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Solid-State Photolysis of α-Azidoacetophenones

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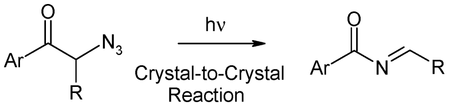
ABSTRACT



1 **2**

Solid-state photolysis of 1 yields 2 in a crystal-to-crystal reaction. The reaction takes place by α-cleavage to form a benzoyl and an azido alkyl radical pair. The azido alkyl radicals rearrange into iminyl radicals and N_2. The iminyl and benzoyl radicals are held in close proximity within the crystal lattice, which allows them to combine and form 2. X-ray structure analysis, molecular modeling and trapping studies support this mechanism.

Crystals can be used to control the reactivity of reactive intermediates such as nitrenes, carbenes, biradicals, and radical pairs.[1] The rigidity of the crystals inhibits movement and diffusion of the intermediates trapped inside, and thus, their reactivity in the solid-state is more selective than in solution. However, despite solid-state reactions being generally both regio- and stereoselective, they are not commonly used in synthetic applications.[2] This is mainly because bimolecular reactions are limited by how the molecules pack in the crystal lattice, and it is difficult to predict crystal packing arrangements. In comparison, unimolecular reactions in the solid-state that are controlled by intrinsic molecular properties rather than crystal packing arrangements can be more easily envisioned. For example, Garcia-Garibay et al. find that ketones with radical stabilizing groups in the α-positions undergo solid-state photodecarbonylation to form a radical pair and CO.[2,3] The constraint of the crystal lattice forces the bonding between the radical pair to take place in a highly chemoselective and stereospecific manner. Thus, Garcia-Garibay et al. used solid-state photodecarbonylation to synthesize natural products.[3]

Nitrogen-centered radicals are less commonly used than carbon-based radicals in organic synthesis.[4] In this paper, we describe a new method to form iminyl radicals within crystals and demonstrate how these radicals can be used to selectively form carbon−nitrogen bonds. Solid-state photolysis of α-azidoacetophenone derivatives **1** (see Scheme 1) yields **2** in a crystal-to-crystal reaction. We propose that the radical-stabilizing effect of the azido group facilitates α-cleavage in **1** to form a benzoyl and azido alkyl radical pair. The azido alkyl radical then rearranges to form an iminyl radical. The iminyl and benzoyl radicals, held in close proximity by the crystal lattice, combine to form **2**.

To support this mechanism, we analyzed the X-ray structure of **1** and trapped the benzoyl radical formed in the solid state with oxygen. Furthermore, we used molecular modeling to verify the radical-stabilizing effect of the azido group. To the best of our knowledge, this is the first time that the reactivity of azido alkyl radicals has been reported.

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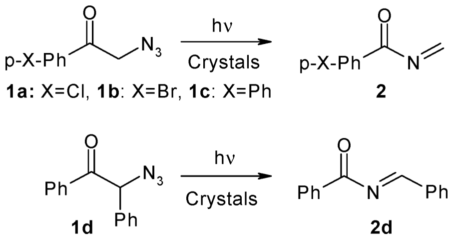
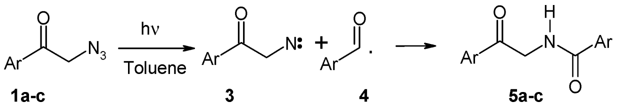
Scheme 1



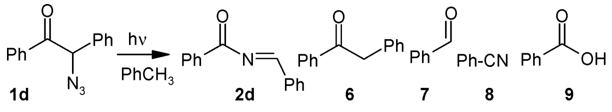
We previously reported the photoreactivity of **1a−c** in solution and found that these molecules undergo triplet energy transfer to form triplet alkyl nitrenes **3** (see Scheme 2).[5] In competition with the triplet energy transfer, **1** undergoes α-cleavage to yield benzoyl radicals **4** and azido methyl radicals. Nitrenes **3** and benzoyl radicals **4** are both long-lived intermediates that mainly combine to form **5**. We were, however, not able to isolate any products that could be attributed to the trapping of azido methyl radicals. Presumably, the α-cleavage comes from the n,π^* configuration of the triplet ketone moiety in **1**,[6] whereas the π,π^* triplet state leads to energy transfer.

Scheme 2



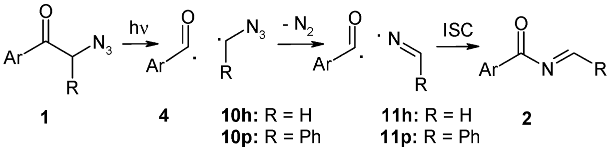
Since we had not previously studied the solution photochemistry of **1d**, we photolyzed it in argon-saturated toluene. The major product formed was **2d**, with a lesser amount of products **6−8** (Scheme 3). All the products can be attributed to α-cleavage of **1d** to form benzoyl and azido benzyl radicals (see Scheme 4). The azido benzyl radical **10p** can transform into **11p** and combine with a benzoyl radical to form **2d**. Abstraction of an H atom from **11p** would yield **8**, whereas **6** and **7** must come from reaction of the benzoyl radical with the solvent. We did not observe any product that corresponded to trapping of triplet alkyl nitrene with a benzoyl radical, indicating that α-cleavage in **1d** is more predominant than nitrene formation. Azide **1d** must undergo α-cleavage more efficiently than **1a−c**, due to the additional radical stabilization effect of the α-phenyl group. However, it is possible that **3d** can undergo 1,2-acyl shift and intersystem cross to form **2d**. Triplet alkyl nitrenes,[5a] like aryl nitrenes,[7] can be trapped with molecular oxygen to form nitro compounds, whereas benzoyl radicals[5a,8] react with molecular oxygen to form benzoic acids. Subsequent photolysis of **1d** in oxygen-saturated toluene yielded **9**, **8**, and **2d** as the major products, thus signifying that the major reactivity of **1d** is α-cleavage.

Scheme 3



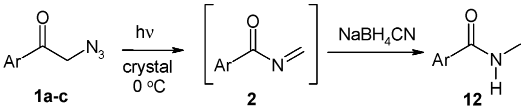
	2d	6	7	8	9
Argon	47	17	11	25	
O$_2$	18	3	4	30	45

Scheme 4



Solid-state irradiation of **1** cracked the crystals and turned them into powder. Dissolution of the irradiated crystals released gas, presumably N$_2$ that must have been trapped in the crystal lattice. GC−MS analysis of irradiated crystals of **1** that were dissolved in anhydrous ethyl acetate indicated that benzamides **2** were the only product, with no remaining starting materials. Padwa et al.[9] have shown that *N*-methylene benzamide is hydrolyzed to benzoic amide in the presence of moisture, and we also found that **2a−c** are not stable in the presence of moisture.[10] To confirm that **2a−c** were the primary photoproducts, the irradiated crystals were reduced with sodium borohydrate cyanide or butyl triphenylphosphonium tetraborate to yield **12a−c** as the only products (Scheme 5). Product **2d**, which is less sensitive to moisture, was characterized directly.

Scheme 5



To further confirm that **2** is the primary photoproduct, we followed the solid-state reaction of **1a** in a KBr pellet (Figure 1) with IR spectroscopy. Irradiation of the pellet led to depletion of the azide band and formation of new bands, the most significant occurring at 1692 and 1643 cm^{-1}. These bands fit with the calculated vibrational bands (with scaling

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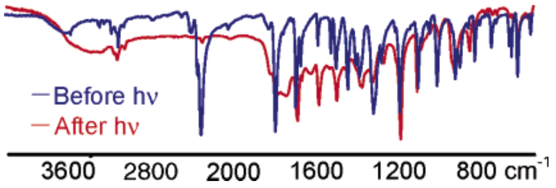

Figure 1. Photoreaction of **1a** in KBr pellets.

of 0.96) for the coupled carbonyl and imine stretches at 1678 and 1646 cm^{-1} in **2a**.[11]

The progress of solid-state reactions are most often limited by the solubility of the products in the reactant crystals.[12] Thus, to prevent any melting of the crystalline phase, the solid-state photolyses of **1** were performed at 0 °C. While photolyzing **1b**, we followed the melting point of the reaction mixture. Azide **1b** melted between 52 and 54 °C, whereas after ~30% conversion, the reaction mixture melted between 49 and 50 °C. At 70% and 100% conversion, the irradiated crystals melted at 62−64 and 65−66 °C, respectively. Thus, the eutectic point for the mixed crystals of **1b** and **2b** must be above 0 °C. Since, the solid-state photolysis of **1b** was done below the eutectic point of **1b** and **2b**, the reaction proceeded to high conversion. Similarly, we expected the eutectic point of **1a**,**c**,**d** and their corresponding products to be above 0 °C; however, it should be pointed out that the crystals of **2d** melt at ambient temperature.

Solid-state photolysis of **1a**−**c** selectively yielded **2a**−**c**; these were not observed in solution. In comparison, solution and solid-state irradiation of **1d** gave the same major product, **2d**, but it was formed exclusively in crystals. To support the notion that formation of **2** in the solid state is a result of α-cleavage of **1**, we analyzed the crystal structures of **1a**−**d** (Figure 2). Compounds **1a**,**b** adopt an approximately planar backbone with the azido group bending out of the plane by ~70° (torsion about C−N1). A similar geometry is observed for **1c** however the *p*-phenyl moiety twists out of the plane by 37.5°. The carbonyl and the azido groups are in the syn arrangement, thus the distance from the carbonyl carbon atom C7 to N1 for the recombination of the radicals formed from α-cleavage is very short: **1a**, 2.48 Å; **1b**−**d**, 2.49 Å. Azides **1a**−**c** adopt a π-stacked motif with the azide groups on adjacent molecules crossing each other. Azide **1d** also packs in a stacked manner with the azide groups pointing toward each other.

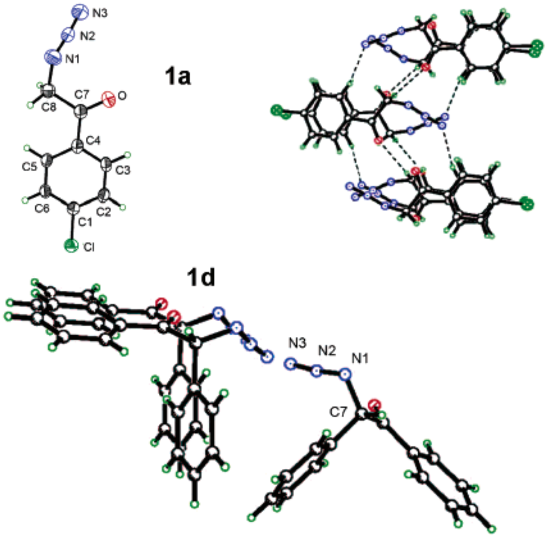

Figure 2. X-ray structures of **1a** and **1d**.

To confirm that the solid-state reactivity of **1** comes from α-cleavage, we trapped the intermediate formed in the solid-state with oxygen. We ground crystals of **1d** to increase their surface area, placed them under oxygenic atmosphere and photolyzed them. GC−MS analysis of the irradiated crystals showed that the major product formed was benzoic acid and benzonitrile, which support that the solid-state reaction takes place via α-cleavage.

Photolyzing **1d** in acetonitrile glass at −77 °C, also yields **2d** in excellent yield and trace amounts of **7** and **8**. Thus, the immobility of the reaction medium is critical to obtain high yields of **2** rather than the crystal packing arrangement of **1**.

Molecular modeling was also used to validate the α-cleavage pathway. Structural optimization of **1** and **2** (see Supporting Information)[11] shows the lowest energy conformations of **1** are similar to those obtained by X-ray analysis. The energies of the triplet-excited states in **1** were calculated using time-dependent density functional theory (TD). The energies of the first and second excited states of the triplet ketone (T1 and T2, see Table 1 and Figure 3) are within 3 kcal/mol of each other in **1a**, **1b**, and **1d**, whereas for **1c**

Table 1. Energies (kcal/mol) of Stationary Points on the Triplet Surface for α-Cleavage of **1**

	T1	T2	TS1	**4** + **10**	TS2	**4** + **11** + N$_2$	**2** + N$_2$
1a	73 (π,π*)	75	77	67	68	23	−48
1b	73 (π,π*)	74	77	67	68	23	−48
1c	67 (π,π*)	74	77	67	68	23	−48
1d	72 (n,π*)	75	73	53	56	15	−60

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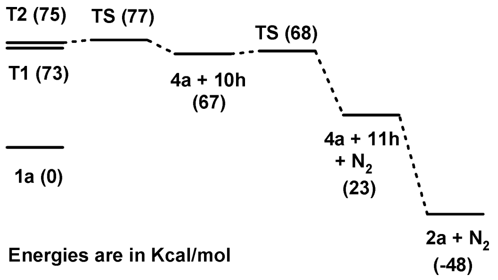

Figure 3. Stationary points on the triplet energy surface for **1a**.

they are slightly further apart. TD assumes a Franck−Condon excitation of the optimized ground-state geometry; therefore, the calculations are not accurate enough to predict whether the n,π^* or the π,π^* configuration is lower in energy, but only to confirm that T1 and T2 are of similar energies in **1a**, **1b**, and **1d**. Our findings are also in agreement with previous estimates of T1 and T2 energies for the valerophenone derivatives.[13]

Furthermore, we calculated the triplet transition state for α-cleavage of **1** into radicals **4** and **10** (see Table 1). The transition states were 1−3 kcal/mol above the n,π^* configuration of the triplet ketone. The calculated transition state for **10h** to form **11h** and N_2 was less than 1 kcal/mol above **10h**, and the transition state for **10p** to form **11p** was 2.5 kcal/mol above **10p**. Thus, both the α-cleavage and the rearrangement of **10** to **11** are easily accessible processes arising from the triplet ketone in **1**. Since we did not observe any products in the solid-state that can be attributed to the formation of triplet alkyl nitrenes, the crystalline phase must be able to stabilize the n,π^* configuration of the triplet ketone better than the triplet π,π^* state that is responsible for the energy transfer to form alkyl nitrenes.

$$^{\bullet}CH_3 + CH_3X \rightarrow {}^{\bullet}CH_2X + CH_4 \qquad \text{(i)}$$

$$\mathrm{RSE}(X) = \Delta_r H = \Sigma\Delta H_{f(prod)} - \Sigma\Delta H_{f(react)} \qquad \text{(ii)}$$

Generally, the radical-stabilizing energy (RSE) of a substituent is defined as the enthalpy change in the isodemic reaction i.[14] The enthalpy change can be obtained as shown in eq ii using molecular modeling to calculate the heats of formation (see the Supporting Information). The RSE for the azido group was calculated to be −15 kcal/mol, demonstrating that the azido methyl radical is more stable than a methyl radical. Thus, the azido group has a similar radical stabilization energy as observed for phenyl and alkenyl substituents.[15] As expected, the calculations also show that α-cleavage for **1d** is more favorable than for **1a**−**c**, due to the additional resonance stabilization of the phenyl substituent. This explains why **1d** undergoes α-cleavage in solution and not nitrene formation.

In conclusion, we have shown that the radical-stabilizing effect of the azido groups in **1** makes α-cleavage to form benzoyl and azido alkyl radicals feasible. The azido alkyl radical rearranges into an iminyl radical and, since the crystal lattice prevents any diffusion, selective bond formation between this radical pair takes place. Thus, α-cleavage of α-azido ketones in the solid-state can be used for selective carbon−nitrogen bond formation.

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Supporting Information Available: Complete crystallographic details for **1a**−**d** (CIF). Details of experimental procedures and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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