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Domino Reaction of α-Acetyl-α-carbamoyl Ketene Dithioacetals with Vilsmeier Reagents: A Novel and Efficient Synthesis of 4-Halogenated 2(1*H*)-Pyridinones

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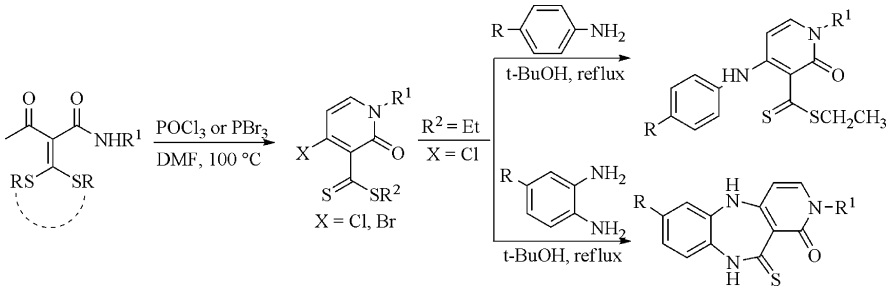

A novel and efficient route to 4-halogenated *N*-substituted 2(1*H*)-pyridinones has been developed via a one-pot domino process of readily available α-acetyl-α-carbamoyl ketene dithioacetals with Vilsmeier reagents. These 4-halogenated-2(1*H*)-pyridinones constitute useful intermediates due to the easy elaboration on either the pyridinone core (by the displacement of the halogen atom) or functionality transformation (dithiocarbonyl functionality) and have proven to be a useful synthetic scaffold in the synthesis of the bio- and pharmacologically important fused-ring diazepine core.

Introduction

Domino reactions are highly efficient processes that allow the synthesis of complex molecules starting from simple substrates and proceeding in a straightforward fashion.[1] During our research on syntheses of heterocyclic[2,3] and carbocyclic compounds[4] by domino reactions, some useful methods have been developed starting from functionalized ketene dithioacetals,[3,4] which are versatile synthons in organic synthesis.[5] In our continuing research, we have found that the polyfunctionalized pyridinones, 4-halogenated *N*-substituted 2(1*H*)-pyridinones, can be easily prepared by a one-pot domino reaction of readily available α-acetyl-α-carbamoyl ketene dithioacetals[4b,6] with Vilsmeier reagents.[7,8] In this paper we describe the results of the synthesis of 4-halogenated *N*-substituted 2(1*H*)-pyridinones and their primary applications in the synthesis of fused-ring diazepine core structures.

2(1*H*)-Pyridone derivatives have attracted considerable attention because of their diverse pharmacological and biological

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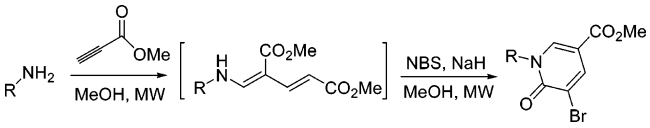
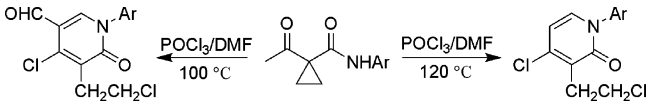
SCHEME 1. Preparation of 3-Bromo-2(1*H*)-pyridinones



activities[9] and their application as intermediates in the construction of complex natural products.[10] In the syntheses of 2(1*H*)-pyridone derivatives, the most general approach for accessing substituted 2-pyridinones is from acyclic substrates which often incorporate a Michael addition as the key step.[11] However, these methods are not general for the preparation of halogenated or *N*-substituted 2(1*H*)-pyridinones which are essential for further elaboration of the 2(1*H*)-pyridinone core.[12] To the best of our knowledge, only one route has been reported in the literature describing the synthesis of halogenated *N*-substituted 2(1*H*)-pyridinones starting from acyclic substrates.[13] In 2002, Dechoux and co-workers reported a synthetic route to this class of compounds which centered on a Michael-type addition between an amine and a methyl propiolate followed by bromocyclization of the ensuing δ-dienaminoester.[13a] This method required long reaction times (ca. 48 h). Later, an extension of this methodology was achieved by Vounatsos and co-workers through the utilization of microwave heating (Scheme 1), and the reaction time was reduced to 30 min but with lower product yields (29−53%).[13b] Most recently, we have reported the preparation of 4-chloro-2(1*H*)-pyridinones via the Vilsmeier−Haack reaction of 1-acetyl,1-carbamoyl cyclopropanes (Scheme 2).[13c] At the same time, as our interest continued in the development of synthetic applications of functionalized ketene dithioacetals,[3−6,14] we also found that 4-chloro/bromo *N*-substituted 2(1*H*)-pyridinones could be prepared via a domino reaction of α-acetyl-α-carbamoyl ketene dithioacetals with Vilsmeier reagents.

SCHEME 2. Preparation of 4-Chloro-2(1*H*)-pyridinones



Results and Discussion

In the initial experiments, based on our previous research on the reactions of α-acetyl ketene dithioacetals with Vilsmeier reagents,[3c,14] the reaction of α-acetyl-α-carbamoyl cyclic ketene dithioacetal **1a1**[6] with Vilsmeier reagent (DMF−$POCl_3$) was selected as the model reaction. It was found that α-chlorovinyl ketene dithioacetal **2a1** was obtained in 90% yield by reacting **1a1** with 2.0 equiv of $POCl_3$ in DMF at room temperature for 4−5 h (Scheme 3). To our delight, when the reaction of **1a1** (1.0 equiv) with $POCl_3$ (2.0 equiv) was performed in DMF at 100 °C for 50 min, the 4-chloro *N*-substituted 2(1*H*)-pyridinone **3a1** could be isolated in 87% yield (Scheme 3 and Table 1, entry 1). On the other hand, it was observed that when **1a1** (1.0 equiv) was treated with excess $POCl_3$ (5.0 equiv) in DMF at 100 °C for a longer reaction time (up to 2 h) under otherwise identical conditions as above, **3a1** was produced in 85% yield and further formylation was not observed. This apparently is due to the stronger electron deficiency of the core of **3a1** and is different from our recent observations on the Vilsmeier−Haack reaction of 1-acetyl-1-carbamoyl cyclopropanes (Scheme 2).[13c] The structure of **3a1** was determined based on its spectroscopic and analytical data and confirmed by X-ray crystal analysis.[15]

The above result indicates a novel and efficient route to 4-halogenated *N*-substituted 2(1*H*)-pyridinones,[13] with the nature of further elaboration of the 2(1*H*)-pyridinone core and an active dithiocarbonyl functionality, from readily available acyclic starting materials. Therefore, the scope of this reaction was extended to some other substrates **1a** (R = −$(CH_2)_3$) or **1b** (R = Et) with variable R and R^1 groups under the above optimal conditions, and the results are described in Table 1. It is obvious that the electronic effects of substituents at the nitrogen (R^1) have little influence on this reaction. All of the selected substrates, bearing an aryl group (with either an electron-donating or electron-withdrawing group on the benzene ring) and an aliphatic group at the nitrogen, could efficiently react with DMF−$POCl_3$ to give the corresponding 4-chloro *N*-substituted 2(1*H*)-pyridinones **3** in high yields (75−87%, Table 1, entries 1−8). More importantly, the reaction also proceeded smoothly even in the case of using the substrates with a sterically hindered ortho-substituted aromatic amine unit, for example **1a4**−**1a7**, and the desired products **3a4**−**3a7** were obtained dominantly in high yields (Table 1, entries 4−7). In addition, the desired 4-bromo-2(1*H*)-pyridinone **3a9** was also obtained under the identical conditions as above in good yield by reacting **1a1** with the DMF−PBr_3 system (Table 1, entry 9).

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(15) Crystal data for **3a1**: $C_{15}H_{12}Cl_3NOS_2$, red crystal, M = 392.75, monoclinic, $P21/c$, a = 8.7752(9) Å, b = 22.221(2) Å, c = 8.8261(9) Å, α = 90.00°, β = 97.234(2)°, γ = 90.00°, V = 1707.3(3) Å^3, Z = 4, T = 293(2), F_{000} = 880, R_1 = 0.0383, wR_2 = 0.0827; for the details please see Supporting Information.

SCHEME 3. Reactions of 1a1 with Vilsmeier Reagent

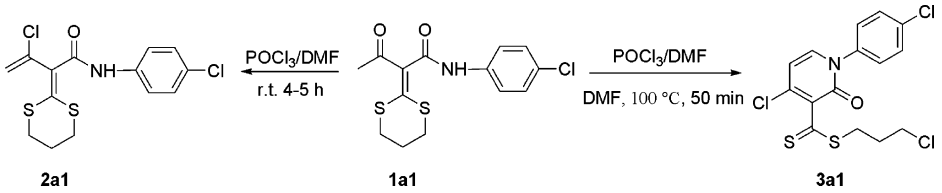
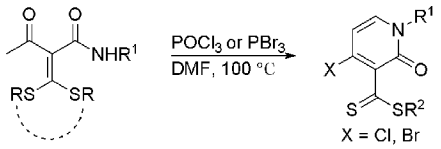


TABLE 1. Synthesis of 4-Halogenated-2(1*H*)-pyridinones 3



1a R = -$(CH_2)_3$-
1b R = Et

3a R^2 = $(CH_2)_2CH_2X$
3b R^2 = Et

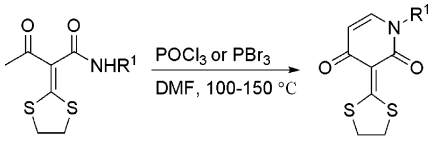
entry	substrate	R, R	R^1	R^2	X	time (min)	yield[a] (%)
1	**1a1**	$(CH_2)_3$	4-Cl-C_6H_4	$(CH_2)_2CH_2Cl$	Cl	50	**3a1** (87)
2	**1a2**	$(CH_2)_3$	C_6H_5	$(CH_2)_2CH_2Cl$	Cl	50	**3a2** (87)
3	**1a3**	$(CH_2)_3$	4-CH_3O-C_6H_4	$(CH_2)_2CH_2Cl$	Cl	50	**3a3** (79)
4	**1a4**	$(CH_2)_3$	2-CH_3-C_6H_4	$(CH_2)_2CH_2Cl$	Cl	55	**3a4** (80)
5	**1a5**	$(CH_2)_3$	2-$(CH_3)_2$-C_6H_3	$(CH_2)_2CH_2Cl$	Cl	60	**3a5** (77)
6	**1a6**	$(CH_2)_3$	2-Cl-C_6H_4	$(CH_2)_2CH_2Cl$	Cl	50	**3a6** (77)
7	**1a7**	$(CH_2)_3$	2-CH_3O-C_6H_4	$(CH_2)_2CH_2Cl$	Cl	45	**3a7** (75)
8	**1a8**	$(CH_2)_3$	CH_3	$(CH_2)_2CH_2Cl$	Cl	50	**3a8** (81)
9	**1a1**	$(CH_2)_3$	4-Cl-C_6H_4	$(CH_2)_2CH_2Br$	Br	30	**3a9** (50)
10	**1b1**	Et	4-Cl-C_6H_4	Et	Cl	50	**3b1** (87)
11	**1b2**	Et	C_6H_5	Et	Cl	50	**3b2** (75)
12	**1b3**	Et	4-CH_3O-C_6H_4	Et	Cl	50	**3b3** (92)
13	**1b4**	Et	2-CH_3-C_6H_4	Et	Cl	55	**3b4** (90)
14	**1b5**	Et	2-$(CH_3)_2$-C_6H_3	Et	Cl	60	**3b5** (72)
15	**1b6**	Et	2-Cl-C_6H_4	Et	Cl	55	**3b6** (87)
16	**1b7**	Et	2-CH_3O-C_6H_4	Et	Cl	45	**3b7** (87)
17	**1b8**	Et	CH_3	Et	Cl	50	**3b8** (77)
18	**1b1**	Et	4-Cl-C_6H_4	Et	Br	30	**3b9** (60)
19	**1b2**	Et	C_6H_5	Et	Br	30	**3b10** (50)
20	**1b7**	Et	2-CH_3O-C_6H_4	Et	Br	30	**3b11** (59)
21	**1b8**	Et	CH_3	Et	Br	30	**3b12** (50)

[a] Isolated yields.

In a further extension of these studies with the consideration of the impact of the ketene dithioacetal moiety, the above reaction was then examined by changing the R group of substrates **1**. From the results shown in Table 1, the reactions of acyclic ketene dithioacetals **1b** with Vilsmeier reagents (DMF−$POCl_3$ or DMF−PBr_3) were also successful and yielded the corresponding 4-chloro/bromo-2(1*H*)-pyridinones **3b** in good to high yields (Table 1, entries 10−21). However, under essentially the same conditions as above, in the case of the reactions of α-acetyl-α-carbamoyl ketene dithioacetals **1c** containing the 1,3-dithiolan moiety with Vilsmeier reagents (DMF/$POCl_3$ or PBr_3), we did not isolate the desired 4-halogenated 2(1*H*)-pyridinones but obtained the corresponding 3-(1,3-dithiolan-2-ylidene)-1-arylpyridine-2,4(1*H*,3*H*)-diones **4c** in high yields (Table 2, entries 1−4). In addition, it was found that no reaction occurred when **3a1** or **4c1** was treated with (DMF/$POCl_3$, 1.0−3.0 equiv) at 100−150 °C for 2−3 h due to the electron-deficient nature of the pyridinone core. However, the existence of the electron-withdrawing dithiocarbonyl group of 4-halogenated *N*-substituted 2(1*H*)-pyridinones **3** can make these compounds good candidates to serve as precursors for further synthetic transformations (see Scheme 6).

In order to gain insight into the mechanism of the reaction, the reactions of α-acetyl-α-carbamoyl ketene dithioacetal **1d** and α-chlorovinyl ketene dithioacetal **2a1** with $POCl_3$ in DMF were conducted, respectively. Under conditions identical to those above, the haloformylation product **5** was exclusively produced in 80% yield by reacting **1d** with $POCl_3$ (2.0 equiv) in DMF followed by treatment with aqueous NaOH (Scheme 4). On the other hand, the reaction of **2a1** (Scheme 3) with 1.0 equiv of $POCl_3$ in DMF at 100 °C for 40 min gave 2(1*H*)-pyridinone **3a1** in 70% yield.

TABLE 2. Synthesis of 1-Arylpyridine-2,4(1*H*,3*H*)-diones 4c



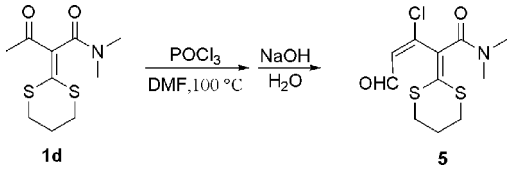
1c **4c**

entry	substrate	R^1	time (h)	product	yield[a] (%)
1	**1c1**	4-Cl-C_6H_4	2	**4c1**	75
2	**1c2**	C_6H_5	2	**4c2**	73
3	**1c3**	2-CH_3-C_6H_4	2	**4c3**	79
4	**1c4**	2-$(CH_3)_2$-C_6H_3	2	**4c4**	70

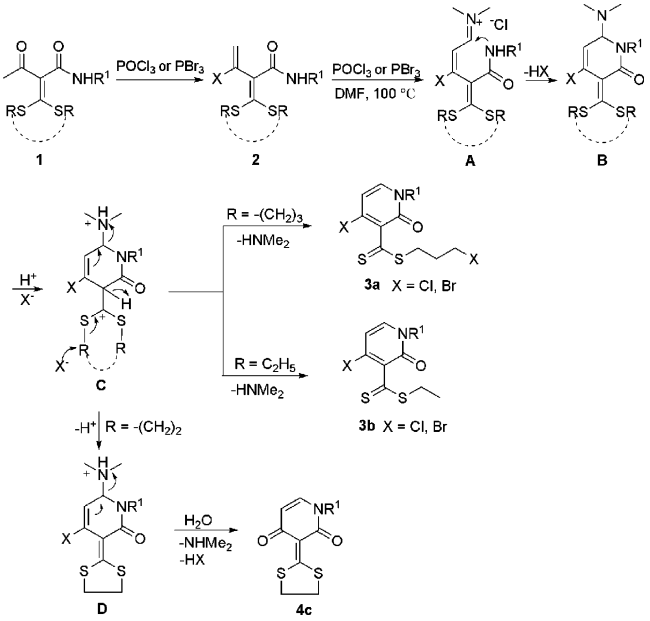
[a] Isolated yields.

On the basis of the above experimental results together with the related reports,[3c,8,14b−14e] the possible mechanisms for the

SCHEME 4. Reaction of 1d with Vilsmeier Reagent



SCHEME 5. Proposed Mechanisms for the Formation of 3 and 4c



formation of pyridinones **3** and **4** are proposed and depicted in Scheme 5. Initially, the α-chlorovinyl ketene-*S*,*S*-acetals **2** would be formed in situ and then react further with excess Vilsmeier reagent to give the ammonium salt intermediate **A**. Then, a nucleophilic attack of the amide nitrogen at the positive carbon of the methylene moiety leads to an intramolecular cyclization of **A** into **B** with elimination of HX (Scheme 5). Under the acidic conditions, the protonation of the carbon−carbon double bond of intermediate **B** may lead to carbocation intermediate **C** (Scheme 5),[16,17] and the further transformations of intermediate **C** would depend on the degree of the overlap of the C−S orbitals of the alkylthio moiety with the carbocation system.

To the intermediate **C** with diethylthio or 1,3-dithiane unit, the overlap of the C−S orbitals of alkylthio moiety with the carbocation system is favorable and the carbocation intermediate **C** is relatively stable. Subsequently, the attack of the halide ion X^- (X = Cl, Br) leads to the cleavage of the C−S bond of intermediate **C**,[17] followed by elimination of dimethylamine to give the corresponding product **3b** and **3a** (Scheme 5). Comparatively, to the intermediate **C** with 1,2-dithiolane moiety (R = $(CH_2)_2$), the overlap of the C−S orbitals with the carbocation system is less favorable than that in the case of the conformationally more mobile 1,3-dithiane and diethylthio systems. Thus, the intermediate **D** would be formed by the reversibility of the protonation process of intermediate **C**,[16a] which is followed by sequential hydrolysis and elimination of dimethylamine and HX (X = Cl, Br) to give the product **4c** (Scheme 5).

In order to get insight into the synthetic potential and further architectural elaboration of the 2(1*H*)-pyridinone core[12] of the reactive 4-halogenated 2(1*H*)-pyridinone **3**, the reactions of compound **3b7** with selected aromatic amines were investigated. It was discovered that the regioselective nucleophilic substitution reactions of **3b7** with phenylamine and 4-methylbenzylamine could easily proceed in refluxing *tert*-butyl alcohol to give the corresponding 4-arylamino-2(1*H*)-pyridinones **6a** and **6b** in 90% and 95% yields, respectively (Scheme 6). On the other hand, when substituted *o*-phenylenediamines were subjected to the identical conditions as above, the corresponding benzo[*b*][1,4]-diazepine-2-thiones **7a** and **7b** were obtained in 60% and 65% yields, respectively (Scheme 6). Therefore, the transformations from **3b7** to **7** provide an efficient route to the biologically important diazepine core.[18]

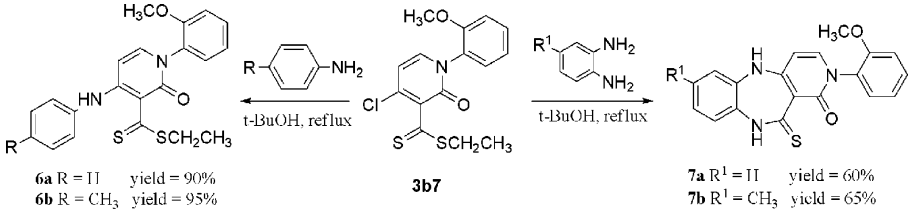
Conclusion

In summary, we have demonstrated a novel and efficient synthesis of 4-chloro/bromo *N*-substituted 2(1*H*)-pyridinones **3** via a one-pot domino reaction of α-acetyl-α-carbamoyl ketene dithioacetals **1a** and **1b** with Vilsmeier reagents. In addition, the 1-arylpyridine-2,4(1*H*,3*H*)-diones **4c** were also obtained in high yields from α-acetyl-α-carbamoyl ketene dithioacetals **1c**. The possible mechanisms of the domino reaction of α-acetyl-α-carbamoyl ketene dithioacetals with Vilsmeier reagents are proposed, and the overlap of the C−S orbitals of the alkylthio moiety of α-acetyl-α-carbamoyl ketene dithioacetals with the π-system seems crucial to the orientation of products. The simplicity of manipulation, good to high yields, high efficiency, and readily available or cheap starting materials make this synthetic strategy most attractive for academic research and potential applications. On the basis of this reaction, the bio- and pharmacologically important diazepine core can be constructed simply by reacting **3** with diamines. Further studies to expand the synthetic applications of these functionalized 4-halogenated 2(1*H*)-pyridinones **3** are in progress.

Experimental Section

General Procedure for Preparation of 3 (3a1 as Example). To a stirred solution of **1a1** (1.0 mmol, 327 mg) in DMF (10 mL) was added $POCl_3$ (2.0 mmol, 0.18 mL) in one portion at room temperature. Then the reaction mixture was heated to 100 °C for 50 min. After **1a1** was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL), followed by basification with saturated aqueous $NaHCO_3$ solution to adjust the pH value of the solution to 7, and extracted with CH_2Cl_2 (10 mL × 2). The combined organic extracts were dried over anhydrous $MgSO_4$,

SCHEME 6. Reactions of 3b7 with Aromatic Amines



filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (acetone/hexane = 1/15, v/v) to give 341 mg (87%) of **3a1** as a red crystal. Mp 119−120 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.25 (quint, J = 7.0 Hz, 2H), 3.56 (t, J = 7.0 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 6.41 (d, J = 7.0 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.33 (q, J = 8.0 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 30.2, 33.6, 43.8, 108.8, 128.1 (2C), 129.8 (2C), 135.2, 135.4, 137.1, 138.3, 142.2, 157.8, 222.8. IR (KBr, cm^{-1}): 842, 931, 1014, 1048, 1102, 1310, 1530, 1583, 1603, 1648, 3446. MS (ESI) *m*/*z* 394 $[(M + 1)]^+$. Anal. Calcd (found) for $C_{15}H_{12}Cl_3NOS_2$: C, 45.87 (45.97); H, 3.08 (3.05); N, 3.57 (3.46).

General Procedure for Preparation of 4c (4c1 as Example). To a stirred solution of **1c1** (1.0 mmol, 313 mg) in DMF (10 mL) was added $POCl_3$ (2.0 mmol, 0.18 mL) in one portion at room temperature. Then the reaction mixture was heated to 100 °C for 2 h. After **1c1** was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL), followed by basification with saturated aqueous $NaHCO_3$ solution to adjust the pH value of the solution to 7, and extracted with CH_2Cl_2 (10 mL × 2). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (acetone/hexane = 1/9, v/v) to give 242 mg (75%) of **4c1** as a yellow crystal. Mp 200−202 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.40−3.48 (m, 4H), 6.01 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 32.8, 33.7, 104.0, 113.5, 123.7 (2C), 125.1 (2C), 129.7, 134.1, 136.2, 157.5, 175.0, 187.4. IR (KBr, cm^{-1}): 708, 954, 1023, 1317, 1410, 1644, 3428. MS (ESI) *m*/*z* 324 $[(M + 1)]^+$. Anal. Calcd (found) for $C_{14}H_{10}ClNO_2S_2$: C, 51.93 (52.11); H, 3.11 (3.14); N, 4.33 (4.45).

General Procedure for Preparation of 6 and 7 (6b as Example). To a stirred solution of **3b7** (1.0 mmol, 339 mg) in *t*-BuOH (15 mL) was added 4-methylbenzylamine (1.0 mmol, 107 mg) in one portion. Then the reaction mixture was heated at reflux for 10−12 h until compound **3b7** was consumed (monitored by TLC). The solution was cooled and then poured into water (50 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (acetone/hexane = 1/6, v/v) to give 390 mg (95%) of **6b** as a yellow crystal. Mp 152−153 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.35 (t, J = 7.5 Hz, 3H), 2.37 (s, 3H), 3.14 (q, J = 7.5 Hz, 2H), 3.79 (s, 3H), 6.04 (d, J = 8.0 Hz, 1H), 7.01 (q, J = 7.0 Hz, 3H), 7.15 (d, J = 8.0 Hz, 1H), 7.16−7.25 (m, 4H), 7.28 (t, J = 7.0 Hz, 1H), 14.29 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 11.5, 21.3, 31.5, 56.1, 96.8, 112.4, 113.1, 121.0, 126.2 (2C), 129.3, 129.6, 130.3, 130.4 (2C), 134.9, 137.0, 140.3, 154.9, 157.0, 161.5, 221.0. IR (KBr, cm^{-1}): 3065, 2921, 2790, 1649, 1536, 1496, 1381, 1302, 1262, 1233, 1104, 1024, 886, 778. MS (ESI) *m*/*z* 411 $[(M + 1)]^+$. Anal. Calcd (found) for $C_{22}H_{22}N_2O_2S_2$: C, 64.36 (64.51); H, 5.40 (5.47); N, 6.82 (6.96).

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Supporting Information Available: Crystallographic data for **3a1** (CIF), and experimental procedures, NMR spectra, and characterization data for new compounds **3**, **4**, **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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