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A triazene-based new photolabile linker in solid phase chemistry

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Abstract—An extension of the T2 linker methodology by showing its applicability as a photocleavable linker is reported. Photocleavage was carried out with 355 nm UV laser irradiation (3ω Nd-YAG) in methanol/diethyl ether and is suitable for protected amino acid derivatives, as well as simple small organic molecules including resin-bound biotin. The linker is stable under a wide range of conditions with the exception of strongly acidic media.

During the last years a wide range of new linkers, including several photolabile linkers, have been developed.[1] The most important advantage is their reagent-free cleavage, which leaves most functional and protecting groups untouched. Orthogonal towards basic, acidic, reductive and oxidative conditions, they display wide applicability.

Nevertheless, most photocleavable linkers suffer from the disadvantage of a rather complicated synthesis, involving multiple steps on the resin. Alternatively, pathways featuring the synthesis of a precursor prior to its attachment to the resin have also been reported.

Research has been conducted on triazene compounds as protecting and anchoring groups for amines. Two different linkers for solid phase organic synthesis (SPOS) have been described (T1 and T2 linker).[2,3]

We wish to give details on the photolabile properties of the T2 linker and its use for photoinduced cleavage. The known linker is easily built in three steps and can be cleaved with 10% TFA in dichloroethane. Such conditions also affect functional groups such as certain carbamates, esters and silyl ethers. The triazene moiety was found to be stable under a wide range of nonacidic reaction conditions. The photochemistry of triazenes has been thoroughly investigated during the nineteen-eighties by Majer et al.[4] and Julliard et al. independently.[5] Majer proposed an ionic mechanism for the photolysis of 1-aryl-3,3-dialkyltriazenes based on spectroscopic studies. Julliard surmised that the reaction proceeded via a radical mechanism, supported by the isolation of intermediates that could have only been generated in radical reactions. Both pathways involve an effervescence of elementary nitrogen and give rise to amines. The chromophore of triazenes, located in the near UV between 300 and 400 nm, depends on the substituents of the aromatic ring. It was therefore anticipated that the photocleavage of the triazene T2 linker is possible.

The linker was synthesised following a known protocol.[3] The Merrifield resin **1** was transformed into the aniline derivative **2** using Williamson's synthesis. It was then converted into an immobilised diazonium salt **3** and subsequently into the triazene moiety **4** by treatment with a secondary amine (Scheme 1).

The optimum conditions in terms of yields of cleavage, purity of the products and successive cleavage procedures were determined by variation of wavelengths, irradiation times, intensities and solvents. All reactions were carried out in cooled open glass vessels containing the resins in suspension.

As a source of light, a 1 kHz pulsed 3ω Nd-YAG laser (355 nm) as well as different excimer lamps (308 and

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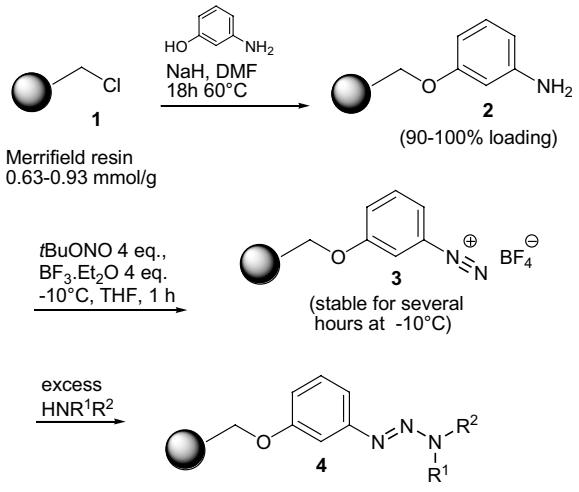
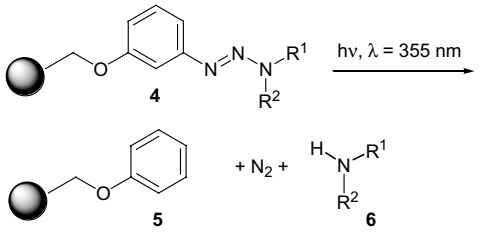


Scheme 1. Synthesis of the T2 linker.



Scheme 2. General reaction scheme for the photolytic cleavage of triazene T2 bound compounds.

222 nm) were used. These investigations on the photolysis wavelength showed that only the Nd-YAG laser at a wavelength of 355 nm was capable of breaking the nitrogen bonds without further decomposition of the products (Scheme 2).

The vertical unfocused beam was directed from above into the open vessel for irradiation times of 1–30 min. Reactions were repeated using different laser power ranging from 0.5 to 1.7 W/cm^2. Various solvents were examined under these conditions, including THF, methanol, diethyl ether and dichloromethane and mixtures thereof. Dichloromethane has the disadvantage of leading to the formation of chlorinated side products appearing upon UV irradiation. A mixture of methanol and diethyl ether turned out to be the optimum solvent.

When the cleavage is carried out with TFA rather than photolysis, reactions can only be monitored by taking out a sample from the reaction vessel and use destructive analytical methods. In terms of combinatorial chemistry this could be a laborious task. In the case of closed microreactors[6] or macrolithic resin portions like Stratosphere Plugs™ monitoring was impossible without severe altering of the reaction set-up. When photolysis is used, a small fraction of the product is cleaved, reducing slightly the resin loading. Most of the material is left unchanged on the resin, available for further reactions.

Acylated piperazines have been chosen as model compounds for cleavage studies. The immobilised piperazine moiety was further treated with different acid halides including cyclohexanoyl chloride and pivaloyl chloride, thus yielding resins **4a** and **4b** (Table 1). During the photolytic experiments the power of the laser was varied, showing that a value below 1.0 W/cm^2 did not yield an adequate amount of product within the irradiation times considered. Values above 1.4 W/cm^2 led to a significant destruction of the resin matrix and to impurities. Accordingly the power of the laser beam was found to be optimum at 1.0 W/cm^2 with a pulse of 1 kHz and a pulse length of 20–25 ns, providing the desired products **6a** and **6b** in moderate yields and high purities. The resin loading has been determined by elementary analysis of the nitrogen content. Photolysis rates and corresponding yields of a selected reaction are shown in Table 2. Reaction times were limited to 30 min for practical reasons. In the current set-up only one sample at a time could be irradiated, even small combinatorial libraries would consume too much time. The use of a beam-splitter for parallel processing is planned. The analytical data of the cleavage products were identical to those of the amides independently synthesised using standard techniques.

Table 1. Photocleavage of T2 moieties with 3ω Nd-YAG laser at 355 nm. (Solvent–purity relationship)

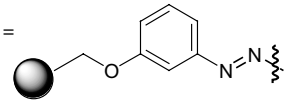
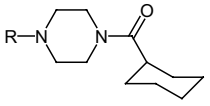
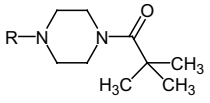
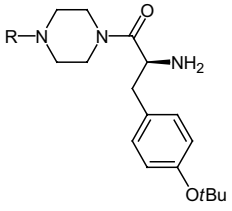
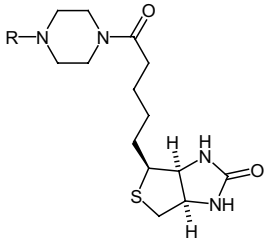
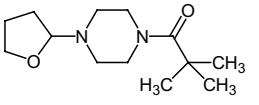
4/6	Resin **4**	Product **6**	Solvent	Purity (%)
	R = 		R = H	
a			Et_2O/MeOH	90
b			Et_2O/MeOH	77
c			Et_2O/MeOH	95
d			Et_2O/MeOH	97
e			THF	100

Table 2. Photolysis rates of the resin **4b** giving **6b**

Irradiation time (min)	Yield of **6b** (%)
10	24
20	38
30	45

Based on our experience of piperazine cleavage, amino acids were immobilised at their C-terminus. Therefore Fmoc-Tyr-(*t*-Bu)-OH was coupled onto the piperazine resin using 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP) as a coupling reagent (Table 1).[7] The photocleavage of this tyrosine derivative **4c** was compared with the classical TFA cleavage. Upon treatment with TFA, the acid-labile *tert*-butyl ether was destroyed, deprotecting the tyrosine hydroxyl moiety. Photocleavage, however, left the ether unscathed. Two peaks were visible in the GC spectrum: one of them corresponding to the Fmoc group, the other one to the Fmoc-deprotected amino acid piperazide (as determined by GC–MS). The basic moiety of the free piperazine amino group present after photolysis, cleaved the Fmoc protecting group, thus delivering the inversely protected product **6c** as obtained by acid cleavage.

As the biotin–streptavidine system is a standard biochemical couple for the investigation of enzyme–substrate interactions, biotin is an interesting substrate for solid phase chemistry. Biotin itself was nearly insoluble in the solvents usually employed with this kind of resins. The use of the biotin tetrafluorophenyl (TFP) active ester, soluble in dichloromethane, allowed successful attachment to the resin (**4d**). From this resin the N-(+)-biotinylpiperazine **6d** was cleaved using our standard photolysis methodology yielding a very pure product (97%).

Interestingly, during the studies on solvent influence, addition of THF to the cleaved amine was observed when irradiation was performed in this solvent (Table 1). It is known that THF is prone to undergo α-hydrogen abstraction in radical reactions; the resulting product **6e** was detected by GC–MS. A similar photochemical addition of THF onto nitrenes was observed by Platz and co-workers.[8] while Bumgardner et al. reported a radical addition of THF onto diimides.[9]

In summary, we have discovered a new advantageous feature of the T2 linker, widening its range of applicability. The linker is selectively cleaved by UV irradiation with a short reaction time to give the desired amines in high purities.[10]

Acknowledgements

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10. General procedure for the photocleavage of resins with a 1 kHz pulsed 3ω Nd-YAG laser at a wavelength of 355 nm: 100 mg of the resin was put into an open glass vessel and suspended in 2 mL of an appropriate solvent. The inner diameter of the open vessel was as wide as the unfocused vertical laser beam (10 mm). The suspension was stirred with a magnetic stirring bar and a H+P Variomag® stirring device and cooled by means of an aluminium cooling block. After irradiation, the solvent was decanted and the resin was washed with the solvent system used during the cleavage. Analyses were performed using TLC, GC–MS and LC–MS techniques.