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# A practical synthesis of aryl tetrafluoroethyl ethers via the improved reaction of phenols with 1,2-dibromotetrafluoroethane

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**Abstract**—An efficient and practical synthesis of various aryl tetrafluoroethyl ethers by the reaction of phenols with 1,2-dibromotetrafluoroethane and the subsequent reduction with zinc dust was described. The nucleophilic substitution of 1,2-dibromotetrafluoroethane with phenols initiated by bromophilic attack was improved by using $Cs_2CO_3$ as a base and DMSO as a solvent.


Aryl tetrafluoroethyl ethers are useful in a number of applications. For instances, they were used as solvents in the deposition of organic active materials in the manufacture of organic electronic devices;[1a] they exhibited important bioactivities such as insecticidal[1b,c] and herbicidal[1d] activities; and they were shown to have potential therapeutic uses in the areas of anti-tumor,[1e] antifungal,[1f] and inhibition of cholesteryl ester transfer protein for the treatment of atherosclerosis and coronary heart disease.[1g–i]

A couple of direct syntheses of these fluorinated aryl ethers have been reported by the reactions of phenols with either tetrafluoroethylene[1a] or tetrafluoroethyl iodide[2] in the presence of a base. However, such methods required either pressure reactor[1a] at high temperature or expensive reagent with limited availability.[2] In our laboratories, a robust and efficient synthesis of aryl tetrafluoroethyl ethers is required. Our effort was directed towards finding an alternative synthesis using 1,2-bromotetrafluoroethane (**2**) as a starting material due to its ready availability and low cost. It was reported that potassium phenoxide reacted with 1,2-dibromotetrafluoroethane (**2**) to provide 2-bromotetrafluoro phenyl ether.[3a–c] In addition, perfluoroalkyl bromide could be reduced in a number of ways to yield perfluoroalkane as described by Dolbier et al.[4] However, the pioneering work by Rico and Wakselman not only resulted in low yields but also required thiophenoxide or mercaptans to promote the reaction of 1,2-dibromotetrafluoroethane (**2**) with potassium phenoxides via bromophilic attack.[3a] Later, Li et al., reported that the nucleophilic substitution reaction could occur spontaneously without using any initiating reagents to give a higher yield if potassium phenoxide and 1,2-dibromotetrafluoroethane (**2**) were carefully purified and dried.[3b] Unfortunately, the detailed procedure was not disclosed. In this Letter, we report our improved and easily scalable synthesis of aryl 2-bromotetrafluoroethyl ethers and their subsequent reduction with zinc dust to aryl tetrafluoroethyl ethers.

Our optimization efforts on the nucleophilic substitution of 1,2-dibromotetrafluoroethane (**2**) with potassium phenoxide were initially focused on the solvent effect. Although HMPA was reported to give a satisfactory yield over diglyme or benzene containing dicyclohexo-[18]crown-6,[3b] it was excluded in our study due to its high toxicity. Thus, dry potassium 3-bromo-5-fluorophenoxide (**1b**) was prepared by the reaction of 3-bromo-5-flourophenol (**1a**) with *t*-BuOK followed by azeotropic removal of *t*-BuOH and water with toluene. The reactions (Scheme 1) of phenoxide **1b** with 2 or 4 equiv of **2** were then carried out under $N_2$ at 50 °C

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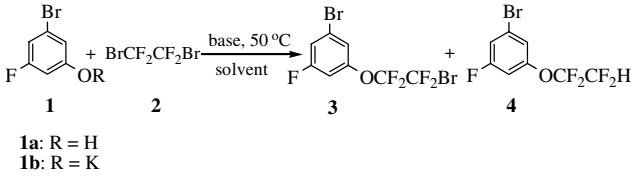
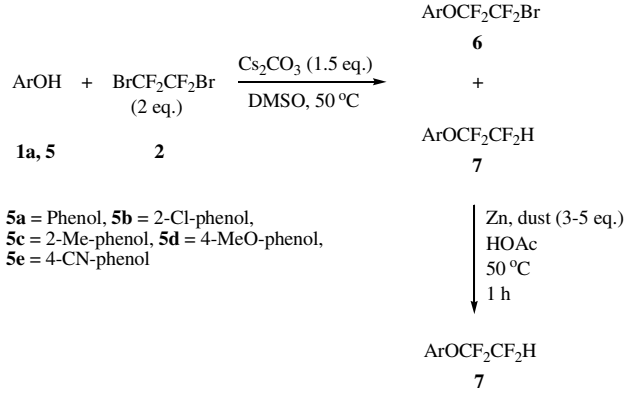



**Scheme 1.**

(slightly above the boiling point of **2**, ~47 °C) for 16 h in various common solvents shown in Table 1. We quickly found DMSO to be the best solvent for the reaction of 1,2-dibromotetrafluoroethane (**2**) with **1b**. In an attempt to scale up the reaction using the potassium phenoxide **1b** stored at room temperature for a couple of days, the desired products **3** and **4** were obtained, but in a significantly lower yield. By careful reexamination of the reaction, we soon found that the potassium salt **1b** was highly hydroscopic, which resulted in a lower conversion. This led us to search for a procedure where the salt such as **1b** could be generated in situ. We first chose $K_2CO_3$ as a base, and were pleased to find that the reaction of phenol **1a** with 2 equiv of dibromotetrafluoroethane (**2**) in the presence of anhydrous $K_2CO_3$ (1.5 equiv) in DMSO at 50 °C proceeded smoothly to give 70% conversion. However, the reaction was still slow. Surprisingly, using $Cs_2CO_3$ (1.5 equiv), the reaction was completed within 5 h in DMSO at 50 °C. Such a clean reaction greatly simplified the work up procedure in which a mixture of the relatively pure products **3** and **4** (>95% HPLC) was isolated by quenching with water, followed by extraction with hexane, and then drying and evaporation of the solvent.

With the optimized condition in hand, we explored the reaction scope with a variety of phenols including those bearing electron withdrawing or donating groups. As shown in Scheme 2 and Table 2, this reaction was quite general (see a typical example in the experimental in the reference).[5] All reactions gave the corresponding desired products **6** and **7** in good to excellent yields. The reaction rate increased as nucleophilicity increased as evidenced by the reaction time. For example, with 4-cyanophenol (**5e**), the reaction took 15 h to complete, while with 4-methoxyphenol (**5c**), the reaction completed in only 2 h. The product ratio of **6** and **7** were quite consistent under this condition. In all cases, we were able to use the mixtures of **6** and **7** directly in the next step without any purification.




**Scheme 2.**

Interestingly, when a mixture of **5d** with **2** (2 equiv) in DMSO in the presence of 1.5 equiv of $Cs_2CO_3$ was heated in a sealed tube under microwave irradiation at 140 °C for 10 min, a product ratio of 2 to 1 of **6d** and **7d** was obtained. This suggested that at high temperature the protonation reaction 7 in Scheme 3 could compete with bromination reactions 5 and 6, and $CsHCO_3$ generated from the reaction might provide additional proton source as illustrated in Scheme 3. It is worth noting that under the above condition (Scheme 2), no ring bromination products,[3c] such as compound **14** shown in equation 8 of Scheme 3, were detected.

It must be pointed out that although the anionic chain mechanism depicted in Scheme 3 rationalizes well the formation of the products **3**, **4**, **6** and **7**, the alternative SRN1 mechanism involving a single electron transfer process from step 2 to step 7 can not be excluded.

Reduction of aryl 2-bromotetrafluoroethyl ethers **6** with zinc dust in acetic acid at 50 °C afforded aryl tetrafluoroethyl ethers **7** in high yields (Scheme 2 and Table 2).[6] The reaction was exothermic, therefore zinc dust was added in portions. In all cases, the reaction was completed in less than an hour. Importantly, the functional groups such as cyano (**5e**), bromo (**1a**), and chloro (**5b**) groups were tolerated under this condition.

This two step synthesis of aryl tetrafluoroethyl ethers **7** was very robust and highly scalable. We have successfully run the reactions in 1.5 mol scales. Since the conversions were very high and the reactions were very

**Table 1.** Optimization of the nucleophilic substitution reactions in Scheme 1

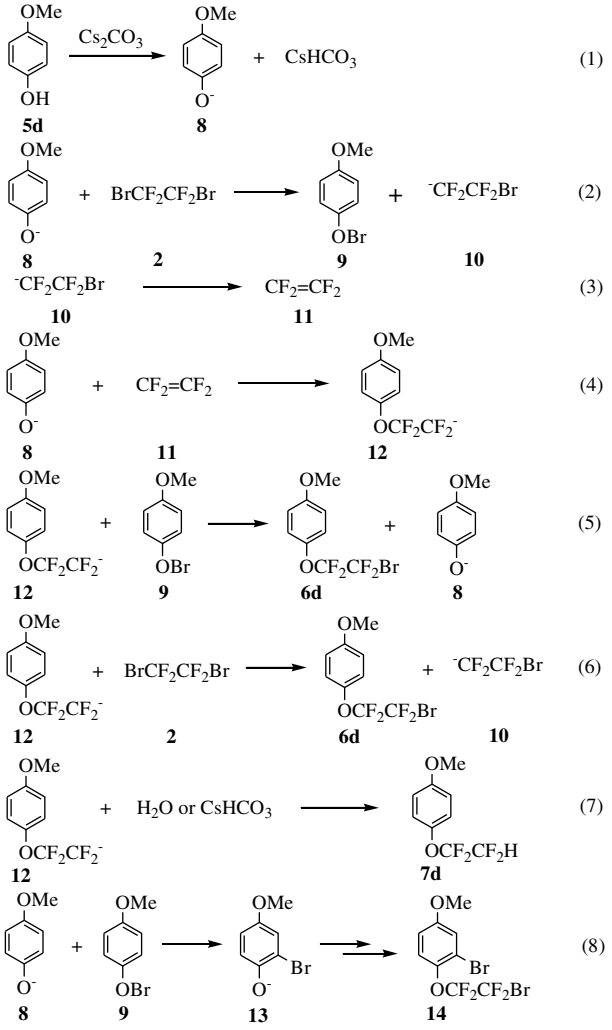
| Entry | Reactant **1** | **2** (equiv) | Base | Solvent | Time (h) | Yield (%) based on **1**[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | **3** | **4** | Total |
| 1 | **1b** | 4 | — | Diglyme | 16 | 21 | 7 | 28 |
| 2 | **1b** | 4 | — | DMF | 16 | 49 | 8 | 57 |
| 3 | **1b** | 2 | — | NMP | 16 | 62 | 3 | 65 |
| 4 | **1b** | 2 | — | DMSO | 16 | 81 | 6 | 87 |
| 5 | **1a** | 2 | $K_2CO_3$ | DMSO | 16 | 65 | 5 | 70 |
| 6 | **1a** | 2 | $Cs_2CO_3$ | DMSO | 5 | 95 | 5 | 100 (94)[b] |

[a] Yield calculated based on LC.
[b] Isolated total yield of **3** + **4**.

**Table 2.** Synthesis of **7** via reaction of phenol **1a** and **5** with **2** and subsequent reduction with Zn dust

| Entry | ArOH | Time (h) | Yield (%) of bromophilic substitution | | | Yield (%) of Zn reduction[c] |
|---|---|---|---|---|---|---|
| | | | **6**[a] | **7**[a] | Total[b] | |
| 1 | **1a** | 5 | 89 | 5 | 94 | 87 |
| 2 | **5a** | 5 | 84 | 4 | 88 | 85 |
| 3 | **5b** | 10 | 89 | 5 | 94 | 85 |
| 4 | **5c** | 5 | 80 | 4 | 84 | 82 |
| 5 | **5d** | 2 | 85 | 5 | 90 | 82 |
| 6 | **5e** | 13 | 94 | 5 | 99 | 86 |

[a] Percentage calculated based on $^{19}F$ NMR.
[b] Isolated yield of **6** + **7**.
[c] Isolated yield.




**Scheme 3.**

clean, fairly pure products **7** (>90% HPLC) were isolated in every case simply after aqueous work up. Without further purification, we were able to use them for potential drug candidate scale up synthesis. More pure products could be obtained either by fine distillation or column chromatography. It should be noted that compounds **7** were highly volatile. Prolonged exposure to high vacuum could result in loss of significant amount of yield.

In conclusion, we have described a practical and convenient synthesis of aryl tetrafluoroethyl ethers from phenols and 1,2-dibromotetrafluoroethane. The new condition using the combination of $Cs_2CO_3$ as a base and DMSO as a solvent for the nucleophilic substitution of phenols with 1,2-dibromotetrafluoroethane not only avoided preparation of moisture sensitive potassium phenoxides, but also gave higher yields. This reaction system could be adopted in other types of nucleophilic replacement initiated by halophilic attack. The use of aryl tetrafluoroethyl ethers in the synthesis of bioactive compounds will be reported in due course.

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5. Typical procedure exemplified by the synthesis of 4-cyanophenyl 2-bromotetrafluoroethyl ether (**6e**) (Table 2, entry 6): A mixture of 4-cyanophenol (**5e**) (11.9 g, 100 mmol), 1,2-dibromotetrafluoroethane (**2**) (51.8 g, 200 mmol) and $Cs_2CO_3$ (48.9 g, 150 mmol) in dry DMSO (100 mL) was heated to 50 °C, under $N_2$, with mechanical stirring, for 13 h. After cooling to rt, $H_2O$ (300 mL) and $CH_2Cl_2$ (300 mL) were added. The resulting mixture was stirred at rt for 15 min. The organic phase was separated and the aqueous phase was extracted with $CH_2Cl_2$ (100 mL). The combined organic extracts were washed with $H_2O$ (2 × 300 mL), brine (300 mL) and dried over $Na_2SO_4$. After filtration, the solution was concentrated in vacuo to give a mixture of products **6e** and **7e** as a colorless liquid at a ratio of 19:1 based on $^{19}F$ NMR (29.5 g, 99%).

This mixture was used for the next step without further purification. An analytical sample **6e** was obtained by column chromatography using 10% $CH_2Cl_2$ in hexane as the eluent. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.32 (d, $J = 9.1$ Hz, 2H), 7.70 (d, $J = 9.1$ Hz, 2H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 110.9, 113.0 (s, 1C), (tt, $J = 312.6$ and 43.8 Hz, 1C), 115.6 (tt, $J = 277.9$ and 32.5 Hz, 1C), 122.0 (s, 2C), 134.0 (s, 2C), 151.8 (s, 1C). $^{19}F$ NMR (282.5 MHz, $CDCl_3$): −86.6, −68.8. Anal. Calcd for $C_9H_4BrF_4NO$: C, 36.27; H, 1.35; N, 4.70. Found: C, 36.31; H, 1.34 N, 4.71.

6. Typical procedure exemplified by the synthesis of 4-cyanophenyl tetrafluoroethyl ether (**7e**) (Table 2, entry 6): A solution of the above mixture of **6e** + **7e** (14.9 g, 50 mmol) in acidic acid (50 mL) was heated to 50 °C. To the solution was added zinc dust (9.8 g, 150 mmol) portion wise. After stirring at 50 °C for 1 h and then cooling to rt, $H_2O$ (150 mL) and $CH_2Cl_2$ (100 mL) were added. The resulting mixture was stirred at rt for 0.5 h before it was filtrated through a Celite pad. The organic phase of the filtrate was separated and the aqueous phase was extracted with $CH_2Cl_2$ (100 mL). The combined organic extracts were washed with $H_2O$ (200 mL), a saturated solution of $NaHCO_3$ (200 mL), brine (200 mL), dried over $Na_2SO_4$, filtered and concentrated in vacuo to give the crude product **7e**, which was purified by column chromatography using 10% EtOAc in hexane as the eluent to afford the pure **7e** as a colorless liquid (9.5 g, 86%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.90 (tt, $J = 52.7$ and 2.9 Hz, 1H), 7.30 (d, $J = 8.8$ Hz, 2H), 7.67 (d, $J = 8.8$ Hz, 2H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 107.3 (tt, $J = 252.2$ and 41.4 Hz, 1C), 110.4 (s, 1C), 116.4 (tt, $J = 274.7$ and 28.7 Hz, 1C), 117.7 (s, 1C), 121.9 (s, 2C), 133.9 (s, 2C), 152.0 (1C). $^{19}F$ NMR (282.5 MHz, $CDCl_3$): −137.5, −88.9. Anal. Calcd for $C_{19}H_5F_4NO$: C, 49.32; H, 2.30; N, 6.39. Found: C, 49.31; H, 2.12; N, 6.46.