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N-CYANO-N'-ALKYLIMIDAZOLIUM YLIDS AS NOVEL INTERMEDIATES TO 2-CYANOIMIDAZOLES

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Abstract: N-Substituted imidazoles were readily converted to 2-cyanoimidazoles by treatment with cyanogen chloride followed by triethylamine. The utilization of the SEM protecting group provided a facile entry to N-unsubstituted 2-cyanoimidazoles.

The synthetic utility of imidazolium ylids has received very little attention[1,2] in contrast to that of thiazole ylides.[3] A number of thiazole ylids have been shown to mimic the chemical properties of vitamin B1 (thiamin ylide)[4] and have been used in the synthesis of 2-substituted thiazoles.

We required a convenient synthetic route to 2-cyanoimidazoles (4) and wish to report a novel entry to this class of compounds via N-cyano-N'-alkylimidazolium ylides (3). There is no direct and high yield method for the preparation of 2-cyanoimidazoles, even though there has been recent interest in this class of compounds.[5] Our route to 4 provides a facile method for carbon-carbon bond formation at the 2-position of imidazoles and the first convenient "one-pot" synthesis of 4 from readily available imidazoles. In addition, we have found the [2-(trimethylsilyl)ethoxy]methyl group (SEM)[6,7] to be a suitable nitrogen protecting group for imidazoles that is readily removed after the introduction of the 2-cyano functionality.

The title compounds were prepared via intermediate N-cyano-N'-alkylimidazolium chlorides (2), which were obtained by the treatment of 1-substituted imidazoles with cyanogen chloride. Subsequent addition of base to the reaction mixture gave 2-cyanoimidazoles (4) in good to excellent yields (see Table).[8] It should be noted that treatment of the anion of N-(diethoxymethyl)imidazole[9] with cyanogen chloride or tosyl cyanide[10] did not provide desired 2-cyanoimidazole. The key to the utilization of N-cyanoimidazolium chlorides (2) for the preparation of the title compounds was the formation of the imidazolium ylide (3) by the treatment of 2 with triethylamine.[2] Other bases including potassium carbonate, N,N-diisopropylethylamine and 4-dimethylaminopyridine were found to be satisfactory substitutes for triethylamine.

SCHEME

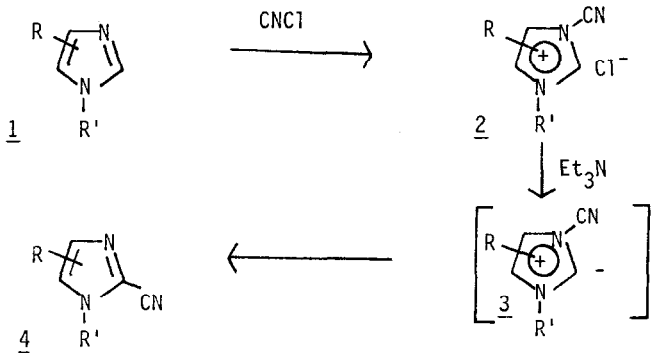

TABLE: Reaction of Imidazoles (1) with Cyanogen Chloride/Triethylamine

Entry	R	R'	Yield of 4(%)	bp or mp (°C)[e]
a	H	CH_2Ph	83[a]	51-52[f,g]
b	H	$CH_2OCH_2CH_2SiMe_3$	66[a]	110-120 (0.4mm)
c	4-CH_3	CH_2Ph	84[b,c]	51.5-52.5
d	5-CH_3	CH_2Ph		112-113[h]
e	H	CH_3	82[b]	65-70 (0.4mm)[g,i]
f	5-Cl	CH_3	59[a]	87-89[j]
g	4-Ph	CH_2Ph	81[b,d]	95-96

[a]Purified by Kugelrohr distillation. [b]Purified by flash chromatography (EtOAc/Hexane, 1:1). [c]Starting material was a mixture of 1c and 1d, but 4c and 4d were separable by flash chromatography. [d]Based on recovered starting material. [e]All solids were recrystallized from cyclohexane. [f]bp 130°C (0.4mm). [g]Isolated in literature as the picrate, see ref. 5j. [h]Literature (ref. 5f) mp 113-115°C. [i]Other references to this compound that do not include physical data include 5a and 5d. [j]Literature (ref. 5i) mp 90-91°C, bp 88°C (0.05 mm).

The following procedure is representative: In a 25 mL 4-neck flask with stirring bar, nitrogen bubbler, gas inlet tube, thermometer, septum and acetonitrile (10 mL) was bubbled cyanogen chloride[11] (1.5 g, 24 mmol) (ice bath was used to avoid mild heat of solution). The solu-

tion was cooled in an ice bath and N-SEMimidazole (1b)[12] (1.0 g, 5 mmol) was added. The colorless solution turned yellow-orange and within a few minutes a yellow-orange crystalline solid started to form. After 1 hour, the thick slurry was cooled to -20°C and triethylamine (4.2 mL, 30 mmol) was added at such a rate to prevent the temperature from rising above 0°C. The mixture was stirred 1 hour while warming to room temperature, and was poured into saturated aq $NaHCO_3$ (100 mL) and extracted with ether (3 x 75 mL). The combined organic layers were dried ($MgSO_4$), evaporated and purified by Kugelrohr distillation. After a forerun of diethylcyanamide, 4b was collected at 110-120°C (0.4 mm) (0.74 g, 66%). IR (thin film) 2230 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0.0 (9H, s), 0.91 (2H, t, J=8.2 Hz), 3.55 (2H, t, J=8.2 Hz), 5.57 (2H, s), 7.3 (1H, d, J=1.5 Hz), 7.84 (1H, d, J=1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.56 ($SiMe_3$), 17.52 (CH_2Si), 67.34 (OCH_2), 75.92 (NCH_2O), 110.63 (C_2), 121.83 (C≡N), 123.06 (C_5), 132.08 (C_4): MS (CI/CH_4) m/e 224 (MH^+). Anal. Calcd for $C_{10}H_{17}N_3OSi$: C, 53.77; H, 7.67; N, 18.81. Found: C, 53.77; H, 7.66; N, 18.43. The SEM protecting group was readily removed from 4b with dilute acid in quantative yield or with tetrabutylammonium fluoride in 70% yield to provide 2-cyanoimidazole.[5b,13] The versatility of the method was increased further by the removal of the benzyl group on 4a with one equivalent of sodium in liquid ammonia.[14]

It is interesting to note that cyanogen bromide in ether has been reported to react rapidly with 1,4-dimethylimidazole to yield exclusively 2-bromo-1,4-dimethylimidazole.[16] Similar reactions with cyanogen chloride in ether, THF or acetonitrile gave the N-cyanoimidazolium chlorides 2 from which only a small amount of 2-cyanoimidazoles could be isolated if the reactions were diluted with DMF and heated at 100°C.

In order to study the mechanism of this reaction, a cross-over experiment with 1-methylimidazole and N-cyano-N'-benzylimidazolium chloride (3a) was performed. The exclusive formation of 1-benzyl-2-cyanoimidazole (4a) would indicate an intramolecular mechanism. However, the formation of 4a and 4e would be inconclusive for the determination of an intra- or intermolecular mechanism, since a transfer of the N-cyano group on 3a to 1-methylimidazole before ylid formation could explain the results. Both 4a and 4e were formed and further work on the mechanism of this new transformation will be reported in due course.

In conclusion, a convenient one-pot preparation of 2-cyanoimidazoles was developed which utilizes N-cyanoimidazolium ylides as intermediates.

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13. Treatment of 4b with a 1 to 1 mixture of 1N HCl and ethanol at 50°C for 5 hours or with 1N tetrabutylammonium fluoride in THF at reflux for 45 minutes provided 2-cyanoimidazole (ref. 5b) in quantative yield and 70% yield, respectively.
14. Treatment of 4a with 1 equivalent of sodium in liquid ammonia provided 2-cyanoimidazole (ref. 5b) in 24% yield. Sodium liquid ammonia has been reported to remove benzyl groups from imidazoles (ref. 13), but not selectively in the presence of cyano groups.
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