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One-Pot Synthesis of Benzoxazole/Benzothiazole-Substituted Esters by Michael Addition: A Selective Construction of C-N/C-S Bonds

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Abstract: An efficient and convenient synthesis of benzoxazole/benzothiazole-substituted esters in a one-pot strategy is reported. In this investigation, a selective construction of C-N and C-S bonds via simple addition is performed. Thus, using substituted 2-aminophenols/2-aminobenzenethiols, TMTD (tetramethylthiuram disulfide) and α,β-unsaturated esters as starting substrates, C-N and C-S bonds can be selectively constructed by means of the Michael addition reaction. This protocol features high selectivity, high atomic economy, mild conditions, good functional tolerance and good to excellent yields, showing the potential value for the preparation of some biologically and pharmaceutically active compounds.

Keywords: benzoxazole; benzothiazole; synthesis; Michael addition; organosulfur

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1. Introduction

Compounds containing C-N/C-S bonds have become a key part in organic synthesis, biomedicine, material chemistry and industrial manufacturing [1–13]. Many heterocyclic compounds bearing C-N/C-S bonds are indispensable in pharmaceutical chemistry due to their unique biological and pharmaceutical activities (Figure 1). These compounds can be used as an anti-inflammatory (**a**) [14], a heat shock protein 90 (Hsp 90) an inhibitor (**b**) [15], a botanical fungicide or insecticide (**c**) [16], a CpIMPDH inhibitor (**d**) [17], a CCR_3 selective antagonist (**e**) [18], a lipoxygenase inhibitor (**f**) [19], an anticancer agent (**g**) [20] and an antinematode drug (**h**) [21]. Therefore, the construction of the C-N bond and the C-S bond has aroused the interest of the organic chemistry community.

So far, various methods for constructing C-N/S bonds have been reported (Scheme 1). Bolm [22], Buchwald [23], Chen [24] and Biswasa [25] realized the construction of the C-N bond by using aryl halides or alcohols to react with nitrogen-containing heterocyclic compounds. The most traditional method to form the C-S bond is the coupling reaction between thiols and aryl halides [26–31]. The Sokolova [32] and Ma [33] group completed the construction of the C-S bond under base conditions. In addition, Yuan and Hajra [34,35] used phenylhydrazine and phenylthiophenol as starting materials to obtain various compounds containing a C-S bond via visible-light-mediated synthesis or aerobic-oxidative coupling. Our laboratory and other groups [36–38] also completed the construction of the C-S bond through the Chan-Lam coupling reaction. To the best of our knowledge, the selective construction of C-N/C-S bonds has rarely been reported [39,40]. Though, efficient, the previously reported methods for the construction of C-N/C-S bonds involved the use of toxic, foul-smelling, and expensive reagents, transition metals as catalysts, a high reaction temperature, a long reaction time, as well as low conversion, which limited the application of these methods in pharmaceutical synthesis. Thus, it is still desirable to

develop efficient protocols for the selective construction of C-N/C-S bonds, especially the ones using a tandem or one-pot synthesis strategy.

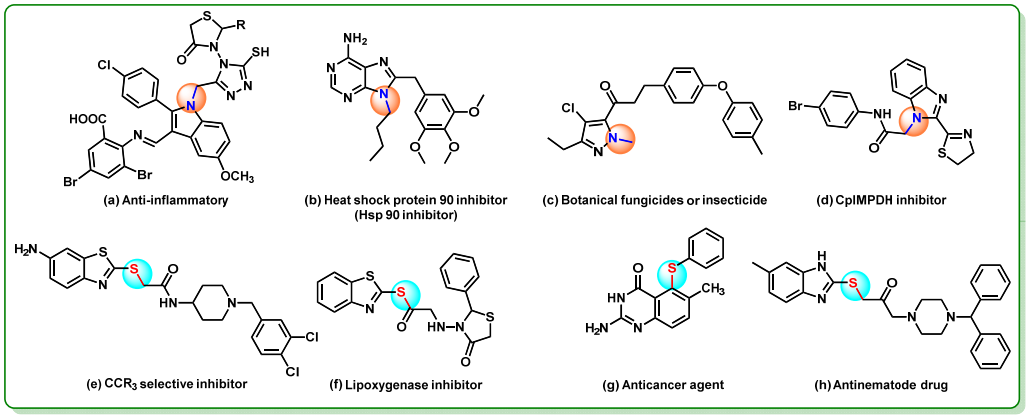
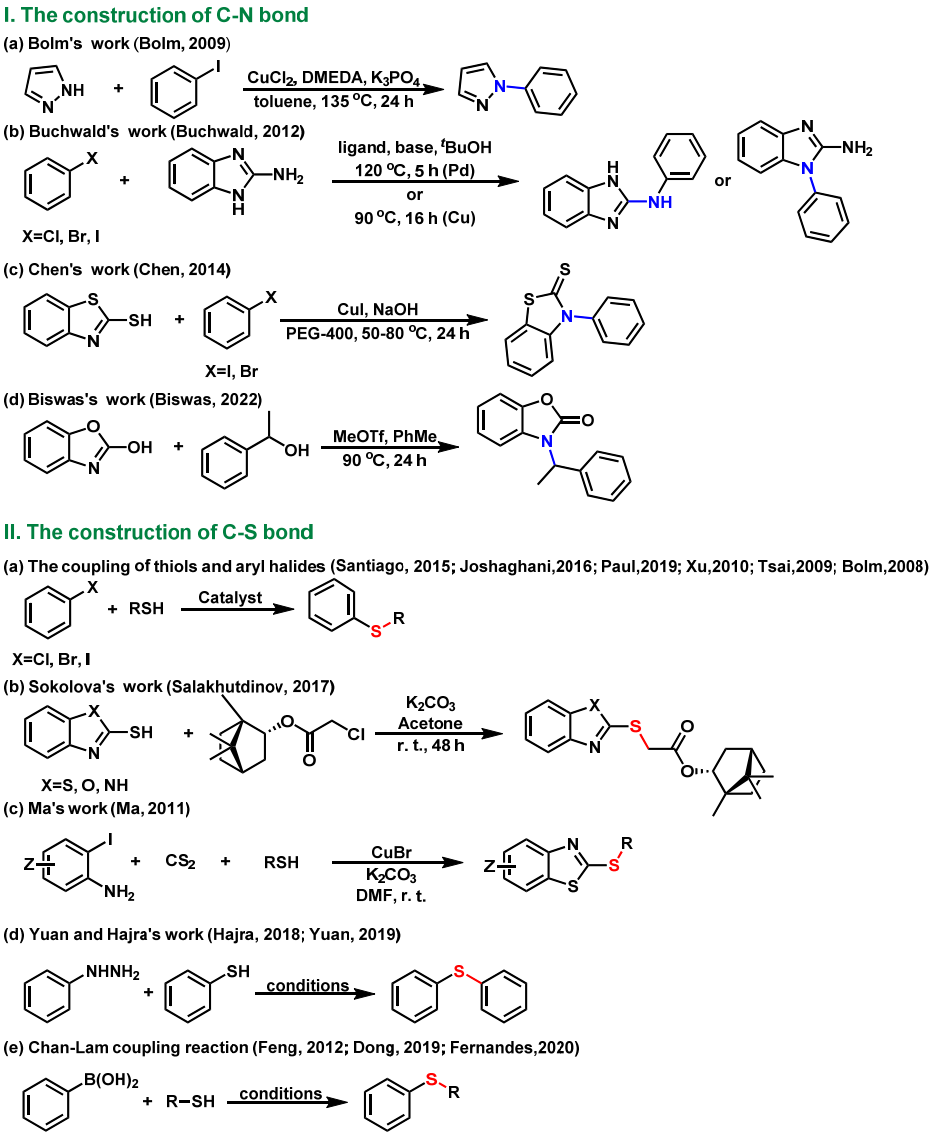
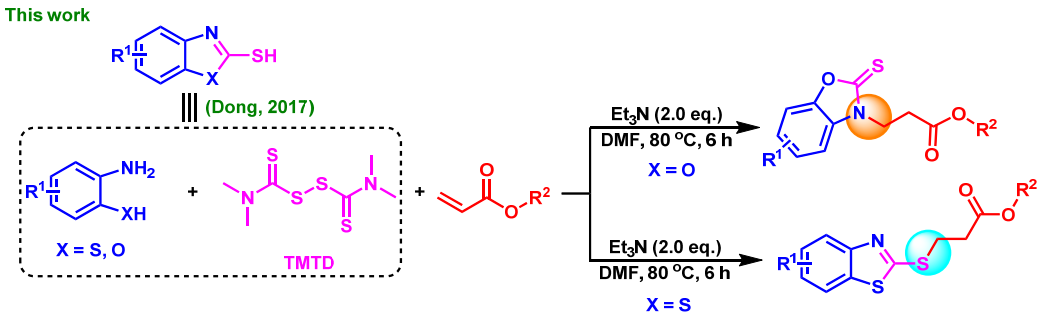


Figure 1. Representative biologically active compounds containing C-N/C-S bonds.



Scheme 1. Previous strategies for the synthesis of C-N/C-S bonds [22–38].

As part of our long-term interest in constructing various C-X (X = O, S, N, P) bonds and studying the synthesis of benzoheterocyclic compounds [41–45], we report here an effective and practical method for the selective formation of C-N/C-S bonds by Michael addition reactions, starting from substituted 2-aminophenols/2-aminobenzenethiols and TMTD (tetramethylthiuram disulfide) with *α*,*β*-unsaturated esters in a one-pot strategy (Scheme 2, the present study).



Scheme 2. Selective formation of C-N/C-S bonds in one-pot strategy [45].

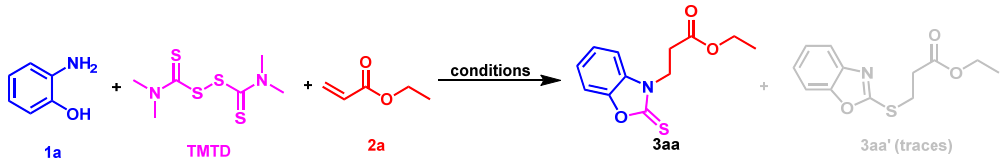
2. Results and Discussion

For our initial study, we chose 2-aminophenol (**1a**), tetramethylthiuram disulfide (TMTD) and ethyl acrylate (**2a**) as the starting materials for the model reaction to explore the optimal reaction conditions (Table 1). Our laboratory has previously made good progress in the synthesis of benzoheterocyclic compounds. The reaction conditions for the first step to produce 2-aminophenols were slightly adjusted based on our previous work [41–45], and our attempts were focused on the second step (the Michael addition reaction). Using CuI as the catalyst and Et_3N as the base in the initial attempt, the ideal product **3aa** was obtained with a 19% yield of EtOH (Entry 1, Table 1). Next we tried other catalysts and found that the catalytic effect of CuI was slightly better (Entries 1–4, Table 1). We were surprised to find that the yield was greatly improved when DMF was used as the solvent (Entry 5, Table 1), and the result was better without adding metal salt as the catalyst (entry 6, Table 1). The screening of bases and reaction temperature showed that Et_3N was the best base and 80 °C was the optimal temperature (entries 7–12, Table 1). Furthermore, the loading of the base and the type of solvent were also investigated, and the results are shown in entries 13–16, Table 1. The optimal reaction conditions are summarized in Entry 10, Table 1. It is worth noting that the model reaction in Table 1 always produced the by-product **3aa'** in traces which formed the C-S bond in the additional step.

According to the optimal conditions obtained above, a variety of related substrates are explored, and the results are presented in Table 2. First, the reaction effect of various substituted 2-aminophenols and ethyl acrylate was investigated, and the experimental results showed that 2-aminophenols with either electron-withdrawing groups (-Br, -Cl) or electron-donating groups ($-CH_3$, $-^tBu$) could react readily with ethyl acrylate to give the desired products with a moderate to good yield (**3aa**–**3ah**). When *tert*-butyl acrylate and cyclohexyl acrylate were used to react with various substituted 2-aminophenols, the reaction also worked well and provided the expected products (**3ai**–**3av**) readily. When 2-amino-3-methylphenol was used as the starting material to react with ethyl acrylate, *tert*-butyl acrylate and cyclohexyl acrylate, the compounds (**3ah**, **3aj**, **3ar**) could only be obtained in 28%, 29% and 36% yields, respectively, which might be due to the steric hindrance.

To further determine the structure of the target products, we performed an X-ray diffraction analysis of **3ai** (CCDC: 2152821, Figure 2) to show the exact C-N bond formation of the product.

Table 1. Optimization of the reaction conditions [a].



Entry	Cat.	Base	Temp. (°C)	Solvent	Yield [b] (%)
1	CuI	Et_3N (2.0 eq.)	60	EtOH	19
2	CuO	Et_3N (2.0 eq.)	60	EtOH	17
3	$CuBr_2$	Et_3N (2.0 eq.)	60	EtOH	15
4	$FeCl_3$	Et_3N (2.0 eq.)	60	EtOH	<10
5	CuI	Et_3N (2.0 eq.)	60	DMF	48
6	-	Et_3N (2.0 eq.)	60	DMF	68
7	-	Na_2CO_3 (2.0 eq.)	60	DMF	53
8	-	$NaHCO_3$ (2.0 eq.)	60	DMF	52
9	-	Et_2NH (2.0 eq.)	60	DMF	60
10	-	Et_3N (2.0 eq.)	80	DMF	85
11	-	Et_3N (2.0 eq.)	100	DMF	84
12	-	Et_3N (2.0 eq.)	110	DMF	80
13	-	Et_3N (1.0 eq.)	80	DMF	70
14	-	Et_3N (3.0 eq.)	80	DMF	72
15	-	Et_3N (2.0 eq.)	80	H_2O	36
16	-	Et_3N (2.0 eq.)	80	DMSO	79

[a] Reaction conditions: Step I: **1a** (0.5 mmol), tetramethylthiuram disulfide (**TMTD**, 0.3 mmol), solvent (2 mL), stirred in a sealed tube for 3 h. Step II: **2a** (1.0 mmol), catalyst (2 eq.), stirred in a sealed tube for 6 h. [b] Isolated yield.

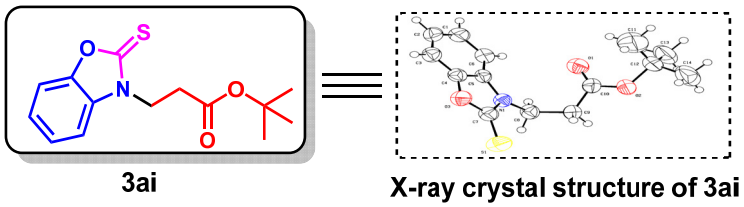


Figure 2. X-ray crystallography of **3ai**.

The above optimal reaction conditions were also applicable to the reactions between various substituted 2-aminobenzenethiols (**1**) and *α*,*β*-unsaturated esters (**2**). However, this reaction would give the C-S formation products (all oily) as major ones via Michael addition, and the C-N formation products were obtained in traces. Thus, under standard conditions, a variety of substituted 2-aminobenzenethiols (**1**) and TMTD could react with ethyl acrylate, *tert*-butyl acrylate and cyclohexyl acrylate, smoothly, giving the target products with a moderate yield (**5aa**–**5ag**, Table 3). To determine the detailed structure of the target product, the X-ray diffraction analysis of by-product **5ag′** (CCDC: 2152790, Figure 3) was performed, showing the existence of the C-N bond formation, which could further indicate the C-S bond formation of the major product **5ag**.

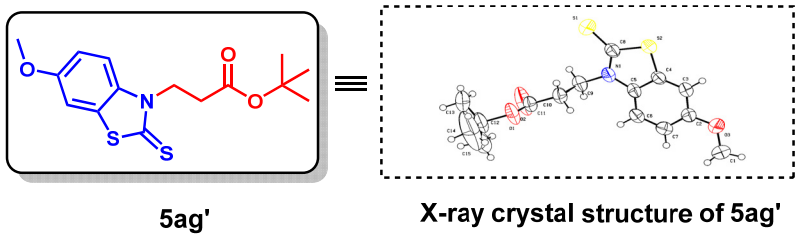
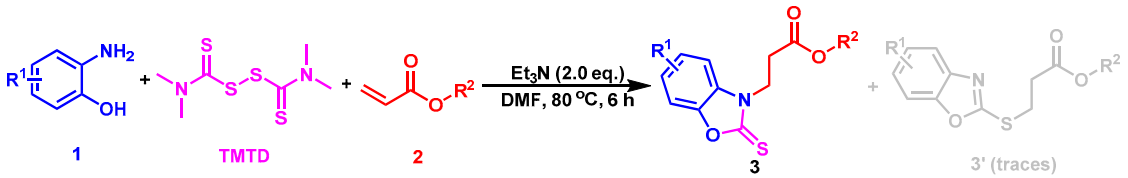
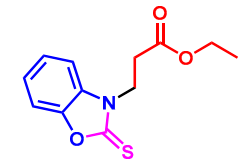


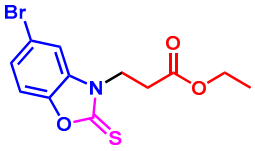
Figure 3. X-ray crystallography of by-product **5ag′**.

Table 2. One-pot synthesis of benzoxazole-substituted ester compounds [a,b].

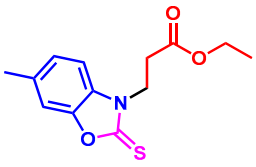




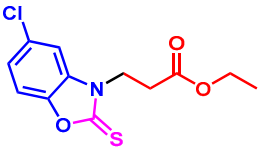
3aa, 85%



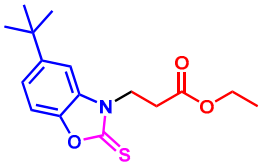
3ab, 84%



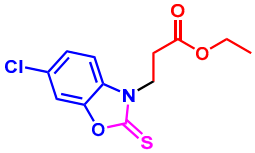
3ac, 82%



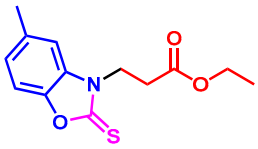
3ad, 78%



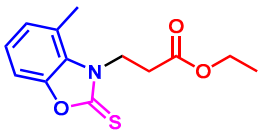
3ae, 88%



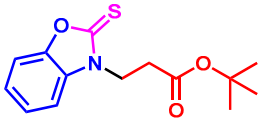
3af, 53%



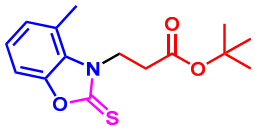
3ag, 70%



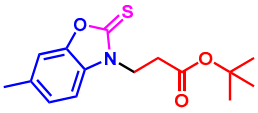
3ah, 28%



3ai, 86%

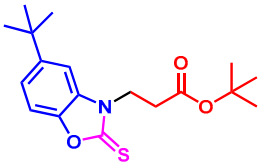


3aj, 29%

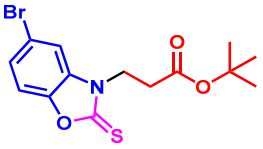


3ak, 89%

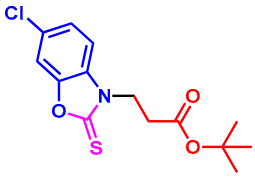
3ak, 89%



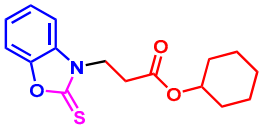
3al, 73%



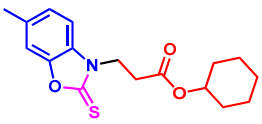
3am, 84%



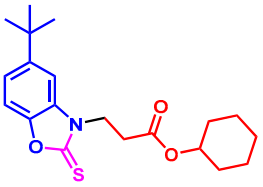
3an, 70%



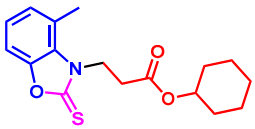
3ao, 89%



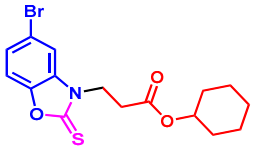
3ap, 69%



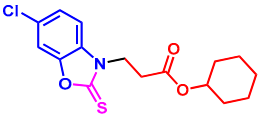
3aq, 70%



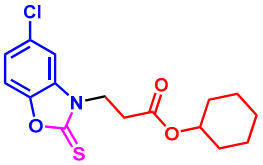
3ar, 36%



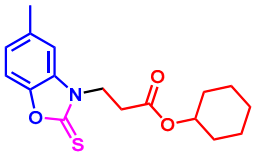
3as, 80%



3at, 88%



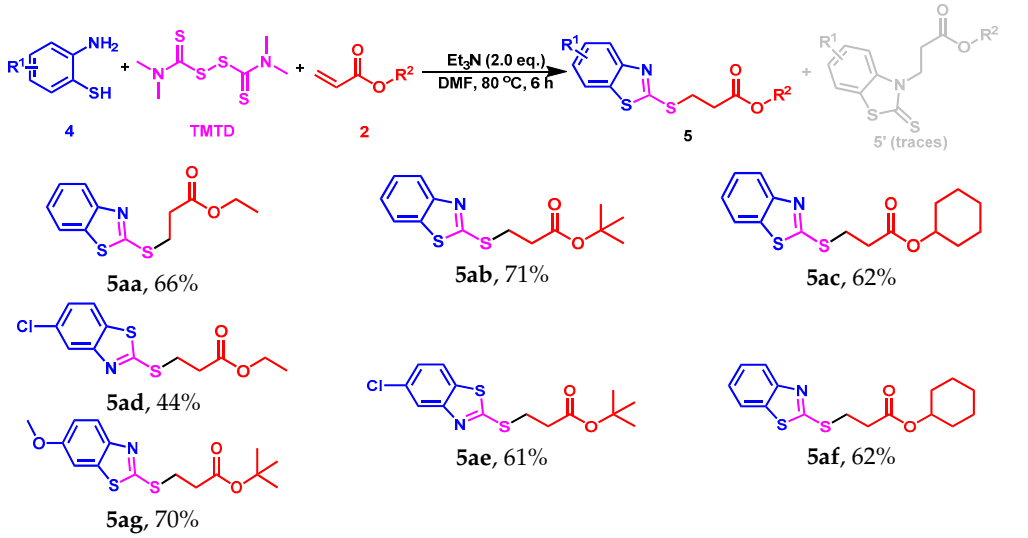
3au, 56%



3av, 87%

[a] Reaction conditions: Step I: **1** (0.5 mmol), tetramethylthiuram disulfide (**TMTD**, 0.3 mmol), DMF (2 mL), 80 °C, stirred in a sealed tube for 3 h. Step II: **2** (1.0 mmol), Et_3N (2.0 eq.), 80 °C, stirred in a sealed tube for 6 h. [b] Isolated yield.

Table 3. One-pot synthesis of benzothiazole-substituted ester compounds [a,b].



[a] Reaction conditions: Step I: **4** (0.5 mmol), tetramethylthiuram disulfide (TMTD, 0.3 mmol), DMF (2 mL), 80 °C, stirred in a sealed tube for 3 h. Step II: **2** (1.0 mmol), Et_3N (2.0 eq.), 80 °C, stirred in a sealed tube for 6 h. [b] Isolated yield.

3. Conclusions

In summary, we developed an efficient and convenient one-pot method to selectively construct C-N and C-S bonds by a simple Michael addition. Using substituted 2-aminophenols/2-aminobenzenethiols, TMTD (tetramethylthiuram disulfide) and α,β-unsaturated esters as starting substrates, a variety of benzoxazole/benzothiazole substituted esters were obtainedwithout problem, forming C-N and C-S bonds selectively. This strategy features high selectivity, high atomic economy, mild conditions, good functional tolerance. and good yields, showing its potential value for the preparation of some biologically and pharmaceutically active compounds.

4. Experimental Section

General Information. All starting materials were commercially purchased. Yields refer to isolated compounds estimated to be >95% pure as determined by ^1H NMR and capillary GC analysis. NMR spectra were recorded on a Bruker AM400 or AM 600 NMR instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in ppm, and coupling constants (J) are given in Hz. All melting points were determined on a RY-1G melting point instrument without correction. High-resolution mass spectra (HRMS) were recorded on a Angilent 6545LC/Q-TOF mass instrument (ESI). TLC was performed using aluminum plates coated with SiO_2 (Merck 60, F-254) and visualized with UV light at 254 nm. Column chromatography was performed on silica gel (200–300 mesh) with PE (petroleum ether)-EA (ethyl acetate) as an eluent.

General procedure for the synthesis of desired products forming C-N bonds (**3aa**–**3av**).

A mixture of substituted 2-aminophenols (**1**, 0.5 mmol) and tetramethylthiuram disulfide (**TMTD**, 0.3 mmol) in DMF (2 mL) was stirred at 80 °C for 3 h until the substrates completely disappeared. Subsequently, the sealed tube was cooled to room temperature. **2** (ethyl acrylate, *tert*-butyl acrylate, or cyclohexyl acrylate, 1.0 mmol) and Et_3N (2.0 eq.) were added, and the mixture was stirred at 80 °C for 6 h. After the reaction was completed, it was quenched with saturated NH_4Cl, and the crude solution was separated after diluting with ethyl acetate and dried-over anhydrous Na_2SO_4. The solvent was removed in a vacuum to obtain the crude product, which was further separated and purified by column chromatography to give the desired products (**3aa**–**3av**).

General procedure for the synthesis of desired products forming C-S bonds (**5aa**–**5ag**).

A mixture of substituted 2-aminobenzenethiols (**4**, 0.5 mmol) and tetramethylthiuram disulfide (TMTD, 0.3 mmol) in DMF (2 mL) was stirred at 80 °C for 3 h until the substrates completely disappeared. Subsequently, the sealed tube was cooled to room temperature, **2** (ethyl acrylate, *tert*-butyl acrylate, or cyclohexyl acrylate, 1.0 mmol) and Et_3N (2.0 eq.) were added, and the mixture was stirred at 80 °C for 6 h. After the reaction was completed, it was quenched with saturated NH_4Cl, and the crude solution was separated after diluting with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed in a vacuum to obtain the crude product, which was further separated and purified by column chromatography to give the desired products (**5aa**–**5ag**).

ethyl 3-(2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3aa**): The target product **3aa** (106.8 mg, 85%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27–7.14 (m, 4H), 4.37 (t, *J* = 6.8 Hz, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 2.88 (t, *J* = 6.8, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 179.0, 169.8, 146.1, 130.8, 123.9, 123.3, 109.3, 109.0, 60.1, 40.4, 30.3, 13.0. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{12}H_{14}NO_3S^+$ 252.0689; Found 252.0682.

ethyl 3-(5-bromo-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ab**): The target product **3ab** (138.7 mg, 84%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.36 (d, *J* = 2.0, 1H), 7.29–7.25 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 4.32 (t, *J* = 6.8, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 179.3, 169.6, 145.1, 132.3, 126.1, 116.8, 112.2, 110.4, 60.2, 40.6, 30.2, 13.1. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{12}H_{13}BrNO_3S^+$ 329.9794; Found 329.9797.

ethyl 3-(6-methyl-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ac**): The target product **3ac** (108.8 mg, 82%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.10–7.01 (m, 3H), 4.35 (t, *J* = 6.8 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 8.6, 2H), 2.35 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 178.9, 169.9, 146.4, 138.7, 133.8, 128.6, 124.6, 109.8, 108.5, 60.1, 40.4, 30.3, 20.4, 13.0. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{13}H_{16}NO_3S^+$ 266.0845; Found 266.0842.

ethyl 3-(5-chloro-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ad**): The target product **3ad** (111.4 mg, 78%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.23 (s, 1H), 7.18–7.08 (m, 2H), 4.32 (t, *J* = 6.6, 2H), 4.04 (q, *J* = 7.2, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 179.4, 169.6, 144.6, 132.0, 129.6, 123.2, 109.9, 109.5, 60.2, 40.7, 30.2, 13.1. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{12}H_{13}ClNO_3S^+$ 286.0299; Found 286.0294.

ethyl 3-(5-(tert-butyl)-2-mercaptobenzo[d]oxazol-3(2H)-yl)propanoate (**3ae**): The target product **3ae** (135.3 mg, 88%) was synthesized as a yellow oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.23–7.13 (m, 3H), 4.40 (t, *J* = 6.8 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.86 (t, *J* = 6.8, 2H), 1.28 (s, 9H), 1.10 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 179.3, 169.9, 147.8, 144.2, 130.5, 120.5, 108.5, 105.9, 60.0, 40.3, 34.1, 30.6, 30.5, 13.0. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{16}H_{22}NO_3S^+$ 308.1315; Found 308.1316.

ethyl 3-(6-chloro-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3af**): The target product **3af** (75.7 mg, 53%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27 (s, 1H), 7.20 (q, *J* = 9.9 Hz, 2H), 4.34 (t, *J* = 6.4 Hz, 2H), 4.03 (q, *J* = 7.1, 2H), 2.89 (t, *J* = 6.4 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 179.1, 169.9, 146.2, 129.9, 129.1, 124.1, 109.9, 109.7, 60.2, 40.6, 30.2, 13.1. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{12}H_{13}ClNO_3S^+$ 286.0299; Found 286.0297.

ethyl 3-(5-methyl-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ag**): The target product **3ag** (92.9 mg, 70%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.20 (d,

J = 8.9 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 4.42 (t, *J* = 6.9, 2H), 4.12 (q, *J* = 7.2, 2H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.44 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.2, 169.8, 144.4, 134.2, 130.8, 124.0, 109.1, 108.9, 60.1, 40.3, 30.3, 20.5, 13.0. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{13}H_{16}NO_3S^+$ 266.0845; Found 266.0851.

ethyl 3-(4-methyl-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ah**): The target product **3ah** (37.1 mg, 28%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 70–72 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.19 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.8, 1H), 7.04 (d, *J* = 7.6, 1H), 4.68 (t, *J* = 7.8, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.93 (t, *J* = 7.8, 2H), 2.63 (s, 3H), 1.23 (t, *J* = 7.1, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.4, 169.3, 146.4, 128.7, 127.0, 123.2, 119.7, 107.5, 60.1, 41.6, 31.2, 16.7, 13.1. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{13}H_{16}NO_3S^+$ 266.0845; Found 266.0843

tert-butyl 3-(2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ai**): The target product **3ai** (120.1 mg, 86%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 88–90 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.28–7.15 (m, 4H), 4.35 (t, *J* = 6.9 Hz, 2H), 2.78 (t, *J* = 6.9 Hz, 2H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.1, 169.0, 146.1, 130.8, 123.9, 123.3, 109.3, 109.1, 80.6, 40.5, 31.5, 27.0. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{14}H_{18}NO_3S^+$ 280.1002; Found 280.1006.

tert-butyl 3-(4-methyl-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3aj**): The target product **3aj** (42.5 mg, 29%) was synthesized as a yellow oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.20 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 4.65 (t, *J* = 7.9 Hz, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.63 (s, 3H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.3, 168.5, 146.4, 128.7, 127.0, 123.2, 119.8, 107.5, 80.7, 41.8, 32.4, 27.3, 16.7. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{15}H_{20}NO_3S^+$ 294.1158; Found 294.1156.

tert-butyl 3-(6-methyl-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ak**): The target product **3ak** (130.6 mg, 89%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 66–68 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.13 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 4.37 (t, *J* = 6.9 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H), 2.41 (s, 3H), 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 178.9, 169.1, 146.4, 133.8, 128.6, 124.5, 109.7, 108.6, 80.6, 40.5, 31.5, 27.0, 20.4. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{15}H_{20}NO_3S^+$ 294.1158; Found 294.1163.

tert-butyl 3-(5-(tert-butyl)-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3al**): The target product **3al** (122.4 mg, 73%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.29–7.26 (m, 2H), 7.24 (d, *J* = 9.0 Hz, 1H), 4.44 (t, *J* = 6.9 Hz, 2H), 2.84 (t, *J* = 6.9 Hz, 2H), 1.38 (s, 9H), 1.36 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 180.4, 170.3, 148.8, 145.2, 131.6, 121.5, 109.6, 107.1, 81.6, 41.4, 35.1, 32.6, 31.6, 28.0. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{18}H_{26}NO_3S^+$ 336.1628; Found 336.1626.

tert-butyl 3-(5-bromo-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3am**): The target product **3am** (150.5 mg, 84%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 136–138 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.43 (d, *J* = 1.8 Hz, 1H), 7.35 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 4.36 (t, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.3, 168.9, 145.1, 132.2, 126.1, 116.8, 112.2, 110.4, 80.9, 40.8, 31.5, 27.0. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{14}H_{17}BrNO_3S^+$ 358.0107; Found 358.0112.

tert-butyl 3-(6-chloro-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3an**): The target product **3an** (109.8 mg, 70%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 88–90 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27 (d, *J* = 1.7 Hz, 1H), 7.21 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 4.31 (t, *J* = 6.6 Hz, 2H), 2.78 (t, *J* = 6.6 Hz, 2H), 1.32 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.1, 169.1, 146.2, 129.8, 129.0, 124.1, 109.9, 109.7, 80.7, 40.7, 31.4, 27.0. HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{14}H_{17}ClNO_3S^+$ 314.0612; Found 314.0606.

cyclohexyl 3-(2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ao**): The target product **3ao** (135.9 mg, 89%) was synthesized as a colorless oil, and purified by column chromatography

(ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.26–7.13 (m, 4H), 4.68–4.60 (m, 1H), 4.37 (t, *J* = 6.8 Hz, 2H), 4.79–4.71 (t, *J* = 6.8 Hz, 2H), 3.47 (t, *J* = 6.8 Hz, 2H), 2.86 (t, *J* = 6.7 Hz, 2H), 1.71–1.64 (m, 2H), 1.61–1.54 (m, 2H), 1.46–1.14 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.1, 169.4, 146.2, 130.9, 123.9, 123.3, 109.3, 109.1, 72.7, 40.5, 30.7, 30.4, 24.2, 22.6. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{16}H_{20}NO_3S^+$ 306.1158; Found 306.1155.

cyclohexyl 3-((6-methylbenzo[d]oxazol-2-yl)thio)propanoate (**3ap**): The target product **3ap** (110.2 mg, 69%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.45 (d, *J* = 8.1 Hz, 1H), 7.23 (s, 1H), 7.08 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.85–4.78 (m, 1H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 1.90–1.81 (m, 2H), 1.76–1.67 (m, 2H), 1.54–1.23 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 162.6, 151.2, 138.7, 133.3, 124.3, 116.7, 109.2, 72.4, 33.7, 30.6, 26.2, 24.3, 22.7, 20.6. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{17}H_{22}NO_3S^+$ 320.1315; Found 320.1316.

cyclohexyl 3-(5-(tert-butyl)-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3aq**): The target product **3aq** (126.5 mg, 70%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.20 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.18–7.14 (m, 2H), 4.68–4.59 (m, 1H), 4.39 (t, *J* = 6.8 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 1.67–1.53 (m, 4H), 1.46–1.06 (m, 16H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.2, 169.4, 147.8, 144.2, 130.5, 120.5, 108.5, 106.0, 72.5, 40.4, 34.1, 30.8, 30.6, 30.4, 24.2, 22.6. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{20}H_{28}NO_3S^+$ 362.1784; Found 362.1777.

cyclohexyl 3-(4-methyl-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3ar**): The target product **3ar** (57.5 mg, 36%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.20 (d, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 4.82–4.75 (m, 1H), 4.68 (t, *J* = 7.8 Hz, 2H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.63 (s, 3H), 1.85–1.78 (m, 2H), 1.73–1.65 (m, 2H), 1.56–1.26 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.3, 168.7, 146.4, 128.7, 127.0, 123.2, 119.8, 107.5, 72.6, 41.7, 31.6, 30.5, 24.3, 22.6, 16.7. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{17}H_{22}NO_3S^+$ 320.1315; Found 320.1313.

cyclohexyl 3-(5-bromo-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3as**): The target product **3as** (153.7 mg, 80%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.42 (d, *J* = 1.8 Hz, 1H), 7.34 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 4.77–4.68 (m, 1H), 4.37 (t, *J* = 6.6 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 1.82–1.73 (m, 2H), 1.69–1.62 (m, 2H), 1.55–1.21 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.3, 169.2, 145.1, 132.3, 126.1, 116.8, 112.3, 110.4, 72.9, 40.7, 30.6, 30.5, 24.2, 22.7. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{16}H_{19}BrNO_3S^+$ 384.0264; Found 384.0266.

cyclohexyl 3-(6-chloro-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3at**): The target product **3at** (149.5 mg, 88%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27 (d, *J* = 1.6 Hz, 1H), 7.22 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 4.68–4.60 (m, 1H), 4.33 (t, *J* = 6.5 Hz, 2H), 2.87 (t, *J* = 6.5 Hz, 2H), 1.72–1.65 (m, 2H), 1.62–1.55 (m, 2H), 1.46–1.14 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.1, 169.4, 146.2, 129.9, 129.0, 124.1, 109.9, 109.7, 72.8, 40.7, 30.5, 30.4, 24.2, 22.6. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{16}H_{19}ClNO_3S^+$ 340.0769; Found 340.0776.

cyclohexyl 3-(5-chloro-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3au**): The target product **3au** (95.2 mg, 56%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30 (d, *J* = 1.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.20 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.77–4.69 (m, 1H), 4.38 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H), 1.82–1.73 (m, 2H), 1.72–1.63 (m, 2H), 1.52–1.20 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 179.5, 169.2, 144.6, 132.0, 129.8, 123.2, 109.9, 109.5, 72.9, 40.7, 30.6, 30.5, 24.2, 22.7. HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{16}H_{19}ClNO_3S^+$ 340.0769; Found 340.0766.

cyclohexyl 3-(5-methyl-2-thioxobenzo[d]oxazol-3(2H)-yl)propanoate (**3av**): The target product **3av** (138.9 mg, 87%) was synthesized as a white solid, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). mp: 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.19 (d, J = 8.2 Hz, 1H), 7.06–7.00 (m, 2H), 4.76–4.69 (m, 1H), 4.41 (t, J = 6.9 Hz, 2H), 2.91 (t, J = 6.9 Hz, 2H), 2.43 (s, 3H), 1.80–1.72 (m, 2H), 1.69–1.63 (m, 2H), 1.54–1.19 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 179.2, 169.3, 144.4, 134.1, 130.8, 124.0, 109.2, 108.8, 72.7, 40.4, 30.7, 30.5, 24.2, 22.6, 20.5. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{17}H_{22}NO_3S^+$ 320.1315; Found 320.1321.

ethyl 3-(benzo[d]thiazol-2-ylthio)propanoate (**5aa**): The target product **5aa** (88.2 mg, 66%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.48 (dd, J = 8.0, 4.0 Hz, 1H), 7.44–7.39 (m, 1H), 7.34–7.27 (m, 2H), 5.00 (t, J = 4.0, 2H), 4.12 (q, J = 8.0 Hz, 2H), 2,87 (t, J = 8.0 Hz, 2H), 1.21 (t, J = 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 186.6, 169.8, 156.5, 134.2, 127.9, 113.4, 112.0, 104.7, 60.1, 54.9, 41.0, 30.3, 13.1. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{12}H_{13}NO_2S_2^+$ 268.0460; Found 268.0463.

tert-butyl 3-(benzo[d]thiazol-2-ylthio)propanoate (**5ab**): The target product **5ab** (104.9 mg, 71%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 7.6, 1H), 7.18–7.09 (m, 2H), 4.49 (t, J = 7.6, 2H), 2.60 (t, J = 7.6 Hz, 2H), 1.25 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 188.1, 169.0, 140.2, 126.7, 126.0, 123.8, 120.4, 111.5, 80.5, 41.0, 31.4, 27.0. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{14}H_{18}NO_2S_2^+$ 296.0773; Found 296.0771.

cyclohexyl 3-(benzo[d]thiazol-2-ylthio)propanoate (**5ac**): The target product **5ac** (99.7 mg, 62%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.40 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.28–7.18 (m, 2H), 4.71–4.64 (m, 1H), 4.61 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 1.73–1.57 (m, 4H), 1.46–1.1.13 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 188.1, 169.2, 140.2, 126.7, 126.0, 123.8, 120.4, 111.5, 72.5, 41.0, 30.6, 30.4, 24.3, 22.6. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{16}H_{20}NO_2S_2^+$ 322.0930; Found 322.0935.

ethyl 3-((5-chlorobenzo[d]thiazol-2-yl)thio)propanoate (**5ad**): The target product **5ad** (66.4 mg, 44%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.21 (dd, J = 8.4, 1.8 Hz, 1H), 4.58 (t, J = 7.4, 2H), 4.09 (q, J = 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 188.9, 169.6, 141.1, 132.4, 124.9, 124.0, 121.0, 111.7, 60.2, 401.1, 30.2, 13.1. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{12}H_{13}ClNO_2S_2^+$ 302.0071; Found 302.0068.

tert-butyl 3-((5-chlorobenzo[d]thiazol-2-yl)thio)propanoate (**5ae**): The target product **5ae** (100.6 mg, 61%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.35 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.26–7.23 (m, 1H), 4.59 (t, J = 7.4 Hz, 2H), 2.74 (t, J = 7.4 Hz, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 188.1, 169.8, 140.2, 126.7, 126.0, 123.8, 120.4, 111.4, 60.1, 40.9, 30.3, 13.1. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{14}H_{17}ClNO_2S_2^+$ 330.0384; Found 330.0386.

cyclohexyl 3-((5-chlorobenzo[d]thiazol-2-yl)thio)propanoate (**5af**): The target product **5af** (99.7 mg, 62%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.39 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.22–7.17 (m, 1H), 4.74–4.66 (m, 1H), 4.64 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 1.87–1.77 (m, 2H), 1.74–1.65 (m, 2H), 1.52–1.18 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 188.8, 169.1, 141.1, 132.4, 124.9, 124.0, 121.0, 111.7, 72.7, 41.2, 30.6, 30.5, 24.3, 22.7. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{16}H_{19}ClNO_2S_2^+$ 356.0540; Found 356.0536.

tert-butyl 3-((6-methoxybenzo[d]thiazol-2-yl)thio)propanoate (**5ag**): The target product **5ag** (113.9 mg, 70%) was synthesized as a colorless oil, and purified by column chromatography (ethyl acetate/petroleum ether = 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.16 (d, J = 8.8 Hz,

1H), 6.93–6.87 (m, 2H), 4.53 (t, J = 7.4 Hz, 2H), 3.75 (s, 3H), 2.69 (t, J = 7.4 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 186.1, 168.5, 156.0, 133.8, 127.4, 112.9, 111.6, 104.1, 80.0, 54.4, 40.6, 30.9, 26.5. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{15}H_{20}NO_3S_2^+$ 326.0879; Found 326.0871.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal13040658/s1, Characterization data for all products, X-ray diffraction analysis of compound **3ai** and **5ag'**, ^{1}H-NMR and ^{13}C-NMR spectra of all products. Deposition Numbers 2152790 (for **5ag'**), 2152821 (for **3ai**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe "http://www.ccdc.cam.ac.uk/structures".

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