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Reactions of 1-alkylsulfanyl- and 1-alkylsulfonyl-2,3,5,6-tetrafluorobenzenes with nitromethane and DBU

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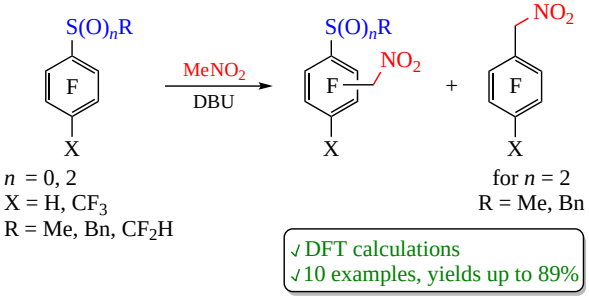
1-Alkylsulfanyl-4-X-2,3,5,6-tetrafluorobenzenes (X = CF_3, H; alkyl = Me, Bn, CHF_2) upon reactions with nitromethane in the presence of DBU undergo replacement of 2 or 3-positioned fluorine atoms by a nitromethyl group to afford the corresponding (nitromethyl)trifluoroarenes. The calculations of the transition states using the DFT method correctly predict the ratios of reaction products. In the cases of relative sulfones, only 2-positioned fluorine atom undergoes substitution; however, the sulfonyl group can also be displaced by a nitromethyl moiety.



Keywords: polyfluoroaromatic compounds, sulfanes, sulfones, nucleophilic substitution, nitromethane, organofluorine compounds.

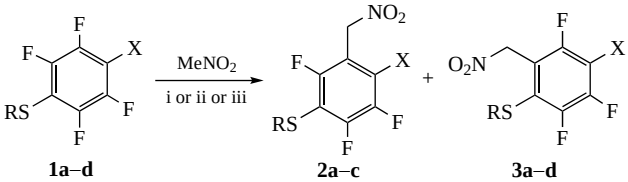
Nowadays organofluorine compounds are used widely in practice.[1–3] Among such compounds, polyfluoroarenes with sulfur-containing functional groups capture special attention.[4–7] In turn, (nitromethyl)arenes attract attention due to their ability for various chemical transformations.[8–11] Nitromethyl-functionalized derivatives can form stable carbanions[12,13] capable of reacting with haloalkanes,[14,15] aldehydes,[16–18] imines[19] as well as Michael acceptors.[20,21] Based on nitromethylfluoroarenes, antibacterial[22,23] and fungicidal[24–26] substances can be accessed.

Among (nitromethyl)fluoroarenes, sulfur-containing derivatives are remarkable due to the wide possibility of modifying the sulfur atom by adding various alkyl groups to it and changing its oxidation state. We recently studied the reaction of sulfanyl-, sulfinyl- and sulfonylpentafluorobenzenes with nitromethane; in all cases, the nucleophilic replacement of the *para*-positioned fluorine atom in relation to the sulfur functional group was observed regardless of the sulfur atom oxidation state.[27]

In this regard, it seems interesting to obtain polyfluoroarenes containing a nitromethyl function in the *ortho*- or *meta*-position relative to the sulfur-containing group. To solve this task, it was necessary to use substrates containing a non-nucleofugic substituent in the *para*-position, for example, a hydrogen atom or a trifluoromethyl group. Among sulfur-containing functions, attention was paid to methyl and difluoromethylsulfanyl groups, simple in structure, as well as their sulfonyl analogues. In addition, polyfluoroarenes containing benzylsulfanyl and benzylsulfonyl groups were of interest, primarily due to the influence of such groups on the direction and rate of some transformations,[28–30] as well as due to the attention to such derivatives in medicine[31–33] and agriculture.[34] Thus, the aim of this work was to study the reactions of 1-alkylsulfanyl- and 1-alkylsulfonyl-4-X-2,3,5,6-tetrafluorobenzenes with nitromethane and DBU to obtain the corresponding nitromethyl derivatives.

In fact, CF_3-containing (alkylsulfanyl)tetrafluorobenzenes **1a**,**b** (alkyl = Me or Bn) reacted with excess nitromethane in the presence of DBU in DMF at 0 °C to afford mainly the products **2a**,**b** of replacement of the *meta*-positioned fluorine atom along with minor quantities of the *ortho*-isomers **3a**,**b** (Scheme 1). At the same time, the transformation of 1-[(difluoromethyl)sulfanyl]-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene **1c** having an electron-withdrawing SCF_2H group (σ_m = 0.33, σ_p = 0.37)[35] in THF at –20 °C gave an essentially equimolar mixture of the corresponding isomers **2c** and **3c** (see Scheme 1). In contrast to trifluoromethyl derivatives **1a**,**b**, 3-methylsulfanyl- and 3-benzylsulfanyl-1,2,4,5-tetrafluorobenzenes did not react with nitromethane and DBU when the process was carried out in DMF, sulfolane and even without a solvent when heated up to 150 °C. However, in the case of more electron-deficient 3-[(difluoromethyl)sulfanyl]-1,2,4,5-tetrafluorobenzene **1d**, exclusively *ortho*-positioned fluorine atom was replaced upon longer processing (27 h at room temperature or 16 h at 30 °C) to produce isomer **3d** (see Scheme 1). Raising the temperature to 50 °C led to tarring of the reaction mass.

The quantum chemical calculations at DFT/B3LYP level in the 6-31G(d) basis, taking into account the DMF solvent,



a R = Me, X = CF_3 (**2a**/**3a** = 93 : 7)
b R = Bn, X = CF_3 (**2b**/**3b** = 93 : 7)
c R = CF_2H, X = CF_3 (**2c**/**3c** = 51 : 49)
d R = CF_2H, X = H (**3d** only)

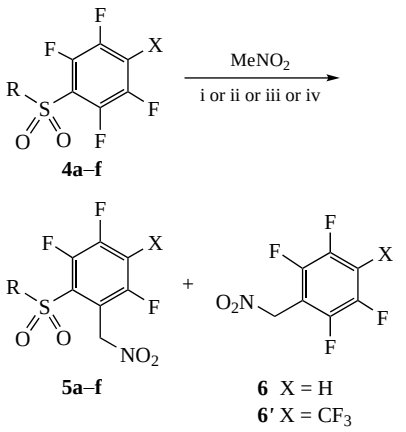
Scheme 1 *Reagents and conditions*: i, DBU, DMF, 0 °C, 6.5–7 h (for **1a**,**b**); ii, DBU, THF, –20 °C, 5 h (for **1c**); iii, DBU, DMF, 30 °C, 16 h (for **1d**). Product ratios were determined from ^{19}F NMR.

Table 1 Calculated [B3LYP/6-31G(d)/PCM-SMD (DMF)] activation barriers E_a for reactions of compounds **1a**,**c**,**d** with nitromethane.

Substrate	Activation energy E_a/kcal mol^{-1}	
	for type **2** TS	for type **3** TS
1a	16.58 (**2aTS**)	17.01 (**3aTS**)
1c	13.97 (**2cTS**)	13.83 (**3cTS**)
1d	19.91 (**2dTS**)	17.0 (**3dTS**)

allowed us to find transition states (TS) for reactions involving substrates **1a**, **1c** and **1d** (Table 1 and Figures S1, S2, S3 of the Online Supplementary Materials). The calculations were carried out with approximations, similar to the reported work.[36] The found transition states are described by the presence of a protonated DBU molecule as a counterion, as well as a distance C(Ar)–C(CH_2NO_2) of about 2 Å. Assuming that the limiting stage of the reaction is the formation of the corresponding transition state (Figure S2), the obtained close corresponding values of activation energies suggest an approximately equal ratio of the products of the nucleophilic substitution of the fluorine atom according to Scheme 1 (products **2** and **3**). In the experiment, this is observed for substrate **1c**. For substrate **1a**, similar activation energies for the transition states **2aTS** and **3aTS** were obtained (see Figure S1), the difference of 0.42 kcal mol^{-1} (see Table 1) favors the reaction pathway to product **2a**. In the experiment, the predominant formation of product **2a** was observed. For the reaction of substrate **1d**, the transition states **2dTS** and **3dTS** were found, when the nucleophile attacked positions 2 and 3, respectively (see Table 1 and Figure S3). In this case, the transition states are also described by the presence of a protonated DBU molecule as a counterion, as well as a C(Ar)–C(CH_2NO_2) bond length of ~2 Å. The difference in the values of activation energies (2.91 kcal mol^{-1}) suggests that the nucleophilic substitution of the fluorine atom should mainly occur along the path with a lower activation energy, with the formation of product **3d** (see Table 1). In the experiment, product **3d** is the only one. It should also be noted that the changes in the calculated activation energies values and the reaction temperatures were also correlated (see Scheme 1).

When an acceptor sulfonyl group was introduced into the aromatic ring of substrate, the enhancement of its reactivity was observed (Scheme 2). When 3-methylsulfonyl-1,2,4,5-tetrafluorobenzene **4a** was reacted with nitromethane in the presence of DBU in THF at room temperature, the fluorine atom was mainly replaced in the *ortho*-position relative to this group giving 3-methylsulfonyl-4-nitromethyl-1,2,5-trifluorobenzene **5a**. 3-Nitromethyl-1,2,4,5-tetrafluorobenzene **6**, a product of substitution of the sulfonyl group, was also found in the reaction mixture in small amounts, the **5a**/**6** ratio having been 91 : 9. Lowering the temperature to 0 °C led to the same result. Replacing the solvent with DMF made it possible to slightly reduce the amount of **6** (the **5a**/**6** ratio became 93 : 7). Close results were obtained for benzyl homologue **4b** (see Scheme 2). In the reaction mass, benzaldehyde was detected (^{1}H NMR and GC-MS data), which was a product of the transformation of benzylsulfinate-anion.[37] When 1,2,4,5-tetrafluoro-3-methylsulfonyl-6-(trifluoromethyl)benzene **4c** was reacted with nitromethane and DBU in DMF at –20 °C, strong tarring was observed and the only product identified was 1,2,4,5-tetrafluoro-3-nitromethyl-6-(trifluoromethyl)benzene **6′**. When DMF was changed for THF, tarring also occurred, however it was possible to obtain the product **5c** of replacement of 2-positioned fluorine atom by a nitromethyl group, the **5c**/**6′** ratio having been 45 : 55. Lowering the temperature to –60 °C made it possible to exclude tarring; the **5c**/**6′** ratio became 65 : 35 (see Scheme 2). Similarly, a **5d** + **6′**



a R = Me, X = H (**5a**/**6** = 93 : 7)
b R = Bn, X = H (**5b**/**6** = 93 : 7)
c R = Me, X = CF_3 (**5c**/**6′** = 65 : 35)
d R = Bn, X = CF_3 (**5d**/**6′** = 34 : 66)
e R = CF_2H, X = H (**5e** only)
f R = CF_2H, X = CF_3 (**5f** only)

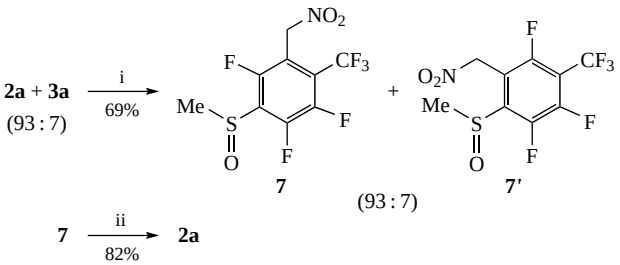
Scheme 2 *Reagents and conditions*: i, DBU, DMF, 0 °C, 3–6.5 h (for **4a**,**b**); ii, DBU, THF, –60 °C, 8.5–12 h (for **4c**,**d**); iii, DBU, THF, –25 °C, 3 h (for **4e**); iv, DBU, THF, –60 °C, 0.5 h (for **4f**). Product ratios were determined from ^{19}F NMR.

(34 : 66) mixture was obtained from 1,2,4,5-tetrafluoro-3-benzylsulfonyl-6-(trifluoromethyl)benzene **4d**, benzaldehyde having been also detected. The formation of compounds **6** and **6′** can probably be explained by the sufficient fugacity of methanesulfinate and phenylmethanesulfinate anions as leaving groups.[37,38]

In the case of difluoromethylsulfonyl-containing tetrafluorobenzenes **4e**,**f**, due to strong acceptor effect of the CHF_2 group (σ_m = 0.75, σ_p = 0.86),[35] the reaction proceeded completely towards the substitution of the fluorine atom giving nitromethyl-containing trifluoroarenes **5e**,**f** as the only products (see Scheme 2).

Compounds **2b**, **5a**–**f** and **3d** were isolated with 80–89% preparative yields. The separation of isomeric pairs **2a**–**3a** and **2c**–**3c** by distillation, sublimation, chromatography or crystallization turned out impossible. To obtain individual compound **2a**, the **2a**–**3a** mixture was oxidized with 100% HNO_3 into a mixture of the corresponding sulfoxides **7** and **7′** (Scheme 3) from which isomer **7** was isolated by crystallization. The further reduction of **7** with AcBr gave pure **2a**. It is of note that during these transformations the nitromethyl group remained intact.

In conclusion, when sulfanyltetrafluorobenzenes reacted with nitromethane and DBU, fluorine atoms in positions 2 or 3 of aromatic ring were replaced. The quantum chemical calculations by the DFT method corresponded to the resulting experimental data. In the case of sulfonyltetrafluorobenzenes, the substitution



Scheme 3 *Reagents and conditions*: i, HNO_3 (100%), room temperature, 0.5 h; ii, MeC(O)Br, PhH, room temperature, 0.5 h.

of fluorine atom proceeded only in the *ortho*-position relative to the sulfur-containing functional group, while in the case of methylsulfonyl- and benzylsulfonyl derivatives the sulfonyl groups are also replaced by nitromethyl moiety.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.021.

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