Dimethyldioxirane Epoxidation of 3-Aryl-1-(3-coumarinyl)propen-1-ones

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Dedicated to the memory of Mrs. Ada Castle

Regioselective epoxidation of 3-aryl-1-(3-coumarinyl)propen-1-ones **1-10** by isolated dimethyldioxirane afforded the appropriate epoxides **11-20** in high (76-87%) yields.

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Coumarins are important and well known naturally occurring oxygen-heterocyclic compounds isolated from various plant sources [1-3]. Owing to their diverse bioactivities, *víz.* anticoagulant [4-6], antibacterial, antifungal [7], etc. activities, natural, semisynthetic and synthetic coumarin derivatives became important substances in drug research. As a result, a wide variety of coumarin type compounds have been synthesized, some of which can be used as versatile intermediates for the synthesis of valuable heterocyclic ring systems as well. Among others, the 3-cinnamoyl coumarins synthesized by the reaction of 3-acetylcoumarins with aromatic aldehydes [6-13] proved to be especially important. Cinnamoyl coumarins obtained in this way have been utilized for the synthesis of various nitrogen-containing heterocyclic compounds, *víz.* pyridine [6] pyrazoline [7] and isoxazoline [13] derivatives. To our knowledge, epoxidation of 3-cinnamoyl coumarins has not hitherto been published in the chemical literature. For this reason, the aim of our present study was to work out a convenient procedure for the regioselective epoxidation of these coumarin derivatives belonging to the α,β-unsaturated ketones.

There are well known nucleophilic and electrophilic oxidants for the epoxidation of α,β-enones. However, since the benzopyrane ring of these coumarin derivatives may be opened by nucleophilic oxidants like alkaline hydrogen peroxide or sodium hypochlorite, an electrophilic oxidant seems to be a convenient reagent for this purpose. As an electrophilic oxidant, the isolated dimethyldioxirane (DMD) is an especially beneficial reagent since it acts under strictly neutral reaction conditions providing epoxides without the formation of by-product. This oxidant was found to be the oxidant of choice for the epoxidation of α,β-unsaturated ketones [14-23] and chromones [24-29]. 3-Cinnamoyl coumarins appear to be challenging substrates for such an epoxidation since they possess two electron deficient olefinic double bonds. In our present paper the regioselective dimethyldioxirane epoxidation of a series of 3-cinnamoyl coumarins is reported.

3-Aryl-1-(3-coumarinyl)propen-1-ones **1-10** dissolved in anhydrous dichloromethane were reacted with isolated dimethyldioxirane (DMD, in acetone solution) at room temperature. The progress of the reaction was monitored by thin-layer chromatography (tlc) until the complete consumption of starting materials **1-10**. The formation of one new substance was detected by tlc in each case. The oxidized products **11-20** have been isolated on the evaporation of the solvent followed by crystallization of the residue from methanol.

Scheme 1

1-10 **11-20**

1, **11:** R = H
2, **12:** R = 3-Me
3, **13:** R = 4-Me
4, **14:** R = 4-iPr
5, **15:** R = 3-MeO
6, **16:** R = 4-MeO
7, **17:** R = 4-F
8, **18:** R = 3-Cl
9, **19:** R = 4-Cl
10, **20:** R = 4-Br

Structure elucidation of all new compounds has been achieved by elemental analyses and spectroscopic measurements. Mass spectroscopic and elemental analyses data unambiguously proved that one oxygen atom has been inserted into the molecules of the starting materials **1-10** in the course of the dimethyldioxirane oxidation resulting in the formation of epoxides **11-20**. Electron impact (70 eV) mass spectra of epoxides **11-20** show abundant molecular ions (10-41%). The initial step in the fragmentation of all compounds involves the loss of a CO and ArCO units. The base peak is mainly the *m/z* 173 ion formed by the loss of an $ArCH_2CO$ part from the molecular ion. In their ^1H nmr spectra the doublets of the 2-H (δ = 4.70-4.80 ppm) and the 3-H (δ = 4.01-4.07 ppm) unequivocally prove the presence of the epoxide moiety. The low coupling constant values (J = 1.6-1.8 Hz) indicate a *trans* arrangement of the protons connected to the oxirane ring as observed for the epoxides of the related (*E*)-α,β-unsaturated ketones [14-23]. In the ^{13}C nmr spectra, chemical shift values of the C-2 (δ = 61.7-61.8 ppm) and the C-3 (δ = 59.9-60.8 ppm) carbon atoms confirm the presence of an epoxide functionality

originating from an α,β-unsaturated ketone unit. Both the ^1H and ^{13}C nmr spectroscopic data also prove that the coumarinyl part of the molecules remained unaltered in the course of the dimethyldioxirane oxidation.

In conclusion, we managed to perform a regioselective epoxidation of 3-aryl-1-(3-coumarinyl)propen-1-ones **1-10** with DMD to afford hitherto unknown epoxides **11-20** of 3-cinnamoyl coumarins. It is worth mentioning that this oxidant provides the above-mentioned epoxides in high (76-87%) yields under neutral reaction conditions and without the formation of any by-product. Our present study is the first example for the epoxidation of coumarin derivatives with dimethyldioxirane.

EXPERIMENTAL

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a Varian Gemini 200 spectrometer at 200/50 MHz in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm) at ambient temperature. Mass spectra were recorded on a VG Trio-2 instrument. Elemental analyses were measured in-house with a Carlo Erba 1106 EA instrument. Tlc was performed on Kieselgel 60 F_{254} (Merck) layer using toluene:ethyl acetate (4:1 v/v) as eluent. Dimethyldioxirane (as acetone solution) was prepared as described [30] by using Caroat as received as a generous gift from the Peroxid-Chemie GmbH (München, Germany) and its peroxide content was determined iodometrically. Starting materials **1-10** were synthesized according to known procedures [6-13].

General Procedure for the Epoxidation of Compounds **1-10**.

One equivalent of isolated dimethyldioxirane (0.05-0.1 *M* acetone solution) was added to a solution of 3-aryl-1-(3-coumarinyl)propen-1-one (**1-10**, 0.50 g, 1.5-1.8 mmoles) in anhydrous dichloromethane (50 ml) at room temperature. The mixture was kept at ambient temperature and the progress of the oxidation was monitored by tlc. Another equivalent of dimethyldioxirane was added every day until the complete conversion of the starting materials **1-10** into the appropriate epoxides **11-20**. Altogether eight equivalents of dimethyldioxirane were used for eight days. The solvent was evaporated under reduced pressure (*ca*. 20 Torr) and the residue was crystallized from methanol to obtain crystalline epoxides **11-20**.

1-(3-Coumarinyl)-2,3-epoxy-3-phenylpropan-1-one (**11**).

This substance was obtained as white needles in 76% yield, mp 175-176°; ^1H nmr ($CDCl_3$): δ 4.07 (d, 1H, J = 1.8 Hz, 3-H), 4.78 (d, 1H, J = 1.8 Hz, 2-H), 7.40-7.70 (m, 9 arom. H), 8.62 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 60.7, 61.7, 117.0, 118.2, 123.4, 125.4, 126.4, 128.7, 128.8, 128.9, 129.1, 130.6, 135.2, 135.6, 148.8, 155.7, 191.9; ms: 292 (M+, 41), 276 (24), 173 (100), 105 (59) *m/z*.

Anal. Calcd. for $C_{18}H_{12}O_4$: C, 73.96; H, 4.14. Found: C, 73.91; H, 4.16.

1-(3-Coumarinyl)-2,3-epoxy-3-(3-methylphenyl)propan-1-one (**12**).

This compound was prepared as white needles in 83% yield, mp 186-187°; ^1H nmr ($CDCl_3$): δ 2.37 (s, 3H, Me), 4.02 (d, 1H, J = 1.7 Hz, 3-H), 4.76 (d, 1H, J = 1.7 Hz, 2-H), 7.0-7.76 (m, 8 arom. H), 8.64 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 21.2, 60.8, 61.7, 116.8, 117.3, 123.4, 124.9, 125.3, 125.4, 126.8, 129.9, 130.6, 131.0, 133.1, 135.4, 142.0, 148.8, 155.7, 192.0; ms: 306 (M+, 23), 290 (15), 173 (100), 119 (75) *m/z*.

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.50, H, 4.61. Found: C, 74.47; H, 4.63.

1-(3-Coumarinyl)-2,3-epoxy-3-(4-methylphenyl)propan-1-one (**13**).

This substance was isolated as white needles in 87% yield, mp 191-192°; ^1H nmr ($CDCl_3$): δ 2.39 (s, 3H, Me), 4.05 (d, 1H, J = 1.7 Hz, 3-H), 4.80 (d, 1H, J = 1.7 Hz, 2-H), 7.19-7.73 (m, 8 arom. H), 8.63 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 21.1, 60.8, 61.7, 117.0, 117.9, 123.5, 125.4, 126.3, 129.5, 130.6, 131.0, 132.6, 132.7, 135.2, 139.0, 142.0, 148.7, 155.7, 192.1, ms: 306 (M+, 27), 278 (14) 173 (100), 119 (68) *m/z*.

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.50, H, 4.61. Found: C, 74.54; H, 4.58.

1-(3-Coumarinyl)-2,3-epoxy-3-(4-isopropylphenyl)propan-1-one (**14**).

This compound was prepared as white plates in 79% yield, mp 159-160°; ^1H nmr ($CDCl_3$): δ 1.24 (d, 6H, J = 6.9 Hz, CH*Me*$_2$), 2.91 (m, 1H, C*H*Me$_2$), 4.04 (d, 1H, J = 1.7 Hz, 3-H), 4.76 (d, 1H, J = 1.7 Hz, 2-H), 7.23-7.72 (m, 8 arom. H), 8.63 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 23.7, 31.6, 33.8, 60.8, 61.6, 116.9, 118.2, 123.4, 124.8, 125.4, 126.4, 126.8, 130.6, 135.1, 148.7, 150.0, 155.6, 192.0; ms: 334 (M+, 11), 186 (19), 173 (100), 147 (41) *m/z*.

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.42. Found: C, 75.45; H, 5.44.

1-(3-Coumarinyl)-2,3-epoxy-3-(3-methoxyphenyl)propan-1-one (**15**).

This compound was obtained as white needles in 77% yield, mp 192-193°; ^1H nmr ($CDCl_3$): δ 3.84 (s, 3H, MeO), 4.02 (d, 1H, J = 1.7, 3-H), 4.73 (d, 1H, J = 1.7 Hz, 2-H), 7.01-7.74 (m, 8 arom. H), 8.64 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 55.1, 60.8, 61.5, 111.8, 115.3, 117.2, 118.5, 119.1, 120.8, 123.2, 125.6, 126.9, 127.9, 131.2, 135.8, 148.8, 155.3, 192.0; ms: 322 (M+, 22), 277 (19), 173 (100), 135 (70) *m/z*.

Anal. Calcd. for $C_{19}H_{14}O_5$: C, 70.80, H, 4.38. Found: C, 70.78; H, 4.36.

1-(3-Coumarinyl)-2,3-epoxy-3-(4-methoxyphenyl)propan-1-one (**16**).

This substance was prepared as white plates in 76% yield, mp 154-155°; ^1H nmr ($CDCl_3$): δ 3.82 (s, 3H, MeO), 4.01 (d, 1H, J = 1.6 Hz, 3-H), 4.77 (d, 1H, J = 1.6 Hz, 2-H), 6.92-7.70 (m, 8 arom. H), 8.62 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 55.3, 60.7, 61.7, 114.2, 116.8, 117.0, 118.2, 123.4, 125.4, 127.5, 127.8, 128.6, 130.6, 135.2, 148.7, 155.7, 160.5, 192.1; ms: 322 (M+, 11), 306 (11), 173 (100), 151 (64) *m/z*.

Anal. Calcd. for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.83; H, 4.39.

1-(3-Coumarinyl)-2,3-epoxy-3-(4-fluorophenyl)propan-1-one (**17**).

This compound was obtained as pale yellow needles in 78% yield, mp 198-199°; ^1H nmr ($CDCl_3$): δ 4.04 (d, 1H, J = 1.8 Hz, 3-H), 4.72 (d, 1H, J = 1.8 Hz, 2-H), 7.04-7.70 (m, 8 arom. H),

8.62 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 60.0, 61.8, 115.6, 116.0, 117.1, 123.3, 125.5, 128.1, 128.3, 130.7, 135.3, 148.9, 155.7, 160.9, 165.9, 191.7; ms: 310 (M+, 34), 294 (26), 173 (51), 123 (100) *m/z*.

Anal. Calcd. for $C_{18}H_{11}FO_4$: C, 69.67; H, 3.57. Found: C, 69.65; H, 3.59.

3-(3-Chlorophenyl)-1-(3-coumarinyl)-2,3-epoxypropan-1-one (**18**).

This substance was isolated as yellow needles in 77% yield, mp 144-145°; ^{1}H nmr ($CDCl_3$): δ 4.03 (d, 1H, J = 1.7 Hz, 3-H), 4.70 (d, 1H, J = 1.7 Hz, 2-H), 7.29-7.71 (m, 8 arom. H), 8.61 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 59.7, 61.7, 117.1, 118.2, 123.3, 124.6, 125.4, 125.5, 126.4, 129.3, 130.0, 130.2, 130.7, 134.9, 135.3, 137.8, 148.9, 191.4; ms: 326 (M+, 11), 310 (19), 173 (100), 139 (46) *m/z*.

Anal. Calcd. for $C_{18}H_{11}ClO_4$: C, 66.17; H, 3.39. Found: C, 66.20; H, 3.36.

3-(4-Chlorophenyl)-1-(3-coumarinyl)-2,3-epoxypropan-1-one (**19**).

This compound was prepared as yellow needles in 81% yield, mp 191-192°; ^{1}H nmr ($CDCl_3$): δ 4.03 (d, 1H, J = 1.7 Hz, 3-H), 4.70 (d, 1H, J = 1.7 Hz, 2-H), 7.26-7.70 (m, 8 arom. H), 8.62 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 59.9, 61.8, 117.1, 117.9, 118.2, 123.3, 125.5, 127.7, 129.0, 130.3, 130.7, 134.2, 135.0, 135.3, 148.9, 191.5; ms: 326 (M+, 12), 310 (17), 173 (72), 139 (100) *m/z*.

Anal. Calcd. for $C_{18}H_{11}ClO_4$: C, 66.17; H, 3.39. Found: C, 66.14; H, 3.41.

3-(4-Bromophenyl)-1-(3-coumarinyl)-2,3-epoxypropan-1-one (**20**).

This substance was obtained as yellow plates in 77% yield, mp 192-193°; ^{1}H nmr ($CDCl_3$): δ 4.02 (d, 1H, J = 1.7 Hz, 3-H), 4.70 (d, 1H, J = 1.7 Hz, 2-H), 7.24-7.70 (m, 8 arom. H), 8.62 (s, 1H, 4'-H); ^{13}C nmr ($CDCl_3$): δ 59.9, 61.8, 116.1, 116.8, 117.1, 118.2, 123.1, 124.9, 125.5, 125.7, 130.7, 131.0, 131.9, 134.7, 135.3, 148.9, 191.5; ms: 370/372 (M+, 10/10), 326/328 (8/8), 186 (52), 173 (100) *m/z*.

Anal. Calcd. for $C_{18}H_{11}BrO_4$: C, 58.24; H, 2.99. Found: C, 58.27; H, 2.97.

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