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

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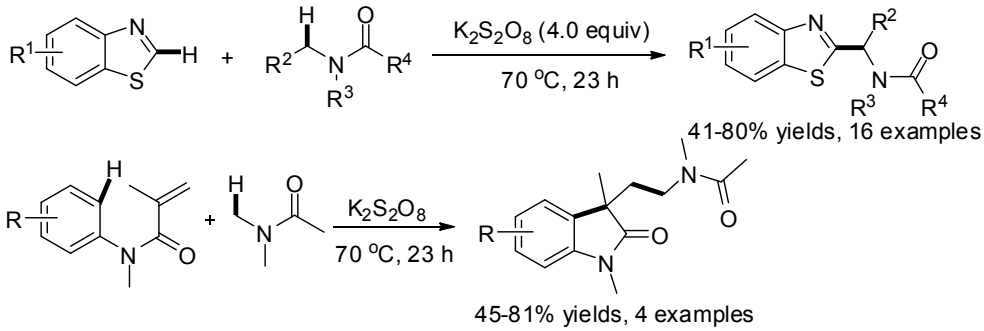


ABSTRACT: A general and practical amidoalkylation reaction, using *N*,*N*-dialkylamides in the presence of potassium persulfate as the sole reagent, has been developed. 2-Amidoalkylated benzothiazole and 3-amidoalkyl substituted indolinone derivatives were obtained by using benzothiazoles and *N*-aryl-*N*-methyl-methacrylamides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

C−C bond formation through direct C−H functionalization is one of the fundamental research topics, owing to its advantages in atom economy and environmental benignity over traditional methods.[1] In this context, activation and coupling of two different C−H centres, 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 catalysed by transition metals including Pd, Ru, Fe, and Sc.[3] However, concerns on cost as well as 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 CDC strategy.[5] And, 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 assembling of drug-like molecules under practical transition-metal-free conditions are still highly desirable.

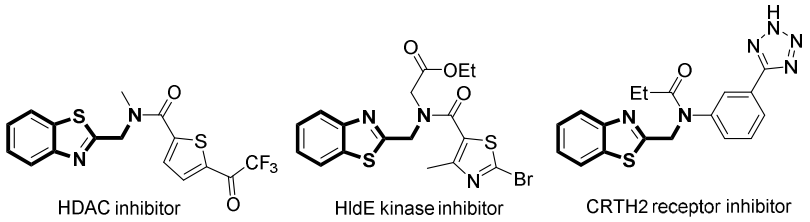
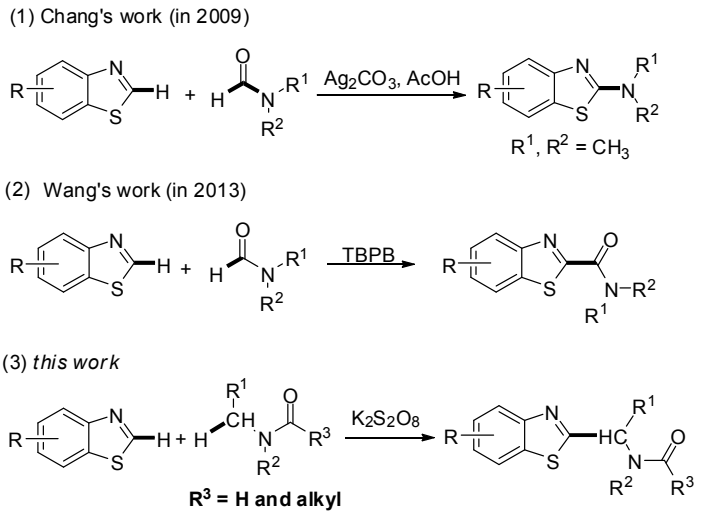


Figure 1. Representative biologically active 2-amidoalkylated benzothiazoles

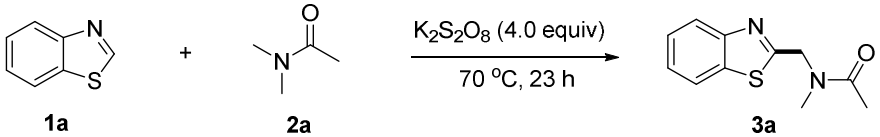
Benzothiazole is an important structural motif that exists in a number of compounds of medicinal interests, natural products, and functional materials.[7] Particularly for 2-amidoalkylated benzothiazole derivatives, they show prominent activities as inhibitors of histone deacetylase (HDAC), HldE kinase, and CRTH2 receptor (Figure 1).[8] To prepare C2 substituted benzothiazole derivatives, 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]

Scheme 1. CDC reactions of benzothiazole with amides



We set out on the study by treating benzothiazole **1a** with 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 out 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 catalytic 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 fewer amounts *N,N*-dimethylacetamide **2a** in nonpolar solvent such as mesitylene or xylene and in polar solvents such as DMF, DMSO, MeOH, or 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 fewer amount of the desired product formation (entry 8). Altering the reaction times to 16 h and 30 h was not helpful for the transformation (entry 9).

Table 1. Optimization of the reaction conditions



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

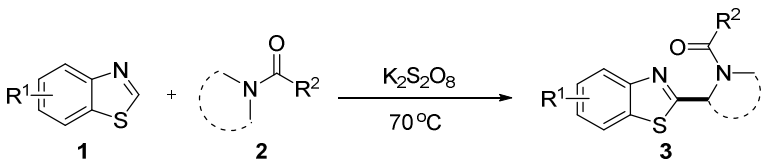
Entry	Change from the ''standard conditions''[a]	Yield (%)[b]
1	**none**	**80 (84)**
2	$Na_2S_2O_8$, instead of $K_2S_2O_8$	trace
3	$PhI(OAc)_2$, instead of $K_2S_2O_8$	n.d.
4	$(NH_4)_2S_2O_8$, instead of $K_2S_2O_8$	n.d.
5	CuBr (20 mol%), TBHP (1.5 equiv)	(12)
6	1.0 equiv of PivOH was added as additive	(4)
7	1.0 equiv of Cs_2CO_3 was added as additive	n.d.
8	at 100 °C	63

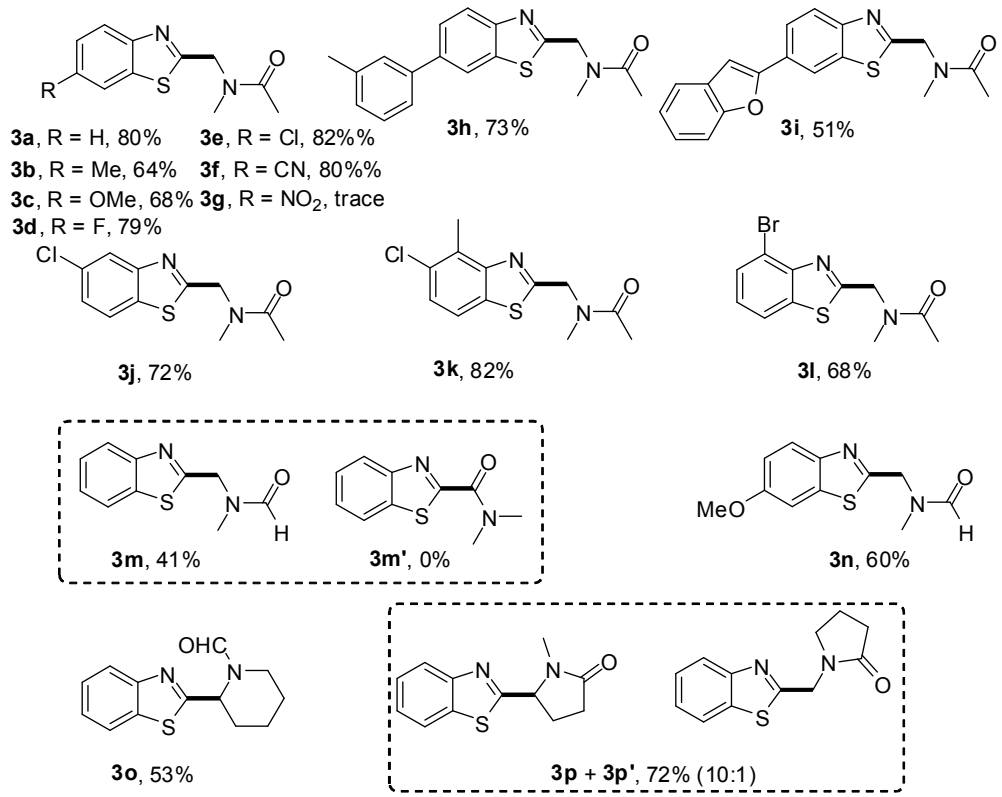
9	The reaction time was 16 h	65
10	The reaction time was 30 h	79

[a] The 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.

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 trace amounts 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 on the products (**3j**-**3l**). To be noted, 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'** in a ratio of 10:1 favouring the secondary amino carbon being arylated.

Table 2. Amidoalkylaion of benzothiazoles with amides[a]

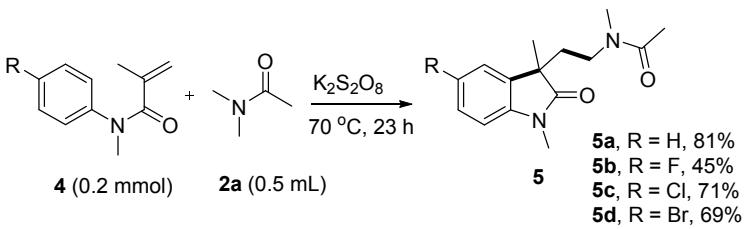




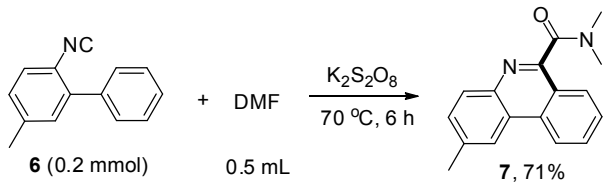
[a] The reaction conditions: **1** (0.2 mmol), **2** (0.5 mL), and $K_2S_2O_8$ (0.8 mmol, 4.0 equiv) at 70 °C, 23 h, in air.

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 formed across the activated double bond sequentially (Scheme 2). It's worth noting that treatment of 2-isocyano-5-methyl-1,1'-biphenyl with DMF gave the corresponding amidated product **7**, while the amidoalkylarylated compound was not observed.

Scheme 2. Cascade amidoalkylarylation of activated alkenes with **2a**



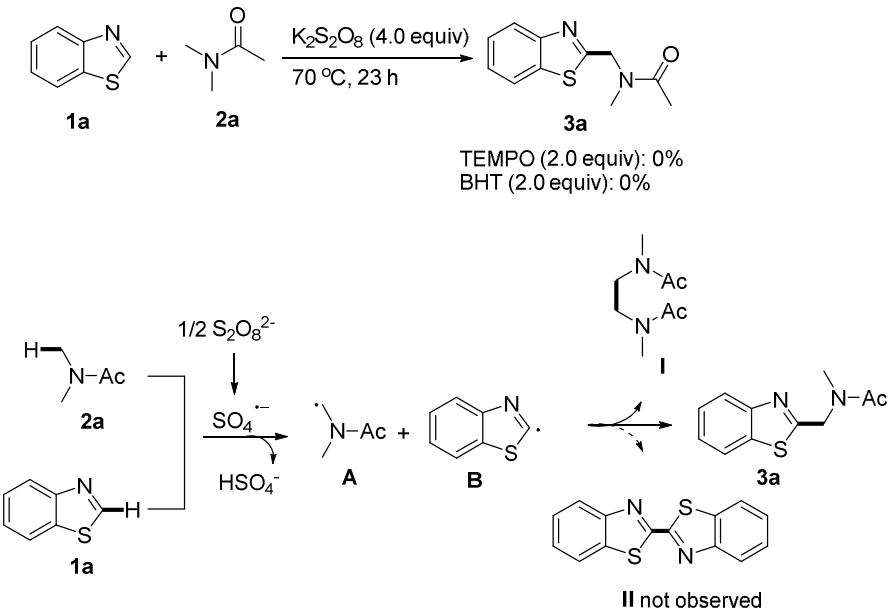
Scheme 3. Cascade amidoarylation of 2-isocyano-5-methyl-1,1'-biphenyl with DMF



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

Scheme 4. Plausible reaction mechanism



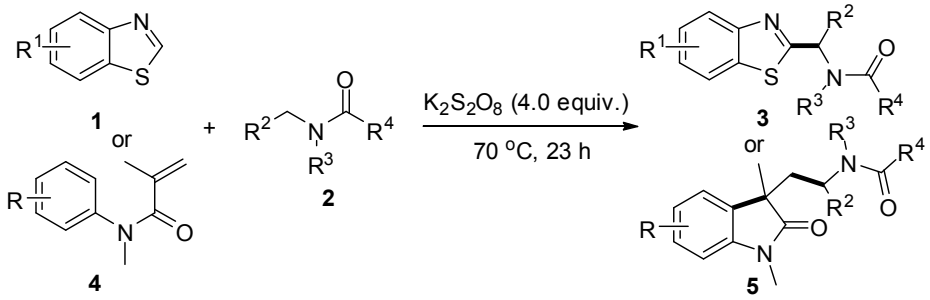
In summary, we demonstrated an efficient and atom economical approach for the synthesis of 2-amidoalkyl benzothiazoles and 3-amidoalkyl oxindoles employing a radical mediated CDC reaction. The process uses inexpensive $K_2S_2O_8$ as the only oxidant under solvent-free condition in open air. Unlike the 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 assembling of drug-like molecules under practical transition-metal-free conditions, but also represents an alternative way of introducing nitrogen atoms to molecules by C−C bond formation.

EXPERIMENTAL SECTION

General Information. Reactions were monitored by 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, 500 MHz (H) and at 101, 126 MHz (C), respectively. 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, m = multiplet. Coupling constant, *J*, was reported in Hertz unit (Hz). Infrared (IR) spectra were recorded on a FT-IR spectrophotometer. Melting points (mp) were taken on an apparatus which is uncorrected. HRMS were recorded using ESI-TOF techniques.

***NOTE*:** *Due to the special structure of amides, most of the products exist as a mixture of two rotamers as shown in NMR charts.*

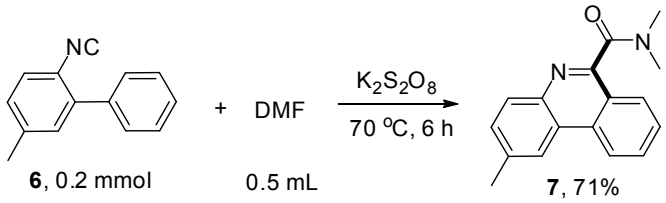
General Procedure for the Preparation of Compounds 3,5



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

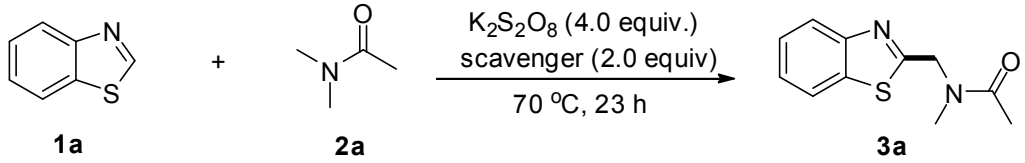
organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/PE = 1:3-1:4) to afford the desired product **3** or **5**.

Procedure for the Preparation of Compounds 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 stirred for about 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 bar = 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 semi-solid, 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 bar = 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 semi-solid, 34 mg, 68% yield. ^1H 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 bar = 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. ^1H 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, $J_{C\text{-}F}$ = 243.6 Hz), 149.3, 136.7, 123.8, 114.6, 107.9, 49.3, 36.4, 21.5; IR (KBr pellet): ν bar = 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. ^1H 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 bar = 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. ^1H 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, 136.2, 129.2, 126.5, 123.7, 118.5, 108.8, 49.6, 36.6, 21.4; IR (KBr pellet): ν bar = 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 bar = 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. ^{1}H 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 bar = 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. ^{1}H 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 bar = 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. ^{1}H 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 bar = 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 semi-solid, 41 mg, 68% yield. ^{1}H 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 bar = 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. ^{1}H 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 bar = 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. ^{1}H 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 bar = 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. ^{1}H 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 bar = 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. ^{1}H 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 bar = 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 semi-solid, 42 mg, 81% yield. ^{1}H 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 bar = 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 ^{o}C. ^{1}H 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 bar = 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. ^{1}H 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 bar = 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 bar = 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 bar = 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.

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Notes

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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