

Synthesis of Benzophenones: Anomalous Friedel–Crafts Reactions

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A Friedel–Crafts reaction between 2,6-dimethoxybenzoyl chloride and benzene yields 2,6-dimethoxybenzophenone and 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone, and under milder conditions, 3-carboxy-2,2',4,6'-tetramethoxybenzophenone. A synthesis and the degradation under acid conditions of 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone are described.

DURING the synthesis of a number of substituted benzophenones for other studies we observed an anomalous Friedel–Crafts reaction. When benzene and 2,6-dimethoxybenzoyl chloride (I) are heated under reflux with aluminium chloride two products are formed, namely 2,6-dimethoxybenzophenone (V) and 3-benzoyl-

2,2',4,6'-tetramethoxybenzophenone (IV). If the reaction is carried out in ether at room temperature, however, the only product is 3-carboxy-2,2',4,6'-tetramethoxybenzophenone [isolated as the methyl ester (III)]. The structures of the products follow from their analysis and u.v., i.r., and n.m.r. spectral data, and were confirmed

Degradation of (IV) by heating under reflux with hydriodic acid yields carbon dioxide, resorcinol, benzoic acid, 1,6-dihydroxyxanthone [isoeuxanthone (VIa)] and 5-benzoyl-1,6-dihydroxyxanthone (VIb). The formation of these products can be explained on the assumption that after initial demethylation at least two reaction sequences occur: (a) cyclisation to the xanthone (VIb) followed by debenzoylation, and (b) cleavage of the diketone at the positions indicated in (IV). Other instances of the cleavage by acids of substituted benzophenones to give phenols and aromatic acids are recorded.¹

¹ J. W. ApSimon, J. A. Corran, N. G. Creasey, W. Marlow, W. B. Whalley, and K. Y. Sim, *J. Chem. Soc.*, 1965, 4144; C. R. Calam, P. W. Clutterbuck, A. E. Oxford, and H. Raistrick, *Biochem. J.*, 1939, **33**, 579; H. Nishikawa, *Acta Phytochim. (Japan)*, 1939, **11**, 167, and earlier references.

⁴ A. Russell and J. R. Frye, *Org. Synth.* 1955, Coll. Vol. 3, 282.

2,6-dimethoxybenzoyl chloride [from the acid (9 g.)] was added in portions, with stirring, to a mixture of aluminium chloride (10 g.), 2,6-dimethoxybenzophenone (5.2 g.), and ether (300 ml.) during 0.5 hr. After 24 hr. the mixture was worked up as in method (b). The product formed colourless plates from light petroleum (b.p. 80–100°), m.p. 222–224° (2.7 g., 29%) [Found: C, 69.6; H, 5.45; OMe, 30.8. $C_{20}H_{10}O_2(OMe)_4$ requires C, 70.9; H, 5.45; OMe, 30.5%].

3-Benzoyl-2,2',4,6'-tetrahydroxybenzophenone.—Solutions of 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone (1.45 g.) and boron tribromide (3.93 g.) in methylene dichloride were cooled to –78° and then mixed. The mixture was warmed to room temperature and water (50 ml.) was added. The product was isolated by extraction into ether and formed pale yellow needles from benzene, m.p. 215.5–218.5° (0.1 g., 10%), ν_{\max} 3500, 3250, 1660, 1615, 1600, and 1590 cm^{-1} (Found: C, 68.3; H, 4.05. $C_{20}H_{14}O_6$ requires C, 68.6; H, 4.05%). 3-Benzoyl-2,2',4,6'-tetrahydroxybenzophenone gave a sherry colour with ferric ions in ethanol.

Action of Hydriodic Acid on 3-Benzoyl-2,2',4,6'-tetramethoxybenzophenone.—The title compound (1 g.) was gently heated under reflux with hydriodic acid (*d* 1.7; 60 ml.) for 3 hr. while a slow stream of nitrogen was passed through the mixture. The effluent gases were passed into a Dreschel bottle containing saturated barium hydroxide solution. A white precipitate of barium carbonate formed as the reaction proceeded. The reaction mixture was diluted with water (60 ml.) and left overnight. Some crystallisation occurred. The suspension was extracted with ether (4 × 50 ml.) and the extract was washed with sodium hydrogen carbonate solution (retained), then a little water, and dried (Na_2SO_4). Removal of the solvent yielded a gum which was dissolved in benzene and chromatographed on a column of silica gel MFC. The eluate yielded resorcinol (0.1 g.), needles, m.p. and mixed m.p. 106–108° [dibenzoate, m.p. 115–116° (lit.,⁵ 117°)], and 5-benzoyl-1,6-dihydroxyxanthone (0.07 g.), pale yellow needles, m.p. 198–201° (from methanol), olive-green colour with ferric ions in ethanol, ν_{\max} 1675, 1650, and 1603 cm^{-1} (Found: C, 71.1; H, 3.45. $C_{20}H_{12}O_5$ requires C, 72.3; H, 3.65%). (Prolonged drying did not improve these figures.) Later fractions yielded 1,6-dihydroxyxanthone (0.02 g.) as pale yellow needles, m.p. 246–248.5° (from methanol) (lit.,⁶ 245–246°), olive-green colour with ferric ions in ethanol, ν_{\max} 1640 and 1603 cm^{-1} , λ_{\max} 231 (log ϵ 4.43), 248 (4.21), 265 (3.98), 305 (4.04), and 351 (3.82)

nm. The sodium hydrogen carbonate extract was acidified with dil. hydrochloric acid and extracted with ether (2 × 50 ml.). Removal of the solvent left colourless needles of benzoic acid (0.025 g.), m.p. and mixed m.p. 120–122°.

2,2',4,6'-Tetramethoxybenzophenone.—Crude 2,6-dimethoxybenzoyl chloride [from the acid (10 g.)] was added with stirring to a mixture of aluminium chloride (10 g.) 1,3-dimethoxybenzene (7.6 g.), and ether (100 ml.). The reaction was carried out as described in method (b). 2,2',4,6'-Tetramethoxybenzophenone (8.2 g., 69%) separated from benzene as colourless prisms, m.p. 125.5–126.5°, ν_{\max} 1645, 1600, and 1580 cm^{-1} , τ 6.38 (s, 2-, 2'-, and 6'-OMe), 6.27 (s, 4-OMe), 3.60 (d, 3-H *meta*-coupled to 5-H; *J* 2.5 Hz), 3.58 (d, 5-H, *J* 9 Hz), 3.48 (d, 3'- and 5'-H, *J* 8 Hz), 2.80 (q, 4'-H, *J* 8 Hz), and 2.32 (d, 6-H, *J* 9 Hz).

1,6-Dihydroxyxanthone.—2,2',4,6'-Tetramethoxybenzophenone (1 g.) was refluxed with hydriodic acid (60 ml.) for 3 hr. The product was isolated by extraction into ether, distillation, and chromatography of the residue on silica gel MFC, with benzene as eluant. 1,6-Dihydroxyxanthone (0.1 g.) separated from methanol as pale yellow needles, m.p. 246–248.5°. Methylation with dimethyl sulphate–potassium carbonate–acetone gave 1,6-dimethoxyxanthone, m.p. 181.5–183° (0.025 g.), colourless needles from light petroleum (b.p. 60–80°), ν_{\max} 1655, 1625, 1605, and 1570 cm^{-1} [Found: C, 70.2; H, 4.65; OMe, 24.7. $C_{13}H_6O_2(OMe)_2$ requires C, 70.3; H, 4.7; OMe, 24.2%].

5-Benzoyl-1,6-dimethoxyxanthone.—Prepared by methylation of 5-benzoyl-1,6-dihydroxybenzophenone (0.057 g.) by the dimethyl sulphate–potassium carbonate method, the product (0.025 g.) separated from light petroleum (b.p. 60–80°) as colourless needles, m.p. 259.5–261°, ν_{\max} 1660, 1620, and 1605 cm^{-1} , τ (Varian A60A) 6.12 and 5.98 (each s, 1- and 6-OMe), 3.33 and 3.20 (each d, 2- and 3-H), 2.96 (d, 7-H, *J* 9 Hz), 2.00–2.58 (5H, m, benzoyl hydrogens), and 1.58 (d, 8-H, *J* 9 Hz) [Found: C, 72.7; H, 4.55; OMe, 16.5. $C_{20}H_{10}O_3(OMe)_2$ requires C, 73.3; H, 4.4; OMe, 17.2%].

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⁵ O. Döbner, *Annalen*, 1881, **210**, 256.

⁶ P. Yates and G. H. Stout, *J. Amer. Chem. Soc.*, 1958, **80**, 1691.