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A New Approach To The Synthesis Of 2-Methylcysteine Using Aziridination

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Abstract

A synthesis of 2-methylcysteine (**1**) has been successfully accomplished starting from methylmethacrylate (**2**). The reaction sequence involves aziridination of methylmethacrylate, regioselective opening of the aziridine ring with thioacetic acid and subsequent hydrolysis with hydrogen bromide in acetic acid.

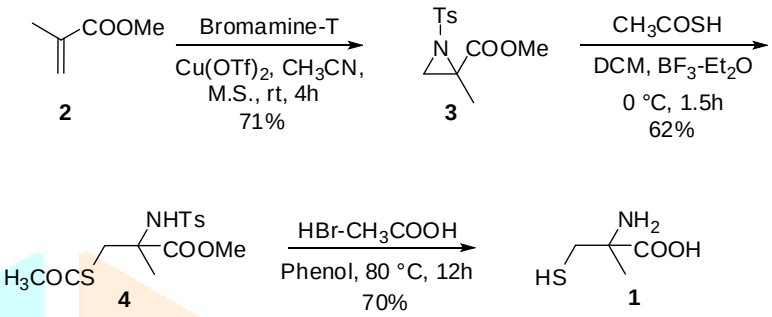
Keywords: Copper triflate, bromamine-T, aziridine, Regioselective, 2-methylcysteine

Introduction

Modified amino acids are valuable building blocks for the synthesis of peptides and peptide analogues[1]. Heathcock and Pattenden showed that 2-methylcysteine is an unnatural amino acid constituting an important building block for natural products such as mirabazoles[2-4], tantazoles[5,6] and thiangazoles[7] which exhibit antitumor and anti HIV activities[8].(*S*)-Desferrithiocin[9] is a naturally occurring ferric iron chelator (siderophore) that incorporates the 2-methylcysteine moiety. 2-Methylcysteine and its derivatives can form constrained cyclic peptide structures via disulphide bridge formation [10], due to the labile nature of the sulfhydryl group. The literature search reveals that, very few reports have been available and successfully developed for the asymmetric synthesis of 2-methylcysteines[11]. Fukuyama[12] obtained the 2-methylcysteine via an enzymatic ester hydrolysis. Ehrler utilized chromatographic separation of a racemate. A stereoselective alkylation and introduce the methyl group was the key step for the synthesis, of Pattenden [13,14] and Heathcock[15]. Other methods include regioselective ring opening of chiral aziridine[10] or β-lactone[11, 12]] with a thiolate nucleophile. Kedrowski synthesized 2-methylcysteine from dimethyl 2-methylmalonate *via* enzymatic resolution followed by a Curtius rearrangement[16]. Ohishi synthesized D- and L-2-methylcysteine starting from chloroacetone under mild conditions [17]. We aimed to devise a simple, facile, industrially scaleable, cost-effective method to produce 2-methylcysteine. The copper-catalyzed reactions[18] to explore copper as a first line catalyst for many organic reactions, copper catalysis in asymmetric synthesis and total synthesis of natural products and heterocycles as well as nanocatalysis.

Results and Discussion

In this communication, we develop a novel synthetic method for synthesis of 2-methylcysteine **1** on regioselective ring opening strategy of aziridine. Synthesis of 2-methylcysteine **1,** started using methyl methacrylate **2** as the alkene source and bromamine-T as a nitrene source [14, 15, 16]. Initially, anhydrous Cu(II) in dry acetonitrile was stirred under nitrogen atmosphere at room temperature[19-20]. Then methyl methacrylate **2** was added to this solution followed by addition of bromamine-T and activated 4Å molecular sieves which afforded aziridine **3**. Aziridination of methyl methacrylate gave 40% and 71 % yield with $CuCl_2$ and $Cu(OTf)_2$ respectively. Regioselective ring opening of **3** with thioacetic acid in presence of boron trifluoride etherate in dichloromethane furnished the protected 2-methylcysteine **4**. protected 2-methylcysteine **4** on global hydrolysis using hydrogen bromide in acetic acid and phenol as an activator to yielded 2-methylcysteine **1** (**Scheme 1**).



Scheme 1: Synthesis of 2-methylcysteine

Experimental Section

Chemistry: NMR spectra were recorded on a Bruker AV-200 spectrometer operated at 200 MHz for ^{1}H-NMR and 50 MHz for ^{13}C-NMR. Spectra were obtained at 25 °C in $CDCl_3$ was referenced to the $CHCl_3$ peak (δ 7.26) and D_2O peck (δ 4.8) for ^{1}H or to the center line of the $CDCl_3$ at δ 77 for ^{13}C-NMR. All chemical shifts are given as δ values (in ppm) relative to TMS. IR spectra were recorded on Perkin-Elmer FT IR instrument. Microanalyses were performed on a Flash EA-1112 Thermo Finnigan Elemental Analyzer Melting points were determined by using a Yanco Micro Melting point apparatus and were uncorrected.

Reactions with moisture-sensitive chemicals were performed under nitrogen in flame-dried reaction flasks. Solvents were dried by standard methods. Column chromatography was carried out using 100-200 mesh silica gel.

Aziridination of methyl methacrylate to N-p-toluenesulphonyl-2-carbomethoxy-2-methylaziridine (3)

Anhydrous $CuCl_2$ (265 mg, 1.97 mmol) in dry acetonitrile (70 ml) was stirred under nitrogen at room temperature. Methyl methacrylate (4.35 g, 3.51 ml, 43 mmol) was then added to this solution followed by addition of bromamine-T (5.37 g, 19 mmol) and 4Å molecular sieves (5 g). The reaction mixture was stirred at room temperature for 4 hours. Then it was diluted with ethyl acetate (250 ml) and filtered through a pad of silica gel. The clear solution was dried over sodium sulphate and solvent concentrated under vacuum. A thick colorless oil was obtained which was purified by silica gel column chromatography using ethyl acetate and light petroleum (1:4) affording the aziridine derivative **3** (2.15 g, 40 %) as a colorless solid, M.P.= 112 °C(sharp); IR ($CHCl_3$): 3020; 1741; 1331; 1215; 1163; 882; 759 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90 (s, 3H); 2.44 (s, 3H); 2.71 (d, *J* = 15 Hz, 1H); 2.79 (m, *J* = 15 Hz, 1H); 3.75 (s, 3H); 7.31 (d, *J* = 8 Hz, 2H); 7.82 (d, *J* = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.04; 21.41; 38.77; 46.28; 52.79; 127.42; 129.45; 136.78; 144.28; 168.71. Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.53; H, 5.51; N, 5.20; S, 11.89. Found: C, 53.41; H, 5.68; N, 4.93; S, 12.09.

Aziridination of methyl methacrylate to N-p-toluenesulphonyl-2-carbomethoxy-2-methylaziridine (3)

Anhydrous $Cu(OTf)_2$ (713 mg, 1.97 mmol) in dry acetonitrile (70 ml) was stirred under nitrogen at room temperature. Methyl methacrylate **2** (4.35 g, 3.51 ml, 43 mmol) was then added to this solution followed by addition of bromamine-T (5.37 g, 19 mmol) and 4Å molecular sieves (5 g). The reaction mixture was stirred

at room temperature for 4 hours. Then it was diluted with ethyl acetate (250 ml) and filtered through a pad of silica gel. The clear solution was dried over sodium sulphate and solvent concentrated under vacuum. A thick colorless oil was obtained which was purified by silica gel column chromatography using ethyl acetate and light petroleum (1:4) affording the aziridine derivative **3** (3.8 g, 71 %) as a colorless solid, M.P.=112 °C (sharp).

Ring opening of the aziridinated product to methyl (2-N-tosylamino-3-acetomercapto) propionate (4)
N-p-Toluenesulphonyl-2-carbomethoxy-2-methyl aziridine **3** (200 mg, 74 mmol) was taken 25 ml two necked round bottom flask under nitrogen and then DCM (5 mL) and thioacetic acid (0.79 ml, 1.11 mmol) was added. Reaction mixture was cooled at 0 °C, followed by addition of $BF_3{\cdot}O(Et)_2$ (1.8 ml, 1.11 mmol) and reaction mixture was stirred for 1.5 hours at 0 °C. It was then diluted with DCM (10 ml); the combined layer was washed with saturated sodium bicarbonate solution and dried. Removal of the solvent under vacuum yielded on oily residue, which was purified by column chromatography yield **4** (160 mg, 62%); IR ($CHCl_3$): 3280; 1740; 1694; 1597; 1331; 1159 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 3H); 2.32 (s, 3H); 2.42 (s, 3H); 3.37 (q, 2H); 3.65 (s, 3H); 7.31 (d, *J* = 8 Hz, 2H); 7.72 (d, *J* = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.46; 21.89; 30.32; 37.52; 53.07; 61.67; 126.97; 129.49; 138.93; 143.40; 172.15; 194.50. Anal. Calcd for $C_{14}H_{19}NO_5S_2$: C, 48.91; H, 5.51; N, 4.06; S, 18.55. Found: C, 48.65; H, 5.27; N, 3.93; S, 18.62.

Hydrolysis to 2-amino-3-mercapto-2-methylpropanoic acid (2-methylcysteine) (1)
Methyl (2-N-tosylamino-3-acetomercapto) propionate **4** (100 mg, 0.28 mmol); phenol (81.73 mg, 0.86 mmol), 10 ml of 32 % hydrogen bromide in acetic acid was charged in a thick walled glass tube. It was sealed and heated in a metallic bomb for 12 hours at 80 °C. The reaction mixture was allowed to cool to room temperature and then was poured into 150 ml of ether and stirred for 5 min. The ether solution was decanted and the residue was dissolved in 6 ml of water. This aqueous solution was stirred with charcoal and filtered. The filtrate was passed through Dowex 50-X8 (Na) bed and washed with 10 ml water. Total aqueous solution was concentrated under vacuum at room temperature to obtain 2-methylcysteine **1** (27 mg, 70 %) as sticky mass.; IR (Nujol): 3615; 2542; 1611; 1511cm^{-1}; ^1H NMR (200 MHz, D_2O): δ 1.74 (s, 1H); 1.72 (s, 3H); 3.25 (m, 1H); 3.62 (m, 1H).

Conclusion

We have developed an efficient and versatile route for synthesis of 2-methylcysteine *via* aziridination of methyl methacrylate followed by regioselective opening of the aziridine with thioacetic acid. Hydrolysis of the N-protected thio-ester in three steps in an overall yield of 30%.

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Supporting Information Available

NMR spectra of all new compounds are available free of charge via the Internet at JSR website

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