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C-TRIFLUOROACYLATION - A CONVENIENT ROUTE TO CARBOXYLIC ACIDS

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SUMMARY

Trifluoroacetic anhydride will trifluoroacylate reactive aromatic and heterocyclic nuclei without the aid of a Friedel-Crafts catalyst. The resulting trifluoromethyl ketone undergoes hydrolysis to yield the corresponding carboxylic acid. This provides a very simple route to aromatic and heterocyclic carboxylic acids.

INTRODUCTION

In 1949 Professor Stacey in collaboration with the late E. J. Bourne and J. C. Tatlow initiated a study of the chemistry of trifluoroacetic acid. It was discovered that solutions of carboxylic acids (RCO_2H) dissolved in trifluoroacetic anhydride were powerful acylating media reacting with hydroxy compounds to yield esters of the solute carboxylic acid and with reactive aromatic compounds to yield ketones (ArCOR) [1, 2]. The mechanism of the reaction was investigated and it was shown that the solute carboxylic acid when dissolved in trifluoroacetic anhydride yielded an equilibrium mixture which ionised very slightly to yield the acylium ion RCO^+ [3].

$$RCO_2H + (CF_3CO)_2O \rightleftharpoons RCO\cdot O\cdot COCF_3 + CF_3CO_2H$$

$$RCO\cdot O\cdot COCF_3 \rightleftharpoons RCO^+ + CF_3CO_2^-$$

In the course of these studies the effect of base on the equilibrium was investigated and it was found that trifluoroacetic anhydride alone reacted with N, N-dimethylaniline to yield the trifluoromethyl ketone [4].

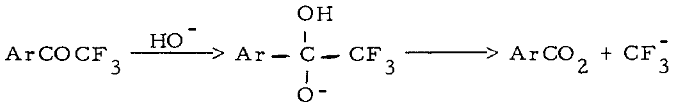
$$Me_2NC_6H_5 + (CF_3CO)_2O \longrightarrow Me_2NC_6H_4COCF_3 + CF_3CO_2H$$

Subsequently the reaction was shown to be extended to other substituted dialkyl anilines [5]. In the years since this work there have been a few isolated accounts of C-trifluoroacetylation [6] but there has been no attempt, as far as we are aware, to develop this reaction for synthetic purposes.

RESULTS AND DISCUSSION

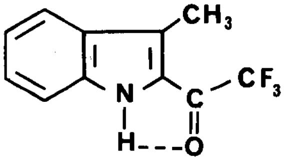
N, N-Dimethyl and N, N-diethylaniline are converted into the p-dialkylamino-α, α, α-trifluoroacetophenones by refluxing amines with excess of trifluoroacetic anhydride in ether. These same conditions were successfully applied to the heterocyclic nuclei pyrrole, indole, 3-methylindole and 2, 4-dimethylthiophen and to the homocyclic 1, 3, 5-trimethoxybenzene. Attempts were made to trifluoroacylate 1, 3-dimethoxybenzene, furan and unsubstituted thiophen without success. It was perhaps surprising the 3-methylindole acylated in the 2-position so easily.

The hydrolyses were performed in a mixture of ethanol and aqueous sodium hydroxide. Two compounds proved completely resistant to this hydrolysis; the trifluoroacetyl ketone derived from 3-methylindole and 1, 3, 5-trimethoxybenzene. Steric hinderance is clearly the cause of resistance of 1, 3, 5-trimethoxy-α, α, α-trifluoroacetophenone to hydrolysis since the tetrahedral intermediate cannot form



$$ArCOCF_3 \xrightarrow{HO^-} Ar-\underset{O^-}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-CF_3 \longrightarrow ArCO_2 + CF_3^-$$

However it is surprising that the trifluoroacetyl group in 3-methyl-2-trifluoroacetyl indole flanked by the 3-methyl group and the hydrogen atom on the nitrogen should also resist hydrolysis when 5-trifluoroacetyl-2, 4-dimethylthiophen hydrolyses readily. Apparently in the former compound a strong hydrogen bond must be formed so that the 3-methyl group prevents a



"back-end" approach to the carbonyl which is available in the 3-tri-fluoroacetylindole.

EXPERIMENTAL

p-Dimethylamino-α, α-α-trifluoroacetophenone (nc)

Trifluoroacetic anhydride (7 ml) was added to a solution of N, N-dimethylaniline (2. 4 g) in 10 ml of ether, and refluxed for three hours. The solution was cooled, washed with water and an aqueous solution of sodium hydrogen carbonate, and then dried over anhydrous sodium sulphate. Evaporation of the ether left a yellow crystalline residue (1. 7 g; 40%) which was recrystallised from aqueous ethanol to yield p-dimethylamino-α, α, α-trifluoroacetophenone [4] as flat yellow plates (1. 36 g) m. p. 74. 5-75. 5°. NMR ($CDCl_3$) δ 3. 0 (s, 6H) AA'BB' 6. 45-6. 6 and 7. 8-7. 95 (4H): (Found: C, 54. 99; H, 4. 71; N, 6. 48. $C_{10}H_{10}NOF_3$ requires C, 55. 3; H, 4. 46; N, 6. 45%) ν_{max} 1665 (C=O); m/e 217 (M^+).

p-Dimethylaminobenzoic acid

p-Dimethylamino-α, α, α-trifluoroacetophenone (0. 8 g) was dissolved in ethanol (7 ml) and sodium hydroxide (20 ml; 5N) was added. The solution was refluxed for 4 hr and the ethanol removed on a rotary evaporator. The residual solution was acidified with concentrated hydrochloric acid added dropwise to give a white precipitate of p-dimethylaminobenzoic acid (0. 45 g; 75%) m. p. 235° (lit. 235° [7]) (from aqueous ethanol); (Found: C, 64. 93; H, 6. 44; N, 8. 19. Calcd. for $C_9H_{11}NO_2$: C, 65. 44; H, 6. 71; N, 8. 48%)

$\nu_{max.}$ 1700 (C=O); m/e 165 (M^+); (CD_3COCD_3) δ 3.0 (s, 6H) AA'BB' 6.65-6.8 and δ 7.75-7.9 (4H) 10-11 (b, H).

p-Diethylamino-α, α, α-trifluoroacetophenone (nc)

Trifluoroacetic anhydride (7 ml) was added to a solution of N, N-diethylaniline (3 g) in 10 ml of ether and refluxed for 3 hr. The solution was cooled, washed with water and an aqueous solution of sodium hydrogen carbonate, then dried over anhydrous sodium sulphate. Evaporation of the ether left a thick viscous liquid (2.1 g; 43%) which resisted attempts at crystallisation. Accurate mass 245.102537; $C_{12}H_{14}OF_3N$ requires 245.102732.

p-Diethylaminobenzoic acid

p-Diethylamino-α, α, α-trifluoroacetophenone (0.9 g) was dissolved in ethanol (7 ml) and sodium hydroxide (20 ml, 5 N) was added. The solution was refluxed for 4 hr and the ethanol removed on a rotary evaporator. The residual solution was acidified with concentrated hydrochloric acid added dropwise to give a white precipitate of p-diethylaminobenzoic acid (0.5 g; 72%) m.p. 190° (lit. 188° [8]; 193° [9]) (from aqueous ethanol). (Found: C, 68.17; H, 7.86; N, 7.50. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25). ν_{max} 1650 (C=O), m/e 193 (M^+); ($CDCl_3$) δ 1.25 (t, 6H); 3.4 (q, 4H) AA'BB' 6.55-6.7 and 7.8-8 (4H).

2, 4, 6-Trimethoxy-α, α, α-trifluoroacetophenone (nc)

Trifluoroacetic anhydride (7 ml) was added to a solution of 1, 3, 5-trimethoxybenzene (3.4 g) in 10 ml of ether, and refluxed for 3 hr. When cool, the solution was washed with sodium hydrogen carbonate solution and with water and dried over sodium sulphate. Evaporation of the ether layer gave a white crystalline residue (4 g; 75.8%) was recrystallised from aqueous ethanol to yield 2,4,6-trimethoxy-α,α,α-trifluoroacetophenone as white crystals (3.5 g) m.p. 56°C. (Found: C, 49.75; H, 4.15; $C_{11}H_{11}O_4F_3$ requires: C, 50.01; H, 4.15%) ν_{max} 1600 (C=O) m/e 264 (M^+); ($CDCl_3$) δ 3.8 (s, 9H); 6.1 (s, 2H).

Attempted hydrolysis of 2,4,6-trimethoxy-α,α,α-trifluoroacetophenone

2,4,6-trimethoxy-α,α,α-trifluoroacetophenone (1.1 g) was dissolved in ethanol (7 ml) and sodium hydroxide (20 ml; 5 N) was added. The solution was refluxed for 4 hr. A test sample was washed with sodium hydrogen carbonate solution and water and the ethanol removed by evaporation. The residual solution was acidified with concentrated hydrochloric acid. No 2,4,6-trimethoxybenzoic acid could be detected. The remaining solution was refluxed for a further 12 hr with similar results.

2-Pyrrolyltrifluoromethyl ketone

Trifluoroacetic anhydride (7 ml) was added to dry ether (60 ml), and a solution of pyrrole (3 g) in 8 ml of ether, was added dropwise. The reaction was run for 6 hr at a temperature just below 0°, with stirring. The solution was washed with an aqueous solution of sodium hydrogen carbonate and water, then dried over anhydrous sodium sulphate. The ether was removed on a rotary evaporator to yield 2-pyrrolyltrifluoromethyl ketone (5 g: 68%), which was recrystallised from ether, m.p. 46°C (lit. 46°C [10]); ($CDCl_3$) δ 6.8-7.1 (m, 2H); 6.0-6.2 (m, 1H); 9.2-10.6 (b, 1H).

Pyrrole-2-carboxylic acid

2-Pyrrolyltrifluoromethyl ketone (0.6 g) was dissolved in ethanol (7 ml) and sodium hydroxide (20 ml; 5 N) was added. The solution was refluxed for 4 hr and the ethanol removed on a rotary evaporator. The solution was acidified by dropwise addition of conc. HCl until a thick pinkish white precipitate was obtained (0. 36 g, 92%) recrystallised from aqueous ethanol. m. p. 207° decomp. (lit. 208. 5 [11]) (Found: C, 53. 8; H, 4. 46; N, 12. 58; Calcd. for $C_5H_5NO_2$: C, 54. 06; H, 4. 54; N, 12. 61%). ν_{max} 1625 (C=O), 3200-3400 (b, -OH), m/e 111 (M^+); ($CDCl_3$) δ 6. 15 (s, 1H), 6. 8-7. 1 (d, 2H); 9. 5 (s, 1H); 10. 1-12. 0 (b, 1H).

3-Indolyl trifluoromethyl ketone (nc)

Trifluoroacetic anhydride (7 ml) to 60 ml of dry ether and a solution of indole (2. 34 g) in 10 ml of dry ether was added dropwise. The reaction mixture was stirred for 6 hr below 0°C washed with sodium hydrogen carbonate solution and water, extracted with ether and dried (Na_2SO_4). Evaporation of the ether gave 3-indolyl trifluoromethyl ketone (3. 85 g; 90%) recrystallised from aqueous ethanol m. p. 208°C. (Found: C, 56. 09; H, 1. 62; N, 6. 51; $C_{10}H_6ONF_3$ requires C, 56. 35; H, 2. 83; N, 6. 57%) ν_{max} 1625 (C=O); m/e 213 (M^+) 184 (M^+ - 29) 144 (M^+ - 69); δ (8. 3-8. 6) (m, 2H); 7. 2-7. 8 (m, 3H); 11. 0-12. 2 (b, 1H).

Indole-3-carboxylic acid

3-Indolyl trifluoromethyl ketone (0. 8 g) was dissolved in ethanol (7 ml) and sodium hydroxide (20 ml; 5N) and the solution was refluxed for 4 hr. The ethanol was evaporated and the residual solution acidified with concentrated hydrochloric acid. Indole-3-carboxylic acid was obtained as a creamy precipitate (0. 45 g, 78%). After recrystallisatior from aqueous ethanol it had m. p. 222°C decomp. (lit. 210-218[10]) (Found: C, 66. 9; H, 4. 43; N, 8. 52; M^+ m/e 161. 0471; calcd. for $C_9H_7O_2N$; C, 67. 076, H, 4. 378; N, 8. 691% M^+ m/e 161. 0469) δ 4. 6-6. 0 (b, H); 7. 0-7. 65 (m, 3H); 7. 95-8. 8 (m, 2H); 10. 0-11. 5 (b, 1H).

2-(3-Methyl)indolyl trifluoromethyl ketone (nc)

Trifluoroacetic anhydride (7 ml) was dissolved in dry ether (60 ml). 3-Methylindole (2.62 g) also in dry ether (10 ml) was added dropwise, and the reaction mixture stirred for 6 hr. below 0°C. The mixture was washed with an aqueous solution of sodium hydrogen carbonate, evaporation of the ether left a brown tarry material which on vacuum distillation gave yellow crystals of 2-(3-methyl)indolyl trifluoromethyl ketone (1.45 g; 32%) m.p. 109-111°C. m/e 227 (M^+), ν_{max} 1630 (C=O); ($CDCl_3$) δ 2.65 (s, 3H); 7.0-7.8 (m, 4H); 8.4-9.2 (b, 1H); (Found: M^+ m/e 227.0561 $C_{11}H_8OF_3N$ requires M^+ m/e 227.0558).

Attempted hydrolysis of 2-(3-Methyl)indolyl trifluoromethyl ketone.

2-(3-Methyl)indolyl trifluoromethyl ketone was added to 7 ml of ethanol and aqueous sodium hydroxide (20 ml; 5 N). The solution was refluxed for 4 hr. Thin layer chromatography carried out on a test sample indicated that the starting product was unchanged. It was refluxed for a further 12 hr whereupon a mixture of the starting product and traces of 3-methylindole were obtained.

Attempted C-Trifluoroacylation of 1, 3-dimethoxybenzene

Trifluoroacetic anhydride (7 ml) was added to resorcinol dimethyl ether (2.8 g) in ether (10 ml). The solution was refluxed for 4 hr and then for a further 12 hr but no product was obtained.

2-(3, 5-Dimethyl)thienyl trifluoromethyl ketone (nc)

Trifluoroacetic anhydride (7 ml) was added to a solution of 2, 4-dimethy thiophen (2.24 g) in 10 ml) of ether and refluxed for 48 hr. The product was washed with sodium hydrogen carbonate solution and with water and dried (Na_2SO_4). A viscous yellow solution was obtained after removal of the ether. A g.l.c. was run and the mass spectrum indicated that the product was mainly the monotrifluoroacetylated dimethylthiophen.

m/e 208 (M^+). On distillation a colourless liquid was obtained (2. 2 g; 53%) b. p. 60°C, 3mm, (Found: M^+ m/e 208. 0157 $C_8H_7OF_3S$ requires m/e 208. 0169 ν_{max} 1630 (C=O).

3, 5-Dimethyl-thiophen-2-carboxylic acid

2-(3, 5-Dimethyl)thienyl trifluoromethyl ketone was dissolved in ethanol (10 ml) and refluxed for 3 hr after adding sodium hydroxide (40 cc; 5 N). The ethanol was evaporated and the residual solution acidified by dropwise addition of concentrated hydrochloric acid, giving a white precipitate (1. 5 g; 96%) which was recrystallised from aqueous ethanol m. p. 168°C (lit. 171-172°C) [12] (Found: C, 53. 38; H, 5. 61; calcd. for $C_7H_8O_2S$: C, 53,83; H, 5. 16%); ν_{max} 1650 (C=O); m/e 156 (M^+); δ 2. 5 (s, 6H); 5. 9 (s, 1H); δ 10. 5-11. 3 (b, H).

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TABLE

The Yields of Trifluoromethyl Ketone and Carboxylic Acid

$$ArH + (CF_3CO)_2O \longrightarrow ArCOCF_3 \longrightarrow ArCO_2H$$

Starting Material	trifluoromethyl ketone	carboxylic acid
$(CH_3)_2N\cdot C_6H_5$	p-$(CH_3)_2N\cdot C_6H_7\cdot COCF_3$ (40%)	p-$(CH_3)_2N\cdot C_6H_4\cdot CO_2H$ (75%)
$(C_2H_5)_2N\cdot C_6H_5$	p-$(C_2H_5)_2N\cdot C_6H_7\cdot COCF_3$ (43%)	p-$(C_2H_5)N\cdot C_6H_4\cdot CO_2H$ (72%)
1, 3, 5-$(CH_3O)_3C_6H_3$	2, 4, 6-$(CH_3O)_3C_6H_2\cdot COCF_3$ (76%)	- (0%)
$C_{10}H_8$ (Azulene)[6]	1-$C_{10}H_7\cdot COCF_3$	1-$C_{10}H_7\cdot CO_2H$
C_4H_7NH (pyrrole)	2-$(CF_3CO)C_4H_3NH$ (68%)	2-$C_4H_3NH\cdot CO_2H$ (92%)
2, 4-$(CH_3)_2C_4H_2S$	3, 5-$(CH_3)_2$, 2-$COCF_3\cdot C_4HS$ (53%)	3, 5-$(CH_3)_2C_4HS\cdot CO_2H$ (96%)
C_8H_6NH (Indole)	3-$(CF_3CO)\cdot C_8H_5NH$ (90%)	3-$C_8H_5NH\cdot CO_2H$ (78%)
3-$(CH_3)C_8H_5NH$	2-(CF_3CO)-3-$(CH_3)\cdot C_8H_9NH$ (32%)	- (0%)