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Iodine-promoted stereoselective amidosulfenylation of electron-deficient alkynes†

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Iodine-promoted three-component synthesis of substituted β -amino sulfides has been developed starting from a propargyl ester, aliphatic secondary amine, and disulfide. This protocol provides a step-economic and highly regioselective entry to trisubstituted olefins with good substrate scope and functional group tolerance.

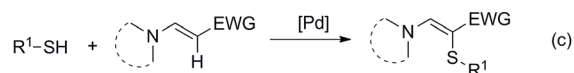
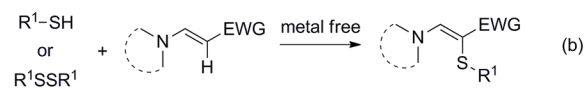
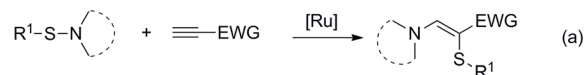
Polysubstituted olefins are ubiquitous structural units among biologically important drugs such as Tamoxifen or Vioxx,¹ and natural products such as Stemona alkaloids and Nileprost analogues.² Importantly, functionalized alkenes also contribute extensively to materials science and as building blocks in organic synthesis.³ In this context, the development of green and efficient methods for olefin synthesis has attracted much attention in recent years. Thereby, difunctionalization of alkynes is one of the most powerful and reliable procedures.⁴ On the other hand, multi-component reactions (MCRs) have been found to show great advantages as efficient protocols because of their general features of convergence, operational simplicity, facile automation, and so forth.⁵ However, regio- and stereoselective synthesis of polysubstituted olefins is still one of the most challenging tasks in organic synthesis, especially in the process of multicomponent reactions.

Organosulfur compounds are widespread in organic and biological research.⁶ Among them, β -amino vinylsulfides are well known to be particularly interesting chemical entities, which can be converted to many other useful compounds.⁷ Due to their importance, various synthetic strategies have been developed to construct these sulfur-containing molecules. For example, in 2004, Mitsudo reported the ruthenium-catalyzed addition of sulfenamides to alkynes, which provides a series of β -amino sulfides under mild reaction conditions (Scheme 1a).⁸ Recently, the groups of Du, Wan, and Prabhu independently disclosed their results of the enamionone sulfenylation with disulfides or thiophenols under metal-free conditions (Scheme 1b).⁹ Loh and co-workers developed a similar transformation through palladium-catalyzed C–H functionalization of enamines by using simple thiols (Scheme 1c).¹⁰ As

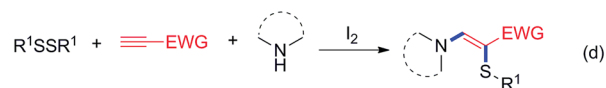
a continuation of our research interest in functionalization of alkenes/alkynes,¹¹ we herein disclose a novel protocol for the preparation of β -amino sulfides through iodine-promoted amidosulfenylation of electron-deficient alkynes involving C–S and C–N bond formation (Scheme 1d).

In our initial study, the reaction of methyl propiolate (**1a**), 1,2-diphenyldisulfane (**2a**), and pyrrolidine (**3a**) was selected as the model reaction to optimize the reaction conditions (Table 1). To our delight, the desired product **4aaa** was obtained in 67% yield when the reaction was performed with NIS (1.5 equiv.) and K_2CO_3 (3.5 equiv.) in CH_3CN at 60 °C for 4 h (entry 1). Lower yields were obtained when NH_4I , KI, and tetrabutylammonium iodide (TBAI) were used as the additive (entries 2–4). The use of molecular I_2 (0.75 equiv.) further enhanced the reaction yield to 90% (entry 5). Other solvents were also

Previous work



This work



Step-economic
Highly regioselective
More than 40 examples
Yields up to 95%

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Scheme 1 New strategy for the synthesis of β -amino sulfides.



Table 1 Optimization of the reaction conditions^a

Entry	Additive	Base	Solvent	Yield ^b (%)
1	NIS	K ₂ CO ₃	CH ₃ CN	67
2	NH ₄ I	K ₂ CO ₃	CH ₃ CN	33
3	KI	K ₂ CO ₃	CH ₃ CN	37
4	TBAI	K ₂ CO ₃	CH ₃ CN	30
5	I ₂	K ₂ CO ₃	CH ₃ CN	90
6	I ₂	K ₂ CO ₃	DMSO	67
7	I ₂	K ₂ CO ₃	DMF	65
8	I ₂	K ₂ CO ₃	Toluene	43
9	I ₂	K ₂ CO ₃	H ₂ O	27
10	I ₂	KOH	CH ₃ CN	56
11	I ₂	K ₃ PO ₄	CH ₃ CN	73
12	I ₂	Cs ₂ CO ₃	CH ₃ CN	65
13	I ₂	Na ₂ CO ₃	CH ₃ CN	83
14	I ₂	<i>n</i> -BuOK	CH ₃ CN	10
15	I ₂	Li ₂ CO ₃	CH ₃ CN	65
16 ^c	I ₂	K ₂ CO ₃	CH ₃ CN	67
17 ^d	I ₂	K ₂ CO ₃	CH ₃ CN	77
18 ^e	I ₂	K ₂ CO ₃	CH ₃ CN	73
19 ^f	I ₂	K ₂ CO ₃	CH ₃ CN	74

^a Conditions: **1a** (0.2 mmol), **2a** (0.15 mmol), **3a** (0.3 mmol), additive (1.5 equiv., for I₂ 0.75 equiv.), base (1.5 equiv.), solvent (0.5 mL), 60 °C, 4 h, under air. ^b Isolated yield based on **1a**. ^c I₂ (0.5 equiv.). ^d K₂CO₃ (1.0 equiv.). ^e 50 °C. ^f I₂ (10 mol%), TBHP (2.0 equiv.).

investigated and showed less efficiency (entries 6–9). The product was observed in 27% yield when H₂O was used as the sole solvent (entry 9). Instead of K₂CO₃, other bases such as KOH, K₃PO₄, Cs₂CO₃, Na₂CO₃, *t*-BuOK and Li₂CO₃ all decreased the reaction yield (entries 10–15). Decreasing the amounts of I₂ or K₂CO₃ or the reaction temperature all could not improve the reaction yield (entries 16–18). We have also studied the optimization of reaction conditions when using catalytic amount of iodine with oxidants (see Table S1 in ESI†).

With the optimized results in hand, we applied this amidosulfenylation conditions to other disulfides and the results are illustrated in Table 2. All of the tested disulfides performed well and gave the desired products **4** in moderate to excellent yields. When disulfides with *para*-substitutions were used, the corresponding β-amino sulfides were obtained in excellent yields in most cases (**4aba**–**4afa**), while the one with an acetylamino group showed modest activity and gave **4aga** in 57% yield. Steric effect of the substituent has no obvious impact on this amidosulfenylation reaction since *o*-MeO- (**2k**), *m*-MeO- (**2n**), and *p*-MeO- (**2b**) disulfides afforded the corresponding products **4aka**, **4ana**, and **4aba**, respectively, in almost the same yields (77–82%). 1,2-Di(naphthalen-2-yl)disulfane (**2p**) was well suited to this amidosulfenylation protocol, and delivered the corresponding product **4apa** in 91% yield. Disulfides **2q** and **2v** with two functional groups were also suitable substrates and

Table 2 Substrate scope with respect to the disulfide and alkynes^a

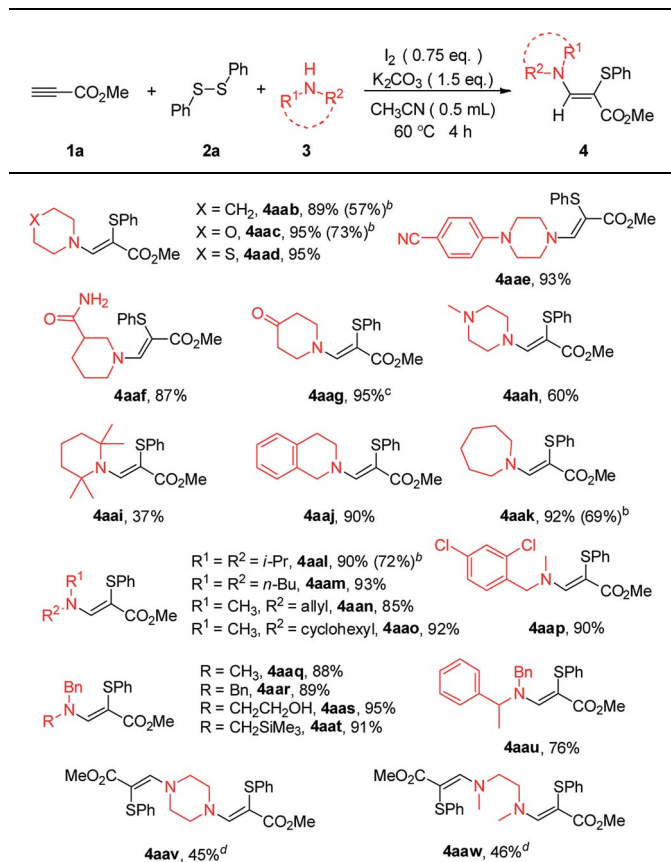
	R = H, 4aaa , 90%		R = OCH ₃ , 4aba , 77%
	R = F, 4aca , 78% (40%) ^b		R = Cl, 4ada , 89%
	R = Br, 4aea , 94%		R = NO ₂ , 4afa , 87%
	R = CH ₃ CONH, 4aga , 57%		R = 2-CH ₃ , 4aia , 93%
	R = 2-Et, 4aja , 89%		R = 2-OCH ₃ , 4aka , 83% (41%) ^b
	R = 2-Cl, 4ala , 92%		R = 3-CH ₃ , 4ama , 84% (65%) ^b
	R = 3-OCH ₃ , 4ana , 82%		R = 2-CH ₃ , 4aia , 93%
	R = 2-Et, 4aja , 89%		R = 2-OCH ₃ , 4aka , 83% (41%) ^b
	R = 2-Cl, 4ala , 92%		R = 3-CH ₃ , 4ama , 84% (65%) ^b
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	R = 2-Cl, 4ala , 92%		R = 3-CH ₃ , 4ama , 84% (65%) ^b
	R = 3-OCH ₃ , 4ana , 82%		R = 2-CH ₃ , 4aia , 93%
	R = 2-CH ₃ , 4apa , 91%		R = 2-OCH ₃ , 4aqa , 93%
	R = 2-Cl, 4ara , 83%		R = 2-CH ₃ , 4aia , 93%

^a Conditions: **1a** (0.2 mmol), **2** (0.15 mmol), **3a** (0.3 mmol), I₂ (0.15 mmol), K₂CO₃ (0.3 mmol), CH₃CN (0.5 mL), 60 °C, 4 h, air. ^b Conditions: **1a** (0.2 mmol), **2** (0.15 mmol), **3a** (0.3 mmol), I₂ (10 mol%), TBHP (2.0 equiv.), K₂CO₃ (0.3 mmol), CH₃CN (0.5 mL), 60 °C, 4 h, air. Isolated yield based on **1a**.

afforded the desired products in 93% and 83% yields (**4aqa** and **4ara**), respectively. Furthermore, heteroaromatic disulfides bearing pyridin-2-yl (**2h**) and thiophen-2-yl (**2o**) functionalities were accommodated, further demonstrating the broad functional-group tolerance of this method. It is noteworthy that ethyl propiolate (**1b**) and but-3-yn-2-one (**1c**) also proved to be suitable coupling partners to provide the corresponding products in high yields.

The scope with respect to the amine was then investigated (Table 3). Under the standard reaction conditions, a broad range of substituted aliphatic secondary amine was successfully coupled with methyl propiolate (**1a**) and 1,2-diphenyldisulfane (**2a**) to give the respective β-amino sulfides in moderate to very good yields (**4aab**–**4aau**). Simple cyclic secondary amines, such as piperidine (**3b**), morpholine (**3c**), thiomorpholine (**3d**) and azepane (**3k**) proceeded smoothly to afford the corresponding β-amino sulfides in excellent yields. When 4-(piperazin-1-yl)benzotrile (**3e**) and piperidine-3-carboxamide (**3f**) were used as the coupling partner, the desired products were obtained in 93% and 86% yields, respectively. 1-Methylpiperazine (**3h**) and 2,2,6,6-tetramethylpiperidine (**3i**) furnished the corresponding products in lower yields. Notably, piperidin-4-one (**3g**) and 1,2,3,4-tetrahydroisoquinoline (**3j**) were well tolerated in the present system, delivering the corresponding products in high yields. Other chain secondary amines (**3l**–**3o**) were also evaluated. Thereby, *N*-methylallylamine (**3n**) was tolerated, and the desired product (**4aan**) was obtained in 85% yield. To our



Table 3 Substrate scope with respect to the amines^a

^a Conditions: **1a** (0.2 mmol), **2** (0.15 mmol), **3a** (0.3 mmol), I_2 (0.15 mmol), K_2CO_3 (0.3 mmol), CH_3CN (0.5 mL), $60^\circ C$, 4 h, air.

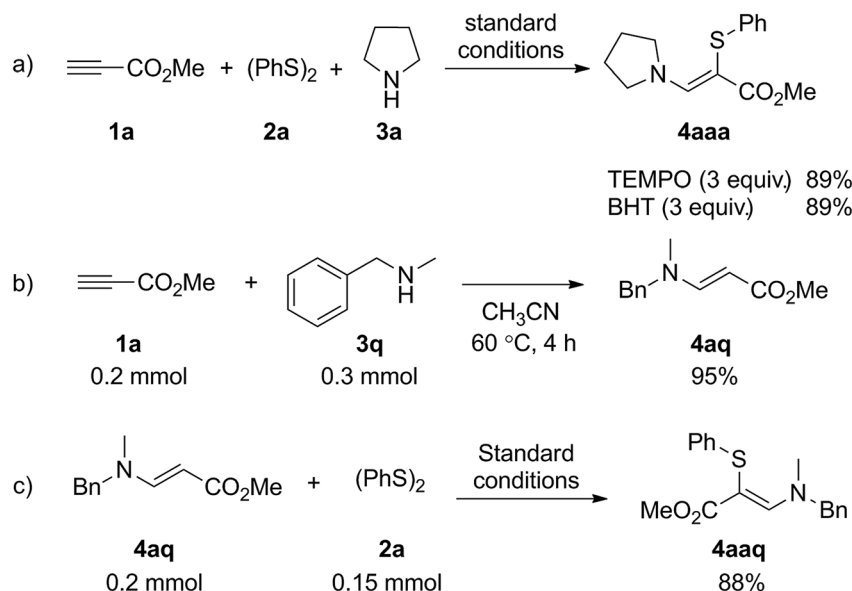
^b Conditions: **1a** (0.2 mmol), **2** (0.15 mmol), **3a** (0.3 mmol), I_2 (10 mol%), TBHP (2.0 equiv.), K_2CO_3 (0.3 mmol), CH_3CN (0.5 mL), $60^\circ C$, 4 h, air. Isolated yield based on **1a**. ^c K_2CO_3 (0.6 mmol).

^d Amine (0.3 mmol).

delight, this reaction system could also be applied to the direct sulfenylation of *N*-substituent benzylamine derivatives (**3p–3u**). Interestingly, the reaction of diamine, such as piperazine (**3v**) and *N,N'*-dimethylethylenediamine (**1w**) with methyl propiolate (**1a**) and 1,2-diphenyldisulfane (**2a**) worked well to afford the corresponding products in moderate yields.

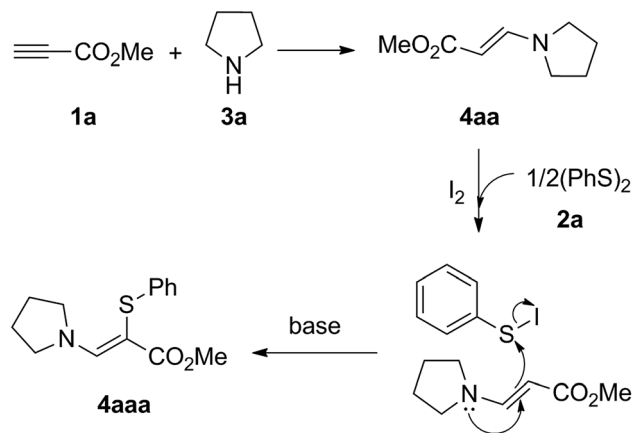
Some control experiments were carried out to gain preliminary insight into the reaction mechanism. First, the addition of a radical scavenger such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) to the reaction system did not inhibit the reaction (Scheme 2a), which suggested that the reaction may not proceed through a radical pathway. Second, the coupling of methyl propiolate (**1a**) with *N*-methyl-1-phenylmethanamine (**3q**) occurred well to afford enamine **4aq** under the standard reaction conditions (Scheme 2b). The product **4aaq** was obtained in 88% yield when **4aq** was used as the substrate with 1,2-diphenyldisulfane (**2a**) (Scheme 2c). On the basis of these results, a plausible mechanism to rationalize this transformation was proposed (Scheme 3). Initially, Michael-type addition of pyrrolidine (**3a**) to methyl propiolate (**1a**) generates the enamine intermediate **4aa**. Meanwhile, the interaction of molecular iodine with disulfide **2a** generated electrophilic species Ph-SI. Finally, nucleophilic displacement of an iodo group by enamionone and subsequent deprotonation form the product **4aaa**.

In summary, we have developed a simple and efficient method for the preparation of β -amino sulfides from propargyl ester, aliphatic secondary amine, and disulfide with moderate to high yields. Halogen, nitro, carbonyl, alkenyl, hydroxyl and amide functional groups were well tolerated under the mild reaction conditions. This method affords an efficient alternative approach for the synthesis of biologically important nitrogen- and sulfur-functionalized olefins.



Scheme 2 Control experiments under various conditions.





Scheme 3 Possible reaction pathway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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