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Base-promoted nucleophilic fluoroarenes substitution of C–F bonds

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ABSTRACT

With the use of KOH/DMSO as the superbase medium, the nucleophilic fluoroarene substitution for C–F bonds is presented. The transformation proceeds smoothly with the use of fluoroarenes bearing not only electron-withdrawing group, but also electron-donating group and a variety of nucleophiles such as alcohols, phenols, amines, amides and nitrogen-heterocyclic compounds. The double nucleophilic substitution using *ortho*-difluoroarenes and nucleophiles bearing *ortho*-dinucleophilic groups results in the formation of 2,3-dihydro-1,4-benzodioxins, dibenzo[b,e][1,4]dioxins and 10*H*-phenoxazines in moderate to good yields.

1. Introduction

Fluoroarenes are one of the important kind of aromatic compounds not only showing special properties in pharmaceutical compounds[1] and organic material molecules,[2] but also being well used as versatile intermediates for the synthesis of functionalized aromatics *via* C–F bond activation.[3] Three major classification of C–F bond activation processes for its functionalization have been developed, including transition-metal-catalyzed/mediated C–F bond activation,[4] *ortho*-directing groups-driven nucleophilic aromatic substitution (S_NAr) reactions of C–F bond with organolithium or Grignard reagents,[5] and base-promoted S_NAr of C–F bond with a variety of nucleophiles. Among of them, the base-promoted S_NAr reactions of fluoroarenes have been recently received particular attention due to using easily available nucleophiles and without use of transition metal catalysts.[6]

The representative reported examples include the KHMDS (potassium bis(trimethylsilyl)amide)-promoted S_NAr reaction of fluroarenes with secondary nitrile anion in toluene to form C–C bond,[6a] P (*i*-BuNCH$_2$CH$_2$)$_3$N-catalyzed the reactions of fluroarenes bearing nitro, cyano, ester, or aldehyde groups with aryl TBDMS (*t*-butyl dimethyl silyl) or TMS ethers in toluene to give diaryl ethers,[6b] Cs$_2$CO$_3$/DMSO-promoted S_NAr reaction between fluoroarenes having electron-withdrawing group(s) and various secondary amines,[6c] KF/CP (potassium fluoride/clinoptilolite)-mediated the coupling of nitro-activated fluroarenes with phenols, anilines and thiophenols in DMSO,[6d] Cs$_2$CO$_3$/DMSO-promoted the synthesis of unsymmetrical polyfluoroaryl ethers *via* selective C4–F bond cleavage of pentafluorobenzene with a wide variety of phenols and benzyl alcohols,[6e] NaOH/DMF-mediated the synthesis of *N*-tetrafluoroarylated heterocyclic compounds *via* selective C4–F bond cleavage of pentafluorobenzene with N–H containing heterocycles,[6f] NaO*t*Bu/DMA-promoted sequential S_NAr reactions of pentafluorobenzenes with azoles or indoles,[6g] and in the presence of Et$_3$N, pentafluoropyridine and 2,4,6-trifluoropyridine underwent S_NAr reactions with a series of primary and secondary amines for the syntheses of a library of simple and complex fluorinated 4-aminopyridine derivatives.[6h]

Encouraged by our previous success in the application of KOH/DMSO as the superbasic medium in the development of a general procedure for the synthesis of five-membered heterocycles *via* the cycloaddition of 1,3-butadiynes with water, primary amines, and Na$_2$S·9H$_2$O,[7] and KOH/DMSO has shown the versatile diverse catalytic activity in a variety of organic transformation reported by Trofimov,[8] Bolm,[9] and other groups,[10] in this paper we investigated the application of KOH/DMSO in the nucleophilic fluoroarene substitution with a variety of nucleophiles to provide an alternative base-promoted S_NAr of C–F bonds.

2. Results and discussion

As shown in Table 1, we firstly studied the reaction of 2-fluorobenzamide (**1a**) with MeOH (4 equiv) in the presence of

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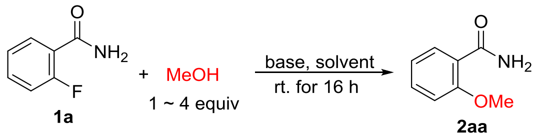
Table 1
Optimizing conditions for nucleophilic substitution of C–F bond with MeOH [a].



entry	MeOH (equiv)	base (equiv)	solvent	yield (%)[b]
1	4	KOH (4)	DMSO	81
2	4	–	DMSO	0
3	4	K_2CO_3 (4)	DMSO	15
4	4	Cs_2CO_3 (4)	DMSO	12
5	4	*t*-BuOK (4)	DMSO	47
6	4	NaOH (4)	DMSO	64
7	4	KOH (4)	THF	36
8	4	KOH (4)	dioxane	22
9	1	KOH (4)	DMSO	45
10	2	KOH (4)	DMSO	77
11	2	KOH (0.2)	DMSO	11
12	2	KOH (1)	DMSO	40
13	**2**	**KOH (2)**	**DMSO**	**80**

[a] 2-fluorobenzamide (0.5 mmol), solvent (2 mL), 16 h.
[b] Isolated yields.

KOH (4 equiv) in DMSO at room temperature. Fortunately, 2-methoxybenzamide (**2aa**) could be isolated from the reaction mixture in 81% yield (entry 1). **2aa** could not form at all without use of KOH (entry 2). Other inorganic bases, such as K_2CO_3, Cs_2CO_3, *t*-BuOK, NaOH in DMSO also promoted the S_NAr reaction, but **2aa** formed in fair to mild yields (entries 3–6). When THF and dioxane were used to replace DMSO as solvents, KOH showed fairly low ability to promote the reaction (entries 7–8). The further studies on the effect of amounts of MeOH and KOH have disclosed that the use of 2 equivalents of MeOH and KOH is the suitable choice for the formation of **2aa** in a satisfactory yield (entries 9–13).

Table 2 summarizes the S_NAr reactions of **1a** with *O*-nucleophiles (2 equivalents) in the presence of 2 equivalents of KOH. In the case of without using additional nucleophile, KOH can act as a nucleophile to generate **2ab** in 55% yield, and the addition of H_2O improved the yield to 83%. It is worth that the direct Pd-catalyzed synthesis of phenols by the reactions of aryl bromides or chlorides with KOH has been developed by Buchwald's group.[11] The use of EtOH and *i*-PrOH afforded the corresponding alkylaryl ethers **2ac** and **2ad** in 63% and 74% yields, respectively. Although it is commonly acknowledged that the alcohols having more alkyl substituents engage higher nucleophilicity, on the basis of the obtained results, methanol shows higher nucleophilicity (the yield of **2aa** in Table 1 of entry 13 *vs* the yields of **2ac** and **2ad** in Table 2). We assume that methanol has less steric hindrance to benefit the S_NAr reactions. Benzyl alcohol also undergoes the substitution to give **2ae** in 55% yield. However, trifluoroethanol shows sluggishly at room temperature, and when the reaction performed at 100 °C, the corresponding ether **2af** could form in 98% yield. In addition, phenols show low reactivity for the S_NAr reactions at room temperature, and at 100 °C, a variety of diaryl ethers could be obtained in 42–86% yield. As expected, the phenols bearing electron-withdrawing group such as 4-chlorophenol and 4-nitrophenol show very low reactivity to afford trace amount of the expected products at 100 °C. Moreover, the substituent position effect on the nucleophilicity of phenols can be also obviously observed (**2ai** *vs* **2aj**). Under the similar reaction conditions, the reaction of **1a** with 1,3,5-trimethylphenol afforded **2ak** in a moderate yield (42%) due possible to the steric hindrance of methyl groups.

Table 3 concludes the S_NAr reactions of 4-nitrofluoroarene (**1b**) with amines and amides. Although all the reactions at room temperature are very sluggish, the formation of C–N bonds at 80 °C is smoothly. **2bl** could be isolated from the reaction mixture in a fair yield by the reaction of **1b** with 2 equiv of dimethylamine hydrochloride in the presence of 4 equiv. of KOH. The use of piperidine led to the formation of **2bm** in 54% yield. When 4-methylaniline and 2-aminopyridine were used, 4-methyl-*N*,*N*-bis(4-nitrophenyl)aniline (**2bn**) and 2-amino-*N*,*N*-bis(4-nitrophenyl)pyridine (**2bo**) were obtained in 48% and 63% yields, respectively, resulting from the subsequent S_NAr reactions of one molecule of primary amines with two molecules of **1b**, and only small amount of diaryl amines could be detected by GC-MS. Pyrrole and its derivatives, such as indole and 5-methoxyindole could be also used as the *N*-nucleophiles to afford the expected products (**2bp**, **2bq** and **2br**) in fair yields. In addition, benzamide shows good reactivity in the S_NAr reaction giving *N*-(4-nitrophenyl)benzamide (**2bs**) in 68% yield. More interestingly, urea could be employed as an efficient precursor of ammonia as *N*-nucleophile to give 4-nitroaniline (**2bt**) in 61% yield.

Table 4 concludes the S_NAr reactions of a variety of fluoroarenes having different substituents with methanol in KOH/DMSO. The reactions of *N*-methyl-2-fluobenzamide (**1c**) and 4-fluorobenzamide (**1d**) at room temperature produced the expected products **2ca** and **2da** in 64% and 56% yields, respectively. Both 4-fluobenzonitrile (**1e**) and 3-fluobenzaldehyde (**1f**) were also able to afford corresponded products **2ea** and **2fa** albeit in relatively low yields with cyano and aldehyde groups untouched. At room temperature, although the reaction of 3,4-difluoronitrobenzene (**1g**) with 2 equiv. of methanol resulted in the formation of a mixture of mono- and di-S_NAr products, and the mono-S_NAr product of 2-fluoro-1-methoxy-4- nitrobenzene (**2ga**) formed as the predominant one. However, when the reaction was performed using 1 equiv. of methanol, **2ga** was obtained in high yield (85%), indicating that the reaction occurred with excellent regioselectivity resulted from the position-effect of two fluoro atoms related to nitro group in benzene ring, and fluoro at *para*-position exhibits significantly high reactivity. Under the similar reaction conditions, the reaction of 2-bromo-4-fluoroacetophenone (**1h**) at room temperature afforded the expected product (**2ha**) in 17% yield, and the reaction of 4-bromofluoroarene (**1i**) at 100 °C produced 1-bromo-4-methoxybenzene (**2ia**) in 45% yield. These results imply that fluorine was exactly a better S_NAr leaving group rather than bromo group.

In addition, although the base-promoted S_NAr reactions of fluoroarenes have been well-documented, the fluoroarenes are limited to bearing electron-withdrawing group(s).[6] To date, it has not reported an efficient reaction conditions for the S_NAr reactions of fluorobenzene, and fluoroarenes having electron-donating group. Therefore, it is very interesting and significant to examine the S_NAr reactions of fluorobenzene (**1j**) and fluoroarenes bearing electron-donating group under the similar reaction conditions. As shown Table 4, it is surprising that **1j**, 2-methoxyfluorobenzene (**1k**) and 4-methoxyfluorobenzene (**1l**) underwent the S_NAr reactions smoothly with methanol to give the corresponding aryl methyl ethers **2ja** ~ **2la** in good yields, when the reactions were carried out at 100 °C.

We also tried to develop a synthetic strategy for construction of 1,4-diheteroatom ring *via* a double S_NAr reaction of **1g** with double nucleophiles. As shown in Table 5, the reactions of **1g** with 1 equiv. of glycol, *ortho*-dihydroxybenzene and 2-aminophenol at 100 °C for 16 h afforded the corresponding 1,4-diheteroatom ring in moderate yields, with the formation of by-product resulted from the mono-S_NAr reaction.

It has been commonly known that most S_NAr reactions occur by addition-elimination reactions involving the formation of a carbanion intermediate.[12] The computational study for the reaction of fluorobenzene with KOMe, generated *in situ* by the reaction of KOH