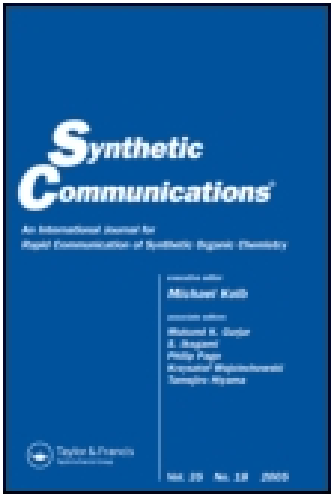

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Efficient Regioselective Oxetane Formation During Photochemical Transformation of spiro[4. n]-2,5-diones

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EFFICIENT REGIOSELECTIVE OXETANE FORMATION DURING PHOTOCHEMICAL TRANSFORMATION OF SPIRO[4. n]-2,5-DIONES

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ABSTRACT : The irradiation of a variety of spirodiones (**3**) in the presence of carbonyl compounds led to the formation of oxetanes (**6**) regioselectively, which upon hydrolysis afforded the corresponding ketoacids (**7**) in excellent yields.

The chemistry of oxetane is well documented in the literature. The oxetane containing materials constitute an important class of biologically relevant compounds such as thromboxane A_2,[1] oxetanocin,[2] taxol [3] and the unique amino acid antibiotic oxetin.[4] The Paterno-Büchi reaction,[5] namely the [2+2]-photoaddition of a carbonyl compound to an olefin is most commonly employed route to functionalized oxetanes.[6] While there are several other methods for oxetane formation including ring expansion,[7] ring contraction[8] and alkylation,[9] the

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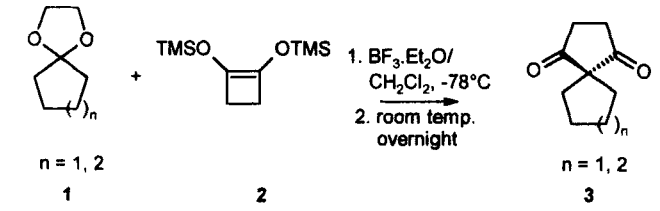
synthesis from the quenching of photochemically excited carbonyl compounds and alkenes is perhaps the most direct and flexible one.[10] Some of the reported syntheses of oxetane involve intermolecular[11] and intramolecular[11] [2+2] cycloaddition with enol ethers and carbonyl compounds which provided substituted oxetanes with modest to good regioselectivity leading mainly to the corresponding 3-alkoxy oxetanes.[12] However, Bach[13] has reported an elegant regio- and diastereoselective synthesis of oxetane by [2+2] cycloaddition of benzaldehyde and substituted trimethylsilyl enol ethers.

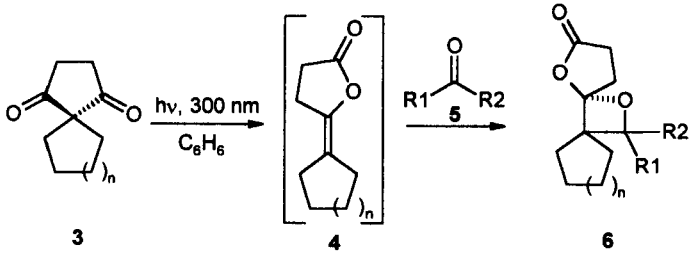
We now report that the photolysis of spiro[4. n]-2,5-dione in the presence of carbonyl compound leads to the regiospecific oxetane formation in quantitative yield which upon hydrolysis affords the ketoacids in excellent yield. As a part of a program for the total synthesis of antitumor antibiotic fredericamycin A,[14] we have recently reported the efficient phototransformation of a variety of model spirodiones to γ-butyrolactones.[15] The synthesis of various spirodiones was accomplished as per recently published methodology involving coupling of 1,2-disilyloxycyclobutene **2** with ethylene glycol ketal of corresponding ketones in the presence of an excess of BF_3. Et_2O at -78°C (Scheme-1).[16]



1 2 3

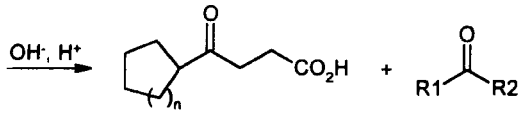
Scheme-1

Irradiation of spirodione **3** at 300 nm Rayonet (*ca.* 0.1 mol dm^{-3} in dry benzene) furnished >90% isolated yields of γ-butyrolactone **4**.[15] With a view to enhance the efficiency and gain some mechanistic insight, the progress of this phototransformation was examined employing standard triplet sensitizers e.g. acetone, acetophenone, benzophenone and benzaldehyde. Thus, irradiation of dione **3** in the presence of sensitizer at 300 nm (Rayonet photoreactor) furnished highly efficient regioselective oxetane **6** *via* **4** in almost quantitative yield. (Scheme-2). The generality of oxetane formation was established with various sensitizers. The structures of various oxetanes were confirmed on the basis of chemical, analytical and spectroscopic evidence. For all the oxetanes, the characteristic IR spectra revealed strong frequencies at ~ 1790 (s), ~ 950 (s), ~ 920 (s). The four protons in lactone moiety appeared as multiplets between ~ 2.15 - 3.05 δ in ^{1}H-NMR



3 **4** **6**

a : R1 = R2 = CH_3, n = 2
b : R1 = CH_3, R2 = Ph, n = 1
c : R1 = CH_3, R2 = Ph, n = 2
d : R1 = H, R2 = Ph, n = 2
e : R1 = R2 = Ph, n = 1
f : R1 = R2 = Ph, n = 2



7 a : n = 1
b : n = 2

Scheme-2

spectrum. ^{13}C-NMR spectrum showed signals at ~ 175 δ for lactone carbon, at ~115 δ for quarternary carbon flanked by two oxygens, at ~ 85 δ for quarternary carbon which is flanked by only one oxygen and at ~ 48 to 54 δ for simple quarternary carbon. The structures were further confirmed by their M^+ base peak appearing as a result of loss of sensitizer as a fragment in their mass spectra.

The reaction mechanism can be visualized as an electrophilic attack of the photoexcited carbonyl compound **5** at the alkene **4** leading to the formation of C-O bond. The photocycloaddition proceeds through the formation of 1,4-biradical, which collapses, to the final product or it cleaves back to the starting material. This mechanism which invokes the direct formation of the biradical without the intermediacy of exciplex or charge-transfer species has been thoroughly investigated by Freilich et. al.[17] with respect to the regio- and stereoselectivity of the reaction. It should be mentioned that the sense of regioselectivity is governed by the ring size of the olefin[10] and also the substitutions in alkenes were found to improve the regioselectivity in a significant manner[13] whereas in our study the regioselectivity is not dependent on the ring size of olefin. It should be noted that the oxetane formation is not only regioselective but also highly stereoselective as only one diastereomer is formed in the case of **6b**, **6c** and **6d**.[18] The application of the present oxetane method for the synthesis of [C, D] ring of taxol is currently in progress.

Interestingly, the oxetanes **6** upon basic hydrolysis in methanol followed by acidic work up gave quantitative yields of ketoacids **7** and corresponding carbonyl compounds (Scheme-2).

The structures of ketoacids prepared were confirmed on the basis of chemical, analytical and spectral evidence and also by comparison with literature data.[19, 20] It should be mentioned that ketoacids serve as useful precursor in the synthesis of variety of compounds of biological interest.[21]

In summary, a highly efficient regio- and stereoselective oxetane formation has been established by the irradiation of spirodione with a variety of carbonyl compounds. The cleavage of oxetanes to ketoacids under basic conditions has been demonstrated.

Experimental : Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 35-70°C was used. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 683 grating infrared spectometer. Proton and ^{13}C-NMR spectra were recorded on Varian FT-80 A, Bruker WH-90 FT NMR and Bruker AC-200 NMR spectrometers. The chemical shifts are reported in parts per million (δ) with tetramethylsilane as internal standard. Mass spectra were obtained with a Finnigan MAT-1020B-70-eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

Typical procedure for the preparation of oxetanes : The spirodione **3** (0.05-0.1mol dm^{-3}) in dry benzene containing 2-5 equiv. of one of the sensitizers (acetone, benzophenone, benzaldehyde or acetophenone) in pyrex tube was purged with nitrogen gas for 15 min. The solution was then photolyzed at 300 nm

(Rayonet photoreactor) for 4 to 6 h. The progress of the reaction was monitored by TLC. After the reaction was complete, benzene was removed under reduced pressure and residue was purified by silica gel column chromatography using acetone : pet. ether mixture (3 : 97) as eluent to get oxetane in >95% yield. During column chromatography, excess sensitizer (80-90%) was recovered.

6a Colorless solid, Yield 97%, mp 61 °C. IR ν_{max} / cm^{-1} (Nujol) : 1790, 1460, 1380, 1290, 1220, 1155, 1018, 955, 920, 860. ^{1}H-NMR ($CDCl_3$) δ : 1.35 (s, 3H), 1.45 (s, 3H), 1.62-1.9 (m, 10H), 2.0-2.78 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ : 174.25 (s), 115.17 (s), 84.87 (s), 48.00 (s), 29.51 (t), 28.40 (t), 27.03 (t), 26.65 (t), 24.69 (t), 24.43 (t), 24.27 (t), 24.01 (q), 22.77 (q). MS : m/z (%) : (M^+- Me_2CO) 166 (100), 137 (22), 124 (80), 109 (38), 95 (13), 85 (11), 81 (26). Anal. Calcd. for $C_{13}H_{20}O_3$ (224.29) : C, 69.61; H, 8.99. Found : C, 69.31; H, 9.2.

6b Colorless solid, Yield 95%, m.p 154-155°C. IR ν_{max} / cm^{-1} (Nujol) : 1775, 1610, 1500, 1460, 1380, 1260, 1215, 1170, 1055, 1040, 955, 930, 900. ^{1}H-NMR ($CDCl_3$) δ : 1.13-1.75 (m, 8H), 1.84 (s, 3H), 2.14-2.93 (m, 4H), 7.20-7.45 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ : 175.45 (s), 144.01 (s), 128.20 (d), 127.12 (d), 124.39 (d), 116.39 (s), 88.43 (s), 59.86 (s), 31.61 (t), 28.99 (t), 28.03 (t), 26.00 (q), 23.77 (t). MS m/z (%) : 228 (3), 172 (22), 157 (21), M^+ - $PhCOCH_3$ 152 (59), 151 (100), 142 (12), 129 (14), 124 (12), 115 (5), 105 (7), 77 (4). Anal. Calcd for $C_{17}H_{20}O_3$ (272.33) : C, 74.97; H, 7.34. Found : C, 74.90; H, 7.23.

6c Colorless solid, Yield 94 %, mp 145 °C. IR ν_{max} / cm^{-1} (Nujol) : 1775, 1700, 1620, 1510, 1460, 1390, 1240, 990, 970, 935, 920, 900. ^{1}H-NMR ($CDCl_3$) δ : 1.00-1.74 (m, 10H), 1.80 (s, 3H), 2.21-2.88 (m, 4H), 7.13-7.45 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ : 175.24 (s), 143.65 (s), 128.07 (d), 127.19 (d), 125.15 (d), 116.59 (s), 88.97 (s), 50.78 (s), 30.92 (t), 30.60 (t), 28.28 (t), 27.91 (t), 25.31 (t), 25.03 (q), 23.69 (t), 23.23 (t). MS (m/z, %) : 186 (15), (M^+- $PhCOCH_3$) 166 (100), 137 (11), 129 (18), 111 (17), 105 (28), 91 (13), 77 (12). Anal. Calcd for $C_{18}H_{22}O_3$ (286.36) : C, 75.49; H, 7.75. Found : C, 75.29; H, 7.68.

6d Colorless solid, Yield 93%, m.p 141°C. IR ν_{max} / cm^{-1} (Nujol) : 1790, 1620, 1470, 1390, 990, 950, 925. ^{1}H-NMR ($CDCl_3$) δ : 0.85-1.65 (m, 8H), 1.87-2.08 (m, 2H), 2.33-2.55 (m, 2H), 2.56-2.61 (m, 1H), 2.62-2.95 (m, 1H), 5.52 (s, 1H), 7.24-7.55 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ : 175.08 (s), 137.91 (s), 128.33 (d), 128.21 (d), 127.20 (d), 126.30 (d), 117.22 (s), 88.13 (d), 50.24 (s), 32.43 (t), 29.93 (t), 27.99 (t), 25.22 (t), 23.08 (t), 22.11 (t). MS (m/z, %) : 172 (19), (M^+ - PhCHO) 166 (100), 138 (13), 128 (18), 115 (19), 104 (26), 91 (28), 77 (34), 67 (18), 55 (15). Anal. Calcd for $C_{17}H_{20}O_3$ (272.33) : C, 74.97; H, 7.34. Found : C, 75.10; H, 7.04.

6e Colorless solid, Yield 96 %, mp 114-116 °C. IR ν_{max} / cm^{-1} (Nujol) : 1795, 1610, 1505, 1460, 1430, 1325, 1275, 1190, 1155, 1090, 1050, 1030, 985, 950, 915. ^{1}H-NMR ($CDCl_3$) δ : 1.40-2.1 (m, 8H), 2.17-2.64 (m, 3H), 2.78-3.00 (m, 1H), 7.15-7.45 (m, 6H), 7.48-7.65 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ :

175.20 (s), 142.76 (s), 142.52 (s), 128.00 (d), 127.88 (d), 127.09 (d), 126.14 (d), 125.70 (d), 115.38 (s), 88.95 (s), 62.32 (s), 31.63 (t), 31.30 (t), 27.97 (t), 23.49 (t), 23.35 (t). MS (m/z, %) : 234 (8), 183 (27), 165 (9), (M^+- Ph_2CO) 152 (100), 105 (9), 97 (9), 77 (12). Anal. Calcd for $C_{22}H_{22}O_3$ (334.40) : C, 79.01; H, 6.63. Found : C, 79.42, H, 6.64.

6f Colorless solid, Yield 96 %, mp 61-63 °C. IR ν_{max} / cm^{-1} (Nujol) : 1795, 1780, 1610, 1500, 1455, 1185, 1150, 990, 955, 910. ^{1}H-NMR ($CDCl_3$) δ : 0.68-2.06 (m, 10H), 2.14-3.05 (m, 4H), 7.00-7.65 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ : 175.15 (s), 142.76 (s), 142.36 (s), 128.81 (d), 128.06 (d), 127.94 (d), 127.42 (d), 127.09 (d), 127.03 (d), 126.09 (d), 125.90 (d), 115.32 (s), 89.15 (s), 53.69 (s), 31.94 (t), 31.72 (t), 31.19 (t), 28.27 (t), 25.26 (t), 24.21 (t), 24.06 (t). MS (m/z, %) : 206 (8), 183 (22), (M^+- Ph_2CO) 166 (100), 137 (15), 124 (15), 111 (24), 105 (56), 91 (30), 85 (45), 82 (70), 77 (65), 69 (52), 55 (77). Anal. Calcd for $C_{23}H_{24}O_3$ (348.42) : C, 79.28; H 6.94. Found : C, 79.36, H 6.61.

Typical procedure for the preparation of 4-alkyl-4-oxobutanoic acids : To a solution of oxetane (1 mmol) in methanol (20 ml) was added 1N sodium hydroxide (5 ml) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was acidified with dil. HCl (pH ~1) and extracted with dicholoromethane. The organic layer was separated, dried over anhydrous sodium sulphate and solvent removed to get the

keto acids in quantitative yield. Further purification of the product was achieved by recrystallization from n-hexane.

7a 4-Cyclopentyl-4-oxobutanoic acid : m.p. 74°C (lit.[19] m.p. 75-76.5°C). IR ν_{max} / cm^{-1} (Nujol) : 3600-2500, 1720, 1420. ^{1}H-NMR ($CDCl_3$) δ : 1.42-2.24 (m, 8H), 2.42-3.04 (m, 5H), 6.00 (bs, 1H). MS : m/z (%) M^+ 170 (8), 129 (15), 111 (50), 101 (55), 85 (35), 69 (100), 55 (52).

7b 4-Cyclohexyl-4-oxobutanoic acid[20] : m.p. 76°C. IR ν_{max} / cm^{-1} (Nujol) : 3600-2500, 1715, 1480, 1420. ^{1}H-NMR ($CDCl_3$) δ : 1.04-2.07 (m, 10H), 2.53-2.91 (m, 5H), 9.01 (br, s, 1H). MS : m/z (%) M^+ 184 (10), 166 (5), 129 (10), 111 (34), 101 (43), 83 (100), 73 (12), 55 (70).

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