choice of dimethylsulfoxide as a solvent for *cine*-substitution seems to be rational.

Good yields of 1,4-dinitroimidazoles *cine*-substitution by *N*-centered nucleophiles were obtained using 1*H*-azoles in slightly alkaline aqueous solutions [9]. In the case of 4(5)-substituted imidazoles one should expect the formation of two isomeric products. However, only one product with a substituent occupying the position 4′ was isolated from the post-reaction mixture [9]. The latter observation drove us to the assumption that not an azole itself but its anion combines with 1,4-dinitroimidazoles to give σ^H complexes. Sodium or potassium salts of azoles are not soluble in dimethylsulfoxide. The use of 1*H*-azole salts with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) enabled us to perform the reactions in homogeneous solutions.

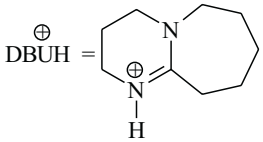
RESULTS AND DISCUSSION

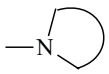
We describe the synthesis of 4(5)-(azol-1′-yl)-5(4)-nitroimidazoles by *cine* substitution of 1-NO_2 group in 2-methyl-1,4-dinitroimidazole **1** (Scheme 1) using salts of 1*H*-azole with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (**2–e**) as nucleophiles in dimethylsulfoxide (DMSO) solutions. DBU deprotonates azoles of pK_a up to over 13 (*e.g.*, pK_a of 5,6-dimethylbenzimidazole = 13.2) to form stable salts [12].

Scheme 1



1 **2a - e** **3a - e**





a - 2-methyl-4(5)-nitroimidazol-1-yl
b - 2-methyl-4,5-dibromoimidazol-1-yl
c - 5,6-dimethylbenzimidazol-1-yl
d - benzotriazol-1-yl
e - 4(5)-nitroimidazol-1-yl

2-Methyl-1,4-dinitroimidazole (**1**), having only one free position 5 at the ring, when treated with twofold excess of the salt **2a–e** in DMSO solution at room temperature for 24 hours gave *cine*-substitution products **3a–e** in moderate to high yields. Removing of the methyl group from the carbon atom 2 resulted, in most cases, in *N*-denitration and ring opening product formation. Only reaction of 1,4-dinitroimidazole with benzotriazole-DBU salt was successful and gave the respective *cine*-substitution product in *ca*. 50% yield.

Separation of the reaction products proved to be somewhat troublesome. When starting dinitroimidazole disappeared (24 hrs), reaction mixture was diluted with water and neutralized by addition of hydrochloric acid (5% aqueous solution). Extraction with ethyl acetate and chromatography on silica gel column was necessary for purification. Both possible regioisomers could be expected for the reactions with unsymmetrically substituted azoles (**2a**, **e**) and benzotriazole **2d**. Basing on inspection of ^{1}H NMR and ^{13}C NMR spectra it appears that the *cine*-substitution of 2-methyl-1,4-dinitroimidazole by DBU salts of unsymmetrically substituted azoles in dimethylsulfoxide led to the formation of only one regioisomer. The absence of regioisomeric 4-nitro-(5′-nitroazol-1′-yl)-imidazole derivative in products of the reaction of **1** with **2** (**a** or **e**) is possibly connected with a lower stability of 5-nitro-1-*H*-imidazoles (in comparison with theirs 4-nitro isomers) also in dimethylsulfoxide solution. Moreover, the position 3, *e.g*. in **2a** or **2e**, is more hindered by the bulky substituents (2-Me and 4(5)-NO_2) than the position 1. Comparing the results presented here with those obtained by us earlier for similar reactions carried out in water or aqueous methanol [11], it seems that (considering yields of products, a scope of the reactions and purification procedures) water is still a solvent of choice for the reaction investigated.

EXPERIMENTAL

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR on a Varian Inova 300 MHz in DMSO-d_6 solution; δ-values are in ppm relative to tetramethylsilane as an internal standard. EI mass spectra were recorded on a Shimadzu GC-MS 2000 (direct inlet, 70 eV). 2-Methyl-1,4-dinitroimidazole [13], 4,5-dibromo-2-methylimidazole [14], 4(5)-nitroimidazole [15], 4(5)-bromo-2-methyl-5(4)-nitroimidazole [16] were obtained according to the reported procedures. Other azoles were purchased from Aldrich. Azole salts with DBU were obtained according to the previously reported methodology [12]. TLC $60F_{254}$ plates and silica gel 60 (0.040–0.063 mm) were purchased from Merck.

4(5)-(Azol-1′-yl)-5(4)-nitroimidazole 3ii (general procedure): To 2-methyl-1,4-dinitroimidazole (**1a**, 0.34 g, 2 mmol) or 1,4-dinitroimidazole (**1b**, 0.32 g, 2 mmol) dissolved in dimethylsulfoxide (5 ml), appropriate azole salts with DBU **2a–e** (4 mmol) was added. Resulting solution was stirred at room temperature to disappearance of dinitroimidazole derivative, then water (25 ml) was added followed by aqueous solution of hydrochloric acid (5%) to reach pH approx. 7. Resulting solution was extracted with ethyl acetate (5 × 10 ml). Organic extract was dried over anhydrous $MgSO_4$ and evaporated, residue was purified on silica gel column using ethyl acetate:chloroform (7:3) as an eluent. The following compounds were obtained:

3aa: Yield 84% (0.42 g); m. p. 269–270°C (H_2O). ^{1}H NMR: 12.20 (broad s, 1H, NH), 8.65 (s, 1H, H-5), 2.42 (s, 3H, Me), 2.34 (s, 3H, Me). ^{13}C NMR: 146.11, 146.06 (C-4, C-4′), 145.11, 144.22 (C-2, C-2′), 123.24, 122.99 (C-5, C-5′), 14.16 (Me), 13.00 (Me). Anal. Calcd. for $C_8H_8N_6O_4$ (252.19): C, 38.10; H, 3.20; N, 33.32. Found: C, 38.10; H, 3.08; N, 33.36.

3ab: Yield 20% (0.15 g); m. p. 198–200°C (decomp., MeOH). ^{1}H NMR: 8.78 (s, 1H, NH), 2.49 (Me), 2.30 (Me). ^{13}C NMR: 147.44, 115.87, 104.13, 14.15 (Me), 13.56 (Me). MS (m/z, %): 365 (M^+, 12), 366 (M^++1, 3), 367 (M^++2, 4), 147 (25), 67 (55), 45 (85). Anal. Calcd. for $C_8H_7Br_2N_5O_2$ (364.99): C, 26.32; H, 1.93; N, 19.19. Found: C, 26.25; H, 2.15; N, 19.40.

3ac: Yield 49% (0.27 g); m. p. 266–267°C (decomp., H_2O). ^{1}H NMR: 8.49 (s, 1H, H-2′), 7.55 (s, 1H, H-4′), 7.36 (s, 1H, H-7′), 2.45 (s, 3H, Me), 2.34 (s, 3H, Me), 2.32 (s, 3H, Me). ^{13}C NMR: 145.61, 143.48, 141.86, 133.15, 132.10, 132.0, 120.36, 112.58, 20.50 (Me), 20.32 (Me), 14.71 (Me). Anal. Calcd. for $C_{13}H_{13}N_5O_2$ (271.28): C, 57.56; H, 4.83; N, 25.82. Found: C, 57.75; H, 4.90; N, 25.82.

3ad: Yield 49% (0.24 g); m. p. 216–217°C (H_2O). ^{1}H NMR: 14.6 (broad s, 1H, NH), 8.24 (d, 1H, J = 8,1 Hz, H-5 or H-8), 7.22 (t, 1H, J = 7.0 Hz, H-6 or H-7), 7.66 (d, 1H, J = 8.1 Hz, H-5 or H-8), 7.56 (t, 1H, J = 7.0 Hz, H-6 or H-7), 2.42 (s, 3H, Me). ^{13}C NMR: 145.72, 145.08, 133.50, 129.57 (2×C), 125.51 (2×C), 120.10, 112.04, 14.69 (Me). Anal. Calcd. for $C_{10}H_8N_6O_2$ x 0.25 H_2O (248.71): C, 48.29; H, 3.44; N, 33.79. Found: C, 48.42, H, 3.19; N, 33.34.

3bd: Yield 52% (0.24 g); m. p. 256–257°C (decomp., MeOH). ^{1}H NMR: 8.29–8.26 (m, 2H, H-2, H-bzt), 7.77–7.56 (m, 3H, H-bzt). ^{13}C NMR: 145.17, 135.97, 133.75, 129.75, 129.07, 125.55, 120.29, 118.92, 112,04. Anal. calcd. for $C_9H_6N_6O_2$ (230.19): C, 46.96; H, 2.63; N, 36.51. Found: C, 46.47; H, 2.49; N, 36.11.

3ae: Yield 66% (0.31 g); m. p. 137–138°C (H_2O). ^{1}H NMR: 12.1 (broad s, 1H. NH), 8.81 (d, 1H, J = 1.2 Hz, H-2), 8.36 (d, 1H, J = 1.2 Hz, H-5), 2.42 (s, 3H, Me). ^{13}C NMR: 147.86, 146.10, 138.02, 136.36, 121.91, 119.51, 14.52 (Me). Anal. calcd. for $C_7H_6N_6O_4$ (238.16): C, 35.30; H, 2.54; N, 35.29. Found: C, 33.65; H, 2.69; N, 34.64.

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