p-nitrobenzoyl chloride,[29] 2,3-di-O-methyl-D-mannose 1,4,6-tri-*p*-nitrobenzoate was obtained: m.p. 192–194°, $[\alpha]^{22}D$ +66° (*c* 0.3, chloroform); lit.[29] m.p. 194°, $[\alpha]D$ +65° (chloroform).

(29) See ref. 12, p. 539.

Acknowledgment.—The author is indebted to Dr. T. Riqué for the gift of the seeds and to Drs. M. Bohner and J. S. Cerezo for the determinations with the ultracentrifuge.

A Method for the Esterification of Hindered Acids[1]

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Received November 23, 1964

The scope, limitations, and mechanism of a simple method for the esterification of hindered aliphatic and aromatic carboxylic acids are discussed.

Need for a quantity of methyl 9-anthroate prompted an examination of techniques for its synthesis other than the conventional esterification methods applicable for sterically hindered acids.[2] Esterification by the reaction[3] of methanol with the unsymmetrical anhydride of 9-anthroic acid and trifluoroacetic acid proved very successful. The extraordinary simplicity of this method led us to study the scope and limitations of the reaction with other hindered acids.[4]

Results and Discussion

Scope of the Reaction.—Two methods which are little different from the techniques useful for unhindered acids[3] were employed. Either the acid is dissolved in trifluoroacetic anhydride and the hydroxy compound is added (method A) or a mixture of the acid and hydroxy compound is treated with the anhydride (method B). In all but a few cases (involving severely hindered acids and hydroxy compounds) esterification is complete in less than 1 hr. The esters prepared by this procedure are summarized in Table I.

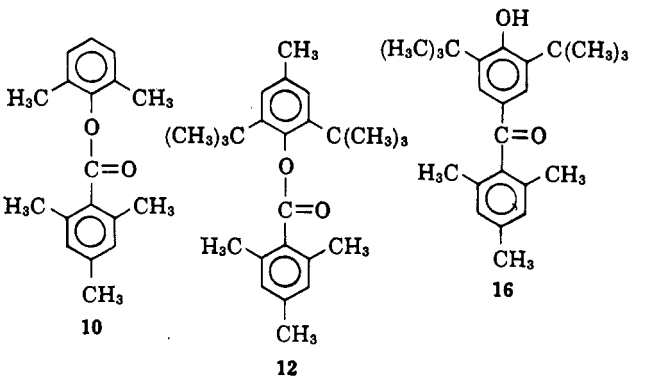
TABLE I

ESTERS PREPARED BY THE MIXED ANHYDRIDE APPROACH

Ester	Acid	Hydroxy compd.	Yield, %[a]
1	9-Anthroic	Methanol	96
2	9-Anthroic	*t*-Butyl alcohol	95
3	9-Anthroic	Phenol	96
4	10-Bromo-9-anthroic	Methanol	95
5	10-Chloro-9-anthroic	Methanol	97
6	10-Methoxy-9-anthroic	Methanol	97
7	Mesitoic	Methanol	89
8	Mesitoic	*t*-Butyl alcohol	72
9	Mesitoic	Phenol	83
10	Mesitoic	2,6-Dimethylphenol	97
11	Mesitoic	Mesitol	94
12	Mesitoic	2,6-Di-*t*-butyl-4-methylphenol	73
13	Pivalic	β-Naphthol	93
14	Triethylacetic	β-Naphthol	93
15	2-*t*-Butyl-2,2,3-trimethylbutyric	β-Naphthol	60

[a] Ester 8 is formed in 52% conversion. Ester 12 is formed in 23% conversion.

Difficulties were encountered in remarkably few cases. Mesitoic acid and 2,6-dimethylphenol readily form **10**, but mesitoic acid and 2,6-di-*t*-butylphenol provide 2,4,6-trimethyl-3′,5′-di-*t*-buty -4′-hydroxybenzophenone (**16**) in 83% yield. No ester is detected in the crude product by infrared. When both the acid and hydroxy compound are highly hindered and an alternate path, acylation of the phenol in this instance,[3c,5] is available, esterification may not occur. 2,6-Di-*t*-butyl-4-methylphenol with the 4-position blocked reacts with mesitoic acid in trifluoroacetic anhydride to yield **12**. As expected, the reaction is slow. Only 23% conversion to **12** occurs in 3 days at ambient temperature in contrast to the complete conversion of 2,6-dimethylphenol to **10** in 5 min.



The fast solvolytic reactions of *t*-alcohols with trifluoroacetic acid[3b] also influence the yields. Thus, *t*-butyl trifluoroacetate is formed competitively with ester **8**. The low conversion (Table I) presumably reflects the importance of this side reaction. The purest product and best conversion are realized with a large excess of *t*-butyl alcohol. When the alcohol is used in 1:1 ratio, olefinic by-products are formed which contaminate the product.

2,4,6-Tribromobenzoic acid (**17**) could not be esterified by this approach. When **17** is dissolved in trifluoroacetic anhydride and allowed to stand (with or without hydroxy compounds) 2,4,6-tribromobenzoic anhydride (**18**) slowly precipitates.

Mechanism.—Solutions of acids in trifluoroacetic anhydride involve several equilibria,[3b] but the major component in solution is the unsymmetrical an-

(1) Supported by Grants G14211 and G25190 from the National Science Foundation.

(2) M. S. Newman, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 204–217.

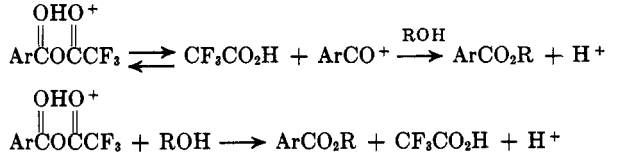
(3) (a) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949); (b) E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall, *ibid.*, 3268 (1958); (c) J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).

(4) A preliminary report of the work has appeared: R. C. Parish and L. M. Stock, *Tetrahedron Letters*, **No. 20**, 1285 (1964).

(5) Acylation of aromatics has been studied: (a) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 718 (1951); (b) M. S. Newman, *J. Am. Chem. Soc.*, **67**, 345 (1945).

hydride.[6,7] Acylation is generally ascribed to the oxocarbonium ion formed by the acid-catalyzed ionization of the anhydride.[3b,8] Support for this hypothesis is the rate retardation by added sodium trifluoroacetate and nonpolar cosolvents,[3b] and the conductivity of solutions of acids in trifluoroacetic anhydride.[9] Further, tri-*i*-propylacetic acid decarbonylates when dissolved in trifluoroacetic anhydride.[10] These observations do not, however, exclude the protonated anhydride[11] as a reactive acylating agent. Several observations suggest its significance. The nucleophilic properties of the hydroxy compound influence the rate of esterification as shown in the reactions of 2,6-dimethyl- and 2,6-di-*t*-butyl-4-methylphenol. Benzoic acid is not esterified by the Newman sulfuric acid method,[2] but is esterified by the anhydride approach. Neither carbon monoxide nor olefins[10] derived from the acid were observed in the preparation of esters of hindered aliphatic acids. Further pivalic acid did not decarbonylate under the reaction conditions. The area ratios in the n.m.r. spectrum of this acid in trifluoroacetic anhydride (with added reference compound) were unchanged after 120 hr. When anisole is added to the solution, *t*-butyl *p*-anisyl ketone[12] (**19**) slowly forms. These findings, although not incompatible with an acylonium ion intermediate, suggest the protonated anhydride might be the actual acylating agent.

We have examined the influence of substituents on the rate of the reaction to distinguish between the oxocarbonium and protonated anhydride paths. Donor



substituents should effect a small increase in the concentration of the protonated anhydride and a major increase in the concentration of the oxocarbonium ion with large accelerating influence on the over-all rate.[13] On the other hand, donor substituents should retard the reaction of the alcohol with the protonated anhydride and the rate should depend only modestly on the polar properties of substituents.

Mesitoic acid and benzoic acid were treated with anisole in trifluoroacetic anhydride under identical conditions (50 hr. at 25°). 2,4,6-Trimethyl-4′-methoxybenzophenone (**20**) is obtained in 65% yield while 4-methoxybenzophenone is formed in 9% yield. A competitive experiment with these acids and insufficient phenol in trifluoroacetic anhydride gave 91% phenyl mesitoate and no phenyl benzoate (v.p.c.). Thus, both carbon and oxygen acylation are far more rapid with mesitoic acid. The greater reactivity of this acid is good evidence for the acylonium ion intermediate in the case of hindered acids. The fact that the nucleophilic path with trifluoroacyl mesitoate is subject to a major steric effect[14] prompted study of substituent effects on the unhindered trifluoroacyl benzoates. *p*-Toluic, benzoic, and *m*-chlorobenzoic acids were treated competitively with phenol in trifluoroacetic anhydride at 25°. The rate sequence was *p*-Me, 12; H, 1.0; and *m*-Cl, 0.062. The substituent effects are large (ρ^+ −3.2 ± 0.1 based on $\sigma_{p\text{-Me}}{}^+$ −0.31 and $\sigma_{m\text{-Cl}}{}^+$ 0.39), indicative of a high electron deficiency in the transition state, and infer the importance of the acylonium ion path for the unhindered acids as well as the hindered acids.

Experimental[15]

Materials.—Commercially available compounds were sufficiently pure with the following exceptions. 2,6-Di-*t*-butylphenol (Ethyl) and 2,6-di-*t*-butyl-4-methylphenol (Matheson Coleman and Bell) were chromatographed on alumina (hexane) prior to use. We are indebted to M. S. Newman for a sample of 2-*t*-butyl-2,3,3-trimethylbutyric acid. Trifluoroacetic anhydride is very conveniently prepared by distillation from a mixture of trifluoroacetic acid and an excess of phosphorus pentoxide.

Procedure.—Two procedures are most useful for the esterification. Benzene is often a desirable cosolvent to hasten the solution of the less soluble acids in trifluoroacetic anhydride.

Method A.—9-Anthroic acid (2.00 g., 9.0 mmoles) was suspended in benzene (40 ml.) and trifluoroacetic anhydride (5.0 ml., 36 mmoles) was added. The acid dissolved after 10 min. of gentle warming. Methanol (5 ml.) was then added. After a short time (see Table II) aqueous sodium hydroxide (10%) was added to extract the acids. The benzene layer was washed with water and dried. Methyl 9-anthroate (**1**) was isolated by removal of the solvent *in vacuo* and by recrystallization from ethanol or hexane.

Method B.—Mesitoic acid (1.00 g., 6.1 mmoles) and mesitol (0.83 g., 6.1 mmoles) were treated with trifluoroacetic anhydride (5.0 ml., 36 mmoles). The resulting solution was stirred at room temperature for 20 min. Benzene (20 ml.) was added and mesityl mesitoate (**11**) was isolated as in method A.

The methods, physical properties, and reaction times employed are summarized in Table II. The spectroscopic observations for previously unknown esters are summarized in Table III.

2,4,6-Trimethyl-3′,5′-di-*t*-butyl-4′-hydroxybenzophenone (16).—Mesitoic acid (1.00 g., 6.1 mmoles) and 2,6-di-*t*-butylphenol (1.26 g., 6.1 mmoles) were treated with trifluoroacetic anhydride (5.0 ml., 36 mmoles). Solution was rapid. After 2 min., benzene (20 ml.) and aqueous sodium hydroxide (10%, 20 ml.) were added and the product was isolated in the usual manner. Crystallization of the slightly yellow compound from ethanol gave **16**: m.p. 136–137°, 1.94 g., 82%.

Anal. Calcd. for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.25.

The infrared spectrum of a dilute solution (carbon tetrachloride) has a sharp absorption at 3635, and a strong carbonyl band at 1660 cm.$^{-1}$. The n.m.r. spectrum consists of six singlets: τ 8.58 (18H), 7.93 (6H), 7.67 (3H), 4.33 (1H), 2.40 (2H), and 2.18 (2H).

Attempts to Esterify 17.—2,4,6-Tribromobenzoic acid[16] (1.00 g., 2.8 mmoles) readily dissolved in trifluoroacetic anhydride (5 ml., 0.036 mole). After treatment with methanol (5 ml.) **17** was recovered unchanged.

(6) W. D. Emmons, K. S. McCallum, and A. F. Ferris, *J. Am. Chem. Soc.*, **75**, 6047 (1953).

(7) E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall, *J. Chem. Soc.*, 2006 (1954).

(8) E. J. Bourne, J. E. B. Randles, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Am. Chem. Soc.*, **76**, 3206 (1954).

(9) J. E. B. Randles, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 436 (1954).

(10) M. S. Newman and T. Fukunaga, *J. Am. Chem. Soc.*, **85**, 1176 (1963).

(11) The unprotonated unsymmetrical anhydride is a trifluoroacylating agent: see E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952).

(12) E. Rothstein and R. W. Saville, *ibid.*, 1951 (1949).

(13) O. P. N. Satchell, *ibid.*, 5404 (1961).

(14) See ref. 2, pp. 218–225.

(15) Infrared spectra were recorded on a Beckman IR7 spectrometer, n.m.r. spectra were recorded on a Varian A60 instrument, and microanalyses were performed by Mr. William Saschek. All melting points are uncorrected.

(16) M. M. Robinson and B. L. Robinson, *Org. Syn.*, **36**, 94 (1956).

TABLE II

PROPERTIES OF THE ESTERS

Ester	Method	M.p., °C., b.p., °C. (mm.) Obsd.	Lit.	Reaction time, min.
1, methyl 9-anthroate	A	114	115[a]	10
2, *t*-butyl 9-anthroate[b]	A	158		30
3, phenyl 9-anthroate[c]	A	144		30
4, methyl 10-bromo-9-anthroate	A	112–112.5	114[a]	300
5, methyl 10-chloro-9-anthroate	A	122–123	123[a]	30
6, methyl 10-methoxy-9-anthroate	A	116–117	117[d]	30
7, methyl mesitoate	B	116 (10) $n^{24}D$ 1.5065	113 (13)[e] $n^{20}D$ 1.5085[e]	60
8, *t*-butyl mesitoate		114 (2) $n^{24}D$ 1.4911	114 (3)[f] $n^{23}D$ 1.4920[f]	15
9, phenyl mesitoate[g]	B	37		10
10, 2,6-dimethylphenyl mesitoate[h]	B	103–104		5
11, mesityl mesitoate	B	71–71.5	70.5–71.5[i]	20
12, 2,6-di-*t*-butyl-4-methylphenyl mesitoate[j,k]	B	127–128		3 days
13, β-naphthyl pivalate	B	65–66	66–66.5[l]	210
14, β-naphthyl triethylacetate[m]	B	33–34		195
15, β-naphthyl 2-*t*-butyl-2,3,3-trimethylbutyrate[n,o]	B	53.5–54.5		60

[a] R. O. C. Norman and P. D. Ralph, *J. Chem. Soc.*, 2221 (1961). [b] *Anal.* Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.74; H, 6.50. [c] *Anal.* Calcd. for $C_{21}H_{14}O_2$: C, 84.54; H, 4.73. Found: C, 84.59; H, 4.78. [d] J. Rigaudy and L. Nedelec, *Compt. rend.*, **246**, 619 (1958). [e] H. L. Goering, I. Rubin, and M. S. Newman, *J. Am. Chem. Soc.*, **76**,7 87 (1954). [f] S. G. Cohen and A. Schneider, *ibid.*, **63**, 3382 (1941). [g] *Anal.* Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.07; H, 6.74. [h] *Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.61; H, 7.46. Found: C, 80.80; H, 7.66. [i] G. W. Thiessen and W. N. Farr, *J. Org. Chem.*, **24**, 559 (1959). [j] *Anal.* Calcd. for $C_{25}H_{34}O_2$: C, 81.90; H, 9.35. Found: C, 81.80; H, 9.39. [k] Based on 77% recovery of starting material. [l] M. Harfenist and R. Baltzly, *J. Am. Chem. Soc.*, **69**, 382 (1947). [m] *Anal.* Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.87; H, 8.37. [n] Performed on a 30-mg. scale. [o] *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.72; H, 9.03. Found: C, 80.61; H, 8.94.

TABLE III

SPECTROSCOPIC PROPERTIES OF NEW ESTERS

Ester	C=O, cm.$^{-1}$[a]	N.m.r.[b]
2	1725	
3	1755	8.35 (s, 9H), 1.5–2.7 (m, 9H)
9	1750	
10	1742	7.70 (s, 6H), 7.65 (s, 3H), 7.43 (s, 6H) 2.98 (s, 2H), 2.83 (m, 3H)
12	1735	8.75 (s, 18H), 7.72 (s, 6H), 7.38 (s, 6H) 3.15 (s, 2H), 3.00 (s, 2H)
14	1750	9.17 (t, 9H), 8.33 (q, 6H), 2.2-3.1 (m, 7H)
15	1742	8.73 (s, 18H), 8.62 (s, 3H), 2.2–3.1 (m, 7H)

[a] In dilute solution in CCl_4. [b] τ-Values; in CCl_4 with tetramethylsilane as internal reference.

When **17** (4.00 g., 11.2 mmoles) and methanol (0.5 ml., 17.2 mmoles) were treated with trifluoroacetic anhydride (5 ml., 36 mmoles) and allowed to stand at room temperature for 36 hr., solid precipitated. The solid dissolved in benzene during the work-up. Unchanged **17**, 2.80 g., was recovered from the aqueous phase. 2,4,6-Tribromobenzoic anhydride (**18**, insoluble in aqueous alkali, 1.0 g., m.p. 147–148°) was isolated from the benzene layer.

Anal. Calcd. for $C_{14}H_4Br_6O_3$: Br, 68.53. Found: Br, 68.58.

The infrared spectrum of **18** (carbon tetrachloride) has absorptions at 1825, 1775, and 1077 cm.$^{-1}$.

Stability of Pivalic Acid in Trifluoroacetic Anhydride.—Pivalic acid (20 mg.), trifluoroacetic anhydride (0.5 ml.), and *t*-butyl trifluoroacetate (one tiny drop) were sealed in an n.m.r. tube. The ratio of the integrated areas of the pivalic trifluoroacetic anhydride resonance to the total resonance was examined at various times. After 120 hr. the area ratio was unchanged.

***t*-Butyl *p*-Anisyl Ketone (19).**—Pivalic acid (2.37 g., 23.3 mmoles), and anisole (2.51 g., 23.3 mmoles) were treated with trifluoroacetic anhydride (10 ml., 72 mmoles) and allowed to stand at room temperature for 93 hr. Benzene (50 ml.) was added and the acids were extracted. The benzene layer was dried and evaporated to yield an orange oil. *t*-Butyl *p*-anisyl ketone (**19**, about 200 mg.), the sole product of the reaction, was isolated by v.p.c. The infrared spectrum (carbon tetrachloride) has a strong carbonyl absorption at 1672 cm.$^{-1}$. The n.m.r. spectrum (carbon tetrachloride) is as follows: τ 8.70 (s, 9H), 6.20 (s, 3H), and 2.77 (q, 4H); J = 9 c.p.s., $\Delta\nu$ = 58.3 c.p.s.

Reaction of Benzoic and Mesitoic Acid with Anisole.—Benzoic acid (0.744 g., 6.1 mmoles) and mesitoic acid (1.00 g., 6.1 mmoles were sealed in separate ampoules each with anisole (0.66 g., 6.1 mmoles) and trifluoroacetic anhydride (5 ml., 36 mmoles). After 50 hr. at room temperature the products were isolated 2,4,6-trimethyl-4′-methoxybenzophenone (**20**) (1.01 g., 65%, m.p. 74–76°, lit.[17] m.p. 77–78°) was isolated from the mesitoic acid reaction. The n.m.r. spectrum is consistent with the assigned structure: τ 7.99 (s, 6H), 7.74 (s 3H), 6.23 (s, 3H), 3.23 (s, 2H), and 2.83 (q, 4H); J = 9 c.p.s., $\Delta\nu$ = 51.2 c.p.s. 4-Methoxybenzophenone (115 mg., 8.9%, m.p. 40–52°, lit.[18] m.p. 61–62°) was isolated from the benzoic acid reaction. The n.m.r. spectrum is consistent with 4-methoxybenzophenone contaminated with about 5% of the 2-isomer.

Competition of Mesitoic and Benzoic Acid for Phenol.—Benzoic acid (1.000 g., 8.2 mmoles) and mesitoic acid (1.344 g., 8.2 mmoles) were dissolved in trifluoroacetic anhydride (10 ml.). The solution was treated with phenol (0.770 g., 8.2 mmoles) in trifluoroacetic anhydride (5 ml.) and benzene (5 ml.). After 1.5 hr., benzene (50 ml.) was added and the reaction mixture was cooled in ice and hydrolyzed. Work-up in the usual manner afforded only phenyl mesitoate (m.p. 33–35°, 91%). Phenyl benzoate could not be detected in the crude product (v.p.c.). Control experiments with phenyl benzoate and mesitoic acid in trifluoroacetic anhydride revealed ester interchange did not occur.

Competitive experiments with *p*-toluic, benzoic, and *m*-chlorobenzoic acids were carried out in a similar manner. The product ratio was determined by v.p.c. and the relative rates were calculated by the equation of Ingold and Shaw.[19]

(17) R. C. Fuson, G. W. Parshall, and E. H. Hess, *J. Am. Chem. Soc.*, **77**, 3776 (1955).

(18) A. W. Smith, *Ber.*, **24**, 4025 (1891).

(19) C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 2918 (1927).