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Yb(OTf)$_3$ catalyzed [3+2] annulations of D−A cyclopropanes with *β*-oxodithioesters: a regioselective synthesis of tetrahydrothiophenes

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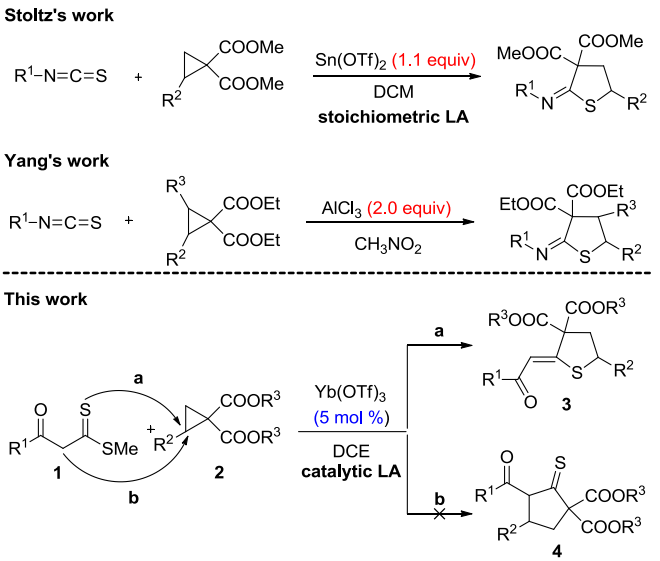
A new route to prepare tetrahydrothiophene derivatives from D−A cyclopropanes and *β*-oxodithioesters catalyzed by Yb(OTf)$_3$ is reported. This is the first example using *β*-oxodithioesters as dipolarophiles to react with D–A cyclopropanes. The method exhibits good regioselectivity.

The methodologies for C−S bond-forming have received extensive attention in transition-metal-catalyzed cross-coupling reactions[1] and metal-free radical-coupling reactions.[2] Organosulfur compounds play important roles in medicinal chemistry.[3] Among them, tetrahydrothiophenes are representative derivatives due to their important biological activities,[4] and as catalysts in asymmetric synthesis.[5] Although a variety of protocols have been reported by a number of organic or pharmaceutical chemists,[6] the development of novel and efficient methods to construct tetrahydrothiophenes with readily available starting materials and catalyst is still in high demand.

Recently, functionalized S,S-ketene acetals[7] and *β*-oxodithioesters (ODEs)[8] have received much attention in construction of heterocycles. ODEs have shown various chemical properties with intriguing five reactive centers. Three nucleophilic centers localize on the oxygen atom, sulphur atom and α-carbon, and two electrophilic centers present on the carbonyl and thiocarbonyl groups. Due to the high reactivity, the reactions of ODEs with various bifunctional reagents could construct diverse heterocyclic compounds.

Donor–acceptor cyclopropanes (D–A cyclopropanes) are versatile building blocks in organic synthesis due to their high reactivity.[9] In the last decade, the annulation of D–A cyclopropanes with various dipolarophiles has become a powerful strategy for the construction of carbo- and heterocyclic compounds. A variety of dipolarophiles, including imines, carbonyls, alkenes, nitriles, and nitrones, have been employed to react with D–A cyclopropanes to construct pyrrolidine,[10] tetrahydrofuran,[11] cyclopentane,[12] pyrroline,[13] and oxazine[14] derivatives. Additionally, the intramolecular [3+2] cycloaddition of functionalized D–A cyclopropanes to construct structurally diverse carbo- or heterocyclic skeletons have been studied systematically.[15] However, there is no report on using ODEs as dipolarophiles to react with D–A cyclopropanes.

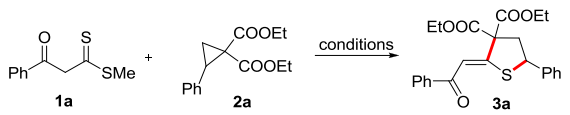


Scheme 1 The comparison of previous reactions and our work

Recently, Stoltz and coworkers[16] developed a methodology to synthesize tetrahydrothiophene derivatives from D–A cyclopropanes and isothiocyanates using stoichiometric Sn(OTf)$_2$ (Scheme 1). A similar reaction was reported by Yang and coworkers[17] using 2.0 equiv AlCl$_3$ as a promoter. The development of catalytic methods that lead to the tetrahydrothiophenes from D-A cyclopropanes remains a challenge to synthetic chemists. In continuation of our interests in *β*-oxodithioesters[18] and constructing heterocycles,[19] herein, we report a novel catalytic methodology to synthesize tetrahydrothiophenes using *β*-oxodithioesters with D-A cyclopropanes. Notably, the tetrahydrothiophene derivatives **3** were generated regioselectively through attacking the cyclopropanes by

the thiocarbonyl group of *β*-oxodithioesters, and the cyclopentanes **4** which formed by the *α*-carbon attacking were not observed. ^{1}H NMR spectrum of compound **3b** shows a singlet peak at δ 7.41 ppm is subject to the olefin proton, and a dd peak at δ 4.75 ppm is assignable to C5-H of the tetrahydrothiophene due to the coupling with adjacent CH_2. Furthermore, the structures of **3** were confirmed by X-ray crystallographic analysis of **3g** and **3j** (see Figures S1 and S2 in SI).

Table 1 Optimization of reaction conditions[a]



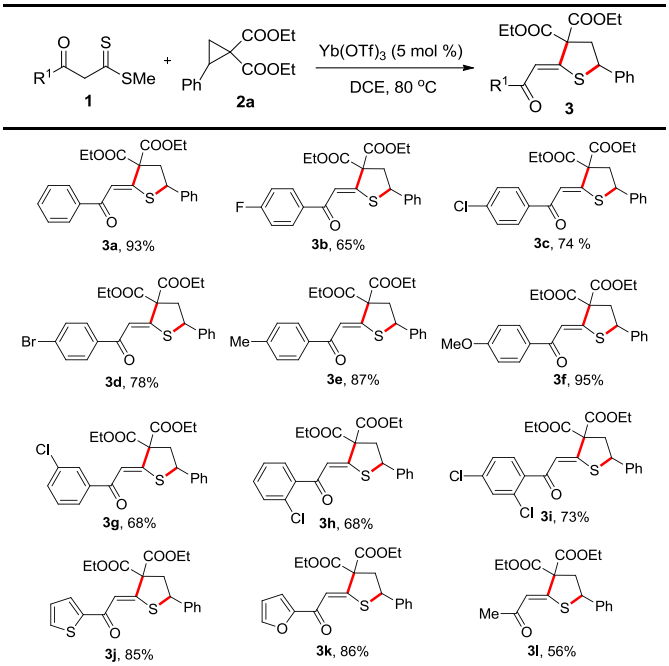
Entry	LA (mol %)	Solvent	Temp (℃)	Time (h)	Yield (%)[b]
1	$Yb(OTf)_3$ (10)	DCM	reflux	14	80
2	$Yb(OTf)_3$ (10)	DCE	reflux	2	93
3	$Yb(OTf)_3$ (10)	$MeNO_2$	reflux	2	mixture
4	$Yb(OTf)_3$ (10)	MeCN	reflux	2	91
5	$Yb(OTf)_3$ (10)	THF	reflux	2	56
6	$Yb(OTf)_3$ (10)	Toluene	reflux	2	86
7	$InCl_3$ (10)	DCE	reflux	6	28
8	$Cu(OTf)_2$ (10)	DCE	reflux	6	mixture
9	$Sc(OTf)_3$ (10)	DCE	reflux	6	75
10	**$Yb(OTf)_3$ (5)**	**DCE**	**reflux**	**2**	**93**
11	$Yb(OTf)_3$ (2)	DCE	reflux	2	48
12	$Yb(OTf)_3$ (5)	DCE	60 ℃	12	76
13	_[c]	DCE	reflux	12	trace

[a] Reaction conditions: The mixture of **1a** (0.2 mmol), **2a** (0.2 mmol) and solvent (2 mL) was stirred in a 25 mL flask. [b] Isolated yield. [c] no catalyst.

Methyl 3-oxo-3-phenylpropanedithioate **1a** and diethyl 2-phenylcyclopropane-1,1-dicarboxylate **2a** were selected as model substrates for the reaction conditions optimization (Table 1). Initially, in the presence of $Yb(OTf)_3$, substrate **1a** was converted to the tetrahydrothiophene **3a** in 80% yield (entry 1). Then different solvents were screening (entries 2-6), and product **3a** was formed up to 93% yield when DCE was used (entry 2). Subsequently, other catalysts, including $InCl_3$, $Cu(OTf)_2$ and $Sc(OTf)_3$, were tested (entries 7-9). Disappointedly, all the yields of **3a** were lower than $Yb(OTf)_3$. Finally, the equivalent of the catalyst was also tested (entries 10-11). When the amount of $Yb(OTf)_3$ was decreased to 5 mol %, the yield of product **3a** was not reduced (entry 10). However, the yield of **3a** was dropped dramatically with further decreasing the catalyst loading to 2 mol % (entry 11). Further optimization of the conditions revealed that the yield was reduced to 76% when lower the temperature to 60 °C (entry 12), and the reaction could not proceed without a catalyst (entry 13).

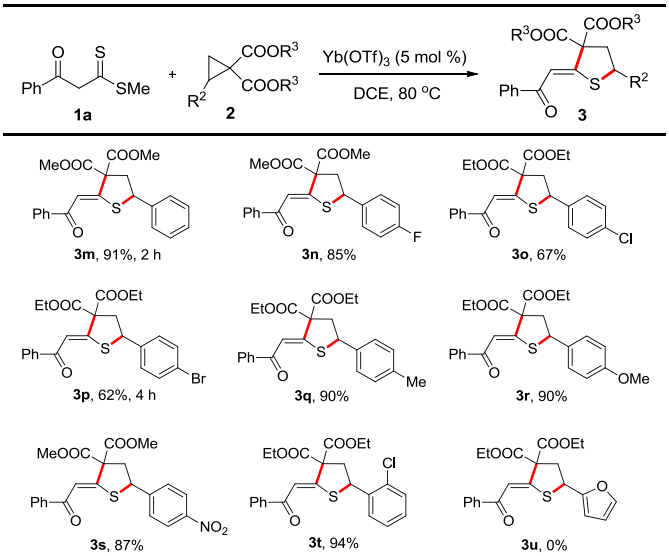
With the optimal conditions in hand, the scope of the reaction was examined using a broad range of substituted ODEs **1** and D–A cyclopropane **2a** (Table 2). ODEs with either electron-donating or electron-withdrawing groups on the phenyl group (R^1) showed similar reactivity and the corresponding tetrahydrothiophenes were formed in high yields (**3b**-**3f**). Additionally, the position of substituents on phenyl ring of **1** did not have significant influence on the yields (**3g**-**3i**). Moreover, furyl and thiophenyl substituted ODEs **1** were tolerated in the reaction and the products (**3j** and **3k**) were isolated in excellent yields. The tetrahydrothiophene **3l** was also obtained with aliphatic ODEs as reactant, albeit in lower yield.

Table 2 Synthesis of tetrahydrothiophenes **3a**-**3l** from various *β*-oxodithioesters **1**[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $Yb(OTf)_3$ (0.01 mmol), DCE (2 mL), 80 ℃, 2 h. [b]Isolated yield.

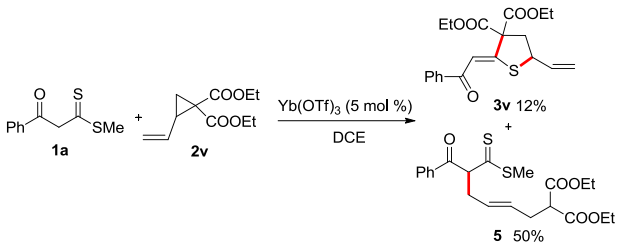
Table 3 Synthesis of tetrahydrothiophenes **3m**-**3u** from various D-A cyclopropanes **2**[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $Yb(OTf)_3$ (0.01 mmol), DCE (2 mL), 80 ℃, 7 h. [b]Isolated yield.

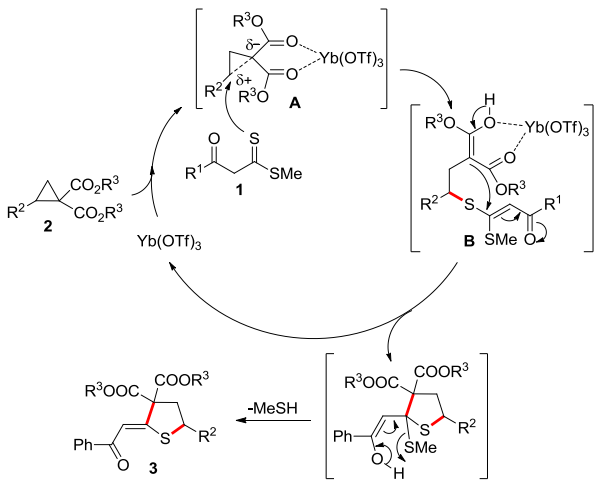
The scope of D–A cyclopropanes **2** was also examined with *β*-oxodithioester **1a** under the optimal conditions (Table 3). The ester group R^2 has no effect on the yields of the reaction (**3m** compared

with **3a**). Subsequently, the cyclopropanes bearing 4-fluoro, 4-chloro, 4-bromo, 4-methyl and 4-methoxy groups on the phenyl ring were employed and the desired tetrahydrothiophenes (**3n-3r**) were afforded in good to excellent yields. Furthermore, excellent yields were obtained when substrates with 2-chloro and highly electron-deficient 4-nitro groups were investigated (**3s-3t**), exhibiting the generality of the method. Unfortunately, no target product **3u** was obtained when furan substituted cyclopropanes was used as reactant.



Scheme 2 Synthetic study towards the vinyl substituted tetrahydrothiophene.

Encouraged by the above results, the substrate scope was extended to vinyl cyclopropane **2v** (Scheme 2). Disappointingly, the reaction exhibited poor selectivity, and the desired vinyl-substituted tetrahydrothiophene **3v** was obtained in only 12% yield. The major product was acyclic compound **5**.



Scheme 3 Proposed reaction mechanism.

Based on the above experimental results, a possible domino-ring-opening-cyclization (DROC)[20] mechanism is proposed in Scheme 3. Initially, the cyclopropane was activated by intimate ion pair, which was generated from 1,3-dicarbonyl group with ytterbium(III) triflate. Then, as nucleophile, the thiocarbonyl group of *β*-oxodithioesters not the *α*-carbon attacked the activated cyclopropane **A** selectively to form the intermediate **B**. Finally, the tetrahydrothiophene was obtained through intramoleculer cyclization, followed by MeSH elimination.

Conclusions

In conclusion, a $Yb(OTf)_3$-catalyzed [3+2] annulation reaction of D–A cyclopropanes with *β*-oxodithioesters has been developed. This methodology has the following advantages: (1) good regioselectivity; (2) catalytic $Yb(OTf)_3$; (3) readily available starting materials; (4) mild reaction conditions. Undoubtedly, this novel reaction is complementary to the [3+2] cycloaddition using D-A cyclopropanes. Efforts to develop new reactions base on *β*-oxodithioesters are currently underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, full spectroscopic data for all new compounds, and crystal data for **3g** and **3j** (CIF). See DOI: 10.1039/c000000x/

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