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Metal-free imination of sulfoxides and sulfides

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Abstract—Using a nitrogen transfer agent obtained in situ by mixing of $NsNH_2$ and $PhI(OAc)_2$, various *N*-nosyl sulfoximines and *N*-nosyl sulfilimines have been prepared under metal-free conditions starting from the corresponding sulfoxides and sulfides, respectively.

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In recent years, various procedures for the imination of sulfoxides and sulfides giving synthetically valuable sulfoximines and sulfilimines,^{1,2} respectively, have been developed (Scheme 1). In general, two approaches metal-catalyzed and metal-free ones—can be distinguished. For the former, a variety of metal complexes proved applicable, and for conversions of (pro)chiral substrates a number of asymmetric and stereospecific versions have been introduced.³ Metal-free imination reactions mostly involve the use of a mixture of sodium azide and sulfuric acid⁴ or MSH (*O*-mesitylenesulfonylhydroxylamine).^{5,6} Those methods are particularly useful for the preparation of 'free' *NH*-derivatives (X = H), which are key building blocks for more complex sulfur-based molecular arrays.²

Despite the wide applications of the aforementioned metal-free methods, a major drawback of them is the use of toxic and potentially explosive reagents. In



Scheme 1.

particular, for large-scale syntheses, finding and development of more practical iminations based on the use of stable, non-toxic reagents are desirable. In this context, a recent report by Yudin and co-workers caught our attention, who described the imination of sulfoxides with N-amino- phthalimide and iodobenzene diacetate as mild oxidant.⁷ Most interestingly and in contrast to previous studies,⁸ no metal was required for this apparently rather facile (formal) nitrene-transfer reaction. This observation was in line with results from our own investigations. During the development of silver-catalyzed sulfoxide imination reactions with mixtures of *p*-nitrobenzenesulfonylamide (Ns-NH₂) and PhI(OAc)₂,^{3g} we had observed the formation of nosyl-protected sulfoximine 2, which under reflux even occurred in the absence of metal catalyst. Since compound 2 had an easy-tocleave protecting group on the sulfoximine nitrogen (allowing access to the corresponding NH-derivative), we wondered about the generality of this metal-free imination process. After optimization of the reaction conditions with methyl phenyl sulfoxide (1) as substrate, a high yield (75%) of N-nosyl sulfoximine 2 was achieved (Scheme 2).

The best conditions involved the use of an acetonitrile solution of all reaction components, which was kept under reflux for 16 h.⁹ Acetonitrile proved superior to



Scheme 2.

Keywords: Asymmetric synthesis; Iminations; Metal-free; Sulfoxides; Sulfoximines.

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the other solvents, such as dichloroethane and THF, which afforded **2** in only 60% and 33% yield, respectively. At room temperature, no reaction occurred. Addition of a base such as MgO did not affect the reaction yield. Unfortunately, no conversions or very low yields were observed with other nitrogen sources such as *p*-toluenesulfonylamide (TsNH₂), *p*-methyl-2-pyridinesulfonylamide, trimethylsilylethyl sulfonyl amide (SesNH₂) and trifluoroacetamide.

In order to investigate the scope of the substrate, the imination of several other sulfoxides with Ns–NH₂ was examined. Gratifyingly, most substrates were converted equally well under the condition described above affording the corresponding *N*-nosyl protected sulfoximines (compounds **3–5**) in good yields (up to 74%). Attempted iminations of benzyl phenyl sulfoxide and phenyl vinyl sulfoxide proceeded inefficiently. Furthermore, the nitrogen transfer onto sulfides was tested and without further optimizing the reaction conditions sulfilimines **6** and **7** were obtained from the corresponding sulfides in 79% and 82% yield, respectively.



As demonstrated previously,^{3g} the deprotection of **2** by treatment with Cs_2CO_3 and thiophenol in acetonitrile at ambient temperature for 16 h proceeded smoothly affording *NH*-free methyl phenyl sulfoximine (**8**) in 76% yield. Unfortunately, when enantiomerically enriched (*S*)-methyl phenyl sulfoxide (**1**) with 83% ee was applied in this two-step reaction sequence, *NH*-sulfoximine **8** with 43% ee was obtained. Since the nosyl deprotection was shown to proceed without epimerization, we attribute this partial racemization to the high reaction temperature (over a period of 16 h), which was required for the metal-free imination.

In conclusion, a metal-free imination of sulfoxides and sulfides with mixtures of NsNH₂ and PhI(OAc)₂ was developed. The discovery of this safe, non-toxic method advances the chemistry of sulfoximines since the resulting *N*-nosyl products can readily be deprotected under standard reaction conditions giving synthetically most valuable *NH*-sulfoximines. Further studies are directed towards the search for new iminating agents avoiding the use of high-molecular weight oxidants.

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- 9. Representative procedure for the imination of sulfoxides: To the solution of sulfoxide 1 (70 mg, 0.5 mmol) in anhydrous acetonitrile (4 mL) was added NsNH₂ (121 mg, 0.6 mmol) and PhI(OAc)₂ (242 mg, 0.8 mmol) at rt under argon, and the reaction mixture was then heated to reflux for 16 h. Subsequently, the mixture was cooled to ambient temperature and concentrated under reduced pressure. Purification of the remaining product by column chromatography gave *N*-nosyl sulfoximine 2 in 75% yield (128 mg).