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4(5)-Nitro-1*H*-imidazole-5(4)-carbonitriles. Synthesis by *Cine*-substitution Reactions.

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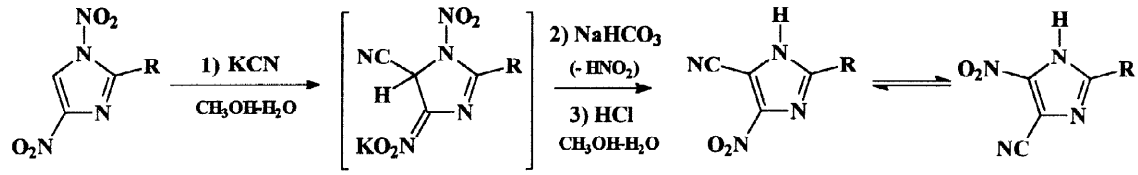
Abstract: The first syntheses of 4(5)-nitro-1*H*-imidazole-5(4)-carbonitrile, its 2-methyl derivative and salts of both compounds with DBU have been described. The carbonitriles have been obtained by a treatment of 1,4-dinitroimidazoles with potassium cyanide in aqueous methanol solution.

Beginning with a discovery of nucleotide biosynthesis pathway through 5-aminoimidazole-4-carboxylic acid **1**, imidazole derivatives have become common starting materials in purine synthesis.[1] Since then, purine syntheses usually involve the use of **1** derivatives; respective carbonitriles being among them.[1] Surprisingly 4(5)-nitro-1*H*-imidazole-5(4)-carbonitrile **2a** (scheme) itself as well as **2b**, in contrast to several *N*-alkyl derivatives of **2**, remain unknown.

Looking for a convenient method of **2a** synthesis we have found that it can be simply obtained in the *cine* nucleophilic substitution of 1,4-dinitroimidazole **3a** with cyanide anion. Beyond a radical reaction of 1,2-dimethyl-5-nitroimidazole with 2-nitropropane[3] it would be the first example of the *cine* substitution of imidazole derivatives with a *C*-centred nucleophile. Until now, only reactions of the *cine* nucleophilic substitution of nitroimidazoles with alcohols, secondary amines, azoles[4] and thiols[5] are known.

Dinitroimidazoles **3a** and **3b** react with potassium cyanide in aqueous methanol at 25° C to give **2a** or **2b** respectively in good yields.[6] The presence of sodium bicarbonate in the solution is not necessary however, it increases rates of formation and yields of the products. Therefore, the reaction mechanism involves base catalysed elimination of nitrous acid from an intermediate **4** forming as a result of cyanide attack on the position 5 of **3a** or **3b**. For a similar *cine* nucleophilic substitution of 1,4-dinitropyrazoles by *N*-centred nucleophiles, the 1,5-sigmatropic hydrogen shift in the respective intermediate was proposed.[7]



3a R = H
3b R = Me

4a
4b

2a (62%)
2b (74%)

Scheme

We have converted compounds **2a** and **2b** into their crystalline salts **5a** and **5b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[8] As we have found earlier, salts of nitroimidazoles as well as other NH-acids with DBU are very convenient reagents for the nucleophilic displacement of terminal tosylate group in sugar derivatives. The latter reaction seems to be the most efficient method of reversed nucleoside synthesis.[9] Compounds **2** can also serve as starting material in syntheses of condensed heterocyclic systems like purines

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containing N-unsubstituted imidazole ring. For example, the use of **2** would shorten a sequence of reactions in the known synthesis of 7-β-D-glucofuranosyl-6-benzylaminopurines,[2] which involves 1-alkylation of 5(4)-bromo-4(5)-nitroimidazole and a displacement of bromine by cyanide group. Recently we have found that 2-methyl-4(5)-nitroimidazole and **3b** labelled in the imidazole ring with ^{15}N-atom are easily available.[10] $K^{13}CN$ and $KC^{15}N$ are commercially produced. Together with the simple synthesis of **2** described here we have in hands a tool for syntheses of differently labelled purines. Work on this topic as well as other uses of **2** is in progress.

References and Notes

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6. **General procedure for 2.** To the solution of sodium bicarbonate (0.02 mole) and potassium cyanide (0.22 mole) in aqueous methanol (1:1, 100 ml) dinitroimidazole **2** (0.02 mole) was added at 25° C while stirring. The resulting mixture was left overnight without heating. Next day it was acidified with hydrochloric acid to pH of 5. The solvents were evaporated to dryness and the residue was treated with water (30 ml) to yield **2** in crystalline form.
   2a: yield 63%, m. p. 241-4° C (from methanol), Elemental analysis calculated for $C_4H_2N_4O_2$: C, 34.79, H, 1.46, N, 40.57; Found C, 34.91, H, 1.33, N, 40.57. MS (*m/z*): M^+ = 138 (100), 122 (6, M-O), 108 (10, M-NO), 92 (36, M-NO_2), 65 (80, M-NO_2-HCN), 53 (68), 38 (73). ^1H NMR (300 MHz, DMSO-d_6): 8.20 (s, 1H, 2-CH), ~11.6 (broad s, 1H, NH).
   2b: yield 77%, m.p. 276-278° C (from methanol, dec.), Elemental analysis calculated for $C_5H_4N_4O_2$: C, 39.48, H, 2.65; N, 36.83; Found C, 39.94; H, 2.60; N, 37.12. MS (*m/z*): M^+ = 152 (35), 136 (1, M-O), 106 (36, M-NO_2), 79 (29, M-NO_2-HCN), 65 (15), 53 (26), 43 (81, CH_3CO), 42 (100), 38 (19), 30 (48). ^1H NMR (300 MHz, DMSO-d_6): 2.40 (s, 3H, CH_3), ~14.4 (broad s, 1H, NH).
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8. General procedure as described in ref. 9 using benzene instead of THF, for **5a**: yield 95%, m. p. 93-95° C, **5b**: yield 97%, m. p. 173-175° C; elemental analyses and spectroscopic data are in full agreement with the proposed structures.
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