# *N,N′*-Di-Boc-Substituted Thiourea as a Novel and Mild Thioacylating Agent Applicable for the Synthesis of Thiocarbonyl Compounds

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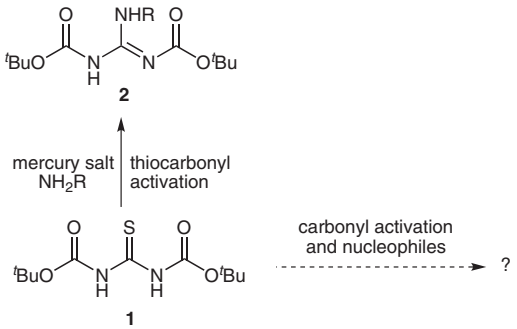
**Abstract:** Stable and readily available *N,N′*-di-Boc-substituted thiourea, when activated with trifluoroacetic acid anhydride, was used as a novel thioacylating agent. Through the thioacylation of nucleophiles, such as amines, alcohols, thiols, sodium benzenethiolate, and sodium malonates with *N,N′*-di-Boc-substituted thiourea, a series of thiocarbonyl compounds were prepared under mild conditions with good chemical selectivity and functional group tolerance.

**Key words:** *N,N′*-di-Boc-substituted thiourea, thioacylating agent, thiocarbonyl

Thiocarbonyl compounds such as thioureas, thiocarbamates, dithiocarbamates, and thioamides, are important compounds and have attracted much attention due to their bioactivities as pesticides and pharmaceutics. For example, a variety of thiourea derivatives and their metal complexes exhibit analgesic,[1] anti-inflammatory,[2] antimicrobial,[3] anticancer,[4] and antifungal activities.[5] Some *O*-alkyl thiocarbamate derivatives demonstrate insecticidal,[6] antimycotic,[7] antiviral[8] and anti-HIV[9] activities. Moreover, thiocarbonyl compounds are important building blocks in the synthesis of heterocycles. For example, 2-amino-1,3-thiazoles can be readily prepared through the condensation of thioureas with α-halocarbonyl compounds.[10] Likewise, arylthioureas can be transformed into benzothiazoles upon treatment with bromine.[11] Other examples include the synthesis of thiazoline from thioamide and dithiocarbamates. Therefore, the synthesis of novel thiocarbonyl compounds and development of new methods for their preparation are of great importance in the search for bioactive molecules as well as in synthetic chemistry.

To date, one of the most common methods for the preparation of such thiocarbonyl compounds involves the reaction of nucleophiles, such as amines, alcohols, thiophenols, and carbanions, with diverse thioacylating agents including thiophosgene,[12] carbon disulfide,[13] 1,1-thiocarbonyldiimidazole,[14] thioacyl-*N*-phthalimide[15] and thiocarbonylbenzotriazoles.[16] However, these thioacylating agents sometimes suffer from some drawbacks and limitations: difficult preparation, instability or harsh reaction conditions such as high temperature, long reaction time, the use of a strong acid or base and noxious reagents such as hydrogen sulfide and carbon disulfide. Therefore, the development of novel, mild, environmentally benign, and especially functional-group-tolerant thioacylating agents is still needed.

*N,N′*-Di-Boc-substituted thiourea **1** is a commonly used reagent in the preparation of guanidine derivatives **2** when its thiocarbonyl is selectively activated by mercury salt and coupled with amines (Scheme 1).[17] However, its synthetic applications in other aspects are seldom reported, especially in the selective activation of its carbonyl group. The activation of the carbonyl group of an amide toward nucleophilic attack has been well studied by adding some activators such as triflic anhydride ($Tf_2O$) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP). These methods have been used extensively in the synthesis of esters, amidines, thiazolines, thioamides, $^{18}O$-labeled amides and so on.[18] Our interest is focused in the selective activation of the carbonyl groups of **1** and its further transformation with nucleophiles to prepare a series of novel, potentially bioactive nitrogen-containing compounds. Herein we report that *N,N′*-di-Boc-substituted thiourea **1** can be used as a novel and mild thioacylating agent applicable for the synthesis of thiocarbonyl compounds.[19]




**Scheme 1** Preparation of guanidine derivatives **2** from *N,N′*-di-Boc-substituted thiourea **1**

Similar to the activation of the carbonyl group of an amide, we activated the carbonyl group of the carbamate unit of **1** with $Tf_2O$ as an activator and pyridine as a base in THF at 0 °C for one hour. The color of the reaction mixture turned to yellow soon after the addition of $Tf_2O$. TLC

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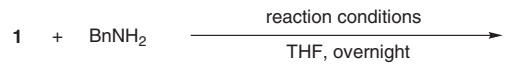
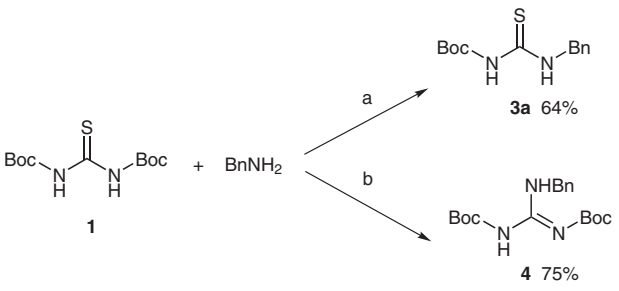
**Table 1** Optimization of the Reaction Conditions of **1** with $BnNH_2$




| Entry | Reaction conditions | Yield (%)[a] |
|---|---|---|
| 1 | BOP (1.1 equiv), pyridine (1.2 equiv), 0 °C; then $BnNH_2$ (1.1 equiv), r.t. | 52 |
| 2 | MsCl (1.1 equiv), pyridine (1.2 equiv), 0 °C; then $BnNH_2$ (1.1 equiv), r.t. | 60 |
| 3 | $Ac_2O$ (1.1 equiv), pyridine (1.2 equiv), 0 °C; then $BnNH_2$ (1.1 equiv), r.t. | 58 |
| 4 | TFAA (1.1 equiv), pyridine (1.2 equiv), 0 °C; then $BnNH_2$ (1.1 equiv), r.t. | 78 |
| 5 | $Tf_2O$ (1.1 equiv), DIPEA (1.2 equiv), 0 °C; then $BnNH_2$ (1.1 equiv), r.t. | 25 |
| 6 | $Tf_2O$ (1.1 equiv), NMM (1.2 equiv), 0 °C; then $BnNH_2$ (1.1 equiv), r.t. | 32 |
| 7 | TFAA (1.1 equiv), NaH (1.2 equiv), 0 °C; then $BnNH_2$ (1.1 equiv), r.t. | 91 |

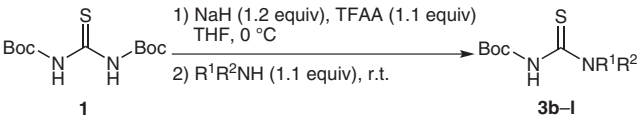
[a] Isolated yield.

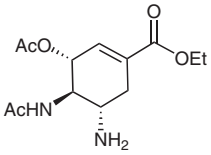
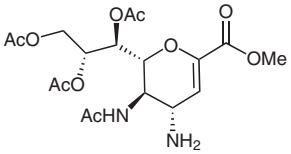
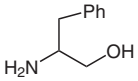
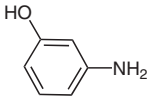
demonstrated that an intermediate was formed, but its isolation by chromatography failed possibly due to its instability. This intermediate can be trapped with $BnNH_2$ and converted into the thiourea **3a** in 64% yield, whose structure was determined by spectroscopic data. In contrast, the coupling of **1** with benzylamine alone gives exclusively the corresponding guanidine **4** in 75% yield (Scheme 2). This unusual but useful result, to the best of our knowledge, provides the first example of applying **1** as a thioacylating agent of amine and a novel access to unsymmetrical thioureas. Further efforts were made to adjust the reaction variants such as activator, base, reaction temperature, and the amount of amine to optimize the reaction conditions. As shown in Table 1, when other activators such as BOP, MsCl, and $Ac_2O$ were used, the yields were lower (entries 1–3), and TFAA (trifluoacetic acid anhydride) as an activator afforded a little higher yield (entry 4). Meanwhile, when other organic base such as DIPEA (*N*,*N*-diisopropylethylamine) or NMM (*N*-methylmorpholine) was used, **3a** was formed in lower yields along with many other unidentified by-products. To our




**Scheme 2** The reaction of **1** with $BnNH_2$ under different reaction conditions. *Reagents and conditions*: (a) $Tf_2O$ (1.1 equiv), pyridine (1.2 equiv), THF, 0 °C, then r.t. (b) THF, r.t.

**Table 2** Synthesis of Thioureas via the Reaction of **1** with Amines

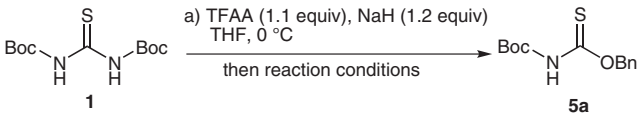



| Entry | $R^1R^2NH$ | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | *i*-$PrNH_2$ | **3b** | 94 |
| 2 |  | **3c** | 78 |
| 3 |  | **3d** | 88 |
| 4 |  | **3e** | 82 |
| 5 |  | **3f** | 90 |
| 6 |  | **3g** | 92 |
| 7 | $(n\text{-Bu})_2NH$ | **3h** | 0 |
| 8 | $PhNH_2$ | **3i** | 91 |
| 9 |  | **3j** | 81 |
| 10 | PhNHMe | **3k** | 0 |
| 11 | $PhNHNH_2$ | **3l** | 85 |

[a] Isolated yield.

delight, when NaH was used as a base to deprotonate and TFFA as an activator, the reaction yield was increased to 91% (entry 7). Based on the results, we concluded that TFAA (1.1 equiv) and NaH (1.2 equiv) at 0 °C, then $BnNH_2$ (1.1 equiv) at room temperature in THF solvent are suitable conditions for this conversion. The scope of the reaction was then examined with different amines, and the results are summarized in Table 2. As can be seen, the steric hindrance of amines influenced the reaction obviously. The reaction of primary amines and cyclic five- or six-membered-ring amines proceeded well with **1** affording the desired compounds **3b–g** in good to excellent yields (entries 1–6). In contrast, more hindered acyclic secondary amines did not lead to the desired products under these conditions (entries 7 and 10). Less nucleophilic primary arylamines also afforded the desired products in excellent yields (entries 8 and 9). With aminophenol, only the thiourea product was isolated and no thiocarbamate was observed (entry 9). Reaction of **1** with phenylhydrazine afforded exclusively the thiohydrozone product **3l**

**Table 3** Optimization of the Reaction Conditions of **1** with BnOH




| Entry | Reaction conditions | Yield (%)[a] |
|---|---|---|
| 1 | BnOH (1.1 equiv), r.t. | 40 |
| 2 | BnOH (1.5 equiv), r.t. | 53 |
| 3 | BnOH (2.0 equiv), r.t. | 55 |
| 4 | BnOH (1.5 equiv), NMM (1.0 equiv), r.t. | 60 |
| 5 | BnOH (1.5 equiv), DIPEA (1.0 equiv), r.t. | 63 |
| 6 | BnOH (1.5 equiv), DMAP (1.0 equiv), r.t. | 75 |

[a] Isolated yield.

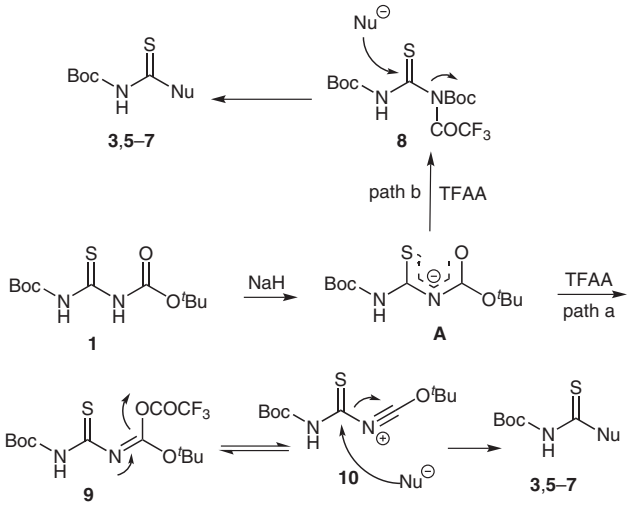
(entry 11). It is worth noting that under these relatively mild reaction conditions, functional groups such as amide, ester, enol ether, and hydroxy are tolerated, which renders the ready access of polyfunctionalized thioureas. Importantly, under these conditions, no epimerization of compounds **3c** and **3d** was observed based on $^1$H NMR spectroscopy (entries 2, 3).

Encouraged by the successful thioacylation of amines, we studied the thioacylation of alcohols with **1** to synthesize *O*-alkyl thiocarbamates. Under the same reaction conditions as for $BnNH_2$, BnOH (1.1 equiv) reacted with **1** providing *O*-alkyl thiocarbamate **5a** in only 40% yield (Table 3, entry 1). When the amount of BnOH was increased to 1.5 equivalents, the yield was improved to 53% (entry 2). More BnOH (2.0 equiv) did not lead to higher yield (entry 3). Addition of organic base DIPEA or NMM as an additive gave rise to higher yields (entries 4, 5). To our delight, when 1.0 equivalent of DMAP [4-(dimethylamino)pyridine] was added, the yield was improved remarkably to 75% (entry 6). DMAP in this coupling might act as a base to activate the alcohol and as a catalyst to activate the thiocarbonyl group.

On the basis of the above results, we concluded that TFAA (1.1 equiv) and NaH (1.2 equiv) at 0 °C, then BnOH (1. 5 equiv) and DMAP (1.0 equiv) at room temperature in THF are suitable conditions for the thioacylation of BnOH. The scope of the reaction was then explored with various alcohols. As can be seen in Table 4, all primary alcohols can be thioacylated to provide the corresponding thiocarbamates in acceptable yields (entries 1–6). Functional groups such as amide, ester, azide, acetal, and nucleobase (uracil) were tolerated (entries 1–6). It is worth noting that the primary alcohol can be selectively thioacylated in the presence of secondary alcohol and no dithioacylated product was observed (entry 6). Due to the acidity of the phenolic hydroxy group, salicyl alcohol was not converted into **5h** (entry 7) under these conditions. Propan-2-ol, a small, slightly sterically hindered secondary alcohol, was thioacylated in lower yield (entry 8), while 1-phenylethanol, a more sterically hindered secondary alcohol, did not lead to the desired product (entry 9).

The thioacylation of thiols was also investigated under the same reaction conditions as used for the amines. Equimolar amounts (1.1 equiv) of $n$-$C_4H_9SH$ and $n$-$C_{12}H_{25}SH$ reacted with **1** providing dithiocarbamate **6a** and **6b** in 78% and 75% yield, respectively (Table 5, entries 1, 2). Possibly owing to their lower nucleophilicity, thiophenols did not react with **1** to provide the desired dithiocarbamates under the same conditions, but their sodium salts reacted well with **1** giving the corresponding dithiocarbamates **6c**–**e** in excellent yield (entries 1–3). The substrate carrying an electron-donating group on the phenyl ring gave slightly higher yield than those with an electron-withdrawing one (**6d** > **6c** > **6e**). Similarly, sodium salt of dimethyl malonate and diethyl malonate as nucleophiles gave the corresponding thioamides in moderate yield (entries 6 and 7). Nevertheless, under the same conditions, when the nucleophile was sodium ethyl acetoacetate, no desired thioamide **7c** was formed (entry 8). The real reason is not clear at present, but may be attributable to the nucleophilicity of sodium acetoacetate being lower than that of sodium malonate.

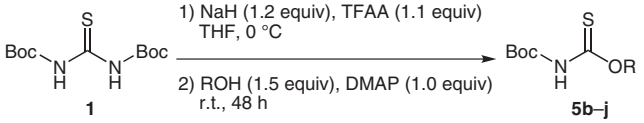
Based on the above results, we propose a possible mechanism for these reactions of thioacylation of nucleophiles with **1** (Scheme 3). Upon deprotonation of **1** by NaH gives rise to ambident ion **A**. TFAA is a hard acid, accordingly, it attacks **A** preferentially at the oxygen or nitrogen terminus, not at sulfur forming O-acylated intermediate **8** or N-acylated intermediate **9**, which was further converted into intermediate **10**. The addition of nucleophiles, such as amines, alcohols, thiols, thiophenols, and activated methylenes, to the thiocarbonyl group of **8** and **10** provides thiocarbonyl compounds **3**, **5**, **6**, and **7**.

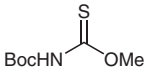
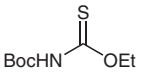
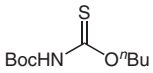
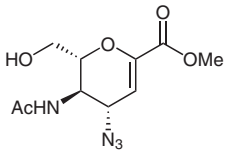
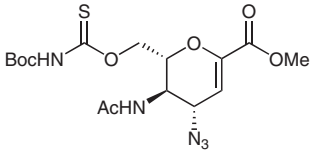
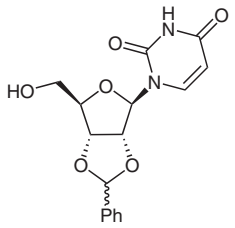
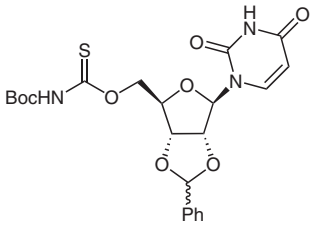
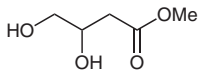
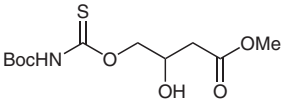
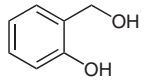
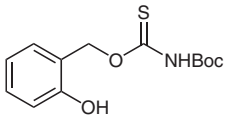
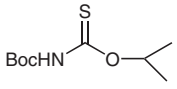
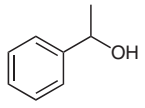
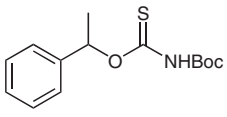



**Scheme 3** Proposed mechanism for the formation of thiocarbonyl compounds

In summary, we have reported *N*,*N*′-di-Boc-substituted thiourea **1**, when activated with TFAA, as a novel thio-

**Table 4** Synthesis of Thiocarbamates via the Reaction of **1** with Alcohols

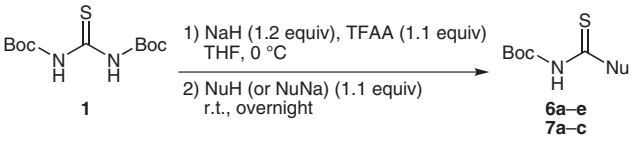


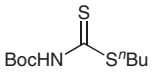
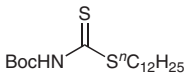
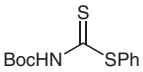
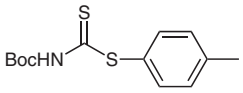
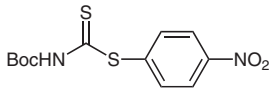
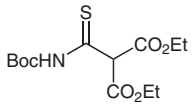
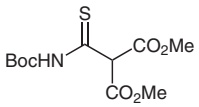
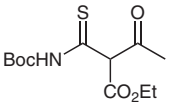

| Entry | ROH | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | MeOH |  **5b** | 71 |
| 2 | EtOH |  **5c** | 68 |
| 3 | *n*-BuOH |  **5d** | 76 |
| 4 |  |  **5e** | 66 |
| 5 |  |  **5f** | 62 |
| 6 |  |  **5g** | 65 |
| 7 |  |  **5h** | 0 |
| 8 | *i*-PrOH |  **5i** | 45 |
| 9 |  |  **5j** | 0 |

[a] Isolated yield.

acylating agent possessing the advantage of stability and ready availability. Through the thioacylation of nucleophiles, such as amines, alcohols, thiols, sodium benzenethiolate, and sodium malonates with **1**, thiocarbonyl compounds (thioureas, thiocarbamates, dithiocarbamates, and thioamide) were prepared under mild conditions with good chemical selectivity and functional group tolerance. In addition, we have proposed a possible mechanism for this thioacylation which might be useful for further design of other novel thioacylating agents. Further studies on the selective activation of the carbonyl or thiocarbonyl group of **3**, **5**, and **6** to prepare novel nitrogen- or sulfur-contain-

**Table 5** Synthesis of Dithiocarbamates and Thioamides




| Entry | NuH (or NuNa) | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | *n*-BuSH |  **6a** | 78 |
| 2 | *n*-$C_{12}H_{25}SH$ |  **6b** | 75 |
| 3 | PhSNa |  **6c** | 92 |
| 4 | 4-$MeC_6H_4SNa$ |  **6d** | 96 |
| 5 | 4-$MeC_6H_4SNa$ |  **6e** | 89 |
| 6 | $NaCH(CO_2Et)_2$ |  **7a** | 64 |
| 7 | $NaCH(CO_2Me)_2$ |  **7b** | 67 |
| 8 | $NaCH(COMe)(CO_2Et)$ |  **7c** | 0 |

[a] Isolated yield.

ing heterocyclic compounds are currently under way in our laboratory and the results will be reported in due course.

IR spectra were recorded with a Perkin-Elmer1 983 or a Shimadzu IR-440 spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded with an AMX-300, DPX-300, Gemini-2000, or IN-OVA-600 spectrometer with TMS as the internal standard. Mass spectra were taken with a Mariner (PE, for ESI), HP5973N or HP5989A instrument. HRMS (EI or ESI) spectra were obtained with a Kratos CONCEPT 1H or Bruker APEXIII 7.0 TESLA mass spectrometer. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. Elemental analyses were carried out in a Heraeus CHN-O-RAPID Elemental Analyzer. Melting points were determined on X-4 Mel-Temp apparatus and were uncorrected. Flash column chromatography was performed on silica gel H (1040 μm) with a PE–EtOAc or EtOAc–EtOH system as eluent.

**Reaction of *N,N′*-Di-Boc-Substituted Thiourea 1 with Amines and Thiols; General Procedure**

To a mixture of **1** (276 mg, 1 mmol) and THF (20 mL) was added 60% NaH (48 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, then TFAA (185 μL, 1.1 mmol) was added and the stirring continued for an additional 1 h. Then, amine or thiol (1.1 mmol) was added and the resulting reaction was stirred at r.t. overnight. $H_2O$ (10 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to afford **3**, **6a**, or **6b** (Tables 2, 5).

**3a**

Yield: 242 mg (91%); white solid; mp 147–148 °C.

IR (film): 3446, 3172, 2971, 1668, 1534, 1250, 1206, 1150, 964, 918, 750 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1 H), 7.94 (s, 1 H), 7.38–7.29 (m, 5 H), 4.86 (d, *J* = 5.6 Hz, 2 H), 1.47 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 179.8, 151.8, 136.5, 128.8, 128.0, 127.9, 83.8, 49.5, 28.1.

ESI-MS: *m*/*z* = 265 (M – H).

Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S, 12.04. Found: C, 58.44; H, 6.86; N, 10.64; S, 12.33.

**3b**

Yield: 204.9 mg (94%); syrup.

IR (film): 3412, 3168, 2973, 1626, 1530, 1244, 1138, 953, 910, 747 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1 H), 7.84 (s, 1 H), 4.53–4.48 (m, 1 H), 1.47 (s, 9 H), 1.28 (d, *J* = 6.4 Hz, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 178.2, 151.9, 83.4, 47.4, 28.0, 21.8.

ESI-MS: *m*/*z* = 219 (M + H).

Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 49.51; H, 8.31; N, 12.83; S, 14.69. Found: C, 49.64; H, 8.25; N, 12.95; S, 14.47.

**3c**

Yield: 345.7 mg (78%); white solid; mp 104–105 °C; $[\alpha]_D^{20}$ +17.6 (*c* 1.0, $CHCl_3$).

IR (film): 3485, 2931, 1725, 1719, 1633, 1557, 1433, 1297, 1031, 774, 659 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.89 (d, *J* = 8.4 Hz, 1 H), 7.94 (s, 1 H), 6.67 (s, 1 H), 6.32 (d, *J* = 8.4 Hz, 1 H), 5.60 (d, *J* = 8.8 Hz, 1 H), 4.87–4.84 (m, 1 H), 4.41–4.36 (m, 1 H), 4.24–4.18 (m, 2 H), 3.00 (dd, *J* = 6.0, 18.0 Hz, 1 H), 2.49–2.42 (m, 1 H), 2.09 (s, 3 H), 1.93 (s, 3 H), 1.48 (s, 9 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 181.1, 170.9, 170.8, 165.2, 151.3, 135.3, 130.7, 84.4, 71.9, 61.3, 53.9, 53.0, 30.4, 28.0, 23.3, 21.0, 20.9, 14.2.

ESI-MS: *m*/*z* = 444 (M + H).

Anal. Calcd for $C_{19}H_{29}N_3O_7S$: C, 51.45; H, 6.59; N, 9.47; S, 7.23. Found: C, 51.67; H, 6.33; N, 9.50; S, 7.10.

**3d**

Yield: 518.5 mg (88%); syrup; $[\alpha]_D^{20}$ +23.4 (*c* 1.0, $CHCl_3$).

IR (film): 3479, 2950, 1722, 1705, 1703, 1638, 1543, 1401, 1257, 1062, 783, 644 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.79 (d, *J* = 8.8 Hz, 1 H), 7.80 (s, 1 H), 6.06 (d, *J* = 8.8 Hz, 1 H), 5.96 (s, 1 H), 5.55 (t, *J* = 8.8 Hz, 1 H), 5.46 (d, *J* = 4.0 Hz, 1 H), 5.29 (m, 1 H), 4.65 (d, *J* = 12.4 Hz, 1 H), 4.40–4.33 (m, 2 H), 4.17–4.07 (m, 2 H), 3.77 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 1.90 (s, 3 H), 1.46 (s, 9 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 181.2, 171.2, 171.1, 170.6, 170.2, 161.6, 151.3, 145.2, 109.0, 84.5, 71.4, 67.7, 62.2, 60.4, 54.0, 52.5, 47.4, 28.0, 23.2, 21.0, 20.9, 14.2.

ESI-MS: *m*/*z* = 590 (M + H).

Anal. Calcd for $C_{24}H_{35}N_3O_{12}S$: C, 48.89; H, 5.98; N, 7.13; S, 5.44. Found: C, 48.76; H, 5.39; N, 7.24; S, 5.69.

**3e**

Yield: 254.3 mg (82%); syrup.

IR (film): 3458, 2932, 1710, 1635, 1569, 1427, 1255, 1038, 771, 637 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 10.00 (d, *J* = 7.6 Hz, 1 H), 8.17 (s, 1 H), 7.30–7.20 (m, 5 H), 4.74–4.69 (m, 1 H), 3.76 (dd, *J* = 11.2, 4.0 Hz, 1 H), 3.65 (dd, *J* = 11.2, 4.0 Hz, 1 H), 3.09 (dd, *J* = 13.2, 5.6 Hz, 1 H), 2.94 (dd, *J* = 13.2, 5.6 Hz, 1 H), 1.48 (s, 9 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 179.5, 151.8, 137.5, 129.4, 128.6, 126.7, 83.7, 62.1, 58.1, 36.2, 28.0.

ESI-MS: *m*/*z* = 309 (M – H).

Anal. Calcd for $C_{15}H_{22}N_2O_3S$: C, 58.04; H, 7.14; N, 9.02; S, 10.33. Found: C, 57.90; H, 7.29; N, 9.29; S, 10.18.

**3f**

Yield: 221.5 mg (90%); white solid; mp 104–105 °C.

IR (film): 3412, 2921, 1626, 1542, 1457, 1235, 1025, 777, 645 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H), 3.88 (m, 4 H), 3.79 (m, 4 H), 1.46 (s, 9 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 180.1, 149.2, 82.7, 66.2, 52.1, 28.2.

ESI-MS: *m*/*z* = 245 (M–H).

Anal. Calcd for $C_{10}H_{18}N_2O_3S$: C, 48.76; H, 7.37; N, 11.37; S, 13.02. Found: C, 48.52; H, 7.39; N, 11.49; S, 13.28.

**3g**

Yield: 211.7 mg (92%); white solid; mp 117–118 °C.

IR (film): 3431, 2924, 1720, 1648, 1537, 1444, 1025, 783, 642 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.26 (s, 1 H), 3.79 (t, *J* = 6.4 Hz, 2 H), 3.66 (t, *J* = 6.0 Hz, 2 H), 1.96 (m, 4 H), 1.46 (s, 9 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.6, 149.4, 82.2, 54.2, 52.4, 28.1.

ESI-MS: *m*/*z* = 229 (M – H).

Anal. Calcd for $C_{10}H_{18}N_2O_2S$: C, 52.15; H, 7.88; N, 12.16; S, 13.92. Found: C, 52.24; H, 7.79; N, 12.33; S, 13.85.

**3i**

Yield: 229.4 mg (91%); white solid; mp 135–136 °C.

IR (film): 3422, 2926, 1635, 1564, 1459, 1217, 1060, 745, 641 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 11.50 (s, 1 H), 8.04 (s, 1 H), 7.64 (d, *J* = 5.7 Hz, 2 H), 7.39 (t, *J* = 5.7 Hz, 2 H), 7.27–7.24 (m, 1 H), 1.54 (s, 9 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.4, 151.9, 137.8, 128.8, 126.7, 124.3, 84.3, 28.0.

ESI-MS: *m*/*z* = 253 (M + H).

Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10; S, 12.71. Found: C, 57.07; H, 6.45; N, 11.24; S, 12.88.

**3j**

Yield: 217.2 mg (81%); white solid; mp 120–122 °C.

IR (film): 3423, 2947, 1639, 1554, 1421, 1235, 1022, 748, 645 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 11.50 (s, 1 H), 8.07 (s, 1 H), 7.35 (s, 1 H), 7.25–7.19 (m, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.72 (dd, *J* = 8.4, 2.4 Hz, 1 H), 1.52 (s, 9 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.2, 156.0, 151.9, 138.7, 129.8, 116.4, 114.0, 111.5, 84.5, 28.0.

ESI-MS: *m*/*z* = 269 (M + H).

Anal. Calcd for $C_{12}H_{17}N_3O_2S$: C, 53.71; H, 6.01; N, 10.44; S, 11.95. Found: C, 53.94; H, 6.28; N, 10.27; S, 11.82.

**3l**

Yield: 227 mg (85%); white solid; mp 143–145 °C.

IR (film): 3417, 2938, 1647, 1558, 1432, 1222, 1054, 743, 649 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 11.15 (s, 1 H), 8.00 (s, 1 H), 7.29–7.25 (m, 2 H), 6.97 (t, *J* = 7.2 Hz, 1 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 1.54 (s, 9 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.8, 151.7, 146.5, 129.3, 122.1, 114.5, 84.4, 28.0.

ESI-MS: *m*/*z* = 266 (M – H).

Anal. Calcd for $C_{12}H_{17}N_3O_2S$: C, 53.91; H, 6.41; N, 15.72; S, 11.99. Found: C, 53.88; H, 6.65; N, 15.84; S, 11.84.

**6a**

Yield: 194.3 mg (78%); syrup.

IR (film): 3471, 3141, 2934, 1744, 1493, 1230, 845, 751 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 1 H), 3.25 (t, *J* = 7.8 Hz, 2 H), 1.75–1.70 (m, 2 H), 1.49 (s, 9H), 1.51–1.46 (m, 2 H), 0.95 (t, *J* = 7.2 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 203.9, 149.2, 83.7, 36.7, 29.3, 28.0, 22.2, 13.6.

ESI-MS: *m*/*z* = 248 (M – H).

Anal. Calcd for $C_6H_{10}NO_2S$: C, 48.16; H, 7.68; N, 5.62; S, 25.71. Found: C, 48.27; H, 7.59; N, 5.57; S, 25.69.

**6b**

Yield: 270.9 mg (75%); syrup.

IR (film): 3465, 3138, 2951, 1746, 1466, 1242, 839, 746 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 3.23 (t, *J* = 7.8 Hz, 2 H), 1.76–1.71 (m, 2 H), 1.52 (s, 9 H), 1.46–1.41 (m, 2 H), 1.37–1.25 (m, 16 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 203.9, 149.2, 83.7, 37.0, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.0, 27.3, 22.7, 14.1.

ESI-MS: *m*/*z* = 360 (M – H).

Anal. Calcd for $C_6H_{10}NO_2S$: C, 59.79; H, 9.76; N, 3.87; S, 17.73. Found: C, 59.65; H, 9.54; N, 3.91; S, 17.88.

**Reaction of 1 with Alcohols; General Procedure**

To a mixture of **1** (276 mg, 1 mmol) and THF (20 mL) was added 60% NaH (48 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, then TFAA (185 μL, 1.1 mmol) was added and the stirring continued for an additional 1 h. Then alcohol (162 mg, 1.5 mmol) and DMAP (122 mg, 1 mol) were added and the resulting reaction was stirred at r.t. for 1 d. $H_2O$ (10 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were

dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to afford compound **5** (Table 4).

**5a**

Yield: 200.3 mg (75%); white solid; mp 143–145 °C.

IR (film): 3442, 3168, 2974, 1674, 1541, 1251, 1066, 644 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.45–7.34 (m, 5 H), 5.57 (s, 2 H), 1.48 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 188.3, 147.9, 134.8, 128.7, 128.6, 128.3, 83.1, 73.7, 28.1.

ESI-MS: *m*/*z* = 266 (M – H).

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24; S, 11.99. Found: C, 58.30; H, 6.27; N, 5.48; S, 12.07.

**5b**

Yield: 135.7 mg (71%); syrup.

IR (film): 3421, 3155, 2969, 1633, 1518, 1233, 1120, 943, 767 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 4.09 (s, 3 H), 1.45 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 189.9, 147.6, 83.0, 59.0, 27.9.

ESI-MS: *m*/*z* = 190 (M – H).

Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32; S, 16.77. Found: C, 43.85; H, 6.69; N, 7.43; S, 16.84.

**5c**

Yield: 139.5 mg (68%); syrup.

IR (film): 3439, 3164, 2958, 1630, 1517, 1238, 1129, 953, 766 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 4.61 (m, 2 H), 1.49 (s, 9 H), 1.42 (t, *J* = 4.8 Hz, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 189.0, 147.6, 82.9, 68.9, 27.9, 13.7.

ESI-MS: *m*/*z* = 204 (M – H).

Anal. Calcd for $C_7H_{13}NO_3S$: C, 46.81; H, 7.37; N, 6.82; S, 15.62. Found: C, 46.96; H, 7.28; N, 6.91; S, 15.55.

**5d**

Yield: 177.1 mg (76%); syrup.

IR (film): 3441, 3173, 2966, 1642, 1518, 1240, 1131, 956, 764 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 4.53 (t, *J* = 6.8 Hz, 2 H), 1.82–1.74 (m, 2 H), 1.49 (s, 9 H), 1.48–1.40 (m, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 188.9, 147.4, 82.6, 72.6, 30.0, 27.8, 18.8, 13.5.

ESI-MS: *m*/*z* = 232 (M – H).

Anal. Calcd for $C_{10}H_{19}NO_3S$: C, 51.48; H, 8.21; N, 6.00; S, 13.74. Found: C, 51.31; H, 8.49; N, 6.21; S, 13.78.

**5e**

Yield: 283.1 mg (66%); syrup; $[\alpha]_D^{20}$ –10.8 (*c* 1.0, $CHCl_3$).

IR (film): 3465, 2957, 1721, 1704, 1700, 1642, 1518, 1128, 949, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.15 (d, *J* = 8.4 Hz, 1 H), 5.69 (t, *J* = 8.0 Hz, 1 H), 4.19 (m, 1 H), 3.92 (d, *J* = 11.2 Hz, 2 H), 3.81 (s, 3 H), 3.76–3.70 (m, 2 H), 2.05 (s, 3 H), 1.51 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 188.8, 171.1, 170.2, 151.2, 147.5, 109.4, 82.9, 71.6, 67.5, 53.8, 52.4, 51.7, 27.9.

ESI-MS: *m*/*z* = 428 (M – H).

Anal. Calcd for $C_{16}H_{23}N_5O_7S$: C, 44.75; H, 5.40; N, 16.31; S, 7.47. Found: C, 44.64; H, 5.29; N, 16.38; S, 7.57.

**5f**

Yield: 304.5 mg (62%); syrup; $[\alpha]_D^{20}$ +7.9 (*c* 1.0, $CHCl_3$).

IR (film): 3480, 2935, 1726, 1718, 1635, 1559, 1430, 1289, 1034, 766 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.52–7.41 (m, 5 H), 7.35–7.33 (m, 1 H), 6.12 (s, 1/3 H), 6.04 (s, 2/3 H), 5.77–5.74 (m, 1 H), 5.66 (d, *J* = 3.0 Hz, 1 H), 5.22 (dd, *J* = 3.0, 7.2 Hz, 2/3 H), 5.16 (dd, *J* = 3.0, 7.2 Hz, 1/3 H), 5.14 (dd, *J* = 3.6, 6.6 Hz, 1/3 H), 5.10 (dd, *J* = 3.6, 6.6 Hz, 2/3 H), 4.47 (m, 2/3 H), 4.34 (m, 1/3 H), 4.02–3.97 (m, 1 H), 3.95–3.82 (m, 1 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 163.2, 150.3, 142.1, 136.2, 129.7, 128.4, 128.3, 126.9, 126.8, 106.5 (2/3 C), 102.6 (1/3 C), 102.0 (1/3 C), 101.7 (2/3 C), 91.3 (2/3 C), 90.4 (1/3 C), 86.4 (2/3 C), 84.4 (2/3 C), 83.9 (1/3 C), 83.0 (1/3 C), 81.9 (2/3 C), 80.1 (1/3 C), 61.4 (1/3 C), 61.3 (2/3 C).

ESI-MS: *m*/*z* = 490 (M – H).

Anal. Calcd for $C_{22}H_{25}N_3O_8S$: C, 53.76, H, 5.13; N, 8.55; S, 6.52. Found: C, 53.70; H, 5.24; N, 8.59; S, 6.48.

**5g**

Yield: 190.5 mg (65%); syrup.

IR (film): 3443, 2924, 1730, 1642, 1520, 1428, 1126, 1044, 775 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 4.44 (m, 2 H), 3.78 (t, *J* = 7.6 Hz, 1 H), 3.68 (s, 3 H), 2.62 (t, *J* = 5.6 Hz, 2 H), 1.49 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 188.9, 172.2, 148.0, 83.0, 74.9, 66.2, 52.2, 37.9, 28.2.

ESI-MS: *m*/*z* = 292 (M – H).

Anal. Calcd for $C_9H_{17}NO_3S$: C, 45.04; H, 6.53; N, 4.77; S, 10.93. Found: C, 45.27; H, 6.61; N, 4.60; S, 10.80.

**5i**

Yield: 98.6 mg (45%); syrup.

IR (film): 3432, 3178, 2967, 1670, 1520, 1241, 1055, 659 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 5.57 (t, *J* = 6.0 Hz, 1 H), 1.49 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 188.2, 147.8, 82.6, 67.9, 27.9, 21.2.

ESI-MS: *m*/*z* = 218 (M – H).

Anal. Calcd for $C_9H_{17}NO_3S$: C, 49.29; H, 7.81; N, 6.39; S, 14.62. Found: C, 49.41; H, 7.74; N, 6.44; S, 14.81.

**Reaction of 1 with Thiophenols and Activated Methylenes; General Procedure**

To a mixture of **1** (276 mg, 1 mmol) and THF (20 mL) was added 60% NaH (48 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, then TFAA (185 μL, 1.1 mmol) was added and the stirring continued for an additional 1 h. Then, sodium benzenethiolate or sodium malonate (2 mmol) in anhyd THF (5 mL) was added and the resulting reaction was stirred at r.t. overnight. $H_2O$ (10 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to afford **6c–e** and **7** (Table 5).

**6c**

Yield: 247.5 mg (92%); yellow solid; mp 127–129 °C.

IR (film): 3466, 3137, 2941, 1740, 1488, 1226, 1145, 1003, 749 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.02 (s, 1 H), 7.51–7.46 (m, 5 H), 1.56 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 205.9, 149.3, 136.0, 131.1, 130.3, 129.4, 84.1, 28.0.

ESI-MS: *m*/*z* = 268 (M – H).

Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.20; S, 23.81. Found: C, 53.67; H, 5.49; N, 4.99; S, 23.74.

**6d**

Yield: 271.7 mg (96%); syrup.

IR (film): 3460, 3132, 2940, 1735, 1479, 1224, 1142, 1011, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 2.46 (s, 3 H), 1.60 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 204.1, 149.1, 140.6, 135.6, 130.1, 127.5, 83.8, 27.8, 21.3.

ESI-MS: *m*/*z* = 282 (M – H).

Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 55.09; H, 6.05; N, 4.94; S, 22.63. Found: C, 55.21; H, 6.17; N, 4.87; S, 22.55.

**6e**

Yield: 279.5 mg (89%); syrup.

IR (film): 3475, 3148, 2936, 1749, 1487, 1143, 1053, 774 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.12 (s, 1 H), 7.99 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 1.62 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 207.8, 151.2, 142.7, 137.9, 132.4, 128.5, 84.9, 28.6.

ESI-MS: *m*/*z* = 313 (M – H).

Anal. Calcd for $C_{12}H_{14}N_2O_4S_2$: C, 45.85; H, 4.49; N, 8.91; S, 20.40. Found: C, 45.79; H, 4.38; N, 8.95; S, 20.28.

**7a**

Yield: 204.1 (64%); syrup.

IR (film): 3451, 2944, 1745, 1723, 1638, 1543, 1420, 1279, 1022, 756 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 5.40 (s, 1 H), 4.25 (q, *J* = 7.2 Hz, 4 H), 1.49 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 6 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 164.9, 149.4, 149.0, 110.2, 84.1, 62.3, 28.0, 14.0.

ESI-MS: *m*/*z* = 320 (M + H, 10), 121 (11).

HRMS: *m*/*z* calcd for $C_{13}H_{21}NO_6S$: 319.1090; found: 319.1077.

**7b**

Yield: 195.2 mg (67%); syrup.

IR (film): 3455, 2947, 1746, 1720, 1633, 1540, 1413, 1274, 1016, 748 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 5.36 (s, 1 H), 3.88 (s, 3 H), 1.48 (s, 9 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 165.2, 149.9, 149.2, 109.5, 84.1, 61.7, 28.2.

ESI-MS: *m*/*z* = 292 (M + H).

Anal. Calcd for $C_{11}H_{17}NO_6S$: C, 45.35; H, 5.88; N, 4.81; S, 11.01. Found: C, 45.47; H, 5.76; N, 4.64; S, 11.14.

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