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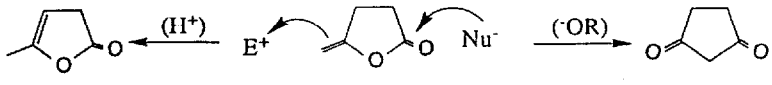
EPOXIDATION OF γ-METHYLENE-γ-BUTYROLACTONES BY DIMETHYLDIOXIRANE

Waldemar Adam, Lazaros Hadjiarapoglou, Volker Jäger * and Bernhard Seidel.*
Institute of Organic Chemistry, University of Würzburg, Am Hubland,
D-8700 Würzburg, Federal Republic of Germany

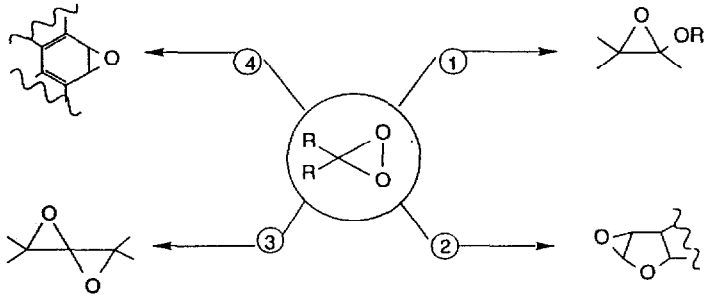
Abstract : Dimethyldioxirane (as acetone solution) converts γ-methylene-γ-butyrolactones and other enol lactones and esters to the corresponding epoxides in excellent yields.

γ-Methylene-γ-butyrolactones **1** constitute a class of compounds that only recently[1] have become accessible, the chemistry of which warrants intensive investigation. An intriguing feature of these enol lactones is the presence of both the C=C and the C=O functionalities, making them susceptible towards attack by electrophiles nucleophiles. This leads normally to 1,4-dicarbonyl derivatives or, in catalytic processes, to the indicated cyclic isomers (Eq. 1) [2]. Of particular relevance to the present study are preliminary results on the bromine addition to



1 (1)

yield highly reactive dibromo compounds [2d,3a] and the reluctance of **1** towards mCPBA epoxidation, making the enol ester C=C bond much less reactive as compared to an (internal) trialkyl-substituted alkene [2c,3b]. Presently we report on the successful epoxidation of enol lactones **1** to afford the labile epoxy esters **2**, which constitute potentially useful building blocks for organic synthesis.



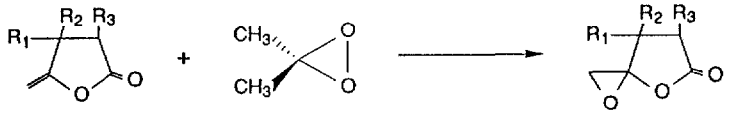
SCHEME 1

A few epoxy esters related to **2** have been prepared directly from enol esters using peroxy acids [4], but in most cases the former have been postulated as transient intermediates, rearranging to keto esters [5]. In one case, a natural product containing this epoxy lactone moiety has been isolated, namely jolkinolide B, and subsequently

its structure elucidated by spectroscopy, chemical transformation, and X-ray crystallography [6], and by total synthesis [7].

An efficient epoxidizing agent, which performs under strictly neutral condition and thus avoids the acid-catalyzed transformations of the epoxide products, a common difficulty with peroxy acids, is dimethyldioxirane. [8] Most recently (Scheme 1) it was shown that dioxiranes (as ketone solutions) [9] convert enol ethers [10] to the corresponding epoxide [1], aflatoxin B_1 [11] to the corresponding epoxide [2], polycyclic aromatic hydrocarbons [12] to arene oxides [3], and allenes [13] to spirodioxides [4]. It was our contention that dimethyldioxirane should be an ideal reagent for the epoxidation of enol lactones.

Indeed, dimethyldioxirane transformed γ-methylene-γ-buyrolactones **1** to the corresponding spiroepoxy lactones **2** (Eq. 2) in high yield (Table 1). Attempts to prepare the spiroepoxy lactones **2** by peroxy acid



1 **2** (2)

epoxidation of these exocyclic enol lactones, even under buffered conditions, led to complete decomposition. The general epoxidation procedure entails adding rapidly a solution of dimethyldioxirane (10-20% molar excess) in acetone (ca. 0.07-0.11 M), which was dried over molecular sieves (4Å), to a cooled (-20 °C), stirred solution of the γ-methylene-γ-butyrolactone (1.06 mmol) in abs. CH_2Cl_2 (10 mL) under N_2. The stirring was continued until complete consumption (cf. Table 1) of the enol lactone **1** and the solvent removed in vacuo, yielding the hitherto unknown, labile spiroepoxy lactones **2** in high purity (NMR,TLC).

Table 1. Epoxidation [a] of the γ-Methylene-γ-butyrolactones 1 to the Spiroepoxy Lactones 2 by Dimethyldioxirane.

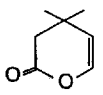
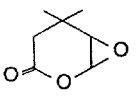
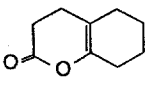
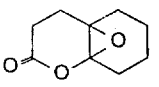
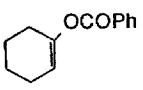
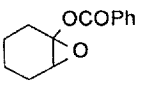
Methylene-lactone	R^1	R^2	R^3	Reaction time (h)	Epoxy lactone 2	Ref.[c]
1					Yield,(%) [b]	
a	H	H	H	2.0	96	14
b	CH_3	CH_3	H	3.0	96	15
c	CH_3	H	H	3.5	95 [d]	16
d	H	H	CH_3	3.5	94 [e]	17

[a] In CH_2Cl_2 / CH_3COCH_3 at -20 °C. [b] Yield of isolated product. [c] Selected spectral data for each of the 1,7-dioxaspiro[2,4]heptan-6-ones **2** are given in the footnotes ; IR data were obtained by using a Perkin Elmer 1420 instrument; ^1H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectral were run on a Bruker WM-250 spectrometer, referring chemical shifts to Me_4Si; MS spectra were obtained on a Varian MAT CH 7 instrument. [d] As a ca. 60:40 mixture of two diastereomers. [e] As a ca. 65:35 mixture of two diastereomers.

As an extension, the three endocyclic enol lactones and esters **3**, **5**, and **7** (cf. Table 2) were examined,

comparing the epoxidation by dimethyldioxirane with that of m-chloroperbenzoic acid. In all cases, dimethyldioxirane proved advantageous in that shorter reaction times and lower temperatures were required, affording the epoxides **4, 6,** and **8** in excellent yield. Thus, in contrast to peroxy acids, dimethyldioxirane (as acetone solution) is an efficient oxygen transfer reagent, permitting the isolation of sensitive epoxides under extremely mild (neutral) conditions. The utilization of the novel spiroepoxides **2** is being actively explored and will be reported subsequently.

Table 2. Epoxidation [a] of Enol-Lactones and Esters by Dimethyldioxirane

Enol Lactone or Ester	Reaction time (h)	Epoxide	Yield [b]	Ref.
 **3**	3.0	 **4**	79 [c]	18
 **5**	3.0	 **6**	83	19
 **7**	3.0	 **8**	96	3a

[a] In CH_2Cl_2/CH_3COCH_3. [b] Isolated yields. [c] m-Chloroperbenzoic acid epoxidized 3,4-dihydro-4,4-dimethyl-pyranone-2 to the corresponding epoxide in 80% yield (^{1}H NMR) in 6 h at room temperature.

Caution: Many epoxides are known to exhibit genetoxic effects, e.g. acetoxyoxirane [20]; therefore the epoxides reported here should be prepared and handled with due care.

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14. **2a**; IR (CCl_4): 1815 cm^{-1} (C=O).- ^1H NMR (250 MHz, $CDCl_3$) : δ = 2.32-2.43 (m, 1H), 2.67-3.01 (m, 3H), 2.97 and 3.31 (AB, J_{AB} = 3.72 Hz, 2H).- ^{13}C NMR (63 MHz, $CDCl_3$): δ = 26.0, 28.1, 50.4 and 88.3 (oxirane C) , 174.1 (C=O).- MS (70 eV): m/z (%) = 114 (M^+, 8), 86 (32), 56 (100).

15. **2b**; IR (CCl_4): 1820 cm^{-1} (C=O) .- ^1H NMR (250 MHz, $CDCl_3$): δ = 1.11 (s, CH_3), 1.25 (s, CH_3), 2.54 and 2.71 (AB, J_{AB} = 17.43 Hz, 2H), 2.95 and 3.23 (CD, J_{CD} = 3.57 Hz, 2H).- ^{13}C NMR (63 MHz, $CDCl_3$) : δ = 21.7, 25.4, 37.3, 42.8, 47.7 and 93.6 (oxirane C) , 173.1 (C=O).- MS (70 eV) : m/z (%) = 142 (M^+, 0.3), 113 (4), 70 (7), 56 (100).

16. **2c**; IR (CCl_4): 1810 cm^{-1} (C=O) ; 60:40 mixture of two diastereomers by NMR. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.05 and 1.21 (2d, J = 6.87 and 7.16 Hz, 3H; CH_3 of minor and major isomers), 2.35-3.12 (m, 3H), 2.93, 3.30 and 3.02, 3.20 (AB of minor and major isomers, J = 3.59 and 3.64 Hz, 2H).- ^{13}C NMR (63 MHz, $CDCl_3$), major isomer: δ = 16.7, 33.2, 36.3, 48.9 and 92.3 (oxirane C), 173.5 (C=O); minor isomer: δ = 13.2, 31.7, 35.7, 48.2 and 90.3 (oxirane C), 173.6 (C=O).- MS (70 eV) m/z (%) = 128 (M^+, 0.6), 99 (6), 70 (25), 42 (100).

17. **2d**; IR (CCl_4): 1815 cm^{-1} (C=O); 65:35 mixture of two diastereomers by NMR.^1H NMR (250 MHz, $CDCl_3$): δ = 1.37 and 1.42 (2d, J = 7.21 and 7.22 Hz, 3H; CH_3 of major and minor isomers), 2.10-3.17 (m, 3H), 2.94, 3.25 and 2.96, 3.31 (AB of minor and major isomers, J = 3.90 and 3.63 Hz, 2H).- ^{13}C NMR (63 MHz, $CDCl_3$), major isomer: δ = 15.5, 33.9, 34.4, 49.5 and 86.3 (oxirane C), 177.4 (C=O); minor isomer: δ = 16.4, 34.1, 34.6, 50.9 and 86.9 (oxirane C), 176.8 ppm (C=O).- MS (70 eV), m/z (%)= 128 (M^+, 1), 99 (6), 70 (19), 42 (100).

18. **4**; IR (CCl_4): 1780 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ = 1.12 (s, CH_3), 1.26 (s, CH_3), 2.17-2.35 (m, 2H), 3.01 (dd, J = 2.55 and 1.56 Hz, 1H) , 5.23 (d, 1H, J = 2.70 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.7, 26.6, 31.3, 58.3 and 77.8 (oxirane C), 167.3 ppm (C=O).- MS (70 eV): m/z (%) = 142 (M^+, 1), 113 (15), 57 (100).

19. **6**; IR (CCl_4): 1775 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ = 1.30 - 2.90 (m).- ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.8, 20.0, 24.7, 27.4, 27.5, 27.8, 61.5 and 87.0 (oxirane C), 168.1 ppm (C=O) .- MS (70 eV): m/z (%) = 168 (M^+, 2), 124 (30), 111 (100).

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