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New Methods for the Synthesis of 2-Aminothiazolones

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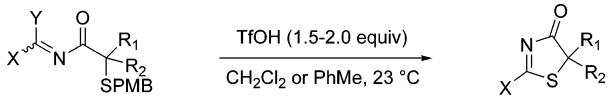


X = NHR, NRR', SMe; Y = SMe, OMe; R_1 and R_2 = H, alkyl, aryl, acyl

Two new methods for the synthesis of 2-aminothiazolones from 2-(4-methoxybenzylthio)acetic acids are described. A single reagent and simple experimental conditions are used in the key tandem deprotection−cyclization process. In the first approach 2-aminothiazolones are directly accessed via cyclization of the corresponding *N*-acylisothioureas. The second complementary approach provides access to a variety of 2-thiomethylthiazolones via cyclization of *N*-acyldithioimidates. The product 2-thiomethylthiazolones are then efficiently converted to 2-aminothiazolones via amine displacement.

The 2-aminothiazolone core structure represents a widely exploited pharmacophore in medicinal chemistry.[1] Compounds containing the 2-aminothiazolone subunit have demonstrated a wide range of biological activity (Figure 1). For example 5-(2,4-dihydroxybenzylidene)-2-(phenylimino)-1,3-thiazolidin (DBPT) is a potential therapeutic agent for colorectal cancer,[2] thiazolone **1** is an antagonist of the $\alpha_v\beta_3$ receptor,[3] and **2** has shown potent herbicidal activity.[4] The majority of biologically active 2-aminothiazolones display a C-5 alkylidene group while alternative substitution at this position is less common.[5]

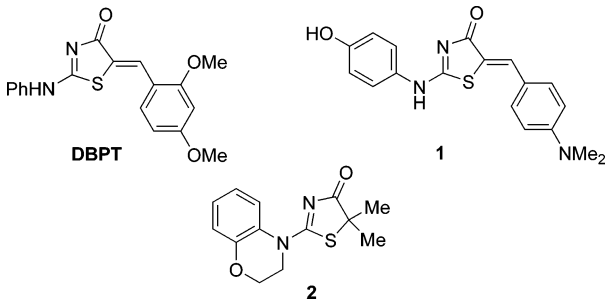
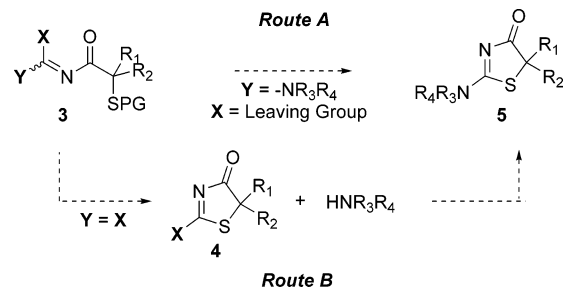


FIGURE 1. Biologically active 2-aminothiazolones.

Given the prominence of the 2-aminothiazolone core structure in biologically relevant molecules, a multitude of methods for their assembly have been reported.[6] The majority of approaches rely on the condensation of substituted thioureas and α-halo acid derivatives in the presence of an exogenous base.[7] However, this approach tends to be inefficient when tertiary α-halo acid derivatives are employed in the reaction. Several reports have appeared detailing the reaction of α-mercaptoacid derivatives and cyanamides to access the 2-aminothiazolone ring system, although the reactions generally proceed in moderate to low yields with a limited substrate scope.[8] Addition of amines to 2-thiothiazolone derivatives has also been reported.[9]

During the course of a recent development program, our group became focused on the discovery of an efficient and modular approach to C-5 mono- and disubstituted 2-aminothiazolones. Considering that C-5 disubstituted 2-aminothiazolones (and C-5 disubstituted 2-thiothiazolones) are difficult to access from the corresponding α-halo acid derivatives, we were interested in the design of alternative methods to synthesize these compounds. We envisioned two complementary cyclization manifolds that would allow ready access to the target, both proceeding via a tandem deprotection−cyclization process (Scheme 1). The first approach (Route A) would emanate from an activated *N*-acylisothiourea derivative **3** (Y = NR_3R_4, X = LG), which upon deprotection and cyclization would supply **5** directly. The second route (Route B) would involve the intermediacy of an activated thiazolone derivative bearing a leaving group in the 2-position (**4**), which would be accessed by the cyclization of *N*-acylimidate **3** (Y = X = LG). Reaction of activated intermediate **4** with the appropriate amine coupling partner would then provide the target 2-aminothiazolones **5**.

SCHEME 1. Proposed Intramolecular Cyclization Strategy



The success of our proposed approaches would rely heavily on judicious choice of the leaving group resident on the *N*-acylimine and the sulfur protecting group. Previous reports

(1) Pulici, M.; Quartieri, F. *Tetrahedron Lett.* **2005**, *46*, 2387−2391.
(2) Teraishi, F.; Wu, S.; Zhang, L.; Guo, W.; Davis, J. J.; Dong, F.; Fang, B. *Cancer Res.* **2005**, *65*, 6380−6387.
(3) Dayam, R.; Aiello, F.; Deng, J.; Wu, Y.; Garofalo, A.; Chen, X.; Neamati, N. *J. Med. Chem.* **2006**, *49*, 4526−4534.
(4) Suzuki, M.; Morita, K.; Yukioka, H.; Miki, N.; Mizutani, A. *J. Pesticide Sci.* **2003**, *28*, 37−43.
(5) Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175−203 and references cited therein.
(6) For an in-depth review, see: Barrett, G. C. *Tetrahedron* **1980**, *36*, 2023−2058. For a recent example, see: Blanchet, J.; Zhu, J. *Tetrahedron Lett.* **2004**, *45*, 4449−4452.
(7) Example using α-bromoester: (a) Mahboobi, S.; Sellmer, A.; Hocher, H.; Eichhorn, E.; Bar, T.; Schmidt, M.; Maier, T.; Stadlwieser, J. F.; Beckers, T. L. *J. Med. Chem.* **2006**, *49*, 5769−5776. Example using α-bromocarboxylic acid: (b) St. Jean, D. J.; Yuan, C.; Bercot, E. A.; Cupples, R.; Chen, M.; Fretland, J.; Hale, C.; Hungate, R. W.; Komorowski, R.; Veniant, M.; Wang, M.; Zhang, X.; Fotsch, C. *J. Med. Chem.* **2007**, *50*, 429−432.

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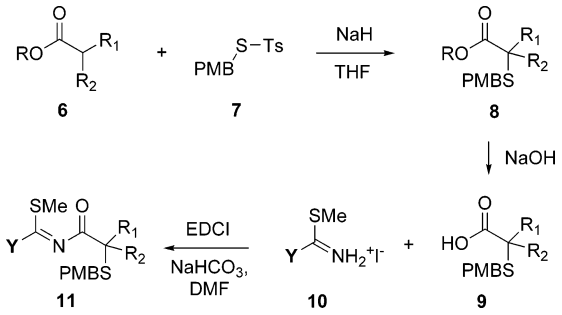
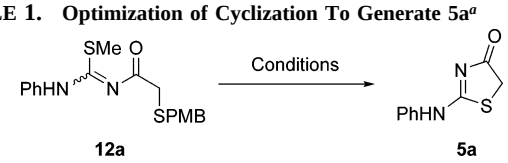
of amine displacements with use of 2-thiomethylthiazolones (**4**, X = SMe)[9] as electrophilic coupling partners and the accessibility of the required isothioureas starting materials led us to investigate the use of thiols as leaving groups. Our synthetic approach to carboxylic acid **9** necessitated introduction of the mercapto moiety as a 4-methoxybenzyl thioether (Scheme 2). Utilization of this functionality bears several advantages: (i) the acid-catalyzed deprotection is followed by in situ acid-promoted cyclization to **4** or **5** and (ii) the 4-methoxybenzyl thioether group can be introduced directly by sulfenylation of the anion of **6**[10] rather than an S_N2 displacement of the corresponding bromide that may be difficult depending on the nature of R_1 and R_2. With mercaptoester **8** in hand, saponification followed by coupling with imine salts[11] **10** provides the desired cyclization substrates (**11**).

SCHEME 2. *N*-Acylimine Substrate Preparation



The deprotection−cyclization was first examined by using *N*-acylisothiourea **12a** (Table 1). *N*-Acylisothiourea **12a** was reacted with 1 equiv of trifluoromethane sulfonic acid (TfOH) and 1 equiv of anisole in trifluoroacetic acid (TFA) at 23 °C for 5 h to afford 2-aminothiazolone **5a** in 71% yield (Table 1, entry 1). The experimental conditions for this transformation were examined in detail. As expected no reaction was observed in the absence of TfOH (entry 2). TFA could be replaced by either toluene (entry 3) or CH_2Cl_2 (entry 4) as the reaction solvent, with toluene affording a higher yield (81%) of **5a**. It was determined that anisole was not required for a clean reaction profile and further evaluation of the reaction parameters in the absence of anisole was performed. A comprehensive solvent survey revealed that $Cl(CH_2)_2Cl$ was also suitable for the reaction, affording a 64% yield of **5a** (entry 6).[12] A number of acids were surveyed as a replacement for TfOH but only methanesulfonic acid (MsOH) gave **5a** albeit in low yield (entry 7). The number of equivalents of TfOH was investigated (entries 8, 9, and 10). With use of 1 equiv of TfOH, no reaction was observed at 23 °C (4 h), with 1.5 equiv the reaction was very sluggish (19% assay yield after 4 h at 23 °C). Increasing the amount of TfOH to 2.0 equiv resulted in a 77% yield of **5a** (entry 10, 23 °C for 4 h).[13]

TABLE 1. Optimization of Cyclization To Generate 5a[a]



entry	acid (equiv)	additive (equiv)	solvent	yield, %
1	TfOH (1)	anisole (1)	TFA	71
2	None	anisole (1)	TFA	NR
3	TfOH (3)	anisole (1)	toluene	81
4	TfOH (3)	anisole (1)	CH_2Cl_2	73
5	TfOH (3)	none	toluene	69
6	TfOH (3)	none	$Cl(CH_2)_2Cl$	64[b]
7	MsOH (10)	none	CH_2Cl_2	28
8	TfOH (1)	none	CH_2Cl_2	NR
9	TfOH (1.5)	none	CH_2Cl_2	19[b]
10	TfOH (2)	none	CH_2Cl_2	77

[a] Reaction conditions: Substrate **12a** was treated with the indicated reagents in 10 mL of solvent per g of substrate at 23 °C for 5 h unless otherwise indicated. Yields are isolated unless otherwise indicated. [b] Assay yields determined by HPLC versus an authentic standard.

Having identified the optimum reaction conditions, the substrate scope of this method was examined (Table 2). After evaluation of the cyclization with substrates **12b** and **12c** (Table 2, entries 2 and 3), CH_2Cl_2 was selected as the preferred solvent since use of toluene resulted in a biphasic reaction mixture[14] thereby decreasing the reaction rates. A study of the substitution at C-5 revealed that unsubstituted, dialkyl-substituted, and monoalkyl-substituted starting materials undergo the cyclization uneventfully (entries 1, 2, and 3). Additionally, a monoaryl-substituted substrate (**12d**) was competent in the cyclization reaction (60% yield, entry 4). Isourea **12e**, synthesized from 4-fluorobenzylamine, successfully underwent the desired transformation to generate **5e** (57%, entry 5). Finally, by using substrate **12f** in which R_3 and R_4 are methyl and phenyl the desired cyclic adduct **5f** was produced in modest yield (49%, entry 6).

With optimized cyclization conditions for *N*-acylisothioureas in hand, we sought to expand the method to the cyclization of *N*-acyldithoimidates to provide 2-thiomethythiazolones (Table 3). The cyclization reactions with substrates **13a**−**e** were studied by using the same reaction conditions described in Table 2, except that 1.5 equiv of TfOH was found to be sufficient. Examination of the substitution at C-5 revealed that unsubstituted, mono- and dialkyl-substituted starting materials are equally competent in undergoing the desired transformation (entries 1, 2, and 3). The reaction conditions allowed the incorporation of other functional groups at the C-5 position. Acyldithioimidates bearing an ester substituent (substrates **13d** and **13e**) underwent the cyclization process efficiently (entries 4 and 5).

Having successfully expanded the scope of the cyclization to include *N*-acyl dithioimidate acceptors in the context of

(8) Example using α-mercaptoester: (a) Ried, W.; Kuhnt, D. *Liebigs Ann. Chem.* **1986**, *4*, 780−784. Example using α-mercaptocarboxylic acid: (b) Kretov, A. E.; Bespalyi, A. S. *Zh. Obshch. Khim.* **1963**, *33*, 3323−3325.

(9) For coupling of 2-thiothiazolones and amines, see: (a) Unangst, P. C.; Connor, D. T.; Cetenko, W. A.; Sorenson, R. J.; Kostlan, C. R.; Sircar, J. C.; Wright, C. D.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1994**, *37*, 322−328. (b) Khodair, A. I. *J. Heterocycl. Chem.* **2002**, *39*, 1153−1160.

(10) For the electrophilic sulfenylation of esters and ketones, see: (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887−4902. (b) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405−4412. (c) Shibata, N.; Baldwin, J. E.; Jacobs, A.; Wood, M. E. *Tetrahedron* **1996**, *52*, 12839−12852. (d) Bischoff, L.; David, C.; Martin, L.; Meudal, H.; Roques, B.-P.; Faournie-Zaluski, M.-C. *J. Org. Chem.* **1997**, *62*, 4848−4850. (e) Hayashi, S.; Furukawa, M.; Yamamoto, J.; Kunihiro, N. *Chem. Pharm. Bull.* **1967**, *15*, 1188−1192.

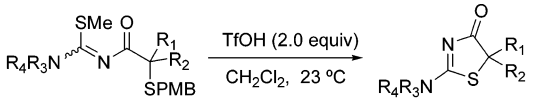
(11) See the Supporting Information for the preparation of imine salts.

(12) Other solvents examined (MTBE, THF, MeOH, acetone, 2-butanone, CH_3CN, DMF, EtOAc) were not effective.

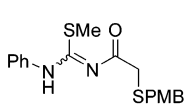
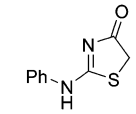
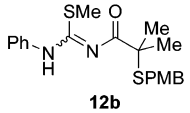
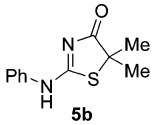
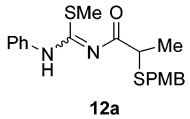
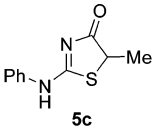
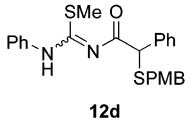
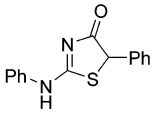
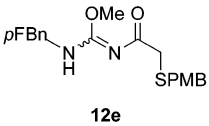
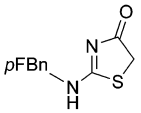
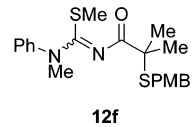
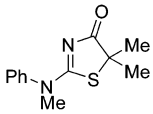
(13) No starting material **12a** remained under these conditions.

(14) We postulate that these insoluble oils are trifluoromethanesulfonic acid salts of the starting materials and products.

TABLE 2. Scope of Cyclization To Form 2-Aminothiazolones[a]

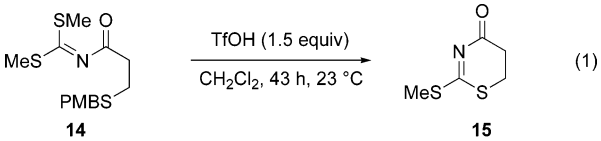


12a-f **5a-f**

Entry	Substrate	Product	Yield (%)
1	 **12a**	 **5a**	77
2	 **12b**	 **5b**	94
3	 **12a**	 **5c**	85
4	 **12d**	 **5d**	60
5	 **12e**	 **5e**	57
6[b]	 **12f**	 **5f**	49

[a] Reaction conditions: Substrates were treated with TfOH (2.0 equiv) in 10 mL of CH_2Cl_2 per g of substrate at 23 °C for 4 h unless otherwise indicated. Isolated yields are reported. Yields represent averages of duplicate experiments. No starting material *N*-acylisothioureas (or *N*-acylisourea) was recovered in these experiments. [b] 2.5 equiv of TfOH was used.

5-membered heterocycle construction, we sought to expand the reaction manifold to the formation of larger rings (eq 1). *N*-acyldithioimidate **14** was prepared and subjected to the prescribed reaction conditions for an extended amount of time providing the desired cyclization adduct **15** in 44% yield.[15]



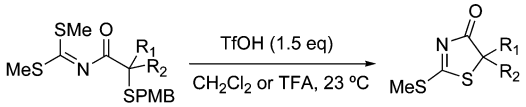
14 **15** (1)

44 % yield

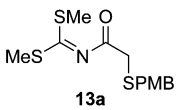
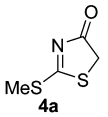
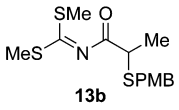
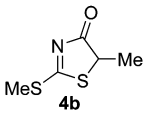
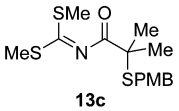
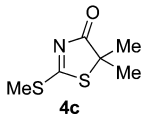
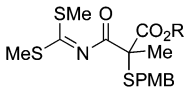
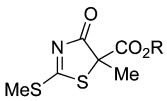
With ready access to a variety of substituted 2-thiomethylthiazolones, we next examined their reaction with amine coupling partners (Table 4). A variety of conditions have been reported to effect the desired transformation, many of which require rigorous conditions.[1,9] It was quickly established that the amine

(15) The corresponding homologated *N*-acylisothiourea did not provide cyclized product upon subjection to the optimized conditions.

TABLE 3. Scope of Cyclization To Form 2-Thiothiazolones[a]



13a-e **4a-e**

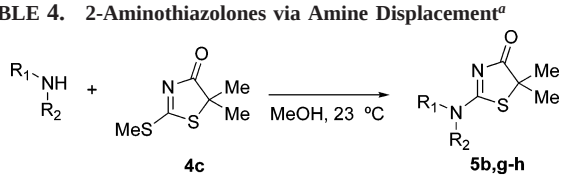
Entry	Substrate	Product	Yield (%)
1	 **13a**	 **4a**	85
2	 **13b**	 **4b**	86
3	 **13c**	 **4c**	95
4[b]	 R = Me (**13d**)	 R = Me (**4d**)	81
5[b]	R = Et (**13e**)	R = Et (**4e**)	73

[a] Reaction conditions: Substrates were treated with the indicated reagents in 10 mL of CH_2Cl_2 per g of substrate at 23 °C for 6−44 h unless otherwise stated. Isolated yields are reported. [b] TFA was used as solvent to simplify sample purification.

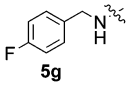
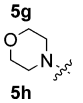
displacement reaction occurred smoothly at ambient temperature in methanol without the requirement of an exogenous base. The coupling of 2-thiomethylthiazolone **4c** with aromatic, benzylic, and secondary amines provided the desired 2-aminothiazolones in uniformly high yield.

In summary, two novel, complementary methods to synthesize 2-aminothiazolones (**5**) have been developed. In the first protocol heterocycles **5a**−**f** were prepared directly from 4-methoxybenzylthioethers (**12a**−**f**) under mild conditions, avoiding the need to perform a bromination−S_N2 displacement sequence to

TABLE 4. 2-Aminothiazolones via Amine Displacement[a]



4c **5b,g-h**

R_1R_2N-	Yield (%)
 **5b**	85
 **5g**	75
 **5h**	93

[a] Reaction conditions: Substrates were treated with the indicated reagents in 10 mL of MeOH per g of substrate at 23 °C. Isolated yields are reported.

introduce the thiol functional group. The second more convergent strategy involves cyclizations of *N*-acyldithioimidates (**13a**−**e**) followed by displacement of the thiomethyl leaving group with amines to produce the desired 2-aminothiazolones (**5b**,**g**,**h**). We anticipate that these methods will find application in the synthesis of enantiomerically enriched C5-disubstituted 2-aminothiazolones and 2-thiothiazolones from enantiomerically enriched carboxylic acids (**9**). Examples of such transformations will be reported in due course.

Experimental Section

Representative Procedure for the Preparation of 2-Aminothiazolones: 5,5-Dimethyl-2-(phenylamino)thiazol-4-(*5H*)-one (5b). To a solution of isothiourea **12b** (0.4 g, 0.001 mol) in CH_2Cl_2 (5 mL) was added TfOH (0.175 mL, 0.002 mol) via syringe under a N_2 atmosphere. The homogeneous mixture was stirred at 23 °C for 4 h during which time its color became deep red. After 4 h, an aliquot of the reaction mixture indicated complete conversion (no starting material **12b** was visible by LC). The reaction mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) and the phases separated. The aqueous phase was extracted with use of EtOAc (3 × 10 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Chromatography of the residue on silica gel (10 to 40% EtOAc/hexanes) afforded the thiazolone **5b** (0.205 g, 94%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (br s, 1H), 7.35−7.43 (m, 2H), 7.16−7.28 (m, 3H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 166.1, 142.6, 129.2, 125.9, 122.5, 56.2, 27.9; IR (neat) 2927, 2833, 1698, 1608, 1573, 1458, 1424, 1260, 1169, 772 cm^{-1}; exact mass ($C_{11}H_{12}N_2OS$ + H) calculated 221.0743, measured 221.0750; mp 128−130 °C.

Representative Procedure for the Preparation of 2-Thiothiazolones: 5,5-Dimethyl-2-(thiomethyl)thiazol-4-(*5H*)-one (4c). To a solution of *N*-acylimidate **13c** (0.994 g, 2.89 mmol) in CH_2Cl_2 (15 mL) was added TfOH (0.390 mL, 4.41 mmol) via syringe under a N_2 atmosphere. The homogeneous mixture was stirred at 23 °C for 6 h during which time its color became deep red. After 6 h, an aliquot of the reaction mixture indicated complete conversion (no starting material **13c** was visible by LC). The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous phase extracted with use of CH_2Cl_2 (1 × 25 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography of the residue on silica gel (5% to 40% EtOAc/hexanes) afforded the thiazolone **4c** (0.482 g, 95%) as a colorless low-melting solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 192.3, 61.6, 27.3, 16.1; IR (neat) 2972, 2930, 1708, 1440, 1229, 1144, 1119, 988 cm^{-1}; exact mass ($C_6H_9NOS_2$ + H) calculated 176.0198, measured 176.0197.

Representative Procedure for the Preparation of 2-Aminothiazolones via Amine Displacement: 5,5-Dimethyl-2-morpholinothiazol-4(5*H*)-one (5h). To a solution of 2-thiomethylthiazolone **4c** (103 mg, 0.59 mmol, 1.0 equiv) in dry MeOH (2 mL) was added morpholine (70 μL, 0.80 mmol, 1.4 equiv). The homogeneous mixture was stirred at ambient temperature for 2 h. The reaction mixture was partitioned between EtOAc (10 mL) and DI H_2O (10 mL). The phases were separated and the aqueous phase was extracted with use of EtOAc (1 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated providing 117 mg (93%) of the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81−4.01 (m, 2H), 3.77−3.79 (m, 4H), 3.47−3.50 (m, 2H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 178.7, 66.3, 66.1, 48.5, 48.2, 27.9; IR (neat) 2962, 2925, 2862, 1696, 1537, 1347, 1284, 1239, 1111, 1027, 892 cm^{-1}; exact mass ($C_9H_{14}N_2O_2S$ + H) calculated 215.0848, measured 215.0852; mp 128−130 °C.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds described in the paper are provided [^{1}H and ^{13}C NMR, FTIR, HRMS, melting points if applicable]. This material is available free of charge via the Internet at http://pubs.acs.org.

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