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Oxazole light triggered protecting groups: synthesis and photolysis of fused heteroaromatic conjugates

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ABSTRACT

Fused oxazole derivatives were synthesized and evaluated as new light triggered protecting groups by using amino acids as model bifunctional molecules. The photosensitivity of ester conjugates was tested under irradiation at 254, 300, and 350 nm. Oxazole conjugates were readily photolyzed with complete release of the amino acid, the best results obtained for naphtho[2,3-*d*]oxazole at 254 and 300 nm, being the first reported application of this type of heterocycles as photocleavable protecting groups for carboxylic acids.

1. Introduction

The need for protecting groups represents a deviation from the concept of an ideal organic synthesis, which should be as fast and efficient as possible from readily available reagents in a simple, safe, and environmentally friendly process. Although very interesting examples of protecting group-free syntheses have been accomplished in recent years,[1] most of the synthetic work is still performed by using classical protecting group chemistry, with its inherent drawbacks. To overcome these limitations, several strategies have been proposed from which light activated protecting groups stand out as an attractive option as no additional reagents are required for deprotection. This feature is appealing in solution and solid phase organic synthesis for the masking of aldehydes and ketones,[2] carboxylic acids,[3] alcohols,[4] thiols,[5] and amines,[6] and especially in biomedical research for the caging of biomolecules.[7–10] There are also reports for the application of photolabile groups and linkers in nanotechnology and materials sciences.[11–15] Numerous types of structures have been proposed with particular emphasis on aromatics, such as 2-nitrobenzyl,[16] benzoin,[17] phenacyl,[18] cinnamyl,[19] 3-nitro-2-naphthalenemethanol,[20] anthracene-9-methanol,[21] phenanthren-9-ylmethoxycarbonyl,[22] anthraquinon-2-ylmethoxycarbonyl,[22] 2-(1′-hydroxyethyl)-anthraquinon,[23] anthraquinon-2-ylethyl-1′,2′-diol,[24] pyren-1-ylmethyl,[25] pyren-1-ylmethoxycarbonyl,[22] and heteroaromatics like acylnitroindolines,[26] xanthones,[6] coumarins (trivial designation for 2-oxo-2*H*-benzopyrans),[27] benzocoumarins,[28] quinolines,[29] and quinolones.[30] Attempts to improve and tune the photolability of the above mentioned groups have been achieved through synthetic tailoring in terms of substituents present in the structure. Recent research by the authors has been focused on the synthesis and application of novel oxygen and nitrogen heterocycles as photolabile protecting groups for the carboxylic and amine functions of amino acids, as well as neurotransmitters.[28,30–34] Bearing these facts in mind, the present work intends to evaluate the use of oxazole as the basis for a novel and alternative protecting group for carboxylic acids, a type of heterocycle, which has never been reported for photriggering applications, to the best of our knowledge. It is now presented the synthesis of novel ester conjugates based on benzo[*d*]oxazole, naphtho[2,3-*d*]oxazole, and oxobenzopyrano[6,7-*d*]oxazole, the latter having the linkage between the heterocycle and the bifunctional model molecule through the oxazole or the oxopyran moieties. The stability of the ester bond to irradiation was evaluated in a photochemical reactor at 254, 300, and 350 nm and photocleavage kinetic data was obtained.

2. Results and discussion

The synthesis of bromomethylated benzo[*d*]oxazole (Box-Br) **1** and naphtho[2,3-*d*]oxazole (Nox-Br) **2** was achieved by condensation reaction between 2-aminophenol and 3-aminonaphthalen-2-ol, respectively, and bromoacetic acid, mediated by polyphosphoric acid (PPA). 4-Aminobenzene-1,3-diol was reacted with ethyl acetoacetate or ethyl 4-chloroacetoacetate through a Pechmann reaction, catalyzed by sulfuric acid at room temperature, yielding the

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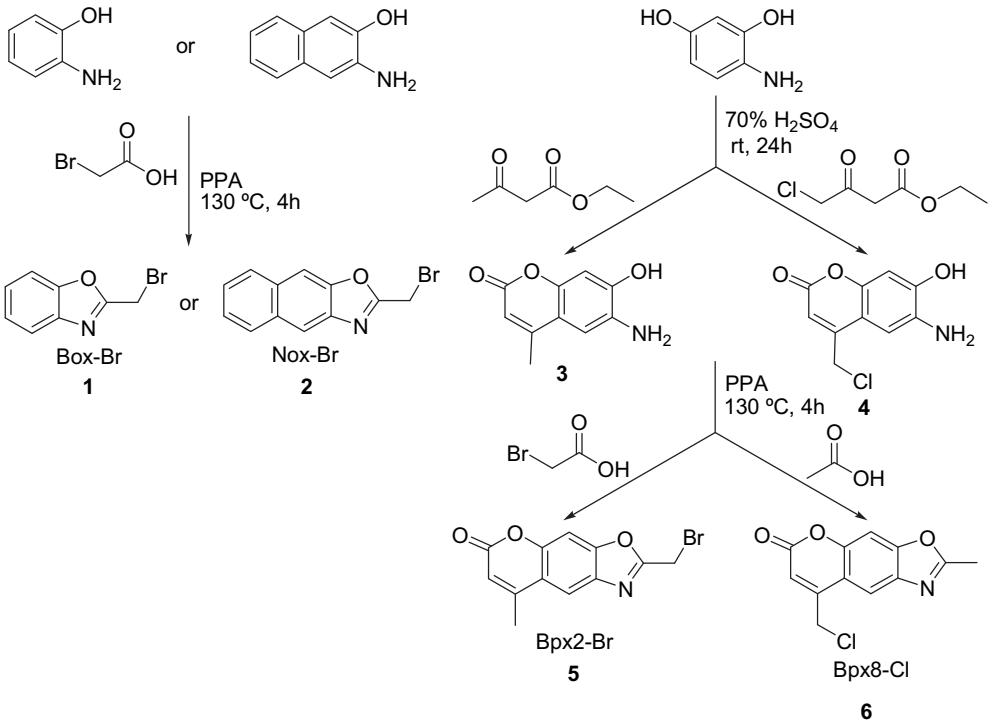
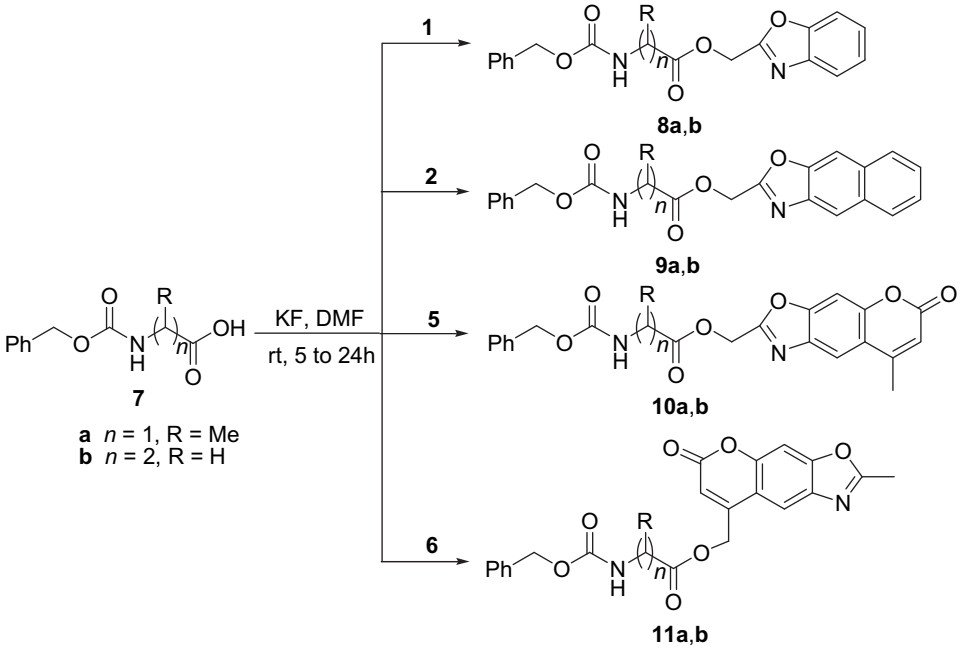
corresponding 6-amino-7-hydroxy-4-methyl-2-oxo-2*H*-benzopyran **3** and 6-amino-4-(chloromethyl)-7-hydroxy-2-oxo-2*H*-benzopyran **4**. Cyclization of compounds **3** and **4** with bromoacetic acid or acetic acid afforded the fused oxazole derivatives 2-(bromomethyl)-8-methyl-6-oxo-6*H*-benzopyrano[6,7-*d*]oxazole (Bpx2-Br) **5** and 8-(chloromethyl)-2-methyl-6-oxo-6*H*-benzopyrano[6,7-*d*]oxazole (Bpx8-Cl) **6** (Scheme 1).

The latter compounds were linked to the model bifunctional moieties either through the oxazole or the oxopyran, allowing the evaluation of the influence of the adjacent heterocycle in the photocleavage process. Compounds **1**, **2**, **5**, and **6**, bearing a reactive halomethyl group, were used in the derivatization at the C-terminus of *N*-benzyloxycarbonyl-protected alanine (**7a**) and β-alanine (**7b**) in the presence of potassium fluoride in DMF, at room temperature,[35] resulting in the model ester conjugates **8**–**11** (Scheme 2). All compounds synthesized were fully characterized by high resolution mass spectrometry, IR, ^{1}H, and ^{13}C NMR spectroscopy.

Considering that the present work involved the evaluation of oxazoles as new photocleavable protecting groups, UV–visible spectroscopic characterization was carried out to obtain the



Scheme 1. Synthesis of functionalized fused oxazoles **1**–**6**.



Scheme 2. Synthesis of model amino acid ester conjugates **8**–**11**.