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One-Pot Telescoped Synthesis of Thiazole Derivatives from β-Keto Esters and Thioureas Promoted by Tribromoisocyanuric Acid

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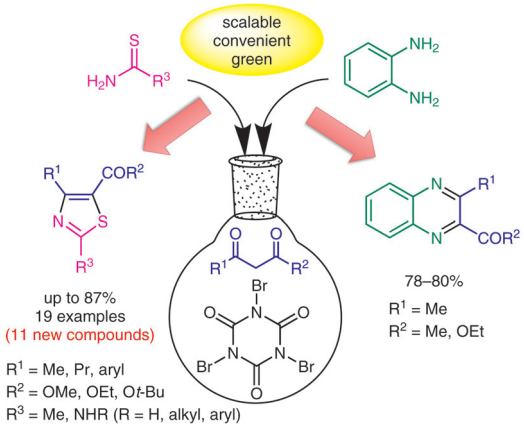
Dedicated to Prof. W. Bruce Kover on the occasion of his 80th anniversary



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Abstract A simple and efficient one-pot protocol has been developed for the synthesis of thiazole derivatives from readily available starting materials. Tribromoisocyanuric acid was successfully used for α-monohalogenation of β-keto esters in aqueous medium, which in the presence of thiourea and DABCO produced the corresponding 2-aminothiazoles in up to 87% yield. Extension of the reaction to thioacetamide and *o*-phenylenediamine led to 2-methylthiazole and quinoxalines, respectively. This approach enables telescoping of the two steps into a single process.

Key words heterocycles, condensation, thiazole, quinoxaline, green chemistry, tribromoisocyanuric acid, pot-ecomomy, thiourea

Thiazole and its derivatives have long inspired researchers.[1] As privileged heterocyclic nucleus, they represent one of the most biologically active classes of compounds owing to their numerous applications in medicinal chemistry (e.g., anti-inflammatory,[2] antitumor,[3] antiparasitic,[4] anticonvulsant,[5] antiviral,[6] to name a few). The thiazole moiety is also a key constituent of many commercial antibiotics.[7] A few examples of important biologically active thiazoles are shown in Figure 1.[8]

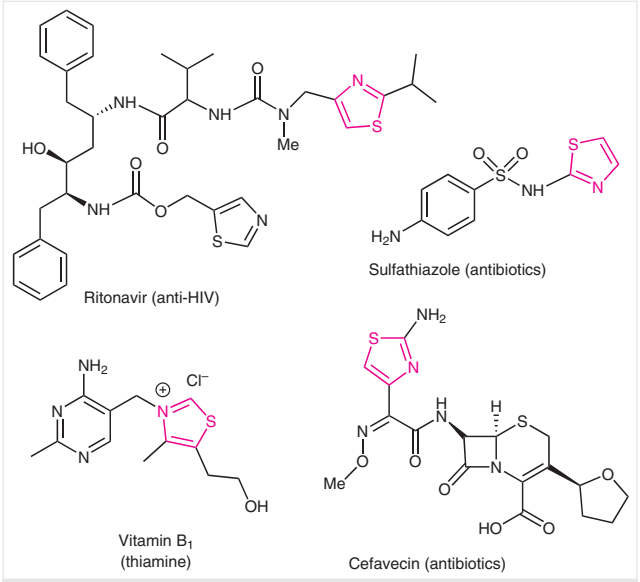
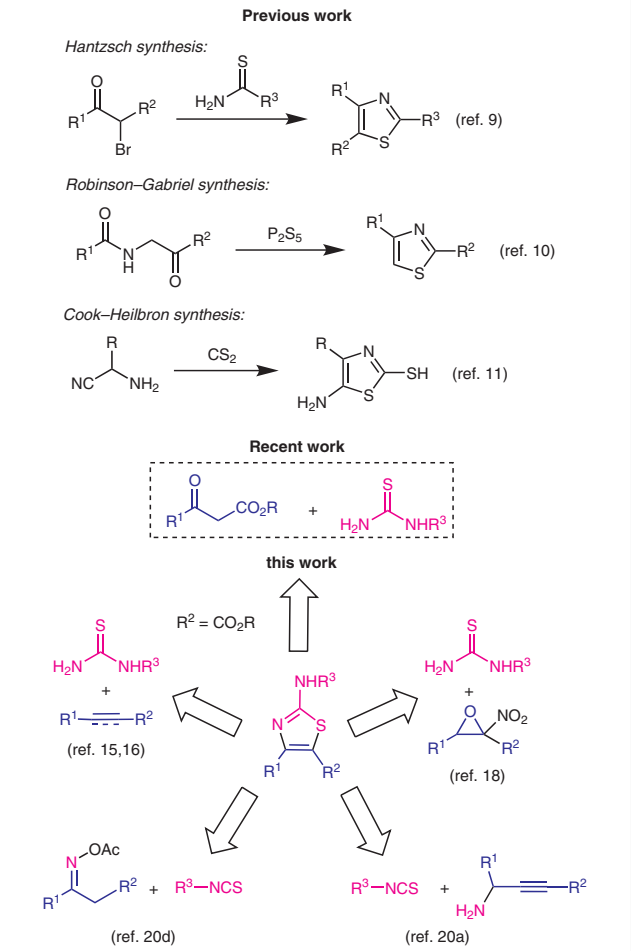


Figure 1 Examples of important biologically active thiazoles

Traditionally, the chosen method for the preparation of these compounds is via the Hantzsch thiazole synthesis, which involves the reaction of thioamides with α-haloketones.[9] However, various other synthetic protocols abound in literature, such as the Robinson–Gabriel[10] and the Cook–Heilborn[11] thiazole synthesis, among others. An inconvenient step of Hantzsch methodology is the preparation or manipulation of toxic haloketones. Therefore, direct one-pot protocols based on the reactions of thioamides/thioureas with ketones,[12] β-keto esters,[13] α,β-unsaturated carbonyl compounds,[14] alkenes,[15] alkynes,[16] α-diazoketones,[17] nitroepoxides[18] and vinyl azides,[19] or reactions of isothiocyanates with different substrates[20] have attracted attention as powerful strategies to prepare the thiazole nucleus. Scheme 1 shows some of these methodologies. Although they are interesting approaches, most of them suffer from drawbacks, especially from the standpoint of the availability of starting materials. Other limitations involve the use of harsh reaction conditions, transition-metal catalysts, and toxic chemicals.



Scheme 1

Therefore, it is desirable and challenging to develop more green reagents and routes to access thiazoles. In this regard, the telescoping of multi-step reactions (i.e., execution of multiple transformations, including quenches and workup procedures without the isolation of intermediates) is often an interesting pot-economical approach that avoids handling and exposure to hazardous or toxic compounds.[21] In addition, telescoped methods simplify many practical aspects, minimizing the number of synthetic steps, purification processes and, thus, chemical waste. In this context, as part of our ongoing studies on the chemistry of trihaloisocyanuric acids,[22] we report herein a novel one-pot synthesis of thiazoles mediated by tribromoisocyanuric acid using a telescoped process from easily available β-keto esters and thioureas.

Tribromoisocyanuric acid[23] (TBCA, Figure 2) is an effective and stable electrophilic brominating reagent that can be prepared from readily accessible material (cyanuric acid, KBr, Oxone™).[24] From the green chemistry point of view, it presents a higher atom economy as being able to transfer up to three bromine atoms to a substrate, corresponding to 65.5% of its mass.[25] In addition, in reactions involving TBCA, cyanuric acid by-product can be reused to produce more of trihaloisocyanuric acid.[26]

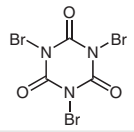
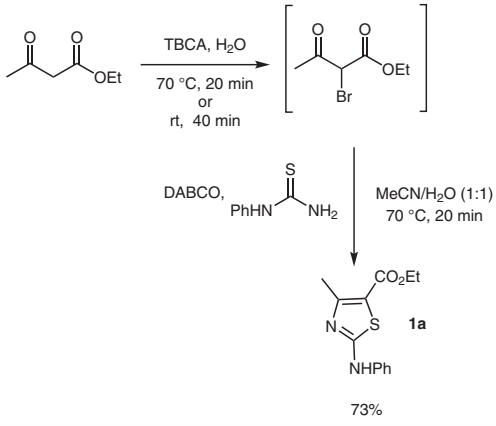


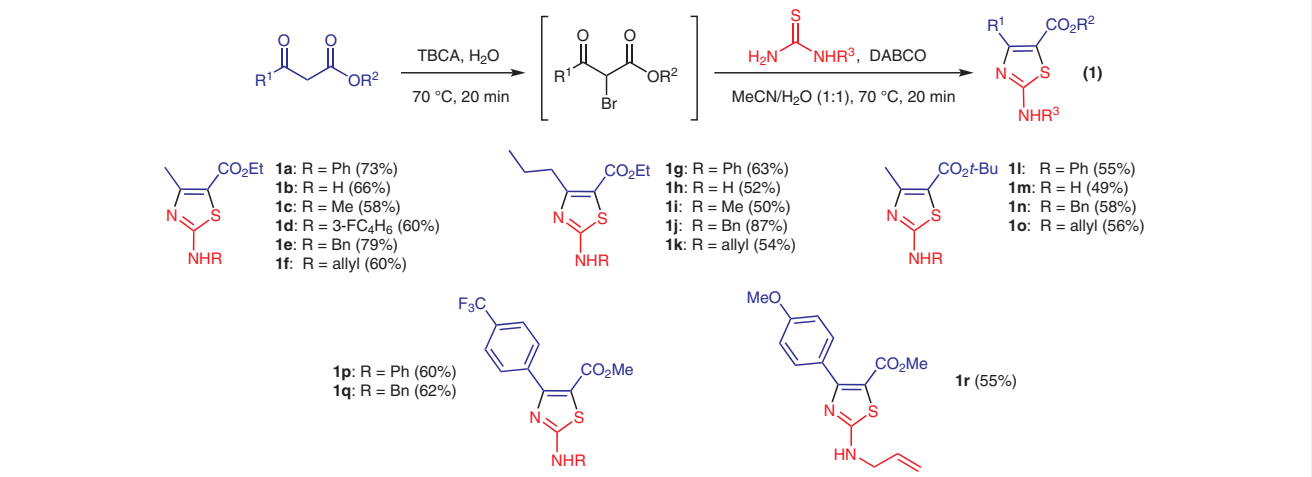
Figure 2 Tribromoisocyanuric acid (TBCA)

Our group has previously presented trihaloisocyanuric acids as effective reagents for regioselective halogenation of β-dicarbonyl compounds.[27] Based on these results, the monobromination of ethyl acetoacetate in aqueous medium by TBCA was chosen as a model reaction. The reaction was successfully performed using 1 mmol of ethyl acetoacetate and 0.4 mmol of TBCA in aqueous medium at 70 °C for 20 minutes (or at r.t. for 40 min). Further addition of *N*-phenylthiourea and DABCO in acetonitrile/water (1:1) led to ethyl 4-methyl-2-(phenylamino)thiazole-5-carboxylate **(1a)** in 73% yield after an additional 20 minutes heating (Scheme 2).



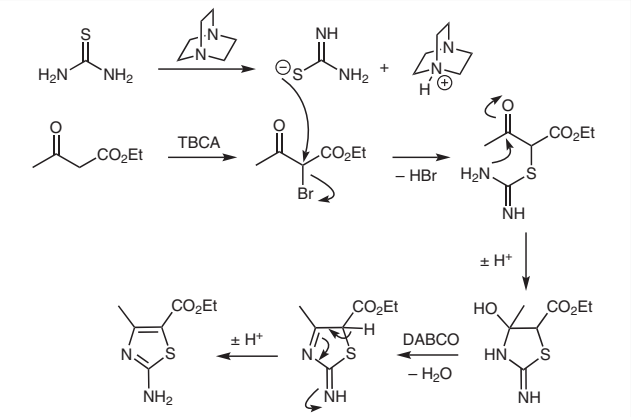
Scheme 2

With these optimized conditions in hand, the scope and generality of the reaction were examined using various thioureas and β-keto esters, and the results are summarized in Scheme 3. To our delight, unsubstituted and diverse N-substituted thioureas, bearing alkyl, allyl, aryl, and benzyl groups tolerated well the conditions employed. At the end of the reaction, the 2-aminothiazoles **1** were obtained in moderate to good yields (49–87%) by means of a simple filtration without the need of further purification. In general, the nature of substituents had no significant effect on the yields.



Scheme 3

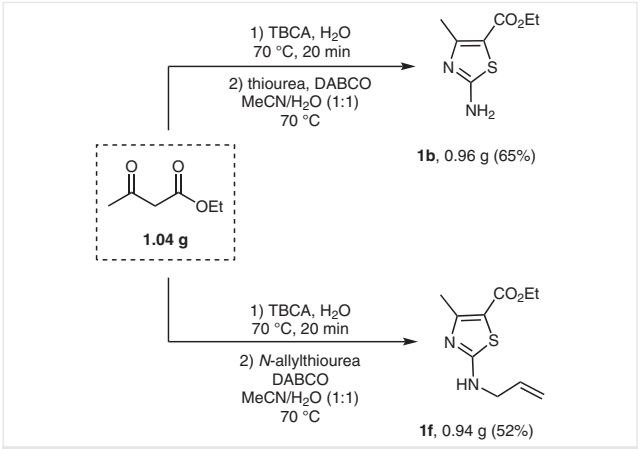
A plausible pathway for these sequential reactions is presented in Scheme 4. Initially, it proceeds with the generation of ethyl 2-bromoacetoacetate via reaction between TBCA and ethyl acetoacetate, followed by a nucleophilic attack of the thiourea, condensation, and elimination to produce the 2-aminothiazole.



Scheme 4

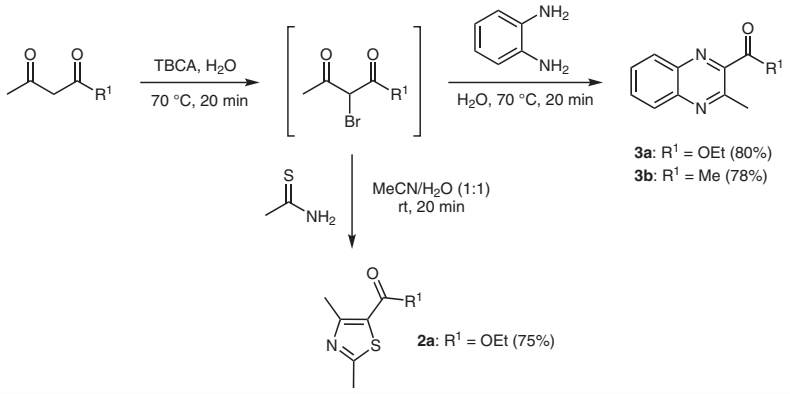
To prove the efficiency of our methodology, a few scaling up experiments were investigated. Hence, reactions of ethyl acetoacetate on a 1 gram scale with TBCA, thiourea or *N*-allylthiourea to produce the corresponding 2-aminothiazoles were carried out under the respective optimized conditions and compounds **1b** (0.96 g, 65%) and **1f** (0.94 g, 52%) were obtained in close yields compared to the reaction performed on a 1 mmol scale. These results attest the scalability of these transformations (Scheme 5).

Encouraged by these results, the substrate scope of the reaction was expanded by varying the nucleophile to react with the bromodicarbonyl compound formed in situ. Interestingly, when these conditions were extended to thioacetamide, the reaction afforded a complex mixture of products. However, performing the second step of the reaction at room temperature in the absence of DABCO, the corresponding thiazole **2a** was obtained as a single product in 75% yield. On the other hand, using *o*-phenylenediamine as nucleophile, the quinoxalines[28] **3** were obtained in 78–80% yield. Scheme 6 summarizes these results.



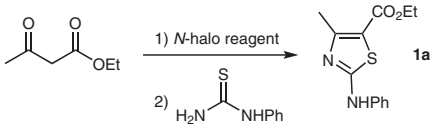
Scheme 5

Compared to the analogue NBS, TBCA provided, in general, the corresponding thiazoles (e.g., **1a**) in higher yields with considerable shortened reaction times. In addition, TBCA has the advantage of being easily accessible (or prepared) and possessing a higher atom efficiency (i.e., atom economy vs chemical yield),[29] which is consistent with the green chemistry principles[30] (Table 1). Also, this method required a simple workup procedure and permitted both recovery and the regeneration of the brominating reagent.



Scheme 6

Table 1 Preparation of **1a** Using Different *N*-Bromo Reagents



N-Halo reagent	Yield (%)	Atom efficiency (%)	Time	Ref.
NBS	50	25	4 h	13
TBCA	73	48	40 min	this work

In conclusion, we have developed an efficient one-pot telescoped protocol for the synthesis of thiazole derivatives. Experimental simplicity, short reaction times, and readily available starting materials all combine to make this method attractive for a wide range of application in organic synthesis and medicinal chemistry.

All chemicals and solvents were purchased and used as received. Tribromoisocyanuric acid was prepared as described.[24] NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C). DMSO-d_6 and $CDCl_3$ were used as solvents and spectra were calibrated using their residual peak. GC-MS analyses were performed on a Shimadzu GCMS-QP2010S gas chromatograph with electron impact (70 eV) using a 30 m DB-5 silica capillary column with 0.25 mm internal diameter and 0.25 µm phase thickness. IR spectra were recorded on a Nicolet 740 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific QExactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer using positive electrospray ionization. Melting points were determined on a Laboratory Device Mel-Temp II and are corrected.

2-Aminothiazoles 1; General Procedure

To a solution of the appropriate β-keto ester (1 mmol) in H_2O (5 mL) held at 70 °C was added TBCA (146 mg, 0.4 mmol) in small portions and the mixture was stirred at 70 °C for 20 min. Then, MeCN (5 mL), the respective thiourea (1 mmol), and DABCO (1 mmol) were successively added and the mixture was stirred at 70 °C for an additional 20 min. After the completion of the reaction, the mixture was poured onto ice and the precipitated solid was collected by filtration to afford the corresponding pure 2-aminothiazole **1**.

Ethyl 4-Methyl-2-(phenylamino)thiazole-5-carboxylate (1a)

Yield: 191 mg (73%); pale yellow solid; mp 134–136 °C (Lit.[31] mp 138–139 °C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.67 (s, 1 H), 7.60 (d, *J* = 8.0 Hz, 2 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 2.52 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.50, 162.30, 159.03, 140.54, 129.60, 123.08, 118.51, 109.41, 60.69, 17.80, 14.75.

MS (70 eV): *m*/*z* = 262 (M^+, 100%), 233, 217, 189, 77.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_2S$: 263.0848; found: 263.0847.

Ethyl 2-Amino-4-methylthiazole-5-carboxylate (1b)

Yield: 122 mg (66%); yellow solid; mp 173–174°C (Lit.[32] mp 174–176 °C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.70 (s, 2 H), 4.15 (q, *J* = 7.3 Hz, 2 H), 2.38 (s, 3 H), 1.23 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.70, 162.43, 159.80, 107.87, 60.19, 17.60, 14.79.

MS (70 eV): *m*/*z* = 186 (M^+), 158, 141 (100%).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{11}N_2O_2S$: 187.0535; found: 187.0535.

Ethyl 4-Methyl-2-(methylamino)thiazole-5-carboxylate (1c)

Yield: 116 mg (58%); beige solid; mp 149–151 °C (Lit.[33] mp 154 °C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.24 (d, *J* = 3.8 Hz, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 2.82 (d, *J* = 4.4 Hz, 3 H), 2.41 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 171.18, 162.42, 160.11, 107.49, 60.23, 31.24, 17.76, 14.78.

MS (70 eV): *m*/*z* = 200 (M^+, 100%), 185, 172, 155, 144, 128.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{13}N_2O_2S$: 201.0692; found: 201.0690.

Ethyl 2-[(3-Fluorophenyl)amino]-4-methylthiazole-5-carboxylate (1d)

Yield: 168 mg (60%); white solid; mp 121–122 °C.

IR (KBr): 3212, 3189, 3060, 2987, 2936, 1712, 1620, 1609, 1567, 1266, 1089 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz): δ = 10.84 (s, 1 H), 7.67 (d, *J* = 11.0 Hz, 1 H), 7.38–7.28 (m, 2 H), 6.84 (t, *J* = 7.5 Hz, 1 H), 4.21 (q, *J* = 6.4 Hz, 2 H), 2.54 (s, 3 H), 1.26 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 164.80, 162.91 (d, $J_{C,F}$ = 241.8 Hz), 158.79, 142.20 (d, $J_{C,F}$ = 11.1 Hz), 131.07 (d, $J_{C,F}$ = 9.6 Hz), 114.04, 110.26, 109.12 (d, $J_{C,F}$ = 21.2 Hz), 105.09 (d, $J_{C,F}$ = 26.7 Hz), 60.81, 17.78, 14.69.

MS (70 eV): *m*/*z* = 280 (M^+, 100%), 251, 235, 207.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}FN_2O_2S$: 281.0754; found: 281.0752.

Ethyl 2-(Benzylamino)-4-methylthiazole-5-carboxylate (1e)

Yield: 218 mg (79%); pale yellow solid; mp 109–110 °C (Lit.[33] mp 112 °C).

^1H NMR (DMSO-d_6, 400 MHz): δ = 8.82 (t, *J* = 5.7 Hz, 1 H), 7.37–7.26 (m, 5 H), 4.46 (d, *J* = 5.7 Hz, 2 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 2.42 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.34, 162.38, 159.81, 138.59, 128.90, 127.87, 127.67, 107.85, 60.68, 48.03, 17.78, 14.79.

MS (70 eV): *m*/*z* = 276 (M^+), 106, 91 (100%).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_2S$: 277.1005; found: 277.1004.

Ethyl 2-(Allylamino)-4-methylthiazole-5-carboxylate (1f)

Yield: 135 mg (60%); white solid; mp 106–107 °C (Lit.[34] mp 109–110 °C).

^1H NMR (DMSO-d_6, 400 MHz): δ = 8.47 (s, 1 H), 5.89–5.82 (m, 1 H), 5.23 (d, *J* = 17.3 Hz, 1 H), 5.14 (d, *J* = 10.3 Hz, 1 H), 4.14 (q, *J* = 6.7 Hz, 2 H), 3.87 (s, 2 H), 2.40 (s, 3 H), 1.22 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.25, 162.39, 159.80, 134.45, 116.75, 107.72, 60.26, 46.86, 17.74, 14.77.

MS (70 eV): *m*/*z* = 226 (M^+, 100%), 211, 198, 181, 154, 112.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{15}N_2O_2S$: 227.0848; found: 227.0847.

Ethyl 2-(Phenylamino)-4-propylthiazole-5-carboxylate (1g)

Yield: 182 mg (63%); pale yellow solid; mp 118–120 °C.

^1H NMR (DMSO-d_6, 400 MHz): δ = 10.68 (s, 1 H), 7.60 (d, *J* = 8.0 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 7.03 (t, *J* = 7.3 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 2.94 (t, *J* = 7.3 Hz, 2 H), 1.68 (sext, *J* = 7.2 Hz, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.61, 163.22, 162.14, 140.61, 129.60, 123.02, 109.48, 60.67, 32.61, 22.36, 14.71, 14.23.

MS (70 eV): *m*/*z* = 290 (M^+), 275, 262 (100%), 190.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_2S$: 291.1161; found: 291.1160.

Ethyl 2-Amino-4-propylthiazole-5-carboxylate (1h)

Yield: 111 mg (52%); yellow solid; mp 133–135 °C (Lit.[35] mp 137–138 °C).

^1H NMR (DMSO-d_6, 400 MHz): δ = 7.70 (s, 2 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 2.80 (t, *J* = 7.3 Hz, 2 H), 1.59 (sext, *J* = 7.3 Hz, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.85, 164.05, 162.28, 107.99, 60.18, 32.52, 22.26, 14.76, 14.23.

MS (70 eV): *m*/*z* = 214 (M^+), 186 (100%), 114.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{15}N_2O_2S$: 215.0848; found: 215.0848.

Ethyl 2-(Methylamino)-4-propylthiazole-5-carboxylate (1i)

Yield: 114 mg (50%); yellow solid; mp 103–105 °C.

IR (KBr): 3210, 3112, 3084, 2971, 2951, 2930, 2869, 1693, 1602, 1534, 1261, 1083, 2061, 763 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz): δ = 8.25 (d, *J* = 4.5 Hz, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 2.84–2.81 (m, 5 H), 1.60 (sext, *J* = 7.2 Hz, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 171.48, 164.41, 162.24, 107.58, 60.20, 32.67, 31.33, 22.34, 14.73, 14.22.

MS (70 eV): *m*/*z* = 228 (M^+), 213, 200 (100%), 183, 155.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{17}N_2O_2S$: 229.1005; found: 229.1003.

Ethyl 2-(Benzylamino)-4-propylthiazole-5-carboxylate (1j)

Yield: 264 mg (87%); reddish brown solid; mp 111–112 °C.

IR (KBr): 3199, 3089, 3065, 3028, 2985, 2966, 2934, 2873, 1683, 1301, 1078 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz): δ = 8.83 (t, *J* = 5.9 Hz, 1 H), 7.25–7.35 (m, 5 H), 4.45 (d, *J* = 5.8 Hz, 2 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 2.83 (t, *J* = 7.3 Hz, 2 H), 1.60 (sext, *J* = 7.3 Hz, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.52, 164.08, 162.21, 138.60, 129.01, 127.95, 127.67, 107.89, 60.26, 48.14, 32.66, 22.32, 14.76, 14.24.

MS (70 eV): *m*/*z* = 304 (M^+), 276, 91 (100%).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_2S$: 305.1318; found: 305.1316.

Ethyl 2-(Allylamino)-4-propylthiazole-5-carboxylate (1k)

Yield: 137 mg (54%); pale yellow solid; mp 90–91 °C.

IR (KBr): 3198, 3092, 2965, 2933, 2872, 1704, 1589, 1534, 1262, 1075 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz): δ = 8.48 (t, *J* = 5.3 Hz, 1 H), 5.91–5.81 (m, 1 H), 5.23 (d, *J* = 17.1 Hz, 1 H), 5.14 (d, *J* = 10.4 Hz, 1 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 3.86 (t, *J* = 5.1 Hz, 2 H), 2.82 (t, *J* = 7.5 Hz, 2 H), 1.59 (sext, *J* = 7.4 Hz, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.47, 164.09, 162.23, 134.40, 116.85, 107.79, 60.24, 47.00, 32.63, 22.33, 14.75, 14.22.

MS (70 eV): *m*/*z* = 254 (M^+), 239, 225 (100%), 211, 154.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}N_2O_2S$: 255.11617; found: 255.11605.

***tert*-Butyl 4-Methyl-2-(phenylamino)thiazole-5-carboxylate (1l)**

Yield: 159 mg (55%); pale yellow solid; mp 150–152 °C.

IR (KBr): 3002, 3175, 3137, 3061, 3010, 2977, 2929, 1681, 1671, 1329, 1100 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.58 (s, 1 H), 7.59 (d, J = 7.9 Hz, 2 H), 7.35 (t, J = 7.7 Hz, 2 H), 7.03 (t, J = 7.2 Hz, 1 H), 2.49 (s, 3 H), 1.49 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.08, 161.79, 157.97, 140.63, 129.57, 122.95, 118.42, 111.24, 81.29, 28.44, 17.78.

MS (70 eV): m/z = 290 (M^+), 234 (100%), 217, 189.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_2S$: 291.11617; found: 291.11598.

***tert*-Butyl 2-Amino-4-methylthiazole-5-carboxylate (1m)**

Yield: 105 mg (49%); yellow solid; mp 170–172 °C.

IR (KBr): 3356, 3308, 3110, 2976, 2933, 2760, 1659, 1647, 1509, 1333, 1107 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.59 (s, 2 H), 2.34 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.27, 161.98, 158.66, 109.90, 109.75, 80.52, 28.48, 17.56.

MS (70 eV): m/z = 214 (M^+), 158 (100%), 141, 112.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{15}N_2O_2S$: 215.08487; found: 215.08479.

***tert*-Butyl 2-(Benzylamino)-4-methylthiazole-5-carboxylate (1n)**

Yield: 176 mg (58%); pale yellow solid; mp 115–117 °C.

IR (KBr): 3195, 3087, 3028, 3005, 2981, 2965, 2934, 2895, 1697, 1286, 1087 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.71 (t, J = 5.33 Hz, 1 H), 7.37–7.27 (m, 5 H), 4.45 (d, J = 5.6 Hz, 2 H), 2.38 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 169.96, 161.94, 158.72, 138.73, 128.88, 127.77, 127.61, 109.70, 80.69, 47.93, 28.48, 17.78.

MS (70 eV): m/z = 304 (M^+), 248, 91 (100%).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_2S$: 305.1318; found: 305.1317.

***tert*-Butyl 2-(Allylamino)-4-methylthiazole-5-carboxylate (1o)**

Yield: 142 mg (56%); pale yellow solid; mp 125–127 °C.

IR (KBr): 3205, 3093, 3011, 2975, 2935, 2892, 2811, 1694, 1281, 1090 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.37 (t, J = 5.0 Hz, 1 H), 5.91–5.81 (m, 1 H), 5.22 (d, J = 17.4 Hz, 1 H), 5.13 (d, J = 10.4 Hz, 1 H), 3.86 (t, J = 5.0 Hz, 2 H), 2.37 (s, 3 H), 1.46 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 169.86, 161.95, 158.75, 134.56, 116.58, 109.51, 80.64, 46.78, 28.48, 17.74.

MS (70 eV): m/z = 254 (M^+), 198 (100%), 183, 170.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{19}N_2O_2S$: 255.1161; found: 255.1160.

Methyl 2-(Phenylamino)-4-[4-(trifluoromethyl)phenyl]thiazole-5-carboxylate (1p)

Yield: 227 mg (60%); pale yellow solid; mp 177–179 °C.

IR (KBr): 3165, 3043, 2929, 2861, 1711, 1620, 1592, 1563, 1539, 1321, 1138, 1077, 1062, 846, 791, 695 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.88 (s, 1 H), 7.95 (d, J = 7.9 Hz, 2 H), 7.79 (d, J = 7.9 Hz, 2 H), 7.63 (d, J = 8.0 Hz, 2 H), 7.36 (t, J = 7.7 Hz, 2 H), 7.06 (t, J = 7.2 Hz, 1 H), 3.70 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.41, 161.70, 156.78, 140.38, 138.65, 130.96, 129.67, 129,53 (q, $J_{C,F}$ = 31.3 Hz), 124.96 (q, $J_{C,F}$ = 3.7 Hz), 124.42 (q, $J_{C,F}$ = 274.6 Hz), 123.32, 118.58, 110.93, 52.39.

MS (70 eV): m/z = 378 (M^+, 100%), 363, 347, 319, 147, 77.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}F_3N_2O_2S$: 379.0722; found: 379.0721.

Methyl 2-(Benzylamino)-4-[4-(trifluoromethyl)phenyl]thiazole-5-carboxylate (1q)

Yield: 243 mg (62%); pale yellow solid; mp 177–179 °C.

IR (KBr): 3213, 3106, 3049, 2974, 2948, 2894, 1712, 1619, 1589, 1575, 1326, 1265, 1146, 1129, 1079, 1065, 736 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 9.07 (s, 1 H), 7.88 (d, J = 7.6 Hz, 2 H), 7.75 (d, J = 7.7 Hz, 2 H), 7.38–7.29 (m, 5 H), 4.52 (d, J = 4.7 Hz, 2 H), 3.64 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.09, 161.79, 157.46, 138.94, 138.38, 130.89, 129.57 (q, $J_{C,F}$ = 31.6 Hz), 128.95, 128.06, 127.78, 124.80 (q, $J_{C,F}$ = 3.6 Hz), 124.48 (q, $J_{C,F}$ = 270.5 Hz), 109.43, 52.08, 48.81.

MS (70 eV): m/z = 392 (M^+), 91 (100%).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{16}F_3N_2O_2S$: 393.0879; found: 393.0876.

Methyl 2-(Allylamino)-4-(4-methoxyphenyl)thiazole-5-carboxylate (1r)

Yield: 167 mg (55%); yellow solid; mp 152–154 °C.

IR (KBr): 3185, 3086, 2951, 1710, 1585, 1497, 1256, 1150, 1072, 1019, 843, 761 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.75 (t, J = 4.6 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 2 H), 6.93 (d, J = 8.6 Hz, 2 H), 5.94–5.85 (m, 1 H), 5.27 (d, J = 17.2 Hz, 1 H), 5.16 (d, J = 10.2 Hz, 1 H), 3.92 (app t, 2 H), 3.80 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 169.57, 162.15, 160.24, 159.23, 134.44, 131.72, 127.29, 116.95, 113.23, 55.62, 51.85, 46.96.

MS (70 eV): m/z = 304 (M^+, 100%), 303, 289, 273, 163, 134, 41.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_3S$: 305.0954; found: 305.0952.

Ethyl 2,4-Dimethylthiazole-5-carboxylate (2a)

To a solution of ethyl acetoacetate (130 mg, 1 mmol) in H_2O (5 mL) held at 70 °C was added TBCA (146 mg, 0.4 mmol) in small portions and the mixture was stirred at 70 °C for 20 min. The mixture was allowed to cool to r.t. and then, MeCN (5 mL) and thioacetamide (75 mg, 1 mmol) were successively added. The reaction mixture was stirred at r.t. for an additional 20 min. After the completion of the reaction, the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue obtained was purified by column chromatography using EtOAc/hexanes as eluent to give the thiazole **2a**; yield: 139 mg (75%); white solid; mp 50–52 °C (Lit.[36] mp 56 °C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 4.32 (q, J = 7.1 Hz, 2 H), 2.69 (s, 3 H), 2.69 (s, 3 H), 1.36 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 168.99, 162.09, 159.66, 121.80, 61.11, 19.31, 17.15, 14.28.

MS (70 eV): m/z = 185 (M^+), 157, 140 (100%), 116, 71.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_{12}NO_2S$: 186.0583; found: 186.0582.

Quinoxaline Derivatives 3; General Procedure

To a solution of the respective 1,3-dicarbonyl compound (1 mmol) in H_2O (7 mL) held at 70 °C was added TBCA (146 mg, 0.4 mmol) in small portions and the mixture was stirred at 70 °C for 20 min. Then, *o*-phenylenediamine (108 mg, 1 mmol) was added and the mixture was stirred at 70 °C for an additional 3 h. After the completion of the reaction, the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography using EtOAc/hexanes as eluent to give the corresponding quinoxaline.

Ethyl 3-Methylquinoxaline-2-carboxylate (3a)

Yield: 173 mg (80%); white solid; mp 65–67 °C (Lit.[37] mp 67 °C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.20 (d, *J* = 8.3 Hz, 1 H), 8.07 (d, *J* = 8.2 Hz, 1 H), 7.86–7.76 (m, 2 H), 4.57 (q, *J* = 7.1 Hz, 2 H), 1.51 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.64, 152.76, 144.50, 142.37, 139.93, 131.82, 129.83, 128.38, 62.47, 23.64, 14.25.

MS (70 eV): *m*/*z* = 216 (M^+), 187, 172, 144 (100%), 102.

1-(3-Methylquinoxalin-2-yl)ethanone (3b)

Yield: 145 mg (78%); white solid; mp 77–79 °C (Lit.[37] mp 78–80 °C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.13 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.85 (t, *J* = 7.6 Hz, 1 H), 7.83 (t, *J* = 7.6 Hz, 1 H), 3.00 (s, 3 H), 2.86 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 201.21, 152.98, 147.27, 142.19, 139.89, 132.20, 129.87, 129.73, 128.17, 27.79, 24.25.

MS (70 eV): *m*/*z* = 186 (M^+, 100%), 158, 144, 143, 117, 102, 77, 75.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610243.

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