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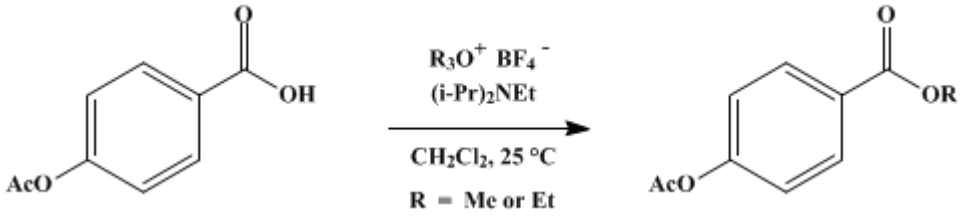
Organic Syntheses, Coll. Vol. 6, p.576 (1988); Vol. 56, p.59 (1977).

ESTERIFICATION OF CARBOXYLIC ACIDS WITH TRIALKYLOXONIUM SALTS: ETHYL AND METHYL 4-ACETOXYBENZOATES

[Benzoic acid, 4-(acetyloxy)-, ethyl and methyl esters]



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Checked by H. Fliri and G. Büchi.

1. Procedure

A. *Ethyl 4-acetoxybenzoate.* A 100-ml., one-necked, round-bottomed flask is charged with 2.09 g. (0.0110 mole) of triethyloxonium tetrafluoroborate (Note 1) and (Note 2), 75 ml. of dichloromethane (Note 3), and 1.80 g. (0.0100 mole) of 4-acetoxybenzoic acid (Note 4). A magnetic stirring bar is added, and the solution is stirred while 1.4 g. (1.9 ml., 0.011 mole) of diisopropylethylamine (Note 5) is introduced with a syringe (Note 6). The flask is then stoppered and allowed to stand at room temperature for 16–24 hours.

Work-up is initiated by extracting the reaction mixture with three 50-ml. portions of 1 *N* hydrochloric acid, three 50-ml. portions of aqueous 1 *N* potassium hydrogen carbonate (Note 7) and (Note 8), and 50 ml. of saturated aqueous sodium chloride. The organic solution is dried over sodium sulfate (Note 9), filtered, and concentrated on a rotary evaporator. Purification of the residue by bulb-to-bulb distillation (Note 10) at about 140° (5 mm.) provides 1.77–1.98 g. (85–95%) of ethyl 4-acetoxybenzoate as a colorless, viscous liquid (Note 11).

B. *Methyl 4-acetoxybenzoate.* A 100-ml., one-necked, round-bottomed flask is charged with 1.63 g. (0.0110 mole) of trimethyloxonium tetrafluoborate (Note 2) and (Note 12), 75 ml. of dichloromethane (Note 3) and (Note 13), and 1.80 g. (0.0100 mole) of 4-acetoxybenzoic acid (Note 4). A magnetic stirring bar is added, and the suspension is stirred while 1.4 g. (1.9 ml., 0.011 mole) of diisopropylethylamine (Note 5) is introduced with a syringe (Note 6). The flask is then stoppered, and stirring is continued at room temperature for 16–24 hours, during which time the oxonium salt dissolves. Work-up exactly as that described in Part A is followed by bulb-to-bulb distillation (Note 10) at about 140° (5 mm.), yielding 1.65–1.84 g. (85–95%) of methyl 4-acetoxybenzoate, m.p. 78–80° (Note 14).

2. Notes

1. Triethyloxonium tetrafluoroborate was prepared according to *Org. Synth.*, **Coll. Vol. 5**, 1080 (1973). The submitters stored this material at −20° under ether in a tightly-stoppered jar and found that the use of a dry box or an inert atmosphere was not required in its handling. A sample of the oxonium salt–ether slurry was transferred to the tared reaction flask, ether was removed on a rotary evaporator, and the resulting solid was weighed and used without further purification. The checkers stored the dry oxonium salt under argon at −15°, maintained an argon atmosphere in all operations involving this reagent, and used dry solvent (Note 3). They obtained 98% yields in two runs of Part A and two runs of Part B.
2. A 10% molar excess of the oxonium salt with regard to the carboxylic acid gives slightly higher yields than does an equimolar quantity.

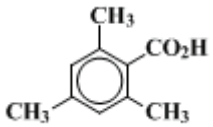
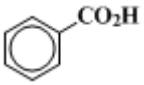
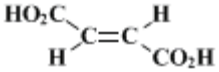
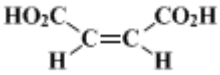
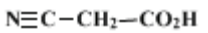
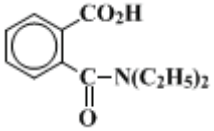
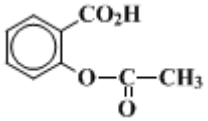
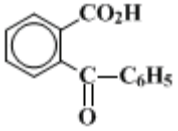
3. The submitters used reagent grade dichloromethane without purification. The checkers dried dichloromethane by distillation from phosphorus pentoxide.
4. This is prepared from 4-hydroxybenzoic acid and acetic anhydride following a procedure for 2-acetoxybenzoic acid.[2] The crude product is conveniently purified by stirring with chloroform (about 15 ml. per gram of acid) and removing any insoluble residue by filtration. Evaporation of the chloroform gives the desired material, m.p. 186–188° (lit.,[3] m.p. 189–190°).
5. This product was obtained from Aldrich Chemical Company, Inc. In many cases, the use of other amines may be satisfactory. Nevertheless, the use of a hindered base minimizes destruction of the oxonium salt by side reaction with the amine. Substitution of triethylamine for diisopropylamine in the procedure gave lower yields of the ester.
6. The use of a syringe affords a convenient method both for measuring the desired quantity of amine and adding it to the reaction mixture. In general, a mildly exothermic reaction takes place during addition of the amine. The submitters, working in an open vessel, suggest that if the reaction is scaled up or if the solution is more concentrated, care should be taken to add the amine gradually so that the reaction mixture does not boil over. For large-scale reactions they recommend the use of a dropping funnel. The checkers, working under argon and introducing the amine through a rubber septum, noted a considerable increase in pressure during the addition. Thus, with this experimental setup a suitable pressure vent is required.
7. Any unreacted carboxylic acid may be recovered by neutralization and extraction of the hydrogen carbonate solution.
8. In preparing ethers of phenols, aqueous 1 *N* sodium hydroxide should be substituted for the sodium hydrogen carbonate solution.
9. In many instances, the dichloromethane solution can be dried adequately by a simple filtration through coarse filter paper.
10. The "Kügelrohr" apparatus sold by Rinco Instrument Company, Inc., or any comparable bulb-to-bulb distillation apparatus is satisfactory. Fractional distillation is unnecessary.
11. The product crystallizes on standing overnight at −20° and melts at 30–32°. GC analysis showed it to be at least 99% pure. Ethyl 4-acetoxybenzoate has been reported to melt at 34°.[4]
12. This compound was prepared according to *Org. Synth.*, **Coll. Vol. 6**, 1019 (1988). Both submitters and checkers stored and handled this material using the techniques outlined for triethyloxonium tetrafluoborate in (Note 1).
13. Trimethyloxonium tetrafluoroborate is only slightly soluble in dichloromethane. However, the use of a two-phase mixture presents no difficulties in either experimental procedure or yield.
14. GC analysis showed this material to be at least 99% pure. The melting point of methyl 4-acetoxybenzoate has been reported[5] as 81–81.6°. In both their runs, the checkers obtained a distilled product which melted from 60° to 74°, resolidified at 74°, and then remelted at 78–79°. A sample recrystallized from hexane showed the same behavior.

3. Discussion

This procedure provides a convenient method for the esterification of a wide variety of carboxylic acids.[6] [7] The reaction proceeds smoothly with sterically hindered acids[6] and with those which contain various functional groups.[7] Esters are obtained in high purity using Kugelrohr distillation as the sole purification technique. In cases where traces of dichloromethane present no problems, the crude product is usually pure enough to be used directly in subsequent reactions. Methyl and ethyl ethers of phenols may also be prepared by this procedure (see (Note 8)).

Examples of polyfunctional carboxylic acids esterified by this method are shown in Table I. Yields are uniformly high, with the exception of those cases (maleic and fumaric acids) where some of the product appears to be lost during work-up as a result of water solubility. Even with carboxylic acids containing a second functional group (e.g., amide, nitrile) which can readily react with the oxonium salt, the more nucleophilic carboxylate anion is preferentially alkylated. The examples described in detail above illustrate the esterification of an acid containing a labile acetoxy group, which would not survive other procedures such as the traditional Fischer esterification.

TABLE I
ESTERIFICATION OF CARBOXYLIC ACIDS WITH TRIALKYLOXONIUM FLUOBORATES

Acid	Triethyloxonium Fluoborate Yield (%)[a]	Purity (%)[b]	Trimethyloxonium Fluoborate Yield (%)[a]	Purity (%)[b]
	90	>99	90	>99
	91	>99	92	>99
	77[c]	>99	80[c]	>99
	70[c]	>99	74[c]	>99
	91	>99	82	95
	88	>99	86	>99
	89	95	85	>99
	95	>99	95	>99

*a*Yield of distilled or crystallized ester.
*b*By GC.
*c*In the esterification of dibasic acids a corresponding increase in equivalents of oxonium salt is employed; the product is the diester.

The great utility of the trialkyloxonium salts is illustrated by the fact that high yields of esters are obtained using reagent which has been stored for up to 6 months under the submitters' conditions (Note 1) and (Note 12). Thus, either trimethyl- or triethyloxonium tetrafluoroborate can be prepared in quantity, stored, and used for esterification as required.

Other examples of esterification with triakyloxonium salts have been reported.[8,9] The present procedure offers the advantages that the reactive carboxylate ion is generated *in situ* and that a low-boiling, nonaqueous solvent is employed, simplifying the experimental procedure considerably. A related method which utilizes a hindered amine with dimethyl sulfate as the alkylating agent has been reported. The present procedure is carried out under somewhat milder conditions and avoids the use of highly toxic reagents.

The only other esterification method which rivals the present procedure in convenience, mildness of conditions, selectivity, and yield is the preparation of methyl esters with diazomethane.[10] Esterification with trialkyloxonium salts, however, allows preparation of both methyl and ethyl esters and avoids the toxicity and explosion hazard[11] of diazomethane.

Furthermore, recent studies indicate that esterifications involving triethyloxonium tetrafluoroborate are often very rapid. For example, subsequent to the checking of this procedure the submitters have found that the reaction time of Part A may be shortened from 16–24 hours to 0.5 hour with no decrease in yield. The longer reaction time is still recommended for esterifications involving the trimethyl salt, such as that of Part B, because of the heterogeneous nature of the reaction mixture in these cases.

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References and Notes

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

amine

Benzoic acid, 4-(acetyloxy)-, ethyl and methyl esters

trimethyl- or triethyloxonium tetrafluoroborate

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

dimethyl sulfate (77-78-1)

dichloromethane (75-09-2)

2-acetoxybenzoic acid (50-78-2)

Diazomethane (334-88-3)

4-hydroxybenzoic acid (99-96-7)

hexane (110-54-3)

triethylamine (121-44-8)

argon (7440-37-1)

potassium hydrogen carbonate (298-14-6)

Triethyloxonium fluoborate,
triethyloxonium tetrafluoroborate (368-39-8)

trimethyloxonium fluoborate,
Trimethyloxonium tetrafluoroborate (420-37-1)

diisopropylamine (108-18-9)

Ethyl 4-acetoxybenzoate (13031-45-3)

4-acetoxybenzoic acid (2345-34-8)

diisopropylethylamine (7087-68-5)

trimethyloxonium tetrafluoborate

Methyl 4-acetoxybenzoate (24262-66-6)

triethyloxonium tetrafluoborate

phosphorus pentoxide (1314-56-3)