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One-Pot synthesis of 2-sustituted-4-methylthiazole-5-carboxylates from ethyl acetoacetate and thiourea by using oxone and Iodobenzene reaction system

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ABSTRACT

A present report expresses that Oxone and Iodobenzene reaction system is useful for the synthesis of several 2-sustituted-4-methylthiazole-5-carboxylates from commercially available starting materials. Ethyl acetoacetate and thiourea in an efficient way instead of the traditional two-step reaction is used for the synthesis of desired product. Advantages of this simple method contain greener and cleaner conditions, shorter reaction time, and excellent yield of products. A simple one-pot protocol has been developed for the synthesis of 2-sustituted-4-methylthiazole-5-carboxylates derivatives from readily available starting materials.

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1. Introduction

Thiazole and its derivatives have play important role in development of heterocyclic chemistry and inspired researchers from long time [1–2]. Thiazoles are most biologically active classes of compounds which have a large number of applications in medicinal chemistry. Thus, thiazole scaffolds have found application in drug development for the treatment of bacterial inflammation antitumor [3], antiparasitic [4], anticonvulsant [5], antiviral. 2-Aminothioazole derivatives shows potential activity, antibacterial, antitubercular, anti-inflammatory, antihypertensive, anti-oxidant, neuroprotective, antifungal, and anti-HIV, anticancer, antidiabetic activities. Several popular drugs containing thiazole moiety proven to be effective for treating multiple diseases. The First report for the synthesis of 2-aminothiazoles was by Hantzsch and Weber [6]. There are numerous methods for the synthesis of 2-aminothiazole which involves condensation of α-haloketones with thiourea in the presence of bromine/iodine [7]. One pot synthesis based on the reactions of Oxidative cyclisation of ketones and thioureas using KI/NH_4NO_3 [8], Silica-supported Preysslernano particles [9], Methyltrioxorhenium (MTO) catalyses [10], silica chloride as a heterogeneous catalyst [11], aqueous $NaICl_2$ [12], oxidative cyclocondensation of ketones using CBr_4 [13] and Nanochitosan: A biopolymer catalytic system [14a,b], have attracted attention as powerful strategies to prepare the thiazole nucleus. Most of methodologies having limitations like availability of starting materials, harsh reaction conditions, use of toxic chemicals. (See Scheme 1.).

Therefore, there is stronger need to develop an attractive and demanding methodology which should have green reagents and greener routes for the synthesis of thiazole derivatives. To the best of our knowledge, there is no protocol for the synthesis of 2-aminothiazole derivatives using oxone and Iodobenzene reaction system. In the recent years hypervalent iodine active species is useful for the various cyclisation reactions in the synthesis of heterocyclic compounds, in our constant works in this field of hypervalent iodine active reagent species. Here we establish as new, stable and excellent reaction system for the synthesis of various 2-aminothiazole derivatives in efficient yield [15],

Our group has formerly presented that oxone and Iodobenzene is an effective reagent for cyclisation reactions based on these results, oxone and Iodobenzene in aqueous acetonitrile solvent system was chosen as a reagent system and stirred for

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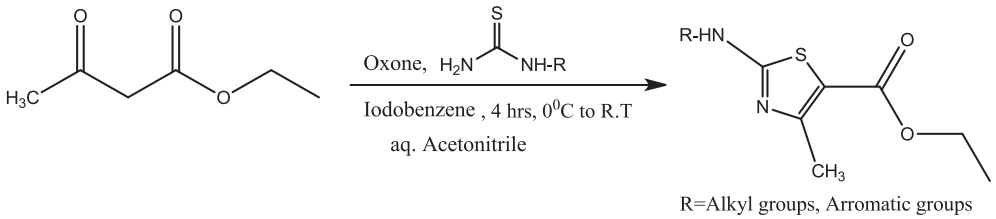


Scheme 1. One pot Synthesis of ethyl 2-substitued-4-methylthiazole-5-carboxylates.

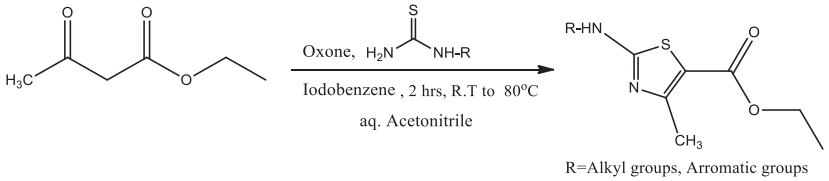
15 min at 0 °C. Then 1 mmol of ethyl acetoacetate was added for the above reaction system and continuous stirring for 2 h at room temperature. Further addition of thiourea 1 mmol to get product **(1a)** in 83% yield after an additional 2 h heating at 80 ^{0}C.

Above Scheme indicates the products of the one-pot reaction and the yield and time related that products. With these set reaction conditions in hand, the scope and generalization of the reaction were examined using various thioureas, ß-keto esters and the results are summarized in Table 1. To our delight, unsubstituted and varied N-substituted thioureas, bearing alkyl, aryl, and benzyl groups tolerated well the conditions employed. At the end of the reaction, the 2-substituted-4-methylthiazole-5-carboxylates derivatives were obtained in moderate to good yields (65-87%) by means of a simple filtration without the need of further purification. In general, the nature of substituent's had no significant effect on the yields.

2. Result and discussion

To explore generality of the reaction variety of substrates were reacted with optimized reaction condition. Various substituted thiourea containing different groups were subjected to this transformation. We observed that electron donating as well as electron withdrawing groups provided significant yield of products. A variety of functional groups including, methyl, isopropyl, were well tolerated and gave good yield (Entry 2, 5). All formed products were characterized by comparing spectral properties and comparing their physical properties with that of reported compounds in the literature. Detail data is presented in the experimental section. All 2-substituted-4-methylthiazole-5-carboxylates derivatives showed characteristic features. The reaction period of substituted thioureas is much longer than that of unsubstituted thiourea (Entry 4–7). N-alkyl- or allyl-substituted thioureas provide as good as the yield of thiourea. (Entry 8–12).

Table 1
One-pot Synthesis of 2-sustituted-4-methylthiazole-5-carboxylates derivatives using substituted thiourea and ethyl acetoacetate.



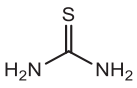
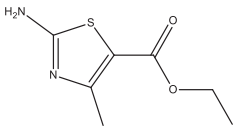
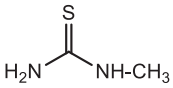
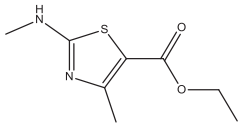
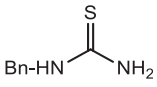
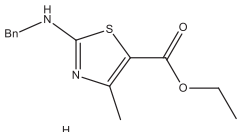
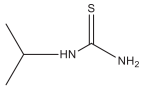
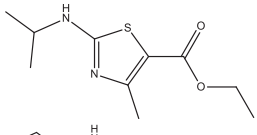
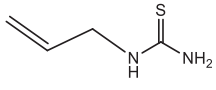
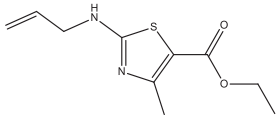
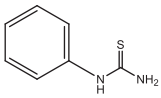
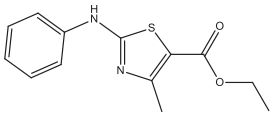
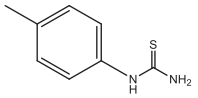
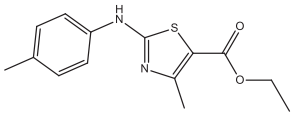
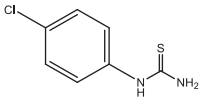
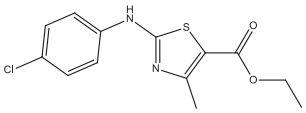
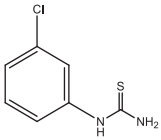
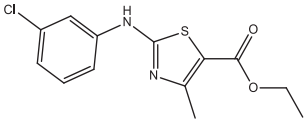
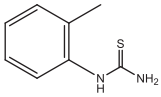
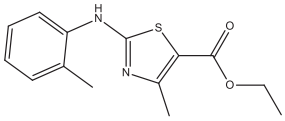
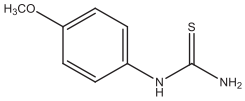
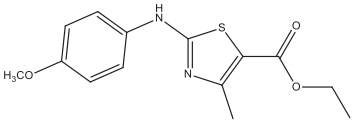
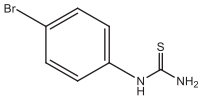
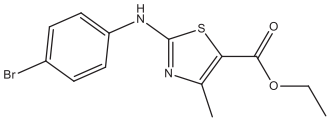
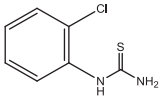
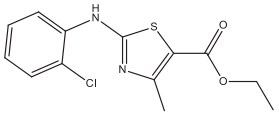
Sr. No.	Material	Product	Time(hrs)	Yield(%)
1[a]			4 h	87
2			5 h	88
3			4 h	79
4			4 h	78
5			5 h	69

Table 1 (*continued*)

Sr. No.	Material	Product	Time(hrs)	Yield(%)
6			5 h	72
7			5 h	77
8			6 h	86
9			4 h	84
10			4 h	79
11			6 h	65
12			6 h	79
13			6 h	81

a: Reaction conditions: ethyl acetoacetate (3.25 g, 0.025 mol), oxone 2 mmol, Iodobenzene 2 mmol and Thiourea (1.9 g, 0.025 mol) and in aq. acetonitrile solvent at room temperature.

3. Conclusions

In summary, a new facile one-pot synthesis method of ethyl 2-amino-4-methylthiazole-5-carboxylate derivatives from the easily available oxone and Iodobenzene as a reaction system has been developed. In addition, this method is probable to be useful for the synthesis of range of substituted heterocyclic compounds with comparable thiazole structures other than simple substituted derivatives of compounds. This method has short reaction time and starting materials are readily available. Combining all these, the method is striking for a wide range of application in organic synthesis and medicinal chemistry.

4. Experimental

4.1. Ethyl 2-amino-4-methylthiazole-5-carboxylate (4a)

Mixture of Oxone (614 mg, 2 mmol) and Iodobenzene (408 mg, 2 mmol) in aqueous acetonitrile stirred at room temperature for 20 min, followed by addition of ethyl acetoacetate (3.25 g, 0.025 mol) was added and continuous stirring for 2 h at room temperature. Thiourea (1.9 g, 0.025 mol) was added and the reaction mixture was heated to 80 °C for 2hrs. After cooling to the root temperature, the reaction mixture was filtered to get rid of the insoluble substance; then $NH_3{\cdot}H_2O$ (4.0 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. (**Ethyl 2-Amino-4-methylthiazole-5-carboxylate, 4a):** Yield: (87%); yellow solid; mp 173–174 °C, ^{1}H NMR (DMSO d_6, 400 MHz): d = 7.70 (s, 2H), 4.15 (q, *J* = 7.3 Hz, 2H), 2.38 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H).^{13}C NMR (DMSO d_6, 100 MHz): d = 171.60, 163.23, 159.85, 108.27,61.19, 17.60, 14.79. MS (70 eV): *m*/*z* = 186 (M +), 158, 141 (100%).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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