OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

N-Alkynylthio Phthalimide: A Shelf-Stable Alkynylthio Transfer Reagent for the Synthesis of Alkynyl Thioethers

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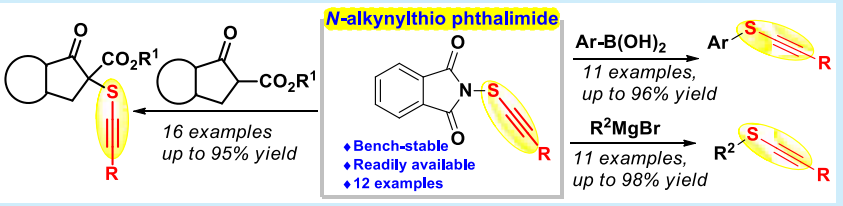
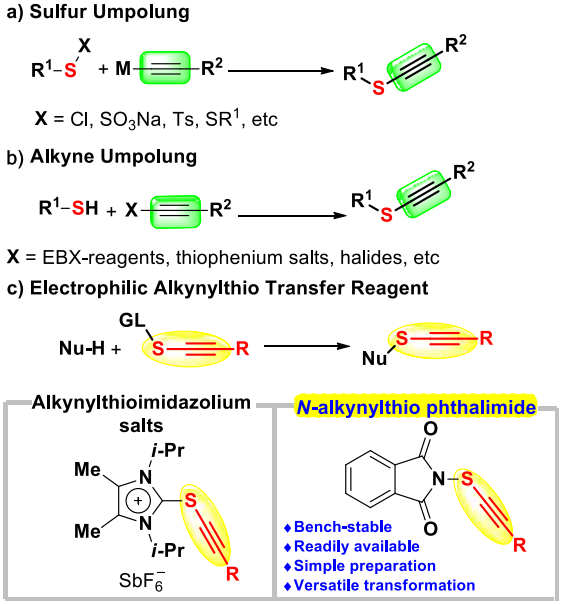
Supporting Information



ABSTRACT: A new kind of electrophilic alkynylthiolating reagent, called *N*-alkynylthio phthalimide, is designed and synthesized herein. This electrophilic sulfenylating reagent can be easily prepared in three steps from commercially available phthalimide and corresponding silver acetylide. Furthermore, the *N*-alkynylthio phthalimides are demonstrated to be efficient alkynylthio transfer reagents that can react with various C-nucleophiles, including *β*-ketoesters, aryl boronic acids, and Grignard reagents to afford a diverse range of alkynyl thioethers under mild conditions.

Development of efficient methods for introducing valuable S-containing structural units has received considerable attention because of the unique properties of sulfur in biology, medicine, and material science.[1,2] Alkynyl thioethers bearing a sulfur atom directly attached to the C−C triple bond serve as a versatile platform for many transformations at both sulfur and alkyne moieties.[3] Furthermore, the electron-rich sulfur atom allows conjugation with its lone electron pair(s) to enhance the reactivity of the C−C triple bond, thereby giving chances for new chemical transformations and the modulation of their physical properties.[4] The most commonly used strategy for the alkyne thioether synthesis is thioalkynylation, which requires both thio and alkyne partners for C−S formation.[5−7] This thioalkynylation process could be realized through direct transition-metal-catalyzed C−S coupling[5] or employing the umpolung-type strategy: one synthetic route involves the umpolung of thio groups through the reaction of terminal alkynes with preactivated thiols, such as sulfenyl chloride, disulfides, and Bunte salts (Scheme 1a);[6] until recently, the umpolung of alkynes based on the thiol alkynylation using active alkynylating reagents has attracted more attention, and alkynes have been modified to ethynyl benziodoxolone reagents,[7a,b] (alkynyl)-dibenzothiophenium triflates,[7c] and haloalkynes[7d,e] (Scheme 1b). All of these strategies focus on the C_{sp}−S bond formation, which required both S-containing compounds and alkynyl equivalents. Nevertheless, access to alkynyl thioethers from molecules without the thiol or alkynyl group remains a great challenge but is still highly desirable.

Scheme 1. Methods for the Synthesis of Alkynyl Thioethers



In the past few years, the reaction of S-electrophiles (*N*-thiosuccinimides, *N*-thiophthalimides, *N*-thiochlorides, etc.)

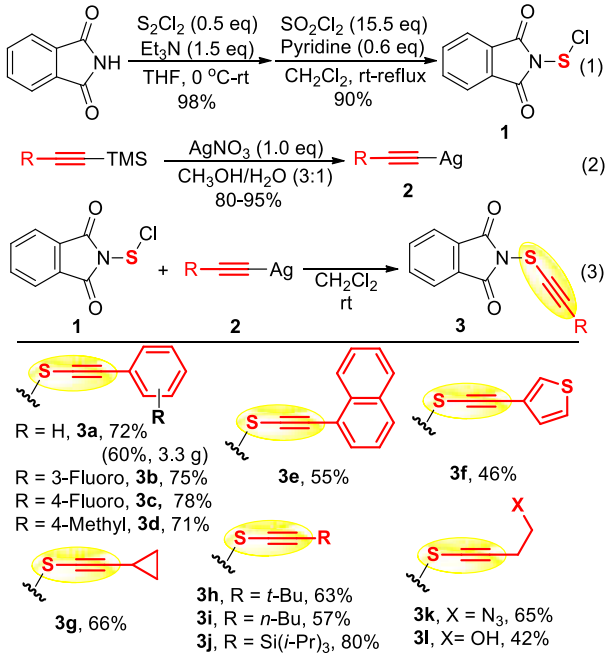
Received: June 24, 2019

DOI: 10.1021/acs.orglett.9b02174
Org. Lett. XXXX, XXX, XXX−XXX

with unactivated arene, alkene, and alkyne derivatives has been well-established and has become a powerful tool for the synthesis of various sulfides.[8] With this strategy, our group has also developed several synthetic methods for the construction of heterocyclic sulfides.[9] However, due to the π-electrophilic nature of thio cations, the compatibility of S-electrophiles with unsaturated C−C bonds still limits the development and utility of unsaturated S-electrophiles. In 2017, Alcarazo et al. prepared one kind of alkynylthioimidazolium salt, which was employed as an alkynylthio electrophile to react with a range of Grignard reagents for thioalkynylation (Scheme 1c).[10] However, the sensitive synthetic procedure and the low solubility of imidazolium salts as well as the narrow reaction scope (only with Grignard reagents) undermined their application to access valuable alkynyl thioethers in synthetic chemistry. We disclose herein a new kind of readily available and bench-stable alkynylthio electrophiles, *N*-alkynylthio phthalimides, which can serve as versatile alkynylthio transfer reagents to access a diverse range of alkynyl thioethers through the alkynylthiolation of different C-nucleophiles, such as β-keto esters, aryl boronic acids, and Grignard reagents, in which neither a thiol nor an alkynyl group is contained.

Considering the nonexistence of alkynylthiol (RC≡CSH),[11] how to obtain the alkynylthio synthetic equivalent is the first issue to address. Additionally, the alkynylthio transfer reagents are inherent electrophiles, and their compatibility with C−C triple bonds imposes another challenge in the preparation. In our design, a convergent synthetic route from an alkynyl equivalent and a thio cation precursor was alternatively employed for the synthesis of *N*-alkynylthio phthalimides **3**. Reagent **3** was precisely prepared from the reaction of silver acetylide **2** and *N*-(chlorosulfenyl)phthalimide **1** through an ion-exchange strategy (Scheme 2) to avoid the interaction of the π-bond of triple bonds with thio electrophiles. Both **1** and **2** could be accessed from commercially available starting materials in one or two steps.[12] Notably, the reaction can be readily scaled up to 20 mmol to afford *N*-alkynylthio reagent **3a** in 60% yield. A range of functional groups, including substituted phenyl rings (**3a**−**d**), 1-naphthyl ring (**3e**), 3-thienyl ring (**3f**), and cyclopropyl ring (**3g**), were well-tolerated in this reaction, and the desired reagents were produced in moderate to good yields. Furthermore, not only the chain alkynylthio phthalimides **3h** and **3i** but also the alkynylthio reagents bearing a terminal siliyl, azide, or hydroxy group could be successfully prepared in moderate to good yields (**3j**−**l**), opening up more opportunities for further derivation. The single crystal of *N*-phenylethynylthio phthalimide **3a** was obtained in the MeCN solvent, and the exact structure of *N*-alkynylthio reagent **3** was unambiguously confirmed (Figure 1).

Scheme 2. Preparation of *N*-Alkynylthio Phthalimides



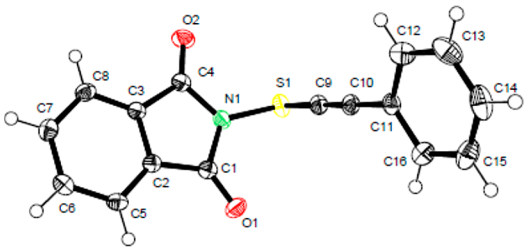
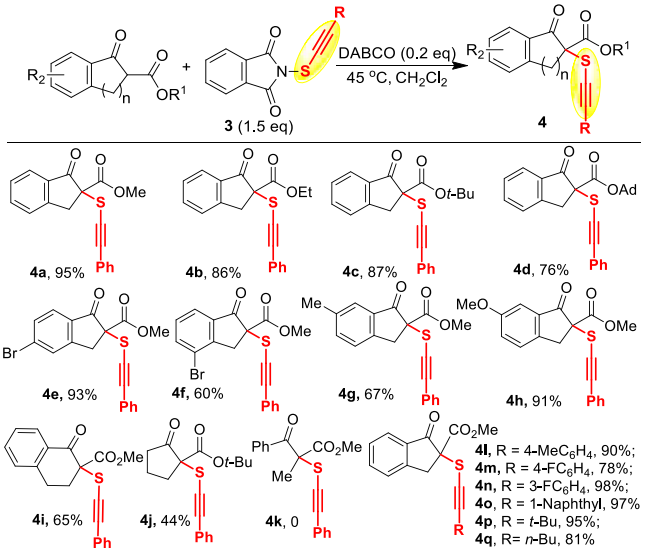


Figure 1. ORTEP drawing of **3a**; ellipsoids shown at a 50% probability level.

With a series of *N*-alkynylthio phthalimides **3** in hand, we first explored its reactivity with soft nucleophiles to accomplish the α-alkynylthiolation of β-keto esters. Methyl 1-indanone-2-carboxylate was selected as a model substrate to explore the reaction conditions for the α-alkynylthiolation of the β-keto esters. The reaction of 1-indanone-2-carboxylate with 1.5 equiv of **3a** in the presence of 0.2 equiv of DABCO could smoothly proceed at 45 °C to provide the desired product **4a** in 95% yield (please see Table S1 in the Supporting Information for details). A range of β-keto esters and *N*-alkynylthio phthalimides were subsequently examined for this transformation under the optimal conditions (Scheme 3). Different esters, including methyl, ethyl, *tert*-butyl, and 1-adamantyl, could be well-tolerated in this reaction.

Scheme 3. Substrate Scope for α-Alkynylthiolation of β-Keto Esters[a]



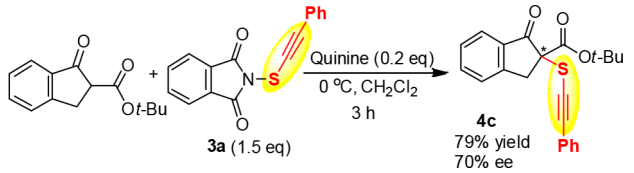
[a]Reaction conditions: β-keto esters (0.1 mmol), **3** (0.15 mmol), DABCO (0.02 mmol) in CH_2Cl_2 (1 mL) stirred at reflux for 2−4 h.

DOI: 10.1021/acs.orglett.9b02174
Org. Lett. XXXX, XXX, XXX−XXX

Moreover, the corresponding α-alkynylthio products were obtained in good to excellent yields (**4a–d**). Substrates with electron-withdrawing or -donating functional groups on the phenyl ring of the indanone moiety were also well-accommodated (**4e–h**), delivering the desired products in moderate to excellent yields. Notably, the β-keto esters derived from α-tetralone or cyclopentanone were also good substrates for this transformation, affording their corresponding products **4i** and **4j** in moderate yields. However, the reaction of **3a** with the noncyclic keto ester could not provide the desired product **4k** under the standard conditions. In addition, various *N*-alkynylthio phthalimides **3** derived from either aliphatic or aromatic alkynes were investigated. All of the reactions smoothly proceeded to give the α-alkynylthiolation products in good to excellent yields (**4l–q**).

Several known S-electrophiles have recently been used for the catalytic enantioselective construction of sulfur-containing carbon stereocenters.[13] Inspired by this progress, we explored the enantioselective α-alkynylthiolation of β-keto esters of four commercially available cinchona alkaloids (i.e., cinchonine, cinchonidine, quinine, and quinidine). Notably, with *tert*-butyl 1-indanone-2-carboxylate as the substrate, the asymmetric α-alkynylthiolation could be achieved in 79% yield with 70% enantioselectivity using quinine as the chiral catalyst (Scheme 4).

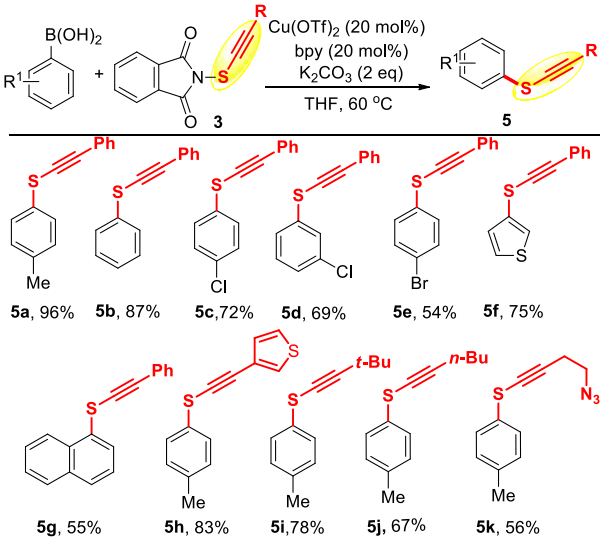
Scheme 4. Enantioselective α-Alkynylthiolation of *tert*-Butyl 1-Indanone-2-carboxylate



As one kind of representative and commercially available C-nucleophile, boronic acids have been widely used in C–S coupling reactions. Reaction of **3** with boronic acids was then explored herein to prepare the unsymmetrical aryl alkynyl sulfides (Scheme 5). With the *p*-tolylboronic acid as the model substrate, product **5a** was provided in 96% yield in the presence of 20 mol % of CuI, 20 mol % of bipyridine (bpy), and 2 equiv of K_2CO_3 in THF at 60 °C (see Table S2 in the Supporting Information for details). A series of aryl boronic acids with *ortho*-, *meta*-, or *para*-substituents were able to react with **3a** to afford the corresponding aryl alkynyl sulfides in moderate to excellent yields (**5a–e**). Additionally, 1-naphthyl and 3-thienyl rings could also be well-tolerated in this system (**5f** and **5g**). Other alkynylthio electrophiles were also tested, and functional groups, including thienyl, *tert*-butyl, and azide groups, could be very compatible in this coupling reaction (**5h–k**), providing more chances for further elaboration. The known Alcarazo reagents were also used to transform an alkynylthio group to β-keto esters and boronic acids, whereas alkynylation, instead of thioalkynylation, occurred as the main pathway (please see Scheme S1 in the Supporting Information for details).

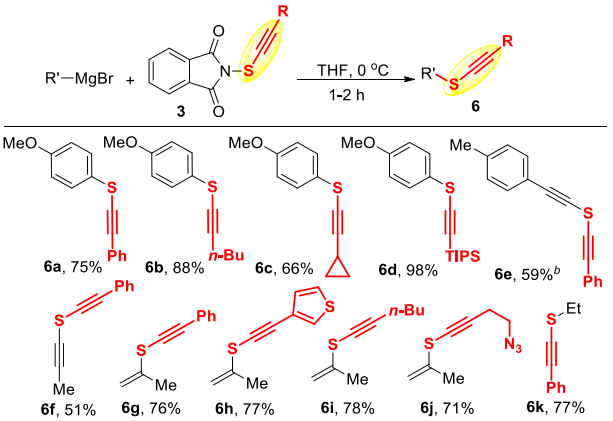
Reaction of *N*-alkynylthio phthalimides with Grignard reagents was subsequently investigated to further expand the synthetic application of reagent **3**. As shown in Scheme 6, various Grignard reagents, including aryl (**6a–d**), alkynyl (**6e–f**), alkenyl (**6g–j**), and alkyl (**6k**), could couple with the alkynylthio reagents to give the corresponding alkynyl thioethers bearing different functional groups in good to excellent yields. The

Scheme 5. Substrate Scope for Cu-Catalyzed Alkynylthiolation of Boronic Acids[a]



[a]Reaction conditions: aryl boronic acid (0.1 mmol), **3** (0.15 mmol), $Cu(OTf)_2$ (20 mol %), 2,2′-bipyridine (20 mol %), and K_2CO_3 (0.2 mmol) in THF (1 mL) at 60 °C for 2–4 h.

Scheme 6. Substrate Scope for Alkynylthiolation of Grignard Reagents[a]



[a]Reaction conditions: Grignard reagent (0.5 M in THF, 0.15 mmol), **3** (0.15 mmol) in THF (1 mL) at 0 °C for 1–2 h. [b]0.2 mmol of (*p*-tolylethynyl)lithium is used instead.

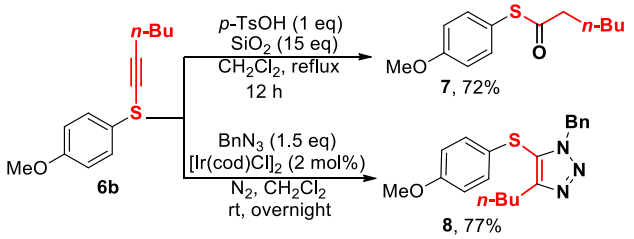
advantage of the present transformation is remarkable because the access to alkynyl–alkynyl thioethers and alkenyl–alkynyl thioethers is a great challenge using other conventional methods.[14]

The resulting alkynyl thioethers could accomplish a series of functionalizing transformations. For example, alkynyl thioether **6b** easily obtained from the reaction of **3a** with 4-methoxyphenylmagnesium bromide could be either transformed to the corresponding thioester **7** under acid hydrolysis or reacted with benzyl azide to furnish the fully substituted 5-thio-1,2,3-triazole **8** through iridium-catalyzed azide–alkyne cycloaddition reaction (Scheme 7).[4b]

In summary, a new kind of electrophilic sulfenylating reagent, called *N*-alkynylthio phthalimide, was developed herein for direct alkynylthiolation. Reagent **3** was bench-stable, easily activated, and readily prepared in three steps from commercially

DOI: 10.1021/acs.orglett.9b02174
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 7. Derivation of Product 6b



available materials. The alkynylthiolation of β-keto esters, boronic acids, and Grignard reagents was well-established by employing the present alkynylthiolating reagents. Furthermore, the enantioselective α-alkynylthiolation of β-keto esters was preliminarily realized using reagent **3a** catalyzed by a natural alkaloid quinine. Transformation of alkynyl thioethers to synthetically useful molecules, such as thioester and 5-thio-1,2,3-triazole, was also demonstrated. Efforts toward biological application with the developed alkynylthio reagents are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02174.

Experimental procedures, optimization tables, crystal structure of **3a**, and the corresponding data and characterization data for all of the products (PDF)

Accession Codes

CCDC 1916070 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support from the Key Research and Development Program of Shanxi Province (International Cooperation) (No. 201803D421093) and China Postdoctoral Science Foundation (No. 2019M651424).

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