

A mild and efficient method for nucleophilic aromatic fluorination using tetrabutylammonium fluoride as fluorinating reagent

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Abstract

Anhydrous tetrabutylammonium fluoride (TBAF_{anh.}) has been found to be a highly efficient fluorinating reagent for nucleophilic aromatic fluorinations such as fluorodenitration or halogen exchange (Halex) reaction. The products were formed in high to excellent yields under surprisingly mild reaction conditions and no phenol or other side-products were detected in these reactions.

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Fluoroaromatics have applications in many sectors, including the pharmaceutical and agrochemical industries due to the unusual properties of the C–F bond [1–4]. Because of the industrial importance of fluoroaromatics, mild and selective methods for their preparation are desirable, thus an expansive set of nucleophilic reagents has been developed to replace various C–X functional groups with C–F via nucleophilic aromatic fluorination. Alkali metal fluoride such as potassium fluoride is the traditional reagent for nucleophilic aromatic fluorination. However, its limited solubility in organic solvent and low nucleophilicity require generally vigorous conditions [5]. CsF being both more reactive and more expensive and LiF and NaF being completely unreactive. Thus, a number of metal fluoride reagents such as KF/18-crown-6, “freeze-dried” KF and “spray-dried” KF have been reported to solve these problems [6]. However, these above-mentioned processes are generally less efficient than those using tetraalkylammonium fluorides [7–10]. TBAF_{anh.} was found to be an efficient fluorinating reagent for the nucleophilic fluorination [11–14]. TBAF_{anh.} is a soluble, highly nucleophilic fluoride-ion source. It can be dissolved in dimethyl sulfoxide (DMSO), CH₃CN and THF, and it can fluorinate primary alkyl halides and tosylates rapidly at low temperature (–35 °C) for 5 min in THF [12]. The rapid rate observed for S_N2 reactions that feature TBAF_{anh.} prompted us to investigate nucleophilic aromatic substitution (S_NAr) reactions with this reagent. Below we describe variants of fluorodenitration and Halex processes for aromatic fluorination. The results show that TBAF_{anh.} permits these reactions to be performed under surprisingly mild conditions.

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1. Experimental

A mixture of TBAF_{anh.} (30 mmol), dried THF (10 mL), nitroaromatics or chloroaromatics (25 mmol) were stirred for certain time at room temperature or refluxed under nitrogen atmosphere. The reactions were trapped by GC. Side-products were obtained by flash column chromatography. 4,4'-Dinitrodiphenyl ether: ¹H NMR (CDCl₃): δ 7.16–7.18 (d, 4 × CH, *J* = 7.5 Hz), 8.29–8.30 (d, 4 × CH, *J* = 7.5 Hz); ¹³C NMR (CDCl₃): δ 160.71, 144.19, 126.19, 119.31; melting point: 145–146 °C; MS (*m/z*): 260, 138, 123, 95, 77; IR (KBr): 3099.91, 1582.87, 1464.64, 1321.93, 1308.05, 1281.75, 1146.28, 1088.96 cm⁻¹. *p*-Nitrophenyl methyl sulfide: ¹H NMR (CDCl₃): δ 2.58 (s, CH₃), 7.31–7.32 (d, 2 × CH, *J* = 8.9 Hz), 8.15–8.17 (d, 2 × CH, *J* = 8.9 Hz); ¹³C NMR (CDCl₃): δ 148.92, 144.74, 124.99, 123.85, 14.82; melting point: 68–69 °C; MS (*m/z*): 169, 139, 111, 108, 77, 45; IR (KBr): 1530.34, 1359.32, 1334.26, 745.42 cm⁻¹.

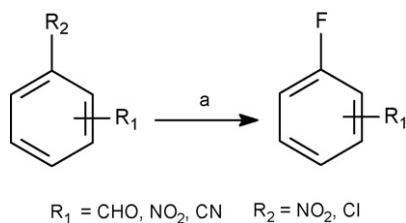
2. Results and discussion

The usual reagents employed to effect fluorodenitration or Halex are spray-dried KF (SD-KF); a high-boiling-point polar aprotic solvent, such as sulfolane; and a phase-transfer catalyst to improve the solubility of the fluoride ion. Prolonged and vigorous heating is often required. Such harsh conditions preclude syntheses in which the late introduction of fluorine substituents is desired. In contrast, many aromatic compounds undergo fluorodenitration or Halex reactions at room temperature in THF upon exposure to TBAF_{anh.} (Scheme 1). Some examples are summarized in Table 1.

As the data in Table 1 indicate, aromatics with electron-withdrawing groups at the 2- or 4-position (entries 2–4, 6, 7 and 9) underwent smooth denitration to afford the corresponding fluoroaromatics after a few hours either at room temperature or at reflux. While aromatics with electron-withdrawing groups at the 3-position required prolong the reaction time to drive completion (entries 1 and 8). A comparison of the meta- ortho- and para-dinitrobenzene examples shows fluorination of meta-dinitrobenzene requires 40 h, whereas ortho- and para-dinitrobenzene are exhaustively fluorinated in 1.5 h under identical conditions. Nitroaromatic substrates bearing more strongly electron-withdrawing (cyano) substituents are also fluorinated rapidly. It is noteworthy that 2- and 4-nitrobenzonitriles are fluorinated quantitatively within 1 h. In addition, TBAF_{anh.} performs fluorinations even on relatively weakly activated arenes, for example, nitrobenzaldehydes and chlorobenzaldehydes, fluorodenitration and Halex fluorinations of 2- and 4-nitrobenzaldehydes and 2- and 4-chlorobenzaldehydes require heating at reflux for ten or twenty hours to give more than 80% yields. Adams and Clark reported that NO₂⁻ is superior to chloride as a leaving group in S_NAr [15], as the data in Table 1 confirmed the conclusion (entries 4, 6, 7, 9, 10 and 12–14). Entries 8 and 15 were chosen as examples of *meta*-substituent, which are of interest due to the difficulty of forming such fluoroaromatics *via* Halex fluorination, thus entries 1 and 8 are established industrial methods of forming such fluoroaromatics.

In order to compare the reaction efficiency for nucleophilic aromatic fluorination of various fluorinating reagents, we chose the conversion of *p*-dinitrobenzene (PDNB) to *p*-fluoronitrobenzene (PFNB). Representative fluorinations are shown in Table 2.

As the data in Table 2 indicate, the activity of KF is the weakest and it needs very high temperature to make the reaction proceed successfully. Attempted displacement of 25 mmol of PDNB by 100 mmol of SD-KF in the presence of 2.5 mmol of Ph₄PBr, 1.25 mmol of TEG-Me₂ and 25 mmol of PDC in 15 mL of DMSO at 189 °C for 1 h gave only 82.7% of PFNB. In the mean time, because of weak stability of NO₂⁻, there will result some by-products, such as phenols and ethers (we had isolated the 4,4'-dinitrodiphenyl ether from the reaction mixture). Generally, side reaction can be controlled effectively by adding NO₂⁻ trapping agent, such as phthaloyl dichloride (PDC) [16]. The high



Scheme 1. Fluorodenitration and Halex reactions of nitro- and chloroaromatic compounds by TBAF_{anh.} (a) TBAF_{anh.}, THF, in RT.

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