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SILICON IN SYNTHESIS: The Use of Trimethylsilyl Cyanide for the Synthesis of Aliphatic Cyanomethylethers

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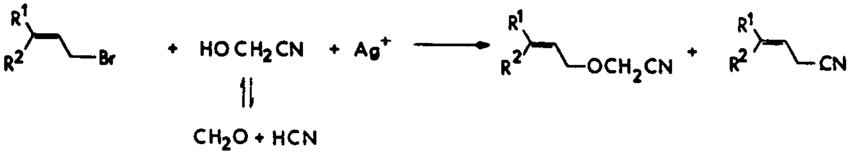
Abstract: The conversion of aliphatic alcohols into cyanomethyl ethers *via* treatment of methylsulfoxymethyl ethers with trimethylsilyl cyanide - zinc iodide is described.

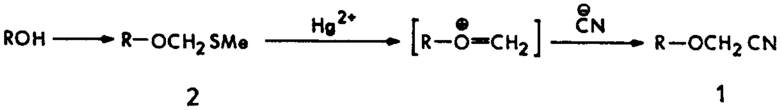
While the conversion of highly nucleophilic species such as thiols, amines and phenols into their derived cyanomethyl ethers 1 is well known, and without complications;[2] the cyanomethyl ethers of simple aliphatic alcohols are virtually unknown.[3-5]

All efforts to prepare cyanomethyl ethers 1 by conventional methods for ether synthesis ($ClCH_2CN$, various bases, KOH, KH, NaH, NPr^i_2Et, phase transfer, silver ion methods, AgO_3SCF_3, and many other methods of ether synthesis) failed. We were unable to repeat the Russian work,[3] (KOH, $ClCH_2CN$) and the procedure described by Julia[4] (SCHEME A) proceeds in low yield (10-20%). Chloromethyl ethers have been converted into cyanomethyl ethers by treatment with cuprous cyanide in dimethylformamide,[5] but for all but the simplest cases, the formation of the required chloromethyl ethers especially from allylic alcohols is problematic.



(SCHEME A)

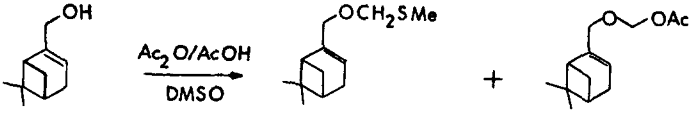
Since methyl thiomethyl ethers 2 are readily available through a number of routes[6] we considered this usual protecting group to be a viable precursor to cyanomethyl ethers 1 (SCHEME B).



$$\mathrm{ROH} \longrightarrow \underset{2}{\mathrm{R{-}OCH_2SMe}} \xrightarrow{\mathrm{Hg^{2+}}} \left[\mathrm{R{-}\overset{\oplus}{O}{=}CH_2}\right] \xrightarrow{\overset{\ominus}{\mathrm{CN}}} \underset{1}{\mathrm{R{-}OCH_2CN}}$$

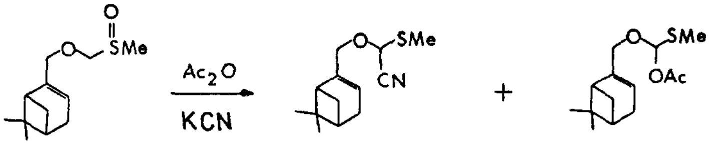
(SCHEME B)

Interestingly, when myrtenol 3 was treated with acetic anhydride/acetic acid in dry dimethylsulfoxide, the methylthiomethyl ether 4 (25%) was formed, along with the acetate 5 (46%). To prevent this unwanted product, the above reaction was run in wet dimethylsulfoxide. In this way the required ether 4 was the major product (64% after distillation and chromatography) and the formation of the acetate 5 completely suppressed. This procedure gave the methylthiomethyl ethers listed in the TABLE in 64 - 90% yield.



3 4 5

Treatment of 4 under a variety of conditions ($HgCl_2$/KCN/DMF; CuCN/DMF; $Hg(CN)_2$/DMF) did not bring about the conversion outlined in SCHEME B. Exposure of 4 to trimethylsilyl cyanide in the presence of stannic tetrachloride surprisingly gave no reaction.[7] Oxidation of 4 with *m*-chloroperbenzoic acid in dichloromethane at 0°C gave the sulfoxide 6. Treatment of the sulfoxide 6 with acetic anhydride containing potassium cyanide in acetonitrile at reflux, gave the two Pummerer rearrangement products 7 and 8. Whereas, when 6 was treated with trimethylsilyl cyanide in dichloromethane containing zinc iodide[8] at 25°C for 16 h a clean transformation to the required cyanomethyl ether 9 took place.



6 7 8

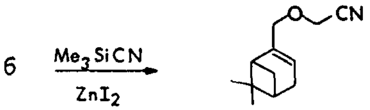


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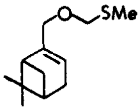
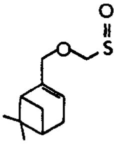
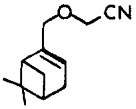
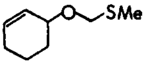
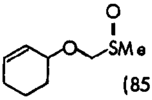
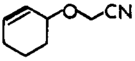
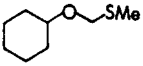
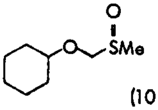
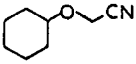
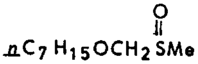
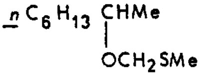
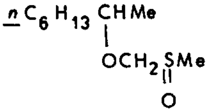
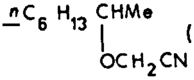
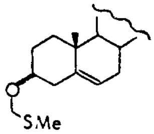
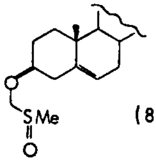
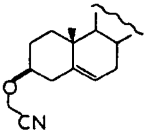
TABLE

METHYLTHIOMETHYL ETHER	SULFOXIDE (YIELD)	CYANOMETHYL ETHER (YIELD)
	 (89%)	 (32%)
	 (85%)	 (67%)
	 (100%)	 (100%)
$\underline{n}C_7H_{15}OCH_2SMe$	 $\underline{n}C_7H_{15}OCH_2\overset{O}{\overset{\Vert}{S}}Me$ (79%)	$\underline{n}C_7H_{15}OCH_2CN$ (91%)
 $\underline{n}C_6H_{13}CHMe(OCH_2SMe)$	 $\underline{n}C_6H_{13}CHMe(OCH_2\underset{O}{\underset{\Vert}{S}}Me)$ (93%)	 $\underline{n}C_6H_{13}CHMe(OCH_2CN)$ (95%)
	 (81%)	 (80%)

Cholesterol cyanomethyl ether: Cholesterol methylsulfoxymethyl ether (85 mg, 0.18 mmole) in dry chloroform (1 ml) was treated with trimethylsilyl cyanide (139 mg, 1.4 mmole) and anhydrous zinc iodide (50 mg). After 5 min the reaction was quenched with 10% aqueous sodium bisulfite solution, and extracted with chloroform. The dried ($MgSO_4$) extract was concentrated in vacuo to give the crude product (81 mg). Chromatography over florisil eluting with pet. ether/ethyl acetate (4:1) gave the cyanomethyl ether (61 mg) m.p. 114-116°C (ethyl acetate), γmax 2940, 2870, 1470, 1265, 1100, 1020, 810 cm^{-1}.

(N.B. The CN absorption is generally too weak to be observed). NMR (δ) 5.39 (1H, bs), 4.26 (2H, s), 3.42 (1H, bs), 2.47-0.77 (40H), 0.70 (3H, s). MS $C_{29}H_{47}NO$. calcd. m/e 425.366; obs. 425.366.

Typical procedure: 2-Octanol methylsulfoxymethyl ether (400 mg, 1.9 mmole) in dry dichloromethane (5 ml) was treated with trimethylsilyl cyanide (218 mg, 2.2 mmole) and anhydrous zinc iodide (50 mg). After 3 h at 25°C the mixture was quenched with 10% aqueous sodium bisulfite solution (30 ml) and extracted with dichloromethane (4 x 20 ml). Drying ($MgSO_4$), evaporation and distillation of the residue gave 2-octanol cyanomethyl ether (305 mg, 95%) b.p. 85°C at 0.5 mm Hg. NMR (δ) 4.23 (2H, s), 3.64 (1H, bs), 1.37 (10H), 1.19 (3H, d, J = 7 Hz), 0.99 (3H, t, J = 5 Hz).

The synthetic value of this type of cyanomethyl ether is exemplified by the [2.3] sigmatropic rearrangements of allylic cyanomethyl ethers[4], and the possibility of intramolecular alkylations to prepare oxygen heterocycles.[9]

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