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Aromatic and Benzylic C–H Bond Functionalization Upon Reaction between Nitriles and Perfluoroalkyl Sulfoxides

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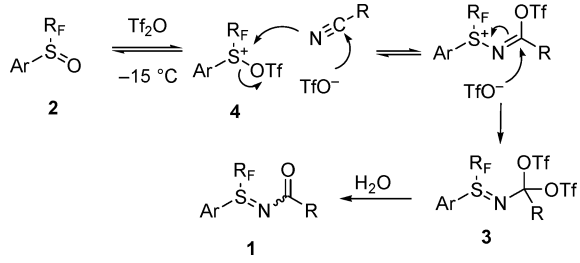
We studied the thermal behavior of some intermediates formed by reaction of nitriles with perfluoroalkyl sulfoxides upon trifluoromethanesulfonic anhydride activation. Bistriflate ketal **3**, precursor of sulfilimine **1**, may undergo a rearrangement to sulfanyl nitrile **5** after triflic acid elimination under thermal conditions. With *p*-tolyl trifluoromethyl sulfoxide, remote triflic acid elimination from intermediate **4** leads to benzamide **8** formation. These reactions involve, respectively, selective functionalization of the aromatic *ortho* C–H bond or the benzylic C–H bond *para* to the sulfoxide group. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

Introduction

The incorporation of perfluoroalkyl groups into molecular structures is an intensive area of chemistry research owing to the unusual properties these groups may confer.[1] Among new reagents, perfluoroalkyl sulfoxides are employed as synthons,[2] fluorous tags, and scavengers.[3] They are also used as precursors of reagents, or reagents themselves able to transfer perfluoroalkyl groups to various substrates either by nucleophilic[4] or electrophilic[5] pathways.

In this context, we recently described easy and flexible access to perfluoroalkylated acylsulfilimines **1** and derived sulfoximines involving a Ritter-like reaction of perfluoroalkylated sulfoxides **2** with nitriles promoted by trifluoromethanesulfonic anhydride (Scheme 1).[6] This reaction was shown to proceed via bistrifluoromethanesulfonic ketal intermediate **3**, which, after hydrolysis, afforded acylsulfilimines **1**, indicating the very high reactivity of activated species **4**.[7]

We thought that besides the hydrolytic pathway, ketal intermediate **3**, which is also a triflate derivative, should be amenable to further functionalization. In particular, alkyl triflates are known to undergo easy thermal triflic acid elimination when there is such a possibility (e.g., when R = CH_2R' in Scheme 1).[8] In our previous study all reactions (and subsequent quenching with water) were performed at –15 °C, leading effectively to the sole isolation, in good yields, of the expected acetyl sulfilimines **1**, thanks to the stability of **3** under these conditions.



Scheme 1. Sulfilimine formation.

In this paper we investigated the behavior of intermediate **3** when the same reaction was performed at higher temperature (between 0 and 50 °C) with substrates possessing hydrogen atoms either at the α position or in a more remote place susceptible to favor thermal triflic acid elimination.[8,9]

Results and Discussion

We first studied the reaction of trifluoromethylated sulfoxides with acetonitrile by mixing the reactants at room temperature followed by heating at 50 °C for 5 h (Table 1, Entries 1 and 4). Under these new conditions, instead of the expected products resulting from a simple elimination of triflic acid, we isolated, along with acylsulfilimines **1**, rearranged (perfluoroalkylsulfanyl)phenyl acetonitrile derivatives **5** in fair to good yields, depending on the substrate.[10] This reaction proved to be applicable to other fluorinated sulfoxides. Higher perfluoroalkyl groups were quite well tolerated (Table 1, Entries 3 and 5).

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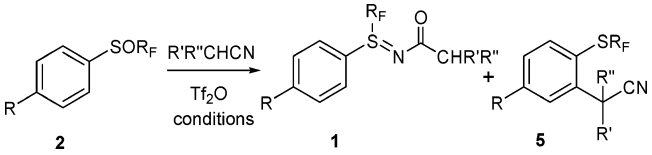
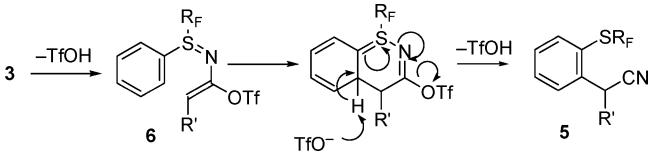
Table 1. Temperature effect on the reaction between nitriles and sulfoxides.[a,b]



Entry	R	R_F	R′	R″	**1**, Yield [%][c]	**5**, Yield [%] [c]
1	H	CF_3	H	H	**1a**, 32	**5a**, 68 (51)
2[d]	H	CF_3	H	H	**1a**, 11	**5a**, 64 (56)
3	H	C_4F_9	H	H	**1b**, 0	**5b**, 100 (63)
4	Br	CF_3	H	H	**1c**, 6	**5c**, 94 (92)
5	Br	C_4F_9	H	H	**1d**, 0	**5d**, 100 (63)
6	H	CF_3	H	Et	**1e**, 16	**5e**, 26 (23)
7[d]	H	CF_3	H	Et	**1e**, 15	**5e**, 85 (70)
8	H	CF_3	H	Ph	**1f**, 54	**5f**, 16 (6)
9[d]	H	CF_3	H	Ph	**1f**, 11	**5f**, 10 (10)
10	H	CF_3	–CH_2CH_2–		**1g**, 4	**5g**, 88 (45)[e]
11[d]	H	CF_3	–CH_2CH_2–		**1g**, 53	**5g**, 23 (18)[e]
12	Me	CF_3	H	H	**1h**, 16 (12)	**5h**, 33 (4)[f]
13[d]	Me	CF_3	H	H	**1h**, 17 (13)	**5h**, 0
14	Me	CF_3	H	Ph	**1i**, 10 (10)	**5i**, 0
15[d]	Me	CF_3	H	Ph	**1i**, 13 (6)	**5i**, 0

[a] Experimental conditions: r.t. to 50 °C, 5 h, unless otherwise noted. [b] Compounds **1a**–**h** were previously described, see ref.[6] [c] ^{19}F NMR spectroscopic yields, isolated yields in brackets. [d] Experimental conditions: 0 °C to r.t., 10 h. [e] A ring-opened chlorinated product was formed, see text and Scheme 3. [f] This product was not isolated in pure form.

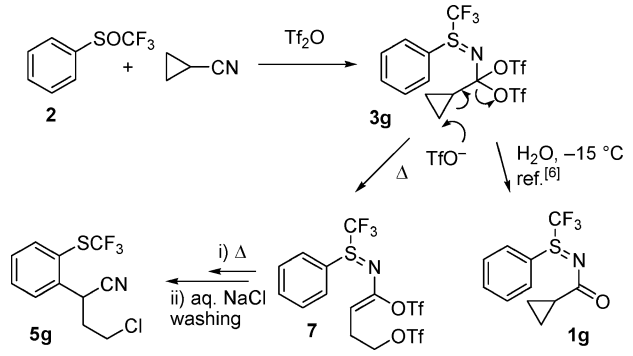
In the case of higher nitriles, it was found that starting the reaction at 0 °C followed by 10 h at room temperature was beneficial to the yield of **5** (Table 1, Entry 6 vs. 7). A minor improvement was observed for the benzylacetonitrile derivative (Table 1, Entries 8 and 9). To rationalize our experimental findings, we propose that when the substituent of the nitrile component bears at least one α-hydrogen atom, there is the possibility, under thermal conditions, of triflic acid elimination from intermediates **3**, leading first to the expected sulfilimino keteneacetals **6** (Scheme 2).



Scheme 2. Thermal rearrangement reaction of sulfilimines **3**.

The latter intermediates **6** proved to be surprisingly prone to undergo an electrocyclic ring closure followed by a further hetero-ring-opening/rearomatization process en route to isolated α-perfluoroalkylthio nitriles **5**. The overall result is net transfer of the alkylated nitrile moiety from sulfur to carbon at the *ortho* position of the newly formed perfluoroalkylsulfanyl group. This process achieves thus the same task as a selective *ortho* C–H aromatic bond activation followed by carbon–carbon bond formation, but without the need for a transition-metal catalyst[11] (C–H bond functionalization sensu Fokin and Schreiner).[12]

In the particular case of cyclopropyl carbonitrile, the rearrangement reaction was accompanied by the ring opening of the cyclopropyl cycle (Table 1, Entries 10 and 11).[13] We thus isolated chlorinated product **5g**, presumably arising by the mechanism shown in Scheme 3.



Scheme 3. Reaction of phenyltrifluoromethyl sulfoxide with cyclopropyl carbonitrile.

Preferential ring opening of intermediate **3g** leading to intermediate **7** occurs. Further "usual" rearrangement of **7** followed by workup with saturated sodium chloride solution exchanging the alkyl triflate group for chlorine then gives rise to observed chloride **5g**.

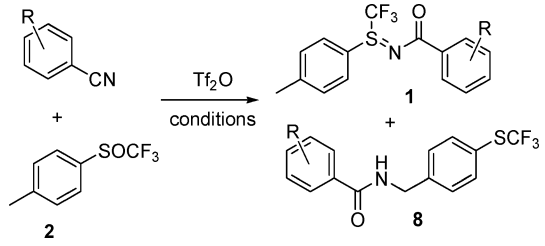
Another notable exception concerning *p*-tolyl trifluoromethyl sulfoxide (Table 1, Entries 12–15) was that disappointingly low yields, or no trace amount, of rearranged products **5** were isolated because of extensive charring of the reaction mixture. We suspected that in this particular case another reaction pathway was operative, possibly involving the benzylic hydrogen atoms of the aromatic methyl group.

To discriminate between thermal vicinal triflic acid elimination leading to the preceding rearrangement and remote elimination from the methyl group, the reaction of *p*-tolyl trifluoromethyl sulfoxide with aromatic nitriles was studied. With such nitriles, a new type of compound was formed and shown to have benzamide structure **8** (Table 2).[14] These amides were isolated in modest to fair yields after hydrolytic workup, along with expected sulfilimines **1**; the optimal temperature for this process was between 0 and 5 °C in most cases. Table 2 shows that the yield of amides **8** increases at the expense of **1** with the less nucleophilic nitriles (Table 2, Entries 7–10). Conversely, lower yields of amides **8** were achieved with the more nucleophilic nitriles (Table 2, Entries 1–6), suggesting a competitive mechanism for the formation of the two types of compounds.

We thus suggest that benzamides **8** and sulfilimines **1** are formed concurrently via a common early intermediate. Activated form **4** of sulfoxide **2** could be the candidate of choice, as shown by the following mechanistic proposal (Scheme 4). This reaction is noteworthy in that it occurs by an intermolecular process at the *para* position of the sulfoxide functionality (aromatic Pummerer).[9]

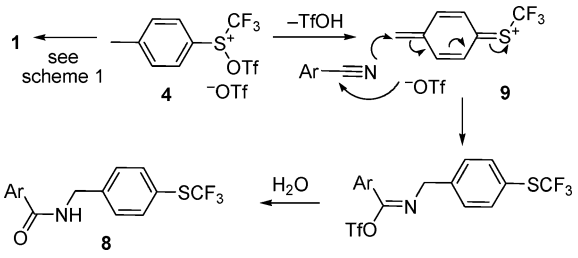
When activated sulfoxide **4** is not captured rapidly enough by reaction at the sulfur center with the nitrile component, it may suffer a competitive deprotonation to give

Table 2. Reaction of *p*-tolyltrifluoromethyl sulfoxide with aromatic nitriles.[a]



Entry	R	**1**, Yield [%][b]	**8**, Yield [%][b]
1	H	**1j**, 56	**8a**, 2
2[c]	H	**1j**, 68	**8a**, 2
3[d]	H	**1j**, 4	**8a**, 12
4	*p*-Me	**1k**, 57	**8b**, trace
5[c]	*p*-Me	**1k**, 61	**8b**, 0
6[d]	*p*-Me	**1k**, 16	**8b**, 0
7	*p*-Br	**1l**, 12	**8c**, 15
8	*o*-Br	**1m**, 4	**8d**, 41
9	*p*-NO_2	**1n**, 0	**8e**, 19
10	*m*-NO_2	**1o**, 0	**8f**, 29

[a] Experimental conditions: 0–5 °C, 5 h, unless otherwise noted. [b] Isolated yields. [c] Experimental conditions: –15 °C, 24 h. [d] Experimental conditions: r.t., 24 h.



Scheme 4. Proposed benzamides **8** formation.

the highly electrophilic benzologous Pummerer-like intermediate **9**.[9] Further efficient reaction of **9** with nitrile (either stepwise or concerted as shown in Scheme 4 for convenience), may then give rise, after hydrolysis, to observed benzamides **8**, involving the functionalization of a remote benzylic carbon–hydrogen bond in a coupled Pummerer/Ritter cascade.

According to this mechanism, more deactivated nitrile groups should give benzamides **8** in better yields and this was observed in our experiments (Table 2, Entries 7–10). In fact, activated intermediate **4** being not immediately captured at the sulfur center by the nitrile enjoys ample time to be converted into highly reactive species **9**.

Conclusions

In summary, fine-tuning of the experimental conditions and substrate choice during the reaction of perfluoroalkylated sulfoxides with nitriles under trifluoromethanesulfonic anhydride activation enables chemical diversity (perfluoroalkylated sulfilimines, perfluoroalkyl sulfanyl acetonitriles, as well as benzamides) through aromatic or (remote) benzylic carbon–hydrogen bond functionalization.

Supporting Information (see footnote on the first page of this article): Experimental procedures and copies of the NMR spectra for all new compounds.

Acknowledgments

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