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Short Note

3-Ethyl-2-(ethylimino)-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate Ethyl Ester

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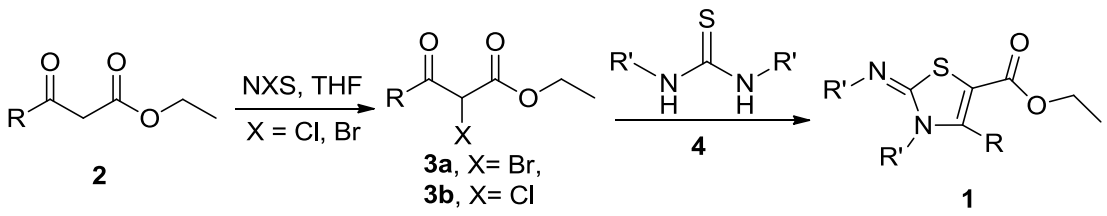
Abstract: An efficient procedure to obtain the new compound **1a** from ethyl acetoacetate (**2a**), NBS and *N*,*N*′-diethylthiourea (**4a**) was reported. In comparison with the traditional method to synthesize its analogues, this efficient, catalyst-free, and one-pot synthetic method is facile. The work-up procedure is easy and gives the pure target compound under milder reaction conditions in a relatively high yield of 75%.

Keywords: 2,3-dihydro-1,3-thiazole; one-pot synthesis; *N*,*N*′-diethylthiourea

1. Introduction

In view of the importance of functionalized 2,3-dihydrothiazole derivatives in both the organic synthesis [1] and the biological fields [2], several preparation methods have been developed [3–6]. The traditional synthetic route to this type of skeleton (**1**) usually involves two steps from β-keto esters (**2**), a halogenated reagent such as *N*-bromosuccinamide (NBS) or *N*-chlorosuccinamide (NCS), and thiourea or its derivatives (**4**) (Scheme 1) [7]. This method usually involves the tedious purification procedures of the halogenated intermediates (**3a** and **3b**). In order to obtain diversely substituted 2,3-dihydrothiazole-4-carboxylate esters efficiently, an improved method employed isothiocyanate, primary alkylamine, and 2-chloro-1,3-dicarbonyl compounds as the starting materials [8]. The latter material could be changed into β-nitroacrylates in ionic liquid [9]. The main material isothiocyanates of those methods usually need to be synthesized and purified ahead of the usage, which hampers the wide use of this method. Recently, a method to synthesize 1,3-thiazol-2-imine derivatives from benzoylphenylthioureas and α-bromoketones generated in situ from the reaction of enolizable ketones with 1,1′-(ethane-1,2-diyl)dipyridinium *bis*tribromide (EDPBT, or 1,2-dipyridinium ditribromide-ethane, DPTBE) has been reported [10,11].



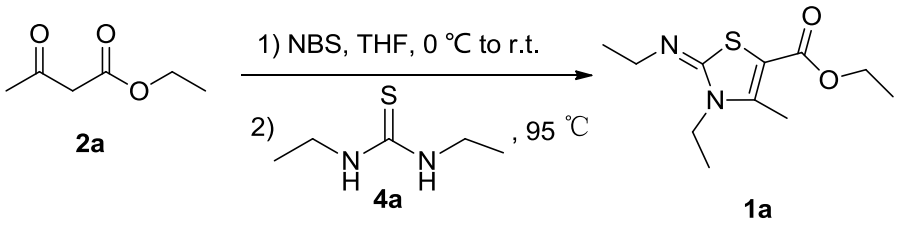
Scheme 1. The reported general synthesis route of 2,3-dihydrothiazole derivatives.

The attempt in our research group to acquire the title compound—3-ethyl- 2-ethylimino-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate ethyl ester (**1a**)—using the reported DBTBE method led to the

complete recovery of the starting materials. The conventional synthesis of **1a** via Scheme 1 involved a tedious work-up with very low overall yield, which could not be used efficiently.

As part of our recent studies on the new biological heterocyclic compounds [12,13], we now report a successful simple procedure to synthesize **1a** from ethyl acetoacetate (**2a**), NBS, and *N*,*N*′-diethylthiourea (**4a**). While **1a** shares a similar structure with the reported analogues [8], it was still reported for the first time by our research group in this paper.

Comparing with the traditional method of synthesizing its analogues, this efficient, catalyst-free, and one-pot synthetic method is facile; the work-up procedure is easy and gives the pure target compound under milder reaction conditions with a relatively high yield of 75%. This method offers an alternative way to provide 2,3-diethyl-2,3-dihydro-1,3-thiazole (**1a**) instead of the traditional two-step method from disubstituted thioureas and β-keto ester derivatives (Scheme 2).



Scheme 2. The efficient one-pot synthesis of the title compound (**1a**).

The methods developed in this paper will enrich the limited arsenal for efficiently constructing various functionalized 2,3-dihydro-1,3-thiazoles, which would be a benefit for further exploration of their potent unknown biological activities. In addition, this method is expected to be useful for the expedient synthesis of a variety of heterocyclic compounds with a thiazole core in more complex structures other than the simple substituted **1a**.

2. Experimental Section

Melting points were taken on an X-4 digital melting point apparatus (Shanghai Yice Apparatus & Equipments Co., Ltd, Shanghai, China) and are uncorrected. Elemental analyses were performed on a Carlo-Erba 1106 elemental analyzer (Thermo Scientific, Waltham, MA, USA). IR spectra were recorded on a Nicolet FT-IR 360 spectrophotometer (Thermo Scientific, Waltham, MA, USA). ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Bruker AM-400 (400 MHz) spectrometer (Brucker Company, Fällanden, Switzerland) with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ. Mass spectra were measured on a HP5988A instrument (Hewlett-Packard, Palo Alto, CA, USA) by direct inlet at 70 eV. All materials were obtained from commercial suppliers and used as received.

Ethyl 3-ethyl-2-(ethylamino)-2,3-dihydro-4-methylthiazole-5-carboxylate (**1a**)

To a mixture of ethyl acetoacetate (**2**, 6.50 g, 50.0 mmol) in water (30.0 mL) and tetrahydrofuran (THF) (28.0 mL) cooled to −5–0°C was added NBS (10.7 g, 60.0 mmol, 1.20 equiv.). The reaction mixture was stirred at room temperature for 1.0 h, and thin-layer chromatography (TLC, petroleum ether-ethyl acetate *v*/*v* = 2:1) showed the disappearance of **2**. *N*,*N*′-diethylthiourea (**4a**, 6.60 g, 50.0 mmol, 1.00 equiv.) was added, and the reaction mixture was heated to 95 °C for 19 h. After cooling to room temperature, the reaction mixture was filtered to remove an insoluble red precipitate, and then $NH_3{\cdot}H_2O$ (8.0 mL) was added to the filtrate. The resulting yellow solid was collected via filtration under the reduced pressure. The filter cake was washed with water (100 mL × 3), recrystallized from ethyl acetate, then dried to give the target compound as the yellow cubic crystals (**1a**, 9.10 g, 75%), mp. 63–64 °C, ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.23–1.29 (m, 6H, $NCH_2CH_3\times$ 2), 1.33 (t, 3H, OCH_2CH_3), 2.57 (s, 3H, thiazole-4-CH_3), 3.17 (q, 2H, 3-N-CH_2CH_3), 3.89 (q, 2H, 2-N-CH_2CH_3), 4.26 (q, 2H,

OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 12.72 (thiazole-4-CH_3), 13.32 (thiazole-3-N-CH_2CH_3), 14.38 (-OCH_2CH_3),15.36 (=NCH_2CH_3), 38.82 (thiazole-3-NCH_2CH_3), 48.91 (=NCH_2CH_3), 60.41 (OCH_2CH_3), 98.62 (thiazole-5-*C*),147.16 (thiazole-2-*C*), 155.74 (thiazole-4-*C*), 162.38 (O=*C*). MS: *m/z* 243 ($M + H^+$). Elemental Analysis. Calcd for $C_{11}H_{18}N_2O_2S$: C, 54.52; H, 7.49; N, 11.56. Found: C, 54.41; H, 7.36; N, 11.42.

3. Conclusions

To summarize, a new compound with the name of 2-ethyl-2-ethylimino-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate ethyl ester was synthesized efficiently via an improved one-pot reaction with a relatively high yield. This method might be useful in further synthesis of the compounds with the similar structure skeleton.

Supplementary Materials: The following are available online at www.mdpi.com/1422-8599/2016/4/M919. The original spectra of the title compound were provided in Figures S1 and S2.

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Author Contributions: Ge Meng was responsible for designing the synthesis method and strategy. Mei Wang synthesized the title compound for the first time using the new one-pot reaction. Ya-Nan Cheng repeated this procedure two years later. Kai Chen repeated the NMR spectral analysis of this compound. Jing Tong has synthesized this compound for the further biological evaluations. Jie-He Zhang has done the biological activity screening test on this compound.

Conflicts of Interest: The authors declare no conflict of interest.

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