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Journal of Fluorine Chemistry 126 (2005) 661–667
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Electrophilic aromatic fluorination with fluorine: *meta*-Directed fluorination of anilines

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Received 5 October 2004; accepted 15 February 2005

Dedicated to Prof. R.D. Chambers for his 70th birthday.

Abstract

Anilines are mainly or selectively fluorinated in the *meta*-position with F_2 when dissolved in triflic acid, sometimes in the presence of small quantities of antimony pentafluoride. The regioselectivity is increased when an electron-donating substituent is present at the *para*-position.

Keywords: Anilines; Fluorine; Fluoroanilines; Triflic acid; Fluorination

1. Introduction

Fluoroaromatics constitute an important class of fluorinated compounds since they are key-intermediates in the manufacture of prominent pharmaceuticals and agrochemicals [1–4]. Usually, they arise from the nucleophilic substitution of diazonium moieties with hydrogen fluoride or that of activated halides with fluoride anions [5–10]. In principle, electrophilic fluorination of unsubstituted aromatic nuclei with fluorine could provide shorter routes to fluoroaromatics.

Nevertheless, the use of fluorine has been hindered, for a long time, for two main reasons. The first one is the hazardous storage and handling of this reagent. Such a problem can be now solved, at least on the laboratory scale, by the commercial availability of bench electrolysers (''Fluorodec®'' from Fluorogas Ltd.), able to deliver fluorine on demand, even at low rates, without any storage of this corrosive gas. Moreover, safety is improved by diluting the fluorine thus generated, with nitrogen (typically, a 10:90, v/v, F_2/N_2 mixture is used). The second problem lies in the difficulty to control the direct fluorination of organic compounds, which was claimed, for a long time, to be a very exothermic radical chain process. Indeed, homolytic dissociation of fluorine is very easy (F–F bond energy = 159 kJ mol^{-1}) [11] and predominates when no polarization of this molecule is induced by its environment. This was especially the case when almost apolar fluorotrichloromethane (CFC-11), which is outstandingly inert to F_2, was chosen as solvent [12–14].

However, during the last decade and especially under the impetus given by Chambers et al., important work has been devoted to the development of new conditions allowing the polarization of fluorine, and thus the tamed electrophilic fluorination of organic substrates. Since this time, a steadily growing number of papers have appeared [15–24]. Concerning electrophilic aromatic fluorination [25–30], an outstanding contribution has been given again by Chambers et al., who demonstrated that aromatics bearing an electron-donating group in *para*-position to an electron-withdrawing group, can be cleanly fluorinated with F_2 at room temperature, provided that a strong acid, such as 98% sulfuric or formic acid, is used as solvent [20,31,32]. Such solvents are polar enough and, more importantly, protic enough to strongly polarize fluorine and avoid uncontrolled

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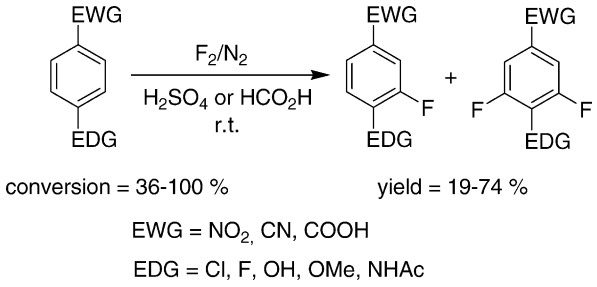
doi:10.1016/j.jfluchem.2005.02.013



Scheme 1. Fluorination of disubstituted benzenes [20,31,32].

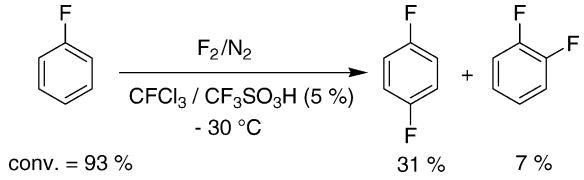
radical processes. This explains why the reaction can be carried out at room temperature. Of course, because of the aromatic substitution pattern, a completely regioselectivity was observed (Scheme 1).

Curiously, few fluorinations have been carried out with perfluoroalkanesulfonic acids as solvents or additives. For example, Hoechst patented results, very similar to those of Chambers et al., from fluorination in perfluorobutanesulfonic acid [22], whereas Coe et al. fluorinated fluorobenzene, at low temperature in fluorotrichloromethane, in the presence of small quantities of triflic acid (CFC-11:TfOH = 95:5 to 90:10) [33] (Scheme 2). It should be noticed that, probably because of the rather low protic character of this medium, chemical selectivity is limited.

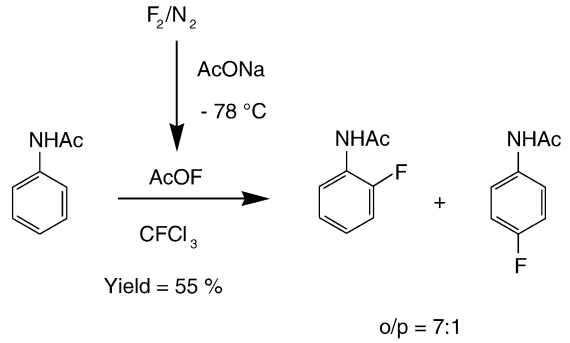
2. Results and discussion

Fluoroanilines are important building blocks for the manufacture of numerous bioactive products. *ortho*- and *para*-fluoroaniline are usually produced, on the industrial scale, through a two-step nitration-reduction of fluorobenzene. *meta*-Fluoroaniline is less easily available, but can be prepared by a *cine*-substitution of *ortho*-chlorofluorobenzene with sodium amide in liquid ammonia [34]. Thus, it would be interesting to examine the possibility to obtain fluoroanilines from direct electrophilic fluorination of anilines.

Of course, the free amino group, as well as the methylamino moiety, cannot survive the action of such an oxidant as F_2, as demonstrated by Purrington and Woodward during the fluorination of *N*-methylaniline, even in the presence of boron or aluminum trichlorides [29]. This is the reason why Rozen and co-workers fluorinated acetanilide, and not aniline, with acetyl hypofluorite, generated in situ



Scheme 2. Fluorination of fluorobenzene [33].



Scheme 3. Fluorination of acetanilide with acetyl hypofluorite [35].

from fluorine and sodium acetate [35]. In this case, *ortho*-fluoroaniline was the major product, may be (but it is not still clear), because of an interaction between the nitrogen atom and the fluorinating agent, at least in the transition state (Scheme 3).

Another strategy could be to protonate anilines strongly enough to protect them against oxidation. Moreover, it could be anticipated that protonated anilines should be fluorinated mainly at the *meta*-position, because of the inductive electron-withdrawing effect of the ammonium substituent.

Thus, we studied the fluorination of aniline itself in strong acidic media, namely pure sulfuric acid, triflic acid or triflic acid with several added Lewis acids [$B(OTf)_3$, SbF_5, $SbCl_5$, 1–4 mol%]. The results are summarized in Table 1.

As resulting from Table 1, aniline was fluorinated, as expected, without extensive oxidation or degradation and *meta*-fluoroaniline was always predominant over its *ortho*- and *para*-isomers. This indicates that aniline was protonated to a large extent during the reaction. However, the results were dependent on the medium composition. Sulfuric acid (entry 1) was not the most suitable solvent since, though conversion of **1a** was rather high (74%), global selectivity (51%) and chemical balance (64%) were not satisfactory. Possibly, water-soluble by-products, arising from sulfonation and oxidation by H_2SO_4, could have been formed and eliminated from the organic phase during the aqueous work up. Better results were obtained in triflic acid (entry 2), which is not an oxidant. In this case, aniline was probably protonated more efficiently. Indeed, reactivity was lower (as indicated by a lower conversion), but the reaction was cleaner, as indicated by a higher global selectivity (70%) and a more satisfying balance of aromatic compounds (80%). Additional proof was brought by a higher *meta*-regioselectivity (*m*-**2a**:*p*-**2a**:*o*-**2a** = 1.5:1.2:1 with TfOH compared to 1.3:1.1:1 with H_2SO_4).

The addition of boron triflate (1 mol%, entry 3) did not change dramatically the conversion, the chemical balance and the isomer ratio but resulted in a lower selectivity. This additive, known as one of the strongest Lewis acids [36], could have activated the fluorine atoms in *p*-**2a** and *o*-**2a** to promote their substitution by free anilines that leads to tarry