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Efficient Preparation of N-Phenylsulfonyl Ketimines from Oximes or Nitro Compounds without Racemization of α-Stereocenters

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ABSTRACT

As N-sulfinyl imines (e.g., RRC=−N=SAr) can be readily transformed to their N-sulfonyl imines (RRC=−N=SOAr), N-sulfonyl imines (RRC=−N=SOAr), and N-sulfonyl oxaziridines, the very mild procedure developed to convert ketoximes and secondary nitro derivatives to N-arenesulfonyl ketimines constitutes a new and efficient route to all these series of compounds. The configuration of the α-stereocenters is retained.

N-Sulfinyl imines1,2 and N-sulfonyl imines3,4 are enjoying an increasing number of applications in asymmetric synthesis (Mannich reactions, α-alkylation via enamine anions, hetero-Diels−Alder reactions, etc.). Chiral N-sulfonyl oxaziridines are also very popular as asymmetric epoxidation and hydroxylation reagents.5 As known,6 N-sulfinyl imines such as sulfinimines 1 are easily oxidized with m-CPBA or other peroxyacids to N-sulfonyl derivatives (sulfinimines 2), subsequently to their N-sulfonyl derivatives (sulfinimines 3), and then to N-sulfonyl oxaziridines (4),6 therefore, any efficient entry to 1 would be extremely useful.7 This is simplified in Scheme 1, where only one stereoisomer is drawn for each species.8 We have focused our attention on ketimines, which have been studied much less than aldimines.

In fact, the success of many asymmetric reactions involving 2−4 relies upon their preparation as stereopure substrates and their configurational stability. Usually, N-sulfinyl ketimines are prepared by condensation of ketones and sulfinamides (RSONH₂ or ArSONH₂) mediated by Ti(OEt)₄ or other peroxoacids to

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dehydrating agents in refluxing THF\(^9\) but also by the above-mentioned oxidation of \(N\)-sulfonyl ketimines and by the reaction\(^{10}\) of metal iminides with sulfinates (RSOOR'). \(N\)-Sulfonyl ketimines are mainly obtained by condensation (with limitations) of sulfonamides and ketones,\(^{3,4}\) from oximes and sulfonyl cyanides,\(^ {11}\) and by oxidation of \(N\)-sulfonyl ketimines.\(^{12}\)

We uncover a very mild method that gives practically quantitative yields of the desired sulfenimines \(1\) at room temperature (rt) from ketoximes and from secondary nitro compounds. It is a significant practical improvement with regard to the reaction of oximes with PBu\(_3/\text{PhSSPh}\) reported by Lukin and Narayanan;\(^{13a}\) these authors showed that sulfonyl ketimines are intermediates in the conversion of oximes to imines\(^{13b}\) and can be cleaved in the presence of suitable acids. Our procedure can be very useful when the direct condensation to obtain \(2\) and \(3\) fails\(^7\) because of the steric hindrance or when it is counter-indicated as concomitant reactions (including stereocenter inversions) take place in the R or R' chains.

When the oximes in Table 1 (usually equilibrium Z/E mixtures) were treated with commercially available \(N\)-(phenylsulfonyl)phthalimide, that is, \(N\)-(phenylthio)phthalimide (PhthN-SPh, a non-stinking solid) and trimethylphosphine (PMe\(_3\)) a trt, \(N\)-phenylsulfenyl ketimines \(1a\) – g were formed quickly. Direct separation and purification of the final mixtures through a short pad of alumina, with hexane as the eluent, afforded excellent isolated yields (86–97%, see Table 1), with no stench, as PhSH was not formed as a co-product or during the workup.

R'-Stereocenters did not epimerize (entry 5), as expected, or did not racemize at all (entries 6 and 7), as checked for \(1f\) and \(1g\) by oxidation to the known, corresponding ketones with oxone (Oxone, 2KHSO\(_4\) â KHSO\(_4\) â K\(_2\)SO\(_4\)) or with ozone;\(^ {14}\) the enantiomeric purities of both ketones were confirmed by polarimetry and chiral HPLC (Chiralpak AD-H column).

In parallel experiments with PBu\(_3\) (220 mol %), only 70% of \(1a\) was obtained after 15 h. With an excess of aromatic phosphine, such as PPh\(_3\) or 1,1’-bis(diphenylphosphino)ferrocene (dpff), no reaction was observed at rt after 15 h.

To achieve a total absence of starting materials in the final products, we had to use stoichiometric amounts of PhthN-SPh. For example, with 0.4 equiv of PhthN-SPh, only 40% of the oximes were converted to sulfenimines; with 0.6 equiv of PhthN-SPh, ca. 60% of conversion occurred. Turnover did not take place, even with an excess of PMe\(_3\).

The method partially failed in one case (Scheme 2). When we applied it to oxime \(5h\), the yield of sulfenimine \(1h\)
reached a maximum of 70%. A fragmentation product (the thiaoacetal shown in Scheme 2) was always formed, even at 0 and −20 °C, in 20–30% yields. It may come from the decomposition of the common intermediate via a benzyl-type cation, which may be trapped by PhSH. Thus, prone to fragmentation oximes (on protonation or by reaction with electrophiles, giving rise to stable carbenic or oxocarbenic cations) may not afford high yields of sulfenimines 1.

Even in this last case (1h), in which the α-stereocenter position is benzylic, no racemization took place. In fact, the oxidation of 1h with oxone gave the corresponding enantiopure ketone, as shown by chiral HPLC.

Secondary nitro groups (6) can also be converted to sulfenimino groups (1) at rt by the same procedure, using 2.2 equiv of PMe 3 instead of 1.1 equiv, as shown in Table 2. One equivalent of PMe 3 is consumed in the first step, that is, the reduction of R 2 CH−NO 2 to R 2 CH−N=O/R 2 C=N−OH catalyzed by PhthN-SPh, which is slower than the second step, the sulfenylation of the oxime group. After 1−3 h of reaction, sulfenimines 1 were isolated in excellent yields. Stereocenter α of 1m did not epimerize.

Moreover, the reaction works in one pot, at rt, in a short time, and using very small amounts of commercially available reagents. The only exception was converting 6m to 1m, as 3.0 equiv of N-(phenylsulfenyl)phthalimide, 6.0 equiv of PMe 3, and 24 h were needed to obtain a good yield.

To gain more insight into the mechanism, the reaction of nitrocyclohexane (6a) with 3 equiv of PMe 3 and 0.2 equiv of PhthN-SPh was followed by 13C NMR spectroscopy in THF (Figure 1). For the sake of simplification, only the signals of the methylene carbons vicinal to the CH−NO2/C=C=NOH/C=NSPh groups are shown. The disappearance of the oxime intermediate was so quick that it could not be detected under these conditions.

To our knowledge, this is the first reported method for obtaining N-sulfenyl imines directly from nitro compounds.

Table 2. From Nitro Compounds to Sulfenyl Ketimines

<table>
<thead>
<tr>
<th>entry</th>
<th>nitro compd</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>1a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>PhNO 2</td>
<td>6b</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>PhNO 2</td>
<td>6i</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>PhNO 2</td>
<td>6j</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>PhNO 2</td>
<td>6k</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>PhNO 2</td>
<td>6l</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>6m</td>
<td>1m</td>
<td>84</td>
</tr>
</tbody>
</table>

(a) The nitro compound (1.0 mmol) was added to a solution of PMe 3 in THF (1.0 M, 1.1 mL). PhthN-SPh (1.2 mmol) was added, and the mixture was stirred at rt for 30 min. The Z/E ratios are those observed (400 MHz 1H NMR spectra) in CDCl 3 at rt. With 3 equiv of PhthN-SPh and 6 equiv of PMe 3 for 24 h.

Figure 1. (a) 13C NMR spectra of nitrocyclohexane (6a) and excess of PMe 3 (3 equiv) in THF. (b–e) After successive additions of 0.2 equiv of PhthN-SPh, only the appearance of sulfenimine 1a was observed. (f) Addition of 0.5 equiv of PhSH to (e); spectrum registered after 10 min. (g) Spectrum registered 30 min after the addition of 0.5 equiv of PhSH.

in the reaction media or water must be added to catalyze or mediate such a N–S bond cleavage.\textsuperscript{13a}

Thus, “the secret of the success” is that the phthalimide anion of [PhthN\textsuperscript{−}PMe\textsubscript{3}(SPh)\textsuperscript{+}] traps the oxime proton, but PhthNH\textsuperscript{−}, in contrast to ArSH, is not acidic enough to help the conversion of sulfenimines 1 to ketimines.

It is likely that many other aromatic and heteroaromatic phthalimide derivatives (PhthN–SAr or PhthN–SHet) may behave similarly. On the other hand, PhthN–S\textsuperscript{t}Bu does not work, as no reaction with nitroalkanes or oximes was observed under our conditions; thus, our method is not useful for the preparation of Ellman’s substrates.\textsuperscript{1c}

In summary, efficient and mild conditions (short times, rt, 84–98\% yields) for the conversion of ketoximes and secondary nitro compounds to sulfinyl ketimines (1) have been uncovered. No epimerization of α-stereocenters takes place. The role of PMe\textsubscript{3} is outstanding (in relation to Bu\textsubscript{3}P and aromatic phosphines). In principle, a plethora of aryl-sulfinyl ketimines (2), arylsulfonyl ketimines (3), and aryl-sulfonyl oxaziridines (4) are available via the new route.

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**Supporting Information Available:** Experimental procedures and NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.