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Iodine- and TBHP-Promoted Acylation of Benzothiazoles under Metal-Free Conditions

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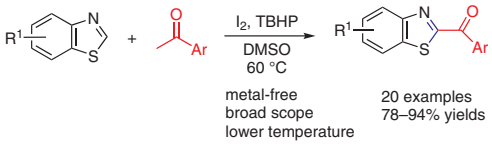

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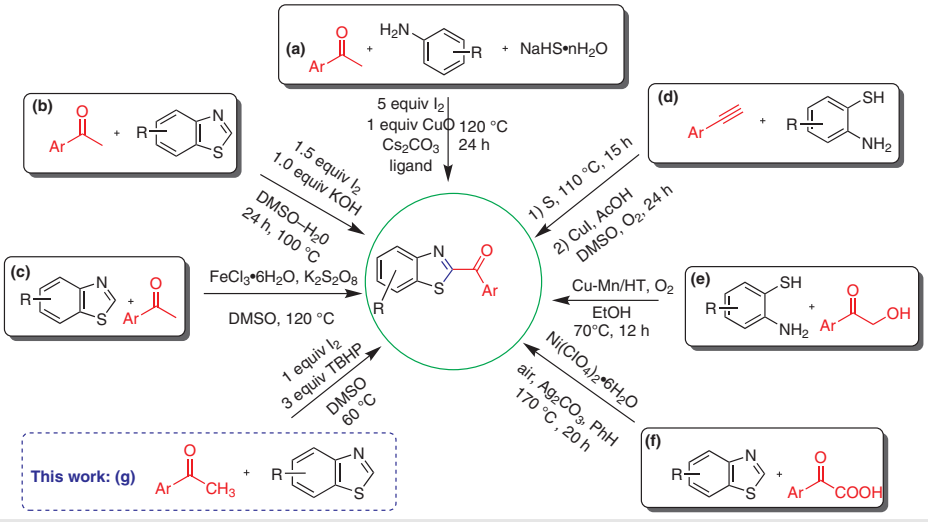
Abstract A simple protocol for the synthesis of 2-acylbenzothiazoles using aryl ketones and benzothiazoles in the presence of I_2 and TBHP is described. Acylation of the benzothiazoles is achieved through a sequence involving oxidation of the aryl ketone to an aryl glyoxal, ring-opening of the benzothiazole followed by condensation of the amino group with the aryl glyoxal, cyclization and oxidation. The method avoids the use of metals and toxic solvents. In addition, this protocol has the advantage of broad scope and provides good to excellent product yields.

Key words benzothiazoles, 2-acylbenzothiazoles, acylation, metal-free, 2-aminothiophenols

The benzothiazole moiety is an important heterocyclic core belonging to five-membered heterocycles. It is often found in diverse natural products[1] and is a common structural unit in synthetic drugs. Numerous research has indicated that compounds containing a thiazole ring exhibit effective pharmacological properties, with examples including ampicillin, amoxicillin, and piperacillin. Studies on benzothiazoles have also shown that they have a wide range of therapeutic activities. Some benzothiazoles can be used as labeling reagents to aid in the diagnosis of Alzheimer's disease (AD) at an early-to-moderate stage and to monitor the efficiency of treatment.[2] In addition, other studies have revealed that several benzothiazoles can serve as promising scaffolds for potent CaMKII[3] and 17β-HSD1



Scheme 1 Previous routes and our strategy for the synthesis of 2-acylbenzothiazoles

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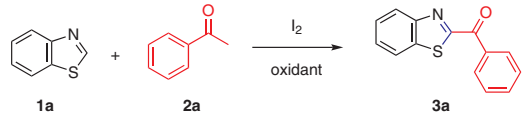
inhibitors.[4] Benzothiazoles also serve as important intermediates for the preparation of antiviral agents,[5] fatty acid amide hydrolase inhibitors[6] and anticancer agents.[7]

Because of the wide application and pharmacological importance of 2-acylbenzothiazoles, a number of different methods for their synthesis have been reported previously (Scheme 1). These methods include the condensation of acetophenones with anilines in the presence of $NaHS{\cdot}nH_2O$ (eq. a),[8] an in situ cross-trapping strategy for the acylation of benzothiazoles with aryl ketones (eq. b),[9] methods catalyzed by copper[10] or by Fe^{3+} (eq. c),[11] reactions of 2-aminothiophenols with phenylacetylenes (eq. d)[12] or α-hydroxyacetophenones (eq. e),[13] and decarboxylative acylation of heteroarenes via sp^2 C–H functionalization (eq. f).[14] It is noted that several different strategies have been developed to assemble benzothiazoles.[15] However, these previous methods usually require high temperatures, a strong base, long reaction times, metal catalysis or toxic solvents. Therefore, in order to overcome these disadvantages, the development of novel routes for the synthesis of 2-acylbenzothiazoles is necessary. Thus, in continuation of our efforts on the synthesis of potentially bioactive key intermediates, we have designed an economic and straightforward strategy for the synthesis of 2-acylbenzothiazoles via the reaction of benzothiazoles with aryl ketones (eq. g).

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3a**

Entry	Oxidant (equiv)	Time (h)	Temp (°C)	Solvent	Yield (%)[b]
1	TBHP (2)	5	80	EtOH	nd
2	TBHP (2)	5	80	DMF	nd
3	TBHP (2)	5	80	MeCN	nd
4	TBHP (2)	5	80	CH_2Cl_2	nd
5	TBHP (2)	5	80	EtOAc	nd
6	TBHP (2)	5	80	DMSO	60
7	DTBP (2)	5	80	DMSO	trace
8	aq H_2O_2 (31%) (2)	5	80	DMSO	trace
9	TBHP (3)	5	80	DMSO	77
10	TBHP (4)	5	80	DMSO	74
11[c]	TBHP (3)	5	80	DMSO	60
12[d]	TBHP (3)	5	80	DMSO	78
13	TBHP (3)	5	90	DMSO	81
14	TBHP (3)	5	70	DMSO	86
15	TBHP (3)	5	60	DMSO	84
16	TBHP (3)	5	50	DMSO	80
17	TBHP (3)	6	60	DMSO	81
18	TBHP (3)	3	60	DMSO	85
19	TBHP (3)	2	60	DMSO	78

[a] Reaction conditions: **1a** (0.4 mmol, 0.0541 g), **2a** (0.4 mmol, 0.0481 g), I_2 (1 equiv), solvent (3 mL).
[b] Yield of isolated product; nd = not detected.
[c] I_2 (0.5 equiv).
[d] I_2 (2.0 equiv).

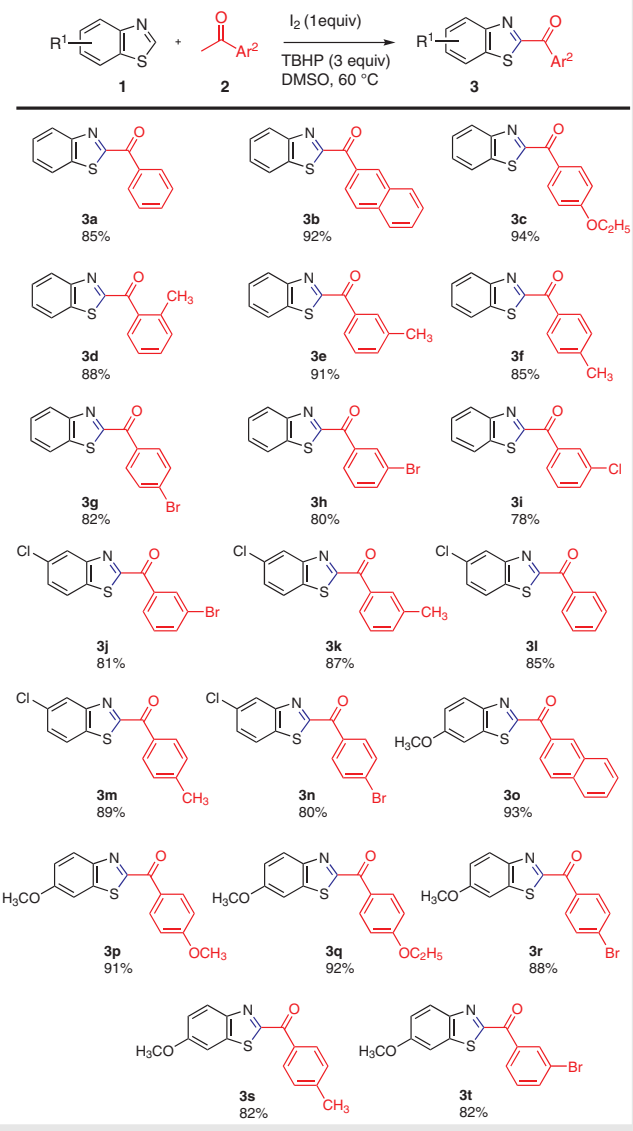
To determine the optimum conditions, the reaction of benzothiazole (**1a**) with acetophenone (**2a**) was chosen as a model reaction in the presence of I_2 and TBHP using different solvents (Table 1, entries 1–6). The results showed that the reaction only occurred in the presence of DMSO, giving the desired product in 60% yield at 80 °C (entry 6). Next, we tested the effect of different oxidants on the reaction and found that low yields of compound **3a** were produced when the oxidant was hydrogen peroxide (H_2O_2) or di-*tert*-butyl peroxide (DTBP) (entries 7 and 8). To our delight, using 3 equivalents of *tert*-butyl hydroperoxide (TBHP, 70% in water) as the oxidant gave compound **3a** in 77% yield (entry 9). However, when the loading of TBHP was more than 3 equivalents the yield did not increase (entries 10). Therefore, TBHP was chosen as the most appropriate oxidant for the reaction. Next, the effect of the loading of I_2 on the reaction yield was explored (entries 11 and 12). Decreased yields were observed when the I_2 loading was reduced to 0.5 equivalents (entry 11) or was increased to 2 equivalents (entry 12).

Furthermore, the effect of the temperature and reaction time on the yield of **3a** was examined (Table 1, entries, 13–19). It turned out that the conversion resulted in an 85% yield when the reaction was run at 60 °C for 3 h (entry 18). However, extending or shortening the reaction time did not improve the yield of **3a** (entries 17 and 19). Thus, equimolar quantities of reactants **1a** and **2a** in DMSO in the presence of 1 equivalent of I_2 and 3 equivalents of TBHP as the oxidant were the optimum conditions for the synthesis of **3a** (entry 18).

Next, with optimized conditions in hand, the substrate scope of this transformation was investigated (Scheme 2). Aromatic ketones bearing electron-donating or electron-withdrawing groups were well tolerated. This showed that the position of the substituent on the phenyl ring of the aromatic ketone had no obvious effect on the reaction yield. Additionally, the scope of the benzothiazoles was also investigated. Both electron-withdrawing and electron-donating groups on the phenyl ring of the benzothiazole were compatible in reactions with different aryl ketones. In all cases, the corresponding products were obtained in good to excellent yields of 78–94% .

To gain insight into the mechanism of this acylation, we carried out several control experiments in DMSO at 60 °C for 3 hours (Scheme 3). At first, acetophenone was replaced with benzaldehyde (eq. 1), however, none of the target compound **3a** was obtained. This proved that the reaction was not a cross-dehydrogenative coupling reaction between the aldehyde and benzoxazole. Next, we explored the mechanism behind the ring-opening of the benzothi-

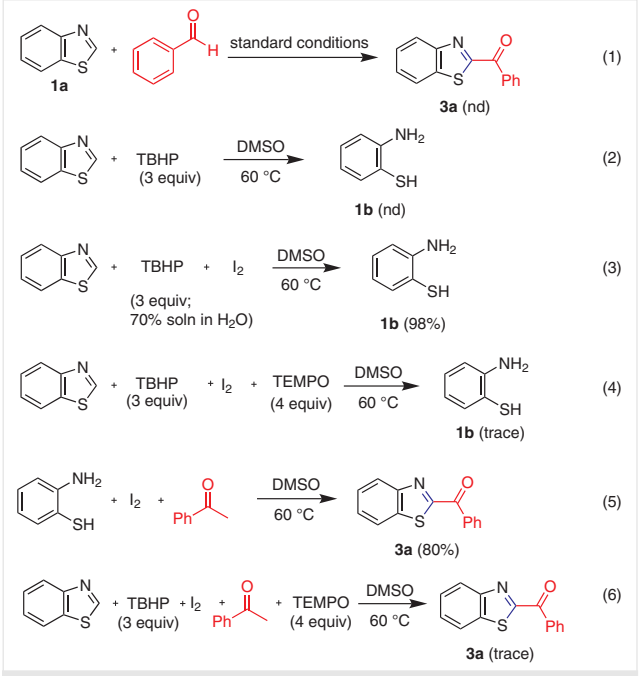
azole (**1a**). The benzothiazole ring remained intact when **1a** was heated in DMSO in presence of 3 equivalents of TBHP (70% in water) without using I_2 (eq. 2). With the addition of 3 equivalents of I_2, benzothiazole (**1a**) was transformed into 2-aminothiophenol (**1b**) (eq. 3). Interestingly, when 4 equivalents of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) were added to the reaction system, 2-aminothiophenol (**1b**) was not observed (eq. 4). As expected, when benzothiazole was replaced with 2-aminothiophenol and reacted in the presence of I_2, compound **3a** was obtained in a yield of 80% (eq. 5). However, only a trace amount of 2-acylbenzothiazole **3a** was obtained when 4 equivalents of TEMPO were added to the template reaction (eq. 6).



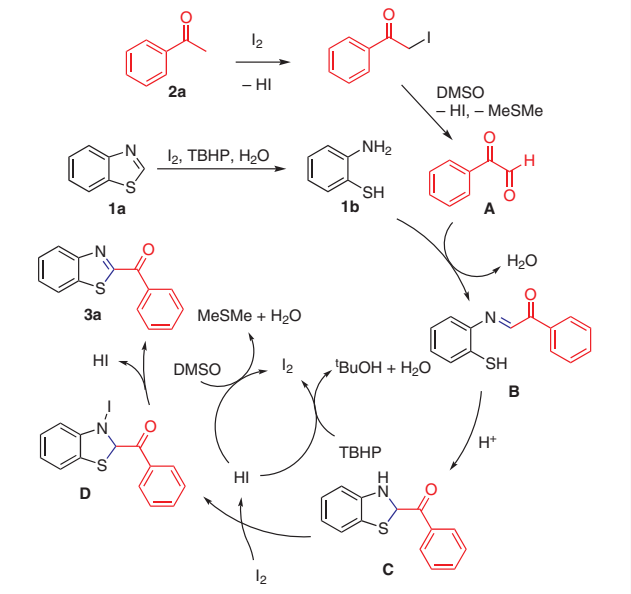
Scheme 2 Scope of the benzothiazoles and aromatic ketones. *Reagents and conditions*: **1** (0.4 mmol), **2** (0.4 mmol), I_2 (0.1015 g, 0.4 mmol, 1 equiv), TBHP (0.1545 g, 70% in water, 3 equiv), DMSO (3 mL), 60 °C, 3 h.

Based on the results from the control reactions described above and previous reports,[16] a proposed mechanism for the formation of 2-acylbenzothiazoles is depicted in Scheme 4. At first, acetophenone can be sequentially converted into phenylglyoxal **A** in the presence of I_2 in DMSO based on a Kornblum oxidation.[15a,17] In the process, the byproduct HI can be oxidized by DMSO or TBHP to regenerate I_2.[18] As 2-aminothiophenol (**1b**) (see Scheme 3, eq. 3) was only detected in the presence of benzothiazole **1a** with TBHP and I_2, we can speculate that the presence of I_2, TBHP and water causes ring opening of the thiazole moiety. Condensation between intermediates **1b** and **A** forms imine intermediate **B**. Next, intermediate **C** is generated by an intramolecular addition reaction. A subsequent substitution reaction between **C** and I_2 generates intermediate **D**, which finally produces the desired product **3a** through elimination of HI.

In summary, we have developed a cheap and efficient method for the metal-free acylation between benzothiazoles and aryl ketones. The products were obtained in high yields using I_2 and TBHP as ring-opening reagents. Compared with previous reports, this method has the advantages of a reduced reaction time and lower temperature, and avoids the use of metals, ligands and toxic solvents.



Scheme 3 Control experiments; nd = not detected



Scheme 4 Proposed mechanism

All reagents and solvents were obtained from commercial sources and were used without further purification. Reactions were routinely carried out under an airtight atmosphere with magnetic stirring. A IKA Plate (RCT digital) heating mantle was used to provide a stable heat source. TLC was conducted with Rushan Taiyang precoated glass-backed plates (silica gel 60 GF254) and visualized by exposure to UV light (254 nm). Flash column chromatography was performed on silica gel (300–400 mesh). Melting points were determined with a SMP3 melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm relative to the solvent signal, coupling constants (*J*) are given in hertz (Hz). Multiplicities are defined by standard abbreviations. High-resolution mass spectra (HRMS) were obtained using ESI ionization (positive) mode.

Benzo[*d*]thiazol-2-arylmethanones 3; General Procedure

A mixture of benzothiazole **1** (0.4 mmol), aryl ketone **2** (0.4 mmol), I_2 (0.4 mmol) and TBHP (70%, 1.2 mmol) was heated at 60 °C in DMSO for 3 h. After completion of the reaction, EtOAc and saturated aqueous $Na_2S_2O_3$ solution were added. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate, 25:1 to 8:1) to give product **3a–t**.

Benzo[*d*]thiazol-2-yl(phenyl)methanone (3a)[9]

Yellow solid; yield: 81 mg, 0.34 mmol (85%); mp 97–99 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61–8.51 (m, 2 H), 8.25–8.18 (m, 1 H), 7.98 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.68–7.61 (m, 1 H), 7.58–7.49 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.30, 167.09, 153.85, 136.98, 133.91, 131.28, 128.50, 127.62, 126.92, 125.72, 122.16.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}NOS$: 240.0477; found: 240.0472.

Benzo[*d*]thiazol-2-yl(naphthalen-2-yl)methanone (3b)[9]

Yellow solid; yield: 106 mg, 0.368 mmol (92%); mp 166–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 8.42 (dd, *J* = 8.7, 1.7 Hz, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 8.09–7.99 (m, 2 H), 7.96 (d, *J* = 8.7 Hz, 1 H), 7.89 (d, *J* = 8.1 Hz, 1 H), 7.66–7.50 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.04, 167.37, 153.91, 137.00, 135.94, 134.36, 132.43, 132.19, 130.22, 129.01, 128.32, 127.76, 127.58, 126.91, 126.72, 125.79, 125.74, 122.16.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{12}NOS$: 290.0634; found: 290.0630.

Benzo[*d*]thiazol-2-yl(4-ethoxyphenyl)methanone (3c)[8]

Yellow solid; yield: 107 mg, 0.376 mmol (94%); mp 112.5–115.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66–8.58 (m, 2 H), 8.24–8.18 (m, 1 H), 8.02–7.93 (m, 1 H), 7.59–7.45 (m, 2 H), 7.02–6.98 (m, 2 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 1.45 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.25, 167.94, 163.82, 153.86, 136.83, 133.83, 127.50, 127.31, 126.74, 125.48, 122.07, 114.28, 63.84, 14.65.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}NO_2S$: 284.0740; found: 284.0735.

Benzo[*d*]thiazol-2-yl(*o*-tolyl)methanone (3d)[11]

Yellow solid; yield: 89 mg, 0.352 mmol (88%); mp 111–113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 9.2 Hz, 1 H), 8.03–7.97 (m, 2 H), 7.58–7.51 (m, 2 H), 7.47 (t, *J* = 6.9 Hz, 1 H), 7.34 (t, *J* = 7.3 Hz, 2 H), 2.52 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.17, 167.56, 153.79, 139.08, 137.25, 135.15, 132.02, 131.56, 131.38, 127.67, 126.93, 125.81, 125.33, 122.24, 20.70.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}NOS$: 254.0634; found: 254.0628.

Benzo[*d*]thiazol-2-yl(*m*-tolyl)methanone (3e)[11]

White solid; yield: 92 mg, 0.364 mmol (91%); mp 73–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 8.3 Hz, 2 H), 8.22 (d, *J* = 7.9 Hz, 1 H), 7.99 (d, *J* = 8.6 Hz, 1 H), 7.60–7.49 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 2.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.87, 167.43, 153.86, 144.98, 136.94, 134.72, 132.38, 131.39, 129.24, 128.37, 127.46, 126.81, 125.64, 122.11, 21.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}NOS$: 254.0634; found: 254.0628.

Benzo[*d*]thiazol-2-yl(*p*-tolyl)methanone (3f)[9]

Yellow solid; yield: 86 mg, 0.34 mmol (85%); mp 95–97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 8.3 Hz, 2 H), 8.24 (dd, *J* = 7.4, 1.4 Hz, 1 H), 8.01 (dd, *J* = 7.6, 1.8 Hz, 1 H), 7.63–7.51 (m, 2 H), 7.39–7.33 (m, 2 H), 2.47 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.87, 167.42, 153.85, 144.99, 136.93, 132.36, 131.39, 129.24, 127.47, 126.82, 125.64, 122.12, 21.85.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}NOS$: 254.0634; found: 254.0628.

Benzo[*d*]thiazol-2-yl(4-bromophenyl)methanone (3g)[9]

Yellow solid; yield: 104 mg, 0.328 mmol (82%); mp 121–123 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.7 Hz, 2 H), 8.19 (d, *J* = 8.7 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 1.9 Hz, 2 H), 7.57–7.47 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.94, 166.72, 153.75, 137.00, 133.57, 132.73, 131.77, 129.46, 127.75, 126.99, 125.72, 122.14.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9BrNOS$: 317.9583; found: 317.9577.

Benzo[*d*]thiazol-2-yl(3-bromophenyl)methanone (3h)

Yellow solid; yield: 102 mg, 0.32 mmol (80%); mp 98–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (t, *J* = 1.8 Hz, 1 H), 8.54 (dt, *J* = 7.8, 1.3 Hz, 1 H), 8.30–8.24 (m, 1 H), 8.05–8.00 (m, 1 H), 7.82–7.77 (m, 1 H), 7.64–7.54 (m, 2 H), 7.45 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.87, 166.35, 153.77, 137.04, 136.65, 136.62, 133.97, 130.01, 129.87, 127.86, 127.06, 125.86, 122.62, 122.17.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9BrNOS$: 317.9583; found: 317.9577.

Benzo[*d*]thiazol-2-yl(3-chlorophenyl)methanone (3i)[11]

Yellow solid; yield: 85 mg, 0.312 mmol (78%); mp 98–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (t, *J* = 2.1 Hz, 1 H), 8.50–8.46 (m, 1 H), 8.29–8.24 (m, 1 H), 8.05–8.01 (m, 1 H), 7.67–7.62 (m, 1 H), 7.62–7.54 (m, 2 H), 7.52 (t, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.00, 166.40, 153.78, 137.04, 136.41, 134.66, 133.76, 131.12, 129.78, 129.40, 127.86, 127.06, 125.85, 122.17.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9ClNOS$: 274.0088; found: 274.0083.

(3-Bromophenyl)(5-chlorobenzo[*d*]thiazol-2-yl)methanone (3j)

Yellow solid; yield: 114 mg, 0.324 mmol (81%); mp 107–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (t, *J* = 1.7 Hz, 1 H), 8.51 (d, *J* = 7.9 Hz, 1 H), 8.25 (d, *J* = 2.0 Hz, 1 H), 7.93 (d, *J* = 8.6 Hz, 1 H), 7.79 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.52 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.43 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.46, 168.14, 154.49, 136.87, 136.29, 135.23, 134.00, 133.19, 130.06, 129.86, 128.48, 125.35, 122.94, 122.68.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_8BrClNOS$: 351.9193; found: 351.9189.

(5-Chlorobenzo[*d*]thiazol-2-yl)(*m*-tolyl)methanone (3k)

Yellow solid; yield: 100 mg, 0.348 mmol (87%); mp 114–116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 7.5 Hz, 1 H), 8.26 (s, 1 H), 8.22 (d, *J* = 2.0 Hz, 1 H), 7.91 (d, *J* = 8.6 Hz, 1 H), 7.52–7.45 (m, 2 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.10, 169.01, 154.55, 138.36, 135.17, 134.95, 134.62, 132.93, 131.46, 128.64, 128.41, 128.12, 125.20, 122.91, 21.44.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}ClNOS$: 288.0244; found: 288.0240.

(5-Chlorobenzo[*d*]thiazol-2-yl)(phenyl)methanone (3l)

White solid; yield: 93 mg, 0.34 mmol (85%); mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (dt, *J* = 8.1, 1.8 Hz, 2 H), 8.24 (d, *J* = 2.0 Hz, 1 H), 7.94 (d, *J* = 8.6 Hz, 1 H), 7.69 (t, *J* = 7.4 Hz, 1 H), 7.57 (t, *J* = 7.7 Hz, 2 H), 7.53 (dd, *J* = 8.6, 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.89, 168.89, 154.57, 135.18, 134.61, 134.11, 132.98, 131.27, 128.54, 128.20, 125.21, 122.93.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9ClNOS$: 274.0088; found: 274.0083.

(5-Chlorobenzo[*d*]thiazol-2-yl)(*p*-tolyl)methanone (3m)

White solid; yield: 102 mg, 0.356 mmol (89%); mp 115–117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 8.3 Hz, 2 H), 8.24 (d, *J* = 2.5 Hz, 1 H), 7.94 (d, *J* = 9.1 Hz, 1 H), 7.52 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 2.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.36, 169.25, 154.57, 145.27, 135.14, 132.88, 132.05, 131.40, 129.29, 128.04, 125.14, 122.89, 21.86.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}ClNOS$: 288.0244; found: 288.0240.

(4-Bromophenyl)(5-chlorobenzo[*d*]thiazol-2-yl)methanone (3n)[15a]

Yellow solid; yield: 113 mg, 0.32 mmol (80%); mp 184–186 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.6 Hz, 2 H), 8.21 (s, 1 H), 7.92 (d, *J* = 8.6 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 2 H), 7.51 (dd, *J* = 8.6, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.75, 168.52, 154.50, 135.21, 133.31, 133.13, 132.73, 131.89, 129.77, 128.38, 125.23, 122.95.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_8BrClNOS$: 351.9193; found: 351.9189.

(5-Methoxybenzo[*d*]thiazol-2-yl)(naphthalen-2-yl)methanone (3o)[9]

Yellow solid; yield: 119 mg, 0.372 mmol (93%); mp 179–182 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 8.41 (d, *J* = 10.3 Hz, 1 H), 8.14 (d, *J* = 9.1 Hz, 1 H), 8.06 (d, *J* = 8.1 Hz, 1 H), 7.95 (d, *J* = 8.7 Hz, 1 H), 7.89 (d, *J* = 8.1 Hz, 1 H), 7.66–7.59 (m, 1 H), 7.59–7.53 (m, 1 H), 7.41 (d, *J* = 2.5 Hz, 1 H), 7.19 (d, *J* = 11.6 Hz, 1 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.85, 164.87, 159.73, 148.56, 139.08, 135.84, 134.04, 132.45, 132.39, 130.16, 128.85, 128.22, 127.73, 126.64, 126.46, 125.84, 117.59, 103.38, 55.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}NO_2S$: 329.0740; found: 329.0735.

(5-Methoxybenzo[*d*]thiazol-2-yl)(4-methoxyphenyl)methanone (3p)

Yellow solid; yield: 109 mg, 0.364 mmol (91%); mp 147–149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 9.0 Hz, 2 H), 8.06 (d, *J* = 9.1 Hz, 1 H), 7.37 (s, 1 H), 7.14 (d, *J* = 11.6 Hz, 1 H), 7.00 (d, *J* = 9.0 Hz, 2 H), 3.88 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.13, 165.35, 164.17, 159.52, 148.48, 138.86, 133.66, 127.89, 126.20, 117.37, 113.77, 103.36, 55.79, 55.50.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}NO_3S$: 300.0689; found: 300.0685.

(4-Ethoxyphenyl)(5-methoxybenzo[*d*]thiazol-2-yl)methanone (3q)

Yellow solid; yield: 115 mg, 0.368 mmol (92%); mp 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69–8.53 (m, 2 H), 8.14–8.05 (m, 1 H), 7.41 (d, *J* = 2.5 Hz, 1 H), 7.18 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.05–6.98 (m, 2 H), 4.16 (q, *J* = 6.9 Hz, 2 H), 3.93 (s, 3 H), 1.47 (q, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.11, 165.35, 163.54, 159.41, 148.40, 138.77, 127.60, 126.12, 117.28, 114.12, 103.26, 63.71, 55.72, 14.56.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_3S$: 314.0845; found: 314.0840.

(4-Bromophenyl)(5-methoxybenzo[*d*]thiazol-2-yl)methanone (3r)

Yellow solid; yield: 123 mg, 0.352 mmol (88%); mp 192–193 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.6 Hz, 2 H), 8.07 (d, *J* = 9.1 Hz, 1 H), 7.67 (d, *J* = 8.6 Hz, 2 H), 7.38 (d, *J* = 2.5 Hz, 1 H), 7.17 (dd, *J* = 9.1, 2.5 Hz, 1 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.96, 164.18, 159.88, 148.43, 139.16, 133.85, 132.63, 131.74, 129.16, 126.47, 117.77, 103.34, 55.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}BrNO_2S$: 347.9688; found: 347.9682.

(5-Methoxybenzo[*d*]thiazol-2-yl)(*p*-tolyl)methanone (3s)

Yellow solid; yield: 93 mg, 0.328 mmol (82%); mp 153–154 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.2 Hz, 2 H), 8.09 (d, *J* = 9.1 Hz, 1 H), 7.40 (d, *J* = 2.5 Hz, 1 H), 7.35 (dd, *J* = 7.8, 0.8 Hz, 2 H), 7.17 (ddd, *J* = 9.0, 2.5, 0.7 Hz, 1 H), 3.92 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.57, 164.83, 159.52, 148.39, 144.58, 138.88, 132.45, 131.16, 129.07, 126.25, 117.38, 103.25, 55.71, 21.71.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}NO_2S$: 284.0740; found: 284.0738.

(3-Bromophenyl)(5-methoxybenzo[*d*]thiazol-2-yl)methanone (3t)

Yellow solid; yield: 114 mg, 0.328 mmol (82%); mp 160–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (t, *J* = 1.8 Hz, 1 H), 8.49 (d, *J* = 7.9 Hz, 1 H), 8.10 (d, *J* = 9.1 Hz, 1 H), 7.79–7.72 (m, 1 H), 7.42 (d, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 2.7 Hz, 1 H), 7.18 (dd, *J* = 9.1, 2.5 Hz, 1 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.60, 163.82, 159.94, 148.43, 139.20, 136.85, 136.39, 133.86, 129.94, 129.75, 126.59, 122.55, 117.82, 103.31, 55.85.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}BrNO_2S$: 347.9688; found: 347.9685.

2-Aminobenzenethiol (1b)

Yellow solid; yield: 49 mg (98%); mp 70–72 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (dd, *J* = 7.7, 0.9 Hz, 2 H), 6.71 (d, *J* = 7.6 Hz, 1 H), 6.63–6.59 (m, 1 H), 4.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.68, 136.84, 131.67, 118.69, 118.24, 115.31.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_6H_8NS: 126.0372; found: 126.0368.

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