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UTILIZATION OF CHLOBENTHIAZONE AND BENAZOLIN-ETHYL AS 4-SUBSTITUTED 2(3*H*)-BENZOTHIAZOL-2-ONE SCAFFOLDS

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Abstract – *N*(3)-Substituted 4-aryl (*or* heteroaryl)-2(3*H*)-benzothiazol-2-ones were synthesized from readily accessible chlobenthiazole and benazolin-ethyl, a couple of *N*(3)-substituted 4-chloro-2(3*H*)-benzothiazol-2-one pesticides, utilizing Suzuki-Miyaura cross-coupling reactions (9 examples; 44–98% yield), although with less reactive stereocongested 4-chloro pendant substituent. In a similar fashion, *N*(3)-substituted 4-anilino (*or* BocNH)-2(3*H*)-benzothiazol-2-ones were synthesized from the 4-bromo analogues of the chlobenthiazole-utilizing Buchwald-Hartwig cross-coupling reactions (3 examples; 50–89% yield). In addition, a short synthesis of the key chloro-type quinone segment in natural mevashuntin with a unique 2(3*H*)-benzothiazol-2-one skeleton, was performed in three short steps with 61% overall yield. The obtained quinone segment functioned as a Diels-Alder reaction dienophile toward the Danishefsky-Kitahara diene as the model experiment. All schemes utilized a common cyclo-condensation using chlorocarbonylsulfonyl chloride for the construction of 4(*ortho*)-substituted 2(3*H*)-benzothiazol-2-one substrates.

INTRODUCTION

2(3*H*)-Benzothiazol-2-ones are important sulfur and nitrogen-containing benzologue heterocycles that are incorporated in various pharmaceuticals and agrochemicals (Figure 1).¹ Among them, *N*(3)- and 4-disubstituted 2(3*H*)-benzothiazol-2-ones **1** are noteworthy due to their synthetic difficulty, compared with the other *N*(3)- and 5- or 6-disubstituted 2(3*H*)-benzothiazol-2-ones;² construction of the stereocongested structure with three contiguous substituents in **1** requires a specific synthetic approach. Nonetheless, several *N*(3)- and 4-disubstituted 2(3*H*)-benzothiazol-2-ones **1** comprise notable biologically active compounds. Chlobenthiazole (**2**) is a potent agrochemical fungicide against rice blast disease³

and benzolin-ethyl (**3**) has been employed as a useful selective herbicide with auxin-like bioactivity.⁴ Mevashuntin (**4**), a unique natural product, was discovered as a unique metabolite of an HMG-CoA reductase inhibitor⁵ and adopted as an interesting target for total synthesis.⁶ We envisaged that the 4-chlorine pendant atom in **2** and **3** would function as a latent and potential scaffold to construct various, less accessible 4-substituted 2(3*H*)-benzothiazol-2-ones utilizing contemporary cross-coupling reactions. This paper reports (i) simple hydrolysis of **2** to give the corresponding carbamate, (ii) Suzuki-Miyaura cross-couplings of **2** and **3** to produce various 4-substituted 2(3*H*)-benzothiazol-2-one derivatives, and (iii) Buchwald-Hartwig cross-couplings using the bromo analogue of **2** to produce 4-anilino-2(3*H*)-benzothiazol-2-one derivatives. In addition, we present a short-step synthesis of one key segment of **4** and an application to Diels-Alder reaction of **4** with Danishefsky-Kitahara diene.

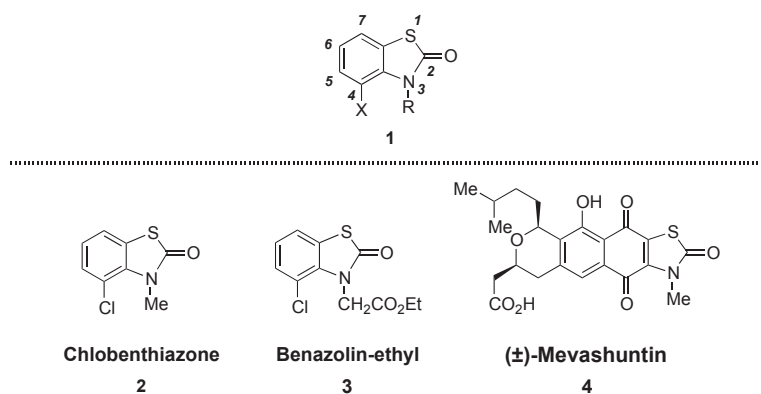


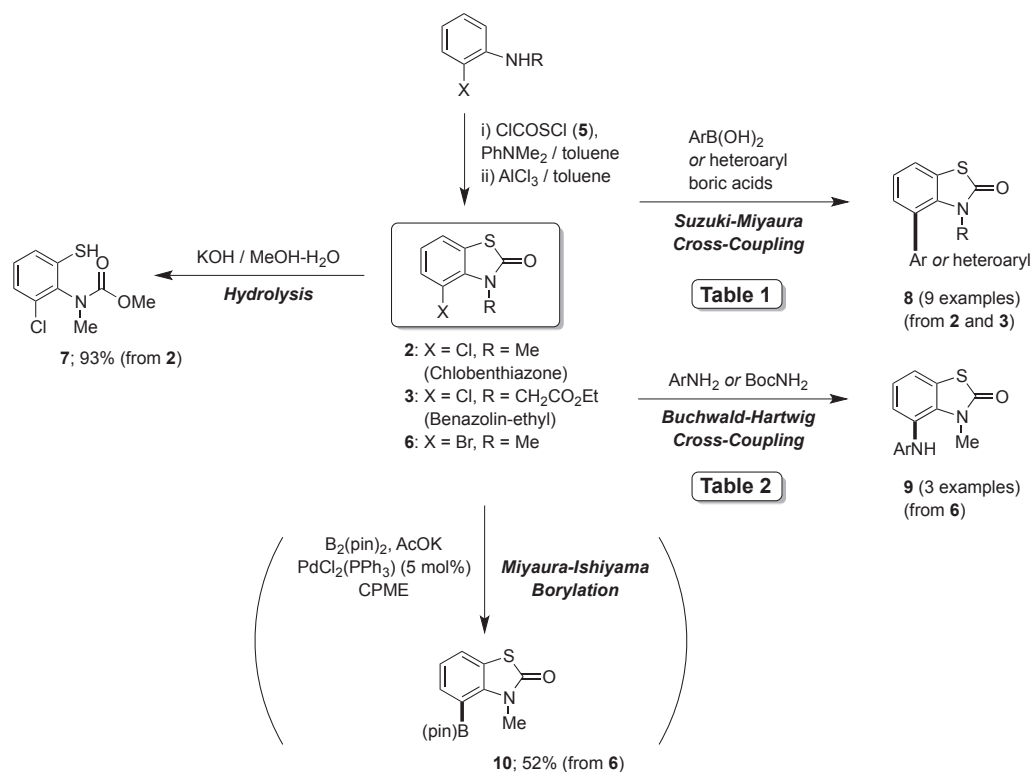
Figure 1. Representative biologically active compounds containing the *N*(3),4-disubstituted 2(3*H*)-benzothiazol-2-one structure

RESULTS AND DISCUSSION

The standard method for the synthesis of *N*(3)- and 4-disubstituted 2(3*H*)-benzothiazol-2-ones **1** is carried out through 5 steps as follows:¹ (i) 2(*ortho*)-substituted anilines are converted to arylthioureas with MSCN and HCl, (ii) oxidative cyclizations using Br₂ or SOCl₂ afford 4-substituted 2-amino-2(3*H*)-benzothiazols, (iii) 2-chlorination through diazotization (NaNO₂ in aqueous HCl) gives 4-substituted 2-chloro-2(3*H*)-benzothiazols, (iv) hydrolysis gives 4-disubstituted 2(3*H*)-benzothiazol-2-ones, (v) final *N*(3)-alkylation affords **1**.

In this study, chlobenthiazone (**2**), benazolin-ethyl (**3**), and the 4-bromo analogue **6** were prepared by the reported straightforward method⁷ utilizing cyclo-condensation of the corresponding *N*-alkylanilines with chlorocarbonylsulfonyl chloride (ClC=OSCl; abbreviated CCSC) (**5**). CCSC (**5**) is a unique, commercially available bifunctional electrophilic reagent⁸ (Scheme 1) and Zumach and Kühle provided a comprehensive review of the synthetic application of **5** for *S,N*-containing heterocyclic compounds.⁹ We previously reported several synthetic studies of these heterocycles with -COS- linkage using **5**.¹⁰

Our recent interests in the synthesis of multi-substituted (*E*)- and (*Z*)-stereodefined olefin scaffolds utilizing various cross-coupling reactions directed toward medicinal and process chemistry,¹¹ led us to investigate the derivatizations of chlobenthiazone (**2**), benazolin-ethyl (**3**), and their bromo analogue **6**. Various derivatizations of **2**, **3**, and **6** were examined: hydrolysis, Suzuki-Miyaura cross-coupling, and Buchwald-Hartwig cross-coupling, as illustrated in Scheme 1. Simple hydrolysis of **2** using KOH/MeOH-H₂O gave the corresponding new carbamate compound **7** in 93% yield.



Scheme 1. Derivatization array of *N*-substituted 4-halo-2(3*H*)-benzothiazol-2-ones **2**, **3**, and **6**

Next, our attention was focused on a couple of Suzuki-Miyaura and Buchwald-Hartwig cross-coupling reactions (Tables 1 and 2). Suzuki-Miyaura cross-coupling of chlobenthiazone (**2**) with several arylboronic acids proceeded smoothly using Pd(OAc)₂ / SPhos / K₃PO₄ catalysis to produce four aryl derivatives **8a–8d** in good to excellent yield (80–98%). The reaction using 3-furyl and 3-thienylboronic acids afforded **8e** and **8f** in moderate 44% and 53% yields, respectively. Benazolin-ethyl (**3**) also underwent the reaction successfully to afford the product **8g** in 88% yield. Two distinctive features are as follows; (i) Despite the lower reactivity of the stereocongested 4(*ortho*)-chloro leaving group, successful results were obtained. (ii) In clear contrast to the reported problematic case using enol tosylate Suzuki-Miyaura cross-coupling partner,^{11a} susceptible product **8c** did not undergo undesirable further Suzuki-Miyaura cross-coupling, indicating that the chlorine reactivity in **2** itself is sufficiently higher than that in **8c**.

Buchwald-Hartwig cross-coupling of **2** failed to proceed,¹² but switching to more reactive bromo analogue **6** solve the problem, and the desired 4-ArNH- and 4-(Boc)NH-products **9a–9c** were afforded in 89%, 84%, and 50% yields, respectively, using Pd₂dba₃ / XPhos / K₂CO₃ catalysis.¹³ A recent study reported that a related Miyaura-Ishiyama borylation of **6** yielded 4-(pinacolato)borone-substituted product **10**.¹⁴

Table 1. Suzuki-Miyaura cross-coupling of chlobenthiazone (**2**) and benazolin-ethyl (**3**)

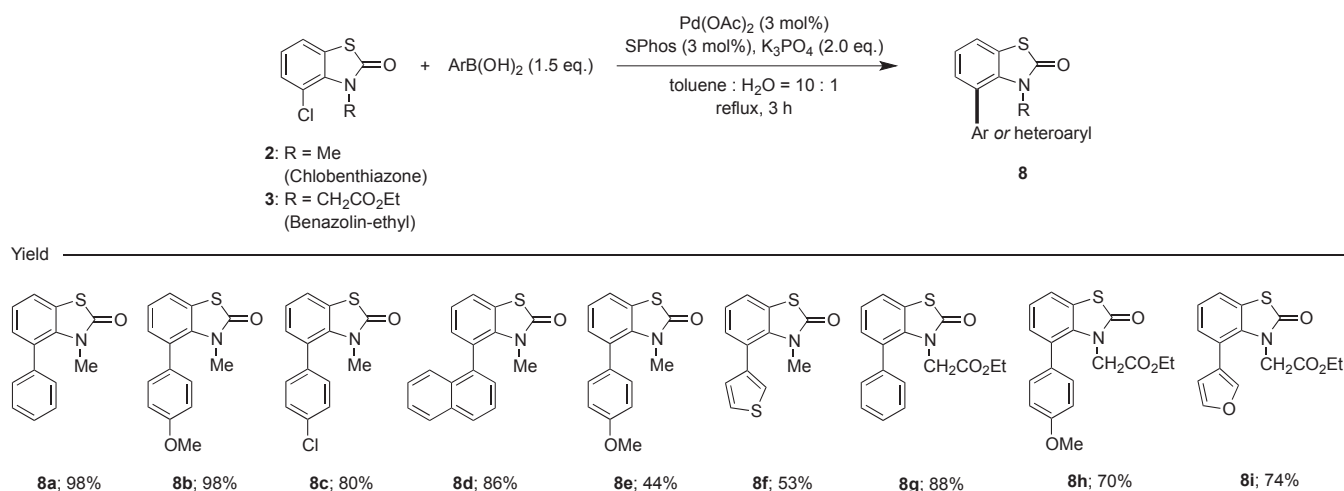
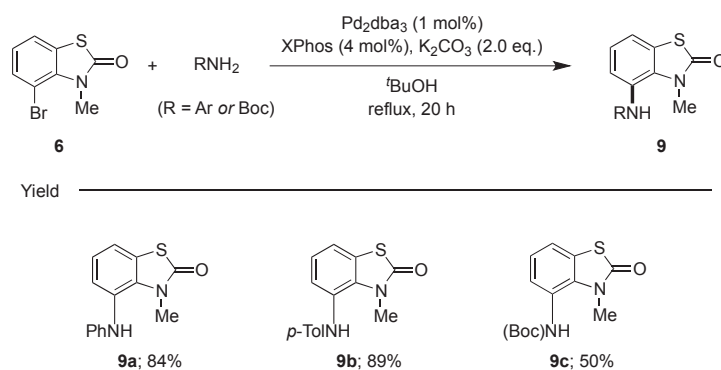
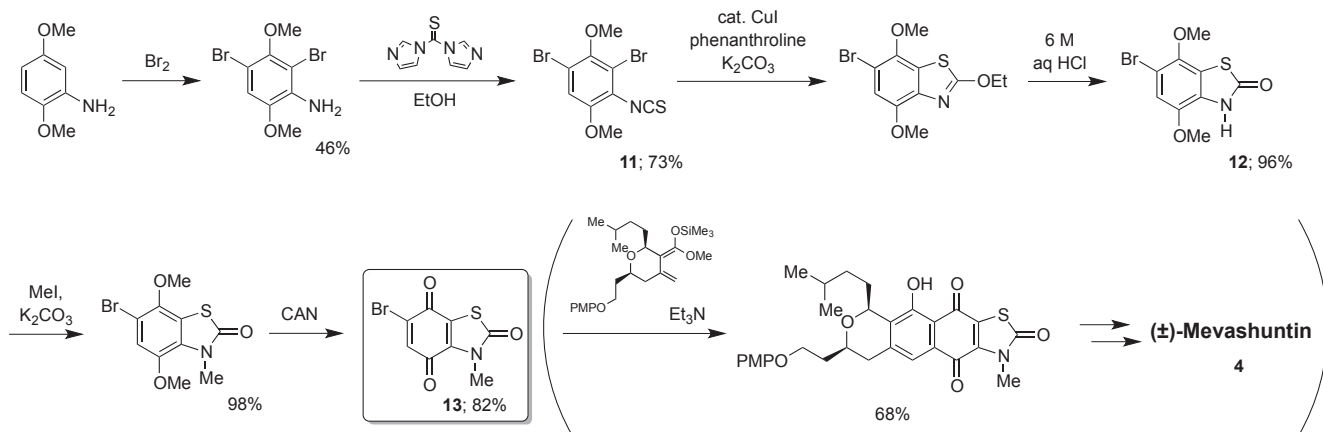


Table 2. Buchwald-Hartwig cross-coupling of the bromo analogue **6**

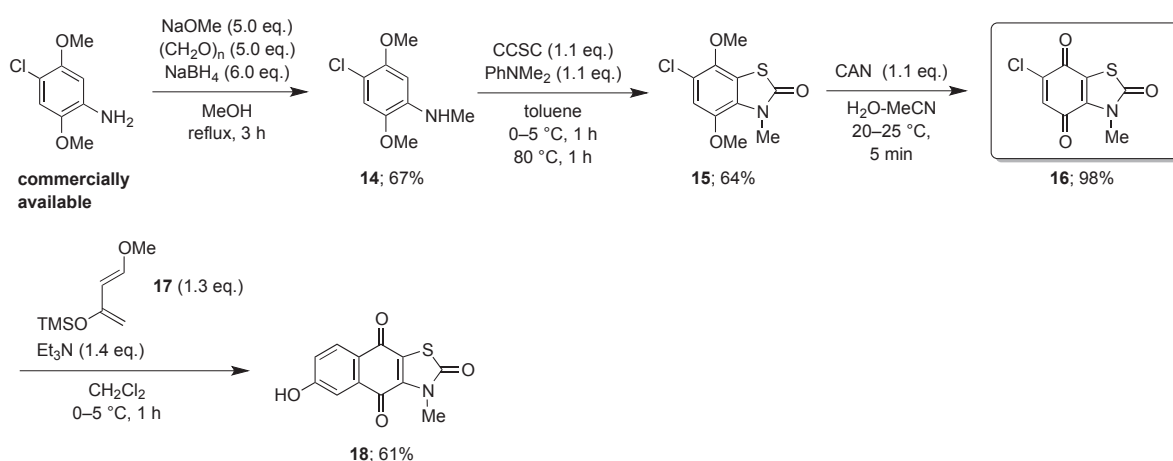


In addition, an alternative synthesis for the key building block in (±)-mevashuntin (**4**) was investigated to demonstrate the utility of cyclo-condensation using CCSC (**5**). The only example so far is Moody and Nawrat's distinctive total synthesis of (±)-mevashuntin,⁶ as illustrated in Scheme 2. 2,5-Dimethoxyaniline was converted to 4,6-dibromophenyl isothiocyanate **11** in two steps (34% yield). Conventional 2-alkoxy-2(3*H*)-benzothiazol formation through the isothiocyanate, followed by acid-hydrolysis afforded 2(3*H*)-benzothiazol-2-one **12**. *N*-Methylation of **12** and subsequent ceric ammonium nitrate (CAN)-oxidation furnished quinone-type segment **13** in six steps with an overall yield of 26%.

The present short synthesis of the key chloro-type segment **16** is depicted in Scheme 3. Commercially available 4-chloro-2,5-dimethoxyaniline was *N*-methylated using the procedure reported by Berluenga's group to afford **14** in 67% yield.^{15,16} Cyclo-condensation of **14** with CCSC (**5**) proceeded smoothly to produce the desired highly substituted *N*-methyl-2(3*H*)-benzothiazol-2-one **15** in 64% yield. Notably, due to the higher electrophilic reactivity of **14**, the addition of the AlCl₃ activating catalyst was unnecessary. CAN-oxidation successfully produced novel quinone-type segment **16** in only three steps with an overall yield of 42%. To evaluate the dienophile reactivity of **16**, Diels-Alder reaction with the Danishefsky-Kitahara diene **17** was examined as a model experiment. As expected, the reaction proceeded smoothly under mild conditions to afford the desired tricyclic quinone product **18** in 61% yield.



Scheme 2. Outline of Moody's total synthesis of (±)-mevashuntin (**4**)



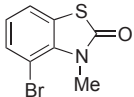
Scheme 3. Alternative short synthesis of chloro analogue segment **16** and Diels-Alder reaction of **16** with the Danishefsky-Kitahara diene (**17**)

In conclusion, a couple of *N*(3)-substituted 4-chloro-2(3*H*)-benzothiazol-2-one pesticides, chlobenthiazone and benazolin-ethyl, contributed as Suzuki-Miyaura cross-coupling partners to afford

several *N*(3)-substituted 4-aryl (or heteroaryl)-2(3*H*)-benzothiazol-2-ones. Similarly, Buchwald-Hartwig cross-coupling was performed using a more reactive 4-bromo analogue to afford 3-methyl-4-anilino (or BocNH)-2(3*H*)-benzothiazol-2-ones. A short-step synthesis of a key chloro-type quinone segment for natural, unique mevashuntin with a 2(3*H*)-benzothiazol-2-one skeleton, was successfully performed as a further application of common cyclo-condensation using CCSC (chlorocarbonylsulfenyl chloride). The quinone precursor served as a Diels-Alder reaction dienophile for the Danishefsky-Kitahara diene as the model experiment.

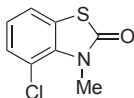
EXPERIMENTAL

4-Bromo-3-methyl-1,3-benzothiazol-2(3*H*)-one (**6**)⁷

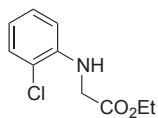
 Chlorocarbonylsulfenyl chloride (CCSC: **5**, 0.9 mL, 11 mmol) was added to a stirred solution of 4-bromo-*N*-methylaniline (1.86 g, 10 mmol) and *N,N*-dimethylaniline (1.33 g, 11 mmol) in toluene (10 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred at same temperature for 1 h. The reaction mixture was filtered through Celite to remove HCl salt of *N,N*-dimethylaniline, and the filtrate was added to a stirred suspension of AlCl₃ (2.00 g, 15 mmol) at room temperature, and the mixture was refluxed for 3 h. After cooling down, water was added to the stirred mixture, which was extracted twice with AcOEt. The organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane / AcOEt = 10 : 1) to give the crude solid. Recrystallization from 2-propanol gave the desired product (**6**; 1.31 g, 54%).

Colorless crystals; mp 137–138 °C (lit.⁷ 139–140 °C); ¹H NMR (500 MHz, CDCl₃): δ = 3.87 (s, 3H), 6.99 (t, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 1.2 Hz, 8.0 Hz, 1H), 7.48 (dd, *J* = 1.2 Hz, 8.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 33.4, 104.0, 121.6, 123.7, 124.9, 132.4, 134.8, 170.0; IR (neat): ν_{max} = 1450, 1435, 1311, 1265, 1257, 1211, 1193, 1149, 1128, 1093, 1072 cm⁻¹.

Chlobenthiazone: 4-Chloro-3-methyl-1,3-benzothiazol-2(3*H*)-one (**2**)^{3,7}

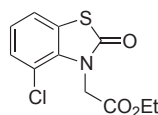
 In a similar procedure for the preparation of **6**, the reaction of 4-chloro-*N*-methylaniline (142 mg, 1 mmol) with CCSC (**5**) (144 mg, 1.1 mmol), using *N,N*-dimethylaniline (133 mg, 1.1 mmol) and AlCl₃ (160 mg, 1.2 mmol) in toluene (3 mL), and the successive purification by silica-gel chromatography (hexane / AcOEt = 10 : 1) gave the desired product (**2**; 170 mg, 85%).

Colorless crystals; mp 130–131 °C (lit.⁷ 124–128 °C); ¹H NMR (500 MHz, CDCl₃): δ = 3.86 (s, 3H), 7.06 (t, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 1.2 Hz, 8.0 Hz, 2H), 7.31 (dd, *J* = 1.2 Hz, 8.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 33.2, 117.5, 121.3, 123.6, 124.9, 129.2, 134.0, 170.1; IR (neat): ν_{max} = 2310, 2250, 1670, 1508, 1471, 1456, 1313, 1261, 1195, 1136, 1080, 1058 cm⁻¹.

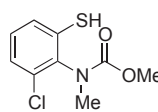
Ethyl (2-chlorophenyl)glycinate¹⁷

Ethyl bromoacetate (3.34 g, 20 mmol) was added to a stirred suspension of 2-chloroaniline (2.55 g, 20 mmol) and NaOAc (1.64 g, 20 mmol) in EtOH (20 mL) at 20–25 °C under an Ar atmosphere, and the mixture was stirred at 80 °C for 20 h. Water was added to the stirred mixture, which was extracted with AcOEt. The combined organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude oil was purified by silica-gel column chromatography (hexane / AcOEt = 5 : 1) to give the desired product (2.45 g, 57%).

Pale yellow oil; ¹H NMR (500 MHz, CDCl₃): δ = 1.30 (t, *J* = 7.5 Hz, 3H), 3.95 (s, 2H), 4.26 (q, *J* = 7.5 Hz, 2H), 4.95 (br s, 1H), 6.50–6.56 (m, 1H), 6.65–6.71 (m, 1H), 7.10–7.17 (m, 1H), 7.21–7.30 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 14.0, 45.4, 61.3, 111.1, 117.9, 119.4, 127.7, 129.1, 142.9, 170.2.

Ethyl 2-(4-chloro-2-oxo-1,3-benzothiazol-yl)acetate (3)⁴

CCSC (**5**; 0.9 mL, 11 mmol) was added to a stirred solution of ethyl (2-chlorophenyl)glycinate (2.14 g, 10 mmol) and *N,N*-dimethylaniline (1.33 g, 11 mmol) in toluene (10 mL) at 0–5 °C, followed by being stirred at same temperature for 1 h under an Ar atmosphere. The reaction mixture was filtered through Celite to remove HCl salt of *N,N*-dimethylaniline, and the filtrate was added to a stirred suspension of AlCl₃ (2.00 g, 15 mmol) in toluene (10 mL) at 20–25 °C, followed by being stirred at reflux for 2 h. After cooling down, water was added to the stirred mixture, which was extracted twice with AcOEt. The organic phase was washed with water, brine, dried (Na₂SO₄), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane / AcOEt = 10 : 1) to give the desired product (**3**; 1.42 g, 52%). Pale yellow crystals; mp 76–78 °C (lit.⁴ 78–79 °C); ¹H NMR (500 MHz, CDCl₃): δ = 1.28 (t, *J* = 7.5 Hz, 3H), 4.26 (q, *J* = 7.5 Hz, 2H), 5.14 (s, 2H), 7.06–7.11 (m, 1H), 7.23–7.28 (m, 1H), 7.31–7.37 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 14.0, 45.9, 61.9, 116.9, 121.4, 123.7, 124.5, 129.0, 132.7, 167.8, 170.1; IR (neat): ν_{max} = 3020, 2310, 2256, 1749, 1680, 1583, 1508, 1498, 1469, 1440, 1375, 1321, 1286, 1209, 1165, 1107, 1020 cm⁻¹.

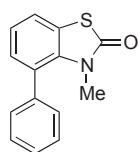
Methyl (2-chloro-6-mercaptophenyl)(methyl)carbamate (7)

5 M KOH aqueous solution (1.0 mL) was added to a stirred solution of chlobenthiazone (**2**; 100 mg, 0.5 mmol) in MeOH (2.5 mL) / H₂O (0.5 mL) at 20–25 °C, followed by being stirred at same temperature for 15 h under an Ar atmosphere. 1 M HCl aqueous solution (5.0 mL) was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na₂SO₄), and concentrated. The obtained crude oil was purified by silica-gel column chromatography (hexane / AcOEt = 5 : 1) to give the desired product (**6**);

108 mg, 93%).

Colorless oil; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 3.18 (s, 3H), 3.56 (s, 1H), 3.68 (s, 3H x 83 / 100), 3.84 (s, 3H x 17 / 100), 7.10 (t, J = 8.0 Hz, 1H), 7.20–7.26 (m, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 34.6, 35.1, 53.2, 53.4, 127.0, 127.4, 127.8, 128.5, 128.7, 128.8, 134.3, 134.4, 134.6, 134.7, 136.8, 137.6, 155.3, 155.9; IR (neat): ν_{max} = 2953, 2544, 1699, 1560, 1437, 1350, 1296, 1194, 1163 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_9\text{H}_{10}\text{ClNO}_2\text{S}$, $[\text{M} - \text{H}]^-$ 230.0043; found: 230.0041.

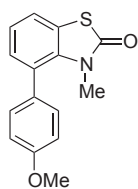
3-Methyl-4-phenylbenzo[*d*]thiazol-2(3*H*)-one (8a)



PhB(OH)₂ (183 mg, 1.5 mmol), K₃PO₄ (424 mg, 2.0 mmol), Pd(OAc)₂ (7 mg, 0.30 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (12 mg, 0.03 mmol) were successively added to a stirred suspension of **2** (200 mg, 1.0 mmol) in toluene (2.0 mL) and H₂O (0.2 mL) at 20–25 °C under Ar atmosphere, and the mixture was stirred at 110 °C for 20 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water and brine, dried (Na₂SO₄) and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane / AcOEt = 5:1) to give the crude solid, which was washed with hexane to remove biphenyl to give the desired product (**8a**; 237 mg, 98%).

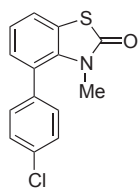
Colorless crystals; mp 82–84 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 2.92 (s, 3H), 7.10–7.18 (m, 2H), 7.30–7.36 (m, 2H), 7.38–7.45 (m, 4H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 33.5, 121.5, 122.1, 123.2, 127.4, 127.8 (3C), 129.6 (2C), 129.7, 135.0, 138.8, 170.7; IR (neat): ν_{max} = 3014, 2310, 1668, 1496, 1471, 1436, 1317, 1282, 1259, 1217, 1197, 1155, 1114, 1060, 1006 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{11}\text{NOS}$, $[\text{M} + \text{H}]^+$ 242.0640; found: 242.0653.

4-(4-Methoxyphenyl)-3-methylbenzo[*d*]thiazol-2(3*H*)-one (8b)



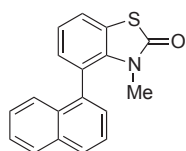
In a similar procedure for the preparation of **8a**, the reaction of **2** (100 mg, 0.50 mmol) with (4-MeO)C₆H₄B(OH)₂ (114 mg, 0.75 mmol), K₃PO₄ (212 mg, 1.00 mmol), Pd(OAc)₂ (7 mg, 0.03 mmol), SPhos (12 mg, 0.03 mmol) in toluene (0.9 mL) / H₂O (0.1 mL), and the successive purification (hexane / AcOEt = 5 : 1) gave the desired product (**8b**; 132 mg, 98%).

Colorless crystals; mp 95–96 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 2.96 (s, 3H), 3.87 (s, 3H), 6.93–6.97 (m, 2H), 7.10–7.16 (m, 2H), 7.23–7.28 (m, 2H), 7.38–7.42 (m, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 33.6, 55.3, 113.3 (2C), 121.4, 122.1, 123.3, 127.2, 130.1, 130.8, 131.1 (2C), 135.3, 159.3, 170.9; IR (neat): ν_{max} = 3016, 2310, 1668, 1610, 1508, 1471, 1440, 1292, 1246, 1215, 1176, 1114, 1060, 1029 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{S}$, $[\text{M} + \text{Na}]^+$ 294.0545; found: 294.0565.

4-(4-Chlorophenyl)-3-methylbenzo[d]thiazol-2(3H)-one (8c)

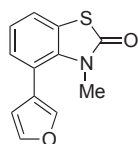
In a similar procedure for the preparation of **8a**, the reaction of **2** (50 mg, 0.25 mmol), 4-chlorophenylboronic acid (43 mg, 0.28 mmol), K_3PO_4 (106 mg, 0.50 mmol), $Pd(OAc)_2$ (2 mg, 0.08 mmol), and SPhos (3 mg, 0.08 mmol) in toluene (0.45 mL) / H_2O (0.05 mL), and the successive purification (hexane / AcOEt = 5 : 1) gave the desired product (**8c**; 55 mg, 80%).

Colorless oil; 1H NMR (500 MHz, $CDCl_3$): δ = 2.96 (s, 3H), 7.09 (dd, J = 1.2, 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.27–7.31 (m, 2H), 7.39–7.42 (m, 2H), 7.44 (dd, J = 1.2, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.7, 121.9, 122.2, 123.5, 126.0, 128.1 (2C), 129.7, 130.9 (2C), 134.1, 135.0, 137.4, 170.6; IR (neat): ν_{max} = 3016, 2310, 1668, 1490, 1471, 1440, 1394, 1319, 1215, 1157, 1114, 1091, 1060, 1014 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{14}H_{10}ClNOS$, $[M + Na]^+$ 298.0081; found: 298.0070.

3-Methyl-4-naphthylbenzo[d]thiazol-2(3H)-one (8d)

In a similar procedure for the preparation of **8a**, the reaction of **2** (100 mg, 0.0 mmol), 1-naphthaleneboronic acid (130 mg, 0.75 mmol), K_3PO_4 (212 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), and SPhos (12 mg, 0.03 mmol) in toluene (0.9 mL) / H_2O (0.1 mL), and the successive purification (hexane / AcOEt = 15 : 1) gave the desired product (**8d**; 125 mg, 86%).

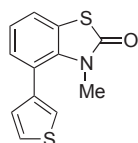
Orange colored oil; 1H NMR (500 MHz, $CDCl_3$): δ = 2.62 (s, 3H), 7.16–7.24 (m, 2H), 7.37–7.48 (m, 3H), 7.49–7.57 (m, 3H), 7.89–7.97 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 31.8, 122.0, 122.3, 123.1, 124.9, 125.1, 125.9, 126.3, 126.9, 127.9, 128.4, 128.6, 130.3, 133.06, 133.08, 136.0, 136.3, 170.6; IR (neat): ν_{max} = 3059, 2250, 1668, 1570, 1506, 1475, 1440, 1394, 1315, 1263, 1205, 1155, 1128, 1105, 1060 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{18}H_{13}NOS$, $[M + Na]^+$ 314.0616; found: 314.0616.

4-(3-Furyl)-3-methylbenzo[d]thiazol-2(3H)-one (8e)

In a similar procedure for the preparation of **8a**, the reaction of **2** (100 mg, 0.5 mmol), 3-furylboronic acid (84 mg, 0.75 mmol), K_3PO_4 (212 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), and SPhos (12 mg, 0.03 mmol) in toluene (0.9 mL) / H_2O (0.1 mL), and the successive purification (hexane / AcOEt = 15 : 1) gave the desired product (**8e**; 48 mg, 44%).

Pale yellow crystals; mp 76–78 °C; 1H NMR (500 MHz, $CDCl_3$): δ = 3.22 (s, 3H), 6.47–6.54 (m, 1H), 7.08–7.19 (m, 2H), 7.39–7.46 (m, 1H), 7.46–7.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.0, 113.3, 117.8, 122.1, 122.2, 122.9, 123.4, 130.7, 135.9, 140.8, 142.6, 170.7; IR (neat): ν_{max} = 3014, 1668, 1506, 1471, 1442, 1319, 1263, 1215, 1199, 1159, 1122, 1058, 1016 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{12}H_9NO_2S$, $[M + H]^+$ 232.0432; found: 232.0436.

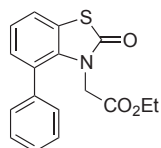
4-(3-Thienyl)-3-methylbenzo[d]thiazol-2(3H)-one (8f)



In a similar procedure for the preparation of **8a**, the reaction of **2** (100 mg, 0.5 mmol), 3-thiopheneboronic acid (96 mg, 0.75 mmol), K_3PO_4 (212 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), and SPhos (12 mg, 0.03 mmol) in toluene (0.9 mL) / H_2O (0.1 mL), and the successive purification (hexane / AcOEt = 15 : 1) gave the desired product (**8f**; 66 mg, 53%).

Colorless crystals; mp 91–93 °C. 1H NMR (500 MHz, $CDCl_3$): δ = 3.02 (s, 3H), 7.08–7.18 (m, 3H), 7.22–7.26 (m, 1H), 7.35–7.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.7, 121.9, 122.1, 122.2, 123.3, 124.2, 125.3, 129.9, 130.0, 135.6, 138.7, 170.7; IR (neat): ν_{max} = 3014, 2310, 1668, 1471, 1440, 1361, 1315, 1265, 1215, 1155, 1112, 1080, 1060, 1008, 916 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{12}H_9NOS_2$, $[M + Na]^+$ 270.0022; found: 270.0023.

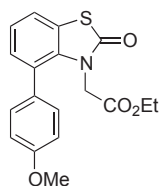
Ethyl 2-(2-oxo-4-phenylbenzo[d]thiazol-3(2H)-yl)acetate (8g)



In a similar procedure for the preparation of **8a**, the reaction of **2** (106 mg, 0.5 mmol) of $PhB(OH)_2$ (92 mg, 0.75 mmol), K_3PO_4 (212 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), and SPhos (12 mg, 0.03 mmol) in toluene (0.9 mL) / H_2O (0.1 mL), and the successive purification (hexane / AcOEt = 7 : 1) gave the desired product (**8g**; 138 mg, 88%).

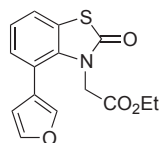
Pale yellow oil; 1H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.5 Hz, 3H), 4.00 (q, J = 7.5 Hz, 2H), 4.24 (s, 2H), 7.03–7.11 (m, 1H), 7.13–7.20 (m, 1H), 7.26–7.30 (m, 2H), 7.37–7.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 45.9, 61.4, 115.2, 121.9, 122.4, 123.1, 127.0, 128.2 (2C), 129.5 (2C), 129.8, 133.8, 138.2, 167.2, 171.1; IR (neat): ν_{max} = 3018, 2310, 1749, 1674, 1433, 1375, 1323, 1215, 1168, 1024 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{17}H_{15}NO_3S$, $[M + Na]^+$ 336.0658; found: 336.0670.

Ethyl 2-(2-oxo-4-(4-methoxyphenyl)benzo[d]thiazol-3(2H)-yl)acetate (8h)



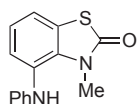
In a similar procedure for the preparation of **8a**, the reaction of **2** (53 mg, 0.25 mmol) of $(4-MeO)C_6H_4B(OH)_2$ (57 mg, 0.38 mmol), K_3PO_4 (106 mg, 0.5 mmol), $Pd(OAc)_2$ (2 mg, 0.02 mmol), and SPhos (3 mg, 0.02 mmol) in toluene (0.45 mL) / H_2O (0.05 mL), and the successive purification (hexane / AcOEt = 5 : 1) gave the desired product (**8g**; 60 mg, 70%).

Colorless oil; 1H NMR (500 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.5 Hz, 3H), 3.86 (s, 3H), 4.01 (q, J = 7.5 Hz, 2H), 4.28 (s, 2H), 6.89–6.94 (m, 2H), 7.06 (dd, J = 1.2, 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.16–7.20 (m, 2H), 7.43 (dd, J = 1.2, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 45.9, 55.3, 61.4, 113.6 (2C), 121.8, 122.4, 123.0, 126.8, 130.2, 130.3, 130.6 (2C), 134.1, 159.5, 167.3, 171.1; IR (neat): ν_{max} = 2982, 2936, 2905, 1748, 1668, 1512, 1296, 1244, 1204, 1167 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{18}H_{17}NO_4S$, $[M + Na]^+$ 366.0776; found: 366.0764.

Ethyl 2-(2-oxo-4-phenylbenzo[d]thiazol-3(2H)-yl)acetate (8i)

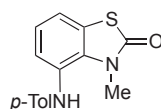
In a similar procedure for the preparation of **8a**, the reaction of **2** (53 mg, 0.25 mmol) of 3-furylboronic acid (42 mg, 0.38 mmol), K_3PO_4 (106 mg, 0.5 mmol), $Pd(OAc)_2$ (2 mg, 0.02 mmol), and SPhos (3 mg, 0.02 mmol) in toluene (0.45 mL) / H_2O (0.05 mL), and the successive purification (hexane / AcOEt = 15 : 1) gave the desired product (**8g**; 56 mg, 74%).

Paled yellow crystals; mp 82–85 °C; 1H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.5 Hz, 3H), 4.10 (q, J = 7.5 Hz, 2H), 4.53 (s, 2H), 6.43–6.46 (m, 1H), 7.09 (dd, J = 1.2, 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.36–7.39 (m, 1H), 7.44 (dd, J = 1.2, 8.0 Hz, 1H), 7.49–7.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 45.6, 61.6, 112.8, 117.3, 122.1, 122.4 (2C), 123.1, 130.8, 134.8, 141.0, 142.9, 167.4, 170.9; IR (neat): ν_{max} = 2982, 2940, 2951, 1748, 1668, 1435, 1204, 1161, 1016 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{15}H_{13}NO_4S$, $[M + Na]^+$ 326.0463; found: 326.0488.

3-Methyl-4-(*p*-tolylamino)benzo[d]thiazol-2(3H)-one (9a)

$PhNH_2$ (47 mg, 0.5 mmol), K_2CO_3 (138 mg, 1.0 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) (16 mg, 0.03 mmol) were successively added to a stirred suspension of 4-bromo-3-methylbenzothiazol-2(3H)-one (**6**; 122 mg, 0.5 mmol) in $tBuOH$ (1.0 mL) at 20–25 °C under Ar atmosphere, and the mixture was stirred at 85–90 °C for 20 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane / AcOEt = 5:1), and washed with hexane to give the desired product (**9a**; 114 mg, 89%).

Orange colored crystals; mp 137–140 °C; 1H NMR (500 MHz, $CDCl_3$): δ = 3.60 (s, 3H), 5.30 (br s, 1H), 6.57–6.62 (m, 2H), 6.80–6.87 (m, 1H), 7.07–7.15 (m, 2H), 7.16–7.23 (m, 2H), 7.28–7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.7, 114.5 (2C), 119.7, 120.5, 123.6, 124.2, 126.9, 127.0, 129.6 (2C), 134.7, 147.2, 170.4; IR (neat): ν_{max} = 3331, 3046, 2951, 1651, 1601, 1582, 1497, 1476, 1449, 1423 cm^{-1} ; HRMS (ESI): m/z calcd for $C_{14}H_{12}N_2OS$, $[M + H]^+$ 257.0755; found: 257.0749.

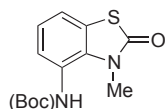
3-Methyl-4-(*p*-tolylamino)benzo[d]thiazol-2(3H)-one (9b)

In a similar procedure for the preparation of **9a**, the reaction of **6** (122 mg, 0.5 mmol), *p*-toluidine (54 mg, 0.5 mmol), K_3PO_4 (138 mg, 2.0 mmol), $Pd_2(dba)_3$ (9 mg, 0.02 mmol), and XPhos (16 mg, 0.03 mmol) in $tBuOH$ (1.0 mL), and the successive purification (hexane / AcOEt = 10 : 1), gave the desired product (**9b**; 114 mg, 84%).

Orange colored crystals; mp 177–179 °C; 1H NMR (500 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 3.62 (s, 3H), 5.24 (br s, 1H), 6.49–6.57 (m, 2H), 6.98–7.05 (m, 2H), 7.06–7.15 (m, 2H), 7.27–7.31 (m, 1H); ^{13}C NMR

(125 MHz, CDCl₃): δ = 20.4, 31.8, 114.8 (2C), 120.0, 123.5, 124.1, 126.4, 127.6, 129.1, 130.0 (2C), 134.4, 144.7, 170.4; IR (neat): ν_{\max} = 3296, 3018, 2310, 1647, 1508, 1475, 1442, 1273, 1215, 1109, 1062 cm⁻¹; HRMS (ESI): m/z calcd for C₁₅H₁₄N₂OS, [M + Na]⁺ 271.0905; found: 271.0924.

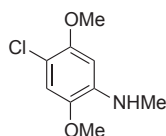
3-Methyl-4-(benzyloxycarbonyl)benzo[d]thiazol-2(3H)-one (9c)



In a similar procedure for the preparation of **9a**, the reaction of **6** (122 mg, 0.5 mmol), BocNH₂ (76 mg, 0.75 mmol), K₃PO₄ (138 mg, 2.00 mmol), Pd₂(dba)₃ (9.2 mg, 0.03 mmol), and XPhos (24 mg, 0.05 mmol) in ^tBuOH (1.0 mL), and successive purification (hexane / AcOEt = 5 : 1), gave the desired product (**9b**; 66 mg, 50%).

Colorless oil; ¹H NMR (500 MHz, CDCl₃): δ = 1.50 (s, 9H), 3.65 (s, 3H), 6.41 (br s, 1H), 7.06–7.15 (m, 2H), 7.28–7.32 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 28.2 (3C), 31.3, 81.2, 121.5 (2C), 122.8, 123.8, 127.6, 134.2, 154.9, 170.9; IR (neat): ν_{\max} = 3292, 2978, 1667, 1659, 1587, 1406, 1393, 1337, 1273, 1194 cm⁻¹; HRMS (ESI): m/z calcd for C₁₃H₁₆N₂O₃S, [M + Cs]⁺ 412.9936; found: 412.9957.

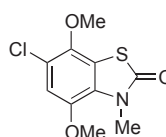
4-Chloro-2,5-dimethoxy-N-methylaniline (14)



According to Berluenga group's procedure,¹⁵ 4-chloro-2,5-dimethoxyaniline (3.75 g, 20 mmol) was added to a stirred solution of NaOMe (5.40 g, 0.10 mol) and paraformaldehyde (3.00 g, 0.10 mol) in MeOH (40 mL) at 20–25 °C under an Ar atmosphere, and the mixture was stirred under reflux for 3 h. After cooling down to 0 °C, NaBH₄ (3.98 g, 0.10 mmol) was added portionwise to the mixture, which was stirred at reflux for 20 h. Water was added to the stirred mixture, which was extracted with AcOEt. The organic phase was washed with water, brine, dried (Na₂SO₄), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane / AcOEt = 3 : 1) to give the desired product (**14**; 2.69 g, 67%).

Colorless crystals; mp 70–71 °C; ¹H NMR (500 MHz, CDCl₃): δ = 2.88 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 6.76 (s, 1H), 6.33 (s, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 30.5, 56.1, 57.2, 96.3, 108.2, 111.7, 138.6, 141.3, 149.9; IR (neat): ν_{\max} = 3446, 3014, 2937, 2831, 1606, 1516, 1456, 1431, 1394, 1205, 1180, 1035, 844, 815 cm⁻¹; HRMS (ESI): m/z calcd for C₉H₁₂NO₂, [M + Na]⁺ 202.0635; found: 202.0656.

6-Chloro-4,7-dimethoxy-3-methylbenzothiazol-2(3H)-one (15)

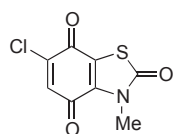


CCSC (**5**; 0.27 mL, 3.3 mmol) was added to a stirred solution of **14** (605 mg, 3.0 mmol) and *N,N*-dimethylaniline (400 mg, 3.3 mmol) in toluene (6 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at same temperature for 1 h at the same temperature and at 80 °C for 1 h. After cooling down, water was added to the stirred mixture, which was extracted twice with AcOEt. The organic phase was washed with 1 M HCl aqueous solution, brine,

dried (Na_2SO_4), and concentrated. The obtained crude solid was purified by silica-gel column chromatography (hexane / AcOEt = 5 : 1) to give the desired product (**15**; 497 mg, 64%).

Colorless crystals; mp 146–149 °C; ^1H NMR (500 MHz, CDCl_3): δ = 3.70 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.82 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ = 32.5, 56.6, 60.5, 111.1, 118.4, 120.1, 126.0, 142.9, 143.6, 169.7; IR (neat): ν_{max} = 3016, 2941, 1732, 1674, 1489, 1446, 1396, 1267, 1213, 1139, 1105, 1074, 1035, 1001 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{10}\text{H}_{10}\text{NO}_3\text{S}$, $[\text{M} + \text{Na}]^+$ 260.0417 found: 260.0148.

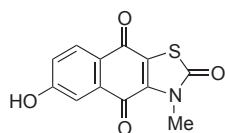
6-Chloro-3-methylbenzo[*d*]thiazole-2,4,7(3*H*)-trione (**16**)



Cerium(IV) ammonium nitrate (CAN) (1.37 g, 2.5 mmol) in water (10 mL) was added to a stirred solution of **15** (260 mg, 10 mmol) in MeCN (10 mL) at 20–25 °C under an Ar atmosphere, and the mixture was stirred at same temperature for 5 min. The reaction mixture was concentrated under reduced pressure to give the residue, which was extracted three times with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the desired product (**16**, 225 mg, 98%), which was used for the next step without purification.

Dark red crystals; mp 137–139 °C; ^1H NMR (500 MHz, CDCl_3): δ = 3.69 (s, 3H), 6.92 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ = 31.8, 122.7, 132.0, 135.7, 144.2, 169.5, 170.9, 174.6.

6-Hydroxy-3-methylnaphtho[2,3-*d*]thiazole-2,4,9(3*H*)-trione (**18**)



1-Methoxy-3-trimethylsiloxy-1,3-butadiene (ca. 70% purity based on q ^1H NMR; 345 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **16** (ca. 75% purity based on q ^1H NMR; 115 mg, 0.38 mmol) and Et_3N (53 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) at 0–5 °C under an Ar atmosphere, and the mixture stirred at same temperature for 1 h. The mixture was poured into 1 M HCl aqueous solution (10 mL), which was extracted three times with CH_2Cl_2 . The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude solid was purified by silica-gel column chromatography (hexane / AcOEt = 3 : 1) to give the desired product (**18**; 80 mg, 61%).

Yellow crystals; mp 279–282 °C; ^1H NMR (500 MHz, Acetone- d_6): δ = 3.85 (s, 3H), 7.38 (dd, J = 2.3, 8.6 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, Acetone- d_6): δ = 33.1, 115.1, 122.1, 125.7, 127.6, 130.4, 136.0, 139.6, 164.5, 170.9, 176.4, 177.5; IR (neat): ν_{max} = 3254, 1668, 1645, 1595, 1558, 1439, 1389, 1337, 1325, 1306 cm^{-1} ; HRMS (ESI): m/z calcd for $\text{C}_{12}\text{H}_7\text{NO}_4\text{S}$, $[\text{M} - \text{H}]^-$ 260.0018 found: 260.0016.

ACKNOWLEDGEMENTS

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12. Although the reaction of **2** using Pd(OAc)₂ / JohnPhos, Pd₂(dba)₂ / BINAP, or / SPhos, or / DavePhos, or / ^tBuXPhos catalysts did not proceed (completely no reaction), XPhos catalyst resulted in ca. 5% yield. This positive result prompted us to examine the use of **6** with XPhos.
13. The reaction of **6** using Pd(OAc)₂ / JohnPhos, Pd₂(dba)₂ / BINAP, or / SPhos, or / DavePhos, or /

^tBuXPhos catalysts did not proceed (completely no reaction).

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