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# SYNTHESIS OF ALKYL HALIDES FROM ALCOHOLS BY THE REACTION WITH 2-ALKOXY-3-ETHYL BENZOTHIAZOLIUM SALTS

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2-Alkoxybenzothiazolium salts, formed in situ from 2-fluorobenzothiazolium salt and alcohols, reacted with iodide, bromide, and chloride ion to give the corresponding alkyl halides in good yields. The present procedure afforded a convenient method for the preparation of highly optically active alkyl halides such as 2-halooctanes.

In the preceding papers, it was demonstrated that 2-halopyridinium salts reacted with carboxylic acids or alcohols to produce 2-acyloxy or 2-alkoxypyridinium salts which in turn reacted with the second nucleophiles to afford condensation products along with N-alkylpyridone. Thus various esters, amides, lactones, sulfides, and alkyl iodides were obtained in good yields according to this procedure.[1a-e)

The effective activation of carboxylic acids or alcohols was also realized using 2-halobenzothiazolium salts.[2) For instance, when 3-ethyl-2-fluorobenzothiazolium tetrafluoroborate (I) was treated successively with an alcohol and sodium iodide, an alkyl iodide was produced in good yield. Concerning similar reactions, Severin and coworkers reported the reactions of 2-methoxy-nitropyridinium salts with various nucleophiles such as sodium methoxide, sodium bromide, sodium iodide, and sodium benzoate in refluxing methanol.[3)

By the present experiment it was made clear that 2-fluorobenzothiazolium salt (I) readily reacted with various alcohols to yield 2-alkoxybenzothiazolium salt (II) at -78°C. The salt II reacted with alkali metal halides to afford the alkyl halides in good yields as summarized in Table 1.

Table 1 Halogenation of Alcohol

| Entry No. | Alcohol | Metal Halide[a] | Alkyl Halide[b] | Isolated Yield(%) |
|---|---|---|---|---|
| 1 | $C_6H_5CH_2CH_2CH_2OH$ | NaI | $C_6H_5CH_2CH_2CH_2I$ | 92 |
| 2 | $C_6H_5CH_2CH_2CH_2OH$ | LiBr | $C_6H_5CH_2CH_2CH_2Br$ | 90 |
| 3 | $C_6H_5CH_2CH_2CH_2OH$ | LiCl | $C_6H_5CH_2CH_2CH_2Cl$ | 90 |
| 4 | $C_6H_5CH_2CH_2OH$ | NaI | $C_6H_5CH_2CH_2I$ | 82 |
| 5 | $C_6H_5CH_2CH_2OH$ | LiBr | $C_6H_5CH_2CH_2Br$ | 87 |
| 6 | dl-$C_6H_5CH_2CH(CH_3)OH$ | NaI | dl-$C_6H_5CH_2CH(CH_3)I$ | 75 |
| 7 | dl-$C_6H_5CH_2CH(CH_3)OH$ | LiBr | dl-$C_6H_5CH_2CH(CH_3)Br$ | 72 |
| 8 | (S)-(+)-$C_6H_{13}CH(CH_3)OH$ | NaI | (R)-(-)-$C_6H_{13}CH(CH_3)I$ | 87 |
| 9 | (R)-(-)-$C_6H_{13}CH(CH_3)OH$ | LiBr | (S)-(+)-$C_6H_{13}CH(CH_3)Br$ | 64 |
| 10 | (S)-(+)-$C_6H_{13}CH(CH_3)OH$ | LiCl | (R)-(-)-$C_6H_{13}CH(CH_3)Cl$ | 56 |

a) Minimum amount of the solvent was used to dissolve the alkali metal halides: acetone for NaI and LiBr: DMF for LiCI and LiF[4]. Following molar ratios of the reagents were used with the salt I, the alcohol, and the metal halide; 1.2:1.0:1.0 and 1.2:1.1:1.0 for the entry 1-7 and 8-10, respectively.

b) All compounds exhibited nmr and ir spectra in agreement with assigned structures.

Table 2 Optical Rotation of 2-Halooctane

| Alcohol[a] used | Observed Rotations of 2-Halooctanes $[\alpha]_D^{23}$(ether)[b], c(g/100 ml) | |
|---|---|---|
| (S)-(+)-2-Octanol | (R)-(-)-2-iodooctane | -53.1° (c 4.07) |
| (R)-(-)-2-Octanol | (S)-(+)-2-bromooctane | +39.9° (c 4.16) |
| (S)-(+)-2-Octanol | (R)-(-)-2-chlorooctane | -33.7° (c 17.0) |

a) Our samples of (S)-(+)- and (R)-(-)-2-octanol had $[\alpha]_D^{20}$ ( 0.1 dm, neat), +9.9°, and -9.7°, respectively. Reported value for each alcohol is $[\alpha]_D^{20}$ +9.9° and -9.9°.[c]

b) Optical rotation measurements of 2-halooctanes were performed in a 0.1 dm tube in ether by the automatic polarimeter. Reported maximum rotations of (R)-(-)-2-halooctanes $[\alpha]_D^{20}$ (neat) are as follows: -64.6° (I)[d]. -44.9° (Br)[d], and -36.2° (Cl)[c].

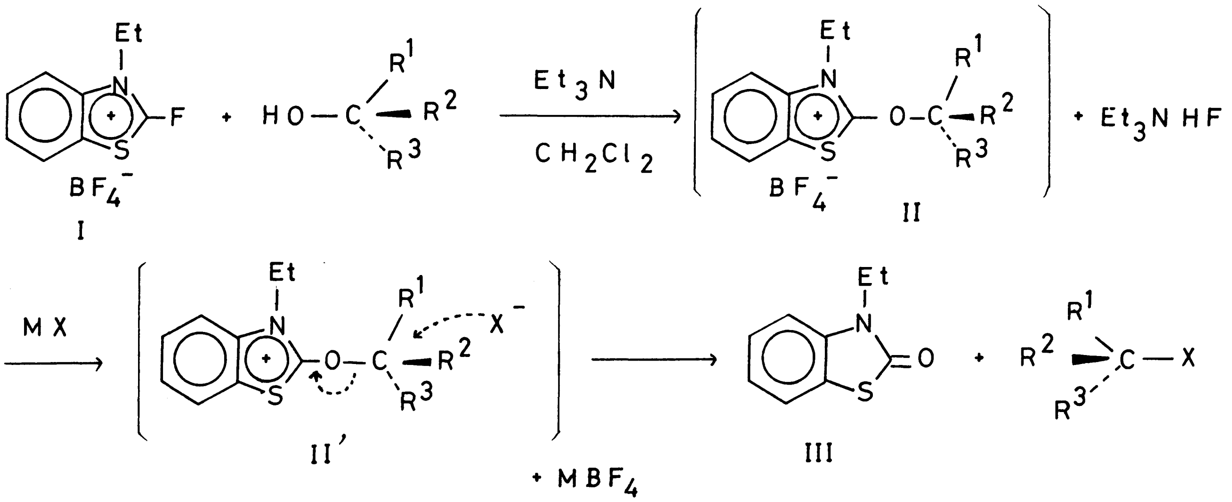
c) H. Brauns, Rec. Trav. Chim. Pays-Bas, <u>65</u>, 799 (1946).

d) E. J. Coulson, W. Gerrard, and H. R. Hudson, J. Chem. Soc., 2364 (1965).

Next, stereochemical course of the present reaction was investigated using optically active alcohols such as (S)-(+)- and (R)-(-)-2-octanol. The results shown in Table 2 clearly indicate that the benzothiazolium moiety of the salt II is displaced by a halide ion with inversion of configuration at the reaction center to give an alkyl halide of high optical purity.

A typical experimental procedure is demonstrated below: to a stirred suspension of I (3.21 g, 12 mmol) in dry $CH_2Cl_2$ (10 ml) was added dropwise a mixture of (S)-(+)-2-octanol (1.43 g, 11 mmol) and triethylamine (1.21 g, 12 mmol) in $CH_2Cl_2$ (20 ml) at -60°C under an argon atmosphere. A pale yellow homogeneous solution was stirred at -60 ∿ -45°C for an additional one hour. A solution of sodium iodide (1.50 g, 10 mmol) in dry acetone (12 ml) was added at -45°C and the reaction mixture was gradually warmed to room temperature over a period of 3 hr. The reaction mixture was concentrated under reduced pressure at 0°C and the residual liquid was chromatographed over silica gel being eluted with petroleum ether. (R)-(-)-2-iodooctane was further purified by distillation. Yield: 2.0 g (87%), bp 98°C/22 mmHg, $[\alpha]_D^{23}$ -53.1° (c 4.07, ether).

The reaction may be explained by considering an initial formation of the intermediate salt II from the alcohol and benzothiazolium salt I through an addition-elimination process. The anion exchange of the salt II took place rapidly on addition of an alkali metal halide (MX) to yield the second intermediate (II').



MX : NaI, LiBr, LiCl

In a final step, the counter anion ($X^-$) entered the reaction center from the site opposite to the benzothiazolium moiety through an $S_N2$ type transition state to give the alkyl halide and 1-ethyl-2-benzothiazolinone (III) as is shown in the scheme.

Although there have been many examples for the preparation of optically active alkyl halides from alcohols, only a few (e.g. the reaction of tosylate carried out under strictly controlled experimental conditions5)) have been shown satisfactory for the practical synthesis of the alkyl halide of high optical purity.6)

It is noted that the present halogenation method has several merits over the others with respect to the generality, yields, and the mildness of the reaction conditions (low reaction temperature, neutral reaction medium, and equimolar amounts of the reagents used etc.) where side reactions and a halide ion exchange are minimized. Therefore it is particularly suited to the preparation of highly optically active alkyl halides.7)

Further investigations are now in progress.

## References and Notes

1) a) T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, Chem. Lett., 1045 (1975).
   b) E. Bald, K. Saigo, and T. Mukaiyama, ibid., 1163 (1975).
   c) T. Mukaiyama, M. Usui, and K. Saigo, ibid., 49 (1976).
   d) T. Mukaiyama, S. Ikeda, and S. Kobayashi, ibid., 1159 (1975).
   e) S. Kobayashi, M. Tsutsui, and T. Mukaiyama, ibid., 373 (1976).

2) T. Mukaiyama and K. Hojo, ibid., 267 (1976).

3) T. Severin, D. Batz, and H. Lerche, Chem. Ber., 103, 1 (1970).

4) No alkyl fluoride was obtained when 2-(3-phenylpropoxy)benzothiazolium salt (II) was treated with LiF overnight at room temperature.

5) J. S. Filippo, Jr., and L. Romano, J. Org. Chem., 40, 1514 (1975).

6) For a recent review of the synthesis of optically active alkyl halides, see H. R. Hudson, Synthesis, 1, 112 (1969).

7) A complete racemization occurred when 2-iodooctane was prepared using 2-fluoropyridinium salt. S. Kobayashi, M. Tsutsui, and T. Mukaiyama, unpublished results. See Ref. 1e for this procedure.

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