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Regioselective Preparation of 3-Alkoxy-4,5-difluoroanilines by S_NAr

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A simple and scalable procedure to introduce alcohols selectively at the 3-position of 3,4,5-trifluoroaniline is described. The procedure uses powdered NaOH as base and catalytic 15-crown-5 in refluxing toluene with a Dean–Stark trap. A short exploration of other nucleophiles and fluoroaryl electrophiles is also described.

Introduction

Nucleophilic aromatic substitution (S_NAr) of fluorine[1] on electron-deficient arenes is well documented and has been extensively exemplified on fluorobenzenes substituted by a variety of activating groups such as, for example, nitro, cyano, sulfonyl, sulfinyl, bromide, keto, or ester groups.[2] In contrast, the displacement of fluoride on nonactivated or deactivated arenes has been scarcely reported.[3] Some procedures include the use of additives,[4] microwave heating,[5,6] photochemical conditions,[7] as well as high boiling point polar aprotic solvents such as NMP, DME, or DMF[3,6,8] and/or addition of cosolvents such as DMPU.[9]

We have recently identified 1,2,4-triazole derivative **1** (Figure 1) as a potent positive allosteric modulator (PAM) of the nicotinic alpha7 (nACh7) receptor.[10] The compound contains 3,4-difluoro-5-methoxyaniline (**2**) as one of the substituents of the triazole ring, for which a simple and efficient synthesis suitable for scale-up purposes was required.

Alkoxyfluoroanilines have been traditionally prepared by S_NAr of the corresponding 2- or 4-fluoronitrobenzene followed by reduction of the nitro group to the amine [Eq. (1), Scheme 1], which respectively affords the *ortho*- or *para*-alkoxy-substituted nitrobenzene as the product.[11] Alternatively, a few examples involving the palladium-catalyzed amination with ammonia of deactivated alkoxyfluoroaryl halides have also been reported [Eq. (2), Scheme 1].[12]

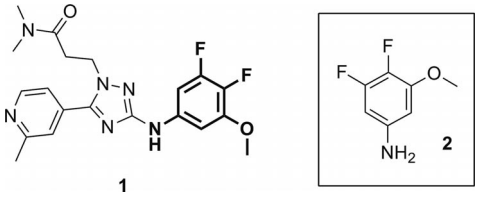
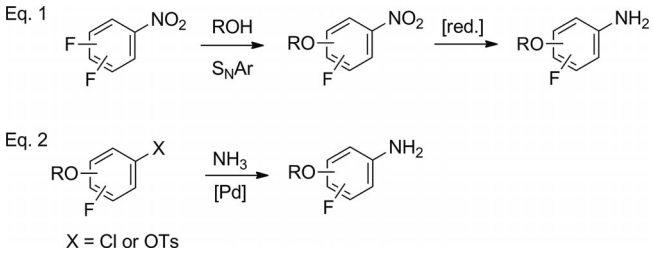


Figure 1. Structure of nACh7 receptor PAM **1** (pEC_{50} = 6.1).



Scheme 1. Reported methods for the preparation of alkoxyfluoroanilines.

To the best of our knowledge, S_NAr of fluorine with alkoxides has never been reported on unprotected fluoroanilines. We present herein the scope and limitations of a general, simple, and efficient method for the preparation of alkoxyfluoroanilines from commercially available polyfluoroanilines.

Results and Discussion

For the preparation of 3,4-difluoro-5-methoxyaniline (**2**), we initially explored the S_NAr of commercially available 3,4,5-trifluoroaniline (**1a**) with sodium methoxide (30 wt.-% in methanol) under several reaction conditions (Table 1). Thus, reaction of **1a** with NaOMe (5 equiv.) for 8 h under reflux led to a partial conversion of **1a** into **2** (Table 1, entry 1). An increase in the number of equivalents of the alkoxide (10 equiv.) and prolonged heating (14 h) led to complete consumption of **1a**. Unfortunately, the formation of

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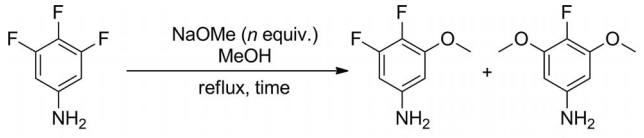
double-substitution product **4a** was also detected in appreciable amount (Table 1, entry 2). After further fine-tuning of the reaction conditions, we found that heating **1a** at reflux in methanol for 13 h with NaOMe (8 equiv.) gave the highest isolated yield of **2** (Table 1, entry 3), although the formation of **4a** could not be completely suppressed. Nevertheless, we were pleased to find that the reaction was reproducible and scalable under these optimized reaction conditions, and **2** could be obtained in 77% isolated yield when starting from 45 g (0.3 mol) of **1a**. To broaden the scope of this simple transformation, we studied the reaction with other alkoxides as nucleophiles. Initially, we selected benzyl alcohol for the nucleophilic substitution reaction, as it would allow diversification upon deprotection of the benzyl group in a later stage of the synthesis. Because the conditions shown in Table 1 involve the use of the alcohol as the reaction solvent, they would not be practical for high boiling point alcohols. Therefore, we decided to look for a more general and equally scalable protocol with the use of benzyl alcohol as the nucleophile but not as the reaction solvent.

Table 1. Nucleophilic substitution of 3,4,5-trifluoroaniline (**1a**) with NaOMe.

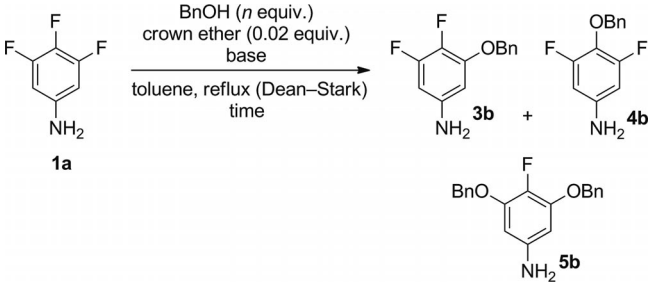


Entry	*n*	**1a** [g]	*t* [h]	LCMS[a] **1a/2/4a**	Yield **2**[b] [%]
1	5	4	8	27:56:0	n.d.[c]
2	10	4	14	0:72:28	60
3	8	45	13	7:78:15	77

[a] Based on UV trace in LC–MS. [b] Yield of isolated product. [c] n.d.: not determined.

For this we envisaged the use of nonprotic solvents combined with additives with the aim to enhance the reactivity of the alkoxide in the reaction media. After initial screening of the solvents and additives, we found that heating a mixture of **1a**, benzyl alcohol (1.2 equiv.), and potassium hydroxide in toluene at reflux in the presence of 18-crown-6 (18C6) led to the formation of a 3:1 mixture of **3b/5b** (Table 2, entry 1). The formation of the double-substitution product **5b** could be suppressed by using NaOH instead of KOH as the base; however, the formation of **3b** was then accompanied by regioisomer **4b** in 4:1 ratio (Table 2, entry 2). The formation of *para*-substituted product **4b** was avoided by decreasing the number of equivalents of NaOH (from 5 to 2) and BnOH (from 1.2 to 1.02), and **3b** was finally obtained in a satisfactory isolated yield of 67% (Table 2, entry 3). Finally, the switch to 15-crown-5 (15C5), which is known to be a better coronand for sodium, accelerated the reaction and reduced the reaction time to 5 h (Table 2, entry 4). Of note is that all reactions were performed with the use of a Dean–Stark trap for azeotropic removal of the water formed during the course of the reaction. This was found to be essential to achieve high conversions and to suppress the formation of isomer **4b** (Table 2, entry 5).

Table 2. Substitution of 3,4,5-trifluoroaniline with benzyl alcohol.



Entry	*n*	Crown ether	Base (equiv.)	*t* [h]	LCMS[a] **1a/3b/4b/5b**	Yield **3b**[b] [%]
1	1.2	18C6	KOH (5)	3	0:73:0:23	n.d.[c]
2	1.2	18C6	NaOH (5)	18	10:68:16:6[d]	56[e]
3[f]	1.02	18C6	NaOH (2)	18	3:79:0:14	67
4	1.02	15C5	NaOH (2)	5	15:81:0:4	67
5[g]	1.02	15C5	NaOH (2)	5	0:46:27:27[d]	n.d.[c]

[a] Conversion of **1a** as determined by LC–MS analysis of the crude reaction mixture. [b] Yield of isolated **3b** in reactions performed with 10 g of **1a**. [c] n.d.: not determined. [d] GC–MS was used to determine relative ratio. [e] **3b**:**4b** = 4:1. [f] A reaction with 250 g of **1a** led to the isolation of **3b** in 53% yield. [g] Performed with 2 g of **1a** *without* the use of a Dean– Stark trap.

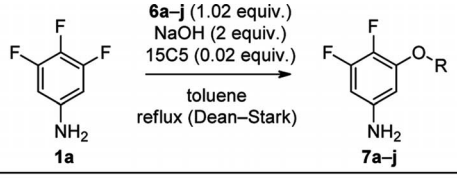
These optimized conditions were selected to extend the scope of this nucleophilic substitution with a diverse set of primary and secondary alcohols (i.e., **6a**–**j**). The results obtained can be found in Table 3. Primary alcohols **6a**–**e** and secondary alcohol **6f** afforded corresponding substitution products **7a**–**f** in moderate to good yields (47–82%; Table 3, entries 1–6). Tertiary *tert*-butyl alcohol **6g** was unreactive under these conditions and even so when sodium *tert*-butoxide was used as the base (Table 3, entry 7). Unfortunately an aromatic alcohol, such as phenol (**6h**), failed to give the substitution product **7h** (Table 3, entry 8). Interestingly, the reaction was compatible with tertiary amine **6i** and primary amine **6j** (Table 3, entries 9 and 10).

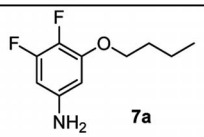
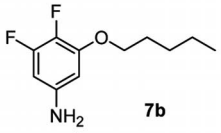
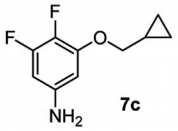
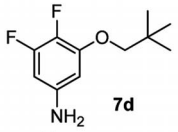
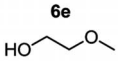
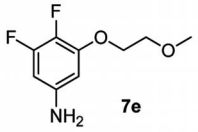
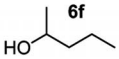
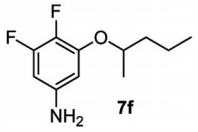
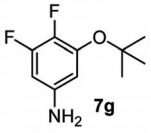
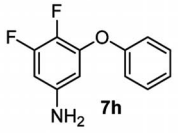
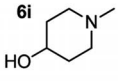
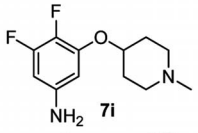
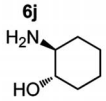
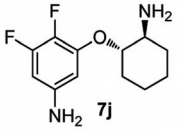
The use of nitrogen nucleophiles was also studied. Thus, different N-nucleophiles **6k**–**n** were selected for the reaction with **1a**. The results obtained are summarized in Table 4.

Benzamide **6k** and imidazole **6l**[6] failed to produce the corresponding substitution products **7k** and **7l** under standard reaction conditions (Table 4, entries 1 and 2). Interestingly, trace amounts of substitution products **7m** and **7n** were observed for piperazine **6m** and morpholine **6n** under the same reaction conditions. Better conversions towards **7m** (47%) and **7n** (46%) were obtained by using amines **6m** an **6n** as the solvent while heating the reaction mixture at 180 °C in a sealed tube (Table 4, entries 3 and 4).

Finally, the scope of the arene electrophile was also studied. For this, fluorobenzenes **1b**–**h** were treated with benzyl alcohol. The reactions were performed under the optimized reaction conditions described above (1.02 equiv. BnOH, 2 equiv. NaOH, 0.02 equiv. 15C5, toluene, reflux/Dean–Stark).

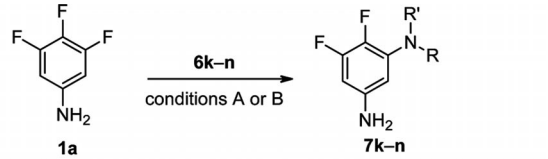
Table 3. Substitution of 3,4,5-trifluoroaniline with various alkoxides.[a]

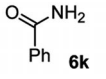
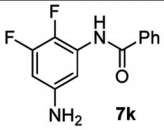
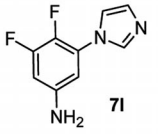
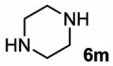
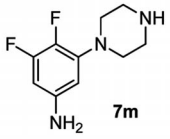
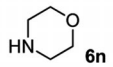
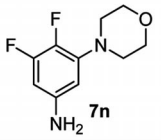


Entry	ROH, 6	t [h]	Product	Yield[b] [%]
1		18		61
2		18		78
3		18		60
4		14		82
5		18		60
6		18		47
7		14		n.r.[c]
8		18		n.r.[c]
9		18		67
10		18		51

[a] The reactions were carried out with 2 g of **1a**. [b] Isolated yield. [c] n.r.: no reaction.

Table 4. Substitution of 3,4,5-trifluoroaniline with nitrogen nucleophiles.[a]



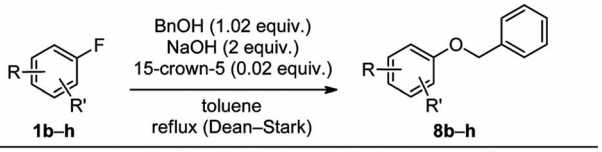
Entry	6	Conditions[d]	t [h]	Product	Yield[b] [%]
1		A	18		n.r.[c]
2		A	18		n.r.[c]
3		A B	18 18		trace 47
4		A B	18 36		trace 46

[a] The reactions were carried out with 2 g of **1a**. [b] Isolated yield. [c] n.r.: no reaction, only self-condensation of **1a** was observed by LC–MS analysis of the reaction crude. [d] Conditions A: **1a** (1.02 equiv.), **6k**–**n** (2 equiv.), NaOH (0.02 equiv.), 15-crown-5, toluene, reflux (Dean–Stark), 18 h; Conditions B: **1a**, amine **6m**–**n** (solvent), sealed tube 180 °C, 18–36 h.

The results of this exploration are shown in Table 5. 1,2,3-Trifluorobenzene (**1b**), which lacks the amino group, reacted smoothly to afford substitution products **8b** and **8b′** in 35 and 16% yield, respectively (Table 5, entry 1). This yield, which is lower than that obtained in the reaction of **1a**, can be explained by the low boiling point of **1b** (94.5 °C), as **1b** may slowly evaporate during the course of the reaction.[13] 3,5-Difluoroaniline (**1c**) gave substitution product **8c** in slightly higher yield (44%; Table 5, entry 2), although an extended heating time of 18 h was required (vs. 5 h for **1a**), which indicates that the *para*-fluoro substituent plays an important activating role in the reaction. Interestingly no selectivity was found with 3,4-difluoroaniline (**1d**), which led to the isolation of **8d** as a 1:1 mixture of the 3- and 4-substitution products (Table 5, entry 3). Simple 4-fluoroaniline (**1e**), lacking the double *meta*-fluorine substitution, gave with very low conversion and isolated yield expected product **8e** (Table 5, entry 4). To our delight, both anisole **1f** and dimethylaniline **1g** gave high-yielding conversions to their respective *meta*-substituted products **8f** and **8g**. Surprisingly, 2,3,4-trifluoroaniline (**1h**) gave only *ortho*- and *para*-substitution products **8h** and **8h′** in 49 and 15% yield, respectively (Table 5, entry 7)[14] without a trace of *meta*-substituted difluoroaniline. When comparing the selectivity observed for **1a** (preferentially *meta*) with that for **1d** (1:1 *meta*/*para*) with benzyl alcohol, it appears the S_NAr

is mostly dictated by the relative rate factors of *ortho*- and *meta*-fluorine substitution ($f_{o\text{-F}}$ = 60 vs. $f_{m\text{-F}}$ = 180) rather than the mesomeric effect of the aniline.[15] In contrast, the preferred *ortho*-substitution of **1g** is in line with previously observed selectivity for xantates and thiolates and can be similarly explained by precoordination of the aniline to the attacking nucleophile.[16] Moreover, as expected, the reactivity appears to be highly controlled by the number of fluorine substituents present.

Table 5. Substitution of fluorobenzenes **1b**–**h** with benzyl alcohol.[a]



1b–h → **8b–h**

Entry	Substrate **1**	*t* [h]	Product (yield[b])
1	**1b**	4	**8b** (35%); **8b'** (16%)
2	**1c**	18	**8c** (44%)
3	**1d**	24	**8d** (1:1 mixture, 53%)
4	**1e**	24	**8e** (7%)
5	**1f**	24	**8f** (84%)
6	**1g**	4	**8g** (81%)
7	**1h**	6	**8h** (49 %); **8h'** (15 %)[c]

[a] Reactions were carried out with 2 g of fluoroarene **1**. [b] Isolated yield. [c] Contained 30% of 2,4-bis(benzyloxy)-3-fluoroaniline (**8h′′**).

Conclusions

3-Alkoxy- and 3-aminodifluoroanilines are easily accessible through simple nucleophilic aromatic substitution of 3,4,5-trifluoroaniline with oxygen and nitrogen nucleophiles. The developed conditions have proven to be unexpectedly mild and easily scalable, which allows the preparation of useful building blocks on a scale up to 250 g. Furthermore, the reported transformations are remarkable, because they depend less on mesomeric deactivation of the aniline than on the relative rate factors of substitution, and precoordination of the aniline when possible. This results in *meta* selectivity for the 3,4,5-trifluoroanilines but in *ortho*/*para* selectivity for 1,2,3-trifluoroaniline. Extending the scope of the reaction with both substrate and nucleophile showed trends confirming the above-mentioned hypothesis. As expected, more bulky and/or less-reactive nucleophiles led to lower yields, whereas more electron-rich substrates reacted smoothly. Similarly, higher fluorination of the arene led to higher reactivity and yields.

Supporting Information (see footnote on the first page of this article): Full experimental details and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

We thank Tom Govaerts and Corina Janssen for performing the scale-up reaction to 250 g. We also thank Michel Carpentier for providing the high-resolution mass spectra.

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