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Visible Light Photorelease of Carboxylic Acids via Charge-Transfer Excitation of *N*-Methylpyridinium Iodide Esters

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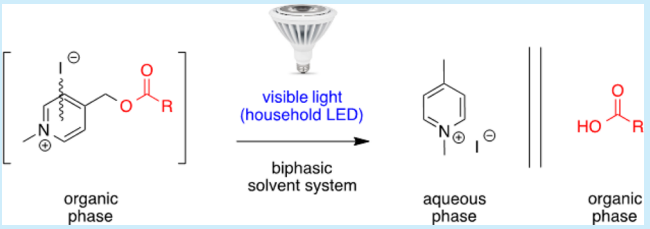
Supporting Information

ABSTRACT: Iodide contrast sensitization to direct irradiation of charge transfer salts incurs carboxylic acid release via visible light absorption. The photochemical reduction of *N*-methyl-4-pyridinium iodide esters to release carboxylic acids is examined using ^{1}H NMR analysis. Photolysis reactions are carried out under mild, biphasic solvent conditions using a household LED lamp. Carboxylic acid release is reported in high yields, and the viability of this method for synthetic chemistry is demonstrated through a macroscale reaction.



Photoreleasable protecting groups (PPGs), which are also referred to as "photocages" or "phototriggers", are light sensitive molecular species that can be covalently linked to a reactive functional group on a substrate molecule in a way that masks its reactivity. Light is then used to release the PPG from the substrate, restoring the latter to its active form. Applications of this technology include organic synthesis,[1−3] photolithography,[4,5] neurobiology,[6,7] drug release,[8−10] and optogenetics.[11,12]

One of the earliest and most commonly used types of PPG is based on the 2-nitrobenzyl chromophore.[13,14] Subsequent developments include (1) the 4-hydroxyphenacyl group,[15−17] which was designed to improve aqueous compatibility and generate more benign byproducts from the photorelease step; (2) the coumarin-4-methyl group, which has an excellent cross section for two-photon absorption;[18−20] (3) the use of fluorescein or BODIPY chromophores, which allow for photorelease using visible wavelengths;[21,22] and (4) other groups which possess alternative mechanisms for photorelease.[23−26]

In a series of reports we have advocated the use of photoinduced electron transfer in the design of PPGs.[27−30] In these systems, release of the protecting group is initiated by electron transfer from an excited state sensitizer group to the protecting group, rather that through direct light absorption. For example, it is possible to effect photorelease of carboxylic acids from *N*-alkyl-4-pyridinium (NAP) esters through irradiation of excited state electron donor molecules. One attractive feature of this approach is that it effectively decouples the light absorption step from the bond-breaking step, allowing both to be optimized independently of each other. And indeed, if the correct donor is utilized, release can be triggered using wavelengths that extend from the near-UV into the visible region of the spectrum.[31−34] A high wavelength spectral response is advantageous because (1) it can reduce side products due to unintended light absorption by products and other additives in the reaction mixture and (2) often such reactions can be carried out using household light sources, which are readily available, inexpensive, and safer to operate than UV sources.[35−40] However, one drawback of the electron transfer approach is that the requirement for an external sensitizer molecule (and/or reductants) can complicate the subsequent isolation of the targeted molecule following the photorelease procedure.

The current report describes investigations into the photochemistry of iodide salts of NAP esters. Specifically it is demonstrated that, in moderately polar solvents, ion pairing leads to formation of charge transfer or Mulliken complexes that absorb visible light. More significantly, excitation of these ion pairs results in single electron transfer reactions that, in turn, promote fragmentation of the ester C−O bond releasing carboxylate anions. On the basis of these mechanistic findings, a protocol for carboxylic acid deprotection was developed that used visible light and eliminated the need for any separation of the released carboxylic acid from the sensitizer, reductant, or PPG residue.

The NAP ester iodide salts used in this study were prepared using previously reported procedures.[32] The corresponding carboxylic acid is coupled with 4-picolylalcohol using *N*-*N*′-dicyclohexylcarbodiimide (DCC) and then alkylated using CH_3I. In the earlier studies these iodide salts were subjected to a metathesis reaction designed to replace the iodide counterion with a tetrafluoroborate. In the current study this step is not necessary.

The photochemical and spectroscopic investigations described below were designed to test the mechanistic proposal outlined in Scheme 1. Related pyridinium iodides have been shown to exhibit a solvent-dependent charge-transfer absorption band in the visible region of the spectrum.[41] This is associated with promoting an electron from the iodide to the

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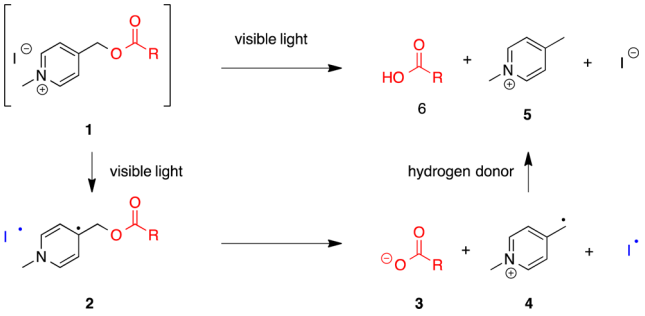
Scheme 1. Predicted Mechanism of NAP–Iodide Ester Charge Transfer Excitation



pyridium ion in the contact ion pair. Such an excitation in the NAP ester iodides should generate the same pyridyl radical that is formed from quenching excited state electron donors such as BODIPY or arylamines.[32,42] As such, the resulting pyridyl radical is expected to fragment generating a carboxylate ion, along with the picolyl radical cation **4**. The latter is of course reactive, and previous work has shown that trapping this intermediate with a good hydrogen atom donor is necessary in order to obtain high yields of the targeted carboxylate anions.

To determine if intimate ion pairs possessing a visible charge transfer band would form, the UV–visible spectra of various pyridinium ions were determined in the presence of varying concentrations of iodide. An example of these experiments is illustrated in Figure 1. In this case, 0 to 458 mM nBu_4N^+ I^- was

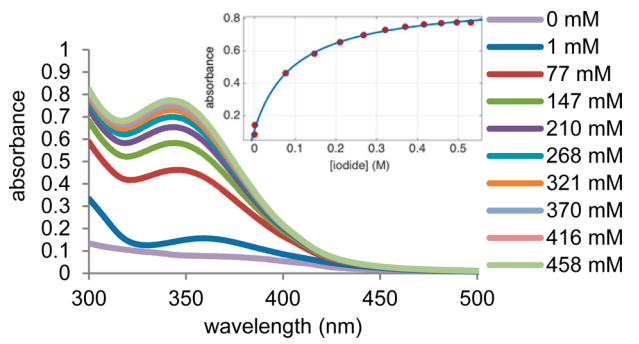


Figure 1. Addition of nBu_4N^+ I^- to 1.0 mM **1a** to form a charge-transfer complex. Inset: Increase in charge-transfer absorbance at 345 nm indicates an asymptotic binding curve. Calculated K_a of NAP–I complex formation is 11 M^{-1}.

added to a 1.0 mM solution of NAP ester **1a** in CH_3CN. Increasing $[I^-]$ results in the growth of a new absorption band at 340 nm that does not appear in the UV–vis spectrum of the corresponding perchlorate salt. This absorption band exhibits a bathochromic shift in increasingly nonpolar solvents (NAP ester **1e** λ_{max} in H_2O: 331 nm, MeOH: 357 nm, MeCN: 360 nm, $CHCl_3$: 363 nm). This behavior is consistent with expected formation of a charge-transfer or Mulliken complex.[43,44] The absorbance at each concentration was modeled using eq 1. The absorbance of the charge-transfer complex, A_{CTC}, can be related to the binding constant, K_a, molar attenuation coefficient, ε_{CTC}, path length, b, the overall concentration of the iodide anion, $[I]$, and the concentration of NAP ester, $[NAP_{total}]$. The results of this analysis, which provide an association constant of 11 M^{-1}, are illustrated in the inset of Figure 1.

$$A_{CTC} = \frac{K_a[I][NAP_{total}]\varepsilon_{CTC}b}{1 + K_a[I]} \quad (1)$$

As seen in Figure 1, the charge transfer complexes formed in CH_3CN have a tail absorption that extends into the low wavelength part of the visible spectrum (>420 nm), implying that the charge transfer reactions described in Scheme 1 could be initiated using inexpensive visible light sources. To test this, a 1.3 mM solution of **1a** in 2.5 mL of $CH_3CN/CHCl_3$ was irradiated using an 18 W household LED lamp. Detection of phenylacetic acid by HPLC determined that production of the acid is rapid over the first 10 min and then slowly increases over the remaining hour with an apparent limit of 50% under these conditions (Figure S-3). The production of acid in this experiment confirms the general predictions of Scheme 1, namely that photolysis into the charge transfer absorption band initiates an electron transfer reaction from I^- to the NAP ester leading to release of the corresponding carboxylic acid. However, from a practical standpoint, yields of the latter are not satisfactory.

The low yields can be attributed to two related effects. First, C–O heterolysis of pyridyl radical **2** generates both the desired carboxylate anion and radical cation **4**, a highly reactive species which, in the absence of efficient radical trapping pathways, can initiate unintended radical reactions, and could degrade the desired product. Similarly, the initial electron transfer generates atomic I. While this species is expected to be less reactive than radical cation **4**, it is known to generate I_3^- (through combination with an additional atomic I and any added I^-). The latter has a strong absorption band in the near-UV region of the spectrum and, thus, could serve as an inner filter, occluding light from the NAP ester iodide. Figure 2 shows

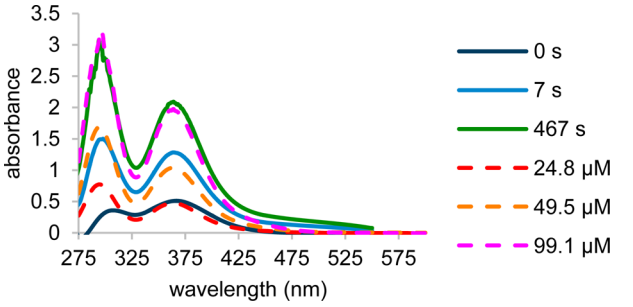


Figure 2. Spectra of various triiodide concentrations (dashed, legend is $[I_3^-]$) overlaid with UV–vis spectra of photolysis spectrum (solid).

UV–vis spectra resulting from the photolysis of the $CH_3CN/CHCl_3$ solutions of **1a** along with spectra measured from preparing varying concentrations of I_3^- in the same solvent. As is apparent from these data, the absorption of I_3^- dominates the spectrum after relatively short photolysis times (in fact these solutions visually develop a strong orange-red color as the photolysis proceeds).

The formation of I_3^-, while consistent with the proposed mechanism, is an impediment to practical implementations of these reactions in situations where recovery of the released acid is desired. Adding reductants, such as ascorbate or starch, directly to the photolysis solution could suppress I_3^- formation, but at the expense of further complicating any subsequent purification procedures. Therefore, we sought methods of directly segregating reductants and byproducts from the reactants and products.

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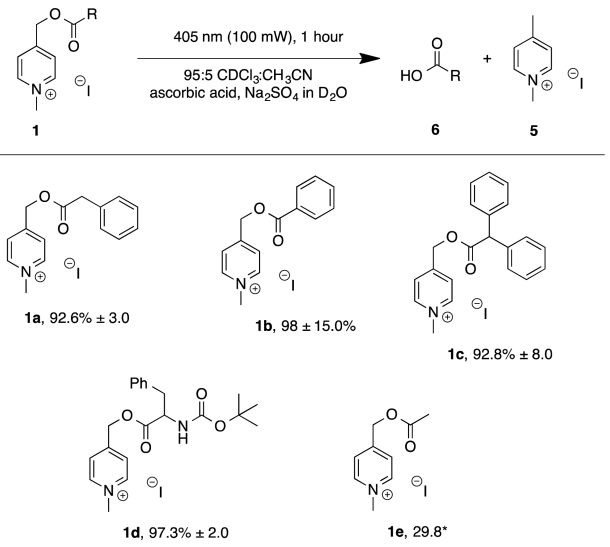
Although the NAP-pyridinium iodide salts are charged, they are, in most cases, sufficiently hydrophobic to partition selectively into organic solvents ($CHCl_3/CH_3CN$). Likewise the PPG residue, 1,4-dimethylpyridinium ion **5**, and the oxidized donor, I_3^-, are highly soluble in H_2O. Therefore, it was reasoned that carrying out the photolysis under biphasic solvent conditions would allow use of a sacrificial reductant (in the aqueous phase) and provide for rapid segregation of the byproducts from the product.

This scheme was realized using an immiscible mixture of water and $CHCl_3/CH_3CN$ (95/5 v/v). Under these conditions the protected molecules **1a**−**1e** selectively partition into the organic phase. Photolysis of a rapidly stirred mixture containing ascorbic acid, Na_2SO_4, and **1a** in the organic phase (using a 100 mW 405 nm diode laser for 1 h or the broad-band output of a household LED lamp for 8 h) produced nearly quantitative yields of the acid in the organic layer (e.g., 92.6% of **6a** using 405 nm diode laser, and deuterated solvents to facilitate NMR analysis) with no side products or byproducts detectable by ^{1}H NMR analysis in the organic layer.

Scheme 2 shows yields for photorelease of several other carboxylic acids determined in a similar manner. Aside from the acetate derivative, **1e**, the yields are close to quantitative. In the case of **1e**, the acetic acid product is sufficiently soluble in the aqueous phase that efficient segregation is not achieved and only a 29.8% yield is detected in the organic layer. This example illustrates a limitation to the biphasic photolysis procedure. Carboxylic acids possessing a high aqueous solubility in their protonated form are unlikely to be recovered in satisfactory yields.

Scheme 2. Visible Light, Biphasic Photolysis of NAP-Esters



To determine the effect of the various additives, ester **1a** was photolyzed for 30 min using each of the conditions shown in Figure 3 and the amounts of phenylacetic acid and unconverted ester in the organic phase were determined by ^{1}H NMR using an internal standard. These photolyses were carried out to incomplete conversions of **1a** (ca. 50% under standard conditions) so that modest differences in rates or yields would be more apparent. In all cases, ^{1}H NMR could detect only **1a** and phenylacetic acid in the organic phase. Reducing the concentration of Na_2SO_4 in the aqueous layer shows a negligible effect on the yield of product. However, the mass

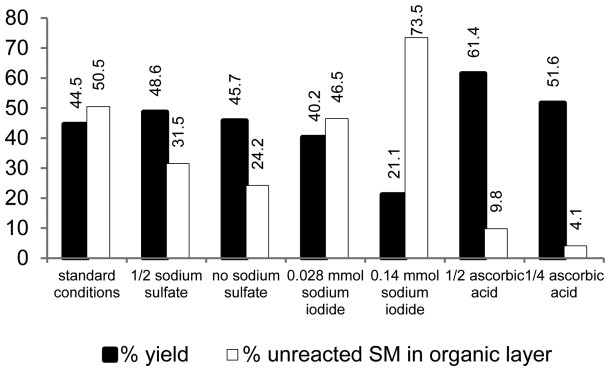


Figure 3. Low conversion biphasic photolyses for **1a**. Standard conditions refer to a 30 min photolysis by 405 nm laser where 28 μmol of NAP ester is solubilized in 1.5 mL of $CDCl_3/CD_3CN$ (95/5 v/v) and 250 μL of D_2O (with 249 μmol of Na_2SO_4 and 217 μmol of ascorbic acid). Other conditions are modifications only of the indicated chemical.

balances in the organic layer were reduced from 95% to 70%. This can be attributed to increased migration of ester **1a** into the aqueous layer when this salting out additive is omitted. Indeed, ^{1}H NMR analysis of the aqueous phase from these experiments showed that significant amounts of **1a** had partitioned into the aqueous phase. Once in the aqueous phase, photolysis is inhibited because this polar medium prevents formation of the contact ion pairs required for formation of the charge transfer complex.

Decreasing ascorbic acid concentration slightly improves the apparent rate at which the deprotection occurs, at the expense of a lower mass balance. Apparently ascorbic acid has a similar effect to that of Na_2SO_4 in that it inhibits ester partitioning into the aqueous phase. While NaI has no discernible effect on the mass balance, and presumably the partitioning ratio for the ester, at very high concentrations (>100 mM in the aqueous) it does appear to inhibit photolysis. This can be attributed to an indirect inhibition of the reduction of I_2 by ascorbic acid. The anion I^- with I_2 is in equilibrium with I_3^-. Increasing concentrations of I^- reduces the effective concentration of I_2, thus reducing the rate of reduction of the latter by ascorbate.

Finally, in order to assess the utility of these reactions for preparative scale ester deprotection, photolysis for 24 h using the 18 W household LED lamp was carried out on a 0.500 g sample of **1a** using the standard biphasic reaction conditions. On this scale 0.140 g (76%) was isolated from the photolysis mixture by separating the organic layer, removing the solvent and recrystallization from petroleum ether.

In conclusion, photolysis of NAP esters by charge-transfer excitation is a facile method for catalyst-free carboxylic acid deprotection triggered by visible light. Photolysis and purification procedures allow this reaction to be performed outside of photochemical laboratories. Protection of carboxylic acids is achieved simply in a two-step process, and deprotection is performed with room light and widely available chemicals and solvents. Under the conditions above, photolysis of many NAP esters could produce high yields. For individual cases, these conditions can be optimized to achieve a near-quantitative release. The byproducts of this reaction appear to be generally nontoxic (**5** is found in ranges of 5 to 25 mg/kg in coffee extract) and nonreactive, a crucial component for protecting groups to be used in biological systems.[45,46] These characteristics suggest the provided method may be of use for

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synthetic chemistry, biochemistry studies, and drug release applications.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedure, additional release studies, characterization data, and NMR spectra for all new compounds The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01490.

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Notes

The authors declare no competing financial interest.

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