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Carbene-Catalyzed Access to Thiochromene Derivatives: Control of Reaction Pathways via Slow Release of Thiols from Disulfides

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Cite This: *Org. Lett.* 2023, 25, 3967−3971 Read Online

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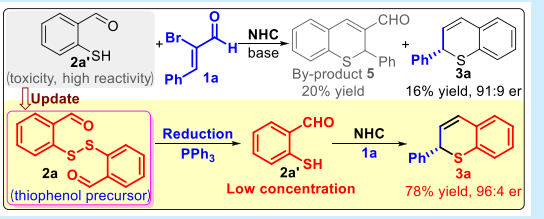
ABSTRACT: Substrates containing disulfide bonds, which are more stable and less smelling, could be used as thiophenol precursors in organic synthesis. Herein, an N-heterocyclic carbene (NHC)-catalyzed reaction between α-bromoenals and 2,2′-dithiodibenzaldehydes was developed. Through the sustained release strategy, the side reaction can be effectively inhibited, and the chiral thiochromene derivatives can be obtained with good yields and high optical purities. Application studies showed encouraging results when the desired products were explored for antimicrobial utilities in pesticide development.



Sulfur-containing heterocyclic compounds, such as thiochromenes, thiochromanes, and their derivatives, are widely found in drugs, pesticides, and natural products[1] (Figure 1). For example, chuangxinmycin is a natural active

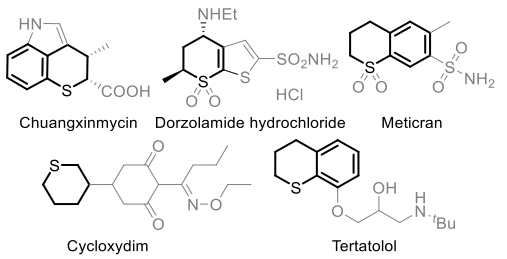


Figure 1. Thiochromene derivatives bioactive molecules.

molecule which is isolated from the actinomycetes *Actinoplanes tsinanens*.[2] It showed broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria *in vitro*. Tertatolol is a prescription drug for the treatment of hypertension and hypertension with renal insufficiency.[3] Cycloxydim is a selective post seedling herbicide,[4] which is used to control annual and perennial gramineous weeds in broadleaf crop fields. Therefore, methods for preparing sulfur-containing molecules continue to receive considerable attentions.[5] One of such methods is to start with thiols (including thiophenols) to make molecules with additional complexities. In recent decades, organic catalysts have been used to mediate these types of reactions involving thiols.[6] Despite the impressive progress, two important challenges remain to be addressed: the bad smell and toxicity of the thiol molecules as well as the high reactivity of thiols that leads to multiple side reactions.[7] It is well-known that thiols can be oxidized to disulfides, and disulfides can be readily reduced back to thiols under various conditions.[8] Typically, disulfides are more stable and less volatile (and less smelling) and thus can be used as thiol precursors in organic synthesis.[9] Here we report a carbene-catalyzed[10] construction of thiochromene derivatives by using disulfide as a thiophenol precursor. With a slow release of thiophenol from the corresponding disulfide under the assistance of triphenylphosphine (PPh_3) and water, undesired side reactions (noncatalytic background reactions) can be avoided.

Our key findings are summarized in Figure 2. When thiophenol **2a′** was employed as nucleophile to react with bromoenal[11] **1a** under the catalysis of pre-NHC **A**,[12] the desired product **3a** was isolated with 16% yield and 91:9 er, while the byproduct **5** was isolated with 20% yield. It suggested that the substrate **2a′** can directly react with **1a** when **2a′** was kept at a high concentration. Inspired by the results, the background reaction may be inhibited by decreasing the concentration of thiophenol. Thus, when 2,2′-dithiodibenzaldehyde **2a** was selected as the thiophenol precursor, the sulfur anion could not be spontaneously generated from the disulfide bond without reductant. PPh_3 can be used to reduce the disulfide bond to *in situ* generate the sulfur anion, which can decrease the concentration of **2a′**.[13] Then, the sulfur anion with low concentration reacted with acyl azolium intermediate

Received: April 28, 2023
Published: May 18, 2023

https://doi.org/10.1021/acs.orglett.3c01414
Org. Lett. 2023, 25, 3967−3971

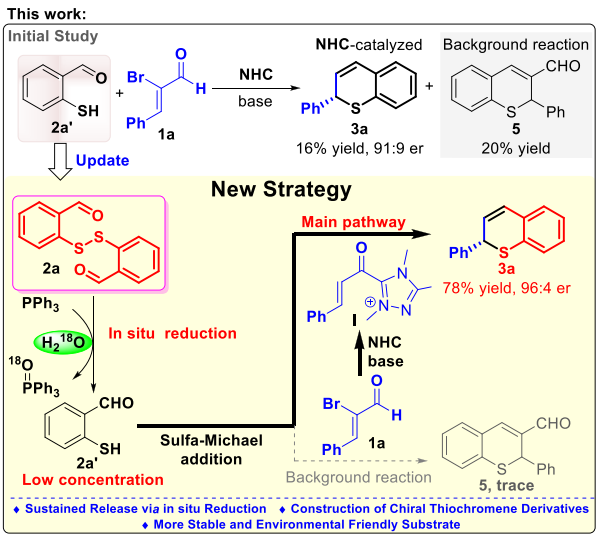
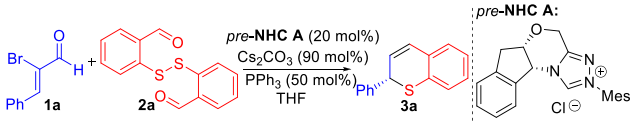


Figure 2. Asymmetric access to chiral sulfur containing heterocycles.

(**I**), and further reactions were carried out to obtain the chiral thiochromene **3a** with 78% yield and 96:4 er.

2,2′-Dithiodibenzaldehyde **2a** was selected as the sulfur nucleophilic precursor to react with bromoenal **1a** under the NHC catalysis. First, the desired product **3a** was obtained with excellent enantioselectivity and 35% yield with the using of aminoindanol-derived triazolium **A**[13] as the NHC precatalyst (Table 1, entry 1). After the addition of 4 Å molecular sieves

Table 1. Effect of Water Addition for Model Reaction[a]



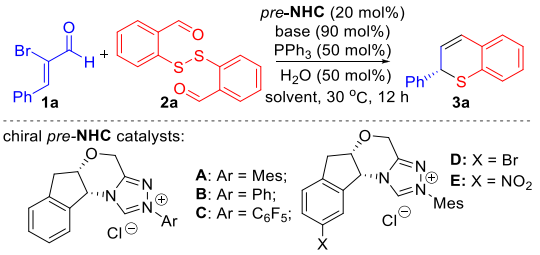
Entry	Additive	Yield (%)[b]	Er[c]
1	no additive	35	95:5
2	4 Å MS (150 mg)	16	97:3
3	H_2O (0.025 mmol)	39	94:6
4	**H_2O (0.050 mmol)**	**67**	**92:8**
5	H_2O (0.100 mmol)	70	88:12

[a]Unless otherwise specified, the reactions were carried under N_2 atmosphere using **1a** (0.12 mmol), **2a** (0.05 mmol), PPh_3 (0.05 mmol), *pre*-NHC **A** (0.02 mmol), Cs_2CO_3 (0.09 mmol), and THF (2.0 mL) at 30 °C (oil bath) for 12 h. [b]Isolated yield of **3a**. [c]The er values of **3a** were determined via HPLC on the chiral stationary phase.

(4 Å MS) (150 mg), the enantioselectivity was slightly improved, but the yield was obviously decreased to 16% (Table 1, entry 2). To our delight, the yield of **3a** was increased to 39% with preserved er value (Table 1, entry 3). It was found that the yield of **3a** was increased with the increasing of water, but the er value was obviously decreased to 88:12 (Table 1, entries 4 and 5). Therefore, the potential reaction condition (Table 1, entry 4) was used to further explore the optimal reaction conditions.

Furthermore, we optimized the reaction conditions in the presence of water. NHC catalysts[14] bearing N-Ph and N-C_6F_5 groups were not efficient for the reactions, which made the yield of **3a** decrease dramatically (low than 10%) (Table 2, entries 2 and 3). It was found that the *pre*-NHC **D**[15] bearing a

Table 2. Condition Optimization[a]



Entry	*Pre*-NHC	Solvent	Base	Yield (%)[b]	Er[c]
1	**A**	THF	Cs_2CO_3	67	92:8
2	**B**	THF	Cs_2CO_3	<10	78:22
3	**C**	THF	Cs_2CO_3	<10	74:26
4	**D**	THF	Cs_2CO_3	70	94:6
5	**E**	THF	Cs_2CO_3	65	93:7
6	**D**	MeCN	Cs_2CO_3	13	92:8
7	**D**	Toluene	Cs_2CO_3	17	68:32
8	**D**	EA	Cs_2CO_3	63	90:10
9	**D**	THF	DBU	35	91:9
10	**D**	THF	Et_3N	24	92:8
11	**D**	**THF**	**K_2CO_3**	**78**	**96:4**

[a]Unless otherwise specified, the reactions were carried under N_2 atmosphere using **1a** (0.12 mmol), **2a** (0.05 mmol), PPh_3 (0.05 mmol), *pre*-NHC (0.02 mmol), base (0.09 mmol), H_2O (0.05 mmol), and solvent (2.0 mL) at 30 °C (oil bath) for 12 h. [b]Isolated yield of **3a**. [c]The er values of **3a** were determined via HPLC on the chiral stationary phase.

bromine atom on the benzene ring gave the desired product **3a** with 70% yield and 94:6 er (Table 1, entry 4). Meanwhile, the *pre*-NHC **E**[16] was examined, and the result was similar to *pre*-NHC **D**. Then, we used the *pre*-NHC **D** to examine the different solvents in this protocol. Switching the THF with MeCN, toluene, and EA, unacceptable enantioselectivities and yields were obtained (Table 2, entries 6−8). Finally, the bases were explored, and it was found that the K_2CO_3 gave excellent yield and enantioselectivity (Table 2, entries 9−11).

With the optimized reaction conditions in hand, the reaction scope of both bromoenals **1** and 2,2′-dithiodibenzaldehyde **2a** was examined (Scheme 1). Different substitution patterns of bromoenals **1** were explored. Substituents with electron-withdrawing groups (**3b**−**3f** and **3i**−**3k**) and electron-donating groups (**3g**, **3h**) could be installed on the *para*- and *meta*-positions of the benzene ring of bromoenals **1**, with the corresponding products afforded in moderate to good yields and excellent enantioselectivities. However, the installation of electron-withdrawing groups (**3l**−**3o**) and electron-donating groups (**3p**) at the *ortho*-position of the benzene ring of **1** led to moderate yields and decreased er values. The same result was also shown when the benzene ring of substrate **1** had multiple electron-withdrawing groups (**3q**). By changing the phenyl group of the bromoenal into a heteroaryl group, the yields and enantioselectivities of the products were slightly dropped (**3r**, **3s**). The *β*-phenyl group of substrates **1** could be replaced with a naphthalene group, and the product was obtained in good yield and excellent enantioselectivity (**3t**). Aliphatic *α*-bromoenals could also be used as a suitable reaction substrate in this reaction, with the desired products afforded in moderate to excellent yields and high optical purities (**3u**−**3w**).

When exploring the substituents' tolerance on the benzene ring of 2,2′-dithiodibenzaldehydes **2**, the yields and enantio-

https://doi.org/10.1021/acs.orglett.3c01414
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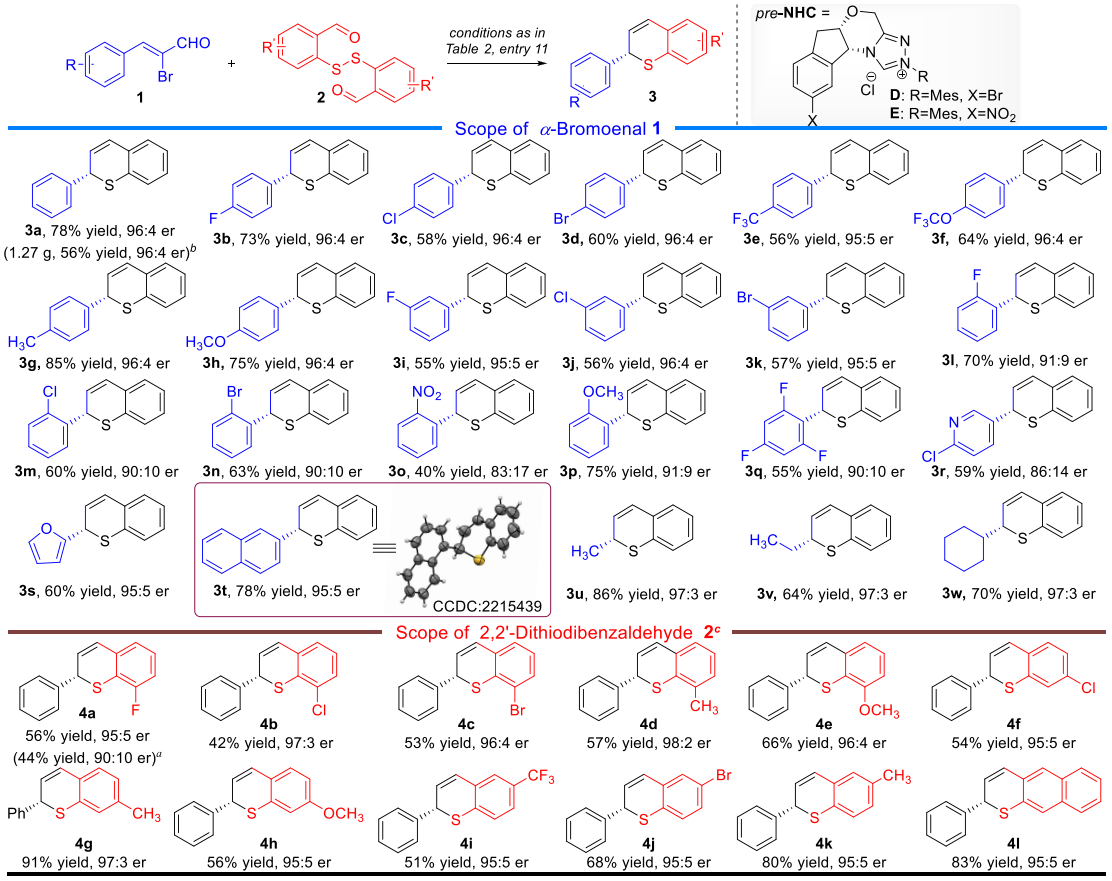
Scheme 1. Scope of α-Bromoenal 1 and 2,2′-Dithiodibenzaldehyde 2[a]



[a]Reaction conditions as stated in Table 2, entry 11. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on chiral stationary phase. [b]The reaction was carried out at 6.0 mmol scale based on **1a**. [c]*pre*-NHC **E** was used as a catalyst for scope of substrates **2**. Ellipsoid contour probability level = 50% (CCDC 2215439).

selectivities of most of the products were reduced under standard reaction conditions. To our delight, when changing *pre*-NHC **D** to *pre*-NHC **E** simply, substituents were also well tolerated on the benzene ring of the 2,2′-dithiodibenzaldehyde **2**, with the desired products afforded in moderate to excellent yields and excellent er values regardless of their electronic properties and substitution patterns (**4a**–**4l**). Subsequently, when the model reaction was conducted on a gram scale, **3a** can be obtained in 56% yield with good enantioselectivity.

In the reaction, it was found that the water played an important role in the pathway control. To understand the effects of the water in the reaction, additional experiments were performed. ^{18}O-labeled water (98% ^{18}O-labeled) was employed as an additive to study the mechanism (Figure 3). Subsequently, the desired product **3a** and triphenylphosphine oxide (TPPO) were isolated, and the TPPO was found with an isotopic anomaly (83% ^{18}O-labeled) via high resolution mass spectroscopy (HRMS). The results suggested that the water participated in the reaction, and the intermediate **III** can be hydrolyzed to form intermediate **II**. The result was similar to Corey-Nicolaou macrolactonization,[17] in which the PPh_3 can be oxidated by the disulfide bond to form TPPO. The concentration of intermediate **II** was significant to the reaction, and with the sustained release strategy, keeping the intermediate **II** at a low concentration can inhibit the byproduct pathway. The addition of the sulfur atom from intermediate **II** to the β-carbon of intermediate **I** gave

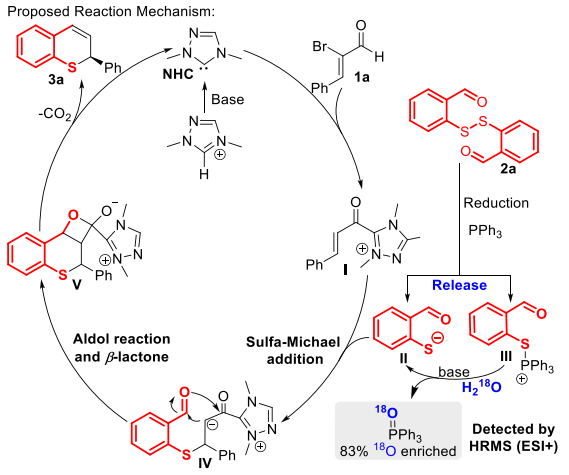


Figure 3. Proposed catalytic cycle.

intermediate **IV** through the thiol-Michael reaction, with a new carbon-sulfur bond formed in a highly enantioselective manner. Additional DFT calculations were performed. It was found that the addition of a thiol anion to the acyl azolium was the enantiodetermining step, and the C-S bond formation was irreversible (details see SI Figure S3). Further reactions of **IV** (through an intramolecular aldol reaction and β-lactone formation) gave intermediate **V**, which undergoes decarbox-

https://doi.org/10.1021/acs.orglett.3c01414
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ylation to afford chiral thiochromene **3a**. Furthermore, the kinetic data were collected. It suggested that the reaction pathway can be modulated via slow release of thiols from disulfides (details see SI Figure S4).

To our delight, the chiral thiochromene derivatives obtained from our method also exhibit interesting biological activities in the turbidimetric test at 100 and 50 μg/mL of the *in vitro* antibacterial activity against *Xanthomonas axonopodis* pv *citri* (*Xac*)[18] (Table 3). Compared with thiodiazole copper (TC)

Table 3. *In Vitro* Inhibitive Activities of the Planar Chiral Compounds against *Xanthomonas axonopodis* pv. *citri* (*Xac*)[a]

	Xac inhibition rate (%)	
Compounds	100 μg/mL	50 μg/mL
3b	75.86 ± 0.51	61.67 ± 0.49
3d	66.56 ± 0.85	59.68 ± 1.21
3e	67.85 ± 0.67	58.44 ± 0.25
3f	72.32 ± 2.13	57.68 ± 2.04
3l	66.38 ± 0.59	54.07 ± 1.65
3n	85.21 ± 0.72	51.24 ± 0.78
3s	77.83 ± 0.95	59.66 ± 0.49
3t	87.82 ± 0.63	62.84 ± 1.05
3u	65.54 ± 0.15	62.20 ± 2.27
3w	61.51 ± 0.87	41.24 ± 0.38
4f	72.71 ± 0.76	52.09 ± 0.23
4g	64.01 ± 1.36	49.55 ± 1.60
TC[b]	57.74 ± 0.82	30.51 ± 1.08

[a]All data were average data of three replicates. [b]TC = thiodiazole copper.

that has been widely used as a commercially available antibacterial agrichemical, 12 of the chiral products obtained from our method have shown obviously superior antibacterial activities and can be regarded as promising candidates in the search for new pesticide structures.

In summary, we have successfully obtained chiral thiochromene derivatives under NHC catalysis by controlling the reaction pathways via slow release of thiols from disulfides. The disulfide-bond-containing substrate was used as a thiophenol precursor to react with corresponding acyl azolium intermediate. The background reaction can be inhibited by the slow release of thiophenol. Water has also been found to play a key role in the hydrolysis of thiosulfate and further slowly release thiophenol to participate in the reaction, which obviously improved the yield of the desired product. Further studies on the bioactivities of chiral thiochromene derivatives obtained from our method for agricultural applications have been evaluated; the preliminary results suggested that these molecules show encouraging *in vitro* activities against *Xac*. Our strategy in controlling reaction pathways via *in situ* sustained release can be further used in developing new reactions, especially those where effective concentration of the substrates matters.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01414.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2215439 and 2244353 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

Q. Wu, S. Wu, and J. Zou contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge funding supports from the National Natural Science Foundation of China (21732002, 22061007 and

22071036); Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY number (2020)004]; The 10 Talent Plan (Shicengci) of Guizhou Province ([2016] 5649); Science and Technology Department of Guizhou Province [Qiankehe-jichu-ZK[2022]zhongdian024], ([2018] 2802, [2019]1020); Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University; Singapore National Research Foundation under its NRF Investigatorship (NRF-NRFI2016-06) and Competitive Research Program (NRF-CRP22-2019-0002); Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG7/20, RG70/21), MOE AcRF Tier 2 (MOE2019-T2-2-117), and MOE AcRF Tier 3 Award (MOE2018-T3-1-003); a Chair Professorship Grant, and Nanyang Technological University.

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https://doi.org/10.1021/acs.orglett.3c01414
Org. Lett. 2023, 25, 3967−3971