Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2024, **22**, 1834

Lewis acid-catalyzed one-pot thioalkenylation of donor–acceptor cyclopropanes using *in situ* generated dithiocarbamates and propiolates†

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Received 10th January 2024,
Accepted 2nd February 2024

DOI: 10.1039/d4ob00053f

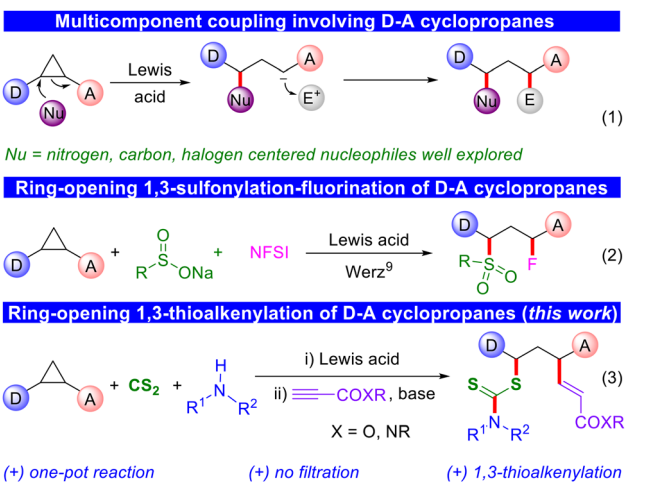
rsc.li/obc

Lewis acid-catalyzed one-pot 1,3-thioalkenylation of donor–acceptor (D–A) cyclopropanes has been demonstrated employing *in situ* generated dithiocarbamates (from amines and CS_2) as nucleophilic triggers and alkyl propiolates as electrophiles. This method addresses the limitations of previously known carbothiolation approach, eliminating the need for extra filtration prior to the subsequent trapping with electrophiles. The anticipated thioalkenylated products were obtained in good to excellent yields with a moderate to good *E*/*Z* ratio. Three new bonds (C–N, C–S, and C–C) are formed during this 1,3-bisfunctionalization reaction. Notably, employing enantiomerically pure D–A cyclopropanes resulted in enantiopure 1,3-thioalkenylated products, underscoring the stereospecific nature of the developed reaction.

Introduction

Donor–acceptor cyclopropanes have been recognized as important three-carbon building blocks in organic synthesis.[1] The merger of ring strain and bond polarization through the adjacent placement of an electron-donating and electron-withdrawing group facilitates a broad spectrum of chemical reactions, which are otherwise difficult to be envisioned.[2] Familiar instances encompass cycloadditions, rearrangements, and ring-opening reactions, providing a quick and efficient means to attain intricate molecular scaffolds.[3] These transformations have already been utilized in several total syntheses, incorporating D–A cyclopropane-derived motifs at intermediate stages.[4] However, there have been limited investigations into the methods of 1,3-bisfunctionalization of D–A cyclopropanes.[5] The primary hurdle involves the controlled delivery of a nucleophile and an electrophile in a manner that directs their preference for reacting with the donor–acceptor cyclopropanes, rather than spontaneously with each other. Achieving ring-opening 1,3-bisfunctionalization reactions can be accomplished using two distinct methods. The first method involves an insertion reaction, which is relatively straightforward due to its low risk of side reactions.[6] The second option is a multi-component coupling, which poses a comparatively greater challenge in execution (Scheme 1, eqn (1)).[7]

Within the realm of 1,3-bisfunctionalization of donor–acceptor (D–A) cyclopropanes, the exploration has primarily focused on nitrogen, carbon, and halogen centred nucleophiles. For instance, Studer and co-workers showcased the 1,3-aminobromination of D–A cyclopropanes,[7a] while Werz and co-workers employed a related strategy to demonstrate the 1,3-aminothiolation of D–A cyclopropanes.[7b] Furthermore, Saha and co-workers revealed a 1,3-bisarylation of D–A cyclopropanes using a multicomponent coupling approach.[7c] However, the utilization of sulfur-based nucleophilic triggers in the



Scheme 1 1,3-Bisfunctionalization of D–A cyclopropanes.

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ob00053f

1,3-bisfunctionalization of D–A cyclopropanes has received limited consideration. Along these lines, our group reported a two-step carbothiolation of D–A cyclopropanes, necessitating a filtration step before the subsequent alkylation.[8] More recently, the Werz group also demonstrated 1,3-sulfonylation–fluorination using sulfinate salts as nucleophiles (eqn (2)).[9] Considering the scarce existing literature on sulfur-based nucleophilic triggers to open D–A cyclopropanes, we conceived a one-pot thioalkenylation method for D–A cyclopropanes (eqn (3)). This method involves the *in situ* generation of dithiocarbamates (from amines and CS_2) as nucleophilic triggers and the use of alkyl propiolates as electrophiles. A significant advantage of this approach is that it overcomes the limitation of the previous two-pot carbothiolation process, which required additional filtration. A similar one-pot strategy for 1,3-carbocarbonation was already reported by Werz and co-workers due to the compatibility issue of nucleophiles and electrophiles.[10] Notably, organosulfur motifs hold considerable importance in pharmaceuticals, materials, and agrochemicals.[11]

Results and discussion

With the envisioned thioalkenylation method for D–A cyclopropanes in mind, the present studies were initiated by the treatment of cyclopropane **1a** with piperidine **2a** and CS_2 in the presence of $Yb(OTf)_3$ in THF at 25 °C for 16 h, and this was followed by the treatment of methyl propiolate **3a** and Cs_2CO_3. Interestingly, under these one-pot reaction conditions, the expected 1,3-thioalkenylated product **4a** was isolated in 77% yield with a 5 : 1 *E*/*Z* ratio (Table 1, entry 1). Changing the stoichiometry of CS_2 led to a reduction in the yield of **4a** to 63% with a 4 : 1 *E*/*Z* ratio (entry 2). Similarly, decreasing the quantities of **2a** and **3a** also resulted in diminished product yields, while maintaining a similar *E*/*Z* ratio (entries 3 and 4). Variations in solvents further resulted in diminished product yields (entries 5 and 6). Further optimizations by reducing the catalyst loading or use of other Lewis acids proved ineffective (entries 7–9). The use of organic bases, such as DBU and DABCO, did not yield any product, and only a 24% yield of **4a** with a 4 : 1 *E*/*Z* ratio was obtained in the presence of K_2CO_3 (entries 10–12).

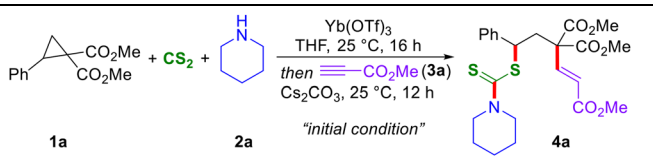
Consequently, entry 1 was selected as the optimized reaction condition and was subsequently employed for further analysis of substrate scope.[12]

With the optimized reaction conditions in hand, first, we evaluated the scope of D–A cyclopropanes (Scheme 2). A diverse range of structurally and electronically different D–A cyclopropanes bearing electron-rich, -neutral, and -poor functional groups at the 4-position of the arene ring on the donor end underwent a smooth reaction, and the corresponding products were formed in good to excellent yields with a good *E*/*Z* ratio (**4a–4e**). Furthermore, D–A cyclopropanes having substitution at the 3- and 2-positions on the benzene ring reacted effectively under the current optimized conditions, leading to the formation of the anticipated products in good yields (**4f–4h**). The presence of a di-substituted aryl ring and naphthyl-containing D–A cyclopropanes resulted in the formation of the desired 1,3-thioalkenylated products in moderate yields and with a moderate *E*/*Z* ratio (**4i** and **4j**). Additionally, the reaction can be extended to incorporate heteroatoms and diverse ester moieties on D–A cyclopropanes, thereby expanding the scope of the reaction (**4k** and **4l**).

Next, we examined the variation on secondary amines. A variety of cyclic secondary aliphatic amines with different ring sizes displayed successful reactivity under the optimized one-pot reaction conditions, resulting in the formation of the corresponding 1,3-thioalkenylated products in good yields and with a moderate *E*/*Z* ratio (**4m–4o**). Moreover, various acyclic secondary aliphatic amines delivered the expected 1,3-bisfunctionalized products in good yields and with a moderate to good *E*/*Z* ratio (**4p–4r**). Notably, alkyl propiolates having different ester substitutions also worked well under the present reaction conditions, thus expanding the scope of the reaction further (**4s** and **4t**). Interestingly, the utilization of *N*,*N*-dibenzyl propiolamide as the electrophilic fourth component resulted in the formation of the anticipated thioalkenylated product **4u** in 73% yield with a >19 : 1 *E*/*Z* ratio.[13]

To gain insight into the mechanism of the present four-component reaction, few mechanistic experiments were performed. Initially, all the components were added together to check whether the desired 1,3-thioalkenylated product is formed or not. As expected, the four-component coupling product **4a** was not formed. Instead, the *in situ* generated dithiocarbamate was directly added to the methyl propiolate to furnish product **5a** in 46% yield (Scheme 3, eqn (4)). This

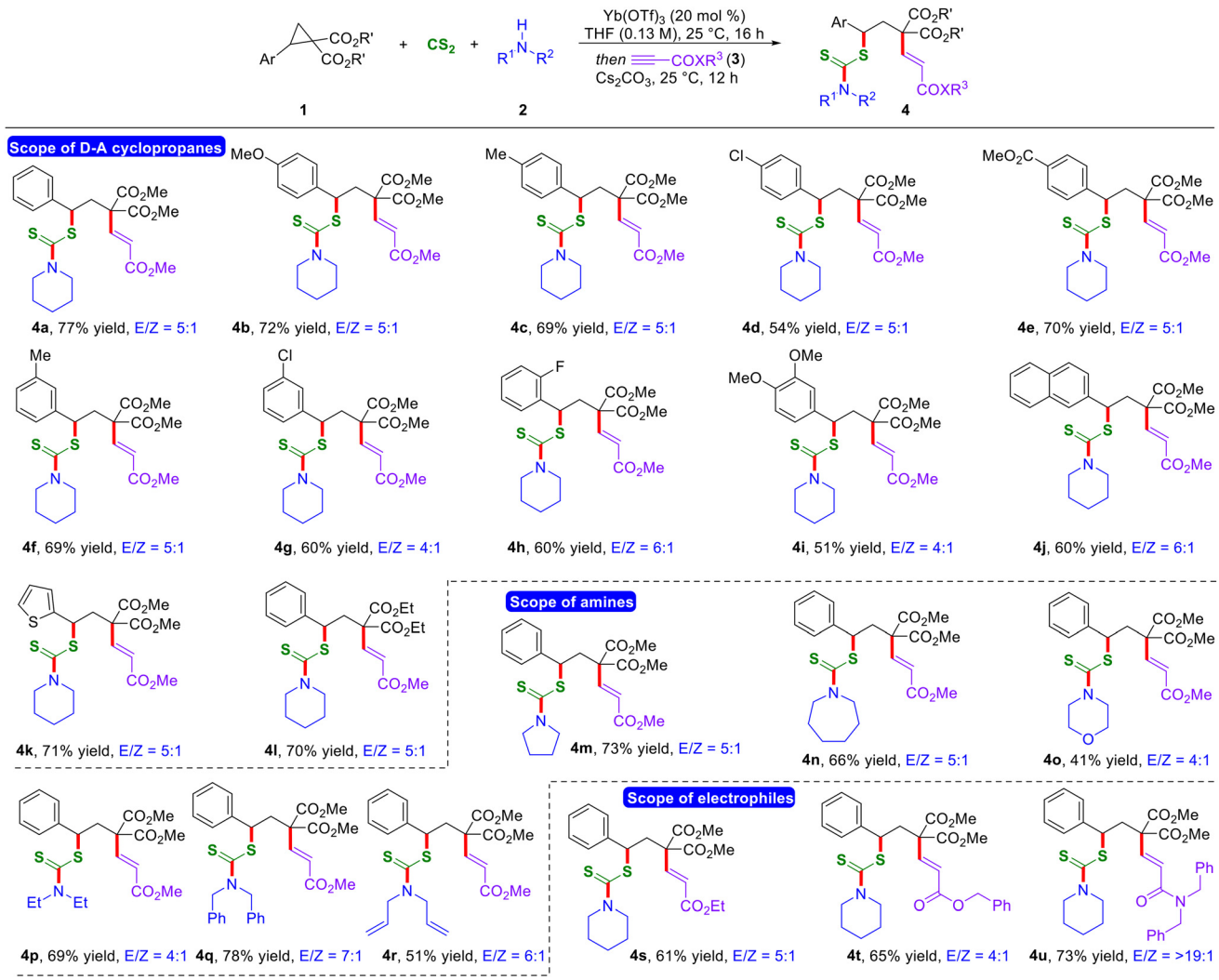
Table 1 Optimization of the reaction conditions[a]



1a 2a 4a

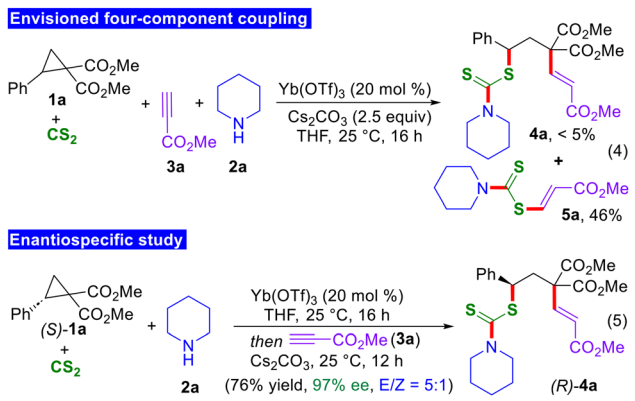
Entry	Variation of the initial conditions[a]	Yield of **4a**[b] (%)	*E* : *Z*[c]
1	*None*	*78 (77)*	*5 : 1*
2	1.5 equiv. of CS_2 instead of 2.0 equiv.	63	4 : 1
3	1.5 equiv. of **2a** instead of 2.0 equiv.	68	4 : 1
4	1.5 equiv. of **3a** instead of 2.0 equiv.	65	4 : 1
5	DCE instead of THF	70	5 : 1
6	CH_2Cl_2 instead of THF	16	4 : 1
7	10 mol% of $Yb(OTf)_3$ instead of 20 mol%	30	4 : 1
8	$Sc(OTf)_3$ instead of $Yb(OTf)_3$	18	5 : 1
9	$Sn(OTf)_2$ instead of $Yb(OTf)_3$	10	4 : 1
10	DBU instead of Cs_2CO_3	<5	Nd
11	DABCO instead of Cs_2CO_3	<5	Nd
12	K_2CO_3 instead of Cs_2CO_3	24	4 : 1

[a] Initial conditions: **1a** (0.2 mmol), CS_2 (0.4 mmol), **2a** (0.4 mmol), $Yb(OTf)_3$ (20 mol%), THF (1.5 mL) for 16 h, and then a base (2.5 equiv.) and **3a** (2.0 equiv.) for 12 h. [b] The yield was determined on the basis of ^{1}H NMR of the crude reaction mixture using CH_2Br_2 as the internal standard. The isolated yield of **4a** is given in parentheses. [c] The *E*/*Z* ratio was determined from ^{1}H NMR of the crude reaction mixture. Nd indicates not determined.



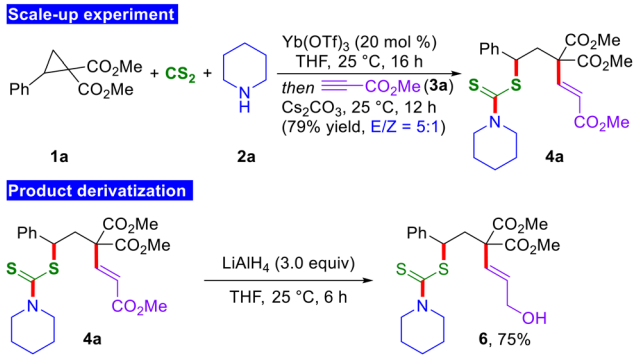
Scheme 2 Substrate scope of the reaction. [a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), CS_2 (0.4 mmol), **2** (0.4 mmol), $Yb(OTf)_3$ (20 mol%), THF (1.5 mL), 25 °C for 16 h, and then Cs_2CO_3 (2.5 equiv.), alkyl propiolate **3** (2.0 equiv.), 12 h. Yields of the isolated products are given. The *E*/*Z* ratio was determined using ^1H NMR of the crude reaction mixture.

observation underscored the significance of the one-pot protocol, wherein the expected thioalkenylated products were consistently obtained as the major products in all cases. Moreover, to elucidate the mode of addition of dithiocarbamates to D–A cyclopropanes, an experiment was performed using enantiomerically pure D–A cyclopropanes. When the bisfunctionalization reaction was conducted in the presence of (*S*)-**1a**, the 1,3-thioalkenylated product (*R*)-**4a** was isolated in 76% yield with 97% enantiomeric excess (eqn (5)). This study provides insights into the S_N2-type addition of the *in situ* generated dithiocarbamates to D–A cyclopropanes.[14,15]

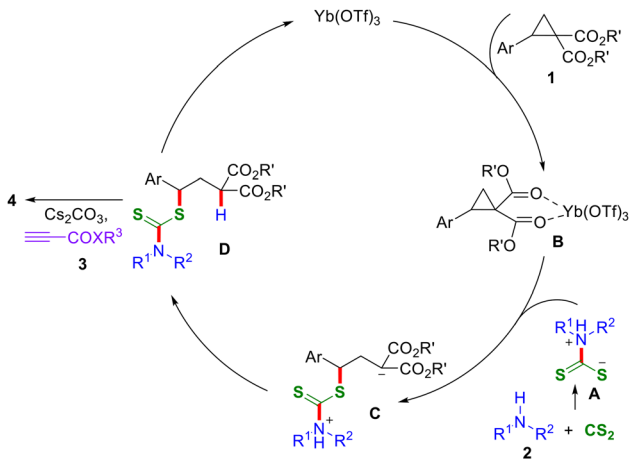


Scheme 3 Mechanistic experiments.

In order to illustrate the practical applicability of the current 1,3-bisfunctionalization reaction, the reaction was conducted on a 2.0 mmol scale. Gratifyingly, during the scale-up experiment, the anticipated product **4a** was generated in a 79% yield and with a 5 : 1 *E*/*Z* ratio, without compromising reactivity and selectivity (Scheme 4). This underscores the practical and scalable nature of the present methodology. In addition, selective reduction of the α,β-unsaturated ester moiety of **4a** was accomplished by treatment with $LiAlH_4$ to furnish the allylic alcohol derivative **6** in 75% yield.



Scheme 4 Scale-up experiment and product derivatization.



Scheme 5 Tentative mechanism of the reaction.

Mechanistically, the reaction proceeds *via* the nucleophilic addition of amine **2** to CS_2, resulting in the formation of a dithiocarbamate intermediate **A** (Scheme 5). This intermediate **A** is then added to the Lewis acid-activated D–A cyclopropane **B**, forming the ring-opened intermediate **C** by the S_N2-type addition. Following this, intermediate **C** undergoes a proton-transfer step to form the monofunctionalized intermediate **D**. Subsequently, deprotonation of intermediate **D** with Cs_2CO_3 followed by alkenylation ultimately resulted in the formation of the thioalkenylated product **4**. The observed diastereoselectivity can be rationalized based on the thermodynamic stability of the diastereomer, wherein the most stable diastereomer forms predominantly.

Conclusions

In conclusion, we have established a versatile and mild one-pot procedure for the 1,3-thioalkenylation of D–A cyclopropanes. The current reaction conditions exhibit compatibility with diverse functional groups, consistently yielding the anticipated products in moderate to good yields and with a good *E*/*Z* ratio in all instances. Notably, enantiopure D–A cyclopropanes produce the corresponding enantiopure products, showcasing the S_N2 type addition of dithiocarbamates to D–A cyclopropanes. Related multicomponent coupling reactions involving D–A cyclopropanes are being explored in the ongoing research in our laboratory.

Data availability

Details on the experimental procedures and the characterization data of all 1,3-thioalkenylation products.

Author contributions

A. G. and A. T. B. conceived the idea and designed the experiments. A. G. performed the optimization studies. S. H. and L. T. K. K. performed the substrate scope analysis and mechanistic studies. A. G. and A. T. B. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support by the Science and Engineering Research Board (SERB), Government of India (File Number: SCP/2022/000837) is greatly acknowledged. A. G. thanks MHRD (for PMRF). We thank Shiksha Deswal (IISc-OC) for helpful discussions.

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13 Disappointingly, the use of activated internal alkynes such as dimethyl acetylene dicarboxylate (DMAD) as the alkyne component did not afford the desired four-component product under the present conditions.

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