Convenient One-Pot Two-Step Synthesis of 1,3-Thiazoles via Organocatalyzed Epoxidation of Nitroolefins

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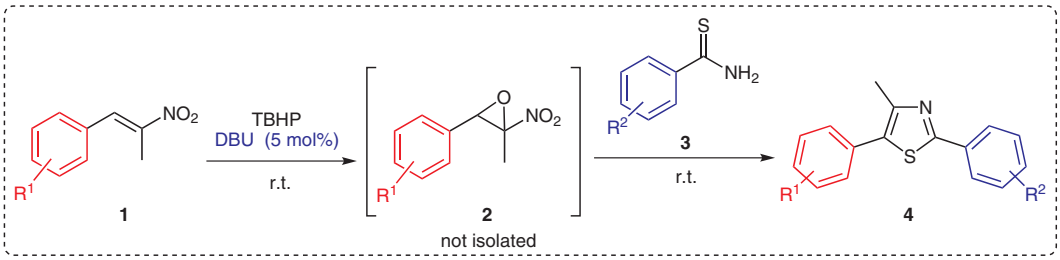
Abstract: A convenient novel one-pot two-step strategy and its substrate scope for the synthesis of 1,3-thiazole heterocycles via organocatalytic epoxidation of nitroolefins with the TBHP/DBU system, and subsequent reaction of α-nitroepoxides with thioamides is reported.

Key words: thiazole, epoxidation, DBU, one-pot reaction, organocatalysis



Scheme 1 One-pot two-step process for the synthesis of 1,3-thiazoles

Thiazole heterocycles are of prominent importance because of their potential as versatile building blocks for pharmaceuticals and natural products.[1–4] It is obvious, furthermore, that compounds with the thiazole ring have potential biological activity.[5,6]

The most salient method to synthesize thiazoles is the Hantzsch thiazole synthesis where α-haloketones are reacted with thioamides.[7] One of the less explored methods is to prepare thiazoles from the corresponding epoxides (e.g., 2-chlorooxiranes, α-nitroepoxides) and thioamides or thioureas.[8] For the synthesis of epoxides diverse approaches to catalytic epoxidations have been developed in recent years.[9] Newman first reported the thiazole synthesis from the corresponding α-nitroepoxides (generated from nitroolefins with H_2O_2/NaOH system).[8a,b] In continuation of our research on organocatalytic epoxidation reactions,[10] we decided to develop an organocatalytic epoxidation of nitroolefins with an intention to further apply the corresponding products, α-nitroepoxides, without workup and purification for the synthesis of 1,3-thiazoles.

Notably, one-pot processes, in which chemical transformations are carried out without intermediate isolation and purification steps, are very attractive and sustainable methods in modern synthetic chemistry due to the reduction of time, costs, materials, and waste generation.[11]

Very recently, we disclosed a facile approach to thiazole derivatives:[12] one-pot two-step synthesis, which involves an organocatalytic epoxidation of nitroolefins with TBPH/DBU (*t*-BuOOH/1,8-diazabicyclo[5.4.0]undec-7-ene) system, followed by reaction with different thiobenzamides at room temperature (Scheme 1).

Herein we report the examined substrate scope (20 examples) in our one-pot two-step process using the optimized reaction conditions, as well as propose a plausible reaction mechanism for 1,3-thiazole formation starting from α-nitroepoxides.

Concerning our idea to develop a one-pot procedure towards thiazole synthesis, we first studied the epoxidation of β-methyl-β-nitrostyrene (**1**). The known strategy for epoxidation of α,β-unsaturated δ-lactones and other enones using anhydrous TBHP as an oxidant and DBU as a base (at 120 mol% loading) at 0 °C[13] was recently extended to the epoxidation of the more challenging nitroolefins as substrates.[12] In order to develop a catalytic epoxidation of β-methyl-β-nitrostyrene (**1**), we used merely catalytic amounts of DBU in combination with TBHP as oxidant. After an optimization series, it was found that DBU could be used in only 5 mol% loading in *n*-hexane at room temperature to generate high conversions of the corresponding α-nitroepoxide **2** after one hour reaction time. Epoxide **2** can be used directly without any

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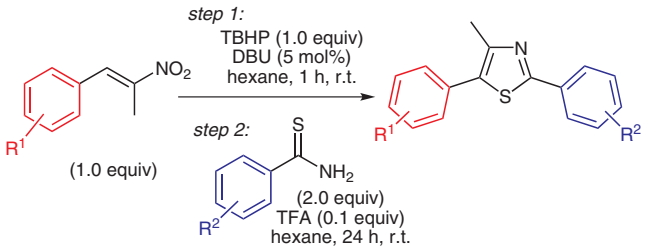
workup procedures for the synthesis of the thiazole heterocycles **4** simply by adding the corresponding thiobenzamide **3** to the reaction mixture. After some investigations, the optimal conditions for the second step of this one-pot procedure proved to be 2.0 equivalents of thiobenzamide with 10 mol% TFA (trifluoroacetic acid) as additive. The corresponding thiazole products were isolated after stirring for 24 hours at room temperature.

We examined the scope of the one-pot process for different aromatic nitroalkenes as well as for different thiobenzamides using the optimized reaction conditions. All reactions investigated could be performed in 22–70% yield, applying DBU at only 5 mol% loading. Higher yields (65–70%) were obtained using β-methyl-β-nitrostyrene and thiobenzamides with R^2 = H, electron-withdrawing, or neutral substituents (Table 1, entries 1–3).

Table 1 Scope of Substrates



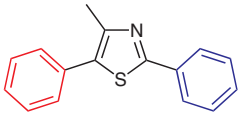
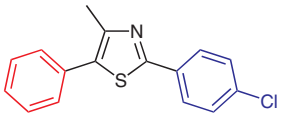
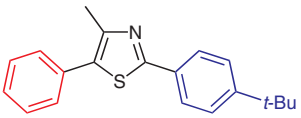
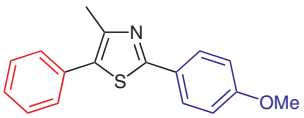
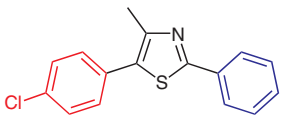
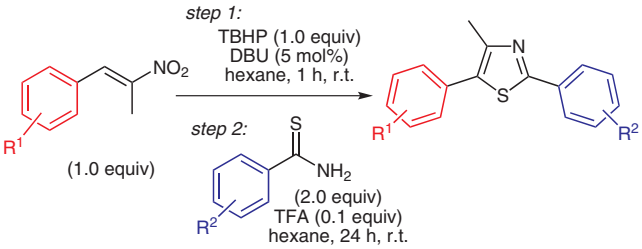
Entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	 **4a**	70
2	H	4-Cl	 **4b**	65
3	H	4-*t*-Bu	 **4c**	65
4	H	4-OMe	 **4d**	41
5[a]	4-Cl	H	 **4e**	50

Table 1 Scope of Substrates (continued)



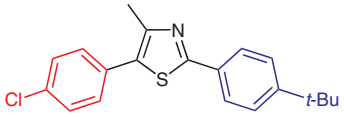
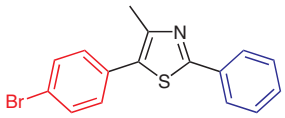
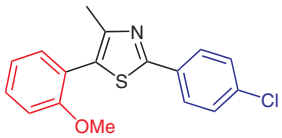
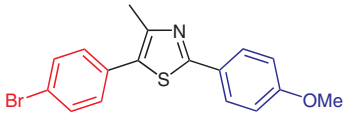
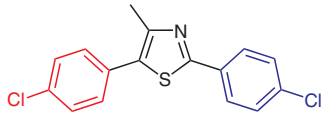
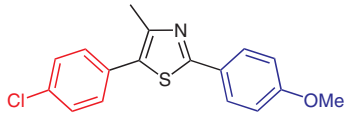
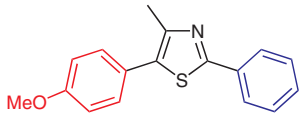
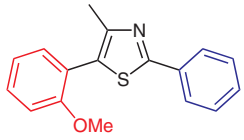
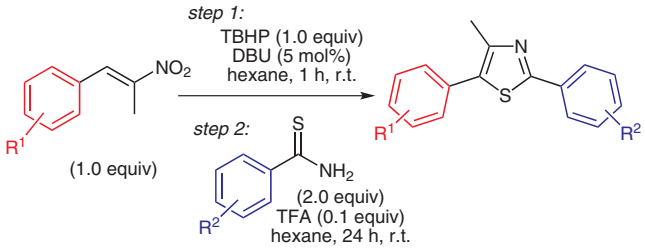
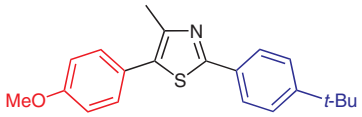
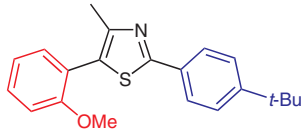
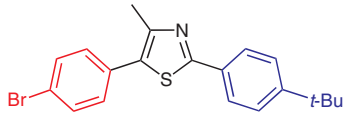
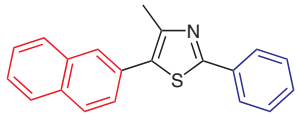
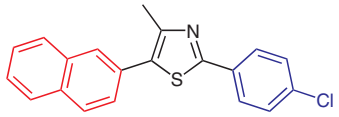
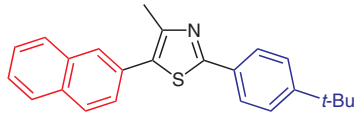
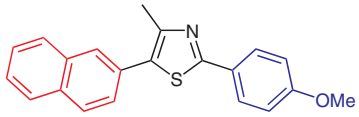
Entry	R^1	R^2	Product	Yield (%)[b]
6[a]	4-Cl	4-*t*-Bu	 **4f**	48
7[a]	4-Br	H	 **4g**	52
8[a]	2-OMe	4-Cl	 **4h**	40
9[a]	4-Br	4-OMe	 **4i**	51
10[a]	4-Cl	4-Cl	 **4j**	40
11[a]	4-Cl	4-OMe	 **4k**	22
12[a]	4-OMe	H	 **4l**	30
13[a]	2-OMe	H	 **4m**	31

Table 1 Scope of Substrates (continued)



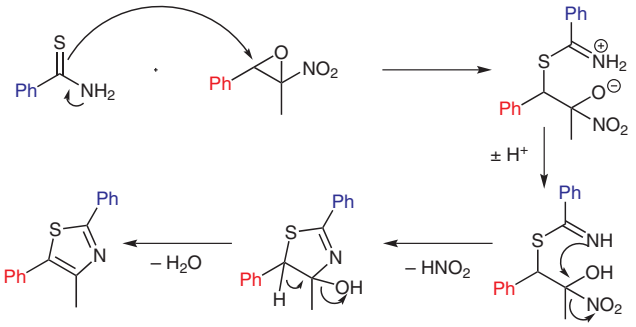
Entry	R^1	R^2	Product	Yield (%)[b]
14[a]	4-OMe	4-*t*-Bu	 **4n**	33
15[a]	2-OMe	4-*t*-Bu	 **4o**	24
16[a]	4-Br	4-*t*-Bu	 **4p**	41
17[a]	3,4-$(CH)_4$	H	 **4q**	35
18[a]	3,4-$(CH)_4$	4-Cl	 **4r**	30
19[a]	3,4-$(CH)_4$	4-*t*-Bu	 **4s**	32
20[a]	3,4-$(CH)_4$	4-OMe	 **4t**	33

[a] MeOH (100 equiv) was added as a second additive.
[b] Isolated yield after column chromatography.

Notably, the presence of OMe group at the aromatic nitroolefin or at the thiobenzamide gave lower yields of the corresponding thiazoles (entries 4, 8, 11–15, 20 vs entries 1–3).

Furthermore, the yields decreased from 65–70% to 30–35% when phenyl moiety in β-methyl-β-nitrostyrene was replaced by naphthyl group and used in the reactions with the same thiobenzamides, where R^2 = H, electron-withdrawing, or neutral substituents (entries 17–19 vs entries 1–3). Interestingly, the reaction conditions using TFA (0.1 equiv) and MeOH (100 equiv) as additive's combination were found to be better suitable (with respect to observed yields) for aromatic nitroolefines with R^1 = electron-withdrawing and/or -donating groups (entries 5–16).

On the basis of related literature known reactions,[15] a proposed mechanism for the thiazole formation could be described as follows (Scheme 2). The thiobenzamide attacks the epoxide at the less hindered carbon atom, followed by ring closure acompanied with release of nitrous acid that presumably decomposes to NO_2 and NO (formation of brown volatiles/gas was observed during the reaction). Finally, aromatization to the thiazole heterocycle occurs under release of water.



Scheme 2 Plausible mechanism for 1,3-thiazole formation using α-nitroepoxides as key starting compounds

In conclusion, the developed one-pot process provides a useful route for the formation of 1,3-thiazoles from easily accessible aromatic nitroolefins. The application of DBU as a readily available organocatalyst for the epoxidation of nitroolefins with TBHP, followed by the reaction with thiobenzamides, and the very mild conditions used for both transformations, make this process a simple and convenient approach to obtain a broad range of 1,3-derived thiazoles in 22–70% yields.

Chemicals were used as received from common commercial sources. All solvents were distilled before use. *n*-Hexane (HPLC grade) was obtained from Fisher Scientific and used as received. Petroleum ether (PE) used refers to the fraction boiling at 40–60 °C. NMR spectra were recorded on Jeol (300 and 400) or Bruker Avance (300 or 400) spectrometer. NMR spectra were referenced to the residual solvent signal (^{1}H: $CDCl_3$, 7.24 ppm; ^{13}C: $CDCl_3$, 77.0 ppm) and recorded at ambient probe temperature. IR spectra were recorded as thin films on a Varian IR-660 spectrometer. FAB mass spectra were measured with a Micromass ZabSpec and EI mass spectra were recorded with a Finnigan MAT 95 XP spectrometer. Gas chromatography was conducted on a Thermo instrument Trace GC Ultra with a 7 m TR5 column. Thin-layer chromatography was carried out on ALUGRAM® SIL G/UV254 (Macherey-Nagel) and visualized by UV. Flash column chromatography was performed using silica gel 60 M (Macherey-Nagel).

One-Pot Two-Step Synthesis of Thiazoles; General Procedure
A round-bottomed flask was charged with *trans*-β-methyl-β-nitrostyrene **1** (0.028 g, 0.170 mmol), DBU (1.3 μL, 0.008 mmol), and *n*-hexane (0.56 mL). Then, TBHP (34.1 μL, 0.170 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 1 h. Then, thiobenzamide (0.047 g, 0.340 mmol) and TFA (1.3 μL, 0.017 mmol) were added, and the mixture was stirred for 24 h at r.t. The crude product was extracted with Et_2O (3 × 3 mL), the solvent evaporated, and the residue purified by column chromatography (SiO_2, PE–EtOAc, 97:3) to yield the desired product.

4-Methyl-2,5-diphenylthiazole (4a)[14]
Yield: 30 mg (70%); white solid; mp 56 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (m, 2 H), 7.49–7.32 (m, 8 H), 2.55 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 148.8, 133.7, 132.2, 129.8, 129.1, 128.9, 128.7, 127.7, 126.3, 16.4.

MS (FAB): *m*/*z* = 252 (100%, M + H$^+$).

2-(4-Chlorophenyl)-4-methyl-5-phenylthiazole (4b)[14]
Yield: 32 mg (65%); white solid; mp 114 °C.

IR (film): 2922, 2360, 1653, 1600, 1572, 1534 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.84 (m, 2 H), 7.48–7.35 (m, 7 H), 2.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 149.0, 135.7, 132.6, 132.2, 131.9, 129.1, 129.1, 128.7, 127.9, 127.4, 16.3.

MS (EI): *m*/*z* = 285 (100%, M$^+$).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{12}ClNS$: 285.0379; found: 285.0372.

Anal. Calcd for $C_{16}H_{12}ClNS$: C, 67.24; H, 4.23; N, 4.90; S, 11.22. Found: C, 66.78; H, 4.55; N, 4.67; S, 12.41.

2-[4-(*tert*-Butyl)phenyl]-4-methyl-5-phenylthiazole (4c)
Yield: 34 mg (65%); white solid; mp 109 °C.

IR (film): 3058, 2961, 2868, 1773, 1736, cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.4 Hz, 2 H), 7.50–7.39 (m, 6 H), 7.36–7.31 (m, 1 H), 2.55 (s, 3 H), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 153.3, 148.7, 132.4, 131.8, 131.1, 129.2, 128.7, 127.7, 126.1, 125.9, 34.8, 31.1, 16.3.

MS (EI): *m*/*z* (%) = 307 (85, M$^+$), 292 (100, M – CH_3).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}NS$: 307.1395; found: 307.1408.

Anal. Calcd for $C_{20}H_{21}NS$: C, 78.13; H, 6.88; N, 4.56; S, 10.43. Found: C, 78.32; H, 6.98; N, 4.55; S, 10.20.

2-(4-Methoxyphenyl)-4-methyl-5-phenylthiazole (4d)
Yield: 19 mg (41%); white solid; mp 63 °C.

IR (film): 3001, 2960, 2931, 2853, 1604, 1574, 1559, 1515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 9.2 Hz, 2 H), 7.48–7.24 (m, 5 H), 6.94 (d, *J* = 9.2 Hz, 1 H), 3.84 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 161.0, 148.4, 132.4, 131.2, 129.1, 128.7, 127.7, 127.6, 126.7, 114.2, 55.4, 16.4.

MS (EI): *m*/*z* = 281 (100%, M$^+$).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{15}NOS$: 281.0874; found: 281.0874.

Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98; S, 11.40. Found: C, 72.50; H, 5.72; N, 5.29; S, 11.25.

5-(4-Chlorophenyl)-4-methyl-2-phenylthiazole (4e)[14]
Yield: 25 mg (50%); white solid; mp 90 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.90 (m, 2 H), 7.43–7.39 (m, 7 H), 2.52 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 148.7, 133.3, 133.0, 130.4, 130.2, 129.9, 129.5, 125.9, 15.9.

MS (EI): *m*/*z* (%) = 285 (100, M$^+$), 182 (75).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{12}ClNS$: 285.0379; found: 285.0389.

2-[4-(*tert*-Butyl)phenyl]-5-(4-chlorophenyl)-4-methylthiazole (4f)
Yield: 28 mg (48%); white solid; mp 95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 9.0 Hz, 2 H), 7.45–7.39 (m, 6 H), 2.52 (s, 3 H), 1.33 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 152.9, 148.5, 133.2, 130.4, 130.3, 129.9, 128.4, 125.6, 125.4, 34.4, 30.7, 15.9.

MS (EI): *m*/*z* = 341 (100%, M$^+$).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{20}ClNS$: 341.1005; found: 341.0993.

Anal. Calcd for $C_{20}H_{20}ClNS$: C, 70.26; H, 5.90; N, 4.10; S, 9.38. Found: C, 69.67; H, 6.35; N, 4.05; S, 9.39.

5-(4-Bromophenyl)-4-methyl-2-phenylthiazole (4g)
Yield: 29 mg (52%); white solid; mp 110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.90 (m, 2 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.43–7.24 (m, 5 H), 2.52 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 161.8, 148.7, 133.0, 131.4, 130.7, 130.2, 129.5, 128.5, 125.8, 15.9.

MS (EI): *m*/*z* = 329 (100%, M$^+$).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{12}BrNS$: 328.9782; found: 328.9797.

Anal. Calcd for $C_{16}H_{12}BrNS$: C, 58.19; H, 3.66; N, 4.24; S, 9.71. Found: C, 57.82; H, 4.22; N, 4.10; S, 10.07.

2-(4-Chlorophenyl)-5-(2-methoxyphenyl)-4-methylthiazole (4h)
Yield: 16 mg (40%); white solid; mp 121 °C.

IR (film): 3002, 2958, 2919, 2831, 1581, 1537 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.4 Hz, 2 H), 7.39–7.31 (m, 4 H), 7.04–6.97 (m, 2 H), 3.84 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 156.5, 150.4, 135.0, 132.0; 131.5, 129.4, 128.6, 127.5, 127.0, 120.1, 120.0, 110.7, 55.1, 15.9.

MS (EI): *m*/*z* = 315 (100%, M$^+$).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}ClNOS$: 315.0485; found: 315.0467.

5-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-methylthiazole (4i)
Yield: 31 mg (51%); white solid; mp 123 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 9.0 Hz, 2 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 3.84 (s, 3 H), 2.50 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 160.6, 148.4, 131.4, 130.8, 130.1, 129.4, 127.3, 126.0, 121.3, 113.8, 55.0, 15.9.

MS (EI): *m*/*z* = 358 (100%, M$^+$).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}ONBrS$: 358.9979; found: 358.9993.

Anal. Calcd for $C_{17}H_{14}ONBrS$: C, 56.67; H, 3.92; N, 3.89; S, 8.90. Found: C, 56.32; H, 3.92; N, 3.87; S, 9.00.

2,5-Bis(4-chlorophenyl)-4-methylthiazole (4j)
Yield: 22 mg (40%); white solid; mp 172 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 9.0 Hz, 2 H), 7.40–7.37 (m, 6 H), 2.51 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 149.5, 136.0, 134.1, 132.2, 131.4, 130.6, 130.5, 129.1, 127.6, 16.5.

MS (EI): *m*/*z* (%) = 320 (20, M$^+$), 321 (80), 319 (100).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{11}Cl_2NS$: 318.9989; found: 318.9931.

Anal. Calcd for $C_{16}H_{11}Cl_2NS$: C, 60.01; H, 3.46; N, 4.37; S, 10.01. Found: C, 59.51; H, 3.27; N, 4.34; S, 10.27.

5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4-methylthiazole (4k)
Yield: 12 mg (22%); white solid; mp 120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31(d, *J* = 9.0 Hz, 1 H), 7.98 (d, *J* = 9.0 Hz, 1 H), 7.86 (d, *J* = 9.0 Hz, 2 H), 6.97–6.91 (dd, *J* = 9.0, 15 Hz, 4 H), 3.84 (s, 3 H), 2.50 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 162.0, 160.7, 160.6, 148.3, 133.1, 131.5, 129.4, 129.1, 128.3, 127.1, 125.0, 114.1, 113.5, 55.0, 15.9.

MS (EI): *m*/*z* = 315 (100%, M^+).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}ClNOS$: 315.04846; found: 315.0485.

5-(4-Methoxyphenyl)-4-methyl-2-phenylthiazole (4l)
Yield: 11 mg (30%); white solid; mp 70 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 6.0 Hz, 2 H), 7.42–7.38 (m, 4 H), 6.97 (d, *J* = 3.0 Hz, 2 H), 3.84 (s, 3 H), 2.52 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 156.5, 150.4, 133.4, 131.5, 129.4, 129.1, 128.3, 127.1, 125.0, 120.0, 110.7, 55.1, 15.9.

MS (EI): *m*/*z* = 281 (100%, M^+).

5-(2-Methoxyphenyl)-4-methyl-2-phenylthiazole (4m)
Yield: 11 mg (31%); white solid; mp 69 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 6.0 Hz, 2 H), 7.41–7.33 (m, 4 H), 7.04–6.99 (m, 2 H), 3.84 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 156.5, 150.2, 133.4, 131.5, 129.3, 129.1 128.3, 127.1, 125.8, 120.2, 120.0, 110.7, 55.1, 15.9.

MS (EI): *m*/*z* = 281 (100%, M^+).

2-(4-*tert*-Butylphenyl)-5-(4-methoxyphenyl)-4-methylthiazole (4n)
Yield: 14 mg (33%); white solid, mp 80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 6.0 Hz, 2 H), 7.43 (d, *J* = 6.0 Hz, 2 H), 7.35 (d, *J* = 6.0 Hz, 2 H), 7.03 (m, 2 H), 3.84 (s, 3 H), 2.40 (s, 3 H), 1.33 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 156.5, 152.4, 150.3, 131.5, 130.8, 129.2, 126.6, 125.6, 120.4, 120.0, 110.7, 55.1, 34.4, 30.7, 16.0.

MS (EI): *m*/*z* = 337 (100%, M^+).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}NOS$: 337.1488; found: 337.1500.

2-(4-*tert*-Butylphenyl)-5-(2-methoxyphenyl)-4-methylthiazole (4o)
Yield: 10 mg (24%); white solid; mp 93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 6.0 Hz, 2 H), 7.41 (d, *J* = 3.0 Hz, 2 H), 7.35 (d, *J* = 3.0 Hz, 2 H), 7.03 (m, 2 H), 3.84 (s, 3 H), 2.41 (s, 3 H), 1.33 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 156.5, 152.4, 150.0, 131.5, 130.8, 129.2, 126.6, 125.6, 125.3, 120.4, 120.0, 110.7, 55.1, 34.4, 30.8, 15.9.

MS (EI): *m*/*z* = 337 (100%, M^+).

2-(4-*tert*-Butylphenyl)-5-(4-bromophenyl)-4-methylthiazole (4p)
Yield: 27 mg (41%); white solid; mp 100 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 3.0 Hz, 2 H), 7.82 (d, *J* = 3.0 Hz, 2 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.30 (d, *J* = 9.0 Hz, 2 H), 2.51 (s, 3 H), 1.33 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 152.9, 148.5, 131.4, 130.8, 130.4, 129.9, 125.6, 125.4, 121.3, 34.4, 30.7, 30.7, 16.0.

MS (EI) *m*/*z* (%) = 385 (50, M^+), 372 (100).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{20}BrNS$: 385.04998; found: 385.0500.

4-Methyl-5-(naphthalen-2-yl)-2-phenylthiazole (4q)
Yield: 18 mg (35%); white solid; mp 130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.85 (m, 6 H), 7.61 (d, *J* = 3.0 Hz, 2 H), 7.53–7.49 (m, 4 H), 2.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 148.6, 133.2, 132.8, 132.1, 131.9, 129.4, 129.1, 128.4, 127.9, 127.6, 127.5, 127.3, 126.6, 126.2, 126.0, 125.9, 16.1.

MS (EI): *m*/*z* = 301 (100%, M + H^+).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{15}NS$: 301.0915; found: 301.0925.

2-(4-Chlorophenyl)-4-methyl-5-(naphthalen-2-yl)thiazole (4r)
Yield: 17 mg (30%); white solid; mp 160 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 6 H), 7.59–7.51 (m, 3 H), 7.41 (d, *J* = 6.0 Hz, 2 H), 2.61 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 148.8, 135.3, 134.7, 132.8, 132.2, 132.1, 131.7, 128.9, 128.7, 128.0, 127.7, 127.6, 127.3, 127.0, 126.5, 126.3, 126.1, 16.0.

MS (EI): *m*/*z* = 335 (100%, M^+).

2-(4-*tert*-Butylphenyl)-4-methyl-5-(naphthalen-2-yl)thiazole (4s)
Yield: 19 mg (32%); white solid; mp 137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.61 (m, 6 H), 7.60 (d, *J* = 6.0 Hz, 1 H), 7.57–7.49 (m, 3 H), 7.47 (d, *J* = 12.0 Hz, 1 H), 2.62 (s, 3 H), 1.34 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 152.7, 148.5, 140.9, 132.8, 132.0, 131.3, 130.5, 129.3, 127.9, 127.6, 127.5, 127.2, 126.6, 126.2, 125.9, 125.6, 125.4, 34.4, 30.7, 16.1.

MS (EI): *m*/*z* = 357 (100%, M^+).

2-(4-Methoxyphenyl)-4-methyl-5-(naphthalen-2-yl)thiazole (4t)
Yield: 18 mg (33%); white solid; mp 119 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51–8.46 (m, 6 H), 8.20–8.10 (m, 3 H), 7.57–7.53 (m, 2 H), 4.46 (s, 3 H), 3.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0, 133.0, 132.0, 131.9, 131.0, 129.3, 128.7, 127.9, 127.5, 127.3, 127.2, 126.6, 126.3, 126.2, 126.1, 125.9, 113.8, 54.9.

MS (EI): *m*/*z* (%) = 331 (80, M^+), 298(100).

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