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Epoxidation of Vinylamides by Dimethyldioxirane: First Spectral Evidence for Enamide Oxides

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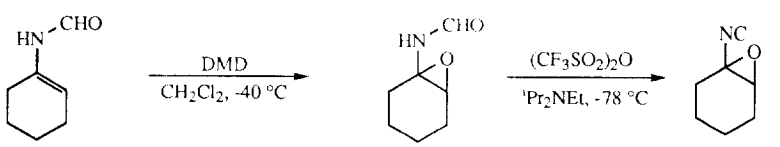
Abstract: The oxidation of the (*E*)- and (*Z*)-*N*-propenylbenzamides (**1**) by dimethyldioxirane (DMD) in acetone solution leads to the α-amido epoxides **2**, which were detected by low-temperature NMR spectroscopy; above -50 °C they dimerize to the diastereomeric dioxanes **3**, in the presence of methanol they are trapped to form the hemiaminal **4**, while *m*CPBA cleaves them to *N*-formylbenzamide and acetaldehyde.

INTRODUCTION

Solutions of dimethyldioxirane (DMD) in acetone[1] are mild and selective oxidants for the epoxidation of C=C bonds.[2] Previously[3] we have shown that enamines, which bear an α hydrogen atom at the double bond, are transformed by DMD into amino-substituted 1,4-dioxanes. The oxygen transfer by dimethyldioxirane occurred selectively at the double bond and not at the amino group, the observed 1,4-dioxanes resulted from dimerization of the thermally labile enamine oxides. Presumably, the destabilizing effect of the α-amino substituent is responsible for the lack of persistence of these enamine oxides. Nonetheless, spectral detection was achieved by disilylation of the nitrogen atom,[4] through which the destabilizing effect of the electron-rich amino group was arrested by the silyl groups due to nitrogen lone pair delocalization onto silicon.

Alternatively, *N*-acylation of the enamine functionality should serve the purpose of stabilizing the corresponding enamide epoxides. This stabilization concept was successful in the preparation of sufficiently persistent indole oxides for spectral detection.[5] Indeed, transient epoxides of *N*-alkylated enamide derivatives have been reported, but their isolation and characterization failed because of too facile rearrangement.[6,7] Nevertheless, Baldwin and O'Neil[8] have reported the DMD oxyfunctionalization of vinyl formamides to afford intermediate epoxy formamides, which were *in situ* dehydrated to yield epoxy isonitriles (eq. 1) without



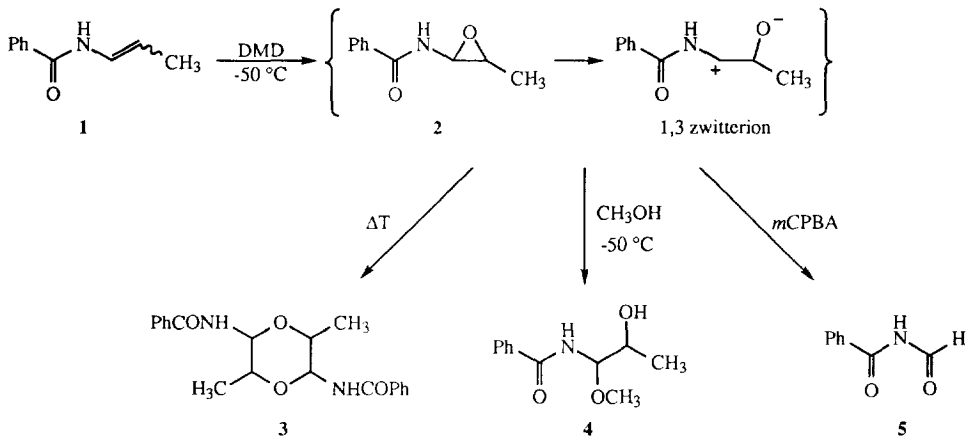
(eq. 1)

rearrangement of the oxirane ring. These novel isonitrile-substituted epoxides are sufficiently stable for isolation and characterization because of the (-I) effect of the isonitrile group in contrast to the (+M) effect of a formamido group. However, epoxy amides have not been observed spectrally until now and we present herein the first such study, in which DMD oxyfunctionalization of enamides leads to the corresponding labile epoxides.

RESULTS AND DISCUSSION

Treatment of the (*E*)- and (*Z*)-enamides **1**[9] with dimethyldioxirane (1.2 equiv.) at -78 °C for 3 h gave after evaporation of the solvent (-20 °C/0.1 Torr) a complex mixture of oxidation products. Unfortunately, even at -20 °C no epoxy enamides were observed spectroscopically.

To avoid the high temperatures (-20 °C) necessary during the evaporation of the solvent (methylene chloride, acetone), the epoxidation was run with deuterated dimethyldioxirane in [D_6]acetone. In this way, the two diastereomeric α-amido epoxides **2** were formed quantitatively (Scheme 1), as manifested by low-



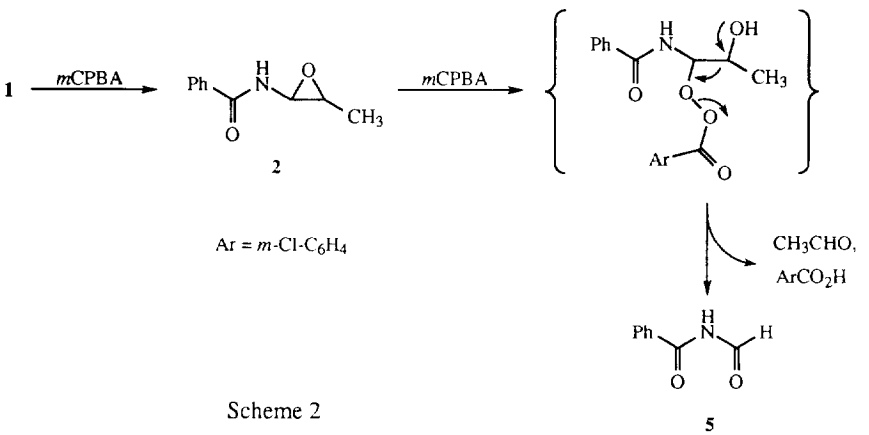
Scheme 1

temperature (-50 °C) NMR spectroscopy. The (*Z*)-propenylbenzamide afforded the *cis* epoxide, while the (*E*)-propenylbenzamide led to the *trans* isomer. The characteristic ^{1}H chemical shifts at δ 3.24 and 5.00 for epoxy amide *cis*-**2** and δ 3.36 and 4.82 for epoxy amide *trans*-**2**, as well as the definitive ^{13}C chemical shifts of the epoxy carbon atoms at δ 53.1 and 60.6 for *cis*-**2** and δ 53.3 and 61.6 for *trans*-**2** unequivocally establish the proposed enamide oxide structures **2**. This constitutes the first direct spectral evidence for α-amido (RCONH) epoxides. Unfortunately, due to the extremely labile nature of these α-amido epoxides, deterioration into intractable, undefined oils took place at temperatures higher than -50 °C.

When warming up the epoxidation reaction mixture to room temperature, besides intractable oxidation material, the diastereomeric 1,4-dioxanes **3** were the only defined products which were isolated (Scheme 1). The structure was established by spectral data and elemental analysis. The ^{1}H chemical shifts at δ 3.88 and 5.33, as well as ^{13}C resonances of the ring carbon atoms at δ 70.2/70.4 [^1J (C,H) = 143.3 Hz] and 78.4/78.5 [^1J (C,H) = 156.0 Hz] are in accord with the proposed 1,4-dioxane structure.[3,10] The yield of 1,4-dioxane **3** (60-80 %) depended on the quality of dioxirane solutions, because traces of water hydrolyze the epoxide **2** and afford higher amounts of undefined oxidation products, but no rearrangement products from hydrogen or alkyl 1,2-shifts, i.e. keto amides, were observed. 1,4-Dioxane **3**, the dimer of the corresponding epoxide **2**, is formed presumably through a 1,3 zwitterion (Scheme 1) and it is unusual that no rearrangement takes place. Apparently, the adjacent benzamido group stabilizes the positive charge sufficiently to build up a high enough steady-state concentration for dimerization.

When the DMD reaction was run in methanol as cosolvent, the hemiaminal **4** was obtained in 20% yield as epoxide trapping product (Scheme 1), which was confirmed by NMR analysis of the crude reaction mixture. Attempts to isolate the hemiaminal **4** by column chromatography failed, presumably due to its lability and easy loss of water or methanol and further reactions during work-up.

In contrast to DMD, the oxidation of enamide **1** by *m*-chloroperoxybenzoic acid (*m*CPBA) gave instead of 1,4-dioxane **3** the C=C cleavage products[11] *N*-formylbenzamide (**5**)[12] and acetaldehyde (Scheme1). As shown in Scheme 2, this C=C cleavage proceeds presumably through an intermediary β-hydroxy perester, formed by



Scheme 2

nucleophilic trapping of *m*CPBA by the epoxide. Subsequent Grob fragmentation affords the observed carbonyl fragments. Indeed, addition of *m*CPBA to the α-amido epoxide **2**, derived from dimethyldioxirane oxidation at -50 °C, led again to the *N*-formylbenzamide (**5**), which provides support for the proposed mechanism (Scheme 2). Moreover, the origin of the traces of imide **5** in the DMD oxidation of enamide **1** is similar in that the epoxide is also cleaved by the dioxirane, for which recently precedents have been reported.[13,14]

In conclusion, we have shown that enamides **1** are selectively oxidized by DMD to the α-amido epoxides **2**. The extremely labile epoxides **2** dimerize to the 1,4-dioxanes **3**, methanol traps them as the hemiaminal **4**, while *m*CPBA leads to the imide **5** as C=C cleavage product.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on a Bruker AC 200 spectrometer (^{1}H: 200 MHz, ^{13}C: 50 MHz) with deuteriochloroform, [D$_6$]acetone or [D$_4$]methanol as internal standards. IR spectra were recorded on a Perkin-Elmer 1420 Ratio Recording IR spectrophotometer. Elemental analyses were carried out by the Microanalysis Laboratory of the Institute of Inorganic Chemistry, University of Würzburg. Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. Solutions of dimethyldioxirane (DMD) in acetone and [D$_6$]dimethyldioxirane in [D$_6$]acetone were prepared according to literature procedures[1]. The known *N*-propenylbenzamides (*Z*)- and (*E*)-**1** were also prepared by following the literature procedure[9] and characterized by their NMR data. All solvents were dried and destilled before use and commercially available reagents were employed as purchased. The oxidations were carried out under dry nitrogen gas.

General Procedure for the Reaction of the Enamides 1 with [D6]dimethyldioxirane:
750 µl (55.9 µmol) of a well-dried (over 4 Å molecular sieves) solution of [D6]dimethyldioxirane in [D6]acetone (0.074 M) was rapidly added to 9.00 mg (55.8 µmol) of the enamide **1** in 50 µl deuteriochloroform at -78 °C. After 1h, the reaction mixture was submitted to low temperature (-50 °C) NMR spectroscopy. The epoxy enamides **2** were obtained quantitatively. At temperatures higher than -50 °C, deterioration into intractable, undefined oils took place.

cis-(2-Methyloxiranyl)benzamide (cis-2): ^{1}H NMR ([D6]acetone, 200 MHz, -50 °C): δ 1.40 (d, *J* = 5.6 Hz, 3H, CH_3), 3.24 (m, 1H, CH), 5.00 (m, 1H, CH), 7.44-7.59 (m, 3H), 7.86-7.91 (m, 2H), 8.28 (br s, 1H, NH); ^{13}C NMR ([D6]acetone, 50 MHz, -50 °C): δ 13.2 (q, CH_3), 53.1 (d, CH), 60.6 (d, CH), 128.1 (2xd), 128.9 (2xd), 132.5 (d), 134,3 (s), 169.6 (s, CO).

trans-(2-Methyloxiranyl)benzamide (trans-2): ^{1}H NMR ([D6]acetone, 200 MHz, -50 °C): δ 1.37 (d, *J* = 6.8 Hz, 3H, CH_3), 3.36 (m, 1H, CH), 4.82 (m, 1H, CH), 7.49-7.59 (m, 3H), 7.86-7.99 (m, 2H), 8.14 (br s, 1H, NH); ^{13}C NMR ([D6]acetone, 50 MHz, -50 °C): δ 16.8 (q, CH_3), 53.3 (d, CH), 61.6 (d, CH), 127.8 (2xd), 129.1 (2xd), 132.6 (d), 134.2 (s), 168.8 (s, CO).

2,5-Dibenzamido-3,6-dimethyl-1,4-dioxane (3):
To a stirred solution of 78.0 mg (0.484 mmol) enamide **1** in 10 ml methylene chloride, cooled to -78 °C, was added rapidly 6 ml (0.570 mmol) of a well-dried DMD solution in acetone (0.095 M). After 3 h, the solvent was removed (-20 °C/0.1 Torr) and the crude product mixture was submitted directly to NMR analysis at low temperature (-20 °C). Full conversion was observed, but no epoxy enamides were detected. The reaction mixture was warmed up to room temperature, the oily residue was taken up in acetone, and after 24 h at -20 °C, 68.0 mg (79%) of 1,4-dioxane **3** precipitated as a colorless, amorphous powder, mp: 86-88 °C (acetone); IR (CCl_4): ν 3400 cm^{-1}, 2950, 2900, 1710, 1690, 1650, 1470, 1230, 900; ^{1}H NMR (CD_3OD, 200 MHz): δ 1.20 (dd, *J* = 6.3, 1.1 Hz, 6H, CH_3), 3.88 (m, 2H, CH), 5.33 (d, *J* = 5.3 Hz, 2H, CH), 7.77 (br s, 2H, NH), 7.85-7.93 (m, 10H); ^{13}C NMR (CD_3OD, 50 MHz) for the 50 : 50 diastereomeric mixture: δ 18.8/19.2 (2xq, CH_3), 70.2/70.4 [2xd, ^1J (C,H) = 143.3 Hz, CH], 78.4/78.5 [2xd, ^1J (C,H) = 156.0 Hz, CH], 128.5 (4xd), 129.6 (4xd), 132.9 (2xd), 135.6 (2xs), 165.8 (2xs, CO); Anal. Calcd. for $C_{20}H_{22}N_2O_4$ (354.4): C, 67.78; H, 6.26; N, 7.90; Found: C, 67.82; H, 6.03; N, 7.42.

Trapping Experiment of Epoxide 2 by Methanol:
To a stirred solution of 106 mg (658 µmol) enamide **1** in 2 ml methanol, cooled to -78 °C, was added rapidly 24 ml (1.30 mmol) of DMD solution in acetone (0.054 M). After 2 h, the solvent was removed (0 °C/ 16 Torr) and the oily residue was submitted to NMR analysis. The hemiaminal **4** (20%) was tentatively assigned on the basis of the following NMR signals: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.27 (d, *J* = 7.4 Hz, 3H, CH_3), 3.42 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.8 (q, CH_3), 56.3 (q, OCH_3). Unfortunately, further assignment was not possible due to severe signal overlap. Several attempts to purify the product by silica gel chromatography failed.

Reaction of the Enamides 1 with m-Chloroperoxybenzoic acid (mCPBA):
To a stirred solution of 172 mg (1.07 mmol) enamide **1** in 10 ml methylene chloride was added 280 mg (1.62 mmol) *m*-chloroperoxybenzoic acid (*m*CPBA), and stirring was continued for 24 h. After filtration, the organic layer was washed with saturated $NaHCO_3$ (2 x 10 ml), dried over $MgSO_4$, and evaporated to yield 130 mg (81%) of the known *N*-formylbenzamide (**5**).[12]

Reaction of the Epoxide 2 with m-Chloroperoxybenzoic acid (mCPBA):
To a stirred solution of 130 mg (806 µmol) enamide **1** in 5 ml methylene chloride, cooled to -78 °C, was added rapidly 10 ml (950 µmol) of DMD solution in acetone (0.095 M). After 3 h, 140 mg (811 µmol) *m*CPBA was added at -50 °C, the reaction mixture was warmed up to 20 °C, and stirring was continued for 24 h. After filtration, the organic layer was washed with saturated $NaHCO_3$ (2 x 10 ml), dried over $MgSO_4$, and evaporated to afford 140 mg of a yellow oil, which contained ca. 50% of the known *N*-formylbenzamide (**5**), based on NMR analysis of the crude reaction mixture.

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