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A New Photocleavable Linker in Solid-Phase Chemistry for Ether Cleavage

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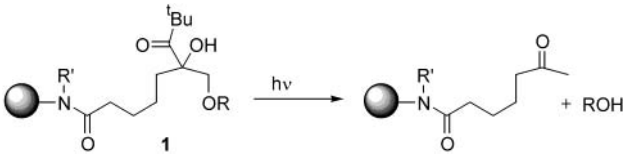
ABSTRACT



We have designed a new linker (1) for the solid-phase synthesis that cleaves ether bonds photolytically. The linker was prepared in nine steps and anchored to the support via an amide bond. Photocleavage is a two-step process in which the immobilized alcohols are released by photolytic generation of a radical that undergoes a spontaneous β-bond scission. The pivaloyl linker (1) was found to cleave off alcohols in high yields and purities. Only traces of acid (pH ~5.5) are necessary for an efficient cleavage.

In the past few years, interest in solid-phase synthesis has increased dramatically due mainly to the importance of the concept of combinatorial chemistry, a powerful tool in the discovery of new biologically active compounds.[1] The use of photolabile linkers[2] became widespread in the generation of combinatorial libraries of organic molecules[3] because this allows a release of the library under mild conditions. This detachment is orthogonal to acidic and basic reaction conditions and therefore affords additional flexibility in the synthesis on solid support.

Whereas much effort was directed toward the development of photolabile linkers for ester cleavage,[4,5] to our knowledge the photolytic ether cleavage on solid support is unknown.[6] All common linkers for ether cleavage are based on acid[7] or base lability,[8] oxidative[9] or reductive cleavage,[10] or fluoride

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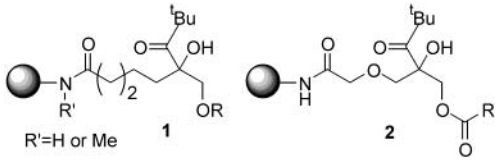
sensitive silyl−oxygen bond cleavage.[11] To our knowledge all photolytical releases of alcohols occur over the indirect way of cleaving carbonates[12] or acetals.[13]

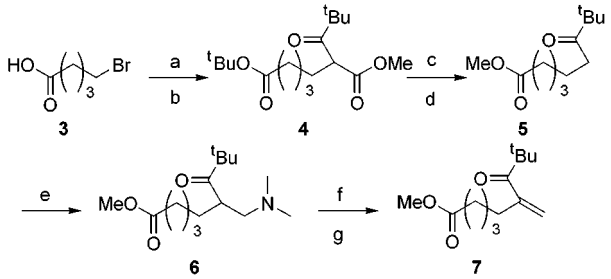
With our newly developed linker **1**, a direct photolytical ether bond cleavage is possible. This linker is a further development of the previous reported pivaloyl glycol linker **2** for ester cleavage.[5]



The new linker **1** differs from **2** mainly in the alkyl chain connection between the cleavage unit and the solid support.

The synthesis of linker **1** is outlined in Scheme 1.

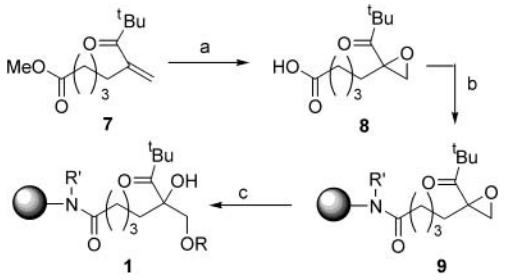
Scheme 1. Synthesis of the Linker Platform[a]



[a] (a) Isobutene, H_2SO_4, 98%; (b) methyl 4,4-dimethyl-3-oxopentanoate, NaH, DMF, 78%; (c) KOH, MeOH, H_2O, Δ, 99%; (d) MeOH, *p*TsOH, 98%; (e) *N*,*N*-dimethylmethyleneiminium chloride, CH_3CN, *p*TsOH, Δ, 90%; (f) CH_3I, 98%; (g) KO^{t}Bu, CH_3CN, 80%.

5-Bromovaleric acid **3** was transformed via esterification with isobutene and subsequent alkylation of methyl 4,4-dimethyl-3-oxopentanoate to the pivaloyl ketone-substituted dicarbonate **4**. Decarboxylation led to ketoester **5** and subsequent Mannich addition with Eschenmoser salt to **6**. Alkylation with methyl iodide and base-induced elimination of trimethylamine yielded the α,β-unsaturated pivaloyl ketone **7**. This approach (overall yield: 52%) requires chromatography only after the alkylation (→ **4**) and the elimination step (→ **7**). The polymer-bound ethers **1** were formed by epoxidation of **7**, connecting **8** with the polymer support, and subsequent nucleophilic epoxide opening (**9** → **1**, Scheme 2).[14]

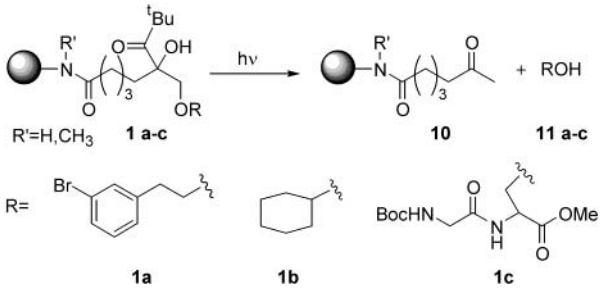
Scheme 2. Attachment to the Solid Support and Modification[a]



[a] (a) 1. KOH, DMF, 95%; 2. DMD, acetone 94%; (b) Tenta Gel S NH_2 or PS-NHMe, DIC, DMAP, CH_2Cl_2; (c) KO^{t}Bu, ROH, THF, Δ or BF_3·Et_2O, ROH, toluene, Δ.

The epoxidation of **7** was performed with a dimethyldioxirane solution[15] yielding epoxide **8** after deprotection of the methyl ester with lithium hydroxide. Coupling of **8** with commercially available amino support (TentaGel or polystyrene), conducted by standard procedures (DIC, DMAP, CH_2Cl_2), yielded the pivaloyl ketone epoxy linker **9**. The anchoring proceeded with complete conversion as determined by the Kaiser test.[16] Epoxide opening with alcohols was performed either with bases (→ **1a**) or acids (→ **1b**, **1c**). The dipeptide coupling forming **1c** was conducted on solid phase after epoxide opening of **9** with FmocSerOMe. In all cases, the epoxide was attacked by the nucleophile regioselectively from the less hindered site. The tertiary hydroxyl group proved to be stable under different reaction conditions. The efficiency of the attachment was estimated by elementary analysis of heteroatoms in the residue, piperidine-mediated cleavage of a Fmoc-protecting group in connection with UV-spectrometric analysis,[17] or picric acid monitoring.[18] The attachment of ethers was additionally checked qualitatively by gel-phase ^{13}C NMR.[19] Photolysis of the linker **1a**−**c** with UV light between 280 and 340 nm released alcohols **11a**−**c** (Scheme 3).

Scheme 3. Photolytic Cleavage of the Substrate



The yields of the alcohols **11a**−**c** were determined by gas chromatography or RP-HPLC after photolysis of the sus-

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(14) Beside the epoxidation, dihydroxylation of **7** with subsequent esterification is possible, too. See also ref 5.

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pended resin beads **1** in quartz cells. The optical equipment used was a 500 W Hg high-pressure lamp with cutoff filters or a Rayonet reactor with up to 16 × 21 W lamps of a spectral energy distribution from 370 to 250 nm with the maximum at 300 nm. The cleavage yields are shown in Table 1.

Table 1. Photolysis of the Resin-Bound Ethers **1a**−**c**

ROH	cleavage conditions	yield[a] (%)
11a[b]	*hν* (300 nm), CH_2Cl_2,[c] 2 h, rt	78
11a[b]	*hν* (300 nm), $CHCl_3$, 2 h, rt	80
11a[b]	*hν* (300 nm), THF, HCl,[d] 2 h, rt	51
11a[b]	*hν* (300 nm), MeOH, HCl,[d] 2 h, rt	65
11b[e]	*hν* (300 nm), CH_2Cl_2,[c] 2 h, rt	68
11b[e]	*hν* (300 nm), $CHCl_3$, 2 h, rt	65
11b[e]	*hν* (300 nm), THF, HCl,[d] 2 h, rt	59
11b[e]	*hν* (300 nm), MeOH, HCl,[d] 2 h, rt	61
11c[b]	*hν* (300 nm), CH_2Cl_2,[c] 2 h, rt	61

[a] Yield determined by GC, HPLC, or UV. [b] Cleaved from polystyrene resin. [c] Contains 0.02% 2-methyl-2-butene. [d] 0.001−0.01% HCl in the corresponding solvent (pH ∼5.0−5.5). [e] Cleaved from TentaGel S resin.

Dichloromethane, chloroform, THF, and methanol were chosen for the photolysis study of the resin-bound ethers **1a**−**c** (Table 1). The cleavage in dichloromethane and chloroform led to alcohols **11a**−**c** in 61−80% yields whereas in THF and methanol the cleavage occurred only in 3−7% yields (data not shown in Table 1). But addition of catalytic amounts of HCl to the THF or methanol solutions (pH ∼5.0−5.5)[20] led to an efficient cleavage also in these solvents.[21] In comparison to the cleavage conditions for acid labile linkers,[7] the slightly acidic medium used here is much milder.[22]

(20) 0.001−0.01% concentrated HCl in the corresponding solvent (pH ∼5.0−5.5); 0.1 equiv of HCl relative to the ether is sufficient to catalyze this reaction.

(21) In CH_2Cl_2 and $CHCl_3$ the photolysis generated small amounts of HCl (pH ∼4.5−5.5).

(22) For example, the release of alcohols from Rink-linker affords 1−5% TFA in CH_2Cl_2. That corresponds to a pH value of 1−2.

To examine the stability of the linker toward different reagents, resin **1a** was treated under various reaction conditions for 2 h. Afterward, the resins were washed, dried, and subjected to photolysis. Yields of the photocleavage were compared with results of the photolysis of untreated resin **1a** and are given in Table 2. The linker showed good to excellent stability toward Brønsted and Lewis acids and bases. Whereas in **2** the ester linkage was unstable toward $LiAlH_4$ and nucleophiles,[5] the ether bond of **1** tolerated these conditions.

Table 2. Stability of the Linker toward Different Reagents

	yield[a] (%)		yield[a] (%)
TFA/CH_2Cl_2, rt	96	DIPEA/THF, 60 °C	91
p-TsOH/toluene, 80 °C	99	DBU/toluene, 80 °C	89
$BF_3{\cdot}Et_2O/CH_2Cl_2$, rt	93	hydrazine/THF, rt	96
$LiAlH_4/Et_2O$, rt	91	KO^{t}Bu/THF, rt	97

[a] Yield of photolysis compared to yield of photolysis of untreated resin.

In summary, the new linker **1** allows the photolytical scission of ether bonds. For an efficient cleavage, a slightly acidic medium (pH 5.0−5.5) is necessary. Because photolysis is conducted by 300 to 340 nm light, easy handling in the laboratory without precautions is possible. The photobyproducts are either volatile (CO and isobutene/isobutane) or inert (resin-bound methyl ketone). Finally, the linker is compatible with many reagents and reactions, which allows broad application in combinatorial chemistry.

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Supporting Information Available: Experimental procedures and full characterization for compounds **1a**−**c**, **3**, and **9** and general photolysis conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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