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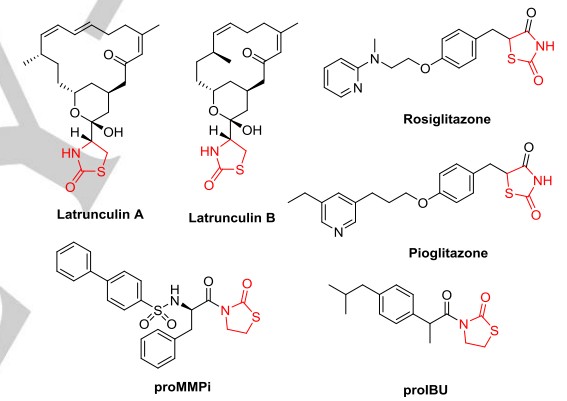
Base-Promoted Sulfur-Mediated Carbonylative Cyclization of Propargylic Amines

Jun Ying,[a]+ Hai Wang,[a]+ Xinxin Qi,[a] Jin-Bao Peng,[a] and Xiao-Feng Wu*[a,b]

Abstract: A ^{t}BuOK mediated carbonylative cyclization of propargylic amines with elemental sulfur has been developed. With benzene-1,3,5-triyl triformate (TFBen) as a convenient CO surrogate, various substituted 1,3-thiazolidin-2-ones were produced in good to excellent yields.

In nowadays, carbonylation reaction has already been accepted as a class of potent transformations in modern organic chemistry. Notably, many carbonylation related processes have been industrialized, such as Fischer-Tropsch process, Cativa process, and hydroformylations.[1] However, transition-metal catalysts are usually obligatory in most of the achieved procedures. Besides the risk of metals contamination on the terminal products, the using metal catalysts will definitely increases the costs of the process. Although metal-free radical mediated carbonylation reactions have been established as well, relative high CO pressure (> 50 bar) is mandatory.[2] Additionally, even though carbon monoxide is a cheap and ideal C1 source for large scale carbonylation chemistry, its high toxicity and smell-less properties lead the related procedures are reluctant to be applied by synthetic chemists in laboratories. Hence, the development of CO surrogates and their applications exploration become a new research topic.[3]

On the other hand, sulfur-containing heterocyclic compounds are one of the central chemicals due to their unusual physical properties and versatile biological activities (Scheme 1).[4] Among the various sulfur-containing heterocycles, 1,3-thiazolidin-2-ones are useful and valuable motifs in various areas.[5] Consequently, much attention has been focused on the development of new synthetic procedures towards thiazolidinones.[6] Various sulfuration agents including thiols, sulfides, and their oxidized derivatives and so on have been applied. However, challenging such as relative harsh reaction conditions, low reaction efficiency and limited substrates scope still exist. Additionally, the compatibility of transition metal catalysts with sulfuration agents is usually problematic as well.[7] This property makes the development of new methodology for sulfur incorporation more challenge. Moreover, among the known sulfuration agents, elemental sulfur (S_8) is obviously the most desirable raw material due to its inexpensive, non-toxic, inodorous and stable characters.[8] Sulfur-involved carbonylation is an intriguing but difficult research topic.[8,9] Not surprisingly, to date there is no research on the carbonylative cyclization of propargylic amines with S_8 been reported. Herein, we disclose a novel procedure for the synthesis of 1,3-thiazolidin-2-ones via a ^{t}BuOK-mediated carbonylative cyclization of propargylic amines with S_8. It is noteworthy that the reaction undergoes smoothly under metal-free conditions to afford the desired 4-alkylidene-thiazolidin-2-ones in good to excellent yields with TFBen as the solid CO source.



Scheme 1. Selected examples of bio-active sulfur-containing motifs.

The initial model reactions were carried out using the propargylic amine **1aa** as a substrate,[10] and the results are summarized in Table 1. When **1aa** was treated with TFBen (2 equiv; benzene-1,3,5-triyl triformate) and sulfur powder (0.5 equiv) in the presence of DBU at 35 ^{o}C, the reaction afforded the corresponding cyclized product **2aa** in 91% yield (Table 1, entry 1). Then, a series of bases were examined (Table 1, entries 2-5). A slightly reduced yield (88%) of **2aa** was obtained with NaOH as the promotor (Table 1, entry 2). We were delighted to find that the using of ^{t}BuOK and DABCO improved the yield to 96% and 93%, respectively (Table 1, entries 3 and 4). A significantly decreased yield (47%) was observed when DMAP was employed (Table 1, entry 5). When the solvent of reaction was changed from DMF to DMSO, over 99% yield was achieved, while MeCN, toluene, 1,4-dioxane, and DCM lead to the formation of a trace or no desired product (Table 1, entries 6-10). Excellent yields (over 99%) were still maintained when the amounts of TFBen (1 equiv) and S_8 (0.375 equiv) were decreased (Table 1, entries 11 and 12). Further reducing the amount of S_8 (0.25 equiv) or ^{t}BuOK (1.5 equiv) slightly decreased the reaction yields (Table 1, entries 13 and 14). It was found that the yield was dramatically decreased to 53% with the use of

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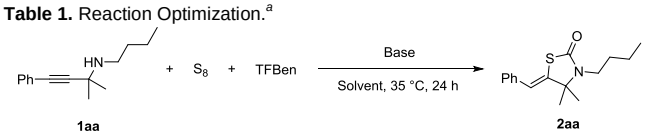
0.5 equivalent of TFBen (Table 1, entry 15). Moreover, in the reaction temperature variations, low conversion of the substrate was observed at room temperature while higher temperature gives no better results.

Table 1. Reaction Optimization.[a]



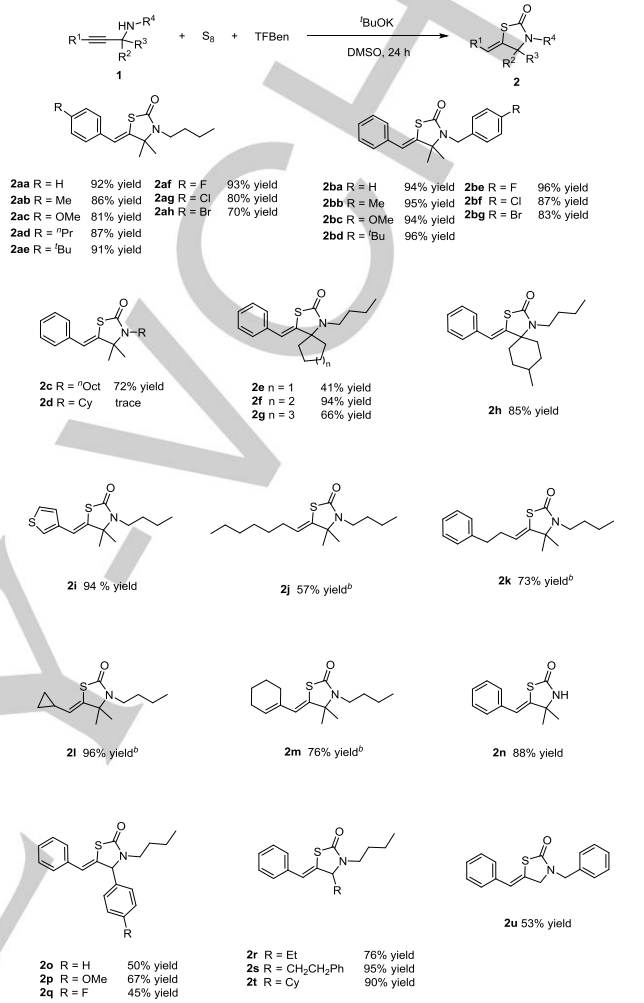
1aa 2aa

Entry	S_8	TFBen	Base	Solvent	Yield[b]
1	0.5 eq	2.0 eq	2.0 eq DBU	DMF	91%
2	0.5 eq	2.0 eq	2.0 eq NaOH	DMF	88%
3	0.5 eq	2.0 eq	2.0 eq ^{t}BuOK	DMF	96%
4	0.5 eq	2.0 eq	2.0 eq DABCO	DMF	93%
5	0.5 eq	2.0 eq	2.0 eq DMAP	DMF	47%
6	0.5 eq	2.0 eq	2.0 eq ^{t}BuOK	DMSO	>99%
7	0.5 eq	2.0 eq	2.0 eq ^{t}BuOK	MeCN	Trace
8	0.5 eq	2.0 eq	2.0 eq ^{t}BuOK	Toluene	0
9	0.5 eq	2.0 eq	2.0 eq ^{t}BuOK	dioxane	0
10	0.5 eq	2.0 eq	2.0 eq ^{t}BuOK	DCM	0
11	0.5 eq	1.0 eq	2.0 eq ^{t}BuOK	DMSO	>99%
12	0.375 eq	1.0 eq	2.0 eq ^{t}BuOK	DMSO	>99% (92%)[c]
13	0.25 eq	1.0 eq	2.0 eq ^{t}BuOK	DMSO	96%
14	0.5 eq	1.0 eq	1.5 eq ^{t}BuOK	DMSO	95%
15	0.375 eq	0.5 eq	2.0 eq ^{t}BuOK	DMSO	53%

[a]Reaction conditions: **1aa** (0.2 mmol), solvent (1 mL). [b]The yield of **2aa** was determined by GC analysis using *n*-dodecane as internal standard. [c]Isolated yield.

The optimal reaction conditions (Table 1, entry 12) were successfully applied to various propargylic amines as follows (Scheme 2). It shows that the propargylic amines bearing both electron-donating and electron-withdrawing substituents underwent cyclization smoothly to give the corresponding products (**2ab-2ah**) in 70-93% yields. The reactions of substrates containing benzyl and alkyl groups on the nitrogen atom afforded the products (**2ba-2bg, 2c**) in high yields. When the propargylic amine with a *N*-cyclohexyl substituent was subjected to the same reaction conditions, only a trace of the desired product **2d** was observed, which could be explained by the steric property on the nitrogen atom. Compounds having a carbocycle on the triple bond were converted to the desired products (**2e-2h**) in moderate to good yields (41-94%). It should be noted that the reaction with a thiophene substituted propargylic amine led to the formation of product **2i** in 94% yield. For compounds containing alkyl groups on the triple bond, good yields of the desired products (**2j-2m**) were obtained under higher temperature (65 °C). Interestingly, primary propargylic amine can be successfully transformed to the product **2n** in 88% yield as well. In addition, we tested the cyclization of substrates with aryl and alkyl substituents (R^2 = aryl, alkyl and R^3 = H), 45-95% yields of the corresponding products **2o-2t** were achieved. It was found that a compound without substituents (R^2, R^3 = H) can also undergo carbonylative cyclization to provide the product **2u** in a moderate yield. The structure of product **2bg** was confirmed by X-ray crystallography as shown in Figure 1 (see the Supporting Information).

Scheme 2. Substrate Scope.[a]



[a]Reaction conditions: substrate (0.2 mmol), S_8 (0.375 eq), TFBen (1.0 eq), ^{t}BuOK (2.0 eq), DMSO (1 mL), 35 °C, 24 h, isolated yields. [b]60 °C.

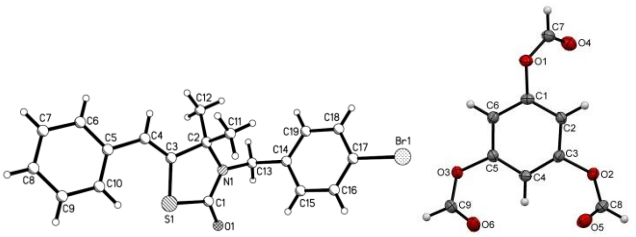
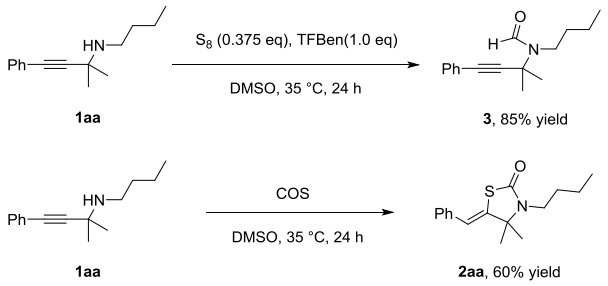


Figure 1. X-ray structures of products **2bg** (CCDC: 1586022), and TFBen (CCDC: 1562894).

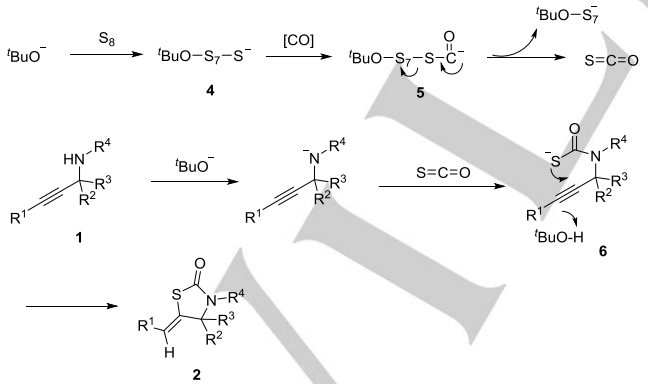
In order to get some insight into the reaction pathway, control experiments of this carbonylative cyclization of propargylic amine and sulfur were performed as well (Scheme 3). First, propargylic amine **1aa** was subjected to the standard reaction conditions in the absence of ^{t}BuOK. No product **2aa** could be observed and the formamide **3** was obtained in 85% yield, which indicated that ^{t}BuOK is essential to activate S_8 in this sulfur-involved carbonylative

cyclization. On the other hand, it was found that carbonyl sulfide (COS), prepared from KSCN and H_2SO_4, can react with **1aa** to give product **2aa** in 60% yield. This result suggested that COS or analogues, which formed from ^{t}BuOK-mediated reaction between S_8 and CO, could be a possible intermediate in this reaction. Additionally, possibility of the involvement of radical intermediates can be excluded by the addition of TEMPO and BHT (2,6-di-*tert*-butyl-*p*-kresol) to the model system which gave the same yields of the desired product.



Scheme 3. Mechanistic Investigations.

On the basis of previous works[8,9] and our preliminary mechanistic studies, a postulated pathway is proposed to account for carbonylative cyclization of propargylic amine and sulfur as follows (Scheme 4). Elemental sulfur is activated in the treatment of ^{t}BuOK, producing the sulfur anion **4**. The reaction of **4** with carbon monoxide, generated *in situ* from TFBen, gives the carbonyl sulfide **5**. Elimination of **5** leads to the formation of the key intermediate COS. In the presence of ^{t}BuOK, the nucleophilic attack of the propargylic amine **1** to COS generates the thiocarbamate **6**. The desired product **2** is obtained through an intramolecular annulation of **6**. The stereoselectivity of product **2** (*Z-isomer*) can be explained by a *trans* addition of sulfur anion to a carbon-carbon triple bond coordinating with bulky ^{t}BuOH.



Scheme 4. Plausible Mechanism.

In summary, we have developed a ^{t}BuOK-mediated transition metal-free carbonylative cyclization of propargylic amines and elemental sulfur. With TFBen as a benign and solid CO source, various desired 1,3-thiazolidin-2-ones were produced in a straightforward manner. Moderate to excellent yields (45-96%) and broad functional groups tolerance can be obtained under mild conditions. Further synthetic applications of this method and more detailed study of the reaction mechanism are under progress.

Experimental Section

S_8 (0.375 equiv.), TFBen (1.0 equiv.) and tBuOK (2.0 equiv.) were added to a 15 mL tube equipped with a magnetic stirrer which was then placed under vacuum and refilled with nitrogen three times. A solution of propargylamine (0.2 mmol) in DMSO (1.0 mL) was added to the reaction tube, then the tube was sealed and the mixture was stirred at 35 ^{o}C for 24 h. After the reaction was completed, the reaction mixture was diluted with 50 mL water and extracted with 30 mL EtOAc three times. The combined organic phases were dried with anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (PE/EtOAc=10/1) to obtain desired (*Z*)-5-benzylidene-3-butyl-4,4-dimethylthiazolidin-2-one.

Acknowledgements

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Keywords: carbonylation • metal-free • sulfur • heterocycle synthesis • cyclization

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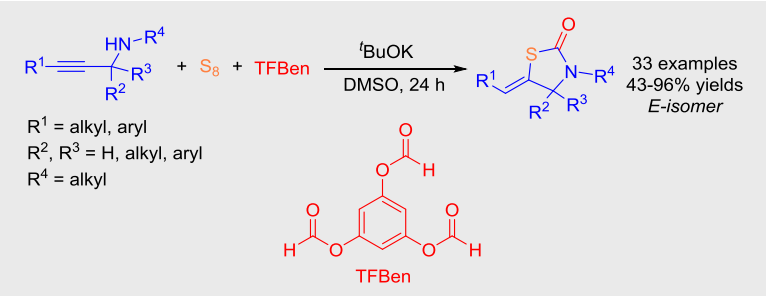

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