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

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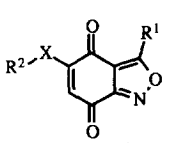
Abstract: On direct irradiation 3-alkoxy[2,1]benzisoxazolequinones **1a**, **1b**, **1c**, **1e** and 3-*N*,*N*-dimethylamino[2,1]benzisoxazolequinone **1d** undergo rearrangement to the corresponding γ-cyano alkylidenebutenolides **3** in high yield. The reaction is highly stereoselective for compounds **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.

[2,1]Benzisoxazolequinones **1** are easily accessible compounds[1] 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 vinilogous 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-quinones[3] 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]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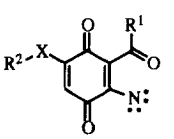
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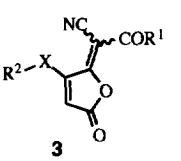
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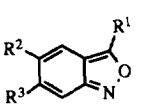
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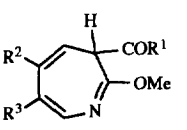
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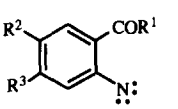
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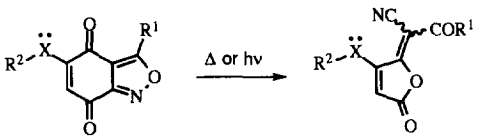
Previous studies on the photoreactivity of anthranils **4** demonstrate that these compounds rearrange to

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.



1 **3**

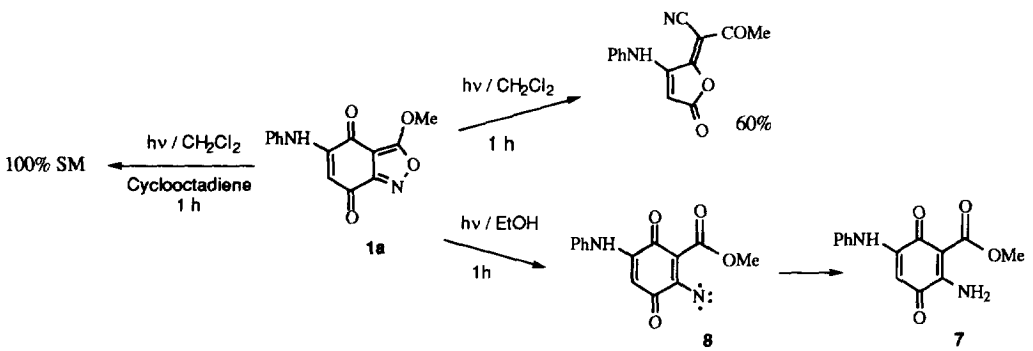
1a, 3a: R^1 = MeO; R^2 = C_6H_5; X = NH
1b, 3b: R^1 = EtO; R^2 = C_6H_5; X = NH
1c, 3c: R^1 = MeO; R^2 = *p*-Br-C_6H_4; X = NH
1d, 3d: R^1 = Me_2N; R^2 = C_6H_5; X = NH
1e, 3e: R^1 = MeO; R^2 = Me; X = O
1f, 3f: R^1 = Me; R^2 = C_6H_5; X = NH

	PHOTOCHEMICAL			THERMAL			
		% Yield			Temp.	% Yield	
Comp.	Time	of **3**	*Z:E*	Time	°C	of **3**	*Z:E*
1a	15 h	85	1:0	40 min	110	85	1:0
1b	15 h	82	1:0	40 min	110	80	1:0
1c	15 h	86	1:0	40 min	110	95	1:0
1d	15 h	76	1:0	120 h	110	10	6:4
1e	1 h	75	1:1	18 h	132	75	7:3
1f	20 h	0	---	5 h	179	90	1:0

Scheme 1

These results demonstrated that the rearrangement of benzisoxazolequinones **1** to γ-cyanomethylidene-butenolides **3** is not only a thermal process but can also take place photochemically. The yields and the stereoselectivy 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).



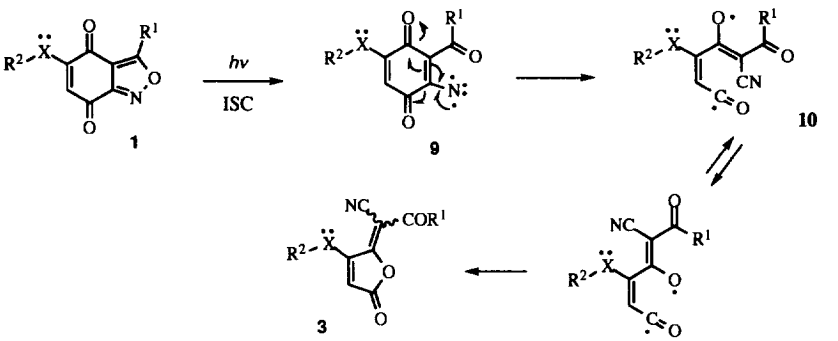
Scheme 2

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

intermediates[11] 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}H-NMR (300 MHz) and ^{13}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 CH_2Cl_2/acetone 50:1 as eluent afforded starting material (3.7 mg, 5%) and 4-anilino-5-cyanomethoxycarbonylmethylidene-2-(5*H*)-furanone[3] **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 CH_2Cl_2/acetone 50:1 as eluent, affords starting material (2.8 mg, 3%) and 4-anilino-5-cyanoethoxycarbonylmethylidene-2-(5*H*)-furanone[3] **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 CH_2Cl_2/acetone 50:1 as eluent gave starting material (3.0 mg, 4%) and 4-(*p*-bromoanilino)-5-cyanomethoxycarbonylmethylidene-2-(5*H*)-furanone[3] **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 CH_2Cl_2/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; ^{1}H NMR ($CDCl_3$) δ 10.10 (broad s, slowly removed by D_2O, 1H), 7.5-7.1 (m, 5H), 5.68 (s, 1H), 3.32 (s, 3H), 3.12 (s, 3H); ^{13}C NMR ($CDCl_3$) 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 $C_{15}H_{13}N_3O_3$: 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 1:1mixture 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 ^{1}H 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 ^{1}H 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 CH_2Cl_2 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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