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A novel photodimerization of 4-aryl-4H-pyrans for cage compounds

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ABSTRACT

Irradiation of 4-aryl-4*H*-pyrans in either the solid state or in solution gave rise to the formation of novel oxa-cage compounds, 3,9-dioxatetraasteranes, derived from a double [2+2] cycloaddition reaction. Meanwhile, an unexpected oxetane formed by the Paternò–Büchi reaction of benzophenone with the pyrans, was established by ¹H NMR data as well as by X-ray crystallographic analysis. Experimental observations and theoretical calculations confirmed that the photodimerization was effectively catalyzed by the triplet excited state of benzophenone, while the Paternò–Büchi reaction was competitive with the process.

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Cage compounds, especially those which possess rigid and highly symmetric structures, such as cubane, pentaprismane, and homocubane, have attracted considerable attention of chemists.¹ These compounds have emerged as important building blocks for the synthesis of polycyclic synthetic and natural products.² Furthermore, the functionalization reactions such as photochemical carboxylation³ have led to the synthesis of new derivatives with interesting pharmacological properties.⁴ However, this only involves derivatives and not new basic structures. Their molecular architecture presents still a challenging subject. Recently, photodimerization of 1,4-dihydropyridines has been reported to yield head-to-tail cage dimers, 3,9-diazatetraasteranes, that hold promise as novel HIV protease inhibitors for their C₂ symmetry.⁵ However, the photochemical reaction of similar heterocyclic systems, 4-aryl-4H-pyrans 1, has not been investigated because of the low photoreactivity. In this Letter, we report a unique double [2+2]photodimerization of 4-aryl-4H-pyrans, in which the centrosymmetric 3,9-dioxatetraasteranes 2 are obtained and enrich the pool of interesting oxa-cage compounds (Scheme 1).

4-Aryl-4*H*-pyrans **1a–h** were prepared by a cyclocondensation reaction of an aryl aldehyde and ethyl acetoacetate, catalyzed by ZnCl₂ under ultrasound irradiation as previously described.⁶ All solid state and solution photoreactions were performed using a 500 W high-pressure mercury lamp fitted with a quartz filter (λ >290 nm). Irradiation of **1a** at room temperature for 72 h afforded the formation of a novel double [2 + 2] photoadduct **2a** in 7% yield

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(Table 1, entry 1). The photoreaction was effectively catalyzed by benzophenone (BP) (entry 2).

When 0.1 M MeOH solutions of **1a–h** contained in a ACE reactor cooled at 3 °C were irradiated in the presence of 0.05 equiv of BP, the cage-dimeric 3,9-dioxatetraasteranes **2a–h** mainly crystallized from the solution during the irradiation and gave final yields of about 10% (entries 3–10). These results suggest that the formation of cage dimers in solution proceeds more effectively than in the solid state owing to the favorable energy transfer in solution. However, irradiation of 4-(3-nitrophenyl)-4H-pyran failed to give the desired [2 + 2] product even after a prolonged reaction time. The similar behavior is observed in the photodimerization of 2-vinylfuran⁷ and 4-azachalcones,⁸ which is attributed to the efficient nonradiative deactivation from nitro groups of the molecules in the excited state.⁹

Much more interestingly, an unexpected oxetane **3c** and other photoproducts (**4** and **5**) were isolated (Scheme 2), along with **2c**.



a: R = H; b: R = 4-OH; c: R = 4-OCH₃; d: R = 4-CH₃; e: R = 3-CI; f: R = 4-CI; g: R = 4-F; h: R = 3-NHCOCH₃

Scheme 1. Formation of 3,9-dioxatetraasteranes 2 from 4-aryl-4H-pyrans 1.





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Table 1	
Photodimerization of 4-aryl-4H-pyrans 1a-h in solid state and solution ^a	

Entry	Pyran	Medium	Sensitizer (equiv)	Time (h)	Product/yield ^b (%)
1	1a	Solid	-	72	2a /7
2	1a	Solid	Ph ₂ CO (0.05)	24	2a /10
3	1a	MeOH	Ph ₂ CO (0.05)	15	2a /10
4	1b	MeOH	Ph ₂ CO (0.05)	15	2b /7
5 ^c	1c	MeOH	Ph ₂ CO (0.05)	15	2c /8
6	1d	MeOH	Ph ₂ CO (0.05)	15	2d /10
7	1e	MeOH	Ph ₂ CO (0.05)	24	2e /12
8	1f	MeOH	Ph ₂ CO (0.05)	24	2f /9
9	1g	MeOH	Ph ₂ CO (0.05)	15	2g /9
10	1h	MeOH	Ph ₂ CO (0.05)	15	2h /8

^a Irradiation was performed with a 500 W high-pressure mercury lamp at room temperature; initial **[1]** = 0.1 M in methanol.

^b Yield of purified products.

^c Other minor products **3c**, **4**, and **5** were isolated.

The formation of compound **5** is unexceptional,¹⁰ being a consequence of hydrogen abstraction by photoexcited BP from the solvent followed by a combination of the resultant ketyl and hydroxymethyl radicals. The formation of benzhydrol **4** is a result of proton transfer from polar solvent (methanol) to ketyl radical.¹¹ It is noteworthy that the oxetane **3c** is formally derived from a Paternò–Büchi photocycloaddition between 4*H*-pyran and triplet BP. The other oxetane products from the reaction were detected in trace by GC–MS but were not isolated.

The structures of 3,9-dioxatetraasteranes **2a-h** were unequivocally determined on the basis of the ESI-MS, ¹H, and ¹³C NMR spectra including DEPT and 2D COSY. First of all, compounds **2** indicate a symmetric structure according to which the number of carbon signals in the ¹³C NMR spectra is halved but the molecular ion in the MS spectrum points to the dimer structure. In the higher field of the ¹H NMR spectrum, a characteristic singlet signal that was assigned to the H-4 and H-4' in the two pyran rings appears at δ 4.2 ppm, whereas the absorption in the starting materials **1** is shifted downfield to 4.7 ppm as a result of the anisotropic effect of the neighboring double bonds. Additionally, the methylene protons at ester groups are nonequivalent probably due to the asymmetric environment around the cage structure. The centrosymmetry of the cage structure is eventually determined by X-ray crystallography of **2g** (Fig. 1).

Regarding the structure of oxetane **3c**, its ¹H NMR spectrum exhibits two singlets at δ = 2.07 and 2.20 ppm attributed to the methyl group of pyran ring at C-6 and C-2, respectively. The signal appearing as a singlet at 4.50 ppm for the H-4 proton is the less affected and displays a small upfield shift upon formation of the oxetane ring, owing to differences in the shielding effect of neighboring groups. In the ¹³C NMR spectra, the characteristic signals for the oxetane ring resonate at 83.6, 105.9, and 113.5 ppm for the bridgehead carbon atoms. Finally, X-ray structural analysis of **3c** was carried out which shows nicely the planarity of the oxetane ring and the anticipated *cis* disposition between the four- and sixmembered rings (Fig. 1).

When photodimerzation of 1 underwent BP-sensitized irradiation, oxetane 3c was obtained via a Paternò-Büchi reaction. The result indicated that BP plays the role of triplet sensitizer, and the triplet excited state of 4-aryl-4H-pyrans is crucial for the photodimerization. In order to obtain direct mechanistic evidence based on the detection of possible reaction intermediates, laser flash photolysis of deaerated acetonitrile solution of BP in the presence of 1c was performed at 355 nm (Nd:YAG, 7 ns laser pulse, unfocused ca. 13 mJ/pulse). The absorption spectrum at 520 nm is made up of two components. The fast component decays with a first-order rate of $1.8 \times 10^6 \text{ s}^{-1}$, which is assigned to the triplet state of BP¹² (Fig. 2). The slow component appears with small signal intensity, and then rapidly decays, which is likely due to the presence of the biradical intermediate¹³ PB-³DR as shown in Scheme 3. At longer times, the transient species at 520 nm is quenched within 1.06 µs to generate new species with an absorption maximum (λ_{max}) at 420 nm. The absorption band at 420 nm is attributed to neither the triplet BP nor the biradical PB-³DR, but the intensity of the absorption increases with the same rate as that for the decay at 520 nm (insert



Scheme 2. Photochemical reaction of 1c in methanol in the presence of benzophenone.



Figure 1. Molecular structures of 2g and 3c (displacement ellipsoids at the 50% probability level).



Figure 2. Transient absorption spectra recorded at 0.2 μ s (\blacksquare), 0.32 μ s (\blacklozenge), 0.47 μ s (\blacktriangle), and 1.06 μ s (\blacktriangledown) upon 355 nm laser excitation of an acetonitrile solution of BP (1.0 M) in the presence of **1c** (0.32 M). Inset: the temporal signal profiles at 420 and 520 nm.

of Fig. 2), suggesting the occurrence of triplet-triplet energy transfer. Therefore, from the above facts, the absorption spectrum at 420 nm is assigned to the triplet state of the pyran **1c**, which was photosensitized by the triplet BP. The change in absorption spectra indicates that triplet energy transfer occurs from triplet BP to **1c**, from which the cage dimer **2c** is produced by photodimerization.

Based on the previous mechanistic studies on the related photochemical reactions,¹⁴ the possible reaction pathways were proposed for our reaction (Scheme 3). The first step in the double [2 + 2] photocycloaddition is the excitation of the 4*H*-pyran **1**, giving the lowest triplet ³**1**^{*} that happens either directly through energy transfer from the triplet BP or by intersystem crossing (ISC) of singlet excited states. After an attack of the triplet excited double bond to the neighboring π bond, an initially formed triplet biradical intermediate PD-³DR can undergo ISC to the ground state biradical which is close to the cycloadduct *syn*. Subsequently, the formation of second cyclobutane ring takes place with a favorable distance between the two radical centers, indicating that their intersystem crossing will be fast.¹⁵ As a consequence, *syn*-dimeric intermediate will be highly photoreactive to absorb another photon for intramolecular [2 + 2] cycloaddition to the final product **2** as described in the previous process.

For the Paternò–Büchi reaction,¹⁶ a triplet biradical is formed during the attack of the triplet-excited benzophenone on the double bond (Scheme 3). The biradical PB-³DR is more stable than the regioisomer derived from the attack by the oxygen at the 3-position of the pyran, since the half-filled n orbital of the oxygen is expected to attack alkenes preferably at the site of higher frontier electron density.¹⁷ The perpendicular orientation of the spin-bearing **2p** orbitals at the radical sites allows fast intersystem crossing,¹⁸ and subsequent ring closure gives the oxetane **3**. On the other hand, hydrogen abstraction occurs from methanol by the triplet BP, and then affords compounds **4** and **5**.

The processes proposed in Scheme 3 are also energetically feasible, as shown in Figure 3. The photodimerization of **1** to triplet **1** is exothermic by 28 kcal mol⁻¹, and all subsequent steps proceed downhill. When BP is involved, endothermic triplet energy transfer



Scheme 3. Proposed mechanism for the photochemical reaction of 4-aryl-4H-pyrans in the presence of benzophenone.



Figure 3. Energy profile for the BP-sensitized photodimerization of 1 at the UB3LYP/6-31G* level of calculation. α_{TET} is the efficiency for the triplet energy transfer.

from triplet BP to **1** occurs with a triplet energy gap of 5 kcal mol⁻¹, which is irreversible due to fast deactivation of the acceptor molecule.¹⁹ Additionally, the Paternò–Büchi reaction between triplet BP and the substrate is expected to be an exothermic process and could compete with the formation of the major product **2**.

In summary, we have successfully achieved the synthesis of C_2 symmetric 3,9-dioxatetraasteranes **2** through the [2 + 2] photodimerization of 4-aryl-4*H*-pyrans for the first time. In the presence of BP as triplet sensitizer, the Paternò–Büchi reaction of BP with the pyrans is competitive with the process and gives the oxetene products. Further studies are concerned with an investigation of the structural variations and biological activity of the functionalized cage compounds.

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Supplementary data

Supplementary data (Experimental details, ¹H and ¹³C NMR spectra of all new compounds, and X-ray crystallographic data for **2g** and **3c**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.016.

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