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A New Practical One-Pot Access to Sulfonimidates

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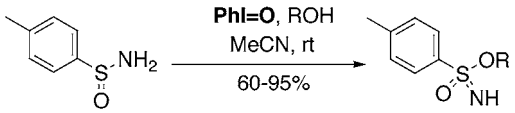
ABSTRACT



Sulfonimidates were prepared from sulfinamides and iodosobenzene in a very mild one-pot procedure in good to excellent yields. This reaction allows quick and efficient access to a class of molecules of important synthetic as well as biological and industrial interest.

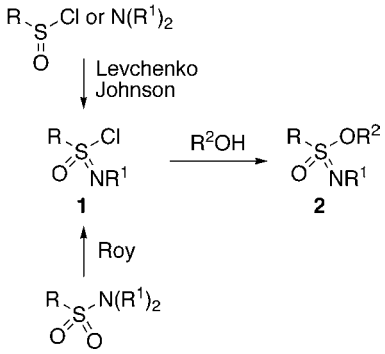
With the exception of sulfonyl derivatives, molecules containing sulfur(VI) atoms—especially those which also include nitrogen—have attracted little attention compared to sulfur(IV) products. This is largely due to stability issues, which derail most of the planned preparations of such compounds.

In our ongoing research program devoted to radical reactions involving sulfur functionalities,[1] we have become interested in finding new ways to rapidly access and subsequently use sulfonimidates **2**. Sulfonimidates are very interesting chiral and nitrogen-containing compounds. They also have applications in material sciences, as monomers of "inorganic polymers" ,[2] and biochemistry, where they could act as inhibitors of human carbonic anhydrase II.[3]

In addition, Johnson has shown that they could be used in asymmetric synthesis as chiral enantiopure sulfoximine precursors.[4] Reggelin developed these precursors with high levels of sophistication by introducing cyclic sulfonimidates.[5]

Most of the preparations of sulfonimidates are achieved via esterification of alcohols with sulfonimidoyl chlorides, obtained by oxidation of arenesulfinyl chlorides[6] or sulfinylamides (Scheme 1).[7] The latter is a very practical method

Scheme 1. Sulfonimidates via Sulfonimidoyl Chlorides



and its asymmetric version has been developed.[8] Alternatively, sulfonimidoyl chlorides **1** can also be synthesized by rearranging sulfonamides.[9]

Our attention was attracted by an isolated 1973 report by Maricich, who evidenced that, in some cases, sulfinylhy-

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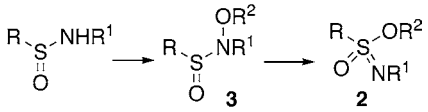
Scheme 2. Rearrangement of Sulfinyl Hydroxylamines



droxylamines **3** underwent spontaneous rearrangement to the sulfonimidates **2**, in which the OR^2 group migrated from nitrogen to sulfur (Scheme 2).[10] Compounds **3** are moderately stable and can be stored for only a few days. They were obtained by coupling sulfinyl chlorides and hydroxylamines, i.e. by starting with the already installed N−O bond.

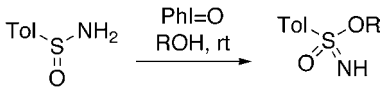
Since sulfinyl amides were much easier to prepare than functionalized hydroxylamines, we decided to focus on the formation of **3** from sulfinyl amides, keeping in mind that the moderate stability of sulfinylhydroxylamines could trigger rearrangement of **3** into **2**, if the conditions we devised allowed it. We would then have a one-pot process rather than a two-step procedure. Thus, our task was to oxidize the sulfinamide to form the N−O bond, with the S−N already in place. We did not expect that to be an easy task because sulfinamides are known to be easily oxidized to sulfonamides by a variety of oxidizing agents (*m*-CPBA being the leading one).[11]

We had to find a reagent that would oxidize the nitrogen position, leaving the sulfur untouched. As it happens, iodine(III) derivatives are very mild oxidants.[12] Furthermore, we knew from previous works that iodosobenzene and iodosobenzene diacetate react with sulfonamides to produce imidoiodinanes (Scheme 3).[13] The initial step is presumably the solvolysis of the initial iodine reagent.[14] Sulfonamides react by nucleophilic substitution on the iodine atom, possibly giving birth to a dissociated intermediate, which would finally be deprotonated.

Now, switching to sulfinamides implies a strong reduction of the amide function acidity.[15] We hoped the methoxide would substitute the iodobenzene moiety at the nitrogen center rather than deprotonate it, thus leading to sulfinyl hydroxylamines.

When submitted to potassium hydroxide in methanol at room temperature, tosylsulfinamide led to the desired sulfonimidate after just a few minutes. This showed not only that our assumption was correct, but also that the one-pot procedure worked. Next, we optimized the reaction conditions: it is unnecessary to use a base if PhI═O is used as the starting iodine reagent. This avoids having to work under overly basic conditions. With the optimized procedure in hand, we looked for the scope and limitations of this reaction. Results are presented in Table 1.

Table 1. Formation of Sulfonimidates from Sulfinamides



entry	R	yield (%)
1	Me	91
2	Et	94
3	*i*-Pr	73[a]
4	allyl	71
5	HC≡C−CH_2	92
6	CH_2═CH−$(CH_2)_2$	85
7	Bn	—[b]
8	*t*-Bu	—[c]

[a] Reaction took 1 h. [b] Tosylbenzylamine (17%) was isolated. [c] Sulfonamide (90%) was obtained.

Entries 1, 2, and 4−7 show that the reaction works well with primary alcohols, with the exception of benzyl alcohol. The only isolated product was tosylbenzylamine in low yield. This product arises from the rearrangement of sulfonimidates.[16] The reaction proved very sensitive to steric hindrance: while the rate diminished with isopropyl alcohol (entry 3), no reaction took place in *tert*-butyl alcohol (entry 8). This could be explained by the impossible solvolysis of iodosobenzene, which is an insoluble polymeric material: when alcohols are not too sterically demanding, dialkoxyiodosobenzene can be formed and the reaction can proceed.

Scheme 3. Reaction of Sulfonamides and Sulfinamides with Dimethoxyiodosobenzene

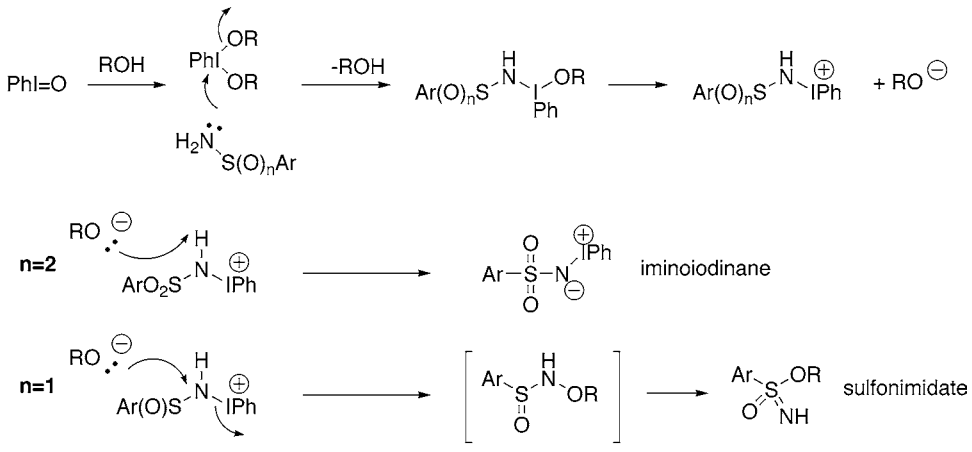
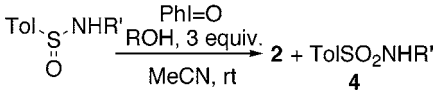


Table 2. Preparation of Sulfonimidates with 3 Equiv of Alcohol



entry	R	R′	**2** (%)	**4** (%)
1	Me	H	85	5
2	Et	H	67	23
3[a]	*i*-Pr	H	39	30
4	allyl	H	60	36
5[a]	$HC{\equiv}CCH_2$	H	76	21
6[a]	$CH_2{=}CH{-}(CH_2)_2$	H	71	13
7	$Ph{-}(CH_2)_4$	H	57	27
8	$HO{-}(CH_2)_3$	H	60	1
9	$HO{-}(CH_2)_5$	H	95	3
10	$Br{-}(CH_2)_2$	H	62	11
11[b]	Ph	H	–	–
12	Me	Bu	52	22

[a] MS 3 Å was also used. [b] Immediate degradation was observed.

The main limitation was, of course, the amount of alcohol needed for the transformation. While this posed no problem when methanol or ethanol were used, it became more troublesome when a more expensive alcohol was targeted. We reasoned that if the limiting step was the solvolysis of the starting material, then we should be able to reduce the equivalents of alcohol used, ideally lowering it to two. Therefore we switched to acetonitrile, anticipating that its polarity could allow the formation of the dialkoxy adducts. Indeed we observed the formation of the desired sulfonimidates, albeit in slightly lower yields. Sulfonamide—arising from the standard oxidation of sulfinamides—was also isolated, and this accounts for the loss in yield. The results are given in Table 2.

The reaction was smooth except in the case of secondary alcohols (entry 3), which led to a dramatic drop in yield of the desired product. We imagined that the water released during the formation of the dialkoxyiodosobenzene was accountable for this loss, but the addition of molecular sieves in the reaction mixture was not entirely conclusive. It may sometimes slightly improve yields, but not as a general rule.

Nonetheless, the result was quite satisfactory for expensive primary alcohols or for those whose physical properties would not allow them to be used as solvents (e.g. entry 7). Propanediol led to a crystalline compound that was unambiguously proven to be the sulfonimidate by X-ray diffraction (entry 8). The ethyl compound was also prepared according to the Roy method; both reactions gave the same product. As stated before, the only observed byproducts were sulfonamides. Lowering the amount of alcohol below 3 equiv leads to an increase of oxidation at the expense of the desired product. This result is still interesting, since to the best of our knowledge no such oxidation involving iodine (III) derivatives has been reported in the literature. Finally, we were pleased to see that our reaction was not limited to primary sulfinamides. The *N*-butyl sulfonimidate is then produced in fair yield (entry 12; when the solvent was methanol, sulfonimidate was obtained in 74% yield), while aromatic alcohols are not suitable: degradation occurs presumably through electrophilic aromatic substitution (entry 11).

In conclusion, we have devised an efficient one-pot procedure to prepare sulfonimidates in good to excellent yields, where the reported methods required two steps. We also observed a dramatic difference in reactivity between sulfinamides and sulfonamides toward iodosobenzene, which can be rationalized by a strong pK_a difference. In addition, sulfonimidates can rearrange to sulfonamides.[16] We are currently looking for conditions that could trigger this rearrangement in the same pot, leading to a one-pot alternative to the Mitsunobu reaction. These results, as well as the asymmetric version of our reaction, will be reported in due course.[17]

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Supporting Information Available: Detailed procedure and full characterization of all new sulfonimidates (including copies of their NMR spectra); crystal structure of the sulfonimidate derived from propanediol. This material is available free of charge via the Internet at http://pubs.acs.org.

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