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# Novel one-pot three-step reaction using supported reagents system: synthesis of 2-aminothiazoles

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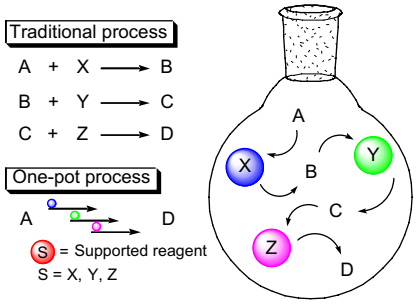
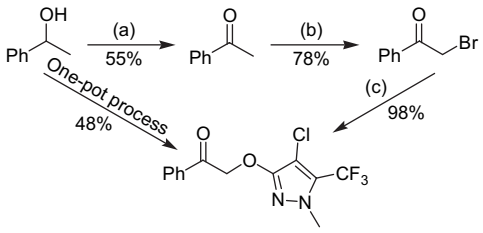
**Abstract**—One-pot tandem three-step reaction has been developed by using supported reagents system. The synthesis of 2-aminothiazoles was selected for confirming the effectiveness of the method using supported reagents system. One-pot three-step reaction effectively proceeded, and the yield of the products is higher than that in step-wise process.


## 1. Introduction

One-pot synthesis, which can carry out multi-step reactions or multiple reactions in one-pot, is very attractive in organic synthesis. In traditional process, the reaction and the isolation of products have to be carried out more than once to synthesize the target compounds. One-pot process, however, can provide the target compounds in not only a single operation and with low cost but also in high total yield. Much effort has been devoted to the development of one-pot reaction processes. One-pot synthesis using inorganic solid-supported reagents is unique because, if three kinds of inorganic solid-supported reagents are used in one-pot, three different reaction stages are able to exist separately in the same vessel.[1] Thus, synthesis of a compound which is prepared step-wise in homogeneous solution could be possible in one-pot if each step in the multi-step reaction can be achieved using inorganic solid-supported reagents (Scheme 1). We have demonstrated the possibility of two-step reactions in one-pot by using a couple of supported reagents, e.g., $ZnCl_2/SiO_2$–$K_2CO_3/Al_2O_3$,[2] $CuBr_2/Al_2O_3$–$KSCN/SiO_2$,[3] $KSCN/SiO_2$–$RNH_3OAc/Al_2O_3$,[4,5] $CuBr_2/Al_2O_3$–$Na_2CO_3/Al_2O_3$,[1] and $Na_2CO_3/SiO_2$–$PPA/SiO_2$.[6,7] If these reagents are not supported on inorganic solids, these reagents react with each other rapidly in solution. Therefore, two-step reaction in one-pot is impossible. In these reports, we realized the possibility of one-pot three-step reaction.[1] One-pot three-step reaction, however, could not proceed in excellent yield. Thus, our efforts were devoted to the development of one-pot three-step reaction which affords products in excellent yields. One-pot three-step reaction using inorganic supported reagents has not been reported. Similar reaction using polymer supported reagents, however, has been reported by Parlow.[8] The desired product was prepared as showed in Scheme 2. But this method could not be extended to the analog synthesis. In this paper, we describe one-pot three-step reactions which constitute a novel method for organic




**Scheme 1**. One-pot multi-step synthesis using supported reagents system.




**Scheme 2**. (a) Poly(4-vinylpyridinium dichromate) in cyclohexane at 60 °C for 12 h. (b) Perbromide on Amberlyst® A-26 in cyclohexane at 65 °C for 12 h. (c) Amberlite® IRA-900(4-chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-ol) in cyclohexane at 65 °C for 12 h.

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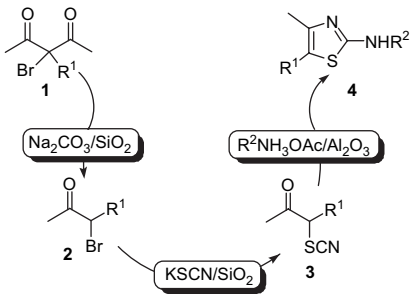


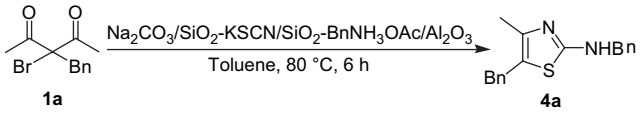

**Scheme 3**.

synthesis. The synthesis of 2-aminothiazoles was selected for confirming the effectiveness of one-pot three-step reaction (Scheme 3). Thiazoles are very useful compounds in medicinal, drug, and agricultural chemistry. For example, aminothiazole ring system is a useful structural element in medicinal chemistry and has found broad application in drug development for the treatment of allergies,[9] hypertension,[10] inflammation,[11] bacterial infection,[12] and HIV.[13]

## 2. Results and discussion

A mixture of 3-benzyl-3-bromopentane-2,4-dione (**1a**: 1 mmol), $Na_2CO_3/SiO_2$ (3 mmol), $KSCN/SiO_2$ (5 mmol), and $BnNH_3OAc/Al_2O_3$ (6 mmol) in toluene was stirred at 80 °C for 6 h to give 2-benzylamino-5-benzyl-4-methylthiazole (**4a**) in 54% yield (Scheme 4). We carried out the three reactions, respectively, using inorganic supported reagents in order to confirm the effectiveness of one-pot reaction. Deacetylation reaction of 2-bromo-1,3-diketones with $Na_2CO_3/SiO_2$ gave α-bromo ketone (**2a**) in 91% yield. Then the product was converted to α-thiocyanato ketone (**3a**) quantitatively by treating with $KSCN/SiO_2$. Cyclization–amination of **3a** with $BnNH_3OAc/Al_2O_3$ gave very low yield of corresponding thiazole (15%). In our previous report,[14] we found that the amination process successfully proceeds in the presence of a large excess of ammonium salt ($RNH_3OAc$). In one-pot process, α-thiocyanato ketone, generated from α-bromo ketone and $KSCN/SiO_2$, reacts immediately with $RNH_3OAc/Al_2O_3$ because large excess of $RNH_3OAc$ to α-thiocyanato ketone is always present. Therefore, the yield in one-pot three-step synthesis is higher than that in step-wise process. We also carried out the reaction of **2a** with $KSCN/SiO_2$–$BnNH_3OAc/Al_2O_3$; **4a** was afforded in 62% yield. The total yield of **4a** from **1a** using $KSCN/SiO_2$–$BnNH_3OAc/Al_2O_3$ pathway was comparable to the yield in one-pot three-step synthesis.

**Table 1**. Preparation of 2-benzylamino-4-methyl-5-phenylthiazoles

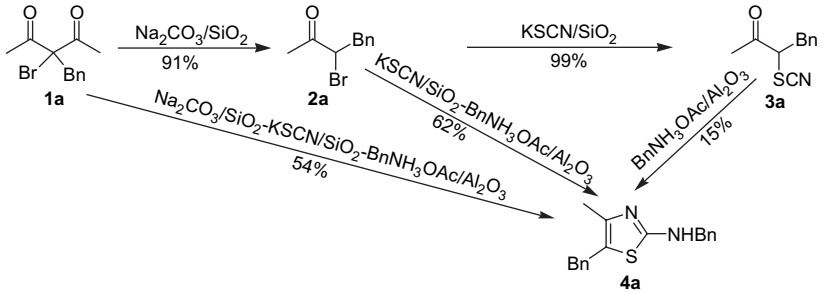



| Entry | $Na_2CO_3/SiO_2$ (mmol) | $KSCN/SiO_2$ (mmol) | $BnNH_3OAc/Al_2O_3$ (mmol) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | 3.00 | 5.00 | 6.00 | 54 |
| 2 | 2.25 | 5.00 | 6.00 | 74 |
| 3 | 1.50 | 5.00 | 6.00 | 50 |
| 4 | 2.25 | 5.00 | 6.00 | 44 |
| 5 | 2.25 | 5.00 | 6.00 | 55 |

[a] Isolated yield.

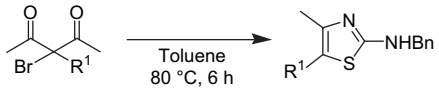
In order to determine the optimum conditions for the synthesis of 2-aminothiazoles in high yields, molar ratios of reagents were investigated (Table 1). Steps of thiocyanation and cyclization–amination reactions have been optimized in our previous report.[14] In the synthesis of **4a**, when 2.25 mmol of $Na_2CO_3/SiO_2$ was used against 1 mmol of **1a**, **4a** was afforded in 74% yield. The use of reduced amount of $Na_2CO_3/SiO_2$ led to a decrease of a yield of **4a**. When a reaction time was prolonged **4a** was given in low yield. When alumina was used as support instead of silica gel, the yield of **4a** was 40%. This result is due to the adsorption of products onto alumina. Thus, we decided to use 2.25 mmol of $Na_2CO_3/SiO_2$, 5.00 mmol of $KSCN/SiO_2$, and 6.00 mmol of $RNH_3OAc/Al_2O_3$ against 1 mmol of 3-alkyl-3-bromopentane-2,4-diones (**1**) for subsequent reactions.

A series of compounds **1** (**b**–**j**) were allowed to react under the optimized conditions (Table 2). When benzylic group in starting diketones has methyl group and chlorine at *para*-position, the yields of products were comparable to the yield of **4a** (entries 3 and 4). Diketones having ester group did not undergo hydrolysis by $Na_2CO_3/SiO_2$. Therefore, desired product **4f** was obtained in good yield. When a diketone which has bromine at the end of alkyl chain instead of ester group was used, desired product (**4g**) and by-product (**4g′**) were obtained in 23% and 42% yields, respectively (entry 6). This reaction was carried out with various amounts of $KSCN/SiO_2$ in order to synthesize selectively **4g** or **4g′**, but selective synthesis could not be achieved. For instance, the use of a small amount of $KSCN/SiO_2$ caused a low yield, and a rate of **4g** did not increase. The yield of the thiazoles decreased with the increase of the length of alkyl substituents at α-position in the starting




**Scheme 4**.

**Table 2**. Preparation of **4** from various 2-bromo-1,3-diketones[a]




| Entry | $R^1$ | Product | Yield[b] (%) |
|---|---|---|---|
| 1 | $C_6H_5$– | **4b** | 60 |
| 2 | $C_6H_5(CH_2)_2$– | **4c** | 49 |
| 3 | 4-$CH_3C_6H_4CH_2$– | **4d** | 75 |
| 4 | 4-$ClC_6H_4CH_2$– | **4e** | 64 |
| 5 | $CH_3CH_2OCO(CH_2)_3$– | **4f** | 76 |
| 6 | $Br(CH_2)_5$– | **4g** | 23 (42)[c] |
| 7 | *n*-$C_8H_{17}$– | **4h** | 48 |
| 8 | *n*-$C_{10}H_{21}$– | **4i** | 33 |
| 9 | *n*-$C_{20}H_{41}$– | **4j** | N.D. |

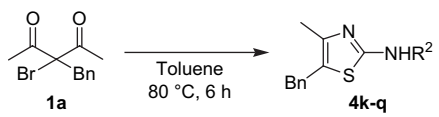
[a] All reactions were carried out using **1** (1 mmol), $Na_2CO_3/SiO_2$ (2.25 mmol), $KSCN/SiO_2$ (5 mmol), and $NH_4OAc/Al_2O_3$ (6 mmol).
[b] Isolated yield.
[c] The figure in parentheses indicates the yield of **4g′** [$R^1$=$NCS(CH_2)_5$–].

diketones. The diketone which has octyl group at α-position gave the desired product in 48% yield, whereas the one having decyl group afforded the desired product in 33% yield. When the diketone having icosyl group was used, no thiazole was yielded and a small amount of thiocyanate was detected (**3j**) (entries 7–9).

A variety of alumina supported alkyl ammonium salts were used for the reaction with **1a** (Table 3). Each of alkyl amines afforded the corresponding thiazole in moderate yields. The successful use of allylamine and ethanolamine indicates that this procedure is unaffected by the presence of a functional group such as a C–C double bond and a hydroxy group in an amine (entries 6 and 7).

In conclusion, we demonstrated a possibility of one-pot three-step reaction using inorganic supported reagents system. Notable advantages are as follows: this one-pot method provides highly efficient synthesis of 2-aminothiazoles than that of step-wise method, and all of three reagents were uneventfully removed from crude products by simple filtration. Moreover, this method is applicable for many analogs. Other one-pot multi-step chemical transformations using this concept are now under investigations.

**Table 3**. Preparation of **4** using various alumina supported alkyl ammonium salt[a]




| Entry | $R^2$ | Product | Yield[b] (%) |
|---|---|---|---|
| 1 | *n*-$C_4H_9$– | **4k** | 50 |
| 2 | *iso*-$C_4H_9$– | **4l** | 65 |
| 3 | *n*-$C_{10}H_{21}$– | **4m** | 51 |
| 4 | *cyclo*-$C_6H_{11}$– | **4n** | 43 |
| 5 | $C_6H_5(CH_2)_2$– | **4o** | 54 |
| 6 | $CH_2$=CH–$CH_2$– | **4p** | 43 |
| 7 | $HO(CH_2)_2$– | **4q** | 38 |

[a] All reactions were carried out using **1a** (1 mmol), $Na_2CO_3/SiO_2$ (2.25 mmol), $KSCN/SiO_2$ (5 mmol), and $NH_4OAc/Al_2O_3$ (6 mmol).
[b] Isolated yield.

## 3. Experimental

### 3.1. General

Melting points were determined on Yanako Micro melting point apparatus or were uncorrected. Elemental analysis was performed on a Yanako CHN corder MT-5. NMR spectra were recorded on a JEOL JNM-GX400 spectrometer. Tetramethylsilane ($\delta$=0) was used as an internal standard for $^1$H NMR. Mass analysis was performed on an Agilent G1969 LC/MDS TOF. IR spectra were recorded on a Thermo Electron Nicolet 380 spectrometer.

**3.1.1. Preparation of $Na_2CO_3/SiO_2$.** Silica gel [Wakogel C-200 (Wako Pure Chemical Ind. LTD.), 16.82 g] was added to a solution of sodium carbonate (30 mmol, 3.18 g) in distilled water, and the mixture was stirred at room temperature for 0.5 h. The water was removed by rotary evaporator under reduced pressure below 60 °C, and the resulting reagent was dried in vacuo (10 mmHg) at room temperature for 5 h.

**3.1.2. Preparation of $KSCN/SiO_2$.** Silica gel [Wakogel C-200 (Wako Pure Chemical Ind. LTD.), 25.70 g] was added to a solution of potassium thiocyanate (250 mmol, 24.3 g) in distilled water, and the mixture was stirred at room temperature for 0.5 h. The water was removed by rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at 150 °C for 2 h.

**3.1.3. Preparation of $NH_4OAc/Al_2O_3$.** Alumina (ICN Biomedical N-Super 1, 9.23 g) was added to a solution of ammonium acetate (10 mmol, 0.77 g) in methanol, and the mixture was stirred at room temperature for 0.5 h. The methanol was removed by rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at room temperature for 2 h.

### 3.2. Typical procedure for the preparation of 2-aminothiazoles

A mixture of 3-alkyl-3-bromopentane-2,4-diones (1 mmol), $Na_2CO_3/SiO_2$ (2.25 mmol), $KSCN/SiO_2$ (5 mmol), and $RNH_3OAc/Al_2O_3$ (6 mmol) was stirred in toluene (15 mL) at 80 °C for 6 h, and then the used supported reagents were removed by filtration. The filtrate was evaporated to leave crude product, which was purified by column chromatography.

**3.2.1. 2-Benzylamino-5-benzyl-4-methylthiazole (4a).** Mp 134 °C (hexane/ethyl acetate). Anal. Calcd for $C_{18}H_{18}N_2S$: C, 73.43; H, 6.16; N, 9.51. Found: C, 73.34; H, 6.19; N, 9.21. HRMS (TOF-CI) calcd for $C_{18}H_{19}N_2S$ ($MH^+$): 295.1269. Found: 295.1268. IR (neat): 3151, 3064, 3025, 2919, 1572, 1452, 1292, 763, 697 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO): $\delta$ 2.08 (3H, s), 3.84 (2H, s), 4.34 (2H, d, $J$=5.8 Hz), 7.15–7.32 (10H, m), 7.73 (1H, t, $J$=5.8 Hz).

**3.2.2. 2-Benzylamino-4-methyl-5-phenylthiazole (4b).** Mp 153–154 °C (hexane/ethyl acetate). Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.64; H, 5.46; N, 9.86. HRMS (TOF-CI) calcd for $C_{17}H_{17}N_2S$ ($MH^+$): 281.1112. Found: 281.1112. IR (neat): 3198, 3060, 3026, 2934, 1589, 1465, 1355, 1301, 761, 702 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.27 (3H, s), 4.48 (2H, s), 6.28 (1H, s), 7.21–7.40 (10H, m).

**3.2.3. 2-Benzylamino-4-methyl-5-phenethylthiazole (4c).** Mp 99–100 °C (hexane/ethyl acetate). HRMS (TOF-CI) calcd for $C_{19}H_{21}N_2S$ ($MH^+$): 309.1425. Found: 309.1434. IR (neat): 3200, 3065, 3025, 2896, 1593, 1494, 1452, 1299, 744, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.97 (3H, s), 2.78–2.88 (4H, m), 4.41 (2H, s), 5.48 (1H, s), 7.13–7.36 (10H, m).

**3.2.4. 2-Benzylamino-4-methyl-5-(4-methylbenzyl)thiazole (4d).** Mp 157–158 °C (hexane/ethyl acetate). Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 73.90; H, 6.67; N, 8.99. HRMS (TOF-CI) calcd for $C_{19}H_{21}N_2S$ ($MH^+$): 309.1425. Found: 309.1426. IR (neat): 3151, 3062, 3029, 2917, 1571, 1512, 1451, 1293, 718, 696 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.18 (3H, s), 2.31 (3H, s), 3.86 (2H, s), 4.38 (2H, s), 5.50 (1H, s), 7.05–7.11 (4H, m), 7.26–7.36 (5H, m).

**3.2.5. 2-Benzylamino-5-(4-chlorobenzyl)-4-methylthiazole (4e).** Mp 151–152 °C (hexane/ethyl acetate). HRMS (TOF-CI) calcd for $C_{18}H_{18}ClN_2S$ ($MH^+$): 329.0879. Found: 329.0884. IR (neat): 3150, 3061, 3023, 2915, 1572, 1489, 1466, 1295, 729, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.16 (3H, s), 3.86 (2H, s), 4.39 (2H, s), 5.59 (1H, s), 7.10 (2H, d, $J$=8.3 Hz), 7.25 (2H, d, $J$=8.0 Hz), 7.27–7.34 (5H, m).

**3.2.6. 2-Benzylamino-5-(4-ethoxy-4-oxobutyl)-4-methylthiazole (4f).** HRMS (TOF-CI) calcd for $C_{17}H_{23}N_2O_2S$ ($MH^+$): 319.1480. Found: 319.1486. IR (neat): 3326, 3030, 2979, 172, 1548, 1479, 1453, 1300, 701 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.24 (3H, t, $J$=7.2 Hz), 1.83 (2H, quint, $J$=7.4 Hz), 2.05 (3H, s), 2.30 (2H, t, $J$=7.4 Hz), 2.59(2H, t, $J$=7.4 Hz), 4.11 (2H, q, $J$=7.2 Hz), 4.40 (2H, s), 6.32 (1H, s), 7.25–7.34 (5H, m).

**3.2.7. 2-Benzylamino-5-(5-bromopentyl)-4-methylthiazole (4g).** HRMS (TOF-CI) calcd for $C_{16}H_{22}BrN_2S$ ($MH^+$): 353.0687. Found: 353.0692. IR (neat): 3204, 2932, 2153, 1699, 1590, 1454, 1358, 1275, 731, 701 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.43–1.57 (4H, m), 1.86 (2H, quint, $J$=6.9 Hz), 2.08 (3H, s), 2.56 (2H, t, $J$=7.3 Hz), 3.39 (2H, t, $J$=6.9 Hz), 4.41 (2H, s), 5.93 (1H, br s), 7.27–7.37 (5H, m).

**3.2.8. 2-Benzylamino-4-methyl-5-(5-thiocyanatopentyl)thiazole (4g′).** Mp 87–88 °C (hexane/ethyl acetate). Anal. Calcd for $C_{17}H_{21}N_3S_2$: C, 61.59; H, 6.39; N, 12.68. Found: C, 61.41; H, 6.18; N, 12.46. HRMS (TOF-CI) calcd for $C_{17}H_{22}N_3S_2$ ($MH^+$): 332.1255. Found: 332.1252. IR (neat): 3198, 3096, 3028, 2917, 2149, 1594, 1466, 1455, 1304, 753, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.44–1.61 (4H, m), 1.83 (2H, quint, $J$=7.3 Hz), 2.10 (3H, s), 2.58 (2H, t, $J$=7.3 Hz), 2.92 (2H, t, $J$=7.3 Hz), 4.42 (2H, s), 5.75 (1H, s), 7.27–7.37 (5H, m).

**3.2.9. 2-Benzylamino-4-methyl-5-octylthiazole (4h).** Mp 63–64 °C (hexane/ethyl acetate). HRMS (TOF-CI) calcd for $C_{19}H_{29}N_2S$ ($MH^+$): 317.2051. Found: 317.2048. IR (neat): 3204, 3103, 3028, 2915, 1593, 1465, 1454, 1301, 719, 696 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.88 (3H, t, $J$=6.8 Hz), 1.26–1.30 (10H, m), 1.50 (2H, quint, $J$=7.3 Hz), 2.08 (3H, s), 2.53 (2H, t, $J$=7.3 Hz), 4.41 (2H, s), 5.87 (1H, s), 7.26–7.37 (5H, m).

**3.2.10. 2-Benzylamino-5-decyl-4-methylthiazole (4i).** Mp 70 °C (hexane/ethyl acetate). Anal. Calcd for $C_{21}H_{32}N_2S$: C, 73.20; H, 9.36; N, 8.13. Found: C, 72.99; H, 9.58; N, 8.10. HRMS (TOF-CI) calcd for $C_{21}H_{33}N_2S$ ($MH^+$): 345.2364. Found: 345.2368. IR (neat): 3205, 3104, 3068, 2917, 1594, 1466, 1454, 1300, 720, 695 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.88 (3H, t, $J$=6.8 Hz), 1.26–1.30 (14H, m), 1.51 (2H, quint, $J$=7.3 Hz), 2.11 (3H, s), 2.54 (2H, t, $J$=7.3 Hz), 4.42 (2H, s), 5.54 (1H, s), 7.27–7.38 (5H, m).

**3.2.11. 5-Benzyl-2-butylamino-4-methylthiazole (4k).** Mp 108–109 °C (hexane/ethyl acetate). Anal. Calcd for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.43; H, 5.70; N, 13.48. HRMS (TOF-CI) calcd for $C_{11}H_{13}N_2S$ ($MH^+$): 205.0799. Found: 205.0792. IR (neat): 3413, 3270, 3062, 1629, 1523, 1494, 1330, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.19 (3H, s), 3.90 (2H, s), 4.88 (2H, s), 7.17–7.31 (5H, m).

**3.2.12. 5-Benzyl-2-isobutylamino-4-methylthiazole (4l).** Mp 108 °C (hexane/ethyl acetate). Anal. Calcd for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76. Found: C, 69.31; H, 7.71; N, 10.68. HRMS (TOF-CI) calcd for $C_{15}H_{21}N_2S$ ($MH^+$): 261.1425. Found: 261.1426. IR (neat): 3205, 3106, 2948, 1592, 1470, 1453, 1330, 759, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.94 (6H, d, $J$=6.8 Hz), 1.81–1.94 (1H, m), 2.19 (3H, s), 2.97 (2H, d, $J$=6.8 Hz), 3.91 (2H, s), 5.33 (1H, s), 7.18–7.32 (5H, m).

**3.2.13. 5-Benzyl-2-decylamino-4-methylthiazole (4m).** Mp 62–63 °C (hexane/ethyl acetate). HRMS (TOF-CI) calcd for $C_{21}H_{33}N_2S$ ($MH^+$): 345.2364. Found: 345.2364. IR (neat): 3153, 3088, 2921, 1565, 1470, 1454, 1297, 761, 699 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.88 (3H, t, $J$=7.0 Hz), 1.25–1.35 (14H, m), 1.58 (2H, quint, $J$=7.0 Hz), 2.19 (3H, s), 3.14 (2H, t, $J$=7.0 Hz), 3.91 (2H, s), 5.08 (1H, s), 7.18–7.31 (5H, m).

**3.2.14. 5-Benzyl-2-cyclohexylamino-4-methylthiazole (4n).** HRMS (TOF-CI) calcd for $C_{16}H_{21}N_2S$ ($MH^+$): 273.1425. Found: 273.1433. IR (neat): 3183, 3064, 2953, 1552, 1452, 1301, 762, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.45–1.53 (2H, m), 1.54–1.63 (2H, m), 1.63–1.72 (2H, m), 1.94–2.03 (2H, m), 2.19 (3H, s), 3.69–3.75 (1H, m), 3.92 (2H, s), 4.91 (1H, s), 7.19–7.32 (5H, m).

**3.2.15. 5-Benzyl-2-phenethylamino-4-methylthiazole (4o).** Mp 139 °C (hexane/ethyl acetate). Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 73.99; H, 6.32; N, 9.17. HRMS (TOF-CI) calcd for $C_{19}H_{21}N_2S$ ($MH^+$): 309.1425. Found: 309.1424. IR (neat): 3096, 3082, 3060, 1590, 1492, 746, 695 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.19 (3H, s), 2.90 (2H, t, $J$=6.8 Hz), 3.44 (2H, t, $J$=6.8 Hz), 3.91 (2H, s), 5.01 (1H, s), 7.18–7.31 (10H, m).

**3.2.16. 2-Allylamino-5-benzyl-4-methylthiazole (4p).** Mp 111–112 °C (hexane/ethyl acetate). Anal. Calcd for

$C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46. Found: C, 68.82; H, 6.58; N, 11.41. HRMS (TOF-CI) calcd for $C_{14}H_{17}N_2S$ ($MH^+$): 245.1112. Found: 245.1110. IR (neat): 3194, 3085, 3062, 2906, 1581, 1469, 1455, 1342, 972, 918, 700 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.19 (3H, s), 3.81 (2H, d, $J$=5.6 Hz), 3.91 (2H, s), 5.16 (1H, dd, $J$=10.5, 1.5 Hz), 5.27 (1H, dd, $J$=17.1, 1.5 Hz), 5.59 (1H, s), 5.84–5.93 (1H, m), 7.18–7.31 (5H, m).

**3.2.17. 2-(2-Hydroxyethyl)amino-5-benzyl-4-methylthiazole (4q).** HRMS (TOF-CI) calcd for $C_{13}H_{17}N_2OS$ ($MH^+$): 249.1061. Found: 249.1070. IR (neat): 3187, 3061, 3028, 2923, 1656, 1494, 1454, 1273, 1075, 701 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO): $\delta$ 2.10 (3H, s), 3.24 (2H, q, $J$=5.6 Hz), 3.53 (2H, t, $J$=5.6 Hz), 3.85 (2H, s), 4.80 (1H, s), 7.16–7.20 (3H, m), 7.26–7.29 (2H, m), 7.28 (1H, t, $J$=5.6 Hz).

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