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PHOTORELEASABLE PROTECTING GROUPS BASED ON ELECTRON TRANSFER CHEMISTRY. DONOR SENSITIZED RELEASE OF PHENACYL GROUPS FROM ALCOHOLS, PHOSPHATES AND DIACIDS

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Abstract. The electron transfer mediated photochemical release of alcohols, phosphates and diacids is examined. The alcohols can be protected as mixed phenacyl carbonate esters. Irradiation of mixtures containing electron donating sensitizers and phenacyl alkyl carbonate ester initiates a series of bond scission reactions that result in clean release of the corresponding alcohols. This was demonstrated for a variety of primary, secondary and tertiary hydroxyl groups, including the 5'-hydroxy group of thymidine. Sensitizers that were effective in promoting photolytic release include 9,10-dimethylanthracene and 9-methylcarbazole. GC/MS and NMR analysis of the by-products formed in these release reactions implicates the intermediacy of radical ion intermediates in these reactions. It is further demonstrated that the electron transfer sensitized release method can be extended to phosphate esters and di-functional acids.

Keywords: Alcohols; Anthracenes; Carbonates; Electron Transfer; Photochemistry; Phosphoric acid derivatives; Protecting Group

INTRODUCTION

Interest in photoreleasable protecting groups (PRPGs) has expanded in recent years as it has become clear that this technology can be applied to a variety of endeavors including, multi-step organic synthesis,[1,2] time resolved x-ray crystallography,[3] photolithographic fabrication of DNA chips,[4-7] photoregulation of proteins and cellular signaling pathways,[8-11] and studies of ion channel dynamics in whole cells.[12-14] There are a number of established strategies for masking and photolytically releasing various functionalities. PRPGs based on derivatives of ortho-nitrobenzyl group are perhaps the most widely used.[15-18] More recent investigations have identified the α-benzoin group and its derivatives as an alternative strategy.[19-26] The latter releases the target functionality more rapidly following absorption of the photon and gives by-products that are generally more inert than those from the ortho-nitrobenzyl family. Lately, Givens, et al.[27,28] have demonstrated the utility of the 4-hydroxyphenacyl group. One problem that remains in this area is control of the wavelengths required for functional group release. Most of the currently available technologies utilize wavelengths in the UV-B region of the spectrum, limiting their applicability in situations where the target molecule or other species in the matrix absorb in the same spectral region.

In a series of recent papers,[29-31] we have advanced a modular approach to the design of PRPGs whereby the light absorption step is controlled by one element (an antenna or a sensitizer) and the bond scission step leading to release of the target molecule is controlled by a separate element (release group). In principle, such a strategy permits separate optimization of the wavelengths of light required for release and the rates and efficiencies of the bond scission process. This concept has been experimentally realized through the release of carboxylic acids from phenacyl esters **1a**.[31] In this case the phenacyl group acts as the release group and the light absorption step is controlled by a separate molecule which functions as an electron donating sensitizer. The initial photochemical step is transfer of an electron from the excited sensitizer to the phenacyl group, generating a phenacyl anion radical **2**. The latter rapidly eliminates a carboxylate anion. It was demonstrated that a variety of carboxylic acids could be released using this strategy.

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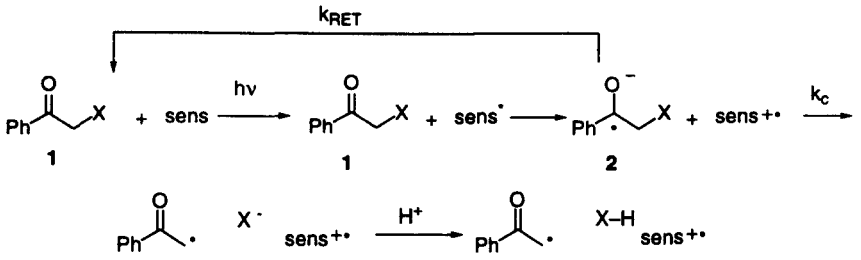
More significantly it was shown this release process couldbe effected with wavelengths approaching the visible region of the spectrum provided an appropriate sensitizer was used.[29]

Scheme 1



a: X=OCOR, **b**: X=OR; **c**: X=OPh; **d**: X=OCO_2R; **e**: X=OP(O)$(OR)_2$

The goal of the current study was to extend the modular method to the photorelease of additional functional groups. Herein are described studies involving photolytic release of alcohols, phosphates and diacids. In each case, electron transfer from an excited state aromatic compound to a phenacyl group is used as the method of photorelease. Extension of this procedure to alcohols requires that the hydroxyl group be masked as a mixed phenacyl carbonate ester (**1d**). Phosphates, on the other hand can be protected as phenacyl esters. It is further demonstrated that this method can be applied to functionally complex systems. Diacids can be doubly masked with phenacyl groups and sequentially released. A variety of excited state donors can be used in these reactions including 9,10-dimethylanthracene The latter allows for photolysis at high wavelengths (>390 nm). Analysis of reaction mixtures by GC/MS and ^1H NMR spectroscopy shows that this sensitizer is consumed in subsequent radical reactions of the fragments.

RESULTS AND DISCUSSION.

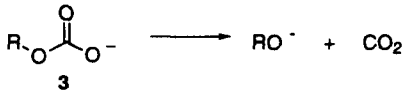
It was clear at the outset of this study that adapting the phenacyl methodology to release of alcohols by simply photolyzing phenacyl ethers (**1b**) was unlikely to be successful. Wayner, et al.[32] have shown that rates of bond scission in anion radicals correlate with the basicity of the anionic fragment, the more basic anions being eliminated much more slowly than less basic anions. It follows then that the more basic alkoxide anion would be eliminated more slowly from a phenacyl ether than the less basic carboxylate from a phenacyl ester. In a practical sense, these slower rates would manifest themselves in a reduction of quantum yields of the release step to the point where unacceptably long exposure times would be required to achieve release of the substrate.

We did carry out preliminary, sensitized deprotection experiments on α–phenoxyacetophenone **1c**. The phenoxide leaving group is less basic than typical alkoxides but more basic than the carboxylates. Therefore, we anticipated that this would represent a best case situation for the phenacyl ethers. In fact laser flash photolysis studies by the Wayner group show that this anion radical does eliminate phenoxide with rate constants $<10^6\ s^{-1}$.[33] Nonetheless exhaustive photolysis of mixtures of our sensitizers and **1c** failed to produce any detectable amounts of phenol . Apparently the release of phenoxide (k_c) is insufficiently rapid to compete with return electron transfer in the geminate solvent cage (k_{RET}).

For these reasons we examined unsymmetric phenacyl carbonates (**1d**). The mechanism in Scheme 1 predicts that the key bond scission step is release of a monoalkyl carbonate anion **3**. These species possess basicities closer to the carboxylates than to the alkoxides and thus the bond scission rate should be rapid enough to allow for good conversions in reasonable exposure times. Monoalkylcarbonates are well known to expel CO_2 ultimately forming the corresponding alcohols (Scheme 2).[34] A similar strategy has been used to extend the capabilities of other PRPG's.[18,21,35]

The phenacylalkyl carbonates can be prepared through the three methods shown in Scheme 3. Where the corresponding chloroformate **4** (for methanol, ethanol, and benzyl alcohol) is available, it is most convenient to couple the latter with phenacyl alcohol. Higher yields could be achieved when the coupling was carried out by first activating the alcohol with N,N-carbonyldiimidazole **5** and then adding phenacyl alcohol. Thymidine and iso-propyl alcohol were protected by the methylimidazolium complex of phenacyl alcohol **6**.[21] The latter was generated from phenacyl alcohol, **5**, and methyltriflate. The yields of the protection step were highly dependent on the presence of traces of water in the solvent. The protection yields in Table 2, which represent typical rather than optimal conditions, ranged from 88 to 38%. The lowest yields were for *tert*-butyl alcohol and thymidine These are attributed to steric hindrance in the first case and the low solubility of the substrate in the second case.

Scheme 2



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Scheme 3

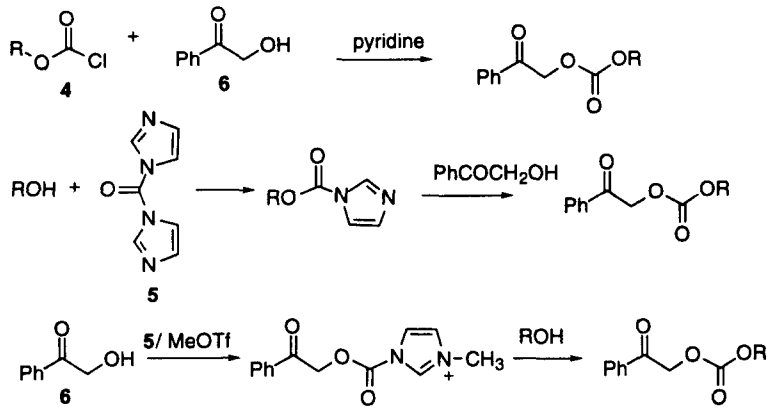


Table 1. Stern-Volmer Quenching Constants ($k_q\tau$) and Relative Quantum Yields for Deprotection of Phenacyl Esters and Carbonates Using 9,10-Dimethylanthracence as the Sensitizer.

Compound	$k_q\tau$ (L/mol)	Φ_{rel}
Phenacyl phenylacetate	180	1.0
Phenacylethyl carbonate	210	0.15
Phenacyl (2-phenylethyl) carbonate	200	0.20

Photolytic release of each alcohol was achieved through irradiation of N_2-purged CH_3CN solutions containing the phenacylalkyl carbonate (40-60 μmol) along with an appropriate electron donor sensitizer (typically 60-90 μmol). For most trials, the mixtures were irradiated in sealed NMR tubes and the consumption of the substrate and the appearance of the product could be monitored at various intervals throughout the photolysis.

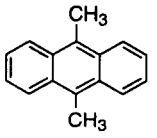
Clean conversion of the carbonate to the alcohol was observed in each case. The yield of alcohol could be calculated by comparison of its ^1H NMR peak integration to that of an internal standard. Modest to excellent yields of the released alcohols are observed. This photorelease strategy does not appear to be strongly

dependent on the type of alcohol. Methyl, primary, secondary and tertiary alcohols were released in reasonable yields. Aryl-substituted alcohols, benzyl and phenethyl alcohols were also released efficiently.

Studies were carried out using the three sensitizers indicated in Chart 1.[29] These are all excited state electron donors which have previously been shown to be effective at reducing the phenacyl group. 9,10-Dimethylanthracene (9,10-dMA) has an excited state oxidation potential of -2.23 V (vs. SCE) and its highest wavelength absorption maximum is at 398 nm. 9-Methylcarbazole (9-MC) is a slightly better donor, having an excited state oxidation potential of -2.46 V but absorbs at lower wavelengths (λ_{max} = 345 nm). Finally N,N,N',N'-tetramethyl-para-phenylenediamine (TMPD) has E_{ox}^* = -3.25 and λ_{max} =332 nm.

While the preparative experiments indicated that the carbonate esters released the alcohols efficiently, it was of interest to obtain a more quantitative comparison between the release efficiencies of the carbonates and the previously studied esters. Relative quantum yields by irradiating solutions containing 9,10-dMA, and a phenacyl carbonate ester with monochromatic light (400±10 nm). The conversion of substrate was monitored at various photolysis times using HPLC. The rates of photolysis for two representative carbonates, phenacylethyl carbonate and phenacyl (2-phenylethyl) carbonate were compared with the rate for phenacyl phenylacetate. The relative quantum yields are shown in Table 1. Changing the carboxlyate leaving group to the less basic monoalkylcarbonate reduces the quantum yield by a factor of 5-6. This can be attributed to a somewhat slower rate constant for bond scission of the corresponding phenacyl anion radical (process k_c in Scheme 1).

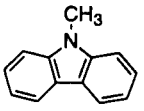
Chart 1: Excited State Electron Donors



9,10-dMA

E_{ox}^* = -2.23 V;

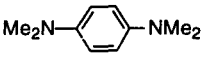
λ_{max} = 398 nm



9-MC

E_{ox}^* = -2.46 V;

λ_{max} = 345 nm



TMPD

E_{ox}^* = -3.25 V;

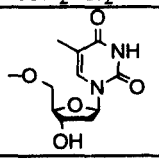
λ_{max} = 332 nm

Scheme 1 predicts that the deprotection step is initiated by electron transfer to the phenacyl group.[31] This follows from our prediction that this group is more easily reduced than the leaving groups and furthermore is not directly conjugated with the leaving group. The influence of the leaving group on this initial step should therefore be minimal. This prediction was verified by two experiments. First we measured the electrochemical reduction potential (E_{red}) for a representative of the carbonate series, phenacylbenzyl carbonate. As anticipated cyclic voltammetry experiments on these compounds show an irreversible reduction wave with a shape virtually indistinguishable from that of the previously studied phenacyl esters. The peak potentials for phenacylbenzyl carbonate is -1890 mV (vs. SCE). This is similar to the peak potentials for simple phenacyl esters; phenacylbenzoate, for example has a peak potential of -1810 mV. Any differences can be attributed to the fact that the electrochemical reductions are irreversible processes and depend in part on the rate constant for the bond scission. In any case, the similar electrochemical behavior confirms that the initial electron transfer event involves the phenacyl group and is relatively insensitive to the leaving group.

Fluoresence quenching rate constants further demonstrate that the initial electron transfer event is localized on the phenacyl group. Addition of the either phenacyl carbonates or esters to solutions of the sensitizer, 9,10-dimethylanthracence quench its fluoresence. A Stern-Volmer analysis of the effect of phenacyl ester or carbonate concentration on the degree of fluorescence quenching gives the Stern-Volmer constant, $k_q\tau$, which indicates the susceptibility of the singlet excited state of sensitizer to reaction with the protected substrates. As expected the measured Stern-Volmer constants ranged from 180-210 L mol^{-1}, showing insignificant variation when the phenacyl esters are compared to the phenacyl carbonates.

One well-established application of photolytic release of alcohols is in the fabrication of solid state combinatorial libraries of oligonucleotides, or "DNA-chips".[20,36,37] For this reason we protected the 5'-(phenacylcarbonate) ester of thymidine and examined its sensitized photorelease. In this case the unprotected alcohol, thymidine was insufficiently soluble in CD_3CN for observation by ^1H NMR. However the product could be conveniently isolated by simply filtering the reaction mixture. In this case the yield was determined by weighing the solid. Its purity was confirmed by ^1H NMR in DMSO-d_6.

Table 2. Photorelease of Alcohols from Sensitized Photolysis of Phenacyl Alkyl Carbonates ($ROCO_2CH_2COPh$) in CH_3CN

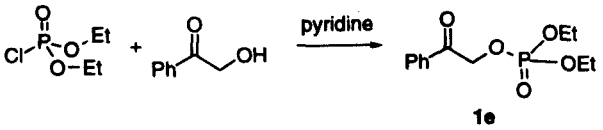
RO–	Sensitizer[a]	Conditions	Protection Yield	Yield of ROH(%)
CH_3O–	9,10-dMA	3 h, >390 nm	64	83
CH_3CH_2O–	9,10 -dMA	1 h, >390 nm	60	66
$(CH_3)_2CHO$–	9-MC TMPD	1.5 h, >320 nm 1.5 h, >320 nm	88	65 84
$(CH_3)_3CO$-	9,10-dMA	2 h, >390 nm	38	61
$PhCH_2O$–	TMPD	2 h, >320 nm	88	72
$PhCH_2CH_2O$–	9,10-dMA	3 h, >390 nm	74	81
	9-MC 9,10-dMA	4 h, >320 nm 4 h, >390 nm	48	81 91

(a) Sensitizers: 9,10-dMA = 9,10-dimethylanthracene; 9-MC = 9-methylcarbazole; TMPD= N,N,N',N'-tetramethyl-*p*-phenylenediamine.

The phosphate group is ubiquitous in biochemistry and many strategies for triggering or otherwise controlling biological systems rely on methods for the photochemical release of this functional group.[38-41] The phenacyl ester of diethyl phosphophosphate **1e** was synthesized by combining diethylphosphoryl chloride with phenacyl alcohol in the presence of pyridine. Irradiation of a mixture of protected phosphate **1e** and 9,10-dMA were carried out using the same conditions employed for the carbonates. As with the carbonates, the consumption of the ester and the growth of the diethyl phosphoric acid could be monitored as the sample was photolyzed in a sealed ^1H NMR tube. Thus the OCH_2–Me resonance at 4.15 ppm was observed to disappear with photolysis and concomitant with the appearance of the same group in diethyl phosphoric acid at 4.01 ppm. The conversion was quantitative and no side products could be detected, other than some aromatic resonances which can be attributed to sensitizer by-products (vide infra). Similar results obtain when **1e** is photolyzed with *N,N*-dimethylaniline, using a 290 nm cutoff filter.

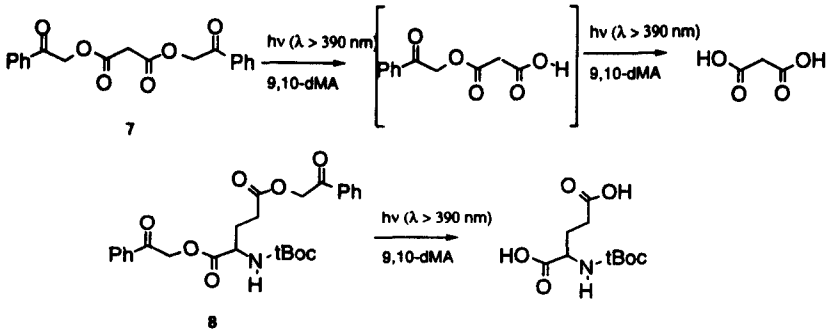
There are many interesting biological molecules which possess several different sites with the same functional group. For example carbohydrates contain several hydroxyl groups, and large proteins will usually possess multiple copies of amino acids with functional side-chains (e.g. serine, glutamate, etc). Phototriggered release of such complex molecules will require that sequential elimination of the two protecting groups occur cleanly and that the released functional group or accumulated by-products do not interfere with subsequent deprotection steps. For this reason it was interesting to determine if it would be possible to release two phenacyl groups from different sites on the same molecule.

Scheme 4



1e

Scheme 5



To this end two diacids, malonic acid and N-t-Boc-glutamic acid were each protected with two equivalents of phenacyl bromide. These protection reactions proceeded cleanly and gave good yields of the diesters **7** and **8**, respectively. Sensitized photolysis (using 9,10-dMA and the same conditions employed for the carbonates) of both **7** and **8** cleanly released the corresponding acids. In the case of malonic acid the overall deprotection yield was 83% and in the case of N-*t*-Boc-glutamic acid the yield was 87%. Monitoring the malonic acid reaction by ^{1}H NMR showed the accumulation of monophenacylmalonate at intermediate times. For example after 15 min of photolysis there was detected the intermediate monoester (34%, observed by its characteristic CH_2 ^{1}H NMR resonance at 3.55 pm), unconverted diester (59%, 3.75 ppm), and malonic acid(5% 3.34 ppm). After 2 h of photolysis only the deprotected diacid was seen. In the case of **8**, ^{1}H NMR analysis of the photolysate at intermediate times during the photolysis also showed additional peaks apparently associated with the two possible monoesters. However the high complexity of the ^{1}H NMR spectrum precluded certain assignment and quantitation of the intermediate peaks. After 2 h of photolysis only the deprotected substrate was seen (along with sensitizer and its by-products).

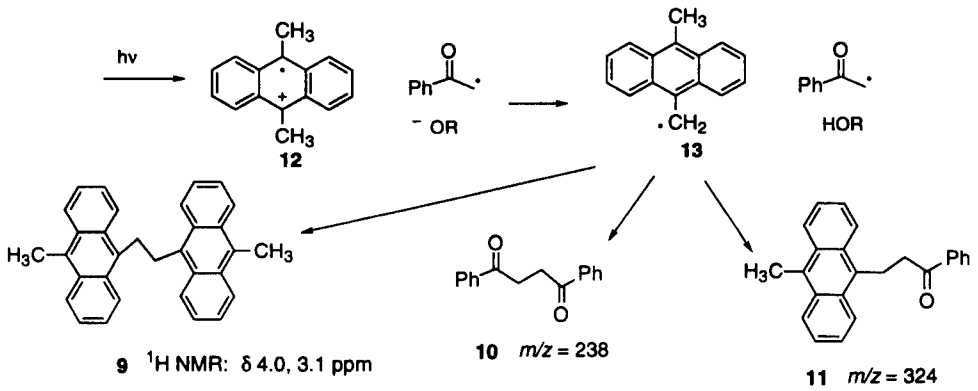
The mechanism in Scheme 1 predicts that a phenacyl radical ($PhCOCH_2$•) and the cation radical of the sensitizer remain after release of the functional group. We have discussed the fates of these species in previous papers for the case where the sensitizer is an alkyl aniline derivative (e.g. N,N-dimethylaniline).[42] Briefly, the arylamine cation radical is deprotonated on the carbon immediately adjacent to the N-atom. This provides a strongly reducing α-amino radical which apparently donates an electron to the phenacyl radical giving acetophenone enolate and an iminium ion.[43] Hydrolysis of the latter and protonation of the former gives the observed products, the de-alkylated aniline derivative along with acetophenone. The sensitizers TMPD and 9-MC are alkylarylamines and therefore we assume that they follow the previously characterized mechanism. The 9,10-dMA sensitizer, on the other hand, is not an alkylaryl amine, and thus the fates of the radicals from this sensitizer also need to be considered.

The by-products detected from the 9,10-dMA sensitized photolyses indicate that analogous free radical and radical ion intermediates are formed. 9,10-Dimethylanthracene was photolyzed in the presence of phenacyl 5'-thymidine carbonate. After the photolysis, the solvent was evaporated under reduced pressure. The resulting white residue was washed twice with $CHCl_3$. ^{1}H NMR analysis of the soluble fraction revealed a mixture of several aromatic compounds, including dMA- dimer **9** . The latter was identified through its characteristic resonances at 4.0 and 3.1 ppm.[44] GC/MS analysis of the same mixture showed peaks with masses characteristic of acetophenone (*m/z* = 120), 1,2-dibenzoylethane **10** (*m/z* = 238), and dMA-phenacyl coupling product, **11** (*m/z* = 324). The same photolysis was carried out with a large excess of 1,4-cyclohexadiene, a good H atom donor. The effect of this trap was to increase the yield of acetophenone and 9,10-dimethylanthracene at the expense of the radical coupling products.

The above results support the mechanism for 9,10-dMA sensitized deprotection shown in Scheme 6. Electron transfer from the excited singlet state of 9.10-dMA to the phenacyl carbonate provides a radical ion

pair. The phenacyl carbonate radical anion (**2**) undergoes a heterolytic C–O scission to give the phenacyl radical ($PhCOCH_2^{\bullet}$) and the cation radical of 9,10-dMA (**12**) . The latter is known to be a rather strong acid (pK_a = -5.0)[45] and would be rapidly deprotonated (either by the monoalkyl carbonate, the alkoxide or the solvent) giving dMA radical (**13**). The observed by-products result from coupling and cross-coupling of radicals $PhCOCH_2^{\bullet}$ and **13.**

Scheme 6



CONCLUSIONS

These results show that is possible to extend the phenacyl/electron-transfer procedure to the photorelease of hydroxyl groups, phosphates and difunctional acids. In the case of the alcohols, it is not possible to deprotect simple phenacyl ethers via the electron transfer route. However the use of mixed phenacyl alkyl carbonates does allow for efficient deprotection. Analysis of the photoproducts from 9,10-dMA sensitized reactions shows that this sensitizer, like the alkylaryl amines, initiates the bond scission reactions via an initial electron transfer reaction. The cation radical of 9,10-dMA decays through deprotonation and subsequent radical coupling processes.

EXPERIMENTAL SECTION

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Acetonitrile and dichloromethane were distilled from CaH_2 under anhydrous N_2 atmosphere through a vacuum sealed column (30 cm) packed with glass helices. ^1H NMR spectra were run at 200 MHz, and ^{13}C NMR spectra at 55.1 MHz on a Bruker AF200 spectrometer unless otherwise indicated. Preparative photolysis reactions were performed using either a 400 W Xe lamp or a Ace-Hanovia 450 W medium pressure Hg vapor lamp. The CW Xe arc lamp was also used to carry out control reactions. 295 nm (corex), 320 nm (Pyrex), 390 nm or 400 nm high pass cutoff filters were used to ensure that the light was absorbed by the sensitizer rather than the substrate. Gas chromatography-mass spectra(GC-MS) were obtained using a XTI®-5 (30 m bonded 5 % phenyl) GC column with 0.25 mm internal diameter and 0.25 μm film thickness. Ar was used as the mobile phase. The temperature was increased from 50 °C to 300 °C in 20 minutes. The mass spectrum of each peak was obtained by EI. Electrochemical experiments were conducted on a BAS-50 electrochemical analyzer operating in cyclic voltammetry mode (CV) with $[Bu_4N][PF_6]$ as the supporting electrolyte. Scan speed for CV data were 100 mV/sec. Fluorescence quenching experiments were performed on a Gilford Fluoro IV fluorimeter. Sample solutions were placed in 10 x 10 mm quartz cuvettes which were then sealed with a rubber septum and purged with N_2 for 10-15 min prior to the experiment. Sample concentrations were adjusted such that their optical densities were 0.07-0.08 at the excitation wavelength.

Phenacyl alcohol (α-hydroxyacetophenone). This procedure was adapted from the one developed by Pirkle and Simmons.[46] 11.62 g (0.1706 moles) sodium formate was stirred in 50 ml ethanol for about 15 minutes. 5.31 g (26.7 mmol) phenacyl bromide was added to it and the mixture was refluxed under nitrogen at 105 °C for nearly 20 h. The reaction mixture was cooled and complete conversion of the starting material was confirmed by TLC. The solvent was evaporated and about 50 ml of boiling water was added and the solution was filtered hot. The filtrate was then cooled to precipitate out the alcohol. Yield 3.11 g (86 %) from 5.31 g phenacyl bromide, white crystalline solid: mp 82-84 °C (lit.[46] mp 84-85 °C); ^{1}H NMR ($CDCl_3$) δ 3.49 (t, J = 4.5), 4.87 (d, J = 4.5), 7.44-7.65 (m, 3H), 7.91 (dd, J_1 = 8, J_2 = 1.3, 2H); ^{13}C NMR ($CDCl_3$) δ 198.4, 134.3, 133.5, 129.0, 127.7, 65.5; EI-MS, m/z (rel. intensity) 136 (M^+, 6), 105 (100), 77 (81), 52 (29).

Phenacyl diethyl phosphate. The synthetic procedure was adapted from the one used by Givens *et al.*[25,26] for the synthesis of desylphosphates. To a solution of 1.38 g (10.1 mmol) phenacyl alcohol in 5 ml pyridine, 3 mL (20.8 mmol) diethyl phosphoryl chloride was added dropwise at -5 °C with constant stirring. The mixture was allowed to warm up to room temperature and stirred overnight under nitrogen. About 10 ml diethyl ether and 50 mL water was added to the mixture. The aqueous layer was extracted with diethyl ether. The organic layer was washed with 3 x 50 mL 1 N H_2SO_4 followed by 3 x 50 mL 5 M $NaHCO_3$ and about 50 ml water. The ether layer was treated with activated carbon, dried over anhydrous $MgSO_4$ and the ether was then evaporated. Yield 0.767 g (28 %) from 1.38 g phenacyl alcohol, yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7, 6H), 4.15 (p, J = 7, 4H), 5.25 (d, J = 10, 2H), 7.38-7.58 (m, 3H), 7.83 (d, J = 7, 2H); ^{13}C NMR ($CDCl_3$) δ 192.3, 192.2, 134.0, 133.9, 128.9, 127.7, 68.7, 68.6, 64.4, 66.3, 16.1,16.0; EI-MS, m/z (rel. intensity) 272 (M^+, 2), 227 (12), 199 (13), 118 (67), 105 (100), 77 (80), 52 (47).

Phenacyl phenoxide (α-phenoxyacetophenone) 1c. Phenol (2.045 g, 21.8 mM) and 2.696 g (19.5 mM) potassium carbonate were dissolved in 40 mL acetone and the mixture was stirred for about 10 minutes. 3.532 g (17.7 mmol) of phenacyl bromide was added to the mixture and the mixture was refluxed for 2 h. The reaction mixture was then quenched with 100 ml water and the phenacyl ether was extracted with (3 x 50 mL) diethyl ether. The organic extracts were washed with 2 M NaOH (3 x 50 ml), and water (3 x 50 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and a white solid was obtained. The crude product was crystallized with ethanol. Yield 2.66 g (71 %) from 3.53 g phenacyl bromide, white crystalline solid: mp 70-72 °C (lit.[47] mp 71-72 °C); ^{1}H NMR ($CDCl_3$) δ 5.26 (s, 2H), 6.92-7.01 (m, 3H), 7.28 (t, J = 7, 2H), 7.45-7.65 (m, 3H), 7.99 (d, J = 7, 2H); ^{13}C NMR ($CDCl_3$) δ 194.5, 158.0, 134.7, 133.8, 129.5, 128.8, 128.1, 121.6, 114.8, 70.8; EI-MS, m/z (rel. intensity) 213 (M+1, 5), 212 (M^+, 29), 106 (16), 105 (100), 91 (13), 77 (90), 65 (15), 50 (45).

Phenacyl *iso*-propyl carbonate. Methyl triflate (1 mL, 8.84 mmol) was added dropwise to a solution of (0.959 g, 5.92 mmol) carbonyl diimidazole dissolved in 20 mL CH_3NO_2. The solution was kept at about 0° C during the addition. The solution was then warmed to room temperature and was allowed to stir for 1 h. The solution was then transferred to a flask containing freshly azeotroped (from benzene) 0.647 g (5.303 mmol) phenacyl alcohol. The resulting mixture was allowed to stir for 2 h at room temperature to form the phenacyl carbonyl-*N*-methylimidazole (not isolated or characterized). Freshly azeotroped iso-propyl alcohol (5.92 mmol) was then added and the reaction mixture was stirred overnight. The solvent was removed by vacuum distillation and the product was purified using silica gel flash chromatography with 80% hexane and 20% ethyl acetate. Yield 1.032 g (88 %) from 0.715 g phenacyl alcohol, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.87 (s, 3H), 5.37 (s, 2H), 7.46-7.62 (m, 3H), 7.92 (d, J = 6, 2H); ^{13}C NMR ($CDCl_3$, 110 MHz) δ 191.9, 154.2, 133.8, 128.7, 127.5, 72.6, 68.2, 21.5; EI-MS, m/z (rel. intensity) 222 (M^+, 1), 163 (27), 118 (32), 105 (100), 91 (60), 77 (66), 65 (13), 50 (44).

Phenacyl 5'-thymidine carbonate. Same procedure as for phenacyl-*iso*-propyl carbonate except 100% ethylacetate was used in the chromatography. Yield 3.7 g (48 %) from 4.6 g thymidine, white solid: mp 179-182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76 (s, 3H), 2.08-2.23 (m, 2H), 3.95-3.97 (m, 1H), 4.27-4.57(m, 3H), 5.49 (d, J = 4, 1H), 5.57 (s, 2H), 6.21 (t, J = 7, 1H), 7.48 (s, 1H), 7.56 (t, J = 7, 2H), 7.70 (t, J = 7, 1H),7.95 (d, J = 7, 2H), 11.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 110 MHz) δ 192.6, 163.7, 154.3, 150.5, 135.8, 134.2, 133.6,

129.0, 127.8, 109.9, 83.8, 83.5, 70.1, 69.3, 67.8, 38.6, 12.1; FAB-MS, m/z (rel. intensity) 405 (M+1, 8), 197 (12), 195 (14), 155 (24), 152 (26), 137 (14), 135 (37), 119 (100), 105 (16), 103 (55), 101 (21), 89 (28), 87 (27), 85 (95), 81 (45), 79 (20), 77 (20), 74 (23), 56 (42), 54 (38); HRMS calcd for $C_{19}H_{21}N_2O_8$: 404.12979, found: 405.12773.

Phenacyl *tert*-butyl carbonate Potassium *tert*-butoxide (0.543 g, 4.83 mM) and *t*-butyl alcohol (0.525 g, 7.08 mM) were stirred in 15 mL dry THF. The mixture was added to a suspension of carbonyldiimidazole (1.5 g, 9.26 mM) in 15 mL dry THF. The mixture was stirred at room temperature for about 14 h. Phenacyl alcohol (0.643 g, 4.73 mM) was added to the reaction mixture and stirred at 0 °C for 2 h. About 30 mL water was added to the mixture and the carbonate was extracted with (3x50 mL) dichloromethane. The carbonate was purified using 4:1 hexane ethyl acetate. Yield 0.429 g (38%) from 0.643 g phenacyl alcohol, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 5.23 (s, 2H), 7.43-7.59 (m, 3H), 7.88 (d, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 192.3, 153.1, 134.1, 133.9, 128.8, 127.7, 83.0, 67.9, 27.7; FAB-MS, m/z (rel. intensity) 237 (M+1, 13), 181 (100), 163 (14), 119 (21), 105 (49), 91 (21), 77 (9), 57 (73); HRMS calcd for (M+1) $C_{13}H_{17}O_4$: 237.1127, found: 237.1135.

Phenacyl (2-phenethyl) carbonate. Same procedure as for phenacyl *tert*-butylcarbonate. Yield 1.11 g (74 %) from 0.65 g phenethyl alcohol, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.02 (t, J = 7, 2H), 4.40 (t, J = 7, 2H), 5.33 (s, 2H), 7.21-7.32 (m, 5H), 7.46-7.63 (m, 3H), 7.89 (d, J = 7, 2H); ^{13}C NMR ($CDCl_3$, 110 MHz) δ 191.7, 154.8, 137.1, 134.0, 129.0, 128.9, 128.6, 127.8, 126.7, 69.0, 68.6, 35.1; FAB-MS, m/z (rel. intensity) 286 (M+2, 3), 284 (M+1, 16), 154 (15), 137 (16), 105 (100), 91 (24), 77 (20); HRMS calcd for $C_{17}H_{17}O_4$: 285.11267, found: 285.11326.

Phenacyl methyl carbonate. To a solution of 0.86 g (6.30 mmol) phenacyl alcohol in 25 mL pyridine, 1.22 g (12.9 mmol) of methyl chloroformate was added dropwise with constant stirring. The mixture was then heated at about 80 °C for 1 h. The reaction mixture was cooled and about 50 ml of diethyl ether was added to it. The mixture was then washed with 3 x 50 mL of 1 N H_2SO_4 followed by 3 x 50 mL sat'd. $NaHCO_3$ and 2 x 50 mL water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent evaporated. The resulting yellow oil was purified by flash chromatography on silica gel using 1:4 mixture of ethyl acetate and hexane. Yield 0.096 g (8 %) from 0.857 g phenacyl alcohol, yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 5.37 (s, 2H), 7.46-7.62 (m, 3H), 7.92 (d, J = 6, 2H); ^{13}C NMR ($CDCl_3$) δ 191.7, 155.5, 134.0, 128.9, 127.7, 68.7, 55.3; EI-MS, m/z (rel. intensity) 194 (M^+, 1), 118 (3), 105 (100), 91 (6), 77 (29), 50 (8).

Phenacyl ethyl carbonate. Procedure same as the methyl carbonate. (5 mL, 52 mM) ethylchloroformate in 10 mL pyridine and 0.7251 g, 5.33 mM phenacyl alcohol. Yield 0.664 g (60%) from 0.7251 g phenacyl alcohol. (mp 41-43 °C).

Phenacyl benzyl carbonate. Benzyl choroformate (3 mL, 21 mM) was added dropwise to a solution of phenacyl alcohol (0.204 g, 1.5 mmol) in 10 mL pyridine at 0 °C. Solution stirred for about 16 h at room temperature. The mixture was dissolved in dichloromethane and was with 10% HCl (3x100 mL), satd $NaHCO_3$ (3x100 mL) and water (2x100 mL). The resulting solution was purified by chromatography (4:1 hexane and ethyl acetate) and recrystallized with diethyl ether. Yield 0.355 g (88%) from 0.204 g phenacyl alcohol, white solid: mp 49-51 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.23 (s, 2H), 5.35 (s, 2H), 7.32-7.62 (m, 8H), 7.89 (d, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 191.7, 154.9, 134.9, 134.0, 133.9, 128.9, 128.6, 128.3, 127.7, 70.2, 68.7; FAB-MS, m/z (rel. intensity) 271.1 (M+1, 11), 181 (12), 120 (5), 105 (28), 91 (100), 77 (12); HRMS calcd for (M+1) $C_{16}H_{15}O_4$: 271.0971, found: 271.0972.

Diphenacyl malonate (7). The procedure for ester synthesis has been published.[31] Yield 3.137 g (46 %) from 8.057 g phenacyl bromide, white solid: mp 84-86 °C; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 2H), 5.43 (s, 4H), 7.46 - 7.70 (m, 6H), 7.91 (d, J = 7.0, 4H); ^{13}C NMR ($CDCl_3$) δ 191.3, 165.6, 134.0, 128.9, 127.8, 66.9, 40.8; EI-MS, m/z (rel. intensity) 340 (M^+, 0.03), 203 (2), 118 (12), 105 (100), 77 (23), 50 (5).

Diphenacyl *N-t*-Boc-glutamate.(8) Yield 0.166 g (82 %) from 0.168 g phenacyl bromide, white solid: mp 110-112 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.20-2.55 (m, 2H), 2.77 (t, J = 7.0 , 2H), 4.50-4.65 (m, 1H), 5.26-5.58 (m, 5H), 7.45 - 7.66 (m, 6H), 7.88-7.94 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 192.1, 191.4, 172.3, 171.7, 155.4, 134.2, 134.0, 133.9, 128.9, 127.8, 80.0, 66.6, 66.1, 52.9, 29.9, 28.3, 27.7; FAB-MS, m/z (rel. intensity) 484 (M+1, 3), 385 (15), 384 (63), 248 (17), 220 (21), 137 (25), 119 (15), 105 (28), 91 (21), 84 (96), 77 (15), 73 (13), 57 (100), 56 (23), 55 (28); HRMS calcd for $C_{26}H_{30}NO_8$: 484.19714, found: 484.19695.

Photorelease and Analysis of Alcohols. About 10-20 mg (~5 x 10^{-5} moles) of the phenacyl ester or the carbonate, and 1.5 equivalents of the sensitizer were dissolved in 1 ml deuterated acetonitrile along with 0.5 equiv. of hexamethyldisiloxane as an internal standard. The solution was then transferred to a sealed NMR tube and purged with N_2 for about 15 minutes. The ^{1}H NMR spectrum of the mixture was taken and the CH_2 peak areas were determined and compared with that of the standard. The solution was then photolyzed with a 350 W Xe-arc lamp with a 395 nm glass cutoff filter (320 cutoff for 9-methylcarbazole) for 2 hours. The ^{1}H NMR spectrum was taken again and the relevant peak areas of the products, unconverted starting materials and the standard were compared and the yields determined. Conversions ranged from 50-100%.

Photolysis of Phenacyl 5'-Thymidine Carbonate and Isolation of the Released Alcohol About 100 mg (2.5 x 10^{-4} mol) of phenacyl 5'-thymidine carbonate and about 5 x 10^{-4} moles (2 equivalents) of the sensitizer were dissolved in freshly distilled CH_3CN, purged with N_2 for 10 minutes and then photolyzed for nearly 3 h using a medium pressure Xe-arc lamp with a 395 nm cutoff filter (320 nm for 9-methylcarbazole and TMPD). The solvent was then removed under reduced pressure and the residue was washed several times with CH_2Cl_2. The insoluble white solid was dried, weighed and confirmed as pure thymidine by ^{1}H NMR.

Quantum Yields The out put from a 1000 W Hg-Xe arc lamp was passed a spectral Energy GM 252 monochrometer set to 400±10 nm and directed onto a 1 cm quartz cell containing 3 mL of the sample solution. Rates of carbonate disappearance were monitored at 0, 10, 20, 30, 60 min of photolysis and were acquired from the peak areas obtained from the HPLC analysis. Light intensities were measured using an International Light Research radiometer model IL 1700. The sensitizer was 9,10-dMA (7.1 x 10^{-6} M) and the initial concentration of carbonate ester was 4.7 x 10^{-6} M. The samples were purged with N_2 for 15 minutes prior to photolysis. HPLC analysis was performed on a Rainin® Gradient HPLC system with a variable wavelength detector (Linear® UVIS 200) set at 254 nm and a Microsorb®-MV 5 μM C-18 column. Chromatographic separation were carried out with a flow rate of 1 mL / min and separations were performed using a mobile phase composition of 70 % MeCN / 30 % H_2O.

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