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Communication

C(aryl)-O Bond Formation from Aryl Methanesulfonates via Consecutive Deprotection and S_NAr Reactions with Aryl Halides in an Ionic Liquid

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Abstract: An efficient K_3PO_4-mediated synthesis of unsymmetrical diaryl ethers using the ionic liquid [Bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) as solvent has been developed. The procedure involves consecutive deprotection of aryl methanesulfonates and a nucleophilic aromatic substitution (S_NAr) with activated aryl halides.

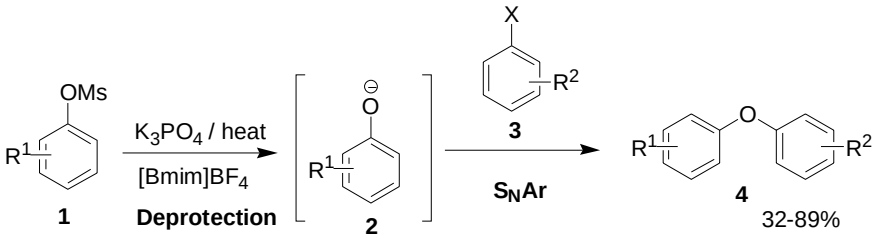
Keywords: C(aryl)-O bond, aryl methanesulfonates, nucleophilic aromatic substitution, diaryl ethers, ionic liquid.

Introduction

In recent years, in the search for green alternatives for traditional organic solvents in chemistry, ionic liquids have generated considerable interest as environmentally benign reaction media, due to their unique properties such as ease of recyclability, ability to dissolve a variety of organic, inorganic and metal complex materials, non-volatile and non-flammable nature and high thermal stability [1]. A growing number of chemical reactions in these media, such as Kabachnik-Fields reaction [2], polymerizations [3], hydrogenations [4], Diels-Alder reactions [5], Michael reactions [6], C-P cross-coupling reactions [7], and Beckmann rearrangements [8], have been reported. Diaryl ethers are very important intermediates in organic synthesis and are known to be present in a variety of natural

compounds of biological interest, such as vancomycin and riccardin [9]. The classical Ullmann reaction for diaryl ether synthesis often requires extremely harsh reaction conditions, i.e. high temperatures (200-300 ^{o}C), strong polar and toxic solvents and the use of stoichiometric quantities of copper, and generally gives low yields [10], so a number of other methodologies for the synthesis of diaryl ethers have been developed in recent years [11]. Meanwhile, the fact that the strategic use of protective groups is a necessary and time-consuming tactic in organic synthesis is well-known, so a merging of protective group chemistry with other transformations that can shorten a reaction sequence and improve synthetic efficiency and convenience is always of great interest. The methanesulfonyl group, as a useful protective group for phenols due to its robust behavior, has been widely used in a variety of reactions [12-13]. On the other hand, aryl methanesulfonates have been used as latent phenols in the nucleophilic aromatic substitution (S_NAr) reaction to prepare diaryl ethers [12], but unfortunately, the reported method requires the use of an excess of expensive Cs_2CO_3 and toxic organic solvents, and is applicable to a only a narrow range of substrates [12], therefore the development of a simpler, greener, cheaper and more efficient route for the synthesis of unsymmetrical diaryl ethers directly from aryl methanesulfonates and aryl halides that would be useful for a wide range of substrates is highly desirable. As part of our program directed at developing efficient and new methodologies for constructing bioactive molecules [14], herein we report a simple and environmentally benign synthesis of unsymmetrical diaryl ethers via a tandem deprotection of aryl methanesulfonates/S_NAr reaction with activated aryl halides using the ionic liquid [Bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) as a solvent (Scheme 1).

Scheme 1. The route of synthesis of unsymmetrical diaryl ethers.



R^1=H, NO_2, Cl, CH_3, Bu-*t*; R^2=NO_2, CN; X=F, Cl, Br

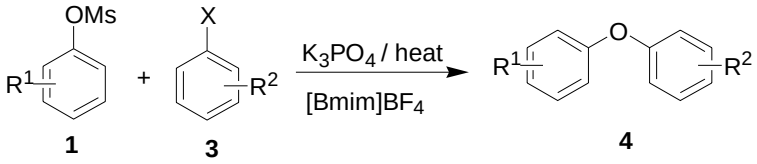
Results and Discussion

As shown in Scheme 1, the C-O bond cross-coupling of phenoxides **2**, generated *in situ* from aryl methanesulfonates **1**, with aryl halides **3** to produce diaryl ethers **4** can be effected in the ionic liquid [Bmim]BF_4 in the presence of anhydrous K_3PO_4. The results for different unsymmetric diaryl ethers are summarized in Table 1. A wide range of aryl methanesulfonates, including those having electron-deficient and electron-rich groups (R^1=H, NO_2, Cl, CH_3, *t*-Bu) were effective for this C-O cross-coupling S_NAr reaction with activated aromatic halides (R^2= NO_2, CN; X=F, Cl, Br) and moderate to good yields (32-89 %) were obtained.

Moreover, it should be recalled that aryl methanesulfonates with electron-withdrawing groups typically behave poorly or are completely inert toward diaryl ether formation, but in our reactions such electron-poor aryl methanesulfonates reacted smoothly with the corresponding aryl halides (X=F, Cl, Br), mediated by anhydrous K_3PO_4, to give the expected products (compounds **4a**, **4c**, **4e**, **4g**, **4i**, **4l**).

Particularly good yields were obtained for compounds **4g**, **4i** and **4c** (85 %, 89 % and 88 %, respectively). When 4-fluoronitrobenzene was reacted with the extremely electron-poor 4'-nitrophenyl methanesulfonate, 4-(4'-nitrophenoxy)nitrobenzene (**4e**) was obtained in 42% yield after being stirred in the presence of anhydrous K_3PO_4 at 110 ^oC for 24.5 h. When 2'-chlorophenyl methanesulfonate was reacted with 4-fluoronitro- or 4-bromonitrobenzene and 2-fluoronitro- or 2-chloronitrobenzene, the corresponding compounds 4-(2'-chlorophenoxy)nitrobenzene (**4c**) and 2-(2'-chlorophenoxy)nitrobenzene (**4i**) were obtained in 72 %/88 % and 89 %/66 % yields, respectively. These results showed that fluoro derivatives may be replaced by the corresponding bromo or chloro derivatives without causing a significant decrease in the yields.

Table 1. Synthesis of diaryl ethers in [Bmim]BF_4 [a]



1 **3** **4**

R^1	R^2	X	Temp. (^oC) [b]	Time (h)	Product	Yield (%) [c]
4'-Cl	NO_2	4-F	100	11	**4a**	70
3'-CH_3	NO_2	4-F	100	20	**4b**	50
2'-Cl	NO_2	4-F	100	7	**4c**	72
4'-*t*-Bu	NO_2	4-F	114	24	**4d**	52
4'-NO_2	NO_2	4-F	110	24.5	**4e**	42
H	NO_2	4-F	110	24.5	**4f**	64
4'-Cl	NO_2	2-F	100	12	**4g**	85
4'-*t*-Bu	NO_2	2-F	100	20	**4h**	32
2'-Cl	NO_2	2-F	105	11	**4i**	89
3'-CH_3	NO_2	2-F	100	20	**4j**	55
4'-*t*-Bu	CN	2-F	110	25	**4k**	63
4'-Cl	CN	2-F	110	24	**4l**	57
2'-Cl	NO_2	2-Cl	110	29	**4i**	66
2'-Cl	NO_2	4-Br	110	25	**4c**	88

[a] All reactions were carried out with **1** (1.5 mmol), **3** (1.0 mmol) and K_3PO_4 (2 mmol) in [Bmim]BF_4 (3 mL) at the appropriate temperature; [b] Reaction temperature; [c] Isolated yield.

Next, we also investigated the reusability and the recycling of the ionic liquid [Bmim]BF_4, and found that it could be easily recovered after the completion of the reaction and reused in the subsequent reactions without any noticeable loss of efficiency. For this purpose the reaction of 2-fluoronitro-benzene with 2'-chlorophenyl methanesulfonate mediated by anhydrous K_3PO_4 in [Bmim]BF_4 was investigated as a model reaction. When the reaction was complete after 11 h at 105 ^oC, as checked by TLC, the reaction mixture was extracted three times with ethyl ether, then the ionic liquid left in the reaction vessel was dissolved with acetone, filtered and washed by acetone to remove the solid, and finally the combined acetone extract was evaporated under reduced pressure to give the recycled ionic liquid, which was reused as the reaction solvent for the next reaction. The ionic liquid activity did not show any significant decrease after 3 runs and the yields were 88%, 89%, and 89% for runs 1-3, respectively.

Conclusions

In summary, we have developed an efficient procedure for the synthesis of unsymmetrical diaryl ethers via a tandem deprotection of aryl methanesulfonates and S_NAr reactions with activated aryl halides mediated by anhydrous K_3PO_4 and using the ionic liquid [Bmim]BF_4 as solvent. The advantages of this method are as follows: 1) moderate to good yields are obtained using a wide range of substrates; 2) a deprotection step is obviated; 3) separation of the products from the ionic liquid during work-up is very easy; 4) the ionic liquid can be recycled without loss of efficiency, making the procedure quite simple, convenient and environmentally benign.

Experimental

General

All the solvents were of analytical grade and the reagents were used as purchased. Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 GF254 (Qingdao Haiyang Chemical Co., Ltd.). Melting points were determined on a digital melting-point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded on a Bruker Avance DMX 400 MHz instrument using TMS as internal standard and $CDCl_3$ as solvent. HRMS and EIMS were carried out with APEX II Bruker 4.7T AS and Thermo DSQ GC/MS instrument respectively. Elemental analysis was executed on Carlo-Erba 1106 CHN microanalyzer.

General procedure for the preparation of unsymmetrical diaryl ethers **4**

The aryl halide (**3**, X=F, Cl, Br, 1 mmol), the aryl methanesulfonate (**1**, 1.5 mmol) and anhydrous K_3PO_4 (2 mmol) were added to [Bmim]BF_4 (3 mL). The reaction mixture was stirred for a given time at the appropriate temperature and monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was cooled to room temperature and extracted with ethyl ether (3 x 40 mL). Then the extracts were combined and evaporated under reduced pressure to give a residue which was purified by using PTLC to obtain the pure diaryl ether. All compounds were characterized by ^{1}H-NMR, HRMS or elemental analysis, EI-MS and m.p.

4-(4'-Chlorophenoxy)nitrobenzene (**4a**). White solid; m.p. 75.8-76.1 ^{o}C; ^{1}H-NMR: δ = 7.00 (4H, m), 7.38 (2H, dd, *J* = 6.8, 2.4 Hz), 8.20 (2H, dd, *J* = 7.2, 2.4 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{12}H_{12}N_2O_3Cl$: 267.0531; found: 267.0532.

4-(3'-Methylphenoxy)nitrobenzene (**4b**). White solid; m.p. 61.9-62.2 ^{o}C; ^{1}H-NMR: δ = 2.78 (3H, s), 6.88 (2H, m), 6.99 (2H, d, *J* = 9.2 Hz), 7.05 (1H, d, *J* = 8.0 Hz), 7.29 (1H, t, *J* = 8.0 Hz), 8.18 (2H, d, *J* = 9.2 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{13}H_{15}N_2O_3$: 230.0812; found: 230.0811.

4-(2'-Chlorophenoxy)nitrobenzene (**4c**). White solid; m.p. 76.8-77.0 ^{o}C; ^{1}H-NMR: δ = 6.93 (2H, m), 7.16 (1H, dd, *J* = 8.0, 1.6 Hz), 7.23 (1H, dt, *J* = 8.0, 1.6 Hz), 7.33 (1H, dt, *J* = 8.0, 1.6 Hz), 7.51 (1H,

dd, *J* = 8.0, 1.6 Hz), 8.19 (2H, m); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{12}H_{12}N_2O_3Cl$: 267.0531; found: 267.0529.

4-(4'-tert-Butylphenoxy)nitrobenzene (**4d**). White solid; m.p. 61.2-61.6 ^oC; ^1H-NMR: δ = 1.35 (9H, s), 6.99 (4H, m), 7.41 (2H, m), 8.18 (2H, d, *J* = 8.8 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{16}H_{21}N_2O_3$: 289.1547; found: 289.1546.

4-(4'-Nitrophenoxy)nitrobenzene (**4e**). Pale yellow solid; m.p. 144.5-144.9 ^oC; ^1H-NMR: δ = 7.15 (4H, m), 8.28 (4H, m); GC/MS (EI, 70eV): m/z (%) = 260 (M^+, 100), 230 (40), 139 (65.1); Anal. calcd. for $C_{12}H_8N_2O_5$: C, 55.39; H, 3.10; N, 10.77. Found: C, 55.21; H, 3.36; N, 10.66.

4-(Phenoxy)nitrobenzene (**4f**). White solid; m.p. 55.9-56.3 ^oC; ^1H-NMR: δ = 6.99 (2H, d, *J* = 12 Hz), 7.08 (2H, d, *J* = 8.4 Hz), 7.24 (1H, t, *J* = 6.8 Hz), 7.41 (2H, t, *J* = 8.4 Hz), 8.18 (2H, d, *J* = 12 Hz); GC/MS (EI, 70eV): m/z (%) = 215 (M^+, 100), 185 (24.9), 77(62.2); Anal. calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.18; N, 6.51. Found: C, 66.75; H, 4.36; N, 6.58.

2-(4'-Chlorophenoxy)nitrobenzene (**4g**). Pale yellow liquid; ^1H-NMR: δ = 6.96 (3H, m), 7.21 (1H, t, *J* = 8.0 Hz), 7.31 (2H, m), 7.51 (1H, dt, *J* = 8.4, 1.6 Hz), 7.95 (1H, dd, *J* = 8.4, 1.6 Hz); GC/MS (EI, 70eV): m/z (%) = 251 (M^+, 10.8), 249 (M^+, 32.5), 122 (100); Anal. calcd. for $C_{12}H_8NO_3Cl$: C, 57.73; H, 3.23; N, 5.61. Found: C, 57.62; H, 3.29; N, 5.54.

2-(4'-tert-Butylphenoxy)nitrobenzene (**4h**). Yellow liquid; ^1H-NMR: δ = 1.32 (9H, s), 6.97 (2H, d, *J* = 8.8 Hz), 6.99 (1H, d, *J* = 8.0 Hz), 7.14 (1H, t, *J* = 7.6 Hz), 7.37 (2H, d, *J* = 8.8 Hz), 7.45 (1H, m), 7.92 (1H, d, *J* = 8.0 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{16}H_{21}N_2O_3$: 289.1547; found: 289.1552.

2-(2'-Chlorophenoxy)nitrobenzene (**4i**). Pale yellow liquid; ^1H-NMR: δ = 6.83 (1H, dd, *J* = 8.4, 1.2 Hz), 7.07 (1H, dd, *J* = 8.0, 1.6 Hz), 7.16 (3 H, m), 7.47 (2H, m), 7.97 (1H, dd, *J* = 8.0, 1.6 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{12}H_{12}N_2O_3Cl$: 267.0531; found: 267.0535.

2-(3'-Methylphenoxy)nitrobenzene (**4j**). Pale yellow liquid; ^1H-NMR: δ = 2.34 (3H, s), 6.83 (2H, m), 6.99 (2H, m), 7.15 (1H, t, *J* =7.6 Hz), 7.23 (1H, t, *J* = 8.0 Hz), 7.46 (1H, dt, *J* = 8.0, 1.6 Hz), 7.93 (1H, dd, *J* = 7.6, 1.6 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{13}H_{15}N_2O_3$: 247.1077; found: 247.1080.

2-(4'-tert-Butylphenoxy)benzonitrile (**4k**). White liquid; ^1H-NMR: δ = 1.33 (9H, s), 6.84 (1H, d, *J* = 8.8 Hz), 7.00 (2H, m), 7.08 (1H, t, *J* = 7.2 Hz), 7.39 (3H, m), 7.63 (1H, dd, *J* = 7.6, 1.6 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{17}H_{21}N_2O$: 269.1648; found: 269.1648.

2-(4'-Chlorophenoxy)benzonitrile (**4l**). White solid; m.p. 85.0-85.7 ^oC; ^1H-NMR: δ = 6.85 (1H, d, *J* = 8.8 Hz), 7.01 (2H, m), 7.14 (1H, t, *J* = 7.2 Hz), 7.35 (2H, m), 7.47 (1H, m), 7.66 (1H, dd, *J* = 8.0, 2.0 Hz); HRMS-FAB: m/z $[M+NH_4]^+$ Calcd. for $C_{13}H_{12}N_2OCl$: 247.0627; found: 247.0633.

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Sample Availability: Samples of the compounds are available from the authors.