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Formation of Unusual Seven-Membered Heterocycles Incorporating Nitrogen and Sulfur by Intramolecular Conjugate Displacement

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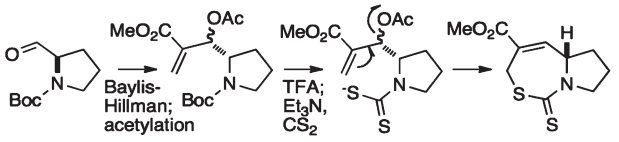
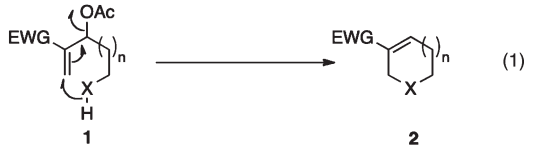
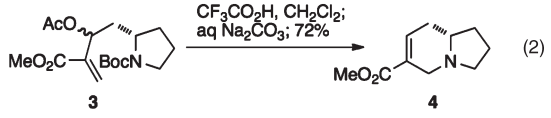
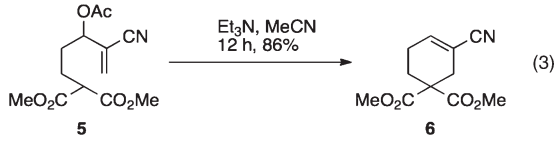


Baylis−Hillman alcohols derived from methyl acrylate or acrylonitrile and carrying an N-Boc group β to the hydroxyl (CH(OH)CHNBoc) can be converted into unusual seven-membered heterocycles containing both nitrogen and sulfur by O-acylation (AcCl or EtOCOCl), N-deprotection (CF_3CO_2H), and reaction with CS_2. In a modification of this process, when the original nitrogen is substituted in the form $PhSCH_2CON(Me)$, an azepine derivative is then generated. The ring closures occur by intramolecular conjugate displacement.

Intramolecular conjugate displacement[1]—the type of cyclization summarized by eq 1—provides a method for making both nitrogen heterocycles and carbocycles along the lines of eqs 2[1] and 3,[2] which show particular examples from the many that have been reported from this laboratory.[1,2]

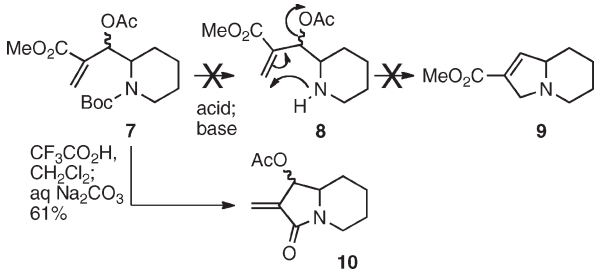




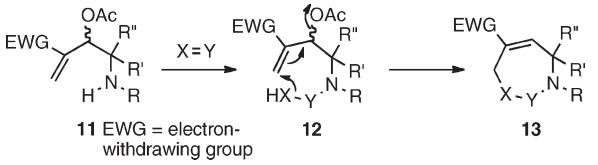


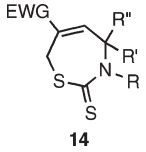
In studying the nitrogen case, we found that one type of starting material, compound **7**, failed to undergo ICD (to give **9**),[1] presumably because such a process would violate Baldwin's rules.[3] In this particular case, an alternative pathway, attack on the methyl ester carbonyl, was followed (**7** → **10**; Scheme 1). The fact that compounds of type **7** would appear to be inherently protected against the intramolecular conjugate displacement pathway suggested that if an unsaturated electrophile could be found that is attacked rapidly by nitrogen to generate a new nucleophilic species, then cyclization would occur as illustrated in Scheme 2, **11** → **12** → **13**, where X=Y represents an electrophile, either by itself or as a subunit of a larger structure. We have examined a number of potential electrophiles (PhNCO, PhNCS, SO_2, $BnN{=}CH_2$, $(Cl_3C)_2C{=}NBn$, CO_2, CS_2, and H_2NCN) and have found that CS_2 satisfies the requirements and gives access to a range of 2-thioxo-1,3-thiazepine derivatives, unusual heterocycles of type **14**. We can find only one example (**14**; EWG = R′ = R″ = H, R = $^+PPh_3$)[4]—formed as a minor (15%) byproduct—of a substance closely related to this compound class.

SCHEME 1. 5-Exo Trigonal Cyclization



SCHEME 2. Intermolecular Addition Followed by ICD





The N-Boc amines we have used were all readily accessible via classical Baylis−Hillman condensation between the appropriate aldehyde and methyl acrylate (second column of Table 1, entries 1−7, 10, and 12) or acrylonitrile (Table 1, entries 8 and 9) in the presence of DABCO at room temperature (2−4 days, > 69%). While this classical approach is not the only route to Baylis−Hillman alcohols,[5] it was convenient for the present study. The alcohols (except that

(1) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem.* **2007**, *72*, 5608–5617.
(2) Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003–6012.

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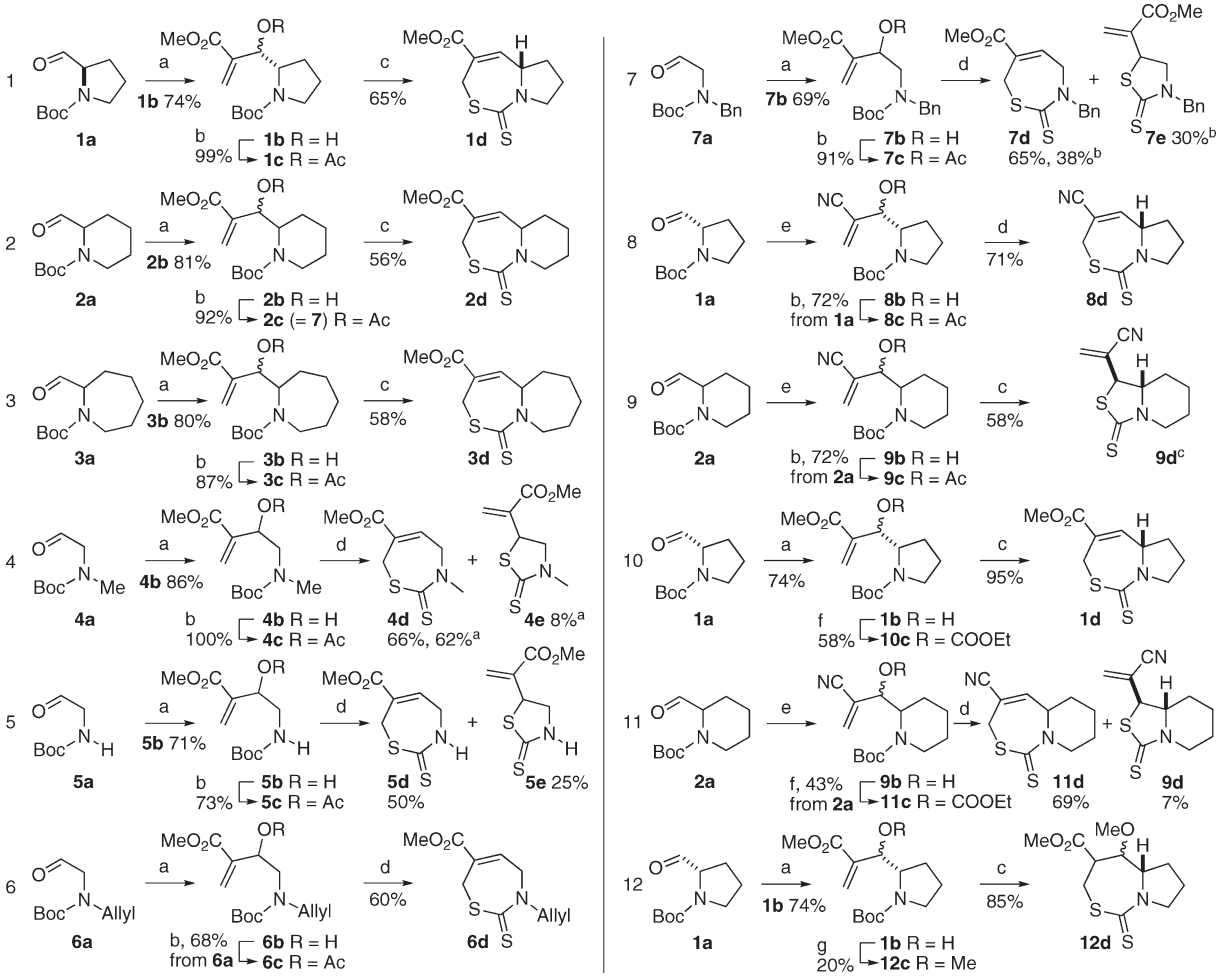
TABLE 1. Baylis–Hillman Reaction, Acylation, and ICD Process



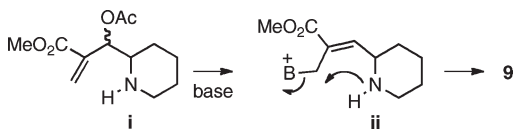
[a] *i*-PrNEt$_2$ gave **4d** (62%) and **4e** (8%); use of 2,6-lutidine gave only **4d** (66%). [b] 2,6-Lutidine gave only **7d** (65%); use of *i*-PrNEt$_2$ gave **7d** (38%) and **7e** (30%). [c] Arbitrary stereochemistry. Reagents and conditions: (a) methyl acrylate, DABCO, CH_2Cl_2; (b) AcCl, pyridine, CH_2Cl_2; (c) TFA, CH_2Cl_2 and CS_2, *i*-PrNEt$_2$, MeCN; (d) TFA, CH_2Cl_2 and CS_2, 2,6-lutidine, MeCN; (e) acrylonitrile, DABCO, CH_2Cl_2; (f) EtOCOCl, pyridine, CH_2Cl_2; (g) NaH, MeI, THF.

of Table 1, entries 10 and 11) were then acylated (> 73% yield), using AcCl/pyridine or (for entries 10 and 11) EtOCOCl/pyridine.

The acylated compounds **1c**–**11c** were each treated with CF_3CO_2H (CH_2Cl_2, room temperature) to remove the N-protecting group and release the trifluoroacetate salt of the corresponding amine. Then CS_2, followed by Hünig's base or 2,6-lutidine, was added to a solution of the crude amine trifluoroacetate in MeCN. Sometimes 2,6-lutidine gave a better result; in the case of **4c**, use of Hünig's base afforded a small amount of **4e** (8%), but with 2,6-lutidine none of this byproduct was isolated. The results summarized in Table 1 show that, with an ester as the electron-withdrawing group and acetate as the leaving group, secondary aliphatic[6] amines undergo the ICD process, but a careful choice of base may be required to optimize the selectivity in favor of the 2-thioxo-1,3-thiazepine derivatives because a competing side reaction is formation of a 2-thiazolidinethione. For example, when **7c** was treated with 2,6-lutidine and CS_2 (1.5 h), **7d** was formed in 65% yield, but with Hünig's base (ca. 12 h) **7e** was isolated (30%) in addition to **7d** (38%).

The nitrogen of the starting amine can be part of a ring or a chain. In the latter case, the reaction is more selective for formation of the seven-membered ring when the deprotected nitrogen is a secondary amine (**4d**/**4e**, **6d**, **7d**/**7e**); when the deprotected nitrogen is primary, a major side product is the 2-thiazolidinethione (**5e**). We noted that if the nitrogen carries an aryl substituent,[6] the ICD did not occur, presumably because of the suppressed nucleophilicity of anilines compared with aliphatic amines.

(3) While the pathway shown in **8** violates Baldwin's rules, we anticipated that **9** might still be accessible by the alternative sequence **i** → **ii** → **9**.



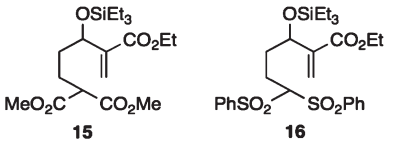
(4) Isoda, T.; Hayashi, K.; Tamai, S.; Kumagai, T.; Nagao, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1616–1619.

(5) For another route, based on selenides, see refs 1 and 2.

(6) We examined one case where the deprotected nitrogen carried a *p*-methoxyphenyl ring; no addition to CS_2 occurred (see the Supporting Information).

As two products are sometimes formed, we determined if the reaction was under thermodynamic or kinetic control. When compound **7d** was subjected to the original conditions of the cyclization, it remained unchanged; likewise **7e** (generated by use of *i*-PrNEt$_2$ instead of 2,6-lutidine) was also unchanged. Consequently, the cyclizations must be kinetically controlled.

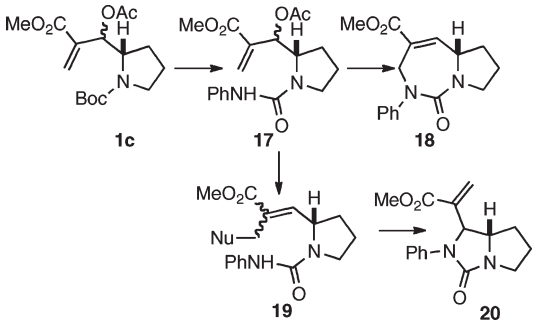
The outcome of the reaction is also sensitive to the nature of both the electron-withdrawing substituent and the allylic leaving group. The nitrile−acetate system **9c** appeared to give only a five-membered ring (58%), for which the indicated stereochemistry is an arbitrary assignment, while the corresponding methyl ester−acetate **2c** provided an almost identical yield (56%) of the seven-membered ring. In the case of nitrile **8c**, reaction at −40 °C gave the single product **8d**, while at room temperature an inseparable 4:1 mixture of two compounds, presumably **8d** and the corresponding pyrrolo-[1,2-*c*]thiazole-3-thione, were formed. The allylic carbonate **10c** afforded the cyclized product **1d** in very high yield—95% versus 65% for the corresponding acetate **1c**. Since in this case the use of a carbonate leaving group favored formation of the seven-membered ring, we examined the ethyl carbonate derived from **9b** and found (Table 1, entry 11) that a 5:1 mixture of the seven-membered and five-membered products was formed at room temperature; this ratio was improved to 10:1 at −40 °C, implying the trend that a carbonate leaving group favors formation of the seven-membered ring. We also evaluated the consequences of using a poor leaving group, by making the methyl ether **12c**; however, this produced only **12d**, the product of Michael addition. Such a pathway had been observed before in related experiments done in this laboratory:[2] use of a poor leaving group, as in **15**, still produced the ICD product on treatment with Cs_2CO_3,[2] although at a lower rate than for the corresponding acetate, while the related substrate **16** underwent both Michael addition without loss of the siloxy group and the normal ICD process.[2]



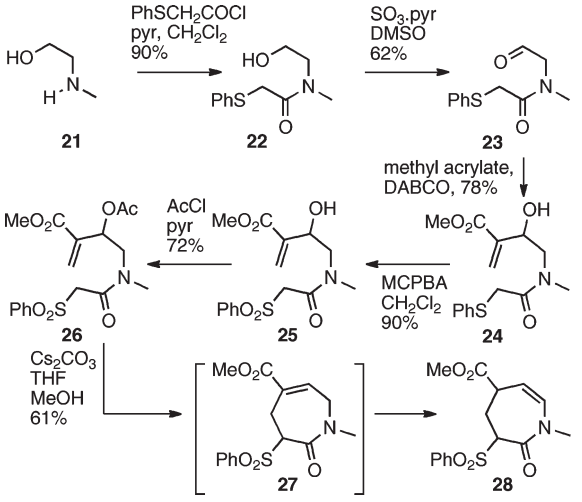
As indicated above, we had examined a number of potential electrophiles and some comment on a few of them is in order. Reaction of **1c** with CF_3CO_2H and then with Hünig's base and PhNCO served only to produce the urea **17** (71%), formed by simple intermolecular addition (Scheme 3). Closure to the ICD product **18** could be achieved, however, by further reaction with $(Me_3Si)_2NK$ (THF, 0 °C), but only in 39% yield. Interestingly, the action of DBU and LiBr on **17** gave **20** (35%). In the pathway from **17** to **20** the first step might be an *intermolecular* conjugate displacement to afford **19**, where the nucleophile is Br^- or DBU.

Each of the final products listed in Table 1 is a cyclic dithiocarbamate, and it was obvious that the utility of the present

SCHEME 3. Reaction with PhNCO



SCHEME 4. Formation of Lactam



ICD process would be increased if heterocycles containing only a single heteroatom in the ring could be generated. To this end, we examined nitroethene,[7] $(MeO_2C)_2CN_2/Rh_2(OAc)_4$,[8] and $(MeO_2C)_2CHBr$[9] as potential formal electrophiles to capture the deprotected nitrogen. Our experiments with these compounds were all unpromising, except for the fact that they steered our attention toward a modified approach, which is illustrated in Scheme 4, and which simply involves attaching the final nucleophile (see the $PhSCH_2CO$ subunit of **22**) at an earlier stage.

N-acylation of 2-(methylamino)ethanol with $PhSCH_2COCl$[10] (pyridine, 90%) and oxidation (Parikh−Doering, 62%) gave **23**, setting the stage for generation of the desired ICD substrate. This was accomplished as follows: reaction of **23** with methyl acrylate in the presence of DABCO gave alcohol **24**, and oxidation (MCPBA) and acetylation (AcCl, pyridine) then afforded sulfone **26**.

Surprisingly, on treatment with Cs_2CO_3 in 10:1 THF−MeOH the sulfone was converted (61%) into the enamide **28**, which was a single isomer whose relative stereochemistry was not established. One possible pathway for its formation is via the expected ICD product **27**, followed by double bond migration. Alternatively, elimination of acetate from **26**, followed by simple Michael addition, would also lead to

(7) Use of nitroethene gave only the result of an initial intermolecular Michael addition (100%) but none of the ICD product.

(8) Cf.: (a) Yamagata, K.; Okabe, F.; Yamazaki, M. J. *J. Prakt. Chem.* **1999**, *341*, 562–567. (b) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 591–600. (c) Falorni, M.; Dettori, G.; Giacomelli, G. *Tetrahedron: Asymmetry* **1998**, *9*, 1419–1426. (d) Gibe, R.; Kerr, M. A. *J. Org. Chem.* **2002**, *67*, 6247–6249. (e) Yang, M.; Wang, X.; Li, H.; Livant, P. *J. Org. Chem.* **2001**, *6*, 6729–6733.

(9) Wolfe, S.; Ro, S.; Kim, C.-K.; Shi, Z. *Can. J. Chem.* **2001**, *79*, 1238–1258.

(10) Kennedy, M. G.; Moody, C. J.; Rees, C. W.; Thomas, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2499–2504.

the observed product **28**. If this is the case, elimination of acetate must give largely (> 61%) the *Z* isomer, and it is not clear why this should be so. When compound **1c**, which we used as a model, was treated under conditions identical with those for **26**, only acetate hydrolysis to **1b** was observed (96% yield) and no elimination product was isolated, suggesting that formation of **28** does indeed occur via a true ICD pathway involving **27**.

The reactions reported here extend the ICD[1,2] process to the generation of unusual seven-membered heterocycles. In a few cases a five-membered heterocycle is formed and we note that a number of potentially significant biochemical properties have been reported for related 2-thiazolidinethiones;[11] the properties of the new seven-membered system are unknown.

Experimental Section

1-[(1,1-Dimethylethoxy)carbonyl]hexahydro-β-hydroxy-α-methylene-1*H*-azepine-2-propanoic Acid Methyl Ester (3b). DABCO (591 mg, 5.28 mmol) was added to a stirred mixture of **3a**[12] (400 mg, 1.76 mmol) and methyl acrylate (1.61 mL, 17.8 mmol), and stirring was continued for 3 days. The mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 2:1 hexane−EtOAc, gave **3b** (440 mg, 80%) as an oil: FTIR ($CDCl_3$, microscope) 3434, 2928, 2854, 1722, 1689, 1676, 1478, 1441, 1414, 1391, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.26−2.16 (m, 17 H), 2.88−3.03 (m, 1 H), 3.48−3.77 (m, 1 H), 3.79 (s, 3 H), 4.13−4.40 (m, 2 H), 5.58−5.89 (m, 1 H), 6.22−6.27 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 25.4, 28.5, 29.0, 29.5, 30.3, 43.2, 44.5, 44.7, 51.7, 59.3, 60.6, 60.8, 74.5, 75.7, 79.6, 79.9, 125.8, 126.3, 140.3, 141.9, 155.5, 157.6, 159.8, 166.9, 167.3; exact mass *m*/*z* calcd for $C_{16}H_{27}NNaO_5$ (M + Na) 336.1781, found 336.1780. The ^1H NMR spectrum consisted of broad signals, and we attribute the extra signals in the ^{13}C NMR spectrum to the presence of rotamers and diastereoisomers.

β-Acetoxy-1-[(1,1-dimethylethoxy)carbonyl]hexahydro-α-methylene-1*H*-azepine-2-propanoic Acid Methyl Ester (3c). AcCl (0.29 mL, 3.27 mmol) was added to a stirred mixture of **3a** (341 mg, 1.09 mmol) and pyridine (0.47 mL, 5.45 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h, and the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 × 15 cm), using 4:1 hexane−EtOAc, gave **3c** (355 mg, 87%) as an oil: FTIR ($CDCl_3$, microscope) 2929, 2855, 1751, 1725, 1692, 1440, 1366, 1232, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.16−2.16 (m, 20 H), 2.81−2.90 (m, 1 H), 3.56−3.70 (m, 1 H), 3.78−3.81 (m, 3 H), 4.29−4.51 (m, 1 H), 5.67−5.81 (m, 2 H), 6.28−6.32 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 20.9, 21.0, 24.8, 25.0, 28.5, 28.6, 28.8, 29.3, 29.7, 29.8, 30.1, 30.3, 43.4, 43.8, 51.9, 52.0, 56.8, 57.0, 51.6, 73.4, 74.0, 79.2, 79.3, 79.8, 80.0, 125.7, 126.0, 126.6, 138.6, 138.8, 155.4, 155.8, 156.2, 165.4, 165.6; exact mass *m*/*z* calcd for $C_{18}H_{29}NNaO_6$ (M + Na) 378.1887, found 378.1890.

5a,6,7,8,9,10-Hexahydro-1-thioxo-3*H*-azapino[1,2-*c*]-[1,3]thiazepine-4-carboxylic Acid Methyl Ester (3d). CF_3CO_2H (0.18 mL, 2.36 mmol) was added to a stirred solution of **3c** (79 mg, 0.236 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h, and the mixture was evaporated. The residue was dissolved in MeCN (5 mL), and CS_2 (72 μL, 0.944 mmol) and *i*-Pr_2NEt (0.13 mL, 0.980 mmol) were added. Stirring was continued overnight, and the mixture was evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 2:1 hexane−EtOAc, gave **3d** (37 mg, 58%) as an oil: FTIR ($CDCl_3$, microscope) 2928, 2854, 1716, 1466, 1437, 1408, 1233, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39−2.18 (m, 8 H), 3.21 (dd, J = 12, 13.5 Hz, 1 H), 3.62 (d, J = 14 Hz, 1 H), 3.79 (s, 3 H), 4.15 (dd, J = 2, 14 Hz, 1 H), 4.89 (ddd, J = 5, 9, 12 Hz, 1 H), 4.97 (dd, J = 5, 14 Hz, 1 H), 6.91 (dd, J = 2, 9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3 (t), 28.6 (t), 28.7 (t), 32.7 (t), 34.8 (t), 50.7 (t), 52.5 (d), 61.3 (q), 129.2 (s), 141.4 (d), 165.2 (s), 195.3 (s); exact mass *m*/*z* calcd for $C_{12}H_{17}NNaO_2S_2$ (M + Na) 294.0593, found 294.0593.

Acknowledgment. We thank the NSERC for financial support.

Supporting Information Available: Text and figures giving detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) E.g.: (a) Alhamadsheh, M. M.; Waters, N. C.; Huddler, D. P.; Kreishman-Deitrick, M.; Florova, G.; Reynolds, K. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 879–883. (b) Yoneda, K.; Ota, A.; Kawashima, Y. *Chem. Pharm. Bull.* **1993**, *41*, 876–881. (c) Znamenskii, V. V.; Grechka, I. I.; Ignatova, Yu. L.; Karimova, N. M. *Pharm. Chem. J.* **1996**, *30*, 617–619.

(12) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109–1117.