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Thiourea participation in [3+2] cycloaddition with donor–acceptor cyclopropanes: a domino process to 2-amino-dihydrothiophenes†

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The Yb(OTf)₃-catalyzed [3+2] cycloaddition of donor–acceptor cyclopropanes with thiourea offers an efficient route to diverse 2-amino-4,5-dihydrothiophenes (up to 92% yield), in which optically active 2-amino-dihydrothiophenes can be produced from enantiomerically pure cyclopropanes. Thiourea, which is an odorless and cheap reagent, provides a C=S double bond, serves as an amino source, and functions as a decarbalkoxylation reagent in this reaction. Preliminary mechanistic studies demonstrate that the reaction undergoes a sequential [3+2] cycloaddition/deamination/decarboxylation process.

2-Aminothiophene is a special structural moiety present in many biologically active molecules.¹ Examples of such molecules are shown in Fig. 1. Olanzapine is an atypical antipsychotic drug used for treating schizophrenia and bipolar disorder.² Tinoridine is an anti-inflammatory drug that has potent antiperoxidative properties.³ T-62 is an allosteric enhancer of the adenosine A1 receptor, and TPCA-1 is a small-molecule IκB kinase β inhibitor.⁴ AX20017 has antituberculosis properties and has been identified as a specific inhibitor of protein kinase G.⁵ 2-Amino-4,5-dihydrothiophene I exhibits antibacterial and antifungal properties.⁶ For most of these 2-aminothiophenes, which exhibit biological activities, it is found that an electron-withdrawing group (e.g., ester, C=O, or CN) is connected to the C3 position of the thiophenes. The most convenient method for preparing 2-aminothiophenes is the Gewald reaction, which involves the condensation of a ketone (or aldehyde) with activated nitrile and elemental sulfur.^{1,7} Although great achievements to construct 2-aminothiophenes have been made through the Gewald reaction, developing an alternative method to synthesize 2-aminothiophenes and their derivatives, which have an electron withdrawing group at the C3 position, is still highly desirable.⁸

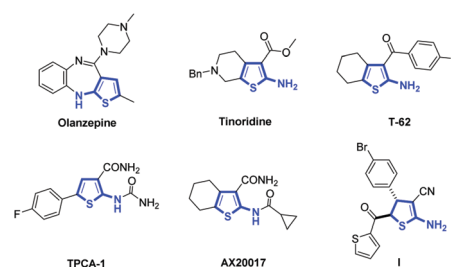


Fig. 1 Examples of bioactive agents with 2-aminothiophene fragments.

Donor–acceptor (D–A) cyclopropanes are exceptionally useful three-carbon building blocks due to their synthetic utility and ease of preparation.⁹ In the presence of a Lewis acid, the normal [3+n] cycloaddition reactions of D–A cyclopropanes with various dipolarophiles, such as C=C, C=O, C=N, N=O, N=N, C≡C, C≡N, nitrones, heterocumulenes, and other dipolarophiles, have proven to be valuable tools for producing highly functionalized cyclic ring systems.^{10–19} However, the C=S double bond has less been employed as a 2π component to react with D–A cyclopropanes.^{20,21} Very recently, the normal [3+2] cycloaddition of thioesters and D–A cyclopropanes has been published concurrently with the preparation of the present manuscript (Scheme 1a).^{20a} Highly substituted tetrahydrothiophenes with two adjacent quaternary carbon atoms were generated in high yields using AlCl₃ as a catalyst. Soon afterwards, a highly efficient Fe(OTf)₃-promoted normal [3+2] cycloaddition of thionoesters with D–A cyclopropanes was developed for the synthesis of *trans*-configured tetrahydrothiophenes (Scheme 1b).²¹ As an odorless, cheap, and easy-to-handle sulfur source,²² thiourea has never previously been employed to react with D–A cyclopropanes. Herein, we report the Yb(OTf)₃-catalyzed [3+2] cycloaddition of thiourea with D–A cyclopropanes to generate 2-amino-4,5-dihydrothiophene derivatives with only one ester group at the C3 position of thiophene (Scheme 1c).

Initially, D–A cyclopropane **1a** and thiourea **2a** were selected as the model reactants (Table 1). When Cu(OTf)₂ or Ni(OTf)₂ was employed as a Lewis acid catalyst, the reaction did not

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Scheme 1 Different C=S 2π components react with D-A cyclopropanes.

Table 1 Optimization of the reaction conditions^a

Entry	LA	Solvent	T (°C)	Base	Yield ^b (%)	
					3aa	4aa
1	Cu(OTf) ₂	CH ₂ Cl ₂	rt	—	NR	—
2	Ni(OTf) ₂	CH ₂ Cl ₂	rt	—	NR	—
3	MgI ₂	CH ₂ Cl ₂	rt	—	9	—
4	Yb(OTf) ₃	CH ₂ Cl ₂	rt	—	15	—
5	Sc(OTf) ₃	CH ₂ Cl ₂	rt	—	—	7
6	Yb(OTf) ₃	CHCl ₃	rt	—	Trace	—
7	Yb(OTf) ₃	DCE	rt	—	29	—
8	Yb(OTf) ₃	DCE	90	—	41	—
9	Yb(OTf) ₃	DCE	90	CS ₂ CO ₃	53	—
10	Yb(OTf) ₃	DCE	90	Na ₂ CO ₃	61	—
11	Yb(OTf) ₃	DCE	90	Rb ₂ CO ₃	65	—
12	Yb(OTf) ₃	DCE	90	Et ₃ N	NR	—
13 ^c	Yb(OTf) ₃	DCE	90	Rb ₂ CO ₃	84	—
14 ^d	Yb(OTf) ₃	DCE	90	Rb ₂ CO ₃	43	—

^a Unless otherwise noted, the reaction conditions were: **1a** (0.2 mmol), **2a** (0.4 mmol), LA (10 mol%), solvent (3.0 mL), and base (20 mol%) at rt for 8 h. ^b Isolated yield. ^c Yb(OTf)₃ (20 mol%). ^d **2a** (0.2 mmol) was used. NR = no reaction.

occur (entries 1 and 2). When MgI₂ was used, 2-amino-4,5-dihydrothiophene **3aa**, which has only one ester group at the C3 position of dihydrothiophene, was obtained in 9% yield (entry 3). When the Lewis acid was changed to Yb(OTf)₃, the yield of **3aa** increased to 15% (entry 4). In the presence of Sc(OTf)₃, only the cyclic imine **4aa**, which has two ester groups at the C3 position of dihydrothiophene, was generated (entry 5). The solvents were then explored, and DCE is the optimal solvent (entries 4, 6 and 7). Increasing the temperature from rt to 90 °C resulted in an enhanced yield (entries 7 and 8). Several bases were then added, and the inorganic base Rb₂CO₃ delivered monoester **3aa** in a better yield (entries 9–12). The cycloadduct **3aa** can be afforded in 84% yield when 20 mol% of Yb(OTf)₃ was employed (entry 13). When 1 equiv. of thiourea **2a** was employed, the yield decreased (entry 14).

Under the optimized reaction conditions (Table 1, entry 13), the scope of D-A cyclopropanes was explored (Scheme 2). For cyclopropanes bearing electron-rich substituents at the aryl moieties, the adducts **3ba–3fa** were produced in 65–83% yields. In the case of naphthalene-2-yl cyclopropane **1g** and tetrahydronaphthalene-derived cyclopropane **1h**, the adducts **3ga** and **3ha**

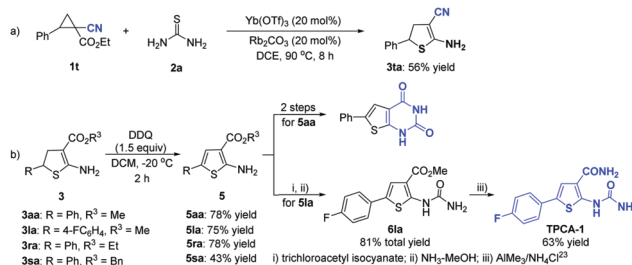


Scheme 2 Substrate scope of D-A cyclopropanes. ^a Unless otherwise noted, the reaction conditions are: **1a–1s** (0.2 mmol), **2a** (0.4 mmol), Yb(OTf)₃ (20 mol%), Rb₂CO₃ (20 mol%), and DCE (3.0 mL) at 90 °C for 8 h. Isolated yields were reported. ^b Reaction time: 24 h.

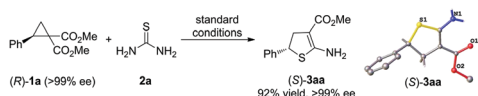
could also be obtained. For the cyclopropanes with electron-withdrawing groups at the aryl moieties, the adducts **3ia–3oa** were given in 62–86% yields. The structure of adduct **3na** was determined by X-ray diffraction analysis. With respect to cyclopropanes with an alkyl group as the donor-substituent, the adducts **3pa** and **3qa** were afforded in 80–82% yields. In addition, D-A cyclopropanes with different ester groups were good reactants. It should be noted that the geminal diesters **4** were not observed in all of the cases.

When ethyl 1-cyano-2-phenylcyclopropane-1-carboxylate **1t** was reacted with thiourea **2a**, the ester group was removed and the cyano group remained, giving the 2-amino-3-cyano-4,5-dihydrothiophene **3ta** in 56% yield (Scheme 3a). Then, several 2-amino-4,5-dihydrothiophenes (**3aa**, **3la**, **3ra**, and **3sa**) were selected as the representative substrates to react with DDQ, and the oxidation products, 2-aminothiophene derivatives (**5aa**, **5la**, **5ra**, and **5sa**), were obtained in 43–78% yields (Scheme 3b). As for 2-aminothiophene **5aa**, the corresponding ring-fused thienopyrimidinone could be afforded in 2 steps.²⁴ With 2-aminothiophene **5la** as the reactant, the desired small-molecule IκB kinase β inhibitor TPCA-1 could be generated in 3 steps (Scheme 3b).²³

Stereospecificity of the cycloaddition was explored using the enantiopure cyclopropane (*R*)-**1a** (>99% ee), and (*S*)-**3aa** was obtained in 92% yield and >99% ee (Scheme 4). The absolute



Scheme 3 (a) Synthesis of 2-amino-3-cyano-4,5-dihydrothiophene; (b) transformation of 2-amino-4,5-dihydrothiophenes.



Scheme 4 Stereospecificity experiments.

configurations of (*R*)-**1a** and (*S*)-**3aa** were determined by X-ray analysis, and these configurations confirmed that an inversion at the stereogenic center was observed.

To understand the cycloaddition process, several control experiments were performed (Fig. 2). When $\text{Sc}(\text{OTf})_3$ was used as the catalyst, the reaction between cyclopropane **1a** and thiourea **2a** generated cycloadduct **4aa** and released NH_3 gas (Fig. 2a(i)). The released NH_3 gas was detected by wet red litmus paper with blue color. When 1-methylthiourea **2b** was used to react with cyclopropane **1a**, NH_3 or CH_3NH_2 could also be released (see ESI† for details). After that, geminal diester **4aa** was then reacted with thiourea **2a** in the presence of $\text{Yb}(\text{OTf})_3$, and the final product **3aa** was formed in 87% yield within 0.5 h, indicating that the geminal diester **4aa** might be an intermediate in the model reaction (Fig. 2b(ii)). Meanwhile, in the formation of monoester **3aa** from geminal diester **4aa**, an esterified thiourea **7aa** was obtained (52% yield) and confirmed by X-ray diffraction analysis, which showed that thiourea **2a** might function as a decarboxylation reagent (Fig. 2b(ii)). In the absence of thiourea **2a**, geminal diester **4aa** could also be converted into monoester **3aa** with the release of CO_2 gas, which was captured by 2-phenyloxirane (Fig. 2b(iii)). By comparing different reaction times (0.5 h vs. 1 h), the decarboxylation step proceeded faster in the presence of thiourea **2a** (Fig. 2b(ii) and (iii)). Finally, the cycloaddition of D-A cyclopropane **1a** with thiourea **2a** produced the monoester **3aa** (78% yield), esterified thiourea **7aa** (45% yield), NH_3 gas, CO_2 gas, and a ring-opened triester **8aa** (see ESI† for details) under the standard conditions (Fig. 2c(iv)). Formation of the esterified thiourea **7aa** in a large proportion indicates that thiourea **2a** participated in the decarboxylation reaction and was the main pathway during the decarboxylation step.

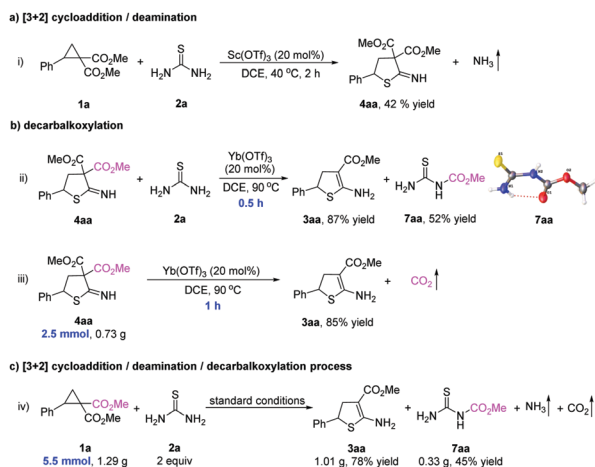
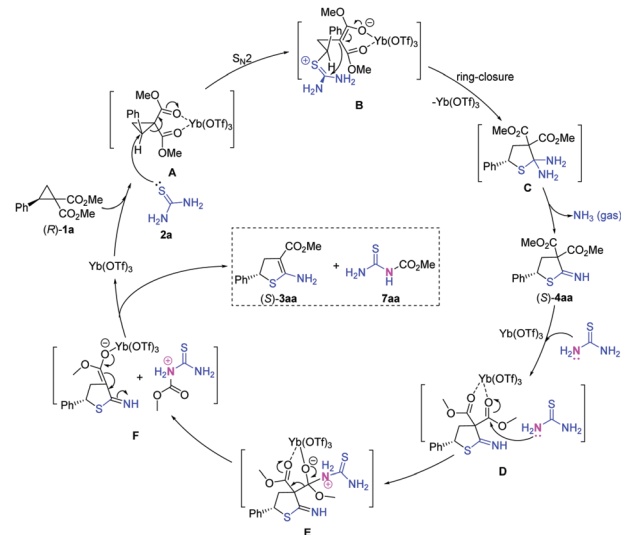


Fig. 2 Preliminary mechanistic studies.



Scheme 5 Proposed reaction pathways for the domino process.

A plausible sequential mechanism of [3+2] cycloaddition/deamination/decarboxylation was proposed for this reaction on the basis of the stereospecificity experiments (Scheme 4) and preliminary mechanistic studies (Fig. 2), and this mechanism is depicted in Scheme 5. First, D-A cyclopropane (*R*)-**1a** is activated by $\text{Yb}(\text{OTf})_3$ via coordination with the geminal diester moiety (**A**). The sulfur atom in thiourea **2a** attacks the activated cyclopropane (*R*)-**1a** in an $\text{S}_{\text{N}}2$ manner to produce the zwitterionic intermediate (**B**),^{11a-c} which generates the cycloadduct 4,5-dihydrothiophene (**C**) through a ring-closure step. Because two amino groups are both connected at the C2 position in the dihydrothiophene (**C**), the dihydrothiophene (**C**) is unstable and produces the cyclic imine (*S*)-**4aa** along with a release of NH_3 gas. The cyclic imine (*S*)-**4aa** is activated by $\text{Yb}(\text{OTf})_3$ via coordination with the geminal diester moiety to enhance the positive charge at the carbonyl group (**D**). The nitrogen atom in another thiourea **2a** attacks the carbonyl group and generates the tetrahedral intermediate (**E**).²⁵ The crowded tetrahedral intermediate eliminates the protonated methyl carbamothioyl-carbamate and generates the dihydrothiophene anion with a single ester group (**F**). Finally, the dihydrothiophene anion deprotonates the protonated methyl carbamothioyl-carbamate, generating 2-amino-4,5-dihydrothiophene (*S*)-**3aa** and the esterified thiourea **7aa** and releasing $\text{Yb}(\text{OTf})_3$.

In summary, thiourea, which is an odorless, cheap, and easy-to-handle sulfur source, was developed to react with D-A cyclopropanes to construct 2-amino-dihydrothiophenes. In this reaction, thiourea exhibited three functions: (1) providing a $\text{C}=\text{S}$ double bond, (2) serving as an amino source for the 2-amino thiophenes, and (3) acting as a decarboxylation reagent. Through a $\text{Yb}(\text{OTf})_3$ -catalyzed [3+2] cycloaddition/deamination/decarboxylation domino process, a range of D-A cyclopropanes could produce 2-amino-4,5-dihydrothiophenes in moderate to good yields (up to 92% yield).

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Conflicts of interest

There are no conflicts to declare.

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