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Photorelease of Primary Aliphatic and Aromatic Amines by Visible-Light-Induced Electron Transfer

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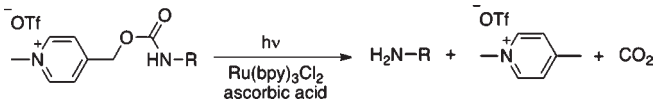
ABSTRACT



Visible-light-absorbing tris(bipyridyl)ruthenium(II) has been used to mediate electron transfer to *N*-methylpicolinium carbamates that undergo C–O bond fragmentation followed by spontaneous carbon dioxide release to give free amines. Release of several aliphatic and aromatic primary amines has been demonstrated under mild conditions using visible light.

Protecting groups (PGs) that are attached to substrates quickly and with readily separated byproducts in addition to clean removal under mild conditions and in high yields are in ever-increasing demand for a variety of applications. The use of photoremovable protecting groups (PRPGs) has attracted much attention as its release step is triggered by exposure to light, rather than a chemical reagent, which allows deprotection in the presence of other protecting groups insensitive to light.[1] Examples of such PRPGs include *o*-nitrobenzyl ethers and esters,[2] phenacyl esters,[3] 3,5-dimethoxybenzoin,[4] and coumarin[5] derivatives. However, some limitations of these groups are that ultraviolet (UV) and near-UV light is required for deprotection, which can cause further photochemical side reactions in the system (especially in the case of using high energy UV light). Some advances have been made in modifying PRPGs to red-shift their absorption profiles; however, this can come at the cost of altering efficiencies and rates of the release reactions.[6]

Recently, Falvey and co-workers have introduced a class of PRPGs that relies on photoinduced electron transfer (PET) to drive deprotection of *N*-alkylpicolinium (NAP) protected carboxylic acids and other substrates with the appropriate choice of a photosensitizer.[7] The NAP group

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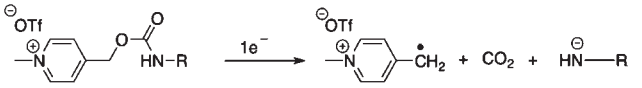
can undergo a one-electron reduction through PET from a photoexcited donor. While the NAP group can be removed in many of these systems using high wavelength UV light, recent results have demonstrated that judicious selection of the photosensitizer allows PET deprotection using visible light (> 400 nm).[7e,f]

Our group has recently applied this approach for the generation of fatty acid molecules leading to spontaneous vesicle formation, which is a process driven only by an external energy source (visible light).[8] The core of the system relies on the use of an 8-oxo-guanine modified [tris(2,2′-bipyridine)Ru(II)] photosensitizer. Interested in extending this protection chemistry toward other functional groups and for other applications, we began to explore use of the NAP group for the protection of aliphatic and aromatic primary amines. While photolabile protecting groups have been developed for amines and anilines,[9] each system displays some limitations. The *o*-nitrobenzyl group has been extensively studied for aliphatic amine protection and deprotection under UV light (254 nm).[9e−h] One limitation of this reaction is that the product amine can react with the aldehydic group of the photoproduct to form an imine, which is not entirely avoidable. One application of this system was in the successful UV-induced cross-linking of protected polymeric amines with formulations containing epoxy groups.[9h] In 1995, Pirrung and Huang extended the use of 3,5-dimethoxybenzoin photoprotecting groups for amines. Protection and deprotection proceeded in good yields; however the reaction was limited to secondary amines, as primary amines were found to undergo intramolecular cyclization leading to byproducts inert to photolysis.[9i] Arylsulfonamides have also been studied as photoremovable protecting groups for amines but suffer from poor deprotection yields.[9j] In all cases UV or near-UV light is required for the photolysis reaction.

The demand for synthesis of complex organic molecules and biomolecules containing amino functionality with increasing complexity requires the need to develop novel protecting groups that are readily cleaved under fundamentally different and mild conditions to ensure selective modifications of specific functional groups. Development of new photoremovable protecting groups that are cleaved under visible light irradiation is one avenue toward increasing viable deprotection pathways of amines under mild conditions.

Herein we report the photorelease of aliphatic and aromatic primary amines by visible-light-induced electron transfer. PET to *N*-methylpicolinium carbamates results in C−O bond fragmentation via one-electron reduction followed by spontaneous carbon dioxide (CO_2) release to give the free amines (Scheme 1). The modest reduction potential of the *N*-methylpicolinium group ($E_{red} = -1.1$ V vs SCE) ensures a thermodynamically feasible electron transfer from many excited photosensitizers. [tris(2,2′-bipyridine) ruthenium(II)] ($[Ru(bpy)_3]^{2+}$) was chosen for the photosensitizer because of its moderate reduction potentials and its absorbance across a wide range of the UV−vis spectrum. Because $[Ru(bpy)_3]^{2+}$ requires an external electron donor to proceed down the reductive quenching pathway, ascorbic acid (H_2Asc) was chosen as it is a known reductant to the Ru metal-to-ligand charge transfer (MLCT) state,[10] and it can also serve as an H-atom donor to trap the *N*-methylpicolinium (NMP) methylene radicals. To understand the thermodynamics of this catalytic reaction, the photoredox properties of $[Ru(bpy)_3]^{2+}$ must be considered and are summarized in Figure 1.[11] The cycle involves in its initial stage the absorption of light by $[Ru(bpy)_3]^{2+}$ and subsequent reductive quenching of its excited state by ascorbate ($HAsc^-$, $k_q = 2 \times 10^7$ M^{-1} s^{-1}).[12] Because the one-electron reduction potential for the $[Ru(bpy)_3]^{2+/+}$ couple is −1.3 V,[13] the $[Ru(bpy)_3]^{+}$ ion is thermodynamically capable of reducing the NMP carbamate to the corresponding NMP methylene radical with C−O bond cleavage to yield the carbamates. The NMP methylene radical will react with the ascorbate radical formed while the carbamate can undergo spontaneous CO_2 release giving the free amine upon abstraction of a proton from the solvent or ascorbic acid.

Scheme 1. Reduction of *N*-Methylpicolinium Group



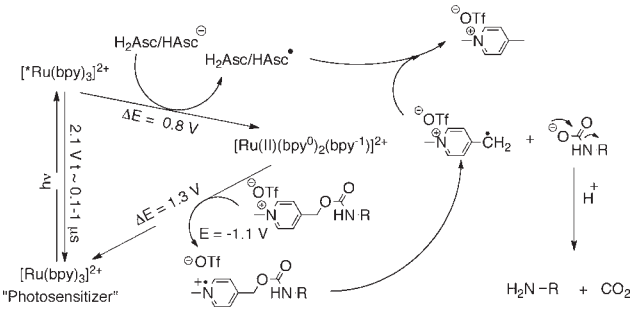


Figure 1. $[Ru(bpy)_3]^{2+}$ photochemistry with respect to ascorbate ($HAsc^-$) electron donor and *N*-methylpicolinium carbamate (NMPC). $HAsc^-$ reduces the MLCT state of Ru, and the NMPC is then reduced to NMP methylene radical.

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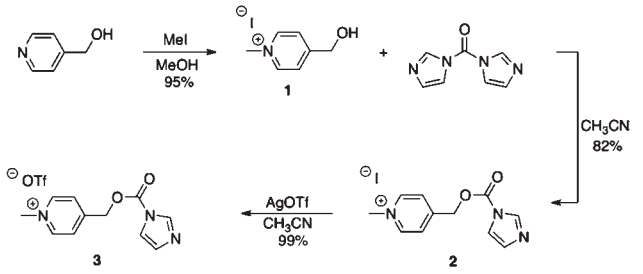
Synthesis of the *N*-methylpicolinium carbamate protecting group precursor is outlined in Scheme 2. Reaction of pyridine-4-methanol with methyliodide in methanol furnishes 4-(hydroxymethyl)-*N*-methylpyridinium iodide, **1**. Subsequent reaction with carbonyldiimidazole in acetonitrile (CH_3CN) precipitates **2** cleanly with no double addition product observed. Counterion exchange with AgOTf in CH_3CN affords **3** in quantitative yield. This three-step overall synthesis of the protecting group precursor proceeds in high yield with no purification steps required.

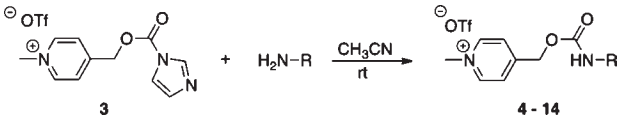
Scheme 2. Synthesis of Protecting Group Precursor

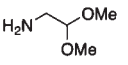
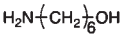
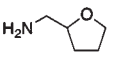
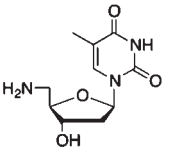
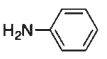
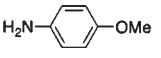
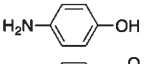
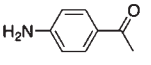
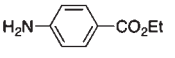
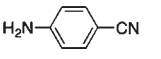


With **3** in hand, its reactivity toward a number of aliphatic and aromatic primary amines was investigated (Table 1). Reaction of **3** with a number of aliphatic amines containing various functional groups in CH_3CN at room temperature gave the *N*-methylpicolinium carbamates. Examples of functional group tolerance include allyl (**4**), aldehyde protected acetal (**5**), hydroxyl (**6**), ether (**7**), and an aminonucleoside (**8**). All the reactions proceed cleanly with purification of the products involving simple washing with tetrahydrofuran (THF) or 1,4-dioxane of the unreacted starting materials and imidazole byproduct from the reaction mixture (see Supporting Information). Of note is the selective reaction of the amine in the presence of hydroxy (**6**) and other more highly functionalized groups (**8**), which is due to the more nucleophilic nature of the primary amine. Aromatic amines containing electron-donating groups react in solution as well. Examples of these include phenyl (**9**), 4-methoxyphenyl (**10**), and 4-hydroxyphenyl (**11**) amines. Purification again involved washing with THF, though higher yields could be obtained from recrystallization (**10**, **11**). Initial attempts to react aromatic amines containing electron-withdrawing groups in CH_3CN at room temperature or reflux resulted in no product formation. However, reaction under pseudoneat conditions at 60 °C (2–3 drops of CH_3CN for the reaction scale investigated, see Supporting Information) facilitated formation of the protected aromatic amines, which could similarly be purified by washing with THF. Examples of protected aromatic amines that contain electron-withdrawing groups include 4-acetylphenyl (**12**), 4-ethylbenzoate (**13**), and 4-cyanophenyl (**14**). Aromatic amines containing *para*-nitro or carboxylic acid functionalities proved to be unreactive under all conditions investigated.

Photolysis solutions containing the protected amines (**4**–**14**, 0.05 mmol), ascorbic acid (1 equiv), and $Ru(bpy)_3Cl_2$ (10 mol %) were prepared in CD_3OD (0.7 mL). The solutions were degassed by two freeze–pump–thaw cycles with argon and irradiated with a 150 W broadband tungsten-filament lamp for a predetermined amount of time. The product mixtures were then analyzed by ^1H NMR spectroscopy to determine free amine yields. Nearly quantitative deprotection was observed in all cases after 2–4 h of irradiation (within error of

Table 1. Synthesis of Protected Amines



entry	amine	product	yield (%)[a]
1		**4**	57
2		**5**	53
3		**6**	59
4		**7**	59
5		**8**	60
6		**9**	62
7		**10**	79
8		**11**	79
9[b]		**12**	67
10[b]		**13**	55
11[b]		**14**	59

[a] Isolated yield for reactions carried out on ~1.0 mmol scale. [b] Reaction heated at 60 °C under pseudoneat conditions.

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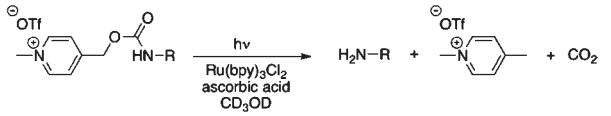
(13) Balzani, V.; Bolletta, F.; Gandolfi, M. T.; Maestri, M. *Top. Curr. Chem.* **1978**, *75*, 31.

Table 2. Photorelease of NMP Carbamates



entry[a]	*N*-methylpicolinium carbamate	irradiation time (h)[b]	amine formed (%)[c]
1	4	4	99
2	5	4	99
3	6	4	98
4	7	4	98
5	8	2	97
6	9	4	95
7	10	2	98 (82)[d]
8	11	4	94
9	12	4	93
10	13	8	96
11	14	4	99

[a] Photolysis solution was 0.7 mL of CD_3OD, (1.0:1.0:0.1) (**NMPC**/ascorbic acid/[$Ru(bpy)_3Cl_2$]). [b] 150 W broad-band tungsten filament lamp. [c] Determined by integration of the ^1H NMR spectrum. [d] Isolated yield on a preparative scale.

integration, Table 2). Control photolysis experiments that lacked either $Ru(bpy)_3Cl_2$ or ascorbic acid or both resulted in no detectable amount of released amine. To confirm the identity of the products, photolysis of **11** was carried out on a preparative scale. The product, *p*-anaside, was isolated in pure form (82% yield), and its ^1H NMR spectrum was found to be indistinguishable from an authentic sample.

In summary, we have demonstrated that the *N*-methylpicolinium PRPG is easily installed on primary aliphatic and aromatic amines. Deprotection proceeds under mild conditions using visible-light-induced electron transfer to drive the photorelease. The most attractive aspects of this system include the development of a protecting group precursor that can be used directly for protection of amines rather than multistep amine protection chemistry, synthesis of the protected amines without the use of column chromatography for purification, and the use of visible light as a mild deprotection route in the presence of multiple functional groups. Current efforts are focused on employing this protection chemistry for biological applications focusing on aminonucleoside protection, which is currently ongoing.

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Supporting Information Available. Experimental procedures, syntheses, ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.