Unsymmetrical Diaryl Ketones from Arenes

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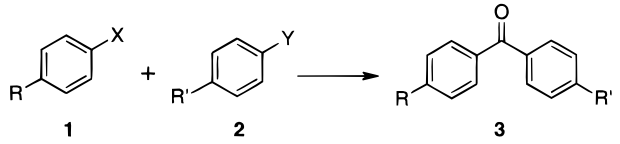
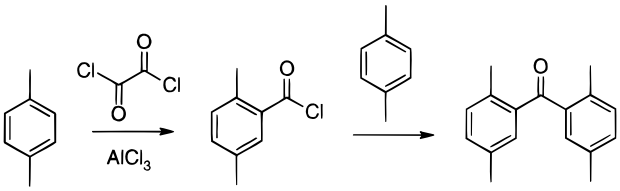
Diaryl ketones serve as valuable intermediates in the synthesis of biologically active compounds. The diarylmethane residue has been seen as a component of such medicinal agents as tolcapone, an inhibitor of catecholamine-*O*-methyl transferase,[1] and the GABA-delivering agent progabide.[2] Usually, such diaryl ketones have been prepared by the aroylation of aryl organometallics (e.g., X = $B(OH)_2$, Y = (C=O)PdI).[3−5] We report here what appears to be a general procedure for a much less expensive approach, the coupling of two arenes (X, Y = H) to make the diaryl ketone **3**.



1 **2** **3**

The $AlCl_3$-mediated chlorocarbonylation of arenes (**4** → **5**) has been known for many years.[6,7] There were a few reports[7c,8,9] of the in situ coupling of the intermediate complexed aroyl chloride with additional arene to prepare the symmetrical benzophenone (e.g., **4** → **6**). We have optimized this procedure (Table 1, entry 1), and have shown that it is easily extended to *unsymmetrical* benzophenones (Table 1, entries 2−6).



4 **5** **6**

As this procedure was optimized, it was found that the best results were obtained when the less activated substrate was used in the initial acylation and the more activated arene was used as the subsequent acceptor. With the less activated substrates, such as chloro- and bromobenzene, the chlorocarbonylation required longer time and higher temperatures. The optimized conditions are summarized in Table 1. In each case, 1.2 equiv of oxalyl chloride were employed. It should be emphasized that the yields reported are for reactions using 1.0 equiv of each arene, not the severalfold excess of one or the other often previously employed.[8]

We have developed what appears to be an efficient approach to both symmetrical and unsymmetrical diaryl ketones. It is especially noteworthy that the conditions of the second Friedel−Crafts reaction are mild enough that even an *o*-methoxy ketone, **17**, often demethylated under Friedel−Crafts conditions,[10] was prepared in satisfactory yield.

Experimental Section

General Procedures. ^{1}H NMR (at 300 MHz) and ^{13}C NMR (at 75 MHz) spectra were obtained as solutions in deuteriochloroform ($CDCl_3$). The infrared (IR) spectra were determined neat or as KBr pellets using a FTIR. R_f values indicated refer to thin-layer chromatography (TLC) on 5.0 × 10 cm, 250 μm analytical plates coated with silica gel 60 F_{254} developed in the solvent system indicated. Elemental analysis was carried out by Quantitative Technologies Inc., P.O. Box 470, Salem Industrial Park, Bldg 5, Whitehouse, NJ 08888. Column chromatography was carried out on an Isco mplc using silica gel 60 particle size 0.015−0.040 μm. The solvent mixtures used are volume/volume mixtures. All reactions were carried out under a flow of nitrogen. Dichloromethane was from EM Science. All reaction mixtures were stirred magnetically, unless otherwise noted. The times and temperatures for the chlorocarbonylations and for the subsequent acylations are summarized in Table 1.

Preparation of Diaryl Ketones. Ketone 6. In a 100 mL side arm round-bottom flask, oxalyl chloride (1.05 mL, 12 mmol) was added dropwise over 5 min to a solution of *p*-xylene (1.23 mL, 10 mmol) in dichloromethane (50 mL) at 5 °C. Aluminum chloride (1.33 g, 10 mmol) was added portionwise over 5 min to give a yellow suspension. The reaction mixture was warmed to room temperature and stirred for 1 h, during which time dissolution of the solid and gas evolution were observed. A second equivalent of *p*-xylene (1.23 mL, 10 mmol) was added dropwise over 5 min, and the reaction mixture was allowed to stir for 13 h at room temperature. The reaction mixture was chilled in an ice/water bath, and 25 mL of H_2O was added dropwise over 10 min. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was chromatographed to give **6**[11] as a clear oil (1.84 g, 77% yield): TLC R_f (10% ethyl acetate/hexanes) = 0.49; ^{1}H NMR δ 7.21−7.14 (m, 4H), 7.11 (s, 2H), 2.37 (s, 6H), 2.29 (s, 6H); ^{13}C NMR δ (CH_3) 19.7, 18.5; (CH) 130.3, 129.4, 129.1; (C) 199.7, 137.6, 133.5, 133.4; IR 1665 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.34; H, 7.28.

Ketone 8: 1.78 g, 74% yield; mp 88−89 °C (lit.[12] mp 88 °C); TLC R_f (10% ethyl acetate/hexanes) = 0.21; ^{1}H NMR δ 7.79 (d, 2H, J = 8.9 Hz), 7.15 (m, 2H), 7.08 (s, 1H), 6.91 (d, 2H, J = 8.9

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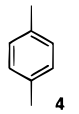
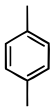
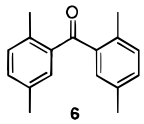
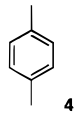
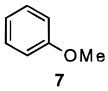
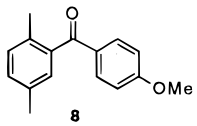
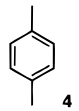
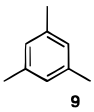
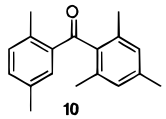
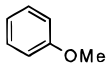
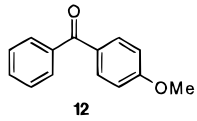
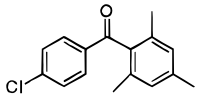
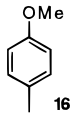
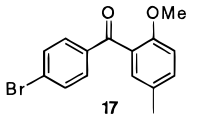
Table 1. Preparation of Diaryl Ketones

	Arene A	Chlorocarbonylation[a]	Arene B	Acylation[b]	Product	Yie
1	 **4**	30 min, 10 °C	 **4**	14 h, rt	 **6**	
2	 **4**	30 min, 10 °C	 **7**	1 h, rt	 **8**	
3	 **4**	30 min, 10 °C	 **9**	14 h, rt	 **10**	
4	 **11**	2 h, rt	 **8**	14 h, rt	 **12**	
5	 **13**	14 h, rt	 **9**	5 h, rt	 **14**	
6	 **15**	14 h, rt	 **16**	14 h, rt	 **17**	

[a] The time and temperature for the initial chlorocarbonylation. [b] The time and temperature for the acylation. [c] The yield given is for a reaction using 1.5 equiv of oxalyl chloride.

Hz), 3.86 (s, 3H), 2.32 (s, 3H), 2.23 (s, 3H); ^{13}C NMR δ (CH_3) 54.0, 19.4, 17.8; (CH) 133.5, 130.9, 129.2, 129.0, 112.2; (C) 196.2, 162.2, 133.3, 131.4, 129.1, 126.8; IR 1657 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.84; H, 6.78.

Ketone 10: 1.72 g, 68% yield; mp 74−75 °C (lit.[13] mp 77−78 °C); TLC R_f (10% ethyl acetate/hexanes) 0.47; ^{1}H NMR δ 7.24−7.15 (m, 3H), 6.86 (m, 2H), 2.60 (s, 6H), 2.32 (s, 3H), 2.23 (s, 3H), 2.09 (s, 3H); ^{13}C NMR δ (CH_3) 19.8, 19.7, 19.3, 18.0; (CH) 131.5, 130.5, 130.2, 127.0; (C) 201.3, 137.1, 136.9, 135.6, 135.2, 133.9, 132.9; IR 1669 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.39; H, 7.97.

Ketone 12: 1.53 g, 72% yield, using 1.5 equiv of oxalyl chloride; mp 62−64 °C (lit.[14] mp 57 °C); TLC R_f (10% ethyl acetate/hexanes) = 0.16; ^{1}H NMR δ 7.85 (d, 2H, J = 8.9 Hz), 7.82 (m, 2H), 7.58−7.47 (m, 3H), 6.98 (d, 2H, J = 8.9 Hz), 3.89 (s, 3H); ^{13}C NMR δ (CH_3) 54.0; (CH) 131.0, 130.4, 128.2, 126.7, 112.0; (C) 194.0, 161.7, 136.8, 128.6; IR 1659 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 78.99; H, 5.85.

Ketone 14: 1.80 g, 70% yield; mp 66−68 °C (lit.[15] mp 68−69 °C; TLC R_f (10% ethyl acetate/hexanes) 0.40; ^{1}H NMR δ 7.75 (d, 2H, J = 8.5 Hz), 7.41 (d, 2H, J = 8.5 Hz), 6.90 (s, 2H), 2.33 (s, 3H), 2.07 (s, 6H); ^{13}C NMR δ (CH_3) 19.6, 17.8; (CH) 129.2, 127.6, 126.9; (C) 197.9, 138.5, 137.2, 134.8, 134.2, 132.6; IR 1671 cm^{-1}.

Ketone 17: 1.65 g, 54% yield; mp 66−69 °C; TLC R_f (10% ethyl acetate/hexanes) 0.21; ^{1}H NMR δ 7.67 (d, 2H, J = 8.6 Hz), 7.57 (d, 2H, J = 8.6 Hz), 7.25 (dd, 1H, J = 8.44, 2.06 Hz), 7.17 (d, 1H, J = 2.06 Hz), 6.89 (d, 1H, J = 8.44 Hz); ^{13}C NMR δ (CH_3) 54.2, 18.8; (CH) 131.2, 130.0, 129.7, 128.5, 110.0; (C) 194.1, 153.8, 135.3, 128.6, 126.5, 126.4; IR 1666 cm^{-1}.

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Supporting Information Available: ^{1}H and ^{13}C spectra of **6, 8, 10, 12, 14,** and **17.** This material is available free of charge via the Internet at http://pubs.acs.org.

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