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PREPARATION OF BROMIDES FROM ALCOHOLS VIA TREATMENT WITH TRIMETHYLSILYL BROMIDE

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Recently we reported the efficient conversion of alcohols and their trimethylsilyl ethers into iodides via treatment with trimethylsilyl iodide.[2] This conversion could be carried out either in the presence or absence of hydrogen iodide by reacting the silyl iodide with either the free alcohol or its silyl ether, respectively. We now report the use of the much less electrophilic trimethylsilyl bromide 1[3] for the simple transformation of alcohols into bromides.

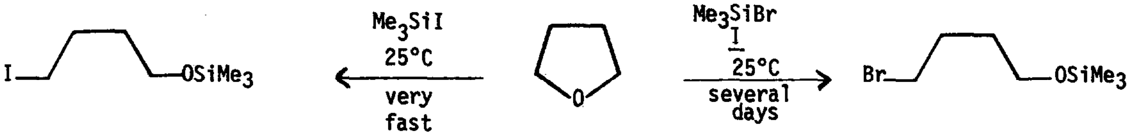
The most commonly employed procedure for the conversion of alcohols into bromides consists of the treatment of the alcohols with hydrogen bromide or phosphorus tribromide.[4] Several milder, non-acidic methods have also been developed recently, using phosphorus and sulfur based reagents.[5] In the course of a general investigation of the comparative reactivity of silicon halides and pseudohalides, we tested the reactivity of trimethylsilyl bromide with various substrates. Contrary to the very electrophilic trimethylsilyl iodide, trimethylsilyl bromide 1 does not dealkylate esters, ethers, or carbamates under mild conditions.[6]

However, when one equivalent of an alcohol 2 is treated with 1.5 to 4 equivalents of trimethylsilyl bromide 1 in chloroform solution at 25°-50°C, a facile reaction occurs which is best monitored by ^{1}H NMR spectroscopy in which the bromide 3 and hexamethyldisiloxane 5 are formed. Tertiary and

$$\underset{\underline{2}}{\mathrm{ROH}} + \underset{\underline{1}}{\mathrm{Me_3SiBr}} \longrightarrow \underset{\underline{3}}{\mathrm{RBr}} + \underset{\underline{4}}{\mathrm{HOSiMe}} \xrightarrow[\mathrm{-HBr}]{\mathrm{Me_3SiBr}} \underset{\underline{5}}{(\mathrm{Me_3Si})_2\mathrm{O}}$$

benzylic alcohols react extremely rapidly at 25°C while primary and secondary alcohols require several hours of heating at 50°C. The reaction proceeds predominantly with inversion of configuration. When (-)-2-octanol 2m was treated with the silyl bromide 1, the 2-octyl bromide 3m obtained (91% yield) was 87.7% optically pure, implying 93.8% inversion.[7]

In contrast to the formation of iodides with trimethylsilyl iodide, it is not possible to convert the trimethylsilyl ethers of alcohols into the corresponding bromides with the silyl bromide 1. For example, the trimethylsilyl ethers of the alcohols 2e, f, g, j, k, and l, were treated with approximately 2 equivalents of the silyl bromide 1 for extended periods (2-4 days) at 50°C with no evidence for the formation of the corresponding bromides. Thus trimethylsilyl bromide 1 must possess very severely reduced electrophilicity when compared to the corresponding iodide as could be expected on the basis of bond strengths.[10] Further evidence of the poor electrophilicity of the bromide versus the iodide is found in the comparison of their reactivity towards tetrahydrofuran (THF). While the iodide reacts with THF extremely rapidly at 25°C,[11] the reaction of THF with the bromide 1 requires several days at 25°C before the formation of 4-bromobutanol trimethylsilyl ether 6 is complete.



The bromide 1 will also convert ortho esters into the corresponding esters. For example, treatment of trimethylorthoformate 7 with 1 at 25°C resulted in the rapid formation (complete in 10 minutes) of methyl formate 8 (with methyl bromide and methyl trimethylsilyl ether as the side products). However, it is not as useful for the transformation of dimethyl ketals into the

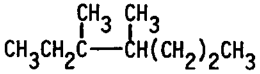
$$\underset{\underline{7}}{\mathrm{HC(OMe)_3}} + \underset{\underline{1}}{\mathrm{Me_3SiBr}} \xrightarrow[10\ \mathrm{min}]{25°\mathrm{C}} \underset{\underline{8}}{\mathrm{HCO_2Me}} + \mathrm{MeBr} + \mathrm{MeOSiMe_3}$$

corresponding ketones as the silyl iodide is.[12] Therefore, in general, the weakened electrophilicity of trimethylsilyl bromide 1 as compared to the iodide causes it to be less useful for dealkylative transformations in which fairly non-nucleophilic substrates are involved.

TABLE

Conversion of Alcohols into Bromides with Trimethylsilyl Bromide

$$\underset{\underline{2}}{ROH} + \underset{\underline{1}}{Me_3SiBr} \longrightarrow \underset{\underline{3}}{RBr} + \underset{\underline{5}}{(Me_3Si)_2O}$$

Compound	R	Time (hr)	Temp (°C)	Ratio 1/2	Yield (%)[a]
a	CH_3	19	25	1.9	> 95
b	CH_3CH_2	307	25	1.6	100
c	$(CH_3)_2CH$	46	50	2	100
d	$(CH_3)_3C$	< 1/6	25	2	100
e	$CH_3(CH_2)_6$	47	50	1.9	86(72)
f	$CH_3(CH_2)15$	95	50	4	100(98)
g	$PhCH_2$	< 1/6	25	1.5	100(95)
h	$CH_3CH(CH_2)_2CH_3$	27	50	2.1	100
i	$CH_3CH_2CH(CH_2)_3CH_3$	20	50	1.6	100
j	cyclohexyl	14	50	1.6	100(90)
k	 $CH_3CH_2\overset{CH_3}{\overset{\vert}{C}}\text{—}\overset{CH_3}{\overset{\vert}{C}}H(CH_2)_2CH_3$	< 1/6	25	1.3	100(79)
l	dl-2-octyl	14	50	2.1	100(81)
m	l-2-octyl	26	50	1.4	100(91)[b]

a) Yields are based on integration of the pertinent peaks in the ^1H NMR. Those in parentheses are for isolated, purified products.

b) The product is predominantly (+)-2-octyl bromide, implying net inversion of configuration. See text and reference 7.

References and Notes

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6. For example, treatment of the following substrates with 1 at 25 °C for 150 hours afforded only partial demethylation: cholestanyl methyl ether, 20-25% demethylated; methyl N-phenylcarbamate, ~15% demethylated; methyl acetate, <5% demethylated. See also: M. Kumada and H. Hattori, *J. Inst. Polytech., Osaka City Univ., Ser. C*, **3**, 77 (1952) [*CA*, **48**, 7542a (1954)]; *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **56**, 269 (1953) [*CA*, **48**, 10543f (1954)].
7. The starting (-)-2-octanol, $[\alpha]_D^{25} = -9.70$, was 93.45% optically pure (rotation of pure (-)-2-octanol, $[\alpha]_D^{25} = -10.38$).[2,8] The (+)-2-octyl bromide obtained had $[\alpha]_D^{25} = +33.30$ compared with the pure (+)-bromide which has $[\alpha]_D^{25} = +40.64$.[9] Thus correcting for impure starting material the bromide obtained was 87.7% optically pure, implying 93.8% inversion.
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