



Stereoselective Synthesis of Functionalized Butenolides by the Photochemical Rearrangement of [2,1]Benzisoxazolequinone Derivatives.

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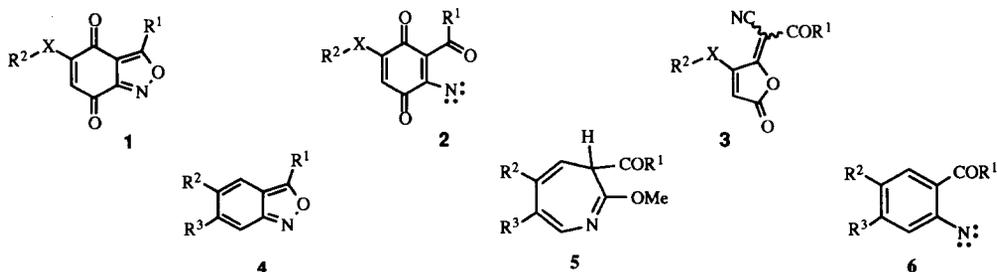
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Abstract: On direct irradiation 3-alkoxy[2,1]benzisoxazolequinones **1a**, **1b**, **1c**, **1e** and 3-*N,N*-dimethylamino[2,1]benzisoxazolequinone **1d** undergo rearrangement to the corresponding γ -cyano alkylidenebutenolides **3** in high yield. The reaction is highly stereoselective for compounds **1a**, **1b**, **1c**, and **1d** yielding the corresponding *Z*-butenolides **3** as the only stereoisomer. A mechanism involving triplet nitrene intermediates is proposed for the reaction.

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[2,1]Benzisoxazolequinones **1** are easily accessible compounds¹ which have a great versatility as synthetic intermediates for the preparation of diverse functionalized quinones and other kinds of heterocyclic systems,²⁻⁷ thus being useful tools for synthetic chemists. The reactivity of benzisoxazolequinones in non-polar solvents may be understood considering these compounds as vinilogenous intramolecular stabilized *o*-carbonyl nitrenes **2**.⁶ The study of these reactive intermediates led us to develop facile procedures for the preparation of γ -alkylidenebutenolides **3**,^{2,3} 1-alkyl[2,1]benzisoxazol-3-(1*H*)-one-4,7-quinones³ and mesoionic compounds derived from indazolones,^{4a} based on thermal rearrangements of such quinone derivatives. Likewise, the reactivity of these singlet nitrenoide species with sulfur and phosphor nucleophiles allowed us to prepare functionalized sulfoximidoquinones,^{5,6} sulfimidoquinones^{5,6} and iminophosphoranoquinones,⁷ respectively. The, iminophosphoranoquinones have been used as substrates in the aza-Wittig reaction.⁴

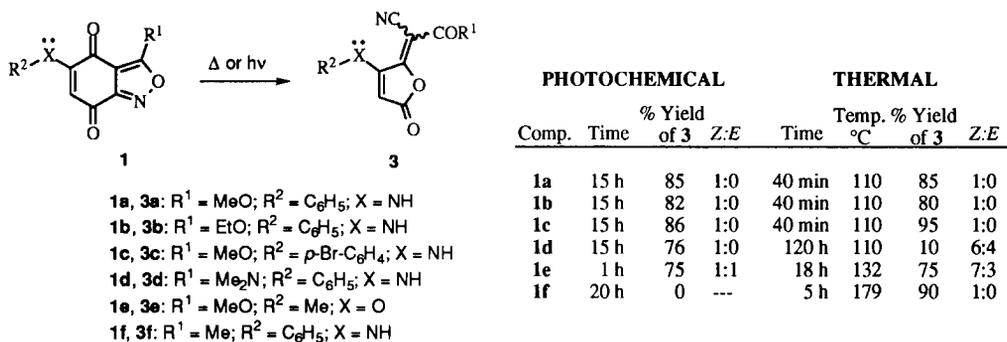


Previous studies on the photoreactivity of anthranils **4** demonstrate that these compounds rearrange to

azepines **5** on irradiation in methanol.^{8,9} Nitrene **6** was proposed as the key intermediate in this reaction. Based on these precedents it was considered of interest to study the possibility of promoting the conversion of compounds **1** into **3** by the photochemical generation of the intermediate nitrene **2**. We wish to report now our results on the photochemical reactivity of the benzisoxazolequinone derivatives **1**.

RESULTS AND DISCUSSION

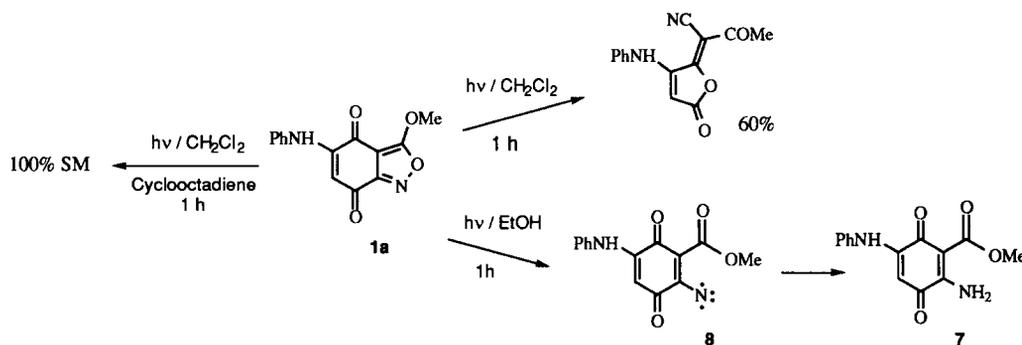
Compounds **1** were synthesized by the methods previously described.¹ Irradiation of dichloromethane solutions of 5-arylamino-3-alkoxybenzisoxazolequinones **1a-c** and 3-(*N,N*-dimethylamino)-5-phenylaminobenzisoxazolequinone **1d** for 15 h, through a Pyrex filter, brought about the formation of the corresponding butenolides (*Z*)-**3a-d** in 76% to 86% isolated yield. Irradiation of 3,5-dimethoxybenzisoxazolequinone **1e**, under the same conditions used for **1a-d**, for 1 h, yielded butenolide **3e** (75%) as a 1:1 mixture of *Z*:*E*-stereoisomers (scheme 1). The identity of the photoproducts was readily determined by comparison with authentic samples previously obtained by us in the thermal rearrangement of compounds **1**.^{2,3,4a} Although quantum yields have not been determined in this study, the efficiency of the photoreactions, in qualitative terms, is low. However, acceptable yields (*c.a.* 60%) of the butenolides **3a-d** were also obtained after 6 h of irradiation only. The analogies and differences in reaction time, yields and stereoselectivity between the thermal and photochemical rearrangements are shown in scheme 1.



Scheme 1

These results demonstrated that the rearrangement of benzisoxazolequinones **1** to γ -cyanomethylidenebutenolides **3** is not only a thermal process but can also take place photochemically. The yields and the stereoselectivity observed in the photorearrangement of compounds **1a-c** are comparable to those obtained in the thermal reactions that gave 85%, 80% and 95% yield of *Z*-**3a-c**, respectively, after heating at 110 °C for 40 min.^{3,4a} The stereoselectivity observed in the thermal reaction was demonstrated to be the result of a thermodynamic control that yields the most stable of the two isomers.³ However, the stereochemical control obtained in the photochemical rearrangement could be due to a selective photoisomerization of the *E*-isomer into the corresponding *Z*-isomer. This possibility was ruled out since irradiation, for 8 h, of a 2:1 mixture of *Z*:*E*-isomers from **3a**, obtained on the thermal rearrangement of **3a** by heating at 61 °C for 48 h,³ afforded unchanged starting material in the same stereoisomeric ratio.

The results mentioned above show clearly the analogy between the thermal and photochemical rearrangements for compounds **1a-c**. However, differences between these two processes were observed in the study of compounds **1d-f** (Scheme 1). Thus, irradiation of **1d**, for 15 h, yields **3d** (76%) as the *Z*-isomer exclusively, while, on heating at 110 °C for 120 h, **1d** gave 10% only of **3d** as a 6:4 mixture of *Z:E* isomers.^{3,4a} The yields of the thermal^{3,4a} and the photochemical reactions for **1e** are identical (75%) although in this instance the photorearrangement proved to be more efficient affording **3e** after 1h of irradiation only. The opposite situation was encountered for **1f**. Thus, compound **1f** affords **3f** in 90% yield thermally, as the *Z*-isomer exclusively,^{4a} while recovered starting material was obtained after 20 h of irradiation. The differences in the efficiency and in the stereoselectivity between the two reactions, in some cases, are still unclear but could be due to a change in the nature of the intermediate nitrene generated by the two alternative paths. The involvement of a singlet nitrene **2** in the thermal reaction has been previously demonstrated by us.²⁻⁴ However, irradiation of **1a** in the presence of 1,3-cyclooctadiene, as a triplet quencher, for one hour, brought about recovered starting material, in contrast to the 60% conversion into **3a** achieved in the absence of quencher in the same period of time (scheme 2).



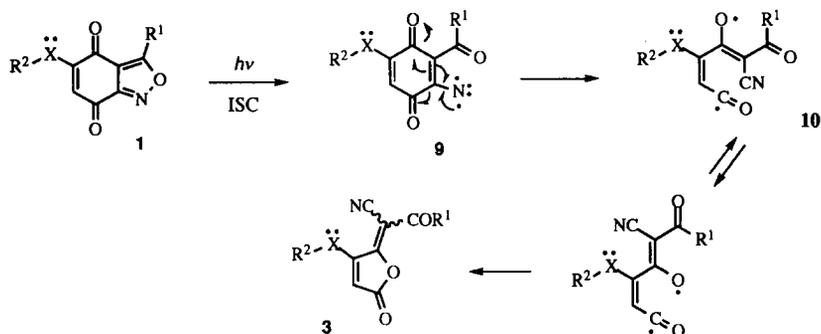
Scheme 2

These results support the involvement of a triplet nitrene intermediate in the photochemical rearrangement. Additional evidence in favor of the participation of the triplet nitrene was obtained in the irradiation of **1a** using ethanol as solvent instead of dichloromethane. Direct irradiation of **1a** under these conditions, for 1 h, afforded the aminoquinone **7**,^{5,6} in 25 % yield, resulting by hydrogen abstraction from ethanol by the triplet nitrene **8**. This is the normal photochemical reactivity reported for triplet nitrenes in the presence of hydrogen donors.^{8, 9, 10}

Based on these results, the mechanism shown in scheme 3 is proposed to account for the photochemical reaction, where excitation of compounds **1** followed by intersystem crossing generates a T_1 state that, by fission of the N-O bond, brings about the formation of the triplet nitrenes **9**. These intermediates ring open to the corresponding biradicals **10** that undergo a conformational change in order to cyclize to the butenolides **3**.

In conclusion, a highly stereoselective synthesis of alkylidenebutenolides **3**, by the photochemical rearrangement of [2,1]benzisoxazolequinones, have been described. This method is an easy and effective alternative for the preparation of functionalized butenolides starting from benzisoxazolequinones whose thermal rearrangement lacks stereoselectivity and/or efficiency. Alkylidenebutenolides are important synthetic

intermediates¹¹ that have been used as precursors of parent physiologically active butenolides such as tetronomicine,¹² piperolides,¹³ and frimbolides.¹⁴



Scheme 3

EXPERIMENTAL

Melting points were determined on a Buchi 530D apparatus in open capillaries and are uncorrected. IR spectra were recorded using a Perkin-Elmer 781 spectrophotometer and band positions are reported in wavenumbers (cm^{-1}). NMR spectra were run at the Servicio de Resonancia Magnética Nuclear de la Universidad Complutense de Madrid. $^1\text{H-NMR}$ (300 MHz) and $^{13}\text{C-NMR}$ (75 MHz) spectra were recorded in CDCl_3 as solvent using a Varian VXR-300S and TMS as internal standard, with chemical shifts δ expressed in ppm. The mass spectra were determined on a VG AutoSpec spectrometer. Combustion analyses were carried out by the Servicio de Microanálisis de la Universidad Complutense de Madrid. Column chromatography was performed by using silica gel 60 (40-63 mm) from Merck. Commercially available starting materials and reagents were purchased from Aldrich Chemical Co.

Preparative Photolysis of [2,1]Benzisoxazol-4,7-quinones 1a-f.

The photolyses were carried out in an immersion well apparatus with Pyrex filter and a 400-W medium-pressure Hg arc lamp. Solutions of the quinones in CH_2Cl_2 (500 mL) were purged for 1 h with argon and irradiated under a positive pressure of argon. After completion of irradiation, the solvent was removed under reduced pressure at room temperature and the residue was purified by chromatography on silica gel.

Irradiation of 1a. A solution of benzisoxazolequinone **1a** (80 mg, 0.30 mmol) was irradiated for 15 h. Chromatography using $\text{CH}_2\text{Cl}_2/\text{acetone}$ 50:1 as eluent afforded starting material (3.7 mg, 5%) and 4-anilino-5-cyanoethoxycarbonylmethylidene-2-(5H)-furanone³ **3a** (68.3 mg, 85%) as the *Z*-isomer exclusively.

Irradiation of 1b. A solution of benzisoxazolequinone **1b** (80 mg, 0.28 mmol) was irradiated for 15 h. Chromatography using $\text{CH}_2\text{Cl}_2/\text{acetone}$ 50:1 as eluent, affords starting material (2.8 mg, 3%) and 4-anilino-5-cyanoethoxycarbonylmethylidene-2-(5H)-furanone³ **3b** (65.6 mg, 82%) as the *Z*-isomer exclusively.

Irradiation of 1c. A solution of benzisoxazolequinone **1c** (80 mg, 0.23 mmol) was irradiated for 15 h. Chromatography using CH₂Cl₂/acetone 50:1 as eluent gave starting material (3.0 mg, 4%) and 4-(*p*-bromoanilino)-5-cyanomethoxycarbonylmethylidene-2-(5*H*)-furanone³ **3c** (69.2 mg, 86%) as the *Z*-isomer exclusively.

Irradiation of 1d. A solution of benzisoxazolequinone **1d** (80 mg, 0.28 mmol) was irradiated for 15 h. Chromatography using CH₂Cl₂/acetone 50:1 as eluent gave starting material (6.6 mg, 8%) and (*Z*)-4-anilino-5-(cyano-*N,N*-dimethylcarbamoyl)methylidene-2-(5*H*)-furanone **3d** (61.1 mg, 76%) as yellow-orange needles: mp 121 °C from chloroform-hexane; ¹H NMR (CDCl₃) δ 10.10 (broad s, slowly removed by D₂O, 1H), 7.5-7.1 (m, 5H), 5.68 (s, 1H), 3.32 (s, 3H), 3.12 (s, 3H); ¹³C NMR (CDCl₃) δ 165.7, 163.7, 162, 152.6, 138.4, 129.7, 125.6, 120.7, 112.1, 89.6, 87.4, 39.9, 36.8; IR (KBr) ν_{max} 3125, 2210 (CN), 1780 (C=O), 1625 (C=O), 1585, 1500, 1300, 1070, 910 cm⁻¹; MS (EI, 70 eV) *m/z* (rel intensity) 283 (M⁺, 57), 240 (30), 212 (14), 145 (17), 144 (100), 117 (17), 116 (17), 94 (10). Anal. Calcd for C₁₅H₁₃N₃O₃: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.63; H, 4.62; N, 14.80.

Irradiation of 1e. A solution of benzisoxazolequinone **7** (50 mg, 0.24 mmol) was irradiated for 1 h. Chromatography using ethyl acetate-hexane 10 : 3 as eluent afforded 5-cyanomethoxycarbonylmethylidene-4-methoxy-2-(5*H*)-furanone^{4a} **3e** (38.0 mg, 75%) as a 1:1 mixture of *Z*: *E* isomers.

Irradiation of 1f. A solution of benzisoxazolequinone **1f** (80 mg, 0.31 mmol) was irradiated for 20 h. After evaporation of solvent at reduced pressure, the ¹H NMR spectrum of the crude showed it to be recovered starting material.

Irradiation of 1a in Ethanol. A solution of benzisoxazolequinone **1a** (80 mg, 0.30 mmol) in absolute ethanol was irradiated for 1 h. After evaporation of solvent at reduced pressure, the ¹H NMR spectrum of the crude showed a mixture of starting benzisoxazolequinone **1a** and aminoquinone **7^{5,6}** in a ratio 3:1, respectively.

Irradiation of 1a in the Presence of 1,3-Cyclooctadiene. A solution of **1a** (80 mg, 0.30 mmol) and freshly distilled 1,3-cyclooctadiene (190 mL) in 230 mL of CH₂Cl₂ was irradiated for 4h. The solvent and the 1,3-cyclooctadiene were removed by distillation under reduced pressure. After this the unchanged starting material was recovered.

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