Photochemistry of α,β-Unsaturated γ,δ-Epoxy Nitrile: A New Methodology for Synthesis of Spiroketals

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Photoinduced intramolecular cyclization of δ-hydroxybutyl-α,β-unsaturated γ,δ-epoxy nitriles **5a, b** provides rapid access to the spiro ketal skeleton.

Spiro ketal derivatives, widely distributed in Nature, have a wide spectrum of biological activity.[1–4] Several syntheses of spiro ketal systems have been reported, most of which involve acid-catalysed ring closure of dihydroxy ketones or their equivalents.[1,2,5]

Since direct irradiation of α,β-unsaturated γ,δ-epoxy nitriles in various alcohols in the presence of aliphatic amine gave the corresponding ketals in moderate yields,[6] we became interested in the possibility of extending our epoxy nitrile photochemistry[6,7] to problems of synthesis. We report here a novel and facile route to a spiro ketal system involving intramolecular nucleophilic addition of a hydroxy group to a photolytically produced carbonyl ylide intermediate **A**. The key compounds **5a, b** were synthesized as follows.

The enone **2a**,† prepared from **1a**[8] and a Grignard reagent[9] in 84% yield, was epoxidized with 35% H_2O_2 in basic media to give the epoxy ketone **3a**† (76%). Wittig–Horner reaction of **3a** afforded the α,β-unsaturated γ,δ-epoxy nitrile **4a**† (*E*:*Z* = 3:2) quantitatively, which was treated with oxalic acid in methanol to give 5-hydroxybutyl-6-oxabicyclo[3.1.0]hex-2-ylidenacetonitrile **5a**† (*E*:*Z* = 3:2) (74%). In a similar manner, 6-hydroxybutyl-7-oxabicyclo[4.1.0]hept-2-ylidenacetonitrile **5b**† (*E*:*Z* = 2:1) was prepared (31%) from **1b**.[9]

Preparative irradiation of **5a** and 1 equiv. triethylamine‡ in tetrahydrofuran (THF) with a low-pressure mercury lamp through a quartz filter at room temperature gave the spiro ketals *E*-**6a**† (5%),§ *Z*-**6a**† (2%)§ and **7a**† (29%).§,¶ Similarly, **5b** was irradiated in MeCN to afford the spiro ketals *E*-**6b**† (4%),§ *Z*-**6b**† (3%)§ and **7b**† (19%),§,‖ which was converted into the spiro ether **8**† (single isomer) quantitatively after SiO_2 chromatography by a [1,3]-sigmatropic rearrangement.[6] On further irradiation, *E*-**6a** was isomerized only to the *Z*-isomer **6a**, and **7a** was unchanged. The results show that the spiroketals **6**, **7** are presumably formed directly from the carbonyl ylide **A**.

Experimental

Typical Procedure for the Synthesis of 5-Hydroxybutyl-6-oxabicyclo[3.1.0]*hex-2-ylidenacetonitrile* **5a**.—To a mixture of magnesium (0.70 g, 29 mmol) in dry ether (1 ml) ethyl bromide (0.25 ml) was added dropwise at room temperature. After the reaction had began, a solution of 4-tetrahydropyranyloxybutyl chloride[9] (5.0 g, 26 mmol) in dry THF (10 ml) was added dropwise at room temperature; the mixture was then heated under reflux for 2 h, and finally cooled. A solution of 3-ethoxycyclohex-2-enone **1a**[9] (2.0 g, 16 mmol) in dry THF (4 ml) was then added to it and the mixture stirred for 3 h at room temperature. The mixture was poured into cold water, acidified with 5% aqueous HCl to pH 5 and extracted with ether. The extract was worked up and the residue subjected to silica gel flash-chromatography (eluted by hexane–ethyl acetate, 1:1) to afford the enone **2a** (3.19 g, 84%) (b.p. 180 °C at 0.15 mmHg). To a mixture of **2a** (500 mg, 2.1 mmol), 20% aqueous NaOH (2 drops) and methanol (2.1 ml), 35% H_2O_2 (0.61 g) was added at 0 °C. The mixture was stirred at room temperature for 4.5 h after which it was poured into cold saturated brine and extracted with CH_2Cl_2. The extract was worked up and the residue subjected to silica gel flash-chromatography (eluted by hexane–ethyl acetate, 1:1) to give the epoxy ketone **3a** (487 mg, 76%) (b.p. 170 °C at 0.2 mmHg). To a suspension of 60% NaH (86.3 mg, 2.16 mmol) in dry dimethylformamide (3.7 ml) was added dropwise diethyl cyanomethylphosphonate (382 mg, 2.16 mmol) at room temperature. After the mixture had been stirred for 20 min, **3a** (500 mg, 1.97 mmol) was added dropwise and stirring was continued at room temperature for 2 h. Ice–water was then added to the mixture and the organic phase was extracted with ether and worked up. The residue was flash-

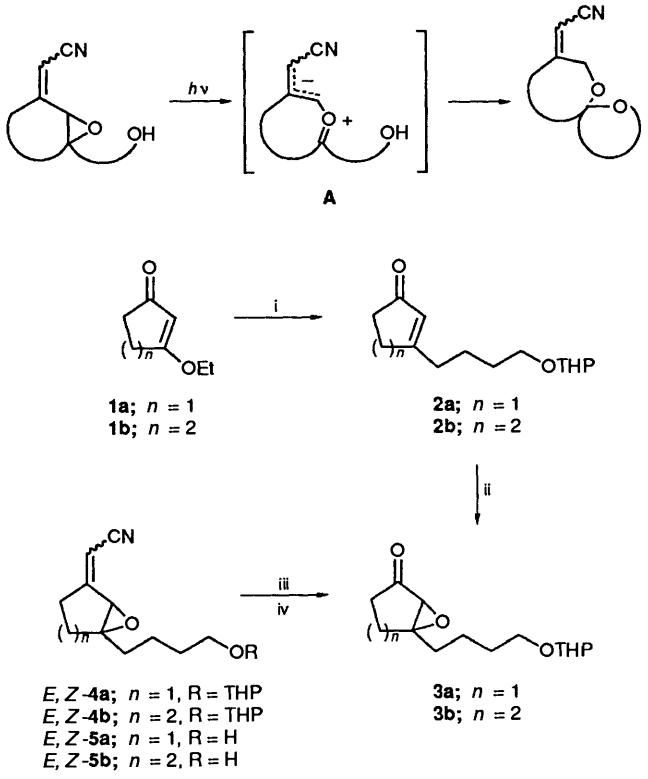
† All new compounds exhibited IR, ^1H NMR, mass and/or ^{13}C NMR spectra which were consistent with the assigned structures, and gave satisfactory elemental analyses or high-resolution mass spectra. Selected NMR data for *E*-**5a**, *E*-**6a**, **7a** and **8** are representative: *E*-**5a**: δ_H($CDCl_3$, 400 MHz) 3.53 (1 H, s), 3.66 (2 H, t) and 5.51 (1 H, br s); δ_C 62.5 (t), 62.7 (d), 71.6 (s), 94.6 (d), 116.0 (s) and 167.3 (s). *E*-**6a**: δ_H 3.92 (1 H, d), 4.29 (1 H, d) and 5.19 (1 H, s); δ_C 61.2 (t), 63.5 (t), 93.4 (d), 95.0 (s), 115.9 (s) and 161.6 (s). **7a**: δ_H 2.97 (1 H, d), 3.00 (1 H, d), 3.62–3.75 (1 H, m), 3.74 (1 H, td) and 6.33 (1 H, s); δ_C 61.7 (t), 95.4 (s), 103.3 (s), 117.6 (s) and 138.7 (d). **8**: δ_H 2.66 (1 H, d), 2.75 (1 H, d), 3.57–3.65 (1 H, m), 3.72–3.77 (1 H, m) and 9.57 (1 H, s); δ_C 62.1 (t), 62.3 (s), 84.2 (s), 118.7 (s) and 200.6 (d).

‡ In our previous report,[6] we showed that amine acts just as a base and stabilizes ketals.

§ Yields for compounds thus indicated throughout the rest of the paper are based on converted starting material.

¶ Photolysis of **5a** afforded apart from **6a** and **7a** a complex mixture.

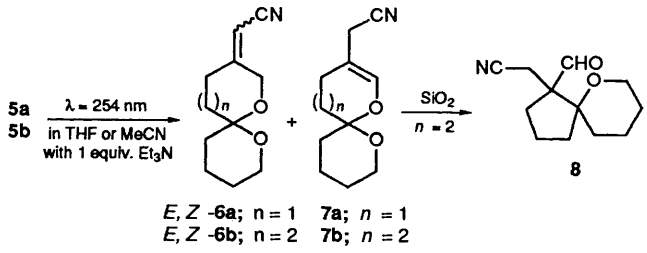
‖ Photolysis of **5b** gave apart from **6b** and **7b** unknown ketones (7%) and intractable material.



Scheme 1 *Reagents and conditions:* i, $Cl(CH_2)_4OTHP$, Mg, THF, room temp.; ii, 35% H_2O_2, 20% NaOH, room temp.; iii, $Et_2P(O)CH_2CN$, NaH, DMF, room temp.; iv, oxalic acid for **5a**, maleic acid for **5b**, MeOH, RT

chromatographed (eluted by hexane–ethyl acetate, 2:1) to give *E*/*Z*-**4a** (*E*/*Z* = 3:2, 534 mg, 98%) (b.p. 195 °C at 0.19 mmHg). A solution of **4a** (1.47 g, 5.30 mmol) and oxalic acid (167 mg) in methanol (130 ml) was stirred for 57 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether and the extract was worked up. The residue was flash-chromatographed (eluted by hexane–ethyl acetate, 1:1) to give *E*/*Z*-**5a** (*E*/*Z* = 3:2, 270 mg, 73%) (b.p. 150 °C at 0.2 mmHg).

Typical Procedure for Photochemical Reaction of **5a**.—A solution of **5a** (665 mg, 3.44 mmol) in dry THF with triethylamine (1 equiv.) was irradiated with a low-pressure mercury lamp (32 W) through a quartz filter (97% conversion) under argon for 1.5 h at room temperature. After removal of the solvent, flash-chromatography (eluted by hexane–ethyl acetate, 4:1→1:4) of the residue yielded *E*-**6a** (35 mg, 5%§), *Z*-**6a** (11 mg, 2%§) and **7a** (187 mg, 29%§).¶



Scheme 2

See footnotes on p. 2057.

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