Photochemical & Photobiological Sciences

An international journal

RSC Publishing

This article is published as part of a themed issue of
Photochemical & Photobiological Sciences in honour of

The contribution of Japanese scientists to photochemistry

Guest edited by **Cornelia Bohne** and **Tadashi Mori**

Published in **issue 9, 2011**

Photochemistry of 2-diphenylmethoxyacetophenone. Direct detection of a long-lived enol from a Norrish Type II photoreaction†‡

Arun Kumar Sundaresan, Steffen Jockusch and Nicholas J. Turro*

Photolysis of 2-diphenylmethoxyacetophenone (**1**) in deaerated acetonitrile at room temperature is expected to proceed *via* Norrish Type II reaction to generate benzophenone (**2**) and acetophenone (**4**) as the main isolated photoproducts. Although the acetophenone enol intermediate (**3**) is generally considered a putative intermediate that is a precursor of acetophenone, there are few reports of the direct spectroscopic detection of **3** when a Type II reaction is conducted in solution at room temperature. Presumably, rapid enol-ketone isomerisation under the reaction conditions causes **3** to have a very short lifetime that lowers its concentration below limits detectable by standard organic spectroscopic methods such as ^{1}H NMR. We report that **3** is readily observed at room temperature by ^{1}H NMR spectroscopy and showed a remarkably long lifetime of almost 1 h under our reaction conditions. It was found that the acetophenone enols from the classic Norrish Type II reactions of valerophenone and butyrophenone could also be readily detected by ^{1}H NMR in acetonitrile at room temperature, but that their lifetimes were similar (tens of minutes) from both precursors, but were considerably shorter than that of **1**. The reason for the differences in the lifetime of the acetophenone enol is probably due to small amounts of adventitious catalysts that arise during the photolysis.

Introduction

Photodeprotection reactions have been widely used in organic synthesis because the deprotection reaction can be performed without affecting other functional groups present in the molecule.[1] We have been interested in designing photolabile protecting groups for ketones and the deprotection reaction for use in 193 nm lithography. Aldehydes and ketones can be protected as acetals with ethylene glycol-based photolabile protecting groups.[2–5] In our work, we directed our attention to the possible utility of the phenacyl ether-based protecting group for ketones using benzophenone as the substrate.[6–8]

We have concentrated our attention on photochemically generating triplet sensitizers for two-stage 193 nm lithography.[9,10] In particular, we examined the photochemistry of 2-diphenylmethoxyacetophenone (**1**, Scheme 1) as a protected ketone. The first step in our strategy was to employ the exhaustively investigated and generally reliable Norrish Type II intramolecular hydrogen abstraction as the key photochemical process to "unprotect" the benzophenone chromophore (Scheme 1). The standard mechanism for the Type II reaction for **1** (Scheme 1) is shown as occurring from the β-cleavage of the 2–3 bond of the 1,4-biradical intermediate to produce benzophenone (**2**) and the acetophenone enol (**3**). The benzophenone produced by cleavage of the 2–3 bond of the 1,4-biradical would then be the key chromophore in a second photochemical step. The second step in our strategy is to utilize this reaction in photolithography, where a photo-inactive acid or base generator will be covalently linked to benzophenone. Thus, the first step of the proposed overall reaction will be the deprotection of phenacyl ether to generate the benzophenone chromophore and the second step will be the sensitized acid or base generation. The objective of the current study was to identify a deprotection reaction that occurred in the absence of other reagents and also regenerated the ketone in good yield.

There are a number of issues to be considered if the deprotection reaction is to be successful. First, the biradical of **1** generated in the Type II process (Scheme 1) is expected to possess two pathways for product formation: (i) cleavage of the 2–3 bond to form the acetophenone enol (**3**) and benzophenone (**2**) and (ii) cyclization to form an oxetane (**5**). The distribution of these two pathways is difficult to predict, so an experimental examination is required. As we describe below, the desired formation of acetophenone enol (**3**) and benzophenone (**2**) product from cleavage of the 2–3 bond is indeed the favored pathway.

As we investigated the photochemistry of **1**, we found that an interesting, and to us unexpected, feature of the results is that the acetophenone enol product **3**, assumed to result from cleavage of the 2–3 bond of the 1,4-biradical produced by the Type II

Department of Chemistry, Columbia University, New York, NY 10027, USA.
E-mail: njt3@columbia.edu

† This article is published as part of a themed issue in honour of Yoshihisa Inoue's research accomplishments on the occasion of his 60th birthday.
‡ Electronic supplementary information (ESI) available: Synthesis and photolysis procedures, NMR characterization, absorbance and phosphorescence spectra, laser flash photolysis data. See DOI: 10.1039/c1pp05095h

Scheme 1 Possible photoproducts from Norrish Type I and II reactions.

reaction, was easily observed directly by ^{1}H NMR spectroscopy; moreover, remarkably to us, **3** was found to be relatively stable under the reaction conditions (lifetime of almost 1 h). A survey of the literature indicated that, although the enols from the Type II reaction have been detected under various conditions,[11] the putative acetophenone enol had not been reported as detectable at room temperature in solution.

Given the enormous number of Type II reactions that produce **3** that have appeared in the photochemical literature, we found it striking that there were no reports of the direct detection of **3** in solution at room temperature by standard organic spectroscopic methods such as ^{1}H NMR.

As a result, we shifted our original goal of studying the photochemistry of **1** as a two stage photosensitizer and decided also to investigate the direct detection of the formation of the acetophenone enol from other classical Type II systems that produced the acetophenone enol, **3**, such as valerophenone and butyrophenone, by ^{1}H NMR spectroscopy.

In order to put the direct detection of enols in Type II reactions in context of organic chemistry, we briefly review the literature on photoproduction of enols.[11–13] The first detection of the enol in a Type II reaction was that of acetone enol in the gas phase through IR detection in 1964.[14,15] A decade later several enols from the Type II reactions of ketones were directly detected by ^{1}H NMR spectroscopy in acetonitrile solution, but only at temperatures below –40 °C.[16] Presumably, these enols were not detected at room temperature because of the rapid enol-ketone isomerization. The enol from a Type II reaction at room temperature in solution has also been detected by CIDNP.[17] In the latter case, the CIDNP signal of the enol disappeared within a few minutes. Furthermore, laser flash photolysis has been widely used to detect enols from Type II reactions.[11]

With this history it is expected that, since it normally takes a few minutes after photolysis to remove a sample from a photolysis cell and to place the sample in an NMR or IR spectrometer, the enols from Type II reactions will be difficult, but not impossible to directly detect. Despite the extensive and classical investigations of the Type II photochemistry of butyrophenone and valerophenone, we were unable to find any reports of the direct identification of the acetophenone enol by standard organic spectroscopic methods such as ^{1}H NMR. However, we will show in this report that [1]H

NMR spectroscopy can readily be employed to directly detect acetophenone enol produced from Type II reactions in solution at room temperature.

Results and discussion

The protected ketone **1** was synthesized following a reported procedure for similar compounds[18] and was characterized by ^{1}H, ^{13}C NMR and GC-MS (see ESI‡ for synthesis procedure and spectra).

To verify that the main chromophore of **1** is similar to acetophenone, absorbance and phosphorescence spectra at 77 K were recorded (Fig. S1, ESI‡). The energy of the triplet states of **1** obtained from the phosphorescence spectra at 77 K were 73.5 kcal mol^{-1} in ethanol and 71 kcal mol^{-1} in methylcyclohexane, which is close to the reported triplet energy of acetophenone (74.3 and 74 kcal mol^{-1} in polar and non-polar solvents, respectively).[19] The phosphorescence lifetime of **1** (77 K) of 3 ms is comparable to the reported value for acetophenone (2 ms).[20] Based on the luminescence spectra and the lifetime, we conclude that the excited state of **1**, from where photoreactions occur, is the triplet state with $n\pi*$ nature.

The photochemistry of substituted acetophenones is known to involve Norrish Type I and/or Type II reactions depending on the details of their structure. While 2-hydroxyacetophenone undergoes α-cleavage (Norrish Type I reaction),[21] with 2-alkoxyacetophenones the Norrish Type II reaction is predominant.[22,23] The mechanisms involved in both processes are well studied.[24–26]

Scheme 1 shows the expected possible photochemistry of **1** and expected photoproducts. The two possible primary photochemical processes are Type I (α-cleavage) and Type II (γ-H abstraction) reactions. Type I reaction is expected to lead to radical combination products such as **6** and **7**. Type II reaction is expected to lead to products from the 1,4-biradical produced by γ-H abstraction, *i.e.*, **2**, **3** and **5**. The acetopheone enol **3** is expected to rapidly tautomerize to acetophenone, **4**. However, we find that when **3** is produced from **1** under our reaction conditions, this enol is remarkably stable and can be detected and tracked by ^{1}H NMR analysis.

Photolysis of **1** was conducted in acetonitrile at room temperature. The products were analyzed by a combination of ^{1}H NMR spectroscopy and gas chromatography (GC). Fig. 1a shows the ^{1}H NMR spectrum before photolysis and Fig. 1b shows the spectrum approximately 5 min after photolysis was terminated. The formation of benzophenone (**2**) and acetophenone (**4**) (Scheme 1) as the major photoproducts was confirmed by comparing the ^{1}H NMR signals of the photoproducts in Fig. 1b with authentic samples of **2** and **4**. The presence of the possible Type II product from 1,4-cyclization, an oxetanol (**5**), was detected in minor amounts ($\leq$10% of all products), although only at higher conversion (Fig. 2 and Fig. S4, ESI‡). No evidence for products **6** and **7** was observed by ^{1}H NMR or GC. Therefore, we conclude that α-cleavage (Type I) reaction is negligible for **1**.
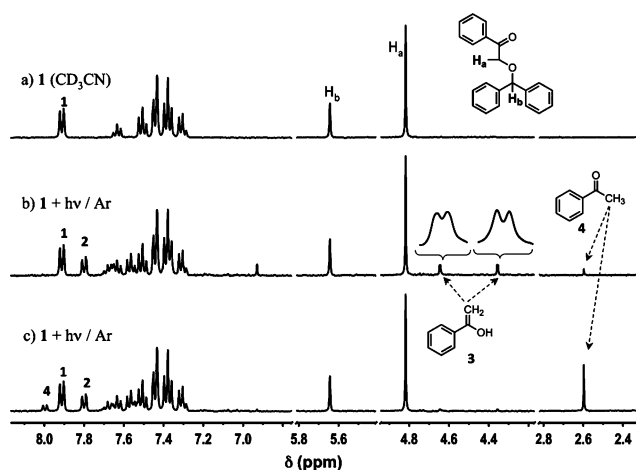

Fig. 1 Partial ^{1}H NMR spectra of (a) **1** (2 mM in CD$_3$CN, 295 K); (b) **1** (deoxygenated) 5 min after photolysis at $\geq$300 nm, 30% conversion; and (c) sample (b) after 2 h in the dark at 295 K. One set of aromatic signals of photoproducts **2** (4H) and **4** (2H) are shown at 7.8 ppm and 8 ppm, respectively. Aliphatic signals of **1**, **3** and **4** are indicated.
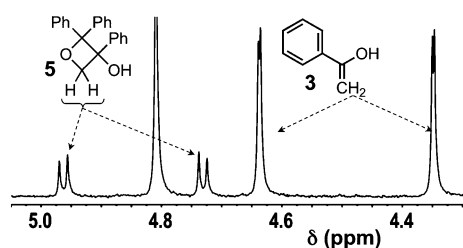

Fig. 2 Partial ^{1}H NMR spectrum of **1** after photolysis (CD$_3$CN, conversion ~ 75%) showing the methylene signals of the oxetane (**5**) and enol (**3**).

Most importantly, the enol intermediate **3** was detected as a major product (Fig. 1b and 2). The two doublets at 4.3 ppm and 4.6 ppm are assigned to the olefinic protons of the enol. The chemical shifts of the enol match well with the literature data.[25] Furthermore, the kinetics of enol-to-ketone conversion (**3** to **4**) was determined by periodically recording ^{1}H NMR spectra of the photolyzed sample. The lifetime of the enol was 51 $\pm$ 8 min at 295 K based on ^{1}H NMR integration (Fig. 4 and Fig. S5, ESI‡). In addition, when **1** was photolyzed in a CD$_3$CN/D$_2$O mixture

(4/1; v/v), acetophenone formed included deuterium (-CH$_2$D in place of -CH$_3$) and the ^{1}H NMR signal of the methyl group of **4** was a triplet (Fig. S6, ESI‡).

GC analysis of the irradiated solutions of **1** showed formation of benzophenone (**2**) and acetophenone (**4**) as the two major end products; the oxetanol (**5**) was not detected by GC at low conversions. Quantum yields for the formation of **2** and **4** (254 nm photolysis) were determined in acetonitrile solutions using valerophenone as actinometer ($\Phi = 0.85$)[27] and GC analysis. The quantum yield of formation of benzophenone was 0.8 and that of acetophenone was 0.65 (conversion < 20%). Control experiments were carried out with up to 75% conversion and the GC analysis showed only **2** and **4** as products formed in a similar ratio. The relative yields of benzophenone and acetophenone (ketone + enol) obtained by NMR integration and by GC were 1 : 0.8. Formation of the two products **2** and **4** from the 1,4-biradical intermediate is expected to be quantitative (1: 1 ratio), but results from two independent analytic techniques (GC and NMR) showed minor loss of acetophenone. We suggest that a fraction of the acetophenone enol (**3**) reacts with **1** or with the photoproducts **2** or **4**, or even with trace amounts of oxygen or other impurities present in the system.

O$_2$ is a ubiquitous impurity in photochemical systems.[28] O$_2$ can quench excited states, such as singlet or triplet states, and O$_2$ can scavenge reactive intermediates, such as radicals or react with electron-rich species such as enols. Because the Type II reaction occurs from the triplet state of **1**, high enough O$_2$ concentrations could quench the triplet state before the Type II reaction occurs. However, laser flash photolysis experiments showed (Fig. S7, ESI‡) that the Type II reaction occurs on a timescale shorter than 20 ns ($k > 5 \times 10^7$ s^{-1}), which is too short for the triplet state to be quenched by dissolved O$_2$.

To investigate if O$_2$ scavenges reactive intermediates, such as the 1,4-biradical or the acetophenone enol, solutions of **1** were prepared for photolysis under the following conditions: (a) saturated with argon, (b) saturated with oxygen or (c) saturated with a mixture of 5% oxygen and 95% nitrogen. The samples were all sealed after preparation. All three samples were irradiated under the same conditions. The NMR spectra recorded after irradiation are shown in Fig. 3. In the absence of O$_2$ **1** was converted to benzophenone and acetophenone (Fig. 3a). However, under O$_2$ saturated condition, no acetophenone was observed after photolysis, *while formation of benzophenone was not affected* (Fig. 3b). This result suggests that adventitious dissolved O$_2$ can scavenge the acetophenone enol. In addition, a new product, formaldehyde (chemical shift 9.6 ppm in Fig. 3b), is formed in the presence of oxygen possibly through an *in situ* oxidation of the acetophenone enol **3**. Another possibility is reaction of oxygen with the 1,4-biradical intermediate,[29,30] where oxygen interacts with the biradical intermediate and inhibits the formation of the enol. When the concentration of oxygen in the system is reduced (Fig. 3c), both acetophenone and formaldehyde are formed, indicating a partial reaction of the acetophenone enol with oxygen. In summary, in the absence of O$_2$, the photodeprotection of **1** occurs efficiently in solution to form benzophenone and acetophenone. High yields of the desired ketones **2** and **4** even at high conversion (up to 75%) and low oxetane formation demonstrate the utility of this group as a photolabile protecting group for ketones.
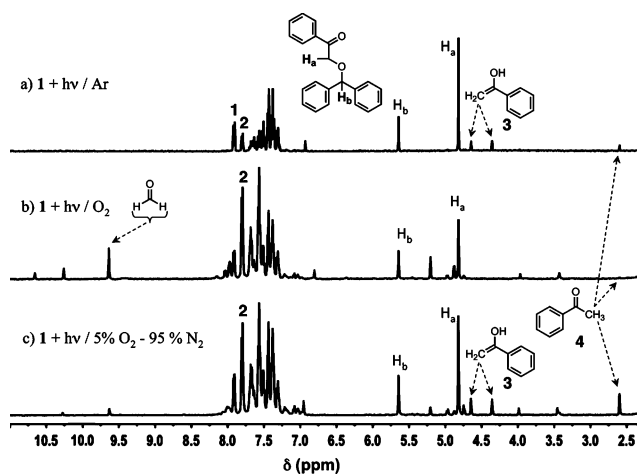
Fig. 3 ^{1}H NMR spectra of **1** (2 mM in CD$_3$CN) recorded 5 min after irradiation was stopped. (a) Argon-saturated solution; (b) oxygen-saturated solution and (c) oxygen-containing solution (5% O$_2$/95% N$_2$).

Since the photochemistry of butyrophenone (**8**) and valerophenone (**9**) hold a special place in the history of photochemistry, we decided to determine whether the enols of acetophenone produced by the Type II reactions of **8** and **9** (eqn (1)) could be directly detected by ^{1}H NMR spectroscopy after photolysis. Indeed, it was found that the acetophenone enol produced in the Type II reactions of valerophenone and butyrophenone both could be readily detected, and that both possess lifetimes of the order ~6–10 min which is significantly shorter compared to the enol from **1**, which had a lifetime of ~51 min under identical conditions of preparation (Fig. 4).
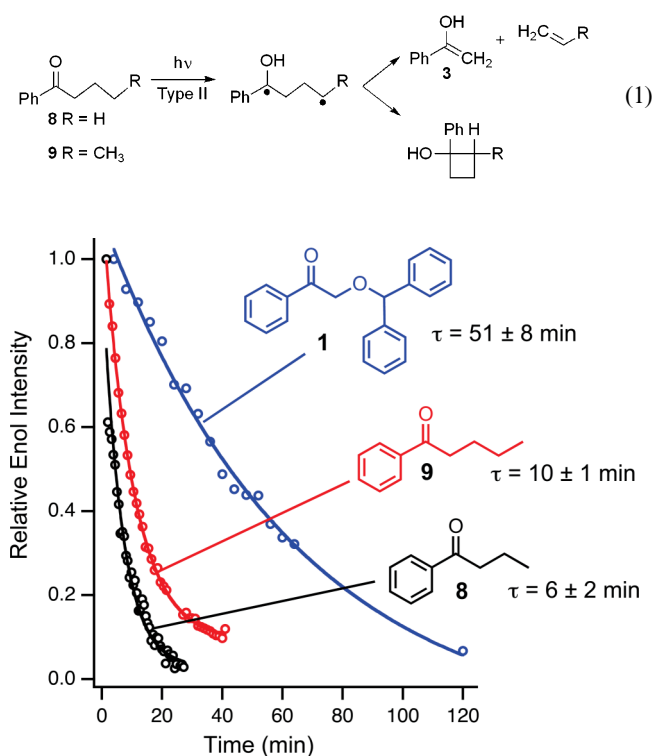

Fig. 4 Time dependence of the ^{1}H NMR signal of the enol (**3**) generated by photolysis of **1**, butyrophenone (**8**) and valerophenone (**9**) at 254 nm in deoxygenated acetonitrile solutions.

Conclusions

Fig. 4 summarizes the directly measured lifetimes of the acetophenone enol produced from Type II precursors **1**, **8** and **9** under as close as possible reaction conditions. Although there are no literature reports of the direct detection by standard ^{1}H NMR of the acetophenone enol from Type II reactions at room temperature, the results reported here indicate that under some circumstances a lifetime of the acetophenone enol in the order of an hour is possible!

The difference between the lifetime of the acetophenone enol from **1** and that of the acetophenone enol produced from **8** and **9** is striking, but its origin is not apparent. In a classic paper demonstrating the direct observation of enols from Type II reactions at low temperatures,[16] Fischer commented: "We believe that the observed lifetimes (*of the enols*) are determined by acid or base catalysis arising from solvent impurities or by-products of UV irradiation." We agree! Especially, catalysis by small amounts of water impurity in aprotic solvents could shorten the enol lifetime.[11]

Acknowledgements

References

1 M. Goeldner, R. Givens, Editors, *Dynamic Studies in Biology: Phototriggers, Photoswitches and Caged Biomolecules*, Wiley-VCH Verlag GmbH & Co KGaA, 2005.
2 J. Hébert and D. Gravel, o-Nitrophenylethylene Glycol: a Photosensitive Protecting Group for Aldehydes and Ketones, *Can. J. Chem.*, 1974, **52**, 187–189.
3 D. Gravel, S. Murray and G. Ladouceur, o-Nitrobenzyl alcohol, a simple and efficient reagent for the photoreversible protection of aldehydes and ketones, *J. Chem. Soc., Chem. Commun.*, 1985, 1828–1829.
4 A. Blanc and C. G. Bochet, Bis(o-nitrophenyl)ethanediol: A Practical Photolabile Protecting Group for Ketones and Aldehydes, *J. Org. Chem.*, 2003, **68**, 1138–1141.
5 P. Wang, H. Hu and Y. Wang, Novel Photolabile Protecting Group for Carbonyl Compounds, *Org. Lett.*, 2007, **9**, 1533–1535.
6 Although utility of the phenacyl ester based protecting groups are well known, this protecting group is not used for the protection of ketones.
7 R. S. Givens, A. Jung, C.-H. Park, J. Weber and W. Bartlett, New Photoactivated Protecting Groups. 7. p-Hydroxyphenacyl: A Phototrigger for Excitatory Amino Acids and Peptides, *J. Am. Chem. Soc.*, 1997, **119**, 8369–8370.
8 R. S. Givens, P. S. Athey, B. Matuszewski, L. W. KueperIII, J. Xue and T. Fister, Photochemistry of phosphate esters: α-keto phosphates as a photoprotecting group for caged phosphate, *J. Am. Chem. Soc.*, 1993, **115**, 6001–6012.
9 N. A. O'Connor, A. J. Berro, J. R. Lancaster, X. Gu, S. Jockusch, T. Nagai, T. Ogata, S. Lee, P. Zimmerman, C. G. Willson and N. J. Turro, Toward the Design of a Sequential Two Photon Photoacid Generator for Double Exposure Photolithography, *Chem. Mater.*, 2008, **20**, 7374–7376.
10 S. Lee, K. Jen, C. G. Willson, J. Byers, P. Zimmerman and N. J. Turro, Materials modeling and development for use in double-exposure lithography applications, *J. Micro/Nanolithogr., MEMS, MOEMS*, 2009, **8**, 011011.
11 J. Wirz, Kinetic studies of keto-enol and other tautomeric equilibria by flash photolysis, *Adv. Phys. Org. Chem.*, 2010, **44**, 325–356.
12 A. C. Weedon, Photochemical reactions involving enols, in *Enols (1990)*, ed. Z. Rappoport, John Wiley & Sons Inc, 2010, pp. 591–638.
13 A. J. Kresge, Flash Photolytic Generation and Study of Reactive Species: From Enol to Ynols, *Acc. Chem. Res.*, 1990, **23**, 43–48.

14 G. R. McMillan, J. G. Calvert and J. N. Pitts, Detection and Lifetime of Enol-Acetone in the Photolysis of 2-Pentanone Vapor, *J. Am. Chem. Soc.*, 1964, **86**, 3602–3605.

15 J. W. Coomber, J. N. Pitts and R. R. Schrock, The detection of ethylketen and enol-crotonaldehyde in the vapour-phase photolysis of trans-crotonaldehyde, *Chem. Commun.*, 1968, 190b–191.

16 A. Henne and H. Fischer, Enols from Norrish Type II Cleavage of Carbonyl Compounds in Solution, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 435–435.

17 S. M. Rosenfeld, R. G. Lawler and H. R. Ward, Photo-CIDNP [chemically induced dynamic nuclear polarization] detection of transient intermediates. Enol of acetophenone, *J. Am. Chem. Soc.*, 1973, **95**, 946–948.

18 R. W. Binkley and H. F. Jarrell, Type II reactions from the photolysis of the phenacyl ether of 1,2:3,4-di-O-isopropylidene-α-D-Galactopyranose, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 347–364.

19 S. K. Ghoshal, S. K. Sarkar and G. S. Kastha, Effects of Intermolecular Hydrogen-bonding on the Luminescence Properties of Acetophenone, Characterization of Emission States, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3556–3561.

20 Photophysical Properties of Organic Compounds, in *Handbook of Photochemistry, Third Edition*, ed. M. Montalti, A. Credi, L. Prodi and M. T. Gandolfi, CRC Press, 2006, pp. 83–351.

21 W. Adam, M. A. Arnold, W. M. Nau, U. Pischel and C. R. Saha-Möller, A Comparative Photomechanistic Study (Spin Trapping, EPR Spectroscopy, Transient Kinetics, Photoproducts) of Nucleoside Oxidation (dG and 8-oxodG) by Triplet-Excited Acetophenones and by the Radicals Generated from α-Oxy-Substituted Derivatives through Norrish-Type I Cleavage, *J. Am. Chem. Soc.*, 2002, **124**, 3893–3904.

22 N. J. Turro and F. D. Lewis, Type II photoelimination and 3-oxetanol formation from α-alkoxyacetophenones, *Tetrahedron Lett.*, 1968, **9**, 5845–5848.

23 F. Lewis and N. Turro, Molecular Photochemistry. XVIII. Type II Photoelimination and 3-Oxetanol Formation from α-Alkoxyacetophenones and Related Compounds, *J. Am. Chem. Soc.*, 1970, **92**, 311–320.

24 N. Mathivanan, L. J. Johnston and D. D. M. Wayner, Photochemical Generation of Radical Anions of Photolabile Aryl Ketones, *J. Phys. Chem.*, 1995, **99**, 8190–8195.

25 W. U. Palm and H. Dreeskamp, Evidence for singlet state β-cleavage in the photoreaction of α-(2,6-dimethoxyphenoxy)-acetophenone inferred from time-resolved CIDNP spectroscopy, *J. Photochem. Photobiol., A*, 1990, **52**, 439–450.

26 J. C. Netto-Ferreira and J. C. Scaiano, Photochemistry of α-phenoxy-p-methoxyacetophenone, *Tetrahedron Lett.*, 1989, **30**, 443–446.

27 P. J. Wagner, Solvent effects on type II photoelimination of phenyl ketones, *J. Am. Chem. Soc.*, 1967, **89**, 5898–5901.

28 N. J. Turro, V. Ramamurthy, and J. C. Scaiano, Molecular Oxygen and Organic Photochemistry, in *Modern Molecular Photochemistry of Organic Molecules*, University Science Books, Sausalito, CA, 2010, pp. 1001–1054.

29 J. Pika, A. Konosonoks, R. M. Robinson, P. N. D. Singh and A. D. Gudmundsdóttir, Photoenolization as a Means To Release Alcohols, *J. Org. Chem.*, 2003, **68**, 1964–1972.

30 A. Konosonoks, P. J. Wright, M.-L. Tsao, J. Pika, K. Novak, S. M. Mandel, J. A. Krause Bauer, C. Bohne and A. D. Gudmundsdóttir, Photoenolization of 2-(2-Methyl Benzoyl) Benzoic Acid, Methyl Ester: Effect of E Photoenol Lifetime on the Photochemistry, *J. Org. Chem.*, 2005, **70**, 2763–2770.

This journal is © The Royal Society of Chemistry and Owner Societies 2011