

[B0003]

## Synthesis of a Photolabile 'Safety Catch' Linker of the 3'-Methoxybenzoin Type

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Received: 14 August 1997 / Uploaded: 114 August 1997

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**Abstract:** Solid supports carrying a photolabile linker of the 3'-methoxybenzoin type were prepared by a rapid solid phase synthesis method. Alternatively, the linker was preassembled in solution by a more lengthy procedure and then coupled onto polystyrene via its carboxymethyl handle. 'Safety catch' linkers of this type are expected to play an important role for the preparation of combinatorial libraries suitable for a variety of miniaturized screening methods, where 'reagentless' release of compounds from the carrier is crucial.

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### Introduction

Photocleavable linkers are of particular interest in combinatorial chemistry, a.o. because of their "reagentless" mode of cleavage for the release of compounds from the *solid synthesis support* into solution.

Screening combinatorial libraries with enhanced efficiency calls for simplified assay protocols (with a minimal number of steps) and for miniaturization.

In *split-and-mix* libraries each bead carries an individual compound.

Photocleavage allows the release of compounds in a dry or semi-dry state, directly from beads into the wet gel-like media of diffusion assays from spread-out beads (e.g. cell lawn assays).

We consider photocleavable linkers an important 'combinatorial technology tool' for the development of miniaturized assay systems in solution.

### Results and Discussion

A safety-catch linker, with the significant advantage of circumventing premature photolysis, was recently developed by *Rock and Chan* (1) and used to keep two peptide moieties covalently linked in solution (but separable upon photocleavage) for the study of conformational transitions between the linked and the individual state.

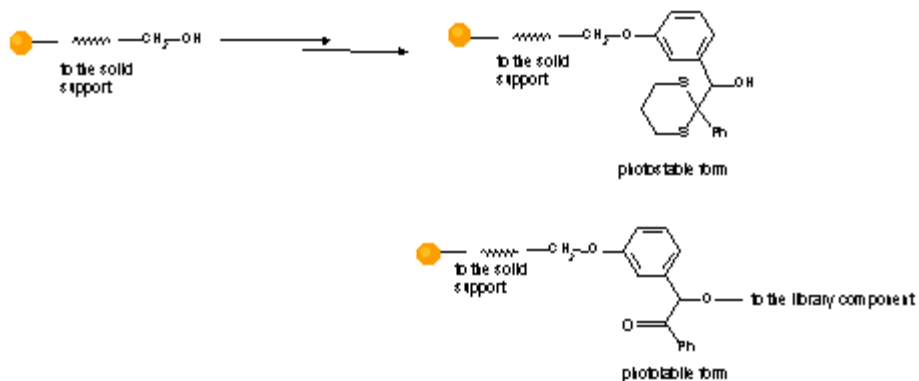
The aim of our work was to graft this linker to *solid phase synthesis supports* and make it available for combinatorial chemistry approaches.

Two alternative approaches were pursued:

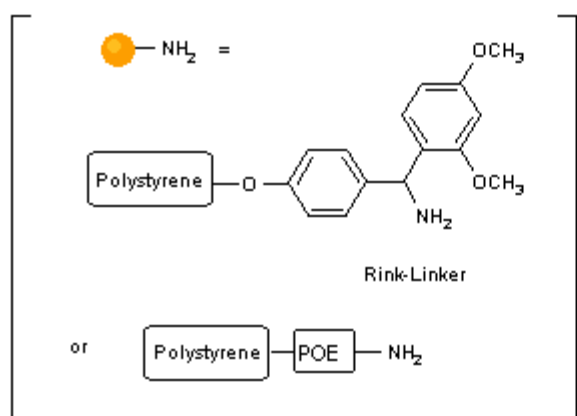
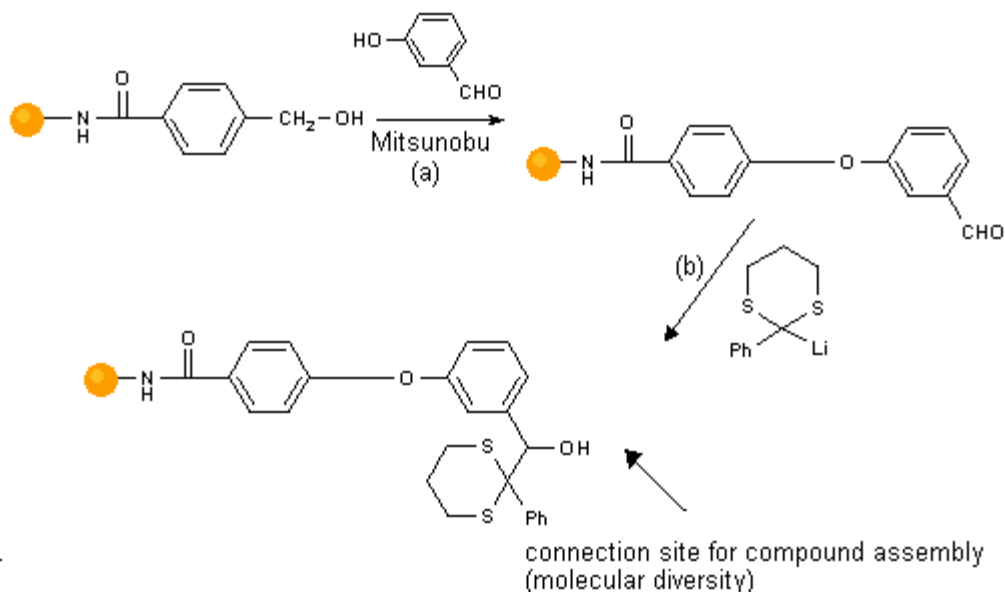
- Approach A: Stepwise assembly of the linker by solid phase synthesis

- Approach B: Coupling of the linker (previously prepared in solution) to the solid support

Outline of the objective



Approach A



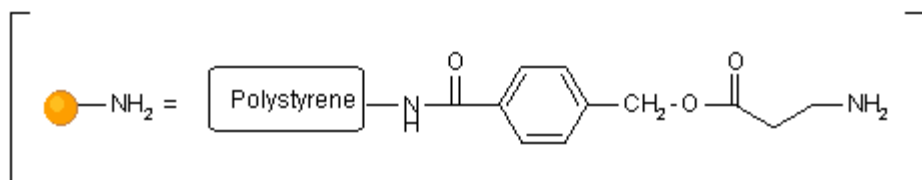
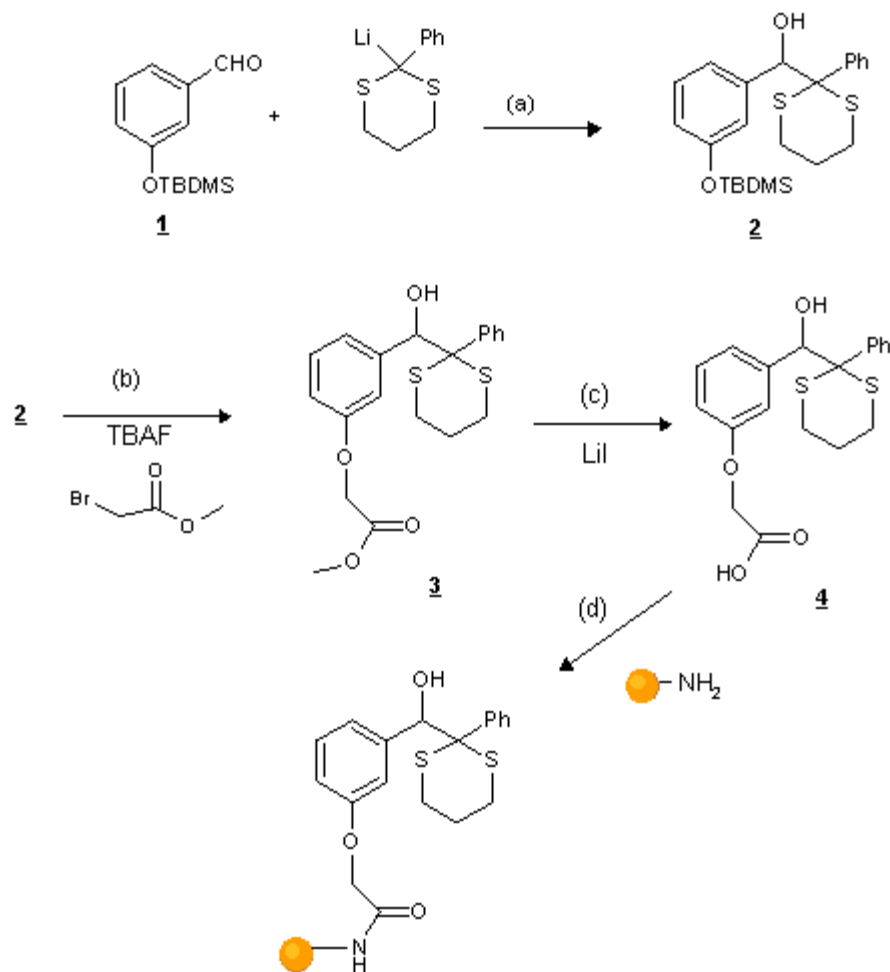
(a) 3-Hydroxybenzaldehyde (10 eq.), TPP (5 eq.), DEAD (5 eq.), DCM/THF, 4h, 87% isol. yield after cleavage (95% TFA)

(b) 2-Phenyl-1,3-dithiane, n-BuLi (8 eq.), THF/cyclohexane, 0°C - RT, 4h, 40% isol. yield after cleavage (2 % TFA, partial decomp.)

**Recently, a similar approach, using NaH oil dispersions on chloromethyl polystyrene was published**

**in the literature (2)**

**Approach B**



(a) 2-Phenyl-1,3-dithiane, n-BuLi (1.1 eq.), **1** (1 eq.), THF / cyclohexane, 0°C, 1h, >95% yield

(b) Br-CH<sub>2</sub>-COOCH<sub>3</sub> (2.3 eq.), TBAF (1.9 eq.), **2** (1 eq.), THF, 16h, 50% yield

(c) LiI (4 eq.), **3** (1 eq.), pyridine, reflux, >95%

(d) **4** (3eq.), HOBT / DIPCPI (3.6 eq.), amino-support (1 eq.), DMA, 2.5h, 90%

## Conclusions

Two alternative approaches were worked out, providing the opportunity to incorporate a safety-catch photolabile linker onto a choice of solid supports used in combinatorial chemistry.

In the course of our investigations we determined an acid lability of the linker, which is more pronounced than expected and needs to be taken into account in planning combinatorial syntheses. The linker is unstable towards trifluoroacetic acid concentrations above 2%.

Improving the overall stability of photolabile linkers remains an area of primary interest for the design of novel application modes in *combinatorial technologies*.

## References

(1) Rock, R.S.; Chan, S.I. *J. Org. Chem.* **1996**, *61*, 1526 - 1529.

(2) Routledge, A.; Abell, C.; Balasubramanian, S. *Tetrahedron Lett.* **1997**, *38*, 1227 - 1230.

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## Comments

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