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α-ALKYLTHIO-NITRILES VIA CYANATION OF THIO-ACETALS AND KETALS

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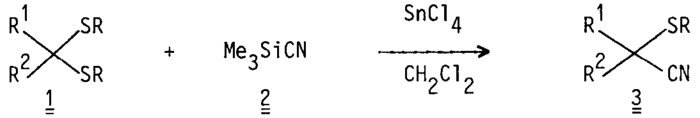
Abstract: The reaction of thio-acetals or ketals with cyanotrimethylsilane in the presence of $SnCl_4$ affords α-alkylthio-nitriles, which can be converted into a variety of other functional groups.

Although C-C bond formation and functional group manipulation via sulfur compounds have been amply exploited1), α-alkylthio-nitriles have received little attention2,3). The parent compound $RSCH_2CN$ is accessible by the reaction of $RSCH_2Cl$ and $Hg(CN)_2$2a), or by an S_N-process involving $ClCH_2CN$ and RSNa2b-c). Also, aliphatic nitriles can be sulfenated by treatment with two equivalents of LDA followed by RSSR3a-b). An interesting process pertains to the reaction of thio-acetals and ketals with $Hg(CN)_2$ and iodine, although the yields are not uniformly acceptable4). We wish to report a new entry into this class of compounds using readily available materials.

Since α-chloro and α-acetoxy ethers as well as acetals can be cyanated by Me_3SiCN5) in the presence of $SnCl_4$ or $SnCl_2$6), we speculated that thio-acetals and ketals, readily accessible from aldehydes and ketones7), could behave similarly. Indeed, stirring 1 and 2 in the presence of 40-50 mol-% $SnCl_4$ leads to smooth cyanation (Table 1). This process is of potential synthetic value because compounds 3 can be transformed in a variety of ways3,4).

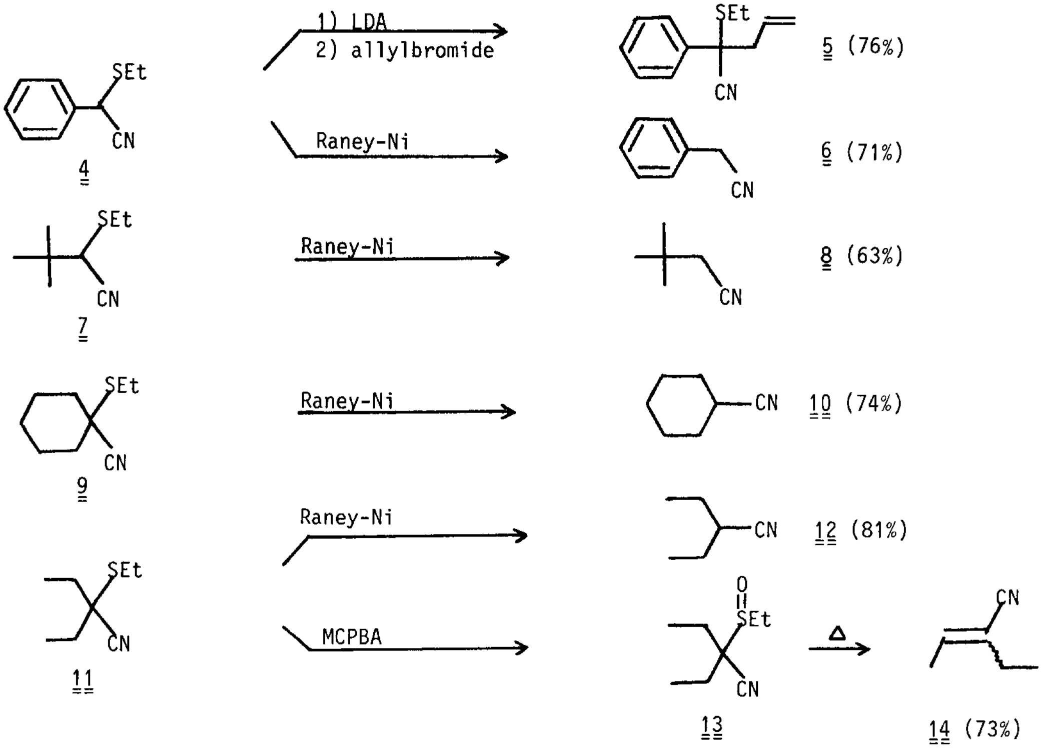


R^1, R^2 = H, alkyl, aryl
R = ethyl, phenyl

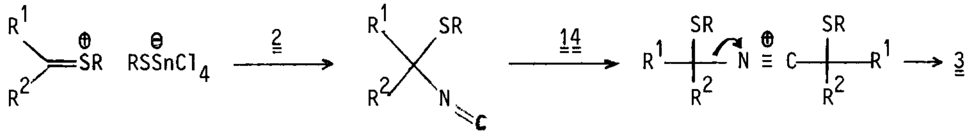
Table 1: Cyanation 1 → 3

R^1	R^2	R	Temp. (°C)	Time (h)	Yield of distilled 3 (%)
$(CH_3)_2CH$	H	Et	0	4	93
$c\text{-}C_6H_{11}$	H	Et	0	4	85
C_6H_5	H	Et	0	4	84
$(CH_3)_3C$	H	Et	0	4	81
$p\text{-}CH_3\text{-}C_6H_4$	CH_3	Et	-20	2	70
$-(CH_2)_5-$		Et	0	4	41
$CH_3CH_2CH(CH_3)$	H	C_6H_5	+22	10	88
CH_3CH_2	CH_3CH_2	C_6H_5	+22	6	78

Several of the adducts were used as model compounds for further reactions. For example, desulfurization using Raney-Nickel provides a means to hydrocyanate aldehydes and ketones[8].



Although $SnCl_4$ is generally believed to be a hard Lewis acid9), the mechanism of the cyanation probably involves intermediate formation of cation 15 10), which adds to 2 at nitrogen to form the isonitrile 16 as the initial product. This rearranges to 3 via catalytic action of 15. A related mechanism has been shown to be operating in the cyanation of tertiary alkyl chlorides by $Me_3SiCN/SnCl_4$ 6a). A typical procedure for cyanation of 1 is given in footnote11) below. Desulfurization was performed using Raney-Nickel W 2 13).



15 16 17

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Footnotes:

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7) Concerning a new variation utilizing the reaction of carbonyl compounds with thioalcohols in the presence of $TiCl_4$, see: V. Kumar and S. Dev, Tetrahedron Lett. 1983, 1289; and lit. cited therein.

8) For a previous method employing TosMIC, see: O.H. Oldenziel, D. van Leusen and A.M. van Leusen, J. Org. Chem. 42, 3114 (1977); A.M. van Leusen and G.P. Oomkes, Synth. Commun. 1980, 399.

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10) a) Silyl enol ethers undergo α-thioalkylation using thio-ketals in the presence of SnCl$_4$: M.T. Reetz and A. Giannis, Synth. Commun. 11, 315 (1981); b) review of these and related α-alkylations using S_N1-active alkylating reagents: M.T. Reetz, Angew. Chem. 94, 97 (1982); Angew. Chem., Int. Ed. Engl. 21, 96 (1982).

11) The mixture of 1.92 g (10 mmol) 1,1-bis(ethylthio)-2,2-dimethylpropane (prepared from pivalaldehyde and thio-ethanol)$^{12)}$ and 1.19 g (12 mmol) cyanotrimethylsilane$^{5)}$ in 25-30 ml dry methylene chloride under an atmosphere of nitrogen is cooled to 0 °C and treated with 1.3 g (5 mmol) of SnCl$_4$ with stirring. After 4 h the mixture is poured on ice water and the aqueous phase extracted twice with methylene chloride. The combined organic phases are washed with water and with 5% NaHCO$_3$ solution. After stripping off the solvent, the residue is Kugelrohr distilled (110 °C/12 torr) to provide 1.27 g (81%) of **7**. ^{1}H-NMR (CCl$_4$):δ= 1.0 (s,9H), 1.2 (t, *J*=7 Hz, 3H), 2.7 (q, *J*=7 Hz,2H), 3.3 (s,1H). A correct elemental analysis was obtained.

12) Thio-acetalization was performed in the presence of chlorotrimethylsilane according to B.S. Ong and T.H. Chan, Synth. Commun. 7, 283 (1977). The compound was isolated by short-path distillation at 57-60 °C/0.6 torr (74% yield).

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