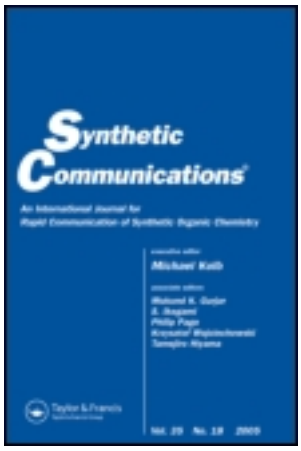

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RAPID MICROWAVE-PROMOTED SYNTHESIS OF FUNCTIONALISED BENZOPHENONES

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RAPID MICROWAVE-PROMOTED SYNTHESIS OF FUNCTIONALISED BENZOPHENONES

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ABSTRACT

Several functionalised benzophenone derivatives have been conveniently obtained in moderate to good yield via the rapid, microwave-promoted Friedel–Crafts acylation of activated arenes with benzoic acids in polyphosphoric acid medium.

Key Words: Friedel-Crafts acylation; Functionalised benzophenones; Polyphosphoric acid; Microwaves; Parallel synthesis

Access to several functionalised (methoxy-substituted) benzophenone derivatives, preferably via simple methodology being both fast and generally adaptable to a parallel synthesis approach would be highly desirable. Several variants of the traditional Friedel–Crafts acylation of arenes with free aromatic carboxylic acids or the corresponding acid chlorides have been frequently used for synthesis of such compounds.[1–6] Scattered reports of the use of microwaves in conjunction with assorted catalysts for Friedel–Crafts acylation exist in the literature.[7–9]

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Polyphosphoric acid (PPA) serves as a highly efficient and cheap catalyst for Friedel–Crafts acylation of aromatic compounds using aromatic carboxylic acids.[10] However, the viscosity of PPA itself and of reactions involving the reagent mean that magnetic stirring is usually not feasible. Elevated temperatures and mechanical agitation are usually required, conditions which are not particularly amenable to parallel synthesis. Encouraged by a few recent reports of the use of PPA in conjunction with microwaves for some unrelated transformations,[7,11,12] the Friedel–Crafts acylation of some (poly)methoxy-benzenes with several benzoic acids in PPA using microwave energy was investigated.

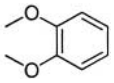
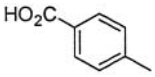
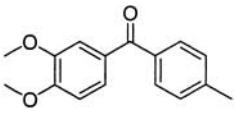
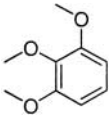
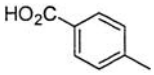
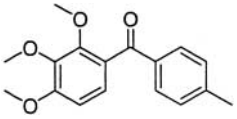
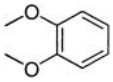
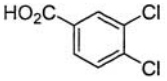
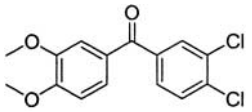
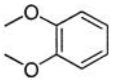
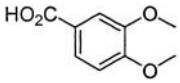
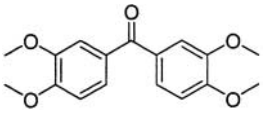
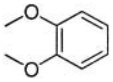
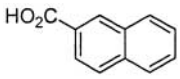
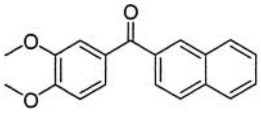
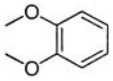
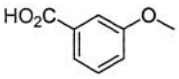
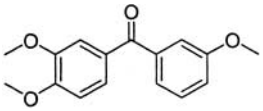
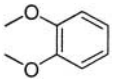
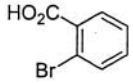
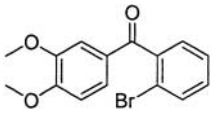
Table 1 summarises the results from these experiments. The reaction was found to be rapid, general applicable and operationally very simple. In short, PPA was added to a mixture of the methoxy–benzene and a small excess of the appropriate benzoic acid in an open round-bottomed flask giving a thick unstirrable suspension. The mixture was placed inside a microwave oven suitably adapted for organic synthesis (see Experimental section). The mixture was irradiated at 100% power for 45 s with the maximum allowed internal temperature set at 120°C (Scheme 1). During each run, the temperature was observed to remain constant and then rise rapidly between 30–35 s causing the reaction mixture to become dark red and mobile such that stirring became possible. TLC analysis confirmed that each reaction was usually complete after 45 s. Work-up consisted simply of hydrolysis of the excess acid by pouring onto water and filtration or extraction of the product and subsequent purification.

Product yields utilizing these reactions were moderate to good and comparable or superior to those obtained using traditional thermal heating. The lowest yield, observed for the 3′,4′-dichlorobenzophenone (Run 3) may be ascribed to the low solubility of 3,4-dichlorobenzoic acid in PPA. Other aromatic carboxylic acids substituted by alkyl, methoxyl or mono-halo groups presented no problems using this method. Similarly, 2-naphthoic acid reacted well under these conditions (Run 5) suggesting that the method is generally applicable. Additionally, the considerably reduced reaction times (45 s), combined with the possibility to carry out several independent reactions in open flasks in parallel at the same time without the need to resort to equipment such as mechanical stirrers make this methodology attractive for the rapid synthesis of functionalised benzophenone derivatives.

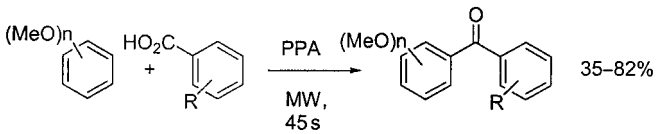
CONCLUSIONS

An operationally simple, economical and rapid method for the synthesis of functionalised benzophenone derivatives involving Friedel–Crafts acylation of (poly)methoxy-benzenes with several aromatic carboxylic acids

Table 1. Synthesis of Functionalised Benzophenone Derivatives[a]

Run	Arene	Aromatic Acid	Product	Yield(%)
1				82
2				60
3				35
4				74
5				79
6				49
7				74

[a]PPA, microwaves (100% power, 45 s).



Scheme 1. Microwave-promoted synthesis of functionalised benzophenone derivatives.

in polyphosphoric acid medium in conjunction with microwave heating has been developed which may be adapted to a parallel synthesis approach.

EXPERIMENTAL SECTION

Melting points were measured in open capillary tubes on an Electrothermal Model 9100 hot stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance DPX (400 MHz) Spectrometer with solvent used as internal standard, and data are reported in the order: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), number of protons, approximate coupling constant in Hertz and assignment of a signal. IR spectra were measured with a Bomem Hartmann & Braun MB Series FTIR spectrometer using KBr tablets. Analytical TLC was performed on precoated silica gel plates (Merck 60 Kieselgel F 254) and visualised with UV light. Preparative chromatography was done on Merck 60 Kieselgel (0.063–0.2 mm). Elemental analyses were performed on a Fisons EA 1110 CHNS instrument and all analyses are consistent with theoretical values to within ±0.4% unless indicated. Solvents and reagents were purchased from Aldrich, Fluka, E. Merck or local sources and used as received. Reactions were run in open borosilicate round-bottom glass vessels at atmospheric pressure in a microwave oven adapted for organic synthesis (focussed microwaves on reaction vessel; continuous un-pulsated power regulation; microwave cavity dimensions: height 210 mm, width 290 mm, depth 320 mm; incorporated magnetic stirrer, infra-red temperature sensor and overfield sensor).

A typical experimental procedure for the microwave-promoted synthesis of benzophenones is exemplified by the following example:

3,4-Dimethoxy-4′-methyl-benzophenone (Run 1): Polyphosphoric acid (15 g) was added to veratrole (1.0 g, 7.25 mmo1) and *p*-toluic acid (1.08 g, 7.97 mmo1) in an open 50 mL round bottom flask equipped with a magnetic stirring bar. The mixture was placed in the cavity of the microwave oven and irradiated at 100% power for 45 s, with the maximum allowed temperature set at 120°C. The resulting deep red mixture was allowed to cool, and then poured onto ice/water (100 mL). The precipitate was filtered off, washed with water and dried in air. Recrystallisation (*i*PrOH) afforded the product as beige crystals, 1.52 g, (82%) of m.p. 127–128°C.

^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H, *o*-Ph), 7.49 (d, 1H, $J = 1.9$ Hz, H-2), 7.39 (dd, 1H, $J = 1.9$ and 8.2 Hz, H-6), 7.29 (d, 2H, *m*-Ph), 6.90 (d, 1H, $J = 8.2$ Hz, H-5), 3.98 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 2.46 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 196.0, 153.4, 149.5, 143.2, 136.0, 131.1, 130.6,

129.4, 125.8, 112.7, 110.3, 56.6, 56.6, 22.2. Found: C, 73.48; H, 6.44%. $C_{16}H_{16}O_3 \cdot 0.25H_2O$ requires: C, 73.69; H, 6.38%.

Using this method there was also obtained:

2,3,4-Dimethoxy-4′-methylbenzophenone (Run 2): pale yellow oil after chromatography (SiO_2, PE/EtOAc, 2 : 1), crystallising on standing, m.p. 77–80°C. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, *o*-Ph), 7.24 (d, 2H, *m*-Ph), 7.12 (d, 1H, $J = 8.5$ Hz, H-6), 6.73 (d, 1H, $J = 8.5$ Hz, H-5), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 195.8, 156.5, 153.1, 144.2, 142.6, 136.3, 130.6, 129.8, 127.3, 125.5, 107.3, 62.4, 61.6, 56.7, 22.3. Found: C, 71.09; H, 6.68%. $C_{17}H_{18}O_4$ requires: C, 71.31; H, 6.33%.

3,4-Dimethoxy-3′,4′-dichlorobenzophenone (Run 3): white crystals (CH_2Cl_2/PE), m.p. 99–101°C. ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 1H, $J = 1.9$ Hz, H-2′), 7.60 (dd, 1H, $J = 1.9$ and 8.4 Hz, H-6′), 7.59 (d, 1H, $J = 8.4$ Hz, H-5′), 7.47 (d, 1H, $J = 2.1$ Hz, H-2), 7.34 (dd, 1H, $J = 2.1$ and 8.4 Hz, H-6), 6.92 (d, 1H, $J = 8.4$ Hz, H-5), 3.99 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 193.6, 154.1, 149.8, 138.5, 137.0, 133.4, 132.1, 130.9, 129.9, 129.4, 126.0, 112.4, 110.4, 56.7, 56.7. Found: C, 57.78; H, 4.12%. $C_{17}H_{18}O_4$ requires: C, 57.90; H, 3.89%.

3,4-Dimethoxy-3′,4′-dimethoxybenzophenone (Run 4): white crystals (EtOH), m.p. 148–150°C. ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 2H, $J = 1.9$ Hz, H-2, H-2′), 7.39 (dd, 2H, $J = 1.9$ and 8.2 Hz, H-6, H-6′), 6.92 (d, 2H, $J = 8.2$ Hz, H-5, H-5′), 3.98 (s, 6H, $2 \times OCH_3$), 3.95 (s, 6H, $2 \times OCH_3$). ^{13}C NMR ($CDCl_3$) δ 195.1, 153.1, 149.4, 131.3, 125.3, 112.8, 110.3, 56.6, 56.6. Found: C, 67.65; H, 5.59%. $C_{17}H_{18}O_4$ requires: C, 67.54; H, 6.00%.

3,4-Dimethoxy-naphthalenone (Run 5): greyish crystals (EtOH), m.p. 122–123°C. ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H, H-1′), 8.0–7.85 (m, 4H, Ar–H), 7.65–7.5 (m, 3H, Ar–H, H-2), 7.47 (dd, 1H, $J = 2.1$ and 8.4 Hz, H-6), 6.94 (d, 1H, $J = 8.4$ Hz, H-5), 4.00 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 196.2, 153.6, 149.6, 136.1, 135.6, 132.8, 131.7, 131.0, 129.8, 128.7, 128.6, 128.4, 127.3, 126.5, 126.1, 112.8, 110.4, 56.7, 56.7. Found: C, 77.98; H, 5.84%. $C_{17}H_{18}O_4$ requires: C, 78.06; H, 5.52%.

3,4-Dimethoxy-3′-methoxybenzophenone (Run 6): beige crystals (CH_2Cl_2/ PE), m.p. 84–85°C. ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 1H, $J = 2.1$ Hz, H-2), 7.45–7.35 (m, 2H, H-6, H-5′), 7.3 (m, 2H, H-2′, H-4′), 7.14 (ddd, 1H, $J = 8.0$, 2.7 and 1.0 Hz, H-6′), 6.90 (d, 1H, $J = 8.4$ Hz, H-5), 3.98 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 195.9, 160.0, 153.6, 149.5, 140.1, 130.7, 129.7, 126.1, 122.9, 118.8, 114.8, 112.6, 110.3, 56.7, 56.6, 56.0. Found: C, 70.42; H, 6.03%. $C_{17}H_{18}O_4$ requires: C, 70.57; H, 5.92%.

3,4-Dimethoxy-2′-bromobenzophenone (Run 7): white crystals (*i*PrOH), m.p. 160–162°C. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1H, H-3′), 7.60 (d, 1H,

$J = 2.1$ Hz, H-2), 7.43 (t, 1H, H-5′), 7.4–7.3 (m, 2H, H-4′, H-6′), 7.21 (dd, 1H, $J = 2.1$ and 8.4 Hz, H-6), 6.85 (d, 1H, $J = 8.4$ Hz, H-5), 3.96 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 195.2, 154.6, 149.9, 141.5, 133.6, 131.4, 129.8, 129.3, 127.7, 127.1, 120.0, 111.4, 110.5, 56.7, 56.6. Found: C, 55.73; H, 4.02%. $C_{17}H_{18}O_4$ requires: C, 56.09; H, 4.08%.

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