JOC Article

$AlCl_3$-Mediated Direct Carbon−Carbon Bond-Forming Reaction of α-Hydroxyketene-*S*,*S*-acetals with Arenes and Synthesis of 3,4-Disubstituted Dihydrocoumarin Derivatives

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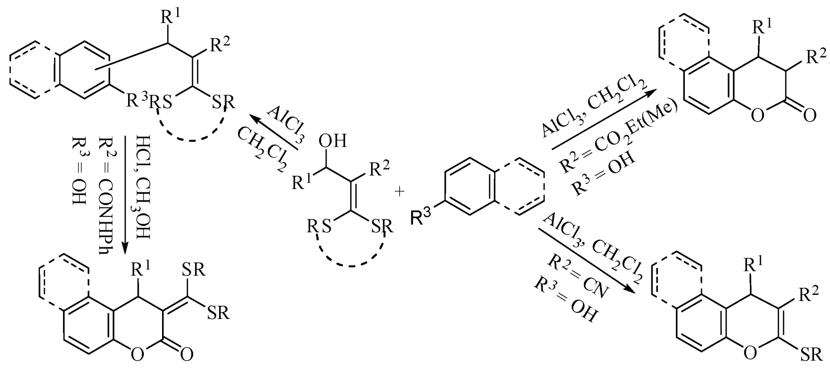
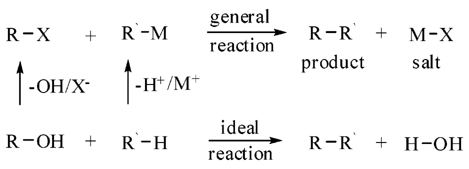


A simple and efficient $AlCl_3$-mediated C−C coupling reaction between readily available α-hydroxyketene-*S*,*S*-acetals and various arenes via direct substitution of the hydroxy group in alcohols has been developed. On the basis of this C−C coupling reaction, a series of bio- and pharmacologically important 3,4-disubstituted dihydrocoumarins, difficult to obtain by other methods, were prepared in high yields by a sequential Friedel−Crafts alkylation and intramolecular annulation reaction of α-hydroxyketene acyclic-*S*,*S*-acetals with phenols under mild conditions.

Introduction

The carbon−carbon bond-forming reaction is one of the most fundamental reactions for the construction of the molecular framework in organic chemistry.[1] From the standpoint of atom efficiency,[2] the direct substitution of a hydroxy group in an alcohol (ROH)[3] by a carbon nucleophile (R′H) via a formal dehydration process is an attractive salt-free method because there is no requirement for the transformation of nucleophiles and alcohols to the corresponding reactive organometallic compounds (R′M) and halides or a related species (RX) (Scheme 1).[4a] Therefore, continuous efforts have been devoted to the direct C−C bond-forming reactions between ROH and R′H in recent years. Among those reported, the C−C coupling reactions between allylic or benzylic alcohols and active methylenes[4] or arenes[5] have proven successful. In this context, the selection of a suitable alcohol component for the carbon−carbon bond-forming reaction is of great significance in achieving the synthetic applications.[3−5]

SCHEME 1



As a special type of allylic alcohol, the α-hydroxyketene-*S*,*S*-acetals have been applied in the synthesis of substituted pyridines,[6] α,*β*-unsaturated dithioesters,[7] and conjugated polyene esters.[8] During the course of our studies on the chemistry of functionalized ketene dithioacetals,[9−12,13a] the α-hydroxyketene-*S*,*S*-acetal intermediates were involved in the Morita−Baylis−Hillman (MBH) type reactions with α-EWG ketene-*S*,*S*-acetals (EWG = electron withdrawing group) as the activated alkenes.[10] Meanwhile, it was found that the resulting α-hydroxyketene-

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[2] (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233−1246.

[3] For reviews, see: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179−4212. (b) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647−2656.

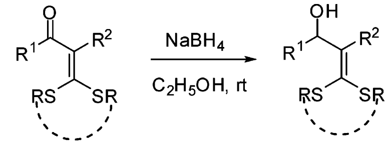
10.1021/jo702414y CCC: $40.75

S,S-acetals can further react with α-EWG ketene-*S,S*-acetals and nitriles to give the corresponding double MBH adducts[10a,b] and aza-MBH adducts, respectively.[10c] Recently, the carbon–carbon bond-forming reaction of α-hydroxyketene-*S,S*-acetals with active methylene compounds was also performed successively in the presence of boron trifluoride etherate.[11] These studies and our continued interest in the development of synthetic applications of α-hydroxyketene-*S,S*-acetals[12] prompted us to explore the feasibility of the C–C coupling reactions between α-hydroxyketene-*S,S*-acetals and arenes.[5] In this paper we describe the results of the C–C coupling reactions between α-hydroxyketene-*S,S*-acetals with various arenes and their applications in the synthesis of 3,4-disubstituted dihydrocoumarins and highly functionalized chromenes.

Results and Discussion

Synthesis of α-Hydroxyketene-*S,S*-acetals 2. Initially, a variety of α-hydroxyketene-*S,S*-acetals **2a–g** were prepared in excellent yields (90–95%) by the reduction reaction of the corresponding α-oxoketene-*S,S*-acetals **1a–g**[13] with sodium borohydride ($NaBH_4$) in ethanol at room temperature[11] (Table, 1).

TABLE 1. Synthesis of α-Hydroxyketene-*S,S*-acetals 2[a]

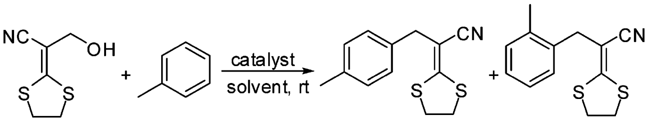


1a-g **2a-g**

entry	substrate	R, R	R^1	R^2	time (min)	product	yield[b] (%)
1	**1a**	$(CH_2)_2$	H	CN	30	**2a**	90
2	**1b**	$(CH_2)_2$	H	CO_2Me	30	**2b**	91
3	**1c**	Et	Me	CO_2Me	30	**2c**	94
4	**1d**	Me	H	CO_2Et	20	**2d**	90
5	**1e**	Et	H	CN	30	**2e**	95
6	**1f**	Et	Me	CN	30	**2f**	90
7	**1g**	Et	Me	CONHPh	60	**2g**	95

[a] The reactions were carried out in ethanol (8.0 mL) with **1** (1.0 mmol) and $NaBH_4$ (1.2 mmol) at room temperature. [b] Isolated yields.

Table 2. Acid-Catalyzed C–C Coupling Reaction of 2a with Toluene 3a under Various Reaction Conditions



2a **3a** **4a1** **4′a1**

entry	catalyst (equiv)	solvent	ratio (**3a**/**2a**)	time (h)	yield[a] (%)
1	$AlCl_3$ (1.0)	CH_2Cl_2	1:1	5	35
2	$AlCl_3$ (1.0)	CH_2Cl_2	4:1	5	75
3	$AlCl_3$ (1.0)	CH_2Cl_2	5:1	5	74
4	$AlCl_3$ (0.5)	CH_2Cl_2	4:1	12	25
5	$AlCl_3$ (1.0)	CH_2ClCH_2Cl	4:1	5	73
6	$AlCl_3$ (1.0)	C_2H_5OH	4:1	12	
7	$AlCl_3$ (1.0)	CH_3CN	4:1	12	
8	BF_3OEt_2 (1.0)	CH_2Cl_2	4:1	5	62
9	$FeCl_3$ (1.0)	CH_2Cl_2	4:1	5	50
10	H_2SO_4 (1.0)	CH_2Cl_2	4:1	12	

[a] Isolated yields.

Carbon–Carbon Bond-Forming Reactions of α-Hydroxyketene Cyclic-*S,S*-acetals 2a and 2b with Arenes 3. With the readily available α-hydroxyketene-*S,S*-acetals **2** in hand, we next turned to the study of the C–C coupling reaction of **2** with various arenes. A model reaction between **2a** with toluene **3a** was first examined to optimize the reaction conditions (Table 2). It was found that, with $AlCl_3$ (1.0 equiv) as a promoter, the C–C coupling reaction of **2a** (1.0 equiv) with toluene **3a** (1.0 equiv) can easily proceed to give a mixture of the 4-/2-alkylated products **4a1** and **4′a1** (the isomer (4-/2-position ratio of 85/15) in 35% yield in CH_2Cl_2 at room temperature for 5 h (Table 2, entry 1). It was pleasing to see that the mixture **4a1** and **4′a1** could be obtained in 75% yield by raising the ratio of **3a/2a** to 4:1 (Table 2, entry 2). However, the yield of the isomers **4a1** and **4′a1** could not be increased by further raising the ratio of **3a/2a** (Table 2, entry 3) and a catalytic amount of $AlCl_3$ (0.5 equiv) led to lower yields (Table 2, entry 4). Among the solvents tested, dichloromethane seemed to be the best choice although comparable results were obtained with 1,2-dichloroethane as the solvent (Table 2, entry 5). No desired product was observed (monitored by TLC) when the reaction was carried out in ethanol or acetonitrile (Table 2, entries 6 and 7). Meanwhile, it was found that other promoters tested, such as $FeCl_3$, $BF_3{\cdot}OEt_2$,

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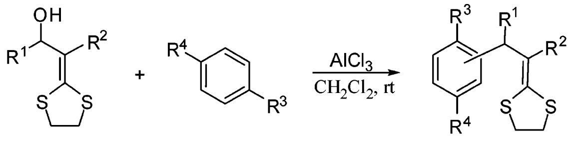
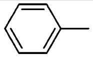
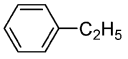
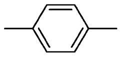
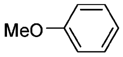
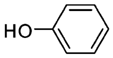
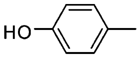
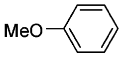
TABLE 3. $AlCl_3$-Catalyzed C−C Coupling Reaction of α-Hydroxyketene Cyclic Dithioacetals 2 with Arenes 3[a]



2 **3** **4 and 4′**

entry	substrate **2**	R^1	R^2	substrate **3**	time (h)	yield[b] (%)	regioselectivity[d] (p/o)
1	**2a**	H	CN		5	**4a1** and **4′a1** (75)	85/15
2	**2a**	H	CN		5	**4a2** and **4′a2** (70)	91/9
3	**2a**	H	CN		2	**4′a3** (72)	---
4[c]	**2a**	H	CN		0.5	**4a4** and **4′a4** (87)	80/20
5[c]	**2a**	H	CN		0.5	**4a5** and **4′a5** (61)	70/30
6[c]	**2a**	H	CN		0.5	**4′a6** (90)	---
7	**2a**	H	CN		5	**4a7** (50)	**---**
8[c]	**2b**	H	CO_2Me		0.5	**4b1** and **4′b1** (85)	90/10

[a] Reaction conditions: **2** (1.0 equiv), **3** (4.0 equiv), $AlCl_3$ (1.0 equiv) in CH_2Cl_2 (5.0 mL) at room temperature. [b] Isolated yields. [c] 2.0 equiv of **3** was used. [d] The isomer (4-/2-position) ratio was determined by the ^1H NMR spectra of the mixture **4** and **4′**.

and H_2SO_4, appeared to be effective but with relatively lower yields (Table 2, entries 8 and 9) or ineffective (Table 2, entry 10).

As is widely known, functionalized arenes are important building blocks and lead structures in medicinal and agricultural chemistry. Obviously, the above results provide an efficient route to functionalized arenes with the nature of further elaboration of the ketene-*S,S*-acetal and related functionality. Therefore, the scope of the C−C coupling reaction was extended to some other substrates **2a** or **2b** and various arenes **3** under optimal conditions (Table 2, entry 2) and the results are described in Table 3. As expected, a variety of electron-rich arenes, such as toluene, ethylbenzene, *p*-xylene, anisole, and phenol, could efficiently react with **2a** to give the corresponding mixture of the 4-/2-alkylated products **4** and **4′** in good to high yields (Table 3, entries 1−5). In the case of the reaction of **2a** with 4-methylphenol, the 2-alkylated product **4′a6** was obtained in 90% yield (Table 3, entry 6). More importantly, even nonactivated arene, benzene, could also afford the alkylated product **4a7** in 50% yield (Table 3, entry 7). In addition, the desired 4-/2-alkylated products **4b1** and **4′b1** were also produced in high yield (85%) by reacting **2b** with anisole under the identical conditions as above (Table 3, entry 8).

Carbon−Carbon Bond-Forming Reactions of α-Hydroxyketene Acyclic-*S,S*-acetals 2c−g with Phenols and Applications in the Synthesis of 3,4-Disubstituted Dihydrocoumarins 5 and 7 and Functionalized Chromenes 6. On the basis of the above results and especially the highly regioselective reaction of **2a** with 4-methylphenol (Table 3, entry 6), together with the consideration of the structural feature of alkylthio as a good leaving group in nucleophilic vinyl substitution reactions,[9a−d] we reasoned that the hydroxyl group of an alkylated phenol from an α-hydroxyketene acyclic-*S,S*-acetal and a suitable phenol may lead to a coumarin derivative via an alkylation and intramolecular addition−elimination sequence. Indeed, under essentially the identical conditions as above, when α-hydroxyketene acyclic-*S,S*-acetals **2c** ($R^2 = CO_2Me$) and **2d** ($R^2 = CO_2Et$) were treated with *β*-naphthol and 4-methylphenol, respectively, the desired products, 3,4-disubstituted dihydrocoumarins **5c1**, **5c2**, and **5d1** were afforded in high yields (Table 4, entries 1−3). It should be noted that coumarin derivatives are found in a variety of biologically important natural products and widely used as intermediates in organic synthesis.[14] Classical routes to coumarins include Pechmann,[15a,b] Perkin,[15c] Knoevenagel,[15d] Reformatsky,[15e] and Wittig[15f] reactions and their variants.[16] In recent years versatile coumarin syntheses could be achieved through transition-metal-catalyzed reactions.[17] However, most of these approaches are focused on monosubstituted coumarins. Though the preparation of 3,4-disubstituted coumarins may be accomplished in different ways,[18] only limited synthesis of 3,4-disubstituted dihydrocoumarins was reported.[19] Undoubtedly, the above one-pot annulation reaction provides a

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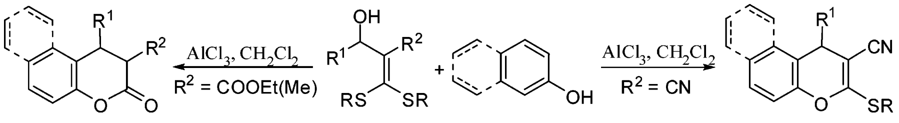
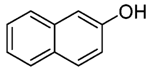
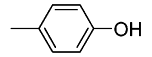
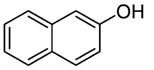
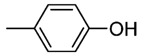
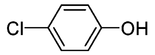
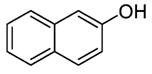
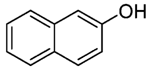
TABLE 4. Synthesis of 3,4-Disubstituted Dihydrocoumarins 5 and Chromenes 6[a]

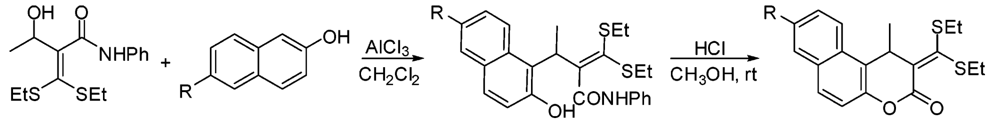


5 **2c-f** **3** **6**

entry	substrate **2**	R	R¹	R²	substrate **3**	time (h)	Yield[b] (%)
1	**2c**	Et	Me	CO_2 Me		0.5	**5c1** (78)
2	**2c**	Et	Me	CO_2 Me		0.5	**5c2** (75)
3	**2d**	Me	H	CO_2Et		0.5	**5d1** (80)
4	**2e**	Et	H	CN		0.5	**6e1** (80)
5	**2e**	Et	H	CN		1	**6e2** (80)
6	**2e**	Et	H	CN		0.5	**6e3** (90)
7	**2f**	Et	Me	CN		0.5	**6f1** (70)

[a] The reactions were carried out in CH_2Cl_2 (5.0 mL) with **2** (1.0 mmol), **3** (2.0 mmol), and $AlCl_3$ (1.0 mmol) at room temperature. [b] Isolated yields.

SCHEME 2. Preparation of Alkylated Products 4g and 3,4-Disubstituted Dihydrocoumarins 7g



2g **3**

4g1 R = H yield = 95%
4g2 R = Br yield = 94%

7g1 R = H yield = 85%
7g2 R = Br yield = 84%

facile and efficient access to 3,4-disubstituted dihydrocoumarins from readily available starting materials under mild conditions.

In further experiments, we found that the substituents R² of α-hydroxyketene acyclic-*S*,*S*-acetals **2** had a significant influence on the above one-pot annulation reaction. As a result, when the reactions of **2e** (R² = CN) with 4-methylphenol, 4-chlorophenol, and *β*-naphthol were carried out under essentially identical conditions as above, the corresponding functionalized chromenes **6e1**, **6e2** and **6e3** were produced in high yields (Table 4, entries 4−6), respectively, which are important organic molecules present in numerous natural products along with wide bio- and pharmacological activities.[20] Similarly, the chromene **6f1** was also successfully prepared in 70% yield by the one-pot annulation reaction of **2f** with *β*-naphthol (Table 4, entry 7).[21] However, in the case of the reactions of **2g** (R² = CONHPh) with *β*-naphthol and 6-Br-*β*-naphthol, the annulation reaction could not occur and only the corresponding alkylated products **4g1** and **4g2** were afforded in 95% and 94% yields, respectively (Scheme 2). Interestingly, when the alkylated products **4g1** and **4g2** were treated with excessive amounts of HCl (10.0 equiv) in CH_3OH at room temperature for 5 h, a novel intramolecular annulation reaction proceeded smoothly to give the corresponding 3,4-disubstituted dihydrocoumarins **7g1** and **7g2** in 85% and 84% yields, respectively (Scheme 2). Indeed, selective synthesis has been a challenge in organic

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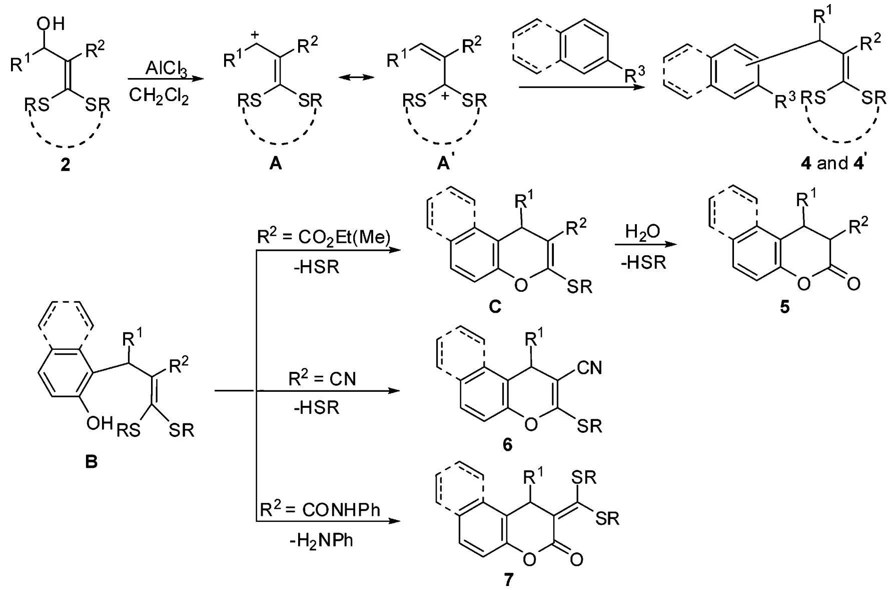
(21) In the further experiments, the transformation feasibility of chromenes **6** to dihydrocoumarins **5** was also examined. We found that, when the chromene **6e3** was treated with Brønsted acid HCl (1.0−5.0 equiv) or Lewis acid $AlCl_3$ (1.0−5.0 equiv) either at room temperature or under reflux conditions in the different solvents, such as CH_3OH, CH_3OH/H_2O (v/v, 10:1), CH_3CN, CH_3CN/H_2O (v/v, 10:1), DMF, and DMF/H_2O (v/v, 10:1), no desired product was produced and **6e3** was recovered in nearly quantitative yield.

SCHEME 3. Proposed Mechanisms for the Formation of 4−7



synthesis, especially controlled highly selective synthesis derived from similar starting materials.[22] Therefore, the above divergent method for the synthesis of 3,4-disubstituted dihydrocoumarins **5** and **7** and highly functionalized chromenes **6** from α-hydroxyketene acyclic-*S*,*S*-acetals **2c−g** is important for academic research and potential applications.

Possible Reaction Mechanism. On the basis of the above experimental results together with the related reports,[4,5,10,11] the possible mechanisms for the formation of **4−7** are proposed and depicted in Scheme 3. Initially, the hydroxyl group in alcohol **2** is activated by $AlCl_3$ to form carbocation intermediate **A**, which is then trapped by arene **3** to give the corresponding alkylated products **4** and **4′** (Scheme 3). To intermediate **B**, generated by the Friedel−Crafts alkylation reaction of α-hydroxyketene acyclic-*S*,*S*-acetals **2c−g** with phenols, the further orientation of reaction may be directed by the electronic effects of substituents R^2 of α-hydroxyketene acyclic-*S*,*S*-acetals **2**. When the R^2 substituent is a stronger electron-withdrawing group (R^2 = CN, CO_2Et or CO_2Me), the hydroxyl group of intermediate **B** would attack the carbon atom bonded to the alkylthio group and then undergo an intramolecular addition−elimination reaction to furnish chromenes **6** (R^2 = CN) or intermediate **C** (R^2 = CO_2Et or CO_2Me), which is followed by further hydrolysis to give the corresponding dihydrocoumarins **5** (Scheme 3). When the R^2 substituent is a relatively weak electron-withdrawing group (R^2 = CONHPh) as in the case of **B** (**4g1** or **4g2**), the hydroxyl group of **B** is likely to attack the carbonyl carbon in the presence of Brønsted acid HCl to produce the dihydrocoumarins **7g1** and **7g2** (Scheme 3). In comparison, for the 2-alkylated products **4′a5** and **4′a6** with a more rigid 1,2-dithiolane unit (Table 3, entries 5 and 6), the attack of the hydroxyl group at the carbon atom bonded to the alkylthio group would have difficulty in proceeding and any further cyclization reaction also would not occur.

Conclusion

In summary, we have developed a new and efficient $AlCl_3$-mediated direct C−C coupling reaction of α-hydroxyketene-*S*,*S*-acetals **2** and various arenes **3** under mild conditions. The simplicity of manipulation, salt-free and energy-saving process, good to high yields, readily available or cheap starting materials, and wide arene components make this direct C−C coupling method most attractive for academic research and potential applications. On the basis of this reaction, a series of bio- and pharmacologically important compounds, such as 3,4-disubstituted dihydrocoumarins **5** and **7** and highly functionalized chromenes **6**, were efficiently prepared in high yields by the annulation reaction of α-hydroxyketene acyclic-*S*,*S*-acetals **2c−g** with phenols. Further studies on the extension of the scope of this C−C bond-forming reaction, as well as synthetic applications, are currently under way in our laboratory.

Experimental Section

General Procedure for Preparation of 4, 5, and 6 (4′a3 for example). To a stirred solution of α-hydroxyketene-*S*,*S*-acetal **2a** (1.0 mmol, 173 mg) and *p*-xylene (4.0 mmol, 0.49 mL) in CH_2Cl_2 (5 mL) was added $AlCl_3$ (1.0 mmol, 132 mg) in one portion. Then the reaction mixture was stirred for 2 h at room temperature. After **2a** was consumed (monitored by TLC), the reaction mixture was poured into water (20 mL), followed by acidification with HCl solution to adjust the pH value of the solution to 3, and extracted with CH_2Cl_2 (2 × 10 mL). 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 (diethyl ether/hexane = 1/20, v/v) to give 188 mg (72%) of **4′a3** as a white solid. Mp 116−118 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 3H), 2.31 (s, 3H), 3.54−3.55 (m, 4H), 3.57 (s, 2H), 6.98 (d, J = 8.0 Hz, 1H), 7.0 (s, 1H), 7.05 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1, 21.0, 37.8, 38.3, 39.4, 95.6, 118.8, 127.9, 129.7, 130.2, 133.2, 134.6, 135.6, 160.8; IR (KBr, cm^{-1}) 2921, 2193, 1546, 816; MS (ESI) m/z 262 $[(M + 1)]^+$. Anal. Calcd (found) for $C_{14}H_{15}NS_2$: C, 64.33 (64.45); H, 5.78 (5.73); N, 5.36 (5.26).

General Procedure for Preparation of 7g (7g1 for example). To a stirred solution of **4g1** (1.0 mmol, 437 mg) in CH_3OH (8

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mL) was added HCl (10.0 mmol) in one portion. Then the reaction mixture was stirred for 5 h at room temperature. After **4g1** was consumed (monitored by TLC), the reaction mixture was poured into water (25 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 (3 × 10 mL). 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 (diethyl ether/hexane = 1/15, v/v) to give 292 mg (85%) of **7g1** as a white solid. Mp 47−49 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, $J = 8.0$ Hz, 3H), 1.30 (t, $J = 7.5$ Hz, 3H), 1.40 (d, $J = 7.0$ Hz, 3H), 2.84 (dd, $J = 7.5$, 13.0 Hz, 1H), 2.97 (q, $J = 7.5$ Hz, 2H), 3.03 (dd, $J = 7.5$, 13.0 Hz, 1H), 5.38 (q, $J = 7.0$ Hz, 1H), 7.25 (d, $J = 9.0$ Hz, 1H), 7.46 (t, $J = 8.5$ Hz, 1H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.5, 15.5, 21.1, 29.9, 30.2, 34.9, 117.4, 121.2, 122.5, 125.1, 127.4, 128.9, 129.1, 129.6, 130.2, 131.2, 147.6, 152.2, 161.5; IR (KBr, cm^{-1}) 2965, 1734, 1513, 1450, 1260, 1217, 813, 747; MS (ESI) m/z 345 $[(M + 1)]^+$. Anal. Calcd (found) for $C_{19}H_{20}O_2S_2$: C, 66.24 (66.43); H, 5.85 (5.80).

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Supporting Information Available: Experimental procedures, NMR spectra, and characterization data for new compounds **2** and **4**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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