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One-pot fluoro-de-diazoniation of anilines in organic medium

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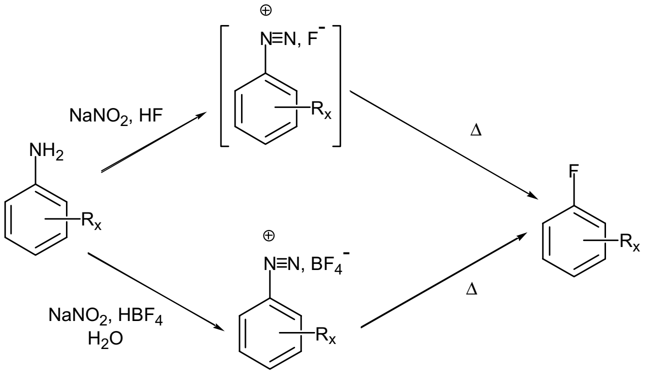
Abstract—Treatment of anilines with *tert*-butyl nitrite in the presence of boron trifluoride in *ortho*-dichlorobenzene leads to in situ fluoro-de-diazoniation and affords the corresponding fluoroaromatics with fair yields. This process, conducted in organic medium without Broensted acids, does not require isolation of hazardous diazonium salts and reduces the amounts of wastes. The results of the first screening are given.

1. Introduction

Fluoroaromatics Ar–F form one of the most important classes of fluorinated compounds used in pharmaceuticals, agrochemicals and performances markets such as liquid crystals.[1] Fluoro-de-diazoniation of anilines is one of the classical routes to fluoroaromatics.[2] It consists of a first step of diazotation of an aniline, followed by the introduction of the fluorine atom directly from the diazonium salt in HF[3] or HF-base media[4] or via thermal decomposition of diazonium tetrafluoroborate salts known as the Balz–Schiemann procedure[5] (Scheme 1).

Fluoro-de-diazoniation in anhydrous HF is limited to non-acid sensitive compounds.[1] The Balz–Schiemann conditions[5] increase the scope of functions in the aromatic ring but require isolation of the diazonium tetrafluoroborates, which are hazardous intermediates. Dryness of diazonium tetrafluoroborates is mandatory to avoid side formations of phenols and biaryl ethers, but this step can be dangerous because of weak thermal stability of these salts. In some cases, diazonium tetrafluoroborate salts are harmful and act as sensitizers.



Scheme 1.

Previous works describe transformations of anilines into fluoroaromatics in non-aqueous medium. $NOBF_4$ was often used to form a diazonium tetrafluoroborate in organic solvents[6] or in ionic liquids,[7] followed by thermal decomposition into fluoroaromatics. This approach is not easily scalable because $NOBF_4$ is expensive and not available in large quantities.

Heterocycles bearing an amino group have been transformed into the corresponding fluoroderivatives with *tert*-butyl-thionitrite as the nitrosing agent and sodium tetrafluoroborate as the fluoride source.[8]

tert-Butyl nitrite was used as the nitrosing agent with SiF_4 as the fluoride source[9] to transform various anilines, but these conditions are limited by the toxicity of SiF_4.[10]

Our goals were, first to synthesize fluoroaromatics Ar–F from anilines without the isolation and the accumulation of diazonium salts due to their toxicity and their potential explosivity and second to work in complete organic medium without acids to minimize aqueous wastes.

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To reach these goals, our strategy was to introduce the nitrosing agent to the reaction medium composed of the aniline, the fluoride source in the solvent at the decomposition temperature of the diazonium salt. In our works, alkyl nitrites[11] (and more specifically *tert*-butyl nitrite stable until 110 °C[12]) and a complex of BF_3 were chosen as nitrosing agents and the fluoride source, respectively.

The first step of the study was to quantify the efficiency of the diazotation of anilines and to determine the temperature of decomposition of the diazonium salts. In the second step, the one-pot transformation of anilines into fluoroaromatics (i.e., diazotation followed by fluoro-de-diazoniation) was studied.

2. Results

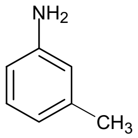
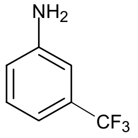
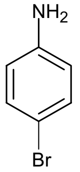
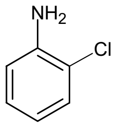
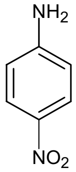
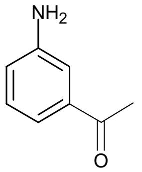
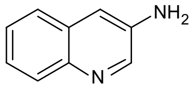
Doyle's procedure[13] seems particularly relevant to synthesize diazonium salts in organic medium. *tert*-butyl nitrite and boron trifluoride etherate were used in this procedure to obtain tetrafluoroborate diazonium salts with good yields in solvents like dichloromethane and ethers. We have extended the scope of this method by using solvents having higher boiling point solvents than dichloromethane or THF. Various solvents were tried in the diazotation reaction of meta-toluidine with *t*-BuONO in the presence of $BF_3{\cdot}OEt$: glyme, and 1,2-dichlorobenzene gave good yields, comparable with the ones obtained in CH_2Cl_2. 1,2-dichlorobenzene was preferred as a scalable solvent since it has a high boiling point (180 °C) consistent with temperatures of decomposition of various tetrafluoroborate salts and it is chemically inert. Thus, several anilines were treated with boron trifluoride etherate and *tert*-butyl nitrite at temperatures between −5 °C and 5 °C to obtain diazonium tetrafluoroborate salts (Table 1).

Satisfactory yields were obtained in our conditions. Temperatures of decomposition of these tetrafluoroborate diazonium salts in 1,2-dichlorobenzene were performed by DSC: globally, they are completely decomposed above 90–100 °C.

In situ fluoro-de-diazoniation was performed by adding *tert*-butyl nitrite to a mixture of aniline and boron trifluoride etherate at a temperature above the measured temperature of decomposition of the intermediate diazonium salt in 1,2-dichlorobenzene. We think that, in these conditions, diazotation of anilines is very fast and that the concentration of diazonium derivative should be very low. The reaction mixture was maintained at elevated temperature until complete transformation of starting anilines. Table 2 summarizes the performances of fluoro-de-diazoniation.

Yields are satisfactory for 3-toluidine and 3-trifluoromethylaniline (entries 1, 2). Since yields of diazotation have been determined before (80% for 3-toluidine and 70% for 3-trifluoromethylaniline, see Table 1), it is possible to estimate the efficiency of the fluorination step: 75% from diazonium intermediate of 3-toluidine and 63% from diazonium intermediate of 3-trifluoromethylaniline. The same orders of fluorination efficiency were obtained on 4-bromoaniline (67%, entry 3), 2-chloroaniline (60%, entry 4) and 3-aminoquinoline (67%, entry 7). These yields obtained for the one-pot procedure, that is, the direct transformation of the anilines into the fluoroaromatics Ar–F, are very similar to the ones obtained for the reactions carried out in water and with isolation of the diazonium salts followed by the Balz–Schiemann step.[5]

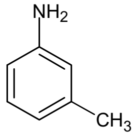
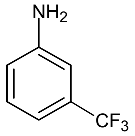
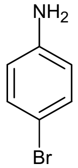
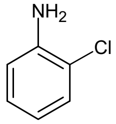
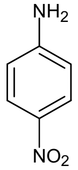
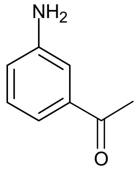
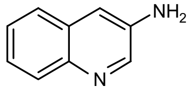
Table 1. Diazonium tetrafluoroborates from anilines with *t*-BuONO and $BF_3{\cdot}OEt_2$[a] in 1,2-dichlorobenzene

Entry	Aniline	ArN_2^+, BF_4^- Isolated yield (%)
1		80
2		70
3		80
4		65
5		80
6		55
7		60

[a] Anilines (5 g) were dissolved in 1,2-dichlorobenzene (30 ml), boron trifluoride etherate (1.5 M equiv) was added at −5 °C, then *tert*-butyl nitrite (1.2 M equiv) was slowly added via a syringe pump maintaining the temperature below 5 °C. The solid was isolated by filtration, washed with pentane and analyzed by NMR (^1H and ^{19}F with internal standard) to measure the yield of formation of diazonium tetrafluoroborate salt.

Concerning 4-nitroaniline (entry 5), yield in 4-nitrofluorobenzene is low (25%). This can come from the

Table 2. In situ fluoro-de-diazoniation of anilines with *t*-BuONO and $BF_3{\cdot}OEt_2$[a] in 1,2-dichlorobenzene

Entry	Aniline	*T* (°C), time	Yield Ar–F (%)
1		100 °C 20 min	60
2		100 °C 40 min	44
3		100–110 °C 120 min	54
4		110–120 °C 90 min	39
5		110–120 °C 60 min	25
6		90 °C 45 min	25
7		100 °C 60 min	40

[a] Anilines (5 g) were dissolved in 1,2-dichlorobenzene (30 ml), boron trifluoride etherate (1.5 M equiv) was added at 20 °C, then the mixture was warmed at the temperature mentioned and *tert*-butyl nitrite (1.2 M equiv) was slowly added in 15 min. The medium was maintained at reaction temperature for the time specified. After cooling at room temperature, water (30 ml) was added. After classical work-up, organic phase was analyzed by GC and NMR (^1H and ^{19}F with internal standard) to measure the yield of fluoroaromatics.

low nucleophilicity of this aniline or from side reactions at elevated temperature during the decomposition of the diazonium intermediate.

3-Fluoro-acetophenone (entry 6) is formed with only 25% yield from 3-aminoacetophenone. The literature[14] gives a 65% yield for the Balz–Schiemann procedure on 3-amino-acetophenone, but in our hands the yield of this reaction was below 30%.

In all our trials, starting anilines were not detected in the final reaction mixture and the only by-products were biaryl compounds coming from cationic or radical pathways, and tars when the yields are low. Arenes Ar–H or phenols derivatives were detected only in very low amount (<1%).

If boron trifluoride etherate is changed for the complex of boron trifluoride with water ($BF_3{\cdot}2H_2O$), the results in terms of yields and profile of impurities are very similar to the ones obtained with $BF_3{\cdot}Et_2O$. It is worth noting that no more phenol derivatives were detected by gas chromatography and NMR.

These results are not optimized but correspond to the first screening efficiency and scope of in situ organic fluoro-de-diazoniation process. Optimizations of conditions to increase the selectivity of fluorination are in progress. We also assume that the amounts of diazonium derivative of starting anilines are very low in our conditions, because the reaction temperature is above the decomposition of diazonium salt. In further work, we will try to measure this amount of diazonium derivatives to show that, in our conditions, we could avoid the accumulation of hazardous diazonium salts.

In conclusion, we have found that it is possible to transform anilines into the corresponding fluoroaromatics with fair yields via in situ fluoro-de-diazoniation in organic medium using *tert*-butylnitrite as the nitrosing agent and a complex of boron trifluoride as the fluoride source. No acid was used and the reaction was performed in complete organic medium. No isolation of intermediate diazonium salts is required and treatment of the reaction medium is easy.

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