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OXONE AND IODOBENZENE ARE USEFUL REACTION SYSTEM FOR SYNTHESIS OF 2-AMINOTHIAZOLE DERIVATIVES FROM EASILY AVAILABLE THIOUREA AND ALKYL / ARYL KETONES

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Keywords:

Heterocyclic Compounds, Aminothiazoles, Oxone, Iodobenzene and thiourea, Hypervalent (III) Compounds

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ABSTRACT: A quick one step, innovative approach for the Synthesis of 2-aminothiazole derivatives from easily available thiourea and alkyl / aryl ketones with the help of Oxone and Iodobenzene reaction system has been developed in aqueous acetonitrile solution. The developed procedure is applicable to several types of substituted 2-aminothiazole derivatives to get the corresponding products. The developed methodology offers mild reaction condition, short reaction time, and moderate to admirable yields. This is one of the most simple and environmentally benign protocols for synthesis of 2-aminothiazole derivatives. When reaction carried out in presence of oxone and Iodobenzene in aq. Acetonitrile solvent system there is formation of active Hypervalent iodine reagent in situ and that reagent is responsible for this conversion but, yield of reaction is less. We go in detailed in Hypervalent reagent study and got some literature in that researcher used catalytic KBr along with oxone and Iodobenzene and there is amplify in activity of Hypervalent iodine reagent because of catalytic amount of potassium bromide. So we decided to use catalytic amount of KBr along with oxone and Iodobenzene reagent and there is increase in yield of desirable product.

INTRODUCTION: Aminothiazoles have been lately identified as a desired structural element that is screened as part of many drug design processes in medicinal chemistry due to their thiourea like properties and tendency to modulate biological targets [1]. Aminothiazole and its derivatives have a broad spectrum of medicinal applications such as antitubercular, [2] anti-inflammatory, [3] antiplatelet, [4] antiviral, [5] anticancer, [6] and human lymphatic filarial parasite [7].

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Aminothiazole analogs have also been reported as ligands at adenosine receptors, [8] Anticonvulsants [9] and Thiazoles are also showed to exhibit numerous pharmacological activities [10]. This heterocyclic core is also reported in many natural products and pharmaceuticals. Various methodologies such as Hantzsch, Cook Heilborn, and Tchernic for the synthesis of aminothiazoles and their derivatives have been reported.

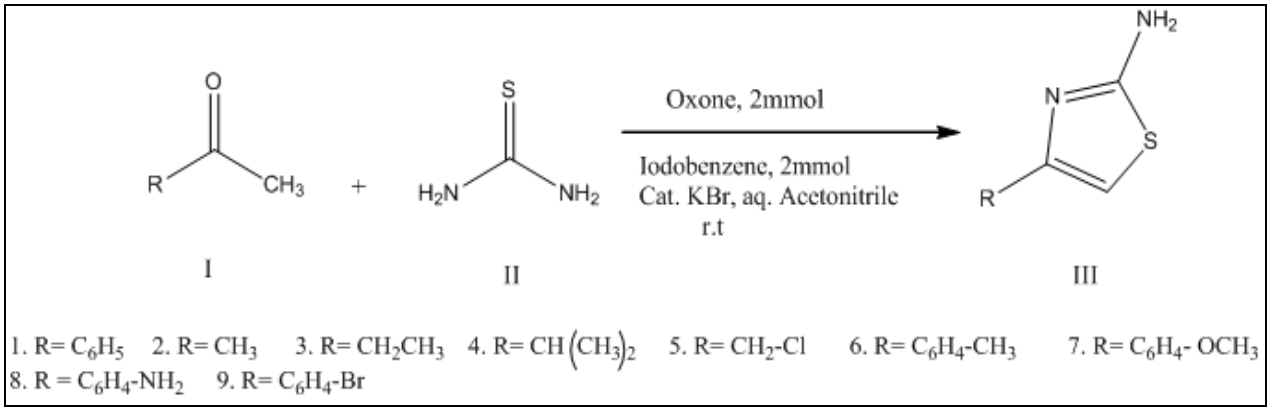
Among these, Hantzsch thiazole synthesis is the Most widely used which involves reaction of α-halo carbonyl compounds with thiourea or thioamides [11]. There are very few reports available in which α-halo carbonyl compounds were generated in situ using ketones and reacted with thiourea to form varieties of aminothiazoles [12].

Recently, aminothiazoles derivatives were also synthesized by aqueous $NaICl_2$, [13] carbon tetrabromaide, [14] nanoclay, [15] Nanochitosan [16], Herein, we report the synthesis of aminothiazoles from thiourea and alkyl / aryl ketones in the presence of Oxone and Iodobenzene and catalytic KBr in aqueous acetonitrile solvent at room temperature. For initial study, we took thiourea and acetophenone as the model substrate **Scheme 1**. The desirable 2-amino-4-(phenyl) 1, 3,-thiazole was formed when 1 eq. of oxone and 1 eq. Iodobenzene in aq. Acetonitrile solvent added 2 eq. thiourea and acetophenone were treated in aqueous acetonitrile solvent system. Further it was observed that in the absence of oxone or Iodobenzene reaction does not proceed. When reaction carried out in presence of oxone and Iodobenzene in aq. Acetonitrile solvent system there is formation of active Hypervalent iodine reagent in situ and that reagent is responsible for this conversion but, yield of reaction is less. We go in detailed in Hypervalent reagent study and got some literature in that researcher used catalytic KBr along with oxone and Iodobenzene and there is amplify in activity of Hypervalent iodine reagent because of catalytic amount of potassium bromide. So we decided to used catalytic amount of KBr along with oxone and Iodobenzene reagent and there is increase in yield of desirable product.

Viktor V. Zhdankin *et al*., found that active iodine (III) species [*i.e.* (hydroxy (phenyl) iodonium ion,)] [17] can be inventively generated in solution by treatment of Iodobenzene with oxone in aqueous acetonitrile at room temperature. Oxone and Iodobenzene reaction system is better reagent for this transformation. This reaction was carried out in Acetonitrile / water reaction system which is helpful for cyclisation and formation of 2-aminothiazole formed in reaction. We have used this combination to present methodology.

MATERIALS AND METHOD: Melting points were determined with melting point apparatus using open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^1H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker spectrometer at 400 MHz. Purity of the compounds was checked by TLC on silica- G plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber.

General Experimental Procedure for Synthesis of 2-aminothiazole Derivatives: Mixture of Oxone (614 mg, 2 mmol) and Iodobenzene (408 mg, 2 mmol) in aqueous acetonitrile stirred at room temperature for 10 min, followed by addition of catalytic amount of KBr (59 mg) under stirring at room temperature followed by addition of Acetophenone (1 mmol) and thiourea (2 mmol) under stirring at room temperature. The resultant reaction mixture was stirred at room temperature until the starting material was completely consumed (TLC). The reaction mixture was diluted with CH_2Cl and washed successively with 10% sodium bicarbonate (2 × 15 mL), followed by water (2 × 20 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtained crude product. The pure product was obtained after silica gel column chromatography (10% EtOAc–Hexane).



SCHEME 1: SYNTHESIS OF 2-AMINOTHIAZOLE DERIVATIVE

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Table 1, Entry 1, (4-phenylthiazol-2-amine), IR (KBr), cm^{-1}: 3325, 3192, 2926, 1616, 1519, 1367 cm^{-1}. 1H NMR (400 MHZ, $CDCl_3$); δ, ppm: 7.77-7.76 (d, j =7.7, 2H), 7.39-7.36 (d, j = 7.4, 2H), 7.30-7.35 (m, 2H), 5.78 (br, s, 2H). Colorless solid.

Table 1, Entry 2, (4-methylthiazol-2-amine), IR (KBr), cm^{-1}: 3225, 3092, 2926, 1616, 1519, 1367 cm^{-1}, 1H NMR (400 MHZ, $CDCl_3$); δ, ppm: 7.67 (d, J = 7.7, 2H), 7.29 (d, J=7.5, 2H), 2.34 (s, 3H), 6.2 (s, 2H).

Table 1, Entry 3, (4-ethylthiazol-2-amine), IR (KBr), cm^{-1}: 3325, 3192, 2926, 1367 cm^{-1}. 1H NMR (400 MHZ, $CDCl_3$); δ, ppm: 1.25 (t, 3H), 3.07 (q, 2H), 6.48 (s, 1H), 6.99 (br, s, 2H).

Table 1, Entry 4, (4-isobutylthiazol-2-amine), IR (KBr), cm^{-1}: 3325, 3192, 2926, 1367 cm^{-1}. 1H NMR (400 MHZ, $CDCl_3$); δ, ppm: 2.28 (s, 3H), 6.48 (s, 1H), 6.99 (s, 2H, NH_2).

Table 1, Entry 5, 4-(chloromethyl) thiazol-2-amine, IR (KBr), cm^{-1}: 3325, 3192, 2926, 1616, 1519, 1367 cm^{-1}. 1H NMR (400 MHZ, $CDCl_3$); δ, ppm: 7.56 (d, j = 7.8, 2H), 7.0 (d, j = 7.4, 2H), 6.27 (s, 2H), 7(br s, 2H).

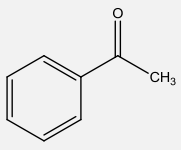
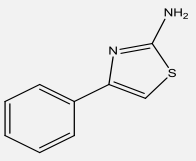
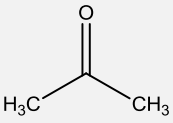
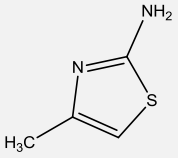
Table 1, Entry 6, 4-(p-tolyl) thiazol-2-amine, IR (KBr), cm^{-1}: 3402, 3240, 1500, 715; 1H NMR (400 MHz, $CDCl_3$); δ, ppm: 6.72 (s, 2H, NH_2), 6.76 (s, 1H, thiazole C-H), 7.2-7.6 (m, 4H, Ar C-H), 2.34 (s, 3H, CH_3),

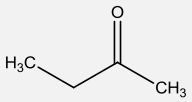
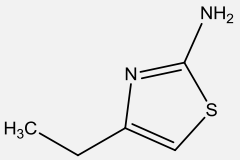
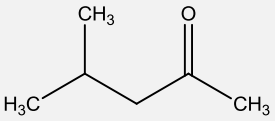
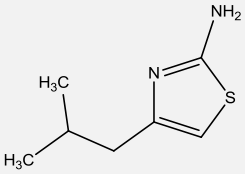
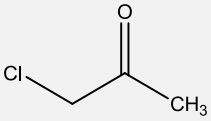
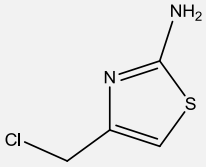
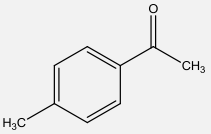
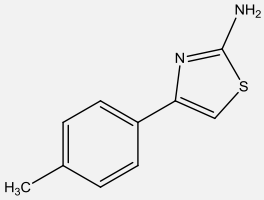
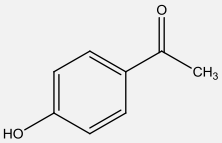
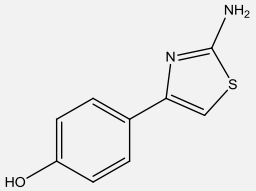
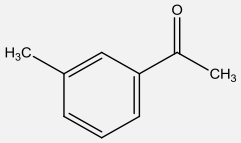
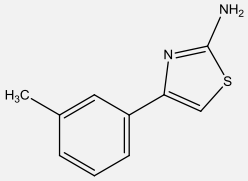
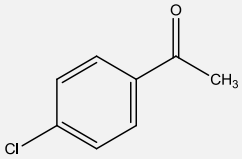
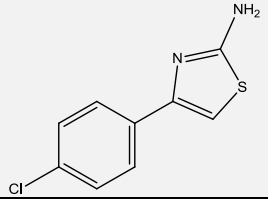
Table 1, Entry 7, 4-(4-Hydroxyphenyl) thiazol-2-amine; IR(KBr), cm^{-1}: 3445, 2917, 1615, 1500, 1435, 834; 1H NMR (400 MHz , $CDCl_3$); δ, ppm: 6.67 (d, J = 8.5 Hz, 2H, Ar-H), 6.72 (s, 1H, thiazole), 6.95 (s, 2H, NH_2), 7.57 (d, J = 8.5 Hz, 2H, Ar-H), 9.50 (s, OH).

Table 1, Entry 8, 4-(3-Methylphenyl) thiazol-2-amine, IR (KBr), cm^{-1}: 3420, 2915, 1600, 1521, 1458, 714; 1H NMR (400 MHz, $CDCl_3$): δ, ppm: 2.48 (s, 3H, CH_3), 6.95 (s, 1H, thiazole), 7.00 (s, 2H, NH_2), 7.02 (d, J = 7.8 Hz, 1H, Ar-H), 7.20 (t, 1H, J = 7.9 Hz, Ar-H), 7.52 (d, J = 7.9Hz, 1H, Ar-H), 7.60 (s, 1H, Ar-H).

Table 1, Entry 9, 4-(4-Chlorophenyl) thiazol-2-amine, IR (KBr), cm^{-1}: 3415, 2900, 1620, 1570, 1487, 735; 1H NMR (400 MHz, $CDCl_3$); δ, ppm: 7.22 (1H, S, thiazole C-H), 7.52 (2H, J= 8.4 HZ Ar-H), 7.70 (2H, J = 8.4 H, Ar-H), 8.82 (s, 2H, NH_2).

TABLE 1: ALIPHATIC AND AROMATIC KETONES ARE CONVERTED INTO AMINOTHIAZOLES

S. no.	Substrate	Product	Time (min)	Yield %
1			180	87
2			190	85

3			195	82
4			195	80
5			185	89
6			165	85
7			160	80
8			190	79
9			185	87

a. Reaction conditions: thiourea 2 eq., ketones 1 eq. and oxone 2 mmol, Iodobenzene 2 mmol and catalytic KBr in aq. Acetonitrile solvent at room temperature.

RESULT AND DISCUSSION: To develop a suitable protocol for formation of 2-aminothiazole, initially the plane acetophenone and thiourea treated with Oxone (2 mmol) and Iodobenzene (2 mmol) in the acetonitrile water solvent system in presence of catalytic amount of KBr at room temperature was chosen as a model reaction as expected product was obtained in exceptional yields in 3 hrs. Completion of the reaction was monitored by Thin Layer Chromatography (TLC). After completion of reaction, workup carried out as given in experimental procedure, pure product was isolated by column chromatography.

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CONFLICT OF INTEREST: No conflict of interest.

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