

Generation and Interception of Isobenzofurans from 2-(α -Bromoalkyl)-benzophenones

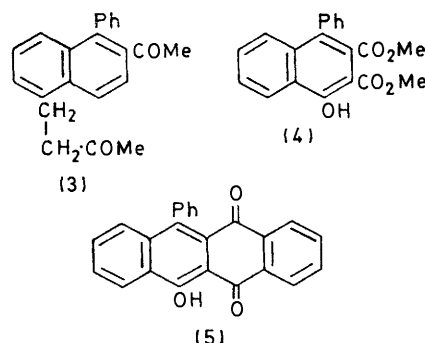
By Roy Faragher and Thomas L. Gilchrist, The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

2-(Bromomethyl)benzophenone, prepared by side-chain bromination of 2-methylbenzophenone, is converted into naphthalene derivatives [(2), (4), and (5)] by heating in tetrachloromethane with olefinic or acetylenic dienophiles. A mechanism is suggested in which 1-phenylisobenzofuran is generated by displacement of bromide by the neighbouring carbonyl group; the isobenzofuran then undergoes cycloaddition and the cycloadducts are aromatised by the hydrogen bromide present. Similar reactions are observed with 2-(2-bromoethyl)benzophenone, but in this case the primary Diels-Alder adducts (7) and (8) can be isolated. Similarly, (*Z*)-4-bromo-1,3-diphenylbut-2-en-1-one (9) is converted into 2,4-diphenylfuran by heating in ethanol.

IN the course of a project involving use of *ortho*-substituted benzyl bromides, we attempted to prepare 2-(bromomethyl)benzophenone. 2-Methylbenzophenone reacted rapidly with bromine but the product was thermally unstable. Irradiation of equimolar amounts of 2-methylbenzophenone and bromine in tetrachloromethane gave a major product which showed an n.m.r. signal at δ 4.67, corresponding to that expected for 2-(bromomethyl)benzophenone; 2-(dibromomethyl)benzophenone was a minor product. When the solution was set aside for a short period, however, the major product began to decompose with evolution of hydrogen bromide.

As the neighbouring carbonyl group in 2-(bromomethyl)benzophenone is well placed to interact with the bromomethyl group, it seemed likely that the instability of the compound was due to its conversion into 1-phenylisobenzofuran (1). We sought evidence for the presence of the isobenzofuran by heating the product of bromination with dienophiles. *N*-Phenylmaleimide, dimethyl maleate, and diethyl fumarate gave the naphthalenes (2a-c) in good yields. With methyl vinyl ketone the

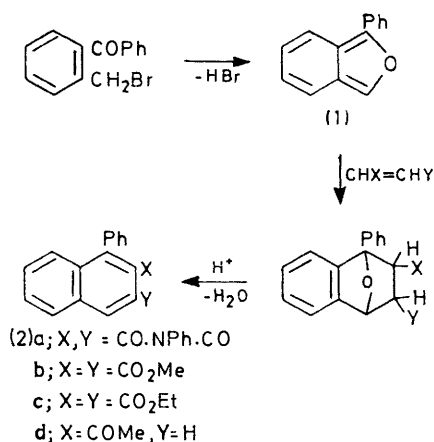
pattern for the hydrogen atoms at C-3 and -4. A minor product of the reaction with methyl vinyl ketone also showed this AB pattern but the mass and ^1H n.m.r. spectra indicated that two molecules of methyl vinyl



ketone had been incorporated. This product is tentatively assigned structure (3), and may be formed by subsequent alkylation of the naphthalene (2d) by methyl vinyl ketone in the presence of hydrogen bromide.

The mechanism suggested for the formation of these naphthalenes is shown in Scheme 1; aromatisation of the Diels-Alder adducts of isobenzofurans in the presence of acids is well known. In a similar way, dimethyl acetylenedicarboxylate reacted to give the naphthol (4) in good yield; with naphthoquinone, aromatisation was achieved by dehydrogenation rather than by dehydration, so that the product was 6-hydroxy-11-phenyl-naphthacene-5,12-dione (5).

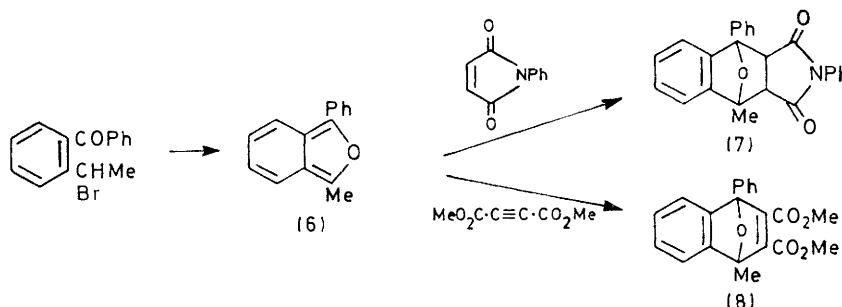
In order to obtain more direct evidence for the intermediacy of isobenzofurans, a similar sequence of reactions was performed with 2-ethylbenzophenone. In this case the isobenzofuran formed is 1-phenyl-3-methylisobenzofuran (6). Since both α -positions are now blocked, the aromatisation of its Diels-Alder adducts with acetylenic dienophiles is much more difficult. Indeed, both with *N*-phenylmaleimide and with dimethyl acetylenedicarboxylate, the isobenzofuran adducts (7) and (8) were isolated (Scheme 2); the structure (7) was supported by the presence of an AB system in the n.m.r. spectrum which corresponded to that expected for the hydrogen atoms at C-2 and -3 of the tetrahydronaphthalene.



SCHEME 1

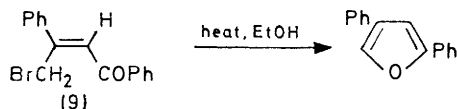
addition appeared to be highly stereoselective: only the ketone (2d) was isolated and none of the 3-acetyl isomer was detected. The structure (2d) was assigned on the basis of the n.m.r. spectrum, which showed an AB

Examples of neighbouring group participation in *ortho*-substituted benzyl bromides have been reported previously,¹ though not, as far as we are aware, involving a neighbouring ketone carbonyl group. On the other hand, a similar sequence of reactions, leading to the



SCHEME 2

formation of monocyclic furans, was reported several years ago.² This, too, is potentially a general reaction; thus, we converted (*Z*)-4-bromo-1,4-diphenylbut-2-en-1-one (9) into 2,4-diphenylfuran in good yield by heating under reflux in ethanol.



The preparation of naphthalenes of this type from 2-alkylbenzophenones complements methods already available involving either photoenolisation^{3,4} or the production of isobenzofurans by other means.⁵

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls with a Pye Unicam SP 200 spectrometer, or (where indicated) for KBr discs with a Perkin-Elmer 125 instrument. ¹H N.m.r. spectra were obtained at 60 MHz with a Perkin-Elmer R12 instrument or at 100 MHz with a Varian HA-100 spectrometer. Kieselgel PF254 (Merck) was used for layer chromatography; petroleum refers to light petroleum, b.p. 60–80°.

Bromination of 2-Methylbenzophenone.—A solution of 2-methylbenzophenone⁶ (0.248 g, 1.27 mmol) in tetrachloromethane (10 ml) was heated under reflux and irradiated with a 300 W sun-lamp while bromine in tetrachloromethane was added. The colour of the bromine was rapidly discharged at first; after the addition of 280 mg (1.75 mmol) a slight yellow colouration persisted, and the irradiation was stopped. Evaporation gave an oil, δ (CCl₄) 4.67, 7.19, and 7.3–7.9 (m). The signals at δ 4.67 and 7.19 (4:1) were assigned to the side-chain hydrogen atoms of 2-(bromo-

methyl)- and 2-(dibromomethyl)-benzophenone, respectively.

A similar experiment involving the use of 2-methylbenzophenone (0.248 g, 1.27 mmol) and bromine (0.203 g, 1.27 mmol) resulted in a mixture containing 2-methyl- (10%;

estimated by n.m.r.), 2-(bromomethyl)- (80%), and 2-(dibromomethyl)-benzophenone (10%). Equimolar amounts of 2-methylbenzophenone and bromine were used in subsequent experiments.

Preparation of Naphthalenes.—(a) *N*,1-Diphenyl-naphthalene-2,3-dicarboximide (2a). Bromine (0.80 g, 5 mmol) in tetrachloromethane (10 ml) was added dropwise to 2-methylbenzophenone (1.00 g, 5 mmol) in tetrachloromethane (10 ml) during 5 min, while the solution was irradiated with a 300 W sun-lamp. The bromination was complete within a further 5 min. *N*-Phenylmaleimide (0.87 g, 5 mmol) in chloroform (10 ml) was added, and the solution was heated under reflux for 19 h. The solvent was removed to leave a yellow oil (2.30 g) which, by trituration with ether and subsequent crystallisation, gave the imide (2a) (1.33 g, 75% based on 2-methylbenzophenone), m.p. 227–228° (from ether–chloroform) (Found: C, 82.1; H, 4.5; N, 4.05. C₂₄H₁₅NO₂ requires C, 82.5; H, 4.3; N, 4.0%), ν_{\max} 1760 and 1720 cm⁻¹ (C=O); δ (CDCl₃) 7.4–8.0 (14 H, m) and 8.55 (1 H); *m/e* 349 (*M*⁺, base), 305, and 304; *m** (349 → 305) 266.5.

(b) *Dimethyl 1-phenyl-naphthalene-2,3-dicarboxylate* (2b). This was prepared as described in (a) from 2-methylbenzophenone (0.250 g, 1.3 mmol), bromine (0.21 g, 1.3 mmol), and dimethyl maleate (0.900 g, 6.2 mmol). Crystallisation gave the dimethyl ester (2b) (0.264 g, 65%), m.p. 120–121° (from methanol) (lit.,⁴ 120–121°); δ (CDCl₃) 3.60 (3 H), 3.97 (3 H), 7.1–8.1 (9 H, m), and 8.63 (1 H).

(c) *Diethyl 1-phenyl-naphthalene-2,3-dicarboxylate* (2c). The method described in (a) was used. 2-Methylbenzophenone (0.250 g, 1.3 mmol), bromine (0.21 g, 1.3 mmol), and diethyl fumarate (0.800 g, 4.6 mmol) gave the diethyl ester (2c) (0.224 g, 51%), m.p. 129–130° (from ethanol) (lit.,⁷ 127–130°; lit.,⁸ 138°); δ (CCl₄) 0.93 (3 H, t, *J* 7 Hz),

⁴ M. Pfau, N. D. Heindel, and T. F. Lemke, *Compt. rend.*, 1965, **261**, 1017.

⁵ J. G. Smith and R. T. Wikman, *J. Org. Chem.*, 1974, **39**, 3648; L. F. Fieser, and M. J. Haddadin, *J. Amer. Chem. Soc.*, 1964, **86**, 2081; D. Wege, *Tetrahedron Letters*, 1971, 2337; R. N. Warrenner and J. W. J. Mijs, *J.C.S. Chem. Comm.*, 1972, 347.

⁶ H. Goldschmidt and H. Stöcker, *Ber.*, 1891, **24**, 2805.

⁷ T. Lanser, *Ber.*, 1899, **32**, 2481.

⁸ W. Herz, R. C. Blackstone, and M. G. Nair, *J. Org. Chem.*, 1966, **31**, 1800.

¹ A. Singh, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, 1962, **84**, 1179; M. J. Strauss, L. J. Andrews, and R. M. Keefer, *ibid.*, 1968, **90**, 3473; M. J. Strauss, I. Horman, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, 1968, **33**, 2194.

² P. S. Bailey and J. C. Smith, *J. Org. Chem.*, 1956, **21**, 628; P. S. Bailey and R. E. Lutz, *J. Amer. Chem. Soc.*, 1945, **67**, 2232.

³ N. C. Yang and C. Rivas, *J. Amer. Chem. Soc.*, 1961, **83**, 2213; F. Nerdel and W. Brodowski, *Chem. Ber.*, 1968, **101**, 1398; S. M. Mellows and P. G. Sammes, *Chem. Comm.*, 1971, 21.

1.40 (3 H, t, J 7 Hz), 3.94 (2 H, q, J 7 Hz), 4.36 (2 H, q, J 7 Hz), 7.3—7.6 (9 H, m), and 8.49 (1 H).

(d) *2-Acetyl-1-phenylnaphthalene* (2d). 2-Methylbenzophenone (0.25 g, 1.3 mmol) and bromine (0.21 g, 1.3 mmol) were used. Methyl vinyl ketone (1.0 g) was added and the mixture was heated under reflux for 21 h, then evaporated to leave an oil (0.55 g) which was subjected to layer chromatography (silica; chloroform-ethyl acetate, 99:1). An oil, obtained from the band at R_F 0.5, slowly solidified to give *2-acetyl-1-phenylnaphthalene* (75 mg, 23%), m.p. 81—82° (from pentane) (Found: C, 87.5; H, 5.7. $C_{18}H_{14}O$ requires C, 87.8; H, 5.7%); ν_{max} 1 672 cm^{-1} (C=O); δ (100 MHz; CCl_4) 1.80 (3 H), 7.26—7.70 (9 H, m), 7.56 (1 H, d, J 8.5 Hz), and 7.80 (1 H, d, J 8.5 Hz); m/e 246 (M^+), 231 (base), and 203. An oil (43 mg), isolated from the band at R_F 0.2, was tentatively identified as *2-acetyl-5-(3-oxobutyl)-1-phenylnaphthalene* (3), ν_{max} 1 708 and 1 685 cm^{-1} (C=O); δ (100 MHz; CCl_4) 1.78 (3 H), 2.13 (3 H), 2.86 (2 H, t, J 7 Hz), 3.25 (2 H, t, J 7 Hz), 7.2—7.7 (8 H, m), 7.65 (1 H, d, J 8.5 Hz), and 8.01 (1 H, d, J 8.5 Hz); m/e 316 (M^+ , base), 301, and 273.

(e) *Dimethyl 1-hydroxy-4-phenylnaphthalene-2,3-dicarboxylate* (4). 2-Methylbenzophenone (0.25 g, 1.3 mmol) was brominated with bromine (0.21 g, 1.3 mmol), and dimethyl acetylenedicarboxylate (1.0 g) was added. The solution was heated under reflux for 20 h, then evaporated to leave an oil (0.73 g). Layer chromatography (silica; ether-petroleum, 3:7) gave (at R_F 0.3) the *naphthol* (4) (0.27 g, 62%), m.p. 149—150° (from methanol) (Found: C, 71.1; H, 4.8. $C_{20}H_{16}O_5$ requires C, 71.4; H, 4.8%); ν_{max} (KBr) 1 735 and 1 655 cm^{-1} (C=O); λ_{max} (EtOH) 283 (ϵ 4 800), 294 (5 400), 306 (5 200), 345 (6 500), and 360 nm (5 900); δ ($CDCl_3$) 3.52 (3 H), 3.96 (3 H), 7.3—7.7 (8 H, m), and 8.45—8.65 (1 H, m); m/e 336 (M^+) and 335. A solution of the *naphthol* in methanol gave a deep blue colouration with iron(III) chloride.

(f) *6-Hydroxy-11-phenylnaphthacene-5,12-dione* (5). 2-Methylbenzophenone (0.25 g, 1.3 mmol) was brominated with bromine (0.21 g, 1.3 mmol). 1,4-Naphthoquinone (0.20 g, 1.3 mmol) was added and the solution was heated under reflux for 15 h. The product, a viscous oil (0.64 g), was dissolved in 1,2-dichloroethane, and ether was added to precipitate an orange solid. Crystallisation gave the *quinone* (5) (88 mg, 19%), m.p. 315—316° (from chloroform-ether) (Found: C, 82.3; H, 4.1. $C_{24}H_{14}O_3$ requires C, 82.3; H, 4.0%); ν_{max} (KBr) 1 662, 1 615, 1 588,

and 1 574 cm^{-1} ; ν_{max} (EtOH) 257 (ϵ 56 000), 284 (20 000), 299 (16 000), and 438 nm (10 000); m/e 350 (M^+) and 349 (base).

1,4-Epoxy-1,2,3,4-tetrahydro-1-methyl-N,4-diphenylnaphthalene-2,3-dicarboximide (7).—2-Ethylbenzophenone⁹ (0.27 g, 1.3 mmol) in tetrachloromethane (10 ml) was heated and irradiated with a 300 W sun-lamp while bromine (0.21 g, 1.3 mmol) in tetrachloromethane (10 ml) was added dropwise. *N*-Phenylmaleimide (0.22 g, 1.3 mmol) in chloroform (10 ml) was added and the solution was heated under reflux for 24 h. The product, an oil (0.58 g), was subjected to layer chromatography (silica; chloroform-ethyl acetate 49:1) and this gave (at R_F 0.6) the *imide* (7) (0.20 g, 40%), m.p. 183—184° (from cyclohexane) (Found: C, 78.2; H, 5.1; N, 3.8. $C_{25}H_{19}NO_3$ requires C, 78.7; H, 5.0; N, 3.7%); ν_{max} 1 718 cm^{-1} (C=O); δ (100 MHz; CCl_4) 2.10 (3 H), 3.48 (1 H, d, J 8 Hz), 3.86 (1 H, d, J 8 Hz), 6.30—6.45 (2 H, m), 6.80—7.40 (10 H, m), and 7.80—7.95 (2 H, m); m/e 208 ($C_{15}H_{12}O^+$) and 173 ($C_{10}H_7NO_2^+$).

Dimethyl 1,4-Epoxy-1,4-dihydro-1-methyl-4-phenylnaphthalene-2,3-dicarboxylate (8).—To 2-ethylbenzophenone (0.27 g, 1.3 mmol) in tetrachloromethane (10 ml) was added bromine (0.21 g, 1.3 mmol) in tetrachloromethane (10 ml), the solution being heated and irradiated with a 300 W sun-lamp. When the addition was complete, dimethyl acetylenedicarboxylate (1.0 g) in tetrachloromethane (15 ml) was added. The solution was heated under reflux for 24 h. The solvent and some of the acetylene were removed by distillation under reduced pressure, and the residual oil (0.76 g) was subjected to layer chromatography (silica; chloroform), which gave (at R_F 0.3) the *imide* (8) (0.26 g, 57%), m.p. 126.5—127° (from cyclohexane) (Found: C, 71.9; H, 5.5. $C_{21}H_{18}O_6$ requires C, 72.0; H, 5.2%); ν_{max} 1 720 cm^{-1} (C=O); δ (100 MHz; CCl_4) 2.10 (3 H), 3.63 (3 H), 3.69 (3 H), and 6.95—7.70 (9 H, m); m/e 350 (M^+) and 208 ($C_{15}H_{12}O^+$, base).

2,4-Diphenylfuran.—(*Z*)-4-Bromo-1,3-diphenylbut-2-en-1-one¹⁰ (9) (0.50 g, 1.66 mmol) was heated under reflux in 95% ethanol for 3 h. Evaporation gave plates of 2,4-diphenylfuran (0.26 g, 70%), m.p. 110—111° (from ethanol) (lit.,¹¹ 110.7—111°).

We thank the S.R.C. for a Research Studentship (to R. F.).

[5/1552 Received, 6th August, 1975]

¹¹ R. C. Fuson, C. L. Fleming, and R. Johnson, *J. Amer. Chem. Soc.*, 1938, **60**, 1994.

⁹ P. A. S. Smith and E. P. Antoniadis, *Tetrahedron*, 1960, **9**, 210.

¹⁰ R. E. Lutz and L. T. Slade, *J. Org. Chem.*, 1961, **26**, 4888.