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A Simple and Efficient Method for the Synthesis of 2-Aminothiazoles Under Mild Conditions

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ABSTRACT
NEt₃ was found to be a simple, mild, and efficient catalyst for the synthesis of 2-aminothiazole derivatives from the reaction of different ketones, thiourea, and iodine in EtOH media under mild conditions for the first time. Present methodology offers several advantages, such as simple procedure, shorter reaction times, and milder conditions, and takes place at reflux temperature, with operational simplicity and with excellent yields.

Introduction
The thiazole ring system is present in various natural materials, and many thiazole derivatives exhibit a broad range of biological activities (1). On the other hand, 2-aminothiazoles are one of the most important classes of heterocycles in the field of pharmaceutical and medicinal chemistry such as antifungal (2, 3), radioprotective (4), insecticidal (3), bactericidal, antiviral (5, 6), and anesthetic (7, 8) activities.

Therefore, in recent times increasing attention has been paid for the synthesis of 2-aminothiazoles. The most straightforward synthesis of thiazole compounds involves treatment of styrene and thiourea with NBS (9), the reaction of α-thiocyanato carbonyl compounds with aromatic or aliphatic aminehydrochlorides (10), condensation of α-bromoketone with thiourea (11), and condensation of aromatic ketone and thiourea with various catalysts (12). Although these protocols reported by others find certain merits of their own, still they suffer from a number of demerits such as the use of expensive catalysts, tedious workup, high reaction temperatures, and undesired side products in reaction, reagents in stoichiometric amounts, low yields, and environmental pollution (13). Therefore, a need still exists for further development of versatile reaction conditions in synthesis of 2-aminothiazoles using an efficient, inexpensive, great, and selective catalyst.

Catalysis plays a central role in chemical processes and lies at the heart of countless chemical transformations, from academic research at laboratories level to the chemical industry level. By using catalytic systems, one can reduce the temperature of a chemical reaction, reduce reagent-based waste, and enhance the yield of a transformation that potentially avoids the unwanted side reactions leading to a green technology (14, 15). Homogeneous catalytic processes are the first choice of chemists because of their high activity and selective chemical...
transformations with excellent product yield. However, it shows difficulty in separating the catalyst from the final reaction product. Examples of these catalysts include mineral acids and bases, and transition metal compounds (15, 16).

However, despite extensive studies on synthesis of 2-aminothiazoles reported in the literature, to the best of our knowledge, there is no report focusing on the development of one-pot synthesis of 2-aminothiazoles using NEt$_3$ under mild conditions. Therefore, this report describes convenient and facile syntheses of 2-aminothiazoles in high yields via the one-pot reaction of various different ketones and thiourea in EtOH under reflux conditions (Scheme 1).

**Experimental**

*Chemicals and apparatus*

Chemicals were purchased from the Merck and Fluka Chemical Companies in high purity. All of the materials were of commercial reagent grade. IR spectra were recorded as KBr pellets on a Perkin–Elmer 781 spectrophotometer and on an Impact 400 Nicolet FTIR spectrophotometer. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker DPX-400 Advanced spectrometer. The melting points were determined by a Yanagimoto micro melting point apparatus. The purity determination of the substrates and reaction monitoring were accomplished by thin layer chromatography (TLC) on silica gel polygram SILG/UV 254 plates.

*Preparation of 2-aminothiazoles using NEt$_3$*

A mixture of the acetophenone (2 mmol), thiourea (3 mmol), and iodine (2 mmol), in the presence of 0.2 mL (0.001 mmol) NEt$_3$ was refluxed in EtOH. The progress of the reaction was monitored by TLC (petroleum ether–ethyl acetate 4:1). After the reaction was completed, the reaction mixture was concentrated on a rotary evaporator under reduced pressure and the solid product obtained was dissolved in boiling water, extracted with ether (3 $\times$ 30 ml), and adjusted to pH = 8 with amount of ammonia to give the solid products. The solid was recrystallized with ethanol-water to give pure 2-aminothiazole product. The products were characterized by IR, $^1$H NMR, and $^{13}$C NMR spectroscopy, and also by comparison with authentic samples.

*Results and discussion*

To achieve suitable conditions for the synthesis of 2-aminothiazoles, various reaction conditions have been investigated in the reaction of acetophenone, thiourea, and iodine as a model reaction in ethanol as solvent. As shown in Table 1, NEt$_3$ were appropriate to catalyze this
reaction and a significant improvement was observed in the yield of 1,3-thiazoles in the presence of 0.2 mL (0.001 mmol) base catalyst. Increase in the amount of catalyst did not improve the yield significantly because NEt$_3$ can act as a nucleophile in the reaction and cause the production of by-product (Table 1, entry 3–5). As can be seen from this table, temperature plays an important role in reaction time and product yield. The yield of the reaction was determined at various temperatures and found to grow with increasing temperature to 80°C (reflux condition). When the reaction was performed at 50°C, the rate of the reaction was slow and at higher temperatures than 80°C the yield of 4b product was reduced (Table 1, entry 12). The general decrease in reaction rates at higher temperatures apparently was due to thermal degradation effects and reversible reaction. A temperature of 80°C was observed to be optimum for the maximum yield of the reaction. In our continued study, we examined the effect of various solvents such as EtOH, DMSO, DMF, THF, MeOH, and CCl$_4$ on a model reaction under reflux conditions. The results were summarized in Table 1. EtOH was chosen as solvent of reaction.

After the optimization of the reaction condition, we turned our focus to the substrate scope and generality of the reaction. A variety of ketones were used under the optimized conditions and the results obtained are summarized in Table 2. The results summarized in this table indicate that the effect of electronic nature and position of substituent on the phenyl rings in aryl ketones did not show strong influence on the reaction and the products were obtained in high yields.

Suggested mechanism is shown in Scheme 2, as the initiation step (1), the acetophenone undergoes the formation of enolate ion A under basic conditions with NEt$_3$ as a basic homogeneous catalyst, and A converts to α-iodoketones B in the presence of I$_2$. Also, thiourea is converted to enol C under basic conditions. Subsequent reaction of B with thiourea C would afford intermediate I, which would undergo an intramolecular nucleophilic addition/dehydration reaction to generate D in the presence of NEt$_3$. Finally, intermediate D
Table 2. Synthesis of 2-aminothiazole derivatives by NEt₃.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)ᵃ</th>
<th>m.p. (°C)</th>
<th>m.p. (°C) (Rep)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetaldehyde</td>
<td>4a</td>
<td>4</td>
<td>90</td>
<td>89–90</td>
<td>90–92 (17)</td>
</tr>
<tr>
<td>2</td>
<td>acetophenone</td>
<td>4b</td>
<td>4</td>
<td>96</td>
<td>150–151</td>
<td>205–207 (12)</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-acetophenone</td>
<td>4c</td>
<td>3.5</td>
<td>98</td>
<td>161–162</td>
<td>162–163 (12)</td>
</tr>
<tr>
<td>4</td>
<td>4-Br-acetophenone</td>
<td>4d</td>
<td>3.5</td>
<td>98</td>
<td>180–183</td>
<td>181–182 (12)</td>
</tr>
<tr>
<td>5</td>
<td>4-OH-acetophenone</td>
<td>4e</td>
<td>4</td>
<td>95</td>
<td>198–200</td>
<td>198–200 (18)</td>
</tr>
<tr>
<td>6</td>
<td>2-OH-acetophenone</td>
<td>4f</td>
<td>4</td>
<td>98</td>
<td>138–139</td>
<td>139–140 (18)</td>
</tr>
<tr>
<td>7</td>
<td>3-Me-acetophenone</td>
<td>4g</td>
<td>3.5</td>
<td>94</td>
<td>88–91</td>
<td>79–92 (18)</td>
</tr>
<tr>
<td>8</td>
<td>4-NO₂-acetophenone</td>
<td>4h</td>
<td>4</td>
<td>80</td>
<td>285–286</td>
<td>286–287 (12)</td>
</tr>
<tr>
<td>9</td>
<td>ethyl acetoacetate</td>
<td>4i</td>
<td>5</td>
<td>93</td>
<td>177–179</td>
<td>177–178 (19)</td>
</tr>
<tr>
<td>10</td>
<td>methyl acetoacetate</td>
<td>4j</td>
<td>5</td>
<td>90</td>
<td>225–226</td>
<td>224–226 (19)</td>
</tr>
<tr>
<td>11</td>
<td>allyl acetoacetate</td>
<td>4k</td>
<td>6</td>
<td>85</td>
<td>148–149</td>
<td>148–150 (19)</td>
</tr>
<tr>
<td>12</td>
<td>acetylacetone</td>
<td>4l</td>
<td>6</td>
<td>83</td>
<td>219–220</td>
<td>219–220 (19)</td>
</tr>
</tbody>
</table>

ᵃ Isolated yields.

Scheme 2. The proposed mechanism of reaction.

undergoes neutralization reaction to give the corresponding products in moderate to excellent yields with high purity (20).

Conclusions

In conclusion, we have developed a simple and convenient procedure for the synthesis of 2-aminothiazoles in the presence of NEt₃ as a homogeneous catalyst under mild condition. Present methodology offers very attractive features such as easy isolation of products, milder and cleaner conditions, higher purity and yields, and easier work-up procedure. This simple method combined with inexpensive homogeneous catalyst makes this protocol economic, benign, and a waste-free chemical process for the synthesis of 1,3-thiazoles.
Funding

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References