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## Accepted Article

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# Sulfur Incorporation using Disulfanes as the Sulfur Atom Source Enabled Metal-free Heteroannulation of 1,7-Enynes

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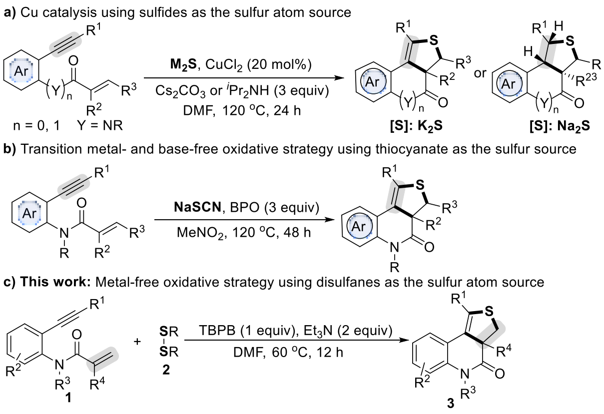
**Abstract:** A new oxidative [2+2+1] heteroannulation of 1,7-enynes with disulfanes promoted by $Et_3N$, producing 3,3*a*-dihydro-thieno[3,4-c]quinolin-4(5*H*)-ones, is described. This reaction is achieved by using equivalent amounts of 1,7-enynes, sulfur atoms (disulfanes), *tert*-butyl peroxybenzoate (TBPB) as an oxidant and $Et_3N$ as the base, and represents an unprecedented strategy to applications of disulfanes as sulfur atom sources in synthesis.

**Keywords:** enynes; disulfanes; heterocycles; oxidant; heteroannulation

Sulfur-containing heterocycles, including thiophene-fuse polyheterocycles, are a class of important organosulfur compounds found in pharmaceuticals, agrochemicals, natural products and functional materials.[1] Additionally, they are versatile building blocks in synthesis.[1] Accordingly, the development of sustainable and efficient methods for sulfur-containing heterocycle framework construction is important and remains an ongoing target of the synthetic community.[1,2] In particular, the annulation cascades of unsaturated molecules that directly incorporated sulfur atoms across the unsaturated bonds have proven to be among the most powerful and straightforward strategies.[2] Although tremendous progress has been documented in the field,[2] examples for the annulation with unsaturated bonds, especially including 1,*n*-enynes, toward thiophene-fuse polyheterocycles through sulfur site-selective incorporation are less abundant and still remain a challenge.[3] Moreover, there have been no report on the use of commercially available disulfanes as the sulfur atom source via the cleavage of the C-S bond and S-S bond for the synthesis of sulfur-containing heterocycles. Recently, our group[3a] employed metal sulfides as the sulfur atom source to achieve a Cu-catalyzed [2+2+1] heteroannulation of 1,7-enynes in the presence of the $Cs_2CO_3$ base via a radical process, where the chemoselectivity toward 3,3*a*-dihydro-thieno[3,4-*c*]quinolin-4(5*H*)-ones and 1,3,3*a*,9*b*-tetrahydrothieno[3,4-*c*]quinolin-4(5*H*)-ones relied on metal sulfides (Scheme 1a). The Hao, Tu and Jiang group has reported a copper catalysis combined with the $^i Pr_2NH$ base that enabled [2+2+1] heteroannulation of 1,6-enynes with $K_2S$[3b] leading to arylated indeno[1,2- *c*]thiophenes (Scheme 1a). Very recently, we demonstrated a oxidative strategy[3c] for the [2+2+1] heteroannulation of 1,7-enynes with NaSCN that serves as the sulfur atom source under transition-metal- and base-free conditions (Scheme 1b). In addition to the requirement of high loadings of Cu catalysts or excess amounts of oxidants, all of these syntheses rely strongly on the use of both a high temperature (120 °C) and an excess amount of sulfur-containing metal salts that form undesired metal-based byproducts, thereby compromising their synthetic applications.[3] Thus, mild, ideal strategies that proceed using equivalent amounts of reaction components would be desirable.

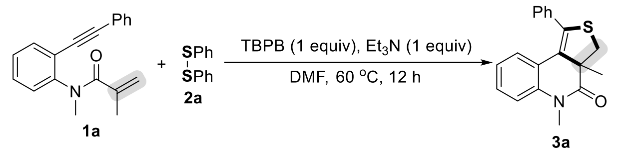


**Scheme 1.** Heteroannulation of 1,*n*-Enynes.

Herein, we report a base-promoted oxidative strategy for [2+2+1] heteroannulation[4-6] of 1,7-enynes with disulfanes for producing 3,3*a*-

dihydrothieno[3,4-*c*]quinolin-4(5*H*)-ones, in which disulfanes serve as the sulfur atom sources (Scheme 1c). This reaction provides an unprecedented strategy to applications of disulfanes in synthesis, and features (i) oxidative cycloaddition with equivalent amounts of 1,7-enynes, sulfur atoms (disulfanes), *tert*-butyl peroxybenzoate (TBPB) oxidant and $Et_3N$ base, (ii) avoidance of the use of excess sulfur-containing metal salts, (iii) excellent levels of selectivity, and mild (60 °C) conditions.

**Table 1.** Optimization of the Reaction Conditions[a]

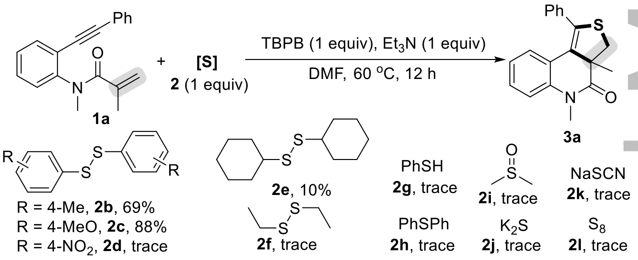


| Entry | Variation from the optimal conditions | Yield [%][b] |
|---|---|---|
| 1[c] | none | 90 |
| 2 | without TBPB | 0 |
| 3 | TBPB (0.5 equiv) | 84 |
| 4 | TBPB (2 equiv) | 89 |
| 5 | BPO instead of TBPB | 77 |
| 6 | DTBP instead of TBPB | 10 |
| 7 | TBHP instead of TBPB | 88 |
| 8 | without $Et_3N$ | 31 |
| 9 | $Et_3N$ (2 equiv) | 90 |
| 10 | pyridine instead of $Et_3N$ | 81 |
| 11 | DBU instead of $Et_3N$ | 82 |
| 12 | $K_2CO_3$ instead of $Et_3N$ | 72 |
| 13 | MeCN instead of DMF | 43 |
| 14 | 1,4-dioxane instead of DMF | 74 |
| 15 | at 80 °C | 91 |
| 16 | at 40 °C | 48 |
| 17[d] | none | 93 |
| 18[e] | none | 88 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.16 mmol), TBPB (1 equiv), $Et_3N$ (1 equiv), DMF (2 mL), 60 °C and 12 h under air or agron atmosphere. [b] Isolated yield. [c] Some by-products, including benzenethiol and diphenylsulfane, were determined by GC-MS analysis. [d] **2a** (0.1 mmol). [e] **1a** (1 mmol) and 36 h.

We started our investigations with the use of *N*-methyl-*N*-(2-(phenylethynyl)phenyl)methacrylamide (**1a**) and 1,2-diphenyldisulfane (**2a**) as the heteroannulation reaction partners in the presence of oxidants (Table 1). Gratifyingly, treatment of enyne **1a** with 0. 8 equiv of disulfane **2a**, 1 equiv of TBPB and 1 equiv of $Et_3N$ in DMF at 60 °C for 12 h generated the desired product **3a** in 90% yield (entry 1). Use of TBPB is crucial as its omission resulted in no reaction (entry 2). Screening the loadings of TBPB showed 1 equiv as the best choice (entries 1, 3 and 4).Other peroxides, such as benzoylperoxide (BPO), di-*tert*-butylperoxide (DTBP) and *tert*-butyl hydroperoxide (TBHP; 6 M in decane), displayed reactivity, and they were less effective than TBPB (entries 5-7). The reaction could occur in the absence of $Et_3N$, albeit with a lower yield (entry 8). The results demonstrated the role of $Et_3N$ as a promoter. A higher loading of $Et_3N$ had no improvement on the yield (entry 9). Other bases, including pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and $K_2CO_3$, could also be used to improve the reaction, but all of them were inferior to $Et_3N$ (entries 10-12). Among the examined solvents and reaction temperatures, a combination of DMF with 60 °C was optimal (entries 13-16). It was noted that the reaction proceeded smoothly when using an equivalent amount of sulfur atoms (0.5 equiv of disulfane **2a**), giving **3a** in 93% yield (entry17). Pleasingly, the reaction scaled up to a 1 mmol scale of enyne **1a** and afforded **3a** in 88% yield after prolonging the reaction time (entry 18).

As shown in Scheme 2, a variety of disulfanes **1b-k** that serve as the sulfur atom sources were evaluated under the optimal reaction conditions. In the presence of TBPB and $Et_3N$, 1,2-di-*p*-tolyldisulfane (**2b**), 1,2-bis(4-methoxyphenyl)disulfane (**2c**) and 1,2-dicyclohexyldisulfane (**2e**) could execute the heteroannulation reaction, and led to the formation of **3a** in 69%, 88% and 10% yields, respectively. However, other sulfur-containing substrates, including 1,2-bis(4-nitrophenyl)disulfane (**2d**), 1,2-diethyldisulfane (**2f**), benzenethiol (**2g**), diphenylsulfane (**2h**), dimethyl sulfoxide (**2i**), $K_2S$ (**2j**), NaSCN (**2k**) and $S_8$ (**2l**), showed no reactivity.

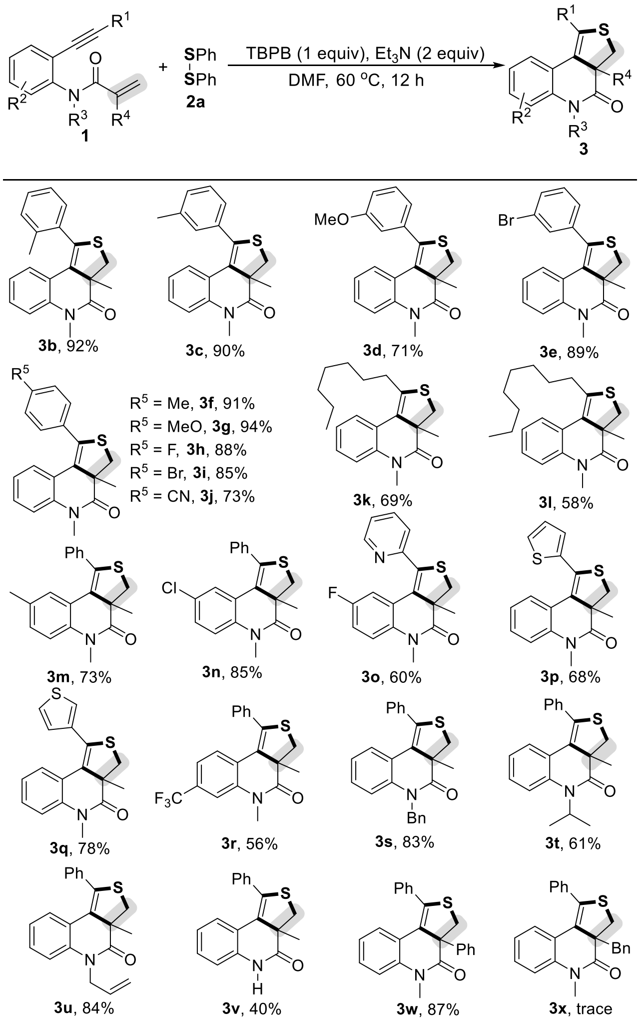


**Scheme 2.** Variation of the Sulfur Sources (**2**).

We next explored the generality of this heteroannulation reaction with 1,7-enynes **1** in the presence of disulfane **2a**, TBPB and $Et_3N$ (Table 2). Initially, the substitution effect at the terminal alkyne of enynes **1b-o** was examined (Products **3b-o**). We found that a series of substituents, including Me, MeO, Br, F and CN, on the aryl ring at the terminal alkyne were inert, thereby producing **3b-j** smoothly in good to excellent yields. The substituent position on the aryl ring had no distinct effect on the reactivity: enynes **1b-c**, **1f** bearing a Me group in the *ortho*, *meta* or *para* position delivered **3b-c**, **3f**, respectively in 90-92% yields. However, enyne **1j** containing a strong electron-withdrawing CN group led to a decrease in the yield (**3j**). Interestingly, tolerance of halogen atoms (e.g., Br, F) provides the chance for transformations of the functional groups (**3e, 3h, 3i**). Notably, enynes **1k-l** bearing an alkyl group at the terminal alkyne were accommodated to the construction of **3k-l**.

A number of substituents, namely, Me, Cl, F and $CF_3$, on the *N*-aryl moiety all were well tolerated, giving the desired products **3m-r** in good yields. Importantly, pyridin-2-yl alkyne **1o** possessing an F group on the *N*-aryl ring was suitable for accessing **3o** in 60% yield. Noatbly, thiophen-2-yl alkyne **1p** and thiophen-2-yl alkyne **1q** were also suitable for this reaction conditions, and provided products **3p** and **3q** in 68% and 78% yields, respectively. High reactivity was also obtained using benzyl, allyl or isopropyl groups to replace the *N*-methyl group, offering **3s-u** in good yields. For enyne **1v** having an N-H free group the reaction proceeded successfully, albeit with a lower yield (**3v**). Replacement of Me by Ph at 2 position of the acrylamide moiety was viable for the formation of **3w** in 87% yield. However, 2-benzyl-*N*-methyl-*N*-(2-(phenylethynyl)phenyl)acrylamide **1x** could not convert to the corresponding product **3x** under this conditions.

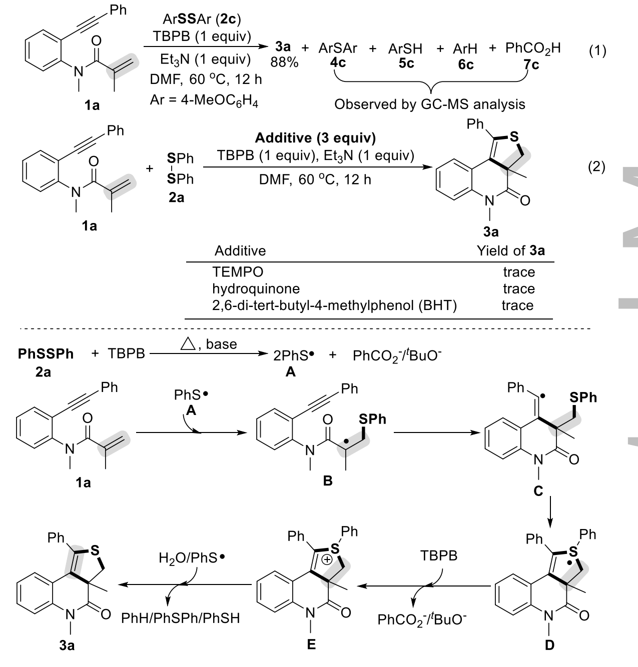
**Table 2.** Variation of the 1,7-Enynes (**1**)[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), TBPB (1 equiv), $Et_3N$ (1 equiv), DMF (2 mL), 60 °C and 12 h.

To understand the mechanism for the heteroannulation reaction, some control experiments were carried out [Eq (1); Scheme 3]. We found that a series of by products, such as ArSSAr (Ar = 4-$MeOC_6H_4$), ArSH, ArH and $PhCO_2H$, were observed from the reaction between enyne **1a** with disulfane **2c** [Eq (1)]. We found that this reaction was completely inhibited in the presence of radical inhibitor reagents, such as TEMPO, hydroquinone and BHT, which suggested a free radical pathway [Eq (2)].

On the basis of the current results and the previous works,[2-6] the possible mechanism for the heteroannulation protocol was proposed as shown in Scheme 3. The PhS· radical **A** is readily generated through single electron transfer (SET) between PhSSPh **2a** and TBPB in the presence of base under heating.[4-6] Addition of the PhS· radical **A** across the C=C bond of enyne **1a** delivers the vinyl radical intermediate **B**, followed by cyclization to form the intermediate **C**[6]. The intermediate **C** undergoes annulation to access the intermediate **D** that subsequently carries out a single electron oxidation by TBPB[4-6] and the S-C($sp^2$) bond cleavage to afford the desired product **3a**.



**Scheme 3.** Control Experiments and Possible Mechanism.

In conclusion, the first example of using disulfanes as the sulfur atom sources for the synthesis of 3,3*a*-dihydrothieno[3,4-*c*]quinolin-4(5*H*)-ones via 1,7-enyne oxidative [2+2+1] heteroannulation reaction has been successfully developed. By employing a TBPB oxidant and an $Et_3N$ promoter, the method proceeds efficiently under metal-free conditions, and enables the formation of three new bonds, two C-S bonds and one C-C bond, with high chemo- and regio-control. A wide range of functional groups can be tolerated and a non-metal sulfur atom source can be efficiently used, thereby making this current strategy highly valuable for the construction of useful complex sulfur-containing heterocycles.

## Experimental Section

### General Considerations:

The $^{1}$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ solvents on an NMR spectrometer using TMS as the internal standard. LRMS was performed on a GC-MS instrument. HRMS was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

### Typical Experimental Procedures

**Typical Experimental Procedure for the Oxidative Heteroannulation Reaction of 1,7-Enynes (1) and Diphenyl disulfide (2a):** To a Schlenk tube were added 1,7-enynes **1** (0.2 mmol), diphenyl disulfide **2a** (0.1 mmol), TBPB (1 equiv), $Et_3N$ (1 equiv), and DMF (2 mL). Then the tube was charged with argon and was stirred at 60 $^{o}$C (oil bath temperature) for the indicated time (approximately 12 h) until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted in EtOAc (15 mL), and washed with brine (3×5 mL）. The aqueous phase was re-extracted with EtOAc (3×10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to afford the desired product **3**.

## Acknowledgements

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## COMMUNICATION

### Sulfur Incorporation using Disulfanes as the Sulfur Atom Source Enabled Metal-free Heteroannulation of 1,7-Enynes

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

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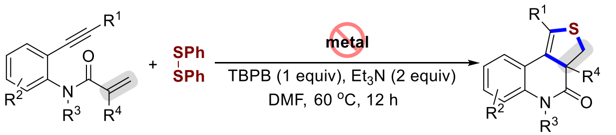

*24 examples of enynes, up to 94%*