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Metal-Free Synthesis of Aryl Ethers in Water

Erik Lindstedt, Raju Ghosh, and Berit Olofsson*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University,
SE-106 91 Stockholm, Sweden

berit@organ.su.se

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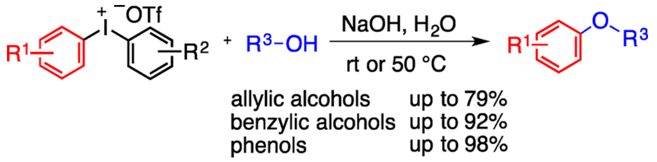
ABSTRACT



The first arylation of allylic and benzylic alcohols with diaryliodonium salts is reported. The reaction yields alkyl aryl ethers under mild and metal-free conditions. Phenols are arylated to diaryl ethers in good to excellent yields. The reaction employs diaryliodonium salts and sodium hydroxide in water at low temperature, and excess amounts of the coupling partners are avoided.

Aryl ethers are important structural motifs in many natural products and drugs, and heteroatom arylation and alkylation rank as the most common transformations in the synthesis of drug candidates.[1] Consequently, there are many synthetic routes to this compound class, ranging from the classical Ullmann coupling to recent copper- and palladium-catalyzed coupling reactions employing alcohols and aryl halides or arylboronic acids.[2] Metal-catalyzed reactions are often high-yielding, but generally suffer from the need for expensive catalysts, ligands, high temperatures, and long reaction times.[3]

Metal-free syntheses of aryl ethers from alcohols include the Williamson ether synthesis,[4] S_NAr reactions with electron-deficient aryl fluorides,[5] and reactions with Mitsunobu type reagents,[6] aryl mesylates,[7] or benzyne intermediates.[8] These reactions are either performed at high temperature, require toxic reagents, or have a limited substrate scope.[9] A metal-free O-alkylation of naphthols under acidic conditions was recently reported, which addressed some of the environmental issues usually associated with ether formation.[10]

We have recently reported an efficient and metal-free synthesis of diaryl ethers by arylation of phenols with diaryliodonium salts at room temperature.[11] The arylation of aliphatic alcohols with these reagents was briefly reported some decades ago,[12] but a synthetically useful method is still lacking. A recent copper-catalyzed monoarylation of

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(1) (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451–3479. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(2) Recent reports: (a) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695. (b) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9943–9947. (c) Maligres, P. E.; Li, J.; Krska, S. W.; Schreier, J. D.; Raheem, I. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 9071–9074. (d) Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 11592–11598.

(3) Recent reviews: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (b) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829–856. (c) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271–2285.

(4) Fuhrmann, E.; Talbiersky, J. R. *Org. Process Res. Dev.* **2005**, *9*, 206–211.

(5) (a) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem.* **1998**, *63*, 9594–9596. (b) Bunce, R. A.; Easton, K. M. *Org. Prep. Proced. Int.* **2004**, *36*, 76–81.

(6) (a) Manivel, P.; Rai, N. P.; Jayashankara, V. P.; Arunachalam, P. N. *Tetrahedron Lett.* **2007**, *48*, 2701–2705. (b) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359–7367.

(7) Sach, N. W.; Richter, D. T.; Cripps, S.; Tran-Dubé, M.; Zhu, H.; Huang, B.; Cui, J.; Sutton, S. C. *Org. Lett.* **2012**, *14*, 3886–3889.

(8) (a) Cano, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654–660. (b) Yuan, Y.; Thomé, I.; Kim, S. H.; Chen, D.; Beyer, A.; Bonnamour, J.; Zuidema, E.; Chang, S.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 2892–2898.

(9) Recent review: Mehta, V. P.; Punji, B. *RSC Advances* **2013**, *3*, 11957–11986.

(10) Cazorla, C.; Pfordt, E.; Duclos, M.-C.; Metay, E.; Lemaire, M. *Green Chem.* **2011**, *13*, 2482–2488.

(11) (a) Jalalian, N.; Petersen, T. B.; Olofsson, B. *Chem.—Eur. J.* **2012**, *18*, 14140–14149. (b) Jalalian, N.; Ishikawa, E. E.; Silva, L. F., Jr.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552–1555.

(12) (a) Beringer, F. M.; Brierley, A.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2708–2712 (5 equiv NaOMe, Ph_2IBr in refluxing MeOH). Mechanistic studies: (b) Lubinkowski, J. J.; Gimenez Arrieche, C.; McEwen, W. E. *J. Org. Chem.* **1980**, *45*, 2076–2079. (c) Lubinkowski, J. J.; Knapczyk, J. W.; Calderon, J. L.; Petit, L. R.; McEwen, W. E. *J. Org. Chem.* **1975**, *40*, 3010–3015.

10.1021/ol402960f

vicinal diols with diaryliodonium salts was inefficient for regular alcohols.[13]

The lack of a general, metal-free arylation methodology for aliphatic alcohols under mild and environmentally benign conditions prompted us to develop an arylation reaction with diaryliodonium salts, which are stable hypervalent iodine reagents of low toxicity.[14,15] Herein our preliminary results are disclosed.

An initial screening revealed that conjugated and regular alcohols displayed rather different reactivity toward diaryliodonium salts. Conjugated alcohols are easily oxidized to the corresponding aldehydes/ketones or carboxylic acids, thus complicating the use of hypervalent iodine reagents, which are powerful oxidants.

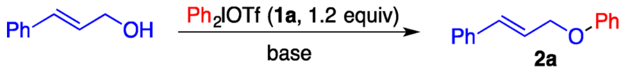
A thorough optimization was performed with cinnamyl alcohol and diphenyliodonium triflate (**1a**), giving ether **2a** in moderate yields using various bases and solvents (Table 1, entries 1−5). Water in combination with the mild base NaOH is ideal for environmental purposes, and these conditions were thus optimized further. Pleasingly, **2a** was obtained in 56% yield at 60 °C (entry 6). Further temperature increases were not fruitful, and ambient temperature was inefficient (entries 7−9).

The yield of **2a** increased to 64% with 2 equiv of base (entries 10−11), and the reaction could be performed at 50 °C for 3 h instead (entry 12). A 1 h reaction time was sufficient, and potassium or lithium hydroxide gave similar results (entries 13−16).

The addition of the radical trap 1,1-diphenylethylene (DPE) did not influence the reaction outcome (entry 17), indicating that neither products nor byproducts are formed *via* a radical pathway.[16] Diphenyliodonium tetrafluoroborate (**1b**) was as efficient as the triflate salt, whereas the corresponding tosylate salt **1c** gave product **2a** in 55% yield.

Symmetric and unsymmetric diaryliodonium salts are easily available,[17] and the arylation scope was subsequently investigated with salts **1** (Scheme 1).[18] Cinnamyl alcohol was chemoselectively arylated with nitrophenyl(phenyl)-iodonium triflate (**1d**) to give **2b**. This reaction was best performed at room temperature to avoid competitive arylation of the base (*vide infra*).

Table 1. Optimization with Cinnamyl Alcohol

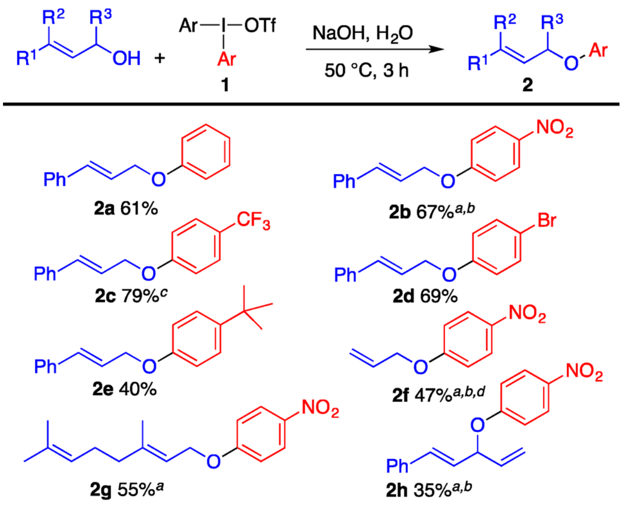


entry	base	(equiv)	solvent	T (°C)	t (h)	yield (%)[a]
1	*t*-BuOK	1.2	toluene	40	4	38
2	NaH	1.2	toluene	40	6	46
3	NaH	1.2	THF	40	6	29
4	NaH	1.2	CH_2Cl_2	40	2	29
5	NaOH	1.2	H_2O	40	3	32
6	NaOH	1.2	H_2O	60	3	56
7	NaOH	1.2	H_2O	80	3	55
8	NaOH	1.2	H_2O	100	3	49
9	NaOH	1.2	H_2O	rt	3	3
10	NaOH	2.0	H_2O	60	3	64
11	NaOH	5.0	H_2O	60	3	65
12	NaOH	2.0	H_2O	50	3	62
13	NaOH	2.0	H_2O	60	1	63
14	NaOH	1.5	H_2O	60	1	60
15	KOH	2.0	H_2O	60	1	61
16	LiOH	2.0	H_2O	60	1	61
17[b]	NaOH	2.0	H_2O	60	3	64

[a] NMR yield with 4-anisaldehyde as the internal standard. [b] 5% DPE added.

4-Trifluoromethylphenyl salt **1e** was highly reactive and delivered product **2c** in high yield. The synthesis of bromo-substituted ether **2d** further illustrates the functional group tolerance of the methodology. Alkyl-substituted salts reacted slower than unsubstituted or electron-withdrawing salts, and **2e** was formed in moderate yield. The arylation of allyl alcohol required a longer reaction time to give ether

Scheme 1. Arylation of Allylic Alcohols



[a] Unsymmetric salt **1d** used. [b] At rt. [c] BF_4 salt **1e** used. [d] 22 h.

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(13) Kuriyama, M.; Hamaguchi, N.; Onomura, O. *Chem.—Eur. J.* **2012**, *18*, 1591–1594.

(14) (a) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, 370–409. (b) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052–9070. (c) Quideau, S.; Wirth, T. *Tetrahedron* **2010**, *66*, 5737–5738.

(15) The biological activities of several diaryliodonium salts have been studied in detail, and the results are summarized in: Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. Diaryliodonium salts have even been found suitable to use in oral mouthwash; see: Goldstein, E. J. C.; Citron, D. M.; Warren, Y.; Merriam, C. V.; Tyrrell, K.; Fernandez, H.; Radhakrishnan, U.; Stang, P. J.; Conrads, G. *Antimicrob. Agents Chemother.* **2004**, *48*, 2766–2770.

(16) Radicals were involved in byproduct formation in the mechanistic studies by McEwen; see refs 12b, 12c.

(17) (a) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602–4607. (b) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610–2618. (c) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592–596. (d) Hossain, M. D.; Kitamura, T. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2213–2219. (e) Hossain, M. D.; Ikegami, Y.; Kitamura, T. *J. Org. Chem.* **2006**, *71*, 9903–9905.

(18) Triflate salts were used, as those are generally easier and more inexpensive to synthesize compared to the tetrafluoroborates (see ref 17). Triflate salts are also efficiently obtained from other salts by anion exchange with NaOTf. See the Supporting Information for structures and synthetic details of salts **1**.

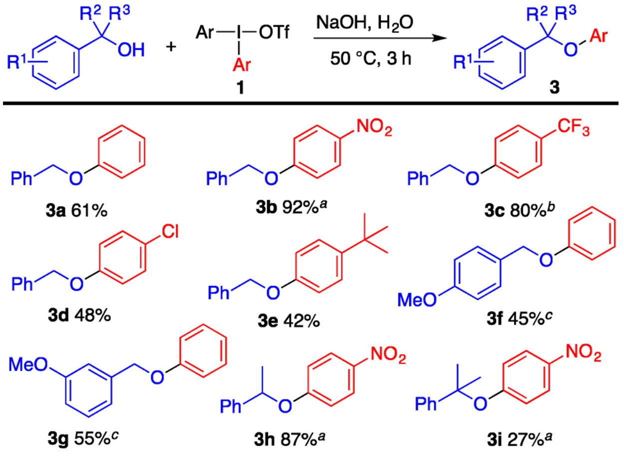
2f, and geraniol proved to be a better substrate (**2g**). Even a sterically hindered, secondary alcohol could be arylated to yield **2h**.

The arylation of benzylic alcohols was subsequently examined (Scheme 2). Benzyl alcohol was arylated in moderate to good yields with a variety of salts, to give products with electron-withdrawing, halide, and alkyl substituents (**3a**–**3e**).

Again, complete chemoselectivity was observed in arylations with 4-nitrophenyl salt **1d**. The reactivity difference of salts **1d** and **1a** is illustrated by the higher yield of nitro product **3b** compared to phenyl product **3a**.

Electron-donating groups on the alcohol were tolerated (**3f**–**3g**), and even sterically hindered secondary and tertiary alcohols were arylated (**3h**–**3i**). Arylations with *ortho*-substituted iodonium salts were poor-yielding.

Scheme 2. Arylation of Benzylic Alcohols

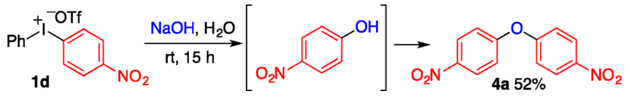


[a] Unsymmetric salt **1d** used. [b] BF_4 salt **1e** used. [c] At 60 °C.

The moderate arylation yields of allylic and benzylic alcohols are explained by competitive oxidation to the corresponding aldehydes/ketones and carboxylic acids, which could not be prevented with these oxidation-prone substrates.[19]

As mentioned above, reactions with nitro-substituted salt **1d** were best performed at room temperature due to the increased reactivity of this salt. The main byproduct was found to be the symmetric di(4-nitrophenyl) ether **4a**, which was formed by sequential arylation of the base and the resulting phenol. In the absence of alcohol, this background reaction provided diaryl ether **4a** in 52% yield (Scheme 3).[20] Arylation of the base was not seen with the other salts.

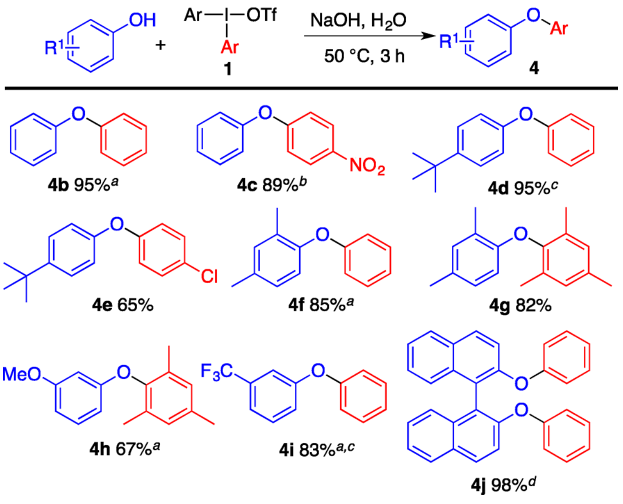
Scheme 3. Synthesis of Diaryl Ether **4a** by Arylation of NaOH



We have recently reported a high-yielding synthesis of diaryl ethers with diaryliodonium salts in THF or toluene.[11] Despite the efficiency of this transformation, the arylation conditions presented herein are preferable for environmental reasons. Phenols have previously been arylated in water under more forcing conditions,[21] and we were therefore keen to see the scope under our mild reaction conditions.

Pleasingly, the arylation of phenols in water was efficient (Scheme 4). Good to excellent yields were obtained with various iodonium salts, tolerating both nitro- and halide substituents (**4b**–**4e**). The reaction proved insensitive to steric hindrance on both coupling partners (**4f**–**4h**). Phenols with electron-donating or -withdrawing substituents were also arylated (**4h**, **4i**).

Scheme 4. Arylation of Phenols



[a] 60 °C for 1 h. [b] Unsymmetric salt **1d** used. [c] 6 h. [d] 17.5 h.

Even diarylation of binaphthol, with substantial steric hindrance, was successful, and the product fell out as a solid during the reaction in almost quantitative yield (**4j**).

We have previously investigated the chemoselectivity of phenol arylations with unsymmetric salts and found them to follow the *ortho*-effect with sterically hindered salts.[11,22] Under the current arylation conditions, the *ortho*-effect was dominant in reactions with phenol (Scheme 5a, **4k:4b**), whereas 2,4-dimethylphenol gave a 1:1 mixture of **4l:4f** in reactions with phenyl(triisopropylphenyl)iodonium triflate (**1f**) (Scheme 5b). This illustrates the delicate balance

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(19) 16% acid, 9% aldehyde, and 3% remaining alcohol were identified in the synthesis of **2a**. Acetophenone was formed in 20% yield in the synthesis of **3h**. Excess alcohol or salt did not improve the yield, nor did an inert atmosphere.

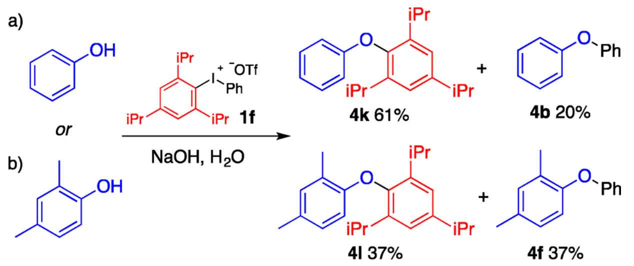
(20) This kind of transformation was reported as a side reaction in: Li, J.; Liu, L. *RSC Advances* **2012**, *2*, 10485–10487. For a Pd-catalyzed version of this reaction with ArX, see ref 2a.

(21) (a) Crowder, J. R.; Glover, E. E.; Grundon, M. F.; Kaempfen, H. X. *J. Chem. Soc.* **1963**, 4578–4585. (b) Teclechiel, D.; Sundström, M.; Marsh, G. *Chemosphere* **2009**, *74*, 421–427. (c) Marsh, G.; Stenutz, R.; Bergman, Å. *Eur. J. Org. Chem.* **2003**, 2566–2576.

(22) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem.—Eur. J.* **2013**, *19*, 10334–10342.

between steric and electronic effects, as product **4g** (Scheme 4) was formed in good yield from symmetric mesityl salt **1g** despite the steric hindrance.

Scheme 5. Chemoselectivity with *Ortho*-Substituents



The iodoarene that is formed in reactions with diaryliodonium salts could be recovered in 87–95% yield in arylations of both alcohols and phenols and reused for the synthesis of the diaryliodonium salt.[23] This facile recovery improves the atom economy and decreases the environmental impact further in large-scale reactions.

Regular aliphatic alcohols were poor substrates in this arylation, likely due to their higher pK_a values, which makes deprotonation with NaOH difficult. The arylation of this substrate class is underway and will be reported in due time.

In conclusion, the first arylation of activated aliphatic alcohols with diaryliodonium salts has been presented. The reaction is simple to perform, takes place in water under mild and metal-free conditions, and does not require excess amounts of the coupling partners.

The yields are moderate to good, and the aryl scope is broader than in S_NAr or benzyne reactions. Aryl groups with electron-deficient, halide, or alkyl substituents are efficiently transferred, while more electron-donating substituents are unsuitable.

Phenols are arylated in good to excellent yields with the same range of diaryliodonium salts, and sterically hindered substrates are well tolerated. Complete chemoselectivity was observed in reactions with unsymmetric salts having different electronic properties, whereas salts with *ortho*-substituents were less selective.

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Supporting Information Available. Experimental details, analytical data, and NMR copies of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] The iodoarene is recovered during product purification by silica gel chromatography; see the Supporting Information for details.

The authors declare no competing financial interest.