155. *Studies of Trifluoroacetic Acid. Part III. The Use of Trifluoroacetic Anhydride in the Synthesis of Aromatic Ketones and Sulphones.*

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Trifluoroacetic anhydride is shown to promote, under mild conditions, the condensation between suitably activated aromatic compounds and carboxylic acids or sulphonic acids, to give ketones or sulphones, respectively.

The discovery that trifluoroacetic anhydride can be employed to promote ester formation between hydroxy-compounds and carboxylic acids (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976) suggested that it might be possible to utilise this halogenated anhydride for the preparation of ketones directly from aromatic compounds and carboxylic acids. Monochloroacetic anhydride (Unger, *Annalen*, 1933, **504**, 267), aluminium chloride (Groggins, Nagel, and Stirton, *Ind. Eng. Chem.*, 1934, **26**, 1317), hydrogen fluoride (Simons, Randall, and Archer, *J. Amer. Chem. Soc.*, 1939, **61**, 1795), and phosphoric anhydride (Kosolapoff, *ibid.*, 1947, **69**, 1651; Hartough and Kosak, *ibid.*, p. 3098) have all been employed as condensing agents in this type of reaction.

The reactions now reported show that mixtures of trifluoroacetic anhydride and carboxylic acids give good yields of ketones from polyalkylbenzenes, phenyl ethers, furan, and thiophen, under mild conditions. Under similar conditions small yields of ketones were obtained from the xylenes, but there was no detectable reaction with benzene or toluene. The carboxylic acids employed were acetic, benzoic, and cinnamic acids.

In general, the aromatic compound (1 mol.) was added to a solution of the carboxylic acid (1—1·5 mols.) in trifluoroacetic anhydride (1·5—2·5 mols.) and left for a few hours, the reaction mixture being gently warmed (maximum, 60°) when necessary. The solution was then poured into aqueous sodium hydrogen carbonate and the ketone isolated by suitable solvent extraction. An attempt to effect the acetylation of toluene by the use of more drastic reaction conditions

(110° for 6 hours) led to considerable charring and still afforded little or no *p*-methylacetophenone.

In two experiments trifluoroacetic anhydride was replaced by heptafluorobutyric anhydride, but with this reagent the yield of *p*-methoxyacetophenone from anisole and acetic acid fell from about 80% to 18%, whilst toluene still could not be acetylated.

In a reaction analogous to the ketone synthesis, trifluoroacetic anhydride can be used for the production of sulphones from aromatic compounds and sulphonic acids, and *p*-methoxyphenyl *p*-tolyl sulphone and mesityl *p*-tolyl sulphone were thus prepared.

It seems probable that, in the above syntheses of ketones and sulphones, and also in the production of esters directly from carboxylic acids and hydroxy-compounds (Bourne, Stacey, Tatlow, and Tedder, *loc. cit.*), the trifluoroacetic anhydride functions by forming a mixed anhydride with the carboxylic acid or sulphonic acid in question. The mechanism of the reaction is now under investigation, and it is already evident that an equilibrium exists in the acid–anhydride system, since an acetic anhydride–trifluoroacetic acid mixture and an acetic acid–trifluoroacetic anhydride mixture show similar properties in that they both react (*a*) with hydroxy-compounds to give acetate esters (Bourne, Stacey, Tatlow, and Tedder, *loc. cit.*, and unpublished results), and (*b*) with suitably activated aromatic compounds to give methyl ketones [cf. Newman (*J. Amer. Chem. Soc.*, 1945, **67**, 345) who has shown that an acetic anhydride–trifluoroacetic acid mixture reacts with anisole to give *p*-methoxyacetophenone].

Experimental.

p-*Methoxyacetophenone.*—(*a*) Anisole (0·52 c.c.) was added to a mixture of trifluoroacetic anhydride (1·20 c.c.) and acetic acid (0·42 c.c.). After being kept at room temperature for 3 hours, the solution was poured into excess of sodium hydrogen carbonate solution and then exhaustively extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated to a syrup, which was distilled at 90—95° (bath-temp.)/0·001 mm. The distillate (0·56 g., 78%), crystallised from light petroleum (b. p. 40—60°), had m. p. 38°. Baranger (*Bull. Soc. chim.*, 1931, [iv], **49**, 1213) gave m. p. 38—39° for *p*-methoxyacetophenone.

(*b*) The experiment was repeated with the same quantities of reagents, but under different reaction conditions, as tabulated below. The product was isolated as its semicarbazone, m. p. 198—200° (Found: C, 57·7; H, 6·1. Calc. for $C_{10}H_{13}O_2N_3$: C, 58·0; H, 6·3%). Baranger (*loc. cit.*) recorded m. p. 202° for this compound.

Reaction temp. (± 2°)	18°	18°	18°	18°	2°	45°	75°
Reaction time (mins.)	10	20	40	150	150	150	150
Yield of semicarbazone (%)	37	64	66	81	57	69	57

(*c*) Anisole (0·26 c.c.) was added to a mixture of heptafluorobutyric anhydride (1·00 c.c.) and acetic acid (0·15 c.c.). The mixture was kept at 18° for 3 hours before being treated with sodium hydrogen carbonate solution as above. The product, isolated as its semicarbazone (0·09 g., 18%), had m. p. 198—199°.

p-*Ethoxyacetophenone.*—Phenetole (0·50 c.c.) was added to a mixture of acetic acid (0·40 c.c.) and trifluoroacetic anhydride (0·70 c.c.), and the mixture was kept at 21° for 3 hours. The solution was neutralised with aqueous sodium hydrogen carbonate and exhaustively extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated to yield a crystalline solid. Recrystallisation from light petroleum (b. p. 40—60°) afforded flat hexagonal plates (0·59 g., 89%), m. p. 36—37° (Found: C, 73·4; H, 7·5. Calc. for $C_{10}H_{12}O_2$: C, 73·1; H, 7·4%). The product gave a semicarbazone, m. p. 182°. Unger (*loc. cit.*) gave m. p. 37—38° for *p*-ethoxyacetophenone and m. p. 181·5° for its semicarbazone.

p-*Methoxybenzophenone.*—Benzoic acid (0·61 g.) was dissolved in trifluoroacetic anhydride (1·60 c.c.), and anisole (0·50 c.c.) was added. The reaction mixture was kept at 50—60° for 5 hours. The crude product, isolated as above, was crystallised from alcohol to give *p*-methoxybenzophenone (0·54 g., 56%), m. p. 62° (Found: C, 79·4; H, 5·5. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%). Rennie (*J.*, 1882, **41**, 220) gave m. p. 61—62°.

ω-Benzylidene-p-*methoxyacetophenone.*—Anisole (0·50 c.c.) was added to a solution of cinnamic acid (0·74 g.) in trifluoroacetic anhydride (1·20 c.c.) and the mixture was warmed at 45° for 1 hour. Extracted as above, the crude ketone was distilled at 285° (bath-temp.)/15 mm. The distillate, recrystallised from alcohol, afforded *ω*-benzylidene-*p*-methoxyacetophenone (0·90 g., 82%), m. p. 106° (Found: C, 81·0; H, 6·0. Calc. for $C_{16}H_{14}O_2$: C, 80·7; H, 5·9%). Stockhausen and Gattermann (*Ber.*, 1892, **25**, 3536) gave m. p. 106—107°.

2 : 4 : 6-*Trimethylbenzophenone.*—Mesitylene (1·00 c.c.) was added to a solution of benzoic acid (0·99 g.) in trifluoroacetic anhydride (1·50 c.c.). The mixture was heated at 60° for 3 hours and the crude ketone was isolated as above. Distillation at 208—212° (bath-temp.)/15 mm. gave a viscous syrup (0·83 g., 52%) (Found: C, 85·4; H, 7·4. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·2%). Nitration gave fine yellow needles, m. p. 203°. Fuson and Armstrong (*J. Amer. Chem. Soc.*, 1941, **63**, 2650) recorded b. p. 135—140°/4 mm. for 2 : 4 : 6-trimethylbenzophenone, and m. p. 202—204° for its trinitroderivative.

2-*Acetylthiophen.*—Thiophen (0·50 c.c.) was added to a solution of acetic acid (0·50 c.c.) in trifluoro-

acetic anhydride (1·00 c.c.) and the mixture was warmed at 40—50° for 1 hour. The crude ketone was isolated as above and converted directly into its semicarbazone. Recrystallised from water, the product (0·59 g., 50%) had m. p. 192° (Found: C, 46·2; H, 5·0. Calc. for $C_7H_9ON_3S$: C, 45·9; H, 5·0%). Steinkopf and Jaffé (*Annalen*, 1917, **413**, 333) gave m. p. 190—191° for 2-acetylthiophen semicarbazone.

2-*Acetylfuran*.—Acetic acid (0·50 c.c.) was mixed with trifluoroacetic anhydride (1·50 c.c.), and furan (0·50 c.c.) was added. After 1 hour at room temperature the crude ketone was isolated as above. Distillation at 75° (bath-temp.)/11 mm. afforded 2-acetylfuran (0·32 g., 43%), m. p. 29—30°. The ketone gave a semicarbazone, m. p. 147—148° (Found: C, 49·8; H, 5·5. Calc. for $C_7H_9O_2N_3$: C, 50·3; H, 5·4%). Bouveault (*Ber.*, 1901, **34**, 1072) gave m. p. 28·5° for the ketone and m. p. 148° for its semicarbazone.

p-*Methoxyphenyl* p-*Tolyl Sulphone*.—Toluene-*p*-sulphonic acid monohydrate (1·05 g.) was warmed with trifluoroacetic anhydride (3·5 c.c.) at 40° for 15 minutes before anisole (0·50 c.c.) was added. Heating was continued at 60—70° for 4 hours and the crude sulphone was isolated as above. Two recrystallisations from aqueous alcohol gave the sulphone (0·55 g., 46%), m. p. 103—104° (Found: C, 63·9; H, 5·5. Calc. for $C_{14}H_{14}O_3S$: C, 64·1; H, 5·4%). Burton and Hu (*J.*, 1948, 601) recorded m. p. 104—105° for this substance.

Mesityl p-*Tolyl Sulphone*.—Mesitylene (0·50 c.c.) was added to a solution of toluene-*p*-sulphonic acid monohydrate (0·89 g.) in trifluoroacetic anhydride (1·50 c.c.). The whole was heated at 50—60° for 4 hours and the crude sulphone was isolated in the manner already described. The pure product (0·64 g., 64%), m. p. 119—120°, was obtained by two crystallisations from light petroleum (b. p. 60—80°) (Found: C, 70·0; H, 6·6. Calc. for $C_{16}H_{18}O_2S$: C, 70·0; H, 6·6%). Meyer (*Annalen*, 1923, **433**, 327) reported m. p. 119° for mesityl *p*-tolyl sulphone.

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