A New Photolabile Linker for the Photoactivation of Carboxyl Groups

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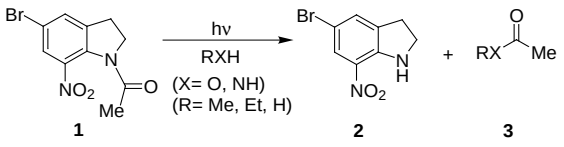
Abstract: A new photolabile linker enabling nucleophilic cleavage of a carboxyl functionality upon irradiation with UV light (>290 nm) was developed. When the photocleavage is carried out in the presence of primary or secondary amines, amides are obtained in high yields and purities, while the intramolecular 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 linkers[1] 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 1976[3] (Scheme 1) and subsequently employed in peptide synthesis and photorelease of carboxylic acids.[4]

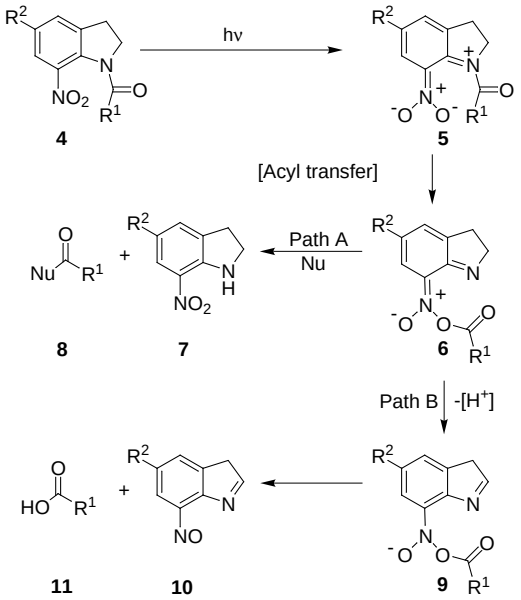


1 **2** **3**

Scheme 1 Photocleavage of the 5-bromo-7-nitroindoline (Bni) group

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).

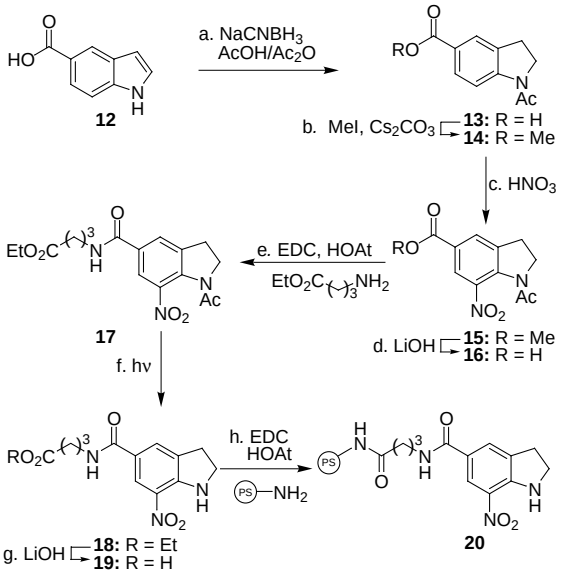
The proposed mechanistic rationale, depicted in Scheme 2, begins with photoexcitation of the starting bromoindoline amide **4** to a highly reactive species **5** which undergoes rapid acyl transfer from the indoline nitrogen to the adjacent nitro group oxygen **5** → **6**.[6,7] The resulting species **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 RNH_2), 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]



Scheme 2 Photolytic fragmentation pathways (A and B) of 1-acyl-7-indolines

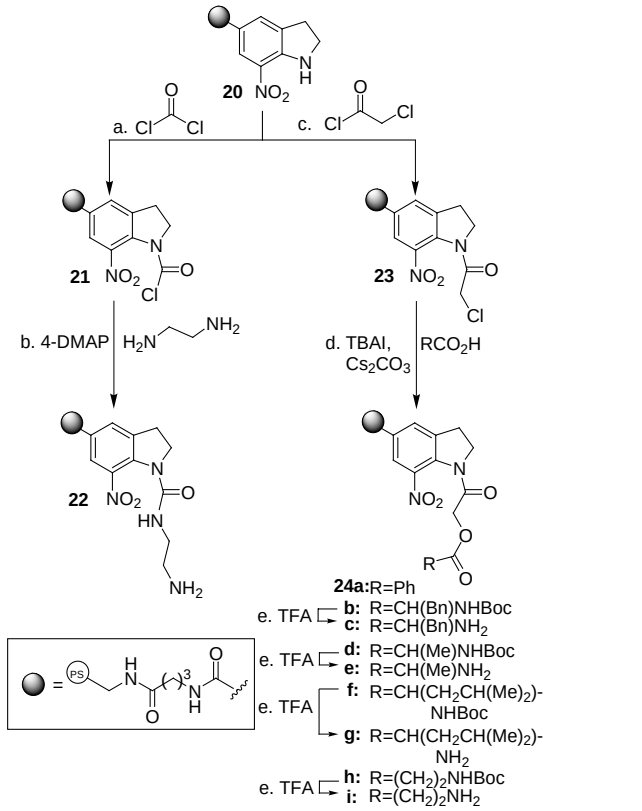
Our interest in the Bni group stemmed from its ability to photochemically activate the otherwise robust amide functionality towards nucleophilic attack, and hence lead to an efficient photolabile linker. It was envisioned that such a linker would be capable of both intermolecular cleavage as well as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



Conditions: (a) 2.0 equiv of $NaCNBH_3$, AcOH, 20 min; then HCl, Ac_2O, 23 °C, 6 h; (b) 10 equiv of MeI, 1 equiv of Cs_2CO_3, DMF, 50 °C, 3 h, 53%, 2 steps; (c) $HNO_3/C_2H_4Cl_4$ (1:2), 50 °C, 1.5 h, 80%; (d) 2.0 equiv of LiOH, THF/H_2O (1:1), 50 °C, 4 h; (e) 1.1 equiv of EDC, 1.1 equiv of HOAt, 1.1 equiv of $EtO_2C(CH_2)_3NH_3Cl$, DMF, 25 °C, 12 h, 83%, 2 steps; (f) hν (pyrex filter), CH_2Cl_2/dioxane/H_2O (2:3:0.05), 6 h, 85%; (g) 1.5 equiv of LiOH, THF/H_2O (1:1), 25 °C, 4 h; (h) 3.0 equiv of EDC, 3.0 equiv of HOAt, 1.0 equiv of aminomethylated polystyrene (0.60 mmol/g), DMF, 25 °C, 24 h, 0.43 mmol/g. Abbreviations: DMF = *N*,*N*-dimethylformamide. THF = tetrahydrofuran. EDC = 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide·HCl. HOAt = 1-hydroxy-7-azabenzotriazole.

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



Conditions: (a) 50 equiv of $COCl_2$, 25 equiv of 4-DMAP, DMF, 25 °C, 1 h; (b) 50 equiv of $NH_2CH_2CH_2NH_2$, 25 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 1 h; (c) 50 equiv of $ClCOCH_2Cl$, 25 equiv of 4-DMAP, DMF, 25 °C, 6 h; (d) 25 equiv of RCO_2H, 2.5 equiv of TBAI, 25 equiv of Cs_2CO_3, DMF, 60 °C, 12 h; (e) 25% TFA in CH_2Cl_2, 25 °C, 30 min. Abbreviations: PS = polystyrene. 4-DMAP = 4-(dimethylamino)pyridine. DMF = *N*,*N*-dimethyl formamide. TBAI = tetra-*n*-butylammonium iodide. TFA = trifluoroacetic acid.

Scheme 4 Solid phase synthesis of resin conjugates

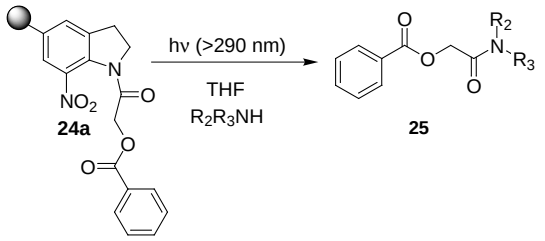
the 5-position favored the desired cleavage pathway A (see Scheme 2). Thus, synthesis of the suitable linker (Scheme 3) began with $NaCNBH_3$ reduction of the commercially available 5-carboxylic acid indole **12**, followed by methylation of the resulting carboxylic acid **13** with Cs_2CO_3 - MeI to furnish ester **14**. Substrate-directed nitration at the 7-position with concentrated nitric acid gave the nitro indoline **15**. Insertion of a four-carbon spacer via ester hydrolysis and standard EDC coupling led to ester **17** via **16**. Photo-removal of the acyl group from **17**, followed by saponification and subsequent attachment to aminomethylated polystyrene resin (1% cross-linked, 100-200 mesh) through EDC coupling completed the synthesis of indoline **20** (via **18** and **19**), with an overall loading of 0.43 mmol/g as estimated by mass gain.

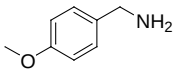
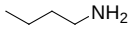
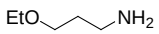
To illustrate the utility of this new resin (**20**), a number of groups capable of undergoing cyclorelease or intermolecular coupling release were loaded on as shown in Scheme 4. Thus, treatment of **20** with phosgene led to **21** which furnished **22** upon reaction with ethylenediamine in the presence 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 $PhCO_2H$, $BocNHCHBnCO_2H$, $BocNHCH(Me)CO_2H$, $BocNHCH(CH_2CH(Me)_2)CO_2H$, $BocNHCH_2CH_2CO_2H$ in the presence of Cs_2CO_3/*n*-Bu_4NI 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 (see 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.

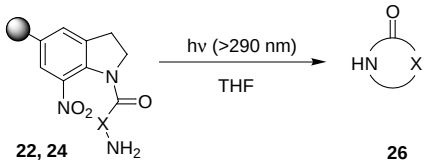
Table 1 Intermolecular photocleavage with amines[a]

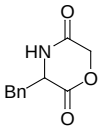
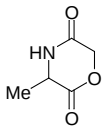
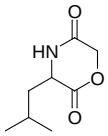
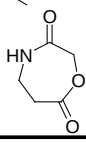


Entry	Amine	Product	Yield(%)[b]	Purity(%)[c]
1		**25a**	>95	95
2		**25b**	>95	95
3		**25c**	>95	95
4		**25d**	67	95
5		**25e**	70	95
6		**25f**	>95	95
7		**25g**	70	90

[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 ^{1}H NMR signals.

Table 2 Intramolecular photocyclizations[a]



Entry	Resin	Product	Yield(%)[b]	Purity(%)[c]
1	**22**	 **26a**	70	75
2	**24c**	 **26b**	90	95
3	**24e**	 **26c**	90	85
4	**24g**	 **26d**	70	80
5	**24i**	 **26e**	50[d]	50

[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 ^{1}H NMR signals.
[d]Yield estimated by integration of ^{1}H NMR signals.

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

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