



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

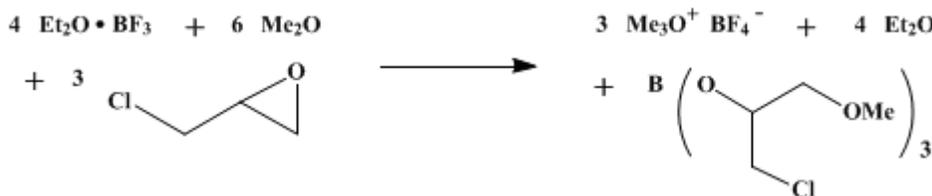
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 6, p.1019 (1988); Vol. 51, p.142 (1971).*

## TRIMETHYLOXONIUM TETRAFLUOROBORATE

[Oxonium, trimethyl- tetrafluoroborate(1-)]



Submitted by T. J. Curphey<sup>1</sup>

Checked by A. Eschenmoser, R. Keese, and A. Daniel.

### 1. Procedure

A 500-ml., three-necked flask fitted with a mechanical stirrer, a Dewar condenser (Note 1) connected by a T-tube to a mineral oil bubbler and a source of dry nitrogen, and a gas-inlet tube connected to a source of dry dimethyl ether (Note 2) is charged with 80 ml. of dichloromethane and 38.4 g. (33.3 ml., 0.271 mole) of boron trifluoride diethyl etherate (Note 3). After establishing a nitrogen atmosphere in the flask, the condenser is filled with an acetone–dry ice mixture. With gentle stirring, dimethyl ether is passed into the solution until approximately 75 ml. has collected (Note 4). The gas-inlet tube is replaced with a pressure-equalizing dropping funnel containing 28.4 g. (24.1 ml., 0.307 mole) of epichlorohydrin, which is added dropwise with vigorous stirring over a 15-minute period. The mixture is stirred overnight under an atmosphere of nitrogen (Note 5). The stirrer is replaced by a filter stick, and the supernatant liquid is drawn off from the crystalline trimethyloxonium tetrafluoroborate, while keeping the mixture under nitrogen. The oxonium salt is washed with two 100-ml. portions of anhydrous dichloromethane and two 100-ml. portions of sodium-dried diethyl ether (Note 6), and dried by passing a stream of nitrogen over the salt until the odor of ether is no longer detected, yielding 28–29 g. (92.5–96.5%) of a white crystalline solid, m.p. (sealed tube) 179.6–180.0° (dec.), (Note 7) and (Note 8).

### 2. Notes

1. A Kontes K-45750 condenser was used.
2. Dimethyl ether and nitrogen were dried by passage through columns of Drierite. Boron trifluoride etherate (Eastman Practical Grade) was redistilled. Epichlorohydrin (Eastman Organic Chemicals) and dichloromethane (Fisher Scientific Company) were used as received.
3. According to <sup>1</sup>H NMR analysis the use of boron trifluoride etherate does not cause any detectable introduction of ethyl groups into the product.
4. This may conveniently be done by placing, prior to conducting the reaction, a mark on the reaction flask at a level of 190 ml., and collecting dimethyl ether up to the mark. The exact amount of dimethyl ether used is not critical.
5. After 2–3 hours of stirring the reaction appears to be over, and the dry ice in the condenser need no longer be renewed. The reaction mixture may be worked up at this point without appreciable reduction in the product yield or purity.
6. According to analysis by <sup>1</sup>H NMR the use of diethyl ether at this point does not cause any detectable exchange of methyl by ethyl groups in the oxonium salt. A user<sup>2</sup> has reported obtaining the best samples of oxonium salt by using boron fluoride dimethyl etherate instead of the diethyl etherate and omitting the diethyl ether washing of the product. Oxonium salt prepared in this way was used to prepare methyl esters (from the corresponding amides) with no detectable (by GC analysis) ethyl esters.
7. The melting point of trimethyloxonium tetrafluoroborate apparently depends upon the procedure by which it is prepared and the method of melting-point determination. It has, for example, been reported to melt at 124.5°,<sup>3</sup> 141–143° [*Org. Synth.*, **Coll. Vol. 5**, 1096 (1973)], and 175°.<sup>4</sup> The <sup>1</sup>H NMR

spectrum, determined (liquid SO<sub>2</sub>, purissimum Fluka AG) in a sealed tube at room temperature shows a single methyl resonance at  $\delta$  4.54; a trace of impurity is discernible as a singlet at  $\delta$  3.39.

8. When prepared as described, the oxonium salt is stable and nonhygroscopic, and may readily be handled in the air for short periods of time. A sample kept in a desiccator over Drierite for 1 month at  $-20^\circ$  showed no change in melting point, and batches stored in this manner for over a year have been successfully used for alkylations.

### 3. Discussion

Trialkyloxonium salts were first discovered by Meerwein,<sup>3</sup> who also investigated much of their chemistry. A discussion of the literature prior to 1963 has been published.<sup>5</sup> Simple trialkyloxonium cations which have been prepared, other than trimethyl, include triethyl,<sup>6</sup> tri-*n*-propyl,<sup>7</sup> and tri-*n*-butyl,<sup>8</sup> with tetrafluoroborate or hexachloroantimonate anions, in most cases. Methods used to prepare trimethyloxonium tetrafluoroborate, which are typical of the class as a whole, include the reaction of boron trifluoride with epichlorohydrin in the presence of dimethyl ether,<sup>3,4,9</sup> the reaction of dimethyloxonium tetrafluoroborate with diazomethane or diazoacetic ester,<sup>10</sup> and the alkylation of dimethyl ether by triethyloxonium tetrafluoroborate<sup>11</sup> or dimethoxycarbonium tetrafluoroborate.<sup>12</sup> Several of these reactions involve the initial formation of a mixed oxonium ion [R<sub>1</sub>R<sub>2</sub>OCH<sub>3</sub>]<sup>+</sup>, which then methylates dimethyl ether, providing R<sub>1</sub>R<sub>2</sub>O and the trimethyloxonium ion. Of the available procedures, the one described here is probably the most convenient, involving as it does a single-step preparation from inexpensive, commercially available, and nonhazardous reagents. Under the proper conditions (Note 8), the resulting product has storage properties comparable to those of the less-accessible trimethyloxonium 2,4,6-trinitrobenzenesulfonate.<sup>13</sup>

The trialkyloxonium salts are powerful alkylating agents. Trimethyl- and triethyloxonium tetrafluoroborates, in particular, have been widely employed for methylation and ethylation of sensitive or weakly nucleophilic functional groups. Alkylations of over 50 such functional groups have been reported in the literature. Examples include amides,<sup>4,7,14,15,16</sup> lactams,<sup>16,17,18,19</sup> sulfides,<sup>3,20</sup> nitro compounds,<sup>9</sup> enols and enolates,<sup>3,21</sup> ethers,<sup>7,11,22</sup> phenols,<sup>3</sup> sulfoxides,<sup>3,7</sup> amine oxides,<sup>3,7,23</sup> carboxylic acids,<sup>3</sup> lactones,<sup>3,4</sup> ketones,<sup>3,16</sup> metal carbonyls,<sup>12,24</sup> thiophenes,<sup>25</sup> and phosphonitriles.<sup>26</sup> Oxonium salts have also been advantageously employed as quarternizing agents for a variety of heterocyclic amines.<sup>27,28,29,30,31,32,33,34</sup> In this way the first diquarternary salts of several heterocyclic diazines have been prepared,<sup>30,31</sup> as have reagents for peptide synthesis,<sup>33,34</sup> for the synthesis of polycyclic ketones,<sup>32</sup> and for cyanine dyes.<sup>28</sup>

One of the major advantages of oxonium salts is that alkylations can be effected under reaction conditions that are generally much milder than those necessary with the more conventional alkyl halides or sulfonates. Triethyloxonium tetrafluoroborate, for example, has usually been employed at room temperature in dichloromethane or dichloroethane solution. Occasionally chloroform<sup>17,23</sup> or no solvent at all<sup>4,21</sup> is used. Difficult alkylations can be effected in refluxing dichloroethane.<sup>30,31</sup> The less soluble trimethyloxonium tetrafluoroborate has been used as a suspension in dichloromethane or dichloroethane, or as a solution in nitromethane or liquid sulfur dioxide. Reports of alkylations in water<sup>24</sup> and trifluoroacetic acid<sup>22</sup> have also appeared. Direct fusion with trimethyloxonium tetrafluoroborate has succeeded in cases where other conditions have failed.<sup>26,31</sup>

Alkylations by oxonium salts have added several new weapons to the synthetic chemist's armamentarium. For example, the *O*-alkylated products from amides [R<sub>1</sub>C(OR)=NR<sub>2</sub>R<sub>3</sub>]<sup>+</sup> (R=CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>) may be hydrolyzed under mild conditions to amines and esters,<sup>15,35</sup> reduced to the amines R<sub>1</sub>CH<sub>2</sub>NR<sub>2</sub>R<sub>3</sub> by sodium borohydride,<sup>14</sup> converted to amide acetals R<sub>1</sub>C(OR)<sub>2</sub>NR<sub>2</sub>R<sub>3</sub> by alkoxides,<sup>4,16</sup> and (for R<sub>3</sub>=H) deprotonated to the imino esters R<sub>1</sub>C(OR)=NR<sub>2</sub>.<sup>17,18,19</sup> Amide acetals and imino esters are themselves in turn useful synthetic intermediates. Indeed, oxonium salts transform the rather intractable amide group into a highly reactive and versatile functionality, a fact elegantly exploited in recent work on the synthesis of corrins.<sup>35</sup>

Other reagents which approach or exceed the oxonium salts in alkylating ability include dialkoxycarbonium ions,<sup>36</sup> alkyl trifluoromethanesulfonates,<sup>37</sup> alkyl fluorosulfonates,<sup>38</sup> dialkylhalonium ions,<sup>39</sup> and alkyl halides in the presence of silver salts.<sup>25,37,40</sup> In terms of availability, stability, and freedom from hazards,<sup>25</sup> oxonium salts often appear to be the reagents of choice. When either

methylation or ethylation is acceptable, methylation may be preferable. [Triethyloxonium tetrafluoroborate](#) must be stored under [ether](#) and handled in a dry box,<sup>6</sup> whereas the trimethyl salt can be stored solvent-free in the freezing compartment of a refrigerator and dispensed in the open atmosphere. Moreover, while information on the relative alkylating ability of the oxonium salts is not extensive, a few cases have been reported in which [trimethyloxonium tetrafluoroborate](#) effected alkylations which the triethyl analog did not.<sup>20,31</sup> The trimethyloxonium salt, therefore, appears to be the more potent alkylating agent.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 5, 1080](#)
- [Org. Syn. Coll. Vol. 5, 1096](#)
- [Org. Syn. Coll. Vol. 5, 1099](#)
- [Org. Syn. Coll. Vol. 6, 576](#)

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**Appendix**  
**Chemical Abstracts Nomenclature (Collective Index Number);**  
**(Registry Number)**

Drierite

boron fluoride dimethyl etherate

liquid SO<sub>2</sub>

dimethoxycarbonium tetrafluoroborate

ether,

diethyl ether (60-29-7)

chloroform (67-66-3)

Epichlorohydrin (106-89-8)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

dimethyl ether (115-10-6)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

Diazomethane (334-88-3)

boron trifluoride (7637-07-2)

boron trifluoride etherate,  
boron trifluoride diethyl etherate (109-63-7)

dichloroethane (75-34-3)

trifluoroacetic acid (76-05-1)

sodium borohydride (16940-66-2)

triethyloxonium tetrafluoroborate (368-39-8)

Trimethyloxonium tetrafluoroborate,  
Oxonium, trimethyl- tetrafluoroborate(1-) (420-37-1)

Trimethyloxonium 2,4,6-trinitrobenzenesulfonate (13700-00-0)

dimethyloxonium tetrafluoroborate