Efficient One-pot Synthesis of Ethyl 2-substitued-4-methylthiazole-5-carboxylates

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General procedures for the synthesis of N-substituted thioureas

Melting points were taken on an X-4 digital melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Elba 1106 elemental analyzer. IR spectra were recorded on a Nicolet FI-IR 360 Spectrophotometer. 1H NMR and 13C NMR spectra were determined on a Bruker AM-400 (400 MHz) spectrometer with TMS as an internal standard. Chemical shifts are reported in δ. Mass Spectra were measured on a HP5988A instrument by direct inlet at 70ev. All materials were obtained from commercial suppliers and used as received. Some N-mono-substituted thioureas are synthesized from substituted aniline derivatives using the methods described in the supporting material.

To a mixture of ethyl acetoacetate (1, 6.50 g, 0.05 mol) in water (50.0 mL) and THF (20.0 mL) below 0 °C was added NBS (10.5 g, 0.06 mol, 1.20 equiv.). The reaction mixture was stirred at room temperature for 2 hrs and thin-layer-chromatography (TLC, petroleum ether-ethyl acetate 2:1, silica gel plate, Rf=0.71, UV lamp detection, λ=254 nm) showed disappearance of compound 1. N-substituted thiourea (3b-3o, 0.05 mol, 1.00 equiv.) was added and the reaction mixture was heated to 80°C for certain amount of time (Table 1). After cooling to r.t., the reaction mixture was filtered to get rid of the insoluble substance, then NH3.H2O (8.0 mL) was added to the filtrate. The resulting yellow floccules were stirred at room temperature for 10 mins and filtered. The filter cake was

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washed with water (100 mL × 3) and recrystallized with ethyl acetate or petroleum ether, then dried to give the target compounds (4b-4o). The related data of some of the new compounds are listed as the following:

**Ethyl 2-(allylamino)-4-methylthiazole-5-carboxylate (4b)**

Yellow needle crystal (4b, 76.0 %), mp.109-110°C, $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.21 (t, 3H, OCH$_2$CH$_3$), 2.39 (s, 3H, thiazole-4-C$_3$H$_3$), 3.86 (d, 2H, CH$_2$CH=CH$_2$), 4.35 (q, 2H, OCH$_2$CH$_3$), 5.13 (d, 1H, CH$_2$CH=CH$_2$-cis), 5.22 (d, 1H, -CH$_2$CH=CH$_2$-trans), 5.83 (m, 1H, CH$_2$CH=CH$_2$), 8.48 (1H, thiazole-2-NH); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 14.12 (OCH$_2$CH$_3$), 16.42 (thiazole-4-C$_3$H$_3$), 21.32 (phenyl-4-C$_6$H$_5$), 60.72 (OCH$_2$CH$_3$), 116.12 (thiazole-5-C), 117.40 (CH$_2$CH=CH$_2$), 135.50 (CH$_2$CH=CH$_2$), 156.54 (thiazole-4-C), 162.55 (O=C), 168.41 (thiazole-2-C), MS: m/z 227 (M+H$^+$).

Anal. Calcd for C$_{10}$H$_{14}$N$_2$O$_2$S: C, 53.08; H, 6.24; N, 12.38. Found: C, 53.18; H, 6.35; N 12.49.

**Ethyl 2-(p-tolylamino)-4-methylthiazole-5-carboxylate (4f)**

Yellow crystal (4f, 65.0 %), mp.151-154°C, $^1$H NMR (CDCl$_3$, 100 MHz): $\delta$ 1.33 (t, 3H, OCH$_2$CH$_3$), 2.38 (s, 3H, Phenyl-4-C$_6$H$_5$), 2.55 (s, 3H, thiazole-4-C$_3$H$_3$), 4.28 (q, 2H, OCH$_2$CH$_3$), 7.20-7.26 (m, 4H, Ph-H × 4), 7.28 (1H, thiazole-2-NH); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 14.16 (OCH$_2$CH$_3$), 16.41 (thiazole-4-C$_3$H$_3$), 21.32 (phenyl-4-C$_6$H$_5$), 60.97 (OCH$_2$CH$_3$), 116.34 (thiazole-5-C), 120.3 (2, 6-C-Ph), 131.20 (4C-Ph), 137.50 (1C-Ph), 129.3 (3, 5-C-Ph), 156.24 (thiazole-4-C), 162.55 (O=C), 159.31 (thiazole-2-C), MS: m/z 277 (M+H$^+$).

Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_2$S: C, 60.85; H, 5.84; N, 10.14. Found: C, 61.02; H, 5.98; N 11.27.

**Ethyl 2-(p-aminosulfonylphenylamino)-4-methylthiazole-5-carboxylate (4g)**

White crystal (4g, 55.9 %), mp.245-247°C, $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.24 (t, 3H, OCH$_2$CH$_3$), 2.53 (s, 3H, thiazole-4-C$_3$H$_3$), 4.20 (q, 2H, OCH$_2$CH$_3$), 7.13 (br, 1H, phenyl-NH-thiazole), 7.25 (br, 2H, -SO$_2$NH$_2$), 7.74-7.78 (m, 4H, Ph-H×4); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 14.13 (OCH$_2$CH$_3$), 16.40 (thiazole-4-C$_3$H$_3$), 60.79 (OCH$_2$CH$_3$),
116.16 (thiazole-5-C), 113.83 (2,6-C-Ph), 129.81 (3,5-C-Ph), 130.98 (4-C-Ph), 143.79 (1-C-Ph), 156.53 (thiazole-4-C), 159.29 (thiazole-2-C), 162.59 (O=C), MS: m/z 342 (M+H+).

**Anal.** Calcd for C13H14N3O4S2: C, 45.73; H, 4.43; N, 12.31. Found: C, 45.92; H, 4.61; N, 12.58.

**Ethyl 2-phenylamino-4-methylthiazole-5-carboxylate (4h)**

Pale red crystal (4h, 50.0%), mp. 191-192°C, \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.33 (t, 3H, OCH\(_2\)C\(\text{H}_3\)), 2.55 (s, 3H, thiazole-4-C\(\text{H}_3\)), 4.28 (q, 2H, OCH\(_2\)CH\(_3\)), 7.20-7.23 (m, 4H, Ph\(_\times 4\)), 7.25 (1H, thiazole-2-NH); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 14.10 (OCH\(_2\)C\(\text{H}_3\)), 16.42 (thiazole-4-C\(\text{H}_3\)), 60.72 (OCH\(_2\)CH\(_3\)), 116.14 (thiazole-5-C), 117.98 (2, 6-C-Ph), 122.42 (4-C-Ph), 129.5 (3, 5-C-Ph), 140.52 (1-C-Ph), 156.34 (thiazole-4-C), 159.30 (thiazole-2-C), 162.95 (O=C), MS: m/z 263 (M+H\(^+\)).

**Anal.** Calcd for C\(_{13}\)H\(_{14}\)N\(_2\)O\(_2\)S: C, 59.50; H, 5.38; N, 10.68. Found: C, 59.65; H, 5.51; N, 10.79.

**Ethyl 2-(4-fluorophenylamino)-4-methylthiazole-5-carboxylate (4i)**

Pale yellow solid (4i, 25.0%), mp. 148-150°C, \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) : 1.37 (t, 3H, OCH\(_2\)C\(\text{H}_3\)), 2.66 (s, 3H, thiazole-4-C\(\text{H}_3\)), 4.18 (q, 2H, OCH\(_2\)CH\(_3\)), 7.17 (br, 1H, thiazole-2-NH), 7.48-8.16 (m, 4H, Ph-\(\times 4\)), \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 14.03 (OCH\(_2\)C\(\text{H}_3\)), 16.49 (thiazole-4-C\(\text{H}_3\)), 60.89 (OCH\(_2\)CH\(_3\)), 116.14 (thiazole-5-C), 116.98 (3, 5-C-Ph), 120.61 (2, 6-C-Ph), 136.18 (1-C-Ph), 157.39 (4-C-Ph), 156.59 (thiazole-4-C), 159.39 (thiazole-2-C), 162.52 (O=C), MS: m/z 281 (M+H\(^+\)).

**Anal.** Calcd for C\(_{13}\)H\(_{13}\)FNO\(_2\)S: C, 55.70; H, 4.67; N, 9.99. Found: C, 55.89; H, 4.51; N, 10.13.

**Ethyl 2-(4-methoxyphenylamino)-4-methylthiazole-5-carboxylate (4m)**

Pale yellow powder (4m, 14.0%), mp. 140-143°C, \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.36 (t, 3H, OCH\(_2\)C\(\text{H}_3\)), 2.54 (s, 3H, thiazole-4-C\(\text{H}_3\)), 2.59 (s, 3H, Ph-4-OCH\(_3\)), 4.30 (q, 2H, OCH\(_2\)CH\(_3\)), 7.26 (d, 2H, \(J = 8.8\), 2,5-Ph-H \(\times 2\)), 7.52 (d, 2H, \(J = 8.8\), 3,5-Ph-H \(\times 2\)), 7.53 (br, 1H, thiazole-2-NH); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 14.22 (OCH\(_2\)CH\(_3\)), 16.58 (thiazole-4-C\(\text{H}_3\)), 55.80 (Ph-4-OCH\(_3\)), 60.23 (OCH\(_2\)CH\(_3\)), 115.10 (3, 5-C-Ph), 116.21 (thiazole-5-C), 127.71 (2,
6-C-Ph), 132.82 (1C-Ph), 153.29 (4C-Ph), 156.54 (thiazole-4-C), 159.32 (thiazole-2-C), 162.55 (O=C), MS: m/z 293 (M+H⁺).

Anal. Calcd for C₁₄H₁₆N₂O₃S: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.63; H, 5.40; N 9.76.

Ethyl 2-(2-methyl-3-chlorophenylamino)-4-methylthiazole-5-carboxylate (4n)

White solid (4n, 23.0 %), mp.116-120°C, lit. 110-120°C, 1H NMR (CDCl₃, 400 MHz): δ 1.37 (t, 3H, OCH₂CH₃), 2.66 (s, 3H, thiazole-4-C₃H₃), 4.18 (q, 2H, OCH₂CH₃), 7.63-7.68 (m, 4H, Ph-CH₃×4), 8.10 (br, 1H, thiazole-2-NH); ¹³C NMR (CDCl₃, 100 MHz): δ 14.02 (OCH₂CH₃), 14.39 (2-Ph-C₃H₃), 16.42 (thiazole-4-C₃H₃), 60.92 (OCH₂CH₃), 116.10 (thiazole-5-C), 118.70 (6C-Ph), 121.98 (5C-Ph), 127.89 (6C-Ph), 130.11 (2C-Ph), 135.20 (3C-Ph), 143.42 (1C-Ph), 156.34 (thiazole-4-C), 159.85 (thiazole-2-C), 162.95 (O=C), MS: m/z 311 (M+H⁺).

Anal. Calcd for C₁₄H₁₅ClN₂O₂S: C, 54.10; H, 4.86; N, 9.01. Found: C, 54.34; H, 4.99; N 9.38.

Ethyl 2-(4-bromophenylamino)-4-methylthiazole-5-carboxylate (4o)

Yellow powder (4o, 26.4 %), mp.151-153°C, ¹H NMR (CDCl₃, 100 MHz): δ 1.33 (t, 3H, OCH₂CH₃), 2.54 (s, 3H, thiazole-4-C₃H₃), 4.26 (q, 2H, OCH₂CH₃), 6.96 (d, 2H, J = 8.8, 2,6-Ph-H×2), 7.30 (d, 2H, J = 8.8, 3,5-Ph-H×2), 7.31 (1H, thiazole-2-NH); ¹³C NMR (CDCl₃, 100 MHz): δ 14.12 (OCH₂CH₃), 16.48 (thiazole-4-C₃H₃), 60.93 (OCH₂CH₃), 116.08 (thiazole-5-C), 117.18 (4C-Ph), 118.95 (2,6-C-Ph), 132.41 (2,6-C-Ph), 139.52 (1C-Ph), 156.58 (thiazole-4-C), 159.38 (thiazole-2-C), 162.59 (O=C), MS: m/z 342 (M+H⁺).

Anal. Calcd for C₁₃H₁₃BrN₂O₂S: C, 45.76; H, 3.84; N, 8.21. Found: C, 46.02; H, 4.17; N 8.45.

The original spectra of Ethyl 2-amino-4-methylthiazole-5-carboxylate (4a) are listed as following:

![](image)

¹H NMR (CDCl₃, 400 MHz):
$^{13}$C NMR (CDCl$_3$, 100 MHz):