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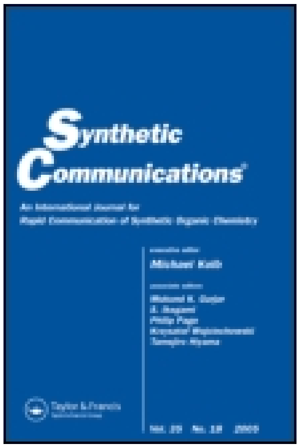

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One-Pot Synthesis of dl-2-Amino-2-thiazoline-4-carboxylic Acid

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One-Pot Synthesis of DL-2-Amino-2-thiazoline-4-carboxylic Acid

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ABSTRACT

DL-2-Amino-2-thiazoline-4-carboxylic acid was prepared in one-pot reaction from 2,3-dichloropropionic acid. Not only the procedure was simplified, but also the yield was increased from less than 63% recorded to 93%.

Key Words: Synthesis; DL-2-Amino-2-thiazoline-4-carboxylic Acid.

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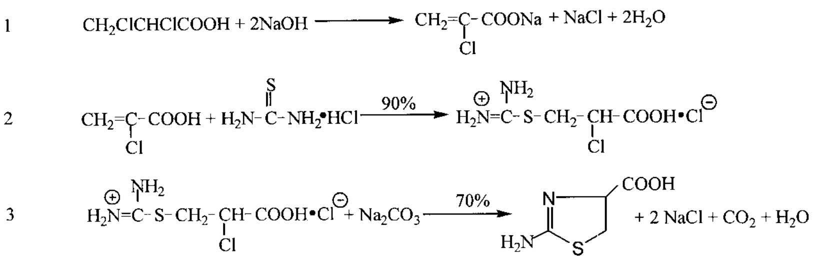
DL-2-Amino-2-thiazoline-4-carboxylic acid is an intermediate for preparing L-cysteine,[1–12] which is widely used in cosmetics, drugs and food industries.

There are three methods of chemical synthesis to prepare DL-2-amino-2-thiazoline-4-carboxylic acid.[12,13] The first method[12] is using HCl salt of thiourea and 2-chloroacrylic acid to isothiuronium salt with 90% yield, and converting the salt to target acid with 70% yield. The second method[12] is using HCl salt of thiourea and methyl 2-chloroacrylate to get isothiuronium salt with 85% yield, and then converting it to the target acid with 30% yield. The third method[12,13] is using thiourea and methyl 2-chloroacrylate to prepare target acid with 70% yield. Among the three methods, the third method has the highest yield, but it is the most complex one. The second method has the lowest yield overall, just about 25%. Though the first method only has relatively lower overall yield of 63% to the third method of 70%, the procedure is relatively simple, and using 2-chloroacrylic acid instead of methyl 2-chloroacrylate. So the first method was chosen in our experiment to prepare DL-2-amino-2-thiazoline-4-carboxylic acid and it should comprise three steps to prepare the compound from 2,3-dichloropropionic acid (Sch. 1). Because the yields of step 2 and 3 are 90% and 70% respectively,[12] the highest yield overall from 2,3-dichloropropionic acid should be not more than 63%.

During the course of preparing DL-2-amino-2-thiazoline-4-carboxylic acid, it was noticed that all three reactions carry out in water solution but with different concentration of base or acid, so it was possible to synthesize the compound in one-pot without isolation any intermediates. Usually, one-pot synthesis has some advantages, such as the procedure can be simplified, the yield might be increased, and the bulk of waste water should be reduced.



Scheme 1.

In fact, the experiment showed it was successful. In one-pot, the title compound was got with 93% yield from 2,3-dichloropropionic acid, its purity was 99.0%, and the bulk of waste water was decreased obviously.

EXPERIMENT

IR spectrum was recorded on Nicolet 5DX spectrometer in KBr disk. ^{1}HNMR and ^{13}CNMR were recorded on VANCE DMX500, the chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane. CHN analysis was obtained by using Carlo Erba elemental analyzer. Melting point determination was performed on XRC-1 melting-point apparatus. Shimadzu LC-10A was used in quantitative analysis. All chemicals are commercial reagents.

2,3-Dichloropropionic acid (114.4 g, 0.8 mol) was placed in a 2 L three-necked flask equipped with a mechanical stirrer and a thermometer. The solution of sodium hydroxide (64.0 g, 1.6 mol) in water (800 mL) was slowly added with stirring. The mixture was stirred for 5 h at 30–35°C, clear yellow solution was got. To the former solution was added thiourea (60.8 g, 0.8 mol)/concentrated hydrochloric acid (204 mL, 2.44 mol) solution, and was stirred for 3 h at 80–85°C. Let the solution cool to room temperature, then solid sodium carbonate (127.2 g, 1.2 mol) was added slowly. After complete addition, the mixture solution was heated and stirred for 3 h at 40–45°C, then its temperature rose to 70°C and kept it for 1 h. The pH of solution was regulated to about 2 with concentrated hydrochloric acid, and the solution was cooled to room temperature again. The reaction product was filtered by suction. Crystalline precipitate was washed with ethanol/water (50:50, v/v) two times, then it was dried. Finally, crystalline product (109 g) was obtained in 93% yield, M.p.: 204–208°C (205–210°C[12]), purity 99.0% (by HPLC). Calcd. for $C_4H_6N_2O_2S$: C, 32.87; H, 4.14; N, 19.16; found: C, 33.29; H, 3.78; N, 19.42. Principal bands in the IR-spectrum (KBr, cm^{-1}): 2940, 1610, 1400, 1300, 800, 700, as same as in the spectrum of Sadtler 21291K. ^{1}H-NMR (D_2O): δ 4.92 (1H, q, C_4), 4.70 (H, s, HDO), 4.08 (1H, q, C_5), 3.88 (1H, q, C_5). ^{13}C-NMR (D_2O): δ 174.70, 173.50, 63.46, 34.24.

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