ChemComm

COMMUNICATION

Check for updates

Cite this: Chem. Commun., 2019, 55, 1580

Received 3rd December 2018, Accepted 7th January 2019

DOI: 10.1039/c8cc09595g

rsc.li/chemcomm

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

Ming-Sheng Xie, D Guo-Feng Zhao, Tao Qin, Yong-Bo Suo, Gui-Rong Qu and Hai-Ming Guo *

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 I κ B 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 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 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-4,5dihydrothiophene 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



View Article Online

Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China. E-mail: ghm@htu.edu.cn

[†] Electronic supplementary information (ESI) available. CCDC 1849437 (3na), 1852130 ((*R*)-1a), 1852128 ((*S*)-3aa), 1852129 (7aa) and 1852131 (8aa). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc09595g

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

Table 1 Optimization of the reaction conditions^a

	Ph CO ₂ Me +		(10 mol%) Solvent ase, 8 h Ph	CO2Me M + NH2 Ph-	eO ₂ C CO ₂ Me	
	1a	2a		3aa	4aa	
					Yield ^{b} (%)	
Entry	LA	Solvent	$T(^{\circ}C)$	Base	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 ₂ CO ₃	61	_
11	Yb(OTf) ₃	DCE	90	Rb_2CO_3	65	_
12	Yb(OTf) ₃	DCE	90	Et ₃ N	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 MgI2 was used, 2-amino-4,5dihydrothiophene 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 $^{\circ}$ 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. ^bReaction time: 24 h.

could also be obtained. For the cyclopropanes with electronwithdrawing 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 IKB 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.



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 NH₃ gas (Fig. 2a(i)). The released NH₃ gas was detected by wet red litmus paper with blue color. When 1-methylthiourea 2b was used to react with cyclopropane 1a, NH₃ or CH₃NH₂ 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 CO2 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), NH₃ gas, CO₂ 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 NH₃ 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).

We are grateful for the financial support from the NSFC (No. 21472037 and 21672055), China Postdoctoral Science Foundation

funded project (2016M592293 and 2018T110726), and the 111 Project (No. D17007).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 Y. Huang and A. Dömling, Mol. Diversity, 2011, 15, 3.
- 2 H. Y. Meltzer and H. C. Fibiger, *Neuropsychopharmacology*, 1996, 14, 83.
- 3 P. D. Kalariya, P. N. Patel, P. Kavya, M. Sharma, P. Garg, R. Srinivas and M. V. N. K. Talluri, *J. Mass Spectrom.*, 2015, **50**, 1222.
- 4 (a) X. Li, D. Conklin, H.-L. Pan and J. C. Eisenach, *J. Pharmacol. Exp. Ther.*, 2003, **305**, 950; (b) P. L. Podolin, J. F. Callahan, B. J. Bolognese, Y. H. Li, K. Carlson, T. G. Davis, G. W. Mellor, C. Evans and A. K. Roshak, *J. Pharmacol. Exp. Ther.*, 2005, **312**, 373.
- 5 A. Walburger, A. Koul, G. Ferrari, L. Nguyen, C. Prescianotto-Baschong, K. Huygen, B. Klebl, C. Thompson, G. Bacher and J. Pieters, *Science*, 2004, 304, 1800.
- 6 E. S. Darwish, Molecules, 2008, 13, 1066.
- 7 (a) K. Gewald, E. Schinke and H. Böttcher, *Chem. Ber.*, 1966, 99, 94;
 (b) R. W. Sabnis, D. W. Rangnekar and N. D. Sonawane, *J. Heterocycl. Chem.*, 1999, 36, 333; (c) H. Özbek, I. S. Veljkovic and H.-U. Reissig, *Synlett*, 2008, 3145.
- 8 P. Gopinath and S. Chandrasekaran, J. Org. Chem., 2011, 76, 700.
- 9 (a) H.-U. Reissig and R. Zimmer, Chem. Rev., 2003, 103, 1151;
 (b) M. Yu and B. L. Pagenkopf, Tetrahedron, 2005, 61, 321;
 (c) C. A. Carson and M. A. Kerr, Chem. Soc. Rev., 2009, 38, 3051;
 (d) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano and J. Waser, Chem. Commun., 2014, 50, 10912; (e) T. F. Schneider, J. Kaschel and D. B. Werz, Angew. Chem., Int. Ed., 2014, 53, 5504;
 (f) M. A. Cavitt, L. H. Phun and S. France, Chem. Soc. Rev., 2014, 43, 804; (g) H. K. Grover, M. R. Emmett and M. A. Kerr, Org. Biomol. Chem., 2015, 13, 655.
- Selected examples with C=C: (a) D. B. England, T. D. O. Kuss, R. G. Keddy and M. A. Kerr, J. Org. Chem., 2001, 66, 4704; (b) F. de Nanteuil and J. Waser, Angew. Chem., Int. Ed., 2011, 50, 12075; (c) B. M. Trost and P. J. Morris, Angew. Chem., Int. Ed., 2011, 50, 6167; (d) H. Xiong, H. Xu, S. Liao, Z. Xie and Y. Tang, J. Am. Chem. Soc., 2013, 135, 7851; (e) F. de Nanteuil, E. Serrano, D. Perrotta and J. Waser, J. Am. Chem. Soc., 2014, 136, 6239; (f) S. Racine, F. de Nanteuil, E. Serrano and J. Waser, Angew. Chem., Int. Ed., 2014, 53, 8484.
- Selected examples with C—O: (a) P. D. Pohlhaus and J. S. Johnson, J. Am. Chem. Soc., 2005, 127, 16014; (b) P. D. Pohlhaus and J. S. Johnson, J. Org. Chem., 2005, 70, 1057; (c) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li and J. S. Johnson, J. Am. Chem. Soc., 2008, 130, 8642; (d) A. T. Parsons and J. S. Johnson, J. Am. Chem. Soc., 2009, 131, 3122.

- 12 Selected examples with C—N: (a) C. A. Carson and M. A. Kerr, J. Org. Chem., 2005, 70, 8242; (b) S. K. Jackson, A. Karadeolian, A. B. Driega and M. A. Kerr, J. Am. Chem. Soc., 2008, 130, 4196; (c) A. T. Parsons, A. G. Smith, A. J. Neel and J. S. Johnson, J. Am. Chem. Soc., 2010, 132, 9688; (d) D.-C. Wang, M.-S. Xie, H.-M. Guo, G.-R. Qu, M.-C. Zhang and S.-L. You, Angew. Chem., Int. Ed., 2016, 55, 14111; (e) J. Preindl, S. Chakrabarty and J. Waser, Chem. Sci., 2017, 8, 7112; (f) M.-C. Zhang, D.-C. Wang, M.-S. Xie, G.-R. Qu, H.-M. Guo and S.-L. You, Chem, 2019, 5, 156.
- With N=O: (a) S. Chakrabarty, I. Chatterjee, B. Wibbeling, C. G. Daniliuc and A. Studer, Angew. Chem., Int. Ed., 2014, 53, 5964With N=N: (b) V. S. Korotkov, O. V. Larionov, A. Hofmeister, J. Magull and A. de Meijere, J. Org. Chem., 2007, 72, 7504.
- 14 Selected examples with C ≡ C: (a) V. K. Yadav and V. Sriramurthy, Angew. Chem., Int. Ed., 2004, 43, 2669; (b) S. Racine, B. Hegedüs, R. Scopelliti and J. Waser, Chem. – Eur. J., 2016, 22, 11997.
- 15 Selected examples with C≡N: (*a*) M. Yu and B. L. Pagenkopf, *Org. Lett.*, 2003, 5, 5099; (*b*) M. Yu and B. L. Pagenkopf, *J. Am. Chem. Soc.*, 2003, **125**, 8122.
- 16 Selected examples with nitrones: (a) I. S. Young and M. A. Kerr, Angew. Chem., Int. Ed., 2003, 42, 3023; (b) M. P. Sibi, Z. Ma and C. P. Jasperse, J. Am. Chem. Soc., 2005, 127, 5764; (c) Y.-B. Kang, X.-L. Sun and Y. Tang, Angew. Chem., Int. Ed., 2007, 46, 3918; (d) P.-W. Xu, J.-K. Liu, L. Shen, Z.-Y. Cao, X.-L. Zhao, J. Yan and J. Zhou, Nat. Commun., 2017, 8, 1619.
- Selected examples with heterocumulenes: (a) C. Brückner and H.-U. Reissig, Angew. Chem., Int. Ed. Engl., 1985, 24, 588; (b) A. F. G. Goldberg, N. R. O'Connor, R. A. Craig II and B. M. Stoltz, Org. Lett., 2012, 14, 5314; (c) Y. Sun, G. Yang, Z. Chai, X. Mu and J. Chai, Org. Biomol. Chem., 2013, 11, 7859; (d) D. Gladow and H.-U. Reissig, J. Org. Chem., 2014, 79, 4492.
- 18 Selected examples with other dipolarophiles: (a) T. P. Lebold, A. B. Leduc and M. A. Kerr, Org. Lett., 2009, **11**, 3770; (b) S.-W. Wang, W.-S. Guo, L.-R. Wen and M. Li, RSC Adv., 2015, **5**, 47418; (c) H. Xu, J.-L. Hu, L. Wang, S. Liao and Y. Tang, J. Am. Chem. Soc., 2015, **137**, 8006; (d) Z. Su, S. Qian, S. Xue and C. Wang, Org. Biomol. Chem., 2017, **15**, 7878.
- 19 Selected examples with nucleophiles: (a) Y. Xia, X. H. Liu, H. F. Zheng, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2015, 54, 227; (b) Y. Xia, L. L. Lin, F. Z. Chang, X. Fu, X. H. Liu and X. M. Feng, *Angew. Chem., Int. Ed.*, 2015, 54, 13748; (c) Y. Xia, L. L. Lin, F. Z. Chang, Y. T. Liao, X. H. Liu and X. M. Feng, *Angew. Chem., Int. Ed.*, 2016, 55, 12228.
- 20 (a) A. U. Augustin, M. Sensse, P. G. Jones and D. B. Werz, Angew. Chem., Int. Ed., 2017, 56, 14293; (b) A. U. Augustin, M. Busse, P. G. Jones and D. B. Werz, Org. Lett., 2018, 20, 820; (c) A. Kreft, P. G. Jones and D. B. Werz, Org. Lett., 2018, 20, 2059.
- 21 Y. Matsumoto, D. Nakatake, R. Yazaki and T. Ohshima, *Chem. Eur. J.*, 2018, **24**, 6062.
- (a) G.-p. Lu, F. Chen and C. Cai, J. Chem. Educ., 2017, 94, 244;
 (b) J. Wang, Q.-Y. Zhang, M.-S. Xie, D.-C. Wang, G.-R. Qu and H.-M. Guo, Org. Lett., 2018, 20, 6578.
- 23 D. C. Cole, U.S. Pat. Appl., US20050038088 A1, 2005.
- 24 J. M. Salamoun, K. E. McQueeney, K. Patil, S. J. Geib, E. R. Sharlow, J. S. Lazo and P. Wipf, *Org. Biomol. Chem.*, 2016, **14**, 6398.
- 25 D. H. Miles and B.-S. Huang, J. Org. Chem., 1976, 41, 208.