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A Highly Chemoselective and Practical Alkynylation of Thiols

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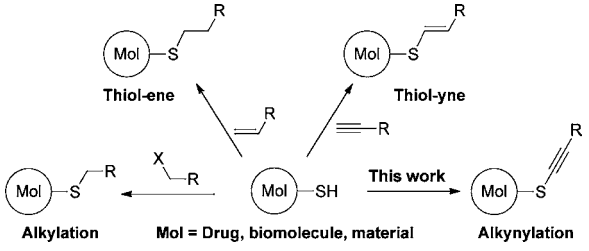
Supporting Information

ABSTRACT: A thiol-alkynylation procedure utilizing the hypervalent iodine alkyne transfer reagent TIPS-ethynyl-benziodoxolone has been developed. This scalable reaction proceeds in five minutes at room temperature in an open flask using commercially available reagents. The scope of the reaction is broad, with a variety of phenolic, benzylic, heterocyclic, and aliphatic thiols undergoing alkynylation in excellent yield. The method is highly chemoselective as a vast array of functional groups are tolerated. The utility of the thiol-alkynylation in postsynthetic elaboration has been demonstrated through the facile installment of a fluorophore tag on a cysteine-containing peptide.

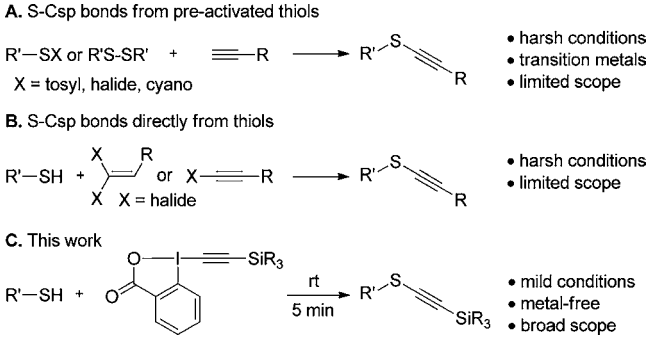
The development and implementation of highly modular reactions that provide near quantitative yields over a wide substrate range with perfect chemoselectivity have a transformational effect in areas extending from material and polymer science, to chemical biology, drug discovery, and small molecule organic chemistry. These ideal reactions should also be experimentally simple to perform, utilize readily available starting materials, be insensitive to water and oxygen, and should not require the use of expensive, sensitive, or toxic metal catalysts. Driven by the exceptional reactivity of sulfur and its importance in biology, medicine, and materials science,[1] recent research efforts targeted a series of thiol-based transformations including thiol alkylations as well as the thiol-ene and thiol-yne reaction among others (Scheme 1).[2]

Scheme 1. Thiol Functionalization for the Modification of Drugs, Biomolecules, and Materials



Unlike the well-established S-Csp[3] and S-Csp[2] bond forming processes, existing methods to construct S-Csp bonds are rare in number and often lack generality or require harsh conditions. Currently, the most common methods to form thio-alkynes require a prefunctionalization of the thiol (Scheme 2A). These methods are generally based on nucleophilic substitutions between highly reactive lithium acetylide intermediates with

Scheme 2. Previously Reported Methods for the Synthesis of Thio-Alkynes (A, B) and Our New Approach (C)



preactivated thiols or disulfide species.[3] Other methods utilize transition-metal catalysts, such as the copper-catalyzed carbon sulfur coupling between terminal alkynes and disulfides,[4] or as in the elegant study by Yamaguchi, the use of catalytic rhodium to achieve C-S bond formation by C-H and S-S bond metathesis.[5] Alternatively, a range of processes utilize alkenyl[6] or alkynyl[7] halides bearing leaving groups that undergo elimination under strongly basic conditions to furnish the desired thio-alkyne (Scheme 2B). Consequently, the limited functional group tolerance exhibited by these methods is not surprising as they require harsh conditions, proceed via highly reactive intermediates, or involve the use of sensitive catalytic systems.

The absence of a broadly applicable thiol-alkynylation process in current literature is further highlighted by the nonexistence of cysteine analogues derivatized with a terminal thio-alkyne at the side chain.[8] This motif would generate great interest as it could serve as a unique point of inception to, for instance, study post-translational modifications, install fluorophore or biotin tags for biotechnological purposes and broadly enable bioconjugation.[2a,b] In general, thio-alkynes represent an ideal platform for drug diversification in light of the versatility of existing acetylene chemistry and, in particular, the extensively used copper-catalyzed azide-alkyne cycloaddition (CuAAC)[9] as well as the privileged position of organosulfur compounds among top-selling pharmaceutical drugs.[1a] Furthermore, the development of a robust, efficient, and orthogonal thiol-alkynylation reaction is particularly attractive to the field of material and polymer science as an alternative tool to the current array of thiol-functionalization reactions.[2] In this context, we set out to investigate the feasibility of more facile and experimentally practical methods to

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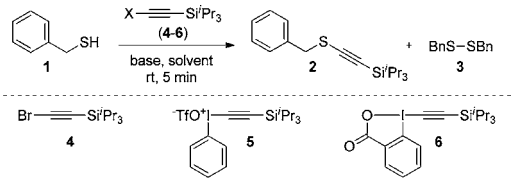
gain access to thio-alkynes, with a particular focus on silyl acetylenes as a direct gateway to the most versatile terminal alkyne (Scheme 2C).

Given the successful exploitation of hypervalent iodine alkyne transfer reagents by our group and others,[10] we speculated that these electrophilic acetylide equivalents could also be applied to the alkynylation of thiols. Unlike methods based on nucleophilic acetylide reagents, electrophilic alkynylation does not require prefunctionalization of the thiol with an activating group. We envisaged that such an umpolung strategy would have the potential to proceed efficiently under mild conditions. Indeed, the mechanism of reactions involving the addition of nucleophiles to alkynyliodonium species is known to proceed via a fast succession of conjugate addition, α-elimination of the aryliodide followed by a 1,2-shift;[11] no long-living anionic or radical intermediates are formed, which in turn could lead to a broad functional group tolerance. However, such a thiol-alkynylation approach has, to the best of our knowledge, only been reported for the reaction between bis-alkynyl iodonium salts and a phenyl thiolate anion to give bis-thioalkynes.[12] The absence of additional reports could be attributed to the oxidative properties of hypervalent iodine reagents, which may lead to the facile oxidation of thiols, resulting in undesired disulfides.

We began our study with benzylthiol (**1**) as our model substrate while screening different alkynylation reagents under mildly basic conditions (Table 1). Less reactive halogenoacetylenes, such as triisopropylsilyl ethynyl bromide (**4**), did not undergo any reaction under these conditions (entry 1). The more reactive alkynyliodonium salt **5** furnished the desired thio-alkynylation (**2**), as minor product (entry 2). Our initial reservations were confirmed as disulfide (**3**), resulting from oxidation, was identified as a major product. However, to our delight, we discovered that benziodoxolone-derived hypervalent iodine reagent 1-[(tri*iso*propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **6**) furnished **2** as the main product (entry 3). This commercially available reagent is highly practical as it is a bench stable solid allowing for simple handling and long-term storage on the multigram scale.[13] While further optimizing our lead result, we discovered that the right choice of solvent and base was crucial to minimizing formation of the undesired disulfide product. We found that 1,1,3,3-tetramethylguanidine (TMG) was superior to triethylamine and aqueous cesium carbonate or sodium hydroxide as base (entries 3–6). Similarly, we discovered that dimethyl sulfoxide (DMSO) or protic solvents, such as methanol and ethanol, produced unsatisfactory levels of the oxidation side reaction, while tetrahydrofuran (THF) was optimal (entries 6–9).[14]

Table 1. Optimization of the Alkynylation Reaction[a]



entry	4–6	base	solvent	yield 2[b]	yield 3[b]
1	**4**	NEt_3	THF	no reaction	
2	**5**	NEt_3	THF	<10%	93%
3	**6**	NEt_3	THF	51%	46%
4	**6**	NaOH	THF	74%	24%
5	**6**	Cs_2CO_3	THF	71%	26%
6	**6**	TMG	THF	>99%	–
7	**6**	TMG	DMSO	81%	15%
8	**6**	TMG	MeOH	12%	85%
9	**6**	TMG	EtOH	80%	17%

[a]Benzylthiol (**1**, 0.40 mmol), alkyne transfer reagent (**4–6**, 0.44 mmol), base (0.48 mmol), solvent (5.0 mL), 23 °C, 5 min, open flask. [b]Isolated yield of spectroscopically pure product.

Under the optimized conditions, **6** (1.1 equiv) was added in one portion to a solution consisting of the corresponding thiol (1.0 equiv), TMG (1.2 equiv), and THF at room temperature and stirred for 5 min in an open flask to give the alkynylation product **2** in quantitative yield (Scheme 3).[15] The reaction was not affected by the addition of water, which was required in some cases for thiol-substrates producing THF insoluble salts with the guanidine base.[16] If desired, the formed 2-iodobenzoic acid coproduct could also be recovered quantitatively and reused to synthesize **6**.[17] The transfer of trimethylsilyl ethyne utilizing benziodoxolone-derivative **7** was also successful, and alkynylation product **8** was obtained in 92% yield (Scheme 3A). Consequently, silyl-protected terminal alkynes with varying stability can be accessed. Due to its commercial availability, **6** was chosen to investigate the scope and limitations of this newly developed thiol-alkynylation reaction (Scheme 3).

Modulating the electronics of the benzylthiol did not change the reaction outcome as both **9** and **10**, bearing an electron-donating methoxy and an electron-withdrawing chloride groups, respectively, were obtained in excellent yields (Scheme 3A). A furan heterocycle was also well tolerated to give product **11** in 97% yield. Furthermore, a highly hydrophobic aliphatic substrate was alkynylated in quantitative yield (product **12**). In addition, aliphatic thiols bearing a hydroxy or carboxylic acid functionality underwent the thio-alkynylation reaction with comparable results (products **13** and **14**), demonstrating that the method was tolerant to nucleophilic oxygen and acidic hydrogens.

Due to the significance of aromatic thiols as important building blocks in the synthesis of natural products and pharmaceutical and medicinal compounds,[18] a range of functionalized thiophenols were then subjected to the optimized conditions (Scheme 3B). The successful formation of products **15–23** in 89–99% yield indicated that substituents, such as halides (products **16** and **17**), methoxy and hydroxy groups (products **18** and **19**), and protected and unprotected amines (products **20** and **21**) as well as carboxylic acids and esters (products **22** and **23**) were well tolerated. This broad functional group tolerance is unprecedented in the field of thiol-alkynylation. Shifting our focus to leading scaffolds of heterocyclic chemistry (Scheme 3C), thiol-substituted thiophene (product **24**), benzoxazole (product **25**), benzimidazole (product **26**), and benzothiazole (product **27**) gave the desired thiol-alkynylation products in 85–99% yields. It is noteworthy that these heterocycles are omnipresent in medicinally relevant compounds, making their facile alkynylation a valuable tool to establish a platform for further diversification.[19] Furthermore, polymers with incorporated thiophene units play a crucial role in organic electronic materials, making alkynylation product **24** a useful building block.[20]

As previously stated, a cysteine side chain derivatized with a terminal thio-alkyne has not yet been reported.[8] At the outset, it was not clear if this was due to insufficient stability or the lack of methods to access such compounds. Thus, the mild thiol-alkynylation conditions permitted by **6** appeared very promising for the functionalization of such challenging and highly important substrates. In this context, N- and C-protected cysteine derivatives were examined as starting materials (Scheme

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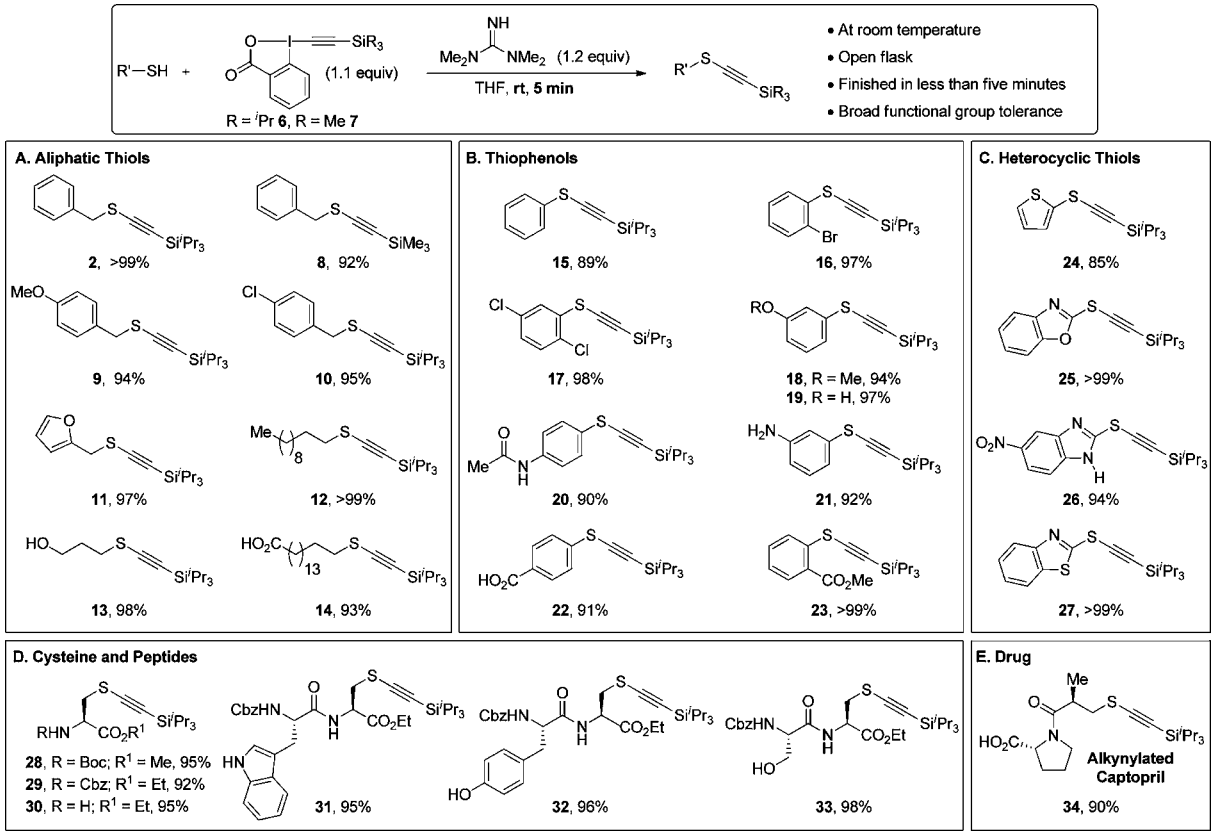
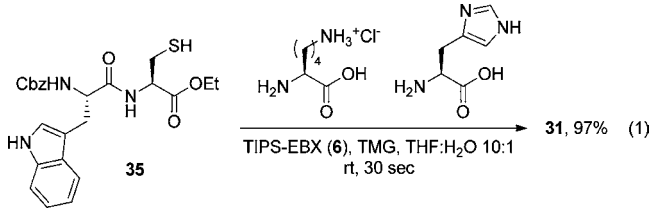
Scheme 3. Scope of the Thiol-Alkynylation Reaction



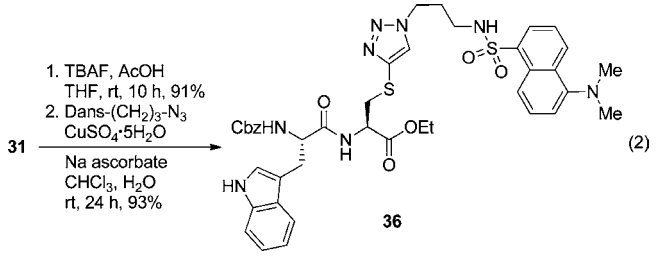
3D). We were able to isolate the corresponding alkynylated products **28** and **29** in 95% and 92% yield, respectively. Moreover, the reaction is scalable, as **28** could also be obtained in quantitative yield on the gram scale.[16] Selective alkynylation of the thiol group in the presence of a free amine also proceeded efficiently to give alkynylation product **30**, demonstrating that protection of the basic aliphatic free N-terminus of peptides is optional.

A subset of cysteine containing dipeptides was also alkynylated successfully, furnishing alkynylation products **31**–**33** in 95–98% yield. These results demonstrated that alkynylation of cysteine was possible in the presence of tryptophan, tyrosine, and serine, respectively. Finally, amino acid-derived marketed drug captopril, an important angiotensin-converting enzyme inhibitor,[21] was successfully converted to the corresponding thio-alkyne **34** (Scheme 3E). The reaction proceeded in 90% yield in the presence of the free carboxylic acid. This example demonstrated the potential utility of this new thiol-alkynylation reaction as a facile entry point to carry out drug diversification studies.

A final competition experiment was carried out to assess the extent of selectivity exhibited by **6** toward thiols (eq 1). For this purpose, unprotected L-histidine and L-lysine (amino acids bearing two of the most nucleophilic substituents present in biomolecules) along with dipeptide **35** were subjected to the optimized reaction conditions. The desired thiol-alkynylation product **31** was still obtained in 97% yield, showcasing the exceptional chemoselectivity of the developed reaction. It is also noteworthy that during the reaction scope exploration, we discovered that the thiol-alkynylation essentially takes place within 30 s upon addition of **6**, which was also the case for the competition experiment (eq 1).



To highlight the utility of the developed thiol-alkynylation process in postsynthetic elaboration of modified peptides, alkynylation product **31** was desilylated using TBAF buffered with acetic acid, furnishing the corresponding terminal alkyne in 91% yield. We found that the free cysteine-acetylene derivative was stable as demonstrated by the complete lack of decomposition observed after stirring a solution of this compound in the presence of a pH = 7 buffer for several weeks at room temperature. Furthermore, the introduction of a dansyl fluorophore was accomplished via a standard CuAAC reaction to give conjugate **36** in 93% yield.[22] To the best of our knowledge, this is the first example of a terminal thio-alkyne participating in the powerful CuAAC process.[23]



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In conclusion, we have developed an operationally practical and highly efficient thio-alkynylation reaction utilizing the electrophilic alkyne transfer reagent **6**. The mild reaction conditions and high chemoselectivity allow for the alkynylation of phenolic, benzylic, heterocyclic, aliphatic, and peptidic thiols while tolerating a vast array of functional groups. Moreover, the potential utility for postsynthetic elaboration of the obtained alkynylated products was demonstrated through the first report of a CuAAC involving a terminal thio-alkyne. The developed method not only allows a highly efficient functionalization of thiols but also provides access to unique alkynes with the potential for further derivatization. Consequently, the thiol-alkynylation presented herein has the potential to achieve a privileged position as a novel tool for various applications in synthetic chemistry, chemical biology, and material science. Ongoing research efforts are aimed at investigating the applicability of other electrophilic alkyne transfer reagents and determining the precise mechanism of this thio-alkynylation process. Further studies to uncover unprecedented applications of terminal and silyl protected thio-alkynes are also progressing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Reaction yields the same outcome under anaerobic conditions using carefully degassed solvents; details in SI.

(16) Details in SI.

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