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A Convenient Synthesis of 2-(9H-Fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic Acid via N-Fmoc-thiourea

Kang Le and Robert A. Goodnow Jr.*

Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey, USA

ABSTRACT

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid has been prepared in high yield from 3-bromopyruvic acid and (aminothioxomethyl)carbamic acid 9H-fluoren-9-ylmethyl ester (*N*-Fmoc-thiourea) that was obtained from potassium thiocyanate.

Key Words: 2-Aminothiazole-4-carboxylic acid; 2-(9H-Fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid; *N-tert*-butoxycarbonylthiourea.

*Correspondence: Robert A. Goodnow, Jr., Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey, USA; E-mail: robert.goodnow@roche.com.

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INTRODUCTION

2-Aminothiazoles have been used in varieties of applications, which cover the fields of agriculture, pharmacy, photography, or related activities.[1] They are also among one of the key building blocks in drug discovery. There are more than 500 structures containing the 2-aminothiazole moiety reported in the Derwent World Drug Index.[2] Therefore, it is of interest to include 2-aminothiazoles in compound library designs for lead generation. Solid phase combinatorial chemistry is a powerful tool for generating novel compounds for lead generation. However, the potential of solid phase combinatorial chemistry is limited by the availability in sufficient quantity of appropriately protected reagents. As of this writing, 2-(9H-fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid is not commercially available at reasonable cost in quantities sufficient for library synthesis. To this end, we sought a convenient method for preparation of multi-gram quantities of 2-(9H-fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid such that the acid component in the molecule could be used as a reactive functionality for loading to solid phase linkers. Subsequent cleavage of the Fmoc group could be easily performed according to standard conditions (1 : 4 vol/vol piperidine/DMF) to expose the terminal amine group. The resin-bound, free amine can then be subjected to a diversity of chemistries generating many structurally diverse molecules.

Conceivably, title compound **5** could be obtained by the reaction of *N*-9-fluorenylmethoxycarbonyl chloride (Fmoc-Cl) and ethyl 2-aminothiazole-4-carboxylate, which is easily prepared from cyclization of ethyl bromopyruvate and thiourea.[3] The ethyl ester could then be carefully hydrolyzed to give the free acid. Although *N*-Boc protection of the ethyl 2-aminothiazole-4-carboxylate has been reported,[4] our efforts to react 2-aminothiazole-4-carboxylic acid with 9H-fluoren-9-ylmethyl chloroformate were not successful (Fmoc-Cl, triethylamine, dimethylaminopyridine, THF, room temperature, 12 hr).

Alternatively, one envisions that compound **5** could be obtained by condensation of *N*-Fmoc-thiourea **3** with bromopyruvic acid **4**. Previously, the preparation of *N-tert*-butoxycarbonylthiourea[5] and *N,N′-bis-tert*-butoxycarbonylthiourea[6] were reported by reaction of the sodium salt of thiourea with di-*tert*-butyldicarbonate. A similar condition was employed to prepare *N*-Fmoc-thiourea. In our hands, this reaction was found to result in a complex mixture and thus was judged not to be a viable route.

In this report, *N*-Fmoc-thiourea **3** was obtained by reacting methanolic and ethanolic ammonia with *N*-Fmoc-thiocyanate (carbon(isothiocyanatidic acid 9H-fluoren-9-ylmethyl ester)) **2**, which was conveniently prepared from potassium thiocyanate and Fmoc-Cl **1** (Sch. 1). Thiourea **3** and bromoketone

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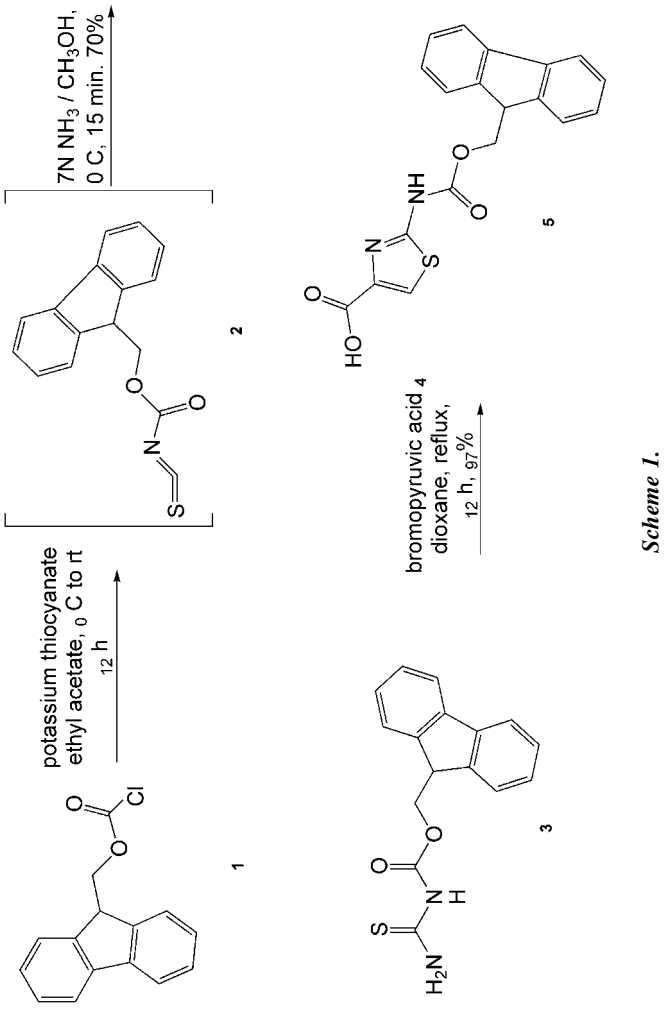

Scheme 1.

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4 were cyclized to afford 2-(9H-fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid **5**. This two-step sequence is easy, convenient, and inexpensive. The overall yield is high. No flash chromatography is required. Both intermediate **3** and the title product **5** were isolated by simple filtration; further purification of product **5** was effected by re-crystallization from methanol.

In practice, 2-(9H-Fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid generated with this method was later used in the solid phase synthesis of several library designs from, which new lead structures have been discovered.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity 400 NMR spectrometer. Infrared spectra were measured on a Perkin Elmer Spectrum GX FT-IR spectrophotometer as KBr pellets. Mass spectra were obtained on a Bruker Apex II FT-ICRmass spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. of Madison, NJ 07910.

***N*-9-Fluorenylmethoxycarbonyl thiourea (3).** To a suspension of potassium thiocyanate (8.55 g, 88 mmol) in ethyl acetate (100 mL) cooled to 0°C was added dropwise a solution of Fmoc-Cl (20.7 g, 80 mmol) in ethyl acetate (100 mL) over a period of 15 min. The resulting stirred suspension was allowed to warm to ambient temperature overnight. The resultant salt was filtered off and the remaining solution was concentrated in vacuo to afford an orange oil. Without further purification, the oil was dissolved in absolute alcohol (50 mL) and treated by dropwise addition with a solution of cold ammonia in methanol (7 N, 91 mL, 640 mmol). A precipitate formed upon addition of the ammonia solution. The suspension was stirred vigorously at 0°C for 15 min and was then filtered, washed with cold ethanol (3 × 20 mL), and dried to afford *N*-9-fluorenylmethoxycarbonyl thiourea (16.8 g, 70%) as an off-white solid. M.P.: 197–200°C. ^{1}H NMR (DMSO-d_6), δ: 4.28 (1H, t, CH), 4.33 (2H, d, CH_2), 7.32–7.45 (4H, m, 4 Ph-H), 7.83–7.91 (4H, m, 4 Ph-H), 8.99 (1H, s, NH-H), 9.33 (1H, s, NH-H), 11.29 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ: 46.00, 67.19, 120.14, 125.62, 127.13, 127.83, 140.70, 143.3, 153.05, 181.34. IR (KBr): 3353, 3249, 1731, 1597, 1530, 1451, 1320, 1204, 1106, 966, 759, 739 cm^{-1}. EI-HRMS m/e calcd for $C_{16}H_{14}N_2O_2S$ (M^+) 298.0776, found 298.0770. Anal. Calcd. For $C_{16}H_{14}N_2O_2S$: C 64.41, H 4.73, N 9.39. Found: C 64.51, H 4.59, N 9.20.

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid (5). A dioxane (40 mL) solution of *N*-9-fluorenylmethoxycarbonyl thiourea

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(5.96 g, 20 mmol) was treated with bromopyruvate (3.34 g, 20 mmol). The reaction mixture was refluxed for 1 hr. At this time the resultant precipitate was filtered and washed with ethyl ether (3 × 20 mL) to afford 2-(9H-fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid (7.1 g, 97%) as a white solid. The crude material was re-crystalized from methanol to provide a white crystalline solid (1.5 g from 2 g, 75%). M.P.: 224–226°C. ^{1}H NMR (DMSO-d_6), δ: 4.32 (1H, t, CH), 4.45 (2H, d, CH_2), 7.34–7.45 (4H, m, 4 Ph-H), 7.77–7.92 (4H, m, 4 Ph-H), 7.97 (1H, s, thiazole-H), 12.29 (1H, s, COOH). ^{13}C NMR (DMSO-d_6), δ: 46.25, 67.19, 120.22, 122.27, 127.18, 127.84, 140.77, 142.48, 143.39, 153.94, 159.52, 162.27. IR (KBr): 3120, 3044, 2967, 2889, 1746, 1721, 1576, 1329, 1259, 1181, 958, 759, 740 cm^{-1}. EI-HRMS m/e calcd for $C_{19}H_{14}N_2O_4S$ (M^+) 366.0674, found 366.0679. Anal. Calcd. For $C_{19}H_{14}N_2O_4S$: C 62.29, H 3.85, N 7.65. Found: C 62.41, H 3.74, N 7.56.

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