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Graphical Abstract

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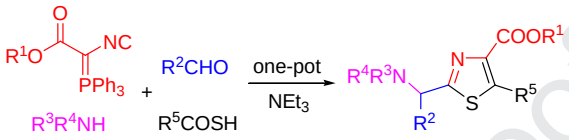

One-Pot Four-Component Synthesis of Polysubstituted Thiazoles via Cascade Ugi/Wittig Cyclization Starting from Odorless Isocyano(triphenylphosphoranylidene)-acetates

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Abstract: A new one-pot four-component preparation of polysubstituted thiazoles by a cascade Ugi/Wittig cyclization has been developed. The four-component reactions of the odorless isocyano(triphenylphosphoranylidene)acetates **1**, aldehydes **2**, amines **3** and thiocarboxylic acids **4** produced 2,4,5-trisubstituted thiazoles **5** in moderate to good yields in the presence of triethylamine. The two-component reactions between isocyano(triphenylphosphoranylidene)acetates **1** and thiocarboxylic acids **4** in the presence of triethylamine provided the corresponding 4,5-disubstituted thiazoles **6** in good yields as well.

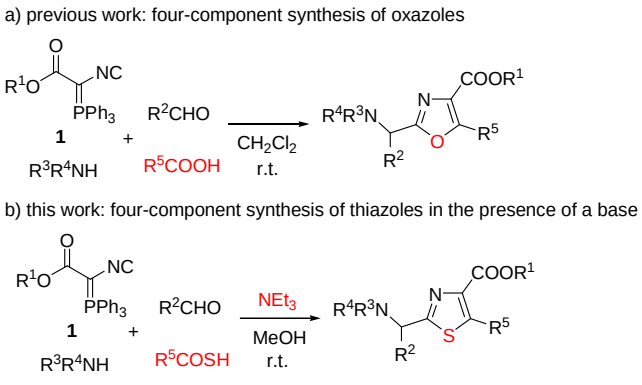
Key words: thiazole; Ugi reaction; Wittig reaction; isocyano(triphenylphosphoranylidene)acetate; thiocarboxylic acid

1. Introduction

Thiazoles are important heterocyclic compounds because they possess highly valuable skeletons widely found in many biologically active compounds and pharmaceuticals[1]. A number of thiazole derivatives have exhibited good biological activities, including antibacterial[2-3], antifungal[4], anticancer[5], antitumor[6-7] and anti-inflammatory activities[8]. Numerous synthetic methods to thiazoles have been developed[9-17]. For examples, some fully substituted thiazoles were prepared by copper-catalyzed

cyclization of α-imino-β-oxodithioesters with α-diazocarbonyls[9]. An efficient synthesis of 2,4,5-trisubstituted thiazoles was provided via the reactions of α-nitroepoxides with thioureas under mild conditions[10]. Recently Zhu and co-workers described a method to 2,4,5-trisubstituted thiazoles by one equivalent of thiocarboxylic acids and two equivalents of isocyanides under the presence of Yttrium Triflate[11]. However, these methods suffer from some drawbacks such as harsh reaction conditions, multistep synthesis and the use of the toxic transition-metal catalysts. Hence, the development of simple and convenient synthetic method to polysubstituted thiazoles is in growing demand for synthetic organic and pharmaceutical chemists.

Owing to their exceptional synthetic efficiency and high atom economy, isocyanide based multicomponent reactions (IMCRs) have attracted great attention in the synthesis of diverse compounds in the past decades[18]. Among the IMCRs, the Ugi reactions have drawn considerable interest in synthesis of organic molecules, especially heterocyclic compounds, under mild one-pot reaction conditions[19]. The Wittig reaction is also a powerful synthetic tool to construct carbon-carbon double bonds between phosphorus ylide and carbonyl compounds[20]. Recently, we have reported the synthesis of new stable Wittig reagent isocyano(triphenylphosphoranylidene)-acetates **1** and its application in one-step four-component preparation of oxazoles (Scheme 1a)[21]. Continuing our interests in synthesis of heterocycles via Ugi and Wittig reactions[22], herein we wish to report a new efficient synthesis of polysubstituted thiazoles by cascade Ugi/Wittig cyclization starting from odorless isocyano(triphenylphosphoranylidene)-acetates **1** by using thio S-acids instead of acids (Scheme 1b).



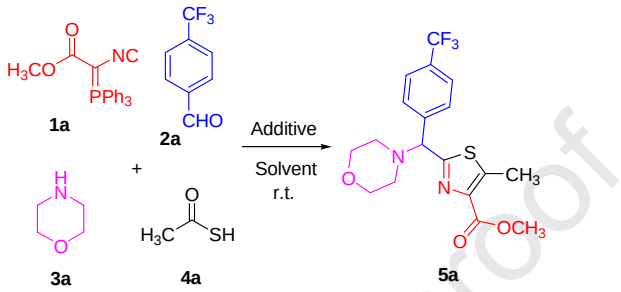
Scheme 1. One-step four-component synthesis of oxazoles and thiazoles

2. Results and discussion

Firstly, we chose the four-component reaction of isocyano(triphenylphosphoranylidene)acetate **1a**, 4-trifluorobenzaldehyde **2a**, diethylamine **3a**, and thioacetic acid **4a** as the model reaction to optimize the reaction condition (Table 1). Though four-component reaction of isocyano(triphenylphosphoranylidene)acetates **1**, aldehydes, amines and acids gave oxazoles successfully as we reported early[21], the using of thio S-acid instead of acid failed to produce the corresponding thiazole **5a** (Table 1, entry 1). We speculated that the thio S-acid was more acidic than the corresponding acid, which might result in the decomposition of isocyano(triphenylphosphoranylidene)acetate **1**. Then a base (NEt_3) was added to the reaction mixture to adjust the solution acidity. As NEt_3 (0.2 equiv) was added to the reaction system, we were pleased to find that the corresponding thiazole **5a** was produced in 27% yield (entry 2). Increasing of the amount of NEt_3 to 0.5 equiv promoted the yield to 58% (entry 3). When NEt_3 (1.0 equiv) was used, the best yield (90%) was obtained (entry 4). Further Increasing of the amount of NEt_3 to 2.0 equiv resulted in a relative lower yield (68%, entry 5). Changing of the solvent from MeOH to CH_2Cl_2, toluene, CH_3CN or DMF gave a relative lower or even no yield (0-71%, entry 6-9) as NEt_3 (1.0 equiv) was added. As CH_2Cl_2 was used as the solvent, the two component (between **1a** and

4a) product **6a** was also produced in minor amount (21% yield, entry 6). Finally, as the inorganic bases (Na_2CO_3, K_2CO_3, NaOH or KOH) were used, relative lower yields (54-78%, entry 10-13) were obtained. Therefore, the optimum reaction condition was identified (Table 1, entry 4).

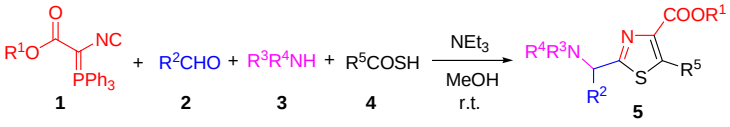
Table 1. Optimization of the Reaction Conditions[a]

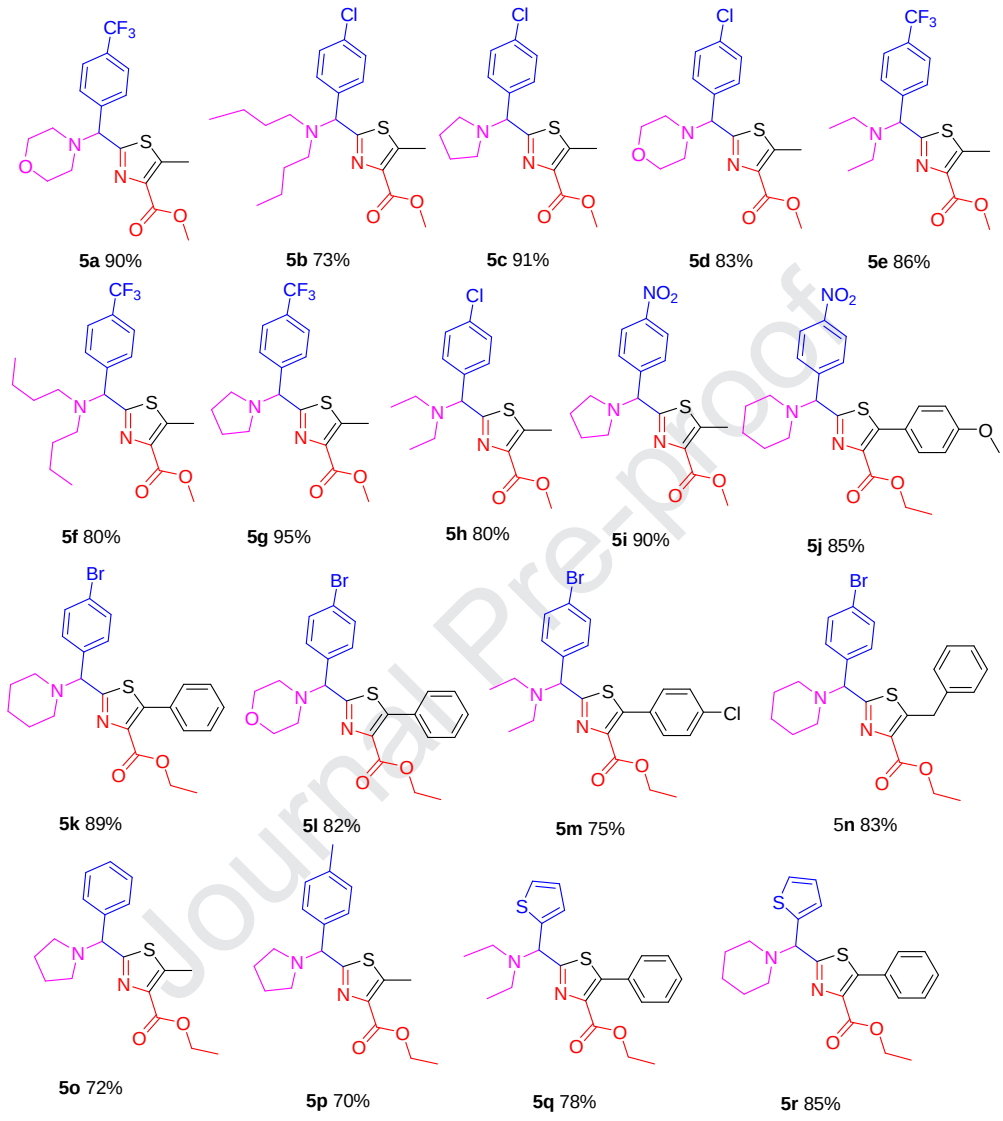


Entry	Solvent	Additive (equiv.)	Yield[b] (%)
1	MeOH	-	0
2	MeOH	NEt_3 (0.2)	27
3	MeOH	NEt_3 (0.5)	58
4	MeOH	NEt_3 (1.0)	90
5	MeOH	NEt_3 (2.0)	68
6	CH_2Cl_2	NEt_3 (1.0)	71(21)[c]
7	Toluene	NEt_3 (1.0)	0
8	CH_3CN	NEt_3 (1.0)	56
9	DMF	NEt_3 (1.0)	0
10	MeOH	Na_2CO_3 (1.0)	54
11	MeOH	K_2CO_3 (1.0)	58
12	MeOH	NaOH (1.0)	62
13	MeOH	KOH (1.0)	78

[a] General conditions: **1a** (3.0 mmol), **2a** (3.0 mmol), **3a** (3.0 mmol), solvent (15 mL), bases (as above), then **4a** (3.0 mmol), stirred in a sealed tube for 12 h at room temperature. [b] Isolated yields based on **1a**. [c] The two component (between **1a** and **4a**) product **6a** was also produced in minor amount (21% yield).

Table 2. Substrate Scope of Thiazoles 5[a][b]





General conditions: **1** (3.0 mmol), **2** (3.0 mmol), **3** (3.0 mmol), solvent (15 mL), NEt_3 (3.0 mmol), then **4** (3.0 mmol), stirred in a sealed tube for 12 h at room temperature. [b] Isolated yields based on **1**.

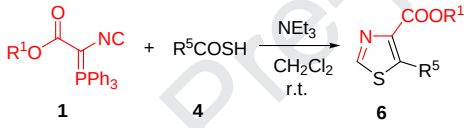
With the optimized conditions in hand, the substrate scope was then explored. The reactions were carried out smoothly to give the corresponding 2,4,5-trisubstituted thiazoles **5** with different substituents of the reactants in moderate to good yields (Table 2). Various substituted aromatic aldehydes **2** bearing electron-withdrawing or electron-donating group were applicable for the four-component reaction. The

aromatic aldehydes substituted by different electron-withdrawing groups, such as chloro (**5a-5d**), trifluoromethyl (**5e-5h**), nitro (**5i-5j**), and bromo (**5k-5n**), readily underwent the four-component reaction to give thiazoles **5a**-**5n** in 73-95% yields. Benzaldehyde and *p*-methylbenzaldehyde were also feasible in this transformation, giving **5o** and **5p** in 70-72% yields. In addition, heterocyclic 2-thiophenformaldehyde was also utilized to synthesize the corresponding thiazoles (**5q**-**5r**) in moderate to good yields (78%-85%). Different secondary amines **3** and thio S-acids **4** may be utilized in above one-pot cyclization to prepare thiazoles **5**. As indicated in Table 2, various cyclic or acyclic acids secondary amines, and aromatic or aliphatic thio S-acids **4** readily occur one-pot cyclization at room temperature, leading to the smooth formation of the trisubstituted thiazoles **5**. These results demonstrated the superior competency of this strategy to access diversely trisubstituted thiazoles **5**.

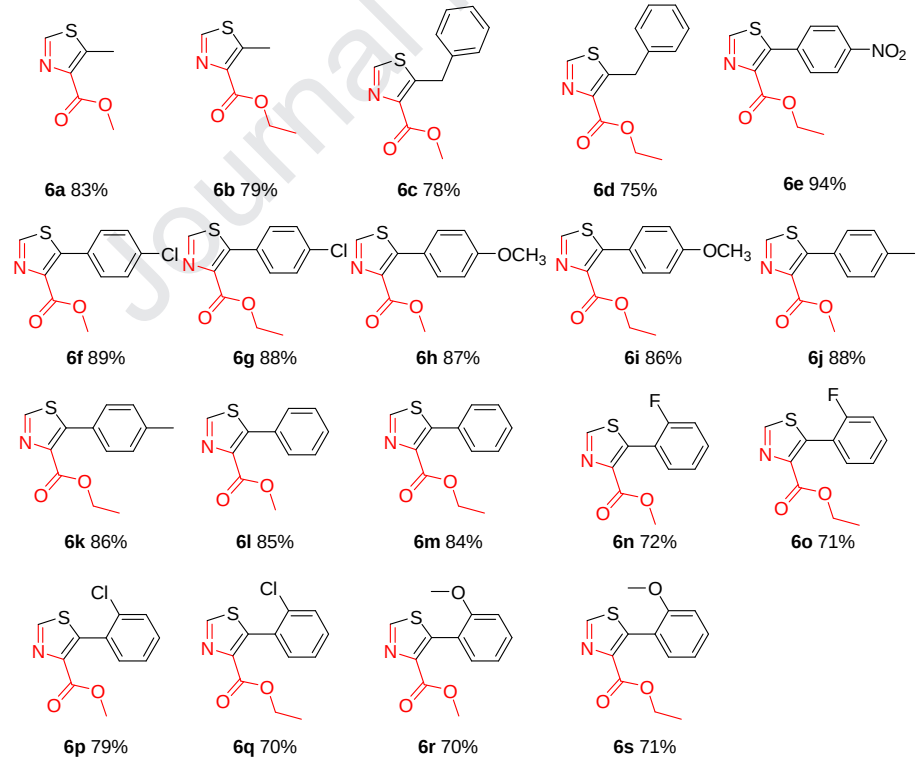
In the process of entry 6 on condition optimization for trisubstituted thiazoles **5**, we found another possible product. Through separation and purification, we confirmed that it was disubstituted thiazole **6a**, and its yield reached 21%. Then direct two-component reaction of ylide **1a** and thio S-acid **4a** was then undertook, however, the reaction gave complex mixture in MeOH or CH_2Cl_2, which might be due to the decomposition of isocyano(triphenylphosphoranylidene)acetate **1** under the acidic condition. In the presence of 1 equiv of triethylamine to adjust the solution acidity, the reaction proceeded smoothly at room temperature and the corresponding 4,5-disubstituted thiazole **6a** was obtained in 51% (in MeOH) or 83% (in CH_2Cl_2) yield. We speculated that the reason might be that the polarity of dichloromethane was smaller than that of methanol. In the two-component reaction, thiocarboxyl anion **8** was more stable in methanol, making it less likely for thiocarboxyl anion **8** to attack isocyanide **12**. In the less polar solvent dichloromethane, thiocarboxyl anion **8** had better activity so that two-component reaction took place smoothly. In the four-component reaction, the polar solvent methanol was more conducive to the

formation of imine cation **9**, while thiocarboxyl anion **8** might be more active for attacking imine cation **9**. We speculated that the formation of imine cation **9** was the rate-determining step for the four-component reaction. The other two-component reactions of ylides **1** and thio S-acids **4** were then carried out in CH_2Cl_2 (Table 3). Gratifyingly, different aliphatic and aromatic thio S-acids can be used in the two-component reactions to produce 4,5-disubstituted thiazoles **6** in moderate to good yields. As shown in Table 3, aliphatic thio S-acids (**6a**-**6d**) and aromatic thio S-acids (**6e**-**6s**), regardless of para-substituted thiobenzoic acids (**6e**-**6k**) or ortho-substituted thiobenzoic acids (**6n**-**6s**), were efficient for the two-component reactions and a series of products **6** were prepared under mild reaction condition.

Table 3. Preparation of Disubstituted Thiazoles 6[a][b]



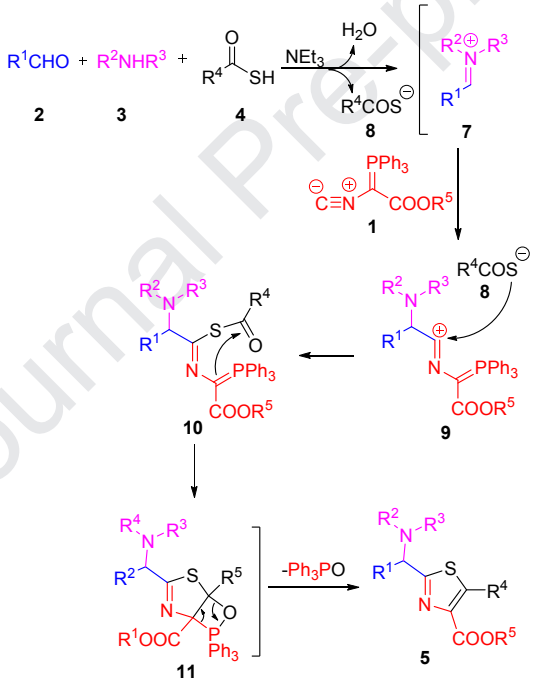
1 **4** **6**



General conditions: **1** (3.0 mmol), solvent (15 mL), NEt_3 (3.0 mmol), then **4** (3.0 mmol), stirred in a sealed tube for 12 h at room temperature. [b] Isolated yields based on **1**.

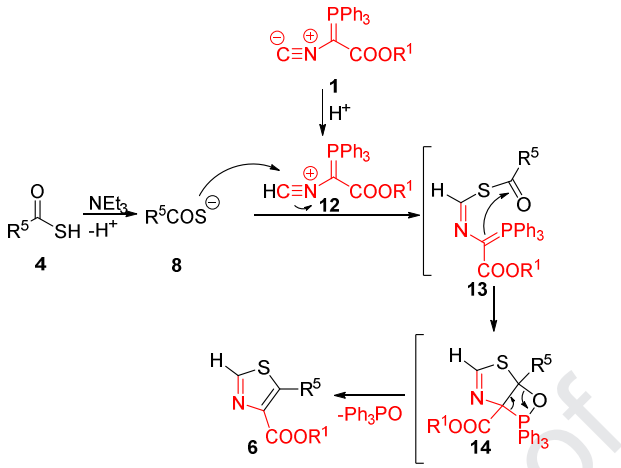
According to these above experiments, the plausible reaction mechanism for 2,4,5-trisubstituted thiazoles **5** is proposed in scheme 2. The reaction involves an initial condensation between aldehyde **2**, amine **3** and thio S-acid **4** to give the iminium cation **7**, with liberating of a molecule of H_2O and conjugate base of the acid **8**. Then the ylide **1** undergoes a nucleophilic addition to the iminium cation **7** to form the intermediate **9**, which is attacked by conjugate base of the thio S-acid **8** via nucleophilic addition to form the intermediate **10**. Finally, an intramolecular Wittig reaction takes place through intermediate **11** to give the product **5**.

Scheme 2. Possible mechanism for the formation of thiazole products 5



Meanwhile, the possible reaction mechanism for disubstituted thiazoles **6** was proposed in scheme 3. In the presence of triethylamine, deprotonation of thiocarboxylic acid **4** could converted into thiocarboxyl anion **8**. Protonation of the isocyanide ylide **1** generates the intermediate **12**, which is attacked by conjugate base of the thio S-acid **8** through nucleophilic addition to give the intermediate **13**. Finally, an intramolecular Wittig reaction takes place through intermediate **14** to produce the final product thiazoles **6**.

Scheme 3. Possible mechanism for the formation of thiazole products 6



3. Conclusion

In conclusion, we have reported the synthesis of 2,4,5-trisubstituted thiazoles and 4,5-disubstituted thiazoles via the four-component or two-component Ugi/Wittig reactions starting from the odorless isocyano(triphenylphosphoranylidene)acetates **1**. The method afforded a facile and efficient strategy to the synthesis of various multisubstituted thiazoles by direct one-pot cyclization under mild condition in moderate to good yields, which makes it significant in synthetic and medicinal chemistry.

4. Experimental

4.1 General

All experiments were carried out under an air atmosphere. Melting points were determined using an X-4 model apparatus and were uncorrected. ^{1}H NMR were recorded in $CDCl_3$ on a Varian Mercury 600 spectrometer and resonances were relative to TMS. ^{13}C {^{1}H} NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 600 (150 MHz) with complete proton decoupling spectrophotometers ($CDCl_3$: 77.0 ppm). MS were measured on a Finnigan Trace MS spectrometer. Elementary analyses were taken on a Vario EL III elementary analysis instrument. The isocyano(triphenylphosphoranylidene)acetates **1** were prepared by the method we reported previously[21].

*4.2 Synthesis of trisubstituted thiazoles **5***

Typical Procedure for the Synthesis of trisubstituted thiazoles 5. A mixture of

isocyano(triphenylphosphoranylidene)acetate **1** (3.0 mmol), aldehyde **2** (3.0 mmol), secondary amine **3** (3.0 mmol) and thio S-acid **4** (3.0 mmol) and triethylamine (0.30 g, 3.0 mmol) was stirred in methanol (15 mL) at room temperature. After completion of the reaction, the solvent was evaporated completely under reduced pressure and the residue was purified by column chromatography with EtOAc/petroleum ether (1:5) as the eluent to afford **5**.

*4.2.1 Methyl 5-methyl-2-(morpholino(4-(trifluoromethyl) phenyl) methyl) thiazole-4-carboxylate (**5a**)*

Light yellow solid (1.080 g, 90%). Mp: 78-79 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.64 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.60 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.85 (s, 1H, CH), 3.91 (s, 3H, OCH_3), 3.73-3.72 (m, 4H, $2OCH_2$), 2.73 (s, 3H, CH_3), 2.52-2.45 (m, 4H, $2NCH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 168.2, 162.5, 146.7, 142.3, 140.0, 130.2 (q, $^{2}J_{F\text{-}C}$ = 30 Hz), 128.7, 125.7, 123.7 (q, $^{1}J_{F\text{-}C}$ = 270 Hz), 72.8, 66.7, 52.2, 52.0, 13.2. MS (EI, 70 eV): m/z (%) = 400 (100, M^+), 315 (18), 283 (9), 255 (21), 159 (14). Anal. Calcd for $C_{18}H_{19}F_3N_2O_3S$: C, 53.99; H, 4.78; N, 7.00. Found: C, 53.75; H, 5.06; N, 7.23.

*4.2.2 Methyl 2-((4-chlorophenyl) (dibutylamino)methyl)-5-methylthiazole-4-carboxylate (**5b**)*

Operation as above. White solid (0.894 g, 73%). Mp: 53-54 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.34-7.28 (m, 4H, Ar-H), 5.17 (s, 1H, CH), 3.89 (s, 3H, OCH_3), 2.74 (s, 3H, CH_3), 2.54-2.49 (m, 2H, NCH_2), 2.42-2.37 (m, 2H, NCH_2), 1.75-1.38 (m, 4H, $2CH_2$), 1.24-1.18 (m, 4H, $2CH_2$), 0.85 (t, *J* = 7.2 Hz, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.6, 162.9, 146.1, 139.9, 137.3, 133.4, 130.2, 128.5, 68.0, 52.0, 49.9, 28.6, 20.4, 14.0, 13.3. MS (EI, 70 eV): m/z (%) = 408 (100, M^+), 280 (9), 245 (21), 220 (18), 128 (11). Anal. Calcd for $C_{21}H_{29}ClN_2O_2S$: C, 61.67; H, 7.15; N, 6.85. Found: C, 61.96; H, 7.37; N, 6.56.

*4.2.3 Methyl 2-((4-chlorophenyl) (pyrrolidin-1-yl) methyl)-5-methylthiazole-4-carboxylate (**5c**)*

Operation as above. White solid (0.956 g, 91%). Mp: 99-100 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.47 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.29 (d, *J* = 7.8 Hz, 2H, Ar-H), 4.71 (s, 1H, CH), 3.90 (s, 3H, OCH_3), 2.72 (s, 3H, CH_3), 2.52-2.48 (m, 4H, $2NCH_2$), 1.79-1.78 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.4, 162.8, 146.4, 139.4, 139.2, 133.5, 129.2, 128.8, 72.2, 53.2, 52.1, 23.4, 13.3. MS (EI, 70 eV): m/z (%) = 350 (100, M^+), 280 (11), 248 (8), 220 (27), 186 (25). Anal. Calcd for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.46; N, 7.98. Found: C, 58.46; H, 5.18; N, 7.76.

*4.2.4 Methyl 2-((4-chlorophenyl) (morpholino)methyl)-5-methylthiazole-4-carboxylate (**5d**)*

Operation as above. White solid (0.911 g, 83%). Mp: 115-116 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.43 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.75 (s, 1H, CH), 3.90 (s, 3H, OCH_3), 3.71 (m, 4H, $2OCH_2$), 2.73 (s, 3H, CH_3), 2.51-2.41 (m, 4H, $2NCH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 168.8, 162.3, 146.7, 139.9, 136.9, 133.9, 129.7, 129.0, 72.7, 66.8, 52.2, 52.1, 13.3. MS (EI, 70 eV): m/z (%) = 366 (100, M^+), 281 (7), 249 (14), 221 (28), 89 (23). Anal. Calcd for $C_{17}H_{19}ClN_2O_3S$: C, 55.66; H, 5.22; N, 7.64. Found: C, 55.39; H, 5.03; N, 7.39.

*4.2.5 Methyl 2-((diethylamino)(4-(trifluoromethyl) phenyl) methyl)-5-methylthiazole-4-carboxylate(**5e**)*

Operation as above. White solid (0.996 g, 86%). Mp: 96-97 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.60-7.55 (m, 4H, Ar-H), 5.25 (s, 1H, CH), 3.89 (s, 3H, OCH_3), 2.74 (s, 3H, CH_3), 2.69-2.63 (m, 2H, NCH_2), 2.56-2.51 (m, 2H, NCH_2), 1.01 (t, *J* = 7.2 Hz, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.2, 162.6, 146.1, 143.1, 139.8, 129.7 (q, $^{2}J_{F\text{-}C}$ = 30 Hz), 128.9, 125.2, 123.8 (q, $^{1}J_{F\text{-}C}$ = 270 Hz), 68.1, 51.8, 43.0, 13.1, 11.0. MS (EI, 70 eV): m/z (%) = 386 (100, M^+), 315 (4), 283 (17), 255 (35), 72 (12). Anal. Calcd for $C_{18}H_{21}F_3N_2O_2S$: C, 55.95; H, 5.48; N, 7.25. Found: C, 56.12; H, 5.70; N, 7.43.

*4.2.6 Methyl 2-((dibutylamino)(4-(trifluoromethyl) phenyl) methyl)-5-methylthiazole-4-carboxylate (**5f**)*

Operation as above. Light yellow oil (1.061 g, 80%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.58 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.53 (d, *J* = 7.8 Hz, 2H, Ar-H), 5.27 (s, 1H, CH), 3.89 (s, 3H, OCH_3), 2.75 (s, 3H, CH_3), 2.56-2.51 (m, 2H, NCH_2), 2.43-2.38 (m, 2H, NCH_2), 1.52-1.41 (m, 4H, $2CH_2$), 1.26-1.22 (m, 4H, $2CH_2$), 0.85 (t, *J* = 7.2 Hz, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.8, 162.7, 146.0, 142.7, 140.0, 129.7 (q, $^{2}J_{F\text{-}C}$ = 30 Hz), 129.1, 125.1, 123.9 (q, $^{1}J_{F\text{-}C}$ = 270 Hz), 68.0, 51.8, 49.8, 28.6, 20.3, 13.8, 13.1. MS (EI, 70 eV): m/z (%) = 442 (100, M^+), 315 (9), 283 (14), 255 (16), 128 (19). Anal. Calcd for $C_{22}H_{29}F_3N_2O_2S$: C, 59.71; H, 6.61; N, 6.33. Found: C, 60.0; H, 6.90; N, 6.10.

*4.2.7 Methyl 5-methyl-2-(pyrrolidin-1-yl(4-(trifluoromethyl)phenyl)methyl)thiazole-4-carboxylate (**5g**)*

Operation as above. Light yellow oil (1.094 g, 95%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.67 (d, *J* = 7.8

Hz, 2H, Ar-H), 7.58 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.81 (s, 1H, CH), 3.90 (s, 3H, OCH_3), 2.72 (s, 3H, CH_3), 2.53-2.51 (m, 4H, $2NCH_2$), 1.81-1.80 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.8, 162.7, 146.4, 144.6, 139.5, 129.9 (q, $^{2}J_{F\text{-}C}$ = 30 Hz), 128.2, 125.6, 123.9 (q, $^{1}J_{F\text{-}C}$ = 270 Hz), 72.4, 53.1, 52.0, 23.4, 13.2. MS (EI, 70 eV): m/z (%) = 384 (100, M^+), 314 (6), 254 (13), 172 (17), 144 (19). Anal. Calcd for $C_{18}H_{19}F_3N_2O_2S$: C, 56.24; H, 4.98; N, 7.29. Found: C, 56.51; H, 5.19; N, 7.01.

4.2.8 *Methyl 2-((4-chlorophenyl) (diethylamino)methyl)-5-methylthiazole-4-carboxylate (**5h**)*

Operation as above. White solid (0.845 g, 80%). Mp: 77-78 °C. ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.40 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.29 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.15 (s, 1H, CH), 3.89 (s, 3H, OCH_3), 2.73 (s, 3H, CH_3), 2.67-2.61 (m, 2H, NCH_2), 2.56-2.50 (m, 2H, NCH_2), 0.99 (t, *J* = 7.2 Hz, 6H, $2CH_3$).^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.0, 162.8, 146.2, 139.8, 137.7, 133.4, 130.0, 128.6, 68.1, 52.0, 43.0, 13.3, 11.1. MS (EI, 70 eV): m/z (%) = 352 (100, M^+), 281 (13), 249 (7), 221 (17), 186 (25). Anal. Calcd for $C_{17}H_{21}ClN_2O_2S$: C, 57.86; H, 6.00; N, 7.94. Found: C, 58.13; H, 6.22; N, 8.12.

*4.2.9 Methyl 5-methyl-2-((4-nitrophenyl) (pyrrolidin-1-yl) methyl) thiazole-4-carboxylate (**5i**)*

Operation as above. Light yellow solid (0.975 g, 90%). Mp: 127-128 °C. ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.19 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.74 (d, *J* = 7.8 Hz, 2H, Ar-H), 4.88 (s, 1H, CH), 3.91 (s, 3H, OCH_3), 2.73 (s, 3H, CH_3), 2.54-2.52 (m, 4H, $2NCH_2$), 1.83-1.82 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.0, 162.7, 147.7, 147.3, 146.7, 139.7, 128.8, 124.0, 72.2, 53.1, 52.1, 23.4, 13.4. MS (EI, 70 eV): m/z (%) = 361 (100, M^+), 292 (15), 260 (8), 232 (14), 70 (16). Anal. Calcd for $C_{17}H_{19}N_3O_4S$: C, 56.50; H, 5.30; N, 11.63. Found: C, 56.73; H, 5.52; N, 11.36.

*4.2.10 Ethyl 5-(4-methoxyphenyl)-2-((4-nitrophenyl) (piperidin-1-yl) methyl) thiazole-4-carboxylate(**5j**)*

Operation as above. Light yellow solid (1.227 g, 85%). Mp: 142-143 °C. ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.21 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.67 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.41 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.93 (d, *J* = 7.8 Hz, 2H, Ar-H), 4.96 (s, 1H, CH), 4.27 (t, *J* = 8.4 Hz, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 2.48-2.44 (m, 4H, $2NCH_2$), 1.61-1.47 (m, 6H, $3CH_2$), 1.21 (t, *J* = 6.0 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.7, 162.1, 160.3, 148.0, 147.3, 146.0, 139.0, 131.1, 129.5, 123.8, 122.5, 113.5, 72.8, 61.2, 55.3, 52.8, 25.9, 24.1, 14.1. MS (EI, 70 eV): m/z (%) = 481 (100, M^+), 397 (30), 351 (9), 323 (14),

276 (21). Anal. Calcd for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.73. Found: C, 62.64; H, 5.91; N, 8.90.

*4.2.11 Ethyl 2-((4-bromophenyl) (piperidin-1-yl) methyl)-5-phenylthiazole-4-carboxylate (**5k**)*

Operation as above. White solid (1.292 g, 89%). Mp: 100-101 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.47-7.35 (m, 9H, Ar-H), 4.79 (s, 1H, CH), 4.27-4.21 (m, 2H, CH_2), 2.47-2.40 (m, 4H, $2NCH_2$), 1.58-1.45 (m, 6H, $3CH_2$), 1.16 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 172.9, 162.1, 147.3, 139.5, 137.7, 131.7, 130.8, 129.8, 128.9, 128.0, 121.7, 72.9, 61.1, 52.9, 26.0, 24.3, 13.9. MS (EI, 70 eV): m/z (%) = 484 (100, M^+), 415 (13), 260 (17), 207 (13), 186 (9). Anal. Calcd for $C_{24}H_{25}BrN_2O_2S$: C, 59.38; H, 5.19; N, 5.77. Found: C, 59.66; H, 5.41; N, 5.55.

*4.2.12 Ethyl 2-((4-bromophenyl) (morpholino)methyl)-5-phenylthiazole-4-carboxylate (**5l**)*

Operation as above. Light yellow solid (1.196 g, 82%). Mp: 82-83 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.50-7.40 (m, 9H, Ar-H), 4.81 (s, 1H, CH), 4.25 (t, *J* = 7.8 Hz, 2H, CH_2), 3.72 (s, 4H, $2OCH_2$), 2.55-2.50 (m, 4H, $2NCH_2$), 1.16 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 171.2, 161.9, 147.5, 139.7, 137.2, 132.0, 130.5, 130.2, 129.8, 129.1, 128.0, 122.2, 72.9, 66.9, 61.2, 52.3, 13.9. MS (EI, 70 eV): m/z (%) = 486 (100, M^+), 401 (22), 329 (16), 188 (13), 77 (9). Anal. Calcd for $C_{23}H_{23}BrN_2O_3S$: C, 56.68; H, 4.76; N, 5.75. Found: C, 56.91; H, 4.98; N, 5.90.

*4.2.13 Ethyl 2-((4-bromophenyl) (diethylamino)methyl)-5-(4-chlorophenyl) thiazole-4-carboxylate (**5m**)*

Operation as above. White solid (1.139 g, 75%). Mp: 90-91 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.48-7.36 (m, 8H, Ar-H), 5.20 (s, 1H, CH), 4.26 (t, *J* = 7.2 Hz, 2H, OCH_2), 2.72-2.66 (m, 2H, NCH_2), 2.58-2.52 (m, 2H, NCH_2), 1.20 (t, *J* = 7.2 Hz, 3H, CH_3), 1.02 (t, *J* = 7.2 Hz, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 174.0, 161.9, 145.8, 139.7, 137.6, 135.1, 131.6, 131.1, 130.5, 129.2, 128.2, 121.7, 68.1, 61.2, 43.1, 14.0, 11.2. MS (EI, 70 eV): m/z (%) = 506 (100, M^+), 434 (19), 362 (7), 155 (13), 72 (9). Anal. Calcd for $C_{23}H_{24}BrClN_2O_2S$: C, 54.39; H, 4.76; N, 5.52. Found: C, 54.65; H, 4.97; N, 5.40.

*4.2.14 Ethyl 5-benzyl-2-((4-bromophenyl) (piperidin-1-yl) methyl) thiazole-4-carboxylate (**5n**)*

Operation as above. White solid (1.240 g, 83%). Mp: 87-88 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm)

7.42-7.25 (m, 9H, Ar-H), 4.71 (s, 1H, CH), 4.52 (s, 2H, CH_2), 4.40 (q, *J* = 7.2 Hz, 2H, OCH_2), 2.38-2.29 (m, 4H, $2NCH_2$), 1.52-1.41 (m, 6H, $3CH_2$), 1.36 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 171.3, 162.3, 150.5, 139.8, 139.1, 137.9, 131.6, 130.2, 128.7, 128.6, 126.8, 121.6, 72.8, 61.1, 52.9, 33.7, 25.9, 24.2, 14.3. MS (EI, 70 eV): m/z (%) = 498 (100, M^+), 417 (17), 369 (9), 147 (12), 84 (19). Anal. Calcd for $C_{25}H_{27}BrN_2O_2S$: C, 60.12; H, 5.45; N, 5.61. Found: C, 60.40; H, 5.57; N, 5.49.

*4.2.15 Ethyl 5-methyl-2-(phenyl(pyrrolidin-1-yl) methyl) thiazole-4-carboxylate (**5o**)*

Operation as above. Light yellow solid (0.713 g, 72%). Mp: 45-46 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.54 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.31 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.24 (t, *J* = 7.2 Hz, 1H, Ar-H), 4.75 (s, 1H, CH), 4.39 (q, *J* = 6.6 Hz, 2H, OCH_2), 2.69 (s, 3H, CH_3), 2.54-2.51 (m, 4H, $2NCH_2$), 1.79 (s, 4H, $2CH_2$), 1.37 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 170.6, 162.5, 145.7, 140.7, 139.8, 128.6, 127.9, 127.8, 72.9, 60.9, 53.2, 23.4, 14.4, 13.4. MS (EI, 70 eV): m/z (%) = 330 (100, M^+), 261 (16), 215 (19), 187 (13), 91 (8). Anal. Calcd for $C_{18}H_{22}N_2O_2S$: C, 65.42; H, 6.71; N, 8.48. Found: C, 65.60; H, 6.49; N, 8.31.

*4.2.16 Ethyl 5-methyl-2-(pyrrolidin-1-yl(p-tolyl) methyl) thiazole-4-carboxylate (**5p**)*

Operation as above. White solid (0.722 g, 70%). Mp: 104-105 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.42 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.12 (d, *J* = 7.2 Hz, 2H, Ar-H), 4.70 (s, 1H, CH), 4.38 (q, *J* = 7.2 Hz, 2H, OCH_2), 2.69 (s, 3H, CH_3), 2.53-2.49 (m, 4H, $2NCH_2$), 2.31 (s, 3H, CH_3), 1.78 (s, 4H, $2CH_2$), 1.37 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 171.0, 162.5, 145.6, 139.8, 137.9, 137.5, 129.3, 127.8, 72.6, 60.9, 53.2, 23.4, 21.1, 14.4, 13.4. MS (EI, 70 eV): m/z (%) = 344 (100, M^+), 275 (17), 229 (14), 201 (12), 105 (9). Anal. Calcd for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.41; H, 7.30; N, 8.00.

*4.2.17 Ethyl 2-((diethylamino)(thiophen-2-yl) methyl)-5-phenylthiazole-4-carboxylate (**5q**)*

Operation as above. Light yellow oil (0.936 g, 78%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.50-7.29 (m, 6H, Ar-H), 7.06-6.96 (m, 2H, Ar-H), 5.57 (s, 1H, CH), 4.27-4.24 (m, 2H, CH_2), 2.72-2.58 (m, 4H, $2NCH_2$), 1.18 (t, *J* = 7.2 Hz, 3H, CH_3), 1.09 (t, *J* = 7.2 Hz, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ

(ppm) 172.2, 162.2, 147.1, 142.1, 139.6, 130.8, 129.8, 128.9, 128.0, 127.1, 126.3, 125.7, 63.3, 61.1, 43.8, 13.9, 12.2. MS (EI, 70 eV): m/z (%) = 400 (100, M^+), 328 (14), 283 (18), 255 (9), 168 (15). Anal. Calcd for $C_{21}H_{24}N_2O_2S_2$: C, 62.97; H, 6.04; N, 6.99. Found: C, 63.13; H, 6.26; N, 7.17.

*4.2.18 Ethyl 5-phenyl-2-(piperidin-1-yl(thiophen-2-yl) methyl) thiazole-4-carboxylate (**5r**)*

Operation as above. Light yellow oil (1.051 g, 85%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.49-7.29 (m, 6H, Ar-H), 7.08-6.95 (m, 2H, Ar-H), 5.19 (s, 1H, CH), 4.28-4.23 (m, 2H, CH_2), 2.55-2.46 (m, 4H, $2NCH_2$), 1.62-1.45 (m, 6H, $3CH_2$), 1.18 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 172.1, 162.1, 147.4, 142.0, 139.5, 130.8, 129.8, 128.9, 128.0, 127.0, 126.5, 125.9, 68.2, 61.1, 52.6, 26.0, 24.3, 14.0. MS (EI, 70 eV): m/z (%) =412 (100, M^+), 329 (13), 283 (12), 255 (9), 80 (17). Anal. Calcd for $C_{22}H_{24}N_2O_2S_2$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.26; H, 6.08; N, 6.51.

*4.3 Synthesis of disubstituted thiazoles **6***

Typical Procedure for the Synthesis of disubstituted thiazoles 6. To a solution of isocyano(triphenylphosphoranylidene)acetate **1** (3.0 mmol) and triethylamine (0.30 g, 3.0 mmol) in dry dichloromethane (15 mL) was added thio S-acid **4** (3.0 mmol) at room temperature. After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by column chromatography with EtOAc/petroleum ether (1:4) as eluent to give **6**.

*4.3.1Methyl 5-methylthiazole-4-carboxylate (**6a**)*

White solid (0.391 g, 83%). Mp: 60-61 °C (lit.[23] mp 62-65 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.59 (s, 1H, CH), 3.96 (s, 3H, OCH_3), 2.82 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.7, 149.0, 144.8, 141.6, 52.0, 12.9. MS (EI, 70 eV) m/z (%) = 157 (100, M^+), 146 (21), 122 (7), 115 (13), 77 (19).

*4.3.2 Ethyl 5-methylthiazole-4-carboxylate (**6b**)*

Operation as above. White solid (0.405 g, 79%). Mp: 85-86 °C (lit.[24] mp 89-90 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.59 (s, 1H, CH), 4.43 (q, *J* = 7.2 Hz, 2H, CH_2), 2.81 (s, 3H, CH_3), 1.43 (t, *J* = 7.2 Hz,

3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.3, 149.0, 144.5, 141.9, 61.0, 14.3, 12.9. MS (EI, 70 eV) m/z (%) = 171 (100), 168 (8), 138 (13), 136 (17), 120 (16).

*4.3.3 Methyl 5-benzylthiazole-4-carboxylate (**6c**)*

Operation as above. Light yellow oil[25] (0.545 g, 78%). ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.59 (s, 1H, CH), 7.33-7.25 (m, 5H, Ar-H), 4.61 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.7, 150.2, 150.1, 140.9, 139.0, 128.7, 128.6, 127.0, 52.2, 33.2. MS (EI, 70 eV): m/z (%) = 233 (100, M^+), 200 (16), 171 (8), 145 (12), 102 (9).

*4.3.4 Ethyl 5-benzylthiazole-4-carboxylate (**6d**)*

Operation as above. White solid (0.558 g, 75%). Mp: 50-51 °C (lit.[26] mp 49-50 °C). ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.62 (s, 1H, CH), 7.33-7.27 (m, 5H, Ar-H), 4.61 (s, 2H, CH_2), 4.45 (q, *J* = 7.2 Hz, 2H, CH_2), 1.43 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.3, 150.3, 149.8, 141.3, 139.1, 128.8, 128.7, 127.0, 61.3, 33.3, 14.3. MS (EI, 70 eV): m/z (%) = 247 (100, M^+), 201 (18), 146 (11), 136 (14), 91 (7).

*4.3.5 Ethyl 5-(4-nitrophenyl) thiazole-4-carboxylate (**6e**)*

Operation as above. White solid (0.784 g, 94%). Mp: 138-139 °C. ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.90 (s, 1H, CH), 8.30 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.71 (d, *J* = 7.8 Hz, 2H, Ar-H), 4.35 (q, *J* = 6.6 Hz, 2H, CH_2), 1.31 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.4, 152.4, 148.0, 143.5, 142.2, 136.8, 131.1, 123.2, 61.7, 14.0. MS (EI, 70 eV): m/z (%) = 278 (100, M^+), 232 (15), 205 (12), 186 (20), 159 (14). Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07. Found: C, 51.53; H, 3.83; N, 10.30.

*4.3.6 Methyl 5-(4-chlorophenyl) thiazole-4-carboxylate (**6f**)*

Operation as above. White solid (0.676 g, 89%). Mp: 88-89 °C (lit.[27] mp 88-90 °C). ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.79 (s, 1H, CH), 7.47-7.41 (m, 4H, Ar-H), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.1, 151.4, 145.6, 140.8, 135.6, 131.2, 128.4, 128.2, 52.3. MS (EI, 70 eV): m/z (%)

= 253 (100, M^+), 221 (13), 194 (15), 167 (17), 123 (32).

*4.3.7Ethyl 5-(4-chlorophenyl) thiazole-4-carboxylate (**6g**)*

Operation as above. White solid (0.705 g, 88%). Mp: 147-148 °C (lit.[28] mp 147-148 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.79 (s, 1H, CH), 7.46-7.40 (m, 4H, Ar-H), 4.33 (q, *J* = 7.2 Hz, 2H, CH_2), 1.30 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.6, 151.4, 145.2, 141.3, 135.4, 131.2, 128.3, 61.4, 14.0. MS (EI, 70 eV): m/z (%) = 267 (100, M^+), 221 (14), 194 (11), 167 (9), 122 (6).

*4.3.8 Methyl 5-(4-methoxyphenyl) thiazole-4-carboxylate (**6h**)*

Operation as above. White solid (0.650 g, 87%). Mp: 88-89 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.72 (s, 1H, CH), 7.48 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.96 (d, *J* = 8.4 Hz, 2H, Ar-H), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.3, 160.4, 150.6, 147.2, 139.8, 131.3, 121.8, 113.6, 55.2, 52.2. MS (EI, 70 eV): m/z (%) = 249 (100, M^+), 218 (5), 191 (14), 164 (21), 119 (18). Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.55; H, 4.19; N, 5.44.

*4.3.9Ethyl 5-(4-methoxyphenyl) thiazole-4-carboxylate (**6i**)*

Operation as above. Light yellow oil[29] (0.679 g, 86%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.73 (s, 1H, CH), 7.46 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.95 (d, *J* = 7.8 Hz, 2H, Ar-H), 4.34 (q, *J* = 6.0 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 1.31 (t, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.0, 160.4, 150.7, 146.8, 140.4, 131.3, 122.0, 113.6, 61.2, 55.3, 14.1. MS (EI, 70 eV): m/z (%) = 263 (100, M^+), 217 (13), 190 (17), 163 (21), 149 (6).

*4.3.10 Methyl 5-(p-tolyl) thiazole-4-carboxylate (**6j**)*

Operation as above. White solid (0.615 g, 88%). Mp: 70-71 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.74 (s, 1H, CH), 7.41 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.8 Hz, 2H, Ar-H), 3.87 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.3, 150.9, 147.3, 140.2, 139.5, 129.7, 128.9, 126.7, 52.2, 21.3. MS (EI, 70 eV): m/z (%) = 233 (100, M^+), 201 (5), 175 (21), 146 (14), 103 (9). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.99; H, 4.94; N, 6.13.

*4.3.11 Ethyl 5-(p-tolyl) thiazole-4-carboxylate (**6k**)*

Operation as above. White solid (0.637 g, 86%). Mp: 78-79 °C (lit.[28] mp 81-82 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.74 (s, 1H, CH), 7.40 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.8 Hz, 2H, Ar-H), 4.33 (q, *J* = 7.2 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.30 (t , *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.8, 150.9, 146.8, 140.7, 139.3, 129.8, 128.8, 126.9, 61.2, 21.2, 14.0. MS (EI, 70 eV): m/z (%) = 247 (100, M^+), 201 (5), 174 (13), 147 (24), 103 (18).

*4.3.12 Methyl 5-phenylthiazole-4-carboxylate (**6l**)*

Operation as above. White solid (0.558 g, 85%). Mp: 99-100 °C (lit.[27] mp 98-100 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.77 (s, 1H, CH), 7.53-7.43 (m, 5H, Ar-H), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.2, 151.2, 146.9, 140.5, 129.9 129.8, 129.3, 128.1, 52.2. MS (EI, 70 eV): m/z (%) = 219 (100, M^+), 187 (6), 160 (25), 132 (15), 89 (9).

*4.3.13 Ethyl 5-phenylthiazole-4-carboxylate (**6m**)*

Operation as above. Light yellow oil [29] (0.587 g, 84%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.74 (s, 1H, CH), 7.49-7.38 (m, 5H, Ar-H), 4.30 (q, *J* = 10.2 Hz, 2H, CH_2), 1.26 (t, *J* = 10.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.8, 151.2, 146.4, 141.1, 130.0, 129.9, 129.2, 128.1, 61.2, 14.0. MS (EI, 70 eV): m/z (%) = 233 (100, M^+), 188 (13), 161 (23), 134 (9), 89 (14).

*4.3.14 Methyl 5-(2-fluorophenyl) thiazole-4-carboxylate (**6n**)*

Operation as above. White solid (0.512 g, 72%). Mp: 77-78 °C (lit.[30] mp 80-82 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.86 (s, 1H, CH), 7.46-7.40 (m, 2H, Ar-H), 7.24-7.17 (m, 2H, Ar-H), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.9, 159.5 (q, $^{1}J_{F\text{-}C}$ = 240 Hz), 152.3, 142.7, 139.0, 131.7, 131.4 (q, $^{2}J_{F\text{-}C}$ = 15 Hz), 123.9, 118.1, 115.8 (q, $^{2}J_{F\text{-}C}$ = 15 Hz), 52.3. MS (EI, 70 eV): m/z (%) = 237 (100, M^+), 205 (15), 175 (8), 151 (11), 107 (14).

*4.3.15 Ethyl 5-(2-fluorophenyl) thiazole-4-carboxylate (**6o**)*

Operation as above. White solid (0.535 g, 71%). Mp: 62-63 °C (lit.[28] mp 65-66 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.86 (s, 1H, CH), 7.45-7.39 (m, 2H, Ar-H), 7.23-7.16 (m, 2H, Ar-H), 4.31 (q, *J* = 7.2 Hz, 2H, CH_2), 1.24 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.5, 159.6 (q, $^{1}J_{F\text{-}C}$ = 255 Hz), 152.3, 143.3, 138.5, 131.7, 131.3 (q, $^{2}J_{F\text{-}C}$ = 15 Hz), 123.8, 118.3, 115.7 (q, $^{2}J_{F\text{-}C}$ = 15 Hz), 61.3, 13.9. MS (EI, 70 eV): m/z (%) = 251 (100, M^+), 205 (7), 178 (13), 151 (20), 107 (9).

*4.3.16 Methyl 5-(2-chlorophenyl) thiazole-4-carboxylate (**6p**)*

Operation as above. White solid (0.600 g, 79%). Mp: 96-97 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.87 (s, 1H, CH), 7.51 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.41-7.33 (m, 3H, Ar-H), 3.82 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.6, 152.3, 143.0, 142.6, 133.9, 131.6, 130.5, 129.6, 129.3, 126.4, 52.3. MS (EI, 70 eV): m/z (%) = 253 (100, M^+), 222 (14), 218 (24), 167 (9), 123 (11). Anal. Calcd for $C_{11}H_8ClNO_2S$: C, 52.08; H, 3.18; N, 5.52. Found: C, 52.24; H, 3.07; N, 5.34.

*4.3.17 Ethyl 5-(2-chlorophenyl) thiazole-4-carboxylate (**6q**)*

Operation as above. White solid (0.561 g, 70%). Mp: 168-169 °C (lit.[28] mp 166-167 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.87 (s, 1H, CH), 7.50 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.40-7.32 (m, 3H, Ar-H), 4.25 (q, *J* = 7.2 Hz, 2H, CH_2), 1.17 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.2, 152.3, 143.6, 142.2, 134.1, 131.6, 130.4, 129.7, 129.5, 126.4, 61.2, 13.8. MS (EI, 70 eV): m/z (%) = 267 (100, M^+), 231 (7), 203 (11), 166 (14), 122 (16).

*4.3.18 Methyl 5-(2-methoxyphenyl) thiazole-4-carboxylate (**6r**)*

Operation as above. White solid (0.523 g, 70%). Mp: 72-73 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.83 (s, 1H, CH), 7.36-7.24 (m, 4H, Ar-H), 3.80 (s, 3H, OCH_3), 2.18 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.7, 151.9, 145.9, 142.1, 137.2, 130.0, 129.9, 129.5, 129.3, 125,4, 52.2, 20.0. MS (EI, 70 eV): m/z (%) = 249 (100, M^+), 233 (7), 201 (12), 174 (15), 146 (21). Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 58.01; H, 4.74; N, 5.74.

*4.3.19 Ethyl 5-(2-methoxyphenyl) thiazole-4-carboxylate (**6s**)*

Operation as above. White solid (0.560 g, 71%). Mp: 138-139 °C (lit.[28] mp 142-143 °C). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.83 (s, 1H, CH), 7.35-7.23 (m, 4H, Ar-H), 4.23 (q, *J* = 7.2 Hz, 2H, CH_2), 2.18 (s, 3H, OCH_3), 1.16 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.4, 151.8, 145.4, 142.6, 137.2, 129.9, 129.8, 129.2, 125.4, 61.1, 20.0, 13.8. MS (EI, 70 eV): m/z (%) = 263 (100, M^+), 247 (5), 201 (17), 174 (6), 146 (9).

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Highlight:

one-pot four-component reactions,

mild reaction conditions,

good yields

Declaration of interests

☐* The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: