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Photorelease of Pyridines Using the Metal-free Photoremovable Protecting Group

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Abstract: Photorelease of bioactive molecules has emerged as a valuable tool in biochemistry. Nevertheless, many important bioactive molecules, such as pyridine derivatives, cannot benefit from currently available organic photoremovable protecting groups (PPGs). We found that inefficient photorelease of pyridines is attributed to intramolecular photoinduced electron transfer (PET) from PPGs to pyridiniums. To alleviate PET, we rationally designed a strategy to drive excited state of PPG from S_1 to T_1 with heavy atom, and synthesized a new PPG by substitution of atom H at 3-position of 7-Dietheylamino-coumarin-4-methyl (**DEACM**) with Br or I. This resulted in an improved photolytic efficiency of the pyridinium with hundreds of times in water solution. The PPG can be applied to various pyridine derivatives. The successful photorelease of a microtubule inhibitor, indibulin, in living cells was demonstrated for the potential application of this strategy in biochemical research.

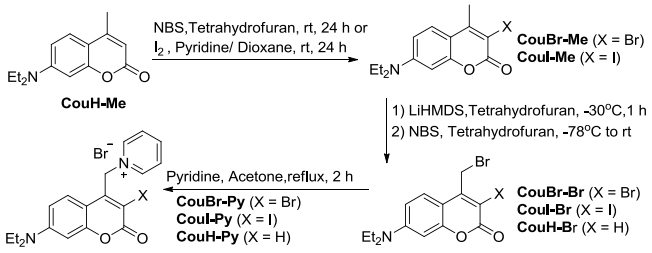
During past decades, the chemistry of PPG has been extensively applied in various fields, including synthesis,[1] material sciences,[2] superresolution imaging, [3] and especially biochemistry .[4] Specifically, when a critical functional group in the bioactive molecule is caged by PPG, it becomes biochemically inert. Upon illumination with light at a specific wavelength, the caged molecule is released, thus recovering its inherent bioactivity. In particular, this strategy can give researchers insight into the dynamics of biological events with high spatial and temporal resolution, as well as the ability in controlled chemical regulation and drug release for targeted therapy. [5]

Currently, the most common leaving groups are restricted to conjugate bases of moderate to strong acids, such as carboxylates, phenolates, phosphates, carbamates, sulfonates, thiolates, etc.[6] Consequently, molecules of interest such as pyridine derivatives without those functional groups, cannot benefit from available PPGs. As N-containing heterocyclic aromatic compounds, many pyridine derivatives emerge as bioactive molecules, and such moieties are involved in aniticancer drugs such as Nilotinib, Neratinib, Axitinib, Entinostat, etc.[7] To cage and uncage bioactive pyridines, PPGs based on Ru(II) polypyridyl complexs have been considerably investigated, and shown potential application in photodelivery and photoactivated chemotherapy.[8] Nevertheless, the possible DNA damage by Ru(II)polypyridyl complexes may limit the practical use.[9] In addition, due to steric hindrance of Ru(II) polypyridyl with coordinate bonds, it is difficult to cage 2-pyridyl compounds and drugs having complicated structures.[10] Up to now, for more promising organic PPGs, successful photorelease of pyridine compounds from corresponding pyridinium has only been reported in acetonitrile.[11] Although leaving ability of pyridine (pK_a = 5.25) is close to that of acetate (pK_a = 4.75), photorelease of pyridines using organic PPGs in water has not been achieved yet. We herein report, for the first time, a coumarin-based organic PPG for photorelease of pyridines in aqueous solution from various pyridiniums. This is realized from the investigation of intramolecular PET effect, which has been ignored in pyridinium photolysis.

Recently, photorelease of tertiary amine using a hydroxyquinoline-based PPG from corresponding quaternary alkylammonium has been reported.[12] In principle, pyridine with a lower pK_a has better leaving ability than that of triethylamine (pK_a = 10.75), however, this hydroxyquinoline-based PPG could not be applied to pyridine photorelease. In our opinion, when alkylating pyridine with the PPG, the resulting pyridinium could serve as a much stronger electron acceptor owing to the existence of π^* orbital. Unlike caged compounds with triethylamine or other common leaving group such as acetate, the pyridinium moiety has efficient intramolecular PET with the excited PPG, followed by deactivation to ground state by back electron transfer.[13] Consequently, the competition of intramolecular PET from PPGs to pyridinium moiety suppresses photolysis reaction. Therefore, we expected that PGGs with high oxidation potential and low excited energy would be required to alleviate PET for pyridinium photolysis.

Using **DEACM** as our model PPG, we tested our assumption by demonstrating its photorelease ability for pyridine. **DEACM** has a higher excited oxidation potential and lower excited energy than the reported hydroxyquinoline-based PPGs for tertiary amine,[12] thus decreasing PET with the pyridinium. It has also shown high photolytic efficiency and large uncaging cross sections with two-photon excitation for many leaving groups.[14] We synthesized **CouH-Py** by reaction of **CouH-Br** with pyridine (Scheme 1). To investigate whether competition of PET with photolysis was involved in the excited state of **CouH-Py**, the reaction was run by 405 nm irradiation in different

solvents. The results showed that the photolytic efficiency ($\varepsilon_{405}\Phi_u$) was decreased with the increase of dielectric constant of solvent (Supporting Information, Table S2). Indeed, it has been reported that photolysis reaction using 7-Dimethylamino-coumarin-4-methyl (**DMACM**) as PPG can be inhibited by its PET with maleamide. [15] Taken together, we proposed that inefficient photolysis reaction of the pyridinium can be attributed to intramolecular PET.



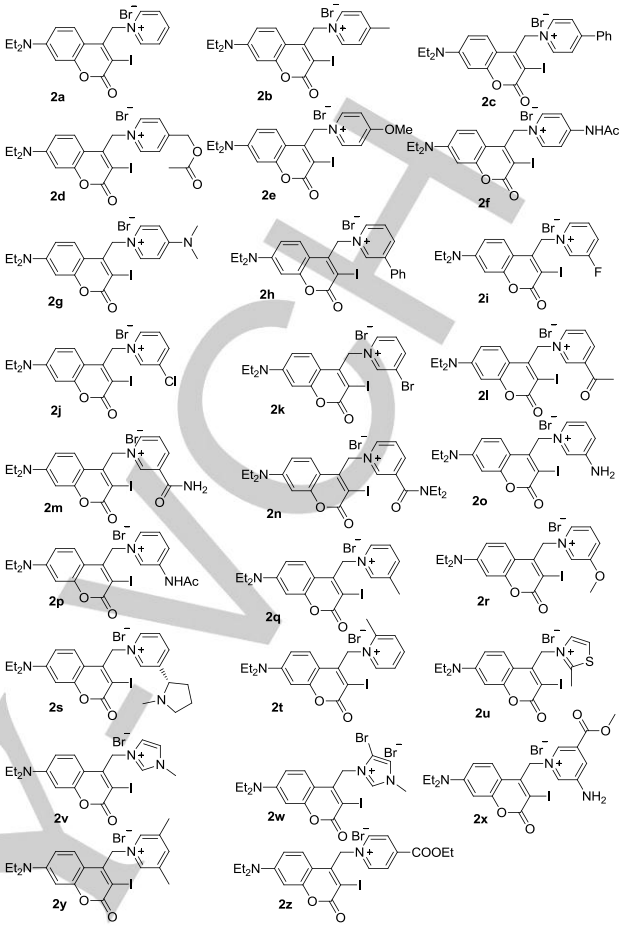
Scheme 1. Synthesis of the DEACM-based PPG and caged pyridine. NBS = N-Bromosuccinimide, rt = room temperature, LiHMDS = Bis(trimethylsilyl)amine lithium.

To further analyze PET between pyridinium and **DEACM**, the energy of PPG moiety, **CouH-Me**, in S_1 state was estimated by intersection of the normalized absorbance and emission spectra. [16] The resulting $E^{S_1}_{0,0}$ (2.89 eV) and oxidation potential (~1.3 V [17]) of **CouH-Me** gave $E^{S_1}_{Ox}$ as -1.59 V, which is much lower than the reduction potential of pyridiniums (> -1.1 V [18]), thus leading to effective electron transfer. According to the result of time-dependent density-functional theory (TD-DFT) calculation of **CouH-Me**, its energy gap between S_1 and T_1 state (ΔE_{ST}) was determined as 0.83 eV, thus, $E^{T_1}_{Ox}$ was increased up to -0.74 V. This indicated that PET between pyridinium and CouH-Me in T_1 state is much weaker compared with that in S_1 state.

Based on TD-DFT calculations and the normalized absorbance and emission spectra (Figure S1), PPG moieties, including **CouH-Me**, **CouBr-Me** and **CouI-Me**, have close energy levels of HOMO orbital (Figure S2), $E^{S_1}_{0,0}$ and ΔE_{ST} (Table S1), so they are estimated to share close $E^{T_1}_{Ox}$. If we used coumarin moiety containing heavy atom Br or I to enable intersystem crossing (ISC) of S_1 to T_1 state, more effective photolytic efficiency could be achieved.

After synthesis of **CouBr-Py**, its photolysis reaction was run in HEPES buffer, and photolytic efficiency was determined with reported procedure. [19] To our delight, $\varepsilon_{405}\Phi_u$ was increased to 135, about 400 times higher than that of **CouH-Py**. Encouraged by this result, **CouI-Py** containing I atom with a stronger ISC effect was synthesized. Excitingly, $\varepsilon\Phi405$ of **CouI-Py** was increased to 202, about 700 times higher than that of **CouH-Py**. The photolysis of **CouI-Py** was also monitored and confirmed by ^{1}H NMR (Figure S3).

With this effective PPG for pyridine in hand, various pyridine derivatives were reacted with **CouI-Br** and afforded corresponding pyridiniums (Scheme 2). Photolysis reactions of all these pyridiniums were run in HEPES buffer at 405 nm irradiation.

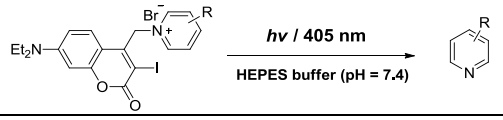


Scheme 2. Chemical structures of the caged pyridines in this work

As listed in Table 1, common substitutes, such as amide, phenyl, alkyl, ester, ketone, amine and halogen, in pyridine were well tolerated in this photolysis reaction. Like general photolysis reactions, photolytic quantum yield (Φ_u) of pyridinium was dependent on pKa of corresponding pyridine. Generally, higher pK_a of pyridine led to less $\varepsilon_{405}\Phi_u$ of corresponding pyridinium. Specifically, photolysis reaction of caged DMAP (pK_a = 9.70) **2g** could not happen, while that of caged 3-bromopyridine (pK_a = 2.84) **2k** showed Φ_u of 1.863%. In addition, Φ_u of pyridinium was also correlated with PET under the influence of electron density of pyridine moiety. Lower electron density of pyridine moiety enhanced its PET with coumarin, resulting in sluggish photolysis reaction. For example, even though 3-acetylpyridine and 3-fluoropyridine have close pK_a, Φ_u of **2l** was much less than that of **2i**. Furthermore, photolysis of corresponding pyridinium **2z** was even inhibited by enhanced PET through the electron-withdrawing ester group at 4-position of pyridine. Surprisingly, although pK_a of protoned 2-methylpyridine was 5.94, Φ_u of corresponding pyridinium (**2t**) was up to 4.546%, which could be attributed to its excellent leaving ability, that is, weak nucleophilicity owing to steric hindrance at 2-position. Besides pyridines, this photolysis reaction can also be applied to cage thiozole (**2u**) and imidazole (**2w**). Recently, caging nicotine with moiety of tertiary amine has been used to investigate membrane current in neurons.[20] In comparison with this strategy, nicotine caged with pyridine moiety (**2s**) was more advantageous as it can be photolyzed with higher $\varepsilon_{405}\Phi_u$ (391 vs 128) by the light

with longer wavelength. For all the reactions in Table 1, apart from products of corresponding pyridines, the same product derived from coumarin moiety was detected by HPLC, indicating excellent chemical selectivity for this photolysis reaction with high yield. Taking pyridinium **2h** as an example, the chemical yield of 3-phenylpyridine was measured about 90% in both HEPES buffer and MeOH (Figure S6, S7).

Table 1. Photophysical properties and photolysis results of pyridiniums in HPEPS buffer



Pyridinium	pK_a [a]	λ_{max} (nm)	$\varepsilon_{405}\Phi_u$ ($mol^{-1}dm^3cm^{-1}$)	ε_{405}	Φ_u (%)
2a	5.14	441	202	15957	1.266
2b	6.02	438	101	16663	0.606
2c	5.45	438	52	13768	0.378
2d	-[b]	439	215	15709	1.369
2e	6.62	436	63	18458	0.341
2f	5.87	437	87	14670	0.593
2g	9.70	432	-	18848	-
2h	4.85	440	353	13556	2.630
2i	3.10	441	338	16289	2.070
2j	2.84	441	281	16590	1.694
2k	2.84	441	276	14818	1.863
2l	3.25	441	47	13544	0.347
2m	3.40	440	56	13647	0.410
2n	3.46	440	324	17636	1.837
2o	5.80	437	65	16324	0.398
2p	4.46	440	376	16184	2.323
2q	5.68	440	125	18124	0.690
2r	4.88	439	388	14976	2.591
2s	3.12	439	391	13506	2.895
2t	5.94	438	749	16102	4.546
2u	3.40	436	405	17853	2.269
2v	6.95	430	-	20422	-
2w	3.70	434	51	17667	0.289
2x	-[b]	438	94	13895	0.677
2y	6.14	437	98	16831	0.582
2z	3.45	438	-[b]	14953	-

[a] pK_a of protoned pyridines, various sources from the literature. [b] pK_a is unavailable

To further verify the mechanism of our photolysis reaction, several control experiments were carried out. First, we found that $\varepsilon_{405}\Phi_u$ of representative pyridiniums were enhanced by a factor of about 1.3 after purging HEPES buffer by N_2, indicating that T_1 is involved in photolysis (Table S3).[21] Second, $\varepsilon_{405}\Phi_u$ of most of pyridiniums in MeOH were increased 1.4 to 36.6 fold over those in HEPES buffer (Table S4). This inverse solvent effect [22] on photolytic efficiency indicated that the photolysis reaction is relatively sensitive to PET, suggesting, in turn, that PPGs in triplet with lower oxidation potential could effectively improve photolytic efficiency. Third, the substitution of pyridine in the reactants by –OH or –OMe was found when photolysis reaction was run in HEPES buffer or MeOH, respectively (Figure S4, S5). Taken together, results demonstrated that this photolysis reaction follows the mechanism of heterolysis contributed mainly from T_1. [23]

Among available PPGs, coumarin-based ones are promising two-photon probes for biological applications. Taking **Coul-Py** as an example, its two-photon uncaging action cross section (δ_u) at 800-900 nm was measured using that of BhOAc at 800 nm as the reference.[24] As shown in Figure 2, the maximum value of δ_u (0.51 GM) was obtained at 880 nm, which was close to that of the most promising two-photo PPG, DEAC450-Glu (δ_u = 0.50 GM at 900 nm). [14d] Therefore, this coumarin-based PPG has potential to serve as a valuable tool for two-photon activation.

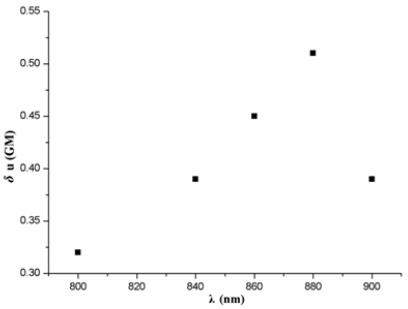


Figure 1. Two-photon uncaging action cross section (δ_u) of **Coul-Py** at 800-900 nm.

Since our photolysis reaction can be realized in water, it has an important advantage for biochemical research. We thus investigated whether our strategy could be applied to photorelease of bioactive molecules in living cells. Indibulin, a bioactive molecule containing a moiety of pyridine, is a microtubule inhibitor which prevents tubulin polymerization. [25] The photorelease of indibulin from **Coul-Indibulin** (Figure 2a) in HEPES buffer was realized under irradiation at 405 nm or 488 nm light (Figure S8 and S9). Then, photorelease of indibulin was applied to living cells. As shown in Figure 2b and 2c, for the control cells without irradiation or **Coul-Indibulin** treatment, the microtubules were clearly visible by confocal imaging. After treatment with **Coul-Indibulin** and subsequent light irradiation, most microtubule networks were disrupted (Figure 2d), a result similar to that of direct indibulin (1×10^{-5} M) administration (Figure 2e and 2f). These results confirmed the successful photorelease of indibulin from **Coul-Indibulin** in living cells. It should be noted that the disruption of microtubules shown in Figure 2d, is more dramatic than that in Figure 2f. This can be explained by the delocalized lipophilic cation in **Coul-Indibulin** which resulted in its faster uptake by cells compared to that of indibulin. [26]

In conclusion, we have, for the first time, achieved photorelease of pyridines from corresponding pyridiniums using an organic PPG in water. Investigations of various pyridiniums demonstrated that photolytic quantum yield is dependent on pK_a and electron density of pyridine moiety. Both experimental results and theoretical calculations suggested that photolysis reaction arises mainly from triplet state of the PPG. In addition, two-photon photorelease of **Coul-Py** was obtained with excellent uncaging action cross section at longer wavelength up to 900nm. Importantly, the successful release of a microtubule inhibitor, indibulin, from corresponding pyrdium with visible light in living

cells showed the promising potential of this photolysis reaction in biochemical research.

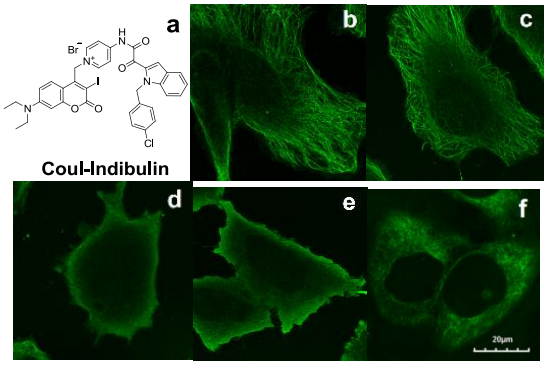


Figure 2. a) Chemical structure of **Coul-Indibulin**. b)-f) are confocal are images of microtubules in HeLa cells were treated by b) **Coul-Indibulin** (+), light (-); c) **Coul-Indibulin** (-), light (+); d) **Coul-Indibulin** (+), light (+); e) indibulin for 3 hours; f) indibulin for 40 minutes.

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Keywords: Photochemistry • Photolysis • Pyridine • Dyes/Pigments • Two-photon activation

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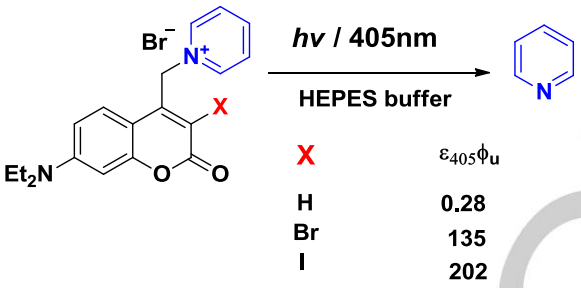

Caging and Uncaging pyridines: Photorelease of pyridines from corresponding pyridiniums in aqueous solution is difficult due to efficient photoinduced electron transfer (PET) from photoremovable protecting groups (PPGs) to pyridiniums. Driving excited state of coumarin-based PPG from S_1 to T_1 by introduction of heavy atom alleviates PET and enhances photolytic efficiency by hundreds of times.