

## An Improved Protocol on the Synthesis of Thiazolo[3,2-a]pyrimidine Using Ultrasonic Probe Irradiation

Sian Hui Tan<sup>‡</sup>, Tse Seng Chuah<sup>‡</sup>, and Poh Wai Chia<sup>§,\*</sup>

<sup>‡</sup>School of Marine Science and Environment, Universiti Malaysia Terengganu, 21030 Kuala Terengganu, Terengganu, Malaysia

<sup>‡</sup>School of Food Science and Technology, Universiti Malaysia Terengganu, 21030 Kuala Terengganu, Terengganu, Malaysia

<sup>§</sup>Institute of Marine Biotechnology, Universiti Malaysia Terengganu, 21030, Kuala Terengganu, Terengganu, Malaysia.

\*E-mail: pohwai@umt.edu.my

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**ABSTRACT.** An improved protocol on the synthesis of thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives are reported. Previously, the thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives were prepared in a two-step procedure. Under the improved procedure, the thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives was readily prepared in a one-step reaction. This procedure was found to be more efficient than the previous protocol and also compared to the ultrasound bath and conventional heating methods in terms of yield and reaction time.

**Key words:** One-pot three component synthesis, Thiazolo[3,2-a]pyrimidine, Ultrasound, Solvent- and catalyst-free reaction

### INTRODUCTION

The thiazolopyrimidine derivatives had received considerable attention among scientists due to their attractive biological activities, such as calcium channel antagonism property,<sup>1</sup> anti-inflammatory activity,<sup>2</sup> anti-fungal activity,<sup>3</sup> CDC25 phosphatase antagonist activity,<sup>4</sup> anti-acetylcholinesterase activity,<sup>5</sup> inhibition to mGluRs property,<sup>6</sup> antioxidant property,<sup>7</sup> anti-viral property,<sup>8</sup> anti-tumor property<sup>8</sup> and insecticide property.<sup>9</sup>

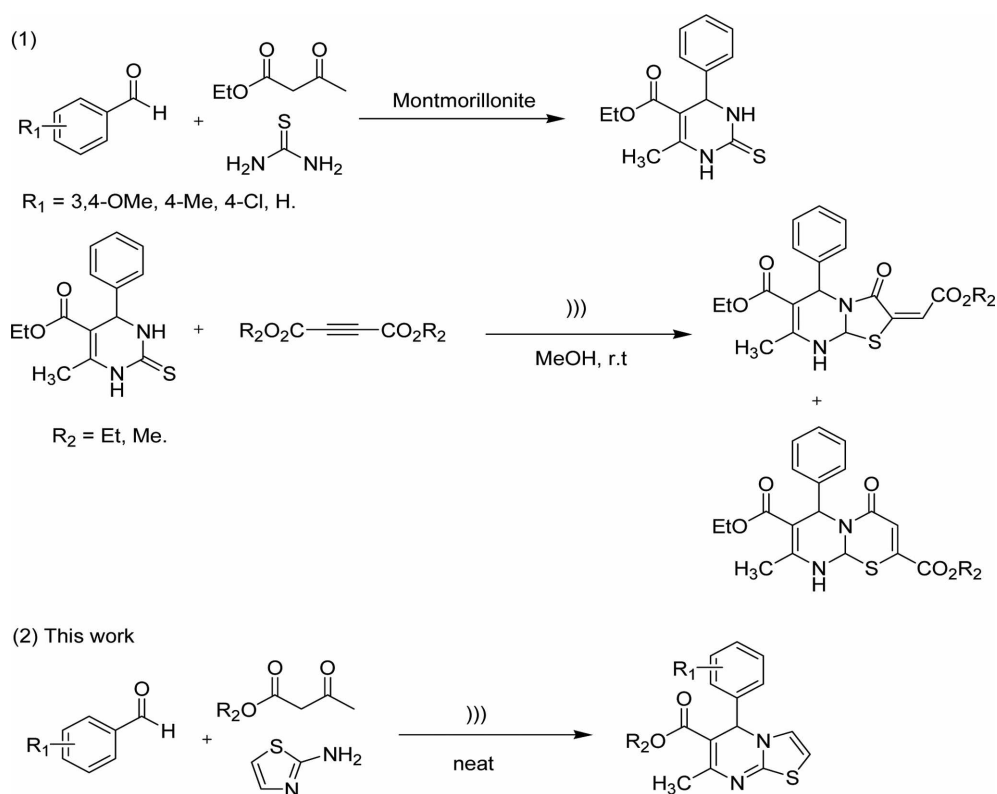
The synthesis of thiazolopyrimidine derivatives could be easily achieved by employing the multicomponent reaction (MCR) method. The MCR has long been used for drugs and herbicide innovation programs.<sup>10</sup> Factors such as the simplicity of this method to generate natural products and drug-like molecules,<sup>11</sup> produce minimal waste as a result of the incorporation of all starting materials into a single product<sup>12</sup> and the shorter reaction time in microwave-assisted MCR reaction<sup>13</sup> have all contributed to the feasibility of this method.

For decades, the ultrasound technology is known for facile access to synthesize molecular complex scaffolds in organic synthesis.<sup>14</sup> The application of ultrasound in organic synthesis has gained overwhelming attention as it offers chemists relatively simple and inexpensive method for chemical activation.<sup>15</sup> In addition, this method is also known to accelerate the rate of a chemical reaction, and at the same time enhance the reaction yield.<sup>16</sup> Recently, there are growing interests in this non-conventional method as it promotes shorter reaction time, eliminate the use of harm-

ful reagents, catalysts- and solvent-free organic transformations, such as in the case exhibited by the synthesis of the 1,4-diazabutadienes<sup>17</sup> and the 1,4-dihydropyridines.<sup>18</sup> Moreover, the inexpensive, fewer synthetic routes and high selectivity of this method has gained interest among the synthetic chemists in the preparation of biologically active scaffold molecules.<sup>19</sup>

The traditional method of preparing thiazolo pyrimidine encompasses the use of acidic conditions or inorganic substances, such as boric acid,<sup>20</sup> microwave irradiation in the presence of acetic acid,<sup>21</sup> potassium fluoride/alumina catalyst<sup>22</sup> and strontium chloride hexahydrate<sup>23</sup> which requires the aid of acids or catalysts in the reaction. In a previous study, an ultrasound synthesis of thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives was published involving a two-step reaction, where the use of montmorillonite catalyst was employed to prepare the pyrimidinone derivative and subsequently treated with acetylenedicarboxylate in methanol under ultrasound irradiation to obtain the desired product (*Scheme 1*, Eq. (1)).<sup>24</sup>

Apart from that, various substituted diesters of thiazolopyrimidine were also prepared by the treatment of 3,4-dihydropyrimidine-2-thione with  $\alpha$ -haloester under reflux condition in ethanol.<sup>25</sup> Another similar approach was found involved the mixture of ethyl acetoacetate, substituted benzaldehyde, 2-aminothiazole and sulphamic acid in ethanol and refluxed for 1.5 h to afford the thiazolopyrimidine carboxylates.<sup>26</sup> Moreover, under the nanoparticle-catalyzed organic synthesis enhancement (NOSE) and solvent free



**Scheme 1.** Synthetic route towards the preparation of thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives.

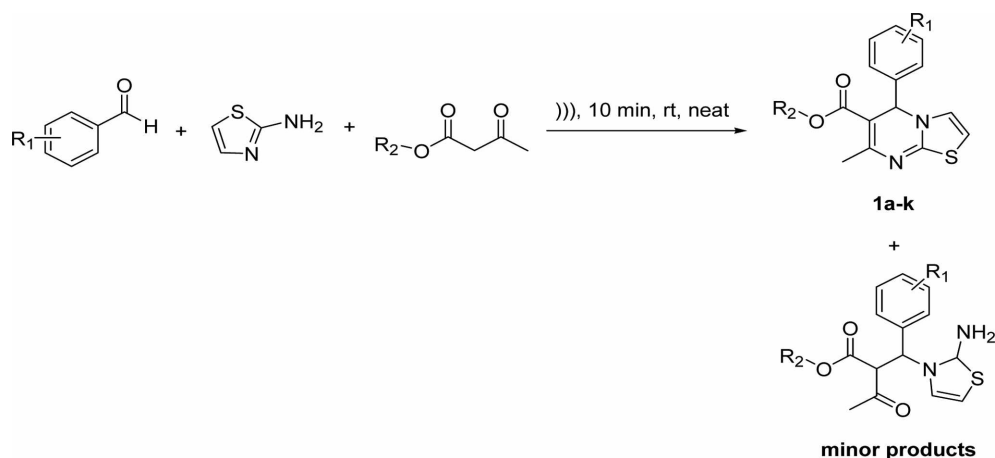
reaction condition (SFRC) approaches, dihydropyrimidine derivatives were synthesized via Biginelli reaction.<sup>27</sup>

In the course of our research in ultrasound synthesis of heterocyclic compounds, our laboratory result showed that the thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives could be readily prepared in a one-step reaction from the starting materials of 2-aminothiazole, ethyl acetoacetate and benzaldehyde derivatives under ultrasound probe irradiation in neat condition as reported in this paper (*Scheme 1*, Eq. (2)).

## EXPERIMENTAL

### Chemicals and analysis

All chemicals and solvents used in this study were purchased from Merck, Acros organic and HmbG<sup>®</sup> chemicals and were used without purification unless stated. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using Bruker AVANCE III NMR spectrometer, with deuterated chloroform as solvent. The mass analysis was performed using Shimadzu



**Scheme 2.** Synthetic route towards the designated compounds (**1a-k**).

GCMS-QP2010 Ultra instrument. The sonication was performed using Microson™ XL2000 Ultrasonic Cell Disruptor (Misonix) at a fixed frequency of 22.5 kHz and a nominal output power of 51 Watts. All the reactions and purity of products were monitored using thin layer chromatography (TLC) on plastic sheets coated with Merck Kieselgel 60 F254 and visualized under UV-visible light.

#### Synthetic procedure for compounds 1a-1k.

The benzaldehyde derivatives (3.00 mmol), 2-aminothiazole (3.00 mmol), and ethyl acetoacetate (3.00 mmol) were added into a 50 mL pyrex round-bottom flask under solvent-free condition and the mixture was irradiated with ultrasonic probe for 20 min at 25±1 °C. After the completion of the reaction, the organic layer was concentrated under reduced pressure. The crude product was then further purified over silica gel column chromatography (Hexane: Ethyl acetate, 6 : 4) to afford the designated compounds 1a-1k. The synthetic route for the designated compounds was illustrated in Scheme 2 and the isolated yield of 1a-1k was summarized in Table 1. All compounds were identified by comparison of their <sup>1</sup>H and <sup>13</sup>C NMR spectra to previous literature and was found to match to those reported in the literature data for the known compounds.<sup>20,21,26,27</sup>

#### 7-Methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester (1a)

Yellow solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.16 (t, 3H, CH<sub>3</sub>, *J* = 7.2 Hz), 2.44 (s, 3H, Ar-CH<sub>3</sub>), 4.06, (m, 2H, CH<sub>2</sub>), 6.18 (s, 1H, Ar-H), 6.26 (d, 1H, Ar-H, *J* = 4.7 Hz), 6.55 (d, 1H, Ar-H, *J* = 4.7 Hz), 7.28–7.36 (m, 5H, Ph-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.23, 23.36, 59.78, 60.71, 99.77, 106.03, 126.70, 126.92, 128.60, 128.86, 142.79, 155.26, 164.82, 166.45. GC-MS: *m/z* 300 [M+H]<sup>+</sup>.

#### 5-(4-Bromo-phenyl)-7-methyl-5H thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester (1b)

Yellow solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.19 (t, 3H, CH<sub>3</sub>, *J* = 7.0 Hz), 2.44 (s, 3H, Ar-CH<sub>3</sub>), 4.08, (m, 2H, CH<sub>2</sub>), 6.16 (s, 1H, Ar-H), 6.33 (d, 1H, Ar-H, *J* = 4.7 Hz), 6.55 (d, 1H, Ar-H, *J* = 4.7 Hz), 7.23 (d, 2H, Ph-H, *J* = 8.5 Hz), 7.45 (d, 2H, Ph-H, *J* = 8.5 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.28, 23.53, 59.91, 60.13, 99.44, 106.25, 122.66, 126.42, 128.58, 132.04, 141.79, 155.67, 164.90, 166.35. GC-MS: *m/z* 377 [M+H]<sup>+</sup>.

#### 5-(4-Chloro-phenyl)-7-methyl-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid ethyl ester (1c)

Yellow solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.19 (t, 3H, CH<sub>3</sub>, *J* = 7.2 Hz), 2.47 (s, 3H, Ar-CH<sub>3</sub>), 4.09, (m, 2H, CH<sub>2</sub>), 6.20 (s, 1H, Ar-H), 6.45 (d, 1H, Ar-H, *J* = 4.7 Hz), 6.62 (d, 1H, Ar-H, *J* = 4.7 Hz), 7.38–7.53 (m, 4H, Ph-H).

Table 1. Isolated yields obtained for compounds 1a-1k

Entry	Product No.	Product	R <sub>1</sub>	R <sub>2</sub>	Isolated yield (%)
1	1a		H	CH <sub>2</sub> CH <sub>3</sub>	90
2	1b		4-Br	CH <sub>2</sub> CH <sub>3</sub>	72
3	1c		4-Cl	CH <sub>2</sub> CH <sub>3</sub>	75
4	1d		2-F	CH <sub>2</sub> CH <sub>3</sub>	84
5	1e		3-F	CH <sub>2</sub> CH <sub>3</sub>	86
6	1f		4-F	CH <sub>2</sub> CH <sub>3</sub>	90
7	1g		3-NO <sub>2</sub>	CH <sub>2</sub> CH <sub>3</sub>	70
8	1h		4-NO <sub>2</sub>	CH <sub>2</sub> CH <sub>3</sub>	80
9	1i		4-CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH <sub>3</sub>	70
10	1j		3-NO <sub>2</sub>	CH <sub>3</sub>	86
11	1k		4-NO <sub>2</sub>	CH <sub>3</sub>	90

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.01, 23.04, 58.50, 62.89, 104.11, 113.32, 128.81, 129.04, 129.27, 129.49, 130.69, 130.93, 131.48, 168.81. GC-MS: *m/z* 334 [M+H]<sup>+</sup>.

#### 5-(2-Fluoro-phenyl)-7-methyl-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid ethyl ester (1d)

Yellow solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.10 (t, 3H, CH<sub>3</sub>, *J* = 7.2 Hz), 2.50 (s, 3H, Ar-CH<sub>3</sub>), 4.02 (m, 2H, CH<sub>2</sub>), 6.29 (d, 1H, Ar-H, *J* = 4.8 Hz), 6.60 (s, 1H, Ar-H), 6.71 (d, 1H, Ar-H, *J* = 4.8 Hz), 7.01–7.44 (m, 4H, Ph-H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.03, 23.43, 52.76, 59.67, 97.62, 105.90, 115.11, 115.33, 125.15, 126.41, 129.59, 130.38, 157.31, 159.85, 164.93, 166.10. GC-MS:  $m/z$  318  $[\text{M}+\text{H}]^+$ .

**5-(3-Fluoro-phenyl)-7-methyl-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid ethyl ester (1e)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.19 (t, 3H,  $\text{CH}_3$ ,  $J = 7.1$  Hz), 2.45 (s, 3H, Ar- $\text{CH}_3$ ), 4.09 (m, 2H,  $\text{CH}_2$ ), 6.19 (s, 1H, Ar-H), 6.34 (d, 1H, Ar-H,  $J = 4.8$  Hz), 6.58 (d, 1H, Ar-H,  $J = 4.8$  Hz), 6.97 (t, 1H, Ph-H,  $J = 8.4$  Hz), 7.05 (d, 1H, Ph-H,  $J = 9.4$  Hz), 7.13 (d, 1H, Ph-H,  $J = 7.8$  Hz), 7.27 (s, 1H, Ph-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.25, 23.74, 59.97, 60.22, 99.42, 106.70, 114.00, 115.66, 122.50, 126.48, 130.51, 130.90, 144.90, 161.81, 164.27, 166.22. GC-MS:  $m/z$  318  $[\text{M}+\text{H}]^+$ .

**5-(4-Fluoro-phenyl)-7-methyl-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid ethyl ester (1f)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.17 (t, 3H,  $\text{CH}_3$ ,  $J = 7.2$  Hz), 2.44 (s, 3H, Ar- $\text{CH}_3$ ), 4.07 (m, 2H,  $\text{CH}_2$ ), 6.17 (s, 1H, Ar-H), 6.29 (d, 1H, Ar-H,  $J = 4.7$  Hz), 6.50 (d, 2H, Ph-H,  $J = 3.7$  Hz), 6.54 (d, 1H, Ar-H,  $J = 4.7$  Hz), 7.06 (d, 2H, Ph-H,  $J = 3.7$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.25, 23.74, 59.84, 99.54, 105.79, 108.39, 115.61, 115.83, 126.47, 128.66, 138.58, 156.15, 166.58, 168.59. GC-MS:  $m/z$  318  $[\text{M}+\text{H}]^+$ .

**7-Methyl-5-(3-nitro-phenyl)-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid ethyl ester (1g)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.21 (t, 3H,  $\text{CH}_3$ ,  $J = 7.1$  Hz), 2.47 (s, 3H, Ar- $\text{CH}_3$ ), 4.10 (m, 2H,  $\text{CH}_2$ ), 6.34 (s, 1H, Ar-H), 6.40 (d, 1H, Ar-H,  $J = 4.8$  Hz), 6.59 (d, 1H, Ar-H,  $J = 4.8$  Hz), 7.53 (t, 1H, Ph-H,  $J = 7.9$  Hz), 7.70 (d, 1H, Ph-H,  $J = 7.7$  Hz), 8.15 (d, 1H, Ph-H,  $J = 8.2$  Hz), 8.19 (s, 1H, Ph-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.25, 23.24, 60.10, 60.20, 99.17, 107.54, 121.73, 123.65, 126.20, 130.30, 133.02, 144.38, 148.37, 155.55, 164.69, 165.92. GC-MS:  $m/z$  345  $[\text{M}+\text{H}]^+$ .

**7-Methyl-5-(4-nitro-phenyl)-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid ethyl ester (1h)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.21 (t, 3H,  $\text{CH}_3$ ,  $J = 7.1$  Hz), 2.45 (s, 3H, Ar- $\text{CH}_3$ ), 4.10 (m, 2H,  $\text{CH}_2$ ), 6.31 (s, 1H, Ar-H), 6.37 (d, 1H, Ar-H,  $J = 4.8$  Hz), 6.55 (d, 1H, Ar-H,  $J = 4.8$  Hz), 7.53 (d, 2H, Ph-H,  $J = 8.7$  Hz), 8.19 (d, 2H, Ph-H,  $J = 8.7$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.32, 23.75, 59.97, 60.12, 99.04, 106.73, 124.25, 126.09, 127.79, 147.95, 149.10, 156.51, 165.19, 166.23. GC-MS:  $m/z$  345  $[\text{M}+\text{H}]^+$ .

**5-(4-Isopropyl-phenyl)-7-methyl-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid ethyl ester (1i)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.18 (t, 3H,  $\text{CH}_3$ ,  $J = 7.1$  Hz), 1.21 (d, 6H, 2( $\text{CH}_3$ ),  $J = 6.9$  Hz), 2.45 (s,

3H, Ar- $\text{CH}_3$ ), 2.86 (m, 1H, CH), 4.07 (m, 2H,  $\text{CH}_2$ ), 6.16 (s, 1H, Ar-H), 6.32 (d, 1H, Ar-H,  $J = 4.7$  Hz), 6.60 (d, 1H, Ar-H,  $J = 4.7$  Hz), 7.16 (d, 2H, Ph-H,  $J = 8.1$  Hz), 7.26 (d, 2H, Ph-H,  $J = 4.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.17, 23.81, 29.70, 33.81, 60.24, 60.83, 97.35, 100.73, 126.90, 127.02, 127.14, 128.81, 149.89, 157.57, 163.27, 165.73. GC-MS:  $m/z$  342  $[\text{M}+\text{H}]^+$ .

**7-Methyl-5-(3-nitro-phenyl)-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid methyl ester (1j)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.47 (s, 3H, Ar- $\text{CH}_3$ ), 3.65 (s, 3H, O- $\text{CH}_3$ ), 6.34 (s, 1H, Ar-H), 6.43 (d, 1H, Ar-H,  $J = 4.8$  Hz), 6.62 (d, 1H, Ar-H,  $J = 4.8$  Hz), 7.27 (s, 1H, Ph-H), 7.53 (t, 1H, Ph-H,  $J = 7.8$  Hz), 7.70 (d, 1H, Ph-H,  $J = 7.6$  Hz), 8.18 (d, 1H, Ph-H,  $J = 4.9$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.63, 51.19, 60.00, 98.82, 107.08, 121.59, 123.61, 126.14, 130.24, 132.94, 144.47, 148.46, 156.55, 165.09, 166.58. GC-MS:  $m/z$  331  $[\text{M}+\text{H}]^+$ .

**7-Methyl-5-(4-nitro-phenyl)-5H thiazolo[3,2-a]pyrimidine-6 carboxylic acid methyl ester (1k)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.45 (s, 3H, Ar- $\text{CH}_3$ ), 3.65 (s, 3H,  $\text{CH}_3$ ), 6.32 (s, 1H, Ar-H), 6.41 (d, 1H, Ar-H,  $J = 4.8$  Hz), 6.57 (d, 1H, Ar-H,  $J = 4.8$  Hz), 7.52 (d, 2H, Ph-H,  $J = 8.6$  Hz), 8.19 (d, 2H, Ph-H,  $J = 8.6$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.73, 51.20, 59.92, 98.83, 106.95, 124.30, 126.12, 127.72, 147.91, 148.96, 156.59, 165.25, 166.67. GC-MS:  $m/z$  331  $[\text{M}+\text{H}]^+$ .

**2-[(2-Amino-thiazol-3-yl)-(4-chloro phenyl)-methyl]-3-oxo-butiric acid ethyl ester (1l)**

Yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.15 (m, 3H,  $\text{CH}_3$ ), 1.93 (s, 2H,  $\text{NH}_2$ ), 2.25 (d, 3H,  $\text{COCH}_3$ ,  $J = 13.1$  Hz), 3.98 (d, 1H, CH,  $J = 5.7$  Hz), 4.11 (m, 2H,  $\text{CH}_2$ ), 5.45 (dd, 1H, CHN,  $J_{ab} = 5.6$  Hz,  $J_{xy} = 7.1$  Hz), 6.48 (d, 1H, CHS,  $J = 3.6$  Hz), 7.06 (d, 1H, CNH,  $J = 3.6$  Hz), 7.28 (s, 1H, CNH), 7.32 (d, 4H, Ph-H,  $J = 12.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.89, 29.36, 57.51, 58.56, 62.00, 64.66, 107.47, 128.21, 128.60, 128.91, 133.93, 166.56, 168.32, 200.41. GC-MS:  $m/z$  354  $[\text{M}+\text{H}]^+$ .

## RESULTS AND DISCUSSION

Initially, the preliminary screening to determine the optimized reaction condition was carried out by using benzaldehyde, 2-aminothiazole and ethyl acetoacetate as a model and was sonicated under various sets of conditions (Table 2). Based on the optimization study, it was found that the yield of **1a** reached a plateau at the 51 W power and recorded a 90% yield after the reaction was sonicated for 10 min. This optimized reaction condition was employed for the synthesis of other

**Table 2.** The ultrasound yields of **1a** under solvent and catalyst free conditions

Entry	Power (W)	Time (min)	Yield <sup>a</sup> (%)
1	48	5	83
2	49	5	83
3	50	5	83
4	51	5	87
5	51	10	90
6	51	20	90
7	52	25	90
8	53	30	90
9	54	25	90
10	55	20	90

<sup>a</sup>Isolated yield.**Table 3.** The yield of **1a** under ultrasonic bath irradiation and silent condition

Time	Yield <sup>a</sup> (%)	
	Sonication	Conventional
10 min	0	-
20 min	0	-
30 min	8	-
2.5 h	-	20
5.0 h	-	50

<sup>a</sup>Isolated yield.

thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives and for other comparative study.

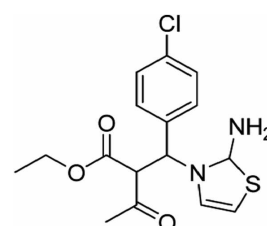
Next, the effectiveness of ultrasonic probe irradiation was evaluated with ultrasonic bath irradiation and conventional heating methods, using **1a** as a model (*Table 3*). No reaction occurred when the synthesis of **1a** was performed using an ultrasonic bath method for 20 min at constant room temperature, whereas only less than 10% yield was isolated if the reaction proceeded until 30 min. Although great disruption was generated in the micro media of the ultrasonic bath environment, the amount of heat produced was insufficient to drive the reaction forward. Thus, a lower yield was recorded under the ultrasound bath method. In contrast, under conventional heating method using methanol as the solvent, only 50% yield of **1a** was recorded when the reaction proceeded for 5 h. Hence, it was apparent that the ultrasound probe irradiation gave the best yield in a shorter reaction time, which was 10 min as compared to the ultrasound bath and conventional heating methods.

To demonstrate the applicability of this procedure and to widen the scope of our study, different substituted benzaldehydes were selected to synthesise a series of thiazolo [3,2-a]pyrimidine-6-carboxylate derivatives. *Table 1* sum-

marised the yields of different thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives under the ultrasound probe irradiation. The condensation of various substituted benzaldehydes, 2-aminothiazole and ethyl acetoacetate proceeded smoothly to afford the designated compounds **1a-1k** in good to excellent yields (70–90%) within 10 min under solvent- and catalyst-free ultrasonic probe irradiation at room temperature. In this procedure, the microenvironment of the reaction without solvents creates a high concentration of local reaction sites, which led to enhanced global efficiency.<sup>18</sup>

As shown in *Table 1*, the activity of benzaldehyde bearing electron-withdrawing groups was higher than that of electron-donating group (*Table 1*, entries 2, 3 vs 9). The obtained results is in agreement with the literature reported by Wang et al., 2008. The yields of the condensation reactions correlated with the position of the substituted benzaldehyde derivatives was also evaluated. Specifically, the yield of the benzaldehyde derivatives bearing electron-withdrawing groups at the para-position gave higher yields compared to that situated at the ortho- and meta- position (*Table 1*, entries 6 vs 4 and 5, 8 vs 7, 11 vs 10). In addition, the electronic effects of substituents such as -F, -Cl and -Br was found to affect the yields of the products. It was found that the benzaldehyde bearing high electronegative substituent gave a higher yield (*Table 1*, 90% vs 75% vs 72%, entries 6 vs 3 vs 2). We have examined the synthesis of thiazolo pyrimidine using methyl acetoacetate (*Table 1*, entries 10 and 11). The reactions gave higher yields of corresponding products in comparison to the reaction with ethyl acetoacetate (*Table 1*, entries 7 and 8). Under the improved protocol, all the thiazolo pyrimidine derivatives were synthesized in one-step, produces higher yield and requires shorter reaction time, which was found to be more superior than the previous reported method.<sup>20</sup>

The only limitation to this procedure was the accompanying side products that was isolated together with the designated compounds (**1a-1k**) when purification work was carried out using column chromatography. The side products of these reactions had a yield in the range from 10 to 20%. *Figure 1* shows one of the side product (**11**) that

**Figure 1.** The minor product **11** produced in this procedure.

belonged to the reaction of 1c, which had been isolated and characterized to identify the structure. This side product were hypothesized to be produced by the incomplete conversion of the MCRs' product during the ultrasound reaction, in which we believed that it might be the intermediate product of Knoevenagel reaction of the reactants. The details of the spectral data is included in the experimental section.

## CONCLUSION

In conclusion, we have demonstrated a convenient, enhanced reaction rate and improved protocol for the preparation of thiazolo[3,2-a]pyrimidine carboxylate derivatives. The present procedure carried out under solvent- and catalyst-free ultrasound probe irradiation has led to higher yields in shorter reaction time and was found to be more efficient than the conventional heating and the ultrasound bath methods for the multicomponent condensation reaction of thiazolo[3,2-a]pyrimidines-6-carboxylate derivatives.

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