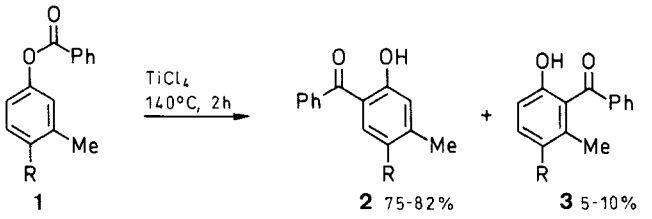
Synthesis of Vicinal 2,3-Dialkyl-6-hydroxybenzophenones by Titanium Tetrachloride Catalyzed Fries Rearrangement of 3,4-Dialkylphenyl Benzoates

Robert Martin,* Pierre Demerseman.
Service de Chimie, CNRS, URA 1387, Institut Curie, Section de Biologie, 26 rue d'Ulm, F-75231 Paris Cedex 05, France

Received 11 November 1991; revised 30 December 1991

The titanium(IV) chloride-mediated Fries rearrangement of 3,4-dialkylphenyl benzoates **1** yields mainly 4,5-dialkyl-2-hydroxybenzophenones **2** in high yield. We describe here a new access to the unknown vicinal 2,3-dialkyl-6-hydroxybenzophenones **3**, which is based on the protection of the most reactive position of **1** by bromination.

The Fries rearrangement[1,2] is generally directed by electronic and steric effects of the substituents of the aryl group.[3-5] Nevertheless, some events can modify the course of the reaction. In particular, Fries rearrangement of phenyl benzoates[6] require high temperatures. This drastic condition may induce migration or elimination of alkyl groups situated on the aryl nucleus, if aluminum chloride is used as the catalyst. For example, with aluminum chloride, the benzoate **1a** yields ketone **2a**,[7] whereas the ester **1b**, by cleavage and migration, affords a very complex mixture. Using titanium(IV) chloride as a catalyst, we were able to obtain ketones **2a,b** in high yields (75% and 82%, respectively) accompanied by 5% and 10%, respectively of the vicinal ketones **3a,b** (Scheme 1).

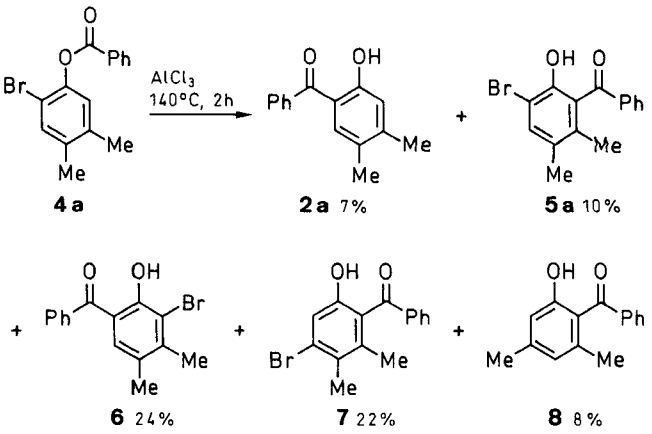


1–3	R
a	Me
b	*i*-Pr

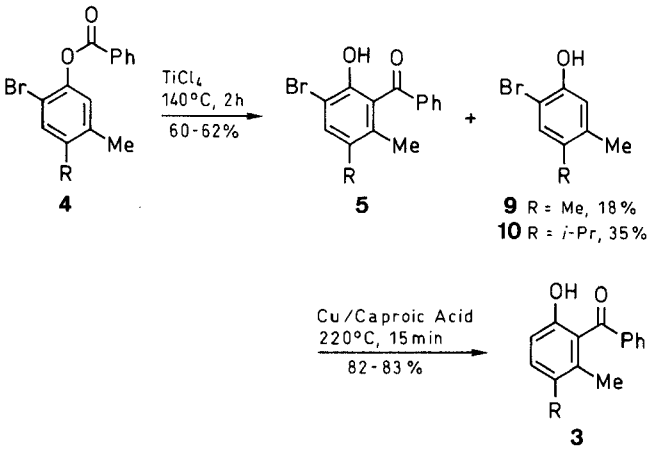
Scheme 1

The vicinally substituted *o*-hydroxybenzophenones **3a,b** are attractive synthetic intermediates and may be considered themselves as potential new light-stable absorbers.[8] For their preparation, a *tert*-butyl group cannot be used to protect the less hindered 6-position[9,10] of the esters **1a,b** because its elimination occurs before the Fries rearrangement takes place. So, we attempted to use a bromine atom instead of the *tert*-butyl group to protect the 6-position of **1a,b**. Unfortunately, the brominated ester **4a** reacts with aluminum chloride at 140°C to give a complex mixture containing only 10% of the vicinally substituted ketone **5a**. (Scheme 2).

We describe here a two-step preparation of the ketones **3a,b** based on the soft catalytic properties of titanium(IV) chloride to carry out the Fries rearrangement of the 6-bromophenyl esters **4a,b**, followed by reductive removal of bromine with copper powder in caproic acid medium[11] (Scheme 3). The byproducts of the Fries rearrangement of **4a** and **4b** were the recovered starting materials (20% and 5%, respectively) and the corresponding bromophenols **9, 10** resulting from heterolysis (18% and 35%, respectively). The side products of the reductive abstraction of bromine were the recovered bromoketones **5a** or **5b**.



Scheme 2



3–5	R
a	Me
b	*i*-Pr

Scheme 3

Melting points (uncorrected) were determined on a Kofler apparatus (> 60°C) or with a capillary tube. IR spectra were obtained using a Perkin-Elmer 1710 spectrometer and the UV spectra on a Varian Techtron 635 spectrometer. ^{1}H NMR spectra were recorded at 90 MHz on a Varian EM 390 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained on a

Table. Compounds **1–10** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C) or bp (°C)/mbar	UV (EtOH) λ_{max} (nm) (log ε)	IR (CH_2Cl_2) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
1b	85	48–49 (EtOH)	$C_{17}H_{18}O_2$ (254.3)	–	1733	1.24 [d, 6H, $(CH_3)_2CH$, J = 6.5], 2.35 (s, 3H, CH_3), 3.13 (m, 1H, CH), 7.32 (m, $6H_{arom}$), 8.20 (m, $2H_{arom}$, $J_{2',6'}$ = 3)	254 (M^+, 9), 105 (100)
2a	75	110–111 (EtOH)	111[7]	–	1636	2.13 and 2.26 (2 br, 6H, $2CH_3$), 6.83 (s, 1H, H-3), 7.27 (s, 1H, H-6), 7.53 (m, $5H_{arom}$), 12.33 (s, 1H, OH)	226 (M^+, 75), 225 (100)
2b	82	48–49 (EtOH)	$C_{17}H_{18}O_2$ (254.3) 152.5[b,15]	203 (4.38), 276 (4.16), 347 (3.65)	1633	1.13 [d, 6H, $(CH_3)_2CH$, J = 6.5], 2.35 (s, 3H, CH_3), 3.03 (m, 1H, CH), 6.85 (s, 1H, H-3), 7.53 (m, $6H_{arom}$), 11.93 (s, 1H, OH)	254 (M^+, 72), 239 (100)
3a	5	124–125 (heptane)	(226.3) 114–115[16]	203 (4.52), 249 (4.16)	1666, 1628	1.90 (s, 3H, CH_3-3), 2.18 (s, 3H, CH_3-2), 6.75 (d, 1H, H-5), 7.15 (d, 1H, H-4, J = 9), 7.42 (m, $3H_{arom}$), 7.72 (m, $3H_{arom}$ + OH)	226 (M^+, 68), 225 (100)
3b	10	142–143 (heptane)	$C_{17}H_{18}O_2$ (254.3) 207/14[b,15]	204 (4.56), 249 (4.17)	1666, 1629	1.20 [d, 6H, $(CH_3)_2CH$, J = 6.5], 1.98 (s, 3H, CH_3), 3.03 (m, 1H, CH), 6.82 (d, 1H, H-5, J = 9), 7.28 (d, 1H, H-4), 7.52 (m, 4H, $3H_{arom}$ + OH), 7.73 (m, $2H_{arom}$)	254 (M^+, 59), 77 (100)
4b	87	68–69 (EtOH)	$C_{17}H_{17}BrO_2$ (333.2)	–	1741	1.23 [d, 6H, $(CH_3)_2CH$, J = 6.5], 2.30 (s, 3H, CH_3), 3.08 (m, 1H, CH), 7.02 (s, 1H, H-3), 7.53 (m, $4H_{arom}$), 8.23 (m, $2H_{arom}$, J = 3)	332 (M^+, 2), 105 (100)
5a	60[c]	157–158 (heptane)	$C_{15}H_{13}BrO_2$ (305.2)	205 (4.66), 250 (4.18)	1672, 1633	1.97 (s, 3H, CH_3–C), 2.22 (s, 3H, CH_3-2), 6.08 (s, 1H, OH), 7.50 (m, $4H_{arom}$), 7.80 (m, $2H_{arom}$)	305 (M^+, 87), 77 (100)
5b	62[c]	119–120 (heptane)	$C_{17}H_{17}BrO_2$ (333.2)	204 (4.70), 250 (4.16)	1670, 1633	1.22 [d, 6H, $(CH_3)_2CH$, J = 6.5], 2.05 (s, 3H, CH_3), 3.07 (m, 1H, CH), 5.92 (s, 1H, OH), 7.48 (m, $4H_{arom}$), 7.82 (m, 2H, H-2, 6)	333 (M^+, 50), 77 (100)
6	24	134–135 (pentane)	134–135[17]	203 (4.43), 282 (4.14), 350 (3.68)	1624	2.22 and 2.43 (2s, 6H, $2CH_3$), 7.27 (s, 1H, H-6), 7.47 (m, $5H_{arom}$), 12.72 (s, 1H, OH)	305 (M^+, 11), 77 (100)
7	22	194–195 (benzene)	$C_{15}H_{13}BrO_2$ (305.2)	204 (4.67), 250 (4.12)	1670, 1632	2.28 and 2.33 (2s, 6H, $2CH_3$), 6.80 (br, 1H, H-5), 7.48 (m, 4H, $3H_{arom}$ + OH), 7.67 (m, $2H_{arom}$)	305 (M^+, 86), 77 (100)
8	8	141–142 (EtOH)	143[7]	204 (4.54), 250 (4.17)	1675, 1630	2.00 (s, 3H, CH_3-4), 2.32 (s, 3H, CH_3-2), 7.53 (m, $7H_{arom}$) 7.87 (s, 1H, OH)	226 (M^+, 70), 225 (100)
10	70[e]	61–62 (pentane)	$C_{10}H_{13}BrO$ (229.1)	–	–[d]	1.17 [d, 6H, $(CH_3)_2CH$, J = 6.5], 2.23 (s, 3H, CH_3), 3.00 (m, 1H, CH), 5.20 (s, 1H, OH), 6.77 (s, 1H, H-6), 7.23 (s, 1H, H-3)	228 (M^+, 32), 213 (100)

[a] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.08, Br ± 0.18.
[b] The previously reported physical constants for ketones **2b** and **3b** are erroneous, since the two structures attributed 34 years ago by one of us[15] on IR basis must be inverted, as we have checked by NMR experiments.
[c] Together with 30–35% of heterolysis product and 5–10% of starting material.
[d] ν_{OH} = 3528 cm^{-1}
[e] Yield refers to the authentic specimen prepared.

Ribermag R-10-10-C apparatus. The purity of all the compounds was checked by TLC. The yields were obtained after isolation of compounds by column chromatography on silica gel (eluent: benzene) and recrystallization. Elementary analyses were performed by the Service Central de Microanalyse, CNRS, Solaise.

3,4-Xylenol and *p*-thymol are commercially available. The benzoates **1a**,[12] **4a**[13] and the 2-bromo-4,5-dimethylphenol (**9**)[14] were prepared according to literature. The synthesis of the benzoates **1b** and **4b** is described below.

3-Methyl-4-(1-methylethyl)phenyl Benzoate (**1b**): To a stirred solution of *p*-thymol (15 g, 0.1 mol) in 10% aq. NaOH solution (140 mL) was added benzoyl chloride (23.9 g, 0.17 mol) at r.t. Stirring was continued for 2 h and, after usual work up, the crude **1b** was recrystallized from ethanol (50 mL), as colorless crystals; yield: 21.6 g (85%); mp 48–49 °C.

2-Bromo-5-methyl-4-(1-methylethyl)phenyl Benzoate (**4b**):

2-Bromo-5-methyl-4-(1-methylethyl)phenol (**10**): This compound was prepared according to the procedure of Selander and Nilsson,[14] starting from *p*-thymol (12.48 g, 83 mmol) and bromine (13.24 g, 83 mmol) in CCl_4 (420 mL) containing 2% Et_2O. After usual work-up, the crude product **10** was recrystallized from pentane (100 mL), as colorless crystals; yield: 19 g (70%); mp 61–62 °C.

Benzoate **4b**: A mixture of **10** (9.2 g, 40 mmol), pyridine (17 mL) and benzoyl chloride (12 mL, 100 mmol) was heated for 4 h at 110 °C, and then allowed to cool to about 80 °C. Water (100 mL) was added, and the mixture was refluxed for 30 min. The mixture was cooled, Et_2O (250 mL) was added, and the organic layer washed successively with 4 N HCl (2 × 20 mL), water (2 × 20 mL), 10% aq $NaHCO_3$ solution (2 × 20 mL) and finally with water (5 × 20 mL). The Et_2O layer was dried (Na_2SO_4), the solvent removed, and the residue was

recrystallized from EtOH (60 mL) as colorless crystals; yield: 11.6 g (87%); mp 68–69°C.

Fries Rearrangement of Aryl Benzoates 1 and 4; General Procedure:
A mixture of ester **1** or **4** (10 mmol) and $TiCl_4$ (1.7 mL, 16 mmol) was stirred at 140°C for 2 h. After cooling to 80°C, the complex was hydrolysed with 4 N HCl (40 mL) and Et_2O (200 mL) added. The organic layer was washed successively with 4 N HCl (3 × 15 mL), water (2 × 15 mL), 10% aq $NaHCO_3$ solution (2 × 15 mL) and, finally, with water (5 × 20 mL). After drying (Na_2SO_4) and evaporation of the solvent, the separation was carried out by column chromatography on silica gel (110 g, eluent benzene). The ketones obtained were recrystallized from appropriate solvent (Table).

The rearrangements of esters **1b** and **4a** (10 mmol) with $AlCl_3$ (2.13 g, 16 mmol) were conducted as described above. Although the rearrangement of **1b** gave an intractable mixture, the separation of the products obtained starting from ester **4a** was successfully carried out in the following manner: The yellow crude product (2.91 g) was treated with boiling benzene (20 mL) and the white crystals obtained after cooling (0.7 g) were treated again with boiling benzene (20 mL) furnishing, after cooling, the ketone **7** (0.67 g). The two benzene extracts were combined, concentrated and chromatographed on silica gel (110 g, eluent benzene) yielding, in the order of elution, the ketones **6** (0.73 g), **2a** (0.22 g), **5a** (0.31 g), **7** (0.01 g) and **8** (0.25 g) (Table).

2,3-Dialkyl-6-hydroxybenzophenones 3; General Procedure:
A mixture of the appropriate ketone **3** (3 mmol), copper powder (6 g, 95 mmol) and caproic acid (8 mL, 65 mmol) was stirred at 220°C for 15 min, and then allowed to cool to about 70°C. After addition of a 10% aq $NaHCO_3$ solution (40 mL), the mixture was heated at 70°C for 30 min. After cooling, Et_2O (150 mL) was added, the organic layer washed with water (3 × 15 mL), dried (Na_2SO_4) and evaporated. The purification of ketones **3** was carried out by column chromatography on silica gel (15 g, eluent CH_2Cl_2). The ketones **3a** and **3b** were recrystallized from heptane (Table).

The authors are grateful to Mrs. N. Sellier for performing mass spectra analyses and to Mrs. G. Flad for the other spectroscopic recordings and analyses.

(1) Fries, K.; Finck, G. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 4271.
(2) Fries, K.; Pfaffendorf, W. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 212.
(3) Edwards, J.D., Jr.; Cashaw, J.L. *J. Am. Chem. Soc.* **1956**, *78*, 3821.
(4) Martin, R. *Bull. Soc. Chim. Fr.* **1977**, 901.
(5) Martin, R.; Gavard, J.-P.; Delfly, M.; Demerseman, P.; Tromelin, A. *Bull. Soc. Chim. Fr.* **1986**, 659.
(6) Martin, R.; Coton, G. *Bull. Soc. Chim. Fr.* **1973**, 1442.
(7) Baddeley, G. *J. Chem. Soc.* **1943**, 273.
(8) Head, F.S.H. *J. Chem. Soc.* (C) **1969**, 34.
(9) Martin, R.; Demerseman, P. *Synthesis* **1989**, 25.
(10) Martin, R.; Demerseman, P. *Monatsh. Chem.* **1990**, *121*, 227.
(11) Smith, W.T., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 2855.
(12) Granger, R.; Orzalesi, H.; Joyeux, P. *C. R. Acad. Sci.* **1965**, *260*, 923.
(13) Crossley, A.W.; Bartlett, D.J. *J. Chem. Soc.* **1913**, 1297.
(14) Selander, H.; Nilsson, J.L. G. *Acta Chem. Scand.* **1971**, *25*, 1178.
(15) Royer, R.; Demerseman, P.; Michelet, R.; Cheutin, A. *Bull. Soc. Chim. Fr.* **1959**, 1148.
(16) Arventiev, B.; Strul, M.; Wexler, H. *Acad. Rep. Populare Romîne, Filiala Jasi, Studii Cercetari Stiint, Chim.* **1960**, *11*, 53; *Chem. Abstr.* **1961**, *55*, 15452
(17) Bartolotti, P.; Linari, A. *Gazz. Chim. Ital.* **1902**, *32*, 271.