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Ammonium chloride catalyzed aqua mediated synthesis of 2-aminothiazoles

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ABSTRACT

We report ammonium chloride catalyzed an efficient and rapid synthesis of 2-aminothiazole derivatives from phenacyl bromide and thiourea in aqueous medium.

Key words: 2-Aminothiazole, Ammonium chloride, Aqueous medium, Phenacyl bromide

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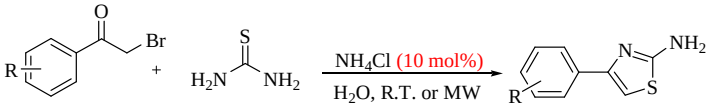
INTRODUCTION

2-Aminothiazole nucleus possesses a broad spectrum of biological activities, comprising of antibacterial [1], anti-inflammatory [2], antifungal [3], pesticidal [4], antiprotozoal [5], antitubercular [6], anti-HIV [7] etc.

Several methods are reported for the synthesis of 2-aminothiazoles derivatives like Hantzsch synthesis, solid supported and solution phase synthesis to generate libraries of these derivatives. Various catalysts are employed such as iodine [8], ammonium-molybdophosphate (AMP) [9], β-cyclodextrin [10], silyl chloride [11], PEG [12], in organic as well as inorganic solvents.

Recently ammonium chloride is emerged as a cost effective catalyst, owing to its greater selectivity under milder reaction conditions and eco-friendly nature. It is used as catalyst for aliphatic Claisen rearrangement [13], synthesis of diindolylmethanes [14], synthesis of spirochromenes and spiroacridines compounds [15] and synthesis of 3, 4-dihydropyrimidinones under solvent-free conditions [16].

Owing to biological significance of 2-aminothiazoles, the development of efficient and ecofriendly chemical processes for the synthesis of 2-aminothiazole derivatives is still a major need. Herein we report ammonium chloride catalyzed synthesis of 2-aminothiazole derivatives in aqueous medium (**Scheme 1**).

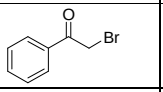
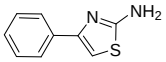
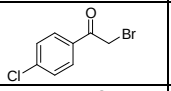
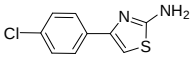
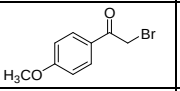
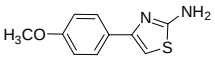
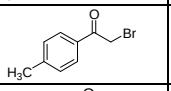
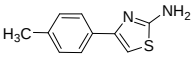
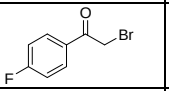
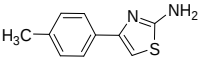
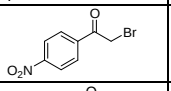
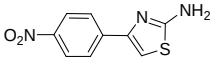
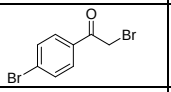
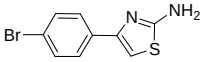
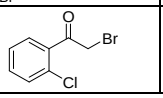
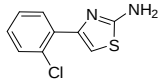


(Scheme 1)

MATERIALS AND METHODS

All research chemicals were purchased from Sigma-Aldrich or Spectrochem and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates (Merck made) and compounds were visualized by exposure to UV. Melting points were determined in open capillaries and were uncorrected. The microwave irradiation was carried out in a scientific microwave oven (CATA-4R-Model No. QW-99, India makes) at 02450 MHz Frequency, with power output of 140-700 W. Infrared (IR) spectra in KBr were recorded on a Perkin-Elmer FT-IR 550 spectrometer. ^{1}H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in $CDCl_3$ as the solvent and chemical shift values were recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

Table 1: Synthesis of 2 aminothiazole from phenacyl bromide and thiourea

Entry	Phenacyl Bromide	Product	Time (min) R.T.	Time (min) MW	Yield (%)	M.P. (°C) [Ref]
1			15	1.30	85	148-150 [17]
2			12	1	92	165-167 [18]
3			11	1	87	206-208 [17]
4			14	1	84	132-134 [18]
5			12	1	92	102-103 [17]
6			10	1	88	232-234 [18]
7			12	1	92	165-167 [19]
8			14	1.30	93	230-232 [17]

General procedure for the synthesis of 2-aminothiazoles:
A mixture of phenacyl bromide (1 mmol), thiourea (1 mmol) and ammonium chloride (10 mol%) was stirred in water (2 mL) at room temperature or kept under microwave irradiation (80 °C, 300 Watt) for the specified time as mentioned in **Table 1**. The progress of reaction was monitored by TLC (30% ethyl acetate: n-hexane). After completion of reaction, the reaction mixture was filtered, washed with water and purified by recrystalization with methanol to afford the pure product.

The spectral data of selected compounds is mentioned below:

4-(4-Methoxyphenyl)- thiazole-2-amine :
IR (KBr): 3436, 3254, 3115, 1598, 1519, 1341, 1040, 715 cm^{-1} 1H NMR ($CDCl_3$, 400 MHz): 3.81 (s, 3H, OMe), 6.81 (s, 1H, thiazole H), 6.93-6.95 (d, 2H, ArH), 7.66-7.68 (d, 2H, ArH), 8.00 (br s, 2H, NH_2).

4-phenyl thiazole-2-amine:
IR (KBr): 3439, 3271, 3118, 1630, 1516, 1260, 1037, 739 cm^{-1}; 1H NMR ($CDCl_3$, 400 MHz): 6.98 (s, 1H, thiazole H), 7.32-7.36 (m, 1H, ArH), 7.39-7.42 (m, 2H, ArH), 7.73-7.75 (m, 2H, ArH), δ = 8.10 (br s, 2H, NH_2).

RESULTS AND DISCUSSION

Phenacyl bromide and thiourea on stirring in presence of ammonium chloride in water at room temperature afforded thiazole-2-amine in just 15 minutes (**Scheme 1**). Progress of reaction was monitored by thin layer chromatography using 30 % ethyl acetate: n-hexane. After completion of reaction, the reaction mixture was filtered, washed with water and recrystallized. There was no need of chromatographic purification technique. The scope and generality of this method was checked using different substituted phenacyl bromides. We also carried the reaction under microwave irradiations. The results are summarized in **Table 1**. All the products were characterized from melting point, IR, ^{1}H NMR spectral analyses. Spectral analysis showed characteristic aromatic stretching vibration between 3000-3150 cm^{-1}; C-N stretching vibration at 1635 cm^{-1}; C-S-C stretching vibration between 710-740 cm^{-1} and NH_2 stretching vibration between 3200-3450 cm^{-1}. ^{1}H NMR was recorded in $CDCl_3$. The compound showed 2 proton singlet of NH_2, One proton singlet of C-H of thiazole ring and 4-H proton signal for aromatic protons between 7.2-7.7.

CONCLUSION

In summary, we have developed a mild, efficient and environmentally benign ammonium chloride catalyzed, water mediated method for the synthesis of biologically important 2-aminothiazole derivatives at room temperature and under microwave irradiation in excellent yield. The present report offers cleaner and simpler experimental and work-up procedure, affording the products in excellent yield.

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