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DBU-Promoted Carbonylative Synthesis of 1,3-Oxathiolan-2-ones from Propargylic Alcohols with TFBen as the CO source

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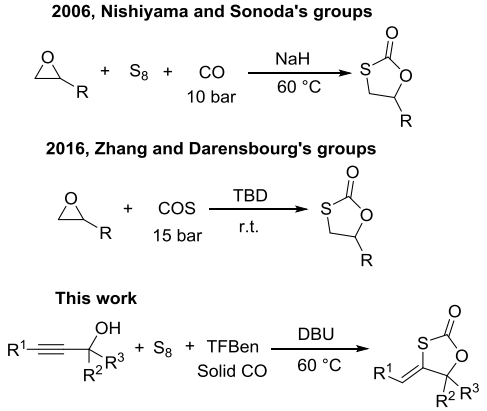
A DBU-promoted carbonylative cyclization of propargylic alcohols with sulfur has been developed. Various 1,3-oxathiolan-2-ones were produced in 61-98% yields under mild conditions in the absence of metal catalysts. TFBen (benzene-1,3,5-triyl triformate) as an efficient and solid CO surrogate and S_8 as an ideal sulfur source were employed and incorporated.

1,3-Oxathiolan-2-ones are useful building blocks in organic[1] and polymer sciences,[2] as well as important structural motifs in biologically active compounds such as quercetin-oxathiolanone,[3] an effective inhibitor of xanthine oxidase. Consequently, extensive efforts have been devoted to the study of a convenient synthesis of 1,3-oxathiolan-2-ones. There are a couple of methods have been reported including the cyclization of *β*-hydroxyl thiol with phosgene, the reaction of epoxides with sulfur and carbon monoxide (CO), the coupling reaction of epoxides with carbonyl sulfide (COS), the base-catalyzed cyclization of the imidazolide derivative, and the acid-assisted cyclization of 2-hydroxyethyl thiocarbonate (Scheme 1). It is obvious that these methods have some obvious drawbacks: including (1) the use of toxic gases (phosgene, CO, COS, etc.); (2) the use of odorous sulfurization reagents (thiols, etc.); (3) limited substrates scope due to the harsh reaction conditions (high temperature and/or high pressure).[4-12]

On the other hand, carbonylation chemistry is an attractive topic from both academia and industry.[13] For the conveniences on small scale applications, many efforts have been attracted on in-situ CO generation, due to the high toxicity and flammable of CO gas.[14] Based on the researches from different research groups, a number of CO surrogates have been developed such as metal carbonyls, formaldehyde, alcohols, formic acid, formates, formamides, etc. Additionally, new reactor systems have been designed and applied as well, such as two-chamber system and *In-Ex* tube.[15] In addition, TFBen (benzene-1,3,5-triyl triformate), a solid, stable, efficient, and convenient CO surrogate, has recently been developed in our group.[16,17] Herein, we wish to report our newly developed procedure for 1,3-oxathiolan-2-ones preparation with TFBen as the CO source. With DBU as the promotor, propargylic alcohols were carbonylatively cyclized with sulfur, which is an inexpensive and odorless sulfurization reagent, under mild reaction conditions.[18,19] Notably, no metal catalyst is needed here.



Scheme 1. Selected examples for the synthesis of 1,3-oxathiolan-2-ones.

Initially, we investigated the reaction of propargylic alcohol **1a** with TFBen and sulfur in the presence of base, and the results are summarized in Table 1. Treatment of compound **1a** with S_8 (0.5 equiv.), TFBen (1.0 equiv.) and DBU (2.0 equiv.) at 30 °C afforded the product **2a** in 49% yield as a *Z-isomer* (Table 1, entry 1). Raising the reaction temperature to 60 °C enhanced the yield of **2a** (79%; Table 1, entry 2). When the amount of DBU was reduced to 1.0 equivalent, the yield was dramatically decreased to 58% (Table 1, entry 3). No product was observed without the addition of DBU, which indicates that DBU as a base is crucial to initiate this sulfur-involved

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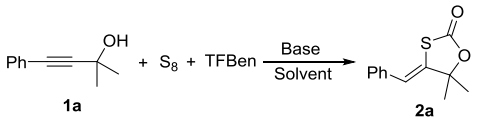
carbonylative cyclization (Table 1, entry 4). Also, decreasing the amount of S_8 (0.25 equiv.) or shortening the reaction time (24 h) gave a remarkably decreased yield (Table 1, entries 5 and 6). Then, a variety of solvents were examined (Table 1, entries 7-12). It shows that the reaction using CH_3CN provided an excellent yield (over 99%, isolated yield 87%), while other solvents (DMSO, DMF, THF, DCM, and 1,4-dioxane) were inferior. Moreover, a series of bases were tested and decreased yields were obtained in comparison with DBU (Table 1, entries 13-16). Notably, the yield of the desired product decreased to 61% when 0.5 equivalent of TFBen was used.

Table 1 Screening of optimal reaction conditions [a]



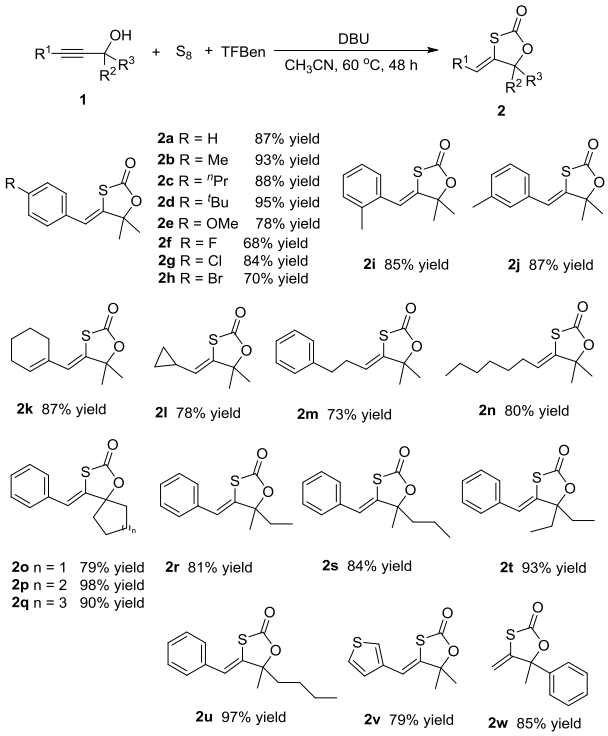
1a 2a (*Z-isomer*)

Entry	S_8	Base	Solvent	Yield[b]
1	0.5 eq	2.0 eq DBU	Toluene	49%[c]
2	0.5 eq	2.0 eq DBU	Toluene	79%
3	0.5 eq	1.0 eq DBU	Toluene	58%
4	0.5 eq	—	Toluene	0
5	0.25 eq	2.0 eq DBU	Toluene	51%
6	0.5 eq	2.0 eq DBU	Toluene	48%[d]
7	0.5 eq	2.0 eq DBU	DMSO	83%
8	0.5 eq	2.0 eq DBU	DMF	9%
9	0.5 eq	2.0 eq DBU	THF	86%
10	0.5 eq	2.0 eq DBU	CH_3CN	>99% (87%)[e]
11	0.5 eq	2.0 eq DBU	DCM	0
12	0.5 eq	2.0 eq DBU	Dioxane	51%
13	0.5 eq	2.0 eq Et_3N	CH_3CN	60%
14	0.5 eq	2.0 eq DABCO	CH_3CN	86%
15	0.5 eq	2.0 eq ^{t}BuOK	CH_3CN	12%
16	0.5 eq	2.0 eq NaOH	CH_3CN	0

[a] Reaction conditions: **1a** (0.5 mmol), solvent (2 mL), TFBen (1 equiv.), 60 °C, 48 h. [b] The yield of **2a** was determined by GC analysis using *n*-dodecane as internal standard. [c] 30 °C. [d] 24 h. [e] Isolated yield.

Subsequently, various propargylic alcohols **1** were prepared and subjected to the optimal reaction conditions. The results are shown in Scheme 2. It was found that the electron-donating *para*-substituted propargylic alcohols **2b-2e** gave yields relatively higher than that of compounds containing electron-withdrawing *para*-substituents **2f-2g**. The reactions of substrates bearing *ortho*- and *meta*-Me group afforded the desired product **2i** and **2j** in good yields. Compounds having an alkyl group on the triple bond could undergo carbonylative cyclization smoothly to give the desired products **2k-2n** in high yields (73-87%). When substrates with a carbocycle unit were tested, excellent yields up to 98% of products **2o-2q** were achieved. Furthermore, the reactions of propargylic alcohols with linear alkyl substituents (R^2, R^3 = alkyl) proceeded to give the corresponding products **2r-2u** in 81-97% yields. Gratifyingly, treatment of a thiophene substituted propargylic alcohol led to the formation of product **2v** in 79% yield. Compound with no substituent on the alkyne carbon (R^1 = H) can also cyclize to form product **2w** in 85% yield.

Scheme 2 Carbonylative synthesis of 1,3-oxathiolan-2-ones.[a]



[a] Reaction conditions: substrate **1** (0.5 mmol), S_8 (0.5 equiv.), TFBen (1.0 equiv.), DBU (2.0 equiv.), CH_3CN (2 mL), 60 °C, 48 h.

On the basis of the above experimental results and previous reports,[18,19] a possible mechanism for this carbonylative cyclization of propargylic alcohol with S_8 is proposed in Scheme 3. Initially, S_8 was activated by DBU and the sulfur anion **3** was formed. The reaction of **3** with carbon monoxide, generated *in situ* from TFBen, gives the carbonyl sulfide **4**. Elimination of **4** can afford the key intermediate COS. In the presence of DBU, deprotonation of propargylic alcohol **1** followed by the nucleophilic attack of its oxygen anion to COS generates the carbonothioate **5**. Subsequent intramolecular cycloaddition of **5** leads to the formation of the final product **2**. The stereoselectivity of product **2** (*Z-isomer*) can be explained by a backside attack of the thionate anion to a carbon-carbon triple bond coordinating with the bulky base DBU. Notably, two sulfur atoms from S8 can be transformed before it forms a stable complex with DBU.

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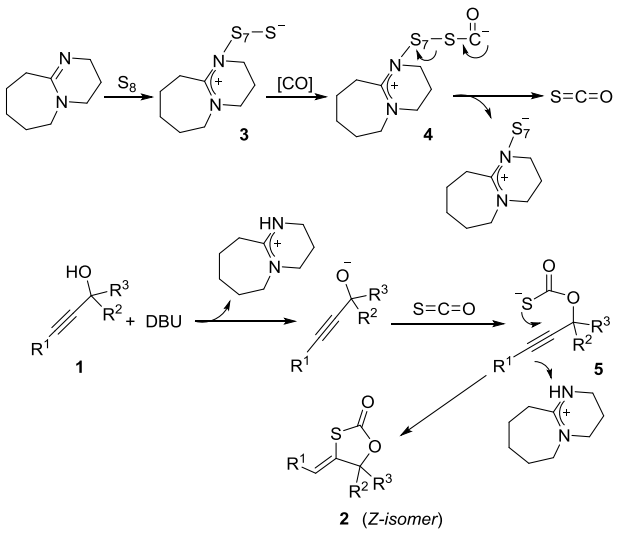

Scheme 3. Possible reaction mechanism.

In conclusion, we have developed a facile and convenient approach for the synthesis of 1,3-oxathiolan-2-ones via carbonylative cyclization of propargylic alcohols with sulfur promoted by DBU. The reactions proceed under mild conditions, affording *Z-isomer* products in high yields (61-98%). This method has some obvious advantages, including metal catalyst-free; with TFBen as a benign CO surrogate; with S_8 as a desirable sulfur source. Further investigation will be focused on synthetic application and mechanistic study of this strategy.

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