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Short and efficient synthesis of 5-aminothiazole-4-carboxamide

Abstract: 5-Aminothiazole-4-carboxamide is a precursor for the synthesis of thiazole [4,5-*d*] pyrimidines. In this work, a new synthesis method with a high total yield (79%) of 5-aminothiazole-4-carboxamide was reported. The starting material is aminocyanacetamide. This synthesis method is environment-friendly and is suitable for industrial production.

Keywords: aminocyanacetamide; 5-aminothiazole-4-carboxamide; synthesis.

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Introduction

Thiazole-5-carboxamide is a key intermediate in the synthesis of thiazole[5,4-*d*]-pyrimidine derivatives. Thiazole [5,4-*d*] pyrimidine compounds are the isostere of purines [1] and precursors to bioactive molecules [2] in the synthesis of antiviral, anticancer, antibacterial, anti-inflammatory, and anti-psychotic drugs [3–7]. Meanwhile, the synthesis of 5-aminothiazole-4-carboxamide (**1** in Scheme 1) has rarely been reported. Tamura et al. [8] have reported the preparation of **1** by cyclization of 2-formamido-2-thiocarbamoylacetamide with acetic formic anhydride, followed by hydrolysis with 5% hydrochloric acid to give compound **1** in 28% yield. In our hands, the method has been difficult to reproduce, and therefore, it appears to be unsuitable for a large-scale preparation. Tamura et al. [8] have also reported another approach to 5-aminothiazole-4-carboxamide by heating 2-formamido-2-thiocarbamoylacetamide in polyphosphoric acid. Unfortunately, the procedure has completely failed in our hands.

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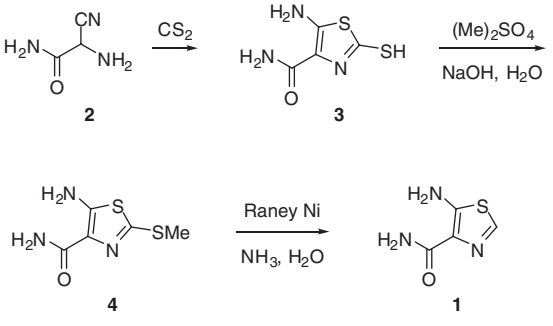
Results and discussion

In this article, we report new synthesis of 5-aminothiazole-4-carboxamide as shown in Scheme 1. The reaction of aminocyanacetamide (**2**) with carbon disulfide furnished the substituted thiazole **3** in a 95% yield. The choice of this reaction was based on the report by Everett that sodium cyanide undergoes a reaction with carbon disulfide to produce thiazole compounds [9]. Methylation of **3** yielded a methylthio derivative **4**. The desired product **1** was obtained in a total yield of 79% after reduction of **4** over a Raney nickel [10]. A direct removal of the thiol from **3** proved to be difficult; hence, the additional methylation step was introduced. It was observed that the concentration of sodium hydroxide is crucial in the methylation of **3** with dimethyl sulfate to give compound **4**. The concentration of 3.5% is optimal for the highest yield of **4**.

Conclusion

A simple and efficient methodology for the synthesis of **1** was developed. The approach is suitable for a large-scale industrial production.



Scheme 1

Experimental

General

All commercial reagents were purchased from Fluka and Sinopharm Chemical Reagent Co. Ltd and used without further purification. Aminocyanoacetamide was prepared using the procedures reported previously [11–13]. Silica gel plates (F254; Sanpont, China) and silica gel (100–200 mesh; SCRC) were used for analytical and column chromatography, respectively. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded in DMSO-d_6 on a Bruker AVANCE 400 spectrometer. Liquid chromatography-mass spectra (LC-MS) were acquired in a positive mode over 100–300 *m/z* range using a Waters Acquity-Quatro Premier spectrometer equipped with an electrospray ionization source. FT-IR spectra were obtained in KBr pellets on a Avatar 360 spectrometer. Elemental analyses were obtained using an Elementar Vario EL-III element analyzer.

5-Amino-2-mercaptothiazole-4-carboxamide (3)

A solution of aminocyanoacetamide (**2**, 6.5 g, 65.6 mmol) in 70 mL of methanol and 12 mL (199 mmol) of carbon disulfide was heated under reflux for **1** and then cooled to 5°C. The resultant yellow crystalline material was filtered and washed with ethyl acetate: yield 10.9 g (95%); mp 234.4–235.2°C; LC-MS: *m/z* 176.4 $[M-H]^+$; ^{1}H-NMR: δ 6.97 (2H, s), 7.08 (2H, s), 12.26 (1H, s); ^{13}C-NMR: δ 176.1, 161.6, 151.6, 109.0; FT-IR (cm^{-1}): 3388.0, 3359.4, 3319.2, 3162.0, 2923.2, 2823.8, 2758.8, 1660.8, 1594.9. Anal. Calcd for $C_4H_5N_3OS_2$: C, 27.42; H, 2.88; N, 23.98; S, 36.60.

5-Amino-2-methylthiothiazole-4-carboxamide (4)

5-Amino-2-mercaptothiazole-4-carboxamide (**3**, 3.5 g, 20 mmol), water (25 mL), and NaOH (0.88 g, 22 mmol) were introduced to a 100-mL three-neck flask, and then the mixture was cooled, stirred, and treated dropwise with dimethyl sulfate (2.1 mL, 22 mmol). After 1 h, yellow solid of **4** that separated was collected, washed with water, and dried: yield 3.6 g (95%); mp 148.1–148.8°C; LC-MS: *m/z* 190.7 $[M-H]^+$; ^{1}H-NMR: δ 2.49 (3H, s), 6.98 (2H, s), 7.08 (1H, s), 7.10 (1H, s); ^{13}C-NMR: δ 166.7, 157.7, 143.6, 123.0, 17.4; FT-IR (cm^{-1}): 3417.0, 3304.5, 3258.8, 3184.4, 2757.0, 1734.3, 1425.9. Anal. Calcd for $C_5H_7N_3OS_2$: C, 31.73; H, 3.73; N, 22.20; S, 33.88. Found: C, 31.75; H, 3.74; N, 22.23; S, 33.85.

5-Aminothiazole-4-carboxamide (1)

A mixture of **4** (30.0 g, 0.158 mol), Raney nickel (300 g), ammonium hydroxide (135 mL, 1.79 mol), and water (2250 mL) was heated under reflux for 3 h and then filtered while hot. The filtrate was cooled and concentrated under reduced pressure. The resultant solid of **1** was washed with ice water, dried (24.0 g), and then purified by column chromatography eluting with dichloromethane/methanol (50:1): yield 19.8 g (88%); mp 139.8–139.9°C (lit mp 140–141°C; [8]; LC-MS: *m/z* 144.7 $[M-H]^+$; ^{1}H NMR: δ 6.94 (2H, s), 7.05 (2H, s), 7.89 (1H, s); ^{13}C-NMR: δ 167.4, 157.1, 135.4, 123.8; FT-IR (cm^{-1}): 3417.1, 3387.6, 3276.1, 3147.6, 3072.1, 2329.7, 1659.7.

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