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1-Acetylpyrene with dual functions as an environment-sensitive fluorophore and fluorescent photoremovable protecting group

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ABSTRACT

A series of new fluorescent ester conjugates of carboxylic acids including amino acids was synthesized by coupling with an environment-sensitive fluorophore 1-acetylpyrene. Interestingly, the fluorescence properties of the ester conjugates and 1-acetylpyrene were found to be highly sensitive to its surrounding environment. The results obtained from the photolysis of the ester conjugates indicated that various factors like solvent, irradiation wavelength, and the structure of the conjugates govern the rate of the photocleavage.

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1. Introduction

Photoremovable protecting groups (PRPGs) for various functional groups are of great interest since they have demonstrated potential applications in synthetic organic chemistry,[1] biochemistry,[2] and materials science.[2a,3] To date several PRPGs have been developed to mask different functional groups including carboxylic acids,[4] alcohols,[5] amines,[6] phosphates,[7] aldehydes,[8] and ketones.[8] The carboxyl group containing molecules can be effectively protected by a variety of PRPGs, such as 2-(dimethylamino)-5-nitrophenol,[9] 3-nitro-2-naphthalenemethanol,[10] α-carboxy nitrobenzyl,[11] *p*-hydroxyphenacyl,[12] α-keto amides,[13] 1-acyl-nitroindolines,[14] anthracene-9-methanol,[15] and derivatives of quinoline[16] as well as coumarin.[17]

Among the aforementioned PRPGs some groups are fluorescent and have greater advantage over non-fluorescent protecting groups since they not only release molecules of interest at desired location for a specific period of time, but also allow us to visualize, quantify and follow the spatial distribution, localization, and depletion of the released molecules.[18] The above strategy of using fluorescent PRPGs has been successfully employed for temporal and spatially controlled delivery of bioactive molecules in the study of numerous processes in biological[19] and medical research field.[20] In particular, labeling of amino acids by fluorescent PRPGs have offered great benefits. Firstly, it allows detection of small aliphatic amino acids with neither fluorescent nor strong absorption in the UV/vis region by a far more sensitive technique than common UV absorption.[21] Secondly, it helps us to visualize the amino acids involved in biological process.[22] Finally, since the amino acids are tagged by fluorescent PRPG, they can be released for a specific period of time at a desired location. For example, release of neuroactive amino acids (e.g., γ-aminobutyric acid, glycine, glutamic acid, etc.) by using fluorescent PRPG in the treatment of neuropsychiatric diseases has been reported.[23]

Although fluorescent PRPGs are of great utility, only limited number of PRPG of above class have been reported. In recent years PRPGs of polycyclic aromatic compounds namely anthraquinone,[24] pyrene,[24,25] phenanthrene,[24] anthracene,[15] and coumarins[18a,b] moieties have been targeted as fluorescent photolabile protecting groups. Among them use of pyren-1-yl methyl as fluorescent photolabile protecting group for alcohols,[24] carboxylic acids,[26] phosphates,[27] and amines[28] has been demonstrated. Although, pyrene is a well known fluorophore, to the best of our knowledge, pyren-1-yl methyl is the only fluorescent PRPG derived from the pyrene skeleton. Hence a search of another set of pyrene derivatives with improved photophysical and photochemical properties led us to investigate, 1-acylpyrenes.

1-Acylpyrenes are used as photoprobes[29,30] since their fluorescence properties are highly sensitive to medium polarity and the hydrogen bonding of the microenvironment. For example, 1-heptanoylpyrene[29] exhibits very low fluorescence in non-polar solvents like hexane or diethyl ether. But as we move to polar solvents like methanol and acetonitrile the fluorescence efficiency of 1-heptanoylpyrene increases and becomes almost identical to

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1-heptylpyrene and also the fluorescence emission band shifts from violet to blue. More interestingly, 1-heptanoylpyrene showed further increase in the fluorescence efficiency and red shift of the fluorescence emission band in binary aqueous mixtures of acetonitrile and methanol. The above fluorescence behavior of 1-heptanoylpyrene is due to their close lying ($\pi-\pi^*$) and ($n-\pi^*$) singlet excited states. Similar fluorescence trends were also observed in 1-octanoylpyrene[30] and pyrene-1-carbaldehyde.[31] Considering 1-acylpyrenes' high fluorescence efficiency, environment-sensitive emission properties and absorption maximum greater than 350 nm prompted us to develop one of its derivatives to act both as an environment-sensitive fluorophore and as a fluorescent PRPG.

In this paper we report a novel environment-sensitive fluorophore namely 1-acetylpyrene (**1**) as a photocage for carboxylic acids and amino acids. The synthesis and the characterization of 1-acetylpyrenyl ester conjugates were discussed. The absorption and emission properties of 1-acetylpyrene and its ester conjugates were also measured. The photorelease ability of 1-acetylpyrene was studied by irradiating the ester conjugates at different UV wavelengths (254, 350, and 410 nm). Further the effect of solvent on the rate of photorelease was also investigated.

2. Results and discussion

2.1. Synthesis of ester conjugates (4a–n)

A series of carboxylic acids including amino acids were protected by 1-(Bromoacetyl) pyrene (**2**) in the form of esters (**4a**–**n**) as outlined in Scheme 1. 1-(Bromoacetyl) pyrene (**2**) was readily prepared from the commercially available 1-acetylpyrene (**1**) by reaction with cupric bromide. Protection of carboxylic acids (**3a**–**g**) was straightforward. Treatment of carboxylic acids with 1 equiv of **2** in the presence of K_2CO_3/KI in dry *N*,*N*-Dimethylformamide (DMF) at 50 °C for a period of 8–12 h afforded the corresponding esters in good to excellent yield (Table 1, entries **4a**–**g**). However, for protecting amino acids (**3h**–**n**) we followed slightly different protocol. Boc-protected amino acids were treated with **2** using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst at 0 °C in 1,4-dioxan, which provided high yield of protection (Table 1, entries **4h**–**n**).

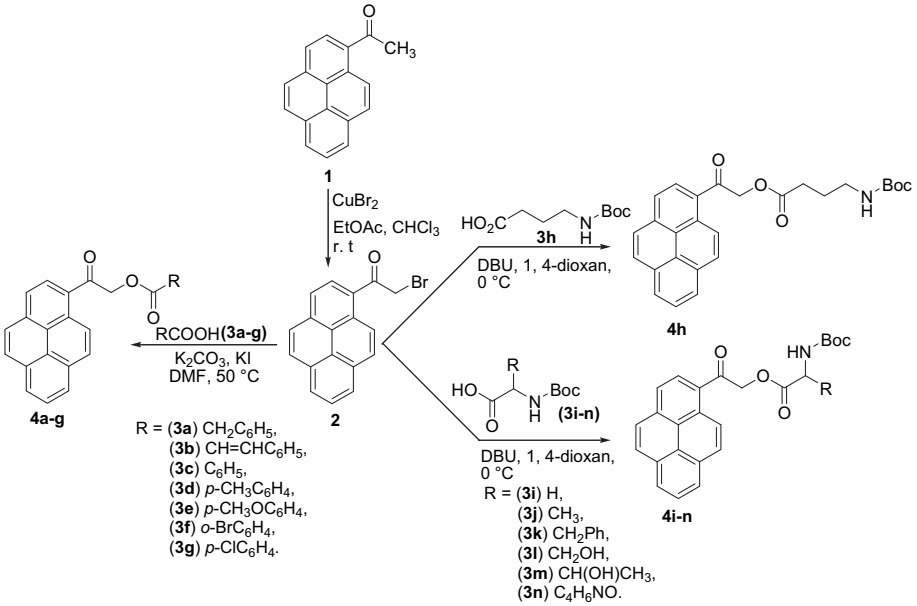
All ester conjugates were characterized by IR, ^{1}H, ^{13}C NMR, and mass spectral analysis. The IR spectra of conjugates **4a**–**n** showed a band at around 1730 cm^{-1} due to the stretching vibration of the newly formed ester carbonyl group. In addition the spectra also showed the carbonyl band of the 1-acetylpyrene protecting group in the range of 1650–1700 cm^{-1}. The confirmation of the presence of the newly formed ester group was further supported by ^{13}C NMR spectra, which showed the ester carbonyl at δ 171 ppm in addition to carbonyl signal of the 1-acetylpyrene at δ 196 ppm.

2.2. Photophyiscal properties of ester conjugates (4a–n)

The photophysical properties of all the ester conjugates and its fluorophore 1-acetylpyrene were investigated. The UV/vis absorption and emission spectra of degassed 2×10^{-6} M solution of esters (**4a**–**n**) and 1-acetylpyrene (**1**) in absolute ethanol (EtOH) were recorded. The absorption and emission maxima, molar absorptivities, and fluorescence quantum yield of the above esters along with 1-acetylpyrene (**1**) are summarized in Table 1. Fluorescence quantum yields were calculated using anthracene as standard (Φ=0.27 in ethanol).[32]

Fig. 1a shows the normalized absorption and the emission spectra of GABA conjugate **4h** in ethanol. The absorption spectrum of **4h** shows an intense band centered at 354 nm with ε 20.7×10^3 mol^{-1} L cm^{-1} while in the emission spectrum the emission maxima was red shifted to about 440 nm. We observed similar absorption and emission maxima for all the other ester conjugates (Table 1), which clearly suggest that 1-acetylpyrene moiety only dictates the position of the absorption and emission maxima ruling out the influence of its counterpart carboxylic acids. The Stokes' shift has been calculated from the difference in the absorption and the emission maxima and the magnitude of the Stokes' shift of all the conjugates varies between 86 and 98 nm. Further the conjugated esters also showed moderate fluorescence quantum yield ($0.028<\Phi<0.056$).

*2.2.1. Fluorescence spectra of ester conjugate (**4h**) in neat solvents.* The GABA ester conjugate **4h** (2×10^{-6} M) was excited at 356 nm and the emission spectra were recorded in various solvents. Fig. 1b indicates the fluorescence of conjugate **4h** is due to the monomeric excited singlet state and displays strong solvent dependence like other 1-acyl derivatives of pyrene.[30,31] The fluorescence solvatochromism of the conjugate **4h** is due to their closely lying $^1\pi-\pi^*$ and $^1n-\pi^*$ single states. In non-polar solvent (e.g.,



Scheme 1. Synthesis of 1-acetylpyrene-carboxylic acid ester conjugates.

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