

Copper(I)-Catalyzed Cascade Synthesis of 2-Substituted 1,3-Benzothiazoles: Direct Access to Benzothiazolones

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An efficient cascade process for the preparation of 2-substituted 1,3-benzothiazoles directly from 2-haloaryl isothiocyanates and O or S nucleophiles by a Cu-catalyzed, intramolecular, C–S bond formation has been developed. This cascade method is viable for the efficient syntheses of both

O- and S-substituted 1,3-benzothiazoles. Furthermore, 1,3-benzothiazol-2(3*H*)-ones having an alkyl group allow easy access to 1,3-benzothiazolones.

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Introduction

The 1,3-benzothiazole scaffold is ubiquitous in the realms of pharmacologically active agents and natural products. Particularly, 2-thio- and oxy-substituted analogues exhibit a wide range of biological activities such as antimycobacterial,^[1a] antimicrobial,^[1b–d] antifouling,^[1e] and antiviral activity.^[1f] Several 2-alkoxy- and 2-(alkylthio)-1,3-benzothiazole derivatives display excellent anti-HRV (human rhinovirus) activity.^[1g] A few substituted thiobenzothiazole derivatives have been screened for human cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibition.^[1h]

Novel 6-arylbenzothiazolones were examined and found to be effective for progesterone receptor (PR) antagonist activities.^[1i] Recent medicinal chemistry applications of substituted 1,3-benzothiazole include leukotriene A4 (LTA4) hydrolase inhibitors (**A**),^[2a,2b] aldolase reductase inhibitors (ARIs) (**B**),^[2c] dual antagonists for the human CCR1 and CCR3 receptors (**C**),^[2d] potent heat shock protein-90 inhibitors (**D**),^[2e] and an inhibitor of Cathepsin-D (**E**, Figure 1).^[2f] The herbicide benazoline (**F**) and fungicides chlobenthiazole (**G**) and 2-(thiocyanatomethylthio)-1,3-benzothiazole (TCMTB, **H**) are widely used in agriculture and are benzothiazole derivatives.^[3a–c] Some 2-substituted mercaptobenzothiazoles have found applications in

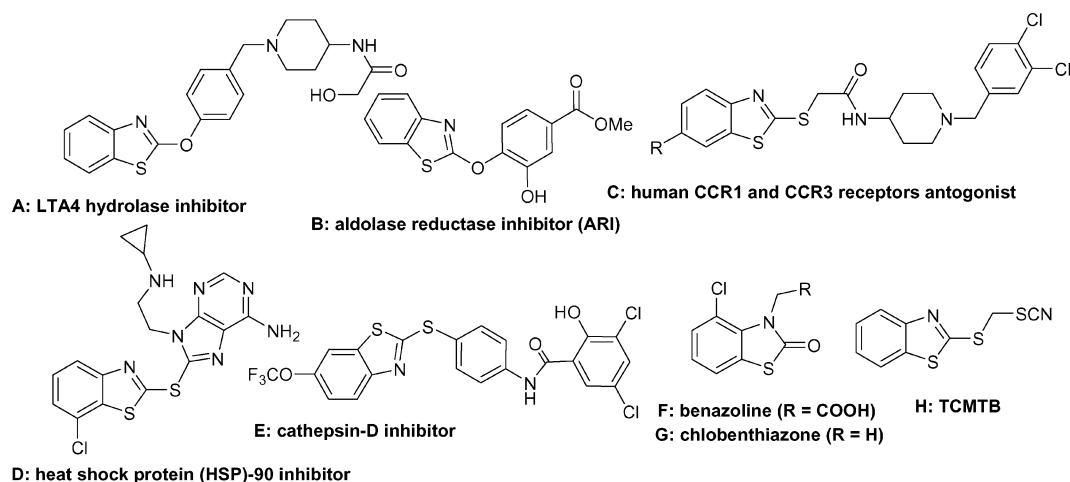


Figure 1. 2-Substituted 1,3-benzothiazoles in medicinal and other applications.

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organic synthesis in Julia olefinations^[4a,4b] and as reagents in Pd-catalyzed, cross-coupling reactions.^[4c]

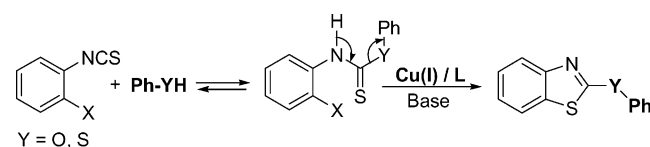
Although 2-oxy- and thio-substituted 1,3-benzothiazoles play an important role in the field of pharmaceutical science, the available synthetic methods for these compounds

are very limited. Traditional methods for the synthesis of this structural moiety include nucleophilic substitution of a 2-chloro-1,3-benzothiazole or its equivalents with either O (alcohols and phenols) or S (thiols and thiophenols) nucleophiles.^[2a,5] Alternatively, S-alkylation of preformed 2-mercaptobenzothiazole with alkylating agents is the common strategy to prepare (alkylthio)benzothiazoles.^[4a,6] However, by this strategy, the synthesis of *S*-(arylthio)benzothiazoles is impossible. They are generally prepared by two types of nucleophilic substitution reactions: by the nucleophilic attack of arylthiols upon preformed 2-halobenzothiazoles or by a nucleophilic attack of mercapto-benzothiazole upon haloarenes containing electron-withdrawing substituents such as -NO₂ and -CN under strongly basic conditions.^[7] An alternative method for the synthesis of 2-(arylthio)benzothiazoles by the *S*-arylation of benzothiazole-2-thiols with diaryliodonium salts in an ionic liquid has been reported.^[8a,8b] Many of these methods rely on harsh reaction conditions with limited functional group tolerance. Recent approaches have focused on the use of transition-metal (Cu, Pd, and Fe)-catalyzed, intermolecular, C–S bond formations for the synthesis of 2-(arylthio)-1,3-benzothiazoles under milder conditions with better efficiency and selectivity.^[9] However, the preparation of substituted 2-oxo and mercapto benzothiazoles using these methods depends largely on the availability of the prerequisites, suitably substituted 2-halobenzothiazole or mercaptobenzothiazoles, which are often difficult to prepare and involve tedious multi-step processes.

Recent advances in the field of transition-metal-catalyzed, C–heteroatom bond formation have proven to be the most efficient method for the construction of various heterocycles.^[10a–e] In general, one-pot, tandem, cascade or domino strategies, whereby multiple bonds can be constructed in a single reaction without the need to isolate the intermediates, are used to improve the efficiency of a chemical reaction.^[10f–i] Numerous heterocycles have been synthesized by one-pot, Cu-catalyzed, C–heteroatom (N, O, and S) bond formations. As compared to C–N and C–O bond formations, C–S bond formations are comparatively less explored because oxidative dimerization (S–S bond formation) and the affinity of thiols towards metals makes the catalyst less efficient.^[11]

An intramolecular, Cu-catalyzed, *S*-arylation of thioacetanilides or thiobenzanilides to produce 2-alkyl- or 2-aryl-1,3-benzothiazoles was first reported by Bowmann et al.^[12a] Later, the same synthesis was achieved by a Pd-catalyzed process in a more efficient manner.^[12b] Batey et al. explored intramolecular C–S bond formation for the synthesis of 2-arylbenzothiazoles and 2-aminobenzothiazoles using either Cu or Pd catalytic systems from the corresponding *o*-halothiobenzanilides or thioureas, respectively.^[12c,12d] Other groups have made further improvements in the Cu-catalytic system for similar reactions.^[12e,12f] Recently, Bao et al. reported a Cu^I-catalyzed synthesis of 2-imino-1,3-benzoxathioles from aryl isothiocyanates and *o*-iodophenols in one pot.^[12g] Our recent success in the Cu-catalyzed synthesis of substituted 2-mercaptobenzimidazoles and 2-(arylthio)-

benzothiazoles by intra/intermolecular C–N and C–S bond formations and our interest in the construction of various heterocycles prompted us to develop a Cu-catalyzed cascade process for easy access to 2-substituted benzothiazoles.^[13] The present strategy involves an initial nucleophilic addition of S or O nucleophiles to isothiocyanate followed by an intramolecular *S*-arylation leading to substituted 2-oxy/thio-benzothiazoles in the same pot (Scheme 1). The success of this strategy depends on the formation of thiocarbamate or dithiocarbamate esters by O or S nucleophiles, respectively. Unlike amino nucleophiles, which quantitatively form stable, isolable thioureas, the corresponding thiocarbamate or dithiocarbamate esters derived from phenol or thiophenol are unstable, particularly under basic conditions due to their better leaving-group ability.^[14] The in-situ-generated thiocarbamate or dithiocarbamate undergoes rapid intramolecular *S*-arylation to give 2-oxy/thio-benzothiazoles.



Scheme 1. Reaction pathway for the formation of 2-substituted benzothiazoles.

Results and Discussion

For the optimization of this cascade process, we selected *o*-bromophenyl isothiocyanate (**1**) and phenol (**a**) as the reaction partners. In the absence of any ligands, we did not observe the desired product (**1a**). Therefore, we carried out an initial ligand screen with different *N,N*-, *N,O*-, and *O,O*-donor ligands by taking CuI as the precatalyst and K₂CO₃ as the base. To our delight, we found 1,10-phenanthroline (**L3**) to be the most effective ligand for the present transformation. This observation is consistent with our previous intramolecular C–N bond formation and similar intramolecular C–heteroarylations observed by others.^[12c,12d,13a] In contrast to our recent finding involving intra and intermolecular C–S bond formation, the 1,2-cyclohexyldiamine (**L7**) ligand was totally ineffective, possibly because thiourea formation outcompeted metal complexation.^[13b] Similar bipyridyl (**L1**), substituted phenanthroline (**L2**), and TMEDA (**L5**) ligands were not very effective, but *L*-proline (**L4**) and ethyleneglycol (**L6**) ligands provided the cyclized product (**1a**) in moderate yields.

This cascade reaction was equally effective in a range of high-boiling, polar, aprotic solvents (DMSO, DMF, and DMA) as well as nonpolar solvents (dioxane and toluene). However, the use of anhydrous dioxane provided a superior conversion to that of other solvents tested. We found the optimum reaction temperature to be 90 °C. Although we achieved faster conversion at higher temperature (100 °C), due to the formation of undesirable side products, we chose 90 °C for all the substrates. From further experimentation,

we achieved the optimum conversion using *o*-haloaryl isothiocyanate (**1**, 1 equiv.), phenol (**a**, 1.2 equiv.), CuI (5 mol-%), **L3** (10 mol-%), and K₂CO₃ (2 equiv.) in dry dioxane (Figure 2).

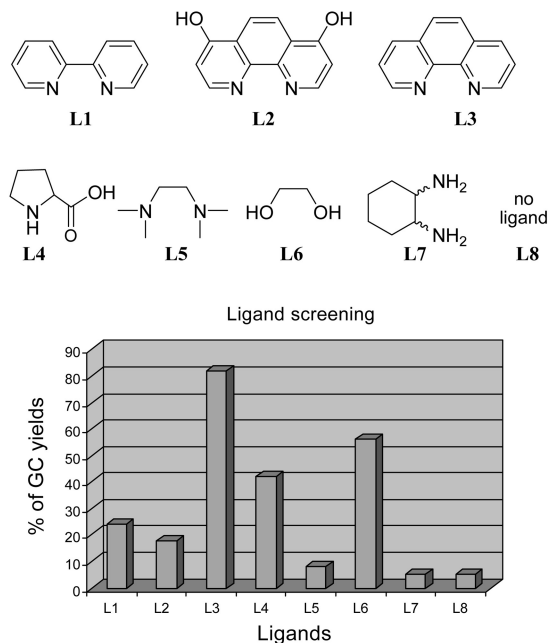


Figure 2. Effect of ligands on Cu-catalyzed, intramolecular *S*-arylation.

With the optimized conditions in hand, we then explored the scope and generality of the method. We were delighted to find that a series of O and S nucleophiles react with *o*-haloaryl isothiocyanates smoothly, giving 2-oxo/thio-substituted benzothiazoles in moderate to high yields (Table 1). We prepared *o*-haloaryl isothiocyanates **1–4** in excellent yields following our recently reported “green” protocol.^[15] The present Cu-catalyzed system is efficient and compatible with various *o*-halo (Br and I) isothiocyanates (**1–4** and **1'**). This intramolecular heteroarylation was equally effective either with *o*-bromo (**1**) and *o*-iodo (**1'**) isothiocyanates. Due to the easy preparation and low cost of *o*-bromo substrates, we performed the reactions mostly with *o*-bromo substrates **1–3**. We confirmed the structure of the product **1b** by X-ray crystallography (Figure 3).^[16]

A wide variety of O and S nucleophiles such as phenols (**a–g**), alcohols (**k–l**), thiophenols (**h–i**), and thiol-containing (**j**), electron-withdrawing (**b**, **c**, and **g**) and electron-donating substituents (**d**, **e**, **f**, and **i**) reacted well with *o*-haloaryl isothiocyanates **1'** and **1–4** to give oxy- and thio-substituted 1,3-benzothiazoles (Table 1). We found both phenols and thiophenols to be equally effective in this cascade process. An aliphatic thiol (**j**) and aromatic alcohols (**k** and **l**) were not that efficient as compared to phenols and thiophenols. Bis-nucleophiles such as 2-mercaptoethanol (**m**) gave the bis-heterocyclic **1m** containing both 2-oxo and 2-thio-substituted 1,3-benzothiazoles in moderate yield. A closer look at Table 1 reveals that phenols having electron-

Table 1. Synthesis of substituted 2-oxa/thio benzothiazoles (reaction conditions: * 12 h at 90 °C; ** 16 h at 90 °C).

Substrate	Nucleophile	Product	% Yield
	a: Y = O, Z = H	1a*	73
	b: Y = O, Z = <i>p</i> -COCH ₃	1b*	81
	c: Y = O, Z = <i>p</i> -NO ₂	1c*	85
	h: Y = S, Z = H	1h*	76
	i: Y = S, Z = <i>p</i> -Me	1i*	79
	j: BnSH	1j**	69
	m: HO-CH ₂ -CH ₂ -SH	1m**	46
	a: Y = O, Z = H	1a*	74
	h: Y = S, Z = H	1h*	75
	a: Y = O, Z = H	2a*	64
	c: Y = O, Z = <i>p</i> -NO ₂	2c**	83
	d: Y = O, Z = <i>p</i> -Me	2d**	72
	e: Y = O, Z = <i>p</i> -OMe	2e**	78
	f: Y = O, Z = <i>m,p</i> -diMe	2f**	65
	g: Y = O, Z = <i>p</i> -CHO	2g*	91
	h: Y = S, Z = H	2h*	68
	i: Y = S, Z = <i>p</i> -Me	2i**	70
		a: Y = O, Z = H	3a*
h: Y = S, Z = H		3h	67
	a: Y = O, Z = H	4a*	78
	h: Y = S, Z = H	4h**	80
	k: HO-CH ₂ -CH ₂ -Ph	4k**	54
	l: HO-CH ₂ -CH ₂ -Ph	4l**	40
	l: HO-CH ₂ -CH ₂ -Ph	4l**	40

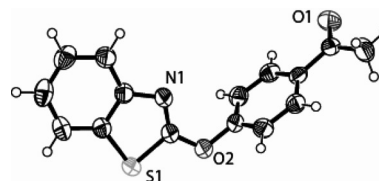


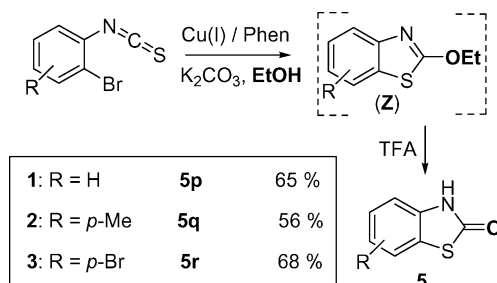
Figure 3. ORTEP molecular diagram of **1b** with ellipsoids at 50% probability.

withdrawing groups (**b**, **c**, and **g**) gave higher yields. This was due to their more facile deprotonation under basic (K₂CO₃) conditions to give the corresponding phenolate ions, which served as better nucleophiles. This also explains why alcohols **k** and **l** and thiol **j** were less reactive. Furthermore, we observed a good correlation between the substituents (*p*-Me, *p*-Cl, and *p*-Br) attached to the isothiocyanates **1'** and **1–4** and their reactivity. A weakly electron-donating substituent (*p*-Me) in the isothiocyanate resulted in lower

yields (**2a** and **2h**) compared to that obtained with weakly electron-withdrawing substituents (*p*-Cl and *p*-Br, **3a**, **3h**, **4a**, and **4h**).

Derivatives of **1j** have been identified as COX-1 and COX-2 inhibitors^[1h] and have antimicrobial activity.^[1a] Additionally, the benzothiazolone core structure can be found in a large number of compounds having a range of biological activities as progesterone receptor (PR) antagonists,^[1i] fungicides, and herbicides.^[3a-c] Traditionally they are synthesized by the condensation of 2-aminothiophenol with ethyl chloroformate,^[17a] urea,^[17b] ammonium thiocarbamate,^[17c] or disuccinimido carbonate.^[17d] Methods are also available for the preparation of benzothiazolones using precursors such as 2-chloro-1,3-benzothiazole and 2-benzothiazolylalkyl sulfide.^[17e-g]

We envisaged an *O*-dealkylation strategy could allow access to these valuable heterocycles. The nucleophilic addition of ethanol to *o*-bromophenyl isothiocyanate (**1**) would give a thiocarbamate ester, which would then undergo an intramolecular *S*-arylation by a CuI–L system to give 2-ethoxy-1,3-benzothiazole (**Z**). In these reactions, ethanol serves the dual purpose of nucleophile and solvent. Since ethanol is a weaker leaving group and is in excess, it drives the reaction forward, giving quantitative yields of (**Z**). The *O*-dealkylation of **Z** using trifluoroacetic acid (TFA) provided 1,3-benzothiazol-2-one **5p** in 65% overall isolated yield. We note that using a similar strategy, 1,3-benzothiazolones have been prepared using benzoic acid at 170 °C for 24 h.^[17f] In an analogous approach, other benzothiazolones **5q** and **5r** were prepared in moderate yields (Scheme 2). We confirmed the structure of the product **5p** by X-ray crystallography (Figure 4).^[18]



Scheme 2. Cascade synthesis of 2-benzothiazolones.

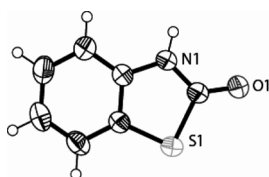


Figure 4. ORTEP molecular diagram of **5p** with ellipsoids at 50% probability.

Conclusions

We have developed an efficient cascade process for the synthesis of a library of 2-substituted 1,3-benzothiazoles. The thiocarbamate or dithiocarbamate generated in situ by the reaction of 2-haloaryl isothiocyanates with O or S nucleophiles undergoes CuI–L-catalyzed intramolecular C–S bond formation giving substituted benzothiazoles. Both phenols and thiophenols reacted with equal ease. On the other hand, alcohols and thiols were less reactive. The rate of the reaction was faster and gave better yields when electron-withdrawing substituents were present in either of the coupling partners. 1,3-Benzothiazolones were prepared in one pot using ethanol as the solvent and nucleophile (O source).

Experimental Section

General Remarks: All reagents were of commercial grade and purified according to commonly used procedures. Organic extracts were dried with anhydrous Na₂SO₄. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh) was used for column chromatography. Reactions were monitored by TLC on silica gel 60 F₂₅₄ (0.25 mm). NMR spectra were recorded in CDCl₃ with tetramethylsilane as the internal standard for ¹H NMR (400 MHz) and CDCl₃ solvent as the internal standard for ¹³C NMR (100 MHz). HR mass spectra were recorded by using a Waters MS system (Q-tof) according to the MS-MS method, and data were analyzed by Mass Lynx 4.1 software (Waters Corporation, USA, 2005). IR spectra were recorded neat or in KBr with a Nicolet Impact 410 spectrophotometer. Melting points were recorded with a Büchi B-545 melting point apparatus and are uncorrected.

Crystallographic Description: Crystal data were collected with a Bruker Smart Apex-II CCD diffractometer by using graphite-monochromated, Mo-*K*_α radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART^[19] software and refined with SAINT^[19] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS.^[20] The structure was solved by direct methods implemented in SHELX-97^[21] and refined by full-matrix least-squares methods on *F*². All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. All the colourless crystals were isolated in rectangular shape from absolute ethanol at room temperature.

General Procedure for the Preparation of 2-(Bromophenyl) Isothiocyanate (1): To a stirred and ice-cooled suspension of the dithiocarbamate of 2-bromoaniline (344 mg, 2 mmol) in acetonitrile (5 mL), was added triethylamine (416 μL, 3 mmol). To this was added iodine (508 mg, 2 mmol) portionwise over a period of 30 min. Acetonitrile was evaporated, and ethyl acetate (15 mL) was added to the mixture, which was washed with HCl (1 N, 2 × 5 mL) and water (1 × 5 mL). The organic layer was dried with anhydrous Na₂SO₄, concentrated under reduced pressure, and purified over a short column of silica gel (100% hexane), and 2-bromophenyl isothiocyanate was isolated (393 mg, 92%).

General Procedure for the Synthesis of 2-Phenoxy-1,3-benzothiazole (1a): A round-bottomed flask with a magnetic stir bar, fitted with

a reflux condenser, was charged with 2-bromophenyl isothiocyanate (**1**, 1 mmol, 214 mg), phenol (**a**, 1.1 mmol, 103 mg), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (**L3**, 0.1 mmol, 18 mg), K₂CO₃ (2 mmol, 276 mg), and dry 1,4-dioxane (3 mL). The mixture was heated at 90 °C for 12 h, protected with a guard tube. The reaction mixture was then cooled and filtered through Celite using ethyl acetate. The filtrate was evaporated to dryness, and the product was purified by column chromatography giving **1a** (166 mg, 73%) as a colourless gum. ¹H NMR (400 MHz, CDCl₃): δ = 7.20–7.45 (m, 7 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 120.8, 121.4, 121.8, 124.2, 126.3, 126.4, 130.1, 132.4, 149.2, 154.8, 172.1 ppm. IR (KBr): ν = 3064, 2753, 1942, 1784, 1683, 1598, 1562, 1528, 1487, 1456, 1440, 1310, 1285, 1230, 1158, 1126, 1066, 1017, 1004 cm⁻¹. C₁₃H₉NOS (227.28): calcd. C 68.69, H 3.99, N 6.16, S 14.11; found C 68.78, H 4.03, N 6.21, S 13.72.

General Procedure for the Synthesis of 1,3-Benzothiazolone (5p): A round-bottomed flask with a magnetic stir bar, fitted with a reflux condenser, was charged with 2-bromophenyl isothiocyanate (**1**, 1 mmol, 214 mg), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (**L3**, 0.1 mmol, 18 mg), K₂CO₃ (2 mmol, 276 mg), and dry ethanol (3 mL). The resulting solution was heated at reflux for 12 h, protected with a guard tube. The reaction mixture was then cooled, TFA (2 mL) was added to it, and the mixture was refluxed for another 5 h. The solvent was removed under vacuum, and the reaction mixture was treated with aq. sodium hydrogen carbonate. The product was extracted with ethyl acetate (2 × 15 mL). The organic phase was dried with Na₂SO₄ and then concentrated. The crude product was purified using a short column of silica gel to give product **5p** (98.3 mg, 65%) as a white solid; m.p. 136–137 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.16 (m, 2 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 10.45 (s, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 112.1, 122.7, 123.4, 124.1, 126.7, 135.7, 173.7 ppm. IR (KBr): ν = 3154, 3110, 3054, 2922, 2853, 1666, 1591, 1463, 1214, 743, 642 cm⁻¹. C₇H₅NOS (151.01): calcd. C 55.61, H 3.33, N 9.26, S 21.21; found C 55.53, H 3.29, N 9.21, S 21.22.

1-(4-(1,3-Benzothiazol-2-yloxy)phenyl)ethanone (1b): White solid; m.p. 106–108 °C. ¹H NMR (400 MHz, CDCl₃): δ = 2.59 (s, 3 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 8.02 (d, *J* = 8.5 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 26.6, 120.2, 121.4, 121.9, 124.5, 126.4, 130.4, 132.3, 134.6, 148.7, 157.9, 170.4, 196.6 ppm. IR (KBr): ν = 3057, 3007, 2913, 1674, 1598, 1520, 1500, 1460, 1442, 1440, 1361, 1300, 1265, 1249, 1226, 1203, 1160, 1105, 1066, 1013, 959, 910, 855, 844 cm⁻¹. C₁₅H₁₁NO₂S (269.32): calcd. C 66.89, H 4.11, N 5.20, S 11.90; found C 66.86, H 4.09, N 5.18, S 11.85.

2-(4-Nitrophenoxy)-1,3-thiazole (1c): White solid; m.p. 111–112 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.33 (t, *J* = 8 Hz, 1 H), 7.42 (t, *J* = 8 Hz, 1 H), 7.57 (d, *J* = 8.8 Hz, 2 H), 7.74 (t, *J* = 8 Hz, 2 H), 8.30 (d, *J* = 8.8 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 120.7, 121.6, 122.2, 125.0, 125.8, 126.7, 132.5, 145.0, 148.6, 159.0, 169.7 ppm. IR (KBr): ν = 3077, 2920, 2851, 1591, 1516, 1488, 1440, 1351, 1250, 1235, 1160, 853, 751 cm⁻¹. C₁₃H₈N₂O₃S (272.28): calcd. C 57.35, H 2.96, N 10.29, S 11.78; found C 57.29, H 2.93, N 10.28, S 11.71.

2-(Phenylthio)-1,3-benzothiazole (1h): Colourless gum. ¹H NMR (400 MHz, CDCl₃): δ = 7.20 (t, *J* = 8.0 Hz, 1 H), 7.33–7.46 (m, 4 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.69 (m, 2 H), 7.87 (d, *J* = 8.4 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 120.7, 121.8, 124.2, 126.0, 129.7, 129.8, 130.4, 135.2, 135.4, 153.8, 169.5 ppm. IR (KBr): ν = 3060, 1582, 1455, 1426, 1310, 1237, 1020, 1007, 752

cm⁻¹. C₁₃H₉NS₂ (243.35): calcd. C 64.18, H 3.73, N 5.76, S 26.35; found C 64.23, H 3.75, N 5.80, S 26.31. HRMS (ESI): calcd. for C₁₃H₉NS₂ [M + H]⁺ 244.0255; found 244.0259.

2-(*p*-Tolylthio)benzothiazole (1i): White solid; m.p. 70–72 °C. ¹H NMR (400 MHz, CDCl₃): δ = 2.38 (s, 3 H), 7.17–7.24 (m, 3 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 3 H), 7.84 (d, *J* = 8.0 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 21.5, 120.8, 121.8, 124.2, 126.1, 126.2, 130.8, 135.4, 135.6, 141.1, 154.0, 170.8 ppm. IR (KBr): ν = 3059, 2916, 1592, 1455, 1422, 1310, 1235, 1005, 816, 757 cm⁻¹. C₁₄H₁₁NS₂ (257.37): calcd. C 65.33, H 4.31, N 5.44, S 24.92; found C 65.41, H 4.29, N 5.39, S 24.90.

2-(Benzylthio)benzothiazole (1j): Colourless gum. ¹H NMR (400 MHz, CDCl₃): δ = 4.60 (s, 2 H), 7.26–7.34 (m, 4 H), 7.39–7.46 (m, 3 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 37.8, 121.2, 121.7, 124.5, 126.2, 127.9, 128.9, 129.3, 135.5, 136.3, 153.3, 166.6 ppm. IR (KBr): ν = 3065, 3027, 2923, 2846, 1494, 1455, 1427, 1309, 1239, 1073, 1017, 993, 754 cm⁻¹. C₁₄H₁₁NS₂ (257.37): calcd. C 65.33, H 4.31, N 5.44, S 24.92; found C 65.27, H 4.27, N 5.39, S 24.84.

2-[2-(1,3-Benzothiazol-2-yloxy)ethylthio]-1,3-benzothiazole (1m): Yellowish solid; m.p. 106–108 °C. ¹H NMR (400 MHz, CDCl₃): δ = 3.84 (t, *J* = 6.8 Hz, 2 H), 4.93 (t, *J* = 6.4 Hz, 2 H), 7.20–7.42 (m, 4 H), 7.60–7.67 (m, 2 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 7.6 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 31.7, 69.7, 121.1, 121.2, 121.5, 121.8, 123.8, 124.6, 126.2, 126.3, 132.2, 135.5, 149.3, 153.2, 165.5, 172.4 ppm. IR (KBr): ν = 3049, 2923, 2851, 1525, 1454, 1440, 1426, 1259, 1218, 960, 754 cm⁻¹. C₁₆H₁₂N₂O₃S (344.47): calcd. C 55.79, H 3.51, N 8.13, S 27.93; found C 55.86, H 3.55, N 8.09, S 27.88.

6-Methyl-2-phenoxy-1,3-benzothiazole (2a): Colourless gum. ¹H NMR (400 MHz, CDCl₃): δ = 2.40 (s, 3 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.2 Hz, 1 H), 7.33 (d, *J* = 8.8 Hz, 2 H), 7.39–7.44 (m, 3 H), 7.61 (d, *J* = 8.4 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 21.6, 120.7, 121.3, 121.4, 126.3, 127.7, 130.1, 132.4, 134.1, 147.0, 154.9, 171.3 ppm. IR (KBr): ν = 3057, 2921, 1593, 1533, 1488, 1464, 1406, 1306, 1234, 1203, 1157, 1004 cm⁻¹. C₁₄H₁₁NOS (241.31): calcd. C 69.68, H 4.59, N 5.80, S 13.29; found C 69.73, H 4.61, N 5.85, S 13.23.

6-Methyl-2-(4-nitrophenoxy)-1,3-benzothiazole (2c): White solid; m.p. 140–142 °C. ¹H NMR (400 MHz, CDCl₃): δ = 2.44 (s, 3 H), 7.22 (d, *J* = 8.4 Hz, 1 H), 7.50 (s, 1 H), 7.54 (d, *J* = 9.2 Hz, 2 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 8.27 (d, *J* = 9.2 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 21.6, 120.5, 121.4, 121.7, 125.7, 128.0, 132.5, 135.0, 144.8, 146.3, 159.0, 168.8 ppm. IR (KBr): ν = 3118, 2924, 2850, 1614, 1591, 1532, 1515, 1488, 1458, 1380, 1349, 1326, 1307, 1294, 1253, 1210, 1182, 1161, 1109, 1057, 862 cm⁻¹. C₁₄H₁₀N₂O₃S (286.31): calcd. C 58.73, H 3.52, N 9.78, S 11.19; found C 58.79, H 3.54, N 9.84, S 11.05. HRMS (ESI): calcd. for C₁₄H₁₀N₂O₃S [M + H]⁺ 287.0490; found 287.0463.

6-Methyl-2-(*p*-tolylthio)-1,3-benzothiazole (2d): Colourless gum. ¹H NMR (400 MHz, CDCl₃): δ = 2.34 (s, 3 H), 2.38 (s, 3 H), 7.15 (m, 1 H), 7.19 (s, 4 H), 7.38 (s, 1 H), 7.60 (m, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 21.0, 21.5, 120.5, 121.2, 121.3, 127.6, 130.5, 132.3, 133.9, 136.0, 147.0, 152.7, 171.7 ppm. IR (KBr): ν = 3032, 2922, 1605, 1535, 1466, 1234, 1200, 1017, 813 cm⁻¹. C₁₅H₁₃NOS (255.33): calcd. C 70.55, H 5.13, N 5.48, S 12.55; found C 70.46, H 5.11, N 5.42, S 12.43. HRMS (ESI): calcd. for C₁₅H₁₃NOS [M + H]⁺ 256.0796; found 256.0734.

2-(4-Methoxyphenoxy)-6-methyl-1,3-benzothiazole (2e): Colourless gum. ¹H NMR (400 MHz, CDCl₃): δ = 2.40 (s, 3 H), 3.80 (s, 3 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.25 (d, *J* =

9.0 Hz, 2 H), 7.41 (s, 1 H), 7.60 (d, $J = 8.0$ Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.7, 55.9, 115.1, 121.4, 122.1, 127.8, 132.5, 134.1, 147.3, 148.7, 157.9, 172.4$ ppm. IR (KBr): $\tilde{\nu} = 3049, 3000, 2928, 2835, 1663, 1609, 1535, 1498, 1459, 1409, 1306, 1229, 1101, 1057, 1033, 920, 850, 816$ cm^{-1} . $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{S}$ (271.33): calcd. C 66.39, H 4.83, N 5.16, S 11.81; found C 66.45, H 4.79, N 5.12, S 11.68. HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{S}$ [M + H] $^+$ 272.0745; found 272.0705.

2-(3,4-Dimethylphenoxy)-6-methyl-1,3-benzothiazole (2f): Colourless gum. ^1H NMR (400 MHz, CDCl_3): $\delta = 2.25$ (s, 3 H), 2.26 (s, 3 H), 2.40 (s, 3 H), 7.03–7.09 (m, 2 H), 7.16 (d, $J = 8.0$ Hz, 2 H), 7.40 (s, 1 H), 7.60 (d, $J = 8.0$ Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.4, 20.1, 21.5, 117.9, 121.2, 121.3, 127.6, 130.9, 132.4, 133.9, 134.9, 138.6, 147.1, 152.9, 171.9$ ppm. IR (KBr): $\tilde{\nu} = 2924, 2857, 1604, 1537, 1496, 1466, 1244, 1225, 1195, 1146, 1056, 1021, 872, 813$ cm^{-1} . $\text{C}_{16}\text{H}_{15}\text{NOS}$ (269.36): calcd. C 71.34, H 5.61, N 5.19, S 11.90; found C 71.43, H 5.59, N 5.17, S 11.88.

4-(6-Methyl-1,3-benzothiazol-2-yloxy)benzaldehyde (2g): White solid; m.p. 99–100 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 2.43$ (s, 3 H), 7.21 (d, $J = 8.0$ Hz, 1 H), 7.48 (s, 1 H), 7.53 (d, $J = 8.6$ Hz, 2 H), 7.63 (d, $J = 8.0$ Hz, 1 H), 7.94 (d, $J = 8.6$ Hz, 2 H), 9.97 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.6, 120.6, 121.4, 121.6, 127.9, 131.8, 132.5, 133.7, 134.8, 146.5, 159.1, 169.3, 190.8$ ppm. IR (KBr): $\tilde{\nu} = 2920, 2833, 1693, 1585, 1534, 1499, 1466, 1455, 1385, 1301, 1231, 1205, 1180, 1157, 1101, 1056, 1010, 963, 917, 851, 823$ cm^{-1} . $\text{C}_{15}\text{H}_{11}\text{NO}_2\text{S}$ (269.32): calcd. C 66.89, H 4.12, N 5.20, S 11.89; found C 66.93, H 4.15, N 5.16, S 11.83.

6-Methyl-2-(phenylthio)-1,3-benzothiazole (2h): Colourless gum. ^1H NMR (400 MHz, CDCl_3): $\delta = 2.40$ (s, 3 H), 7.19 (d, $J = 8.4$ Hz, 1 H), 7.41–7.47 (m, 4 H), 7.70–7.76 (m, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.7, 120.9, 121.7, 127.9, 130.1, 130.4, 130.6, 134.7, 135.4, 136.0, 152.2, 168.3$ ppm. IR (KBr): $\tilde{\nu} = 3056, 2919, 1582, 1468, 1439, 1242, 1012, 813, 749, 689$ cm^{-1} . $\text{C}_{14}\text{H}_{11}\text{NS}_2$ (257.37): calcd. C 65.33, H 4.31, N 5.44, S 24.92; found C 65.25, H 4.29, N 5.38, S 24.83.

6-Methyl-2-(*p*-tolylthio)-1,3-benzothiazole (2i): White solid; m.p. 80–81 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 2.41$ (s, 3 H), 2.43 (s, 3 H), 7.20 (d, $J = 8.4$ Hz, 1 H), 7.28 (d, $J = 8.0$ Hz, 2 H), 7.41 (s, 1 H), 7.61 (d, $J = 8.0$ Hz, 2 H), 7.74 (d, $J = 8.4$ Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.6, 120.8, 121.5, 126.7, 127.7, 130.8, 134.5, 135.6, 135.8, 141.1, 152.3, 169.3$ ppm. IR (KBr): $\tilde{\nu} = 2918, 2852, 1594, 1438, 1003, 810, 504$ cm^{-1} . $\text{C}_{15}\text{H}_{13}\text{NS}_2$ (271.40): calcd. C 66.38, H 4.83, N 5.16, S 23.63; found C 66.46, H 4.84, N 5.20, S 23.56.

6-Bromo-2-phenoxy-1,3-benzothiazole (3a): White solid; m.p. 109–111 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.26$ (s, 1 H), 7.31–7.37 (m, 2 H), 7.45–7.50 (m, 3 H), 7.59 (d, $J = 8.8$ Hz, 1 H), 7.79 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 117.1, 120.8, 123.1, 124.0, 126.7, 129.9, 130.2, 134.0, 148.2, 154.7, 172.4$ ppm. IR (KBr): $\tilde{\nu} = 3056, 2924, 1589, 1522, 1489, 1440, 1393, 1303, 1250, 1234, 1202, 1153, 1050, 915, 807$ cm^{-1} . $\text{C}_{13}\text{H}_8\text{BrNOS}$ (306.18): calcd. C 50.99, H 2.63, N 4.57, S 10.47; found C 50.86, H 2.57, N 4.54, S 10.35.

6-Bromo-2-(phenylthio)-1,3-benzothiazole (3h): Colourless gum. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.49$ (m, 3 H), 7.69 (s, 1 H), 7.20 (m, 2 H), 7.75 (m, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 118.0, 122.8, 123.1, 123.5, 129.5, 130.3, 131.0, 135.7, 137.2, 153.0, 171.0$ ppm. IR (KBr): $\tilde{\nu} = 3059, 2924, 2851, 1581, 1528, 1494, 1456, 1429, 1390, 1093, 1013, 813, 748$ cm^{-1} . $\text{C}_{13}\text{H}_8\text{BrNS}_2$ (322.24): calcd. C 48.45, H 2.50, N 4.35, S 19.90; found C 48.41, H 2.47, N 4.31, S 19.78.

6-Chloro-2-phenoxy-1,3-benzothiazole (4a): White solid; m.p. 88–90 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.26$ –7.34 (m, 4 H), 7.40–7.46 (m, 2 H), 7.58–7.61 (m, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 120.7, 121.0, 122.6, 126.6, 127.0, 129.6, 130.1, 133.4, 147.7, 154.6, 172.2$ ppm. IR (KBr): $\tilde{\nu} = 3057, 2962, 1672, 1598, 1529, 1490, 1445, 1399, 1304, 1255, 1155, 1097, 915$ cm^{-1} . $\text{C}_{13}\text{H}_8\text{ClNOS}$ (261.73): calcd. C 59.66, H 3.08, N 5.35, S 12.25; found C 59.71, H 3.13, N 5.40, S 12.17.

6-Chloro-2-(phenylthio)-1,3-benzothiazole (4h): White solid; m.p. 72–74 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.32$ (d, $J = 8.6$ Hz, 2 H), 7.40–7.52 (m, 2 H), 7.56 (d, $J = 2.0$ Hz, 1 H), 7.70–7.75 (m, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 120.5, 122.6, 126.9, 129.5, 130.2, 130.9, 135.6, 136.6, 152.6, 170.7$ ppm. IR (KBr): $\tilde{\nu} = 3064, 2967, 2922, 2851, 1585, 1542, 1456, 1431, 1397, 1300, 1260, 1172, 1061, 1103, 1061, 1013, 851, 829$ cm^{-1} . $\text{C}_{13}\text{H}_8\text{ClNS}_2$ (277.79): calcd. C 56.21, H 2.90, N 5.04, S 23.08; found C 56.27, H 2.89, N 5.11, S 22.93.

6-Chloro-2-(phenyloxy)-1,3-benzothiazole (4k): White solid; m.p. 96–98 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 3.16$ (t, $J = 6.8$ Hz, 2 H), 4.75 (t, $J = 6.8$ Hz, 2 H), 7.24–7.33 (m, 5 H), 7.50–7.60 (m, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 35.3, 72.6, 121.1, 121.7, 126.7, 126.9, 128.8, 129.0, 129.1, 133.2, 137.4, 148.0, 172.9$ ppm. IR (KBr): $\tilde{\nu} = 3061, 2921, 1595, 1536, 1498, 1452, 1436, 1402, 1371, 1303, 1254, 1242, 1217, 1198, 1096, 1052, 977, 816$ cm^{-1} . $\text{C}_{15}\text{H}_{12}\text{ClNOS}$ (289.78): calcd. C 62.17, H 4.17, N 4.83, S 11.06; found C 62.10, H 4.13, N 4.78, S 10.91.

6-Chloro-2-(3,4-dichlorobenzoyloxy)-1,3-benzothiazole (4l): White solid; m.p. 220–222 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.62$ (s, 2 H), 7.29 (d, $J = 8.4$ Hz, 2 H), 7.42 (d, $J = 1.6$ Hz, 1 H), 7.48 (d, $J = 8.4$ Hz, 1 H), 7.59 (m, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 70.1, 121.2, 121.9, 126.9, 127.5, 129.3, 131.0, 131.6, 133.4, 134.6, 135.4, 147.8, 172.4$ ppm. IR (KBr): $\tilde{\nu} = 3088, 2922, 2852, 1682, 1599, 1565, 1540, 1509, 1458, 1447, 1336, 1253, 1232, 1211, 1187, 1148, 1096, 1052, 1006, 812$ cm^{-1} . $\text{C}_{14}\text{H}_8\text{Cl}_3\text{NOS}$ (344.64): calcd. C 48.78, H 2.34, N 4.06, S 9.30; found C 48.82, H 2.35, N 4.01, S 9.27.

6-Methyl-1,3-benzothiazol-2(3*H*)-one (5q): White solid; m.p. 169–170 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 2.23$ (s, 3 H), 6.93 (m, 2 H), 7.04 (s, 1 H), 10.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 20.4, 110.9, 121.7, 123.2, 126.4, 131.6, 133.4, 170.9$ ppm. IR (KBr): $\tilde{\nu} = 3148, 3070, 3017, 2915, 2850, 1660, 1485, 1229, 802, 665$ cm^{-1} . $\text{C}_8\text{H}_7\text{NOS}$ (165.21): calcd. C 58.16, H 4.27, N 8.48, S 19.41; found C 58.23, H 4.25, N 8.51, S 19.32.

6-Bromo-1,3-benzothiazol-2(3*H*)-one (5r): White solid; m.p. 230–231 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.02$ (d, $J = 8.8$ Hz, 1 H), 7.32 (d, $J = 8.8$ Hz, 1 H), 7.49 (s, 1 H), 11.62 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 112.5, 114.0, 124.0, 125.4, 128.4, 134.9, 170.2$ ppm. IR (KBr): $\tilde{\nu} = 3139, 3074, 3013, 2890, 1673, 1597, 1463, 1210, 801, 648$ cm^{-1} . $\text{C}_7\text{H}_4\text{BrNOS}$ (230.08): calcd. C 36.54, H 1.75, N 6.09, S 13.94; found C 36.48, H 1.73, N 5.98, S 13.86.

Supporting Information (see also the footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra.

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