OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Thiocarbonyl Surrogate via Combination of Potassium Sulfide and Chloroform for Dithiocarbamate Construction

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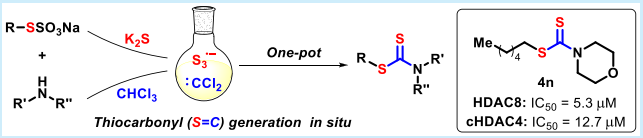
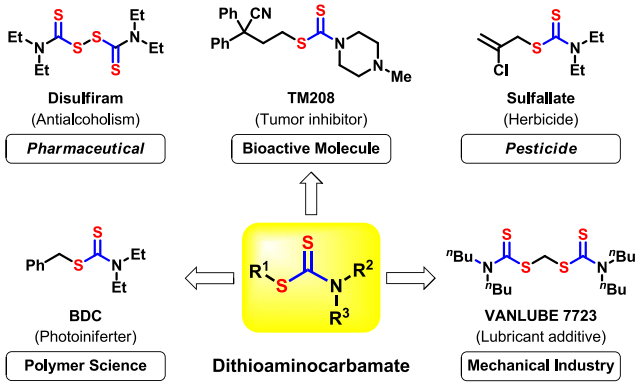
Supporting Information

ABSTRACT: An efficient and practical thiocarbonyl surrogate via combination of potassium sulfide and chloroform was established. A variety of dithiocarbamates were afforded along with four new chemical bond formations in a one-pot reaction in which the thiocarbonyl motif was generated in situ. Furthermore, these readily accessed molecules showed promising activity against HDAC8, opening a potential gateway to discover a new type of nonhydroxamate and isoenzyme-selective HDAC inhibitors.



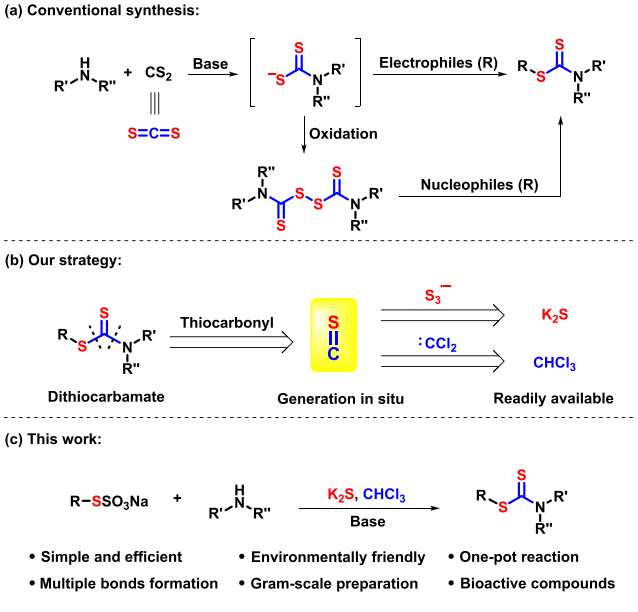
Dithiocarbamate is an important class of molecule with extensive value in pharmaceuticals, agrochemicals, and organic materials (Scheme 1).[1−5] Disulfiram with a dithiocarbamate motif is a famous molecule previously applied for alcoholism treatment[1a] and recently as a drug candidate for its anticancer activity in preclinical models.[1b] Moreover, other dithiocarbamates are attracting more and more attention based on their variety of biological activities[2] such as antitumor,[2a] antibacterial,[2b] cholinesterase inhibition,[2c] etc. Sulfallate is a chlorinated dithiocarbamate derivative that is used as an herbicide.[3] Meanwhile, dithiocarbamate also serves a unique role in material science, such as a radical chain transfer agent BDC in reversible addition−fragmentation chain transfer (RAFT) polymerizations.[4] VANLUBE 7723 is a nonnegligible chemical widely applied as a lubricant additive in the mechanical industry.[5]

Scheme 1. Representative Dithiocarbamates



Accordingly, numerous procedures have been developed for the synthesis of dithiocarbamate. Most of these strategies revolved around the reactions of volatile and flammable carbon disulfide[6] with electrophiles through a dithiocarbamic acid salt intermediate[7] in which the electrophiles included alkyl halides,[7a] epoxides,[7b] alkynes,[7c] alkyl vinyl ethers,[7d] etc. (Scheme 2). Furthermore, there is an alternative procedure[8] involving the reaction of pre-prepared tetramethylthiuram

Scheme 2. Strategies for Dithiocarbamate Construction



Received: August 6, 2019

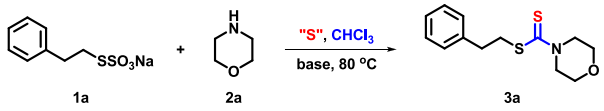
DOI: 10.1021/acs.orglett.9b02784
Org. Lett. XXXX, XXX, XXX−XXX

disulfide and organozinc[8a] or organolithium[8b] reagents as nucleophiles that are sensitive to air and moisture. However, the development of a practical and environmentally friendly process for dithiocarbamate construction is still highly desirable. Based on our continuous study on organosulfur chemistry[9] especially in thiocarbonyl chemistry,[10] we envisioned that dithiocarbamate can be assembled from a combination of sulfur, carbon, and amino sources in one pot along with the direct generation of a thiocarbonyl group in situ, avoiding the use thiocarbonyl reagents. Following our concept, potassium sulfide provides trisulfur radical anion ($S_3^{\bullet-}$)[11] as an inorganic sulfur source and chloroform[12] provides dichlorocarbene as one carbon source. Herein, we developed a straightforward method for preparation of dithiocarbamate with potassium sulfide and chloroform in the presence of readily available thiosulfate salts[9c,13] and organic amines, in which a library of valuable bioactive molecules was well established.

We commenced our studies with *S*-phenethyl thiosulfate sodium salt **1a** and morpholine **2a** as the model substrate in combination with potassium sulfide and chloroform. The desired product **3a** could be obtained in 56% yield by using lithium hydroxide as a base and *N*-methylpyrrolidone (NMP) as a solvent at 80 °C under nitrogen atmosphere (Table 1, entry 1). When the odorous phenylethyl mercaptan or *S*-phenethylethanethioate was employed in the corresponding conditions, the product **3a** was only formed in 38% or 13% yields, respectively (Table 1, entries 2 and 3). The results indicated that odorless *S*-phenethyl thiosulfate salt **1a** had a distinct advantage not only for the ecofriendly procedure but also for the chemical "mask" effect.[9c] When the reaction was carried out under air atmosphere, the yield decreased (Table 1, entry 4 vs entry 1). Meanwhile, other inorganic sulfur sources were examined, and only a trace amount of product could be observed by substituting elemental sulfur or sodium thiosulfate for potassium sulfide while potassium thioacetate afford product in 47% yield (Table 1, entries 5–7). Various polar solvents were explored, in which the target product **3a** could be afforded in 55% yield with *N*,*N*-dimethylformamide (DMF) (Table 1, entries 8–11). Subsequently, barium hydroxide octahydrate was employed as a base in the reaction, and the compound **3a** was isolated in 81% yield with a significant elevation compared to other base usage (Table 1, entries 12–16). Finally, the product **3a** was obtained in 85% yield with a slight improvement by adjusting the base amount and solvent concentration (Table 1, entries 17–19).

On the basis of the optimized conditions, the scope of amines was examined as shown in Scheme 3. First, various cyclic amines (**3a**–**3k**) were tested, and the corresponding products were formed in moderate to good yields, in which the hydrolyzable lactam (**3g**), amide (**3j**), and sulfone groups (**3k**) under alkaline conditions were tolerable in the reaction system. Meanwhile, the structure of product **3a** was further confirmed through X-ray crystallographic analysis. Noncyclic amines could also perform as amino sources (**3l**–**3o**). Diethylamine could give the related product **3l** in 52% yield, while dibenzylamine (**3m**) and *N*-methylbenzylamine (**3n**) afforded their respective products in good yields. Moreover, *N*-

Table 1. Optimization for the Synthesis of Dithiocarbamate[a]

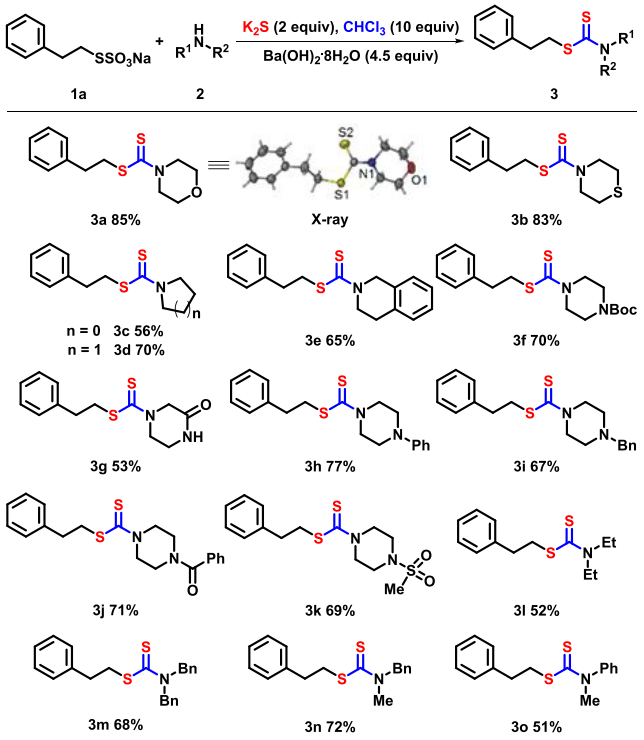


1a 2a 3a

entry	"S"	base	solvent	yield[b] (%)
1	K_2S	LiOH	NMP	56
2[c]	K_2S	LiOH	NMP	38
3[d]	K_2S	LiOH	NMP	13
4[e]	K_2S	LiOH	NMP	47
5	S_8	LiOH	NMP	trace
6	$Na_2S_2O_3$	LiOH	NMP	trace
7	KSAc	LiOH	NMP	47
8	K_2S	LiOH	DMF	55
9	K_2S	LiOH	MeCN	trace
10	K_2S	LiOH	DMSO	19
11	K_2S	LiOH	1,4-dioxane	nd
12	K_2S	KOH	NMP	17
13	K_2S	K_3PO_4	NMP	41
14	K_2S	^{t}BuOLi	NMP	53
15	K_2S	^{t}BuOK	NMP	33
16	K_2S	$Ba(OH)_2{\cdot}8H_2O$	NMP	81
17[f]	K_2S	$Ba(OH)_2{\cdot}8H_2O$	NMP	81
18[g]	K_2S	$Ba(OH)_2{\cdot}8H_2O$	NMP	76
19[f,h]	**K_2S**	**$Ba(OH)_2{\cdot}8H_2O$**	**NMP**	**85**

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), "S" (0.4 mmol), $CHCl_3$ (2 mmol), and base (1.2 mmol) in solvent (1 mL) was stirred at 80 °C for 12 h under nitrogen atmosphere. [b]Isolated yields. nd = not detected. [c]Phenylethyl mercaptan is instead of **1a**. [d]*S*-Phenethylethanethioate is instead of **1a**. [e]Air is instead of nitrogen atmosphere. [f]$Ba(OH)_2{\cdot}8H_2O$ (0.9 mmol). [g]$Ba(OH)_2{\cdot}8H_2O$ (0.6 mmol). [h]NMP (2 mL).

Scheme 3. Scope of Amines[a]

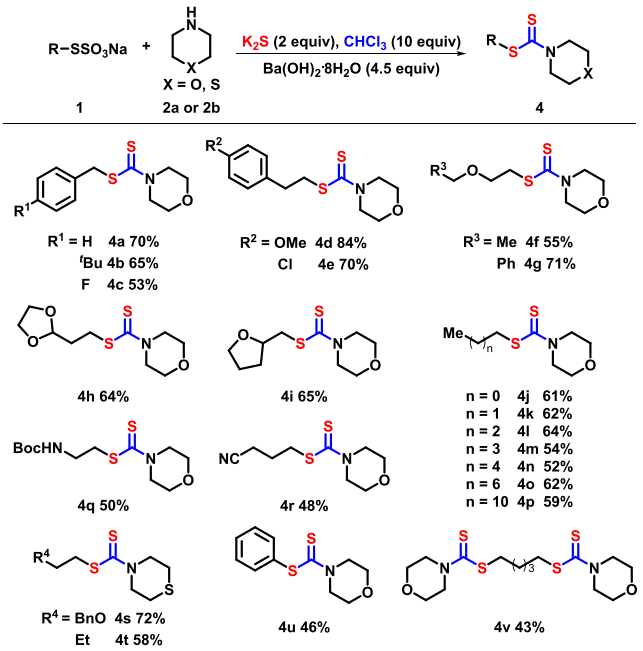


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), K_2S (0.4 mmol), $CHCl_3$ (2 mmol), and $Ba(OH)_2{\cdot}8H_2O$ (0.9 mmol) in NMP (2 mL) was stirred at 80 °C for 8–12 h under nitrogen atmosphere. Isolated yields.

DOI: 10.1021/acs.orglett.9b02784
Org. Lett. XXXX, XXX, XXX–XXX

methylaniline as an aromatic amine could be efficiently transformed to the desired product **3o** in moderate yield, and it seems that the yield of the product with *N*-arylamine was slightly lower than those of the *N*-alkyl-supplied product. On the other hand, when the primary amine was employed in the reaction, the target product could not be obtained.[14] Subsequently, various thiosulfate salts were successfully employed, as shown in Scheme 4. When the electron-

Scheme 4. Scope of Thiosulfate Salts[a]

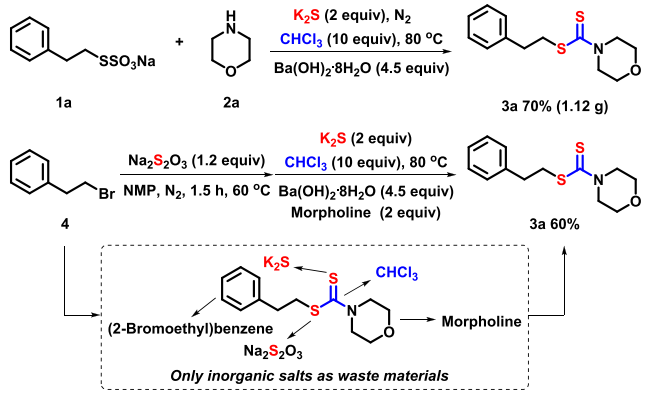


[a]The reaction conditions: **1** (0.2 mmo l), **2a** (0.4 mmol), K_2S (0.4 mmol), $CHCl_3$ (2 mmol), and $Ba(OH)_2{\cdot}8H_2O$ (0.9 mmol) in NMP (2 mL) was stirred at 80 °C for 8−12 h under nitrogen atmosphere. Isolated yields.

withdrawing group was connected to the aromatic ring on substrate at the para position, the yield of the reaction seemed to decrease (**4a**−**4e**). Then *S*-alkylether thiosulfate salts (**4f**−**4i**) were tested, and notably the acetal group used as a protective group for aldehydes was compatible in the multicomponent reaction (**4h**). Meanwhile, *S*-alkyl thiosulfate salts with alkyl chains of different lengths (**4j**−**4p**) were examined, and the corresponding products could be obtained in similar yields. Moreover, *tert*-butyl carbonate (**4q**) and cyano (**4r**) groups were tolerable in the reaction as well. In addition, *S*-phenyl thiosulfate salts could also be transformed into the desired product (**4u**) in a moderate yield, and this method could be applied to the synthesis of a dithiocarbamate containing a double thiocarbonyl motif (**4v**).

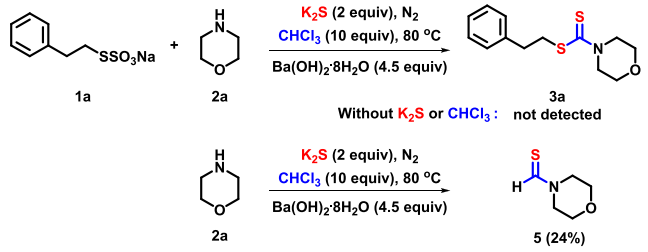
To further explore the potential practicability of this method (Scheme 5), the gram-scale operation was performed on a 6 mmol scale for the synthesis of phenethyl morpholine-4-carbodithioate **3a**, and the desired product could be obtained in 70% yield. On the other hand, (2-bromoethyl)benzene **4** was investigated as a substrate to afford compound **3a** in 60% yield through a multicomponent reaction in one pot, in which each component was effectively embedded in the target structure and only inorganic salts as waste materials were discharged.

Scheme 5. Gram-Scale Preparation and Further Exploration



Afterward, control experiments were carried out (Scheme 6). When the model reaction was carried out in the absence of

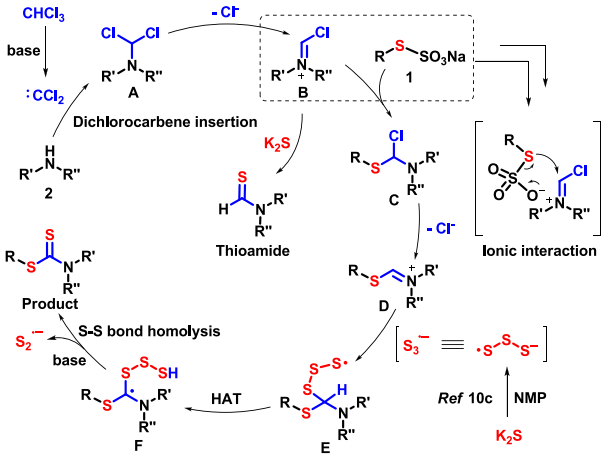
Scheme 6. Control Experiments



potassium sulfide or chloroform, no desired product could be detected. The results indicated that potassium sulfide and chloroform are indispensable in the transformation for thiocarbonyl motif construction. Moreover, if the reaction was performed in the absence of *S*-alkyl thiosulfate salt **1a**, the thioamide **5** could be formed in 24% ^1H NMR yield, which implied that a thiolcarbonyl byproduct could be generated from reaction intermediates on certain conditions.

According to the results of experiments, a possible reaction mechanism is depicted in Scheme 7. First, dichlorocarbene[12] was generated from chloroform in the presence of base and inserted into the H−N bond of the starting amine to form **A**, which provides monochlorinated imine cation **B** readily. Then the reaction occurred between imine **B** and the thiosulfate salt

Scheme 7. Proposed Mechanism



DOI: 10.1021/acs.orglett.9b02784
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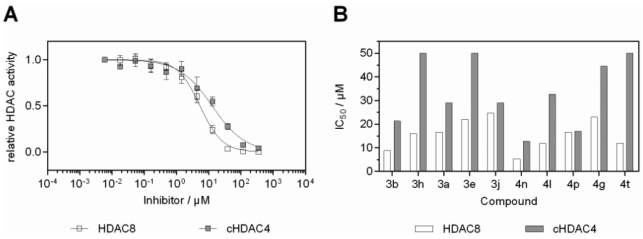
to afford another imine cation **D** via intermediate **C**. Trisulfur radical anion ($S_3^{\bullet-}$) could be formed from potassium sulfide in NMP solvent, which had been demonstrated by detection experiments in our previous work.[10c] Herein, trisulfur radical anion ($S_3^{\bullet-}$) generating from K_2S in the solvent of NMP interacted with imine cation **D** to produce intermediate **E** along with the establishment of the C−S bond. Next, the α-aminoalkyl radical **F** was obtained through an intramolecular hydrogen atom transfer (HAT) process of intermediate **E**.[15] Finally, homolysis of the S−S bond in the intermediate **F** provides the target product in the presence of base along with the generation of disulfur radical anion ($S_2^{\bullet-}$).

The pyrimido[1,2-*c*][1,3]benzothiazin-6-imine PD-404,182 was recently shown to be a potent and selective inhibitor of the established cancer target human histone deacetylase 8 (HDAC8).[16] However, this compound class turned out to be unstable in the presence of thiol groups in aqueous solution, and the reaction of PD-404,182 leads to chemical modifications of HDAC8 cysteine residues such as cyanylation and the formation of mixed disulfides.[16b] What attracted our attention is that the thiocarbonyl analogues of PD-404,182 still retain their activity against HDAC8.[16a] This inspired us to explore the biological activity of the noncyclic dithiocarbamate compounds of this study against human HDAC8 and the catalytic domain of human HDAC4 (cHDAC4). Most interestingly, some of these compounds exhibited promising bioactivity against HDAC8 with less activity against cHDAC4, in which **4n** showed impressive activity with an IC_{50} value in the low micromolar range (Scheme 8; see the SI for more details). The results indicated potential for the development of novel nonhydroxamate- and isoenzyme-selective HDAC8 inhibitors with a dithiocarbamate core, which is different from the widely studied HDAC inhibitors with a hydroxamate warhead.

Scheme 8. IC_{50} Values on HDAC8 and cHDAC4[a]



[a](A) Representative dose−response curves of **4n** on HDAC8 and cHDAC4. (B) Comparison of the selected compounds with an IC_{50} < 25 μM on HDAC8 with cHDAC4.

In summary, we have developed an efficient and practical thiocarbonyl surrogate via combination of potassium sulfide and chloroform, in which the thiocarbonyl motif was generated in situ under this novel synthesis strategy. A variety of dithiocarbamates were straightforwardly established along with four new chemical bond formations in a one-pot reaction in which each component was effectively embedded in the target structure. Meanwhile, a preliminary biological study indicated that the dithiocarbamates obtained from this reaction exhibit promising activity against HDAC8, which is a potential gateway to discover a new type of nonhydroxamate and isoenzyme-selective HDAC inhibitors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02784.

Experimental procedures, NMR spectral, X-ray, and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1935361 contains 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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support provided by the National Key Research and Development Program of China (2017YFD0200500), NSFC (21971065, 21722202, 21672069), the S&TCSM of Shanghai (Grant 18JC1415600), Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning, and the National Program for Support of Top-notch Young Professionals.

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DOI: 10.1021/acs.orglett.9b02784
Org. Lett. XXXX, XXX, XXX−XXX