A New Photolabile Linker for the Photoactivation of Carboxyl Groups

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Abstract: A new photolabile linker enabling nucleophilic cleavage of a carboxyl functionality upon irradiation with UV light (>290 nm) was developed. When the photocleavage is carried out in the presence of primary or secondary amines, amides are obtained in high yields and purities, while the intramolecular version of this reaction leads to heterocycles via a cyclorelease mechanism.

Key words: solid phase synthesis, photolabile linker, amides, cyclizations

The scope of combinatorial chemistry is constantly expanding by the development of new linkers1 capable of allowing for the facile adoption of new synthetic strategies on solid phase. A rich repertoire of such linkers is necessary in order to provide the practitioner with the opportunity of orthogonality often needed to achieve the desired selectivity for solid phase library construction. Photolabile linkers are particularly attractive by virtue of the green chemistry conditions associated with their cleavage, rendering them compatible with most functional groups found in biologically relevant compounds.2

In an effort to develop a photolabile linker for deployment in cyclorelease and related strategies, we considered the unique photochemical properties of the 5-bromo-7-nitroindoline (Bni) moiety 1, first introduced by Amit et al. in 19763 (Scheme 1) and subsequently employed in peptide synthesis and photorelease of carboxylic acids.4

![Scheme 1](image)

In addition to serving as a protecting group,5 the Bni group has the ability to activate the amide carbonyl group towards nucleophilic attack by hydroxy or amino compounds upon irradiation with UV light (see Scheme 1).

The proposed mechanistic rationale, depicted in Scheme 2, begins with photoexcitation of the starting bromoindoline amide 4 to a highly reactive species 5 which undergoes rapid acyl transfer from the indoline nitrogen to the adjacent nitro group oxygen 5 → 6.5,7 The resulting species 6 has two options available to it, both of which result in the species regaining aromaticity (Scheme 2). Thus, in the presence of a nucleophile (ROH or RNH2), the now activated carboxyl group may react to afford an ester or an amide 8 and indoline 7 (Path A) or it can lose a proton and provide 9 which collapses to the carboxylic acid 11 and nitroso indoline 10 (Path B). It was shown that in aqueous media pathway B predominates over nucleophilic attack, whereas in organic solvents containing traces of water (ca. 1%) pathway A dominates thereby releasing the carboxylic acid.7

Our interest in the Bni group stemmed from its ability to photochemically activate the otherwise robust amide functionality towards nucleophilic attack, and hence lead to an efficient photolabile linker. It was envisioned that such a linker would be capable of both intermolecular cleavage as well as cyclorelease via an intramolecular ring closure.

In the process of creating a solid phase version of the Bni group 1, preliminary experiments suggested that a substituent capable of deactivated the aromatic ring at
the 5-position favored the desired cleavage pathway A (see Scheme 2). Thus, synthesis of the suitable linker (Scheme 3) began with NaCNBH₃ reduction of the commercially available 5-carboxylic acid indole 13 with Cs₂CO₃, MeI to furnish ester hydrolysis and standard EDC coupling led to ester hydrolysis and standard EDC coupling

**Scheme 3** Synthesis of the new photolabile linker 20

The 5-position favored the desired cleavage pathway A (see Scheme 2). Thus, synthesis of the suitable linker (Scheme 3) began with NaCNBH₃ reduction of the commercially available 5-carboxylic acid indole 13 with Cs₂CO₃, MeI to furnish ester hydrolysis and standard EDC coupling led to ester hydrolysis and standard EDC coupling. 4. Thus, treatment of 20 with phosgene led to 21 which furnished 22 upon reaction with ethylenediamine in the presence of 4-DMAP. On the other hand, derivatization of 20 with chloroacetyl chloride allowed the loading of a number of carboxylic acids via intermediate 23. Thus, the reaction of 23 with PhCO₂H, BocNHCH₂CO₂H, BocNHCH₂CH₂(Me)₂CO₂H, BocNHCH₂CH₂MeCO₂H in the presence of Cs₂CO₃/n-Bu₄NI led to conjugates 24a, 24b, 24d, 24f and 24h, respectively. Exposure of these compounds to TFA produced the free amines 24c, 24e, 24g and 24i, respectively.

Preliminary solution phase intermolecular cleavage experiments of the nonpolymer-bound counterpart of 24a with various primary and secondary amines resulted in efficient conversion (>95%) to the desired amide product. However, when methanol was used as a nucleophile, a mixture of the carboxylic acid (Scheme 2) and the ester were obtained along with decomposition products. In light of these findings, only amines were chosen for initial solid phase photorelease studies.

Table 1 illustrates the generality and scope of the photocleavable linker with a number of primary and secondary amines (25a–g). Depending on the nucleophilicity and steric environment of the amino group, yields ranging from 67–95% and purities over 90% were observed.
Intramolecular photo-induced cycloreleases were also demonstrated with a number of resins as shown in Table 2. Especially notable are the cycloreleases of 24c and 24e (entries 2 and 3), leading to the corresponding 6-membered heterocycles in high yields and purities. In an attempt to form macrocycles by this reaction, however, we observed a significant drop in efficiency as demonstrated with entry 5, Table 2. Formation of the 7-membered heterocycle 26e proceeded only in ca. 50% yield and ca. 50% purity, the product being contaminated with the acyclic carboxylic acid (see Scheme 2).

In conclusion, we have constructed a novel polystyrene-based photolabile linker based on the Bni moiety (1) and demonstrated its utility in loading a number of building blocks for further elaboration. Photo-induced releases of a variety of compounds were also demonstrated utilizing a variety of external or internal nucleophiles (e.g. amines) to produce amides or lactams, respectively. Further explorations along these lines may lead to useful applications to organic synthesis and combinatorial chemistry.

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References and Notes


In Table 2 Intramolecular photocyclizations a

<table>
<thead>
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<th>Entry</th>
<th>Resin</th>
<th>Product</th>
<th>Yield(%) b</th>
<th>Purity(%) c</th>
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<td>X</td>
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<td>75</td>
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<tr>
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<td>MeN</td>
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<tr>
<td>5</td>
<td>24i</td>
<td>O</td>
<td>50</td>
<td>50</td>
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</table>

a Conditions: General Procedure: A suspension of 24c (30 mg, 0.013 mmol) in THF (3 mL) was irradiated with UV light (450W, Hg, 4.3" arc lamp, Ace Glass Inc.; 7830-60 power supply, Ace Glass Inc.), wave length >290 nm (lamp equipped with pyrex filter), while stirring for 6-12 h at 25 °C.

b Yields of entries 1-4 are for chromatographically and spectroscopically pure compounds.
c Purity was estimated by integration of 1H NMR signals.

*Acknowledgement*

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*References and Notes*


**Table 1** Intermolecular photocleavage with amines a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Yield(%) b</th>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td></td>
<td>25c</td>
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<tr>
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<td></td>
<td>25d</td>
<td>67</td>
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<td></td>
<td>25g</td>
<td>70</td>
<td>90</td>
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</table>

a Conditions: (a) General Procedure: To a suspension of 24a (30 mg, 0.013 mmol) in THF (3 mL) was added an amine (10 equiv or further excess if volatile) and irradiated with UV light (450W, Hg, 4.3" arc lamp, Ace Glass Inc.; 7830-60 power supply, Ace Glass Inc.), wave length >290 nm (lamp equipped with pyrex filter), while stirring for 6-12 h at 25 °C.
b Yields are for chromatographically and spectroscopically pure compounds.
c Purity was estimated by integration of 1H NMR signals.
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