Tetrahedron Letters 56 (2015) 4689–4693

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Synthesis of fluorinated aryl ethers via selective C–F functionalization with polyfluorobenzenes and carbonates under mild conditions

Guanghui Yang, Zhiqun Yu, Xinpeng Jiang, Chuanming Yu *

*Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, College of Pharmaceutical Sciences, Zhejiang University of Technology, Chao Wang Road 18th, Hangzhou 310014, China*

ARTICLE INFO

*Article history:*
Received 22 April 2015
Revised 8 June 2015
Accepted 11 June 2015
Available online 17 June 2015

*Keywords:*
Fluorinated aryl ethers
C–F bond functionalization
Polyfluorobenzene
Carbonate

ABSTRACT

A facile and efficient method to synthesize fluorinated aryl ethers with polyfluorobenzenes and carbonates without metal catalyst has been developed. Selective C–F bond and aryl fragment of carbonate participate in the reaction. The desired products were obtained in moderate to excellent yields with good substrates compatibility.



## Introduction

The carbon–oxygen bond-forming reaction has gained significant attention during past few years and is widely applied in organic and pharmaceutical chemistry.[1] The most straightforward procedures to synthesize these ethers includes classic Ullmann coupling,[2] palladium catalyzed coupling reaction of aryl halides with phenols,[3] Williamson ether synthesis,[4] and some other methods.[5] However, these strategies often require high temperatures, expensive metal catalysts, long reaction times, and mostly used to active aryl halides, such as chloride, bromide, and iodide,[6] with low selectivity. While fluorine atom can increase the biological activity, the bioavailability, and the potency of biologically active molecules.[7] Perfluoro- or polyfluoro-substituted aryl ethers have drawn great interest especially in materials science,[8] agricultural and pharmaceutical areas due to their unique chemical and physiological properties,[9,10] such as lapatinib and crizotinib (Scheme 1). The activation and functionalization of carbon–fluorine bonds by transition metals is an effective method for synthesizing these compounds.

Recently, Cao and co-workers found a new method of preparing unsymmetrical biaryl ethers using polyfluoroarenes and arylboronic acids through nickel catalysts.[5b] Later, Weng and co-workers have reported palladium-catalyzed cross coupling reaction between pentafluorobenzene and phenols.[3b] Shortly after that, Adonin and Bardin found the reaction also could be achieved without palladium catalysis.[11] Inevitably, it still needs a higher reaction temperature. Zhang has reported a transition metal-free method of synthesizing polyfluoroaryl ethers by using pentafluorobenzene with phenols and benzyl alcohols.[12]

Moreover, our group engaged in the research of fluorochemicals and has successfully developed some useful methods to synthesize fluorinated thioethers, tetrafluorophenoxathiins, biphenyl compounds by using copper catalysis, and fluorinated nitriles and diaryl ketones via selective C–F bond functionalization.[13]

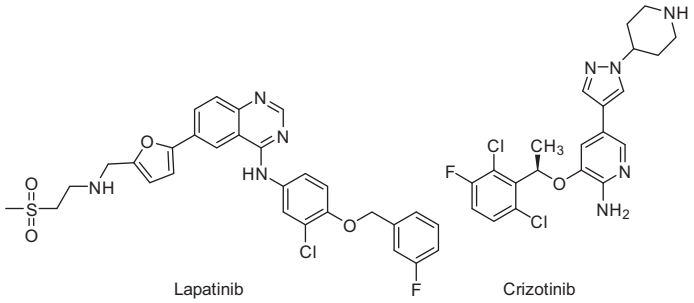
As mentioned above, it is meaningful to synthesize these aryl ethers via functionalization of C–F bond with higher selectivity under milder conditions. Herein, we report another convenient and effective procedure to synthesize fluorinated aryl ethers via selective C–F functionalization of polyfluorobenzenes with carbonates without metal catalyst.

## Results and discussion

At the early stage of our research, we intended to selectively active C–H bond of pentafluorobenzene under metal catalyzed. However, when the alkalinity of base was enhanced, we found the existence of benzyl ether products even when the temperature dropped to room temperature. So we found another easy way to

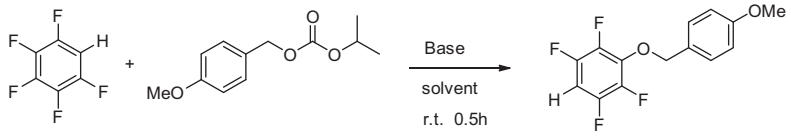
* Corresponding author. Fax: +86 571 88320867.
*E-mail address:* ycm@zjut.edu.cn (C. Yu).

http://dx.doi.org/10.1016/j.tetlet.2015.06.032
0040-4039/




**Scheme 1.** Representative drugs of fluorinated aryl ethers.

**Table 1**
Optimization of selective C-F functionalization to synthesize fluorinated aryl ethers[a]

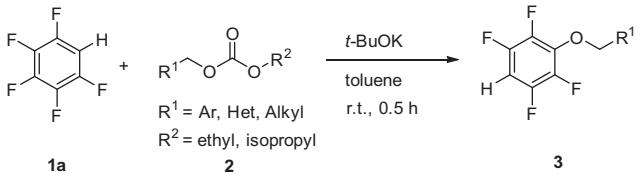



**1a** **2b** **3b**

| Entry | Base | Solvent | Yield%[b] |
|---|---|---|---|
| 1 | *t*-BuOLi | Toluene | NR |
| 2 | NaH | Toluene | NR |
| 3 | *t*-BuONa | Toluene | 57 |
| 4 | *t*-BuOK | Toluene | 93 |
| 5[c] | *t*-BuOK | Toluene | 76 |
| 6 | *t*-BuOK | Xylene | 85 |
| 7 | *t*-BuOK | THF | 81 |
| 8 | *t*-BuOK | DMF | 40 |
| 9 | *t*-BuOK | DMA | 37 |
| 10 | *t*-BuOK | DMSO | 31 |
| 11 | *t*-BuOK | 1,4-Dioxane | 68 |
| 12 | *t*-BuOK | $CH_3CN$ | 16 |

[a] Reaction condition: **1a** (2 mmol), **2b** (1 mmol), solvent (3 mL), base (1.5 mmol), rt, 0.5 h.
[b] Isolated yield base on **2b**.
[c] 1 equiv *t*-BuOK.

**Table 2**
Substrate scope of carbonates[a]




**1a** **2** **3**

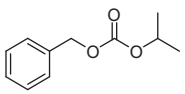
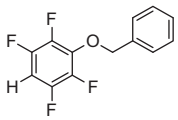
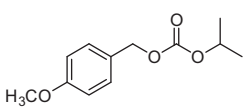
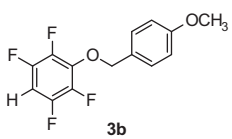
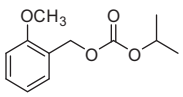
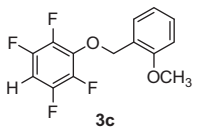
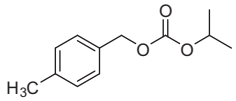
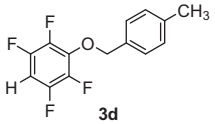
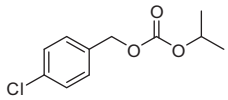
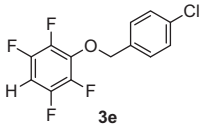
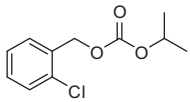
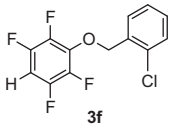
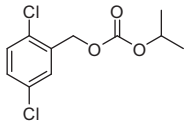
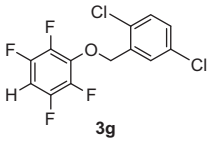
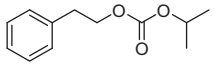
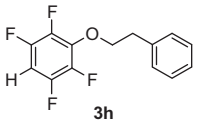
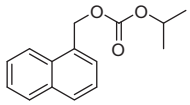
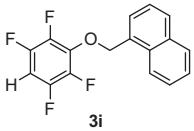
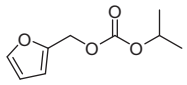
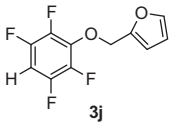
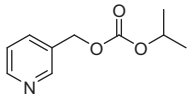
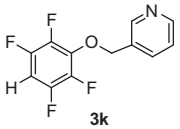
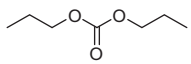
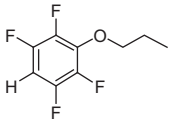
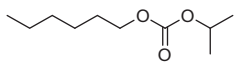
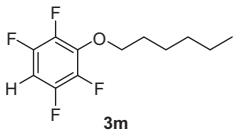
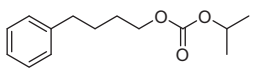
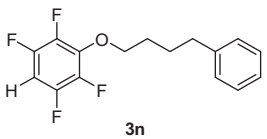
| Entry | Carbonate | Product | Yield%[b] |
|---|---|---|---|
| 1 |  |  **3a** | 86 |
| 2 |  |  **3b** | 93 |
| 3 |  |  **3c** | 90 |

**Table 2** (*continued*)

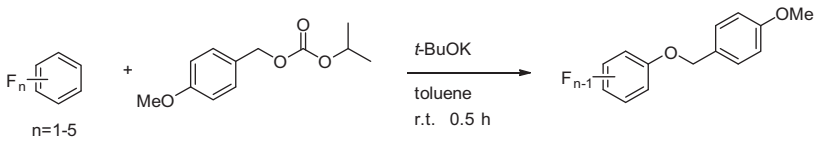
| Entry | Carbonate | Product | Yield%[b] |
|---|---|---|---|
| 4 |  |  **3d** | 84 |
| 5 |  |  **3e** | 95 |
| 6 |  |  **3f** | 90 |
| 7 |  |  **3g** | 77 |
| 8 |  |  **3h** | 94 |
| 9 |  |  **3i** | 83 |
| 10 |  |  **3j** | 85 |
| 11 |  |  **3k** | 80 |
| 12 |  |  **3l** | 87 |
| 13 |  |  **3m** | 93 |
| 14 |  |  **3n** | 90 |

[a] Reaction condition: **1a** (2 mmol), **2** (1 mmol), solvent (3 mL), base (1.5 mmol), rt, 0.5 h.
[b] Isolated yield base on **2**.

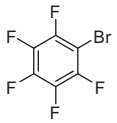
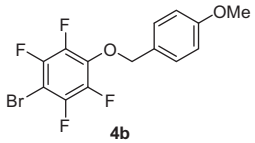
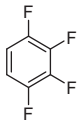
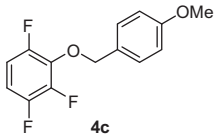
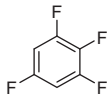
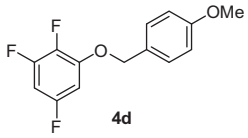
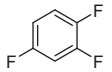
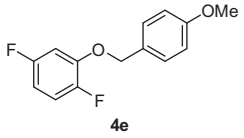
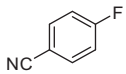
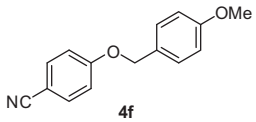
form C–O bond via selective C–F functionalization of polyfluorobenzenes with carbonates under mild conditions without metal catalyst.

Pentafluorobenzene (**1a**) and isopropyl (4-methoxybenzyl) carbonate (**2b**) were chosen as the substrates in our following exploration. The reaction did not proceed when *t*-BuOLi and NaH were used in this reaction (Table 1, entries 1 and 2). While *t*-BuONa was used as the base with toluene as the solvent, corresponding product **3b** was obtained in 57% yield (Table 1, entry 3). When the base was changed to *t*-BuOK, the yield was increased

**Table 3**
Substrate scope of polyfluorobenzenes[a]




1 2b 4

| Entry | Fluorobenzene | Product | Yield%[b] |
|---|---|---|---|
| 1 |  |  **4b** | 92 |
| 2 |  |  **4c** | 85 |
| 3 |  |  **4d** | 81 |
| 4 |  |  **4e** | 62 |
| 5 |  |  **4f** | 55 |

[a] Reaction condition: **1** (2 mmol), **2b** (1 mmol), solvent (3 mL), base (1.5 mmol), rt, 0.5 h.
[b] Isolated yield base on **2b**.

to 93% (Table 1, entry 4).[14] The yield was reduced to 76% as the quantity of base was decreased to 1 equiv. (Table 1, entry 5). A variety of solvents (e.g., xylene, THF, DMF, DMSO, 1,4-dioxane, etc.) were screened, and toluene was found to be the best solvent (Table 1, entries 6–12). Xylene, THF, and 1,4-dioxane also gave good yields with 85%, 81%, and 68%.

We further examined the scope and limitations of substituted carbonates with the optimal reaction conditions in hand, the representative results are summarized in Table 2. As described, various carbonates were found to participate in the reaction, and the electronic nature showed no pronounced effect on the efficiency of the reaction. When the aryl group had no substituent, the reaction proceeded smoothly and 86% yield of the product was obtained (Table 2, **3a**). Carbonates with electron-donating substituents afforded the corresponding products in 93%, 90%, and 84% (Table 2, **3b**–**3d**). Electron-withdrawing groups on different positions of the aromatic ring could also react well, the yields of desired products were 95% and 90% (Table 2, **3e**–**3f**). It was worth mentioning that the yields were decreased a little due to the effect of steric hindrance (Table 2, **3g** and **3i**). The reaction proceeded well when phenylethyl and 4-phenylbutyl carbonates were used instead of benzyl carbonate (Table 2, **3h** and **3n**). Alkyl carbonates also showed good activity and provided the desired products in 87% and 93% yields (Table 2, **3l** and **3m**). Furthermore, other heterocyclic substrates, such as furan and pyridine, were also investigated and the corresponding products were obtained in good yields (Table 2, **3j** 85% and **3k** 80%).

To expand the scope of the substrates, we proceeded to examine a series of fluorobenzenes. When bromopentafluorobenzene was used, selective C–F functionalization product was obtained in 92% (Table 3, **4b**). 1,2,3,4-Tetrafluorobenzene and 1,2,3,5-tetrafluorobenzene could also undergo the reaction to afford the corresponding products **4c** and **4d** in good yields. The yields were in decline as the number of fluorine atoms in polyfluorobenzenes decreased. As shown in Table 3, the desired products **4e** and **4f** of 1,2,4-trifluorobenzene and 4-fluorobenzonitrile were generated in moderate yields. Unfortunately, we did not observe the ether products when 1,2-difluorobenzene and 1,3-difluorobenzene were examined.

## Conclusion

In conclusion, we have developed a facile and efficient route to synthesize fluorinated aryl ethers with polyfluorobenzenes and carbonates. Various functional groups are tolerated in this reaction with moderate to excellent yields. Moreover, selective C–F bond and aryl fragment of carbonate participated in the reaction. Further investigation and its application are in progress.

## Acknowledgments

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China (NSFC) (grant number 21176222) and the Public Projects of Zhejiang Province (grant number 2014C31133).

## Supplementary data

Supplementary data (characterization of the products and copies of spectras) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.032.

## References and notes

1. (a) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973; (b) Ma, D. W.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799; (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
2. (a) Ullmann, F.; Dtsch, B. *Chem. Ges.* **1904**, *37*, 853; (b) Ullmann, F.; Sponagel, P.; Dtsch, B. *Chem. Ges.* **1905**, *38*, 2211; (c) Yang, S. L.; Wu, C. Q.; Zhou, H.; Yang, Y. Q.; Zhao, Y. X.; Wang, C. X.; Yang, W.; Xu, J. W. *Adv. Synth. Catal.* **2013**, *355*, 53.
3. (a) Milton, E. J.; Fuentes, J. A.; Clarke, M. L. *Org. Biomol. Chem.* **2009**, *7*, 2645; (b) Sun, L. B.; Rong, M. G.; Kong, D. D.; Bai, Z. S.; Yuan, Y. F.; Weng, Z. Q. *J. Fluorine Chem.* **2013**, *150*, 117.
4. (a) Williamson, A. W. *J. Chem. Soc.* **1852**, *4*, 229; (b) Paul, S.; Gupta, M. *Tetrahedron Lett.* **2004**, *45*, 8825.
5. (a) Peng, D. P.; Yu, A. J.; Wang, H. L.; Wu, Y. J.; Chang, J. B. *Tetrahedron Lett.* **2013**, *69*, 6884; (b) Zhang, J.; Wu, J. J.; Xiong, Y.; Cao, S. *Chem. Commun.* **2012**, *48*, 8553; (c) Lanning, M. E.; Fletcher, S. *Tetrahedron Lett.* **2013**, *54*, 4624.
6. (a) Cheng, A. Y.; Hsieh, J. C. *Tetrahedron Lett.* **2012**, *53*, 71; (b) Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett* **2005**, 1101; (c) Swapna, K.; Murthy, S. N.; Jyothi, M. T.; Nageswar, Y. V. D. *Org. Biomol. Chem.* **2011**, *9*, 5978; (d) Wang, M.; Yuan, B. Z.; Ma, T. M.; Jiang, H. F.; Li, Y. W. *RSC Adv.* **2012**, *2*, 5528; (e) Niu, J. J.; Zhou, H.; Li, Z. G.; Xu, J. W.; Hu, S. J. *J. Org. Chem.* **2008**, *73*, 7814.
7. (a) Wang, F.; Luo, T.; Hu, J. B.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Surya Prakash, G. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7153. *Angew. Chem.* **2011**, *123*, 7291; (b) Itoh, T. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Oxford, UK, 2009; pp 313–334.
8. Cargill, M. R.; Sandford, G.; Tomlinson, D. J.; Hollfelder, N.; Pleis, F.; Nelles, G.; Kilickiran, P. *J. Fluorine Chem.* **2011**, *132*, 829.
9. Jones, L. H.; Randall, A.; Barba, O.; Selby, M. D. *Org. Biomol. Chem.* **2007**, *5*, 3431.
10. Behniafar, H.; Sedaghatdoost, M. *J. Fluorine Chem.* **2011**, *132*, 276.
11. Adonin, N. Y.; Bardin, V. V. *J. Fluorine Chem.* **2013**, *153*, 165.
12. Liu, C. B.; Cao, L. M.; Yin, X. G.; Xu, H. L.; Zhang, B. *J. Fluorine Chem.* **2013**, *156*, 51.
13. (a) Yu, C. M.; Zhang, C. L.; Shi, X. J. *Eur. J. Org. Chem.* **2012**, 1953; (b) Yu, C. M.; Hu, G. B.; Zhang, C. L.; Wu, R.; Ye, H. W.; Yang, G. H.; Shi, X. J. *J. Fluorine Chem.* **2013**, *153*, 33; (c) Zhu, X. Y.; Li, F.; Su, W. K. *Tetrahedron Lett.* **2013**, *54*, 1285; (d) Yang, G. H.; Liu, M.; Li, N.; Wu, R.; Chen, X.; Pan, L. L.; Gao, S.; Huang, X.; Wang, C.; Yu, C. M. *Eur. J. Org. Chem.* **2015**, 616.
14. *Procedure for the synthesis of compounds* ***3*** *and* ***4*** *(****3b*** *as an example):* In a 15 mL sealed tube, isopropyl (4-methoxybenzyl) carbonate (0.224 g, 1 mmol), *t*-BuOK (0.168 g, 1.5 mmol), were added to toluene (3 mL) at room temperature. 10 min later, pentafluorobenzene (0.336 g, 2 mmol) was following added in one portion. The reaction mixture was monitored by TLC until the carbonate compound was consumed, and then poured into water (10 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl, dried with anhydrous Na2SO4, and concentrated. The crude product was purified by flash chromatography on a silica gel column (petroleum ether/EtOAc, 32:1 v/v) to afford the desired pure product.
*1,2,4,5-Tetrafluoro-3-((4-methoxybenzyl)oxy)benzene* **3b**: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33 (d, $J$ = 8.6 Hz, 2H), 6.87 (d, $J$ = 8.6 Hz, 2H), 6.72 (tt, $J$ = 10.0, 7.0 Hz, 1H), 5.17 (s, 2H), 3.80 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.0, 146.3 (dm, $J_{C-F}$ = 243.0 Hz, 2C), 141.3 (dd, $J_{C-F}$ = 243.1, 14.6 Hz, 2C), 137.7–137.1 (m), 130.0 (2C), 127.6, 113.9 (2C), 99.6 (t, $J_{C-F}$ = 23.0 Hz), 76.1, 55.3. $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −140.08 to −140.47 (m, 2F), −155.64 to −156.00 (m, 2F). HRMS (APCI): calcd for $C_8H_9O^+$ (Positive) 121.0648; found 121.0650; $C_6HF_4O^-$ (Negative) 164.9969; found 164.9974.