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Na_2CO_3-promoted thioesterification via N–C bond cleavage of amides to construct thioester derivatives

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Abstract

A mild, efficient, and transition-metal-free catalytic strategy is developed to construct thioesters via selective N–C bond cleavage of Boc_2-activated primary amides. This strategy is successfully carried out with stoichiometric Na_2CO_3 as the base and provides the corresponding products in moderate to excellent yields.

Keywords

selective N–C bond cleavage, stoichiometric Na_2CO_3, thioesters, transition-metal-free catalytic strategy

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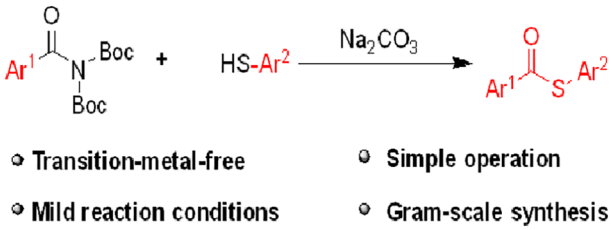

Introduction

The thioester group is a fundamental structural motif which is found widely in polymers, agrochemicals, pharmaceuticals, and natural products (Figure 1).[1–7] This class of compound is usually employed as key intermediates to synthesize some important skeletal units, such as β-lactams,[8] β-lactones[9] esters,[10,11] aldehydes,[12] and ketones.[13,14] Thioesters also play important roles in several biological processes.[3,15,16] During the past decades, significant research efforts have focused on the synthesis of thioesters. The condensation reaction between carboxylic acid derivatives and thiols was the initial synthetic strategy toward thioesters (Scheme (1a)).[15,17–20] In 1997, Xiao and Alper[21] reported the first palladium-catalyzed method for the synthesis of thioesters via carbonylation of aryl iodides and *n*-BuSNa. Since then, transition-metal-catalyzed thiocarbonylation processes have attracted much attention and various methods have been explored to construct thioester compounds using aryl halides and *S*-nucleophiles (Scheme (1b)).[22–31] Moreover, oxidative coupling between aldehydes and thiols (or disulfides) has also offered a reliable solution to obtain thioester compounds (Scheme (1c)).[32,33] However, in principle, metal catalysts or stoichiometric oxidants were needed in the above reaction

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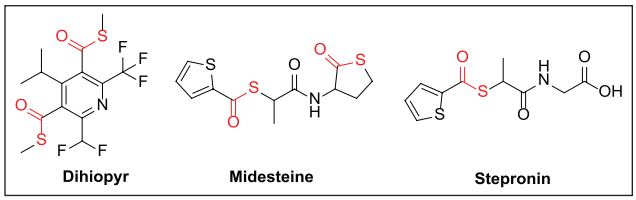
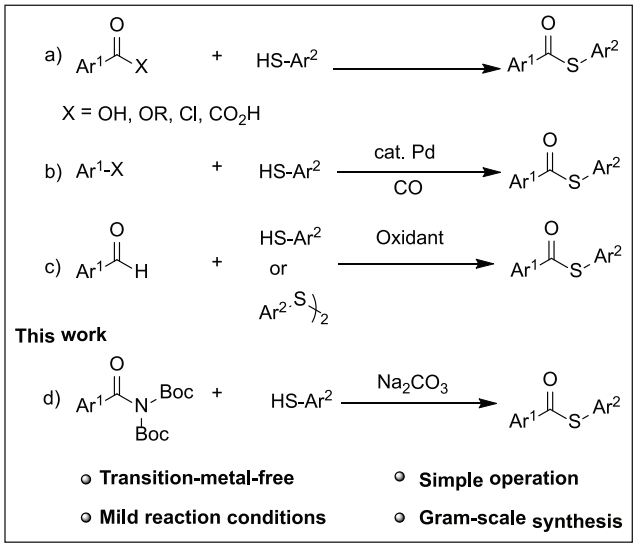


Figure 1. Examples of pharmaceuticals containing a thioester motif.



Scheme 1. Synthesis of thioesters.

processes. In view of environmental concerns, metal-free and oxidant-free synthetic methods are highly desirable for the preparation of thioesters.

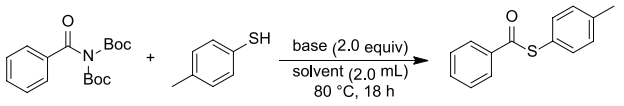
In recent years, significant breakthroughs have been exploited to construct C–C or C–X bonds via transition-metal-catalyzed amide N–C bond cleavage.[34–38] In 2015, Hie et al.[39] reported the first nickel-catalyzed conversion of amides into esters via selective N–C bond cleavage. Soon after, Suzuki,[40–48] Negishi,[49–51] borylation,[52,53] Heck,[53,54–60] Sonogashlira,[61] and other cross-coupling reactions[54,52,62–73] have been extended by this means.

However, the geometries of typical amide bonds are planar as a result of amidic resonance, which results in amides having very stable chemical bonds (15–20 kcal mol^{-1}).[40] Many studies have shown that distortion of amide bonds greatly affects the stability and reactivity of amides. In recent work, cross-coupling of twisted amides with arenes,[67] amines,[74–77] alcohols,[48,58] and phenols[78] have been successfully explored and the twisted amide bond is considered as a controlling factor in selective amide bond activation.[79–81] Considering the reactivity of twisted amides, herein, we report a synthetic strategy for the preparation of thioesters using twisted amides and thiols without a transition-metal-catalyst.

Results and discussion

Initially, we carried out the reaction with *N,N-di*-Boc-activated amide[82–85] **1a** and *p*-toluenethiol (**2a**) as substrates (Table 1), and Et_3N (2.0 equiv.) as the base in 1,4-dioxane

Table 1. Optimization of the Reaction Conditions.[a]



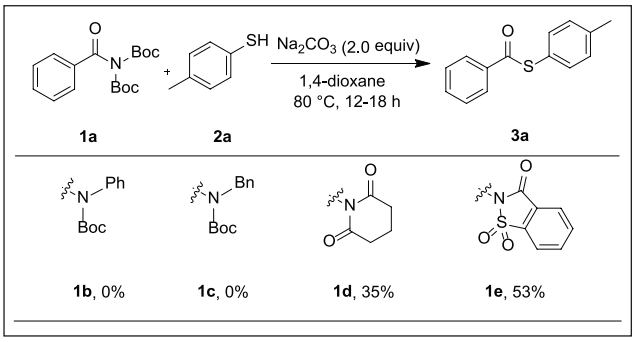
1a 2a 3a

1a	2a		3a
Entry	Base	Solvent	Yield (%)[b]
1	Et_3N	1,4-Dioxane	68
2	DABCO	1,4-Dioxane	63
3	DBU	1,4-Dioxane	60
4	***Na_2CO_3***	***1,4-Dioxane***	***95***
5	K_3PO_4	1,4-Dioxane	85
6	Cs_2CO_3	1,4-Dioxane	78
7	*t*BuONa	1,4-Dioxane	Trace
8	Na_2CO_3	CH_3CN	70
9	Na_2CO_3	THF	63
10	Na_2CO_3	DCE	78
11	Na_2CO_3	DMF	80
12[c]	Na_2CO_3	1,4-Dioxane	50
13[d]	Na_2CO_3	1,4-Dioxane	80
14[e]	Na_2CO_3	1,4-Dioxane	33
15	–	1,4-Dioxane	N.D.

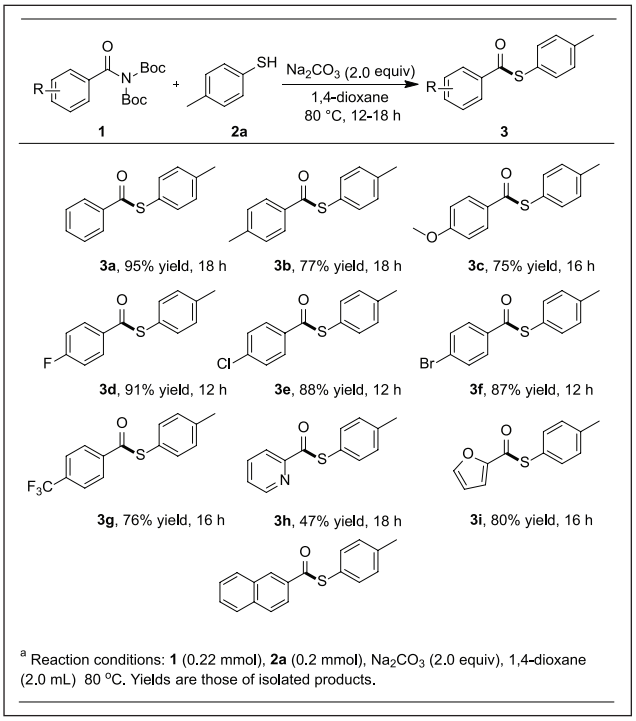
DABCO: 1,4-diazabicyclo[2.2.2]octane; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; THF: tetrahydrofuran; DCE: 1,2-dichoroethane; DMF: dimethylformamide; N.D.: not detected.
[a]Reaction conditions: **1a** (0.22 mmol, 1.1 equiv.), **2a** (0.2 mmol), base (2.0 equiv.), solvent (2.0 mL), 80 °C, 18 h.
[b]Isolated yield.
[c]Base (0.5 equiv.).
[d]Base (1.0 equiv.).
[e]rt.

(2 mL) at 80 °C for 18 h, which resulted in the formation of product **3a** in 68% yield (Table 1, entry 1). Other amides **1b–e** were also tested under the same reaction conditions, but their reaction efficiencies were poor (Scheme 2). Second, various organic bases (1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) and inorganic bases (Na_2CO_3, K_3PO_4, Cs_2CO_3, ^{t}BuONa) were evaluated (Table 1, entries 2–7). When Et_3N was replaced with Na_2CO_3, the product **3a** was obtained in 95% isolated yield (Table 1, entry 4). Third, screening of the solvent indicated that other solvents (CH_3CN, tetrahydrofuran (THF), 1,2-dichoroethane (DCE), and dimethylformamide (DMF)) resulted in slightly decreased yields (Table 1, entries 8−11). Fourth, the yield of product **3a** was obviously lower when the amount of base was decreased to 1.0 equiv. and 0.5 equiv. (Table 1, entries 12 and 13), and the reaction did not work without a base (Table 1, entry 15). In addition, the reaction efficiency was the best at 80 °C, while a poor yield was observed at rt (33%, Table 1, entry 14).

With optimized reaction conditions in hand, the substrate scope of the amides was evaluated. As shown in Scheme 3, the reactions of electron-rich amides were well-tolerated and afforded the corresponding thioesters **3b,c** in 77% and 75% yields. Delightfully, halogen substituents (such as F, Cl, and Br) were tolerated in this transformation and good yields were obtained (**3d,e,f**), which implied a potential possibility for further functionalization of thioesters. A slightly lower yield was obtained using a 4-trifluoromethyl-substituted



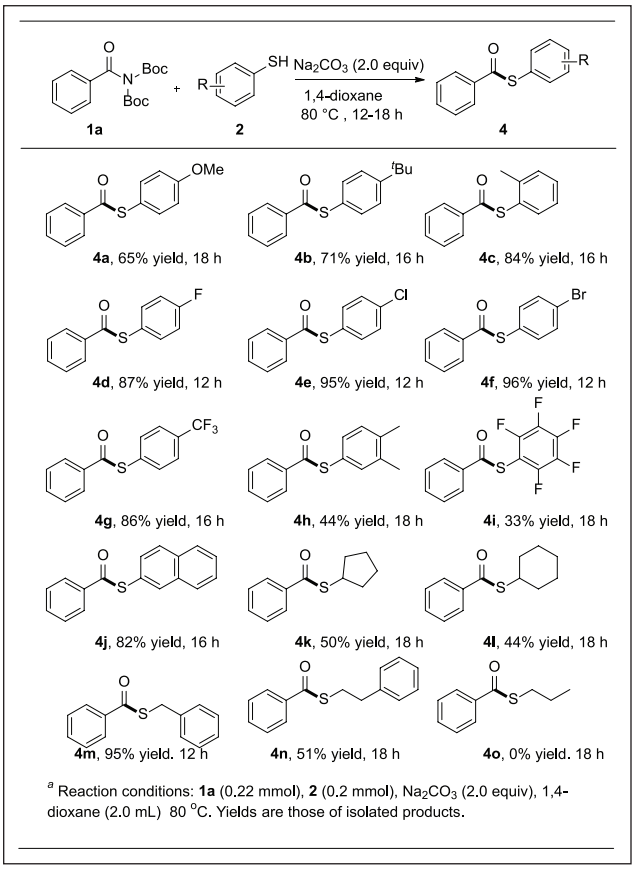
Scheme 2. Evaluating different amides.



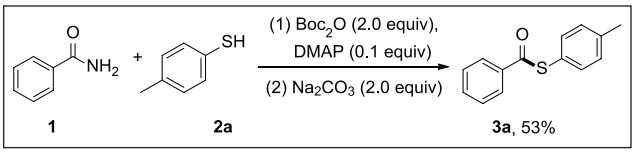
Scheme 3. Substrate scope of amides.

amide as the substrate (**3g**). Other amides, including heterocycles, and polyarenes were also tolerated and afforded products **3h–j** in acceptable yields.

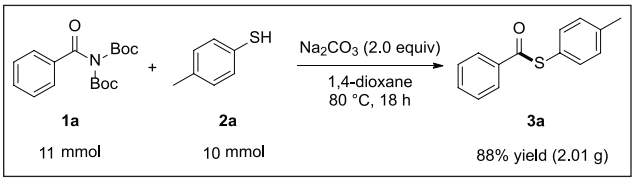
Next, we tested the tolerance of thiols under the optimized conditions (Scheme 4). Both electron-donating and electron-withdrawing substituents on the phenyl afforded the desired products **4a**–**c,g** in good yields. The halogen substituents (F, Cl, and Br) were tolerated under the standard conditions and afforded the desired products in excellent yields (**4d**–**f**). Multi-substituted thiophenols, such as 3,4-dimethyl and perfluoro, could be transformed into the corresponding thioesters **4h**,**i** in acceptable yields. 2-Naphthalenethiol afforded the corresponding thioester **4j** in 82% yield. Some alkyl-type thiols were also transformed into thioesters **4k**–**n** under standard conditions in 44%–95% yields. Unfortunately, an aliphatic alkyl-type thiol **4o** did not react under the optimized conditions. Finally, a one-pot reaction was carried out under the current conditions and product **3a** was obtained in a 53% total yield (Scheme 5). This suggests that the synthetic strategy can be achieved with a common primary amide.



Scheme 4. Substrate scope of thiols.



Scheme 5. One-pot experiment.



Scheme 6. Scale-up experiment.

To check the practicality of this transformation, a gram-scale reaction (10 mmol) was carried out (Scheme 6). The reaction afforded product **3a** in 88% yield under standard conditions, which demonstrates that this protocol has potential application value in industrial production.

Conclusion

In summary, we have reported a transition-metal-free cross-coupling reaction for the preparation thioester compounds using commercial primary amides and thiols *via* activated N–C bond cleavage under exceedingly mild conditions. The transformation is accomplished efficiently with the

assistance of stoichiometric Na_2CO_3 under an air atmosphere. A high-yielding gram-scale reaction demonstrated the potential value of the synthetic utility of this method.

General procedure

All reagents and solvents were commercially available and used without further purification. Unless otherwise noted, all reactions were run under a nitrogen atmosphere. Purification of all products was carried out by flash chromatography using brand 200–300 mesh silica gel. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Ascend instrument at 400, 100 and 376 MHz, respectively. Chemical shifts were reported in δ (ppm) referenced to an internal tetramethylsilane (TMS) standard for ^{1}H NMR (δ 0.00), and $CDCl_3$ (δ 77.16) for ^{13}C NMR. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptaplet, m = multiplet, and br = broad. High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using electrospray ionization-time of flight (ESI-TOF). GC-MS spectra were recorded on a Shimdazu-GC-MS 2010QP-Ultra instrument.

Preparation of the starting materials

General procedure for N,N-Boc$_2$-amide synthesis. A previously published procedure was followed. An oven-dried round-bottomed flask (100 mL) equipped with a stir bar was charged with the primary amide (8.26 mmol, 1.0 equiv.), 4-dimethylaminopyridine (DMAP) (typically, 0.10 equiv.), and dichloromethane (typically, 25 mL), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles under high vacuum.[84] Di-*tert*-butyl dicarbonate (typically, 2.0 equiv.) was added portion-wise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred overnight at room temperature. After the indicated time, the reaction mixture was concentrated and unless stated otherwise, purified directly by chromatography on silica gel (hexanes/ethyl acetate) to give analytically pure product. ***N,N*-Boc$_2$-benzamide (1a)**. White solid. Yield 85.2%. MS = 321.2.

*General procedure for synthesis of N-Boc amides from secondary amides (**1b, 1c**).* An oven-dried round-bottomed flask (100 mL) was charged with a secondary amide substrate (5.0 mmol, 1.0 equiv.), DMAP (0.1 equiv.), and dichloromethane (typically, 0.20 M).[86] Di-*tert*-butyl dicarbonate (1.0 equiv.) was added in one portion, and the reaction mixture was allowed to stir at room temperature for 15 h. After the indicated time, the reaction mixture was quenched with $NaHCO_3$ (aq, 10 mL), extracted with EtOAc (3 × 20 mL), washed with H_2O (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried, and concentrated. Unless stated otherwise, purification by flash chromatography (EtOAc/hexanes) afforded the pure product. In our hands, the *N*-Boc activation of secondary amides typically proceeds in average yields of >80%. ***tert*-Butyl benzoyl(phenyl)carbamate (1b)**. White solid. Yield 81%. MS = 297.1. ***tert*-Butyl benzoyl(benzyl)carbamate (1c)**. Colorless oil. Yield 76%. MS = 311.1.

*General procedure for N-acyl-glutarimide synthesis (**1d**).* An oven-dried round-bottomed flask (100 mL) equipped with a stir bar was charged with amine (8.84 mmol, 1.0 equiv.), triethylamine (typically, 2.0 equiv.), DMAP (typically, 0.25 equiv.), and dichloromethane (typically, 50 mL), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles under high vacuum.[87] Acyl chloride (typically, 1.1 equiv.) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred overnight at room temperature. After the indicated time, the reaction mixture was diluted with Et_2O (20 mL) and filtered. The organic layer was washed with HCl (1.0 N, 30 mL) and brine (30 mL), dried, and concentrated. Unless stated otherwise, the crude product was purified by recrystallization (toluene) to give analytically pure product. **Benzoylpiperidine-2,6-dione (1d)**. White solid. Yield 87%. MS = 217.1.

*General procedure for saccharinamide synthesis (**1e**).* A previously published procedure was followed.[88] An oven-dried flask (25 mL) equipped with a stir bar was charged with the amine (typically, 3.0 mmol, 1.0 equiv.), triethylamine (typically, 1.0 equiv.), and *N,N*-dimethylacetamide (DMAc, typically, 0.75 M), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles under high vacuum. The acyl chloride (typically, 1.0 equiv.) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. After the indicated time, the reaction mixture was diluted with H_2O (5 mL). The resulting solid was collected by filtration, washed with Et_2O (1 × 10 mL), and dried. The crude product was purified by recrystallization (methanol or toluene) to give analytically pure product. ***N*-Benzoylsaccharin (1e)**. Yield 85%. MS = 287.0.

*General procedure for the synthesis of S-p-tolyl benzothioate (e.g. **3a**).* A mixture of **1a** (0.22 mmol, 1.1 equiv.), **2a** (0.2 mmol, 1.0 equiv.), and Na_2CO_3 (0.4 mmol, 2.0 equiv.) in 1,4-dioxane (2 mL) for 12–18 h at 80 °C. After the disappearance of **2a** (detected by TLC), the reaction mixture was washed with ethyl acetate (3 × 5.0 mL), and the combined organic phase was concentrated in vacuo and the residue purified by column chromatography on silica gel (eluted with PE/EtOAc = 50:1) to provide the desired product **3a**.

One-pot experiment. To a dry flask was added primary amide **1a** (0.22 mmol, 1.1 equiv.), DMAP (typically, 0.10 equiv.), and dichloromethane (typically, 2 mL), and the mixture placed under a positive pressure of nitrogen. Di-*tert*-butyl dicarbonate (typically, 2.0 equiv.) was added portion wise with vigorous stirring at 0 °C, and the reaction mixture was stirred overnight at room temperature. The combined organic phase was concentrated in vacuo, a mixture of **2a** (0.2 mmol, 1.0 equiv.) and Na_2CO_3 (0.4 mmol, 2.0 equiv.) in 1,4-dioxane (2 mL) for 12–18 h at 80 °C. After the disappearance of **2a** (detected by TLC), the reaction mixture was washed with ethyl acetate (3 × 5.0 mL), the combined organic phase was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluted with PE/EtOAc = 50:1) to provide the desired product **3a** (53%).

S-(p-tolyl) benzothioate (**3a**)[89]: A pale white crystalline solid; yield 95% (42.3 mg); m.p. 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 2.28 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 139.8, 136.8, 135.1, 133.6, 130.2, 128.8, 127.5, 123.9, 21.4 ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{13}OS$ $[M + H]^+$: 229.0687; found: 229.0690.

S-(p-tolyl) 4-methylbenzothioate (**3b**)[90]: A pale white crystalline solid; yield 77% (37.3 mg); m.p. 123.5–124.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.27–7.23 (m, 4H), 2.41 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 144.6, 139.8, 135.2, 134.3, 130.2, 129.5, 127.7, 124.1, 21.8, 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{15}H_{15}OS$ $[M + H]^+$; 243.0844; found: 243.0840.

S-(p-tolyl) 4-methoxybenzothioate (**3c**)[91]: A pale white crystalline solid; yield 75% (38.7 mg); m.p. 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 166.1 (d, $^1J_{C\text{-}F}$ = 255.2 Hz), 140.0, 135.1, 133.1 (d, $^4J_{C\text{-}F}$ = 2.6 Hz), 130.3, 130.1 (d, $^3J_{C\text{-}F}$ = 9.3 Hz), 123.6, 116.0 (d, $^2J_{C\text{-}F}$ = 22.1 Hz), 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{15}H_{15}O_2SNa$ $[M + Na]^+$: 281.0612; found: 281.0599.

S-(p-tolyl) 4-fluorobenzothioate (**3d**): A pale white crystalline solid; yield 91% (44.8 mg); m.p. 71–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.02 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.27–7.24 (m, 2H), 7.14 (t, J = 8.4 Hz, 2H), 2.39 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −104.26 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 166.1 (d, $J_{C\text{-}F}$ = 255.2 Hz), 140.0, 135.1, 133.1 (d, J = 2.6$_{C\text{-}F}$ Hz), 130.3, 130.1 (d, $J_{C\text{-}F}$ = 9.3 Hz), 123.6, 116.0 (d, $J_{C\text{-}F}$ = 22.1 Hz), 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{12}FOSNa$ $[M + Na]^+$: 269.0412; found: 269.0394.

S-(p-tolyl) 4-chlorobenzothioate (**3e**): A pale white crystalline solid; yield 88% (46.1 mg); m.p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.30–7.22 (m, 2H), 2.39 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 140.1, 140.0, 135.2, 135.1, 130.3, 129.1, 128.9, 123.5, 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{12}ClOS$ $[M + H]^+$: 263.0297; found: 263.0309.

S-(p-tolyl) 4-bromobenzothioate (**3f**): A pale white crystalline solid; yield 87% (53.1 mg); m.p. 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.24–7.12 (m, 2H), 2.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 140.1, 135.6, 135.1, 132.1, 130.3, 129.0, 128.7, 123.4, 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{12}BrOS$ $[M + H]^+$: 306.9792; found: 306.9780.

S-(p-tolyl) 4-(trifluoromethyl)benzothioate (**3g**): A pale white crystalline solid; yield 76% (45.1 mg); m.p. 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 2H), 2.41 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.09 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 140.3, 139.7, 135.1, 135.0 (q, $^2J_{C\text{-}F}$ = 32.8 Hz), 130.4, 127.9, 125.9 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 123.6 (q, $^1J_{C\text{-}F}$ = 272.7 Hz), 123.1, 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{15}H_{12}F_3OS$ $[M + H]^+$: 297.0561; found: 297.0542.

S-(p-tolyl) pyridine-3-carbothioate (**3h**): A pale white crystalline solid; yield 47% (21.5 mg); m.p. 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.8 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.86 (t, J = 7.2 Hz, 1H), 7.57–7.52 (m, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 151.9, 149.3, 139.7, 137.5, 135.0, 130.2, 128.1, 124.7, 120.9, 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{13}H_{12}NOSNa$ $[M + Na]^+$: 252.0459; found: 252.0455.

S-(p-tolyl) furan-2-carbothioate (**3i**): A pale white crystalline solid; yield 80% (34.9 mg); m.p. 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.29–7.17 (m, 3H), 6.55 (dd, J = 3.2, 1.6 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 150.5, 146.5, 140.1, 135.2, 130.2, 122.7, 116.2, 112.5, 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{12}H_{11}O_2S$ $[M + H]^+$: 219.0479; found: 219.0465.

S-(p-tolyl) naphthalene-2-carbothioate (**3j**): A pale white crystalline solid; yield 81% (45.1 mg); m.p. 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.01 (dd, J = 8.4, 1.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.87 (t, J = 8.4 Hz, 2H), 7.63–7.48 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 139.9, 136.0, 135.2, 134.1, 132.6, 130.2, 129.7, 129.0, 128.70, 128.67, 127.9, 127.1, 124.0, 123.4, 21.5 ppm. HRMS (ESI-TOF) calcd for $C_{18}H_{15}OS$ $[M + H]^+$: 279.0844; found: 279.0847.

S-(4-methoxyphenyl) benzothioate (**4a**)[92]: A pale white crystalline solid; yield 65% (31.5 mg); m.p. 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 160.9, 136.8, 136.7, 133.7, 128.8, 127.6, 118.0, 115.1, 55.5 ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{13}O_2SNa$ $[M + Na]^+$: 267.0456; found: 267.0465.

S-(4-(tert-butyl)phenyl) benzothioate (**4b**): A pale white crystalline solid; yield 71% (38.4 mg); m.p. 77–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.46–7.43 (m, 6H), 1.34 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 152.9, 136.9, 134.8, 133.7, 128.8, 127.6, 126.5, 124.0, 34.9, 31.4 ppm. HRMS (ESI-TOF) calcd for $C_{17}H_{19}OS$ $[M + H]^+$: 271.1157; found: 271.1157.

S-(o-tolyl) benzothioate (**4c**): A yellow oily liquid; yield 84% (38.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 3H), 7.41–7.33 (m, 2H), 7.32–7.20 (m, 1H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 142.8, 136.9, 136.5, 133.7, 130.9, 130.3, 128.8, 127.7, 126.9, 126.8, 20.9 ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{13}OS$ $[M + H]^+$: 229.0687; found: 229.0685.

S-(4-fluorophenyl) benzothioate (**4d**)[91]: A pale white crystalline solid; yield 87% (40.4 mg); m.p. 51–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.51–7.45 (m, 4H), 7.15 (t, J = 8.8 Hz, 2H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −111.02 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 163.8 (d, $^1J_{C\text{-}F}$ = 250.1 Hz),

137.3 (d, $^{3}J_{C\text{-}F}$=8.5 Hz), 136.6, 133.9, 128.9, 127.6, 122.8 (d, $^{4}J_{C\text{-}F}$=3.4 Hz), 116.7 (d, $^{2}J_{C\text{-}F}$=22.1 Hz) ppm. HRMS (ESI-TOF) calcd for $C_{13}H_{10}FOS$ $[M+H]^+$: 233.0436; found: 233.0431.

S-(4-chlorophenyl) benzothioate (**4e**)[90]: A pale white crystalline solid; yield 95% (47.2 mg); m.p. 73–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J*=7.2 Hz, 2H), 7.63–7.55 (m, 3H), 7.48 (t, *J*=7.6 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 136.6, 136.5, 134.0, 132.6, 128.9, 127.6, 126.6, 124.4 ppm. HRMS (ESI-TOF) calcd for $C_{13}H_{10}ClOSNa$ $[M+Na]^+$: 270.9960; found: 270.9950.

S-(4-bromophenyl) benzothioate (**4f**)[93]: A pale white crystalline solid; yield 96% (56.1 mg); m.p. 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J*=7.3 Hz, 2H), 7.61 (t, *J*=7.4 Hz, 1H), 7.48 (t, *J*=7.8 Hz,2H), 7.45–7.40 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 136.5, 136.4, 136.1, 134.0, 129.6, 128.9, 127.6, 126.0 ppm. HRMS (ESI-TOF) calcd for $C_{13}H_{10}BrOS$ $[M+H]^+$: 292.9636; found: 292.9623.

S-(4-(trifluoromethyl)phenyl) benzothioate (**4g**)[94]: A pale white crystalline solid; yield 86% (48.5 mg); m.p. 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J*=7.4 Hz, 2H), 7.70 (d, *J*=8.2 Hz, 2H), 7.65–7.61 (m, 3H), 7.50 (t, *J*=7.6 Hz, 2H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.83 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 136.4, 135.3, 134.2, 132.3, 131.6 (q, $^{2}J_{C\text{-}F}$=32.6 Hz), 129.0, 127.7, 126.1 (q, $^{3}J_{C\text{-}F}$=3.7 Hz), 124.0 (q, $^{1}J_{C\text{-}F}$=272.5 Hz) ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{10}F_3OS$ $[M+H]^+$: 283.0404; found: 283.0405.

S-(3,4-dimethylphenyl) benzothioate (**4h**): A pale white crystalline solid; yield 46% (22.3 mg); m.p. 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J*=7.2 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 2H), 7.23–7.20 (m, 3H), 2.294 (s, 3H), 2.286 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 138.7, 137.9, 136.9, 136.2, 133.6, 132.7, 130.7, 128.8, 127.6, 123.9, 19.9, 19.8 ppm. HRMS (ESI-TOF) calcd for $C_{15}H_{15}O$ $[M+H]^+$: 243.0843; found: 243.0832.

S-(perfluorophenyl) benzothioate (**4i**)[95]: A pale white crystalline solid; yield 33% (20.1 mg); m.p. 47–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J*=7.6 Hz, 2H), 7.66 (t, *J*=7.6 Hz, 1H), 7.53 (t, *J*=8.0 Hz, 2H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.82 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.7, 139.0, 136.2, 135.8, 134.6, 132.7, 129.2, 129.0, 128.0 ppm. HRMS (ESI-TOF) calcd for $C_{13}H_6F_5OS$ $[M+H]^+$: 305.0060; found: 305.0047.

S-(naphthalen-2-yl) benzothioate (**4j**)[91]: A pale yellow crystalline solid; yield 82% (42.3 mg); m.p. 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J*=7.6 Hz, 3H), 7.91–7.80 (m, 3H), 7.59 (t, *J*=7.2 Hz, 1H), 7.56–7.44 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 136.8, 135.0, 133.8, 133.7, 133.6, 131.5, 128.9, 128.9, 128.1, 127.9, 127.6, 127.3, 126.7, 124.8 ppm. HRMS (ESI-TOF) calcd for $C_{17}H_{13}OS$ $[M+H]^+$: 265.0687; found: 265.0675.

S-cyclopentyl benzothioate (**4k**): A white oily liquid; yield 50% (20.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J*=7.6 Hz, 2H), 7.55 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 4.00–3.85 (m, 1H), 2.20 (d, *J*=5.6 Hz, 2H), 1.85–1.58 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 137.5, 133.2, 128.6, 127.3, 42.8, 33.5, 25.0 ppm. HRMS (ESI-TOF) calcd for $C_{12}H_{15}OS$ $[M+H]^+$: 207.0844; found: 207.0827.

S-cyclohexyl benzothioate (**4l**): A white oily liquid; yield 44% (19.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J*=7.6 Hz, 2H), 7.55 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 3.73 (s, 1H), 2.02 (d, *J*=9.2 Hz, 2H), 1.77 (s, 2H), 1.69–1.42 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 137.6, 133.2, 128.7, 127.3, 42.7, 33.3, 26.2, 25.8 ppm. HRMS (ESI-TOF) calcd for $C_{13}H_{17}OS$ $[M+H]^+$: 221.1000; found: 221.0998.

S-benzyl benzothioate (**4m**)[92]: A pale white crystalline solid; yield 95% (43.3 mg); m.p. 36–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J*=7.2 Hz, 2H), 7.54 (t, *J*=7.2 Hz, 1H), 7.42 (t, *J*=7.6 Hz, 2H), 7.37 (d, *J*=7.6 Hz, 2H), 7.30 (t, *J*=7.6 Hz, 2H), 7.27–7.21 (m, 1H), 4.31 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4, 137.6, 136.9, 133.5, 129.1, 128.8, 128.7, 127.4, 127.4, 33.5 ppm. HRMS (ESI-TOF) calcd for $C_{14}H_{13}OS$ $[M+H]^+$: 229.0687; found: 229.0693.

S-phenethyl benzothioate (**4n**)[92]: A white oily liquid; yield 51% (24.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J*=7.6 Hz, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 7.43 (t, *J*=7.3 Hz, 2H), 7.33–7.18 (m, 5H), 3.31 (t, *J*=7.5 Hz, 2H), 2.97 (t, *J*=7.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 140.2, 137.3, 133.4, 128.8, 128.7, 128.7, 127.3, 126.7, 36.1, 30.6 ppm. HRMS (ESI-TOF) calcd for $C_{15}H_{15}OS$ $[M+H]^+$: 243.0844; found: 243.0854.

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Supplemental material

Supplemental material for this paper is available online.

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