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Photoinduced Reactions of 1-Acetylisatin with Phenylacetylenes

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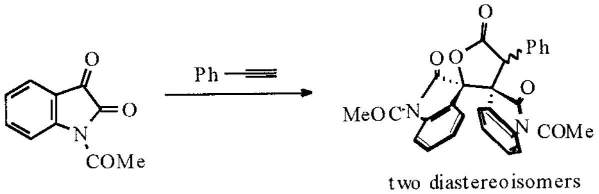
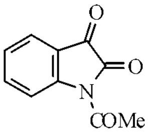
ABSTRACT

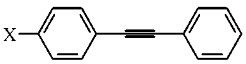


Photoinduced reactions of 1-acetylisatin 1 with diphenylacetylenes 2a–2c afforded the corresponding 3-methylene-2-indolones 4a–4e and 5a–5e in 80–90% yields via a spirooxetene intermediate. Similar irradiation of 1 with phenylacetylene, on the other hand, resulted in efficient formation of two diastereoisomeric dispiro[3*H*-indole-3,2′-furan-3′,3′′-(3*H*)-indole]-2,5′,2′′(2*H*,5′*H*,2′′*H*)triones 6 and 7 via a reaction sequence with initial formation of the spirooxetene intermediate. The regioselectivity in the photocycloaddition of 1 with phenylacetylene and the reaction mechanism for the formation of 6 and 7 are discussed.

Photoinduced reactions of quinones[1] and aromatic ketones[2] with diphenylacetylene are known to give quinone methides and α,β-unsaturated ketones, respectively, via the unstable oxetene intermediates[3] formed by [2 + 2] cycloaddition of the carbonyl $C{=}O$ bond with the acetylenic $C{\equiv}C$ bond. This process can be viewed as a variant of the Paterno−Büchi reaction.[4] The scope of these reactions, however, has not been extensively explored for carbonyl addends of diverse structures. 1*H*-2,3-Indoledione (isatin) derivatives have various biological activities[5] and have been widely used as precursors or building blocks of many natural and unnatural products.[6] However, their photochemical reactions have scarcely been investigated.[7] Isatin derivatives strongly absorb in the UV−visible region (λ_{max} 304 nm, ϵ_{max} 7540; $\lambda_{shoulder}$ 385 nm, ϵ 513), and their $n\pi^*$ triplet excited states[8] are good electron acceptors owing to a rather high triplet energy (e.g., 64 kcal mol^{-1} for **1**)[9] and a small negative reduction potential (−0.75V for **1**, SCE).[9] With the aim of further exploring the scope of the photoreactions of carbonyl compounds with alkynes, we have carried out an investigation of the photoinduced reactions of 1-acetylisatin **1** with diarylacetylenes **2a**−**2c** and phenylacetylene **3**.



1



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

Irradiation of a solution of **1** (0.05 M) and diphenylacetylene **2a** (0.10 M) in dry benzene under argon with light of λ greater than 400 nm for 24 h results in complete conversion

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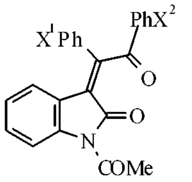
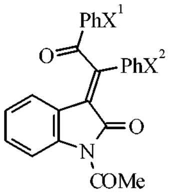
of **1** and the formation of *E*- and *Z*-3-(benzoylphenylmethylene)-2-indolones **4a** (43% yield) and **5a** (37% yield). These two products could not be fully separated by flash chromatography on silica gel; thus this ratio was determined by ^{1}H NMR measurement of the product mixture. An X-ray crystallographic analysis of **4a**, obtained by fractional crystallization, showed that it has the *Z*-configuration (Figure 1). These quinone methide products have a more extended π-conjugation system than that of **1** and are brightly yellow-colored. Since these compounds have strong absorptions in the wavelength region used for photolysis, photoinduced *E*/*Z*-isomerizations occur after their formation. Consequently, the *E*/*Z* product ratio is the result of secondary photointerconversion between **4a** and **5a**. By analogy with reactions of photoexcited quinones with diphenylacetylenes, we propose that **4a** and **5a** are derived by [2 + 2] cycloaddition of the acetylene to the carbonyl C═O bond in the n → π* triplet state of **1**, followed by electrocyclic ring opening of the oxetene intermediate **8a**.



4a $X^1=X^2=H$
4b $X^1=p\text{-OMe}, X^2=H$
4c $X^1=H, X^2=p\text{-OMe}$
4d $X^1=p\text{-Cl}, X^2=H$
4e $X^1=H, X^2=p\text{-Cl}$



5a $X^1=X^2=H$
5b $X^1=p\text{-OMe}, X^2=H$
5c $X^1=H, X^2=p\text{-OMe}$
5d $X^1=p\text{-Cl}, X^2=H$
5e $X^1=H, X^2=p\text{-Cl}$

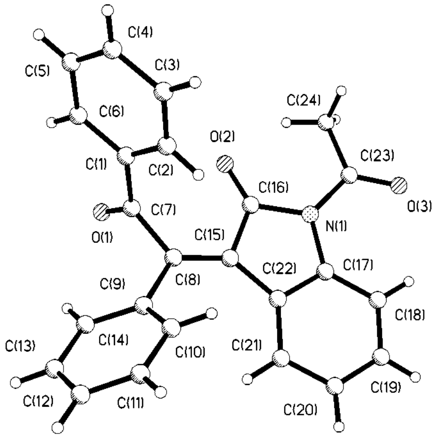
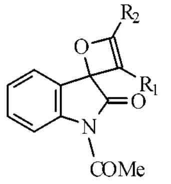


Figure 1. ORTEP drawing of compound **4a**.

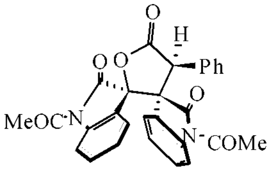


8a $R_1=Ph, R_2=Ph$
8b $R_1=Ph, R_2=H$

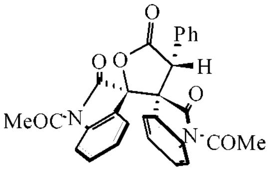
Photoinduced reactions of **1** with the monosubstituted diphenylacetylenes **2b** and **2c** were also investigated. Irradiation of a benzene solution of **1** (0.05 M) with **2b** (0.1 M) gives the quinone methides **4b**, **4c**, **5b**, and **5c** in a ratio of 16:9:3:2 and a total yield of 90%. These products derive from the two regioisomeric spirooxetene intermediates. Isomers **4b** and **5b**, obtained from the oxetene intermediate with the methoxy-substituted phenyl linked to C_3 at the oxetene ring, are in a slight excess over isomers **4c** and **5c** with a ratio (**4b** + **4c**)/(**5b** + **5c**) of 19/11. In each case, the *Z*-isomer predominates over the *E*-isomer. Photoreactions of **1** with **2c** also give the four possible quinone methides, **4d**, **4e**, **5d**, and **5e**, in a total yield of 84% and a ratio of 2.8:5.4:1:1.8.

These reactions allow efficient access to 3-arylydin-2-indolone derivatives, which are important starting materials for the synthesis of spirocyclohexenindole derivatives.[10−12]

We have also found that, in sharp contrast to the sluggish reactions of excited quinones[1] and aromatic ketones[2] with phenylacetylene, photoinduced reactions of 1-acetylisatin with phenylacetylene proceed smoothly to give the diastereoisomeric 2:1 coupling products **6** (52% yield) and **7** (27% yield) in a rather high total yield. The steric structure of **6** was established by an X-ray crystallographic analysis (Figure 2) which demonstrated that in this racemate the three chiral



6



7

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(5) See, for example: Bieck, P. R.; Antonin, K. H.; Schulz, R. In *Monoamine Oxidase*; Yasuhara, H., Ed.; VSP: Utrecht, The Netherlands, 1993; p 177.

(6) For reviews, see: (a) Popp, F. D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; VSP Academic Press: New York, 1975; Vol. 18, p 1. (b) Shvekhgeimer, M. A. *Khim. Geterotsikl. Soedin.* **1996**, 291 (Russ); *Chem. Abstr.* **1996**, *125*, R195450b.

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(9) Acetylisatin has no measurable phosphorescence either at room temperature or at 77 K in glassy ethanol. Its triplet energy was estimated to be ~64 kcal/mol by quenching experiments with a series of triplet quenchers of different triplet energies. Photoreaction of **1** with phenylacetylene was found to be fully quenched by naphthalene (E_T: 60.9 kcal/mol), diphenylacetylene (E_T: 62.5 kcal/mol) and *p*-hydroxydiphenyl (E_T: 63.6 kcal/mol) and not able to be quenched by *m*-diphenylbenzene (E_T: 64.3 kcal/mol), biphenyl (E_T: 65.7 kcal/mol), and benzophenone (E_T: 68.5 kcal/mol) in the wavelength region used for photolysis. The reduction potential ($E_{1/2}^{\mathrm{ox}}$) of 1-acetylisatin **1** was measured by cyclic voltammetry to be −0.75V (SCE) in MeCN.

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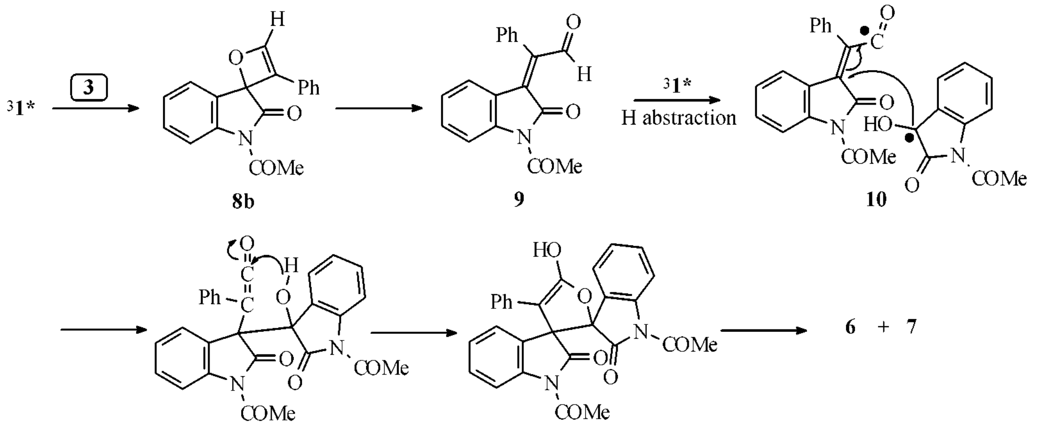
Scheme 1



carbon atoms C$_7$, C$_{12}$, and C$_{22}$ (following the numbering scheme in Figure 2) have the *S*,*R*,*R* and *R*,*S*,*S* configurations, respectively, and the two isatin frameworks are staggered in the opposite direction. Steric consideration suggests that **7** should be another racemate with the C$_7$, C$_{12}$, and C$_{22}$ having *R*,*S*,*R* and *S*,*R*,*S* configurations, respectively, so that the two isatin frameworks are also staggered with respect to each other. The other two possible racemates were not found.

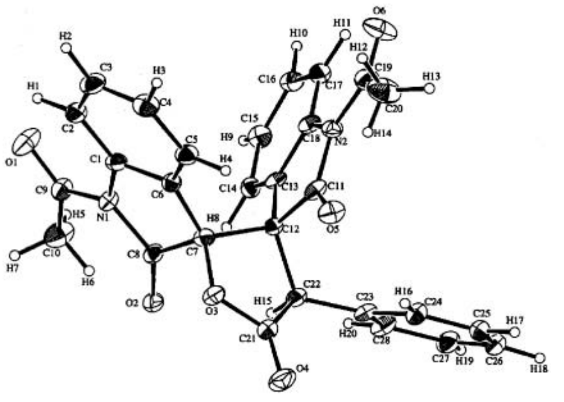


Figure 2. ORTEP drawing of compound **6**.

Products **6** and **7** are proposed to be formed by the mechanism shown in Scheme 1. The structures of products **6** and **7** indicate that the primary spirooxetene intermediate has a regiochemistry as shown in **8b**. This regioselectivity can be rationalized by consideration of the frontier molecular orbital (FMO) interactions[13] of the two addends. For this purpose, ab initio calculations on **1** have been carried out by using Gaussian 94 and a 6-31G basis set.[14] The calculated HOMO energy and the coefficients are shown in Figure 3 together with that of phenylacetylene.[15] Peterno−Büchi reactions of $n\pi^*$ triplet carbonyl compounds with alkene are initiated by bonding between the low-lying half filled n orbital on the excited ketone oxygen (the original HOMO) and the occupied π orbital (the HOMO) of the alkene.[16] It is shown in Figure 3 that in this LSOMO$_{1*}$(HOMO$_1$)−HOMO$_3$ interaction, maximum positive overlap demands a regioselectivity in agreement with that found in **8b**. This regioselectivity is also consistent with the formation of the most stable 1,4-diradical intermediate.

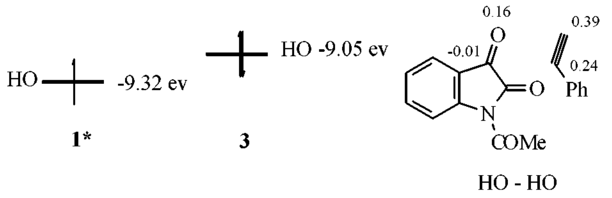


Figure 3. FMO interactions between **1*** and **3**.

Following the formation of the α,β-unsaturated aldehyde **9** from the spirooxetene intermediate, hydrogen abstraction by another ^{3}**1*** from the aldehydic C−H bond gave a triplet radical pair, **10**. Similar hydrogen abstractions of $n\pi^*$ triplet carbonyl compounds from an aldehyde in which the (O=)C−H bond has an especially low bond dissociation enthalpy (87 kcal/mol)[17] have been reported such as in the

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coupling reactions of triplet quinones with aldehydes.[18] Intersystem crossing and radical combination in **10** followed by intramolecular nucleophilic attack of the hydroxy group toward the ketene functionality furnish the products.

The principal n (ketone)−π (alkene) orbital interaction in the Peterno−Büchi reaction of nπ* triplet ketones with alkenes implies that the charge transfer interaction between the two addends plays important role in these reactions. Although a complete electron transfer as evidenced by direct detection of ion radical pairs (as in the photocycloadditions of α-diketones with the highly electron rich enol ethers[19] and dichlorobenzoquinone with diarylacetylenes[1g] in polar solvent) is less common, quenching rate constants of ketone triplets by alkenes have been found to correlate with the alkene ionization potential.[19,20] The feasibility of the reactions of ^{3}**1*** with phenylacetylene, in contradiction to the low reactivity of quinones and aromatic ketones toward the same alkyne, could therefore be attributed to the stronger electron acceptor ability of ^{3}**1***, which makes the electron (charge) transfer interaction with the alkyne more likely to take place. As an example, the free energy change for electron transfer (ΔG_{ET}) between phenylacetylene ($E_{1/2}^{ox}$: 2.04 V, SCE, MeCN)[21] and triplet benzoquinone ($E_{1/2}^{red}$: −0.57 V, SCE; $E_T \sim 50$ kcal/mol)—the strongest excited electron acceptor of all carbonyl compounds whose photoreactions with phenylacetylene have been investigated—is 19 kcal/mol in benzene as estimated by the Weller equation,[22] while ΔG_{ET} between ^{3}**1*** and **3** is 9 kcal/mol. However, the positive ΔG_{ET} value and the nonpolar solvent used suggest that ion radical formations are not involved in the reactions of **1** with phenylacetylene.

The mechanistic details and synthetic applications of these reactions are being further investigated.

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Supporting Information Available: Experimental procedures and full characterization for compounds **4a**, **4b**, **4e**, **6**, and **7**. Crystal data of **4a**, **4b**, and **6**. ^{1}H NMR spectra for compounds **4a**, **4b**, **4e**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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