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Zheng Lu, Yong-Qing Yang, Jiu-Hui Li, Jun-Nan Wei & Yi-Zhu Wang

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A convenient approach to chiral 4-monosubstituted 1,3-oxazolidine-2-thiones

Zheng Lu

School of Pharmacy, Jiangsu University, Zhenjiang, Jiangsu, China

Yong-Qing Yang*

School of Pharmacy, Jiangsu University, Zhenjiang, Jiangsu, China

Jiu-Hui Li

School of Pharmacy, Jiangsu University, Zhenjiang, Jiangsu, China

Jun-Nan Wei

School of Pharmacy, Jiangsu University, Zhenjiang, Jiangsu, China

Yi-Zhu Wang

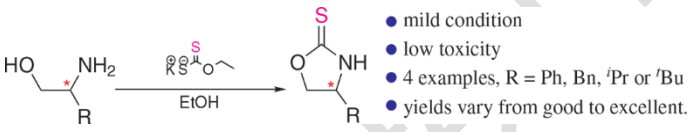
School of Pharmacy, Jiangsu University, Zhenjiang, Jiangsu, China

*Address correspondence to Yong-Qing Yang, School of Pharmacy, Jiangsu University, Zhenjiang, Jiangsu, 212013, China. E-mail: yqy@ujs.edu.cn

ABSTRACT

Chiral 4-monosubstitued 1,3-oxazolidine-2-thiones are regarded as one of the modified version of Evans auxiliaries in asymmetric aldol condensation, which can generate two adjacent chiral carbon centres in one time They have advantages over Evans auxiliaries in some aspects, however their application is highly limited by their preparation approaches as toxic or flammable chemicals are involved. Here, a mild and applicable procedure for preparing the chiral oxazolidine-2-thione auxiliaries has been developed in this article. Potassium ethylxanthate and the corresponding chiral amino alcohols as the starting material in absolute ethanol are mixed and the mixture are heated under reflux for one hour in open air to provide 1,3-oxazolidine-2-thiones chiral auxiliaries in moderate to excellent yields.

GRAPHICAL ABSTRACT



KEYWORDS: 1,3-oxazolidine-2-thione, chiral auxiliaries, environmentally-benign, xanthates

Subject classification codes: include these here if the journal requires them

Introduction

Homochiral 4-monosubstituted 1,3-oxalidine-2-thiones are chiral auxiliaries applied in the enantioselective syntheses,[1] compared to classical chiral 1,3-oxazolidinones (Evans auxiliaries[2]), 1,3-oxalidine-2-thiones show advantage of easier cleavage[3] and better selectivity in the acetate-like aldol reaction.[4] Recent studies have shown that oxalidine-2-thiones could also

act as convenient sulfur suppliers[5] and Michael donors[6] as well. Approaches to preparation of 1,3-oxazolidine-2-thiones have been developed by several research groups.[1e,7,8] The source of sulfur contains three types, CS_2,[7] $CSCl_2$[1e] and 1,1-thiocarbonyldiimidazole.[8] In the preparations of 4-monosubstituted 1,3-oxalidine-2-thiones starting from corresponding amino alcohols, which are commercially available are especially studied broadly.[1c,7a–c] CS_2[7] and $CSCl_2$[1e] are currently employed as the sulfur source(**Figure 1**). Carbon disulfide (CS_2) is employed as the major source of sulfur by many groups,[7] as it is inexpensive and easily accessible. Under basic conditions,[4,7a] amino alcohols react with CS_2 under refluxing to form 1,3-oxalidine-2-thiones in good to excellent yields. However, regarding low boiling point (46^{o}C) and low flash point (-30^{o}C) of CS_2,[9] refluxing condition would inevitably be potential danger to researchers. Although addition of hydrogen peroxide (H_2O_2) to this basic system could shorten the reaction duration and improve the reaction yield remarkably,[7c] usage and storage of CS_2in the laboratory is still a serious safety concern.

Thiophosgene ($CSCl_2$) was once reported by Crimmins group[1e] as source of sulfur leading to excellent yield of (*S*)-4-benzyl-1,3-oxalidine-2-thione. However, the application of this reaction is restricted by the high toxicity of $CSCl_2$.[10] Therefore, the need for an environmentally-benigh access to 1,3-oxalidine-2-thiones still remains. Interestingly, it was reported that xanthates (potassium ethylxanthate (KSCSOEt)[11a–d] or potassium isopropylxanthate (KSCSO^{i}Pr)[11e] could convert 2-aminophenol to 3*H*-benzooxazole-2-thione in moderate to excellent yields.

Furthermore, KSCSOEt has even been applied in the preparation of indene-based thiazolidinethione chiral auxiliary.[12] However, to the best of our knowledge, their applications to forming chiral oxalidine-2-thiones auxiliaries have not been reported yet. Here we are keen to explore xanthates as safer and milder surrogates of CS_2 to the preparation of homochiral 4-monosubstituted 1,3-oxazolidien-2-thione.

Results and Discussion

With (*R*)-2-phenylglycinol as our model substrate, investigation on search for optimal conditions for the formation of (*R*)-4-phenyl-1,3-oxazolidine-2-thione has been conducted. Our experimental results are summarized in **Table 1**. Initially the amino alcohol was dissolved in ethanol and KSCSOEt was added to the solution, the reaction was performed at room temperature, it turned out that no cyclization compound was obtained at all within one hour (entry 1), no change was observed even after 12 hours. To our delight, when the reaction temperature was raised to 50^{o}C, desired product was isolated with 31% yield (entry 2). Further heating the oil bath to 100^{o}C (the reaction mixture was heated at reflux) lead to an outcome of 88% yield (entry 3). Prolonged reaction time (> 1 hr, up to 18 hrs) caused deteriorating yield (entries 4-6). Polar solvents (e.g. THF, MeCN&DMF) have been tested in this system, however none of them showed superiority over ethanol (entries 11-13). Then the amount of KSCSOEt was tested, and 2.5 eq. of xanthate seems to be necessary. Increasing the amount of xanthate did not improve the yield, while lower

the amount of xanthate lead to drop of the yield (entries 3, 7, 8&9). If the reaction proceeded under N_2 instead of open air, the yield decreased by 13% (entry 10).

The optimal condition is that (*R*)-2-Phenylglycinol was mixed with KSCSOEt with the molar ratios as 1:2.5 in ethanol and reacted at 100°C (oil bath) for one hour in open air. We were satisfied with this result and the application of this reaction in preparation of chiral auxiliaries from commercial amino alcohols was explored.

In general, homochiral 4-monosubstituted 1,3-oxazolidine-2-thiones (R = Ph, Bn, ^{i}Pr and ^{t}Bu) could be prepared in good to excellent yield. The steric hindrance of the substituent at the 4-position shows some effect on the outcome of the reaction. When R = Bn, which is more flexible compared to Ph, ^{i}Pr and ^{t}Bu, the corresponding product **2b** was isolated only in moderate yield. The bulkiest one (R = ^{t}Bu) gives excellent yield in the meanwhile. It shows the more steric hindrance 4-substitute bears, the better turnout the reaction gives.

In conclusion, a mild and safe procedure to prepare homochiral 4-monosubstituted 1,3-oxazolidine-2-thione auxiliaries has been developed by employment of KSCSOEt in place of CS_2 (or $CSCl_2$). It has been successfully applied to preparation of widely used chiral auxiliaries (4-Ph, 4-Bn, 4-^{i}Pr&4-^{t}Bu 1,3-oxazolidine-2-thiones) from corresponding amino alcohols. This protocol will contribute to wider application of this type of chiral auxiliary in asymmetric synthesis.

Experimental

The starting materials used were purchased from Energy Chemical. All chemicals were analytical reagent and used as purchased. The reactions described in this manuscript were performed in standard laboratory glassware. Melting points were recorded on a WRS-1B digital melting point recorder from Shanghai Precision Scientific Instrument Corporation. Optical rotations were measured on an Automatic Polarimeter WZZ-2A from Shanghai Precision Scientific Instrument Corporation. Infrared spectra were recorded on a Nicolet Avatar 370 DTGS machine. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AV400 equipment. ESI-MS data were recorded on a Shimadzu LCMS-2010EV mass spectrometer. Column chromatography was performed on silica gel (300–400 mesh) under slightly positive pressure. PE = petroleum ether (b.p. 60–90^{o}C).

General procedure for preparation of homochiral 4-monosubstituted 1,3-oxzlidine-2-thiones

Potassium ethylxanthate (400mg , 2.5 mmol) was added to the solution of (*R*)-D-phenylglycinol (**1a**, 137mg , 1.0 mmol) in ethanol (2.0mL), then the resulting suspension was heated to reflux (oil bath at 100^{o}C). The reaction was completed in one hour, which was monitored by TLC. Then it was cooled to r.t. and diluted with EtOAc (40 mL), and washed with H_2O (10mL *3) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the crude product was obtained, which was purified through

flash chromatography (rinsed with PE/EtOAc = 5:1) to afford (*R*)-4-phenyl-1,3-oxazolidine-2-thione[7a] (**1b**) as white solid (158mg , 0.88 mmol), yield 88%.

Mp 120.0-120.4 ºC (lit. [7a] Mp 121-122 ºC); $[\alpha]_D^{27}$-70.0 (*c* 0.70, $CHCl_3$) (lit. [7a] $[\alpha]_D^{20}$ -79.3 (*c* 0.21, $CHCl_3$)); R_f = 0.3 (PE-EtOAc, 3:1). ^{1}H NMR (400MHz , $CDCl_3$) δ 7.45-7.36 (m, 3H, Ar-H), 7.33-7.29 (m, 2H, Ar-H), 5.12 (dd, *J* = 8.4, 6.8Hz , 1H, OCH_2), 5.00 (t, *J* = 9.2Hz , 1H, OCH_2), 4.48 (dd, *J* = 8.8, 6.8Hz , 1H, NCH). ^{13}C NMR (100MHz , $CDCl_3$) δ 189.6, 137.9, 129.2, 129.0, 126.2, 77.6, 60.1. IR (KBr, solid) ν_{max} 3436, 2922, 1525, 1268, 1170, 763cm^{-1}. MS (ESI) *m/z* 178.0 ($[M-H]^-$).

Supplemental material

Full experimental details, IR, ^{1}H NMR, and ^{13}C NMR data for this article can be accessed on the publisher's website.

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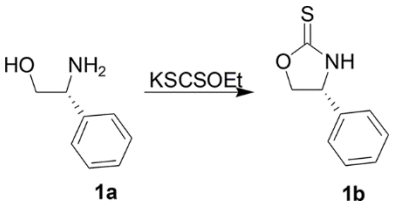
Table 1. Investigation of synthesis of **1b** from the corresponding amino alcohol **1a**.

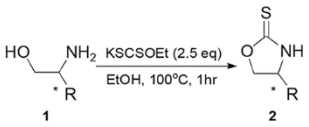


1a **1b**

Entry[a]	Solvent	Reagent/eq.[b]	Time/h	Yield/%[c]
1	EtOH	2.5	1[d]	0
2	EtOH	2.5	1[e]	31
3	EtOH	2.5	1	88
4	EtOH	2.5	3	73
5	EtOH	2.5	7	72
6	EtOH	2.5	18	24
7	EtOH	3.0	1	87
8	EtOH	2.0	1	70
9	EtOH	1.5	1	64
10	EtOH	2.5	1[f]	75
11	THF	2.5	1	7
12	ACN	2.5	1	2
13	DMF	2.5	1	12
14	EtOH	1.1	1	41

[a]Reactions were performed in oil bath at 100°C if there's no other indication. [b]The quantity of the reagent is given in molar equiv. with respect to **1a**. [c]Isolated yield. [d]Room temperature. [e]Oil bath at 50°C. [f]The reaction is carried out under N_2.

Table 2. Scope of synthesizing 1,3-oxazolidine-2-thiones from corresponding amino alcohols



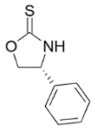
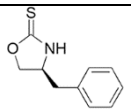
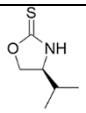
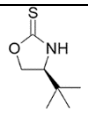
 **2a**, 88%	 **2b**, 60%	 **2c**, 80%	 **2d**, 91%

Figure 1. Accesses to 1,3-oxazolidine-2-thiones from corresponding amino alcohols.