Acylation of Arenes and Heteroarenes with *in situ* Generated Acyl Trifluoroacetates

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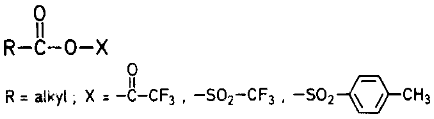
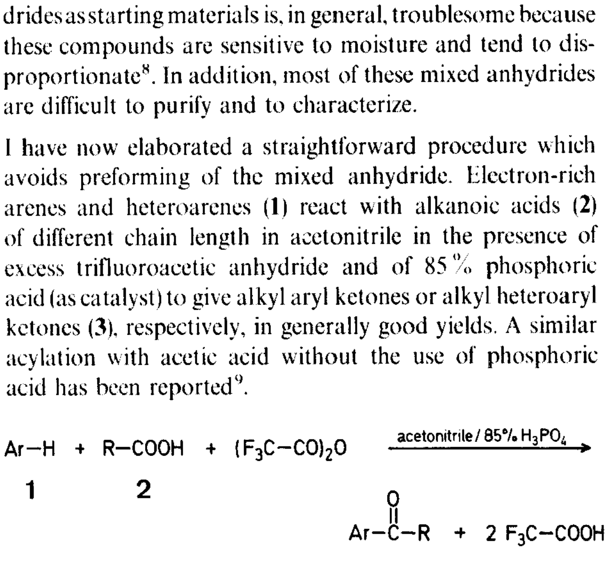
The use of carboxylic anhydrides as *C*-acylating agents[1] is practically limited to acetylation, propanoylation, and occasionally butanoylation. In order to avoid this limitation, mixed anhydrides of the type



have been employed[2–7]. However, the use of mixed anhydrides as starting materials is, in general, troublesome because these compounds are sensitive to moisture and tend to disproportionate[8]. In addition, most of these mixed anhydrides are difficult to purify and to characterize.

I have now elaborated a straightforward procedure which avoids preforming of the mixed anhydride. Electron-rich arenes and heteroarenes (**1**) react with alkanoic acids (**2**) of different chain length in acetonitrile in the presence of excess trifluoroacetic anhydride and of 85% phosphoric acid (as catalyst) to give alkyl aryl ketones or alkyl heteroaryl ketones (**3**), respectively, in generally good yields. A similar acylation with acetic acid without the use of phosphoric acid has been reported[9].



$$\underset{\mathbf{1}}{Ar{-}H} + \underset{\mathbf{2}}{R{-}COOH} + (F_3C{-}CO)_2O \xrightarrow{\text{acetonitrile / 85\% } H_3PO_4} \underset{\mathbf{3}}{Ar{-}\overset{O}{\overset{\|}{C}}{-}R} + 2\,F_3C{-}COOH$$

The nature of the acylating agent was studied in a separate experiment. The reaction with dodecanoic (lauric) acid was carried out in the absence of an aromatic or heteroaromatic substrate under the conditions given in the experimental procedure. The expected mixed anhydride, dodecanoyl trifluoroacetate, could be isolated and characterized by I.R. spectrometry according to Ref. [3]. Reaction of the isolated mixed anhydride with 3-methylthiophene afforded a 3:1 mixture of 3-methyl-2-(1-oxododecyl)- and 4-methyl-2-(1-oxododecyl)-thiophene (**3d**) in 58% yield.

The acylation proceeds also in the absence of 85% phosphoric acid; however, in these cases it requires significantly longer reaction times and gives lower yields (see **3c**). No reaction takes place when the catalyst and trifluoroacetic acid are used in a 1:1 molar ratio; a ratio of 1:3 was found to be suitable. The role of phosphoric acid is at present not completely understood; the intermediacy of a phosphoric alkanoic anhydride cannot be ruled out[10]. It is interesting to note that replacement of phosphoric acid by trifluoroacetic acid results in yields similar to those which are obtained without catalysis.

The following concentrations of reaction components and reagents were found to be optimum:
substrate: 0.1–0.3; alkanoic acid: 0.1; phosphoric acid: 0.1; trifluoroacetic anhydride: 0.4.

Ketones **3** are readily formed starting from C_2–C_{12} alkanoic acids. Even with the sterically hindered pivalic acid, the acylation products (**3e**) were obtained in 69% yield. With trifluoroacetic acid, acylation was only observed in the case of benzoic acid (which shows only low reactivity in the reaction). The attempted formylation of 2-methylthiophene with formic acid failed under our conditions[11].

The reactivity of the aromatic and heteroaromatic substrates decreases from furan and the methylthiophenes to polymethylbenzenes and benzenoid-type substrates. In cases, in which mixtures of isomers may be formed, the isomer ratios are as expected from the literature[12].

The products prepared under mild conditions are practically pure (by T.L.C., G.L.C., I.R., and N.M.R.) and are obtained in high yields. When the reaction is carried out under more vigorous conditions, chromatographic separation of the product from tarry material is necessary.

The present method is advantageous in terms of the mild conditions employed, the ease of performance, and the ready availability of the starting materials. It avoids the separate preparation of the mixed anhydride or the conversion of the carboxylic acid to its chloride which is the most common reagent in most Friedel-Crafts acylations. The yields are generally good and reproducible. The homogeneous reaction conditions proved to be suitable for a kinetic study of acylations to be reported in a forthcoming publication.

3- and 4-Methyl-2-(1-oxododecyl)-thiophene (3d); Typical Procedure:

A dried three-neck flask with stirrer, calcium chloride drying tube, and dropping funnel is charged with dodecanoic acid (**2**, R = *n*-$C_{11}H_{23}$; 0.45 g, 2.3 mmol), 3-methylthiophene (0.70 g, 7.1 mmol), 85% phosphoric acid (0.27 g, 2.3 mmol), and anhydrous acetonitrile (15 ml; distilled from phosphorus pentoxide). The mixture is stirred at 50° and a solution of trifluoroacetic anhydride (1.25 ml, 8.7 mmol) in anhydrous acetonitrile (6 ml) is rapidly added from the dropping funnel. The clear solution becomes opaque and, eventually, pink. After 30 min, water (40 ml) is added and the mixture is extracted with ether (3 × 30 ml). The organic extract is extracted with aqueous sodium hydrogen carbonate, washed with water, and dried with sodium sulfate. The solvent is removed under reduced pressure to leave a mixture of the isomeric compounds **3d** as a pale yellow liquid which gives only two spots on T.L.C. (silica gel, benzene as eluent, Rf 0.41 and 0.48); yield: 0.63 g. The product is purified by distillation in vacuo; yield: 0.54 g (85%); b.p. 162–166°/0.7 torr; n_D^{22}: 1.5083.

$C_{17}H_{28}OS$	calc.	C 72.80	H 10.06
(280.5)	found	72.63	9.81

I.R. (CCl_4): $\nu_{C=O}$ = 1670 cm^{-1}.

^{1}H-N.M.R. (CCl_4, 60 MHz):

2,3-Isomer: δ = 7.20 (d, 5-$H_{thiophene}$, J = 6 Hz); 6.80 (d, 4-$H_{thiophene}$, J = 6 Hz); 2.50 ppm (s, 3H, thiophene-$C\underline{H}_3$).

2,4-Isomer: δ = 7.45 (bs, 5-$H_{thiophene}$); 7.05 (bs, 3-$H_{thiophene}$); 2.25 ppm (s, 3H, thiophene-$C\underline{H}_3$).

The integrals of these signals (5H overall) are consistent with an isomer ratio of 3:1 with the 2,3-isomer predominating.

G.L.C. analysis (1 m column packed with 2% SE 30 plus 0.4% FFAP on silanized chromosorb W 60–80, operated at 176°) of the mixture gives only two peaks in a 3:1 ratio.

Besides the ^{1}H-N.M.R. signals listed above, the following signals are present in the spectrum: δ = 2.8 (t, 2H, $C\underline{H}_2$–CO); 1.4–1.2 (bs, 18H, 9 "central" CH_2); 0.9 ppm (t, 3H, ω-$C\underline{H}_3$).

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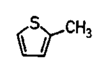
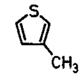
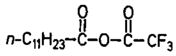
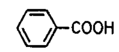
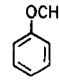
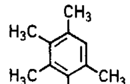
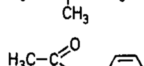
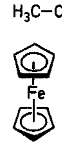
Table. Ketones (**3**) by Acylation of Arenes and Heteroarenes (**1**) with *in situ* Generated Mixed Anhydrides of Alkanoic Acids (**2**) and Trifluoroacetic Acid

	1	**2**	Temperature	Time [min]	Yield of **3**[a] [%]	b.p./torr[b] or m.p. (n_D)	Molecular formula[c] or Physical data reported
a		$n\text{-}C_3H_7-COOH$	20°	30	75	b.p. 100–101°/23 torr (n_D^{19}: 1.4950)	b.p. 95–97°/19 torr[13] (n_D^{25}: 1.4922)
b		$n\text{-}C_4H_9-COOH$	20°	4	78	b.p. 144–145°/17 torr (n_D^{18}: 1.5358)	$C_{10}H_{14}OS$ (182.3)
		$n\text{-}C_{11}H_{23}-COOH$	50°	8	81	m.p. 37–39° (methanol)	$C_{17}H_{28}OS$ (280.5)
c		$n\text{-}C_4H_9-COOH$	50°	10	79[d]	b.p. 141–143°/19 torr (n_D^{15}: 1.5358)	$C_{10}H_{14}OS$ (182.3)
			50°	40	34[e]	—	—
d		$n\text{-}C_{11}H_{23}-COOH$	50°	30	85[d]	b.p. 162–166°/0.7 torr (n_D^{22}: 1.5083)	$C_{17}H_{28}OS$ (280.5)
		 $n\text{-}C_{11}H_{23}-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CF_3$	50°	80[f]	58[d]	—	
e		$t\text{-}C_4H_9-COOH$	50°	60	69[g]	b.p. 123–125°/19 torr (n_D^{20}: 1.5286)	$C_{10}H_{14}OS$ (182.3)
f			reflux	180	48[h]	—	—
g		$H_3C-COOH$	reflux	20	77	b.p. 107–108°/19 torr (n_D^{23}: 1.5640)	b.p. 77°/4 torr[12] (n_D^{20}: 1.5666)
h		$n\text{-}C_{11}H_{23}-COOH$	50°	120	82	b.p. 153–160°/0.8 torr (n_D^{21}: 1.5074)	$C_{16}H_{26}OS$ (266.4)
i		$H_3C-COOH$	reflux	80	66[i]	b.p. 146–148°/25 torr[j]	b.p. 139°/15 torr[14]
j		$H_3C-COOH$	reflux	15h	23[i]	m.p. 80–82° (methanol)	m.p. 85° (ethanol)[15]
k		$H_3C-COOH$	50°	15h	none[k]		
l		$H_3C-COOH$	20°	30	70[i]	m.p. 81–83° (cyclohexane)	m.p. 85–86° (isooctane)[16]

[a] Yield of distilled product, based on **2**.

[b] Uncorrected.

[c] The microanalyses of the new compounds (except **3c**) were in satisfactory agreement with the calculated values; maximum deviations: C, ±0.34; H, ±0.25; **3c:** C, −0.48; H, −0.19.

[d] 2,3- to 2,4-isomer ratio is 3:1.

[e] Without phosphoric acid.

[f] The reaction was carried out with isolated dodecanoyl trifluoroacetate.

[g] 2,3- to 2,4-isomer ratio is 1.5:1.

[h] Yield of crude product, estimated from I.R. spectrum. A ~1:1 mixture of **3f** and the trifluoroacetylated compound was obtained; the mixture was not seperated.

[i] Yield of pure product obtained from column chromatography.

[j] 4-Methoxyacetophenone, 99% pure by G.L.C. analysis.

[k] Quantitative recovery of acetanilide.

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[1] G. A. Olah, *Friedel-Crafts and Related Reactions*, Vol. III, Part 1, Interscience Publishers, New York, 1964.
D. E. Pearson, C. A. Buehler, *Synthesis* **1972**, 533.
C. W. Schellhammer, in: Houben-Weyl, *Methoden der Organischen Chemie*, 4th Ed., E. Müller, Ed., Vol. VII/2a, Georg Thieme Verlag, Stuttgart, 1973, p. 311.

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

[3] E. J. Bourne, M. Stacey, J. C. Tatlow, R. Worrall, *J. Chem. Soc.* **1954**, 2006.

[4] R. J. Ferrier, J. M. Tedder, *J. Chem. Soc.* **1957**, 1435.

[5] F. Effenberger, G. Epple, *Angew. Chem.* **84**, 294 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 299 (1972).

[6] C. G. Overberger, E. Sarlo, *J. Am. Chem. Soc.* **85**, 2446 (1963).

[7] For comprehensive reviews, see:
J. M. Tedder, *Chem. Rev.* **55**, 787 (1955).
D. P. N. Satchell, *Quart. Rev.* **17**, 160 (1963).
G. Marino, *Adv. Heterocyclic Chem.* **13**, 235 (1971).

[8] C. D. Hurd, M. F. Dull, *J. Am. Chem. Soc.* **54**, 3427 (1932).

[9] E. J. Bourne, M. Stacey, J. C. Tatlow, J. M. Tedder, *J. Chem. Soc.* **1951**, 718.

[10] For similar cases, see:
W. E. Parham et al., *J. Am. Chem. Soc.* **76**, 4957 (1954).
J. Lamy, D. Lavit, N. P. Buu-Hoi, *J. Chem. Soc.* **1958**, 4202.

[11] H. D. Hartough, A. I. Kosak, *J. Am. Chem. Soc.* **69**, 3098 (1947).

[12] H. D. Hartough, A. I. Kosak, *J. Am. Chem. Soc.* **69**, 3093 (1947).

[13] H. Gilman, N. O. Calloway, *J. Am. Chem. Soc.* **55**, 4197 (1933).

[14] C. R. Noller, R. Adams, *J. Am. Chem. Soc.* **46**, 1893 (1924).

[15] O. Jacobsen, *Ber. Dtsch. Chem. Ges.* **22**, 1218 (1889).

[16] V. Weinmayr, *J. Am. Chem. Soc.* **77**, 3009 (1955).