

Nitric Acid Promoted Metal-Free Bromothiolation of Internal Alkynes with Hydrobromic Acid and Disulfides

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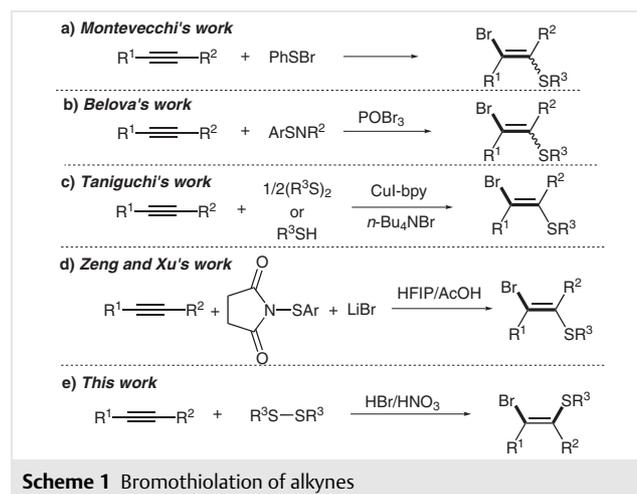
Abstract A novel, metal-free bromo-thiolation of internal alkynes with hydrobromic acid and disulfides has been developed. The reaction is promoted by commercial-grade nitric acid and is used to construct a series of unexplored β -bromoalkenyl sulfides in moderate to good yield. Most products were obtained with high stereoselectivity as *syn*-configured tetrasubstituted alkenes. Both sulfide groups of the disulfide reagent were used in this method.

Key words bromo-thiolation, internal alkynes, hydrobromic acid, disulfides, nitric acid, β -bromoalkenyl sulfides, *syn*-configuration

Alkenyl sulfides are widely utilized as versatile building blocks¹ and key components in the synthesis of many natural products and biologically active molecules.² Consequently, new effective synthetic methods for these convenient intermediates has attracted much attention,³ especially for β -haloalkenyl sulfides, which are easily converted into various alkenes and alkynyl sulfides as coupling partners in nucleophilic substitutions and transition-metal-catalyzed cross-coupling reactions.⁴ Since the original work reported by Modena's group,⁵ numerous methods have been developed to prepare a variety of β -haloalkenyl sulfides, including chloro,⁶ bromo,⁷ and iodo⁸ groups. However, approaches that can be used to access β -bromoalkenyl sulfides have been less extensively investigated.⁹

Typically, β -bromoalkenyl sulfides are synthesized by bromo-thiolation of alkynes using different sulfonylating agents (Scheme 1a–d). Montevecchi and co-workers realized the addition of sulfonyl bromine to alkynes in 1993.^{7a} Belova's group developed the reactions of alkynes and sulfonamides activated by phosphorus oxohalides (POCl₃, POBr₃).^{7b} Subsequently, Taniguchi reported copper-catalyzed addition of halides and sulfide groups to alkynes utilizing

disulfides and thiols.^{7c,d} Recently, Zeng and Xu's group developed a regio- and stereoselective halothiolation of alkynes using lithium halides (Br, Cl, I) and *N*-thiosuccinimides as starting materials.^{7f} Nevertheless, the products of these strategies were *anti*-configured, while the other *syn*-additive isomers come out as byproducts. Moreover, terminal and dialkyl alkynes are more tolerant to these preparations, and diaryl acetylenes are not so compatible. Furthermore, some of them suffer from the disadvantages of requiring metal catalysts and unstable sulfonylating agents, which are hard to transfer to an industrial scale. Therefore, the development of metal-free catalyzed, easy-to-handle, stereo- and regioselective synthetic methods for *syn*-configured bromoalkenyl sulfides remains a significant and challenging task.

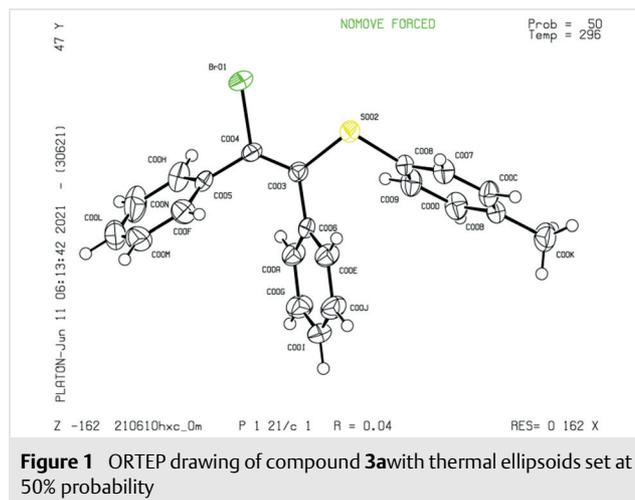


Scheme 1 Bromothiolation of alkynes

Herein, we present a method for direct bromo-thiolation of internal alkynes using hydrobromic acid (40% aqueous solution) and disulfides, only promoted by commercial-

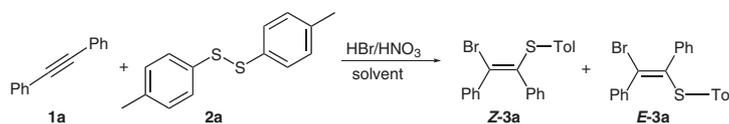
grade nitric acid (65% aqueous solution) (Scheme 1e). The reported reaction can selectively afford the corresponding *syn*-configured tetrasubstituted alkenes containing two good leaving groups, a thiolate and a bromide, and uses both sulfide groups of the disulfide reagent. Notably, the method can be scaled up to gram-scale with no loss in yield.

Initially, we chose the reaction of diphenylacetylene (**1a**) and *p*-toyl disulfide (**2a**) as the model, given that the *Z/E* ratio of the corresponding product can be determined by ¹H NMR analysis more clearly (Table 1). It should be noted that the reaction did not occur in the absence of HNO₃, which suggested that HNO₃ played an important role in this transformation (entry 1). Screening of solvents showed that the solvent was crucial to the transformation (entries 2–6). CH₂Cl₂ proved to be the best option and improved both the yield and *Z/E* selectivity significantly (entry 3), whereas the use of either THF or DMSO did not produce **3a** at all (entries 5 and 6). NaBr and NH₄Br could also be used as bromine sources with excellent selectivity, while TBAB did not work (entries 7–9). When HNO₃ was replaced with H₂SO₄ and HClO₄, only a trace amount of product could be detected by



GC-MS (entries 10 and 11). Lower and higher temperature resulted in poor yield of the product (entries 12 and 13). In addition, when the amounts of HNO₃ and HBr were decreased to 0.25 equiv and 5.0 equiv, respectively, the prod-

Table 1 Optimization of reaction conditions^a



Entry	[Br] (equiv)	Additive (equiv)	Solvent	Yield (%) ^b	<i>Z/E</i> ^c
1	HBr (10.0)	–	DCE	0	–
2	HBr (10.0)	HNO ₃ (0.5)	DCE	50	40:60
3	HBr (10.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	91	99:1
4	HBr (10.0)	HNO ₃ (0.5)	CHCl ₃	28	50:50
5	HBr (10.0)	HNO ₃ (0.5)	THF	0	–
6	HBr (10.0)	HNO ₃ (0.5)	DMSO	0	–
7	NaBr (10.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	26	99:1
8	NH ₄ Br (10.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	22	99:1
9	TBAB (10.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	0	–
10	HBr (10.0)	H ₂ SO ₄ (0.5)	CH ₂ Cl ₂	trace	–
11	HBr (10.0)	HClO ₄ (0.5)	CH ₂ Cl ₂	trace	–
12 ^d	HBr (10.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	50	38:62
13 ^e	HBr (10.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	trace	–
14	HBr (10.0)	HNO ₃ (0.25)	CH ₂ Cl ₂	80	86:14
15	HBr (5.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	67	72:28
16 ^f	HBr (10.0)	HNO ₃ (0.5)	CH ₂ Cl ₂	88	91:9

^a Reaction conditions: **1a** (0.40 mmol), **2a** (0.22 mmol), mixture of HBr and HNO₃, solvent (4 mL), under air, 40 °C, 8 h.

^b Isolated yield.

^c *Z/E* ratio determined by ¹H NMR analysis.

^d At 20 °C.

^e At 60 °C for 1 h.

^f **1a** (4.0 mmol), **2a** (2.2 mmol), solvent (30 mL), 6 h.

uct yield and selectivity decreased to 80% (*Z/E*: 86/14, entry 14) and 67% (*Z/E*: 72/28, entry 15). To our delight, the reaction could be scaled up to 4.0 mmol, and 1.3 g **3a** (88%) was isolated with only slightly loss in selectivity (*Z/E*, 91:9, entry 16 and the Supporting Information).

To confirm the configuration of (*Z*)-**3a** unambiguously, the product was purified by using column chromatography and analyzed by single-crystal X-ray crystallography (Figure 1).

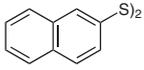
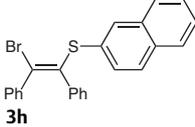
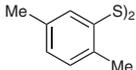
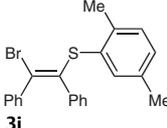
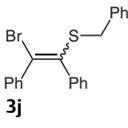
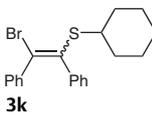
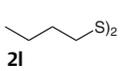
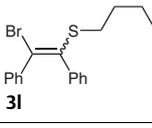
With the optimized conditions in hand, various disulfides were applied in the reaction to establish the scope of this protocol (Table 2). The results disclosed that numerous combinations of diaryl or dialkyl disulfides and diphenylacetylene (**1a**) could produce the corresponding β -bromoalkenyl sulfides in moderate to excellent yields. In gen-

eral, diaryl disulfides afforded a higher yield and had good *syn*-selectivity (entries 1–8); however, a strong electron-donating group (OMe) adversely affected the regioselectivity (entry 2). Lower yields were observed when *ortho*-substituted substrates were used as coupling partner, because of increased steric hindrance. For example, **2e**, **2g**, and **2i**, bearing an *o*-fluoro, *o*-bromo, and *o*-methoxy group, respectively, reacted with **1a** to give desired products in 78, 67, and 53% yield (entries 4, 6, and 8). Regrettably, dialkyl disulfides showed lower reactivity and selectivity. When dibenzyl and dicyclohexyl disulfides participated in the reaction, yields and *Z/E* ratio decreased to 77% (50:50) and 60% (33:67), while a substrate with a *n*-dibutyl substituent gave the product in 43% yield (entries 9–11).¹⁰

Table 2 Scope of Disulfides for the Synthesis of β -Bromoalkenyl Sulfides^a

Entry	Disulfide 2	Product 3	Yield (%) ^b (<i>Z/E</i>) ^c
1			90 (99:1)
2			88 (83:17)
3			82 (99:1)
4			78 (99:1)
5			84 (99:1)
6			67 (99:1)

Table 2 (continued)

Entry	Disulfide 2	Product 3	Yield (%) ^b (<i>Z/E</i>) ^c
7	 2h	 3h	71 (99:1)
8	 2i	 3i	53 (99:1)
9	 2j	 3j	77 (50:50)
10	 2k	 3k	60 (33:67)
11	 2l	 3l	43 (61:39)

^a Reaction conditions: **1a** (0.40 mmol), **2** (0.22 mmol), mixture of HBr (4.0 mmol) and HNO₃ (0.2 mmol), in CH₂Cl₂ (4 mL), under air, 40 °C, 8 h.

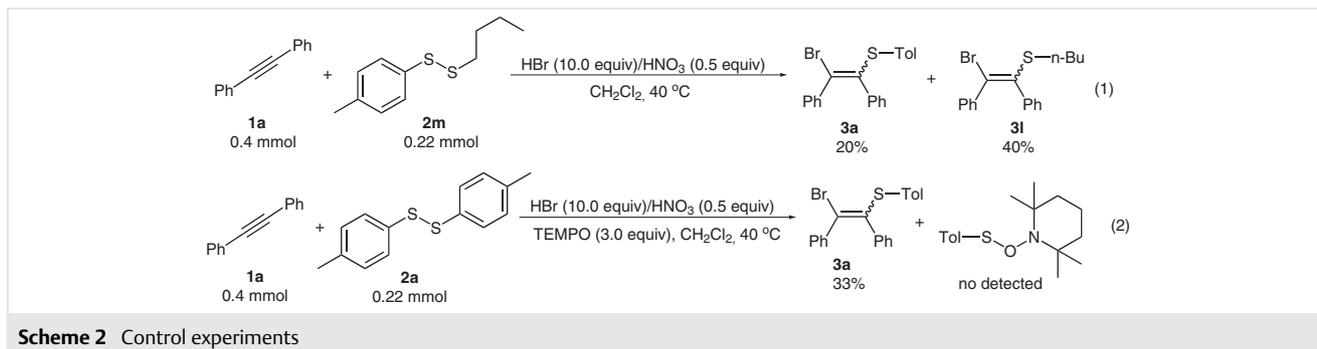
^b Isolated yield.

^c *Z/E* ratio determined by ¹H NMR analysis.

Subsequently, a series of alkynes were further examined for the bromothiolation of **2a**. As showed in Table 3, symmetrical arylacetylenes, substituted at the *para*-position including chloro and bromo groups, reacted smoothly, while fluoro and methyl substituents gave a mixture of the *Z/E* isomers (entries 1–4). To our delight, unsymmetrical alkynes **1f** and **1g** could be used to selectively produce the β -bromoalkenyl sulfides in 54 and 41% yields, respectively, although the configurations were not confirmed (entries 5 and 6). When dialkylacetylene **1h** was examined, the *anti*-configured product (*E*)-**3t**^{7c,d} was afforded in 49% yield. Un-

fortunately, terminal alkynes, phenylacetylene and 1-heptyne, were not suitable for the reaction (entries 8 and 9).

To identify the possible reaction mechanism, control experiments were conducted (Scheme 2). Firstly, we introduced unsymmetrical disulfide¹¹ **2m** into the reaction with diphenylacetylene (**1a**). Both sulfide groups were added to alkyne, and afforded the corresponding products **3a** in 20% yield and **3l** in 40% yield (based on 0.4 mmol of **1a**; Eq. 1). Then, the radical scavenger 2,2,6,6-tetramethylpiperidinoxy (TEMPO) was added to the model reaction. The reaction was not inhibited in the presence of TMEPO (3 equiv), giv-



ing **3a** in 33% yield.¹⁰ Moreover, no adduct of radical quencher was detected, which indicated a radical pathway was unlikely (Eq. 2).¹²

Based on the above results, a proposed mechanism for bromothiolation of diphenylacetylene (**1a**) with diary disulfide **2a** is illustrated (Scheme 3). Initially, nitric acid mixes with excess hydrobromic acid to generate nitrosyl bromide,¹³ which can react with **1a** to form *p*-toluensulfonyl

bromide **A**.¹⁴ Then, the addition of **A** to alkyne **2a** gives a thiirenium intermediate, which is represented as a covalent species **B** or a tight ion pair **C**.⁵ Finally, the intermediate complex collapses to afford the product **3a**, yielding the *syn*-configured adduct. The high *Z*-selectivity of reaction can be rationalized by the tight ion pair **C**, which may dissociate into free thiirenium ion without the influence of good solvent for Br⁻ and the stabilizing effect of aryl groups.

Table 3 Scope of Diarylacetylenes for the Synthesis of β -Bromoalkenyl Sulfides^a

Entry	Diarylacetylene 1a	Product 3	Yield (%) ^b (<i>Z/E</i>) ^c
1			72 (99:1)
2			77 (95:5)
3			66 (61:39)
4			52 (68:32)
5			54 (99:1)

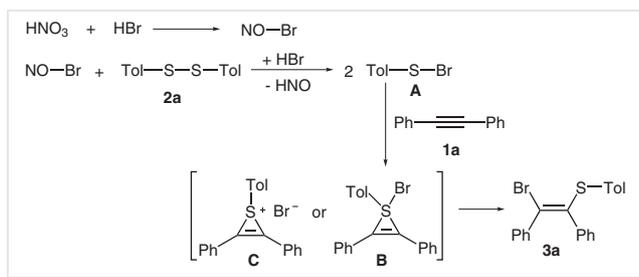
Table 3 (continued)

Entry	Diarylacetylene 1a	Product 3	Yield (%) ^b (Z/E) ^c
6			41 (89:11)
7			49 (1:99)
8			trace
9			trace

^a Reaction conditions: **1a** (0.40 mmol), **2** (0.22 mmol), mixture of HBr (4.0 mmol) and HNO₃ (0.2 mmol), in CH₂Cl₂ (4 mL), under air, 40 °C, 8 h.

^b Isolated yield.

^c Z/E ratio determined by ¹H NMR analysis.



Scheme 3 Proposed reaction mechanism

In summary, we have developed a metal-free bromothiolation of internal alkynes with disulfides under simple and mild conditions. This unprecedented protocol offers β -bromoalkenyl sulfides with good functional tolerance and high *syn*-stereoselectivity, and showed great promise for the synthesis of bioactive complex alkenyl sulfides. In addition, a scale-up experiment revealed the potential application value of this protocol.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1719934>.

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- (10) **Synthesis of 3; General procedure:** Alkyne **1** (0.40 mmol) and disulfide **2** (0.22 mmol) were added into a 25 mL oven-dried flask and dissolved in dichloromethane (4 mL), then hydrobromic acid (40% aqueous, 10 equiv) mixed with nitric acid (65% aqueous, 0.5 equiv) was added dropwise. The solution was then stirred for 8 h at 40 °C. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted in diethyl ether (15 mL), and washed with brine (2 × 15 mL). The aqueous phase was re-extracted with diethyl ether (15 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuum and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford product **3**. Spectroscopic data of (Z)-(2-bromo-1,2-diphenylvinyl)(p-tolyl)sulfane (**3a**): Yield: 136.7 mg (91%); white solid; mp 105.0–106.1 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.56 (d, J = 8.0 Hz, 2 H), 7.34–7.43 (m, 5 H), 7.17–7.27 (m, 3 H), 7.00 (d, J = 8.0 Hz, 2 H), 6.88 (d, J = 8.0 Hz, 2 H), 2.19 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.7, 139.7, 137.2, 136.4, 131.9, 130.1, 129.7, 129.3, 129.2, 128.6, 128.2, 127.8, 127.7, 121.5, 21.0. HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₈^{78,9183}BrS: 381.0307; found: 381.0298. HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₈^{80,9163}BrS: 383.0287; found: 383.0273. See the Supporting Information for **3a–s**.
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