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Transition Metal-Free Amidoalkylation of Benzothiazoles and Amidoalkylarylation of Activated Alkenes with *N,N*-Dialkylamides

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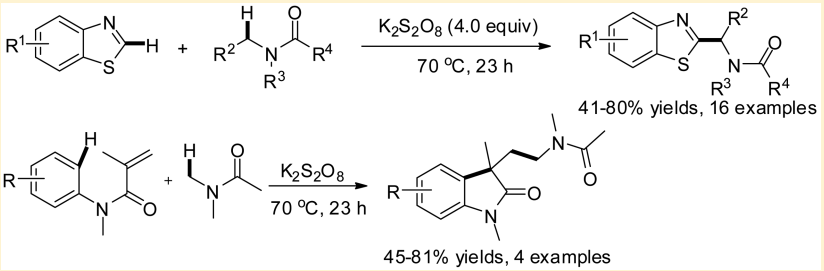
Supporting Information



ABSTRACT: A general and practical amidoalkylation reaction, using *N,N*-dialkylamides in the presence of potassium persulfate as the sole reagent, has been developed. 2-Amidoalkylated benzothiazole- and 3-amidoalkyl-substituted indolinone derivatives were obtained by using benzothiazoles and *N*-aryl-*N*-methyl-methacrylamides as substrates, respectively. The transformation proceeded smoothly through amidoalkyl radical intermediates that were trapped by benzothiazoles or activated alkenes.

The formation of a C−C bond through direct C−H functionalization is a fundamental research topic because of its advantages in atom economy and environmental benignity over traditional methods.[1] In this context, activation and coupling of two different C−H centers, known as oxidative cross-dehydrogenative-coupling (CDC), has been recognized as an ideal approach to build C−C bonds in terms of bond-forming efficiency and atom economy.[2] Over the past decade, substantial progress has been made in CDC reactions mainly catalyzed by transition metals, including Pd, Ru, Fe, and Sc.[3] However, concerns over cost as well as the toxicity of transition metal contaminants from either catalyst and/or oxidant make transition metal-free CDC processes more attractive. For example, Antonchick and Burgmann developed a $PhI(OCOCF_3)/NaN_3$-promoted oxidative cross-coupling reaction of heteroarenes with simple alkanes.[4] Recently, Liu reported an I_2-catalyzed olefination of oxindoles with simple alkenes to give 3-alkenyl-2-oxindoles via the CDC strategy.[5] Furthermore, several protocols for C−C bond construction via free radical-mediated CDC processes have been developed by Han and others.[6] Although considerable advances in this field have been made, more CDC reactions leading to quick assembly of drug-like molecules under practical transition metal-free conditions are still highly desirable.

Benzothiazole is an important structural motif that exists in a number of compounds of medicinal interests, natural products, and functional materials.[7] 2-Amidoalkylated benzothiazole derivatives in particular show prominent activities as inhibitors of histone deacetylase (HDAC), HldE kinase, and CRTH2 receptor (Figure 1).[8] For preparing C2-substituted benzothiazole derivatives, a CDC reaction between benzothiazole and another C−H species is probably the most atom economical and efficient approach.[9] For example, Chang and co-workers developed a silver-mediated decarbonylative amination of benzothiazoles using formamides as nitrogen sources (eq 1, Scheme 1).[10] Recently, Wang and co-workers reported a metal- and base-free approach to prepare C2-amidated benzothiazoles with formamides via double C−H activation (eq 2, Scheme 1).[11] However, the synthesis of 2-amidoalkylated benzothiazoles through the strategy of CDC has not been reported. In continuing our interest in transition metal-free transformations,[12] we herein report a practical amidoalkylation of benzothiazoles with simple *N,N*-dialkylamides using potassium persulfate as the sole reagent (eq 3, Scheme 1). In addition, this amidoalkylation method is also accessible to amidoalkyl-substituted oxindoles, which are closely related to a variety of biologically active molecules, such as anti-inflammatory natural product convolutamydine A and PDE10A inhibitor BMS 204352 (MaxiPost).[13]

We started the study by treating benzothiazole **1a** with an excess amount of *N,N*-dimethylacetamide **2a** under solvent-free conditions. After a brief survey of catalyst, additive, and oxidant, we were delighted to find that the reaction proceeded well in the presence of potassium persulfate ($K_2S_2O_8$) at 70 °C to afford *N*-(benzo[*d*]thiazol-2-ylmethyl)-*N*-methylformamide **3a** in 80% isolated yield (entry 1, Table 1). Other oxidants, including $Na_2S_2O_8$, $PhI(OAc)_2$ and $(NH_4)_2S_2O_8$, were also surveyed. It was intriguing that these oxidants were far less effective than $K_2S_2O_8$ (entries 2−4), probably due to their poor solubility under the experimental conditions. A combination of a catalytic

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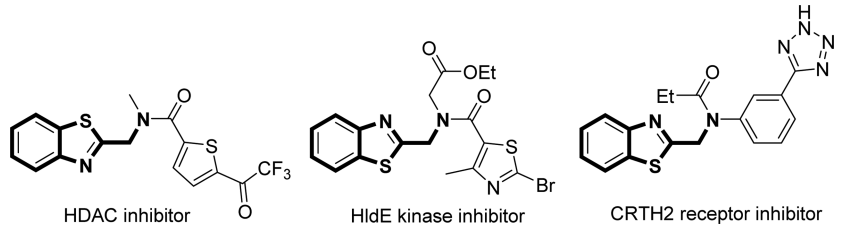


Figure 1. Representative biologically active 2-amidoalkylated benzothiazoles.

Scheme 1. CDC Reactions of Benzothiazole with Amides

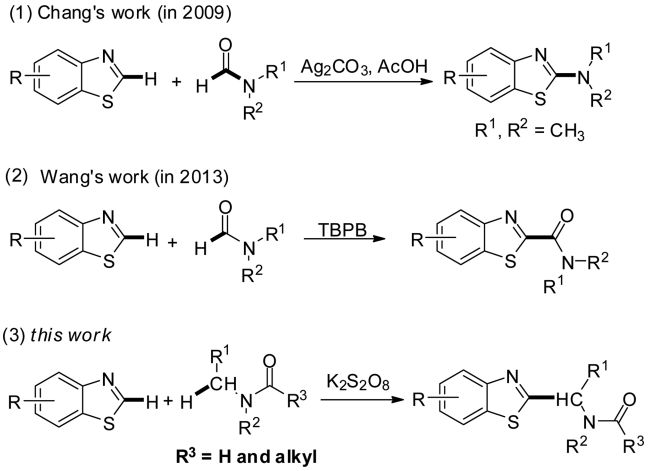
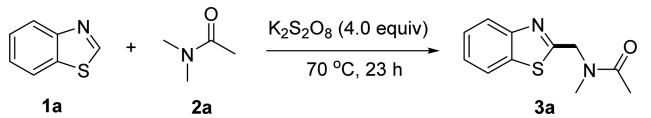


Table 1. Optimization of the Reaction Conditions



1a 2a 3a

entry	change from the "standard conditions"[a]	yield (%)[b]
1	none	80 (84)
2	$Na_2S_2O_8$ instead of $K_2S_2O_8$	trace
3	$PhI(OAc)_2$ instead of $K_2S_2O_8$	n.d.
4	$(NH_4)_2S_2O_8$ instead of $K_2S_2O_8$	n.d.
5	CuBr (20 mol %), TBHP (1.5 equiv)	(12)
6	1.0 equiv of PivOH added as additive	(4)
7	1.0 equiv of Cs_2CO_3 added as additive	n.d.
8	at 100 °C	63
9	reaction time of 16 h	65
10	reaction time of 30 h	79

[a]Standard reactions conditions: **1a** (0.2 mmol), **2a** (5.3 mmol, 0.5 mL), and $K_2S_2O_8$ (0.8 mmol, 4.0 equiv) at 70 °C in air. TBHP = ^{t}butyl hydroperoxide (5.5 M in decane). [b]Isolated yield; yields in parentheses are based on ^{1}H NMR analysis of the crude product using 4-iodoanisole as an internal standard.

amount of CuBr and 1.5 equiv of TBHP can also promote the coupling reaction, albeit in only 12% yield (entry 5). The attempt of using a smaller amount of *N*,*N*-dimethylacetamide **2a** in nonpolar solvents, such as mesitylene and xylene, and in polar solvents, such as DMF, DMSO, MeOH, and isopropanol, was unsuccessful (results not shown in Table 1). Either acidic or basic additive deteriorated the reaction (entries 6 and 7). Elevating the reaction temperature to 100 °C resulted in a smaller amount of the desired product formation (entry 8). Altering the reaction times to 16 and 30 h was not helpful for the transformation (entry 9).

With the optimized conditions established, the scope of benzothiazole was investigated first in reactions with *N*,*N*-dimethylacetamide (**2a**) in the presence of $K_2S_2O_8$ (Table 2). Benzothiazoles bearing electron-donating Me and OMe substituents at the C6 position tolerated the oxidative conditions, furnishing **3b** and **3c** in 64 and 68% yields, respectively. Substrates substituted at the same site with electron-withdrawing groups, such as F, Cl, and CN, provided the corresponding products **3d**−**3f** in better yields (79−82%). However, 6-nitrobenzothiazole was not compatible with the oxidative conditions, and only a trace amount of **3g** was detected by GC-MS (most of the starting material decomposed). In addition, aryl- and heteroaryl-substituted benzothiazoles were also suitable substrates for this CDC amidoalkylation reaction in acceptable yields (**3h**, 73%; **3i**, 51%). C4- and C5-halogenated benzothiazoles were amidoalkylated smoothly, providing opportunities for further modification of products **3j**−**3l**. Of note, when *N*,*N*-dimethylformamide (DMF), a common organic solvent, was used in coupling with benzothiazole, the corresponding aminoalkylated product **3m** was obtained selectively, albeit in moderate yield. No amidated benzothiazole **3m**′ or decarbonylative amination product as described in Chang's work[10] was detected. Cyclic formamide coupled with **1a** to provide piperidinyl-substituted benzothiazole **3o** in 53% yield. It was notable that *N*-methylpyrrolidin-2-one (NMP) containing two different amino carbons gave a mixture of **3p** and **3p**′ at a ratio of 10:1, favoring the secondary amino carbon being arylated.

Recently, transition metal-catalyzed cyclizations as well as radical-initiated cascade reactions have been developed to prepare 3,3-disubstituted oxindoles, which represent a class of *N*-heterocycles exhibiting remarkable bioactivities.[14] It was expected that 3-amidoalkyloxindoles could be accessed by using *N*-aryl-*N*-methyl-methacrylamides as substrates under the same reaction conditions. Indeed, 3-methyl-3-amidoethyloxindole derivatives **5a**−**5d** were obtained in moderate to good yields in which two C−C bonds were sequentially formed across the activated double bond (Scheme 2). It is worth noting that treatment of 2-isocyano-5-methyl-1,1′-biphenyl with DMF gave corresponding amidated product **7**, whereas the amidoalkylarylated compound was not observed (Scheme 3).

For confirmation that the current amidoalkylation reaction proceeds through radical intermediates, radical-trapping experiments were carried out (Scheme 4). When radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction, the coupling process was completely inhibited, suggesting that a radical pathway is likely involved in this transformation.

On the basis of experimental results and literature reports,[11,15] a plausible radical mechanism was proposed (Scheme 4). Initially, a sulfate anion radical was generated through homolytic cleavage of a peroxydisulfate dianion. Then, the sulfate anion radicals grab one of the hydrogen atoms in *N*,*N*-dialkylamide (using DMA as an example) and the C2 hydrogen atom in

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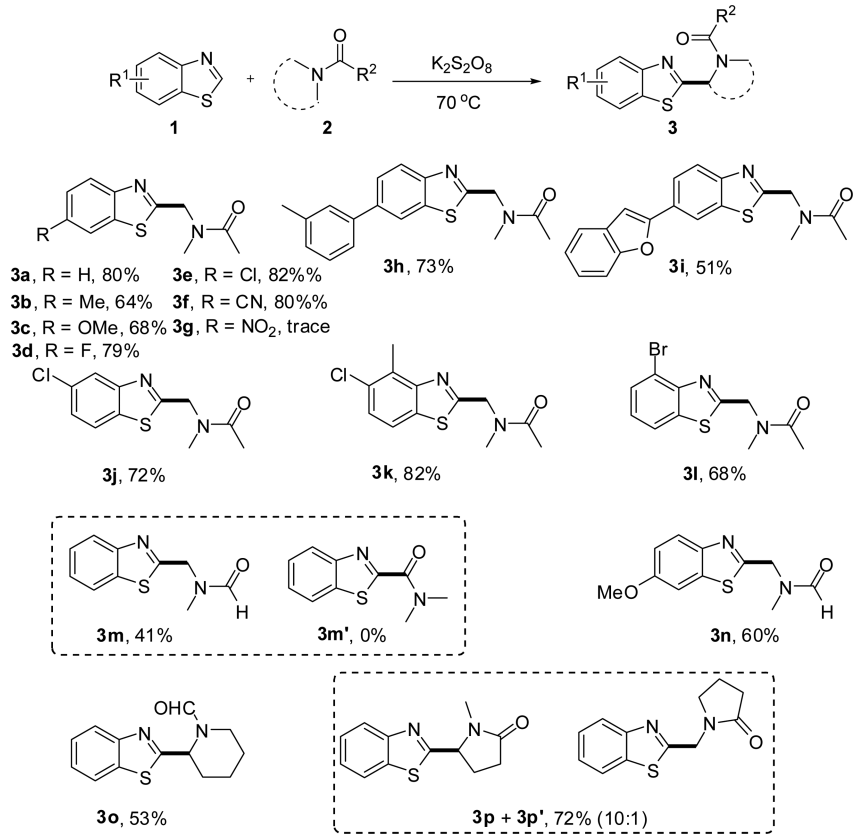
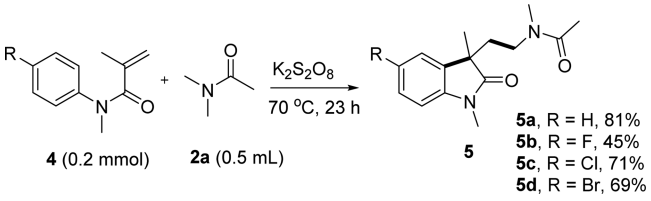
Table 2. Amidoalkylaion of Benzothiazoles with Amides[a]

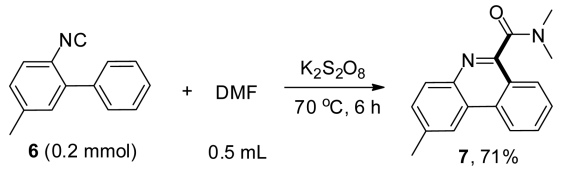


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.5 mL), and $K_2S_2O_8$ (0.8 mmol, 4.0 equiv) at 70 °C, 23 h, in air.

Scheme 2. Cascade Amidoalkylarylation of Activated Alkenes with 2a



Scheme 3. Cascade Amidoarylation of 2-Isocyano-5-methyl-1,1′-biphenyl with DMF



benzothiazole **1a**, generating the respective radicals **A** and **B**, which react with each other to generate the corresponding cross-coupling product **3a**.[11] Homocoupling product **I** was also detected by GC-MS; however, the other homocoupling product **II** was not observed. When *N*-aryl-*N*-methyl-methacrylamide was applied instead of benzothiazole, a similar cascading radical process involving addition of amidoalkyl radical **A** to activated alkene and intramolecular homolytic aromatic substitution (HAS) of the resulting carbon radical took place (not shown in the scheme).

In summary, we demonstrated an efficient and atom economical approach for the synthesis of 2-amidoalkyl benzothiazoles and 3-amidoalkyl oxindoles employing a radical-mediated CDC reaction. The process uses inexpensive $K_2S_2O_8$ as the only oxidant under solvent-free conditions in open air. Unlike the reported decarbonylative amination and amidation of benzothiazoles with formamides, the corresponding amidoalkylation products were formed selectively using simple *N*,*N*-dialkylamides including formamides. This method not only provides a quick assembly of druglike molecules under practical transition metal-free conditions but also represents an alternative method of introducing nitrogen atoms to molecules by C−C bond formation.

EXPERIMENTAL SECTION

General Information. Reactions were monitored using thin-layer chromatography (TLC) on commercial silica gel plates (GF 254). Visualization of the developed plates was performed under UV lights (GF 254 nm). Flash column chromatography was performed on silica gel (200−300 mesh). NMR spectra were recorded at 400 and 500 MHz (H) and at 101 and 126 MHz (C). Chemical shifts (δ) were reported in ppm referenced to the $CDCl_3$ residual peak (δ 7.26) or the DMSO-d_6 residual peak (δ 2.50) for ^{1}H NMR. Chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.5). The following abbreviations were used to describe peak splitting patterns when appropriate: br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constant, *J*, was reported in hertz (Hz). Infrared (IR) spectra were recorded on an FT-IR spectrophotometer. Melting points (mp) were taken on an apparatus that was uncorrected. HRMS were recorded using ESI-TOF techniques.

Of note, because of the special structure of amides, most of the products exist as a mixture of two rotamers as shown in the NMR charts.

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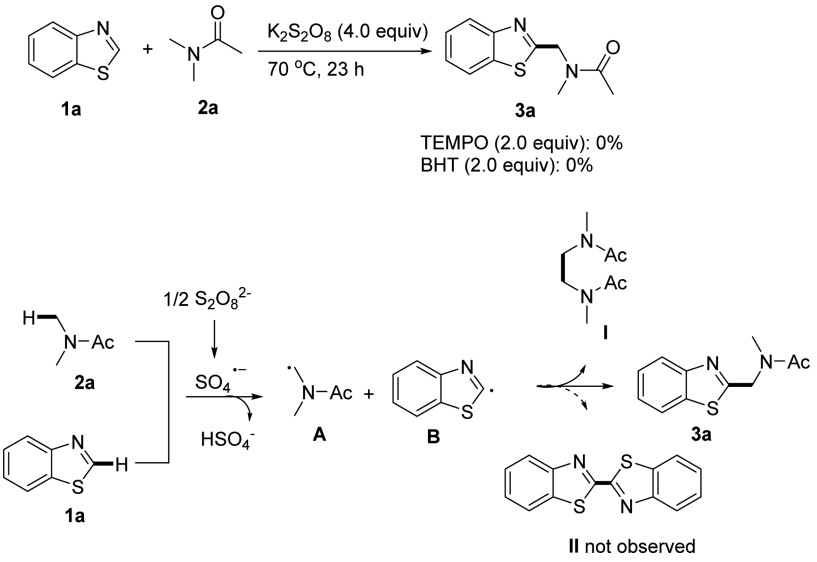
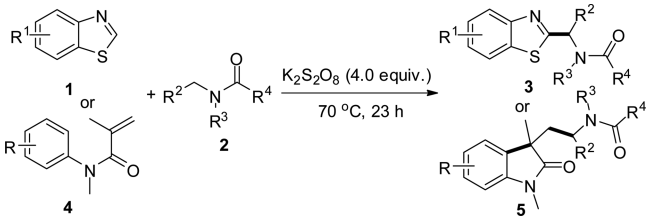
Scheme 4. Plausible Reaction Mechanism

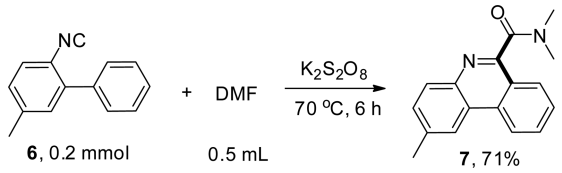


*General Procedure for the Preparation of Compounds **3** and **5**.*



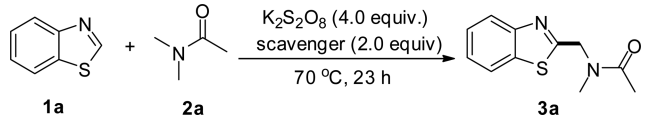
To a mixture of benzothiazole **1** or *N*-methyl-*N*-phenylmethacrylamide **4** (0.2 mmol) and amides **2** (0.5 mL) in a reaction tube was added $K_2S_2O_8$ (4.0 equiv). The reaction mixture was stirred for 23 h at 70 °C in air. The reaction mixture was quenched with H_2O (10 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/PE = 1:3−1:4) to afford the desired products **3** and **5**.

*Procedure for the Preparation of Compound **7**.*



To a solution of 2-isocyano-5-methyl-1,1′-biphenyl **6** (39 mg, 0.2 mmol) in 0.5 mL of DMF was added $K_2S_2O_8$ (3.0 equiv). The reaction mixture was stirred for 6 h at 70 °C in air. Then, 2 mL of saturated aqueous $NaHCO_3$ was added carefully to quench the reaction, and the mixture was stirred for approximately 5 min. The mixture was extracted with EtOAc, and the combined organic layers were evaporated under vacuum. The residue was purified by column chromatography on silica gel to give *N,N*,2-trimethylphenanthridine-6-carboxamide **7**.

Experiments on Free Radical Inhibition.



A mixture of benzothiazole **1a** (0.2 mmol), $K_2S_2O_8$ (4.0 equiv), and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) (2.0 equiv) in 0.5 mL of DMA was heated at 70 °C for 23 h. The reaction was monitored by TLC, and no desired compound was detected by GC-MS.

*N-(Benzo[d]thiazol-2-ylmethyl)-N-methylacetamide (**3a**).* Yellow solid, 35 mg, 80% yield. Mp: 53−55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−8.04 (m, 1H), 7.86−7.92 (m, 1H), 7.47−7.52 (m, 1H), 7.38−7.43 (m, 1H), 4.99 (s, 2H), 3.15 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 168.0, 153.2, 135.6, 126.4, 125.5, 123.1, 121.8, 49.3, 36.3, 21.4. IR (KBr pellet) ν: 3124, 3060, 2931, 1651, 1517, 1433, 1384, 1334, 1286, 1239, 1126, 1062, 989, 869, 762 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{11}H_{12}N_2OS$ $[M + H]^+$, 221.0743; found, 221.0741.

*N-Methyl-N-((6-methylbenzo[d]thiazol-2-yl)methyl)acetamide (**3b**).* Yellow semisolid, 30 mg, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 4.96 (s, 2H), 3.12 (s, 3H), 2.49 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 166.6, 150.8, 135.9, 135.4, 127.6, 122.4, 121.4, 53.0, 49.3, 36.3, 21.4. IR (KBr pellet) ν: 3125, 3048, 2930, 1655, 1517, 1436, 1390, 1338, 1285, 1241, 1128, 998, 876, 768 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{12}H_{15}N_2OS$ $[M + H]^+$, 235.0900; found, 235.0903.

*N-((6-Methoxybenzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3c**).* Yellow semisolid, 34 mg, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 4.95 (s, 2H), 3.90 (s, 3H), 3.13 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 165.1, 157.7, 147.7, 137.1, 123.5, 115.7, 104.3, 55.7, 52.9, 49.2, 36.2, 21.5. IR (KBr pellet) ν: 3020, 2926, 1653, 1579, 1546, 1460, 1361, 1342, 1236, 1098, 1070, 886, 846, 754 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{12}H_{15}N_2O_2S$ $[M + H]^+$, 251.0849; found, 251.0848.

*N-((6-Fluorobenzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3d**).* Yellow solid, 38 mg, 79% yield. Mp: 95−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93−7.97 (m, 1H), 7.53−7.60 (m, 1H), 7.20−7.25 (m, 1H), 4.95 (s, 2H), 3.15 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 167.4, 160.4 (d, J_{C-F} = 243.6 Hz), 149.3, 136.7, 123.8, 114.6, 107.9, 49.3, 36.4, 21.5. IR (KBr pellet) ν: 3090, 3069, 2937, 1649, 1632, 1566, 1453, 1385, 1337, 1287, 1249, 1196, 1115, 1026, 990, 880, 763, 681, 642 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{11}H_{12}FN_2OS$ $[M + H]^+$, 239.0649; found, 239.0647.

*N-((6-Chlorobenzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3e**).* Yellow oil, 42 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 4.95 (s, 2H), 3.15 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 168.5, 151.8, 136.8, 131.5, 127.2, 123.8, 121.4, 49.4, 36.4, 21.4. IR (KBr pellet) ν: 3076, 2937, 1631, 1543, 1482, 1407, 1337,1282, 1228, 1176, 1103, 1059, 994, 937, 865, 765 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{11}H_{12}ClN_2OS$ $[M + H]^+$, 255.0353; found, 255.0350.

*N-((6-Cyanobenzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3f**).* Yellow oil, 39 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 5.00 (s, 2H), 3.19 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 171.1, 155.1,

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136.2, 129.2, 126.5, 123.7, 118.5, 108.8, 49.6, 36.6, 21.4. IR (KBr pellet) ν: 3080, 2948, 1648, 1565, 1490, 1438, 1330,1289, 1236, 1176, 1158, 1119, 998, 937, 898 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{12}H_{12}N_3OS$ $[M + H]^+$, 246.0696; found, 246.0693.

N-Methyl-N-((6-(m-tolyl)benzo[d]thiazol-2-yl)methyl)acetamide (**3h**). Yellow oil, 45 mg, 73% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 8.03−8.06 (m, 1H), 7.69−7.75 (m, 1H), 7.46 (s, 1H), 7.35−7.43 (m, 2H), 7.20−7.23 (m, 1H), 5.00 (s, 2H), 3.15 (s, 3H), 2.45 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 168.1, 152.5, 140.5, 139.2, 138.6, 136.4, 128.8, 128.4, 128.2, 126.2, 124.5, 123.1, 120.1, 49.4, 34.4, 21.5. IR (KBr pellet) ν: 3021, 2923, 1651, 1585, 1517, 1452, 1359, 1333, 1236, 1097, 1066, 872, 828, 752, 681 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{18}H_{19}N_2OS$ $[M + H]^+$, 311.1213; found, 311.1215.

N-((6-(Benzofuran-2-yl)benzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3i**). Yellow solid, 34 mg, 51% yield. Mp: 175−178 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.96−8.07 (m, 2H), 7.55−7.64 (m, 2H), 7.27−7.35 (m, 2H), 7.12 (s, 1H), 5.01 (s, 2H), 3.18 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 168.7, 155.2, 155.0, 152.8, 136.6, 129.2, 127.8, 124.7, 123.7, 123.2, 123.1, 121.1, 118.0, 111.2, 102.0, 49.5, 34.4, 21.5. IR (KBr pellet) ν: 3425, 3110, 2967, 2927, 1647, 1573, 1454, 1396, 1335, 1296, 1228, 1167, 1109, 968, 857, 831 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{19}H_{17}N_2O_2S$ $[M + H]^+$, 337.1005; found, 337.1006.

N-((5-Chlorobenzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3j**). Yellow oil, 37 mg, 72% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 4.96 (s, 2H), 3.15 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 169.8, 153.6, 133.9, 132.1, 125.7, 122.8, 122.4, 49.4, 36.5, 21.5. IR (KBr pellet) ν: 3139, 2926, 2854, 1645, 1513, 1482, 1399, 1384, 1276, 1261, 1170, 1103, 1069, 989, 811, 763 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{11}H_{12}ClN_2OS$ $[M + H]^+$, 255.0353; found, 255.0352.

N-((5-Chloro-4-methylbenzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3k**). Yellow solid, 44 mg, 82% yield. Mp: 93−95 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 4.98 (s, 2H), 3.16 (s, 3H), 2.79 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 168.3, 153.3, 133.7, 131.5, 131.2, 126.4, 119.3, 49.4, 36.4, 21.5, 15.7. IR (KBr pellet) ν: 3065, 2932, 1647, 1557, 1516, 1420, 1363, 1336, 1276, 1236, 1169, 1025, 990, 874, 823 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{12}H_{14}ClN_2OS$ $[M + H]^+$, 269.0510; found, 269.0507.

N-((4-Bromobenzo[d]thiazol-2-yl)methyl)-N-methylacetamide (**3l**). Yellow semisolid, 41 mg, 68% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80−7.86 (m, 1H), 7.67−7.73 (m, 1H), 7.23−7.32 (m, 1H), 5.02 (s, 2H), 3.17 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 169.1, 151.7, 136.5, 129.9, 126.3, 121.0, 116.5, 49.5, 36.4, 21.5. IR (KBr pellet) ν: 3060, 2930, 1651, 1583, 1479, 1399, 1308, 1287, 1210, 1171, 988, 860, 788, 772, 740 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{11}H_{12}BrN_2OS$ $[M + H]^+$, 298.9848; found, 298.9849.

N-(Benzo[d]thiazol-2-ylmethyl)-N-methylformamide (**3m**). Yellow oil, 17 mg, 41% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.90−7.93 (m, 1H), 7.56−7.88 (m, 1H), 7.40−7.55 (m, 2H), 4.96 (s, 2H), 3.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 162.6, 152.7, 135.6, 126.4, 125.6, 123.2, 121.8, 46.1, 34.6. IR (KBr pellet) ν: 3337, 3033, 2933, 2856, 1681, 1516, 1483, 1434, 1335, 1281, 1240, 1123, 1014, 731, 707 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{10}H_{11}N_2OS$ $[M + H]^+$, 207.0587; found, 207.0589.

N-((6-Methoxybenzo[d]thiazol-2-yl)methyl)-N-methylformamide (**3n**). Yellow oil, 28 mg, 60% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.08−7.14 (m, 1H), 4.91 (s, 2H), 3.90 (s, 3H), 3.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 162.4, 157.8, 147.1, 137.0, 123.5, 115.5, 104.1, 55.7, 45.9, 30.2. IR (KBr pellet) ν: 2922, 2865, 1677, 1608, 1558, 1518, 1444, 1392, 1307, 1281, 1119, 960, 866 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{11}H_{13}N_2O_2S$ $[M + H]^+$, 237.0692; found, 237.0692.

2-(Benzo[d]thiazol-2-yl)piperidine-1-carbaldehyde (**3o**). Yellow oil, 26 mg, 53% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.02−8.06 (m, 1H), 7.86−7.91 (m, 1H), 7.37−7.52 (m, 2H), 5.12−6.03 (m, 1H), 3.60−4.45 (m, 1H), 3.37−3.44 (m, 1H), 2.69−2.92 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 161.8, 153.6, 135.5, 126.0, 125.1, 123.1, 121.6, 50.3, 43.8, 27.9, 25.9, 20.6. IR (KBr pellet) ν: 3061, 2940, 2861, 1674, 1557, 1350, 1246, 1157, 1121, 1056, 1013, 986, 825, 761 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{13}H_{15}N_2OS$ $[M + H]^+$, 247.0900; found, 247.0900.

5-(Benzo[d]thiazol-2-yl)-1-methylpyrrolidin-2-one (**3p**). Yellow oil, 31 mg, 66% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.28−7.54 (m, 2H), 5.02−5.06 (m, 1H), 2.89 (s, 3H), 2.62−2.70 (m, 2H), 2.48−2.54 (m, 1H), 2.21−2.24 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 172.2, 153.0, 134.7, 126.4, 125.6, 123.2, 121.9, 62.7, 47.1, 30.4, 28.9, 26.6. IR (KBr pellet) ν: 3543, 3061, 2952, 1696, 1557, 1436, 1421, 1391, 1312, 1277, 1239, 1111, 1036, 935, 799, 763 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{12}H_{13}N_2OS$ $[M + H]^+$, 233.0743; found, 233.0745.

N-(2-(1,3-Dimethyl-2-oxoindolin-3-yl)ethyl)-N-methylacetamide (**5a**). Yellow semisolid, 42 mg, 81% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.27−7.35 (m, 1H), 7.22−7.24 (m, 1H), 7.09−7.15 (m, 1H), 6.85−6.91 (m, 1H), 3.25 (s, 3H), 2.8−3.3 (m, 2H), 2.82 (s, 3H), 1.9−3.3 (m, 2H), 1.90 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.0, 170.2, 143.1, 133.1, 128.3, 122.8, 122.5, 108.4, 46.9, 43.6, 36.1, 34.5, 26.2, 24.4, 21.7. IR (KBr pellet) ν: 2960, 2924, 1705, 1639, 1484, 1468, 1380, 1350, 1265, 1176, 1118, 1010, 989, 886 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{15}H_{21}N_2O_2$ $[M + H]^+$, 261.1598; found, 261.1597.

N-(2-(5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)ethyl)-N-methylacetamide (**5b**). Yellow solid, 25 mg, 45% yield. Mp: 103−105 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 6.96−7.04 (m, 2H), 6.75−6.84 (m, 1H), 3.21 (s, 3H), 2.8−3.3 (m, 2H), 2.84 (s, 3H), 1.9−2.3 (m, 2H), 1.91 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.7, 170.2, 160.4 (d, J_{F-C} = 237.9 Hz), 139.1, 135.0, 114.7, 110.6, 108.9, 47.1, 43.4, 36.1, 34.6, 26.4, 24.2, 21.7. IR (KBr pellet) ν: 2968, 2929, 1709, 1644, 1494, 1470, 1383, 1352, 1277, 1183, 1118, 1012, 904, 872 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{15}H_{20}FN_2O_2$ $[M + H]^+$, 279.1503; found, 279.1503.

N-(2-(5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)ethyl)acetamide (**5c**). Yellow oil, 40 mg, 71% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.27−7.33 (m, 1H), 7.22 (s, 1H), 6.77−6.84 (m, 1H), 3.21 (s, 3H), 2.9−3.2 (m, 2H), 2.83 (s, 3H), 1.9−2.3 (m, 2H), 1.90 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.4, 178.9, 170.1, 141.7, 134.9, 127.9, 122.9, 109.3, 46.8, 43.3, 36.0, 34.5, 26.3, 24.4, 21.6. IR (KBr pellet) ν: 2968, 2930, 1720, 1650, 1609, 1488, 1453, 1360, 1348, 1276, 1178, 1138, 1118, 890 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{14}H_{18}ClN_2O_2$ $[M + H]^+$, 281.1051; found, 281.1053.

(2-(5-Bromo-1,3-dimethyl-2-oxoindolin-3-yl)ethyl)-N-methylacetamide (**5d**). Yellow oil, 47 mg, 69% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.48 (m, 1H), 7.40 (s, 1H), 6.72−6.79 (m, 1H), 2.8−3.3 (m, 2H), 3.20 (s, 3H), 2.82 (s, 3H), 1.9−2.3 (m, 2H), 1.88 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.3, 170.1, 142.3, 135.3, 131.2, 125.6, 115.5, 109.8, 46.7, 43.3, 36.0, 33.8, 26.3, 24.5, 21.6. IR (KBr pellet) ν: 2967, 2928, 1712, 1643, 1606, 1487, 1446, 1363, 1345, 1273, 1173, 1129, 1108, 879 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{15}H_{20}BrN_2O_2$ $[M + H]^+$, 339.0703; found, 339.0705.

N,N,2-Trimethylphenanthridine-6-carboxamide (**7**). Colorless oil, 37 mg, 71% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 8.4 Hz, 1H), 8.40 (s, 1H), 8.09 (t, J = 7.2 Hz, 2H), 7.88 (t, J = 7.2 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.60−7.62 (m, 1H), 3,32 (s, 3H), 2.94 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 158.7, 138.0, 137.5, 135.2, 134.3, 133.1, 132.1, 131.3, 129.3, 129.1, 128.0, 121.6, 118.6, 29.6, 20.8, 20.7. IR (KBr pellet) ν: 3026, 2920, 2866, 1693, 1592, 1517, 1442, 1290, 1153, 1024, 770, 629, 607 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{17}H_{17}N_2O$ $[M + H]^+$, 265.1335; found, 265.1336.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00096.

^1H and ^{13}C NMR spectra of all of the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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