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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]

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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 thioketones 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 $AlCl_3$ 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_2Cl_2	rt	—	NR	
2	$Ni(OTf)_2$	CH_2Cl_2	rt	—	NR	
3	MgI_2	CH_2Cl_2	rt	—	9	—
4	$Yb(OTf)_3$	CH_2Cl_2	rt	—	15	—
5	$Sc(OTf)_3$	CH_2Cl_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_2CO_3	53	—
10	$Yb(OTf)_3$	DCE	90	Na_2CO_3	61	—
11	$Yb(OTf)_3$	DCE	90	Rb_2CO_3	65	—
12	$Yb(OTf)_3$	DCE	90	Et_3N	NR	
13[c]	$Yb(OTf)_3$	DCE	90	Rb_2CO_3	84	
14[d]	$Yb(OTf)_3$	DCE	90	Rb_2CO_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 MgI_2 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 Rb_2CO_3 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%), Rb_2CO_3 (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 thienopyrimidinedione 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 $Sc(OTf)_3$ 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 $Yb(OTf)_3$, 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 $Yb(OTf)_3$ *via* coordination with the geminal diester moiety (**A**). The sulfur atom in thiourea **2a** attacks the activated cyclopropane (*R*)-**1a** in an S_N2 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 $Yb(OTf)_3$ *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 carbamothioylcarbamate and generates the dihydrothiophene anion with a single ester group (**F**). Finally, the dihydrothiophene anion deprotonates the protonated methyl carbamothioylcarbamate, generating 2-amino-4,5-dihydrothiophene (*S*)-**3aa** and the esterified thiourea **7aa** and releasing $Yb(OTf)_3$.

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 C═S double bond, (2) serving as an amino source for the 2-amino thiophenes, and (3) acting as a decarboxylation reagent. Through a $Yb(OTf)_3$-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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