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Phosphine Mediated Conjugation of S-Nitrosothiols and Aldehydes

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Abstract

S-Nitrosothiols (SNO) and their biological implications as an important post-translational modification are under active investigation. In our work on bioorthogonal reactions of protein SNO we have uncovered chemistry of this functionality that shows synthetic promise. Herein we report a phosphine-mediated reaction between SNO and aldehydes to form thioimines. A simple synthesis of benzoisothiazole based on this reaction is presented.

Graphical Abstract

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Keywords

S-Nitrosothiols; Thioazaylide; Thioimine; Aldehyde; Conjugation

In the past two decades S-nitrosothiol (SNO) formation, mainly on protein cysteine residues, has received considerable attention in redox biology. This reaction is an important post-translational modification and plays essential roles in nitric oxide-related signal transductions.^{1,2} Extensive studies have been carried out to understand how SNO are formed in different protein environments, how SNO can be detected in complex biological systems, and what their functions are.^{1,2} In contrast, SNO seems to be ignored by synthetic chemists, probably because SNO compounds are thought to be too unstable and therefore not useful for synthesis.³ To the best of our knowledge, only very few reactions utilize SNO as

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synthetic intermediates. Such examples include radical additions of SNO to alkenes to form α -thio oximes or thioepoxides,⁴ and the reactions with carbanions (RLi or RMgX) to form thioethers.⁵ Other synthetic applications have not been well studied.

In our recent work on SNO bio-orthogonal reactions (aiming at the development of novel detection methods for proteins SNO),⁶ we have realized some unique reactivity/properties of SNO. The reaction between SNO and triarylphosphines (2 equiv) can generate reactive thioazaylides in high yields under mild conditions (Scheme 1). Thioazaylides are potent nucleophilic species. Upon manipulating the electrophilic groups on the phosphine reagents, we could trap the thioazaylides as stable products.⁶ In one example, we trapped relatively stable tertiary SNO substrates with thioesters to form thioimidates (Scheme 1).⁷ We expected similar reactions with appropriate electrophiles would have unique synthetic applications. In this communication, we report the reactions between SNO-derived thioazaylides and selected aldehydes. We found such reactions could precede both intra-molecularly and inter-molecularly.

Aldehydes are highly reactive electrophiles and expected to react with thioazaylides. We also envisioned the intramolecular reaction would be feasible. Therefore 2-(diphenylphosphanyl)-benzaldehyde (**2**) was selected as the first substrate to be tested. As for SNO, trityl-SNO (**1**) makes for a convenient platform for exploring SNO chemistry as it can be easily prepared and stored as a stable solid for months in the dark at 0°C. In this study, two equivalents of phosphine **2** was treated with trityl-SNO. We screened a series of solvents and different reaction temperatures. The results were summarized in Scheme 2. Dichloromethane and chloroform were found to be the optimum solvents, which gave the desired product **4** with the best yield (57%). The progress of the reaction was monitored by TLC. The consumption of the SNO by phosphine to form the thioazaylide was completed within three hours by TLC. The subsequent intramolecular aza-Wittig reaction was somewhat slow, requiring overnight reaction times.

Next we tested the reactions with a range of SNO substrates and the results are summarized in Scheme 3. In general, the reaction worked well for tertiary SNOs (entries 1-4) and the corresponding products were stable for purification by flash column chromatography. Some products derived from secondary SNOs (entries 5 and 6) were stable enough for purification and characterization. The products from **4e** and primary SNO **4f** were found to be unstable. Crude NMR analysis showed the presence of the products in the reaction but attempts to isolate resulted in decomposition. These results indicated that there is a correlation between the stability of the starting SNO and the stability of the final product.

Having demonstrated the intramolecular coupling between thioazaylides and aldehydes, we set out to study the application of this reaction in intermolecular bond formation. Attempts to couple a series of benzaldehyde derivatives (Scheme 4) (benzaldehyde, p-methoxybenzaldehyde, and 4-trifluoromethylbenzaldehyde) with TrSNO-derived thioazaylide produced none of the anticipated product (Scheme 4). Heating this reaction proved unproductive, TrSNH₂, the decomposition product from thioazaylide, was observed by ESI-MS, but no trace of the product was observed. We ascribe the lack of any observed product to the excessive steric bulk of the phenyl rings in close proximity.

We then turned to α,β -unsaturated aldehyde substrates for this reaction as such substrates were found to react well in the analogous Wittig cross couplings.⁸ Cinnamaldehyde proved to be a more suitable substrate for this reaction, and under the same conditions produced the desired product (**6**) in a modest yield (57%, Scheme 5). *t*-Butyl SNO was also used to react with cinnamaldehyde to produce the desired product **7** in a similar yield (64%). We also found that the use of excess of SNO (1.5 equiv.) could improve the yield to 89%. Presumably the unavoidable decomposition of the *S*-nitrosothiols into their corresponding disulfide should occur over the reaction times used. These disulfides can be expected to react with and consume the phosphine reagent. However simply adding more SNO and phosphine should force the reaction to completion. Under these conditions, *t*-butyl SNO even reacted successfully with *p*-methoxybenzaldehyde to produce the corresponding product **8**, albeit the yield was not high (18%). Interestingly employing a more nucleophilic phosphine, i.e. EtPPh₂, led to a significantly improved yield (54%). With this optimized protocol benzaldehyde and *p*-trifluoromethylbenzaldehyde were also successfully coupled with *t*-butyl SNO.

Finally we set out to explore the application of this chemistry in making *-S-N-* containing molecules. Benzoisothiazole is a fused, two-ring heterocycle with a unique *S-N* bond. Benzoisothiazole derivatives have been reported to act as antibacterials,⁹ anti-HIV¹⁰ as well as some other activities.¹¹ For example, the antipsychotics Ziprasidone and Lurasidone contain benzoisothiazole rings. Current synthetic methods for this heterocycle (Scheme 6) are either low yielding and inefficient, or require the insertion of an amine at the 3-position.¹² Starting from 1,2-benzisothiazole-3(2H)-one (**13**) is undesirable as this compound and its 3-chlorinated derivative (not shown) are both strong dermal, ocular and nasal irritants which require special containment and handling.¹²

We envisioned that our SNO-mediated aldehyde condensation could be used to access benzoisothiazole. Retro-synthetically the target molecule **12** could be synthesized from SNO-mediated intramolecular aza-Wittig reaction (Scheme 7). As such omercaptobenzaldehyde **17** should be the starting material. We tested this idea by starting from the commercially available omercaptobenzoic acid **18**, which was converted to omercaptobenzol **19** upon reduction with lithium aluminum hydride (LAH). Subsequent oxidation of **19** to the aldehyde **17** caused the formation of disulfide-aldehyde **20**. Disulfide formation is often an unavoidable consequence of working with thiols, especially under oxidative conditions.

Our initial plan called for the reduction of **20** to aldehyde **17**, and then *S*-nitrosation and ring closure by phosphine-mediated aza-Wittig reaction. We recognized that PPh₃ would be used in step 1 and 3 in this 3-step process; and *S*-nitrosation by organonitrite should proceed in the presence of PPh₃. As such it might be possible to achieve the 3-step transformation in one-pot with all the reagents presented. This was found to be the case. Simply dissolving the disulfide-aldehyde **20** (1.0 equiv.) in a THF/H₂O system with excess phosphine (6.0 equiv.) and isoamyl nitrite (2.5 equiv.) led to the complete conversion to benzoisothiazole (**12**) in an excellent yield. The lower isolated yield of 81%, as compared to almost quantitative conversion observed by NMR, is ascribed to the fact that benzoisothiazole easily evaporates during solvent removal. This route is highly preferable to handling the free thiols, as their

odor, propensity to act as a nucleophile or oxidize to their corresponding disulfides can be painful problems to deal with.

To conclude, we have presented a facile method for the formation of thioimine bonds from aldehydes and S-nitroso compounds, readily obtained via nitrosation of thiols. This reaction proceeds under mild conditions and should find applications in the preparation of some pharmaceutically important molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

$$\text{RSNO} + \text{R}'\text{CHO} \xrightarrow[\text{CH}_2\text{Cl}_2, 25^\circ\text{C, overnight}]{\text{PR}_3} \text{R}'\text{CH=N-S-R}$$

entry	SNO	aldehyde	PR ₃	product	% yield
1	 1 equiv.		PPh ₃	 6	57
2	 1 equiv.		PPh ₃	 7	64
3	 1.5 equiv.		PPh ₃	 7	89
4	 1.5 equiv.		PPh ₃	 8	18
5	 1.5 equiv.		EtPPh ₂	 8	54
6	 1.5 equiv.		EtPPh ₂	 9	68
7	 1.5 equiv.		EtPPh ₂	 10	44

Scheme 5.

Scheme 6.

Scheme 7.