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 (3S,4S)-[(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 fivemembered 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.



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 method⁹ involves the

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466 • Vol. 11, No. 3, 2007 / Organic Process Research & Development Published on Web 04/03/2007 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 method¹⁰ 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 4,4dimethyl 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 $^{\circ}$ 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 procedure⁹ 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 $^{\circ}$ 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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 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, 5 μ) column with a UV detector (240 nm) and mobile phase phosphate buffer (pH 6.5)/ acetonitrile(1:9) with flowrate 1.5 mL/min. ¹H 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.



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IR (ν cm⁻¹, KBr) 3200, 1520. MS (m/e): 131.

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