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Diaryl iodonium 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 arylation of allylic and benzylic alcohols in water at 50 °C for 3 h. Herein, we report the first general arylation of aliphatic alcohols with diaryliodonium salts (Figure 1 B).

The arylation of 1-pentanol with diphenyliodonium salts a–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). 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-diphenyl

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**Table 1.** Optimization with 1-pentanol.15

| Entry | Base solvent | 1a–c X | T (°C) | t (h) | Yield [%] |
|-------|-------------|--------|--------|-------|----------|
| 1     | NaOH toluene| 1a–c   | 80     | 2.0   | 47       |
| 2     | NaH toluene | 1a–c   | 80     | 2.0   | 75       |
| 3     | tBuOLi toluene| 1a–c | 80     | 2.0   | 45       |
| 4     | tBuOK toluene| 1a–c | 80     | 2.0   | 62       |
| 5     | tBuONa toluene| 1a–c | 80     | 2.0   | 80       |
| 6     | tBuONa CH₂Cl₂ | 1a–c | 40     | 2.0   | 70       |
| 7     | tBuONa THF  | 1a–c   | 40     | 2.0   | 24       |
| 8     | NaOH H₂O     | 1a–c   | 40     | 2.0   | 95       |
| 9     | tBuONa toluene| 1a–c | 80     | 0.5   | 81       |
| 10    | tBuONa toluene| 1a–c | 80     | 0.5   | 81       |
| 11    | tBuONa toluene| 1a–c | 80     | 0.5   | 74       |
| 12    | tBuONa toluene| 1a–c | 80     | 0.5   | 67       |
| 13    | tBuONa toluene| 1a–c | 80     | 0.5   | 52       |

[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.
nylethylene (DPE) was found to not influence the reaction much (Entry 12), and addition of crown ether lowered the yield. 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.\[13\]

The optimized phenylation conditions (Table 1, Entry 10) were subsequently applied on various aliphatic alcohols (Scheme 1). Several aryl ethers were successfully obtained from 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 (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 21 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 benzyl- and allylic alcohols were efficiently arylated with this salt, 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 antidepressant...
sants in the world. The commercially available, un-
protected amino alcohol was successfully arylated with diaryliodonium salt 1f to give fluoxetine (2u) in 55% yield without competing N-arylation.[32] We have previously demonstrated the efficient recovery of the iodoarene formed in arylation with diaryliodonium salts.[31]

The methodology was subsequently applied in the synthesis of Butoxycaine, which is a local anesthetic drug. The target has previously been synthesized by Pd-catalyzed arylation of butanol with methyl 4-bromo-mobenzofurate, followed by hydrolysis to the carboxylic acid and N,N-dicyclohexylcarbodiimide (DCC) coupling to butoxycaine.[24]

In our formal synthesis of butoxycaine, n-butanol was chemoselectively arylated with salt 1g at room temperature, giving nitrile 2v 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 aryl aryl ethers have been synthesized. Compared to nucleophilic aromatic substitutions, alkyl aryl ethers, 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.

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 tBuONa (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 Et2O (5.0 mL), filtered through a short silica plug and eluted with Et2O. The combined filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel, using pentane, pentane/EtOAc or CH2Cl2/MeOH as eluent, to yield ether 2.

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

[1] a) R. A. D. Arancon, C. Sze Ki Lin, C. Vargas, R. Luque, Org. Biomol. Chem. 2014, 12, 10–35; b) Y. F. Mehta, B. Punji, RSC Adv. 2013, 3, 11957–11966; c) M. Raj, V. K. Singh, Chem. Commun. 2009, 6687–6703.
[2] Recent reports: a) P. E. Maligres, J. Li, S. W. Krska, J. D. Schreier, I. T. Raheem, Angew. Chem. 2012, 124, 9205–9208; Angew. Chem. Int. Ed. 2012, 51, 9071–9074; b) J. X. Qiao, P. Y. S. Lam, Synthesis 2011, 829–856; c) D. Maiti, Chem. Commun. 2011, 47, 8340–8342; d) X. Wu, B. P. Fons, S. L. Buchwald, Angew. Chem. 2011, 123, 10117–10121; Angew. Chem. Int. Ed. 2011, 50, 9943–9947; e) S. Goweriank, A. G. Sergeev, P. Arbanas, A. Spannenberg, H. Neumann, M. Beller, J. Am. Chem. Soc. 2010, 132, 11592–11598; f) F. Monnier, M. Taillefer, Angew. Chem. 2009, 121, 7088–7105; Angew. Chem. Int. Ed. 2009, 48, 6954–6971; g) G. Evano, N. Blanchard, M. Toumi, Chem. Rev. 2008, 108, 3054–3131.
[3] E. Fuhrmann, J. Talberries, Org. Process Res. Dev. 2005, 9, 206–211.
[4] a) R. Cano, D. J. Ramón, M. Yus, J. Org. Chem. 2011, 76, 654–660; b) B. Xu, J. Xue, J. Zhi, Y. Li, Chem. Lett. 2008, 37, 202–203.
[5] a) P. Manivel, N. P. Rai, V. P. Jayashankara, P. N. Arunachalam, Tetrahedron Lett. 2007, 48, 2701–2705; b) T. Shintou, T. Mukaiyama, J. Am. Chem. Soc. 2004, 126, 7359–7367; c) N. W. Sach, D. T. Richter, S. Cripps, M. Tran-Dubé, H. Zhi, B. Huang, J. Cui, S. C. Sutton, Org. Lett. 2012, 14, 3886–3889.
[6] a) S. G. Ouellet, A. Bernardi, R. Angelaud, P. D’Ouhea, Tetrahedron Lett. 2009, 50, 3776–3779; b) A. Kim, J. D. Powers, J. F. Toczek, J. Org. Chem. 2006, 71, 2170–2172; c) R. A. Bunce, K. M. Easton, Proc. Prep. Int. Drug. 2004, 36, 76–81; d) T. F. Woiwode, C. Rose, T. J. Wandleiss, J. Org. Chem. 1998, 63, 9594–9596.
[7] Results from studies of the biological activities of several diaryliodonium salts are summarized in: a) P. J. Stang, V. V. Zhdankin, Chem. Rev. 1996, 96, 1123–1178; Diaryliodonium salts have even been found suitable to use in dental materials and oral mouthwash, see: b) L. S. Gonçalves, R. M. Moraes, F. A. Ogliari, L. Boaro, R. R. Braga, S. Consani, Dent. Mater. 2013, 29, 1251–1255; c) E. J. C. Goldstein, D. M. Citron, Y. Warren, C. V. Merriam, K. Tyrell, H. Fernandez, U. Radhakrishnan, P. J. Stang, G. Conradi, Antimicrob. Agents Chemother. 2004, 48, 2766–2770.
[8] a) M. S. Yusubov, A. V. Maskarev, V. V. Zhdkhanov, ARKIVOC 2011, 370–409; b) E. A. Merritt, B. Olofsson, Angew. Chem. 2009, 121, 9214–9234; Angew. Chem. Int. Ed. 2009, 48, 9052–9070.
[9] a) F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, C. C. Lumpkin, J. Am. Chem. Soc. 1993, 75, 2708–2712 (5 equiv NaOMe, PH2Br in refluxing MeOH); Mechanistic studies with MeOH, ETOH and iPrOH using radical traps: b) I. J. Lubinkowski, C. Gimenez Arricue, W. E. McEwen, J. Org. Chem. 1980, 45, 2076–2079; c) J. J. Lubinkowski, J. W. Knapczyk, J. L. Calderon, L. R. Petit, W. E. McEwen, J. Org. Chem. 1975, 40, 3010–3015.
[10] C. Cazorla, E. Pfirldr, M. C. Duclos, E. Metay, M. Lemare, Green Chem. 2011, 13, 2462–2468.
[11] a) N. Jalalian, T. B. Petersen, B. Olofsson, Ophfchem. Eur. J. 2012, 18, 14140–14149; b) T. B. Petersen, R. Khan, B. Olofsson, Org. Lett. 2011, 13, 3462–3465; c) N. Jalalian, E. Ishikawa, L. F. Silva, Jr., B. Olofsson, Org. Lett. 2011, 13, 1552–1555; d) E. Lindstedt, R. Ghosh, B. Olofsson, Org. Lett. 2013, 15, 6070–6073; e) R. Ghosh, B. Olofsson, Org. Lett. 2014, 16, 1830–1832.
[12] The low reactivity with NaOH was expected due to the similar pKa values of water and 1-pentanol. Anhydrous conditions were used in subsequent reactions to avoid formation of NaOH in situ.

[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.

[14] The small pKa difference between secondary alcohols and tBuOH might explain the moderate yield, but use of NaH did not improve the results.

[15] a) M. Bielawski, D. Aili, B. Olofsson, J. Org. Chem. 2008, 73, 4602–4607; b) M. Zhu, N. Jalalian, B. Olofsson, Synlett 2008, 592–596; c) M. Bielawski, M. Zhu, B. Olofsson, Adv. Synth. Catal. 2007, 349, 2610–2618.

[16] a) R. Dey, N. Mukherjee, S. Ahammed, B. C. Ranu, Chem. Commun. 2012, 48, 7982–7984; b) A. M. Tafesh, J. Weiguny, Chem. Rev. 1996, 96, 2035–2052.

[17] For a chemoselectivity discussion, see J. Malmgren, S. Santoro, N. Jalalian, F. Himo, B. Olofsson, Chem. Eur. J. 2013, 19, 10334–10342 and references therein.

[18] Arylation of the base was not seen in the phenylation reactions.

[19] Several of the compounds in Scheme 2 have never been synthesized by SnAr, but 2n was formed in 88% yield using ArF, K₂CO₃ in N,N-dimethylformamide (DMF) at 100 °C for 24 h, and 2α was obtained in 92% yield using ArF with KOH and 10% phase-transfer catalyst without solvent at 80 °C for 1 h, see a) T. Doura, Q. An, F. Sugihara, T. Matsuda, S. Sando, Chem. Lett. 2011, 40, 1357–1359; b) A. Loupy, N. Philippon, P. Pigeon, J. Sansoulet, H. Galons, Synth. Commun. 1990, 20, 2855–2864.

[20] a) O. A. Tomashenko, V. V. Grushin, Chem. Rev. 2011, 111, 4475–4521; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 2008, 37, 320–330.

[21] a) B. Ahmed-Omer, A. J. Sanderson, Org. Biomol. Chem. 2011, 9, 3854–3862; b) H. Kakei, T. Nemoto, T. Ohshima, M. Shibasaki, Angew. Chem. 2004, 116, 321–324; Angew. Chem. Int. Ed. 2004, 43, 317–320.

[22] Arylation of amines with diaryliodonium salts is known under metal-free and metal-catalyzed conditions, see a) J. Li, L. Liu, RSC Adv. 2012, 2, 10485–10487; b) S.-K. Kang, S.-H. Lee, D. Lee, Synlett 2000, 1022–1024.

[23] Arylation in the presence of tBuOHa as base gives 2v in 98% yield, but with 2% inseparable byproduct from arylation of the base.

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