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IMPROVED Cs_2CO_3 PROMOTED *O*-ALKYLATION OF PHENOLS

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ABSTRACT: Cesium carbonate mediated *O*-alkylation of phenols was carried out under mild conditions to give the corresponding phenol ethers exclusively. The methodology is more efficient than previous methods since harsh conditions such as higher temperatures and longer reaction times are avoided.

Alkyl phenyl ethers are usually prepared by *O*-alkylation of phenols, which are ubiquitously found in a large number of syntheses. Recently, cesium base promoted phenol alkylations have attracted much attention,[1] and these techniques have been applied extensively to the syntheses of various macrocyclic targets including crown ethers.[2] Nonetheless, these methodologies have shown limitations due to their relatively harsh reaction conditions, requiring high

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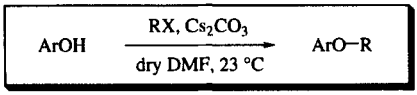
temperatures or prolonged reaction times, and most *O*-alkylation reactions need reactive electrophiles such as methyl, allyl, and benzyl halides.

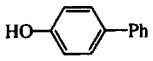
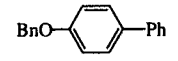
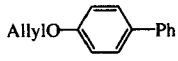
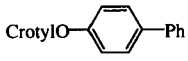
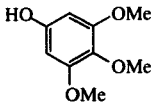
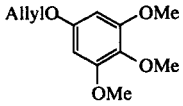
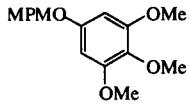
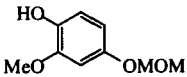
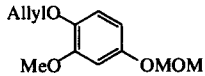
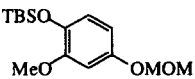
Scheme I



In the course of aromatic alkaloid synthesis, we found the aforementioned techniques can be garnered under mild conditions. Reported herein is an improved procedure as depicted in Scheme I. Using cesium carbonate in anhydrous DMF, *O*-alkylations proceeded to completion smoothly at room temperature, affording the desired phenyl ethers exclusively. Representative examples are listed in Scheme II.

Using active halides such as benzyl, allyl, and crotyl halides (entry 1 – 3), alkylations of 4-phenylphenol were efficient and rapid, providing exclusively the desired ethers **2**, **3**, and **4**, respectively. When our synthetic intermediates were subjected to *O*-alkylations, phenyl ethers were prepared successfully (entry 4 – 7). Interestingly, this methodology was also used to introduce common protecting groups such as MPM (4-methoxyphenyl methyl) and TBS (*t*-butyldimethylsilyl) ethers, which was not always possible using previously reported methods due to

Scheme II

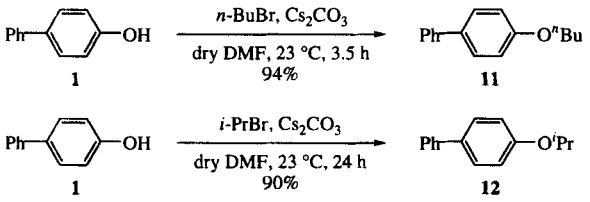
entry	ArOH	R'X	ArOR'	Time	Yield
1	 **1**	BnBr	 **2**	1 h	92%
2		Allyl bromide	 **3**	1 h	97%
3		Crotyl chloride	 **4**	5 h	97%
4	 **5**	Allyl bromide	 **6**	1 h	98%
5		MPMCl	 **7**	12 h	61%
6	 **8**	Allyl bromide	 **9**	1 h	91%
7		TBSCl	 **10**	2 h	73%

the labile properties of the halides used under harsh reaction conditions (entry 5 and 7).

Subsequently, the developed protocols were extended to alkylations with unreactive halides as illustrated in Scheme III. Using *n*-butyl bromide, phenol alkylation was completed in 3.5 hours at ambient temperatures, generating the

butyl aryl ether **11** in 94% yield. Amazingly, secondary bromides including isopropyl bromide exhibited great reactivities under similar conditions, resulting in the exclusive formation of the desired ether **12** in excellent yield.

Scheme III



Our improved conditions using cesium carbonate in anhydrous DMF demonstrate superiority over the known methodologies, enabling various alkyl bromides to be utilized. Under mild conditions, active halides and secondary bromides were tolerant to decomposition and elimination. *O*-Alkylation was promoted in anhydrous polar solvent, presumably by "naked" anions, which would behave as strong nucleophiles.[3] Thus, these techniques are practical and convenient alternatives to the precedented *O*-alkylation methods.

General Experimental Procedure

All reactions were run under standard conditions, utilizing 1.5 equivalents of cesium carbonate and 1.5 equivalents of halide regardless of their reactivities. The reactions were run under anhydrous conditions, and progress of these

reactions were monitored by thin layer chromatography of crude mixtures. These samples were attained by standard aqueous work-up of aliquots taken from the reaction. The representative experimental is described below.

Preparation of 2: Under an atmosphere of nitrogen, 4-phenylphenol **1** (1.00 g, 5.88 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (30 mL), and cesium carbonate (2.87 g, 8.82 mmol) was added in one portion to the solution. After benzyl bromide (1.05 mL) was added, the white suspension was stirred at ambient temperatures for an hour under N_2. The reaction was quenched by adding 1 N HCl solution slowly, then the resulting solution was extracted with hexanes-EtOAc (3:1 v/v mixture). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography on silica provided exclusively the *O*-alkylation product, 4-phenylphenyl benzyl ether **2** (1.48 g, 92%) as a white solid: R_f 0.65 (5:1 hexanes-EtOAc); **IR** (thin film) 3059, 2907, 1925, 1883, 1607, 1453, 1286, 1008, 825, 692 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 5.17 (s, 2 H), 7.14 (d, J = 8.7 Hz, 2 H), 7.35-7.65 (m, 12 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 70.1, 115.2, 126.7, 127.5, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 135.2, 140.8, 158.4.

Data for 3: R_f 0.60 (5:1 hexanes-EtOAc); **IR** (thin film) 3059, 2853, 1980, 1889, 1604, 1486, 1248, 991, 830, 693 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 4.62 (d, J = 5.3 Hz, 2 H), 5.36 (d, J = 10.5 Hz, 1 H), 5.50 (d, J = 17.3 Hz, 1 H), 6.13

(ddt, J = 17.3, 10.5, 5.3 Hz, 1 H), 7.04 (d, J = 8.8 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.8 Hz, 2 H), 7.57 (d, J = 8.8 Hz, 2 H), 7.61 (d, J = 8.1 Hz, 2 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 68.8, 114.9, 117.7, 126.6, 126.7, 128.1, 128.7, 133.2, 133.9, 140.7, 158.1.

Data for 4: R_f 0.63 (5:1 hexanes-EtOAc); **IR** (thin film) 3098, 3033, 2947, 2868, 1950, 1890, 1845, 1611, 1493, 1275, 1006, 834, 755 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 1.83 (d, J = 5.4 Hz, 3 H), 4.54 (d, J = 5.7 Hz, 2 H), 5.81 (m, 1 H), 5.94 (m, 1 H), 7.04 (d, J = 8.6 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.57 (d, J = 8.7 Hz, 2 H), 7.61 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 17.9, 68.7, 114.9, 126.0, 126.6, 126.7, 128.1, 128.7, 130.6, 133.7, 140.8, 158.3. Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.83; H, 7.21.

Data for 6: R_f 0.43 (5:1 hexanes-EtOAc); **IR** (thin film) 3082, 2939, 2837, 2008, 1980, 1880, 1596, 1504, 1422, 1229, 1030, 812 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 3.68 (s, 3 H), 3.71 (s, 6 H), 4.38 (d, J =5.0 Hz, 2 H), 5.17 (d, J = 10.4 Hz, 1 H), 5.31 (d, J = 16.3 Hz, 1 H), 5.94 (m, 1 H), 6.07 (s, 2 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 55.8, 60.7, 68.9, 92.3, 117.3, 118.0, 133.2, 153.5, 155.1. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.22; H, 7.14.

Data for 7: R_f 0.47 (5:1 hexanes-EtOAc); **IR** (thin film) 3007, 2868, 1591, 1509, 1252, 1125, 1023, 822 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 3.80 (s, 3 H),

3.82 (s, 3 H), 3.84 (s, 6 H), 4.95 (s, 2 H), 6.24 (s, 2 H), 6.93 (d, J = 8.5 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 55.2, 56.0, 60.9, 70.2, 92.6, 113.9, 128.8, 129.3, 132.3, 153.6, 155.4, 159.5. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.01; H, 6.56.

Data for 9: R_f 0.58 (5:1 hexanes-EtOAc); **IR** (thin film) 3080, 2946, 1950, 1860, 1598, 1510, 1221, 1154, 1018 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 3.48 (s, 3 H), 3.84 (s, 3 H), 4.54 (d, J = 5.4 Hz, 2 H), 5.11(s, 2 H), 5.25 (d, J = 10.4 Hz, 1 H), 5.37 (d, J = 17.2 Hz, 1 H), 6.06 (ddt, J = 17.2, 10.5, 5.4 Hz, 1 H), 6.54 (dd, J = 8.7, 2.7 Hz, 1 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.79 (d, J = 8.7 Hz, 1 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 55.7, 55.8, 70.6, 95.1, 102.1, 106.7, 114.6, 117.7, 133.6, 143.0, 150.3, 152.1. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.06; H, 7.21.

Data for 10: R_f 0.58 (5:1 hexanes-EtOAc); **IR** (thin film) 2998, 2857, 1592, 1510, 1229, 1154, 1020, 896 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.01 (s, 9 H), 3.49 (s, 3 H), 3.79 (s, 3 H), 5.11 (s, 2 H), 6.52 (dd, J = 8.6, 2.4 Hz, 1 H), 6.60 (d, J = 2.4 Hz, 1 H), 6.76 (d, J = 8.6 Hz, 1 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ −7.0, 18.3, 25.7, 55.3, 55.8, 95.1, 102.0, 107.2, 120.6, 139.8, 151.3, 152.2. Anal. Calcd for $C_{15}H_{26}O_4$: C, 60.37; H, 8.78. Found: C, 60.28; H, 8.82.

Data for 11: R_f 0.67 (5:1 hexanes-EtOAc); **IR** (thin film) 3085, 2967, 2914, 2875, 1950, 1880, 1611, 1453, 1269, 1071, 755, 690 cm^{-1}; **^{1}H NMR** (360 MHz,

$CDCl_3$) δ 1.09 (t, J = 7.4 Hz, 3 H), 1.62 (m, 2 H), 1.89 (m, 2 H), 4.08 (t, J = 6.5 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 7.39 (t, J = 7.3 Hz, 1 H), 7.50 (t, J = 7.4 Hz, 2 H), 7.61 (d, J = 8.8 Hz, 2 H), 7.65 (d, J = 7.1 Hz, 2 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 16.3, 19.1, 31.2, 69.3, 117.1, 126.3, 126.5, 128.2, 128.7, 136.4, 141.3, 158.1. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.96; H, 8.01.

Data for 12: R_f 0.65 (5:1 hexanes-EtOAc); **IR** (thin film) 3072, 3039, 2986, 2934, 1935, 1875, 1611, 1486, 1368, 1269, 1124, 959, 755 cm^{-1}; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 1.39 (d, J = 6.1 Hz, 6 H), 4.62 (septet, J = 6.1 Hz, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.33 (t, J = 7.3 Hz, 1 H), 7.45 (t, J = 7.4 Hz, 2 H), 7.55 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 7.1 Hz, 2 H); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 22.0, 69.9, 116.0, 126.5, 126.6, 128.1, 128.6, 133.5, 140.8, 157.4.

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