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A NEW SYNTHETIC METHOD FOR THE TRANSFORMATION OF ALCOHOLS TO ALKYL CHLORIDES USING 2-CHLOROBENZOXAZOLIUM SALT

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2-Chloro-3-ethylbenzoxazolium tetrafluoroborate reacts smoothly with a variety of alcohols in the presence of tetraethylammonium chloride to afford the corresponding alkyl chlorides in high yields. Replacement of a hydroxyl group at an asymmetric carbon atom with chlorine proceeds in a stereospecific manner.

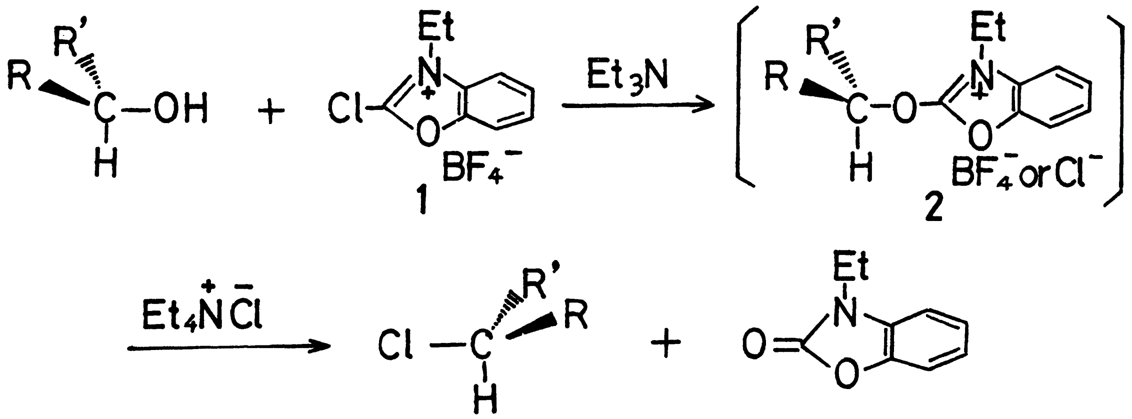
Replacement of a hydroxyl group of alcohols in a stereospecific manner is important particularly in the fields of steroids and carbohydrates.1) Recently, we have reported that alkyl halides including optically active ones are obtained by the reaction of 3-ethyl-2-fluorobenzothiazolium salt with alcohols in the presence of lithium chloride.2) When the method was applied to alicyclic alcohols, however, unsatisfactory results were obtained.

We now found that 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**1**), readily available from 2-aminophenol in three steps,3) reacted smoothly with various kinds of alcohols in the presence of tetraethylammonium chloride and triethylamine to afford the corresponding chlorides in high yields. The following is a typical procedure for the preparation of alkyl chlorides by the present method.

To a stirred suspension of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (1.3 mmol) and tetraethylammonium chloride (1.0 mmol) in dichloromethane (2 ml) cooled to 0°C was added triethylamine (1.3 mmol) in dichloromethane (1 ml) under an argon atmosphere. To the yellow suspension was added dropwise 3β-cholestanol (1.0 mmol) in dichloromethane (1.5 ml) and the resulting mixture was stirred at the same temperature for additional 4 h. After evaporation of the solvent under reduced pressure, the residue was directly chromatographed on silica gel eluting with hexane to give 3α-chlorocholestane in 85 % yield, m.p. 105-107°C (lit.[4] m.p. 105°C).

As shown in Table, alicyclic alcohol (3β-cholestanol) as well as acyclic alcohols (primary and secondary) were converted to the corresponding chlorides in high yields. Moreover, the reaction of 3β-cholestanol or (R)-(-)-2-octanol proceeded clearly with inversion of configuration at the reaction center.

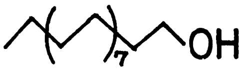
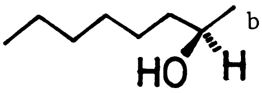
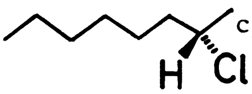
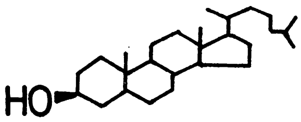
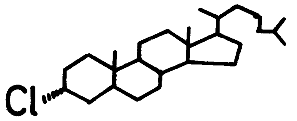
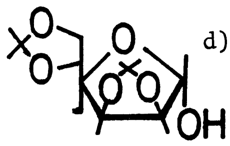
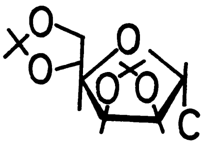
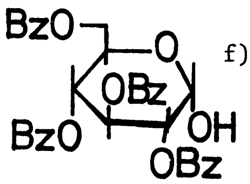
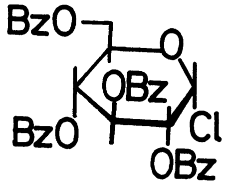
The reaction may be explained by assuming the initial formation of 2-alkoxybenzoxazolium salt 2, which in turn reacts with chloride ion to afford alkyl chloride and 3-ethyl-2-benzoxazolinone. The high stereospecificity in the reactions of cholestanol and 2-octanol indicates strongly that the present substitution reaction proceeds through an S_N2 type process at the stage of the reaction of intermediate 2 with chloride ion.



In order to examine the utility of the present method, we employed two carbohydrates as substrates. When 2,3-5,6-di-O-isopropylidene-α-D-mannofuranose or 2,3,4,6,-tetra-O-benzyl-α-D-glucopyranose was treated with 1 and tetraethylammonium chloride, one isomer which had the same configuration with the starting material was exclusively obtained in excellent yield.[5]

It is noted that the present method is applicable effectively to the transformation of a wide variety of alcohols including alicyclic alcohols such as steroid alcohol and carbohydrate. Thus, the present reaction using benzoxazolium salt 1 promises to be a unique and useful method for the preparation of various optically active chlorides from the correspondig alcohols in respects of (i) high yield, (ii) high stereospecificity, and (iii) mild reaction conditions.

Table Synthesis of Alkyl Chlorides

Alcohol	Conditions Temp.	Time	Alkyl Chloride[a]	Yield (%)
	r.t.	2h		97
	r.t.	2h		96
 b)	0°C	4h	 c)	76
	0°C	4h		85
 d)	0°C then r.t.	3h overnight	 e)	86
 f)	0°C then r.t.	3h overnight	 g)	89

a) These compounds were identified by NMR, IR, and in some cases, physical constant (melting point or optical rotation).

b) The alcohol used in the present experiment had 98 % of optical purity.

c) $[\alpha]_D^{19}$ + 33.0° (c 0.8, ether).
Reported maximum value for (R)-(-)-2-chlorooctane which has opposite configuration to the product obtained here is $[\alpha]_D^{20}$ - 36.2° (neat).

d) This sample was provided from Prof. Y. Ishido of Tokyo Institute of Technology.

e) $[\alpha]_D^{19}$ + 67.2° (c 5.7, acetone).
The product had NMR spectrum which showed the same pattern as that reported by Lee and Nolan for the structure depicted in the table [J. B. Lee and T. J. Nolan, Tetrahedron, 23, 2789 (1967)].

f) Bz = Benzyl.
This compound was prepared according to the following literature: T. D. Perrine, C. P. J. Glaudemans, R. K. Ness, Y. Kyle, and H. G. Fletcher, Jr., J. Org. Chem., 32, 664 (1967).

g) $[\alpha]_D^{17}$ + 63.6° (c 1.9, chloroform).
The product was identified by comparison of NMR spectrum and specific rotation with those reported by Grob et al. [V. D. Grob, T. G. Squires, and J. R. Vercelloti, Carbohydr. Res., 10, 595 (1969)].

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References and Notes

1) A. K. Bose and B. Lal, Tetrahedron Lett., 3937 (1973).

2) K. Hojo and T. Mukaiyama, Chem. Lett., 619 (1976).

3) a) Preparation of 2-mercaptobenzoxazole: J. A. van Allan and B. D. Deacon, Org. Synth., Coll. Vol. IV, 569 (1963).

b) Preparation of 2-chlorobenzoxazole: H. N. McCoy, J. Am. Chem. Soc., 21, 123 (1899).

c) Benzoxazolium salt 1 was obtained according to Balli and Kersting's method: H. Balli and F. Kersting, Justus Liebigs Ann. Chem., 647, 1 (1961).

4) C. W. Shoppee and J. C. Coll, J. Chem. Soc. (C), 1124 (1970).

5) Each result may be accounted for by the following reasons; (i) the reaction proceeded with retention of configuration because of steric hindrance, and/or (ii) β-anomer initially formed via S_N2 process epimerized to α-one during the reaction and the procedure of isolation because of anomeric effect.$^{6)}$

6) R. U. Lemieux in "Molecular Rearrangements", Ed., by P. de Mayo, Wiley-Interscience, New York, N. Y. (1964), P.735.

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