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An Unexpected Paternò-Büchi Reaction in the Crystalline State

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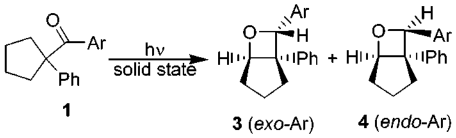
ABSTRACT

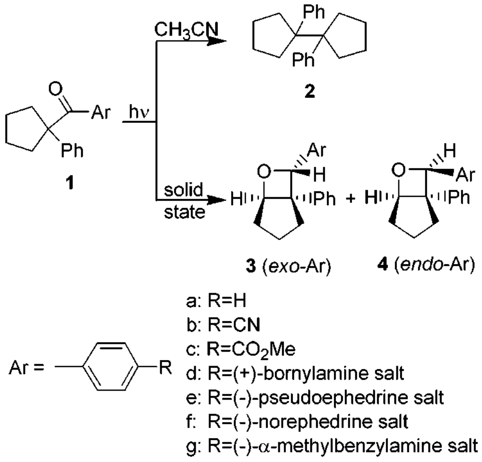


The solution and solid-state photochemistry of a series of aryl 1-phenylcyclopentyl ketones (1) was investigated. While typical Norrish type I products were formed in solution, irradiation of crystals of 1 afforded the novel oxetanes 3 and 4 regiospecifically. The formation of the oxetanes is believed to occur through Norrish type I cleavage and hydrogen abstraction, producing an alkene and an aldehyde, followed by a Paternò-Büchi reaction within the crystal lattice cage.

Unlike reactions in solution, where many processes can take place because of relatively free bond rotations and molecular movement, chemical transformations in the solid state can only access certain pathways owing to the highly restricted atomic and molecular motion imposed by the crystal lattice. This results in a reduced number of products and enhanced selectivity.[1] In some circumstances, the "latent reactivity"[2] of the starting material, which cannot be observed in solution, is brought about in the solid state and new products are obtained. Although unpredictable, this rare type of discovery is one of many topics of interest in the study of solid-state reactions. In this letter, we report the first example of the selective formation of oxetanes in the solid state, which can be considered an instance of "latent reactivity" because photolysis of the starting materials in solution yields only typical Norrish type I products.[3]

Ketones **1a**–**c** (Scheme 1) were prepared by standard synthetic methods[4] from commercially available 1-phenyl-1-cyclopentane carboxylic acid. Hydrolysis of **1b** afforded the corresponding keto acid (R = COOH), which was then reacted with various optically pure amines to form chiral salts **1d**–**g** through acid–base chemistry. All solution and solid-state photolyses were performed using a 450-W Hanovia medium-pressure mercury lamp fitted with a Pyrex filter (λ >290 nm). Samples in solution were photolyzed to complete conversion and the crystalline samples were irradiated to various degrees of conversion as determined by gas chromatography (GC). Solid-state photolyses were conducted at room temperature without observable melting

Scheme 1. Photochemical Reactions of Ketone **1**



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(1) *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991.

(2) Cheung, E.; Kang, T.; Scheffer, J. R.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **2000**, 2309.

(3) The Norrish type I photoreaction was first reported by: Bamford, C. H.; Norrish, R. G. W. *J. Chem. Soc.* **1938**, 1521.

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except for ketone **1a**, where low temperatures were required. The photochemical results for ketones **1a**−**c** are summarized in Table 1.

Table 1. Photochemical Results for Ketones **1a**−**c**

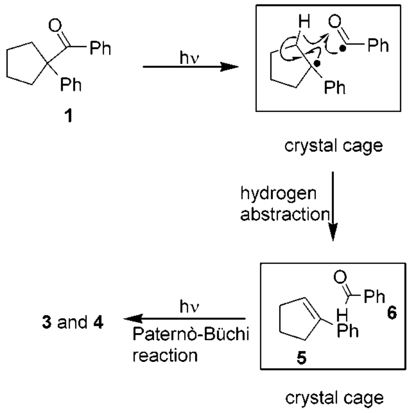
ketone	reaction medium	temp (°C)	reaction time (h)	conv[a] (%)	**2** (%)[b]	**3** (%)[b]	**4** (%)[b]
1a	CH_3CN[c]	rt	15	100	43	0	0
	crystal	−20	2	38	0	91	6
			10	95	0	59	13
			22.5	100	0	63	12
		−30	2	39	0	92	4
			7	53	0	83	8
1b	CH_3CN[c]	rt	5.5	100	60	0	0
	crystal	rt	46	100	0	13	28
1c	CH_3CN[c]	rt	3	100	47	0	0
	crystal	rt	24	48	0	19	12
			51.5	73	0	20	11

[a] Based on total GC integral due to remaining starting material. [b] Percentage of total GC integral due to a given product in the product mixture. [c] Typical concentrations for solution-phase photolyses were 30−100 mg of ketone in 5 mL of acetonitrile.

Solution photolysis of phenyl ketone **1a** afforded compound **2**, which was formed via a typical Norrish type I α-cleavage pathway, as the only isolable product. In the solid state, ketone **1a** showed different reactivity and the oxetanes were formed very efficiently, with *exo*-isomer **3a** as the major component and *endo*-isomer **4a** as the minor component. The structures of products **3a** and **4a** were determined on the basis of spectroscopic measurements (IR, LRMS, HRMS, ^{1}H NMR, ^{13}C NMR, COSY, HMQC, and NOE difference) and elemental analysis. Similar behavior was observed in the solid-state photolysis of ketones **1b** and **1c** (Table 1), although the yield of oxetanes was considerably lower owing to the formation of numerous minor (<5% each) side products.

Solid-state oxetane formation is unprecedented and a possible mechanism is presented in Scheme 2. In this mechanism, irradiation of crystals of **1a** results in Norrish type I cleavage of the α carbon−carbon bond to form a benzoyl radical and a 1-phenylcyclopentyl radical. Subsequent hydrogen atom transfer to the benzoyl radical from the C2 position of the adjacent alkyl radical affords two neutral molecules, 1-phenylcyclopentene (**5**) and benzaldehyde (**6**). Because the process takes place in the crystalline state, the radical pair and molecules **5** and **6** are formed within a crystal cage, with the relative orientation between **5** and **6** resembling the starting ketone **1a**.[5] It therefore seems reasonable to suggest that the C═O double bond of benzaldehyde and the C═C double bond of alkene **5** are favorably oriented for oxetane formation. Under the reaction conditions, benzaldehyde is able to absorb a photon and undergo a Paternò-Büchi reaction,[6] presumably through its n−π^* triplet excited state, with the ground-state alkene **5** to form the observed oxetanes **3** and **4**. The regioselectivity of the process is what one would expect (in solution) on the basis of formation of the more stable biradical intermediate. This mechanism is supported by the detection of trace amounts of intermediates **5** and **6** in the reaction mixture by GC−MS. It is likely that these two species do not accumulate owing to the efficient formation of the oxetanes in the crystal lattice.

Scheme 2. Proposed Mechanism for Solid-State Oxetane Formation



For purposes of comparison, the solution-state photoreaction of benzaldehyde (**6**) with 1-phenylcyclopentene (**5**) was studied in benzene. The reaction was very slow and produced a number of products as evidenced from the GC trace of the reaction mixture (Figure 1a). After 69 h of irradiation, benzaldehyde **6** was almost entirely consumed, but the product mixture contained only 6% of *exo*-oxetane **3** and 13% of *endo*-oxetane **4**. The preference for formation of *endo*-oxetanes in the solution-phase Paternò-Büchi reactions of benzaldehyde with cyclic olefins has been noted and explained on the basis of faster spin−orbit coupling in the 1,4-triplet biradical leading to the *endo* product.[7] This makes the preferred *exo* stereochemistry observed in the solid state

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(4) Ketone **1b** was obtained by heating fluoro-substituted ketone **1** (R = F) with potassium cyanide in dimethyl sulfoxide (DMSO). When R = F, ketone **1** is a liquid and its solid-state photochemistry could not be studied. The details of the preparation of compounds **1a**−**g** will be given in a subsequent full paper.

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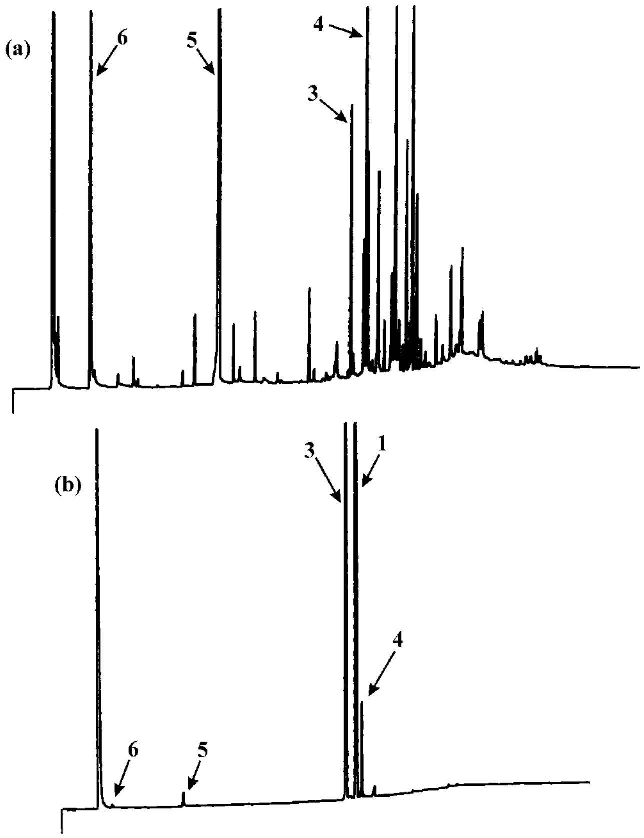

Figure 1. (a) The GC trace of the solution-state photoreaction of compounds **5** and **6** after 25 h of irradiation. (b) The GC trace of the solid-state photolysis of ketone **1a** after 2 h of irradiation at −20 °C. The retention times of identical compounds in the two diagrams do not match owing to different temperature programs used.

all the more noteworthy. Also noteworthy is the fact that the formation of oxetanes **3** and **4** is much cleaner in the solid state than in solution (Figure 1b).

The other products from the solution photoreaction were not isolated or identified. The complex nature of the solution-phase reaction mixture is not surprising because benzaldehyde (**6**) has a higher triplet energy ($E_T = 298-301$ kJ/mol) than that of the conjugated alkene **5** ($E_T = 248$ kJ/mol).[8] Therefore, triplet−triplet energy transfer becomes an important process that not only slows down oxetane formation but also causes other reactions.

These observations are consistent with studies of other similar systems.[9,10] It has been found that when the triplet energy of a conjugated alkene is lower than that of an aromatic carbonyl compound, solution-state oxetane formation is inefficient, either being excluded[9] or becoming a side reaction to other processes such as *cis*−*trans* isomerization of the alkene, alkene dimerization, or intermolecular hydrogen atom abstraction.[10] The corresponding reactions of aliphatic ketones and aldehydes have been shown to be more effective owing to the involvement of the singlet excited states of the carbonyl compounds.[11]

An interesting aspect of the photochemical transformation of ketone **1** into oxetanes **3** and **4** is that it represents an achiral-to-chiral transformation. Since this is a solid-state reaction, if the crystals of the starting material are chiral, enantioselectivity in the formation of oxetanes **3** and **4** would be expected.[12] For this purpose, the “ionic chiral auxiliary”[13] approach was applied, and chiral salts **1d**−**g** were prepared. Each salt was photolyzed in the crystalline state and treated with an ethereal diazomethane solution to convert the ionic starting material and products into the corresponding methyl esters, so that the reaction mixture could be subjected to GC for percentage conversion analysis. All of the salts afforded oxetanes **3c** and **4c** in the solid state, indicating the generality of this reaction. However, the product distribution varies among these photolyses, with product **3c** as the major oxetane in some cases (**1d** and **1g**) and compound **4c** as the major component in the others (**1e** and **1f**). Unfortunately, we were not able to resolve the racemic *endo*-oxetane **4c**. Therefore, enantiomeric excesses (ee) are reported only for **1d** and **1g** in Table 2.

Table 2. Asymmetric Induction in the Solid State[a]

salt	conv %[b]	**3c** (%)[c]	**4c** (%)[c]	ee % of **3c**[d]
1d	17	57	10	6.8
	56	44	8	9.9
	61	41	9	9.1
1e	29	3	42	
	65	2	57	
	96	2	25	
1f	16	3	28	
	29	5	38	
	35	4	30	
1g	23	31	11	52
	41	28	9	45
	67	17	5	42

[a] All photolyses were performed at room temperature. [b] Based on total GC integral due to remaining starting material. [c] Percentage of total GC integral due to a given product in the product mixture. [d] The ee’s were obtained on a custom chiral GC column (50% 6-TBDMS-2,3-dimethyl-□-cyclodextrin dissolved in OV-1701, 20 m × 0.25 mm i.d.) with column head pressure of 30 psi.

Because it was not possible to obtain a crystal structure for any of the salts, structure−reactivity correlation[14] studies

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could not be performed. Previous studies on crystals exhibiting low to mediocre ee's have shown that conformational enantiomerism is responsible for the observed results,[15] and it is possible that a similar effect occurs in this system. Nevertheless, the dual function of the chiral crystal lattice in this reaction is clearly seen. It not only serves as the medium for the reaction (the ability to form oxetanes is lost in solution) but also carries the asymmetric information and transfers this information to the reactive intermediates (compounds **5** and **6)** to lead to enantiomerically enriched products. The present enantioselectivity studies extend the generality of using crystals as chiral "messengers" in photochemical asymmetric induction reactions.

In conclusion, the first example of a Paternò-Büchi reaction in the solid state is reported. The reaction is efficient, regiospecific and takes place only in the crystal lattice. When a chiral auxiliary is used, the final products can be formed enantioselectively.

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Supporting Information Available: Characterization of photoproducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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