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Vicarious Nucleophilic Substitutions of Hydrogen in 1,1,1-Trifluoro-*N*-[oxido(phenyl)(trifluoromethyl)-λ⁴-sulfanylidene]methanesulfonamide

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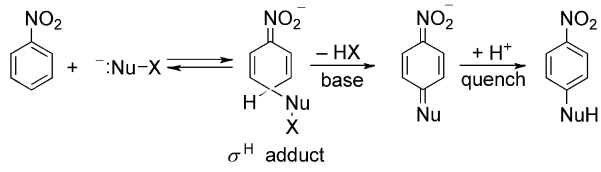
1,1,1-Trifluoro-*N*-[oxido(phenyl)(trifluoromethyl)-λ⁴-sulfanylidene]methanesulfonamide reacts with carbanions bearing a leaving group to give vicarious nucleophilic substitution (VNS) of hydrogen products with moderate yields. This is the first example of the VNS process at a benzene ring activated by an electron-withdrawing group other than a nitro group. The orientation of the substitution is exclusively *para*. Findings open a large possibility for exploration of the scope of the VNS reaction on to compounds activated with sulfur-based electron-withdrawing groups.

Introduction

Vicarious nucleophilic substitution (VNS) was discovered at the end of 1970s and subsequently studied mainly by Mąkosza and coworkers, and it became a powerful synthetic tool in organic synthesis.[1–6] This reaction was primarily designed for arenes activated by a nitro group. Later, the scope was extended to electrophilic heterocyclic compounds as well as electrophilic alkenes.[7,8] Numerous C, N, and O anions were applied as nucleophilic substrates for VNS. The general scheme of the reaction involves nitro-substituted arenes that form σ^H adducts, which then undergo base-promoted 1,2-elimination of HX (Scheme 1). Until the end of the 20th century, it was believed that such σ^H adducts are "short-lived species" and could not be observed.[1] In 2003, Lemek et al.[2] proved by direct spectrophotometric (UV and NMR) observation that σ^H adducts of VNS type are relatively stable compounds. Despite an intensive search for alternative activating groups enabling the VNS reaction, only the nitro group seemed to provide sufficient electron-withdrawing power and charge capacity to stabilize efficiently the intermediate σ^H adducts. Although the trifluoromethylsulfonyl group exhibits even higher electron-withdrawing force than the nitro group[9] and the fact that it was successfully used in S_NAr reactions, attempts of using it for VNS failed.[10] The reason was that the nucleophilic attack of a carbanion took place primarily on the CF_3 group or on the sulfur atom of the trifluoromethylsulfonyl group and not on the aromatic ring. The only successful example of the VNS reaction on a homocyclic aromatic ring activated by a group other than nitro is the reaction of α-chlorosulfone and sulfonamide carbanions with phenyl azoxysulfones described by Goliński.[11] A decade ago, Yagupolskii et al.[12] introduced to organic chemistry a new super-strong electron-withdrawing substituent – the *N*-trifluoromethylsulfonyl-*S*-trifluoromethylsulfoximidyl group [$CF_3S(O)=NSO_2CF_3$]. The comparison of its electron-withdrawing power with the nitro and another groups gives the Hammett constant value for this new group σ_p = 1.4, calculated from ^{19}F NMR spectroscopic data, which reflects the static molecular state. This value is even higher than that obtained for the "super-strong" electron-withdrawing trifluoromethylsulfonyl group.[12] Taking into account this promising information, we synthesized the model compound 1,1,1-trifluoro-*N*-[oxido(phenyl)(trifluoromethyl)-λ⁴-sulfanylidene]methanesulfonamide (**1**) and used it in reactions with a series of classical nucleophiles for VNS. Here we present the preliminary results of our investigations.



Scheme 1. Vicarious nucleophilic substitution of hydrogen.

Results and Discussion

The reaction of **1** with carbanions **2a**–**f** (generated in situ by adding an excess amount of *t*BuOK to CH acids) carried out with an excess amount of the base yielded VNS prod-

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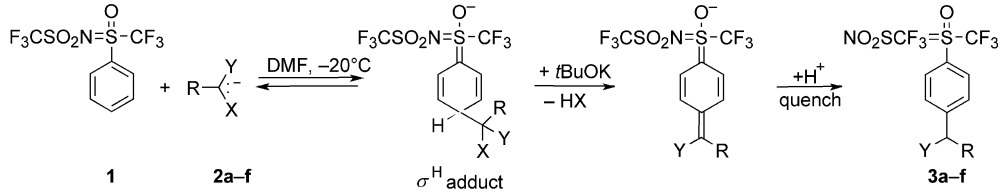


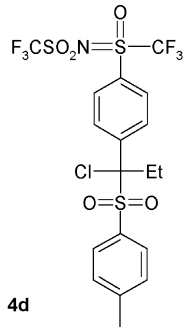
Scheme 2. Vicarious nucleophilic substitution in 1,1,1-trifluoro-*N*-[oxido(phenyl)(trifluoromethyl)-λ⁴-sulfanylidene]methanesulfonamide (**1**).

ucts **3a**–**f** (Scheme 2, Table 1). Contrary to the classical VNS reaction, orientation of this substitution was exclusively *para*. Under preliminary, unoptimized conditions, the yields ware moderate to low. For comparison, the yields of the VNS reaction for nitro-activated compounds range between 60 and 80%.[13] In our experiments, the remaining electrophile as well as the carbanion precursors were not recovered after workup except for **2d**. The formation of foams and emulsions during the workup could indicate that there is competition between the VNS reaction and nucleophilic attack of the carbanion on the *N*-trifluoromethylsulfonyl-*S*-trifluoromethylsulfoximidyl group of the electrophile or that the VNS products undergo decomposition, which leads to unidentifiable products. Isolated product **3a** after dissolving in DMSO partially dissociates (without the presence of a base) with formation of a band at λ_{max} = 418 nm. The addition of *t*BuOK causes total deprotonation of **3a** (log ε = 4.7). The carbanion generated by this way showed limited stability, and the UV absorption disappeared completely after 1 h. In the case of carbanion **2d**, oxidative nucleophilic substitution of hydrogen (ONSH) was observed as a side process (product **4d** was isolated). The reason for the competition between the ONSH and VNS reactions is a result of slow 1,2-elimination of HCl from the σ^H adduct caused by steric hindrance. The reaction of $CHCl_3$ as a carbanion precursor with electrophile **1** yielded only trace amounts of the VNS product. The reaction of (4-chlorophenoxy)acetonitrile with **1** gave exclusively the product of the Thorpe condensation: 3-amino-2,3-bis(4-chlorophenoxy)acrylonitrile.[13]

Table 1. The VNS reaction of electrophile **1** with carbanions **2a**–**g**.

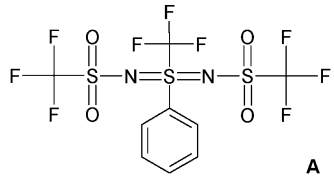
Entry	Carbanion				Product	
	No	X	Y	R	No	Yield [%]
1	**2a**	Cl	4-Ts	H	**3a**	28
2	**2b**	Cl	CO_2Me	Me	**3b**	22
3	**2c**	Br	CN	Me	**3c**	38
4[a]	**2d**	Cl	4-Ts	Et	**3d**	9
5	**2e**	Cl	COO*t*Bu	H	**3e**	31
6	**2f**	Br	SO_2Ph	H	**3f**	5
7	**2g**	Cl	SO_2Ph	Cl	**3g**	very low

[a] ONSH product **4d** was isolated (9%), and carbanion precursor **2d** was recovered (20%).



Conclusions

The results show that the *N*-trifluoromethylsulfonyl-*S*-trifluoromethylsulfoximidyl group activates efficiently the benzene ring towards nucleophilic attack of carbanions. This is the first example of the VNS reaction in a homocyclic aromatic ring activated by a group other than a nitro group. The orientation of the substitution is *para*. Presumably, this is because of the steric effect caused by the bulky *N*-trifluoromethylsulfonyl-*S*-trifluoromethylsulfoximidyl group and because of competitive nucleophilic attack at this electron-withdrawing group. The yields under the chosen reaction conditions are moderate to low. One can expect that compounds similar to **1**, for example, trifluoro-*N*-[phenyl(trifluoromethyl){[(trifluoromethyl)sulfonyl]imino}-λ⁶-sulfanylidene]methanesulfonamide (**A**), would also enter the VNS process.



Experimental Section

Instruments and Materials: Chemical shifts in the ^1H and ^{13}C NMR spectra are expressed in ppm and are reported relative to Me_4Si (δ_H = 0.00 ppm, δ_C = 0.00 ppm). Chemical shifts in the ^{19}F NMR spectra are expressed in ppm and are reported relative to $CFCl_3$ (δ_F = 0.00 ppm). Coupling constants are in Hz. Melting points are uncorrected. The yields refer to isolated products without optimization of the procedures. DMF was dried with CaH_2 and distilled under reduced pressure. Compound **1** and carbanion precursors

2a–**g** were prepared according to literature procedures or were commercially available. Substrates were commercially available. Silica gel (230–400 mesh) was used for column chromatography.

1,1,1-Trifluoro-*N*-[oxido(phenyl)(trifluoromethyl)-λ⁴-sulfanylidene]-methanesulfonamide (1): Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79–7.82 (m, 2 H, CH-*meta*), 7.97–8.00 (m, 1 H, CH-*para*), 8.15 (d, J = 7.9 Hz, 2 H9, CH-*ortho*) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 118.9 (q, J = 320.6 Hz), 119.9 (q, J = 328.4 Hz), 128.8, 130.5, 130.7, 138.1 ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –79.2, –75.9 ppm. Compound **1** was obtained from [*S*-(trifluoromethyl)-sulfonimidoyl]benzene in 45% yield by using procedure described for substituted [*S*-(trifluoromethyl)sulfonimidoyl]benzenes.[14] [*S*-(Trifluoromethyl)sulfonimidoyl]benzene [^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.6 (s, 1 H, NH, flat), 7.57–7.67 (m, 2 H, CH-*meta*), 7.73–7.81 (m, 1 H, CH-*para*), 8.11–8.16 (m, 2 H, CH-*ortho*) ppm] was prepared from phenyl trifluoromethyl sulfoxide by the reaction with NaN_3 in oleum.[15]

Reactions of 1 and 2a–f: To a stirred solution of *t*BuOK (337 mg, 3 mmol) in DMF (2 mL) at –30 °C and under an argon atmosphere was added, by cannula, a solution of CH acid **2a**–**g** (1 mmol) in DMF (2 mL) and a solution of electrophile **1** (341 mg, 1 mmol) in DMF (1 mL). After 10 min stirring, the mixture was poured into cooled 3% aqueous HCl (100 mL). The precipitate was filtered off, washed with water, and dried in the air, or in case of oil was extracted with AcOEt, washed with brine, and dried with Na_2SO_4. Crude products **3a**–**g** were isolated as oils, or as powders, and purified by column chromatography (hexane/ethyl acetate) and recrystallized.

1,1,1-Trifluoro-*N*-[(4-{[(4-methylphenyl)sulfonyl]methyl}phenyl)-(oxido)(trifluoromethyl)-λ⁶-sulfanylidene]methanesulfonamide (3a): M.p. 127–128 °C (143 mg, 28%, acetonitrile/petroleum ether). IR (KBr): $\tilde{\nu}$ = 3098, 2997, 2929, 1595, 1378, 1297, 1223, 1207, 1133, 1095, 1052, 602 cm^{-1}. ^{1}H NMR (300.1 MHz, [D$_6$]acetone): δ = 2.42 (s, 3 H, CH_3), 4.85 (s, 2 H, CH_2), 7.38 (d, J = 8.0 Hz, 2 H7), 7.59 (d, J = 8.2 Hz, 2 H8), 7.82 (d, J = 8.6 Hz, 2 H4), 8.25 (d, J = 8.5 Hz, 2 H2) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]acetone): δ = 21.0, 61.6, 119.9 (q, J = 319.9 Hz), 120.8 (q, J = 327.7 Hz), 128.0, 128.8, 130.1, 131.0, 134.1, 135.9, 141.8, 145.6 ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –78.8, –75.4 ppm. MS (EI, 70 eV): *m*/*z* (%) = 509 (10) [M]$^+$, 440 (5.3), 293 (7.5), 191 (11), 155 (90), 138 (49), 91 (100). HRMS (EI, 70 eV): calcd. for $C_{16}H_{13}F_6NO_5S_3$ [M]$^+$ 508.9860; found 508.9859. $C_{16}H_{13}F_6NO_5S_3$ (509.45): calcd. C 37.72, H 2.57,N 2.75; found C 37.72, H 2.25, N 2.72.

Methyl 2-(4-{*S*-(Trifluoromethyl)-*N*-[(trifluoromethyl)sulfonyl]-sulfonimidoyl}phenyl)propanoate (3b): Oil (94 mg, 22%). IR (film): $\tilde{\nu}$ = 3096, 1738, 1591, 1376, 1293, 1199, 1047 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.59 (d, J = 7.2 Hz, 3 H, CH_3-CH), 3.72 (s, 3 H, CH_3O), 3.91 (q, J = 7.2 Hz, 1 H, CH_3-C*H*), 7.72 (d, J = 8.4 Hz, 2 H), 8.09 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 18.4, 45.6, 52.6, 118.9 (q, J = 320.6 Hz), 119.9 (q, J = 328.5 Hz), 127.4, 130.1, 131.0, 151.7, 172.9 ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –79.0, –75.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 427 (10) [M]$^+$, 382 (25), 358 (100), 266 (18), 211 (10), 166 (56). HRMS (EI, 70 eV): calcd. for $C_{12}H_{11}F_6NO_5S_2$ [M]$^+$ 426.9983; found 426.9965.

***N*-{[4-(1-Cyanoethyl)phenyl](oxido)(trifluoromethyl)-λ⁶-sulfanylidene}-1,1,1-trifluoromethanesulfonamide (3c):** Oil (150 mg, 38%). IR (film): $\tilde{\nu}$ = 3096, 1594, 1375, 1295, 1199, 1045 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.75 (d, J = 7.3 Hz, 3 H, CH_3), 4.11 (q, J = 7.3 Hz, 1 H, CH), 7.81 (d, J = 8.5 Hz, 2 H), 8.19 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.0, 31.5, 118.8 (q, J = 320.5 Hz), 119.4, 119.9 (q, J = 328.5 Hz), 128.9, 129.3, 131.6, 148.0 ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –78.9, –75.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 395 (1) [M]$^+$, 325 (100), 378 (12), 146 (10), 130 (16), 103 (12).

1,1,1-Trifluoro-*N*-[(4-{1-[(4-methylphenyl)sulfonyl]propyl}phenyl)-(oxido)(trifluoromethyl)-λ⁶-sulfanylidene]methanesulfonamide (3d): Oil (59 mg, 11%). IR (film): $\tilde{\nu}$ = 2930, 1592, 1376, 1288, 1201, 1046 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.88–0.93 (m, 3 H, CH_3), 2.20–2.26 (m, 1 H, CH_2), 2.399 and 2.404 (2 × s, 3 H, CH3), 2.46–2.57 (m, 1 H, CH_2), 4.09–4.14 (2 × dd, 1 H, CH), 7.21 (d, J = 8.1 Hz, 2 H), 7.37–7.41 (m, 2 H), 7.52–7.54 (m, 2 H), 8.00–8.02 (m, 2 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 11.47 and 11.50 (*C*H_3CH$_2$), 21.22 and 21.38 (CH$_3$*C*H$_2$), 21.55 and 21.59 (*C*H$_3$C), 72.83 and 72.87 (*C*H), 118.9 (q, J = 320.3 Hz), 119.8 (q, J = 328.7 Hz), 128.83 and 128.93 (CH arom.), 129.02 and 129.08 (C arom.), 129.70 and 129.75 (CH arom.), 130.47 (CH arom.), 132.02 and 132.03 (CH arom.), 133.63 and 133.67 (C arom.), 144.27 and 144.34 (C arom.), 145.54 and 145.59 (C arom.) ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –79.0, –78.9, –75.7, –75.6 ppm. MS (EI, 70 eV): *m*/*z* (%) = 468 (2), 382 (100), 305 (35), 160 (60), 115 (30).

***N*-[(4-{1-Chloro-1-[(4-methylphenyl)sulfonyl]propyl}phenyl)oxido-(trifluoromethyl)-λ⁴-sulfanylidene]trifluoromethanesulfonamide (4d):** Oil (50 mg, 9%). IR (film): $\tilde{\nu}$ = 2980, 1595, 1318, 1146, 1070 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.97 (2 × d, J = 7.25, 7.25 Hz, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 2.53 (dq, J = 14.6, 7.3 Hz, 1 H, CH_2), 2.98 (dq, J = 14.4, 7.2 Hz, 1 H, CH_2), 7.14 (d, J = 8.2 Hz, 2 H), 7.28–7.31 (m, 2 H), 7.35–7.37 (m, 2 H), 7.46–7.47 (m, 2 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 8.2 (*C*H_3CH$_2$), 21.6 (*C*H$_3$C), 28.4 (CH$_3$*C*H$_2$), 118.9 (q, J = 320.5 Hz), 119.9 (q, J = 331.9 Hz), 92.6 (CCl), 127.9 (CH arom.), 128.8 (CH arom.), 129. 5 (CH arom.), 131.3 (CH arom.), 130.0 (C arom.), 130.6 (C arom.), 132.0 (C arom.), 145.2 (C arom.) ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –78.9, –75.6 ppm. MS (EI, 70 eV): *m*/*z* (%) = 382 (1), 348 (4), 153 (100), 117 (56), 91 (50).

***tert*-Butyl (4-{*S*-(Trifluoromethyl)-*N*-[(trifluoromethyl)sulfonyl]-sulfonimidoyl}phenyl)acetate (3e):** Oil (141 mg, 31%). IR (film): $\tilde{\nu}$ = 2981, 1729, 1593, 1371, 1200, 1090, 1047 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, C(CH$_3$)$_3$], 3.73 (s, 2 H, CH_2), 7.70 (d, J = 8.6 Hz, 2 H, CH-arom.), 8.09 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 27.9 [C(*C*H$_3$)$_3$], 42.4 [*C*(CH$_3$)$_3$], 82.4 (CH$_2$), 118.9 (q, J = 321 Hz, CF_3), 119.9 (q, J = 328 Hz, CF_3), 127.1 (C arom.), 130.7 (CH arom.), 131.7 (CH arom.), 146. 3 (C arom.), 168.6 (CO) ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –79.1, –75.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 440 (12) [M – CH_3]$^+$, 386 (32), 382 (60), 355 (72), 330 (100), 152 (32).

1,1,1-Trifluoro-*N*-[oxido{4-{(phenylsulfonyl)methyl}phenyl}(trifluoromethyl)-λ⁶-sulfanylidene]methanesulfonamide (3f): M.p. 118–121 °C (25 mg, 5%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 4.48 (s, 2 H, CH_2), 7.52–7.58 (m, 4 H), 7.68–7.72 (m, 3 H), 8.08 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]acetone): δ = 62.4, 118.8 (q, J = 322.0 Hz), 119.8 (q, J = 327.0 Hz), 128.5, 129.4, 130.7, 133.0, 134.6, 137.3, 139.4, 146.1 ppm. ^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –78.92, –75.51 ppm. MS (EI, 70 eV): *m*/*z* (%) = 495 (40) [M]$^+$, 426 (20), 410 (6), 354 (7), 175 (19), 152 (30), 141 (100), 90 (18), 77 (42). HRMS (EI, 70 eV): calcd. for $C_{15}H_{11}F_6NO_5S_3$ [M]$^+$ 494.9704; found 494.9673.

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