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Efficient one-pot synthesis of ethyl 2-substitued-4-methylthiazole-5-carboxylates

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A new and practical one-pot procedure for the synthesis of several 2-sustituted-4-methylthiazole-5-carboxylates from commercially available starting materials is described. Under mild reaction conditions, some of the products with alkyl group on the 2-amino group or with various groups on 2-substituted phenyl ring were obtained in good yields from ethyl acetoacetate, *N*-bromosuccinimide, thiourea, or its *N*-substituted derivatives in an efficient way instead of the traditional two-step reaction.

Keywords: *N*, *S*-heterocyle; thiourea; ethyl 2-substituted-4-methylthiazole-5-carboxylates; cyclization

Introduction

Among the heterocyclic compounds, sulfur- and nitrogen-containing 1,3-thiazoles are very important class of heterocyclic compounds (*1*, *2*), which are well known for their biological properties (*3–6*). 2-Amino-1,3-thiazoles ring system (*7*) has found application in drug development for the treatment of allergies (*8*), hypertension (*9*), inflammation (*10*, *11*), schizophrenia (*12*), and bacterial (*13*) and HIV (*14*) infections. Especially, ethyl 2-amino-4-methylthiazole-5-carboxylate (**4a**) and its 2-substituted derivatives are building blocks in organic synthesis especially in the preparation of biologically important and medicinally useful agents (*15*, *16*), of which **4a** is also an intermediate for synthesis of 4-methyl-5-formylthiazole, a key intermediate for cefditoren pivoxil (*17–19*). The derivatives of ethyl 2-amino-4-methylthiazole-5-carboxylate have been reported to have shown significant antileukemic activity on various human cells and exhibited a promising antineoplastic potential (*15*).

The conventional synthesis of **4a** usually starts from ethyl acetoacetate (**1**) and *N*-bromosuccinimide (NBS) (*20–22*) in dichloromethane to give the intermediate ethyl 2-bromo-3-oxobutanoate (**2**), which was then reacted with thiourea (**3a**) to give the target molecule (**4a**) (Scheme 1; *23*). This two-step synthesis of **4a** was limited by the tedious work-ups and low overall yield (11%; *24*). Xanthan sulfuric acid has been used a solid acid catalyst to assist the formation of 2-amino-thiazole (*25*). Benzoyl peroxide was also used as radical initiator to furnish 2-aminothiazoles (*26*). All these two methods need extra reagent including peroxide and acid beside the necessary materials. In order to overcome these shortcomings, an alternative one-step synthesis of **4a** has been designed by using **1**, **3a** and iodine as the materials (Scheme 1; *27*). This method also involves tedious work-ups and the excessive amount of iodine, which could cause harm to the environment. The lab-scale synthesis of **4a** via the latter method ends up with no target molecule, which is not practical. The one-pot method also needs using β-cyclodextrin as supramolecular catalysis (*28*). Therefore an efficient alternative way is still needed for industrial purpose.

Based on the similar procedures involving using unsaturated ethyl β-ethoxyacrylate as different starting material (*29*) and our research experience in synthesis of the thiazole heterocyles (*30*, *31*), we envisioned that these two steps could be carried out in one pot (Scheme 2). By using water and tetrahydrofuran (THF) as the mixable solvent instead of CH_2Cl_2 and using NBS instead of I_2, compound **4a** of sufficiently high quality was obtained by using less time and higher overall yields than conventional methods. Compared with the related methods, this newly developed method saves these special reagents by just using the water-mediated solvent system to avoid using the extra-toxic reagent in order to achieve the green purpose. Encouraged by this efficient improvement in overall yield (72% vs. <11%) of **4a** via this procedures, we decided to explore the scope and the condition of this one-pot method to synthesize the related 2-substituted amino-4-methylthiazole-5-carboxylate derivative. Several substrates including *N*-alkyl thioureas and *N*-aryl thioureas have been used to synthesize the related derivatives (Scheme 2). The results are shown in Table 1.

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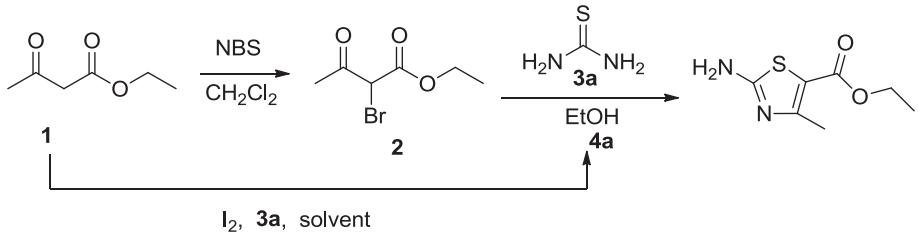
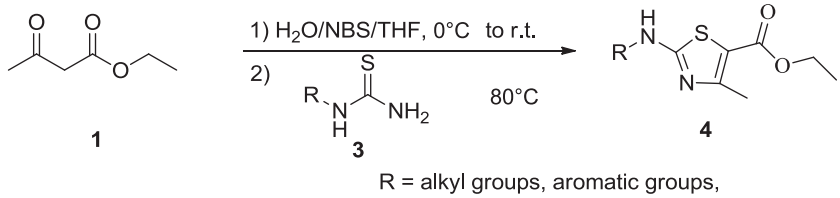


Scheme 1. Conventional synthesis routes of **4a.**



Scheme 2. Improved one-pot synthesis of compounds **4.**

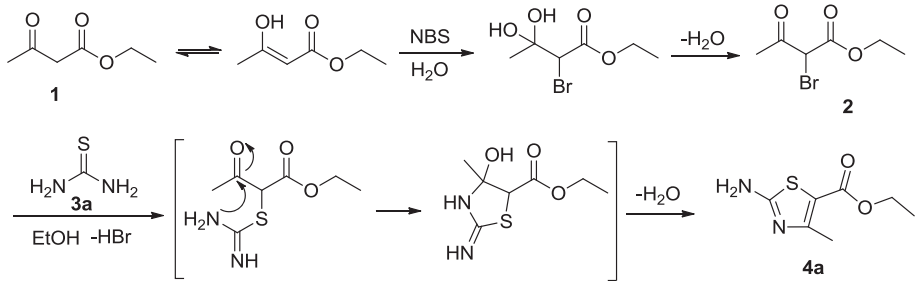
Herein, we report this novel efficient one-pot procedure from the readily available ethyl acetoacetate with NBS and thiourea or its *N*-substituted derivatives for the preparation of the title compounds **4**. Compared to the conventional methods, the yields of this facile method have been increased greatly (from less than 11% to 72% for Entry 1), the manipulation procedures have also been substantially improved.

Results and discussion

The reaction times of substituted thioureas (Entry 2–14) are much longer than that of unsubstituted thiourea (Entry 1). *N*-alkyl- or allyl-substituted thioureas (Entry 2, 3) give as good as the yield of thiourea (Entry 1), except for the one with long side chain (Entry 4). Generally speaking, compared with unsubstituted phenyl compound (Entry 8), *N*-aryl thioureas with electron-withdrawing groups on phenyl ring usually give lower yields (Entry 9–13), aryl thiourea with electron-donating group on phenyl ring provides higher yield (Entry 6). Although in some special circumstance, the substrates with two chloro on both *meta*- and *para*-position (Entry 5) or with a sulfonamide group in *para*-position of phenyl ring (Entry 7) offered unusual higher yields. Methyl group on *ortho*-position (Entry 14) instead of chloro on *para*-position (Entry 5) could drastically decrease the yield from 73% to 23%. The results showed that the yields are associated with many aspects such as steric effects, electronic properties, and substituted position of groups on aromatic rings. A plausible mechanism was proposed to explain the one-pot reaction with Entry 1 as an example based on related literature (Scheme 3; *29*).

Conclusions

In summary, a new facile one-pot synthesis method of ethyl 2-amino-4-methylthiazole-5-carboxylate derivatives from the commercially available materials has been developed in this paper. Compared to the previous syntheses, the efficient method is not only manipulatively simpler, but also affords higher overall



Scheme 3. Plausible mechanism of forming **4a** in H_2O/THF.

Table 1. Scopes of the one-pot reaction and the properties of the related products.

Entry	R (in **3** and **4**)	Materials	Products	Time (h)	Form	Recrystallization solvent	Yield (%)	M.p. (°C)
1	H	**3a**	**4a**	4	Pale yellow crystal	EA	72	178–179
2*	Allyl	**3b**	**4b**	20	Yellow needle crystal	EA	76	109–110
3	*i*-Pr	**3c**	**4c**	20	Yellow solid	PE	62	99–104
4	Diethylamino ethyl	**3d**	**4d**	20	Yellow plate crystal	PE	27	122–123
5	C_6H_3Cl-*m*, Cl-*p*	**3e**	**4e**	20	Pale yellow solid	PE	73	186–188
6*	C_6H_4Me-*p*	**3f**	**4f**	16	Yellow crystal	EA	65	151–154
7*	$C_6H_4SO_2NH_2$-*p*	**3g**	**4g**	23	Brown powder	EA	56	245–247
8*	Phenyl	**3h**	**4h**	20	Pale red crystal	EA	50	191–192
9*	C_6H_4F-*p*	**3i**	**4i**	15	White solid	PE	25	148–150
10	C_6H_4F-*o*	**3j**	**4j**	20	Pale yellow solid	PE	25	103–104
11	$C_6H_4NO_2$-*p*	**3k**	**4k**	18	Yellow crystal	EA	21	125–128
12	$C_6H_4CF_3$-*o*	**3l**	**4l**	15	Yellow needle crystal	EA	21	121–124
13*	$C_6H_4OCH_3$-*p*	**3m**	**4m**	20	Pale yellow powder	PE	14	140–143
14*	C_6H_3Me-*o*,Cl-*m*	**3n**	**4n**	20	Yellow crystal	EA	23	116–120
15*	C_6H_4Br-*p*	**3o**	**4o**	36	Yellow powder	PE	26	151–153

Note: The asterisks in column means that the related spectra data and physical properties of the product have been supplied in the Supplementary Material.
EA, ethyl acetate; PE, petroleum ether.

yields for the substrates including *N*-alkyl-substituted thioureas and some of the *N*-aryl thioureas bearing both electron-donating groups or electron-withdrawing groups on the phenyl ring. In addition, this method is expected to be useful for the expedient synthesis of a variety of substituted heterocyclic compounds with similar thiazole structures other than simple substituted derivatives of compounds **4**.

Experimental

General methods and materials

Melting points were taken on an X-4 digital melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Erba 1106 elemental analyzer. Infrared (IR) spectra were recorded on a Nicolet FI-IR 360 Spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were determined on a Bruker AM-400 (400 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ. Mass Spectra were measured on a HP5988A instrument by direct inlet at 70 ev. All materials were obtained from commercial suppliers and used as received. Some *N*-mono-substituted thioureas are synthesized from substituted aniline derivatives using the methods described in the Supplementary Material.

General procedures are described as for compound **4a**, while other target molecules could be obtained by the similar method, except for the different recrystallization solvents which have been shown in Table 1.

*Ethyl 2-amino-4-methylthiazole-5-carboxylate (**4a**)*
To a mixture of ethyl acetoacetate (**1**, 6.50 g, 0.05 mol) in water (50.0 mL) and THF (20.0 mL) below 0°C was added NBS (10.5 g, 0.06 mol, 1.20 equiv.). The reaction mixture was stirred at room temperature for 2 h and thin-layer chromatography (TLC, petroleum ether–ethyl acetate 2:1, on silica gel plate, UV lamp λ = 254 nm, R_f = 0.71) showed disappearance of **1**.Thiourea (**3**, 3.80 g, 0.05 mol, 1.00 equiv.) was added and the reaction mixture was heated to 80°C for 2 hrs. After cooling to r.t., the reaction mixture was filtered to get rid of the insoluble substance, then $NH_3{\cdot}H_2O$ (8.0 mL) was added to the filtrate. The resulting yellow floccules were stirred at room temperature for 10 min and filtered. The filter cake was washed with water (100 mL × 3) and recrystallized with ethyl acetate, then dried to give the target compound (**4a**, 6.70 g, 72.0%), m.p. 178–179°C, *lit*. 175–177°C (*32*, *33*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.36 (s, 3H, thiazole-4-CH_3), 4.13 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 7.69 (2H, thiazole-2-NH_2); ^{13}C NMR ($CDCl_3$, 100

MHz): δ 14.32 (thiazole-4-*C*H_3), 17.12 (OCH_2*C*H_3), 59.72 (O*C*H_2CH$_3$), 107.34 (thiazole-5-*C*), 159.34 (thiazole-4-*C*), 161.95 (O = *C*), 170.21 (thiazole-2-*C*), MS: *m*/*z* 187 ($M + H^+$).

Anal. Calcd for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.41; N, 15.04. Found: C, 45.29; H, 5.49; N 15.15.

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Supplemental Material

All Supplemental Material is available alongside this article on www.tandfonline.com – go to http://dx.doi.org/10.1080/17518253.2014.895858

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