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Electrophilic fluorination of *N*,*N*-dimethylaniline, *N*,*N*-dimethylnaphthalen-1-amine and 1,8-bis(dimethylamino)naphthalene with N–F reagents

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ABSTRACT

Reaction of *N*,*N*-dimethylaniline, *N*,*N*-dimethylnaphthalen-1-amine and 1,8-bis(dimethylamino)-naphthalene (proton sponge) with 1-chloromethyl-4-fluorodiazonia-bicyclo[2.2.2]octane bis(tetra-fluoroborate) (Selectfluor) and *N*-fluorobenzenesulfonimide (NFSI) has been studied under various conditions. Unlike the proton sponge, which is fluorinated rather selectively at the *ortho*-position to NMe_2 group, producing 2-fluoro derivatives in moderate yield, two other amines react with Selectfluor and NFSI with strong tarring and the formation of complex mixtures of the corresponding biaryls, biarylmethanes and *N*-demethylated products. 2-Fluoro and 4-fluoro derivatives are also formed in minor quantities with the former isomer being predominant. Using the NFSI–$ZrCl_4$ system results in competitive chlorination of the aromatic ring.

1. Introduction

Direct fluorination of aromatic compounds has been of interest to organic chemists for several decades. This is caused by wide application of fluoroorganics in such important areas as polymers, drugs, pesticides, functional dyes, liquid crystals, etc. [1]. Until late 1980s, a typical set of reagents for electrophilic fluorination of aromatic C–H bonds included F_2 [2,3], $CsSO_4F$, CF_3OF, RCO_2F, ArIF, XeF_2 and some others [2]. They, however, suffer from such drawbacks as bad handling and rather strong oxidative ability.

A significant contribution into this field had been done by Umemoto who introduced in 1986 *N*-fluoropyridinium salts as the first N–F fluorinating agents [4]. Now this class of compounds encounters about 100 representatives; many of them are commercially available. Unlike the above fluorinating agents of the first generation, the N–F reagents are less aggressive, easily stored and generally more selective [5]. Along with *N*-fluoropyridinium salts, the most used among them are 1-chloromethyl-4-fluorodiazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate) (trademark Selectfluor, **1**) and *N*-fluorosulfonimides, e.g. *N*-fluorobenzenesulfonimide (NFSI, **2**) (Fig. 1).

Although quite some time has passed since introducing the N–F reagents, many aspects of their application remain unexplored. This is especially true for fluorination of strongly activated aromatic compounds such as arylamines. In the present paper, we describe results of electrophilic fluorination of three typical dimethylaminoarenes: *N*,*N*-dimethylaniline (**3**), *N*,*N*-dimethylnaphthalen-1-amine (**4**) and 1,8-bis(dimethylamino)naphthalene (known as "proton sponge", **5**). These amines differ from one another by the number of conjugated rings and NMe_2 groups allowing investigation of influence of these factors on ease and regioselectivity of fluorination. In most experiments, compounds **1** and **2** were used as fluorinating reagents. Additionally, an NFSI–$ZrCl_4$ system suggested by Yamamoto [6] has been tested in some instances.

2. Results

Table 1 summarizes experimental results that allow comparing the chosen arylamines in fluorination reaction. The reactions were conducted in $CHCl_3$ for NFSI and in MeCN for Selectfluor and the temperature varied from ambient to 60–61 °C.

2.1. N,N-*Dimethylaniline*

In all experiments, a significant tarring and low selectivity were observed with this substrate.

The formation of fluorodimethylanilines was observed only with NFSI (entries 1–3), and the *ortho*-isomer was predominant (entry 3). The main reaction products were diphenylmethane **6** and

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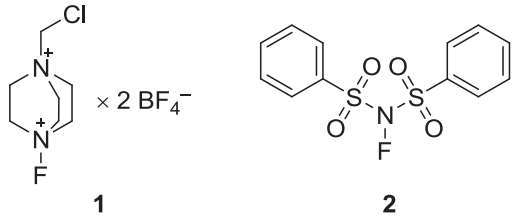


Fig. 1. Structures of Selectfluor (**1**) and NFSI (**2**).

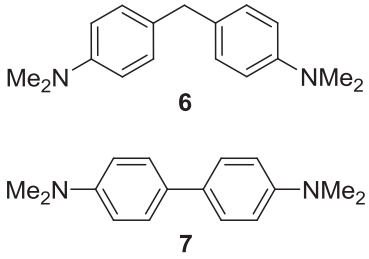


Fig. 2. Main reaction products on fluorination of amine **3**.

biphenyl **7** (Fig. 2) along with their numerous *N*-demethylated and ring-fluorinated derivatives. The total amount of diphenylmethane and biphenyl derivatives in volatile fractions, independently on the temperature, was about 20% and 12%, respectively. Among other reaction products identified in experiments with NFSI were the starting **3** (4% at 25 °C), *N*-methylaniline (1.3%), *N*,*N*,4-trimethylaniline (1.9%), *N*,4-dimethylaniline (1.3%), *N*-formyl-*N*-methylaniline (1.4%), 4-methylaminobenzaldehyde (7%) and 4-dimethylaminobenzaldehyde (8%). Additionally, the sulfur derivatives **8** and **9** were detected in ~2% yields each (Fig. 3).

Surprisingly, but in the case of NFSI–$ZrCl_4$ system, along with the above-mentioned products, 2-chlorodimethylaniline (10%) together with phenylsulfonyl halides **10** (3%) and **11** (6%) were also produced.

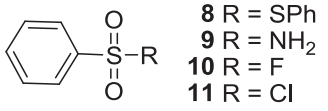


Fig. 3. Side products when using NFSI and NFSI–$ZrCl_4$ mixtures.

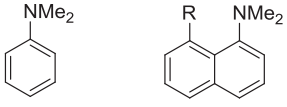
On lowering the temperature to 0 or −15 °C, a significant drop in the yield of 2- and 4-fluorodimethylanilines (from 10–13% down to 1–2% total) was observed. Regardless on the conditions used, diphenylmethanes and biphenyls were the only reaction products in the experiments with Selectfluor (entries 4, 5).

2.2. N,N-*Dimethylnaphthalen-1-amine*

As in the case of **3**, a considerable tarring occurs at fluorination of **4**. At the same time, there are two notable differences between these substrates. First, amine **4** is less reactive towards both fluorinating agents. Thus, about 60 and 50% of unchanged **4** were detected in volatile fractions when using NFSI and Selectfluor at room temperature, respectively (entries 6 and 9). The second notable difference is a higher selectivity of **4**. This conclusion results from the larger total yield of ring-fluorinated compounds for **4** if compared with that for **3** (*cf*. entries 1 and 2 with 6 and 7, respectively). A lesser number of side-products in the case of **4** also agrees with this point. Indeed, unlike **3**, no *N*-demethylated or ring-methylated compounds were noticed in the reaction mixtures, although the formation of coupling products **12** and **13** (11% and 4%, respectively, almost independent on temperature), was observed (Fig. 4). As for **3**, the benzenesulfonic acid derivatives **8** and **9** have been also detected after NFSI fluorination.

We were unable to isolate the ring-fluorinated products of **4** in pure state to estimate the regioselectivity of the process. However, from indirect arguments one can suggest that the 2-fluoro-*N*,*N*-dimethylnaphthalen-1-amine is the isomer that prevails. Thus, the ^{19}F NMR spectrum of a crude reaction mixture in $CDCl_3$ contained the doublet-of-doublets signal of the fluorine

Table 1
Selected results of fluorination of dimethylaminoarenes (amine/N–F reagent ratio is 1:1).



3 **4** R = H, **5** R = NMe_2

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Entry	Amine	N–F reagent	Conditions	*ortho: para* Selectivity by GC (%)	Number of products by GC
1	**3**	NFSI	$CHCl_3$, 25 °C, 10 h	4:2	16
2	**3**	NFSI	$CHCl_3$, reflux, 5 h	10:3	17
3	**3**	NFSI	$CHCl_3$, reflux, 5 h [a]	7:1	17
4	**3**	Selectfluor	MeCN, 25 °C, 10 h	[b]	15
5	**3**	Selectfluor	MeCN, 60 °C, 5 h	[b]	18
6	**4**	NFSI	$CHCl_3$, 25 °C, 10 h	11:1	21
7	**4**	NFSI	$CHCl_3$, reflux, 5 h	14:1	17
8	**4**	NFSI	$CHCl_3$, reflux, 5 h [a]	6 [c]	19
9	**4**	Selectfluor	MeCN, 25 °C, 10 h	9:2	17
10	**4**	Selectfluor	MeCN, 60 °C, 5 h	23:3	20
11	**5**	NFSI	$CHCl_3$, 25 °C, 10 h	59(26)[c,d]	10
12	**5**	NFSI	$CHCl_3$, reflux, 5 h	49(16)[d]:2	16
13	**5**	NFSI	$CHCl_3$, reflux, 5 h [a]	8 [c]	18
14	**5**	Selectfluor	MeCN, 25 °C, 10 h	47(15)[d]:9	11
15	**5**	Selectfluor	MeCN, 60 °C, 5 h	52(17)[d]:10	16

[a] 20 mol% of $ZrCl_4$ as catalyst.
[b] Neither starting nor fluorinated amines were detected.
[c] Only *ortho*-isomer was detected.
[d] Isolated yield in parenthesis.