Chlorotrimethylsilane in Combination with Sodium Sulfide as the Equivalent of Sodium Trimethylsilanethiolate in Organic Reactions

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Introduction

Reagent sodium trimethylsilanethiolate (Me_3SiSNa) has been used in reduction of aromatic nitro compounds to amines,[1] conversion of nitriles to thioamides,[2] and removal of a methyl group from methoxypyridines.[3] This reagent can be generated by reaction of $(Me_3Si)_2S$ with NaOMe.[1] Toxicity and stink associated with the expensive $(Me_3Si)_2S$ reagent, however, limits its applicability.[4,5] Consequently we developed a method for the generation of Me_3SiSNa, in which such disadvantages do not exist.

Olah et al.[6] reported that the mixture of Me_3SiCl and Li_2S in acetonitrile can be used as a powerful silylating agent. Herein we report our findings that the combination of Me_3SiCl and Na_2S can be used as a substitute for Me_3SiSNa in the performance of various types of organic reactions.

Results and Discussion

In a sealed tube, we treated an organic substrate with a mixture of Me_3SiCl and anhydrous Na_2S in 1,3-dimethyl-2-imidazolidinone (DMEU), ethanol, or CH_2Cl_2 at elevated temperature. After normal workup and purification, the desired product was obtained in good to excellent yields for most reactions. By employing the conditions listed in Table I, we were able to accomplish the following transformations: conversion of organic nitriles to thioamides, reduction of aromatic nitro compounds to amines, deoxygenation of sulfoxides to sulfides, demethylation of methyl aromatic ethers to alcohols or pyridones, and sulfurization of organic halides to dialkyl or diaryl sulfides.

Conversion of Organic Nitriles to Thioamides. Aryl, pyridyl, and benzyl nitriles can be converted to the corresponding thioamide in 58–73% yields (entries 1–4 and 6–8 in Table I) under the currently reported conditions. The same reaction with use of an alkanecarbonitrile (i.e., *n*-pentanecarbonitrile) as the starting material, however, gave a poor yield (28%, entry 5). This may be due to the low activity resulting from the nonconjugated cyano group.[7,8] In comparison with the same transformation with use of $(Me_3Si)_2S$ and NaOMe,[2] the current method gave a comparable yield.

We also found that both the polar aprotic solvent DMEU and the commonly used protic solvent ethanol were appropriate media for the conversion. Although the reaction between Me_3SiCl and Na_2S proceeded much faster in DMEU than in ethanol, complete removal of DMEU often required chromatography and would increase difficulty for isolation of some desired products of high polarity.

Reduction of Aromatic Nitro Compounds to Amines. Upon treatment with Me_3SiCl and Na_2S, aryl and pyridyl nitro compounds were reduced to the aromatic amines (entries 9–14 in Table I). The capability for Me_3SiSNa to remove a methyl group from methoxypyridines has been established.[3] We found that reduction of the nitro group in 2-methoxy-3-nitropyridine, however, prevailed over the demethylation by use of Me_3SiCl and Na_2S. This was evidenced by the isolation of 3-amino-2-methoxypyridine as the major product (61% yield, entry 14).

The new method was sensitive to steric congestion. The yields dropped from 75 to 45% in reduction of the nitro group on benzene bearing a methyl substituent at the ortho position (cf. entries 9 and 10).

Deoxygenation of Sulfoxides to Sulfides. Silicon-containing reagents Me_3SiI[9,10] and $(Me_3Si)_2S$[11] have been applied in the reduction of sulfoxides to sulfides. Nevertheless, use of Me_3SiSNa for the same reduction is not reported.

We found that deoxygenation of sulfoxides occurred under neutral and mild conditions by a direct use of Me_3SiCl and Na_2S at 50–60 °C. The desired sulfides were isolated in 63–90% yields. This newly developed reduction procedure was applicable to dialkyl, diaryl, and dibenzyl sulfoxides (entries 15–17 and 19–21), as well as a "mixed-substituted" sulfoxide (i.e., MeS(=O)Ph, entry 18). In addition to DMEU, CH_2Cl_2 can also be used as the solvent for the reduction.

Demethylation of Methyl Aromatic Ethers to Alcohols or Pyridones. Demethylation of monomethoxy aromatic compounds by use of Me_3SiCl and Na_2S proceeded smoothly to afford the corresponding alcohols or pyridones in good yields (entries 22–26 in Table I). Among the three regioisomeric dimethoxybenzenes, bis-*O*-demethylation occurred to the ortho isomer only (entry 27). In the presence of excess Me_3SiCl and Na_2S in DMEU, *m*- and *p*-dimethoxybenzenes gave the corresponding monodemethoxy products in good yields (i.e., *m*- and *p*-methoxyphenols in entries 28 and 29, respectively).

Reagent Me_3SiSNa, prepared from $(Me_3Si)_2S$ and NaOMe, can sequentially remove two methyl groups from *o*-, *m*-, and *p*-dimethoxybenzenes.[12] These results deviated from those obtained by use of the combination of Me_3SiCl and Na_2S in the demethylation of dimethoxybenzenes.

Sulfurization of Organic Halides to Dialkyl and Diaryl Sulfides. Reagent $(Me_3Si)_2S$ can react with alkyl

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Table I. Conditions and Yields for Various Organic Reactions by Use of Me_3SiCl and Na_2S

entry	reaction[a]	ratio of equivalents substrate/Me_3SiCl/Na_2S	solvent	temp, °C	time, h	yield, %
	$RC{\equiv}N \rightarrow RC({=}S)NH_2$					
1	R = Ph	1:1.9:7.0	DMEU	80	24	68
2	R = 4-MeC_6H_4	1:1.9:7.0	DMEU	80	24	59
3	R = 3-py	1:1.9:7.0	DMEU	80	24	58
4	R = $PhCH_2$	1:1.9:7.0	DMEU	80	24	64
5	R = n-C_5H_{11}	1:1.9:7.0	DMEU	80	24	28
6	R = Ph	1:1.5:7.5	EtOH	100	24	73
7	R = 4-MeC_6H_4	1:1.5:7.5	EtOH	100	24	66
8	R = 3-py	1:1.5:7.5	EtOH	100	24	61
	$ArNO_2 \rightarrow ArNH_2$					
9	Ar = Ph	1:3.0:6.0	DMEU	160	24	75
10	Ar = 2-MeC_6H_4	1:3.0:6.0	DMEU	160	24	45
11	Ar = 3-py	1:3.0:6.0	DMEU	160	24	71
12	Ar = Ph	1:1.5:7.5	EtOH	100	24	69
13	Ar = 3-py	1:1.5:7.5	EtOH	100	24	60
14	Ar = 2-MeO-3-py	1:1.5:7.5	EtOH	100	24	61
	$RR'S{=}O \rightarrow RR'S$					
15	R = R′ = Ph	1:4.5:4.5	DMEU	50	24	81
16	R = R′ = n-Bu	1:4.5:1.5	DMEU	60	24	90
17	R = R′ = $PhCH_2$	1:4.5:1.5	DMEU	60	24	70
18	R = Ph; R′ = Me	1:4.5:1.5	DMEU	60	24	85
19	R = R′ = Ph	1:4.5:1.5	CH_2Cl_2	60	36	80
20	R = R′ = n-Bu	1:4.5:1.5	CH_2Cl_2	60	36	81
21	R = R′ = $PhCH_2$	1:4.5:1.5	CH_2Cl_2	60	24	63
	ArOMe → ArOH or pyridones					
22	R = 2-py	1:1.9:1.7	CH_2Cl_2	60	24	68
23	R = 6-Me-2-py	1:1.9:1.7	CH_2Cl_2	60	24	61
24	R = 6-Cl-2-py	1:1.9:1.7	CH_2Cl_2	60	24	62
25	R = 2-quinonyl	1:1.9:1.7	CH_2Cl_2	60	24	89
26	R = 2-naphthyl	1:1.9:7.0	DMEU	170	24	75
27	o-$C_6H_4(OMe)_2 \rightarrow$ o-$C_6H_4(OH)_2$	1:3.5:12	DMEU	170	24	81
28	m-$C_6H_4(OMe)_2 \rightarrow$ m-$C_6H_4(OH)(OMe)$	1:3.5:12	DMEU	170	24	70
29	p-$C_6H_4(OMe)_2 \rightarrow$ p-$C_6H_4(OH)(OMe)$	1:3.5:12	DMEU	170	24	72
	$RX \rightarrow R_2S$					
30	R = $PhCH_2$; X = Cl	1:1.5:4.5	DMEU	60	24	76
31	R = $PhCH_2$; X = Br	1:1.5:4.5	DMEU	30	24	93
32	R = 3-py; X = Br	1:1.5:4.5	DMEU	160	24	76
33	R = $PhCH_2$; X = Cl	1:1.5:4.5	CH_2Cl_2	30	36	86
34	R = $PhCH_2$; X = Br	1:1.5:4.5	CH_2Cl_2	30	36	89
35	R = n-Bu; X = Br	1:1.5:4.5	CH_2Cl_2	60	24	80

[a] The physical properties and spectroscopic characteristics of all isolated products were consistent with those of an authentic sample or published data.

halides directly,[13] or along with NaOMe,[14] to afford the corresponding dialkyl sulfides. We found that the reaction of alkyl chlorides or bromides with the mixture of Me_3SiCl and Na_2S in situ allowed generation of the corresponding symmetric sulfides in 76–93% yields (entries 30, 31, 33–35). These reactions proceeded at 30–60 °C in DMEU or CH_2Cl_2.

To apply the newly developed conditions to aromatic halides in DMEU at 190 °C, we found that bromobenzene led to diphenyl disulfide (30% yield), instead of diphenyl sulfide. Similarly, 2-bromopyridine was converted at 160 °C to di(2-pyridyl) disulfide in 51% yield, together with di(2-pyridyl) sulfide as the byproduct (11% yield). The disulfides could be generated through a radical process. These findings, however, diverged from the results obtained from the reaction of 3-bromopyridine with Me_3SiCl and Na_2S in DMEU at 160 °C affording di(3-pyridyl) sulfide (76% yield, entry 32).

Control Experiments Regarding the Roles of Chlorotrimethylsilane and Ethanol. We carried out a series of control experiments by employing the conditions shown in Table I except that Me_3SiCl was not used. We found that none of the expected products were detected in a significant amount by use of Na_2S alone in these experiments, including the conversion of benzonitrile to thiobenzoamide (cf. entry 1), reduction of 3-nitropyridine to 3-aminopyridine (cf. entry 11), deoxygenation of di-n-butyl sulfoxide to di-n-butyl sulfide (cf. entry 16), demethylation of 2-methoxypyridine to 2-pyridone (cf. entry 22), and sulfurization of benzyl chloride to dibenzyl sulfide (cf. entry 30). Consequently, we believe that the first step of the entire transformation involved the reaction between Me_3SiCl and Na_2S to give Me_3SiSNa as the intermediate,[4a] which has a better solubility than Na_2S in organic solvents.[15–17] In situ, this intermediate reacted with an organic substrate to produce the desired product.

When ethanol was used as the solvent, we cannot exclude the possibility that Me_3SiSNa reacted with ethanol to give HSNa and Me_3SiOEt. Thus we carried out a control experiment, in which p-toluenecarbonitrile was treated

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with a mixture of HSNa (7.5 equiv) and Me_3SiOEt (1.5 equiv) in ethanol at 100 °C for 24 h. The corresponding thioamide was obtained in 12% yield only (cf. 66% yield in entry 7). The results indicate that, in ethanol, the Me_3SiSNa species played a direct role during the transformation.

Conclusions

A practical and convenient method was developed for generation of the Me_3SiSNa equivalent by reaction of Me_3SiCl with Na_2S in 1,3-dimethyl-2-imidazolidinone, ethanol, or CH_2Cl_2. This mixture has been used successfully to conduct the following transformations: conversion of organic nitriles to thioamides, reduction of aromatic nitro compounds to amines, deoxygenation of sulfoxides to sulfides, demethylation of methyl aromatic ethers to alcohols or pyridones, and sulfurization of organic halides to dialkyl or diaryl sulfides. These transformations often led to the desired products in good to excellent yields.

Experimental Section

Standard Procedure: To a tube were added Me_3SiCl (3.0–9.0 mmol) and anhydrous Na_2S (3.0–24 mmol) in DMEU, EtOH, or CH_2Cl_2 (3.0 mL). The mixture was stirred efficiently for 30 min to which was added an organic substrate. After the tube was sealed and heated, the reaction mixture was diluted with water and then extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 (s) and the solvents were removed under reduced pressure. The residue was chromatographed on a column of silica gel to give the expected products. The detailed conditions and yields are shown in Table I.

The physical properties and spectroscopic characteristics of all isolated products were consistent with those of an authentic sample or published data. The authentic samples[5] included the disulfides in entries 15–21, 30, 31, and 33–35, 2-naphthol (entry 26), diphenyl disulfide, and di(2-pyridyl) disulfide. The published data are related to the thioamides[2] in entries 1–8, the aromatic amines[1] in entries 9–14, the pyridones[3] in entries 22–25, *o*-dihydroxybenzene[12] (entry 27), *m*- and *p*-methoxyphenol[18] (entries 28 and 29), di(3-pyridyl) sulfide[19] (entry 32), and di(2-pyridyl) sulfide.[20]

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