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Desulfurization of Thiols for Nucleophilic Substitution

Mu-Xian Fu, Jin-Hong Lin,* and Ji-Chang Xiao*

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ABSTRACT: Although the desulfurization of thiols is a topic of great importance and has received significant attention, most efforts have focused on the hydrodesulfurization of thiols. In this work, we describe the desulfurization of thiols for nucleophilic substitution. This process occurs rapidly, promoted by the Ph_3P/ICH_2CH_2I system, and can be extended to a wide range of nucleophiles. Notably, free amines can be employed as nucleophiles to synthesize various secondary and tertiary amines. This method tolerates a wide array of functional groups, including hydroxyl groups in amination reactions. Benzyl thiols are particularly reactive and can be completely converted at room temperature within 15 min. Although alkyl thiols show lower reactivity, they can also be converted smoothly at a reaction temperature of 70 °C overnight.

R-SH + Nu-H $\xrightarrow[\text{NMP, rt}]{Ph_3P/ICH_2CH_2I}$ R-Nu

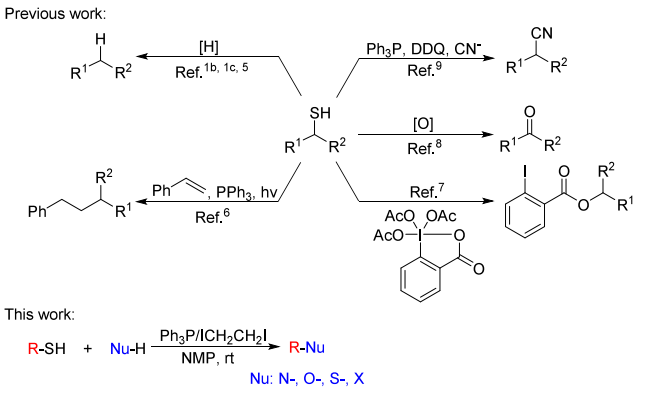
Nu: N-, O-, S-, X 45 examples, up to 97% yield

Desulfurization of thiols is a topic of great value in peptide synthesis,[1] drug developments[2] and fossil fuel treatments.[3] The combination of thiol-mediated ligation with a desulfurization is an attractive strategy for the synthesis of protein targets.[1] Desulfurization-based structural modification of thiol-containing biologically active molecules, including pharmaceuticals like Captopril[2a,b] and Glutathione,[2c,d] could significantly bolster drug development initiatives. Desulfurization plays a crucial role in eliminating thiols from crude fossil fuels, preventing the release of environmentally damaging sulfur oxides generated from thiols upon combustion.[3] Consequently, substantial efforts are being invested in developing efficient methods for desulfurization of thiols.

Some effective desulfurization strategies have been developed (Scheme 1, Previous work).[4] Extensive studies have focused on the hydrodesulfurization process for converting alkyl thiols into alkanes,[1b,c,5] a strategy pioneered by Hoffmann and his colleagues, who demonstrated that thermal or UV light conditions can facilitate this process in the presence of $P(OEt)_3$.[5a] Due to the low bond energy of the RS-H bond, homolytic cleavage may occur under light irradiation to generate a RS• radical, which would be readily trapped by a trivalent phosphorus, resulting in the cleavage of the C−S bond to generate an alkyl radical for hydrogenation.[1c,5a,h] Based on these findings, it has been determined that hydroalkylation of alkenes with primary thiols can also be successfully achieved through a radical desulfurization process.[6] Primary benzyl thiols can attack a hypervalent iodine, such as Dess−Martin periodinane (DMP), and the subsequent elimination affords esters, in which the $ArCO_2$− and R^1R^2CH− moieties are derived from the DMP reagent and thiols, respectively.[7] Primary and secondary benzyl thiols can be desulfurized and oxidized to aldehydes and ketones, respectively. The reaction is highly effective, but the complex reaction conditions involving three oxidants and light irradiation may be a drawback of this method.[8] The Ph_3P/DDQ system can be used for cyanation of thiols with $^nBu_4N^+CN^-$.[9] Both primary and secondary thiols are reactive under these conditions. However, DDQ's strong oxidative properties and moisture sensitivity might narrow its applicability due to its low compatibility with functional groups and the risk of releasing highly toxic HCN when it reacts with water.[10] Overall, while desulfurization has received considerable interest, the focus has predominantly been on hydrodesulfurization, leaving other reactions largely unexplored.

We have previously demonstrated that the R_3P/ICH_2CH_2I system is effective in activating alcohols to cleave the C−OH bond, facilitating various nucleophilic substitution,[11] such as halogenation,[11a] fluorination[11d] and sulfonylation.[11f] Notably,

Scheme 1. Desulfurization of Thiols



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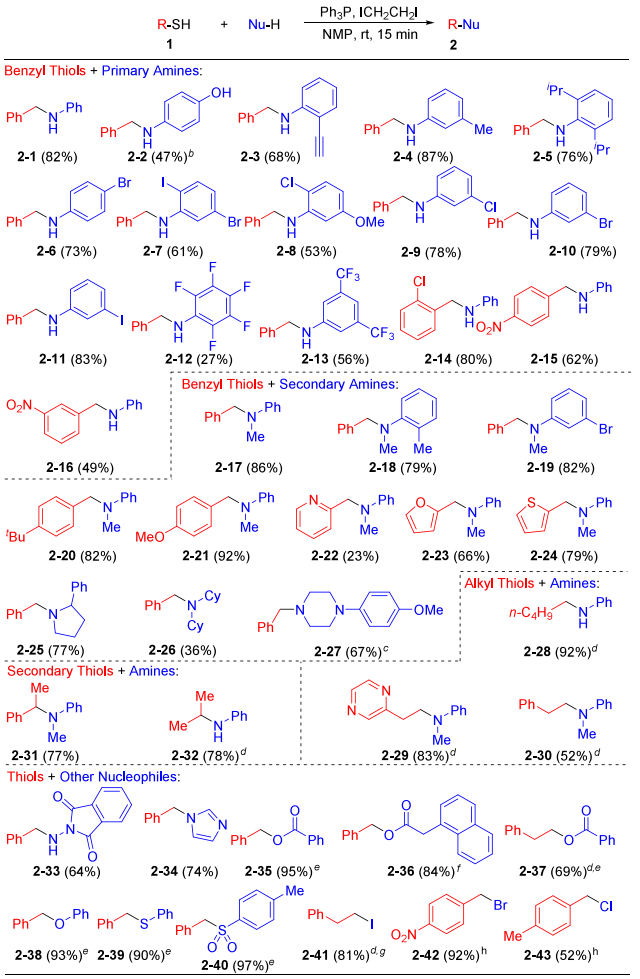
the halogenation method was effectively utilized in the total synthesis of Clionastatins A and B during the chlorination step, a result unattainable with other commonly employed methods.[12] We hypothesized that the C−SH bond in thiols could potentially be activated by the R_3P/ICH_2CH_2I system for nucleophilic substitution, given that oxygen and sulfur belong to the same chemical family. However, the differences between the hydroxyl and the thiol groups should be considered. While the bond energy of C−S is lower than that of C−O (with a bond energy of 74 kcal/mol for the CH_3−SH bond compared to 92.3 kcal/mol for the CH_3−OH bond),[13] thiols are significantly more acidic than alcohols (with a pK_a of 9.8 for CH_3SH[14] compared to 15.54 for CH_3OH[15]). The high acidity of thiols can lead to the protonation of nucleophiles, reducing their nucleophilicity and potentially inhibiting nucleophilic substitution. Surprisingly, the nucleophilic substitution of thiols promoted by the R_3P/ICH_2CH_2I system can accommodate a wide range of nucleophiles, such as amines, carboxylate, phenolate and halides. Especially, free amines can function as nucleophiles, sharply contrasting with traditional alkyl halide amination methods, which commonly face challenges in preventing side reactions such as the alkylation of the amination products with alkyl halides. The reactions proceeded rapidly under an air atmosphere and moderate to high yields were obtained (Scheme 1, this work).

The optimal conditions for the desulfurized nucleophilic substation of thiols were identified after systematic screening of the amination of benzyl thiol (**1-1**) (see Supporting Information). The reaction promoted by the Ph_3P/ICH_2CH_2I system proceeded very quickly under an air atmosphere, achieving the desired product in just 15 min with a 91% yield. Ph_3P was converted into the nonreusable byproducts $Ph_3P{=}O$ and $Ph_3P{=}S$ in this reaction, which is further discussed in the mechanistic investigation section. With the optimal conditions in hand, we proceeded to explore the substrate scope of the Ph_3P/ICH_2CH_2I-promoted desulfurized nucleophilic substitution of thiols. As shown in Scheme 2, the substitution process can be extended to a wide variety of nucleophiles, showcasing extensive substrate scope and significant tolerance for various functional groups. Notably, all of these reactions were performed under an air atmosphere, eliminating the need for an inert gas environment, which is very convenient for operation. Benzyl thiols are highly reactive, and a 15 min or reaction time can give moderate to high yields. It is quite surprising to see that 4-aminophenol can also act as a nucleophile, with the hydroxyl group remaining unaffected, despite the potential for the hydroxyl group to attack the electrophilic center (**2-2**). The compatibility with alkynyl (**2-3**) and halide (**2-6** to **2-11**) groups may allow for further transformations. Electron-deficient phenyl amines tended to result in lower yields, probably because of reduced nucleophilicity (**2-12** and **2-13**). Benzyl thiols with electron-deficient groups also produced lower yields, due to the decreased nucleophilicity of the thiol group, which prevents it from being activated by attacking the iodophosphonium salt generated in situ (see the mechanism section) (**2-15** and **2-16**). In addition to primary amines, secondary amines are also well-suited for the substitution reaction despite a higher steric hindrance (**2-17** to **2-27**). However, the use of highly sterically hindered amines resulted in low yields (**2-26**). While heterocyclic thiols generally undergo smooth conversion, exceptions occur with pyridinyl thiol, where the pyridinyl group may act as a nucleophile, leading to side reactions (**2-22**). For the amine containing two amino groups, a secondary alkyl amino and a tertiary aryl amino groups, the tertiary amino group exhibited no significant side effects, likely attributable to its lower nucleophilicity (**2-27**). Alkyl thiols show lower reactivity, resulting in almost no desired product under the conditions for the amination of benzyl thiols. Fortunately, they can also be successfully converted at a reaction temperature of 70 °C overnight (**2-28** to **2-30**). This process can also be extended to secondary thiols (**2-31** to **2-32**).

Scheme 2. Desulfurization of Thiols for Nucleophilic Substitution[a]



[a]Isolated yields are shown. Reaction conditions: **1** (0.5 mmol), nucleophile (2.5 equiv), Ph_3P (1.2 equiv), ICH_2CH_2I (1.2 equiv) in NMP (5 mL) at room temperature for 15 min. [b]4 equiv of the nucleophile was used. [c]The reaction time was 2 h. [d]The reaction was performed at 70 °C overnight. [e]Na^+ Nu^- was used as a nucleophile and the reaction time was 1 h. [f]K^+ Nu^- was used as a nucleophile and the reaction time was 1 h. [g]No additional iodide nucleophile was needed as the iodide anion was generated from the reaction system. [h]For chlorination and bromination, $^nBu_4N^+$ X^- (X = Cl or Br) was used as a nucleophile.

Since amines are fundamental products and building blocks in chemistry with particular importance for the pharmaceutical and agrochemical industries, amination has become a highly active research topic.[16] Many amination methods have been developed, such as reductive amination,[17] Buchwald−Hartwig amination[18] and traditional amination of alkyl halides.[19] All of these amination methods have found widespread applications,

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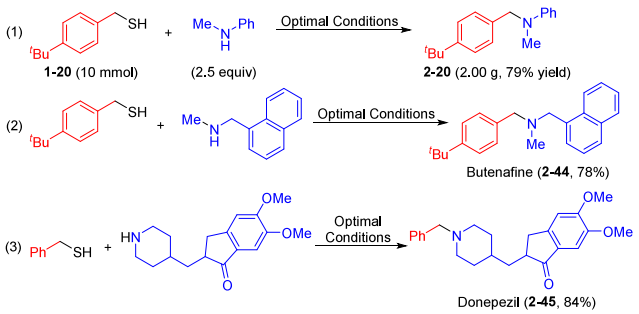
but they may still have some drawbacks. For instance, in reductive amination, the reducibility of the carbonyl group can diminish the reaction's efficiency. Similarly, in the traditional amination of alkyl halides, the resultant product is typically a mixture of alkylated derivatives, as the amination product is prone to further alkylation by alkyl halides.[19] In this regard, our protocol is quite appealing because it allows for easy access to various amines under mild conditions with convenient operations.

In addition to amine nucleophiles, other nucleophiles were also examined (Scheme 2, **2-33** to **2-43**). *N*-nucleophiles, like hydrazine and imidazole, were directly employed in the Nu-H form (**2-33** and **2-34**). For esterification and etherification, nucleophiles were used in their salt forms to increase nucleophilicity (**2-35** to **2-39**). Sodium sulfinates as nucleophiles would give sulfones (**2-40**), which are also are important structural motifs that are prevalent in diverse biologically active molecules[20] and organic reagents/intermediates.[21] For iodination, no additional iodide nucleophile was needed as the iodide anion was generated from the reaction system (**2-41**). Bromination and chlorination occurred smoothly with the use of $^{n}Bu_4N^+$ X^- (X = Cl or Br) as nucleophiles (**2-42** and **2-43**).

In order to further demonstrate the synthetic utility of this protocol, a gram-scale reaction was performed and two pharmaceuticals were synthesized by this method (Scheme 3). The gram-scale reaction was also very rapid, yielding the

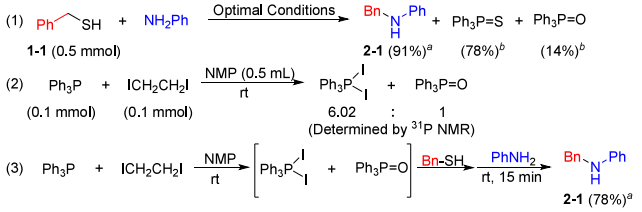
Scheme 3. A Gram-Scale Reaction and the Synthesis of Two Pharmaceuticals



desired product in just 15 min with a 79% yield (Scheme 3, eq 1). This reaction was conducted in an open flask under an air atmosphere, enhancing operational convenience. Butenafine, a medication used for the topical treatment of various fungal infections like tinea versicolor,[22] was synthesized using this desulfurization method in a good yield (Scheme 3, eq 2). Similarly, Donepezil, which is used to treat Alzheimer's-type dementia,[23] was also synthesized effectively using this protocol (Scheme 3, eq 3).

In our previous studies on dehydroxylative substitution of alcohols, we propose that mixing Ph_3P and ICH_2CH_2I together in DMF would immediately produce Vilsmeier−Haack type intermediates for activating the hydroxyl group, a process involving the conversion of Ph_3P into $Ph_3P{=}O$, where the oxygen atom originates from the DMF solvent.[11b,c] Given the structural similarities between NMP and DMF, it is conceivable that the Vilsmeier−Haack type mechanism may also apply to the desulfurization process in this work. If so, Ph_3P would predominantly be converted into $Ph_3P{=}O$, with the oxygen atom sourced from the solvent, NMP. However, we found that under the optimal conditions, Ph_3P was mostly converted into $Ph_3P{=}S$, with only a low yield of $Ph_3P{=}O$ (Scheme 4, eq 1). Apparently, the sulfur atom in $Ph_3P{=}S$

Scheme 4. Role of the Ph_3P/ICH_2CH_2I System

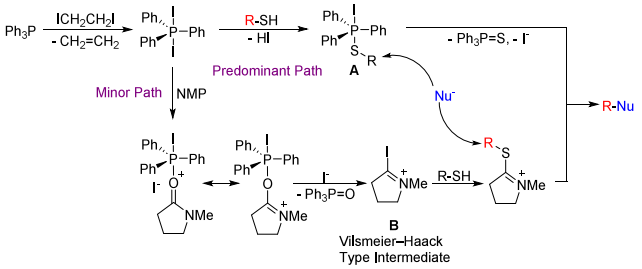


[a]The yield was determined by GC; [b]Isolated yields are shown.

comes from thiol substrate **1-1**, indicating that the Vilsmeier−Haack type intermediate is not critical in the desulfurization process. We speculated that the solvents NMP and DMF have distinctly different effects. In NMP, the immediate mixing of Ph_3P with ICH_2CH_2I resulted in the complete conversion of both compounds, similar to the case in DMF. However, in NMP, Ph_3P was converted into two identifiable phosphorus species, $Ph_3P{=}O$ and a pentacoordinate phosphorus, Ph_3PI_2, which dominates as the major phosphorus species, as confirmed by ^{31}P NMR spectroscopy (Scheme 4, eq 2). Ph_3PI_2 is stable enough to be detected by ^{31}P NMR spectroscopy in NMP, unlike in DMF where it rapidly reacts with DMF to form Vilsmeier−Haack type intermediates. After Ph_3PI_2 was produced, sequentially adding substrate Bn-SH and nucleophile $PhNH_2$ resulted in the desired product with a good yield, further suggesting that Ph_3PI_2 is a key intermediate for this desulfurization reaction (Scheme 4, eq 3).

Based on the above results, we propose the reaction mechanism shown in Scheme 5. Mixing Ph_3P and ICH_2CH_2I

Scheme 5. Proposed Reaction Mechanism



together would immediately release ethylene $CH_2{=}CH_2$ and generate the key intermediate Ph_3PI_2, a process which has been studied in our previous reports.[11] Ph_3PI_2 can effectively activate thiols by forming the P−S intermediate (**A**), which is the predominant path. The high energy of the P=S bond makes the formation of $Ph_3P{=}S$ energetically favorable, which facilitates the substitution of thiols via the cleavage of the C−S bond. Even though Ph_3PI_2 shows some stability in NMP, it may still coordinate with NMP, leading to the formation of the Vilsmeier−Haack type intermediate (**B**), which can also activate thiols for nucleophilic substitution (minor path).

In summary, we have detailed a desulfurization process for thiols promoted by Ph_3P/ICH_2CH_2I, suitable for nucleophilic substitution with a broad spectrum of nucleophiles. Notably, free amines can be employed as nucleophiles to synthesize various secondary and tertiary amines. Benzyl thiols are particularly reactive and can be completely converted at

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room temperature within 15 min. This method tolerates a wide array of functional groups, including hydroxyl groups in amination reactions. Given the widespread availability of thiols, this desulfurization approach holds significant potential for synthetic applications.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c02256.

Experimental procedures and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

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