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A METHOD FOR THE ESTERIFICATION OF STERICALLY HINDERED CARBOXYLIC ACIDS

Roger C. Parish and Leon M. Stock
Department of Chemistry, University of Chicago
Chicago 37, Illinois

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The problems associated with the acid-catalyzed esterification of sterically hindered carboxylic acids are well known.[1] Moreover, the techniques which have been found useful for the preparation of these esters are subject to important restrictions in the character of the carboxylic acid or the hydroxy compounds.

In a search for a general method, we have observed that the known[2] esterification reaction of an unsymmetrical anhydride (prepared *in situ*) of trifluoroacetic acid and a carboxylic acid with an hydroxy compound proceeds very easily with highly hindered acids and hindered hydroxy compounds of diverse structure.

The synthetic results are summarized in the table. Elemental analyses and the infrared and magnetic resonance spectra were used to establish the structure of the previously unknown esters.

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[1] M. S. Newman, *Steric Effects in Organic Chemistry*, M. S. Newman, editor, John Wiley and Sons, New York (1956). p.204-217.

[2a] E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949). [b] J. M. Tedder, *Chem. Rev.*, 55, 787 (1955). [c] E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall, *J. Chem. Soc.*, 3268 (1958).

Yields and Properties of Esters Prepared by the Mixed Anhydride Approach

Acid	Hydroxy Compound	°/o Yield of Es
9-Anthroic	Methanol	96[b]
	t-Butyl alcohol	95[c]
	Phenol	96[d]
10-Bromo-9-anthroic	Methanol	95[b]
10-Methoxy-9-anthroic	Methanol	97[e]
Mesitoic	Methanol	89[f]
	t-Butyl alcohol	38[g]
	Phenol	83[h]
	2,6-Dimethylphenol	97[i]
	Mesitol	94[j]
	2,6-Di-*t*-butyl-4-methylphenol	73[k]
Pivalic	β-Naphthol	93[l]
Triethylacetic	β-Naphthol	93[m]
2-t-Butyl-2,3,3-tri-methylbutyric[n]	β-Naphthol	60[o]

[a] The physical properties of known esters were in agreement with literature values.

[b] R. O. C. Norman and P. D. Ralph, *J. Chem. Soc.*, 2221 (1961).

[c] M.p. 158°. Calcd. for $C_{19}H_{18}O_2$: °/oC 81.98, °/oH 6.52; Found: °/oC 81.74, °/oH 6.50.

[d] M.p. 144°. Calcd. for $C_{21}H_{14}O_2$: °/oC 84.54, °/oH 4.73; Found: °/oC 84.59, °/oH 4.78.

[e] J. Rigandy and L. Nedeles, *Compt. rend.*, **246**, 619 (1958).

[f] H. L. Goering, T. Rubin, and M. S. Newman, *J. Am. Chem. Soc.*, **76**, 787 (1954).

[g] S. G. Cohen and A. Schneider, *ibid.*, **63**, 3382 (1941).

[h] M.p. 37°. Calcd. for $C_{16}H_{16}O_2$: °/oC 79.97, °/oH 6.71; Found: °/oC 80.07, °/oH 6.74.

[i] M.p. 103-104°. Calcd. for $C_{18}H_{20}O_2$: °/oC 80.61, °/oH 7.46; Found: °/oC 80.80, °/oH 7.66.

[j] G. W. Thiessen and W. N. Farr, *J. Org. Chem.*, **24**, 559 (1959).
[k] Based on recovery of 77°/o starting material, m.p. 127-128°. Calcd. for $C_{25}H_{34}O_2$: °/oC 81.90, °/oH 9.35; Found: °/oC 81.80, °/o H 9.39.
[l] M. Harfenist and R. Baltzly, *J. Am. Chem. Soc.*, **69**, 362 (1947).
[m] M.p. 33-34°. Calcd. for $C_{18}H_{22}O_2$: °/oC 79.96, °/oH 8.20; Found: °/oC 79.87, °/oH 8.37.
[n] We are indebted to M. S. Newman for a sample of this acid.
[o] Performed on 30 mg. scale, m.p. 53.5-54.5°. Calcd. for $C_{21}H_{28}O_2$: °/oC 80.72, °/oH 9.03; Found: °/oC 80.61, °/oH 8.94.

In a typical preparation, mesitoic acid (1.0 g., 0.0061 mole) and mesitol (0.83 g., 0.0061 mole) were treated with trifluoroacetic anhydride (5.0 ml., 0.036 mole) and the resulting solution allowed to stand at room temperature for 20 min. Benzene (25 ml.) was then added and the solution washed with aqueous sodium hydroxide (10°/o) and with water. The organic layer was dried over sodium sulfate and evaporated to yield 1.62 g. (94°/o) mesityl mesitoate (m.p. 70.5-71.5°). Recrystallization of the product changed the m.p. only slightly (71-71.5°).

A modified procedure was used with less soluble acids. In a typical preparation, 9-anthroic acid (2.00 g., 0.009 mole) was suspended in benzene (40 ml.) and treated with trifluoroacetic anhydride (5.0 ml., 0.036 mole). All of the 9-anthroic acid had dissolved after ten minutes of gentle warming. Methanol (5 ml.) was then added and methyl 9-anthroate (96°/o) isolated in the usual manner.

In the preparation of *t*-butyl mesitoate, the reaction of *t*-butyl alcohol with trifluoroacetic acid to form *t*-butyl trifluoroacetate[2c] may account for the poor yield of this ester in contrast to the high yields obtained with other more hindered esters. We have observed the method to fail in only two cases. When a 1:1 mixture of mesitoic acid and 2,6-di-*t*-butylphenol was treated with trifluoroacetic anhydride acylation of the phenol, rather than esterification, occurred to provide 2,4,6-trimethyl-3',5'di-*t*-butyl-4'-hydroxybenzophenone[3] (m.p. 136-137°) in 82% yield. This result is not surprising in view of the extreme hinderance of the hydroxy group and the fact that carboxylic acids in the presence of trifluoroacetic anhydride are known to acylate activated aromatic nuclei.[2b,4] When the reaction was carried out with this activated position blocked by a methyl group, the reaction proceeded to give the expected ester, 2,6-di-*t*-butyl-4-methylphenyl mesitoate. The reaction however, was quite slow.

In a number of attempts, this procedure failed to produce esters of 2,4,6-tribromobenzoic acid. Surprisingly, however, a solution of 2,4,6-tribromobenzoic acid in a minimum amount of trifluoroacetic anhydride was observed to slowly deposit crystals of 2,4,6-tribromobenzoic anhydride[5] (m.p. 147-148°) upon standing at room temperature for several days.

The scope of the reaction is indicated by the nearly quantitative formation of such remarkably hindered esters as mesityl mesitoate and *t*-butyl-9-anthroate. The method is apparently applicable to highly hindered aliphatic acids as illustrated by the preparation of β-naphthyl 2-*t*-butyl-2,3,3-trimethylbutyrate.

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[3] Calculated for $C_{24}H_{32}O_2$ %C 81.77, %H 9.15; Found: %C 81.72, %H 9.25.

[4] E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 718 (1951).

[5] Calcd. for $C_{14}H_4Br_6O_3$: %Br 68.53; Found: %Br 68.58

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