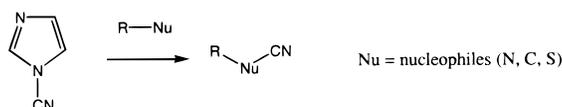


1-Cyanoimidazole as a Mild and Efficient
Electrophilic Cyanating AgentYong-qian Wu,* David C. Limburg, Douglas E. Wilkinson, and
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ABSTRACT



A mild and high-yielding cyanating reaction of amine, sulfur, and carbanion nucleophiles is reported here using 1-cyanoimidazole as an electrophilic cyanating agent.

Compounds containing cyano functional groups are found among many pharmaceuticals and their intermediates.^{1,2} For instance, the guanidine group is readily synthesized through a cyanoamine precursor.² There are a limited number of reagents that can serve as a cyano cation (CN⁺) equivalent when reacted with nucleophiles. Several reagents which have

been reported in the literature include cyanogen chloride/bromide,² 2-chlorobenzyl thiocyanate,³ tosyl cyanide,⁴ and most recently 1-cyanobenzotriazole.^{5,6} 1-Cyanoimidazole

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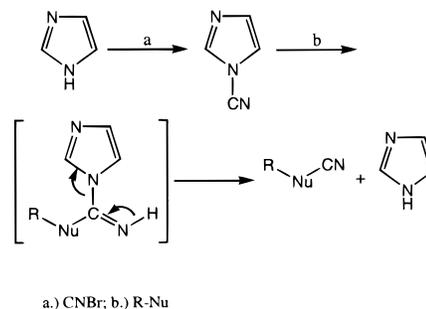
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(9) **Typical Experimental Procedure. Normal addition:** A solution of 1-cyanoimidazole (47 mg, 0.5 mmol) in 1 mL of DMA was added to a solution of *N*-methylaniline (54 mg, 0.5 mmol) in 5 mL of DMA under N₂. The mixture was allowed to stir at 100 °C, and the reaction was monitored by TLC. After 24 h, the reaction was complete. The mixture was poured into 10 mL of water, followed by CH₂Cl₂ extraction. Further workup and silica gel purification yielded 53 mg (80%) of product: GC-MS gave molecular ion (M⁺) 132; R_f = 0.7 (50% EtAc in hexane); ¹H NMR (CDCl₃) δ 7.43 (dt, 2H, J = 6.0, 8.0 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.12 (t, 1H, J = 6.5 Hz), 3.34(s, 3H); ¹³C NMR (CDCl₃) δ 140.7, 130.0, 123.4, 115.1, 114.3, 36.8. Inverse addition: 0.4 mL (2.5 M, 1 mmol) of *n*-BuLi was added slowly to a solution of phenylacetylene (102 mg, 1 mmol) in 5 mL of THF at –78 °C under N₂. The solution was allowed to warm to 0 °C and continued to stir for 30 min. After cooling to –78 °C again, the solution was transferred via cannula to a precooled (–78 °C) solution of 1-cyanoimidazole (93 mg, 1 mmol) in 5 mL of THF. The reaction was complete after 30 min of stirring. The mixture was poured into 10 mL of saturated NH₄Cl, followed by CH₂Cl₂ extraction. Further work up and silica gel purification gave the pure product (118 mg, 94% yield): GC-MS gave molecular ion (M⁺) 127; R_f = 0.3 (10% EtAc in hexane); ¹H NMR (CDCl₃) δ 7.58 (d, 2H, J = 7.5 Hz), 7.47 (t, 1H, J = 7.3 Hz), 7.35 (t, 2H, J = 7.5 Hz); ¹³C NMR (CDCl₃) δ 132.5, 129.7, 126.4, 116.3, 105.0, 83.1, 64.3.

Scheme 1



was previously reported⁷ as a useful coupling agent for the formation of polynucleotides. We now wish to report 1-cyanoimidazole as an electrophilic cyanating reagent toward various amine, sulfur, and carbon nucleophiles.

animidazole (93 mg, 1 mmol) in 5 mL of THF. The reaction was complete after 30 min of stirring. The mixture was poured into 10 mL of saturated NH₄Cl, followed by CH₂Cl₂ extraction. Further work up and silica gel purification gave the pure product (118 mg, 94% yield): GC-MS gave molecular ion (M⁺) 127; R_f = 0.3 (10% EtAc in hexane); ¹H NMR (CDCl₃) δ 7.58 (d, 2H, J = 7.5 Hz), 7.47 (t, 1H, J = 7.3 Hz), 7.35 (t, 2H, J = 7.5 Hz); ¹³C NMR (CDCl₃) δ 132.5, 129.7, 126.4, 116.3, 105.0, 83.1, 64.3.

Table 1

Entry	Nucleophile	Conditions	Products	Yield ^a
1		CH ₂ Cl ₂ 24hr Δ		82 ^{bc}
2		DMA 24hr Δ		80% ^c
3		CH ₂ Cl ₂ 3hr room temp.		89% ^c
4		CH ₂ Cl ₂ 3hr room temp.		83% ^{bc}
5		THF 30 min. -78°C		90% ^{bd}
6		n-BuLi THF 30 min. -78°C		86% ^{bd}
7		n-BuLi THF 30 min. -78°C		94% ^d
8		CH ₂ Cl ₂ 1.5hr room temp.		48% ^{bc} 70% ^{bd}
9		CH ₂ Cl ₂ 1.5hr room temp.		32% ^{bc} 50% ^{bd}

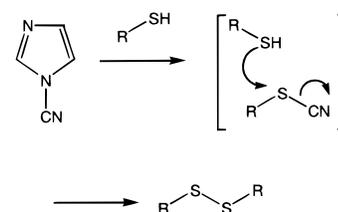
^a Isolated yield. ^b The products compared with authentic samples using GC-MS. ^c Normal addition. ^d Inverse addition.

1-Cyanoimidazole was synthesized by treating cyanogen bromide with imidazole based on a modified literature procedure (Scheme 1).⁸ The reaction between 1-cyanoimidazole and different nucleophiles is described by an addition–elimination process shown in Scheme 1, and the results are summarized in Table 1.

As shown in the Table 1, the cyano group was transferred from 1-cyanoimidazole to the nucleophile in a smooth reaction. Both primary and secondary amines (entries 1–4) gave cyanoamines in good to excellent yields (80–89%). However, less nucleophilic aromatic amines (entries 1 and 2) needed longer reaction times and heated condition to complete. In the case of the aromatic secondary amine (entry 2), the reaction failed to complete in refluxing dichloromethane but was able to be completed in the polar aprotic solvent DMA (*N,N*-dimethylacetamide) heated at 100 °C over 24 h.⁹ Similarly, carbanions (sp, sp², and sp³), which were generated either by direct lithiation or lithium/halogen

exchange or from a Grignard reagent, gave excellent yields (>86% in all cases) of the cyanated products (entries 5–7). We chose to select the inverse addition method in the cases where the carbanion was slowly added to the cyanating agent.⁹ It was suggested that limiting nucleophiles would limit the production of byproduct, imines presumably, resulting in the better yields.⁷ In the reactions with thiols

Scheme 2



(entries 8 and 9), lower yields were observed, as significant amount of disulfides were generated as side products. The inverse addition method gave somewhat better yields but could not eliminate their formation. This is consistent with what has been previously reported in the literature⁴ where sulfonyl cyanides were used as cyanating agents. The

disulfides were generated by further addition of thiol to the thiocyanate product as depicted in Scheme 2.

In summary, we have found and successfully demonstrated the variability of 1-cyanoimidazole as a useful cyanating reagent for many nucleophiles.

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