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Synthesis of CF_3-Substituted Sulfoximines from Sulfonimidoyl Fluorides

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ABSTRACT

N-Protected trifluoromethyl-substituted sulfoximines have been prepared by treatment of sulfonimidoyl fluorides with a combination of the Ruppert–Prakash reagent ($TMSCF_3$) and tetrabutyl ammonium fluoride (TBAF). The starting materials were accessed following two synthetic routes, and for each reaction sequence the substrate scope was evaluated. Accordingly, a wide variety of aryl-substituted products were obtained in moderate to good yield.

The introduction of fluorine can substantially change the chemical and physical properties of an organic compound.[1] For example, fluorinated molecules show improved stability toward oxidation, increased solubility in lipid membranes without loss of polarity, and enhanced organization in enzyme receptor sites by interactions of C–F bonds with NH–, CH–, and CO– moieties. As a consequence, organic fluorine compounds have attracted a great deal of attention in the fields of medicinal and crop protection chemistry.[2] For synthetic chemistry, the directed introduction of fluorine atoms and fluoroalkyl groups has emerged as an interesting challenge.[3,4]

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(1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem Soc. Rev.* **2008**, *37*, 320. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (e) O'Hagan, H; Rzepa, H. S. *Chem. Commun.* **1997**, 645. (f) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (g) Kirsch, P. *Modern Fluororganic Chemistry*; Wiley-VCH: Weinheim, 2004.

(2) (a) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071. (b) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15. (c) Shofield, H. *J. Fluorine Chem.* **1999**, *100*, 7. (d) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Blackwell: Oxford, 2009. (e) Béguè, J. P.; Bonnet-Delpont, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons: Hoboken, NJ, USA, 2008. (f) Maienfisch, P.; Hall, R. G. *Chimia* **2004**, *58*, 93.

(3) For some reviews concerning introduction of fluorine or fluoroalkyl groups, see: (a) Harschneck, T.; Kirsch, S. F. *Nachr. Chem.* **2010**, *58*, 892. (b) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (c) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 1. (d) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (e) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. (f) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (g) Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185. (h) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431. (i) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (j) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (k) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189. For reviews concerning stereoselective fluorinations or trifluoromethylations, see:(l) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (m) Iseki, K. *Tetrahedron* **1998**, *54*, 13887.

(4) For a recent topical issue on organofluorine chemistry, see: Togni, A. *Adv. Synth. Catal.* **2010**, *352*, 2689 and articles referred to therein. (b) For a recent themed series in organo-fluorine chemistry, see: O'Hagan, D. *Beilstein J. Org. Chem.* **2010**, *6*, 36.

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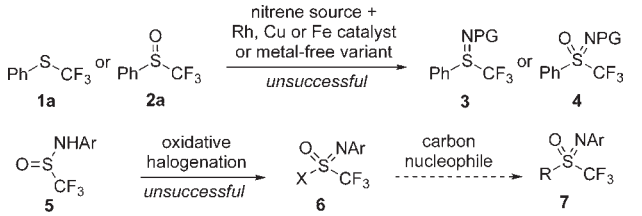
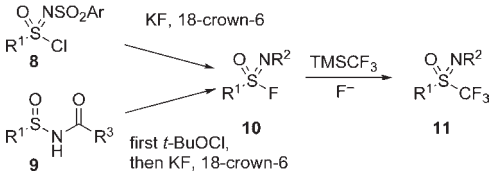
Sulfoximines have found applications as auxiliaries in asymmetric synthesis, chiral ligands in enantioselective metal catalysis, and structural units in pseudopeptides.[5] Their recent wide emergence in the patent literature is remarkable.[6] Derivatives with perfluoroalkyl substituents at sulfur have been used as neutral or electrophilic CF_3 transfer agents by Hu and Shibata, respectively.[3c,7] Furthermore, they were recognized as attractive compounds in material science.[8] However, perfluoroalkyl sulfoximine derivatives remain relatively rare: early syntheses involved iminations of the corresponding sulfoxides with NaN_3 and H_2SO_4 or oleum. These protocols proved difficult due to low-yielding sulfide oxidations to afford the required sulfoxides and the need of a significant fine-tuning of the nitrogen transfer step.[8,9] Recently, Magnier reported an alternative approach based on a Ritter-type sulfoxide-to-sulfilimine conversion as the key step.[10] Subsequent selective oxidation of the intermediately formed *N*-acylsulfilimines afforded trifluoromethyl- and nonafluorobutyl-substituted aryl sulfoximines in moderate to good yields.[11] Based on our expertise in catalyzed sulfur iminations,[12] we wondered if our previously developed protocols were also applicable in the preparation of perfluoroalkyl sulfilimines and sulfoximines. Unfortunately, the use of rhodium, copper, or iron catalysts or the recently introduced metal-free variant[13] did not lead to success in attempted iminations of both phenyl trifluoromethyl sulfide (**1a**) and the corresponding sulfoxide **2a** (Scheme 1, top), and the desired products **3** and **4**, respectively, remained inaccessible. Alternatively, oxidative halogenation of N-arylated trifluoromethyl sulfinamide **5** was attempted analogous to the work of Yagupolskii,[14] with the goal to apply carbon

Scheme 1. Attempted Preparations of Trifluoromethyl Phenyl Sulfilimine **3** and Sulfoximines **4** and **7**



Scheme 2. Synthesis of Trifluoromethyl Sulfoximines **11** via Sulfonimidoyl Fluorides **10** Starting from Sulfonimidoyl Chlorides **8** or Sulfinamides **9**



nucleophiles subsequently in substitution reactions on **6** to provide **7** (Scheme 1, bottom). Oxidants NCS, NBS, chloramine T, trichloroisocyanuric acid, and 1,3-dichloro-5,5-dimethyl hydantoin were used, but none of them proved applicable for the synthesis of target structures **6**. Treatment of **5** with the stronger oxidant chlorine led to decomposition of the starting material.

Hypothesizing that the sulfur iminations of **1a** and **2a** and the oxidative halogenations of **5** were hampered by the low nucleophilicity of the sulfur reagents induced by the fluoro substituents, we pursued an alternative strategy. Accordingly, sulfonimidoyl halides became key targets with the vision to convert those into trifluoromethyl sulfoximines **11** by nucleophilic substitution with a formal CF_3^- reagent. For the latter transformation, the Ruppert–Prakash reagent ($TMSCF_3$)[3e,f] appeared suitable (Scheme 2) as suggested by a single example described by Yagupolskii, who had described the reaction between $TMSCF_3$ and a highly activated N-Tf sulfonyl fluoride with tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) as a catalyst.[15]

Two routes were followed for the synthesis of sulfonimidoyl fluorides **10**. The first involved the corresponding sulfonimidoyl chlorides **8**, which were available by a known protocol via sulfinic chlorides **12** starting from thiols,[16] disulfides,[17] and sulfinic acids.[18] The conversions of **12a–e** into **8a–g** are summarized in Table 1.

The second route made use of *N*-benzoyl and *N*-Boc sulfinamides **9** (R^3 = Ph or O*t*-Bu),[19] which were first oxidized with *t*-BuOCl to provide the corresponding

(5) Reviews: (a) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (b) Harmata, M. *Chemtracts* **2003**, *16*, 660. (c) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (d) Bolm, C. In *Asymmetric Synthesis with Chemical and Biological Methods*; Enders, D., Jaeger, K.-E., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 149. (e) Worch, C.; Mayer, A. C.; Bolm, C. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008; p 209.

(6) See refs 3 and 4 in: Garcia Mancheño, O.; Dallimore, J.; Plant, A.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 309.

(7) (a) Zhang, W.; Wang, F.; Hu, J. *Org. Lett.* **2009**, *11*, 2109. (b) Zhang, W.; Huang, W.; Hu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9858. (c) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465.

(8) (a) Kirsch, P.; Lenges, M.; Kühne, D.; Wanczek, K.-P. *Eur. J. Org. Chem.* **2005**, 797. (b) For use as superacidifiers, see: Terrier, F.; Magnier, E.; Kizilian, E.; Wakselman, C.; Buncel, E. *J. Am. Chem. Soc.* **2005**, *127*, 5563.

(9) (a) Kondratenko, N. V.; Radchenko, O. A.; Yagupolskii, L. M. *Zh. Org. Khim.* **1984**, *20*, 2250. (b) Magnier, E.; Wakselman, C. *Synthesis* **2003**, 565.

(10) Macé, Y.; Urban, C.; Pradet, C.; Marrot, J.; Blazejewski, J.-C.; Magnier, E. *Eur. J. Org. Chem.* **2009**, 3150.

(11) For a recent extension of this work, see: Urban, C.; Macé, Y.; Cadoret, F.; Blazejewski, J.-C.; Magnier, E. *Adv. Synth. Catal.* **2010**, *352*, 2805.

(12) Rh: (a) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305. Ag:(b) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983. Fe:(c) García Mancheño, O.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349. (d) García Mancheño, O.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 6674. (e) García Mancheño, O.; Dallimore, J.; Plant, A.; Bolm, C. *Org. Lett.* **2009**, *11*, 2429.

(13) (a) García Mancheño, O.; Bolm, C. *Org. Lett.* **2007**, *9*, 2951. (b) García Mancheño, O.; Bistri, O.; Bolm, C. *Org. Lett.* **2007**, *9*, 3809. (c) Pandey, A.; Bolm, C. *Synthesis* **2010**, 2292.

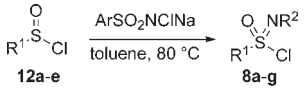
(14) Garlyauskayte, R. Y.; Bezdudny, A. V.; Michot, C.; Armand, M.; Yagupolskii, Y. L.; Yagupolskii, L. M. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1887.

(15) Garlyauskajte, R. Y.; Sereda, S. V.; Yagupolskii, L. M. *Tetrahedron* **1994**, *50*, 6891.

(16) Youn, J.-H.; Herrmann, R. *Synthesis* **1987**, 72.

(17) Youn, J.-H.; Herrmann, R. *Tetrahedron Lett.* **1986**, *27*, 1493.

Table 1. Preparation of Sulfonimidoyl Chlorides **8** from Sulfinic Chlorides **12**[a]



entry	R^1 (starting material)	R^2	product	yield (%)[b]
1	4-MeC_6H_4 (**12a**)	Ts	**8a**	80
2	4-MeC_6H_4 (**12a**)	Ns	**8b**	64
3	C_6H_5 (**12b**)	Ts	**8c**	81
4	C_6H_5 (**12b**)	Ns	**8d**	56
5	4-*t*-BuC_6H_4 (**12c**)	Ts	**8e**	65
6	Me (**12d**)	Ts	**8f**	63
7	Bu (**12e**)	Ts	**8g**	80

[a] Reaction conditions: sulfinyl chloride (1 equiv), chloramine (1 equiv), toluene, 80 °C, 1−2 h under Ar. [b] After filtration through a pad of silica gel.

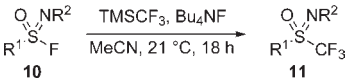
Table 2. Preparation of Sulfonimidoyl Fluorides **10** According to Scheme *2* (**9a**−**g**: R^3 = Ph, **9h**: R^3 = O*t*-Bu)[a]

entry	starting material	R^1	R^2	product	yield (%)[b]
1	**8a**	4-MeC_6H_4	Ts	**10a**	81
2	**8b**	4-MeC_6H_4	Ns	**10b**	87
3	**8c**	C_6H_5	Ts	**10c**	76
4	**8d**	C_6H_5	Ns	**10d**	72
5	**8e**	4-*t*-BuC_6H_4	Ts	**10e**	79
6	**8f**	Me	Ts	**10f**	35
7[c]	**8f**	Me	Ts	**10f**	74
8[c]	**8g**	Bu	Ts	**10g**	67
9	**9a**	4-MeC_6H_4	Bz	**10h**	89
10	**9b**	2-MeC_6H_4	Bz	**10i**	71
11	**9c**	C_6H_5	Bz	**10j**	75
12	**9d**	4-ClC_6H_4	Bz	**10k**	86
13	**9e**	2-ClC_6H_4	Bz	**10l**	78
14	**9f**	4-FC_6H_4	Bz	**10m**	78
15	**9g**	4-*t*-BuC_6H_4	Bz	**10n**	81
16	**9h**	4-MeC_6H_4	Boc	**10o**	79

[a] Reaction conditions: sulfonimidoyl chloride (1 equiv), KF (2 equiv), 18-crown-6 (cat.), MeCN, 21 °C, 16 h. [b] After column chromatography. [c] Use of AgF (1.05 equiv) instead of KF.

sulfonimidoyl chlorides in situ.[20] Sulfonimidoyl fluorides **10** were then obtained from **8** or **9** (after *t*-BuOCl oxidation) by treatment with a combination of potassium fluoride and catalytic amounts of 18-crown-6 (Scheme 2).[21] In reactions with alkyl-substituted sulfonimidoyl fluorides **8f** and **8g** use of AgF instead of KF proved beneficial. Table 2 summarizes the results of this study.

Table 3. Preparation of Trifluoromethyl Sulfoximines **11** Using Sulfonimidoyl Fluorides **10** and $TMSCF_3$ (Ruppert−Prakash Reagent) in Combination with TBAF[a]



entry	starting material	R^1	R^2	product	yield (%)[b]
1	**10a**	4-MeC_6H_4	Ts	**11a**	70
2[c]	**10a**	4-MeC_6H_4	Ts	**11a**	53
3	**10b**	4-MeC_6H_4	Ns	**11b**	55
4	**10c**	C_6H_5	Ts	**11c**	72
5	**10d**	C_6H_5	Ns	**11d**	52
6	**10e**	4-*t*-BuC_6H_4	Ts	**11e**	67
7	**10f**	Me	Ts	**11f**	--
8	**10h**	4-MeC_6H_4	Bz	**11h**	76
9	**10i**	2-MeC_6H_4	Bz	**11i**	69
10	**10j**	C_6H_5	Bz	**11j**	79
11	**10k**	4-ClC_6H_4	Bz	**11k**	74
12	**10l**	2-ClC_6H_4	Bz	**11l**	59
13	**10m**	4-FC_6H_4	Bz	**11m**	54
14	**10n**	4-*t*-BuC_6H_4	Bz	**11n**	51
16	**10o**	4-MeC_6H_4	Boc	**11o**	75

[a] Reaction conditions: slow addition of a TBAF solution in THF (1 M, 0.5 equiv) to a mixture of sulfonimidoyl fluoride (1 equiv) and $TMSCF_3$ (2 equiv as THF solution) at 0 °C for 30 min, then stirring at 21 °C for 18 h. [b] After column chromatography. [c] Use of only 0.2 equiv of TBAF.

Attempts to use sulfonimidoyl chlorides **8** in reactions with $TMSCF_3$ remained unsuccessful under a variety of conditions. To our delight, however, most reactions between sulfonimidoyl fluorides **10** and the $TMSCF_3$ proceeded well, affording the corresponding trifluoromethyl sulfoximines **11** in moderate to good yields (Table 3). In contrast to the system studied by Yagupolskii, simple tetrabutylammonium fluoride (TBAF) was applicable for the activation of the CF_3-transfer agent, thereby avoiding the use of the expensive and water-sensitive TASF.[22] No additional solvent was required when commercially available THF solutions of $TMSCF_3$ and TBAF were used. Commonly, 0.5 equiv of TBAF was sufficient for the activation. Smaller quantities of this reagent led to reduced yields (Table 3, entries 1 and 2).

Various substituents on the aryl groups and the imino nitrogens of the sulfonimidoyl fluorides were tolerated. Electronic effects induced by electron-withdrawing or -donating groups on the arene appeared to have a minor impact. Even substrates **10i** and **10l** with sterically demanding methyl or chloro groups, respectively, in the ortho position (Table 3, entries 9 and 12) reacted well, albeit the yields were slightly lower than those observed in transformations of comparable substrates with para substituents (Table 3, entries 8 and 11).

(18) Krasnova, L. B.; Yudin, A. K. *J. Org. Chem.* **2004**, *69*, 2584.

(19) Their syntheses protocols are outlined in: (a) Brownbridge, P.; Jowett, I. C. *Synthesis* **1988**, 252. (b) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403. (c) Backes, B. J.; Dragoli, D. R.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 5472. (d) Worch, C.; Atodiresei, I.; Raabe, G.; Bolm, C. *Chem.—Eur. J.* **2009**, *16*, 677.

(20) Johnson, C. R.; Wambsgans, A. *J. Org. Chem.* **1979**, *44*, 2278.

(21) For such a conversion, see also: Johnson, C. R.; Bis, K. G.; Cantillo, J. H.; Meanwell, N. A.; Reinhard, M. F. D.; Zeller, J. R.; Vonk, G. P. *J. Org. Chem.* **1983**, *48*, 1.

(22) Attempts to use CsF, KO*t*Bu, or trimethylamine *N*-oxide for the activation failed.

(23) Johnson, C. R.; Jonsson, E. U.; Bacon, C. C. *J. Org. Chem.* **1979**, *44*, 2055.

Attempts to convert alkyl-substituted sulfonimidoyl fluoride **10f** failed (Table 3, entry 7). Presumably, the methyl hydrogens were too acidic, and the fluoride ions acted as a base, resulting in deprotonation followed by unselective decomposition as observed by Johnson in analogous reactions of sulfonimidoyl chlorides.[23]

In summary, we have developed a flexible synthetic approach toward aryl trifluoromethyl sulfoximines using readily available commercial reagents. As a wide variety of useful intermediates are accessible starting from various precursors,[24] the introduced reaction sequences appear attractive for library syntheses. Related studies are currently ongoing in our laboratories.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet http://pubs.acs.org.

(24) For examples for synthetic approaches toward sulfonimidoyl chlorides or sulfinamides with various *N*-protecting groups, see: (a) Toth, J. E.; Grindey, G. B.; Ehlhardt, W. J.; Ray, J. E.; Boder, G. B.; Bewley, J. R.; Klingerman, K. K.; Gates, S. B.; Rinzel, S. M.; Schultz, R. M.; Weir, L. C.; Worzalla, J. F. *J. Med. Chem.* **1997**, *40*, 1018. (b) Kluge, R.; Hocke, H.; Schulz, M.; Schilke, F. *Phosphorus, Sulfur and Silicon* **1999**, *149*, 179. (c) Savile, C. K.; Maglorie, V. P.; Kazlauskas, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 2104.