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C—O bond formation in a microfluidic reactor: high yield S_NAr substitution of heteroaryl chlorides

Mohammad Parvez Alam, Barbara Jagodzinska, Jesus Campagna, Patricia Spilman, Varghese John *

Drug Discovery Laboratory, Department of Neurology, Mary S. Easton Center for Alzheimer's Disease Research, University of California, Los Angeles, CA 90095, United States

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ABSTRACT

This study describes our development of a novel and efficient procedure for C—O bond formation under mild conditions, for coupling heteroaryl chlorides with phenols or primary aliphatic alcohols. We utilized a continuous-flow microfluidic reactor for C—O bond formation in electron-deficient pyrimidines and pyridines in a much more facile manner with a cleaner reaction profile, high yield, quick scalability, and without the need for the transition metal catalyst. This approach can be of general utility to make C—O bond containing intermediates of industrial importance in a continuous and safe manner.

Introduction

In both academia and industry, carbon—oxygen (C—O) bond forming reactions are of great utility as these bonds are ubiquitous in natural products, polymers, and biologically active molecules.[1] Some examples of bioactive molecules incorporating the C—O bond are shown in Figure 1. Puromorphamine is a Hedgehog-signaling pathway activator, an important regulator of stem cell renewal and cancer growth,[2] BMS-777607 at therapeutic doses acts as a multi-kinase inhibitor,[3] and bispyribac-sodium is used as a herbicide.[4]

Traditionally, C—O bonds are formed using nucleophilic aromatic substitution (S_NAr). Copper-mediated Ullmann coupling has typically been used for the synthesis of aryl ethers from aryl bromides/iodides and phenols, but it is characterized by a harsh reaction conditions and the need for stoichiometric amount of metal.[5] In the last decade, many groups have switched to Buchwald methodology, which utilizes a catalytic amount of copper and various ligands to generate the aryl ethers.[6] There are substantial precedents where S_NAr reactions were performed on activated aryl halides in flow under both traditional and microwave heating.[7] More recently, Charaschanya et al. have reported high-temperature and high-pressure S_NAr reactions of heterocycles with various nitrogen nucleophiles.[8] Although significant advances have been achieved in this area, the development of a more efficient, mild, economical, and green strategies for the C—O bond formation still constitutes a significant synthetic challenge. Pertinent to our hit-to-lead optimization work, improvement of such strategies would facilitate synthesis of analogs for biological analysis as part of our drug discovery efforts. Our interest is in finding an alternative, green chemistry approach to the precious transition-metal catalyzed C—O coupling reactions. To the best of our knowledge microfluidic reactor-based, rapid and high yield C—O bond formation under mild conditions, as described in this manuscript, has not been previously reported. Our approach, described herein, supplements the traditional C—O bond-forming reactions described above. Furthermore, it also reveals the benefits of using a continuous-flow microfluidic reactor, which include the following: short reaction times, superior mixing, efficient heat transfer, increased pressures, and the use of less reactive reagents that result in a high yield reaction.[9–17]

Results and discussion

In conventional batch reactions, dichloropyrimidine exhibits a low reactivity as compared to its bromo- or iodo-counterpart.[18] Consequently, the C—O bond formation using this intermediate is slow and takes many hours even under the metal catalysis.[19] In the initial phase of development of our method, we used 4,6-dichloro-2,5-dimethylpyrimidine and 4-methoxy-2-methylphenol to study the effects of temperature, pressure, and solvent on the yield of C—O bond formation (Table 1) in the continuous-flow microreactor. Traditionally, 4,6-dichloro-2,5-dimethylpyrimidine is coupled with 4-methoxy-2-methylphenol after treatment with sodium hydride (60% suspension in oil) in DMF for 5–10 h.[20]

* Corresponding author. Tel.: +1 (310) 206 4345; fax: +1 (310) 794 3148.
E-mail address: VJohn@mednet.ucla.edu (V. John).

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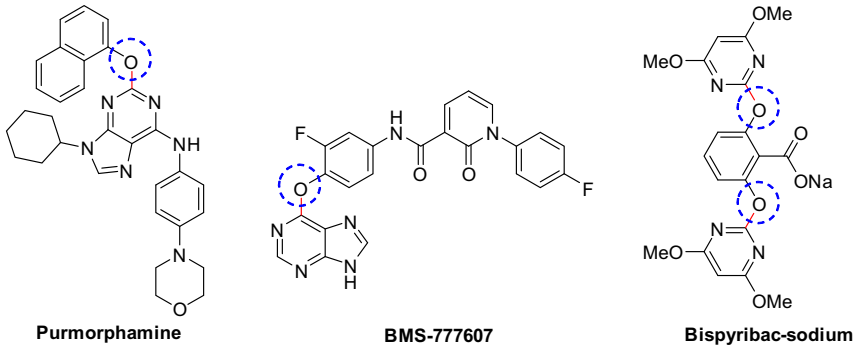
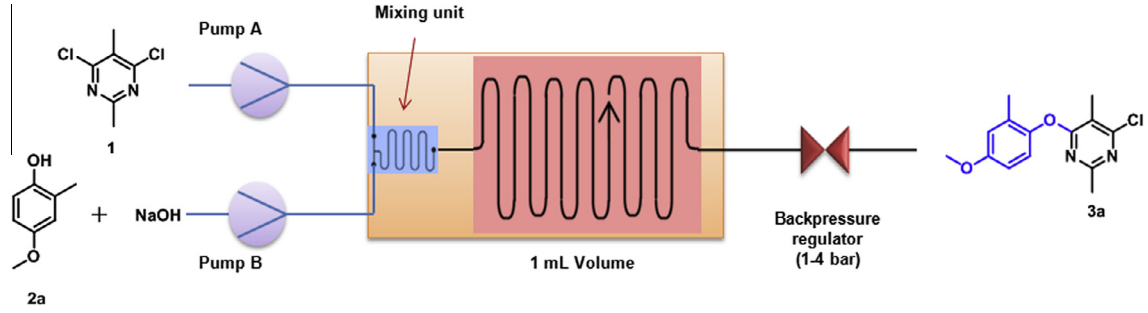


Figure 1. Examples of bioactive molecules containing C—O bond.

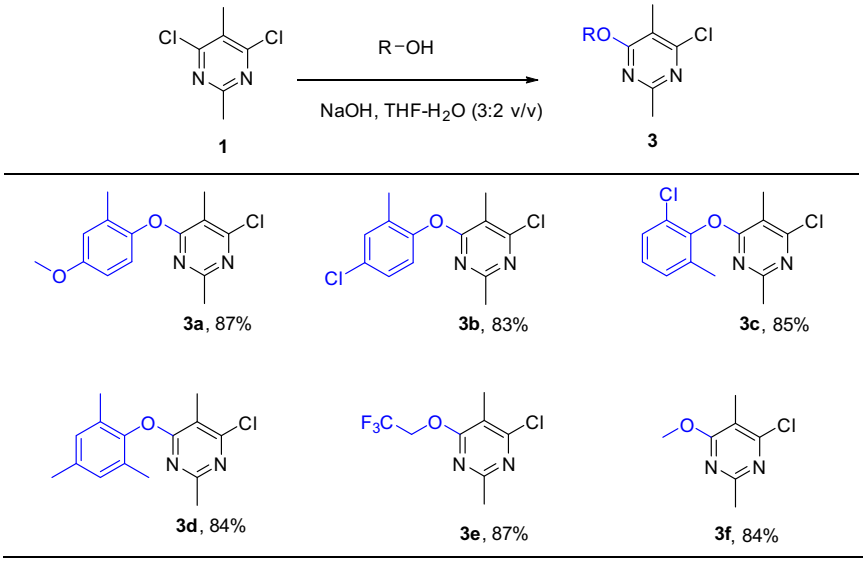
Table 1
Effect of temperature and pressure on yield of C—O bond formation



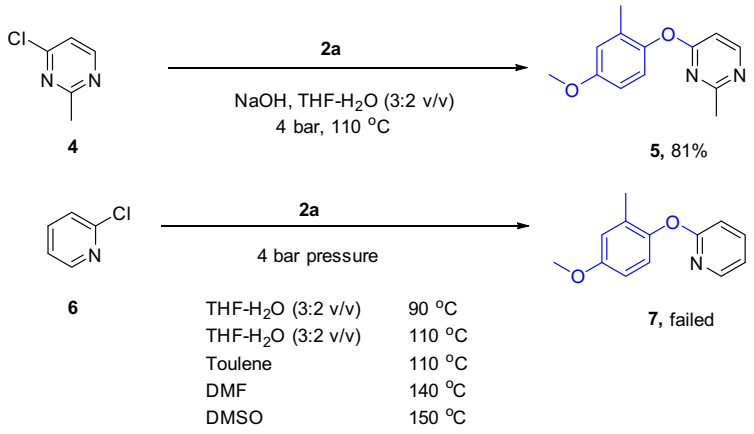
Entry [a]	Solvent	T (°C)	P (bar)	Flow rate[b] (μL/min)	t_R[c] (min)	Yield[d] (%)
1	THF	66	1	500	2	6
2	THF	66	1	250	4	12
3	THF	66	1	100	10	19 (*c*log)
4	THF	66	1	50	20	30 (*c*log)
5	THF	76	2	50	20	45 (*c*log)
6	THF	90	4	50	20	55 (*c*log)
7	THF–H_2O	90	4	50	20	54
8	THF–H_2O	100	4	50	20	71
9	THF–H_2O	110	4	50	20	87

[a] Synthesis of compound **3a** was done under varying conditions (entries 1–9); two solutions were prepared and introduced by Pump A & B into the Asia microfluidic reactor; one contained the aryl halide **1** (0.56 mmol, 1.0 equiv) in THF–H_2O (2.5 mL, 3:2 v/v) and the other contained a mixture of phenol **2a** (0.84 mmol, 1.5 equiv) and NaOH (0.84 mmol, 1.5 equiv) in THF–H_2O (2.5 mL, 3:2 v/v).
[b] Flow rates of the combined solutions.
[c] Retention time (in a 1 mL microfluidic reactor).
[d] Yield determined by LCMS.

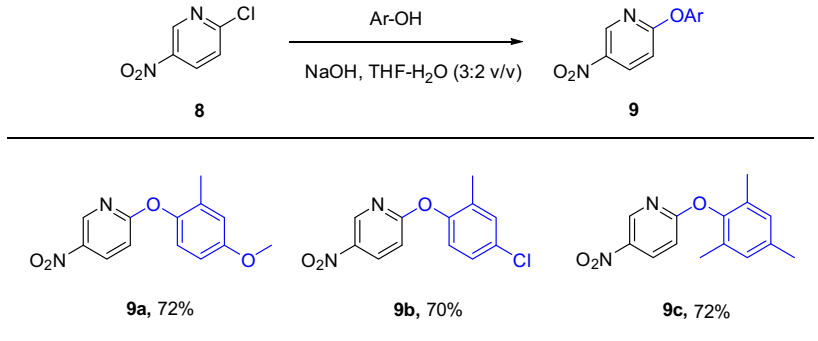
However, sodium hydride (60% suspension in oil) cannot be used in a microfluidic reactor due to clogging of either the back pressure regulator or the microfluidic reactor chip. Thus, we used THF as the solvent and NaOH as the base to generate the required phenoxide. Under these conditions, using a temperature of 60 °C, and 1 bar pressure, the expected monophenoxy derivative, **3a**, was formed in varying yields depending on residence time in the reactor. We obtained yields of 6%, 12%, 19% and 30% with flow rates of the combined solution being 500 μL/min, 250 μL/min, 100 μL/min, and 50 μL/min, respectively (Table 1, entries 1–4). This corresponded to residence times of 2, 4, 10, and 20 min, respectively, in the 1 mL microfluidic reactor. To improve yields we evaluated the reaction at 76 °C and 90 °C under 2 bar and 4 bar pressure, respectively. The temperature and/or pressure changes in the microreactor were done easily, using the Asia chip climate controller (−10 °C to +150 °C range) and the Asia pressure controller (1–10 bar range). Using the higher temperature and pressure, the product yield was shown to be increased to 45% and 55%, respectively (Table 1, entries 5 and 6). However, under these conditions, clogging of the microfluidic reactor or back pressure regulator was observed after a few runs, likely due to the deposition of NaCl. To solve the clogging issue, the reaction solvent was combined with water to remove NaCl formed as a byproduct. Switching the solvent to THF–H_2O (3:2 v/v) provided a similar yield of 54% at 90 °C, 4 bar pressure, using the combined flow rate of 50 μL/min without any observed clogging. Further increase of temperature while maintaining the 4 bar pressure was also evaluated to determine if there was any improvement of reaction yield. To our delight, using the THF–H_2O solvent system and the combined flow rate of 50 μL/min (Pump A & B at 25 μL/min each), the target coupling product yield increased to 87% when reactor temperature was maintained at 110 °C and 4 bar pressure (entry 9). Under these conditions no clogging of the glass microfluidic reactor chip or the back pressure regulator was observed. Additional increases in reactor temperature to 120 °C and above did not improve the product yield and, interestingly, clogging of the microfluidic reactor chip was once again observed. Therefore, for further studies with pyrimidine **1**, temperature, pressure and combined flow rate were



Scheme 1. C—O bond formation using compound **1** with different phenols and alcohols.[a,b] [a]For synthesis of various **3** derivatives, two solutions were prepared and introduced by Pump A & B into the Asia microfluidic reactor; one contained the aryl halide **1** (0.56 mmol, 1.0 equiv) in THF–H_2O (2.5 mL, 3:2 v/v) and the other contained a mixture of corresponding phenols (0.84 mmol, 1.5 equiv) and NaOH (0.84 mmol, 1.5 equiv) in THF–H_2O (2.5 mL, 3:2 v/v). [b]Product yield determined by LCMS.



Scheme 2. C—O bond formation using mono chloropyrimidine and pyridine.[a,b,c] [a]For synthesis of **5** & **7**, two solutions were prepared and introduced by Pump A & B into the Asia microfluidic reactor; one contained the aryl halide **1** (0.56 mmol, 1.0 equiv) in THF–H_2O (2.5 mL, 3:2 v/v) and the other contained a mixture of phenol **2a** (0.84 mmol, 1.5 equiv) and NaOH (0.84 mmol, 1.5 equiv) in THF–H_2O (2.5 mL, 3:2 v/v). [b]For attempted synthesis of **7** Toulene, DMF and DMSO neat were also used. [c]Yield determined by LCMS.



Scheme 3. C—O bond formation using 2-chloro-5-nitropyridine with different phenols.[a,b] [a]For synthesis of various **9** derivatives, two solutions were prepared and introduced by Pump A & B into the Asia microfluidic reactor; one contained the aryl halide **1** (0.56 mmol, 1.0 equiv) in THF–H_2O (2.5 mL, 3:2 v/v) and the other contained a mixture of corresponding phenols (0.84 mmol, 1.5 equiv) and NaOH (0.84 mmol, 1.5 equiv) in THF–H_2O (2.5 mL, 3:2 v/v). [b]Yield determined by LCMS.

maintained at 110 °C, 4 bar and 50 μL/min, respectively, in THF–H_2O (3:2 v/v) solvent system.

After optimizing reaction conditions, we investigated C—O bond formation with different phenols and alkyl alcohols. 4-Chloro-2-methylphenol, 2-chloro-6-methylphenol, 2,4,6-trimethylphenol, sodium 2,2,2-trifluoroethoxide and sodium methoxide all reacted with 4,6-dichloro-2,5-dimethylpyrimidine to generate the monophenoxy (**3a**–**3d**) or monoalkoxy compounds (**3e**–**3f**) in a

high yields. Notably as shown in Scheme 1, the reaction proceeds regioselectively and only a mono-isomer was formed.

Encouraged by the above results, we tried to extend the same protocol to 2-chloropyridine and 4-chloropyrimidine. Interestingly, while 4-chloro-2-methylpyrimidine reacted smoothly to generate the C—O coupled product **5** in 81% yield; no conversion was observed with 2-chloropyridine, even with different solvent systems, and varying temperature and pressure conditions (Scheme 2). Switching the solvent system to toluene or DMF did not furnish any coupled product. Only a trace amount of coupled product **7** was observed as detected in mass spectrometry when DMSO was used as solvent.

Reactions of 2-chloro-5-nitropyridine, **8**, were explored with three different phenols and done in the microfluidic reactor to furnish products in good yield. Coupling with 4-methoxy-2-methylphenol produced **9a** in 72% yield whereas 4-chloro-2-methylphenol produced **9b** in 70% yield and 2,4,6-trimethylphenol gave 72% of coupled product **9c** (Scheme 3). In the pyridine series C—O bond formation was found to be dependent on the electronic property of the ring. The presence of an electronegative nitro group in the pyridine ring facilitated C—O bond formation.

Conclusion

The use of a microfluidic reactor dramatically decreases the reaction time needed for the C—O bond (aryl or alkyl) formation and led to products in reasonably high yield. We were able to accelerate the process by increasing temperature and pressure to achieve 70–90% product yield within a 20 min residence time in the microfluidic reactor as compared to 5–24 h needed for traditional C—O bond coupling reactions by batch chemistry. This green chemistry methodology should facilitate continuous synthesis of alkyl/aryl ethers and can potentially be coupled with additional microfluidic reactors in series for multistep synthesis as needed by a specific synthetic scheme. This novel approach will allow for more rapid, efficient synthesis of key intermediates and aid in the discovery of new drug candidates. We are currently investigating C—O bond formation using other aryl- and heteroaryl halides, and anticipating reporting these results in the near future.

Notes

The authors declare no competing financial interest.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.095.

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