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NUCLEOPHILIC AROMATIC SUBSTITUTION IN 4,5-DICYANOIMIDAZOLES

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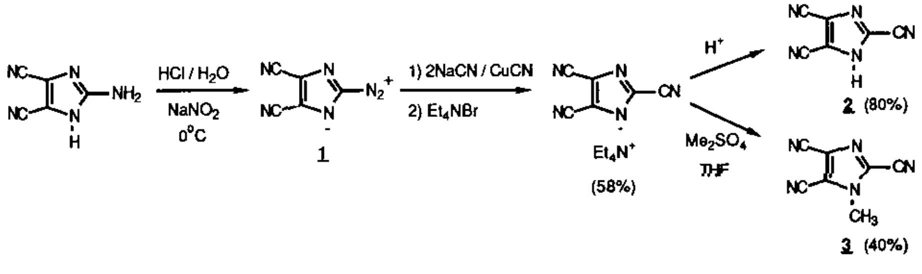
Abstract- Nucleophilic aromatic substitution reactions in 4,5-dicyanoimidazoles are described. For example, reaction of 1-methyl-2-bromo-4,5-dicyanoimidazole (**5**) with good nitrogen nucleophiles, such as n-butylamine, piperidine and imidazole, gave the highly functionalized 2-substituted 1-methyl-4,5-dicyanoimidazoles (**6-10**). Reaction of **5** with weaker nucleophiles, such as carbazole, did not occur.

Nucleophilic aromatic substitution (NAS) reactions in benzene and in various six-membered ring heteroaromatics are well documented[1]. Although less common, there are several examples of NAS reactions in five-membered ring heteroaromatics[2]. It is known that the presence of electron-withdrawing groups greatly enhances NAS . Imidazoles, for example, show a marked increase in reactivity when substituted with a nitro group[3].

Here, we report the displacement of halide in 1-methyl-2-bromo-4,5-dicyanoimidazole (**5**) giving the 2-substituted products (**6-10**) in fair to good yields. In our investigations, we have found that the electron-withdrawing ability of the nitrile groups has a great effect on the physical and chemical properties of cyanoimidazoles. For example, these compounds are moderately strong organic acids[4] (unlike imidazole, $pK_a = 14.2$) and NAS is possible under fairly gentle conditions.

Nucleophilic aromatic substitutions in 4,5-dicyanoimidazoles have previously been observed by Webster and co-workers in the 2-diazo derivative (**1**)[5,6]. In this case, a variety of substitution reactions are possible. For example, displacement by cyanide affords 2,4,5-tricyanoimidazole which can be isolated as its tetraethylammonium salt[5,6]. This salt can be protonated to give the moderately strong parent acid (**2**) ($pK_a = 2.1$) or it can be alkylated by strong electrophiles, such as dimethylsulfate, to give **3**. As shown in Scheme I, we have obtained compounds **2** and **3** in fair yields.

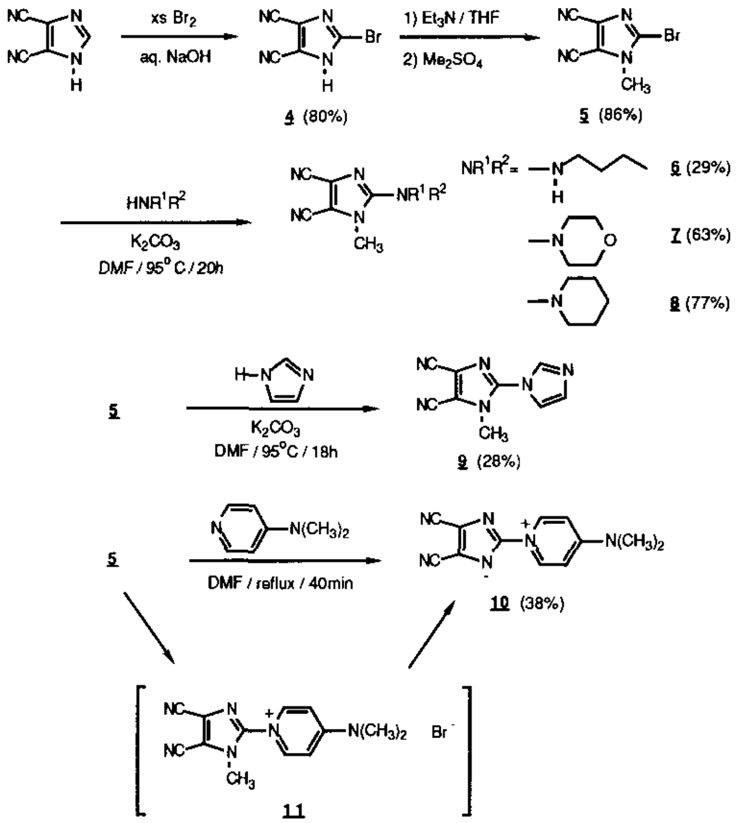
SCHEME I



We have since been investigating the behavior of **5** in NAS reactions. We have displaced bromide with a number of nitrogen containing nucleophiles including n-butylamine, piperidine, morpholine, imidazole, and N,N-dimethylaminopyridine (DMAP).

In Scheme II, the synthesis of **5** from simple starting materials is shown. Bromination in aqueous base gives 2-bromo-4,5-dicyanoimidazole (**4**) (pK_a = 2.7) which can be alkylated to give **5**. Displacement of halide with various nucleophiles gives the 2-substituted products (**6-10**)[7]. Particularly interesting is the reaction of **5** with DMAP to give the zwitterionic salt (**10**). The structure of **10** is unambiguously established by the spectral and analytical data. Although, the mechanism of this reaction has not been investigated, the loss of the methyl group from the proposed *intermediate (**11**) is consistent with the known ability of 4,5-dicyanoimidazoles to form stable anions and, as a result,* act as good leaving groups. The unique zwitterion (**10**) precipitates from the reaction mixture upon cooling and can be recrystallized from DMF to give colorless needles[8].

SCHEME II



Attempts to substitute halide in **5** with weaker nucleophiles (e.g. carbazole or 4,5-dicyanoimidazole) have failed. Even in refluxing DMF (up to 2 days), none of the desired 2-substituted products were observed.

We are now using NAS as a general method for functionalizing 4,5-dicyanoimidazoles. We intend to exploit this methodology in the design and synthesis of new molecular materials and polymers[9].

EXPERIMENTAL

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Thin layer chromatography was done on Eastman Kodak silica gel sheets equipped with fluorescent indicator. Infrared spectra were recorded on a Nicolet 5-DX FTIR spectrophotometer. Nmr spectra were recorded on a Bruker AM-300 NMR spectrometer (300 MHz). Chemical shift values are reported relative to TMS in the appropriate solvent. Nominal mass spectra were recorded on a Finnigan model 4021 quadrapole mass spectrometer. Hrms were recorded on a VG analytical model 70-250S mass spectrometer. Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY.

Solvents were purified prior to use. THF was distilled from sodium benzophenone ketyl. DMF was distilled from BaO and stored over 4A molecular seives. Other reagents were used as purchased.

The tetraethylammonium salt of 2,4,5-tricyanoimidazole was prepared according to the method of Sheppard and Webster.[6]

Isolation of 2,4,5-tricyanoimidazole (**2**). The tetraethylammonium salt of tricyanoimidazole (0.268g, 0.99mmol) was dissolved in 50ml of H_2O, acidified to pH=1 with 10%HCl and extracted with diethyl ether (4x10ml). Combined organics were dried over Mg_2SO_4, and concentrated to give a pale yellow solid which, after drying, gave 0.113g of **2** (80%). Pale yellow powder; mp 161-163°C; tlc acetone R_f=0.50; ir(KBr): 3600-3400(br.), 3000-2400(v.br.), 2251, 1618, 1402, 901, 819, 451cm^{-1}; ms(EI)m/z 143(M^+,100%), 116, 91, 64, 53, 38; Anal. calcd for C_6HN_5, C,50.35; H,0.70; found C,50.31; H,0.87.

1-Methyl-2,4,5-tricyanoimidazole (**3**). To a solution of 0.265g of the tetraethylammonium salt of tricyanoimidazole (1.0mmol) in 15ml of THF was added 0.10ml of Me_2SO_4 (1.0mmol). The reaction mixture was stirred overnight at 25°C. A precipitate was filtered. Solvent was removed and the viscous oil remaining was taken up in CH_2Cl_2, washed with aq.NH_4OH and then H_2O. The organic layer was dried (Na_2SO_4) and concentrated to give a tan solid. This was purified by sublimation (85°C / 0.8torr) to give 0.065g of **3** (40%). White powder; mp 115-116°C; tlc 1/1 EtOAc/hex R_f=0.50; ir(KBr): 2966, 2924, 2246, 1476cm^{-1}; ^1H nmr($CDCl_3$) δ 4.05(s); ms(EI)m/z 157(M^+,100%), 156, 116, 105, 76, 67; hrms calcd for $C_7H_3N_5$, 157.0388; found 157.0390.

2-Bromo-4,5-dicyanoimidazole (**4**). To a 500ml flask was added 11.80g of 4,5-dicyanoimidazole (0.100mol) and 250ml of 0.1M NaOH and then 18ml of Br_2 (0.351mol). The mixture was stirred overnight at ambient temperature and then acidified with dilute HCl. The off-white solid was filtered, rinsed with H_2O and recrystallized from H_2O to give 16.10g of pure product (82%) after drying. White solid; mp 141-143°C; tlc 4/1 EtOAc/MeOH R_f=0.65; ir(KBr): 3490, 3300-2400(v.br.), 2247, 1498, 1394, 1289cm^{-1}; ms(EI)m/z 196, 198(M,M+2), 169, 171, 91, 64, 53, 38; Anal. calcd for C_5HN_4Br, C,30.49; H,0.51; N,28.44; found C,30.44; H,0.66; N,28.33.

1-Methyl-2-bromo-4,5-dicyanoimidazole (5). To a flask with 3.178g of **4** (16.1mmol) in 30ml of THF was added 2.3ml of Et_3N (1eq.) dropwise. Stirred for 30min at room temperature, cooled to 0^oC, and then added 1.53ml of Me_2SO_4 (1eq.) dropwise slowly. The reaction mixture was stirred overnight at room temperature and poured into aq.NH_4OH. This was extracted with EtOAc (3x50ml). Organics were combined, washed with aq.NH_4OH and H_2O, dried (Na_2SO_4) and solvent was removed to give a white solid. This was recrystallized from 95% EtOH to give 2.87g of **5** after drying (86%). White needles; mp 135-136^oC; tlc 1/1 EtOAc/hex R_f=0.62; ir(KBr): 2924, 2241, 1468, 1373, 1311cm^{-1}; ^1H nmr($CDCl_3$) δ 3.89(s); ms(EI)m/z 210, 212(M,100%,M+2), 131, 79, 67; hrms calcd for $C_6H_3N_4{}^{79}Br$, 209.9541; found 209.9543.

General procedure for NAS reactions in **5**. Synthesis of compounds **6-9**. A three-necked flask, under N_2, was charged with equimolar amounts (1-5mmol) of **5**, the desired amine, and K_2CO_3 in 5-6ml of DMF. The reaction mixture was heated to 90^oC for 18-24h and then poured into brine and extracted with EtOAc. Organics were combined, dried(Na_2SO_4), and concentrated to give the crude product.

1-Methyl-2-(1-n-butylamino)-4,5-dicyanoimidazole(6). The crude solid was subjected to column chromatography (SiO_2, EtOAc) and then recrystallized from MeOH/H_2O to give 0.302g of the desired product (29%). White crystals; mp 130-131^oC; tlc EtOAc R_f=0.60; ir(KBr): 3371, 2960, 2938, 2234, 2219, 1610, 1461cm^{-1}; ^1H nmr($CDCl_3$) δ 4.26(br.s,1H), 3.48(s,3H), 3.41(t,2H,J=5.7Hz), 1.60(m,2H), 1.40(m,2H), 0.96(t,3H,J=7.3Hz); ms(EI)m/z 203(M^+), 188, 174, 160, 147(100%), 133, 119, 67; hrms calcd for $C_{10}H_{13}N_5$, 203.1171; found 203.1171.

1-Methyl-2-(1-morpholino)-4,5-dicyanoimidazole(7). Recrystallization of the crude product from 95% EtOH gave 0.103g of product after drying (63%). Colorless plates; mp 149-150^oC; tlc 2/1 EtOAc/hex R_f=0.43; ir(KBr): 2977, 2924, 2864, 2233, 1561, 1542, 1532, 1467, 1446, 1119cm^{-1}; ^1H nmr($CDCl_3$) δ 3.84(t,4H,J=4.7Hz), 3.65(s,3H), 3.22(t,4H,J=4.7Hz); ms(EI)m/z 217(M^+), 202, 186, 173, 160(100%), 132; Anal. calcd for $C_{10}H_{11}N_5O$, C,55.28; H,5.10; N,32.24; found C,55.26; H, 4.98; N,32.31.

1-Methyl-2-(1-piperidino)-4,5-dicyanoimidazole(8). The crude product was taken up in Et_2O, washed with H_2O, dried($MgSO_4$), and solvent concentrated to give a white solid which can be recrystallized from an EtOH/H_2O mixture. Upon drying, 0.155g of the desired product was obtained (77%). White crystals; mp 80-81^oC; tlc 2/1 EtOAc/hex R_f=0.78; ir(KBr): 2960, 2926, 2857, 2235, 1543, 1530, 1473cm^{-1}; ^1H nmr($CDCl_3$) δ 3.60 (s,3H), 3.13(t,4H,J=5.3Hz), 1.73-1.60(m,6H); ms(EI)m/z 215(M^+), 200, 186(100%), 173, 160, 146, 133, 119; Anal. calcd for $C_{11}H_{13}N_5$, C,61.37; H,6.09; N,32.54; found C,61.27; H,6.11; N,32.48.

1-Methyl-2-(1-imidazolyl)-4,5-dicyanoimidazole(9). The crude product was taken up in CH_2Cl_2, washed with H_2O, dried ($MgSO_4$) and concentrated to give 0.063g of product . Purification by column chromatography (SiO_2, 4/1 EtOAc/hex) or crystallization from iPrOH/pentanol/hexane gave pure product (28%). Off-white crystals; mp 134-135^oC; tlc 3/1 EtOAc/hex R_f=0.21; ir(KBr): 3130, 3122, 3113, 2958, 2242, 1553, 1527, 1521, 1487, 1328cm^{-1}; ^1H nmr(acetone-d_6) δ 8.09(s,1H), 7.64(d,1H,J=1.4Hz), 7.21(d,1H,J=1.4Hz), 3.98(s,3H); ms(EI)m/z 198(M^+), 171, 158, 131 ,104, 77, 67, 43(100%); Anal. calcd for $C_9H_6N_6{\bullet}0.5H_2O$, C,52.17; H,3.38; N,40.57; found C,52.86; H,2.94; N,39.89.

Synthesis of the 2-(N,N'-dimethylaminopyridinium)-4,5-dicyanoimidazolate betaine salt (**10**). A flask, equipped with reflux condenser and under N_2, was charged with 0.225g of **5** (1.07mmol) and 0.130g of DMAP (1eq.) in 5ml of DMF. Solution was heated to reflux for 40min and then allowed to cool to room temperature. A white solid was filtered and washed with acetone to give 0.096g of product (38%). Product can be recrystallized from DMF to give pure **10**. White needles; mp 355-356°C; ir(KBr): 3116, 2223, 1651, 1589, 1414, 1218, 1126, 829cm^{-1}; ^{1}H nmr(DMSO-d_6) δ 8.87(d,2H,J=8.1Hz), 7.10(d,2H,J=8.1Hz), 3.27(s,6H); ms(EI)m/z 238(M$^+$,100%), 223, 195, 167, 119, 105, 91, 78; Anal. calcd for $C_{12}H_{10}N_6$, C,60.50; H,4.23; N,35.27; found C,59.88; H,4.13; N,34.73.

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