Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric synthesis of linezolid thiazolidine-2-thione derivatives *via* CS_2 mediated decarboxylation cyclization

De-Yun Cui [a,b,#], Hong-Tao Kong [a,#], Yi Yang [a], Jianfeng Cai [c], Bo-Yuan Shen [a], Da-chao Yan [a], Xiu-Juan Zhang [a], Ying-Long Qu [a], Meng-Meng Bai [a], En Zhang [a,c,*]

[a] School of Pharmaceutical Sciences, Institute of Drug Discovery and Development, Key Laboratory of Advanced Pharmaceutical Technology, Ministry of Education of China, Zhengzhou University, Zhengzhou 450001, China
[b] West China School of Pharmacy, Sichuan University, Sichuan 610041, China
[c] Department of Chemistry, University of South Florida, 4202 East Fowler Avenue, Tampa, FL 33620, USA

ARTICLE INFO

Article history:
Received 18 February 2020
Revised 12 March 2020
Accepted 13 March 2020
Available online xxxx

Keywords:
Asymmetric synthesis
Cyclization
Stereoselectivity
Chirality
Linezolid thiazolidine-2-thione

ABSTRACT

A mild and cost-effective decarboxylation cyclization method was developed for the synthesis of chiral 5-substituted thiazolidine-2-thione derivatives from β-amino oxazolidinones. This reaction was mediated by CS_2 and allowed a highly stereoselective synthesis of linezolid thiazolidine-2-thione derivatives. The chirality of the linezolid base was completely retained in the final product.

Introduction

The thiazolidine-2-thione motif is a key substructure of various organic compounds that have central roles in multiple domains [1,2]. Thiazolidinethiones (Fig. 1, **1**) are well known as powerful chiral auxiliaries [3–5]. These efficiently complement the Evans' chiral *N*-acyl oxazolidinones [6] with high stereoselective control for specific substrates, including acetate [7]. Thiazolidinethione chiral auxiliaries can be transformed into various functional groups [8]. These chiral auxiliaries have been successfully applied to the synthesis of natural products [9,10] and antibiotic skeletons [11].

Compounds that contain thiazolidine-2-thione fragments have a wide range of biological activities, such as regulation of apoptosis in cancer chemotherapy (Fig. 1, BH3I-1Br), [12] antifungal activity (Fig. 1, Fezatione) [1], *Escherichia coli* β-ketoacyl-(acyl-carrier-protein) synthase III inhibition and antimalarial activity (Fig. 2, **2**) [13], and hepatoprotective effects [14]. Acyl-1,3-thiazolidine-2-thione has also been used for selective etherification of the primary alcohols of diols and polyols [15–17].

To date, various methods have been reported for the synthesis of thiazolidine-2-thiones. Commonly, thiazolidine-2-thione can be synthesized by the reaction of carbon disulfide with β-amino alcohols [18,19], β-amino thiols [20,21] or azridines [22,23]. Both the electrogenerated-base method [24] and microwave-assisted method [25] can improve the reaction yield and time. Multicomponent reactions have also been used for the synthesis of thiazolidine-2-thiones [26–28]. However, few studies have investigated the synthesis and further applications of 5-substituted thiazolidine-2-thiones [29,30]. Hence, there is still a need for the effective synthesis of chiral 5-substituted thiazolidine-2-thiones.

Oxazolidinones are a novel class of orally active synthetic antibacterial agents [31]. Linezolid is a representative oxazolidone antibacterial drug that has excellent activity against almost all Gram-positive pathogens [32,33]. However, reversible myelosuppression has been reported with high doses of linezolid [33]. To improve the safety profile, various efforts have been made to modify linezolid. Besides tedizolid phosphate (Fig. 2), several other oxazolidinone drug candidates are currently undergoing clinical phase trials (Fig. 2, MRX-1 and Radezolid) [34]. Racemic thiazolidinethione analogs of linezolid with good activity against fungi have been prepared by transforming the oxazolidinone ring oxygen into a bulkier sulfur atom [35]. The development of new and efficient synthetic approaches towards chiral thiazolidine-2-thione substructures will help medicinal chemists to modify linezolid.

* Corresponding author at: School of Pharmaceutical Sciences, Institute of Drug Discovery and Development, Key Laboratory of Advanced Pharmaceutical Technology, Ministry of Education of China, Zhengzhou University, Zhengzhou 450001, China.
E-mail address: zhangen@zzu.edu.cn (E. Zhang).
# De-Yun Cui and Hong-Tao Kong contributed equally.

https://doi.org/10.1016/j.tetlet.2020.151847
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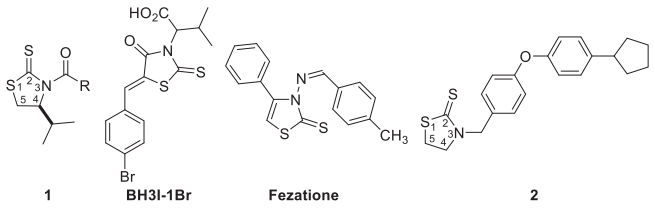


Fig. 1. Representative compounds containing the thiazolidine-2-thione substructure.

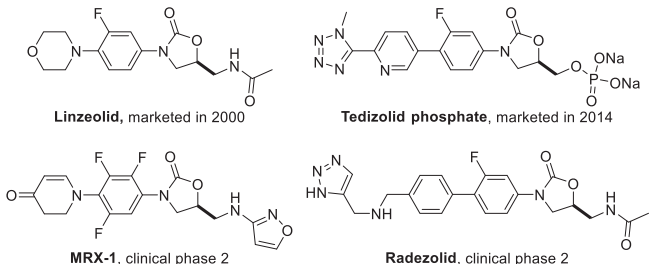


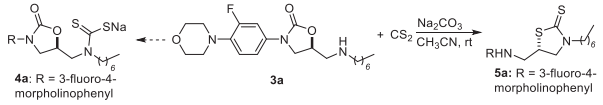
Fig. 2. Structures of linezolid and other biologically active oxazolidinones.

Results and Discussion

In our endeavor to identify more potent compounds with excellent antimicrobial activity against drug-resistant bacteria [36–40], dithiocarbamate derivatives [41,42] and picolinic acid derivatives [43] were found to be good metallo-beta-lactamase inhibitors that could improve meropenem antimicrobial activity up to 2569 times against strains containing *bla*$_{NDM-1}$ genes [41]. Inspired by the extensive application of linezolid against major Gram-positive pathogenic bacteria, including vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumonia* [44], dithiocarbamate derivatives based on the linezolid skeleton were designed as metallo-beta-lactamase inhibitors (Scheme 1). However, an unexpected product, thiazolidinethione **5a**, was obtained in 65% yield instead of oxazolidinone **4a** when **3a** was reacted under weakly basic conditions (Scheme 1, entry 1 in Table 1).

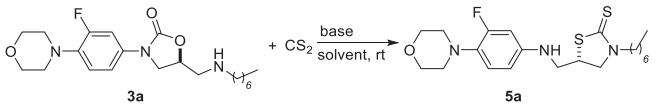
On the basis of this unexpected finding, the reaction conditions were optimized using different bases and solvents to improve the efficiency of the reaction (Table 1, Entries 1–7). The results showed that NaOH and *N*,*N*-diisopropylethylamine (DIPEA) slightly improved the yield compared with Et_3N (Table 1, entries 2–4). The use of $Na_3PO_4{\cdot}12H_2O$ as a base also gave a better yield (74%). Screening a series of solvents showed that acetone performed better than other solvents (Table 1, entries 8–15). Product **5a** was obtained in the lowest yield in EtOH and only traces were observed in toluene. A small increase in the yield (Table 1, entry 16) was obtained when the reaction time was increased to 24 h. No reaction was observed in the absence of a base (Table 1, entry 17).

After optimization of the reaction conditions, the substrate scope of the reaction was investigated (Table 2). First, substrates **3a**–**c** with various alkyl substituents were screened. Although all alkyl substrates reacted successfully, the yield decreased with increasing length of the alkyl chain (**5a**–**c**). Unsaturated alkane and cyclopropane substituents were suitable for this reaction and gave the product in moderate yields (**5u** and **5v**). Next, the effect of aromatic benzyl substituents was examined. The reaction proceeded smoothly both for substrates bearing an electron-donating group on the benzyl group (**5d**–**g**) and those with electron-withdrawing mono- and disubstituted substituents on the benzyl



Scheme 1. Unexpected one-pot decarboxylation reaction.

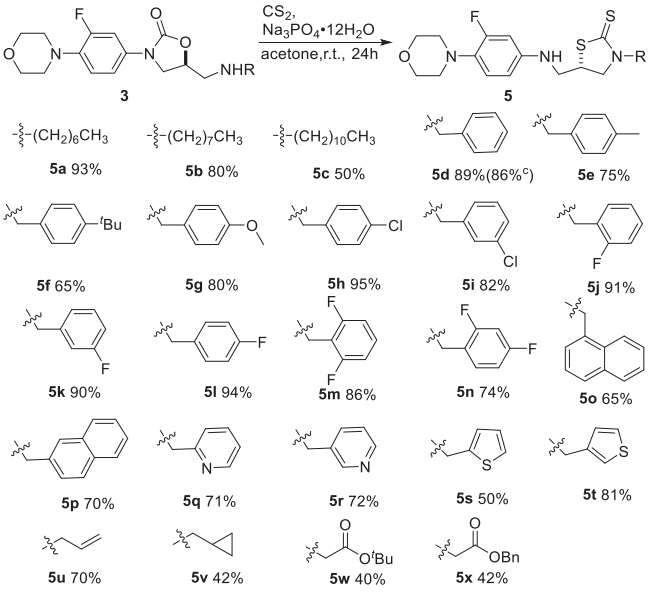
Table 1
Optimization of the reaction conditions[a].



Entry	Base	Solvent	Yield[b] **5a** (%)
1	Na_2CO_3	MeCN	65
2	DIPEA	MeCN	71
3	Et_3N	MeCN	57
4	NaOH	MeCN	69
5	$NaHCO_3$	MeCN	53
6	$Na_3PO_4{\cdot}12H_2O$	MeCN	74
7	K_2CO_3	MeCN	58
8	$Na_3PO_4{\cdot}12H_2O$	Acetone	90
9	$Na_3PO_4{\cdot}12H_2O$	DCE	25
10	$Na_3PO_4{\cdot}12H_2O$	EtOH	14
11	$Na_3PO_4{\cdot}12H_2O$	Toluene	Trace
12	$Na_3PO_4{\cdot}12H_2O$	DMSO	80
13	$Na_3PO_4{\cdot}12H_2O$	DCM	28
14	$Na_3PO_4{\cdot}12H_2O$	THF	67
15	$Na_3PO_4{\cdot}12H_2O$	DMF	35
16	$Na_3PO_4{\cdot}12H_2O$	Acetone	93[c]
17	None	Acetone	n.r.[d]

[a] Reagents and conditions: **3a** (150 mg, 0.38 mmol, 1 equiv.), CS_2 (0.38 mmol, 1 equiv.), base (0.38 mmol, 1 equiv.), solvent (5 mL), r.t., 18 h.
[b] Isolated yield based on **3a**.
[c] 24 h.
[d] n.r. = no reaction.

Table 2
Substrate scope of thiazolidine-2-thione analogs of linezolid.[a,b]



[a]Reagents and conditions: **1** (0.38 mmol, 1 equiv.), CS_2 (0.38 mmol, 1 equiv.), $Na_3PO_4{\cdot}12H_2O$ (0.38 mmol, 1 equiv.), acetone (5 mL), r.t., 24 h. [b]Isolated yield based on **1**. [c]Yield on a gram scale.

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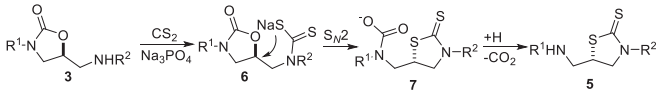
group. In most cases, the products were obtained in >80% yield (**5h**–**n**). Notably, with electron-withdrawing substituents such as F and Cl, a higher yield was obtained when substitution was in the *para*-position than in the *ortho*- or *meta*-position. Methylnaphthalene and various substituted naphthalene and heterocyclic aromatics such as picoline and thiophene were also viable for this reaction and gave the corresponding products (**5o**–**t**). Different esters, which were sensitive to base, were also suitable for this process and gave moderate yields of the products (**5w**–**x**). Unfortunately, primary amino or acetyl substrates did not react at all. Substrates containing ether or cyano groups also failed in this reaction. An experiment with reaction scale on the gram level indicated that this had little influence on the yield (**5d**).

To confirm whether the stereochemistry of the product was lost in this reaction and to explore the mechanism of the CS_2-mediated one-pot decarboxylation reaction, racemic **5d** was prepared by the same method as **5d**. Compared with racemic **5d**, HPLC using an appropriate column showed the enantioselectivity of compound **5d** was >99% enantiomeric excess. The absolute configuration of thiazolidinethione **5d** was established as (*S*) by X-ray crystallography (Fig. S1) [45].

Based on the stereochemistry of **3a** and **5a**, a plausible reaction mechanism for the CS_2 mediated decarboxylation cyclization is shown in Scheme 2. Oxazolidinone **3** reacts with CS_2 under weakly basic conditions to form dithiocarbamate **6**. Oxazolidinone ring opening of dithiocarbamate **6** gives intermediate **7** *via* nucleophilic substitution (S_N2). In this step, **6** undergoes configuration inversion. Finally, **5** was obtained by the decarboxylation of **7** [46].

To our delight, selected compounds showed anticancer effects on human esophageal cancer cells (EC109), human bladder cancer cells (EJ) and human gastric cancer cell lines (MGC803) (Fig. 3). Compound **5v** exhibited the best cytotoxicity on EJ (IC_{50} = 61.607 ± 1.790 μg/mL) and MGC803 (IC_{50} = 65.584 ± 1.817 μg/mL) (Fig. 4). In addition, the antibacterial activities of thiazolidine-2-thione **5a**-**x** against three Gram-positive bacteria *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus Subtilis* and four Gram-negative *Escherichia coli*, *Pseudomonas maltophilia*,



Scheme 2. Proposed mechanism.

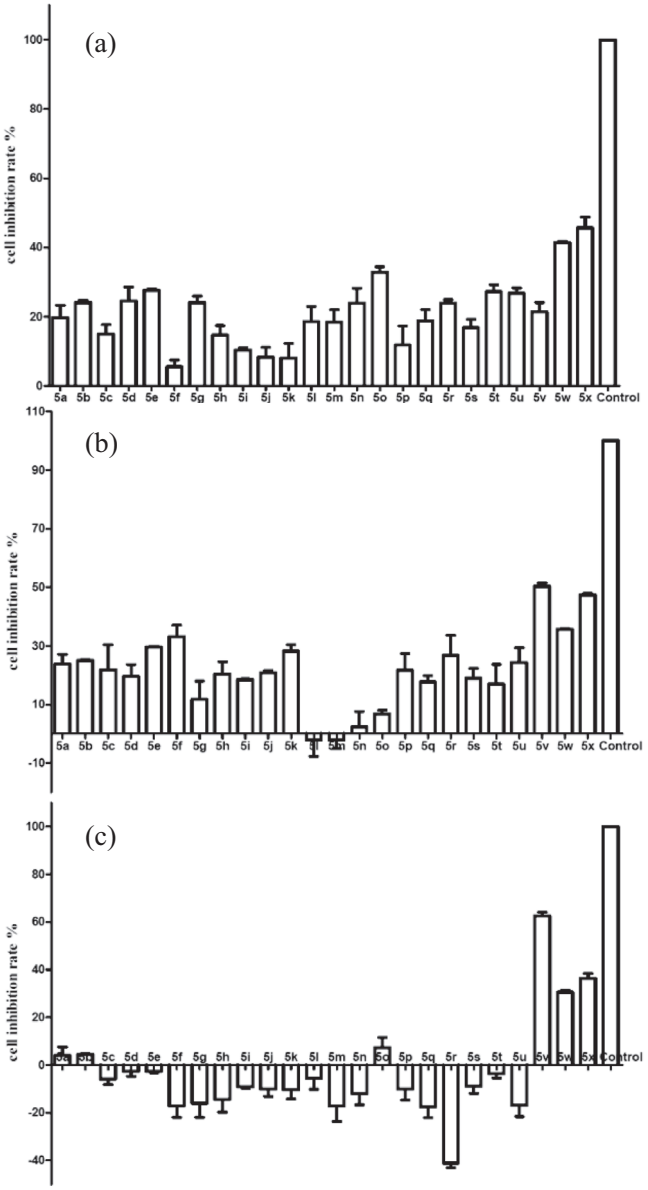


Fig. 3. Cell inhibition rates for 72 h treatment at 64 μg/mL. (a) human esophageal cancer cells (EC109). (b) human bladder cancer cells (EJ). (c) human gastric cancer cells (MGC803).

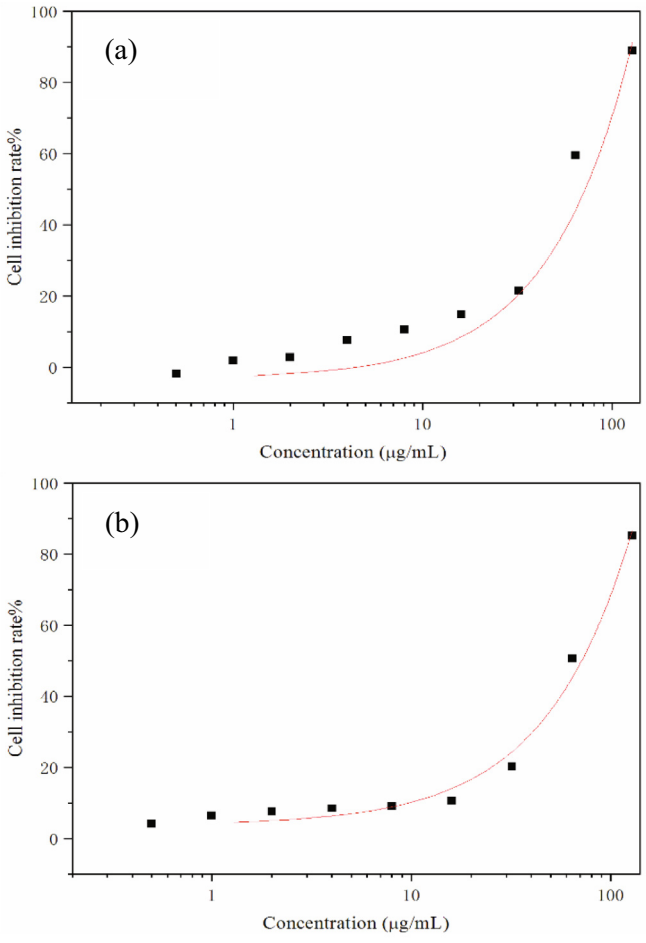


Fig. 4. Fit curve of IC_{50} (50% inhibitory concentration) of compound **5v**. (a) human gastric cancer cell lines (MGC803). (b) human bladder cancer cells (EJ).

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Table 3
MICs of compounds and commercial antibiotics.

MIC (μg/mL) Gram-positive bacteria							
Com.	*S.a*[a]	*E.f*[b]	*B.s*[c]	*E.c*[d]	*P.m*[e]	*K.p*[f]	*Se*[g]
5a	>64	>64	>64	>64	>64	>64	>64
5a	>64	>64	>64	>64	>64	>64	>64
5c	>64	>64	>64	>64	>64	>64	>64
5d	>64	>64	>64	>64	>64	>64	>64
5e	>64	>64	>64	>64	>64	>64	>64
5f	>64	>64	>64	>64	>64	>64	>64
5g	>64	>64	>64	>64	>64	>64	>64
5h	>64	>64	>64	>64	>64	>64	>64
5i	>64	>64	>64	>64	>64	>64	>64
5j	>64	>64	>64	>64	>64	>64	>64
5k	>64	>64	>64	>64	>64	>64	>64
5l	>64	>64	>64	>64	>64	>64	>64
5m	>64	>64	>64	>64	>64	>64	>64
5n	>64	>64	>64	>64	>64	>64	>64
5o	>64	>64	>64	>64	>64	>64	>64
5p	>64	>64	>64	>64	>64	>64	>64
5q	>64	>64	>64	>64	>64	>64	>64
5r	>64	>64	>64	>64	>64	>64	>64
5s	>64	>64	>64	>64	>64	>64	>64
5t	>64	>64	>64	>64	>64	>64	>64
5u	>64	>64	>64	>64	>64	>64	>64
5v	>64	>64	>64	>64	>64	>64	>64
5w	>64	>64	>64	>64	>64	>64	>64
5x	>64	>64	>64	>64	>64	>64	>64
V[h]	1	—[j]	—[j]	—[j]	—[j]	—[j]	—[j]
M[i]	—[j]	—[j]	0.0625	—[j]	—[j]	—[j]	—[j]

[a] Staphylococcus aureus.
[b] Enterococcus faecalis.
[c] Bacillus subtilis.
[d] Escherichia coli.
[e] Pseudomonas maltophilia.
[f] Klebsiella pneumonia.
[g] Salmonella.
[h] Vancomycin.
[i] Meropenem.
[j] Not determined.

Klebsiella pneumonia, *Salmonella* were evaluated. However, the minimum inhibitory concentration (MIC) of these compounds were >64 μg/mL (Table 3).

Conclusion

In summary, we have developed a new route toward the asymmetric synthesis of thiazolidine-2-thione analogs of linezolid *via* a one-pot reaction. The reaction is efficient, simple, and gives good to high yields of chiral 5-substituted thiazolidine-2-thione products. The enantiopurity of the starting material in this reaction was retained.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 21702190), the China Postdoctoral Science Foundation (001803014, 2018 M640685, 2019 T120642) and Henan province (No. 17A350004). We thank Gabrielle David, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151847.

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