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Regioselective S_NAr reactions of substituted difluorobenzene derivatives: practical synthesis of fluoroaryl ethers and substituted resorcinols

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ABSTRACT

In this Letter, we describe a practical and highly selective method for the preparation of fluoroaryl ethers and differentially substituted resorcinol derivatives. This synthetic strategy relies on a selective S_NAr of substituted difluorobenzene derivatives with various alcohols.

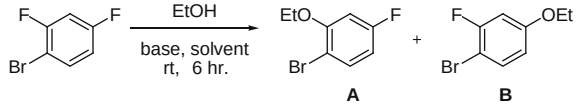
Aryl ether functionality is a prevalent structural motif found in many natural products and in biologically active compounds.[1] In the past few decades, several new methods for the preparation of aryl-aryl[2] and aryl–alkyl ethers have been described. While significant progress has been made in the field of metal-catalyzed reaction (mostly Cu and Pd), nucleophilic aromatic substitution (S_NAr) of aryl fluorides by alkoxides remains a highly efficient and useful strategy for the construction of aryl ethers.[3] The fact that a wide range of fluorinated aromatic compounds are commercially available certainly enhances the synthetic potential of the S_NAr approach for the preparation of functionalized aromatic compounds.

In support of a drug development program, we required a method for the preparation of substantial quantities of 2-substituted-5-fluoroanisoles. We were interested in identifying a methodology that would be highly selective, that would use readily available starting materials, and also enable facile preparation of a large array of differentially substituted aryl ethers. A survey of commercial sources confirmed that a wide variety of substituted-2,4-difluorobenzene derivatives are available. We felt that if we could achieve good levels of regioselectivity for the nucleophilic aromatic substitution of these substrates, it would provide a very efficient method for the preparation of 2-substituted-5-fluoroanisoles. Examination of the literature revealed that while a number of isolated examples have been reported, the selectivities and/or the yields were often moderate.[4–6] Moreover, the generality of this transformation has not been well established. This synthetic strategy could also provide access to differentially substituted resorcinol derivatives which find a broad range of applications in the pharmaceutical industry.[7] In this Letter, we wish to disclose the application of this general and highly selective S_NAr reaction of substituted-2,4-difluorobenzene derivatives with alkoxides to generate fluoroaryl-alkyl ethers. We have also demonstrated that this approach can be used to prepare fully differentiated resorcinol derivatives.

Our investigation into an efficient and selective S_NAr reaction began with commercially available 2,4-difluorobromobenzene using ethanol as the nucleophile. To find the optimal reaction conditions, a number of bases and solvents were evaluated. We found that inorganic bases such as potassium carbonate were inefficient in promoting this transformation. The selectivity observed was generally greater when a potassium alkoxide was used as base (Table 1, see entries 2 vs 3).

We observed acceptable conversions (81 $\geqslant$ 95% in 6 h at rt) and encouraging isomeric ratios when either potassium hydride or *t*-butoxide was used in THF. For ease of handling, we selected potassium *t*-butoxide as the base of choice for further study. We next evaluated the effect of the solvent on the reactivity and regioselectivity. We found that solvents with a low dielectric constant such as toluene or hexanes provided only modest conversion. Rapid consumption of the starting material was seen in polar

Table 1
Optimization of the selective S_NAr reaction using 2,4-difluorobromobenzene



A B

Entry	Base	Solvent	Conversion[a] (%)	Ratio[a] (A:B)
1	K_2CO_3	THF	N.R.	—
2	KH	THF	81	17:1
3	NaH	THF	13	13:1
4	*t*-BuOK	THF	39	17:1
5	*t*-BuOK	Toluene	N.R.	—
6	*t*-BuOK	DMF	>95	6:1
7	*t*-BuOK	DMSO	>95	7:1
8	*t*-BuOK	Dioxane	71	38:1

[a] Determined by GC.

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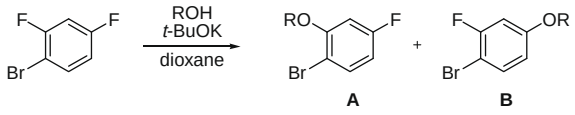
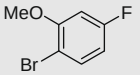
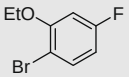
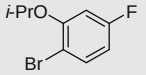
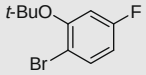
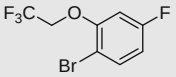
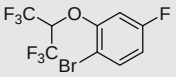
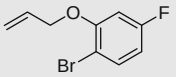
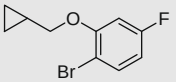
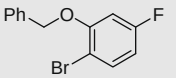
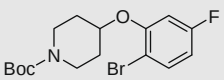
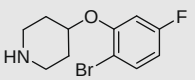
non-protic solvent (Table 1, entries 6 and 7), however the selectivity was significantly lower. The best selectivities were obtained in etheral solvents with dioxane providing the highest regioselectivity (38:1) and acceptable rates.

To extend the scope of this transformation, we next evaluated the influence of various alcohols on the regioselectivity of the S_NAr reaction, again using 2,4-difluorobromobenzene as a model aryl fluoride. Based on the results of Table 1, we selected *t*-BuOK as the base of choice and subsequent bench scale reactions were conducted in dioxane at room temperature.[8] As shown in Table 2, a wide variety of alcohols were added with excellent chemical yields and with very high selectivities.

Table 2
Substrate scope for the selective S_NAr reaction of 2,4-difluorobromobenzene with a variety of alkoxides

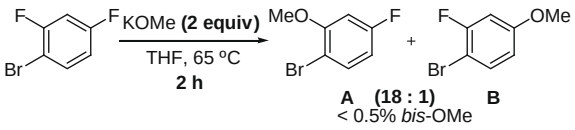


Entry	Product	Yield (%)	Ratio[a] (A:B)
1		83	54:1
2		85	47:1
3		82	72:1
4		99	128:1
5		60[b]	77:1
6		N.R.	—
7		87	59:1
8		98	52:1
9		96	55:1
10		98	79:1
11		92[c]	30:1

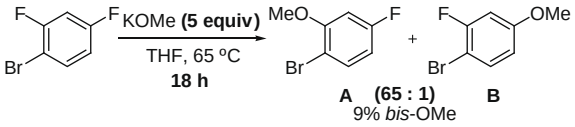
Typical conditions: 3 equiv of alcohol, 2.9 equiv of *t*-BuOK in dioxane at rt for 6–24 h.
[a] Determined by GC.
[b] Reaction carried out at 45 °C with 4 equiv of alcohol for 24 h.
[c] Reaction carried out in THF, HPLC assay yield.

In general, regioselectivity increases with the sterics of the alkoxide used. When primary alcohols were used, selectivities of about 50:1 were observed (entries 1, 2, and 7–9). The selectivity increased to approximately 75:1 when secondary alkoxides were used (entries 3 and 10) and finally selectivities exceeding 125: 1 were observed for sterically hindered nucleophiles such as *t*-BuOK (entry 4). We also observed that the nucleophilicity/basicity of the alkoxide impacted both the rate and the selectivity of this S_NAr displacement. This trend becomes obvious when we compare the entries 2, 5, and 6. In the case of trifluoroethanol, a significantly slower reaction was observed. Hexafluoro-2-propanol was found to be unreactive, even under forcing conditions (entry 6, 100 °C, for 2 days). Finally, we also demonstrated that high level of chemoselectivity in the nucleophile could be obtained as shown in entry 11 where an unprotected piperidine alcohol was added in excellent chemical yield.[9] These reactions are operationally simple and are typically very clean. No byproducts were observed arising from displacement of the bromide[10] and we never observed more than 1% of the double addition product under these conditions.

For preparative scale purposes, we decided to use THF as solvent instead of dioxane and commercial availability of KOMe obviated the use of *t*-BuOK. However, the selectivity in THF was somewhat lower than that observed in dioxane (Table 1, entry 2). To overcome this setback, we studied the effect of the reaction time, temperature and the stoichiometry of the alkoxide used. We observed a significant improvement in selectivity as we increased the amount of alcohol used (Eq. 1 vs 2). The improved selectivity arises from the favored consumption of the undesired isomer (**B**) which reacts faster in a second addition than the desired isomer (**A**). The bis-addition product formed could easily be removed by fractional distillation to provide a highly enriched mixture of isomer **A**.[11]



(1)



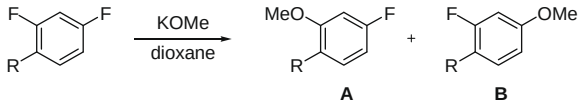
(2)

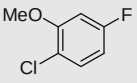
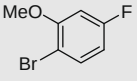
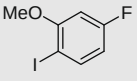
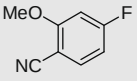
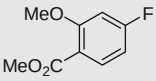
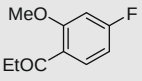
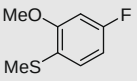
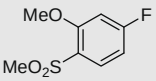
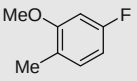
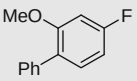
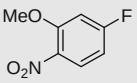
Table 3 demonstrates the wide range of 1-substituted 2,4-difluorobenzenes which can be successfully used to prepare 3-fluoroanisole derivatives in good chemical yields and with high levels of regioselectivity. Both the aryl chloride and bromide were found to undergo selective S_NAr reaction using KOMe with excellent selectivity (Table 3, entries 1 and 2). The reaction of 1-iodo-2,4-difluorobenzene was slower and required more forcing conditions, resulting in decreased selectivity (entry 3). Substrates bearing electron-withdrawing groups such as nitrile, ester, ketone, sulfone, and nitro provided the desired anisole derivatives with good to excellent regioselectivity.

Not surprisingly, the electronic characteristics of the substituent on the aryl ring had a profound influence on the reactivity. This was confirmed in the case of methyl and phenyl-substituted difluorobenzene substrates where no reactions were observed (entries 9 and 10). We also found that more vigorous conditions (100 °C) were necessary in order to promote the addition of KOMe onto 2,4-difluorothioanisole (entry 7).

Finally, we set out to evaluate the possibility of preparing differentially substituted resorcinol derivatives by sequential addition of alkoxides. The synthesis of fully differentially substituted resorcinol is still a nontrivial task. While interesting methods have been

Table 3
Substrate scope for the selective S_NAr of substituted 2,4-difluorobenzenes with KOMe



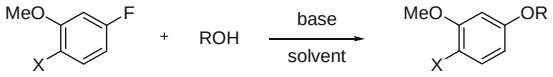
Entry	Product	Time, temp.	Yield (%)	Ratio[a] (A:B)
1		5 h, rt	74	53:1
2		24 h, rt	83	54:1
3		48 h, 45 °C	79	11:1[b]
4		48 h, 45 °C	75	14:1
5		h, 40 °C	80	22:1
6		5 h, 45 °C	44	37:1
7		48 h, 100 °C	66	8:1[b]
8		3 h, rt	75	11:1
9		—	N.R.	—
10		—	N.R.	—
11		10 min, 60 °C	97	99:1[b]

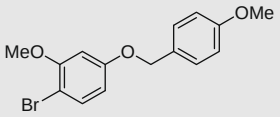
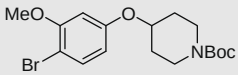
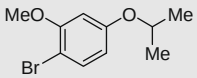
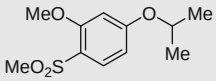
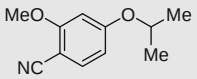
Typical conditions: 2.5–3.5 equiv of KOMe in dioxane at rt (<2% of bis-OMe product observed).
[a] Determined by GC.
[b] Between 2.5% and 4% of bis-OMe.

reported for the preparation of resorcinol derivatives,[12,13] their functionalization to access a 1,2,4-substitution pattern is typically unselective.[14] The chemistry we have disclosed herein constitutes a practical and modular strategy to access this class of compounds, which are versatile building blocks for a variety of interesting biologically active compounds. As shown in Table 4, a second S_NAr reaction is possible and it provides good yields of the desired trisubstituted aryls. We have demonstrated that a number of activating groups such as nitrile, sulfone, and bromide can be successfully used.

In summary, we have developed a general and practical methodology for the selective S_NAr reaction using a broad range of commercially available 1-substituted-2,4-difluorobenzene derivatives.

Table 4
Preparation of fully differentially substituted resorcinol derivatives



Entry	Product	Condition	Yield (%)
1		A	75
2		A	69
3		A	66
4		B	91
5		B	90

Typical conditions: (A) 2.0 equiv of alcohol and 2.4 equiv of NaH in DMF at 100 °C. (B) 2.0 equiv of alcohol and 1.9 equiv of *t*-BuOK in THF at rt.

This approach was used in the kilo-scale preparation of 2-bromo-5-fluoroanisole in high yield and selectivity. This strategy also enables the preparation of fully differentially substituted resorcinol derivatives.

Acknowledgments

Mélina Girardin is thanked for her experimental work on the unprotected piperidine substrate. Ravi Sharma, Chad Dalton, and Wayne Mullett are thanked for their analytical support.

Supplementary data

Supplementary data (Experimental procedures and spectral data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.204.

References and notes

1. (a) Zhu, J. *Synlett* **1997**, 133; (b) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544; (c) Kase, H.; Kaneko, M.; Yamado, K. *J. Antibiot.* **1987**, *40*, 450; (d) Franklin, M. A.; Penn, S. G.; Lebrilla, C. B.; Lam, T. H.; Pessah, I. N.; Molinski, T. F. *J. Nat. Prod.* **1996**, *59*, 1121.
2. For a review on diaryl ether synthesis, see: (a) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5545; (b) Frlan, R.; Kikelj, D. *Synthesis* **2006**, *14*, 2271.
3. (a) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718; (b) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498; (c) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, SL. *Org. Lett.* **2002**, *4*, 973.
4. For polyfluorinated benzene derivatives, see: (a) Burdon, J.; Coe, P. L.; Marsh, C. R.; Tatlow, J. C. *Tetrahedron* **1966**, *22*, 1183; (b) Zhang, Y.; Wen, J. *J. Fluorine Chem.* **1991**, *52*, 333; (c) Chen, Y.; Yekta, S.; Martyn, L. J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433.
5. For substituted-2,4-difluorobenzene derivatives, see: (a) Umezu, K.; Tabuchi, F.; Kimura, Y. *J. Fluorine Chem.* **2003**, *121*, 97; (b) Guzzo, P. R.; Buckle, R. N.; Chou, M.; Dinn, S. R.; Flaugh, M. E.; Kiefer, A. D., Jr.; Ryter, K. T.; Sampognaro, A. J.; Tregay, S. W.; Xu, Y.-C. *J. Org. Chem.* **2003**, *68*, 770.

6. During the internal clearance process of this manuscript, this article appeared: Dirr, R.; Anthaume, C.; Désaubry, L. *Tetrahedron Lett.* **2008**, *49*, 4588.
7. Kuo, M. S.; Bock, M. G.; Freidinger, R. M.; Guidotti, M. T.; Lis, E. V.; Pawluczyk, J. M.; Perlow, D. S.; Pettibone, D. J.; Quigley, A. G.; Reiss, D. R.; Williams, P. D.; Woyden, C. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3081.
8. In presence of an excess of primary or secondary alcohol, no *t*-BuOH addition product was observed.
9. No N addition product was detected by HPLC.
10. Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633.
11. This was also observed if we compare entry 8 (Table 1) and entry 2 (Table 2).
12. Kim, A.; Powers, J. D.; Toczko, J. F. *J. Org. Chem.* **2006**, *71*, 2170.
13. Rodriguez, J. R.; Agejas, J.; Bueno, A. B. *Tetrahedron Lett.* **2006**, *47*, 5661.
14. Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2002**, *43*, 6331.