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LETTERS

Photoinduced reactions of 1,3,4(2*H*)-isoquinolinetriones with diphenylacetylenes—an efficient one pot syntheses of dibenz[*de*,*g*]-(2*H*)-isoquinoline-4,6-dione derivatives

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Abstract

Photoinduced reactions of 1,3,4(2*H*)-isoquinolinetriones with diphenylacetylenes afforded the corresponding dibenz[*de*,*g*]-(2*H*)-isoquinoline-4,6-dione derivatives in moderate to high yields via a reaction sequence involving [2+2] photocycloaddition, ring opening rearrangement of the oxetene intermediate and dehydrogenative cyclization in one pot. © 2000 Elsevier Science Ltd. All rights reserved.

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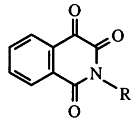
Reactions of triplet excited quinones[1] and aromatic ketones[2] with diphenylacetylenes are known to give quinone methides and α,β-unsaturated ketones, respectively, via an oxetene intermediate[3] formed by [2+2] cycloaddition of the carbonyl group with the alkyne C≡C bond. The scope of these reactions, however, has not been extensively explored. 1,3,4(2*H*)-Isoquinolinetrione derivatives have a variety of biological activities and are synthetic precursors for many naturally occurring alkaloids.[4] Therefore, investigations on structural elaborations of isoquinolinetriones have been attracting much research interest recently.[5] To explore further the scope of the photoinduced reactions of carbonyl compounds with alkynes and their synthetic applications, we report here photoinduced reactions between 1,3,4(2*H*)-isoquinolinetriones **1a**–**c** and diphenylacetylenes **2a**–**c**, which gave the dibenz[*de*,*g*]-(2*H*)–isoquinoline-4,6-dione derivatives **3a**–**g** via sequential reactions in one pot.



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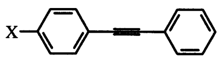
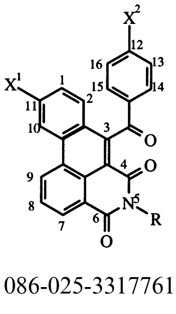
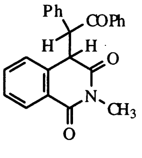
1b R=H
1c R=Ph



2a X=H
2b X=Cl
2c X=OMe



3a R=Me,X¹=X²=H
3b R=H,X¹=X²=H
3c R=Ph,X¹=X²=H
3d R=Me,X¹=Cl, X²=H
3e R=Me,X¹=H,X²=Cl
3f R=Me,X¹=OMe,X²=H
3g R=Me,X¹=H,X²=OMe



4a, 4b

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Irradiation of a solution of **1a** (0.05 mol dm^{-3}) and **2a** (0.1 mol dm^{-3}) in MeCN with light of λ>400 nm under an argon atmosphere led to the formation of the tetracyclic product **3a** (82% yield) and a mixture of two diastereoisomeric hydrogenated 4-[benzoylphenylmethylene]-isoquinoline-1,3-diones **4a** and **4b** in a ratio of $\sim$2.8:1 in a total yield of 8%. In the ^{1}H NMR spectrum of **3a**, the protons in the 'bay' area (H_9 and H_{10}) which are deshielded by all the three phenyl rings of the phenanthrene framework, and H_7 which is deshielded by the nearby carbonyl group resonate at the lowest field (δ 8.7–9.1 ppm). The MS spectrum is characterized by a strong molecular ion peak at *m*/*z* 365. This dibenz[*de*,*g*]-(2*H*)-isoquinoline-4,6-dione structure was further unambiguously proved by an X-ray crystallographic analysis of product **3f** (vide infra) as shown in Fig. 1. The structure of **4a** was also established by an X-ray crystallographic analysis as shown in Fig. 2.

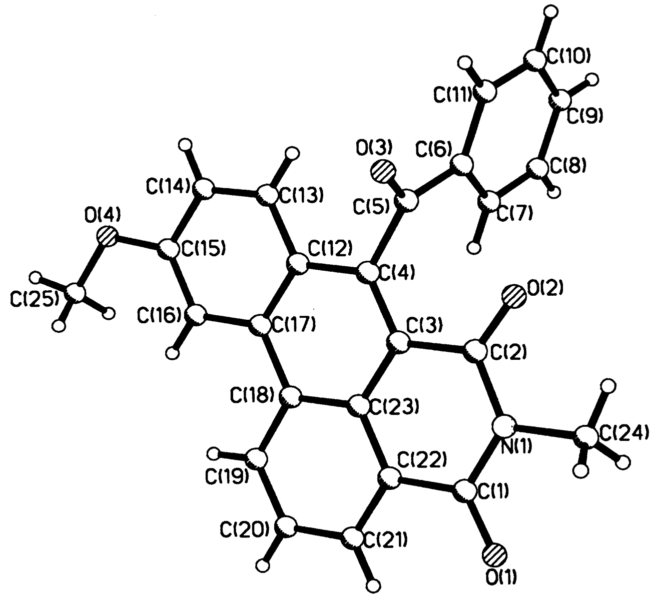


Figure 1. ORTEP drawing of compound **3f**

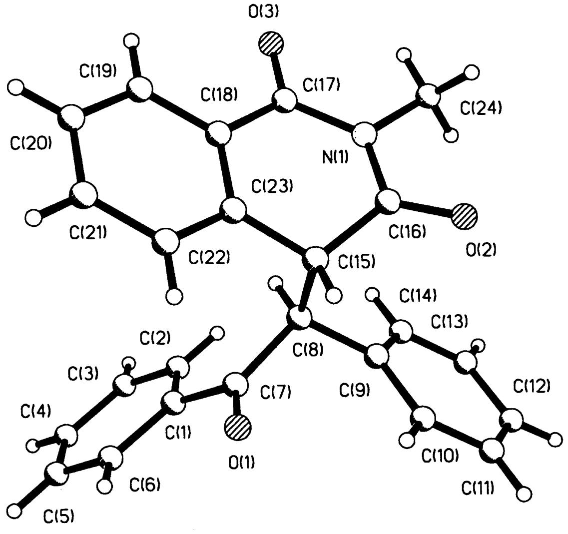


Figure 2. ORTEP drawing of compound **4a**

Table 1
Photoinduced reactions of 1,3,4(2*H*)-isoquinolinetriones **1** with alkynes **2**[a]

1	$E_{1/2}^{\mathrm{red}}$ (V)[b]	2	$E_{1/2}^{\mathrm{ox}}$ (V)[b]	ΔG_{ET}[c] (kcal mol^{-1})	Irrad. time (h)	Conversion (%)	Products and yield[d]
1a	−1.24	**2a**	1.81	6.0	48	100	**3a** (82%), **4a** (6%), **4b** (2%)
1b	−0.99	**2a**	1.81	0.2	48	81	**3b** (83%), **5a**, **6a** (7.5%)
1c	−1.18	**2a**	1.81	4.5	48	84	**3c** (68%), **7** (2%), **5b**, **6b** (5%)
1a	−1.24	**2b**	1.97	9.6	60	51	**3d** (50%), **3e** (40%). **5c**, **5d**, **6c**, **6d** (7%)
1a	−1.24	**2c**	1.48	8.5	60	30	**3f** (44%), **3g** (4%), **5e**, **5f**, **6e**, **6f** (2%), **8** (40%)

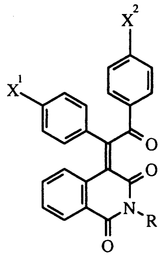
[a] All the reactions were conducted in MeCN except for the photoreaction of **1a** with **2c**, which was carried out in benzene. The concentration of **1** was 0.05 mol dm^{-3}, and **2** was 0.1 mol dm^{-3}.

[b] Measured by cyclic voltammetry in MeCN with tetrabutylammonium perchlorate (0.1 M) as supporting electrolyte and platinum as working and auxiliary electrodes versus a saturated calomel electrode (SCE).

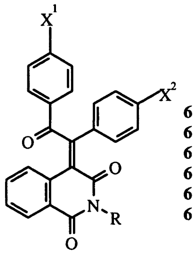
[c] Estimated by the Weller Equation.[8]

[d] Yields of isolated products based on consumed **1**. The ratios of the stereoisomers were determined from ^{1}H NMR spectra of the product mixtures.

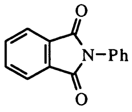
Similar irradiation of **1b** and **1c** with **2a**, respectively, in MeCN gave the corresponding tetracyclic products (**3b**, **3c**) and a mixture of *E*- and *Z*-4-[benzoylphenylmethylene]-1,3-isoquinolinediones (**5a**, **6a** and **5b**, **6b**), respectively (Table 1). A small amount (2% yield) of **7** was also obtained as a by-product in the reactions of **1c** with **2a**. The isomers **5a** and **6a**, as well as **5b** and **6b** are inseparable by flash chromatography on a silica gel column and the ratio of the two isomers was determined by ^{1}H NMR measurement of the product mixture.



5a R=H,X1=X2=H
5b R=Ph,X1=X2=H
5c R=Me,X1=H,X2=Cl
5d R=Me,X1=Cl, X2=H
5e R=Me,X1=OMe,X2=H
5f R=Me,X1=H,X2=OMe



6a R=H,X1=X2=H
6b R=Ph,X1=X2=H
6c R=Me,X1=H,X2=Cl
6d R=Me,X1=Cl, X2=H
6e R=Me,X1=OMe,X2=H
6f R=Me,X1=H,X2=OMe



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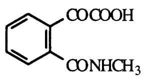

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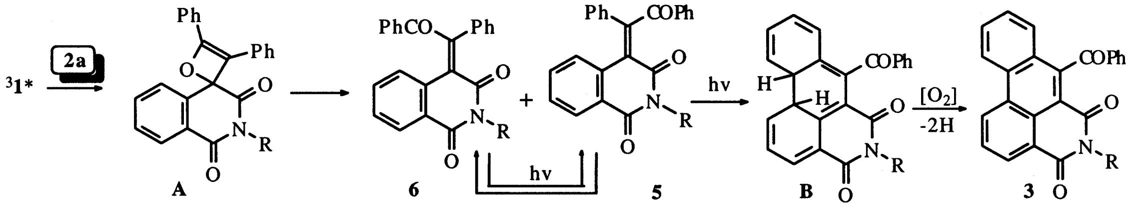
The structure of the products **3** and the isolation of the 4-methylene-1,3-isoquinolinedione products **5** and **6** suggest that a reaction sequence shown in Scheme 1 is involved in the formation of the products. [2+2] Cycloaddition of ^{3}**1*** with diphenylacetylene via a diradical intermediate may give an unstable spirooxetene, which rearranges to the *E*- and *Z*-4-methylene-



Scheme 1.

1,3-isoquinolinediones. The E-isomer could be photoisomerized to the Z-isomer which is then irreversibly transformed to product **3** by cyclization and oxidative dehydrogenation, which is a further example of the much investigated stilbene–phenanthrene photo-transformation[6] in the presence of a trace amount of oxygen in the solution.

That the triplet nπ* state[7] of **1** is the reactive excited state was proved by quenching experiments in which the reactions were found to be fully quenched by such quenchers as styrene (E_T 61.7 kcal mol^{-1}) and quinoline (E_T 62.8 kcal mol^{-1}). The intermediacy of **5** and **6** in the formation of **3** by electrocyclic reactions was supported by a control experiment where independent irradiation of a pure sample of **5a** in MeCN under conditions as mentioned above afforded **3b** quantitatively.

Photoinduced reactions of **1a** with the monosubstituted diphenylacetylenes **2b** and **2c** were also investigated. Photolysis of **1a** with **2b** in acetonitrile gave two tetracyclic products **3d** (50% yield) and **3e** (40% yield) as well as all the four possible 4-methylene-1,3-isoquinolinedione isomers **5c**, **5d**, **6c** and **6d** in a total yield of 7%. The two tetracyclic products **3d** and **3e** were obtained in a ratio of 5/4, indicating that the two isomeric oxetene intermediates are formed with low regioselectivity. On the contrary, photocycloaddition of **1a** with **2c** proceeded with high regioselectivity to afford the corresponding tetracyclic products **3f** and **3g** (total yield 48%) in a ratio of 11:1, together with a small amount (2%) of a mixture the isomeric 4-methylene-1,3-isoquinolinediones. In this case, serious hydrolysis of **1a** accompanied the reaction and the acid **8** was obtained in 40% yield. The structure of **3f**[9] was established by an X-ray crystallographic analysis as shown in Fig. 1.

To assess the possibility of single electron transfer (SET) interaction between ^{3}**1*** and the alkynes, free enthalpies for SET (ΔG_{ET}) in MeCN have been estimated by the Weller equation.[8] Although the ΔG_{ET}s are slightly positive in most cases, the following facts suggest that an electron transfer (charge transfer) interaction between ^{3}**1*** and the alkyne may play an important role in these reactions: (1) compounds **1a**–**c** could hardly take part in photocoupling reactions with electron deficient alkynes such as ethyl phenylpropiolate and 1,3-diphenyl-2-propyn-1-one, and irradiation under the same conditions as mentioned above resulted in a very sluggish reaction. (2) Photo reactions of **1a** with **2c** in MeCN, where the ΔG_{ET} is -1.6 kcal mol^{-1}, are extremely slow, while reactions in benzene (ΔG_{ET} 8.5 kcal mol^{-1}) proceed substantially faster. In MeCN, further dissociation of the triplet solvent separated ion radical pair (SSIP) prevails, leading to a much diminished reaction efficiency.

In summary, photoinduced reactions of **1a**–**c** with diphenylacetylenes **2a**–**c**, respectively, resulted in the efficient formation of the dibenz[*de*,*g*]-(2*H*)-isoquinoline-4,6-diones **3a**–**g** via a reaction sequence of photoinduced [2+2] cycloaddition-ring opening rearrangement—E-, Z-isomerization of the 4-methylene-1,3-isoquinolinedione-electrocyclic cyclization-dehydrogenative aromatization, with all these reactions accomplished in one pot. These dibenz[*de*,*g*]-(2*H*)-isoquinoline-4,6-diones are interesting targets for biological activity investigation in view of their structural similarity with the wide range of dibenzoannelated isoquinoline alkaloids (e.g. apomorphine etc.).[10] The mechanistic details of these reactions are being further investigated.

Acknowledgements

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References

1. (a) Zimmerman, H. E.; Craft, L. *Tetrahedron Lett.* **1964**, 2131; (b) Bryce-Smith, D.; Fray, G. I.; Gilbert, A. *Tetrahedron Lett.* **1964**, 2137; (c) Bryce-Smith, D.; Gilbert, A.; Johnson, M. G. *Tetrahedron Lett.* **1968**, 2863; (d) Farid, S.; Kothe, W.; Pfundt, G. *Tetrahedron Lett.* **1968**, 4147; (e) Pappas, S. P.; Portnoy, N. A.; *J. Org. Chem.* **1968**, *33*, 2200; (f) Bardamova, M. I.; Berus, E. I.; Vlasov, A. A.; Kotlyarevskii, I. L.; *Izv. Akad. Nauk SSSR, Ser. Khim.* (Russ) **1977**, 912; (g) Bosch, E.; Hubig, S. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1998**, *120*, 386.
2. Polman, H.; Mosterd, A.; Bos, H. J. T. *Rec. Trav. Chim.* **1973**, *92*, 845 and references cited therein.
3. (a) Friedrich, L. E.; Lam, P. Y. *J. Org. Chem.* **1981**, *46*, 306. (b) Friedrich, L. E.; Schuster, G. B. *J. Am. Chem. Soc.* **1971**, *93*, 4602.
4. See, for example: (a) Malamas, M. S.; Hohman, T. C.; Millen, J. *J. Med. Chem.* **1994**, *37*, 2043; (b) Hall, I. H.; Chapman, J. M.; Wong, O. T. *Anticancer Drugs* **1994**, *5*, 75.
5. See, for example: (a) Ling, K. Q.; Cai, H.; Ye, J. H.; Xu, J. H. *Tetrahedron* **1999**, *55*, 1707; (b) Cornforth, J.; Du, M. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, *5*, 1463.
6. For reviews, see, (a) Mallory, F. B.; Mallory, C. W. *Organic Reactions* **1984**, *30*, 1 (b) Laarhoven, W. H., In *Organic Photochemistry*, Padwa, A. Ed. Marcel Dekker: New York, 1983; Vol. 6, p. 1.
7. (a) Suau, R.; De Innstrosa Villatoro, E. P. *Tetrahedron* **1994**, *50*, 4987. (b) Suau, R.; De Innstrosa Villatoro, E. P. *Tetrahedron* **1995**, *51*, 6293.
8. Weller, A. Z. *Phys. Chem.* (*Wiesbaden*) **1982**, *133*, 193.
9. Spectral data of Compound **3f**: colorless crystals from chloroform, mp 296–298°C IR(KBr): 3050, 2950, 1680, 1650, 1610, 1580, 1520, 1360, 790, 760, 740, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, H–H COSY): 3.47 (3H, s, N–CH_3), 4.08 (3H, s, O–CH_3), 7.25 (1H, d, $J=9.2$, H_1), 7.45 (2H, t, $J=7.3$, 7.3, H_{13}, H_{16}), 7.59 (1H, t, $J=7.3$, H_{12}), 7.75 (1H, d, $J=9.2$, H_2), 7.89 (2H, d, $J=7.3$, H_{14}, H_{15}), 7.95 (1H, dd, $J=7.3$, 8.2, H_8), 8.12 (1H, s, H_{10}), 8.73 (1H, d, $J=7.3$, H_7), 8.97 (1H, d, $J=8.2$, H_9) m/z (EI): 395 (M^+, 55), 366 (23), 318 (100), 275 (11), 190 (6), 105 (32), 77 (38) (found: C, 75.81, H, 4.44, N, 3.55%. $C_{25}H_{17}O_4N$ requires C, 75.95; H, 4.30; N, 3.54%). Crystal structure of **3f**: triclinic, space group P-1 with $a=8.4046(4)$, $b=11.4204(5)$, $c=12.4969(6)$ Å, $\alpha=77.150(2)$, $\beta=89.217(1)$, $\gamma=83.092(2)°$, $V=1160.86(9)$ Å^3, $Z=2$, $D_c=1.473$ g cm^{-3}. Absorption coefficient 0.430 mm^{-1}, $F(000)=528$. A crystal of 0.28×0.12×0.04 mm was used. Data were collected on an Siemens SMART CCD area detector diffractometer equipped with graphite-monochromated Mo Kα radiation in the range of θ 1.67–28.31°. The structure was solved by direct method (SHELXL-97) and refined on F^2 by full-matrix least-squares method. A total of 8008 independent reflections [R(int)$=0.0515$] were used in the refinement which converged with $R=0.0706$ and $wR=0.1720$.
10. Shamma, M. In *Chemistry of the Alkaloids*; Pelletier S. W. Ed. Van Nostrand Reinhold: New York, 1970; Chapter 3, p. 31.