Epoxidation of Enamines by Dimethyldioxirane: Formation of 1,4-Dioxanes by Enamine Epoxide Dimerization

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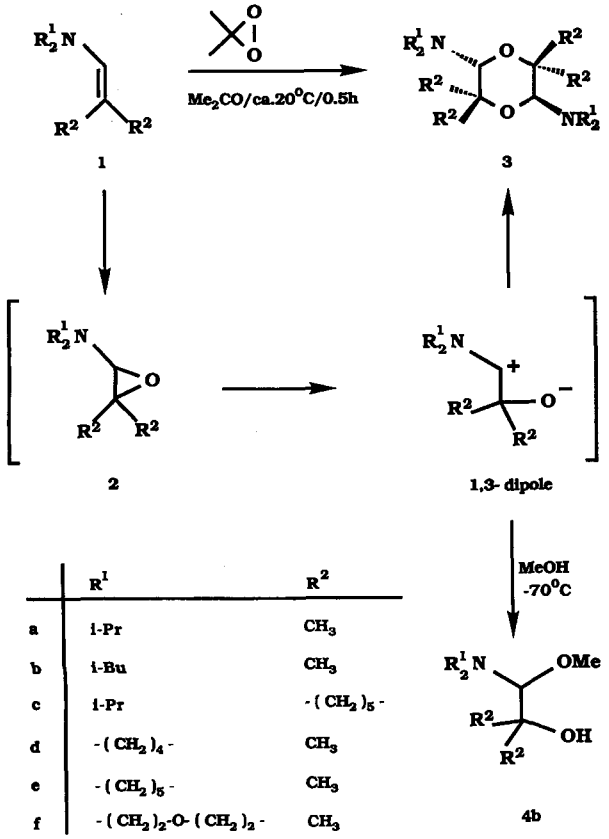
The 1,4-dioxanes **3a–f**, which constitute dimers of the enamine epoxides **2a–f**, were obtained in excellent yields as crystalline products during the oxygen transfer to the corresponding enamines by dimethyldioxirane (DMD) in acetone. In methanol at −78°C, enamine **1b** gave with dimethyldioxirane the β-hydroxy acetal **4b** as the expected trapping product of the intermediary enamine epoxide **2b**.

Solutions of dimethyldioxirane (DMD) in acetone[1] are mild and selective oxidants for the epoxidation of C=C bonds[2]. For example, the epoxidation of enol silyl ethers, enol phosphates, unsaturated esters, and lactones afforded in all cases the corresponding epoxides in high yields[3]. On the other hand, while primary amines are transformed by DMD into the corresponding nitro compounds[4–8], secondary amines are oxidized to hydroxylamines and/or nitroxides[9–11]; however, the reaction of enamines with DMD appears not to have been studied until now. Herein we present our results on the oxy functionalization of the enamines **1a–f** by DMD, in which we demonstrate that instead of nitrogen lone-pair oxidation, the epoxidation of the π bond prevails (Scheme 1).

Scheme 1



	R^1	R^2
a	i-Pr	CH_3
b	i-Bu	CH_3
c	i-Pr	$-(CH_2)_5-$
d	$-(CH_2)_4-$	CH_3
e	$-(CH_2)_5-$	CH_3
f	$-(CH_2)_2-O-(CH_2)_2-$	CH_3

Results and Discussion

The enamines **1a–f** were transformed in very good yields by DMD into the dimers **3a–f** of the corresponding epoxides **2a–f**. After evaporation of the solvent, in all cases the dimeric epoxides **3a–f** (1,4-dioxanes) were isolated as colorless crystalline solids. While they are insoluble in polar solvents such as methanol or acetone (except for **3f**), they can readily be handled in *n*-pentane solutions. The structures of the 1,4-dioxanes **3a–f** were established by spectral data and elemental analyses. In the case of **3b**, its configuration was proven by an X-ray structure determination (Figure 1).

The epoxidation reaction must be carried out with rigorously dry (!) solutions of DMD, because traces of water hydrolyzed the epoxides **2** and led to complex mixtures of oxidation products. Even at low temperatures (−20°C), only the dimers **3a–f** were observed with no spectral evidence for the monomeric epoxides **2**. Since the corresponding enol ether **5** yielded with DMD the monomeric epoxide **6** [Eq. (1)], the exclusive formation of the dimers in the enamine epoxidation speaks for the very labile nature of the enamine epoxides.

To elucidate the reaction mechanism of the formation of dimer **3b**, logically formed from the intermediary epoxide

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2b, the enamine **1b** was oxidized by DMD in the presence of excess methanol. Indeed, the hydroxy acetal product **4b** was obtained exclusively at −78 °C by trapping of the epoxide-derived 1,3-dipole, as confirmed by NMR spectral data (Scheme 1). Product **4b** is quite sensitive towards moisture and decomposes at room temperature and also during attempted silica gel column chromatography, so that rigorous purification was not possible.

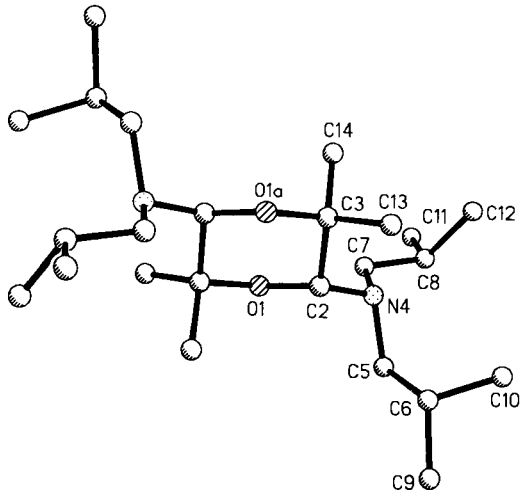
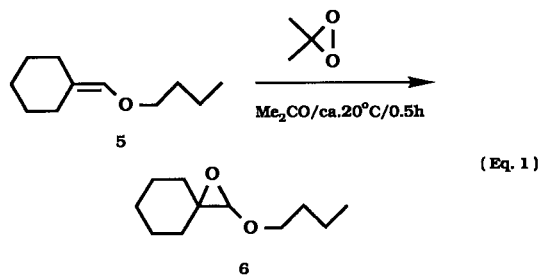


Figure 1. Perspective drawing of the crystal structure of **3b**: the numbering of the atoms corresponds to that in Table 1; selected bond lengths [pm] and angles [°]: O(1)−C(2) 143.5(2), C(2)−C(3) 154.2(3), C(3)−C(13) 152.5(3), C(3)−O(1A) 145.0(3), N(4)−C(7) 147.7(3), C(6)−C(9) 153.1(3), C(7)−C(8) 152.4(4), C(2)−N(4) 144.2(3); C(2)−O(1)−C(3A) 114.7(2), O(1)−C(2)−N(4) 110.0(2), C(2)−C(3)−C(13) 109.5(1), C(13)−C(3)−C(14) 110.7(2), C(13)−C(3)−O(1A) 104.3(2), C(2)−N(4)−C(5) 110.0(1), C(5)−N(4)−C(7) 110.9(2), O(1)−C(2)−C(3) 110.7(1), C(3)−C(2)−N(4) 116.6(1), C(2)−C(3)−O(1A) 105.3(1), C(2)−N(4)−C(7) 114.9(1)

In summary, DMD is an efficient and selective oxidant for the oxygen transfer exclusively to the C=C bond rather than the nitrogen atom of the enamines investigated here. The formation of the trapping product **4b** with methanol indicates that the epoxide **2** is the intermediate, which dimerizes via the corresponding 1,3-dipole (Scheme 1).



(Eq. 1)

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Experimental

Melting points: Reichert Thermovar hot stage. — IR: Perkin-Elmer 1420. — ^{1}H and ^{13}C NMR: Bruker AC 200 (200 MHz) or AC 250 (250 MHz); chemical shifts refer to C_6D_6. — CI MS: Finnigan MAT 90. — Solutions of dimethyldioxirane (DMD) in acetone were prepared according to literature procedures[1]; the known enamines **1a**[13], **1b**[14], **1c**[15], **1d**[16], **1e**[17], and **1f**[16] were also prepared in analogy to literature procedures[16] and characterized by their NMR and MS data.

N,N-Diisopropyl-2-methyl-1-propen-1-ylamine (**1a**): Yield 50%; b.p. 52 °C/20 Torr. — *N,N-Diisobutyl-2-methyl-1-propen-1-ylamine* (**1b**): Yield 80%; b.p. 75 °C/10 Torr. — *N,N-Diisopropyl(cyclohexylidenemethyl)amine* (**1c**): Yield 23%; b.p. 92 °C/6 Torr. — *N-(2-Methyl-1-propen-1-yl)pyrrol* (**1d**): Yield 70%; b.p. 65 °C/17 Torr. — *N-(2-Methyl-1-propen-1-yl)piperidin* (**1e**): Yield 70%; b.p. 65 °C/12 Torr. — *N-(2-Methyl-1-propen-1-yl)morpholine* (**1f**): Yield 60%; b.p. 60 °C/10 Torr. — *(Butoxymethylene)cyclohexane* (**5**) was obtained in 45% yield by reaction of cyclohexanecarboxaldehyde and excess butanol in the presence of *p*-toluenesulfonic acid[18] after distillation, b.p. 215−220 °C/760 Torr.

General Procedure for the Reaction of Dimethyldioxirane (DMD) with the Enamines **1a**−**f**: A well-dried (over 4 Å molecular sieves) 0.083 M (0.078 M, 0.067 M) solution of DMD in acetone was rapidly added at room temperature (ca. 20 °C) while stirring and under dry N_2 to the pure enamines **1a**−**f**. After complete consumption of the DMD (ca. 30 min), the solvent was removed (20 °C/17 Torr). The products **3a**−**f** were obtained as crystalline solids, which were purified by washing with methanol and recrystallization from petrolcum ether/aceton (1:20).

trans-2,5-Bis(diisopropylamino)-3,3,6,6-tetramethyl-1,4-dioxane (**3a**): According to the general procedure, 151 mg (0.97 mmol) of **1a** and 12.5 ml of 0.083 M (1.10 mmol) DMD in acetone afforded 155 mg (93%) of **3a** as colorless prisms; m.p. 164−165 °C. — IR (CCl_4): $\tilde{\nu}$ = 2995 cm^{-1}, 1415, 1385, 1270, 1200, 1115, 1100, 1040. — ^{1}H NMR (250 MHz, C_6D_6): δ = 0.86 (d, 12H), 1.04 (d, 12H), 1.08 (s, 6H), 1.22 (s, 6H), 3.12 (m, 4H), 4.14 (s, 2H), — ^{13}C NMR (63 MHz, C_6D_6): δ = 18.5 (q), 20.8 (q), 23.8 (q), 27.5 (q), 44.7 (d), 75.6 (s), 83.2 (d). — MS (70 eV): *m/z* (%) = 343.4 (11.2) [M^+ + 1], 173 (13), 172 (100), 155 (19), 130 (14), 113 (11), 112 (9), 81 (10), 73 (21), 71 (9).

$C_{20}H_{42}N_2O_2$ (342.6) Calcd. C 70.12 H 12.36 N 8.18
Found C 69.65 H 12.67 N 7.88

trans-2,5-Bis(diisobutylamino)-3,3,6,6-tetramethyl-1,4-dioxane (**3b**): According to the general procedure, 165 mg (0.90 mmol) of **1b** and 12.5 ml of 0.083 M (1.10 mmol) DMD in acetone gave 162 mg (91%) of **3b** as colorless prisms; m.p. 142−143 °C. — IR (CCl_4): $\tilde{\nu}$ = 2950 cm^{-1}, 1465, 1380, 1215, 1180, 1150, 1070, 1035. — ^{1}H NMR (200 MHz, C_6D_6): δ = 0.89 (d, *J* = 6.7 Hz, 12H), 1.04 (d, *J* = 6.5 Hz, 12H), 1.37 (s, 6H), 1.43 (s, 6H), 1.70 (m, 4H), ABX system [δ_A = 2.60 (dd, 4H, J_1 = 13.4 Hz; J_2 = 13.4 Hz); δ_B = 2.27 (dd, 4H, J_1 = 13.4 Hz; J_2 = 13.4 Hz)], 4.23 (s, 2H). — ^{13}C NMR (63 MHz, C_6D_6): δ = 20.0 (q), 20.8 (q), 21.2 (q), 27.1 (q), 27.7 (d), 60.0 (t), 76.5 (s), 89.4 (d). — MS (70 eV): *m/z* (%) = 399.5 (16.9) [M^+ + 1], 200 (52), 147 (27), 144 (30), 130 (94), 105 (90), 92 (27), 88 (44), 75 (100), 73 (22).

$C_{24}H_{50}N_2O_2$ (398.7) Calcd. C 72.30 H 12.64 N 7.03
Found C 72.07 H 12.53 N 6.98

Crystallographic data and data-collection details: empirical formula: $C_{24}H_{50}N_2O_2$; molecular mass: 398.68; *a* = 905.6(3), *b* = 985.0(3), *c* = 832.2(2) pm; α = 94.90(2), β = 113.62(2), γ =

81.20(2)°; V = 671.9(3) × 10^6 pm^3; Z = 1; d(calcd.) = 0.985 g cm^{-3}; crystal system: triclinic; space group: $P\bar{1}$; diffractometer: Siemens R3m/V; radiation: Mo-K_α; monochromator: graphite; crystal size: 0.4 × 0.4 × 0.7 mm; data collection mode: Wyckoff scan; Θ range: 1.75–27.5°; reciprocal lattice segment: h = −11 to 10, k = −12 to 12, l = 0 to 10; number of reflexions measured: 3296; number of unique reflexions: 3083; number of reflexions with $F > 3\sigma(F)$: 2652; linear absorption coefficient: 0.06 mm^{-1}; absorption correction: ψ scan; direct phase determination; method of refinement: full-matrix least squares; hydrogen atom positions; by riding model with fixed isotropic U; data-to-parameter ratio: 18.29; R = 0.057. R_w = 0.054; program used; Siemens SHELXTL PLUS (Micro VAX II). The atomic and equivalent isotropic displacement parameters are given in Table 1[12].

Table 1. Atomic parameters (× 10^4) and equivalent isotropic displacement parameters (× 10^{-1}) [pm^2] of **3b**

	x	y	z	U(eq)
O(1)	4563(2)	440(1)	1377(2)	41(1)
C(2)	5150(2)	-979(2)	1207(2)	37(1)
C(3)	4745(2)	-1398(2)	-736(2)	41(1)
N(4)	4638(2)	-1813(2)	2183(2)	38(1)
C(5)	5808(2)	-1873(2)	4032(3)	47(1)
C(6)	7298(2)	-2952(2)	4337(3)	56(1)
C(7)	2961(2)	-1401(2)	2066(3)	46(1)
C(8)	2207(2)	-2578(2)	2388(2)	59(1)
C(9)	8580(3)	-2759(2)	6189(3)	89(1)
C(10)	6841(3)	-4391(3)	4036(4)	96(2)
C(11)	585(3)	-2024(3)	2508(5)	99(2)
C(12)	2000(3)	-3725(3)	988(4)	78(1)
C(13)	5703(3)	-2791(2)	-857(3)	59(1)
C(14)	2938(2)	-1391(3)	-1912(3)	56(1)

trans-8,16-Bis(diisopropylamino)-7,15-dioxadispiro[5.2.5.2]hexadecane (**3c**): According to the general procedure, 152 mg (0.78 mmol) of **1c** and 12.0 ml of 0.083 M (1.00 mmol) DMD in acetone provided 158 mg (96%) of **3c** as colorless rhombohedrons; m.p. 194–195.5°C. – IR (CCl_4): $\tilde{\nu}$ = 2930 cm^{-1}, 2860, 1450, 1360, 1230, 1210, 1190, 1147, 1125, 1045, 1020. – ^{1}H NMR (250 MHz, C_6D_6): δ = 0.97 (d, J = 6.8 Hz, 12H), 1.19 (d, J = 6.6 Hz, 12H), 1.78 (m, 20H), 3.30 (m, 4H), 4.42 (s, 2H). – ^{13}C NMR (63 MHz, C_6D_6): δ = 21.5 (q), 22.1 (t), 22.5 (t), 24.9 (q), 26.6 (t), 33.0 (t), 33.1 (t), 45.8 (d), 79.1 (s), 82.8 (d). – MS (70 eV): m/z (%) = 423.5 (0.07) [M$^+$], 421 (0.2), 322 (6), 213 (2), 212 (15), 210 (6), 196 (14), 195 (100), 180 (12), 152 (12).

$C_{26}H_{50}N_2O_2$ (422.7) Calcd. C 73.88 H 11.92 N 6.63
Found C 74.02 H 12.11 N 6.48

trans-2,5-Dipyrrolidino-3,3,6,6-tetramethyl-1,4-dioxane (**3d**): According to the general procedure, 126 mg (1.00 mmol) of **1d** and 14 ml of 0.078 M (1.10 mmol) DMD in acetone yielded 135 mg (95%) of **3d** as colorless prisms; m.p 124–125°C. – IR (CCl_4): $\tilde{\nu}$ = 3000 cm^{-1}, 2890, 1475, 1395, 1385, 1165, 1045, 985. – ^{1}H NMR (250 MHz, C_6D_6): δ = 1.35 (s, 6H), 1.40 (s, 6H), 1.58 (m, 8H), 2.82 (m, 4H), 3.00 (m, 4H), 4.33 (s, 2H). – ^{13}C NMR (63 MHz, C_6D_6); δ = 19.8 (q), 27.2 (q), 25.2 (t), 49.2 (t), 76.2 (s), 88.7 (d).

$C_{16}H_{30}N_2O_2$ (282.4) Calcd. C 68.04 H 10.71 N 9.92
Found C 68.05 H 10.90 N 9.88

trans-2,5-Dipiperidino-3,3,6,6-tetramethyl-1,4-dioxane (**3e**): According to the general procedure, 69.8 mg (0.50 mmol) of **1e** and 7 ml of 0.078 M (0.55 mmol) DMD in acetone afforded 65.9 mg (85%) of **3e** as colorless prisms; m.p. 178–179°C. – IR (CCl_4): $\tilde{\nu}$ = 3005 cm^{-1}, 2970, 2870, 1445, 1385, 1185, 1130, 1090, 1070, 1025. – ^{1}H NMR (250 MHz, C_6D_6): δ = 1.30–1.60 (m, 4H), 1.33 (s, 2H), 2.55 (m, 4H), 2.89 (m, 4H), 4.01 (s, 2H). – ^{13}C NMR (63 MHz, C_6D_6): δ = 19.1 (q), 25.3 (t), 26.9 (q), 27.2 (t), 51.7 (t), 76.8 (s), 92.9 (d).

$C_{18}H_{34}N_2O_2$ (310.5) Calcd. C 69.63 H 11.04 N 9.02
Found C 69.47 H 11.07 N 8.92

trans-2,5-Dimorpholino-3,3,6,6-tetramethyl-1,4-dioxane (**3f**): According to the general procedure, 141 mg (1.00 mmol) of **1f** and 14 ml of 0.078 M (1.10 mmol) DMD in acetone gave 94.5 mg (61%) of **3f** as colorless prisms (well soluble in acetone); m.p. 190–191°C. – IR (CCl_4): $\tilde{\nu}$ = 2980 cm^{-1}, 2860, 1455, 1375, 1255, 1270, 1160, 1135, 1070, 1035. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.10 (s, 6H), 1.20 (s, 6H), 2.48 (m, 4H), 2.75 (m, 4H), 3.55 (m, 8H), 3.78 (s, 2H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.0 (q), 26.4 (q), 50.3 (t), 67.5 (t), 76.4 (s), 91.8 (d).

$C_{16}H_{30}N_2O_4$ (314.4) Calcd. C 61.12 H 9.62 N 8.91
Found C 60.81 H 9.94 N 8.90

2-Butoxy-1-oxaspiro[2.5]octane (**6**): According to the general procedure, 171 mg (1.00 mmol) of **5** and 15 ml of 0.067 M (1.10 mmol) DMD in acetone provided 185 mg (98%) of **6**. – IR (CCl_4): $\tilde{\nu}$ = 2940 cm^{-1}, 2860, 1470, 1240, 1225, 1145, 1115, 920. – ^{1}H NMR (250 MHz, C_6D_6): δ = 0.84 (t, 3H), 1.18–1.92 (m, 14H), 3.40 (m, 1H), 3.60 (m, 1H), 4.16 (s, 1H). – ^{13}C NMR (63 MHz, C_6D_6): δ = 14.2 (q), 19.9 (t), 25.1 (t), 25.3 (t), 26.3 (t), 29.5 (t), 32.4 (t), 33.8 (t), 63.3 (s), 69.3 (t), 87.6 (d).

$C_{11}H_{20}O_2$ (184.3) Calcd. C 71.70 H 10.93
Found C 71.71 H 10.75

Trapping Experiment of Epoxide **2b** *by Methanol:* To a stirred solution of 183 mg (1.00 mmol) of **1b** in 160 mg (5.00 mmol) of methanol, cooled to −78°C, was added rapidly 24 ml (2.00 mmol) of a 0.083 M DMD solution in acetone. After 20 min, the solvent was removed (0°C/17 Torr), and the residual, colorless oil (210 mg, 90%) was submitted to NMR spectral analysis, which showed only the signals expected for the trapping product *1-(Diisobutylamino)-1-methoxy-2-methyl-2-propanol* (**4b**): ^{1}H NMR (250 MHz; $CDCl_3$): δ = 0.81 (d, J = 6.7 Hz, 6H), 0.86 (d, J = 6.5 Hz, 6H), 1.10 (s, 3H), 1.14 (s, 3H), 1.67 (m, 2H), 2.10 (s, 1H), 2.45 (m, 4H), 3.43 (s, 3H), 3.62 (s, 1H). – ^{13}C NMR (63 MHz, C_6D_6): δ = 20.6 (q), 21.0 (q), 25.7 (q), 26.8 (q), 59.6 (q), 61.2 (t), 72.3 (s), 101.1 (d).

CAS Registry Numbers

1a: 23297-04-3 / **1b**: 19244-89-4 / **1c**: 76886-47-0 / **1d**: 2403-57-8 / **1e**: 673-33-6 / **1f**: 2403-55-6 / (*trans*)-**3a**: 139462-48-9 / (*trans*)-**3b**: 139462-49-0 / (*trans*)-**3c**: 139462-50-3 / (*trans*)-**3d**: 139462-51-4 / (*trans*)-**3e**: 139462-52-5 / (*trans*)-**3f**: 139462-53-6 / **4b**: 139462-55-8 / **5**: 91212-51-0 / **6**: 139462-54-7 / dimethyldioxirane: 74087-85-7

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