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ESTERIFICATION OF STERICALLY HINDERED CARBOXYLIC ACIDS WITH TRIETHYLOXONIUM FLUOROBORATE

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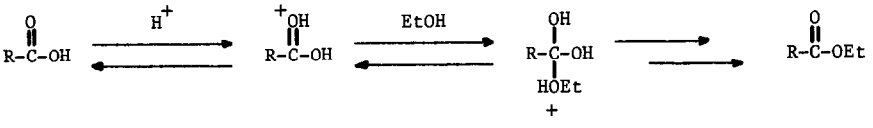
The esterification of carboxylic acids is a commonplace reaction which often presents unexpected difficulties. For instance, other functionality in the molecule may be sensitive to the acidic conditions of the standard[1] esterification procedures, the equilibrium between the acid and the ester may be unfavorable,[2] or the reaction may proceed only very slowly as is frequently found with sterically hindered acids.[3] Various approaches have been used to avoid such difficulties, but these either have suffered from a lack of generality or have presented new disadvantages. For example, Newman's[4] method for esterification using 100% sulfuric acid succeeds with only a limited number of carboxylic acids, while procedures utilizing such intermediates as the acid chloride, the n-butyl chlorosulfite,[5] or the tetramethylammonium salt[6] all require additional synthetic and purification steps and lead to corresponding decreases in yield, convenience, and generality.

Since the difficulty in esterification of hindered acids is apparently a consequence of the generation of increased nonbonded interactions in the tetrahedral intermediate III, we felt that the use of trialkyloxonium salts[7] (e.g., VI) would alleviate this difficulty as



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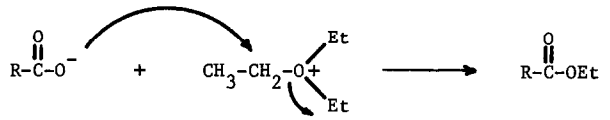
attack would take place at the more remote oxygen atom of the carboxyl group (i.e., V ⟶ IV) rather than at the acyl carbon atom. Meerwein reported several examples of esterification using



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trialkyloxonium salts and found that a better yield was obtained with an aqueous solution of sodium benzoate than with the free acid;[8] in support of this finding preliminary kinetic studies in our laboratory indicate that carboxylate anion does react considerably more rapidly than the free acid.

We have found that hindered (as well as unhindered) carboxylic acids can be easily esterified with triethyloxonium fluoroborate[10] in dichloromethane, generating the carboxylate anion in situ by the addition of the bulky organic base, diisopropylethylamine.[9] The hindered tertiary amine (which reacts at most only slowly with the oxonium salt) serves the added purpose of effectively neutralizing the fluoroboric acid which would be formed in its absence. Note should be made of the similarity of this method to the esterification procedure of Stodola[11] using diethyl or dimethyl sulfate; however, the utility of the latter method is decreased by the high toxicity of the reagents. Similar arguments can be made regarding esterification with diazomethane; although it is an extremely versatile reagent, it presents an explosive hazard[12] in addition to its high toxicity.

The Table summarizes the results of a series of esterification reactions of both hindered and unhindered carboxylic acids, and our standard procedure is described below for the preparation of ethyl 2,4,6-trimethylbenzoate.

Preparation of ethyl 2,4,6-trimethylbenzoate. To a solution of 0.94 g (5.7 mmole) of 2,4,6-trimethylbenzoic acid and 1.2 g (6.3 mmole) of triethyloxonium fluoroborate[10] in 75 ml of dichloromethane was added 1.0 ml (5.7 mmole) of diisopropylethylamine,[9] and the resulting solution was allowed to stand at room temperature in a stoppered flask for 24 hr. The reaction mixture was then extracted with three 50 ml portions of 1 N hydrochloric acid, three 50 ml portions of 1 N potassium bicarbonate, and a single 50 ml portion of saturated aqueous sodium chloride. The resulting dichoromethane solution was dried over sodium sulfate

and evaporated at reduced pressure to give 1.04 g of crude product. Bulb to bulb distillation (1 mm at ca. 90°) afforded 0.99 g (90%) of ethyl 2,4,6-trimethylbenzoate. The purity of the product was greater than 99% by nmr and gas chromatographic analyses.

Table. Esterification of Carboxylic Acids with Triethyloxonium Fluoroborate/ Diisopropylethylamine / Dichloromethane.[a]

Carboxylic Acid[b]	Yield (%)[c]	Purity[d]
2,4,6-triemthylbenzoic	90	>99%
triphenylacetic	81[e]	mp 115-116° (lit,[f] 116-117°)
9-decalincarboxylic[g] (mixture of cis and trans)	89	>99%
triethylacetic	90	>99%
2-phenylisobutyric[h]	86	>99%
benzoic	91	>99%
phenylpropiolic	90	>99%
o-benzoylbenzoic	95	mp 57-58° (lit,[i] 59-61°)

[a]Ca. 1 g of the acid and an equivalent amount of diisopropylethylamine in 50-75 ml of dichloromethane were allowed to react with a 10% excess of the oxonium salt. [b]Commerically available except as noted. [c]Distilled or crystalline product. [d]Estimated by glpc. [e]89% based on recovered acid. [f]Ref. 13 [g]Ref. 14 [h]Ref. 15 [i]Ref. 16

In summary esterification with triethyloxonium fluoroborate / diisopropylethylamine / dichloromethane is carried out conveniently and leads to good yields of the esters in a high degree of purity. Since the mild conditions (room temperature and essentially neutral medium) are compatible with a wide variety of functional groups in addition to the carboxyl moiety, this procedure offers great potential as a general method for the esterification of carboxylic acids.[17]

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17. Methyl esters can also be prepared by this method. Although trimethyloxonium fluoroborate is relatively insoluble in dichloromethane, good yields of methyl esters are obtained with the same procedure outlined for the ethyl esters but using a suspension rather than a solution of the oxonium salt in dichloromethane.