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Technical Notes

An Improved Process for the Preparation of 4,4-Dimethyloxazolidine-2-thione

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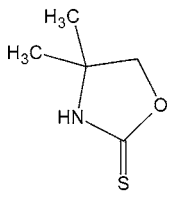
Abstract:

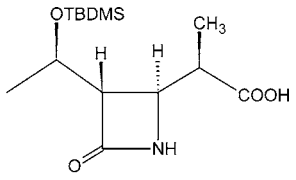
An improved process for the preparation of 4,4-dimethyloxazolidine-2-thione (1), an auxiliary used in the synthesis of (3*S*,4*S*)-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (2), a key intermediate for carbapenem synthesis is reported.

Introduction

Oxazolidine-2-thiones have been used as chiral auxiliaries for a wide variety of synthetic transformations.[1] These five-membered heterocycles are commonly prepared by the condensation of carbon disulphide with β-amino alcohols.[2−4] Oxazolidine-2-thiones are used in the synthesis of (3*S*,4*S*)-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-azetidinone (**2**), a key carbapenem intermediate.[5−7] In the course of our ongoing project for the synthesis of **2**, a method for production of the auxiliary 4,4-dimethyloxazolidine-2-thione (**1**) on a multikilogram scale was required. In this report an efficient and scalable synthesis of **1** is described.



1



2

Results and Discussion

Literature survey reveals that **1** is prepared from 2-methyl-2-aminopropanol (**3**), ammonium hydroxide, carbon disulphide, and chloroacetic acid.[8] Another method[9] involves the preparation of dithiocarbamic acid **4** in benzene followed by heating of the isolated **4** to result in **1** (Scheme 1). Benzene being carcinogenic cannot be used on a commercial scale, and direct heating of solid dithiocarbamic acid **4** is not recommended on a commercial scale. Another recent literature method[10] for synthesis of oxazolidine-2-thiones involves reaction of amino alcohol with carbon disulphide in the presence of sodium carbonate. However our attempts to prepare **1** using the above methodology gave poor yields and quality due to precipitation of sodium carbonate along with the product.

The present process describes the synthesis of 4,4-dimethyl oxazolidine-2-thione (**1**) in one step from reaction of 2-amino-2-methylpropanol (**3**) in toluene with carbon disulphide (entry 2). In a typical experiment carbon disulphide is added to 2-amino-2-methylpropanol (**3**) dropwise. As the reaction proceeds the intermediate **4** separates as a solid. The solid is dissolved in water and heated in the presence of aqueous sodium hydroxide (10%) at 95−100 °C for 1−2 h followed by cooling of the reaction mixture to yield **1** in 38% yield. During the optimization studies we have carried out the reaction under different conditions, and the results are tabulated in Table 1. The preparation of **1** without any organic solvent (entry 1) gives better yields but can have scale up issues. The preparation of **1** following the reported procedure[9] using toluene instead of benzene as solvent results in 32% yield (entry 3). However the reaction carried out in toluene (entry 2) results in better yields (38%). The reaction using water and a water/toluene mixture as solvent gave no product (entry 5, 8). Reaction with dichloromethane as solvent also results in lower yields (25%) (entry 4).

On a commercial scale, the addition of carbon disulphide should be carried out under water blanketing and a nitrogen atmosphere. The rate of addition of carbon disulphide should be such that the temperature of the reaction mixture does not rise above 40 °C.

The present method has the following advantages over the reported methods. The reaction is carried out in one step without filtration of dithiocarbamic acid **4** which prevents exposure to carbon disulphide on a commercial scale, and direct heating of **4** is avoided.

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Scheme 1

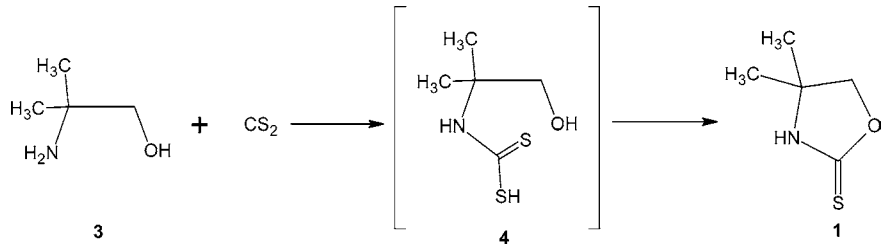

Table 1. **Preparation of 4,4-dimethyl oxazolidine-2-thione (1) under different conditions**

entry	solvent (times)	base	yield (%)
1	neat	−	40
2	toluene (2T)	−	38
3	toluene (7T)[a]	−	32
4	DCM (2T)	−	25
5	water	−	no reaction
6	water[b]	Na_2CO_3	15
7	water	NaOH	10
8	toluene + water	−	no reaction
9	DCM	triethylamine	20

[a] Dithiocarbamic acid is isolated and dissolved in water for further reaction. [b] Sodium carbonate precipitates out along with the product.

In conclusion, an improved single step scalable process for the preparation of 4,4-dimethyloxazolidine-2-thione (**1**) is reported.

Experimental Section

General. Reagents are used as such without purification. HPLC is performed with a Waters instrument using an ACE C-18 (150 mm × 4.6 mm, 5μ) column with a UV detector (240 nm) and mobile phase phosphate buffer (pH 6.5)/acetonitrile(1:9) with flowrate 1.5 mL/min. ^{1}H NMR spectra are recorded using a Bruker 300 MHz instrument. The chemical shift data are reported as δ (ppm) downfield from tetramethylsilane which is used as an internal standard. Infrared spectra are recorded using Perkin-Elmer FTIR (Spectrum One) instrument. Mass spectra are recorded using an API 2000(MDS SCIEX) instrument.

Preparation of 4,4-Dimethyloxazolidine-2-thione (1). Carbon disulphide (1.88 kg, 24.73 mol) was added dropwise to 2-amino-2-methylpropanol (**3**) (2.0 kg, 22.47 mol) in toluene (4.0 L) with vigorous stirring over a period of 1−2 h. (The rate of addition of carbon disulphide was maintained in such a way that the reaction temperature does not exceed 40 °C.) After 1 h, distilled water (4.0 L) was added and the reaction mixture was stirred until complete dissolution of the solid in water takes place. The layers were separated, and to the aqueous layer 10% NaOH (500 mL) was added; the resulting solution was heated at 95−100 °C for 1−2 h. The colour of the solution changes from red to light green, and evolution of H_2S gas ceases (H_2S gas generated is trapped by passing through an aqueous NaOH solution). The resulting reaction mixture on cooling gave a crystalline solid which was filtered, washed with cold water (2 × 500 mL), and dried to yield **1** (1.12 kg, 38%). Chromatographic purity by HPLC > 99%. ^{1}H NMR ($CDCl_3$) δ 8.5 (s, 1H, NH), 4.4 (s, 2H, $-CH_2$), 1.4 (s, 6H, 2 × CH_3). IR (ν cm^{-1}, KBr) 3200, 1520. MS (*m*/*e*): 131.

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