A New and Efficient Access to Oxazoline-5-carboxylates and Amino Acid Derivatives with Cyclopropyl Groups[1]

Marcus W. Nötzel,[†] Markus Tamm,[†] Thomas Labahn,[‡] Mathias Noltemeyer,[‡] Mazen Es-Sayed,[§] and Armin de Meijere*,[†]

Institute für Organische und Anorganische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2−4, D-37077 Göttingen, Germany and Bayer AG, Landwirtschaftszentrum, Alfred-Nobel-Strasse 50, Geb. 6510, D-40789 Monheim, Germany

Received January 29, 1999

Cyclopropyl groups containing homologues of natural amino acids are gaining an ever increasing interest as potential enzyme inhibitors[2] and conformationally restricted building blocks for peptidomimetics.[3] A wide range of biological activities has been uncovered for such unnatural amino acid analogues and small peptides containing them.[4] Quite a variety of such cyclopropane amino acids and their derivatives have been prepared via sequences of Michael addition, nucleophilic substitution, and possible further transformations[5−8] from the highly reactive acrylate analogues methyl 2-chloro-2-cyclopropylideneacetates **1**.[9] In view of the fact that even weakly nucleophilic deprotonated oxazolidinones add to **1** under appropriate conditions,[7] it was of interest to study the addition of primary carboxamides to **1**, as the adducts would have the potential to undergo ring closure to oxazolines **5** by intramolecular substitution of the α-chlorine.[10] Such ring closures are well documented,[11] but this would be the first case in which an oxazoline would be formed in a domino process consisting of a Michael addition and immediately ensuing ring closure by intramolecular nucleophilic substitution. The resulting spirocyclopropanated oxazolinecarboxylates **5** would be protected 2-hydroxy-2-(1'-aminocyclopropyl)acetic acid derivatives with an interesting combination of functionalities for further elaboration.

When methyl 2-chloro-2-cyclopropylideneacetate (**1a)** in acetonitrile solution was treated with benzamide (**2a**) in the presence of sodium hydride at 0 °C and the mixture was allowed to warm to room temperature overnight, the methyl 2-phenylspirocyclopropane-1',4-oxazoline-5-carboxylate (**5a**) was isolated in 60% yield (Scheme 1). The structure could be assigned on the basis of its ^{1}H and ^{13}C NMR and MS data, and it was rigorously proved by X-ray crystallography.[12]

Nicotinamide (**2b**), furan-2-carboxamide (**2c**), and substituted benzamides **2d**−**o** under the same conditions gave the corresponding oxazolines **5b**−**o** in yields ranging from 38% to 77% (Table 1).

It is remarkable that of four possible diastereomers only two are formed in the Michael additions of the deprotonated amide **2** to the 2'-substituted 2-cyclopropylideneacetates **1b,c**, and of these two one is highly favored in the cases of **5p**−**r,t** [diastereomeric ratio (dr) up to 17:1]. This means one chiral center was formed diastereoselectively during the addition of **2** to the two prochiral centers of **1b,c**. The relative configuration of the major diastereomer of the 4-nitrophenyl-substituted oxazolinecarboxylate **5s** was proved by an X-ray crystal structure analysis[12] to be 4*S**,5*R**,2'*R**.

The new oxazolinecarboxylates **5** are suitable precursors to 2-(1'-aminocyclopropyl)-2-hydroxyacetic acid (**7**). While hydrolysis of **5a** under basic conditions (NaOH in THF) led only to the oxazolinecarboxylic acid **6**, the free amino acid **7** could be obtained under acidic conditions. However, **7** was not isolated but immediately benzoylated to the more easily purified *N*-benzoyl derivative **8** (Scheme 2).

This benzoyl derivative **8** can be viewed as a cyclopropanated analogue of the side chain in Taxol (**9**). It remains to be seen whether replacement of the natural side chain in Taxol with the acyl residue of **8** would lead to interesting properties of the pharmacophor.[13]

Simple alkanecarboxamides do not form the corresponding oxazolinecarboxylates **5** in good yield, which is probably a result of their C,H acidity α to the carbonyl group. Acetamide (**2p**) gave only 6% of **5w**, whereas propionamide (**2q**), butyramide (**2r**), and pivalamide (**2s**)

[†] Institut für Organische Chemie.
[‡] Institut für Anorganische Chemie.
[§] Bayer AG.

(1) Part 56 in the series "Cyclopropyl Building Blocks in Organic Synthesis". For Part 55 see: Winsel, H.; Gazizova, V.; Kulinkovich, O.; Pavlov, V.; de Meijere, A. *Synlett* **1999**, 1999−2003. For Part 54 see: de Meijere, A.; Nüske, H.; Es-Sayed, M.; Schroen, M.; Labahn, T.; Bräse, S. *Angew. Chem.* **1999**, *111*, 3881−3884; *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3669−3672.

(2) (a) Pirrung, M. C.; Cao, J.; Chen, J. *J. Org. Chem.* **1995**, *60*, 5790−5794. (b) Pirrung, M. C.; Han, H.; Chen, J. *J. Org. Chem.* **1996**, *61*, 4527−4531. (c) Pirrung, M. C.; Kaiser, L. M., Chen, J. *Biochemistry* **1993**, *32*, 7445−7450.

(3) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett* **1994**, 575−583.

(4) (a) Salaün, J. *Top. Curr. Chem.* **1999**, *207*, 1−88. (b) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511−542. (c) Huang, Z.; He, Y.-B.; Raynor, K.; Tallent, M.; Reisine, T.; Goodman, M. *J. Am. Chem. Soc.* **1992**, *114*, 9390−9401. (d) Zhu, Y.-F.; Yamazaki, T.; Tsang, J. W.; Lok, S.; Goodman, M. *J. Org. Chem.* **1992**, *57*, 1074−1081.

(5) For reviews see: (a) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20−32. (b) de Meijere, A. In *New Aspects of Organic Chemistry II*, Proceedings of the Fifth International Kyoto Conference on New Aspects of Organic Chemistry−IKCOC 5, Kyoto, Nov 11−15 1991; Oshiro, Y., Ed.; Kodansha: Tokyo, 1992; p 181. (c) de Meijere, A.; Kozhushkov, S. I.; Hadjiarapoglou, L. *Top. Curr. Chem.* **1999**, *207*, 149−227.

(6) (a) Wessjohann, L.; Krass, N.; Yu, D.; de Meijere, A. *Chem. Ber.* **1992**, *125*, 867−882. (b) Tamm, M.; Thutewohl, M.; Ricker, C.; Bes, M. T.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, 2017−2024.

(7) (a) Es-Sayed, M.; Gratkowski, C.; Krass, N.; de Meijere, A. *Synlett* **1992**, 962−964. (b) Es-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 289−292.

(8) Wessjohann, L.; Giller, K.; Zuck, B.; Skattebøl, L.; de Meijere, A. *J. Org. Chem.* **1993**, *58*, 6442−6450.

(9) Liese, T.; Seyed-Mahdavi, F.; de Meijere, A. *Org. Synth.* **1990**, *69*, 148−153.

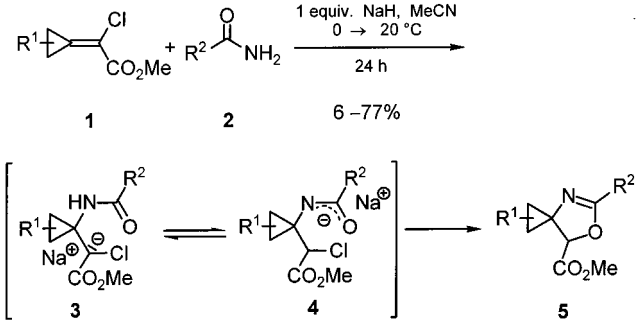
(10) de Meijere, A.; Teichmann, S.; Yu, D.; Kopf, J.; Oly, M.; von Thienen, N. *Tetrahedron* **1989**, *45*, 2957−2972.

(11) For examples see: (a) Gabriel, S.; Elfeldt, P. *Chem. Ber.* **1891**, *24*, 3213−3228. (b) Cassebaum, H.; Uhlig, K. *J. Prakt. Chem.* **1973**, *315*, 1057−1066. (c) Flouzat, C.; Guillaumet, G. *Synthesis* **1990**, 64−66. (d) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306−4309. (e) Perry, J. R.; Wilson, B. D. *J. Org. Chem.* **1992**, *57*, 6351−6354. (f) Minami, T.; Isonaka, T.; Okada, Y.; Ichikawa, J. *J. Org. Chem.* **1993**, *58*, 7009−7015.

(12) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication CCDC-113834 (**5a**) and CCDC-135542 (**5s**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (a) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467. (b) Sheldrick, G. M. *SHELXL-93*, program for crystal structure refinement: University of Göttingen: Göttingen, 1993.

10.1021/jo990170y CCC: $19.00
Published on Web 05/23/2000

Scheme 1[a]



[a] For details, see Table 1.

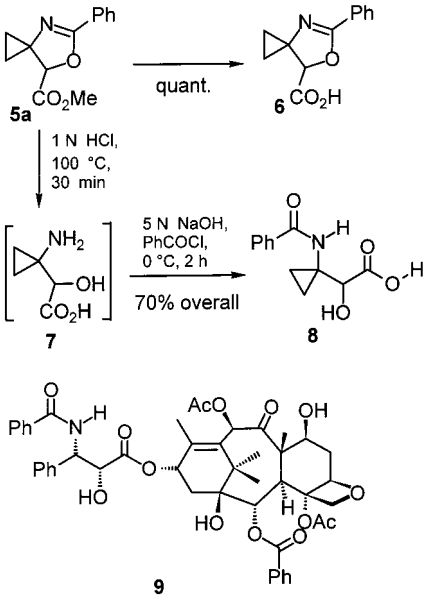
Table 1. Synthesis of Oxazolinecarboxylates 5 from Acid Amides 2 and Methyl 2-Chloro-2-cyclopropylideneacetates 1

Michael acceptor	amide	R^1	R^2	product	yield (%)	dr
1a	**2a**	H	Ph	**5a**	60	
1a	**2b**	H	3-C_5H_4N[a]	**5b**	38	
1a	**2c**	H	2-C_4H_3O[b]	**5c**	49	
1a	**2d**	H	*p*-CN-C_6H_4	**5d**	74	
1a	**2e**	H	*o*-Me-C_6H_4	**5e**	70	
1a	**2f**	H	*m*-Me-C_6H_4	**5f**	58	
1a	**2g**	H	*p*-Me-C_6H_4	**5g**	50	
1a	**2h**	H	*m*-F-C_6H_4	**5h**	75	
1a	**2i**	H	*p*-Br-C_6H_4	**5i**	73	
1a	**2j**	H	*o*-NO_2-C_6H_4	**5j**	47	
1a	**2k**	H	*p*-NO_2-C_6H_4	**5k**	47	
1a	**2l**	H	*o*-Cl-C_6H_4	**5l**	77	
1a	**2m**	H	*p*-Cl-C_6H_4	**5m**	68	
1a	**2n**	H	*o*-I-C_6H_4	**5n**	72	
1a	**2o**	H	*m*-I-C_6H_4	**5o**	49	
1b	**2a**	Et	Ph	**5p**	56	9:1
1b	**2e**	Et	*o*-Me-C_6H_4	**5q**	68	17:1
1b	**2n**	Et	*o*-I-C_6H_4	**5r**	55	17:1
1b	**2k**	Et	*p*-NO_2-C_6H_4	**5s**	40	2:1
1b	**2h**	Et	*m*-F-C_6H_4	**5t**	46	7:1
1b	**2b**	Et	3-C_5H_4N[a]	**5u**	25	5:1
1c	**2k**	CH_2CH_2OBn	*p*-NO_2-C_6H_4	**5v**	41	2:1
1a	**2p**	H	Me	**5w**	6	
1a	**2q**	H	Et	**5x**	24	
1a	**2r**	H	*n*-Pr	**5y**	24	
1a	**2s**	H	*t*-Bu	**5z**	25	

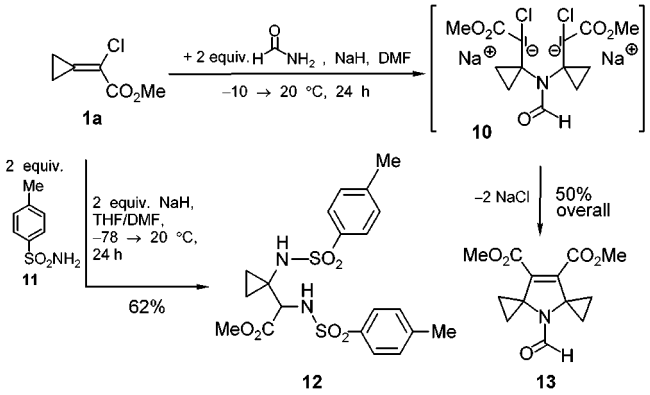
[a] Nicotinic acid amide. [b] Furan-2-carboxamide.

gave **5x**–**z** in a moderate yield of 24% and 25%. Interestingly, formamide in its reaction with methyl 2-chloro-2-cyclopropylideneacetate (**1a**) did not yield the 2-unsubstituted oxazolinecarboxylate of type **5** but the bis-spirocyclopropanated pyrrolinedicarboxylate **13**. The latter apparently must have formed via the 1:2 Michael adduct of formamide onto **1a**. On the other hand, *p*-toluenesulfonyl amide (**11**) reacted with **1a** under the same conditions to give the Michael addition–substitution product **12** rather than the *N*-*p*-toluenesulfonyl-substituted analogue of **13**. This product **12** dominated even when only 1 equiv

Scheme 2



Scheme 3



of **11** was used; with 2 equiv of **11** the bissulfonyl-protected α,*β*-diamino acid **12** was obtained in 62% yield (Scheme 3).

In conclusion, methyl 2-chloro-2-cyclopropylideneacetates **1a**–**c** upon treatment with carboxamides under basic conditions undergo a domino transformation involving a Michael addition followed by an intramolecular nucleophilic substitution to afford 4-spirocyclopropane-annelated oxazoline-5-carboxylates **5**. The reactions of the 2'-substituted compounds **1b,c**, with two prochiral centers, are remarkably diastereoselective in that only two of four possible diastereomers are formed, and one of the two in most cases is highly favored (dr up to 17:1). The oxazoline-5-carboxylates **5** are protected α-hydroxy-*β*-amino acids.

Experimental Section

General. All chemicals used are commercially available except for methyl 2-chloro-2-cyclopropylideneacetates **1a**–**c**,[14] which were prepared by the literature method,[8] and some of the benzamides, which were prepared according to a general procedure.[15] All reactions were performed in anhydrous solvents under an atmosphere of N_2. Solvents were distilled under N_2

(13) (a) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597–1599. (b) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599–1600. (c) Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1381–1384. (d) Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Clowers, J. S.; Vander Velde, D. G.; Himes, R. H. *J. Org. Chem.* **1996**, *61*, 2664–2676. (e) Li, L.; Thomas, S. A.; Klein, C. M.; Yeung, C. M.; Maring C. J.; Grampovnik, D. J.; Lartey, A.; Plattner, J. J. *J. Med. Chem.* **1994**, *37*, 2655–2663.

(14) The immediate precursor to **1a**, 1-chloro-1-(trichloroethenyl)-cyclopropane, is commercially available from Merck-Schuchardt.

(15) Autorenkollektiv *Organikum*, 15. Aufl., VEB Dt.; Verlag der Wissenschaften: Berlin 1984.

from sodium benzophenone (THF), 3 Å molecular sieve (acetonitrile), or CaH_2 (DMF). All other reagents and solvents such as light petroleum and diethyl ether were purified by standard procedures. Reactions were monitored by thin-layer chromatography. Eluents for column chromatography were distilled before use. NMR spectra were run at 250 MHz (^{1}H) and 62.9 MHz (^{13}C) in $CDCl_3$; for the oxazolinecarboxylic acid **6**, DMSO-d_6 was used as solvent. Melting points are uncorrected.

General Procedure. Methyl 2-Phenylspiro(cyclopropane-1',4-oxazoline)-5-carboxylate (5a). A solution of methyl 2-chloro-2-cyclopropylideneacetate (**1a**) (510 mg, 3.48 mmol) and benzamide (421 mg, 3.48 mmol) in 15 mL of anhydrous acetonitrile was treated with NaH (160 mg, 4.00 mmol, 60% dispersion in mineral oil) at 0 °C. The suspension was subsequently stirred for 24 h and allowed to warm to room temperature. After filtration (200 mL Et_2O, column 1.5 cm × 3 cm; 5 g of silica gel) the solvent was evaporated in vacuo. The dark yellow residue was purified by chromatography (light petroleum/Et_2O = 3:1, 300 mL; 1:1, 500 mL; column 1.5 cm × 30 cm; 30 g of silica gel) to yield 486 mg (60%) of **5a** as a colorless solid, mp 47 °C, R_f 0.34 (light petroleum/Et_2O 1:1): IR (KBr) 3073 (C−H), 3004 (C−H), 2949 (C−H), 1726 (C═O), 1652 (C═N) cm^{-1}; ^{1}H NMR δ 0.87−1.03 (m, 2 H), 1.16−1.25 (m, 1 H), 1.30−1.38 (m, 1 H), 3.77 (s, 3 H), 4.91 (s, 1 H), 7.37−7.51 (m, 3 H), 7.92−7.97 (m, 2 H); ^{13}C NMR (DEPT) δ 10.4 (−), 14.7 (−), 52.2 (+), 53.2 (C_{quat}), 79.6 (+), 126.9 (C_{quat}), 127.9 (+), 128.3 (+), 131.4 (+), 163.4 (C_{quat}), 169.4 (C_{quat}); MS *m*/*z* (%) 231 (47) [M$^+$], 172 (100) [M$^+$ − CO_2Me], 144 (49) [M$^+$ − CO_2Me − C_2H_4]. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.05. Found: C, 67.46; H, 5.55; N, 6.00.

2-Phenylspiro(cyclopropane-1',4-oxazoline)-5-carboxylic Acid (6). To a solution of oxazoline **5a** (250 mg, 1.08 mmol) in 20 mL of THF was added at room temperature 3 mL of 5 N NaOH. The solution was subsequently stirred for 24 h, then 5 mL of 100% acetic acid was added, and the solvent was evaporated in vacuo. The residue was dissolved in dichloromethane and filtered over 10 g of silica gel. Crystallization from Et_2O gave 239 mg (quantitative) of the carboxylic acid **6**, mp 171 °C (dec): IR (KBr) 3305 (O−H), 3030 (C−H), 2924 (C−H), 1652 (C═N) cm^{-1}; ^{1}H NMR δ 0.93−1.19 (m, 4 H), 4.99 (s, 1 H), 7.45−7.59 (m, 3 H), 7.82−7.86 (m, 2 H); ^{13}C NMR (DEPT) δ 9.7 (−), 14.1 (−), 53.0 (C_{quat}), 78.7 (+), 126.7 (C_{quat}), 127.4 (+), 128.7 (+), 131.6 (+), 162.4 (C_{quat}), 170.2 (C_{quat}); MS *m*/*z* (%) 217 (52) [M$^+$], 172 (100) [M$^+$ − COOH], 144 (63) [M$^+$ − COOH − C_2H_4]. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.10; N, 6.44. Found: C, 66.33; H, 5.16; N, 6.33.

2-Hydroxy-2-(1'-benzoylaminocyclopropyl)acetic Acid (8). A solution of oxazoline **5a** (1.00 g, 4.32 mmol) in 10 mL of 1 N HCl was heated to 100 °C for 30 min. Subsequently 15 mL of 5 N NaOH was added to the hot solution, which was then cooled to 0 °C, and 1.00 g (7.11 mmol) of benzoyl chloride was added dropwise. The mixture was then stirred for 2 h and allowed to warm to room temperature. Next, 3 N HCl was added until a pH of under 2 was reached, and the water phase was extracted with 3 × 50 mL of Et_2O. After drying of the organic phases over Na_2SO_4, the solvents were evaporated in vacuo, and the residue was chromatographed on silica gel (column 1.5 cm × 20 cm; 20 g of silica gel; light petroleum/Et_2O 1:1, 200 mL; Et_2O, 200 mL; $CHCl_3$, 200 mL; to each eluent 0.1% of acetic acid was added). After crystallization from $CHCl_3$/light petroleum 3:1 at −20 °C, 710 mg (70%) of **8** was obtained as a colorless solid, mp 140 °C, R_f 0.24 (Et_2O): IR (KBr) 3435 (OH), 3318 (NH), 3080 (CH), 2880−2530 (br. COOH assoc.), 1713 (COOH), 1625 (CONH), 1536 (CONH), 1314 (OH) cm^{-1}; ^{1}H NMR δ 0.73−1.09 (m, 4 H), 3.37 (br s, 1 H), 4.03 (s, 1 H), 7.39−7.54 (m, 3 H), 7.80−7.83 (m, 2 H), 8.78 (s, 1 H), 12.30 (br s, 1 H); ^{13}C NMR (DEPT) δ 10.6 (−), 11.6 (−), 35.7 (C_{quat}), 72.4 (+), 127.5 (+), 128.2 (+), 131.4 (C_{quat}), 134.1 (+), 168.4 (C_{quat}), 173.9 (C_{quat}); MS *m*/*z* (%) 235 (1) [M$^+$], 218 (8) [M$^+$ − OH], 190 (63) [M$^+$ − COOH], 172 (7) [M$^+$ − H_2O − COOH], 105 (100) [PhCO$^+$]. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57. Found: C, 61.20; H, 5.54.

Methyl *p*-Toluenesulfonamido(1-*p*-toluenesulfonamidocyclopropyl)acetate (12). To a solution of *p*-toluenesulfonamide (**11**) (1.20 g, 7.01 mmol) in a mixture of 15 mL of THF and 5 mL of DMF was added NaH (280 mg, 7.00 mmol, 60% dispersion in mineral oil) at 0 °C, and the mixture was subsequently stirred for 2 h and then cooled to −78 °C. A precooled solution of methyl 2-chloro-2-cyclopropylideneacetate **1a** (500 mg, 3.41 mmol) in 5 mL of THF was added dropwise. The mixture was stirred for 24 h and allowed to warm to room temperature. Then 150 mL of saturated $NaHCO_3$ (aqueous) was added, and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and the solvents were evaporated in vacuo. Column chromatography (column 1.5 × 30 cm; 30 g of silica gel; Et_2O) yielded 950 mg (62%) of **12** as a colorless solid, mp 160 °C, R_f 0.34 (Et_2O): IR (KBr) 3283 (NH), 2962 (C−H), 1732 (C═O), 1352 (SO_2), 1157 cm^{-1} (SO_2); ^{1}H NMR δ 0.60−0.89 (m, 4 H), 2.41 (s, 3 H), 2.42 (s, 3 H), 3.51 (s, 1 H), 3.56 (s, 3 H), 5.65 (s, 1 H), 6.11 (s, 1 H), 7.26−7.30 (m, 4 H), 7.67−7.73 (m, 4 H); ^{13}C NMR (DEPT) δ 12.6 (−), 13.5 (−), 21.5 (+), 21.5 (+), 37.7 (C_{quat}), 52.8 (+), 61.5 (+), 127.1 (+), 127.2 (+), 129.6 (+), 129.7 (+), 136.9 (C_{quat}), 138.4 (C_{quat}), 143.6 (C_{quat}), 143.8 (C_{quat}), 169.5 (C_{quat}); MS *m*/*z* (%) 393 (4) [M$^+$ − CO_2Me], 297 (65) [M$^+$ − MePhSO$_2$], 155 (58) [MePhSO$_2^+$], 142 (46) [M$^+$ − 2MePhSO$_2$]. Anal. Calcd for $C_{20}H_{24}N_2O_6S_2$: C, 53.08; H, 5.35; N, 6.19; S, 14.17. Found: C, 53.16; H, 5.31; N, 6.21; S, 14.15.

Dimethyl 4-Formyl-4-azadispiro[2.1.2.2]non-8-ene-8,9-dicarboxylate (13). To a solution of formamide (310 mg, 6.89 mmol) and methyl 2-chloro-2-cyclopropylideneacetate (**1a**) (500 mg, 3.41 mmol) in 20 mL of DMF was added NaH (180 mg, 4.50 mmol, 60% dispersion in mineral oil) at −10 °C. The light grey suspension was subsequently stirred for 15 h and allowed to warm to room temperature. Then 20 mL of H_2O was added, and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, and the solvents were evaporated in vacuo. Column chromatography (light petroleum/Et_2O 10:1, 500 mL; 1:1, 500 mL; column 30 cm × 1.5 cm; 30 g of silica gel) yielded as a first fraction 80 mg of **1a** (16% recovered) and, as a second fraction, 227 mg (50%) of **13**, which could be crystallized from Et_2O at −20 °C as colorless sharp needles, mp 75 °C, R_f 0.22 (light petroleum/Et_2O 1:1): IR (KBr) 3015 (C−H), 2958 (C−H), 1722 (C═O), 1673 (C═O), 1635 (C═C), 1261 (C−O) cm^{-1}; ^{1}H NMR δ 0.97−1.23 (br s, 4 H), 1.37−1.63 (br s, 2 H), 2.12−2.40 (br s, 2 H), 3.72 (s, 6 H), 7.63 (s, 1 H); ^{13}C NMR (DEPT) δ 9.6 (−), 14.0 (−), 48.1 (C_{quat}), 50.8 (C_{quat}), 52.4 (+), 130.9 (C_{quat}), 140.5 (C_{quat}), 155.3 (+), 161.4 (C_{quat}), 162.8 (C_{quat}); MS *m*/*z* (%) 265 (12) [M$^+$], 147 (23) [M$^+$ − 2CO_2Me], 119 (43) [M$^+$ − 2CO_2Me − C_2H_4], 91 (36) [M$^+$ − 2CO_2Me − 2C_2H_4]. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.89; H, 5.68; N, 5.26.

Acknowledgment. This work was supported financially by the Deutsche Forschungsgemeinschaft (SFB 416, Project A3), the Fonds der Chemischen Industrie, and the Bayer AG, as well as through generous gifts of chemicals by the BASF AG. M.N. is particularly grateful to the Bayer AG for a two months stay in their Agriculture Research Station. The authors are indebted to Dr. Burkhard Knieriem, Göttingen, for his careful reading of the final manuscript.

Supporting Information Available: Experimental procedures and characterizations for compounds **5b**−**z**, ORTEP drawings for **5a** and (4*S**,5*R**,2'*R**)-**5s** and details of the data acquisition. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990170Y