Lactic acid mediated tandem one-pot synthesis of 2-Aminothiazole derivatives: A rapid, scalable and sustainable process


Environmentally benign and biodegradable lactic acid is identified as an alternative solvent and catalyst for the tandem one-pot synthesis of Hantzsch 2-aminothiazole derivatives in good to excellent isolated yields (up to 96%) within 10-15 min from aralkyl ketones through in situ regioselective α-bromination using NBS followed by heterocyclization using thiourea at 90-100°C.

Lactic acid as alternative solvent and catalyst
Avoids use of lachrymatory α-bromoketones
Example for Wender's "ideal synthesis"
Practical and sustainable process
Free from column purification

R = Aryl, Naphthyl

15 examples
up to 96%
2-Aminothiazole derivatives

ORGANIC CHEMISTRY | RESEARCH ARTICLE

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Lactic acid-mediated tandem one-pot synthesis of 2-aminothiazole derivatives: A rapid, scalable, and sustainable process

Mohan Reddy Bodireddy¹, P.Md. Khaja Mohinuddin¹, Trivikram Reddy Gundala¹ and N.C. Gangi Reddy¹*

Abstract: Environmentally benign and biodegradable lactic acid is identified as alternative solvent and catalyst for the tandem one-pot synthesis of Hantzsch 2-aminothiazole derivatives (4) from readily available aralkyl ketones (1) through in situ regioselective α-bromination using N-bromosuccinimide (2) followed by heterocyclization using thiourea (3) at 90–100°C. The major advantages of the present method include short reaction times (10–15 min), practical, simple to perform, easy work-up, good yield of products (up to 96%), productive for large-scale applications, free from apply of α-bromoketones (lachrymator) as substrates, avoids column purification. Hence, the present method meets with the concepts of both Wender’s “ideal synthesis” and sustainable chemical process.

Subjects: Environmental Chemistry; Medicinal & Pharmaceutical Chemistry; Organic Chemistry

Keywords: 2-aminothiazole; lactic acid; NBS; thiourea, α-bromination; scale-up process

ABOUT THE AUTHORS
N.C. Gangi Reddy was born in 1981 in Naravakati Palle village, Kadapa, Andhra Pradesh, INDIA. He has been awarded the PhD degree from Sri Venkateswara University, Tirupati, INDIA in April 2007. Later, he joined as an assistant professor in the Department of Chemistry, Yogi Vemana University, Kadapa in June 2007. His research interests are design and synthesis of medicinally valuable organic compounds and development of catalyst-based synthetic methodologies. He published more than 25 research papers in journals of international repute. He completed two major research projects as principal investigator.

PUBLIC INTEREST STATEMENT
The reported method provides wide scope and quick access to Hantzsch 2-aminothiazole derivatives in good to excellent isolated yields within a short period of time from readily available aralkyl ketones through in situ regioselective α-bromination using NBS and subsequent heterocyclization using thiourea in presence of environmentally benign and biodegradable lactic acid at 90–100°C in a single step operation. Major advantages of the present method include scale-up process, non-explosive, easy to perform, simple work-up, easy isolation of products, improved worker safety and use of environmentally benign, non-volatile and biodegradable lactic acid as an alternative solvent and catalyst. Further, the present protocol is free from (i) column purification, (ii) the use of hazardous solvents and (iii) the isolation of lachrymatory α-bromoketones. Hence, the present method meets the concept of Wender’s “ideal synthesis”. Finally, it is concluded that the present method is an attractive addition to the sustainable chemical processes.
1. Introduction

The growing interest in developing simple, more convenient methods for the synthesis of medici-
nally important thiazole moiety has great demand both in academic, chemical, and pharmaceutical
domains (Donadoni, 1985). Consequently, extensive use of conventional solvents and hazardous
catalysts became mandatory for their preparation which is leading to environmental pollution.
Besides, these are mostly prepared from α-bromoketones that are difficult to store and not easily
accessible. Further, these α-bromoketones are lacrimary and cause other severe health hazards
to the operating chemists. As a result, the growing interest in developing simple, safe, more conveni-
ent, and sustainable scale-up methods for the synthesis of these thiazole synthetic precursors from
readily available ketones has great demand in academic, chemical, and pharmaceutical domains.
The Hantzsch thiazole synthesis (Hantzsch & Weber, 1887) is a powerful synthetic tool for the con-
struction of the five-membered 2-aminothiazole derivatives. Even though it was introduced more
than one century ago, still the development of new Hantzsch-based methods is warranted. As a re-
result, numerous methods have been reported with the improvement of many aspects of the original
synthetic protocol for their syntheses from either ketones or α-brominated ketones or other key
starting materials (Jacques & Vernin, 2008). 2-aminothiazole derivatives possess broad range of
pharmacological activities (Biagetti et al., 2010; González Cabrera et al., 2011; Jaen et al., 1990;
Parekh, Juddawala, & Rawal, 2013; Patt et al., 1992; Shah, Shah, Patel, & Patel, 2012; Shao et al.,
2013; Singh et al., 2014; Spector, Liang, Giordano, Sivaraja, & Peterson, 1998; Yang et al., 2010) and
plant growth activities (An Tran, Anil Kumar, Jung-Ae, Lee, & Park, 2015). Recently, 2-aminothiazole
derivatives are identified as a prodrug for the treatment of type 2 diabetes (I and II) (Erion et al.,
2005), anti-tuberculosis agent (III) (Makam & Kannan, 2014), and anti-Parkinsonian agent-prami-
pexole (IV) (Chau, Cooper, & Schapira, 2013) as shown in Figure 1. Consequently, thiazole moiety is
considered as “Important Structural motif” and the desirable properties of 2-amino thiazole deriva-
tives render them attractive targets for new drug discovery. There are many reports on the synthesis
of thiazole derivatives from ketones or their derivatives (Kumar, Minh An, Lee, Park, & Lee, 2015;
Heravi, Poormohammad, Beheshtihao, & Baghernejad, 2011; Huang, Zhu, & Zhang, 2002; Janardhan,
Krishnaiah, Rajitha, & Crooks, 2014; Kidwai, Chauhan, & Bhatnagar, 2011; Meshram, Thakur, Madhu
Babu, & Bangade, 2012; Nitta et al., 2012; Potewar, Ingale, & Srinivasan, 2008; Zhuravel, Kovalenko,
Vlasov, & Chernykh, 2005; Zhu et al., 2012) and thiourea or substituted thiourea. However, most of
the reported methods suffer from one or more disadvantages including use of hazardous and toxic
reagents, long reaction times, low selectivity of the products, use of toxic and volatile solvents as
well as catalysts, environmentally hazardous processes, low yields and difficulties in work-up and
isolation of products and oppressive operational procedures.

On the other hand, now-a-days, recycle and reduce of solvent usage or change to other solvents
with better environmental profiles (Jessop, 2011; Kerton, 2009) become prominent. Accordingly, we
found that environmentally benign lactic acid (Yang, Tan, & Gu, 2012) can act as catalyst cum sol-
vent for in situ regioselective α-bromination and subsequent heterocyclization in the synthesis of
pharmacologically active 2-aminothiazole derivatives. The present method is scale-up process and
also meets the concept of “ideal synthesis” as described by Wender, Handy, and Wright (1997).
Herein, we report a simple, more convenient, practical method in which lactic acid acts as green catalyst and solvent for the one-pot synthesis of Hantzsch 2-aminothiazole derivatives (4) within 10–15 min from readily available aralkyl ketones (1) through *in situ* regioselective α-bromination using *N*-bromosuccinimide (2) followed by heterocyclization using thiourea (3) at 90–100°C (Scheme 1).

2. Results and discussion

It is planned to develop a simple, more convenient method for the preparation of Hantzsch 2-aminothiazole derivatives (4). For this purpose, initially we have chosen to synthesize the 4-(4-bromophenyl)thiazol-2-amine (4a) using 4′-bromoacetophenone (1a). It is used as model substrate for the optimization of reaction conditions as discussed below.

2.1. Selection of suitable catalyst and solvent

For the success of the present hypothesis, an acidic organic liquid which can function as a catalyst and solvent is needed to identify for the accomplishment of both *in situ* regioselective α-bromination and heterocyclization in a single step operation, as the solubility of key reactants and their α-bromination and subsequent heterocyclization become easy in the presence of acidic organic liquid compared to solid catalysts alone. At the same time, it is evident that both the α-bromination and heterocyclization processes proceed in the presence of acidic catalysts.

Toward this direction, a reaction is carried out using 4′-bromoacetophenone (1a) and *N*-bromosuccinimide (2) followed by addition of thiourea (3) in the presence of acetic acid (entry 1, Table 1) and the isolated yield of desired product (4a) is 30% at RT (entry 1, Table 1) and 58% at 90–100°C. To increase the yield of 4a, the same reaction is carried out in lactic acid and the obtained yield of product (4a) is increased to 45% at RT (entry 3). The same reaction at 90–100°C provided 96% yield (entry 4, Table 1). It may be due to more acidic nature of lactic acid compared to acetic acid. The evaluation of suitable acidic organic liquid which acts both as catalyst and solvent disclosed that lactic acid is the best option to obtain maximum yield (96%) of the desired product (4a) (entry 4, Table 1) compared to acetic acid (entry 2, Table 1).

### Table 1. Screening of suitable acidic organic liquid (act as catalyst and solvent) for the synthesis of 4-(4-bromophenyl)thiazol-2-amine (4a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalystb</th>
<th>Temperature</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yieldc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetic acid</td>
<td>RT</td>
<td>7 h</td>
<td>4a</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Acetic acid</td>
<td>90–100°C</td>
<td>90 min</td>
<td>4a</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>Lactic acid</td>
<td>RT</td>
<td>1.2 h</td>
<td>4a</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Lactic acid</td>
<td>90–100°C</td>
<td>13 min</td>
<td>4a</td>
<td>96</td>
</tr>
</tbody>
</table>

Notes: *Reaction conditions: 4′-bromoacetophenone (1a) (25.0 mmol), *N*-bromosuccinimide (2) [(30.0 mmol) is added in 4 portions], thiourea (3) (30.0 mmol) and dual functional weak organic acid (20 mL) at 90–100°C.

*bAct as catalyst and solvent.

+cIsolated yield.
Later, other reaction conditions such as effect of brominating agent and mode of addition of brominating agent on the course of in situ regioselective α-bromination and also the effect of temperature both on in situ regioselective α-bromination and subsequent heterocyclization is investigated and the results obtained are discussed below.

In the present method, the in situ α-bromination reaction plays a vital role as the yield of target 2-aminothiazoles (4) is directly proportional to the yield of in situ generated α-brominated ketone (5). For this reason, various brominating agents and their mode of addition are studied. In particular, greater attention has been paid to improve the efficiency of α-bromination of ketones in terms of regioselectivity to generate α-monobrominated ketones exclusively compared to α-dibrominated ketones and also to achieve maximum conversion. The results obtained are presented in Tables 2 and 3.

### 2.2. Screening of suitable brominating agent

The effect of brominating agent is studied on the course of in situ regioselective α-bromination and the results obtained are presented in Table 2. Accordingly, a reaction is carried out using molecular bromine and obtained lower yield (55%) of product 5a (entry 1, Table 2). The toxicity, difficulties in handling and low selectivity of molecular bromine encouraged us to use other user-friendly and readily available brominating agents such as HBr-H2O2, dioxane dibromide, N-bromosuccinimide (NBS) and CuBr2 which provided 60, 76, 97, and 81% yields of product 5a, respectively (entries 2–5, Table 2).

The study revealed that NBS is the best brominating agent as it gave maximum yield (97%) of product 5a when added in 4 portions (entry 3, Table 3).

### 2.3. Effect of temperature

In general, the solubility of reactants and products, rate of reaction, efficiency and selectivity of catalyst are highly dependent on operating temperature of the reaction. Hence, we desired to study the effect of temperature on the course of both in situ α-bromination (A) and subsequent heterocyclization (B) process. Accordingly, reactions are conducted at various ranges of temperature and the results obtained are presented in Table 4.

### Table 2. Effect of brominating agent on the course of in situ α-bromination reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Brominating agent</th>
<th>Time (min)</th>
<th>Temperature (°C)</th>
<th>Product (5a)</th>
<th>Yield (%)</th>
<th>Selectivity (%) (5a:6a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br2</td>
<td>25</td>
<td>10–15</td>
<td>5a</td>
<td>55</td>
<td>55:16</td>
</tr>
<tr>
<td>2</td>
<td>HBr-H2O2</td>
<td>31</td>
<td>RT</td>
<td>5a</td>
<td>60</td>
<td>60:13</td>
</tr>
<tr>
<td>3</td>
<td>Dioxane dibromide</td>
<td>20</td>
<td>90–100</td>
<td>5a</td>
<td>76</td>
<td>76:12</td>
</tr>
<tr>
<td>4</td>
<td>N-bromosuccinimide</td>
<td>12</td>
<td>90–100</td>
<td>5a</td>
<td>97</td>
<td>97:02</td>
</tr>
<tr>
<td>5</td>
<td>CuBr2</td>
<td>25</td>
<td>90–100</td>
<td>5a</td>
<td>81</td>
<td>81:10</td>
</tr>
</tbody>
</table>

Notes: *Reaction conditions: 4′-bromoacetophenone (1a) (25.0 mmol), brominating agent (2) [(30.0 mmol) is added in 4 portions] and lactic acid (20 mL) at 90–100°C.

*Isolated yield.

*Unreacted substrate.
For instance, when the reaction is carried out at room temperature, the rate of α-bromination (A) process is slow (3 h) and provided lower yield (53%) of product 5a (entry 1, Table 4) and subsequent heterocyclization (B) using thiourea (3) provided only 40% yield of final product 4a (entry 1). This may be due to partial solubility of the reactants. To improve the solubility of reactants and yield of α-bromoketone (5a) further, the reaction is conducted at different temperatures, for example at

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mode of NBS addition (Portions)</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Selectivity (%) (5a:6a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Once</td>
<td>7</td>
<td>5a</td>
<td>67</td>
<td>67:16</td>
</tr>
<tr>
<td>2</td>
<td>Two</td>
<td>9</td>
<td>5a</td>
<td>76</td>
<td>76:14</td>
</tr>
<tr>
<td>3</td>
<td>Four</td>
<td>12</td>
<td>5a</td>
<td>97</td>
<td>97:02</td>
</tr>
</tbody>
</table>

Notes: *Reaction conditions: 4′-bromoacetophenone (1a) (25.0 mmol), N-bromosuccinimide (2) (30.0 mmol) is added in 4 portions and lactic acid (20 mL) at 90–100°C.

For instance, when the reaction is carried out at room temperature, the rate of α-bromination (A) process is slow (3 h) and provided lower yield (53%) of product 5a (entry 1, Table 4) and subsequent heterocyclization (B) using thiourea (3) provided only 40% yield of final product 4a (entry 1). This may be due to partial solubility of the reactants. To improve the solubility of reactants and yield of α-bromoketone (5a) further, the reaction is conducted at different temperatures, for example at
Table 5. Tandem one-pot synthesis of 2-amino thiazole derivatives (4a-o) from readily available aralkyl ketones (1a-o)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (1)</th>
<th>Product (4)</th>
<th>Time (min)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O(\text{Br})(1a)</td>
<td>O(\text{S})N(\text{NH}_2)(4a)</td>
<td>13</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>O(\text{Br})(1b)</td>
<td>O(\text{S})N(\text{NH}_2)(4b)</td>
<td>14</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>O(\text{Cl})(1c)</td>
<td>O(\text{S})N(\text{NH}_2)(4c)</td>
<td>13</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>O(\text{F})(1d)</td>
<td>O(\text{S})N(\text{NH}_2)(4d)</td>
<td>14</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>O(\text{Cl})(\text{Cl})(1e)</td>
<td>O(\text{S})N(\text{NH}_2)(4e)</td>
<td>15</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>O(\text{Cl})(\text{Cl})(1f)</td>
<td>O(\text{S})N(\text{NH}_2)(4f)</td>
<td>15</td>
<td>78</td>
</tr>
<tr>
<td>7(^c)</td>
<td>O(\text{O})(\text{2N})(1g)</td>
<td>O(\text{S})N(\text{NH}_2)(4g)</td>
<td>14</td>
<td>53</td>
</tr>
<tr>
<td>8(^c)</td>
<td>O(\text{O}_2)(\text{N})(1h)</td>
<td>O(\text{S})N(\text{NH}_2)(4h)</td>
<td>14</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>O(\text{2N})(1i)</td>
<td>O(\text{S})N(\text{NH}_2)(4i)</td>
<td>15</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>O(\text{Me})(1j)</td>
<td>O(\text{S})N(\text{NH}_2)(4j)</td>
<td>15</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>O(\text{Et})(1k)</td>
<td>O(\text{S})N(\text{NH}_2)(4k)</td>
<td>15</td>
<td>77</td>
</tr>
</tbody>
</table>

(Continued)
Table 5. (Continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (1)</th>
<th>Product (4)</th>
<th>Time (min)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1l</td>
<td>4l</td>
<td>14</td>
<td>79</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>4m</td>
<td>13</td>
<td>88</td>
</tr>
<tr>
<td>14</td>
<td>1n</td>
<td>4n</td>
<td>15</td>
<td>81</td>
</tr>
<tr>
<td>15</td>
<td>1o</td>
<td>4o</td>
<td>14</td>
<td>90</td>
</tr>
</tbody>
</table>

Notes: aReaction conditions: Aralkyl ketone (1a-o) (25.0 mmol), N-bromosuccinimide (2) [(30.0 mmol) is added in 4 portions], thiourea (3) (30.0 mmol) and lactic acid (20 mL) at 90–100°C.
bIsolated yield.
c45.0 mmol of N-bromosuccinimide is used.

40–50, 50–60, 70–80, 80–90, and 90–100°C provided 65, 69, 75, 84, and 97% isolated yield of α-bromoketone (5a) (entries 2–6).

While we consider heterocyclization (B) step alone, this stage is also slightly influenced by the operating temperature. For example, at room temperature, the yield of product 4a (40%) is decreased (entry 1, Table 4) significantly due to the partial solubility of thiourea (3) in lactic acid. When the same reaction is conducted at 40–50°C, improved yield (58%) of product 4a is obtained compared to RT (entry 2). But, when the reaction is operated at 50–60, 70–80, 80–90, and 90–100°C provided yields of 62, 71, 82, and 96% of product 4a, respectively (entries 3–6, Table 4).

These results indicate that the isolated yield of product 4a is directly proportional to the percentage of formation of in situ regioselective α-bromoketone 5a (entries 2–6, Table 4).

When we consider the overall reaction i.e. both in situ regioselective α-bromination (A) and heterocyclization (B), the optimum operating temperature is 90–100°C for maximum conversion and isolated yield (96%) of target product 4a (entry 7, Table 4). Based on our present study, we found that in case of laboratory scale, the optimum temperature is 90–100°C for the synthesis of 2-aminothiazoles (4).

2.4. Scope of the method
The substrate scope of the present method is studied with the help of above optimized reaction conditions using different types of aralkyl ketones (1a-o) as key starting substrates and the results obtained are presented in Table 5. The study disclosed that the substrate with fluoro, chloro, and bromo groups at para-position provided excellent yields (90–96%) of the products 4a, 4c, 4d (entries 1, 3, and 4, Table 5), but meta monohalogenated substrate, for example 1-(3-bromophenyl)
ethanone (1b) provided good yield (85%) of the product 4b (entry 2, Table 5). Whereas the dihalogenated substrates, 1-(2,4-dichlorophenyl)ethanone (1e) and 1-(3,4-dichlorophenyl) ethanone (1f) provided moderate yields of products 4e and 4f in 74% and 78%, respectively (entries 5 and 6, Table 5). It is found that the isolated yield of the respective products depends on the position of halogen(s) on aromatic ring of aralkyl ketone (entries 1–6, Table 5).

Interestingly, substrates, 1-(4-nitrophenyl)ethanone (1g) and 1-(3-nitrophenyl)ethanone (1h) with high deactivating groups (-NO$_2$) provided lower yields of product 4g (53%) and 4h (46%) (entries 7 and 8, Table 5) compared to all other substrates used in the present study. This may be due to the presence of strong electron withdrawing groups on the aromatic ring cause to reduce the percentage of formation of in situ α-brominated ketones which play vital role on yield of final product. Simple aralkyl ketones, for instance acetophenone (1i) and propiophenone (1l) provided good yields of the products 4i (92%) and 4l (84%) (entries 9 and 12, Table 5) and the substrates with moderate activating groups, for example 1-(p-tolyl)ethanone (1j), 1-(4-phenylethyl)ethanone (1k) provided acceptable yields (79–84%) of respective products (4j and 4k) (entries 10–11, Table 5). But, the substrate with high activating group, for example 1-(4-methoxyphenyl)ethanone (1m) provided good yield (88%) of the product 4m (entry 13, Table 5). Interestingly, in case of acenaphthanones (1n and 1o), the 1-acetyl naphthalene (1n) gave lower yield (81%) of product 4n when compared to 2-acetyl naphthalene (1o) which afforded higher yield (90%) of product 4o (entries 14 and 15, Table 5). It may be due to steric effects.

3. Conclusions

In summary, the developed method provides wide scope and quick access to Hantzsch 2-aminothiazole derivatives (4) in good yields within 10–15 min from readily available aralkyl ketones (1) through in situ regioselective α-bromination using NBS (2) and subsequent heterocyclization using thiourea (3) in the presence of lactic acid at 90–100°C in a single step operation when compared to an alternative two-step procedures or other reported one-step methods. Major advantages of the present method include scale-up process, non-explosive, easy to perform, simple work-up, easy isolation of products, improved worker safety and use of environmentally benign, non-volatile and biodegradable lactic acid as alternative solvent and catalyst. Further, the current protocol is free from (i) column purification, (ii) the use of hazardous solvents, and (iii) the isolation of lachrymatory α-bromoketones.

Finally, it is concluded that the present method is an attractive addition to the sustainable chemical processes.

4. Materials and method

4.1. Materials

Melting points of various obtained products are determined and uncorrected. $^1$H NMR spectra are recorded on a Varian 400 MHz and $^{13}$C NMR spectra on a Jeol/AL-100 MHz. Chemical shifts were expressed in parts per million (ppm), coupling constants are expressed in Hertz (Hz). Splitting patterns describe apparent multiplicities and were designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). High-resolution mass spectra (HRMS) and compound purity data are acquired on a Exactive Orbitrap Mass Spectrometer (ThermoScientific, Waltham, MA, USA) equipped with electro spray ionization (ESI) source. Thin-layer chromatography is performed on 0.25 mm Merck silica gel plates and visualized with UV light. Column chromatography is performed on silica gel. Chemicals and solvents are purchased from Sigma Aldrich and Merck. Isolated compounds are identified on the basis of spectroscopic data ($^1$H & $^{13}$C NMR, Mass and HRMS).

4.2. Method for the synthesis of 2-aminothiazole derivatives (4a–o)

In a 100-mL 3 necked round bottom flask, aralkyl ketone (1) (25.0 mmole) and lactic acid (20 mL) are taken. The substrate (1) is partially soluble in lactic acid at room temperature. The temperature of the reaction mass is raised to 90–100°C. At this temperature, the reaction mass became homogeneous and N-bromosuccinimide (2) (30.0 mmol) is added in 4 portions (7.5 × 4 = 30 mmol). On addition of each portion of NBS (3.0 mmol), the color of the reaction mass is changed from colorless to orange
red. This indicates that the bromonium ion is released from NBS (2). Later, within few minutes, the disappearance of the orange red color is observed. The same situation is observed when another 3 portions of NBS (2) is added. After the completion of α-bromination as per TLC, thiourea (3) (30.0 mmol) is added and stirred at the same temperature for 1 min. Then, the reaction mass is slowly cooled down to RT. As the temperature of the reaction mass is below 80°C, the final product (4) is slowly thrown out from the lactic acid. At room temperature, 20 mL of water is added for the precipitation of product (4). Then, it is filtered-off and washed with 10 mL of water. The crude solid product (4) is collected and to this 100 mL of cold water is added and quenched with NaHCO3. Again, it is filtered-off and washed twice with water (2 × 25 mL) for the removal of by-product and inorganic salts. The pure solid product (4) is collected and dried in vacuum oven at ambient temperature and the isolated yields of respective products are presented in Table 5. All the prepared products (4a-o) are characterized by physical and spectroscopic data (1H & 13C NMR, Mass, and HRMS).

### 4.3. Characterization data of the corresponding compounds are as follows

#### 4.3.1. 4-(4-bromophenyl) thiazol-2-amine (4a)
Off-white solid, yield: 96%; m.p. 180–181°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 7.73 (2H, dd, J = 6.8 Hz, J = 2.0 Hz, arom H), 7.69 (2H, br s, -NH2), 7.61 (2H, dd, J = 6.8 Hz, J = 2.0 Hz, arom H), 7.16 (1H, s, thiazole H); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 169.12, 144.39, 131.59 (3C), 127.61 (2C), 121.09, 102.91; HRMS (ESI): calcd for C9H8BrN2S [M + H]+ 254.9586, found 254.9596; [M + H + 2]+ 256.9572.

#### 4.3.2. 4-(3-bromophenyl) thiazol-2-amine (4b)
Yellow solid, yield: 85%; m.p. 162–163°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 7.98 (1H, s, arom H), 7.79 (1H, d, J = 7.6 Hz, arom H), 7.44 (1H, d, J = 6.8 Hz, arom H), 7.32 (1H, t, J = 8.0 Hz, arom H), 7.16 (1H, s, thiazole H), 7.15 (2H, br s, -NH2); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 168.35, 148.06, 137.11, 130.62, 129.73, 124.32, 103.10; HRMS (ESI): calcd for C9H8BrN2S [M + H]+ 254.9507, found 254.9596; [M + H + 2]+ 256.9550.

#### 4.3.3. 4-(4-chlorophenyl) thiazol-2-amine (4c)
Off-white solid, yield: 95%; m.p. 166–167°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 7.80 (2H, d, J = 8.4 Hz, arom H), 7.41 (2H, d, J = 8.8 Hz, arom H), 7.09 (2H, s, -NH2), 7.07 (1H, s, thiazole H); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 168.39, 148.56, 133.71, 131.57, 128.45 (2C), 127.20 (2C), 125.20 (1C, d, J = 3.3 Hz), 116.08 (2C, d, J = 21.4 Hz), 102.82; HRMS (ESI): calcd for C9H8N2ClS [M + H]+ 211.0091, found 211.0082.

#### 4.3.4. 4-(4-fluorophenyl) thiazol-2-amine (4d)
Off-white solid, yield: 94%; m.p. 101–102°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.8 (2H, br s, -NH2), 7.82 (2H, m, arom H), 7.34 (2H, t, J = 6.8 Hz, arom H), 7.21 (1H, s, thiazole H); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 170.33, 162.51 (1C, d, J = 246.2 Hz), 137.66, 128.17 (2C, d, J = 8.3 Hz), 125.20 (1C, d, J = 3.3 Hz), 116.08 (2C, d, J = 21.4 Hz), 102.82; HRMS (ESI): calcd for C9H8N2FS [M + H]+ 195.0387, found 195.0377.

#### 4.3.5. 4-(2, 4-dichlorophenyl) thiazol-2-amine (4e)
Off-white solid, yield: 74%; m.p. 189–191°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.6 (2H, br s, -NH2), 7.79 (1H, d, J = 2.4 Hz, arom H), 7.71 (1H, d, J = 8.4 Hz, arom H), 7.57 (1H, dd, J = 8.4 Hz, J = 2.0 Hz, arom H), 7.14 (1H, s, thiazole H); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 169.21, 135.40, 134.92 (2C), 129.65, 127.81, 127.58, 108.13; MS (ESI) m/z: [M + H]+ 245.00, [M + H + 2]+ 247.00.

#### 4.3.6. 4-(3, 4-dichlorophenyl) thiazol-2-amine (4f)
Off-white solid, yield: 78%; m.p. 193–194°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.016 (1H, d, J = 2.0 Hz, arom H), 7.78 (1H, dd, J = 8.8 Hz, J = 1.6 Hz, arom H), 7.61 (1H, d, J = 8.4 Hz, arom H), 7.23 (1H, s, arom H), 7.16 (2H, br s, -NH2); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 168.58, 146.95, 134.92, 131.38, 130.59, 129.44, 127.19, 125.44, 103.76; HRMS (ESI): calcd for C9H7N2Cl2S [M + H]+ 244.9702, found 244.9691; [M + H + 2]+ 246.9658.
4.3.7. 4-(4-nitrophenyl) thiazol-2-amine (4g)
Orange solid, yield: 53%; m.p. 285–286°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.23 (2H, d, J = 8.8 Hz, arom H), 8.04 (2H, d, J = 8.8 Hz, arom H), 7.42 (1H, s, thiazole H), 7.25 (2H, br s, -NH2); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 168.79, 146.85, 146.02, 140.28, 126.32 (2C), 124.00 (2C), 106.67; HRMS (ESI): calcd for C9H8O2N3S [M + H]+ 222.0332, found 222.0341.

4.3.8. 4-(3-nitrophenyl) thiazol-2-amine (4h)
Yellow solid, yield: 46%; m.p. 282–283°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.60 (1H, s, arom H), 8.23 (1H, d, J = 7.6 Hz, arom H), 8.14 (1H, d, J = 8.0 Hz, arom H), 7.69 (1H, t, J = 7.6 Hz, arom H), 7.38 (1H, s, thiazole H); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 169.03, 148.19, 144.93, 134.93, 131.69, 130.19, 122.19, 120.05, 104.65; MS (ESI) m/z: [M + H]+ 222.00.

4.3.9. 4-phenylthiazol-2-amine (4i)
Off-white solid, yield: 92%, m.p. 149–151°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.6 (2H, br s, -NH2), 7.73 (2H, d, J = 7.6 Hz, arom H), 7.48 (2H, d, J = 8.6 Hz, arom H), 7.41 (1H, d, J = 7.6 Hz, arom H), 7.21 (1H, s, thiazole H); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 170.30, 138.53, 129.54, 129.10 (2C), 128.46, 125.80 (2C), 103.06; HRMS (ESI): calcd for C9H9N2S [M + H]+ 177.0481, found 177.0486.

4.3.10. 2-Amino-4-(4-methylphenyl) thiazole (4j)
Off-white solid, yield: 84%; m.p. 136–137°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.7 (2H, br s, -NH2), 7.62 (2H, d, J = 8.4 Hz, arom H), 7.32 (2H, d, J = 8.6 Hz, arom H), 7.15 (1H, s, thiazole H), 2.34 (3H, s, -CH3); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 170.27, 139.28, 138.46, 129.61 (2C), 125.66 (3C), 102.05, 20.88; HRMS (ESI): calcd for C10H11N2S [M + H]+ 191.0637, found 191.0644.

4.3.11. 4-(4-ethylphenyl) thiazol-2-amine (4k)
Off-white solid, yield: 77%; m.p. 140–141°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.75 (2H, br s, -NH2), 7.67 (2H, d, J = 8.4 Hz, arom H), 7.32 (2H, d, J = 8.6 Hz, arom H), 7.14 (1H, s, thiazole H), 2.64 (2H, q, J = 7.6 Hz, -CH2-), 1.19 (3H, t, J = 7.6 Hz, -CH3); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 168.14, 149.97, 142.71, 142.71, 132.57, 127.82 (2C), 125.56 (2C), 100.58, 27.92, 15.50; HRMS (ESI): calcd for C11H13N2S [M + H]+ 205.07940, found 205.07976.

4.3.12. 5-methyl-4-phenylthiazol-2-amine (4l)
Off-white solid, yield: 79%, m.p. 118–120°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.96 (2H, br s, -NH2), 7.57–7.48 (5H, m, arom H), 2.28 (3H, s, -CH3); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 179.46, 167.66, 133.12, 129.43, 128.95 (2C), 128.45 (2C), 114.83, 11.70; HRMS (ESI): calcd for C10H11N2S [M + H]+ 191.0637, found 191.0642.

4.3.13. 4-(4-methoxyphenyl) thiazol-2-amine (4m)
Off-white solid, yield: 88%; m.p. 205–206°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.9 (2H, br s, -NH2), 7.57–7.48 (5H, m, arom H), 2.28 (3H, s, -OCH3); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 170.38, 160.12, 138.14, 127.26 (2C), 120.91, 114.49 (2C), 100.49, 55.42; HRMS (ESI): calcd for C10H11ON2S [M + H]+ 207.0587, found 207.0593.

4.3.14. 4-(naphthalen-1-yl) thiazol-2-amine (4n)
Brown solid, yield: 81%; m.p. 164–165°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 9.06 (2H, br s, -NH2), 8.10–8.02 (4H, m, arom H), 7.69 -7.60 (3H, m, arom H), 7.05 (1H, s, thiazole H), 7.05 (1H, d, J = 8.8 Hz, arom H), 3.81 (3H, s, -OCH3); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 170.38, 160.12, 138.14, 127.26 (2C), 120.91, 114.49 (2C), 100.49, 55.42; HRMS (ESI): calcd for C13H11N2S [M + H]+ 227.06375, found 227.06416.

4.3.15. 4-(naphthalen-2-yl) thiazol-2-amine (4o)
Brown solid, yield: 90%; m.p. 151–152°C; 1H NMR (400 MHz, DMSO-d6, δ/ppm): 8.32 (1H, s, arom H), 7.96–7.87 (4H, m, arom H), 7.52–7.47 (2H, m, arom H), 7.17 (1H, s, arom H), 7.13 (2H, br s, -NH2); 13C NMR (100 MHz, DMSO-d6, δ/ppm): 170.38, 153.37, 133.01, 132.74, 132.36, 128.36, 127.80, 127.49, 126.58, 126.42, 125.66, 123.53, 103.63; HRMS (ESI): calcd for C13H11N2S [M + H]+ 227.0637, found 227.0645.
4.3.16. 2-bromo-1-(4-bromophenyl)ethanone (5a)

Off-white solid, yield: 97%; m.p. 108–110°C; 1H NMR (400 MHz, CDCl3): δ = 7.53 (d, J = 8.8 Hz, 2H, arom H), 7.64 (d, J = 8.4 Hz, 2H, arom H), 4.39 (s, 2 H, -CH2-).2011/37C/52/BRNS/2264

Supplementary material

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Notes

1. NaHCO3 is added slowly, because of rapid effervescences.
2. If the reaction mass contains unreacted substrate (1), after water wash, it is to be washed again with petroleum ether.

References


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