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Photochemical Hydrolysis of *o*-Acetylphenylacetonitriles

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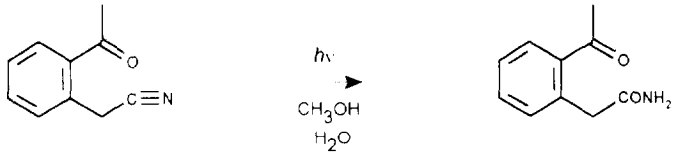
Abstract: Irradiation of **1** and its methyl derivative **10a** (λ >280 nm) in methanol leads to photohydrolysis of the nitrile group and formation of the related ketal amides **3** and **11a**, respectively. Similar treatment of the dimethyl derivative **10b** and of the parent nitrile **13** fails to yield corresponding products of hydrolysis. A mechanism is proposed for these novel hydrolyses.

Irradiation of *o*-acetylphenylacetonitrile (**1**)[1] with λ >280 nm in methanol containing a few percent water, followed by chromatography over silica gel, led to the corresponding amide **2**[2] in a yield of greater than 80%. Because this photohydrolysis was to our knowledge unprecedented, and because conversion of nitriles specifically to primary amides can be synthetically useful, we have investigated this transformation in greater detail and report our preliminary findings below.

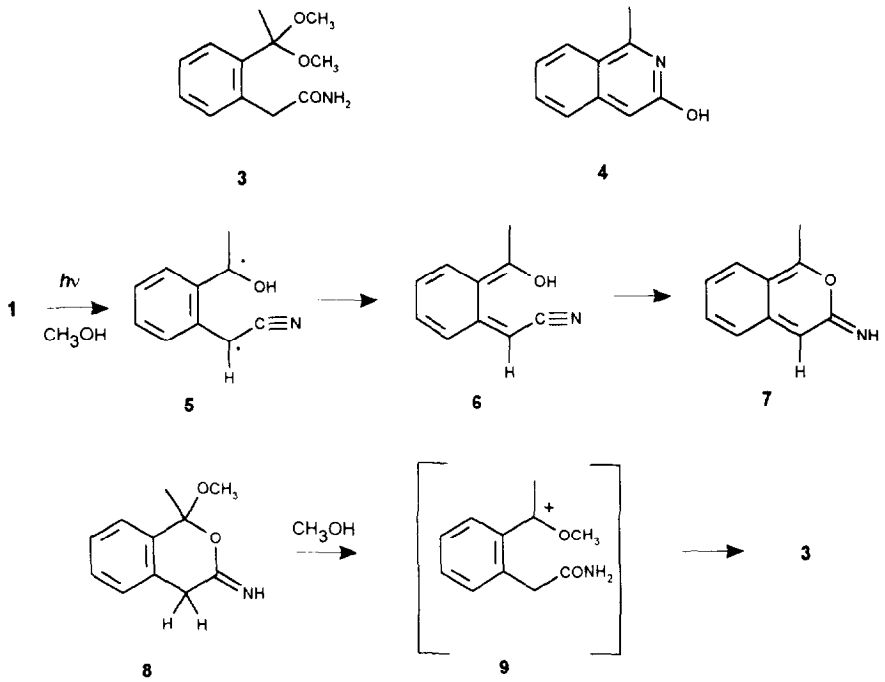


1 **2**

When the above conditions were modified so that the solvent contained only 0.02% water and the reaction mixture was worked up without use of acid or silica gel chromatography, the major product proved to be the dimethyl ketal **3**[2] instead of **2**. Brief acid-catalyzed hydrolysis of **3** yielded **2**, as expected, while more vigorous acid treatment converted **2** further into the previously reported[3] 3-hydroxy-1-methylisoquinoline (**4**).[4]

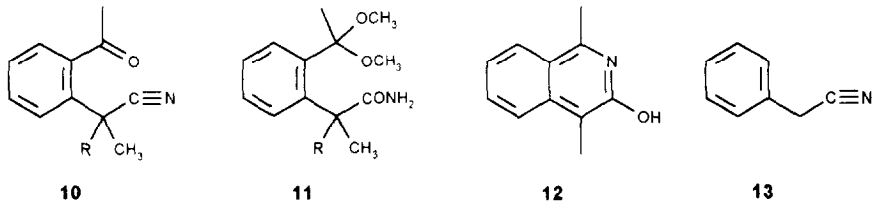
Formation of **3** as the primary product of photohydrolysis of **1** suggests that the reaction proceeds as shown below. Thus, we suggest that irradiation of **1** leads through unexceptional hydrogen abstraction[5] to biradical **5**, which relaxes to **6** as well as isomers of **6** with alternative stereochemistry about the double bonds.

The other isomers presumably revert to **1**, but the stereochemistry of the hydroxyl and cyano groups of **6** permits cyclization to the corresponding iminolactone **7**. This intermediate then rearomatizes to **8** through 1,4



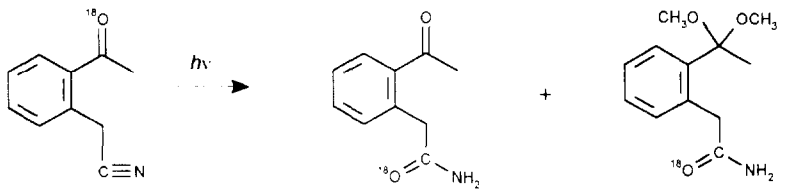
addition of methanol. Compound **8** can add another molecule of methanol, probably by way of tertiary benzylic oxycarbocation **9** formed on protonation and cleavage, finally furnishing the isolated ketal amide **3**.

In keeping with this proposed sequence of transformations, the monomethylated keto nitrile **10a**[6] underwent similar hydrolysis, yielding primarily **11a**[2] along with a small amount of **12**,[2] but the dimethyl derivative **10b**[7] failed to hydrolyze photochemically to **11b** or any other amide-containing product.[8] Phenylacetonitrile (**13**) was recovered unchanged from exposure to these reaction conditions.



a, R = H; **b**, R = CH_3

Further evidence suporting the suggested mechanism of this novel photohydrolysis comes from labelling experiments. Irradiation of **1-L** containing ~55% ^{18}O in the carbonyl group[9] yielded **2-L** and **3-L** in which,



1-L **2-L** **3-L**

according to mass spectral and ^{13}C NMR measurements,[10] the label had been transferred without loss from the ketone to the amide carbonyl groups.[11]

Footnotes and References

1. Compound **1** was prepared from the ethylene ketal of *o*-methylacetophenone through bromination with N-bromosuccinimide followed by reaction with sodium cyanide (Friedman, L.; Schechter, H., *J. Org. Chem.* **1960**, *25*, 877) and subsequent deketalization.

2. This new compound was characterized by its ^1H- and ^{13}C-NMR spectra and by M^+ in its high resolution mass spectrum. For **2**: ^1H NMR (acetone-d_6, 300 MHz): d 7.79 (dd, 1H, J = 7.5, 1.2 Hz), 7.46-7.31 (m, 3H), 6.81 (bs, 1H), 5.15 (bs, 1H), 3.76 (s, 2H), 2.55 (s, 3H), ^{13}C NMR (acetone-d_6, 75 MHz): d 201.8, 171.8, 139.0, 135.1, 131.8, 130.9, 128.7, 126.6, 40.0, 28.5; MS *m/z* 177.0790 (M^+, calcd 177.0790). For **3**: ^1H NMR ($CDCl_3$, 300 MHz): d 7.56-7.52 (m, 1H), 7.28-7.24 (m, 3H), 6.24 (bs, 1H), 5.81 (bs, 1H), 3.77 (s, 2H), 3.21 (s, 6H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): d 174.8, 140.7, 133.3, 132.5, 128.2, 127.9, 127.2, 102.9, 48.7, 41.8, 25.2; MS *m z* 246.1119 [(M + Na)$^+$, calcd 246.1106]. For **11a**: ^1H NMR ($CDCl_3$, 300 MHz): d 7.51 (dd, 1H, J=7.8, 1.8 Hz), 7.44 (dd, 1H, J = 7.8, 1.8 Hz), 7.32- 7.20 (m, 2H), 6.12 (bs, 1H), 5.80 (bs, 1H), 4.49 (q, 1H, J=7.2), 3.37 (s, 3H), 3.24 (s, 3H), 1.61 (s, 3H), 1.42 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): d 177.2, 140.8, 139.2, 128.7, 128.5, 127.1, 126.5,

103.1, 49.5, 48.7, 40.6, 25.0, 18.5; MS *m/z* 260.1276 [(M + Na)$^+$, calcd 246.1263]. For **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): d 7.87 (d, 1H, *J* = 8.4 Hz), 7.74 (d, 1H, *J* = 9.0 Hz), 7.54-7.49 (m, 1H), 7.21-7.16 (m, 1H), 2.95 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): d 159.4, 149.9, 140.0, 130.6, 126.3, 123.0, 122.0, 119.9, 109.8, 18.2, 10.4; MS *m/z* 173.0837 (M$^+$, calcd 173.0841).

3. Alpha, B.; Anklam, E.; Deschenaux, R.; Lehn, J.-M. *Helv. Chim. Acta* **1988**, *71*, 1050. The ^{1}H NMR spectrum of our sample of **4** was compatible with that on record.

4. For related cyclizations leading to 3-hydroxyisoquinolines, see Jones, D. W., *J. Chem. Soc. (C)* **1969**, 1729. For a review, including discussion of the equilibrium between the lactam and lactim forms in this series, see Hazai, L. *Adv. Heterocycl. Chem.* **1991**, *52*, 155.

5. Wagner, P. J. *Pure Appl. Chem.* **1977**, *49*, 259

6. Nitrile **10a** was prepared by base-catalyzed methylation of the ethylene ketal of **1**, using a modification of a procedure described in Bloomfield, J. J. *J. Org. Chem.* **1961**, *26*, 4112.

7. Nitrile **10b** was prepared by base-catalyzed dimethylation of the ethylene ketal of **1**, using a modification of a procedure described in MacPhee, J.-A.; Dubois, J.-E. *Tetrahedron* **1980**, *36*, 775. Subsequent deketalization was based on the method of Huet, F., Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.

8. Irradiation of **10b** leads to other sorts of photoproducts, which are currently under investigation.

9. Ketone **1-L** was prepared by hydrolyzing the corresponding ethylene ketal with $H_2{}^{18}O$, following a known procedure: Risley, J. M.; DeFrees, S. A.; Van Etten, R. L. *Org. Magn. Res.* **1983**, *21*, 28 and references cited therein.

10. For discussion of the shift of carbonyl signals owing to ^{18}O-substitution in ^{13}C NMR spectra, see ref. 9.

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