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Synthesis of fluorofurazans

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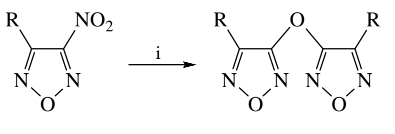
Furazans bearing fluoro atoms are easily obtained by nucleophilic displacement of a nitro group at the furazan ring upon treatment with TEAHF in a solution of [BMIM][BF$_4$].

The fluorodenitration reaction of activated substituted nitro(hetero)aromatic compounds is well known (Scheme 1).[1–4] The most commonly used methodologies for this transformation employ alkali metal fluorides in polar aprotic solvents, such as DMF, *N*-methylpyrrolidinone, DMSO and sulfolane.

$$\mathrm{Ar{-}NO_2} \xrightarrow{\mathrm{F^-}} \mathrm{Ar{-}F}$$

Scheme 1

Chemically, nitrofurazans are the activated nitroheteroaromatic compounds, and it has always been assumed that the nitro group can be easily replaced by a nucleophile.[5,6] However, it is known that 3-nitro-4-R-furazans reacted with NaF or KF in MeCN to give derivatives of symmetrical difurazanyl ethers (Scheme 2).[7–9] This unusual reaction pathway to ether bond formation was identified, and a mechanism was proposed.[7] The transformation of the nitro group is made possible by the presence of another electron-withdrawing function, R, and by the use of solid anhydrous bases (heterogeneous mixture) under dry conditions.



Scheme 2 *Reagents and conditions*: i, NaF or KF, MeCN, 60–80 °C.

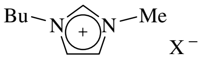
The question arose of whether the preparation of fluorofurazan was conceivable in principle. Note that other halofurazans are rarity.[5] General methods for preparation of chloro-[10] and iodofurazans[11] have been described only recently. The results of these studies helped us to understand necessary requirements for the successful halofurazan synthesis. The requirements involved (i) dry conditions, (ii) homogeneous reaction mixture, (iii) acidic media, (iv) mild temperature, and (iv) exception of common polar solvents. Here, we report the synthesis of fluorofurazan by the fluorodenitration reaction at the furazan ring.

The key to the implementation of the fluorodenitration reaction was the selection of the fluorine source and solvent. The solubility of alkali metal fluorides in dried common solvents is low. In contrast, fluorides of organic bases are more soluble in the reaction media. For example, tetraalkylammonium fluorides have been successfully used for the fluorodenitration of several nitroarenes.[12,13] However, tetraalkylammonium fluorides are highly basic. Moreover, the fluorine source was also used in common polar solvents. The conditions are not applicable to the synthesis of fluorofurazans. The reaction mixture of 3,4-dinitrofurazan **1a** with anhydrous tetramethylammonium fluoride in DMSO or DMF was observed to turn dark brown, the only compound isolated (< 10%) was 3-hydroxy-4-nitrofurazan.

When this reaction was carried out with triethylamine hydrofluoride (TEAHF) in DMF, and then analysed by GC-MS, desired 3-fluoro-4-nitrofurazan **2a** was detected. However, attempted isolation of compound **2a** from the solvent failed. This clearly illustrated the importance of solvent properties in the fluorodenitration process. Thus, an alternative solvent is necessary.

Recently, Sandford *et al.*[14] have reported an interesting solution to similar problem involving the use of room temperature ionic liquids (RTILs) as a medium for halogen exchange processes with CsF as a fluorine source; attempts using KF, KHF_2 or CaF_2 were unsuccessful.

RTILs have been widely investigated as potential replacement common solvents for a variety of chemical processes.[15–17] RTILs, such as [bmim][X] (Figure 1), may be advantageous reaction media because they are the most widely available, fire-resistant, recyclable and have a limited vapour pressure, allowing efficient recovery of organic products.



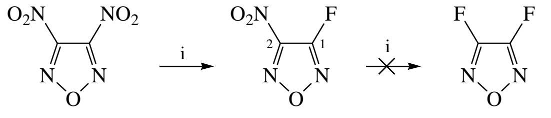
[bmim] = butylmethylimidazolium
X = BF_4, PF_6

[bmim][X]

Figure 1 Room temperature ionic liquids (RTILs).

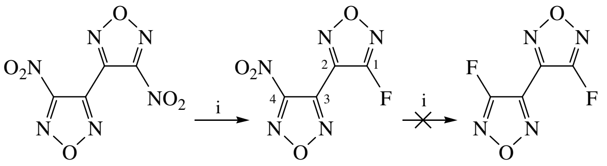
We found that a nitro group at a furazan ring was displaced by fluoride when heated with TEAHF in a solution of $[bmim][BF_4]$ or $[bmim][PF_6]$.[†] A variety of fluorofurazans can be produced in moderate to good yields from 3-nitro-4-R-furazans bearing electron withdrawing group R. Thus, when 3,4-dinitrofurazan **1a**[18] was treated with the fluorine source at 50 °C for 4 h, 3-fluoro-4-nitrofurazan **2**[‡] was obtained in *ca.* 50% yield (Scheme 3). The influence of RTIL anion on the yield is unimportant. Product **2** was isolated by simple distillation directly from the RTIL. GC-MS analysis showed the absence of 3,4-difluorofurazan **3** in the reaction. Similar conversions were observed using Py·3HF as a fluorine source, but the reaction times were longer. Compound **2** is a highly volatile and reactive liquid.

The reaction of 4,4′-dinitrobifurazan **1b**[18] with TEAHF in a solution of $[bmim][BF_4]$ at 50 °C for 24 h behaves similarly, producing monofluro product **4** (36%) along with some recovered starting compound **1b** (60%). A related reaction occurred using $[bmim][PF_6]$ resulting in the formation of a 2:5 mixture of compounds **4** and **1b**. The same reaction gave a higher yield (58%) of fluoro product **4** when it was done at 50 °C for 56 h. However, the reaction did not afford difluoro product **5** (Scheme 4).



1a **2** **3**

Scheme 3 *Reagents and conditions*: i, $NEt_3\cdot3HF$, [bmim][X], 50–100 °C.



1b **4** **5**

Scheme 4 *Reagents and conditions*: i, $NEt_3\cdot3HF$, [bmim][X], 50 °C.

In sharp contrast to this result, treatment of 4,4′-dinitroazofurazan **1c**[16] with TEAHF in a solution of $[bmim][BF_4]$ at 50 °C for 8 h afforded a 3:1 mixture of monofluoro **6** (59%) and difluoro derivative **7** (Scheme 5), which was readily separated by silica gel chromatography. The fluorodenitration reaction for a longer period (24 h) delivered a lower yield (38%) of monofluoro product **6**, together with some increase in the yield (47%) of difluoro compound **7**.

When a mixture of 4-amino-4′-nitroazofurazan **1d**[18] was heated at 80 °C with the same reagent for 6 h, fluoro compound **8** was the only product isolated (73%) (Scheme 5).

The nucleophilic displacement reactions in 4,4′-dinitroazoxyfurazan **1e**[18] have been recently reported to occur at the carbon bonded with the nitro group proximate to N-oxide of the azoxy group and carbon bonded with N(O) atom of azoxy group.[10,19,20] Indeed, the treatment of compound **1e** with TEAHF in the above manner for 24 h afforded about 30% yield of 4-fluoro-4′-nitroazoxyfurazan **9** and about 30% yield of 3-fluoro-4-nitrofurazan **2**, which resulted from the nucleophilic displacement of the azoxyfurazanyl moiety (Scheme 6). The reaction contained none of the difluoro derivatives such as 4,4′-difluoroazoxyfurazan or 3,4-difluorofurazan **3**.

[†] *General procedure for the preparation of fluorofurazans.* To a mixture of $NEt_3\cdot3HF$ (10–20 mmol) and [bmim][X] (10 ml) corresponding nitrofurazan **1a–e** (10 mmol) was added under an atmosphere of argon and anhydrous conditions. The reaction mixture was then heated at 50 °C with stirring for 4–24 h. The product was separated from the residue by distillation or by sublimation onto a dry ice cooled cold finger when heated to 35–55 °C (0.1 Torr).

[‡] All fluoro compounds gave satisfactory combustion analyses and accurate mass measurements. These structures were also confirmed by IR and NMR spectroscopy.

For **2**: oil; R_f 0.7 (pentane–CH_2Cl_2, 5:2). ^{13}C NMR ($CDCl_3$) δ: 159.0 (d, C-1, $^1J_{CF}$ 291.2 Hz), 150.5 (C-2). ^{14}N NMR ($CDCl_3$) δ: –35.4 (NO_2, $\Delta\nu_{1/2}$ 9 Hz). ^{19}F NMR ($CDCl_3$) δ: –138.1. MS, *m/z*: 133 (M^+), 87 ($M^+ - NO_2$), 57 ($M^+ - NO_2 - NO$).

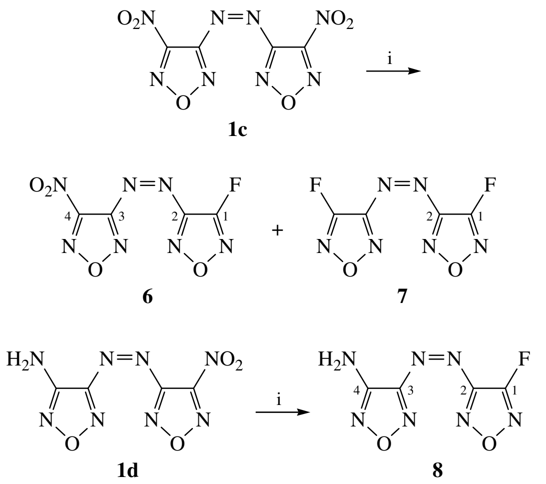
For **4**: oil. ^{13}C NMR ($CDCl_3$) δ: 164.7 (d, C-1, $^1J_{CF}$ 276.1 Hz), 158.4 (C-4), 136.7 (C-3), 132.5 (d, C-2, ^2J 21.6 Hz). ^{14}N NMR ($CDCl_3$) δ: –40.3 (NO_2, $\Delta\nu_{1/2}$ 15 Hz). ^{19}F NMR ($CDCl_3$) δ: –140.0. MS, *m/z*: 201 (M^+), 155 ($M^+ - NO_2$).

For **6**: oil. ^{13}C NMR ($CDCl_3$) δ: 159.1 (d, C-1, $^1J_{CF}$ 280.5 Hz), 153.3 (d, C-2, ^2J 13.8 Hz), 153.0 (C-3), 153.4 (C-4). ^{14}N NMR ($CDCl_3$) δ: –39.7 (NO_2, $\Delta\nu_{1/2}$ 22 Hz). ^{19}F NMR ($CDCl_3$) δ: –141.3. MS, *m/z*: 229 (M^+).

For **7**: mp 72–73 °C. ^{13}C NMR ($CDCl_3$) δ: 159.2 (d, C-1, $^1J_{CF}$ 281.7 Hz), 153.4 (d, C-2, ^2J 14.1 Hz). ^{19}F NMR ($CDCl_3$) δ: –141.6. MS, *m/z*: 202 (M^+). Found (%): C, 23.81; N, 41.57. Calc. for $C_4F_2N_6O_2$ (202.08) (%): C, 23.77; N, 41.59.

For **8**: mp 94–95 °C. ^1H NMR ([$^2H_6$]DMSO) δ: 6.87. ^{13}C NMR ([$^2H_6$]DMSO) δ: 163.0, 157.5 (d, C-1, $^1J_{CF}$ 100 Hz), 154.3, 154.0 (d, C-2, ^2J 10 Hz), 156.1 (C-4), 149.3 (C-3). ^{19}F NMR ([$^2H_6$]DMSO) δ: –142.6 ($\Delta\nu_{1/2}$ 10 Hz). MS, *m/z*: 199 (M^+). Found (%): C, 24.16; H, 0.99; N, 49.21. Calc. for $C_4H_2FN_7O_2$ (199.10) (%): C, 24.12; H, 1.01; N, 49.25.

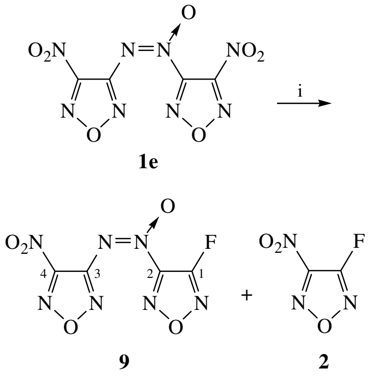
For **9**: mp 49–51 °C. ^{13}C NMR ($CDCl_3$) δ: 159.1 (d, C-1, $^1J_{CF}$ 279.2 Hz), 155.0 (C-4), 148.0 (d, C-2, ^2J 22.1 Hz), 128.3 (C-3). ^{14}N NMR ($CDCl_3$) δ: –38.7 (NO_2, $\Delta\nu_{1/2}$ 13 Hz), –66.1 (N→O, $\Delta\nu_{1/2}$ 62 Hz). ^{19}F NMR ($CDCl_3$) δ: –136.6. IR (ν/cm^{-1}): 1616, 1572, 1516, 1500, 1352, 1220, 1160, 1036, 876, 836. MS, *m/z*: 245 [M^+], 229 [$M^+ - O$], 158 [$O_2NFuN_2O^+$], 153 [$M^+ - O - NO_2 - NO$], 142 [$O_2NFuN_2^+$], 117 [$FFuNO^+$], 115 [$FFuN_2^+$], 96, 95, 70, 69, 68. Found (%): C, 19.55; N, 39.97. Calc. for $C_4FN_7O_5$ (245.09) (%): C, 19.60; N, 40.01.



Scheme 5 *Reagents and conditions*: i, $NEt_3 \cdot 3HF$, [bmim][X], 50 °C.

Attempts to synthesise fluorofurazans from 3-nitro-4-R-furazans bearing electron-donating groups R, such as methyl and amino, were unsuccessful.

The structures of the products were confirmed by ^{13}C, ^{14}N and ^{19}F NMR spectroscopy and by their high resolution mass spectra and/or elemental analyses. A characteristic ^{19}F NMR resonance appeared as a singlet at δ –142 to –137 ppm. Furthermore, in the ^{13}C NMR spectra of fluorofurazans, the resonances attributed to C-1 and C-2 can be assigned at *ca.* 159 and 132–153 ppm, respectively, because of the presence of diagnostic coupling patterns ($^1J_{CF}$ 276–281 Hz and $^2J_{CF}$ 13–20 Hz, respectively).



Scheme 6 *Reagents and conditions*: i, $NEt_3 \cdot 3HF$, [bmim][X], 50 °C.

In conclusion, the first method for fluorofurazan synthesis has been developed. As a result, such interesting key precursors as 3-fluoro-4-nitrofurazan, 4-fluoro-4′-nitrobifurazan and 4,4′-fluoroazofurazans are now readily accessible.

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