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One-Pot Approach for S_NAr Reaction of Fluoroaromatic Compounds with Cyclopropanol

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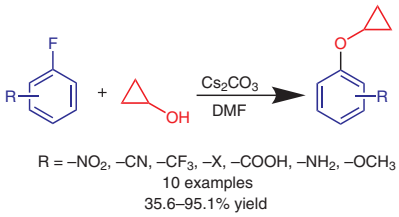

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Abstract A novel method for preparing aromatic compounds containing cyclopropoxy via nucleophilic aromatic substitution reaction (S_NAr) of fluoroaromatic compounds with cyclopropanol under relatively mild conditions is presented. As compared to the approaches reported previously for preparing 1-(cyclopropyloxy)-2-nitrobenzene, the one proposed in this work is simplified without sacrificing the yields: When the reaction was performed at 75 °C with Cs_2CO_3 as the base and DMF as solvent, after 6 h the yield was up to 90%. Finally, various fluoroaromatic compounds were employed as substrates for a test that proves a wide application scope of the method.

Key words fluoroaromatic compounds, nucleophilic aromatic substitution reaction (S_NAr), cyclopropanol, Cs_2CO_3, DMF

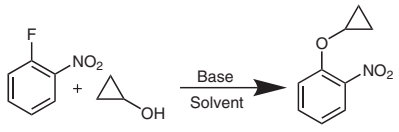
Aromatic compounds containing cyclopropoxy are widely used in pesticides, pharmaceuticals, and other fields. For instance, dienone cyclopropoxy curcumin analogues with anti-angiogenic properties stay in the spotlight for preclinical development regarding the treatment of cancer.[1] *N*-[5-(2-Chloro-4-cyclopropoxyphenyl)pyridine-2-yl]-4-methylnicotinamide are particularly useful for immunosuppression or to treat/prevent inflammatory conditions, immune disorders, and allergic disorders;[2] some ALK kinase inhibitor compounds are also effective for treating cancer.[3] Thus, the preparation of aromatic compounds containing cyclopropoxy continues to attract keen research interest. However, due to the interaction of steric forces and electronic configurations in cyclopropoxy,[4] it is difficult to prepare aromatic compounds containing cyclopropoxy groups.

At present, there are mainly two methods for preparing cyclopropoxy-containing compounds. The first is the preparation of halogenated aryl cyclopropyl ethers by methylenation of halogenated aryl vinyl ethers;[5–7] this protocol suffers from drawbacks such as long reaction time, cumbersome operations, and the rather low yield (<20%). An alternative route is to react bromocyclopropane with phenol to produce phenyl cyclopropyl ether.[8–10] This approach also has many shortcomings. For example, the involvement of bromine affords a rather low atom economy; besides, the evaporation of bromocyclopropane due to its low boiling point (69 °C) relative to the temperature required by the reaction results in a low yield.

Herein, we report an efficient and mild method for the synthesis of aryl cyclopropyl ether via nucleophilic aromatic reaction of halogenated aromatic compound with cyclopropanol in the presence of Cs_2CO_3 and DMF. Unlike the traditional S_NAr reaction of alkyl alkoxides with halogenated aromatic hydrocarbons,[11–14] we treat halogenated aromatic compound and cyclopropanol in a one-pot reaction in the presence of a suitable base (Cs_2CO_3) as well as a matching solvent (DMF) thus producing aryl cyclopropyl ether. Given the thermodynamic instability of cyclopropyl alkoxide,[4] we directly use cyclopropanol as a nucleophile. This method works well for various substances with product yields up to >90%. A general and reliable procedure with high selectivity is preferably performed under mild conditions and requires convenient manipulation and isolation. The efficiency of the nucleophilic reaction of aromatic halides is related to the nature of halogen. When the electronegativity of the halogen atom increases, the electron density at the attacked site decreases thus favoring nucleophilic reaction. Accordingly, the fluorinated substrate affords the highest reaction efficiency, and the aromatic nucleophilic reactions of fluoronitrobenzene and cyclopropanol is selected as a model reaction.[15] Further, the application scope of this proposal is tested with various fluorinated aromatic compounds[16,17] as substrates.

Initially, the model reaction of 2-fluoronitrobenzene with cyclopropanol is performed at 75 °C for 6 h under nitrogen atmosphere (Table 1).[18] Because both the base and the solvent affect much the nucleophilic substitution of halogenated aromatic compounds, we have screened different bases, such as inorganic bases (potassium carbonate and cesium carbonate) and organic bases (sodium tert-butoxide), as well as different solvents like DMSO, DMF, and THF.[19,20]

Table 1 Screening for Base and Solvent for S_NAr Reaction of 2-Fluoronitrobenzene with Cyclopropanol[a]



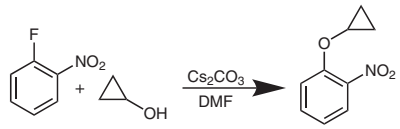
Entry	Base	Solvent	Conversion (%)[b]	Yield (%)[b]
1	Cs_2CO_3	DMF	96.0	92.6
2	Cs_2CO_3	THF	72.9	71.3
3	Cs_2CO_3	DMSO	13.7	6.3
4	K_2CO_3	DMF	16.5	15.4
5	K_2CO_3	THF	5.4	3.6
6	K_2CO_3	DMSO	24.2	13.7
7	t-BuONa	DMF	97.6	76.9
8	t-BuONa	THF	96.3	90.4
9	t-BuONa	DMSO	12.2	5.4

[a] Typical conditions: 1.5 equiv. of cyclopropanol, 1.5 equiv. of base in solvent at 75 °C for 6 h under nitrogen atmosphere.
[b]Determined by HPLC (Hypersil ODS, 30 °C, λ = 254 nm, acetonitrile/H_2O = 50:50) analysis.

As shown in Table 1, both Cs_2CO_3 and t-BuONa are proven to be the suitable base, while DMF turns out to be the best solvent facilitating a higher yield. Thus, the combination of Cs_2CO_3 and DMF as employed in Table 1, entry 1 was selected for further study. Table 2 summarizes the results of the condition-optimization experiments for the S_NAr reaction of 2-fluoronitrobenzene with cyclopropanol. To find the optimal reaction conditions, one-variable method was used to analyze process parameters. We observed that the increase of temperature under 75 °C favors both the yield and the selectivity for the target product (Table 2, entries 1–3), while an even higher temperature exerts an inverse effect (Table 2, entry 4).

An optimum temperature for this reaction is confirmed to be 75 °C, at which both the conversion and the yield increase at a longer reaction time (Table 2, entries 3, 5–8), whereas the time-elongation protocol loses its efficiency above 6 h; the latter may thus be ideal for an efficient approach. Next, it is notable that a high feed-in ratio of cyclopropanol vs 2-fluoronitrobenzene (>1.5) results in a reduced yield of the target product (Table 2, entries 3, 9–11).

Table 2 Reaction Optimization for the S_NAr Reaction of Cyclopropanol on 2-Fluoronitrobenzene



Entry	Cyclopropanol (equiv.)	Temp (°C)	Time (h)	Conversion (%)[b]	Yield (%)[b]
1	1.5	25	6	71.3	69.2
2	1.5	50	6	72.6	70.0
3	1.5	75	6	96.0	92.6
4	1.5	100	6	89.8	80.6
5	1.5	75	2	70.6	69.3
6	1.5	75	4	92.5	82.0
7	1.5	75	8	98.1	93.8
8	1.5	75	10	98.9	94.6
9	2	75	6	80.1	63.5
10	3	75	6	93.1	72.1
11	4	75	6	98.0	73.0

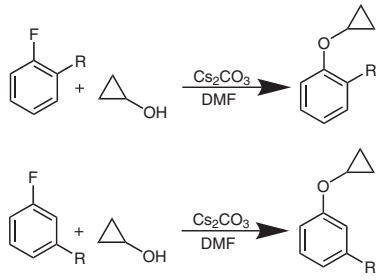
[a]Typical conditions: 1.5 equiv. of Cs_2CO_3 in DMF (4 mL) under nitrogen atmosphere.
[b]Determined by HPLC (Hypersil ODS, 30 °C, λ = 254 nm, acetonitrile/H_2O = 50:50) analysis.

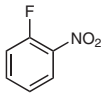
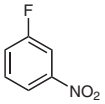
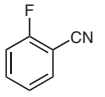
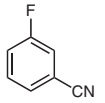
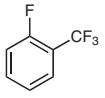
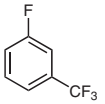
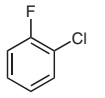
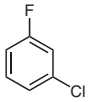
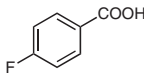
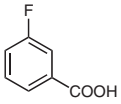
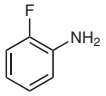
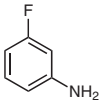
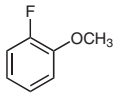
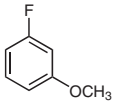
We speculate that this is due to the substantial heat released when excessive cyclopropanol is added at the beginning of the reaction thus rendering, e.g., higher local temperature and side reaction; the deterioration of more cyclopropanol thus results. Thus, the optimal reaction conditions for S_NAr reaction is: 2-fluoronitrobenzene/cyclopropanol/Cs_2CO_3 = 1:1.5:1.5, reacting at 75 °C for 6 h in DMF.

With the optimized conditions in hand, a series of substituted fluorobenzenes have been employed to probe the application scope of the protocol. It is indicated in Table 3 that the factors like substitution position, electronegativity, and steric effect of the substituent matter for the efficiency of the reaction.[21,22] Generally, the electron-withdrawing groups such as nitro, cyano, halogen (like chloro), and carboxyl at the *ortho* or *para* position of the fluorobenzenes facilitate moderate to good yields of the desired products (Table 3, entries 1, 3, 7, and 9). The presence of these groups in *meta* position, however, does not give rise to the generation of the desired products (Table 3, entries 2, 4, 8, and 10). This is, most likely, due to the reduced electron density on the *ortho* or *para* position of the electron-withdrawing group such that these positions are more prone to be attacked by the nucleophile cyclopropanol. Of course, not all substrates bearing electron-withdrawing groups lead to good yields. For strong electron-withdrawing groups such as nitro and cyano groups, the reactions are very effective (Table 3, entries 1 and 3). However, for the groups of relatively weak

electron-withdrawing effects, such as chloro and carboxyl, poor reaction efficiencies are expected (Table 3, entries 7 and 9). Notably, despite of the rather strong electron-withdrawing effect of trifluoromethyl, its presence on the benzene ring fails to give the corresponding product even at a high temperature (150 °C) and a long reaction time (16 h; Table 3, entry 5 vs entries 1 and 3). Here, the steric hindrance of trifluoromethyl to the nucleophile may matter.[23]

Table 3 Substrate Scope for the Selective S_NAr Reaction of Substituted Fluorobenzenes with Cyclopropanol[a]



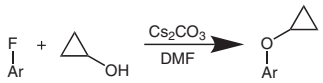
Entry	Substrate	Time (h)	Temp (°C)	Conversion (%)[b]	Yield (%)[b]
1		6	75	96.0	92.6
2		6	75	0	0
3		6	75	96.9	95.1
4		6	75	50.9	0
5		16	150[c]	44.5	0
6		16	150[c]	25.7	0
7		15	135	40.1	39.6
8		15	135	23.2	0
9		15	100	52.6	38.1
10		15	100	22.1	0
11		16	150[c]	0	0
12		16	150[c]	19.3	0
13		16	150[c]	0	0
14		16	150[c]	16.5	0

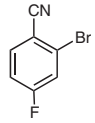
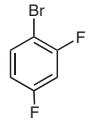
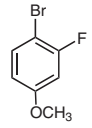
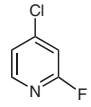
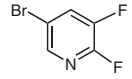
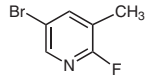
[a] Typical conditions: 1.5 equiv. of Cs_2CO_3 and 1.5 equiv. of cyclopropanol in DMF (4 mL) under nitrogen atmosphere.
[b] Determined by HPLC (Hypersil ODS, 30 °C, λ = 254 nm, acetonitrile/H_2O = 50:50) analysis.
[c] Using suffocating can.

As to the electron-donating substituents such as amino and methoxy, regardless of their position on the benzene ring, the associated yields are poor. The inverse effect vs that induced by the electron-withdrawing groups prevail.

Finally, as further probe, several other fluoroarenes with substituents have been examined with regard to the S_NAr reaction with cyclopropanol, and the results are summarized in Table 4. In these cases, the current protocol works well, giving respective target products with moderate to good yields. In particular, reacting 2-bromo-4-fluorobenzonitrile with cyclopropanol at 25 °C for 4 h gives rise to a yield of 80.3% (Table 4, entry1). For pyridine derivatives, 4-chloro-2-fluoropyridine, 5-bromo-2,3-difluoropyridine and 5-bromo-2-fluoro-3-methylpyridine, the protocol give respective target products with moderate yields (Table 4, entries 4–6). Note that room temperature and 2 h are sufficient for the reaction of 4-chloro-2-fluoropyridine with cyclopropanol to achieve a moderate yield (about 62.7%; Table 4, entry 4). The other two substrates, 2,4-difluorobromobenzene and 1-bromo-2-fluoro-4-methoxybenzene, bring about relatively less efficient S_NAr reactions (Table 4, entries 2 and 3). What's more, the reaction of 2,4-difluorobromobenzene with cyclopropanol at 125 °C for 15 h mainly leads to 1-bromo-4-(cyclopropyloxy)-2-fluorobenzene (about 35.6% yields) because of steric hindrance (Table 4, entry 2).

Table 4 Reaction of some Substituted Fluoroarenes with Cyclopropanol[a]



Entry	Substrate	Cyclopropanol (equiv.)	Time (h)	Temp (°C)	Yield (%)[b]
1		1.6	4	25	80.3
2		1.5	15	125	35.6
3		1.4	10	120	36.8
4		1.5	2	rt	62.7
5		1.5	5	50	68.1
6		1.6	8	85	56.5

[a] Typical conditions: 1.5 equiv. of Cs_2CO_3 in DMF under nitrogen atmosphere.
[b] Determined by HPLC (Hypersil ODS, 30 °C, λ = 254 nm, acetonitrile/H_2O = 50:50) analysis.

In summary, we have developed a general and practical method for preparing arylcyclopropyl ether derivatives via selective S_NAr reaction of various commercially available substituted fluoroarenes with cyclopropanol; the presence of 1.5 equiv. of Cs_2CO_3 and the solvent DMF as well as relatively mild conditions are required. The scope and generalizability of this method were assessed. We found that the position, electronic character, and steric effect of the substituent on the aryl ring may influence the reactivity. The substrates bearing strong electron-withdrawing groups on the *ortho* or *para* positions of fluorine give excellent selectivity and high yield. Meanwhile, this S_NAr reaction is also valid for selected fluoropyridine derivatives. This work may offer an alternative and general strategy for organic and medicinal chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611768.

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(17) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013.
(18) **The Synthesis of 1-(Cyclopropyloxy)-2-nitrobenzene under the Optimal Reaction Conditions – General Procedure**
Into a 25 mL single-necked round-bottom flask 2-fluoronitrobenzene (0.30 g, 2.1 mmol), DMF (4 mL), and cyclopropanol (0.18 g, 3.2 mmol) were successively added under N_2 protection. After that, the mixture was stirred. And Cs_2CO_3(1.04 g, 3.2 mmol) was put into the flask at nitrogen atmosphere. Then the resulting mixture started to be heated to 75 °C in a water bath. The reaction was followed by TLC and HPLC. After the reaction was complete, the resulting mixture was diluted with H_2O (30 mL) and extracted with AcOEt (3 × 10 mL). Then the combined organic phase was washed with saturated aqueous NaCl (3 × 10 mL) and dried over Na_2SO_4 for 0.5 h. After that, the organic phase was concentrated under reduced pressure to give crude product. Further, column chromatography (eluent: petroleum ether/ethyl acetate = 10:1) on silica gel was needed to afford the pure product as a yellow oily liquid in 92.6% yield (0.35 g).
Data for 1-(Cyclopropyloxy)-2-nitrobenzene as Typical Example
^{1}H NMR (600 MHz, $CHCl_3$-*d*): δ = 7.83 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.55 (m, 1 H), 7.48 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.08–7.03 (m, 1 H),

3.90 (m, 1 H), 0.91–0.86 (m, 4 H) ppm. ^{13}C NMR (151 MHz, $CHCl_3$-*d*): δ = 152.48, 139.72, 133.92, 125.44, 120.53, 115.56, 52.36, 6.43 ppm. MS (EI): *m/z* = 178.0 $[M]^+$.

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