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A new facile synthesis of 2-aminothiazole-5-carboxylates

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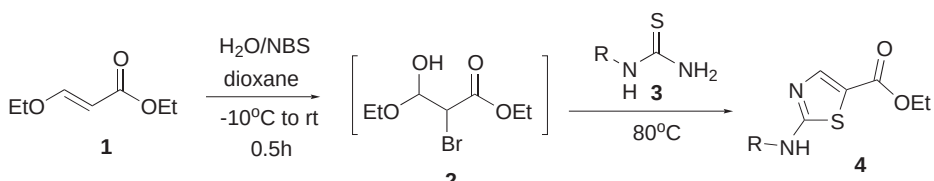
Abstract—A new facile method has been developed for the synthesis of 2-aminothiazole-5-carboxylates. The new method involves reaction of ethyl β-ethoxyacrylate with *N*-bromosuccinimide (NBS) to give a novel intermediate, α-bromo-α-formylacetate hemiacetal. Cyclization of the in situ formed hemiacetal with thioureas afforded 2-aminothiazole-5-carboxylates in 60–98% yields.

2-Aminothiazole-5-carboxylates are an important class of heterocycles in organic synthesis especially in the preparation of biologically important and medicinally useful agents such as angiotensin II antagonists,[1] DNA minor groove binding analogs of netropsin,[2] in addition to many others.[3] Previously, 2-aminothiazole-5-carboxylates were prepared in two steps from α-chloroacetates through α-formyl-α-chloroacetate intermediates.[2,4] For example, treatment of ethyl α-chloroacetate and ethyl formate using potassium ethoxide generated from potassium metal and absolute ethanol gave ethyl α-formyl-α-chloroacetate in 25% isolated yield which after reaction with thiourea in water afforded ethyl 2-aminothiazole-5-carboxylate in 67%.[2] Although this procedure can be carried out in gram scale, it is limited by its low overall yield (17%). Alternatively, α-formyl-α-bromoacetate has been used for the synthesis of 2-aminothiazole-5-carboxylates.[5] The second method however suffered from similar problems, i.e. the preparation and isolation of the generally unstable α-formyl-α-haloacetates.[6] In a project of our drug discovery programs, we required a rapid access to various 2-aminothiazole-5-carboxylates. Herein, we report a new facile synthesis of the titled compounds.

Our synthesis of 2-aminothiazole-5-carboxylates entails the use of the readily available ethyl β-ethoxy acrylate **1** (Scheme 1). Thus, treatment of **1** with *N*-bromosuccinimide (NBS) in a mixture of water and dioxane gave α-formyl-α-bromoacetate hemiacetal **2** which was confirmed by LC/MS analysis of the reaction mixture (M+H = 240). Addition of thiourea **3a** in situ to hemiacetal **2** and heating the resulting mixture at 80°C for 1 h cleanly afforded ethyl 2-aminothiazole-5-carboxylate **4a** which was isolated in 90% yield.[7]

The new one-pot method worked well also for the preparation of *N*-substituted 2-aminothiazole-5-car-



a, R=H
b, R=Pr-i
c, R=Bu-t
d, R=Bn
e, R=C_6H_4OMe-p

Entry	3/4	Time (h)	Yield % (4)
1	**a**	1h	90%
2	**b**	16h	60%
3	**c**	16h	75%
4	**d**	16h	70%
5	**e**	16h	98%

Scheme 1.

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boxylates as shown in Scheme 1. *N*-Alkyl, *N*-benzyl and *N*-aryl 2-aminothiazole-5-carboxylates **4b–e** were all readily prepared in good to excellent yields.[8]

In summary, a new facile synthesis of 2-aminothiazole-5-carboxylates has been developed. Compared to the previous two-step syntheses, the new one-pot method not only is manipulatively simpler, but also affords higher overall yields (60–98% versus <25%). In addition, the new intermediate, α-formyl-α-bromoacetate hemiacetal **2**, is expected to be useful for the synthesis of a variety of heterocycles other than 2-aminothiazole-5-carboxylates **4**.

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7. Typical procedure: To a mixture of ethyl β-ethoxyacrylate **1** (144.2 g, 1.0 mol) in water (500 mL) and dioxane (500 mL) at −10°C was added NBS (195.7 g, 1.1 mol, 1.1 equiv.). The reaction mixture was stirred at rt for 1 h and HPLC showed disappearance of **1**. Thiourea **3a** (76.0 g, 1.0 mol, 1.0 equiv.) was added and the reaction mixture was heated to 80°C for 1 h. After cooling to rt, conc. NH_4OH (200 mL) was added. The resulting slurry was stirred at rt for 10 min and filtered. The cake was washed with water (3×500 mL) and dried to give 2-aminothiazole-5-carboxylate **4a** (155.1 g, 90% yield), mp 159°C, lit.[2] 156–158°C. The NMR spectrum data were consistent with those reported for this compound.[2]
8. ^{1}H NMR ($CDCl_3$) spectrum data for new compounds: **4b**, δ 7.72 (s, 1H), 6.72 (br s, 1H), 4.24 (q, $J=7.1$ Hz, 2H), 3.55 (m, 1H), 1.29 (t, $J=7.1$ Hz, 3H), 1.27 (d, $J=6.3$ Hz, 3H); **4c**, δ 7.82 (s, 1H), 5.90 (br s, 1H), 4.29 (q, $J=7.1$ Hz, 2H), 1.45 (s, 9H), 1.34 (t, $J=7.1$ Hz, 3H); **4d**, δ 10.50 (br s, 1H), 7.87 (s, 1H), 7.52 (m, 5H), 4.67 (s, 2H), 4.46 (q, $J=7.1$ Hz, 2H), 1.47 (t, $J=7.1$ Hz, 3H); **4e**, δ 8.18 (br s, 1H), 7.91 (s, 1H), 7.29 (d, $J=8.9$ Hz, 2H), 6.95 (d, $J=8.9$ Hz, 2H), 4.29 (q, $J=7.1$ Hz, 2H), 3.83 (s, 3H), 1.33 (t, $J=7.1$ Hz, 3H).