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Room Temperature, Metal-Free Arylation of Aliphatic Alcohols

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Diaryliodonium salts are demonstrated as efficient arylating agents of aliphatic alcohols under metal-free conditions. The reaction proceeds at room temperature within 90 min to give alkyl aryl ethers in good to excellent yields. Aryl groups with electron-withdrawing substituents are transferred most efficiently, and unsymmetric iodonium salts give chemoselective arylations. The methodology has been applied to the formal synthesis of butoxycaine.

Efficient transition metal-free transformations are of high importance in organic synthesis, for example in the pharmaceutical industry where trace amounts of remaining metal in biologically active compounds must be avoided. Furthermore, many metal-free reactions utilize inexpensive, readily available reagents of low toxicity.[1] The synthesis of alkyl aryl ethers is a central theme in organic chemistry, as this structural moiety is present in many drugs and natural products. Several copper- and palladium-catalyzed arylations of aliphatic alcohols with aryl halides or aryl boronic acids have been reported.[2] Drawbacks with metal-catalyzed methods include high temperatures, long reaction times or the need for excess starting materials and/or reagents (Figure 1 A).

Alkyl aryl ethers can also be synthesized by metal-free methods,[1b] including the Williamson ether synthesis,[3] reactions via benzyne intermediates[4] or Mitsunobu-type reagents.[5] Nucleophilic aromatic substitution is often efficient, but requires strong electron-withdrawing substituents or forcing conditions.[6] Diaryliodonium salts are stable and low-toxic[7] hypervalent iodine compounds that have recently been utilized as electrophilic arylation agents with a wide range of nucleophiles.[8] Despite this, the arylation of aliphatic alcohols with these reagents has only briefly been reported with the alcohol in large excess or as solvent, thus lacking synthetic utility.[9] Vicinal diols have been monoarylated with iodonium salts under Cu-catalyzed conditions, but regular alcohols could not be arylated.[10]

We have recently developed several O-arylations with diaryliodonium salts, including an environmentally benign arylation of allylic and benzylic alcohols in water at 50 °C for 3 h.[11] Herein, we report the first general arylation of aliphatic alcohols with diaryliodonium salts (Figure 1 B).

The arylation of 1-pentanol with diphenyliodonium salts **1a–c** to give alkyl phenyl ether **2a** was investigated as model reaction (Table 1). Contrary to our previous O-arylations,[11] sodium bases were found superior to both lithium and potassium bases (Entries 1–5).[12] Toluene was a better solvent than dichloromethane and tetrahydrofuran (THF), while no reaction took place in water (Entries 6–9).

Reactions at room temperature for only 30 min provided **2a** in equally good yield, and excess amounts of the reagents were not beneficial (Entries 10–11). The radical trap 1,1-diphe-

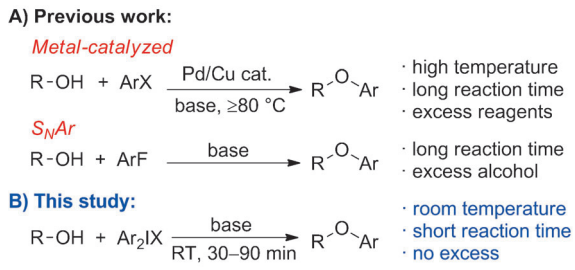
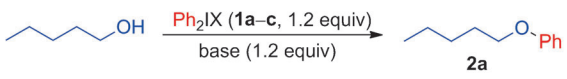


Figure 1. Synthesis of alkyl aryl ethers.

Table 1. Optimization with 1-pentanol.[a]



Entry	Base	Solvent	1a–c X	T [°C]	t [h]	Yield [%][b]
1	NaOH	toluene	1a OTf	80	2.0	47
2	NaH	toluene	1a OTf	80	2.0	75
3	*t*BuOLi	toluene	1a OTf	80	2.0	45
4	*t*BuOK	toluene	1a OTf	80	2.0	62
5	*t*BuONa	toluene	1a OTf	80	2.0	80
6	*t*BuONa	toluene	1a OTf	40	2.0	80
7	*t*BuONa	CH_2Cl_2	1a OTf	40	2.0	70
8	*t*BuONa	THF	1a OTf	40	2.0	24
9	NaOH	H_2O	1a OTf	40	2.0	0[c]
10	*t*BuONa	toluene	1a OTf	RT	0.5	81
11[d]	*t*BuONa	toluene	1a OTf	RT	0.5	81
12[e]	*t*BuONa	toluene	1a OTf	RT	0.5	74
13	*t*BuONa	toluene	1b BF_4	RT	0.5	67
14	*t*BuONa	toluene	1c OTs	RT	0.5	50

[a] *Reagents and conditions*: 1-Pentanol (0.5 mmol), base, solvent (2.5 mL), 0 °C, under argon atmosphere; after 15 min at RT, salt **1** was added. [b] NMR yield with 4-anisaldehyde as internal standard. [c] No reaction. [d] 2 equiv **1a**, 2 equiv base. [e] 1 equiv DPE added.

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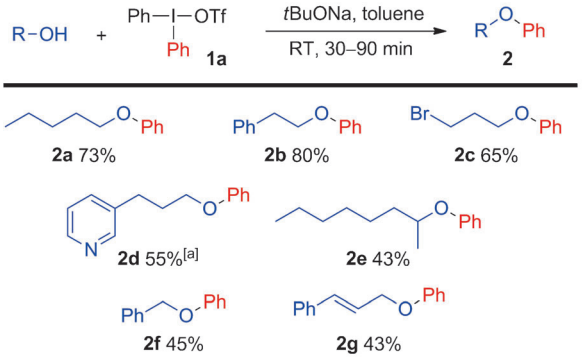
nylethylene (DPE) was found to not influence the reaction much (Entry 12), and addition of crown ether lowered the yield.[13] Diphenyliodonium tetrafluoroborate (**1b**) and tosylate (**1c**) provided **2a** in inferior yields to the triflate **1a** (Entries 13–14). This is surprising, as tetrafluoroborates often are superior to triflates, whereas tosylates can be inferior in arylation reactions.[8]

The optimized phenylation conditions (Table 1, Entry 10) were subsequently applied on various aliphatic alcohols (Scheme 1). Several aryl ethers were successfully obtained from



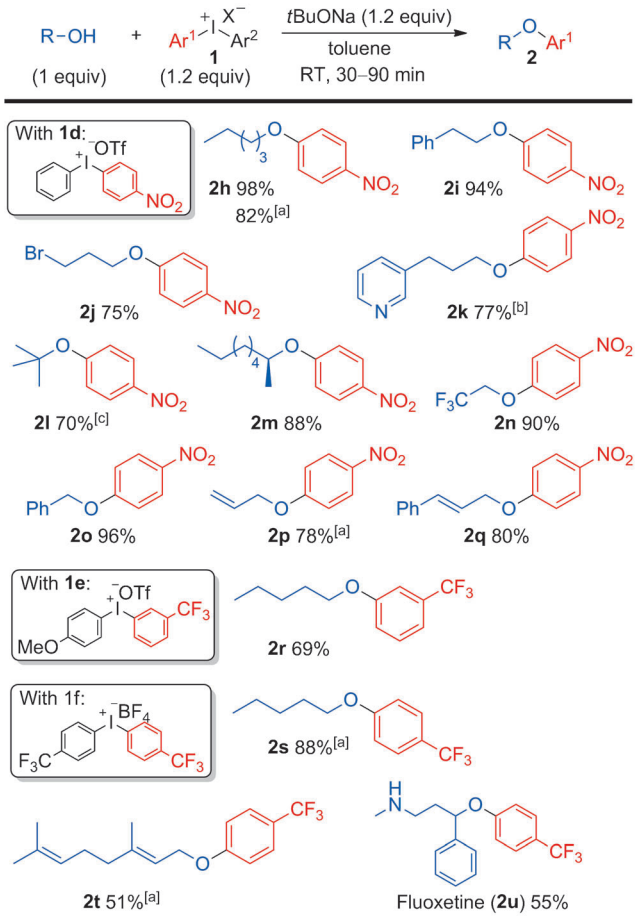
Scheme 1. Phenylation of aliphatic alcohols. [a] At 40 °C.

primary alcohols, including bromo-substituted ether **2c**. A pyridyl substituent was also tolerated; ether **2d** was synthesized at 40 °C due to solubility problems at room temperature. Secondary alcohols were phenylated in moderate yield (**2e**).[14] Benzyl ether **2f** was formed in 45%, and cinnamyl alcohol delivered **2g** in similar yield; these products are obtained in better yields using the recently reported NaOH/water conditions.[11d]

Unreacted alcohol could be recovered in most phenylations, but attempts to achieve complete conversion by using excess reagents failed (Table 1, Entry 11). The synthesis of ethers **2f** and **2g** was accompanied by formation of minor amounts of the corresponding aldehydes, as previously noted.[11d]

Selected diaryliodonium salts[15] were then utilized to synthesize a range of alkyl aryl ethers **2** (Scheme 2). Nitrophenyl ethers can be selectively transformed into a range of functionalized arenes, and are valuable precursors in the production of pharmaceuticals, agrochemicals and dyes.[16] The unsymmetric nitro salt **1d** gave chemoselective transfer[17] of the 4-nitrophenyl group in excellent yields (**2h**–**k**). This salt was so reactive that ether **2l** was often obtained as byproduct in trace amounts.[18] NaH was a more convenient base in reactions where **2l** was difficult to separate from the product, despite slightly lower yields (**2h** 98% versus 82%).

Indeed, product **2l** was isolated in 70% yield in the absence of added alcohol. As expected, no erosion of enantiomeric excess was seen in the arylation of *(S)*-2-octanol to give **2m**. Alcohols with electron-withdrawing substituents, such as trifluoroethanol, were also excellent substrates (**2n**). Even benzylic and allylic alcohols were efficiently arylated with this salt,



Scheme 2. Chemoselectivity aspects and arylation scope. [a] NaH was used. [b] At 40 °C. [c] No alcohol was added.

providing **2o**–**q**. These products were obtained in better yields with this methodology than in the water system, as the nitro salt reacted with NaOH to provide the corresponding diaryl ether in water.[11d]

Chemoselective arylation was also obtained with salt **1e**, which transferred the 3-trifluoromethylphenyl moiety to yield ether **2r**. The symmetric 4-trifluoromethylphenyl tetrafluoroborate **1f** could be employed to arylate 1-pentanol and geraniol to **2s**–**t**, indicating that tetrafluoroborate salts are efficient in transfer of electron-withdrawing aryl groups.

Alkyl aryl ethers with electron-withdrawing substituents, such as nitro groups, are generally obtained by nucleophilic aromatic substitution. While the yields in Scheme 2 are similar to those obtained by S_NAr reactions, our conditions are significantly milder.[19] *Ortho*-substituted and electron-rich diaryliodonium salts surprisingly gave sluggish reactions with byproduct formation, and a mechanistic study of these reactions is currently performed in our laboratory.

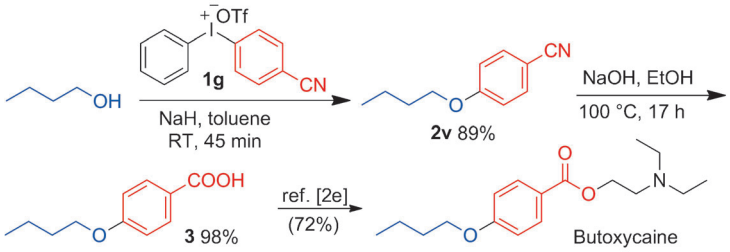
Trifluoromethylated arenes are important building blocks in medicinal chemistry,[20] and the methodology for selective introduction of such a moiety in the presence of other functional groups is versatile in the synthesis of drug candidates. This feature was demonstrated in the synthesis of fluoxetine (Prozac),[21] which is one of the most prescribed antidepres-

sants in the world. The commercially available, unprotected amino alcohol was successfully arylated with diaryliodonium salt **1 f** to give fluoxetine (**2 u**) in 55% yield without competing N-arylation.[22] We have previously demonstrated the efficient recovery of the iodoarene formed in arylations with diaryliodonium salts.[11]

The methodology was subsequently applied in the synthesis of Butoxycaine, which is a local anestethic drug. The target has previously been synthesized by Pd-catalyzed arylation of butanol with methyl 4-bromobenzoate, followed by hydrolysis to the carboxylic acid and *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling to butoxycaine.[2e]

In our formal synthesis of butoxycaine, *n*-butanol was chemoselectively arylated with salt **1 g** at room temperature, giving nitrile **2 v** in 89% yield within 45 min (Scheme 3).[23] The nitrile was hydrolyzed to the carboxylic acid **3** in almost quantitative yield, completing the formal synthesis. Compound **3** was thus synthesized under metal-free conditions in 87% overall yield from butanol, which should be compared to the previous Pd-catalyzed strategy yielding **3** in 74%.

In conclusion, the first efficient arylation of aliphatic alcohols with diaryliodonium salts has been developed, employing mild and metal-free conditions. Aryl groups with electron-withdrawing substituents are transferred in excellent yields for a wide range of alcohols. Phenylation works best for unactivated, primary alcohols, but also secondary, benzylic and allylic alcohols are tolerated, and several novel alkyl aryl ethers have been synthesized. Compared to nucleophilic aromatic substitutions, the present arylation methodology does not require excess reagents, elevated temperature or long reaction time. The efficiency of the methodology is demonstrated in a high-yielding formal synthesis of butoxycaine. Investigations into the mechanism and the full scope of this transformation are currently being performed in our laboratory and will be reported in due time.



Scheme 3. Formal synthesis of butoxycaine.

Experimental Section

Synthesis of alkyl aryl ethers 2: Alcohol (0.5 mmol) was added dropwise at 0 °C under argon atmosphere to a solution of *t*BuONa (0.6 mmol) in dry toluene (2.5 mL), and the solution was stirred for 15 min at RT. Diaryliodonium salt **1** (0.6 mmol) was added at 0 °C, and the solution was stirred for 0.5–1.5 h at RT. The reaction mixture was diluted with Et_2O (5.0 mL), filtered through a short silica plug and eluated with Et_2O. The combined filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel, using pentane, pentane/EtOAc or CH_2Cl_2/MeOH as eluent, to yield ether **2**.

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Keywords: aliphatic alcohols · alkyl aryl ethers · arylation · diaryliodonium salts · hypervalent iodine

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[13] When DPE was added to reactions in THF, the yield increased considerably. Radicals were involved in byproduct formation in the mechanistic studies by McEwen, see ref. [9]. See the Supporting Information for details on DPE and crown ether experiments.
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