by X-ray crystallography and matches the assignments proposed herein for C-2, C-4, and C-9 in **5** and **7**.

Careful examination of three collections of *Dysidea etheria* has yielded no sign of spirodysin or herbadysidolide, although furodysinin is abundant and lesser amounts of the related furodysin[5,10] are always present. Dysetherin might represent an oxidative shunt in the biosynthetic pathway to this family of sesquiterpenes.

Experimental Section

The IR spectrum was recorded on a Beckman IR-20 spectrophotometer, while mass spectral analyses were performed on VG MM16F and 7070 EHF mass spectrometers. NMR spectra were obtained with a Bruker WM-250 Fourier transform spectrometer; chemical shifts are reported in δ units relative to Me_4Si (δ 0).

Collection and Extraction of *Dysidea etheria*. *Dysidea etheria* was collected in relatively shallow (2–5 m), calm inshore waters in Bermuda, primarily along the coastline of Harrington Sound, in August, 1983. The sponge was chopped and stored in acetone at −10 °C until extracted. The acetone was removed by suction filtration, and the sponge was ground with MeOH in a Waring blender. After removal of the MeOH by filtration, the marc was steeped in CH_2Cl_2 (thrice, 24 h each). The acetone and MeOH extracts were combined and reduced to an aqueous suspension, which was then equilibrated with the CH_2Cl_2 extracts. The CH_2Cl_2 phase was reduced, in vacuo, to a thick brown oil, 6.565 g (8.3% of dry weight).

Isolation of Dysetherin. The CH_2Cl_2-soluble extracts were chromatographed on Florisil (225 g, column 3 × 60 cm) with a hexane–EtOAc–MeOH gradient; 24 fractions were collected. Fraction 4, 492 mg, eluted with hexane–EtOAc (24:1), was permeated through Bio-Beads S-X4 (4 × 80 cm) with hexane–CH_2Cl_2–EtOAc (4:4:1) to give six fractions. Fraction 6, 93 mg, was chromatographed under low pressure (~10 psi of N_2) on silica gel (Whatman LPS-2, 2.5 × 34 cm) with a hexane–Et_2O gradient, yielding 12 fractions. Fraction 1, 48 mg, eluted with hexane–Et_2O (22:3), was permeated through Sephadex LH-20 (1.5 × 130 cm) with MeOH–CH_2Cl_2 (1:1). The seventh of seven fractions yielded dysetherin (**5**), 30 mg colorless oil: $[\alpha]_D$ −28.5° (*c* 0.85, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 2940, 1783, 1430, 1370, 1330, 1063 cm^{-1}; MS, *m/z* (relative intensity) 248.1407 (M^+, 6%, calcd for $C_{15}H_{20}O_3$ 248.1412), 233 (6), 215 (6), 203 (100), 189 (10), 159 (15); NMR data in Table I.

Acknowledgment. We thank Dr. Klaus Ruetzler for identifying the sponge. This investigation was supported by PHS Grant 1 R01 CA35905-01A1, awarded by the National Cancer Institute. The NMR spectrometer was acquired via NSF Grant CHE 79-26160 and the mass spectrometry facility was developed with funds from NSF Grant CHE 81-15565 and a grant from the M.J. Murdock Charitable Trust.

Registry No. **5**, 97920-19-9.

(10) Cardellina, J. H., II; Meng, M. W., unpublished data.

A Practical Access to Methyl 3,3-Dimethoxypropionates, *N*-Protected β-Aminoacrylates, and β-Aminoacrylonitrile Using an Electrochemical Procedure

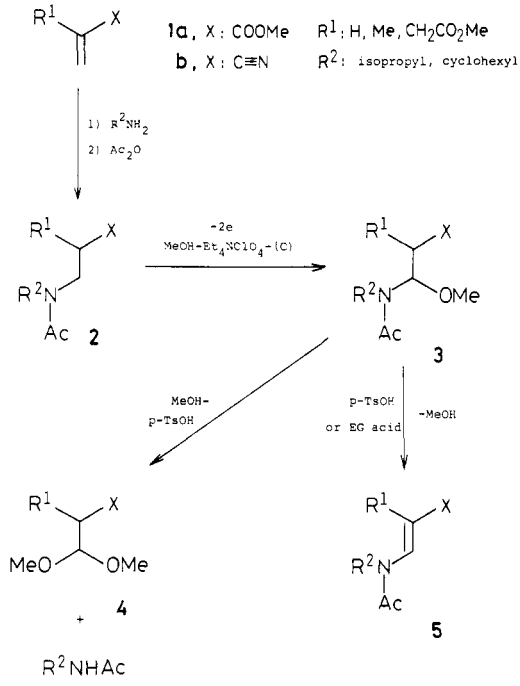
Sigeru Torii,* Tsutomu Inokuchi, and Minoru Kubota

Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama 700, Japan

Received March 26, 1985

Methyl 3,3-dimethoxypropionate (**4a**, R^1 = H) is a sheltered form of the unstable methyl formylacetate and is useful for the synthesis of a variety of compounds including coumarins,[1] porphyrins,[2] and spermine metabolites.[3] Reported methods for the preparation of **4a** and its homologues involve (a) copper(I) triflate catalyzed addition of alcohol to ethyl propiolate,[4] (b) acetalization of ethyl formylacetate,[5] (c) AIBN initiated addition of carbon tetrachloride to ethyl vinyl ether,[6] (d) oxo reaction of acrylate with palladium catalyst in the presence of alkylnitrite,[7] and others.[8] These reported methods, however, are not satisfactory owing to high costs of their starting materials, low overall yields of the processes, or low efficiency of the transition-metal catalyst. We disclose here a facile preparative access to the acetal **4a** (R^1 = H) and its C(2) alkylated derivatives from methyl acrylate (**1a**, R^1 = H) and the related α,β-unsaturated esters (**1a**). In addition, the preparation of N-protected β-aminoacrylates **5a**[9] and β-aminoacrylonitriles **5b**, versatile intermediates for the preparation of a variety of nitrogen containing heterocycles,[10] is also described (Scheme I).

Scheme I



The electrochemical methoxylation at the α position of N-protected amines was employed as a means of obtaining the key precursors **3** of the desired products **4** and **5**. The procedure known as Ross–Eberson–Nyberg method[11g] has

(1) Crosby, D. G.; Berthold, R. V. *J. Org. Chem.* **1962**, *27*, 3083.

(2) Collman, J. P.; Chong, A. O.; Jameson, G. B.; Oakley, R. T.; Rose, E.; Schmittou, E. R.; Ibers, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 516.

(3) Israel, M.; Zoll, E. C.; Muhammad, N.; Modest, E. J. *J. Med. Chem.* **1973**, *16*, 1.

(4) Bertz, S. H.; Dabbagh, G.; Cotte, P. *J. Org. Chem.* **1982**, *47*, 2216.

(5) McElvain, S. M.; Clarke, R. L. *J. Am. Chem. Soc.* **1947**, *69*, 2657.

(6) Holý, A. *Collect. Czech. Chem. Commun.* **1974**, *39*, 3177.

(7) Matsui, K.; Uchiumi, S.; Iwayama, A.; Umezu, T. (Ube Industries, Ltd.) Eur. Pat. Appl. EP 55 108; *Chem. Abstr.* **1982**, *97*, 162364b.

(8) (a) Croxall, W. J.; Schneider, H. J. *J. Am. Chem. Soc.* **1949**, *71*, 1257. (b) Croxall, W. J.; Van Hook, J. O.; Luckenbaugh, R. *Ibid.* **1949**, *71*, 2736.

(9) For recent reports on the preparaton of β-aminoacrylates: (a) Slopianka, M.; Gossauer, A. *Liebigs Ann. Chem.* **1981**, 2258. (b) Bredereck, H.; Simchen, G.; Funke, B. *Chem. Ber.* **1971**, *104*, 2709. (c) Gupton, J. T.; Lizzi, M. J.; Polk, D. *Synth. Commun.* **1982**, *12*, 939. (d) Huisgen, R.; Giese, B.; Huber, H. *Tetrahedron Lett.* **1967**, 1883.

(10) Newkome, G. R.; Paudler, W. W. "Contemporary Heterocyclic Chemistry, Syntheses, Reactions, and Applications"; John Wiley and Sons: New York, 1982.

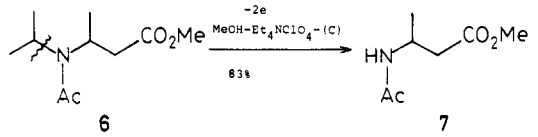
0022-3263/85/1950-4157$01.50/0

Table I. Results of Electrochemical Methoxylation of 2, Methanolysis of 3, and Demethoxylation of 3

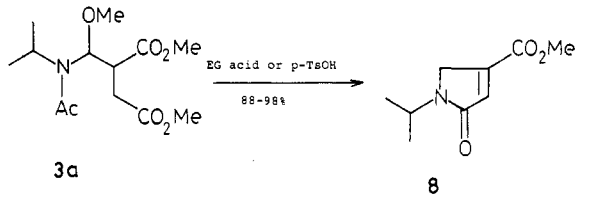
				2→3	3→4	3→5	
entry	compd	R^1	R^2	yield (%)	yield (%)	method[a]	yield (%)
1	**2a**	H	isopropyl	96	90	A	93
						B	94
2	**2a**	Me	cyclohexyl	93	80	A	90
3	**2a**	CH_2CO_2Me	isopropyl	91	84	A	88[c]
						B	98[c]
4	**2b**	H	cyclohexyl	97	10[b]	A	63
5	**10**			60[d]		A	93[e]

[a] Method A: heating at reflux in benzene with a catalytic amount of *p*-TsOH. Method B: treatment with an electrogenerated acid (EG acid) in MeOH at room temperature. [b] The product is unstable in this conditions. [c] Compound **8** was isolated as a sole product. [d] Compound **11** was obtained. [e] Compound **12** was produced.

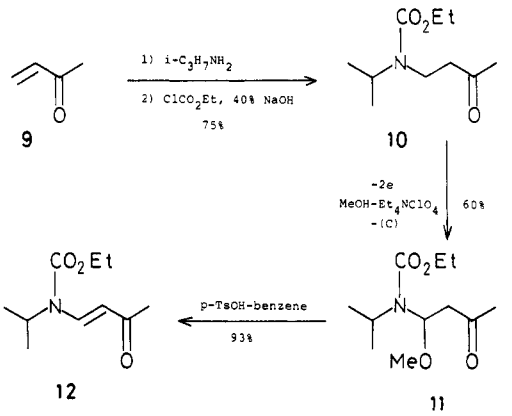
Scheme II



Scheme III



Scheme IV



been intensively employed for the functionalization of nitrogen containing compounds,[11] and by usng this procedure, N-protected amines can be converted to acetals of the corresponding carbonyl compounds.[12] We developed further exquisite use of this reaction for the preparation of synthetically significant β-functionalized propionates **4** and propenoates **5**.

As shown in Scheme I, the starting olefins **1** were converted to N-protected amines **2** in 85–92% yields by 1,4-addition of secondary amines and the subsequent acetylation with acetic anhydride or ethoxycarbonylation with ethyl chloroformate of the resulting amine adducts. The electrooxidation of **2a** (R^1 = H, R^2 = isopropyl) was carried out in methanol using perchlorate salts such as Et_4NClO_4 or $LiClO_4$ as an electrolyte with carbon electrodes. Thus, passage of 7 F/mol of electricity under a constant current of 200 mA (ca. 20 mA/cm^2, terminal voltage: 7–15 V) in an undivided cell at about 15 °C with external cooling provided the desired methoxylated **3a** (R^1 = H, R^2 = isopropyl) in 95% yield. The reaction proceeded exclusively at the methylene group linked to nitrogen, giving **3a**, and no reaction has been observed at the branched carbon atom α to the nitrogen. Meanwhile, the electrooxidation of **6**, bearing a methyl group at the C(3) position of **2a** (R^1 = H, R^2 = isopropyl), resulted in the dealkylation of the nitrogen substituents[13] to produce **7** in 83% yield and no methoxylated product was detected (Scheme II). The results of electrochemical methoxylation of **2** are summarized in Table I.

The transformation of **3** to the acetal **4** was carried out by heating with a catalytic amount of *p*-toluenesulfonic acid in methanol, and the results are summarized in Table I. Although β-methoxy-β-amino esters **3a** have been converted into the corresponding acetals **4a** in good yields, 3,3-dimethoxypropionitrile (**4b**) could not be obtained efficiently from **3b** (R^1 = H, R^2 = cyclohexyl) owing to its instability in the acidic conditions. *N*-Isopropyl- and *N*-cyclohexylacetamides, a counterpart of the methanolysis product from **3**, could be collected after the reaction and the starting amines were recovered by alkaline hydrolysis.

Demethoxylation of **3**, giving the enamine **5**, was performed by treatment with either *p*-toluenesulfonic acid in benzene at 80 °C (method A) and/or with an electrogenerated acid (EG acid) in methanol at room temperature (method B),[14] and the results are listed in Table I. In contrast, the treatment of **3a** (R^1 = CH_2COOMe, R^2 = isopropyl) with the same acids afforded only γ-lactam **8**, due to the migration of C=C double bond of the initially formed enamine (Scheme III).

The present procedure can be applicable for the conversion of α,β-unsaturated enone to enaminone.[15] By analogy with the preparation of **2**, the starting enone **9** was converted into the carbamate **10** in 75% yield. The electrolysis of **10** in an MeOH–Et_4NClO_4–(C) system provided the desired **11** in 60% yield whose demethoxylation by treatment with *p*-toluenesulfonic acid in

(11) (a) Weinberg, N. L.; Brown, E. A. *J. Org. Chem.* **1966**, *31*, 4058. (b) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Org. Chem.* **1966**, *31*, 133. (c) Cedheim, L.; Eberson, L.; Helgèe, B.; Nyberg, K.; Servin, R.; Sternerup, H. *Acta Chem. Scand., Ser. B* **1975**, *B29*, 617. (d) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. (e) Nyberg, K.; Servin, R. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 640. (f) Mitzlaff, M.; Warning, K.; Jensen, H. *Liebigs Ann. Chem.* **1978**, 1713. (g) Palasz, P. D.; Utley, J. H. P.; Hardstone, J. D. *Acta Chem. Scand., Ser. B* **1984**, *B38*, 281. (h) Blum, Z.; Ekström, M.; Wistrand, L. *Ibid.* **1984**, *B38*, 297. (i) Malmberg, M.; Nyberg, K. *Ibid.* **1984**, *B38*, 85. (j) Ban, Y. *Yuki Gosei Kagaku Kyokaishi* **1982**, *40*, 866. (k) Shono, T. *Tetrahedron*, **1984**, *40*, 811, and references cited therein.

(12) Shono, T.; Matsumura, Y.; Kashimura, S. *J. Org. Chem.* **1983**, *48*, 3338.

(13) (a) Barnes, K. K.; Mann, C. K. *J. Org. Chem.* **1967**, *32*, 1474. (b) Smith, P. J.; Mann, C, K. *Ibid.* **1969**, *34*, 1821. (c) Portis, L. C.; Bhat, V. V.; Mann, C. K. *Ibid.* **1970**, *35*, 2175.

(14) Torii, S.; Inokuchi, T.; Kondo, K.; Ito, H. *Bull, Chem. Soc. Jpn.* **1985**, *58*, 1347.

(15) (a) Matsuyama, Y.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 6312. (b) Murashashi, S.; Tsumiyama, T.; Mitsue, Y. *Chem. Lett.* **1984**, 1419 and references cited therein.

benzene at 80 °C afforded **12** in 93% yield (Scheme IV).

Experimental Section

Melting points are uncorrected and boiling points are indicated by an air-bath temperature without correction. IR spectra were recorded with a JASCO IRA-1 grating spectrometer. Unless otherwise noted, ^{1}H NMR spectra were determined at 60 MHz with a Hitachi R-24 spectrometer. ^{13}C NMR spectra were recorded with a JEOL FX-100 (25.05 MHz) spectrometer. Samples were dissolved in $CDCl_3$ and the chemical shifts are expressed in δ values relative to Me_4Si as an internal standard. Elemental analyses were performed in our laboratory.

Materials. Methyl 3-(acetylamino)propionates (**2a**), 3-(acetylamino)propionitrile (**2b**), and 3-[(ethoxycarbonyl)amino]-2-butanone (**10**) were prepared by the 1,4-addition of secondary amines[16] to **1a,b** and **9** in the presence or absence of a catalytic amount of Triton B followed by acetylation with acetic anhydride at 120–140 °C or ethoxycarbonylation with ethyl chloroformate in 75–92% yields.[17]

Electrolysis Apparatus. An undivided cell was equipped with a gas lead pipe, a stirring bar, a thermometer, and two carbon plate electrodes (10 cm^2) placed parallel to each other 5 mm apart. The vessel was immersed in a water bath cooled to 10–15 °C.

General Procedure for Electrochemical Methoxylation of N-Protected Amines 2. A solution of **2a** (R^1 = H, R^2 = isopropyl, 3.0 g, 16 mmol) in MeOH (30 mL) containing Et_4NClO_4 (150 mg) as a supporting electrolyte was electrolyzed under a constant current of 200 mA (terminal voltage: 10–15 V) at 15 °C. After passage of 7.0 F/mol of electricity, the mixture was concentrated in vacuo, and the residue was taken up in benzene–AcOEt (1:1). The extracts were washed with brine, dried (Na_2SO_4), and concentrated on a rotary evaporator. The crude product was purified by column chromatography (SiO_2, hexane–AcOEt, 3:1) to give 3.3 g (95%) of **3a** (R^1 = H, R^2 = isopropyl): bp 120–123 °C (2 mm); IR (neat) 2820, 1740 (ester C=O), 1640 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.32, 1.39 (d, J = 6.5 Hz, 6, CH_3), 2.17 (s, 3, CH_3CO), 2.74 (dd, J = 6.5, 2 Hz, 2, CH_2CO), 3.32 (s, 3 OCH_3), 3.50–3.90 (m, 1, CH—N), 3.67 (s, 3, OCH_3), 5.19 (t, J = 6 Hz, 1, CH—O); ^{13}C NMR ($CDCl_3$) δ 20.5 (q, 2C), 23.7 (q), 39.4 (t), 45.5 (d), 52.0 (q), 55.7 (q), 86.3 (d), 170.1 (s), 170.4 (s). Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81. Found: C, 55.17; H, 8.78.

Results of elecrochemical methoxylation of **2** and **10** are given in Table I and the physical properties along with spectral data of the products are as follows.

3a (R^1 = Me, R^2 = cyclohexyl): bp 109–112 °C (0.02 mm); IR (neat) 2840, 1740 (ester C=O), 1655 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.10–2.10 (m, 10, CH_2), 1.17 (d, J = 7 Hz, 3, CH_3), 2.18 (s, 3, $COCH_3$), 2.30–3.35 (m, 2, COCH, CH-N), 3.33 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 4.83 (d, J = 10 Hz, 1, CH-O). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29. Found: C, 61.83; H, 9.35.

3a (R^1 = CH_2COOMe, R^2 = isopropyl): bp 129–132 °C (0.025 mm); IR (neat) 2820, 1740 (ester C=O), 1705 (ester C=O), 1645 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.21, 1.37 (d, J = 7 Hz, 6, CH_3), 2.16 (s, 3 $COCH_3$), 2.40–2.85 (m, 2, $COCH_2$), 2.97–4.35 (m, 2, COCH, CH-N), 3.35 (s, 3, OCH_3), 3.67, 3.74 (s, 6, OCH_3), 4.75–5.20 (m, 1, CH-O). Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01. Found: C, 53.70; H, 7.88.

3b (R^1 = H, R^2 = cyclohexyl): bp 132–135 °C (0.02 mm); IR (neat) 2250 (C≡N), 1655 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.05–2.35 (m, 10, CH_2), 2.19 (s, 3, $COCH_3$), 2.83 (dd, J = 7, 1 Hz, 2, CH_2C≡N), 3.05–3.80 (m, 1, CH-N), 3.38 (s, 3, OCH_3), 5.22 (m, 1, CH-O). Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99. Found: C, 64.43; H, 9.01.

11: bp 105–108 °C (2 mm); IR (neat) 2820, 1720, 1705 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3, CH_3), 1.31, 1.36 (d, J = 7 Hz, 6, CH_3), 2.18 (s, 3, $COCH_3$), 2.09–2.38 (m, 2, $COCH_2$), 3.56 (m, 1, CH-N), 4.18 (q, J = 7 Hz, 2, CH_2O), 5.56–5.78 (m, 1, CH-O). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15. Found: C, 57.19; H, 9.11.

7: bp 81–83 °C (1 mm); IR (neat) 3280, 3070, 1740 (ester C=O), 1660 (C=O), 1555, 1440, 1375, 1300, 1260, 1205, 1150, 1100, 1005, 975 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.22 (d, J = 7 Hz, 3, CH_3), 1.96 (s, 3, $COCH_3$), 2.52 (d, J = 5 Hz, 2, CH_2CO), 3.68 (s, 3, OCH_3), 4.32 (m, 1, CH-N), 6.05 (br, 1, NH). Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23. Found: C, 52.96; H, 8.36.

General Procedure for Methanolysis of 3, Leading to 4. A solution of **3a** (R^1 = H, R^2 = isopropyl, 10 g, 46 mmol) and *p*-TsOH (1.0 g) in MeOH (12 mL) was heated at reflux for 2.5 h. After having been cooled to 0 °C, the mixture was quenched with isopropylamine (4–5 mL) and concentrated in vacuo. The residue was subjected to fractional distillation to give 6.13 g (90%) of **4a** (R^1 = H) at boiling range of 78–79 °C (36 mm) and 4.46 g (96%) of *N*-isopropylacetamide at boiling range of 90–98 °C (31 mm). **4a** (R^1 = H): bp 97–99 °C (55 mm); IR (neat) 2830, 1735 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ 2.62 (d, J = 6 Hz, 2, $COCH_2$), 3.33 (s, 6, OCH_3), 3.67 (s, 3, OCH_3), 4.79 (t, J = 6 Hz, 1, CH-O); ^{13}C NMR ($CDCl_3$) δ 38.8 (t), 51.8 (q), 53.5 (q, 2C), 101.4 (d), 170.3 (s). Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.60; H, 8.25.

Results of methanolysis of **3** are listed in Table I and physical properties along with spectral data of **4** are as follows.

4a (R^1 = Me): bp 101–103 °C (42 mm); IR (neat) 2830, 1735 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J = 7 Hz, 3, CH_3), 2.77 (m, 1, COCH), 3.34, 3.36 (s, 6, OCH_3), 3.68 (s, 3, OCH_3), 4.38 (d, J = 8 Hz, 1, CH-O). Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.47; H, 8.79.

4a (R^1 = CH_2COMe): bp 89–92 °C (0.025 mm); IR (neat) 2820, 1735 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ 2.63–2.77 (m, 2, $COCH_2$), 3.04–3.20 (m, 1, COCH), 3.37, 3.39 (s, 6, OCH_3), 3.68, 3.74 (s, 6, OCH_3), 4.56 (d, J = 6 Hz, 1, CH-O). Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.24; H, 7.40.

4b (R^1 = H): bp 113–116 °C (25 mm); IR (neat) 2840, 2230 cm^{-1} (C≡N); ^{1}H NMR ($CDCl_3$) δ 2.67 (d, J = 5 Hz, 2, CH_2C≡N), 3.39 (s, 6, OCH_3), 4.65 (t, J = 5 Hz, 1, CH-O).

General Procedure for Acid-Catalyzed Elimination of Methanol from 3, Leading to 5. Method A. A solution of **3a** (R^1 = H, R^2 = isopropyl, 2.0 g, 9.2 mmol) and *p*-TsOH (200 mg) in benzene (15 mL) was heated at reflux for 6 h. The mixture was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (SiO_2, hexane–AcOEt, 5:1) to give 1.58 g (93%) of **5a** (R^1 = H, R^2 = isopropyl) as an oil.

Method B. A solution of MeOH (8 mL) and $LiClO_4$ (20 mg, 0.19 mmol) was electrolyzed with platinum electrodes under a constant current of 10 mA in an anode compartment of an H-shaped divided cell. After being electrolyzed for 30 min, a portion of an anolyte (ca. 2 mL) was transferred to **3a** (R^1 = H, R^2 = isopropyl, 217 mg, 1 mmol) in another flask. The mixture was stirred at room temperature for 2 h, and the reaction was quenched with pyridine (0.05 mL). Evaporation of the solvent followed by chromatography (SiO_2) gave 174 mg (94%) of **5a** (R^1 = H, R^2 = isopropyl): bp 110–113 °C (3 mm); IR (neat) 3080, 1700 (ester C=O), 1615 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 7 Hz, 6, CH_3), 2.29 (s, 3, $COCH_3$), 3.66 (s, 3, OCH_3), 4.43 (m, 1, CH-N), 5.33 (d, J = 14 Hz, 1, CH=C), 7.76 (d, J = 14 Hz, 1, CH=C); ^{13}C NMR ($CDCl_3$) δ 19.2 (q, 2C), 23.4 (q), 47.6 (d), 51.4 (q), 99.5 (d), 141.9 (d), 168.1 (s), 170.6 (s). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16. Found: C, 58.21; H, 8.19.

Results of demethoxylation of **3** and **11** are listed in Table I and the physical properties along with spectral data of **5**, **8**, and **12** are as follows.

5a (R^1 = Me, R^2 = cyclohexyl): bp 103–105 °C (0.04 mm); IR (neat) 1715 (ester C=O), 1660 (C=O), 1635 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 1.00–2.20 (m, 10, CH_2), 1.80 (d, J = 1.5 Hz, 3, CH_3), 1.97 (s, 3, $COCH_3$), 3.81 (s, 3, OCH_3), 4.15–4.70 (m, 1, CH-N), 7.15 (m, 1, CH=C); ^{13}C NMR ($CDCl_3$) δ 13.2 (q), 22.5 (q), 25.4 (t), 25.9 (t, 2C), 30.5 (t, 2C), 52.1 (q), 55.0 (d), 129.9 (s), 136.5 (d), 167.5 (s), 168.8 (s). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84. Found: C, 65.06; H, 8.91.

5b (R^1 = H, R^2 = cyclohexyl): mp 128–129 °C; IR (Nujol) 3080, 3040, 2220 (C≡N), 1680 (C=O), 1612 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 1.00–2.15 (m, 10, CH_2), 2.30 (s, 3, $COCH_3$), 3.55–4.15 (m, 1, CH-N), 5.42 (d, J = 15 Hz, CH=C), 7.28 (d, J = 15 Hz,

(16) (a) Pearson, D. E.; Jones, W. H.; Cope, A. C. *J. Am. Chem. Soc.* **1946**, *68*, 1227. (b) Holley, R. W.; Holley, A. D. *Ibid.* **1949**, *71*, 2124. (c) Bruson, H. A. "Organic Reactions", John Wiley and Sons: New York, 1949; Vol. 5, p 79.

(17) (a) Hartman, W. W.; Brethen, M. R. "Organic Syntheses"; John Wiley and Sons: New York, 1943; Collect. Vol. II, p 278. (b) Hipkin, J.; Satchell, D. P. N. *J. Chem. Soc. B* **1966**, 345.

1, HC≡C). Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39. Found: C, 68.80; H, 8.46.

8: mp 122-123 °C; IR (Nujol) 3050, 1695 (C=O), 1605 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 6.5 Hz, 6, CH_3), 3.32 (d, J = 2 Hz, 2, CH_2N), 3.76 (s, 3, OCH_3), 4.37 (m, 1, CH-N), 7.53 (t, J = 2 Hz, 1, CH=C). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15. Found: C, 58.90; H, 7.22.

12: bp 86-88 °C (1 mm); IR (neat) 3080, 1720 (ester C=O), 1682, 1618, 1588 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3, CH_3), 1.38 (d, J = 7 Hz, 6, CH_3), 2.21 (s, 3, $COCH_3$), 4.22 (m, 1, CH-N), 4.25 (q, J = 7 Hz, 2, CH_2O), 5.78 (d, J = 14 Hz, 1, CH=C), 7.93 (d, J = 14 Hz, 1, HC=C). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.34; H, 8.56.

Registry No. **1a** (R^1 = H), 96-33-3; **1a** (R^1 = CH_2CO_2Me), 617-52-7; **1b** (R^1 = Me), 80-62-6; **1b** (R^1 = H), 107-13-1; **2a** (R^1 = H, R^2 = *i*-Pr), 98013-99-1; **2a** (R^1 = Me, R^2 = c-C_6H_{11}), 98014-00-7; **2a** (R^1 = CH_2CO_2Me, R^2 = *i*-Pr), 98014-01-8; **2b** (R^1 = H, R^2 = c-C_6H_{11}), 17526-82-8; **3a** (R^1 = H, R^2 = *i*-Pr), 98014-02-9; **3a** (R^1 = Me, R^2 = c-C_6H_{11}), 98014-03-0; **3a** (R^1 = CH_2CO_2Me, R^2 = *i*-Pr), 98014-04-1; **3b** (R^1 = H, R^2 = c-C_6H_{11}), 98014-05-2; **4a** (R^1 = H), 7424-91-1; **4a** (R^1 = Me), 76526-43-7; **4a** (R^1 = CH_2CO_2Me), 98014-06-3; **4b** (R^1 = H), 57597-62-3; **5a** (R^1 = H, R^2 = *i*-Pr), 98014-07-4; **5a** (R^2 = Me, R^2 = c-C_6H_{11}), 98049-90-2; **5b** (R^1 = H, R^2 = c-C_6H_{11}), 98014-08-5; **6**, 98014-09-6; **7**, 43135-01-9; **8**, 98014-10-9; **9**, 78-94-4; **10**, 98014-11-0; **11**, 98014-12-1; **12**, 98014-13-2; cyclohexylamine, 108-91-8; *N*-isopropylacetamide, 1118-69-0; isopropylamine, 75-31-0; *N*-cyclohexylacetamide, 1124-53-4.

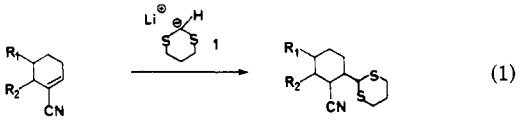
1,4-Addition of Certain 2-Lithio-1,3-dithianes to α,β-Unsaturated Nitriles

Fatima Z. Basha, John F. DeBernardis,* and Steven Spanton

Division of Cardiovascular Research, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064

Received December 20, 1984

The metallated 1,3-dithiane derivatives are among the most widely used Umpolung reagents.[1] The 1,4-addition of these acyl anion equivalents to α,β-unsaturated aldehydes,[2] ketones,[3] and amides[4] resulting in the formation of a new C-C bond has received considerable attention. However, the use of the 1,3-dithiane anion in the 1,4-addition to unsaturated nitriles is virtually unexplored. We now report the first examples of the 1,4-addition of 1,3-dithianes to a series of α,β-unsaturated nitriles as shown in eq 1.



(1)

Formation of 2-lithio-1,3-dithiane (**1**) was accomplished by the dropwise addition of *n*-butyllithium to a solution of 1,3-dithiane in THF at -20 °C under nitrogen. The reaction mixture was allowed to stir at this temperature for 30 min and then cooled to -78 °C. The solution of the unsaturated nitrile in THF was added dropwise to the anion **1**, resulting in immediate discharge of a dark color. This afforded, after workup, the desired 1,4 Michael products **2** and **3** in a ratio of 2.2:1 (cis/trans) in 90% overall yield.

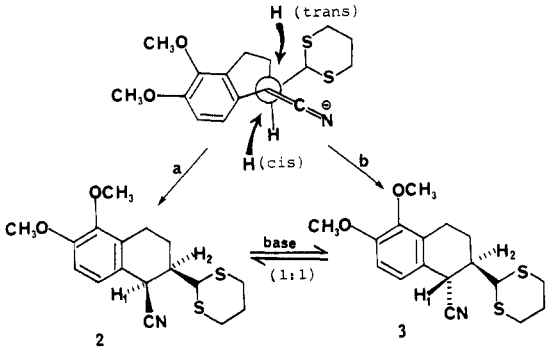
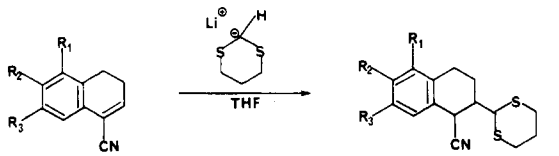


Figure 1. Equilibration of **2** with DBU/CH_2Cl_2 or 2 N NaOH/CH_2Cl_2/THF gave a 1:1 equilibrium mixture consisting of the trans-**3** and cis-**2** isomers, respectively.

Table I. NOE Difference Data for Compound 9

proton	case 1	case 2	case 3
2	IRR (-100)	3.1	8.0
I-CH_3	2.9	IRR (-100)	6.0
8		3.7	
9	5.5		IRR (-100)
10 axial			4.8
12 axial			6.1

Table II. Addition of 1,3-Dithiane Anion to α,β-Unsaturated Nitriles[a,b]



R_1	R_2	R_3	product	c/t[a]	yield,[b] %
CH_3O	CH_3O	H	**2**	2.2/1	90
H	H	H	**4**	2/1	90
CH_3O	H	H	**5**	3/1	90
H	CH_3O	H	**6**	2.2/1	85
H	CH_3O	CH_3O	**7**	2/1	70

[a] Cis/trans ratio based on high field NMR. [b] No attempts were made to optimize yield.

The stereochemistry of **2** was assigned to be cis on the basis of a coupling constant of H_1 and H_2 ($^3J_{H_1-H_2}$ = 4.6 Hz) and a W coupling constant of H_1 and H_3 eq ($^4J_{H_1-H_3}$ eq = 1.8 Hz), consistent with an equatorial arrangement for H_3 relative to an axial H_1. The stereochemistry of **3** was assigned trans on the basis of a $^3J_{H_1-H_2}$ coupling constant of 9.0 Hz and the lack of a W coupling.[5]

The formation of **2** as the major product is in agreement with the results of the alkylation of α-cyano carbanions,[6] which undergo equatorial protonation/alkylation as shown in path a (Figure 1). The alternative path b would lead to the trans product **3**.

The intermediate carbanion from compound **2** has been trapped with D_2O, affording product **8** with a cis/trans ratio of 2.1/1 (95% yield). Trapping the carbanion with CH_3I gave only the cis product **9** in 70% yield, with no detectable trans isomer by high field nuclear magnetic resonance (NMR). The stereochemistry of **9** was determined from coupling constant and NOE difference data. The proton H-2 shows three coupling constants of $^3J_{2,9}$ =

(1) For excellent review on this subject, see: (a) Groebel, B.-t., Seebach, D. *Synthesis* **1977**, 357. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639.
(2) Wartski, L.; et al. *Tetrahedron* **1982**, *38*, 3285.
(3) (a) Brown, C. A.; Tamaichi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100. (b) Ostrowski, P. C.; Kane, V. V. *Tetrahedron Lett.* **1977**, 3549. (c) Luchetti, J.; et al. *Tetrahedron Lett.* **1979**, 2695.
(4) Mango, G. B., Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823 and references cited therein.
(5) Bovey, F. A. "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1969; pp 133-143.
(6) Bare, T. M.; Hershey, N. D.; House, H. O.; Swain, C. G. *J. Org. Chem.* **1972**, *37*, 997.

0022-3263/85/1950-4160$01.50/0