

2-HALO-3-ETHYLBENZOTHAZOLIUM SALTS AS REACTIVE COUPLING REAGENTS

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2-Halobenzothiazolium fluoroborate, when treated with a mixture of equimolar amounts of carboxylic acids and alcohols in the presence of base such as tertiary amines, gave the corresponding carboxylic esters in good yields.

In the preceding papers, it was demonstrated that 1-methyl-2-halopyridinium salts effectively produce esters,<sup>1)</sup> amides,<sup>2)</sup> and sulfides<sup>3)</sup> in good yields from equimolar amounts of the reacting molecules. Characteristics of these reactions are as follows: (1) Nucleophiles carrying a hydroxyl group readily displace a halogen atom on an  $sp^2$ -carbon adjacent to a quaternized nitrogen atom of a pyridinium salt: (2) A highly reactive intermediate thus formed is in turn subjected to attack of various nucleophiles to yield thermodynamically stable N-methylpyridone and the condensation-products.<sup>4)</sup>

Based on these results, our investigation was extended to explore some other coupling reagents which react readily with nucleophiles to produce highly reactive intermediates capable of undergoing further reactions with the second nucleophiles under extremely mild conditions.

After examinations on various onium salts of azaaromatics utilizing esterification of carboxylic acid as a model reaction, it was revealed that 2-halobenzothiazolium salt (I) is one of the most reactive reagents.<sup>5)</sup> This paper concerns the reactions of I applied primarily to esterification of carboxylic acid.

2-Halo-3-ethylbenzothiazolium fluoroborates (Ia X=Cl, Ib X=F) are readily available,<sup>6)</sup> and soluble in a variety of aprotic solvents. When a mixture of carboxylic acid and alcohol was treated with I in the presence of tertiary amine, an exothermic reaction took place rapidly to afford the corresponding carboxylic

ester (III) and 1-ethyl-2-benzothiazolinone(IV) as illustrated in the following scheme.<sup>7)</sup>

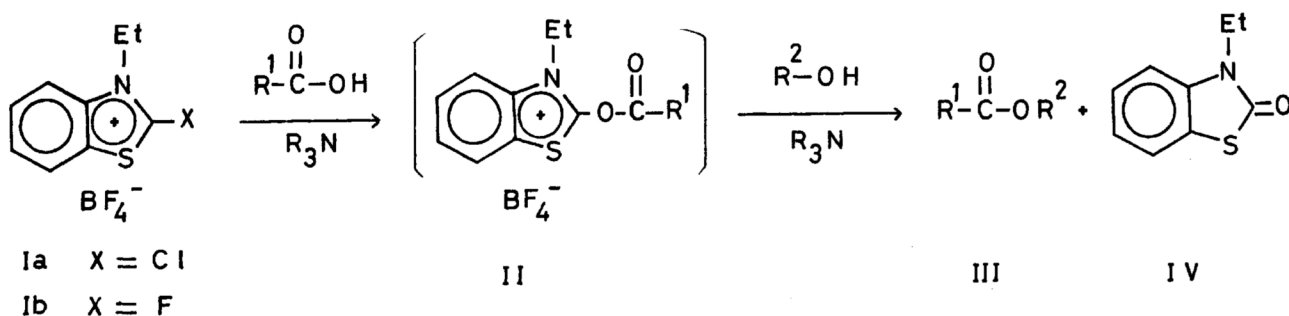


Table. Esterification of Carboxylic Acid with Alcohol<sup>a)</sup>

| Entry No. | Acid $R^1$           | Alcohol $R^2$        | Coupling Agent I | Base <sup>b)</sup> | Isolated <sup>c)</sup> yield (%) |
|-----------|----------------------|----------------------|------------------|--------------------|----------------------------------|
| 1         | $C_6H_5CH_2$         | $CH_3CH_2$           | Ia               | A                  | 98                               |
| 2         | $C_6H_5CH_2$         | $C_6H_5CH_2$         | Ia               | A                  | 92                               |
| 3         | $C_6H_5CH_2$         | $C_6H_5CH(CH_3)$     | Ia               | A                  | 92                               |
| 4         | $C_6H_5CH_2$         | $C_6H_5$             | Ia               | A                  | 71                               |
| 5         | $C_6H_5$             | $C_6H_5CH_2CH_2CH_2$ | Ib               | B                  | 71 <sup>d)</sup>                 |
| 6         | $C_6H_5CH_2CH_2$     | $C_6H_5CH_2CH_2CH_2$ | Ib               | B                  | 75                               |
| 7         | $C_6H_5CH(CH_2CH_3)$ | $C_6H_5CH_2CH_2CH_2$ | Ib               | B                  | 73                               |
| 8         | $C_6H_5CH_2$         | $(CH_3)_3C$          | Ia               | A                  | 47 <sup>e)</sup>                 |
| 9         | $C_6H_5CH_2$         | $(CH_3)_3C$          | Ib               | B                  | 42 <sup>e)</sup>                 |

a) Unless otherwise indicated, reactions were performed at  $0^\circ C$  in  $CH_2Cl_2$ .

b) Either tri-n-butylamine(A) or triethylamine(B) was used as a base.

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

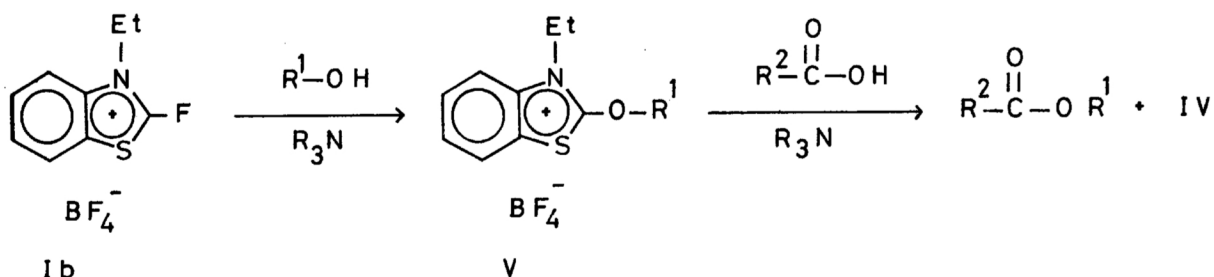
d) The reaction was carried out at  $-78^\circ C$ .

e) Unidentified material also formed. Either toluene or a mixture of toluene and  $CH_2Cl_2$  was used as a solvent.

A typical experimental procedure is demonstrated below: To a stirred suspension of Ia (342 mg, 1.2 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (1 ml) maintained at  $0^\circ\text{C}$ , was added a mixture of phenylacetic acid (136 mg, 1.0 mmol) and benzyl alcohol (108 mg, 1.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2 ml), followed by dropwise addition of tri-n-butylamine (444 mg, 2.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) under an argon atmosphere. Stirring was continued for half an hour at  $0^\circ\text{C}$  and one hour at room temperature. The solvent was removed in vacuo and the residue was subjected to preparative thin layer chromatography on silica gel developed with benzene, affording benzyl phenylacetate and 1-ethyl-2-benzothiazolinone(IV) in 92% and quantitative yields, respectively.

As shown in the table, 2-chloro salt(Ia) gave good to excellent yields of esters when primary or secondary alcohols were treated with phenylacetic acid. For sterically hindered carboxylic acids or benzoic acid, the use of more reactive 2-fluoro salt (Ib) gave more favorable results, where formation of alkyl halides and acid anhydrides was minimized. When t-butyl alcohol was used, esterification apparently suffered from serious side reactions to give only modest yield of ester.

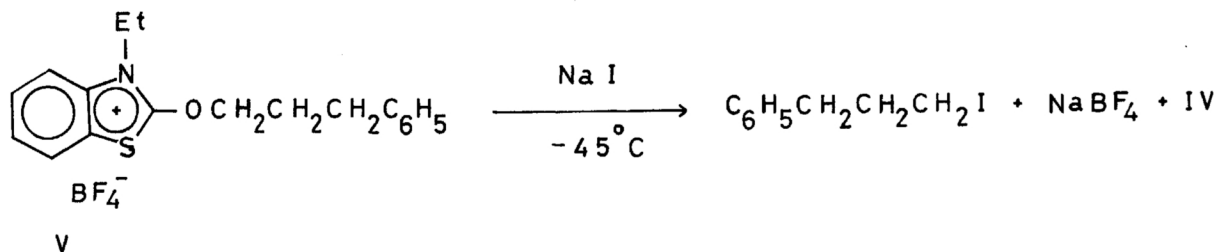
Important findings related to esterification reactions are that Ib reacted with alcohol in the presence of base to yield reactive 2-alkoxybenzothiazolium salt(V); upon treatment with carboxylic acid, corresponding ester was produced in fairly good yields as is indicated in the following example.



A mixture of 3-phenyl-1-propanol (1.0 mmol) and triethylamine (1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was added to Ib (1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml) at  $-45^\circ\text{C}$  to produce a yellow colored solution. A mixture of phenylacetic acid (1.0 mmol) and triethylamine (1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was added at the same temperature, and the solution was warmed to room temperature.

The Ester, 3-phenylpropyl phenylacetate, was obtained in 80% yield after preparative thin layer chromatography.

The formation of 2-alkoxy salt(V) in this reaction was verified by the fact that V, generated in situ and treated with sodium iodide under the similar conditions as those mentioned above, afforded 3-phenylpropyl iodide in 92% yield.



Further investigations are now in progress.

#### REFERENCES

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4. General concept: T. Mukaiyama, *Angew. Chem.*, in press.
5. Other salts examined: 2-chloro-1-methyl-pyrimidinium methylsulfate (64%), 2-chloro-3-methylthiazolium methylsulfate(88%), 2-chloro-3-ethyl-benzoxazolium fluoroborate(58%): numbers in parentheses designate per cent yields of an ester obtained when phenylacetic acid and benzyl alcohol were employed.
6. Ia and Ib were prepared by quaternization of 2-halobenzothiazoles with triethyl-oxonium fluoroborate; H. Balli and F. Kersting, *Ann.*, 647, 1 (1961).  
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7. The reaction appeared to take place even at  $-78^\circ\text{C}$

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