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Chlorotrimethylsilane/Lithium Bromide and Hexamethyldisilane/Pyridinium Bromide Perbromide: Effective and Selective Reagents for the Conversion of Alkyl (Cycloalkyl and Aralkyl) Alcohols into Bromides[1]

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Alkyl bromides were obtained in high yield in the reaction of the corresponding alcohols with chlorotrimethylsilane/lithium bromide. The reaction was equally applicable to primary, secondary, and tertiary alcohols as well as to allylic and benzylic alcohols. High regioselectivity was observed in related conversions in which hexamethyldisilane/pyridinium bromide perbromide was used. Tertiary alcohols, for example, were converted selectively into the corresponding tertiary bromides in the presence of primary and secondary hydroxylic functions. The reactions were also highly stereoselective.

Recently, we reported the efficient in situ generation of iodotrimethylsilane and its equivalents using chlorotrimethylsilane/sodium iodide[2] and hexamethyldisilane/iodine.[2,3] These reagents were found to be more effective than iodotrimethylsilane itself in the cleavage of ethers,[2,3] in the deoxygenation of sulfoxides,[4] and in the conversion of alcohols to the corresponding iodides.[2,3] The last transformation encouraged us to study the reactions with other added nucleophiles. In the presence of such added nucleophiles as sulfide ion, however, silylation was the major reaction.[5] We now report the convenient conversion of alcohols to bromides with chlorotrimethylsilane/lithium bromide and the regio- and stereoselective conversion of alcohols with hexamethyldisilane (HMDS)/pyridinium bromide perbromide.

The most commonly used reagents for the conversion of alcohols to bromides involve HBr,[6] PBr_3,[7] and Ph_3PBr_2[8] and are of limited selectivity. Although some of the recent methods involve more selective phosphorus[9] and sulfur[10] based reagents as well as the use of bromotrimethylsilane,[11] there is still a need for new regio- and stereoselective reagents. It was with this goal in mind that we have developed the reagents described in this report.

Results and Discussion

When a mixture of the corresponding alcohol, chlorotrimethylsilane, and lithium bromide in acetonitrile was heated under reflux, the desired bromide was obtained in high yield (eq 1). The reaction appears to be general, converting primary, secondary, and tertiary as well as allylic and benzylic alcohols into bromides in quantitative yield (Table I).

Table I. Conversion of Alcohols to Bromides with Chlorotrimethylsilane/Lithium Bromide Reagent (Eq 1)

$$\underset{\mathbf{1}}{ROH} \xrightarrow[\quad]{\underset{\mathbf{3}\qquad\mathbf{4}}{ClSiMe_3/LiBr}} \underset{\mathbf{2}}{RBr}$$

alcohol 1	molar ratio of 1:3:4	reacn time,[a] h	% yield of bromide 2[b]
c-$C_6H_{11}OH$	1:2.5:2	16	98
1-$C_9H_{19}OH$	1:2.5:2	20	95
$C_6H_5CH_2OH$	1:2.5:2	12	98
$C_6H_5CH{=}CHCH_2OH$	1:2.5:2	12	93
C_2H_5OH	1:2.5:2	12	(100)[c]
2-methylnorbornan-2-ol	1:2.5:2	8	100
phenylisopropylcarbinol	1:2.5:2	8	93

[a] All reactions were carried out in refluxing acetonitrile. [b] Isolated yield of the pure product. The IR and NMR spectra and the boiling point of the isolated products were in agreement with those of the authentic samples. [c] Yield determined by NMR.

$$\underset{\mathbf{1}}{ROH} \xrightarrow{Me_3SiCl/LiBr} \underset{\mathbf{2}}{RBr} \tag{1}$$

The reaction could also be carried out with sodium bromide. However, due to its comparatively lower solubility in acetonitrile, longer reaction times were required to effect complete conversion. The reactions proceeded faster than with bromotrimethylsilane itself,[11] presumably due to catalysis by the bromide ion, similar to the iodide ion catalysis observed in the preparation of iodides.[2,4] Further, in contrast to bromotrimethylsilane, chlorotrimethylsilane is an easily available, inexpensive reagent, making the in situ method attractive. The reaction mechanism is probably similar to the one proposed for the conversion of alcohols to iodides.[2,4]

These results also encouraged us to study the reaction of hexamethyldisilane (HMDS) and bromine. Hexamethyldisilane is known to react with bromine to form bromotrimethylsilane. Several byproducts resulted from the reaction of alcohols with $HMDS/Br_2$, probably due to

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Table II. Conversion of Alcohols to Bromides with HMDS/Pyridinium Bromide Perbromide Reagent (Eq 2)

$$\underset{\mathbf{1}}{\mathrm{ROH}} \xrightarrow[]{\underset{\mathbf{5}\quad\ \ \mathbf{6}}{\mathrm{HMDS/PyH^+Br_3^-}}} \underset{\mathbf{2}}{\mathrm{RBr}}$$

alcohol 1	molar ratio of 1:5:6	reacn time,[a] h	% yield of bromide 2[b]
$C_6H_5CH_2OH$	1:1.25:1.25	0.5	100
$C_6H_5CH{=}CHCH_2OH$	1:1.25:1.25	0.5	100
2-methylnorbornan-2-ol	1:1.25:1.25	0.5	100
phenylisopropylcarbinol	1:1.25:1.25	0.5	100
l-2-octanol	1:1.25:1.25	96	95[c]
2-methyl-2,4-pentanediol	1:0.625:0.625	3	78[d]

[a] All reactions were carried out at 25 °C. [b] Isolated yield of the pure product. The IR and NMR spectra and the boiling point of the isolated products were in agreement with those of the authentic samples. [c] The product obtained was 76.4% optically pure, implying 88.2% inversion.[13] [d] The only product obtained was 2-bromo-2-methylpentan-4-ol.

the oxidizing nature of bromine. This led us to explore alternative and more selective bromine sources. It was found that pyridinium bromide perbromide serves as an excellent in situ source of bromine. When alcohols were treated with HMDS/pyridinium bromide perbromide in chloroform solution, tertiary alcohols reacted extremely readily to give the corresponding bromides at ambient temperature (eq 2) (Table II).

$$\underset{\mathbf{1}}{\mathrm{ROH}} \xrightarrow[\text{pyridinium bromide perbromide}]{\text{HMDS}} \underset{\mathbf{2}}{\mathrm{RBr}} \qquad (2)$$

On the other hand, primary and secondary alcohols reacted very slowly, giving, after refluxing in chloroform for several hours, only low (~20%) conversion. Benzylic and allylic alcohols, on the other hand, also reacted rapidly.

These observations indicate the feasibility of regioselective conversion of a tertiary alcohol into its corresponding bromide in the presence of primary and secondary hydroxyl groups. Indeed, when a mixture of 2-methylnonan-2-ol and cyclohexanol was reacted with HMDS/pyridinium bromide perbromide, 2-bromo-2-methylnonane was obtained in excellent yield. Cyclohexanol remained unreacted and was completely recovered. As an example of related intramolecular regioselectivity, the reaction of 2-methylpentane-2,4-diol with the reagent afforded 2-bromo-2-methylpentan-4-ol in high yield (eq 3).

$$\mathrm{CH_3C(CH_3)(OH)CH_2CH(OH)CH_3} \xrightarrow[\mathrm{PyH^+Br_3^-}]{\text{HMDS}} \mathrm{CH_3C(CH_3)BrCH_2CH(OH)CH_3} \quad (3)$$

These results demonstrate that HMDS/pyridinium bromide perbromide can be used in the regioselective transformation of alcohols into bromides. This approach forms one of the few methods available for achieving such selective transformations.[12] The reagent was also found to be highly stereoselective. When *l*-2-octanol was reacted with HMDS/pyridinium bromide perbromide at ambient temperature, the reaction required 4 days for completion and afforded optically active bromide with 88.2% inversion.[13]

In conclusion, we have found extremely simple, efficient reagents for the conversion of alcohols to bromides. The regio- and stereoselective nature of HMDS/pyridinium bromide perbromide reagent should find particularly useful application in organic synthesis.

Experimental Section

Starting Materials. All the alcohols used in this work were commercially available in generally 98% or higher purity and were used without further purification. Chlorotrimethylsilane was obtained from Aldrich and used after distillation over sodium hydroxide. Hexamethyldisilane was purchased from PCR Inc. or prepared by the method of Seitz et al.[14] Acetonitrile was purified by the usual methods and stored over molecular sieves.

NMR and IR spectra were obtained on Varian EM360L and Perkin-Elmer 297 spectrometers, respectively. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. Mass spectra were obtained on a Hewlett-Packard 5984 GC/MS spectrometer.

General Procedure for the Conversion of Alcohols into Bromides with Chlorotrimethylsilane/Lithium Bromide. Chlorotrimethylsilane (2.7 g, 25 mmol) was added to a solution of lithium bromide (1.74 g, 20 mmol) in dry acetonitrile (20 mL) with good stirring under a nitrogen atmosphere. The corresponding alcohol (10 mmol) was then added and the reaction mixture was heated under reflux. The progress of the reaction was monitored by TLC on silica gel plates with hexane as eluent or by ^{1}H NMR spectroscopy. In general, the reactions were complete in 8–20 h. Upon completion of the reaction, the reaction mixture was taken up in ether (50 mL), washed successively with water (25 mL × 2), sodium bicarbonate solution (10%, 50 mL), and finally brine and dried over anhydrous sodium sulfate. Evaporation of ether afforded pure bromides in good yields (Table I). The obtained bromides showed expected physical and spectral characteristics.

Procedure for the Conversion of Benzyl Alcohol to Benzyl Bromide Using HMDS/Pyridinium Bromide Perbromide. HMDS (1.83 g, 12.5 mmol) and benzyl alcohol (1.08 g, 10 mmol) were added to a suspension of pyridinium bromide perbromide (4.0 g, 12.5 mmol) in dry chloroform (25 mL) with continuous good stirring under a nitrogen atmosphere. Soon, an exothermic reaction took place with the dissolution of all insoluble salts, and the solution turned colorless. The reaction was complete within 30 min, as indicated by TLC on silica gel with hexane as eluent. The reaction mixture was then taken up in ether (50 mL), washed thoroughly with water (25 mL × 4) to remove all water-soluble pyridinium salts, and dried over anhydrous sodium sulfate. Removal of the volatile materials from the dried extracts gave spectroscopically pure benzyl bromide (1.71 g, 100%).

A similar procedure was employed in reactions with other alcohols (Table II).

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Registry No. c-$C_6H_{11}OH$, 108-93-0; 1-$C_9H_{19}OH$, 143-08-8; $C_6H_5CH_2OH$, 100-51-6; $C_6H_5CH{=}CHCH_2OH$, 104-54-1; C_2H_5OH, 64-17-5; 2-methylnorbornan-2-ol, 5240-73-3; phenylisopropylcarbinol, 611-69-8; *l*-2-octanol, 5978-70-1; 2-methyl-2,4-pentanediol, 107-41-5; c-$C_6H_{11}Br$, 108-85-0; 1-$C_9H_{19}Br$, 693-58-3; $C_6H_5CH_2Br$, 100-39-0; $C_6H_5CH{=}CHCH_2Br$, 4392-24-9; C_2H_5Br, 74-96-4; 2-bromo-2-methylnorbornane, 72985-06-9; 1-bromo-2-methyl-1-phenylpropane, 57181-82-5; *d*-2-bromooctane, 1191-24-8; 2-bromo-2-methylpentan-4-ol, 72985-07-0; chlorotrimethylsilane, 75-77-4; lithium bromide, 7550-35-8; hexamethyldisilane, 1450-14-2; pyridinium bromide perbromide, 72985-09-2.

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