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Cyclization of Active Methylene Isocyanides with α-Oxodithioesters Induced by Base: An Expedient Synthesis of 4-Methylthio/Ethoxycarbonyl-5-acylthiazoles

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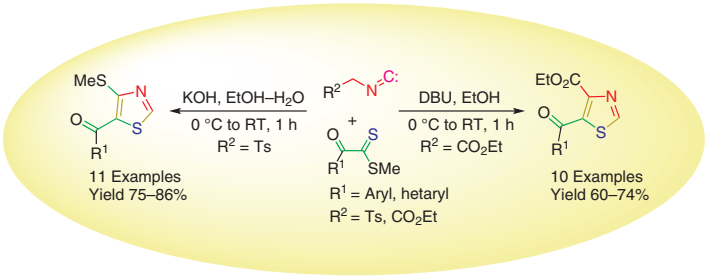

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Abstract Cyclization of tosylmethyl isocyanide with α-oxodithioesters in the presence of KOH is reported for the synthesis of 4-methylthio-5-acylthiazoles. Similarly, ethyl isocyanoacetate underwent cyclization with α-oxodithioesters to form 4-ethoxycarbonyl-5-acylthiazoles in the presence of DBU/EtOH. Mechanisms for the formation of thiazoles are proposed. These thiazoles can also be obtained by Takeda reaction, in which thiazole-4,5-anhydride is acylated with aromatic compounds followed by esterification; however, that approach requires two steps and suffers from the formation of a regioisomeric mixture of products.

Key words thiazole, TosMIC, ethyl isocyanoacetate, α-oxodithioester, cyclization

Thiazoles are among the most important members of the azaheterocycle family. Derivatives of these ring systems exhibit therapeutic properties including anticancer,[1] antimicrobial,[2] anti-inflammatory,[3] antimalarial,[4] antiprotozoal,[5] antiprion[6] and psychotrophic activities.[7] They also show inhibitory action against HIV-1 NNRT,[8] PIN1,[9] and histone acetyl transferase.[10] Some of them have fluorescence[11] and photochromic properties.[12] In addition, they are used in the detection of heavy metals,[13] RNA duplex formation,[14] and for determination of hydrophobic 1° and 2° amines.[15] Thus, the aforementioned properties mark thiazoles as privileged moieties. A selection of important drugs that are approved by FDA with their biological activities and some naturally occurring and synthetically important thiazole containing molecules are given in Figure 1.

The conventional method for the synthesis of thiazoles is the Hantzsch method,[16] which involves cyclocondensation of α-bromo acetophenones with thiourea. Other methods include cyclization of *N*,*N*-diformylaryl ketone with P_2S_5,[17] Cu-catalyzed annulation of amine with aldehyde,[18] condensation of oxime with anhydride and thiocyanide,[19] Pd/Fe-catalyzed condensation of vinyl azides with KSCN,[20] the Ugi reaction,[21] reaction of α-amido-β-keto esters with Lawesson's reagent,[22] and the reaction of thiourea with propargyl bromides.[23] However, these available methods suffer from limitations such as the use of hazardous starting materials, toxic/non-ecofriendly solvents, need for high temperature, long reaction time and tedious workup procedures. Hence, more synthetic methods are required for the synthesis of thiazole moieties.

Notably, thiazoles unsubstituted at the 2-position can be synthesized by the cycloaddition of isocyanide with thiano esters,[24] carbon disulfides,[25] and isothiocyanates[26] or caboxymethyldithioates.[27] Recently, we have reported the synthesis of thiazoles unsubstituted at the 2-position by cyclization of active methylene isocyanides with aryldithiocarboxylates (Scheme 1a)[28] and xanthate esters (Scheme 1b).[29] On the other hand, α-oxodithioesters are a special class of synthons[30] and their synthetic properties have not been much explored. To our knowledge, reaction of active methylene isocyanides with α-oxodithioesters has not been reported. In continuation of our work on the development of new synthetic methods for the synthesis of heterocyclic compounds,[31] we herein report the cyclization of some active methylene isocyanides with α-oxodithioesters (Scheme 1).

In the beginning of our study, we considered the reaction of methyl 2-oxo-2-phenylethanedithioate (**1**) with tosylmethyl isocyanide (**2**) in the presence of various bases (NaH, *t*-BuOK, KOH, K_2CO_3 and DBU) with EtOH as solvent

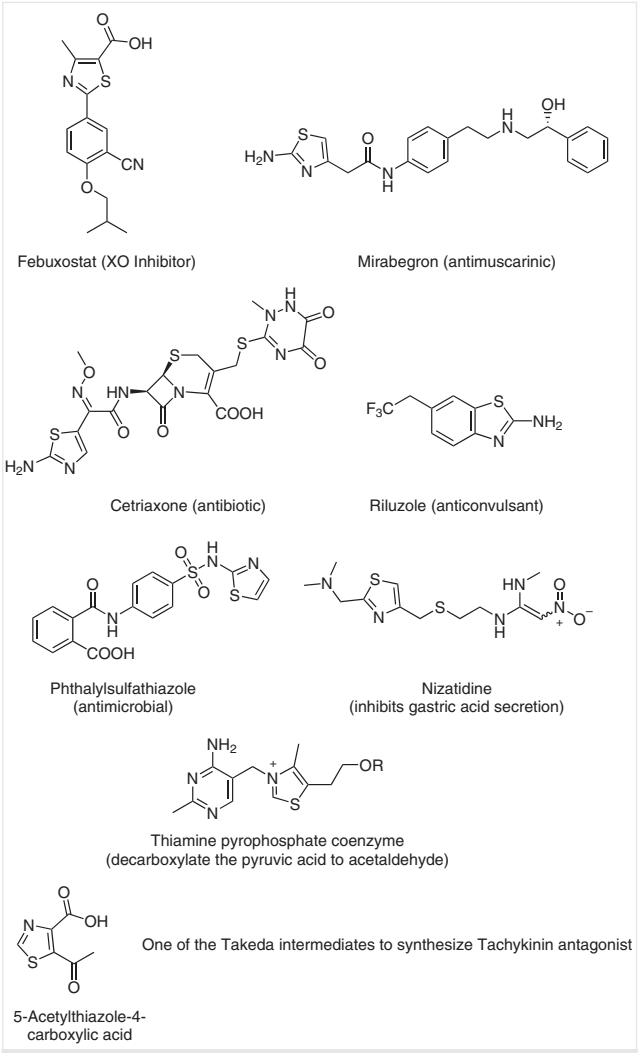
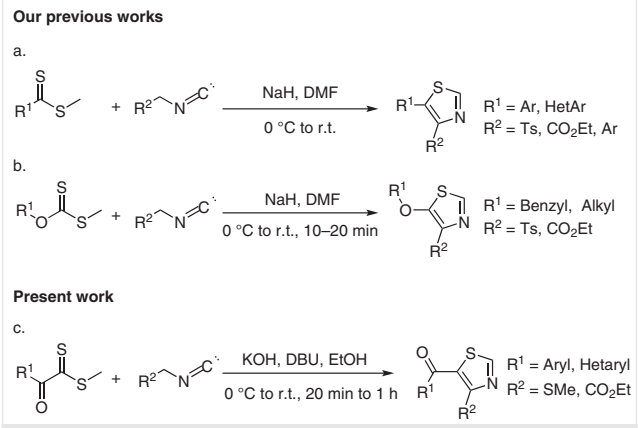


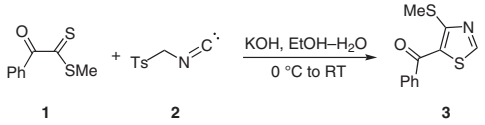
Figure 1 Some significant FDA-approved drugs and naturally occurring thiazoles



Scheme 1 Our previous work and the present work

(Table 1, entries 1–5). Among the bases, KOH was found to be optimal. For the same reaction, variation of solvents (THF, DMSO, acetonitrile and toluene) in the presence of KOH base did not improve the yield (entries 6–9). Finally, aqueous alcoholic KOH gave product in the highest yield, 82% (entry 10).

Table 1 Optimization of the Synthesis of 4-Methylthio-5-phenylthiazoles[a]



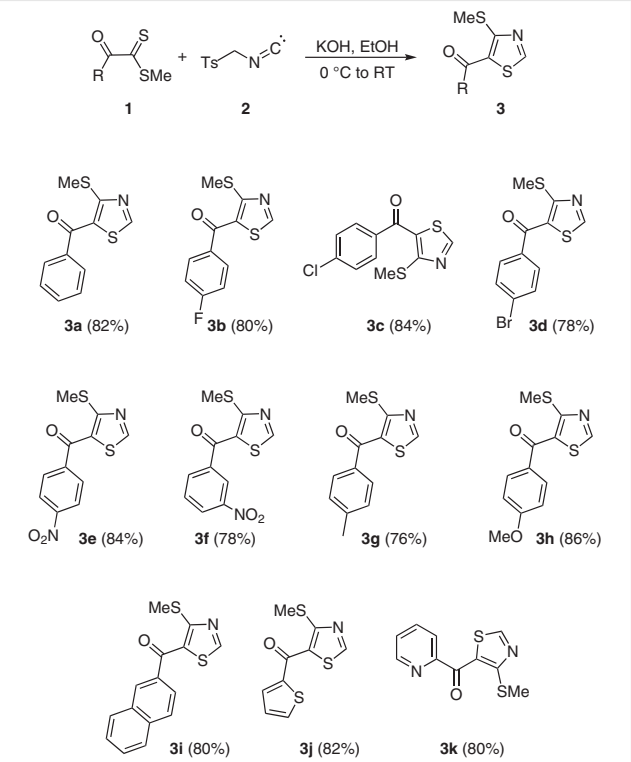
Entry	Solvent	Base	Yield of **3** (%)
1	EtOH	NaH	12
2	EtOH	*t*-BuOK	24
3	EtOH	KOH	75
4	EtOH	K_2CO_3	50
5	EtOH	DBU	43
6	THF	KOH	23
7	DMSO	KOH	16
8	MeCN	KOH	trace
9	toluene	KOH	trace
10	EtOH–H_2O	KOH	82

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), KOH (1 mmol), EtOH/H_2O (3 mL/3 drops), 0 °C to r.t.

Thus, with the combination of KOH base and EtOH solvent, we explored the potential of the reaction by taking various substrates. To our delight, α-oxodithioesters substituted with F, Cl and Br substituents formed the respective products **3b–d** in 78–84% yield (Scheme 2). The methyl 2-(4-nitrophenyl)-2-oxoethanedithioate also underwent smooth cyclization with **2** to form (4-(methylthio)thiazol-5-yl)(4-nitrophenyl)methanone (**3e**) in 84% yield. Similarly, substrates with electron-donating groups (Me and OMe) also furnished the corresponding products **3g** and **3h** in 76 and 86% yield, respectively.

Finally, α-oxodithioesters containing naphthyl and thienyl groups also afforded desired thiazoles **3i** and **3j** in 80 and 82% yield, respectively. In the ^{1}H NMR spectra, all compounds showed a characteristic peak of thiomethyl around δ = 2.7 ppm and a characteristic peak of thiazole around δ = 8.0 ppm.

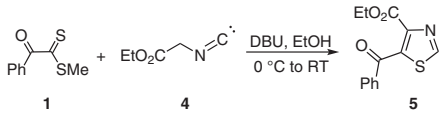
We also considered the reaction of methyl 2-oxo-2-phenylethanedithioate (**1**) with ethyl isocyanoacetate (**4**) in the presence of various bases (NaH, *t*-BuOK, KOH, K_2CO_3 and DBU) with EtOH as solvent (Table 2, entries 1–5). Among the bases, DBU was found to be optimal. Performing the reaction in various solvents (THF, DMSO, acetonitrile



Scheme 2 Synthesis of 4-methylthio-5-acylthiazoles **3** from α-oxodithioesters **1**. *Reagents and conditions*: **1** (1 mmol), **2** (1 mmol), KOH (2 mmol), EtOH (3 mL), 1 h.

and toluene) in the presence of DBU base did not improve the yield (entries 6–9). Thus, DBU in ethanol was found to be the best combination (entry 5).

Table 2 Optimization for the Synthesis of Ethyl 5-Benzoylthiazole-4-carboxylate[a]

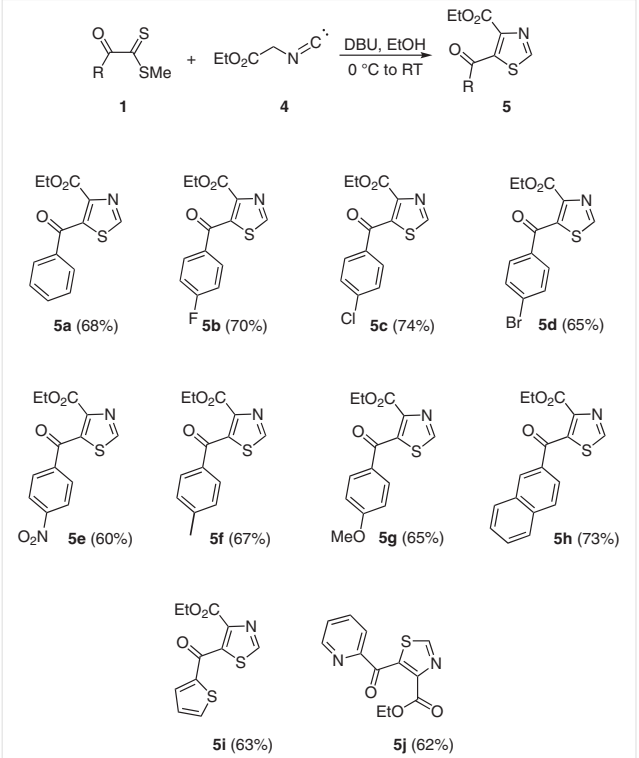


Entry	Solvent	Base	Yield of **5** (%)
1	EtOH	NaH	26
2	EtOH	*t*-BuOK	38
3	EtOH	KOH	18
4	EtOH	K_2CO_3	52
5	EtOH	DBU	68
6	THF	DBU	32
7	DMSO	DBU	41
8	MeCN	DBU	52
9	toluene	DBU	18

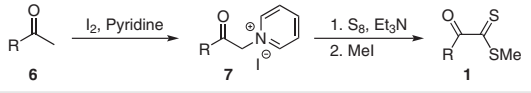
[a] Reaction conditions: **1** (0.5 mmol), **4** (0.5 mmol), DBU (1 mmol), EtOH (3 mL), 0 °C to room temperature.

To establish the scope of the protocol, we investigated the reaction of various dithioesters **1** bearing halogens (F, Cl and Br), electron-withdrawing groups (NO_2), electron-donating groups (Me and OMe), naphthyl and thienyl dithioesters; the reactions furnished the respective ethyl 5-acylthiazole carboxylates **5a–j** in 60–74% yield, respectively (Scheme 3). Similar products can be obtained by using the Takeda reaction, which involves Friedel–Crafts acylation of thiazole-4,5-anhydride with aromatic compounds to give 5-acyl-thiazole-4-carboxylic acid followed by esterification.[32] To obtain **5** by using the Takeda approach requires two steps. Furthermore, regioisomeric products are formed during acylation. Thus, our method is superior over the Takeda approach. All compounds were characterized by analytical techniques. For instance, the NMR spectra showed signals around δ = 1.5 ppm for methyl as a triplet, δ = 4.5 ppm for methylene as a quartet and around δ = 8.4 ppm for the thiazole proton as singlet.

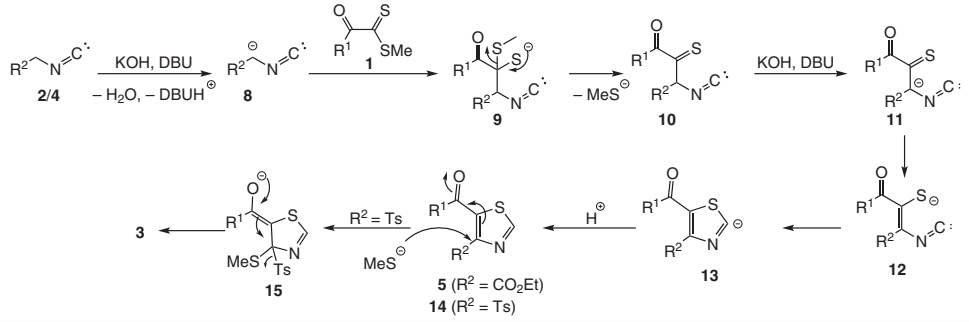
The required substrates were synthesized by a slight modification of the reported protocol, which involves the



Scheme 3 Synthesis of ethyl 5-acylthiazole carboxylates **5** from α-oxodithioesters **1**. *Reagents and conditions*: **1** (1 mmol), **4** (1 mmol), KOH (2 mmol), EtOH (3 mL), 1 h.



Scheme 4 Synthesis of α-oxodithioesters from methyl ketones



Scheme 5 Probable mechanisms for the formation of thiazoles **3** and **5**

reaction of methyl ketones with iodine and pyridine to form pyridinium salts, which were converted into α-oxo-dithioesters after treatment with sulfur and methyl iodide in the presence of triethyl amine (Scheme 4).

A probable mechanism for the formation thiazoles **3** and **5** is given in Scheme 5. The pathway involves reaction of active methylene isocyanides **2** and **4** with KOH/DBU to form the respective anions **8**. Nucleophilic attack on the thiocarbonyl group of **1** forms anion **9**. Elimination of methanethiolate from **9** furnishes the condensation intermediate **10**. Abstraction of another active hydrogen by KOH/DBU forms anion **11**, which is resonance stabilized to give enethiolate **12**. Cyclization of **12** forms thiazole anion **13**. In the latter, the tosyl group is substituted with methanethiolate to form thiazole **3** *via* the Michael addition intermediate **15**, which is formed after the protonation of **14**. On the other side, ethyl carboxylate was retained in thiazole **5**. Intermediate anion **13** was protonated from either water or alcohol to give thiazoles **3** and **5**.

All reagents and solvents were purchased from commercial suppliers and used as such. The methyl α-oxo-dithioates[31e] and ethyl isocyano acetate[32] were prepared by following reported procedures. All the reactions were monitored by TLC using commercially available precoated plates (MERCK 60F254, 0.25 mm thickness) and visualized under UV light. ^{1}H and ^{13}C NMR spectra were obtained with an AGILENT NMR spectrometer. Chemical shift (δ) are given in ppm using $CDCl_3$ solvent as reference relative to TMS, coupling constant (*J*) values are given in Hz, mass spectral analysis was performed with a Water-Synapt G2 mass spectrometer. The single-crystal X-ray diffraction data of the compound was generated with a Rigoku SMART Lab model, Japan, using a Cu source at r.t. with the monochrome beam method. The structure was established by full matrix least square methods using SHELKS program. Melting points were determined with a SELACO melting-point apparatus and are uncorrected.

Synthesis of 3; General Procedure

A solution of KOH (1.01 mmol) in EtOH was placed in an ice bath for 10 minutes. To the cooled solution was added a mixture of the oxodithioate (0.51 mmol) and TosMIC (0.56 mmol) in EtOH, and the reaction mixture was allowed to reach to r.t. The reaction was quenched with ice-cooled water and the mixture was extracted with EtOAc (3 × 25 mL), washed with brine solution, dried over Na_2SO_4 and evaporated. The crude material was subjected to column chromatography using hexane/EtOAc solvent system to give the desired compound.

Synthesis of 5; General Procedure

A solution of DBU (1.01 mmol) in EtOH was placed in an ice bath for 10 minutes A mixture of the oxodithioate (0.51 mmol) and ethyl cyanoacetate (0.56 mmol) in EtOH was added, the mixture was allowed to attain r.t. The reaction was quenched with ice cooled water and the mixture was extracted with EtOAc (3 × 25 mL), washed with brine solution, dried over Na_2SO_4, and evaporated. The crude material was subjected to column chromatography using hexane/EtOAc solvent system to give the desired compound.

(4-(Methylthio)thiazol-5-yl)(phenyl)methanone (3a)

Yield: 82% (98 mg); yellow solid; mp 110–112 °C.

IR (KBr): 2968, 1623, 1348, 1308, 1277 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H, Ar-H), 7.82 (t, *J* = 6.8 Hz, 2 H, Ar-H), 7.60 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.50 (t, *J* = 8.0 Hz, 2 H, Ar-H), 2.74 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.5, 176.2, 149.1, 138.6, 137.6, 132.8, 128.9, 128.7, 16.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9NOS_2$: 236.0198; found: 236.0190.

(4-Fluorophenyl)(4-(methylthio)thiazol-5-yl)methanone (3b)

Yield: 80% (95 mg); pale-yellow solid; mp 134–136 °C.

IR (KBr): 2944, 1624, 1597, 1349, 1314 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, Ar-H), 7.87 (dd, *J* = 5.6, 3.2 Hz, 2 H, Ar-H), 7.18 (t, *J* = 8.8 Hz, 2 H, Ar-H), 2.74 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9, 166.8 and 164.2 (*J* = 254 Hz), 148.8, 145.9, 138.3, 133.9, 131.5 and 131.4 (*J* = 9.2 Hz), 115.9 and 115.8 (*J* = 21 Hz), 16.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8FNOS$: 254.0104; found: 254.0100.

(4-Chlorophenyl)(4-(methylthio)thiazol-5-yl)methanone (3c)

Yield: 84% (98 mg); pale-yellow solid; mp 145–147 °C.

IR (KBr): 2948, 1625, 1347, 1312 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.48 (d, *J*=8.4 Hz, 2 H, Ar-H), 2.74 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1, 176.6, 148.9, 139.3, 138.2, 135.9, 130.3, 129.0, 16.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8ClNOS_2$: 269.9809; found: 269.9816.

(4-Bromophenyl)(4-(methylthio)thiazol-5-yl)methanone (3d)

Yield: 78% (89 mg); pale-yellow solid; mp 128–130 °C.

IR (KBr): 2948, 1630, 1347, 1311, 681 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, Ar-H), 7.70 (dd, *J* = 4.8, 2.0 Hz, 2 H, Ar-H), 7.66–7.63 (m, 2 H, Ar-H), 2.74 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.3, 176.7, 149.0, 138.1, 136.3, 132.0, 130.4, 127.8, 16.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8BrNOS_2$: 313.9303 and 315.9283; found: 313.9301 and 315.9298.

(4-(Methylthio)thiazol-5-yl)(4-nitrophenyl)methanone (3e)

Yield: 84% (98 mg); pale-yellow solid; mp 182–185 °C.

IR (KBr): 2976, 1633, 1346, 1310, 1280 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 8.4, 2 H, Ar-H), 7.98 (t, *J* = 8.8 Hz, 3 H, Ar-H), 2.76 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.5, 178.6, 150.1, 149.7, 142.7, 137.7, 129.7, 123.9, 16.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8N_2O_3S_2$: 281.0049; found: 281.0052.

(4-(Methylthio)thiazol-5-yl)(3-nitrophenyl)methanone (3f)

Yield: 78% (90 mg); pale-yellow solid; mp 173–175 °C.

IR (KBr): 2987, 1644, 1351, 1323, 1277 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 1 H, Ar-H), 8.47 (d, *J* = 8.0 Hz, 1 H, Ar-H), 8.15 (s, 1 H, Ar-H), 8.05 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.77–7.69 (m, 1 H Ar-H), 2.78 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 151.4, 148.8, 140.9, 139.4, 136.2, 131.9, 128.8, 128.6, 125.5, 18.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8N_2O_3S_2$: 279.9976; found: 279.9985.

(4-(Methylthio)thiazol-5-yl)(*p*-tolyl)methanone (3g)

Yield: 76% (90 mg); pale-yellow solid; mp 80–82 °C.

IR (KBr): 2964, 1620, 1499, 1350, 1297 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, Ar-H), 7.72 (d, *J* = 7.6 Hz, 2 H, Ar-H), 7.26 (d, *J* = 8.0 Hz, 2 H, Ar-H), 2.70 (s, 3 H, SMe), 2.40 (s, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0, 175.7, 148.6, 143.6, 138.7, 134.9, 129.3, 129.0, 21.6, 16.5.

HRMS (ESI): *m*/*z* [M + H]$^+$calcd for $C_{12}H_{11}NOS_2$: 250.0335; found: 250.0339.

(4-Methoxyphenyl)(4-(methylthio)thiazol-5-yl)methanone (3h)

Yield: 86% (101 mg); pale-yellow solid; mp 116–118 °C.

IR (KBr): 2983, 1642, 1453, 1376, 1285 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, Ar-H), 7.85 (dd, *J* = 5.2, 2.0 Hz, 2 H, Ar-H), 6.97 (dd, *J* = 4.8, 2.0 Hz, 2 H, Ar-H), 3.88 (s, 3 H, OMe), 2.73 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.0, 175.4, 163.5, 148.2, 138.7, 131.3, 130.2, 113.9, 55.5, 16.6.

HRMS (ESI): *m*/*z* [M + H]$^+$calcd for $C_{12}H_{11}NO_2S_2$: 266.0304; found: 266.0300.

(4-(Methylthio)thiazol-5-yl)(naphthalen-2-yl)methanone (3i)

Yield: 80% (93 mg); pale-yellow solid; mp 82–84 °C.

IR (KBr): 2963, 1640, 1568, 1432, 1307 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, Ar-H), 8.13 (s, 1 H, Ar-H), 7.93 (dd, *J* = 12.8, 6.8 Hz, 4 H, Ar-H), 7.63–7.55 (m, 2 H, Ar-H), 2.76 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 176.1, 149.0, 138.7, 135.3, 134.9, 132.3, 130.4, 129.3, 128.8, 128.5, 127.9, 127.1, 124.8, 16.6.

HRMS (ESI): *m*/*z* [M + H]$^+$calcd for $C_{15}H_{11}NOS_2$: 286.0335; found: 286.0332.

(4-(Methylthio)thiazol-5-yl)(thiophen-2-yl)methanone (3j)

Yield: 82% (98 mg); pale-yellow solid; mp 108–110 °C.

IR (KBr): 2920, 1610, 1500, 1413, 1347 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, Ar-H), 7.84 (d, *J* = 3.2 Hz, 1 H, Ar-H), 7.71 (d, *J* = 4.8 Hz, 1 H, Ar-H), 7.19 (t, *J* = 4.4 Hz, 1 H, Ar-H), 2.75 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 175.5, 147.3, 142.4, 137.9, 133.9, 132.8, 128.2, 16.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_7NOS_3$: 241.9763; found: 241.9769.

(4-(Methylthio)thiazol-5-yl)(pyridin-2-yl)methanone (3k)

Yield: 80% (96 mg); pale-yellow solid; mp 120–122 °C.

IR (KBr): 2970, 1646, 1560, 1480, 1365 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1 H, Ar-H), 8.72 (d, *J* = 4.4 Hz, 1 H, Ar-H), 8.19 (d, *J* = 7.6 Hz, 1 H, Ar-H), 7.91–7.87 (m, 1 H, Ar-H), 7.50 (dd, *J* = 2.4, 12.4 Hz, 1 H, Ar-H), 2.76 (s, 3 H, SMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2, 154.7, 153.5, 150.2, 139.2, 139.1, 135.0, 128.9, 125.4, 18.2

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8N_2OS_2$: 237.0156; found: 237.0157.

Ethyl 5-Benzoylthiazole-4-carboxylate (5a)

Yield: 68% (90 mg); mp 92–94 °C.

IR (KBr): 3051, 2946, 1616, 1414, 1350 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H, Ar-H), 7.90–7.87 (m, 2 H, Ar-H), 7.66 (dd, *J* = 7.6, 1.6 Hz, 1 H, Ar-H), 7.56–7.52 (dd, *J* = 6.4, 1.6 Hz, 2 H, Ar-H), 4.53–4.48 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.8, 162.9, 159.4, 148.9, 143.2, 136.9, 133.6, 129.2, 128.9, 63.1, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}NO_3S$: 262.0582; found: 262.0585.

Ethyl 5-(4-Fluorobenzoyl)thiazole-4-carboxylate (5b)

Yield: 70% (91 mg); pale-yellow solid; mp 138–140 °C.

IR (KBr): 3025, 2951, 1736, 1631, 1406 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H, Ar-H), 7.93 (dd, *J* = 5.6, 5.2 Hz, 2 H, Ar-H), 7.22 (t, *J* = 8.8 Hz, 2 H, Ar-H), 4.53–4.48 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.45 (t, *J* = 7.6 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.2, 167.3 and 164.7 (*J* = 260 Hz), 163.0, 159.4, 148.7, 143.0, 133.2, 132.0, and 131.9 (*J* = 10 Hz), 116.4 and 116.1 (*J* = 30 Hz), 63.3, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}FNO_3S$: 280.0438; found: 280.0442.

Ethyl 5-(4-Chlorobenzoyl)thiazole-4-carboxylate (5c)

Yield: 74% (95 mg); pale-yellow solid; mp 106–110 °C.

IR (KBr): 3033, 1648, 1453, 1363, 1308 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H, Ar-H), 7.83 (t, *J* = 8.4 Hz, 2 H, Ar-H), 7.51 (d, *J* = 8.4 Hz, 2 H, Ar-H), 4.49 (d, *J* = 7.2 Hz, 2 H, CH_2), 1.44 (t, *J* = 7.2 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5, 163.2, 159.3, 148.8, 142.9, 140.2, 135.2, 130.6, 129.3, 63.2, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}ClNO_3S$: 296.0143; found: 296.0140.

Ethyl 5-(4-Bromobenzoyl)thiazole-4-carboxylate (5d)

Yield: 65% (80 mg); pale-yellow solid; mp 102–104 °C.

IR (KBr): 2936, 1631, 1305, 1276, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H, Ar-H), 7.76 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.69 (d, *J* = 8.8 Hz, 2 H, Ar-H), 4.54–4.48 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.46 (t, *J* = 7.6 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.7, 163.2, 159.3, 148.8, 142.7, 135.6, 132.3, 130.7, 128.9, 63.2, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}BrNO_3S$: 339.9638 and 341.9707; found: 339.9643 and 341.9701.

Ethyl 5-(4-Nitrobenzoyl)thiazole-4-carboxylate (5e)

Yield: 60% (76 mg); pale-yellow solid; mp 128–130 °C.

IR (KBr): 2952, 1634, 1532, 1409, 1303 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (t, *J* = 12 Hz, 3 H, Ar-H), 8.03 (d, *J* = 8.8 Hz, 2 H, Ar-H), 4.54–4.48 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.45 (t, *J* = 6.8 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.3, 164.1, 159.1, 150.5, 149.5, 142.3, 141.7, 130.1, 124.1, 63.4, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}N_2O_5S$: 307.0383; found: 307.0390.

Ethyl 5-(4-Methylbenzoyl)thiazole-4-carboxylate (5f)

Yield: 67% (88 mg); pale-yellow solid; mp 94–96 °C.

IR (KBr): 2998, 1663, 1598, 1417, 1397 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H, Ar-H), 7.80 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.34 (d, *J* = 8.0 Hz, 2 H, Ar-H), 4.51 (d, *J* = 7.2 Hz, 2 H, CH_2), 2.46 (s, 3 H, Ar-Me), 1.45 (t, *J* = 7.6 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 162.6, 159.5, 148.6, 144.7, 143.5, 134.3, 129.6, 129.4, 63.1, 21.7, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}NO_3S$: 276.0689; found: 276.0695.

Ethyl 5-(4-Methoxybenzoyl)thiazole-4-carboxylate (5g)

Yield: 65% (84 mg); pale-yellow solid; mp 134–136 °C.

IR (KBr): 3021, 1723, 1568, 1461, 1357 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, Ar-H), 7.91 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.01 (d, *J* = 8.8 Hz, 2 H, Ar-H), 4.53–4.48 (q, *J* = 7.2 Hz, 2 H, CH_2), 3.90 (s, 3 H, OMe), 1.45 (t, *J* = 7.2 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1, 164.1, 162.3, 159.5, 148.2, 143.6, 131.8, 129.5, 114.2, 63.2, 55.6, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}NO_4S$: 292.0638; found: 292.0635.

Ethyl 5-(2-Naphthoyl)thiazole-4-carboxylate (5h)

Yield: 73% (92 mg); pale-yellow solid; mp 78–80 °C.

IR (KBr): 3017, 1703, 1616, 1484, 1360 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 15.6 Hz, 2 H, Ar-H), 7.99–7.91 (m, 4 H, Ar-H), 7.67–7.58 (m, 2 H, Ar-H), 4.54–4.49 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.45 (t, *J* = 7.2 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.7, 162.8, 159.5, 148.9, 143.4, 135.7, 134.3, 132.3, 131.3, 129.6, 129.0, 127.9, 127.3, 124.6, 124.3, 63.2, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}NO_3S$: 312.0689; found: 312.0695.

Ethyl 5-(Thiophene-2-carbonyl)thiazole-4-carboxylate (5i)

Yield: 63% (83 mg); pale-yellow solid; mp 96–98 °C.

IR (KBr): 3080, 1744, 1734, 1606, 1505, 1469 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1 H, Ar-H), 7.91 (d, *J* = 5.4 Hz, 1 H, Ar-H), 7.80 (d, *J* = 4.8 Hz, 1 H, Ar-H), 7.24 (t, *J* = 4.8 Hz, 1 H, Ar-H), 4.54–4.49 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.46 (t, *J* = 7.2 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 162.4, 159.4, 147.6, 142.6, 142.3, 135.3, 134.1, 128.5, 63.2, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9NO_3S_2$: 268.0097; found: 268.0096.

Ethyl 5-Picolinoylthiazole-4-carboxylate (5j)

Yield: 62% (82 mg); pale-yellow solid; mp 110–112 °C.

IR (KBr): 3067, 1756, 1782, 1623, 1534, 1480 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (s, 1 H, Ar-H), 8.78 (d, *J* = 4.8 Hz, 1 H, Ar-H), 8.24 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.96–7.92 (m, 1 H, Ar-H), 7.57 (dd, *J* = 1.6, 12.4 Hz, 1 H, Ar-H), 4.54–4.48 (q, *J* = 7.2, 21.6 Hz, 2 H, CH_2), 1.47 (t, *J* = 7.6 Hz, 3 H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9, 167.3, 162.2, 153.8, 153.7, 150.4, 139.4, 138.7, 129.7, 125.5, 64.7, 16.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}N_2O_3S$: 263.0490; found: 263.0485.

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Supporting Information

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