ALKYLATION OF 5-CYANOIMIDAZOLE-4-CARBOXAMIDE

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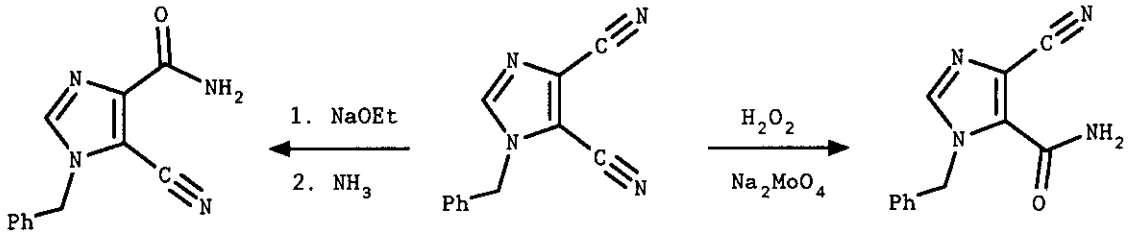
Abstract - Alkylation of 5-cyanoimidazole-4-carboxamide under alkaline conditions occurs with extremely high regioselectively at the nitrogen atom adjacent to the cyano group. The reaction is demonstrated to be useful for the synthesis of imidazo[1,5-*a*]pyrazines.

Recently we reported the preparation of 1-benzyl-5-cyanoimidazole-4-carboxamide (**1**) and it's use in the synthesis of a novel cyclic homolog of xanthine.[1] The key step in the preparation of **1** was the reaction of the dinitrile (**2**) with sodium ethoxide, which occurs regioselectively at the 4-cyano group. Ammonolysis of the intermediate then yields **1**. For some of the derivatives we required it became important to avoid the strongly basic conditions of this reaction sequence. Two other approaches to **1** can be envisaged, direct hydrolysis of **2** under very mild conditions or benzylation subsequent to hydrolysis of 4,5-dicyanoimidazole. Herein we report our investigation of these methods, and our observation that the latter alkylation occurs with high regioselectivity. This useful reaction appears general and was applied to a synthesis of imidazo[1,5-*a*]pyrazines. Direct mild hydrolysis of **2** using hydrogen peroxide in the presence of sodium molybdate was found to give 1-benzyl-4-cyanoimidazole-5-carboxamide

(**3**) as the major product, with small amounts of **1** and the diamide.[2] The isomeric imidazoles (**1**) and (**3**) are easily distinguished by carbon-13 nmr spectroscopy. The C-5 resonance is readily identified by coupling to the

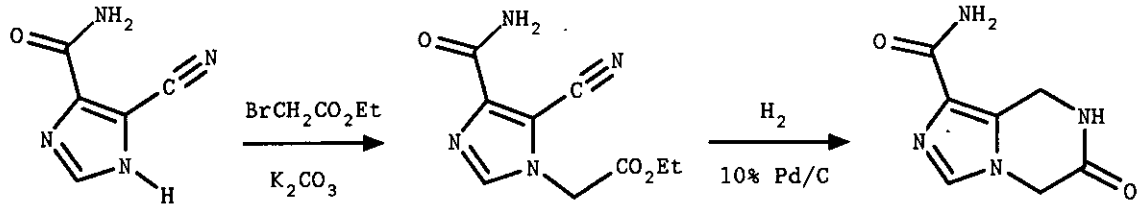


1 2 3

benzyl methylene protons and occurs at 105.2 ppm in **1** and at 134.0 ppm in **3**, while C-4 resonates at 145.1 ppm in **1** and at 113.7 ppm in **3**. These shifts are consistent with predicted substituent effects.[2]

5-Cyanoimidazole-4-carboxamide (**4**) was prepared from 4,5-dicyanoimidazole by alkaline hydrolysis.[3] Reaction of **4** with benzyl bromide in DMF in the presence of potassium carbonate gave **1** in 85% isolated yield. The isomer **3** could not be detected in the reaction mixture. The excellent regioselectivity observed in this reaction probably results from both the electronic and steric effects of the amide group directing toward the vicinal nitrogen atom.[4]

The high regioselectivity observed in this alkylation suggested a facile entry to the imidazo[1,5-*a*]pyrazine ring system. Reaction of **4** with ethyl bromoacetate gave ethyl 4-carbamoyl-5-cyanoimidazole-1-acetate (**5**). The



4 5 6

carbon-13 nmr spectrum was consistent with the expected structure, with the C-5 resonance at 106.4 ppm and the C-4 resonance at 144.6 ppm. Again,

the regioisomer was not observed. Reduction of the cyano group by hydrogenation over 10% palladium-on-carbon was accompanied by ring closure, and 1-carbamoyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-6-one (**6**) was isolated in excellent yield. This ring closure also provides conclusive confirmation of the regiochemistry of the alkylation reaction.

EXPERIMENTAL

1-Benzyl-4-cyanoimidazole-5-carboxamide (3). Compound (**2**)(5.0 g, 24 mmol) was dissolved in 95% ethanol (800 ml) and sodium molybdate (0.15 g, 0.6 mmol) was added, followed by 30% hydrogen peroxide (25 ml, 220 mmol). The solution was stirred at ambient temperature for 7 h then evaporated to an oil. The oil was dissolved in hot ethanol and a small amount of compound (**1**) was removed by filtration. Compound (**3**)(3.33 g, 61%) crystallized on cooling, and an analytical sample was obtained on recrystallization from aqueous ethanol, mp 185-187°C. *Anal.* Calcd for $C_{12}H_{10}N_4O$: C: 63.71; H: 4.46; N: 24.77. Found: C: 63.45; H: 4.35; N: 24.63. ^{1}H Nmr (DMSO-d_6, 300 MHz): 5.47 (s, 2H, PhC$\underline{H}_2$), 7.18 - 7.38 (complex, 5H, Ph), 7.99 (s, 1H, NH), 8.19 (s, 2H, NH and H-2). ^{13}C-Nmr (DMSO-d_6, 75 MHz): 48.9, 113.7, 114.4, 127.4, 128.0, 128.7, 134.0, 136.3, 141.5, 159.3.

1-Benzyl-5-cyanoimidazole-4-carboxamide (1). Compound (**4**)(12 g, 88 mmol) was dissolved in DMF (120 ml). Potassium carbonate (22 g, 160 mmol) and benzyl bromide (11.4 ml, 96 mmol) were added. The mixture was stirred at ambient temperature for 18 h, then water (200 ml) was added. The precipitate was filtered, washed with water, and recrystallized from acetic acid to give **1** (17 g, 85%), mp 260-262°C. *Anal.* Calcd for $C_{12}H_{10}N_4O$: C: 63.71; H: 4.46; N: 24.77. Found: C: 63.69; H: 4.49; N: 24.59. ^{1}H Nmr (DMSO-d_6, 300 MHz): 5.39 (s, 2H, PhC$\underline{H}_2$), 7.26 - 7.40 (complex, 5H, Ph), 7.62 (s, 1H, NH), 7.75 (s, 1H, NH), 8.30 (s, 1H, H-2). ^{13}C-Nmr (DMSO-d_6, 75 MHz): 49.6, 105.2, 110.6, 127.5, 128.3, 128.8,

135.2, 141.2, 145.1, 161.3.

Ethyl 4-carbamoyl-5-cyanoimidazole-1-acetate (5). Compound (**4**)(1.0 g, 7.3 mmol) was dissolved in DMF (10 ml). Potassium carbonate (1.8 g, 13 mmol) and ethyl bromoacetate (0.9 ml, 8 mmol) were added. The mixture was stirred at ambient temperature for 18 h, then water (50 ml) was added. The precipitate was filtered, washed with water, and recrystallized from 95% ethanol to yield **5** (1.2 g, 74%), mp 214-215°C. *Anal.* Calcd for $C_9H_{10}N_4O_3$: C: 48.64; H: 4.54; N: 25.22. Found: C: 48.49; H: 4.52; C: 25.01. ^{1}H Nmr (DMSO-d_6, 300 MHz): 1.22 (t, J = 7 Hz, 3H, CH_3), 4.21 (q, J = 7 Hz, 2H, OCH_2), 5.20 (s, 2H, NCH_2), 7.66 (br s, 1H, $CONH_2$), 7.77 (br s, 1H, $CONH_2$), 8.07 (s, 1H, H-2). ^{13}C-Nmr (DMSO-d_6, 75 MHz): 13.9, 47.1, 61.8, 106.4, 110.3, 141.7, 144.6, 161.3, 166.8.

1-Carbamoyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-6-one (6). Compound (**5**)(1.25 g, 5.6 mmol) was dissolved in acetic acid (100 ml). 10% Palladium-on-carbon (0.25 g) was added, and the mixture was shaken under hydrogen (40 psi) for 4 h. The mixture was filtered, and the filtrate was concentrated. The residue was crystallized from water to yield **6** (0.85 g, 85%), mp >320°C (decomp). *Anal.* Calcd for $C_7H_8N_4O_2$: C: 46.66; H: 4.47; N: 31.10. Found: C: 46.75; H: 4.40; N: 30.94. ^{1}H Nmr (DMSO-d_6, 300 MHz): 4.60 (s, 2H, $C\underline{H}_2NH$), 4.65 (s, 2H, CH_2CO), 7.11 (br s, 1H, $CONH_2$), 7.23 (br s, 1H, $CONH_2$), 7.64 (s, 1H, H-3), 8.41 (br s, 1H, $C\underline{H}_2NH$). ^{13}C-Nmr (DMSO-d_6, 75 MHz): 37.7, 45.8, 126.3, 128.6, 134.0, 164.5, 164.7.

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