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Visible light promoted organic reaction on a solid support

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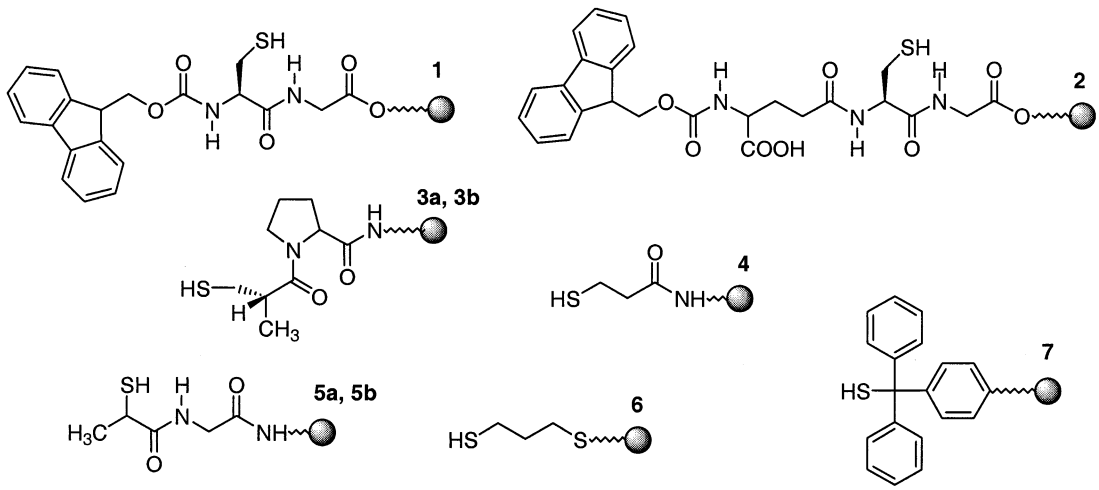
Abstract—The first example of a photochemical reaction promoted by visible light irradiation on a solid support is described.

A principal aim of contemporary synthetic chemistry is to devise methods that maximize the potential for preparing large and diverse product libraries.[1] Polymer-supported chemistry or solid-phase organic synthesis (SPOS)[2] is best suited to these purposes for reasons that include easy work-up procedures, high yields by employing an excess of reagents and amenability to automation.

Examples of light-mediated processes on solid supports are still scarce and mainly concern peptide chemistry. Early and well known cases are the photolabile linkers,[3] which continue to be useful in achieving milder and cleaner cleavage steps in solid-phase peptide synthesis (SPPS). All these mild photochemical methodologies commonly use UV irradiation. However, visible light mediated processes would be advantageous because of cleaner reaction products and energy savings, thereby constituting progress towards a greener chemistry. Several reactions of synthetic importance have been satisfactorily performed under visible light irradiation,[4] but none of them on solid supports.

Methods for thiol desulfurization[5] are also very uncommon and as in early examples,[6] most require harsh conditions (i.e. high temperatures) that make them difficult to adapt to solid phase procedures.[7] Consequently, examples of such desulfurization processes have not yet been carried out on solid supports.

Here we report a light-induced photochemical desulfurization method[8] of solid-phase anchored thiol groups.



Scheme 1.

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This new method in SPOS is, to our knowledge, the first example of a photochemical reaction promoted by visible light irradiation on a solid support. Unique features of this method are the mild reaction conditions (room temperature) and the broad substrate structures that can be used with visible rather than UV light.

For the purpose of this work, a series of polymer-bound thiols were prepared, comprising molecules such as peptidyl resins and other small alkyl thiols anchored to a solid support (Scheme 1). Among the peptide derivatives, glutathione was selected since it is the simplest biologically active peptide model with a free Cys residue. A cysteine-containing dipeptide (Cys-Gly) peptidyl resin derivative **1** was prepared using a Wang resin. The corresponding bioactive tripeptide (γ-Glu-Cys-Gly) peptidyl resin (**2**) was synthesized from a Merrifield resin by standard SPPS techniques. In addition, the orally active angiotensin-converting enzyme inhibitor and antihypertensive drug captopril was anchored to 4-methylbenzhydrylamine (MBHA) and Rink resins (**3a** and **3b**, respectively).

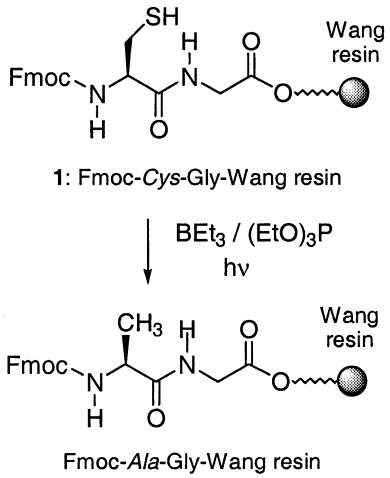
Thiol derivatives of small organic molecules were chosen owing to the present interest in polymer bound thiols and the techniques available to prepare them.[9] Accordingly, 3-mercaptopropionic acid and *N*-(2-mercaptopropionyl)glycine were anchored to a MBHA resin following known procedures[10] (**4** and **5a**, respectively). Similarly, *N*-(2-mercaptopropionyl)glycine was also coupled to a Rink resin (**5b**). A Merrifield resin bound 1,3-propanedithiol derivative **6** was also synthesized by sulfide bond formation.[11] Finally, a commercially available thiol-4-methoxytrityl Merrifield resin **7**, bearing a tertiary thiol function, was included in this study.

The desulfurization process was essentially effected as in previous experiments in solution.[12] However, since it was suspected that mass transfer effects of reagents may reduce the reaction rates, several kinetic measurements were performed. No such effect was observed and after a period of 48 h most of the reactions came to a halt, so reaction conversions are referred to this point (see Table 1).

Table 1. Desulfurization of thiol derivatives **1**–**7** anchored on various solid supports

Entry	No.: type of resin	Conversion[a] (%)	Yield (%)
1	**1**: Wang	100	86
2	**2**: Merrifield	100	84
3	**3a**: MBHA	100	85
4	**3b**: Rink	100	89
5	**4**: MBHA	95	65
6	**5a**: MBHA	72	72
7	**5b**: Rink	82	69
8	**6**: Merrifield	88	N.d.[b]
9	**7**: Merrifield	31 at 17 h 44 at 42 h 52 at 49 h 61 at 72 h	N.d.

[a] At 48 h unless specified.
[b] N.d. (not determined).



Scheme 2.

As seen from Table 1, conversions of anchored L-cysteine derivative **1** and glutathione **2** correlate with results in solution since they are always quantitative. Quantitative conversions have also been recorded while testing the peptidyl resin related products captopril **3a** and **3b**. From the four resins assayed (Merrifield, MBHA, Rink and Wang) it was not possible to see any resin or linker influence. These experiments are the first examples of Cys to Ala conversions on solid supported peptide sequences performed by photochemical means employing a visible light source (Scheme 2).

Among the small organic thiol molecules studied, none showed full conversion as in the case of the peptidyl resin substrates. Moreover, no significant conversion differences could be attributed to the primary or secondary nature of thiols (**4**, **5** and **6**), but rather variations may come from resin and linker effects (**5a**, **5b**).

It is interesting to note that in assessing the performance of this method, attempts to desulfurate the highly hindered tertiary thiol 4-methoxytrityl resin **7** were also successful. As seen from data in Table 1, conversions were moderate and reaction rates low.

Among the different methods available for monitoring the reaction progress on resin supports,[13] it was found that elemental analysis provided the most reproducible results. Accordingly, reaction conversions were calculated from the sulfur content in initial and treated resin samples. This method is most convenient since it reduces sample preparation to a minimum by avoiding the cleavage/isolation procedures required for other chromatographic/spectroscopic analytical methods. The progress of the desulfurization of propanedithiol resin samples (**6**) has also been directly monitored on crushed beads by diffuse reflectance infrared Fourier Transform spectroscopy (DRIFTS).[14] Thus, the band corresponding to ν(S–H) stretch at 2555 cm^{-1} faded away as the reaction progressed.

In summary, a visible light-assisted solid-phase organic reaction is reported here for the first time. The proce-

dure selectively removes thiol groups from solid supported substrates by using triethylborane and triethyl phosphite under visible light irradiation. This new tool in SPOS allows easy access to a variety of desulfurated organic molecules starting from even highly hindered tertiary thiol precursors. In addition, this photochemical procedure is the first example of a light-mediated solid-phase post-synthetic modification of Cys residues on a solid-phase anchored peptide. Finally, the present investigation may certainly provide a new method for traditional solid-phase structure–activity optimization studies and combinatorial library synthesis. The specificity and mild reaction conditions of this process may also open new perspectives in the modulation of the interfacial properties of thiol bound polymeric materials and structural studies in protein science involving thiol groups.

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12. *Typical procedure*: Resin bound thiol substrates (0.1 g) were suspended in acetonitrile (0.5 mL) under an argon atmosphere, followed by the addition of triethylborane in 1 M THF solution (0.2 mL) and triethylphosphite (0.1 mL). The resulting mixtures were irradiated with a 300 W visible light bulb located about 20 cm from the flasks, under stirring for 48 h. The resins were filtered, washed with acetonitrile (4×2 mL) and dried under vacuum. For characterization purposes, the amides from Rink amide (**3b**, **5b**) and MBHA resins (**3a**, **5a**) and the peptide acids (**1**, **2**), obtained by cleavage of the corresponding resins after the light-induced photochemical desulfurization reaction were submitted to HPLC analysis, ^{1}H NMR characterization and MALDI-TOF-MS analysis. Cys to Ala conversion on peptide acids **1** and **2** were corroborated by independent synthesis of FmocAla-Gly-OH and γ-Glu-Ala-Gly-OH peptides, respectively. Furthermore, amino acid analyses of the treated peptidyl glutathione Merrifield resins (**2**) also confirmed the completeness of the reaction by showing the presence of L-Ala in the right proportion.
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