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A New *o*-Nitrobenzyl Photocleavable Linker for Solid Phase Synthesis

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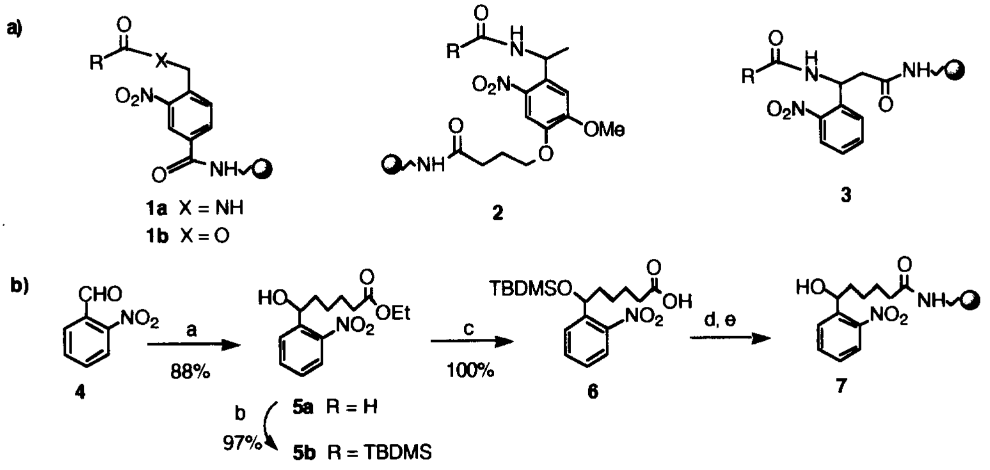
Abstract: A new photolabile linker, **7**, was synthesized in high yield from commercially available starting materials. Irradiation of polymer supports containing **7** produced the desired amino acid and sugar products in high yields. The utility of **7** was demonstrated through the synthesis and photocleavage of a branched trimannan from a polymer support. © 1997 Elsevier Science Ltd.

The use of photolabile linkers based on the *o*-nitrobenzyl moiety for the cleavage of peptides from solid supports is a valuable tool in combinatorial chemistry.[1] Although the original photolabile supports **1a** and **1b** have been useful for the production of carboxamides and carboxylic acids, respectively,[2] they often suffer from slow cleavage kinetics.[3] Recently, improved linkers such as **2** and **3** which produced high yields of amides upon photolysis were reported separately by Holmes et al. and Brown et al., respectively (Scheme 1a).[4,5] However, few improvements in alcohol linker **1b** have been reported. In our recent studies on the solid phase synthesis of carbohydrates, a method for the facile cleavage of polymer-bound oligosaccharides was needed.[6] Herein, we report a new alcohol photocleavable linker which represents substantial improvement in the rate of cleavage and yields, for the production of carboxylic acids or reducing sugars.

Scheme 1



(a) 1. ZnI_2, naphthalene, Li, THF, 16 h; then ethyl 5-bromovalerate; 2. Zn reagent, **4**, BF_3•OEt_2, THF; (b) TBDMSCl, imidazole, DMF; (c) Na_2CO_3, MeOH:H_2O; (d) DIC, DMAP, amine resin, NMP; (e) TBAF, THF.

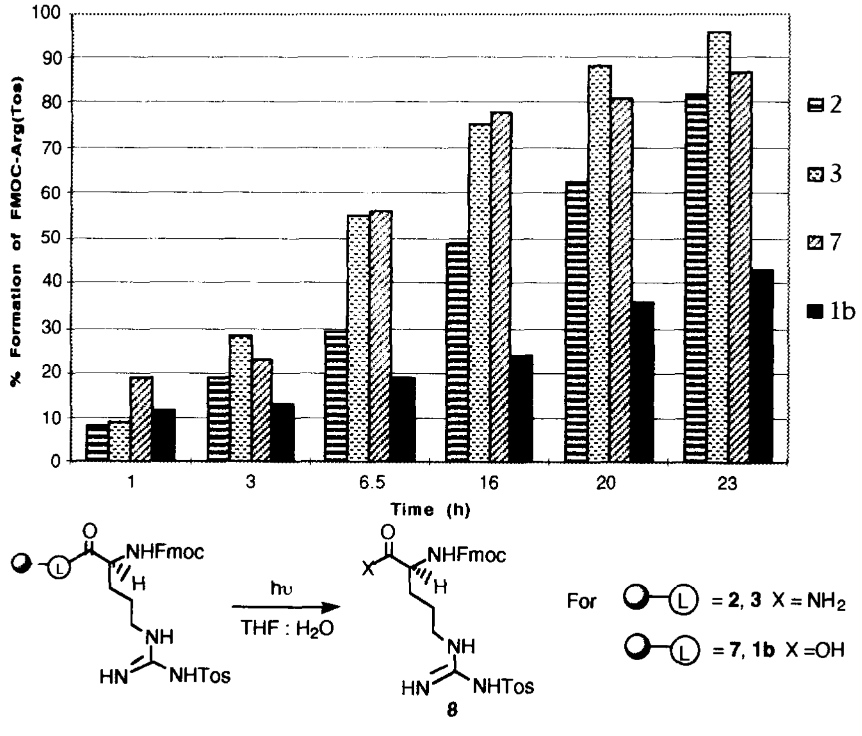
On the basis of the mechanism for photocleavage of *o*-nitrobenzyl derivatives,[7] a secondary benzylic hydrogen should be more easily abstracted than a primary, which would translate into improved cleavage kinetics and yield of product received. Accordingly, the primary alcohol in the Rich linker **1b** was changed to a secondary benzylic alcohol, the linkage to the solid support now being through an alkyl chain rather than an amide function attached directly to the phenyl ring. Thus, **7** was constructed as shown in Scheme 1b.

Commercially available *o*-nitrobenzaldehyde **4** was condensed with the zinc reagent prepared from action of Rieke zinc[8] upon ethyl bromovalerate, to afford **5a** in 88% yield.[9] The length of the six carbon chain in **5** was designed to prevent elimination to form an α/β unsaturated system as well as lactonization of the alcohol onto the carboxyl moiety. The alcohol was then protected as the TBDMS ether, and the ethyl ester saponified for installation onto the support. After condensation of the resulting acid linker to the amine polymer, the TBDMS group was removed uneventfully with TBAF to afford **7**.

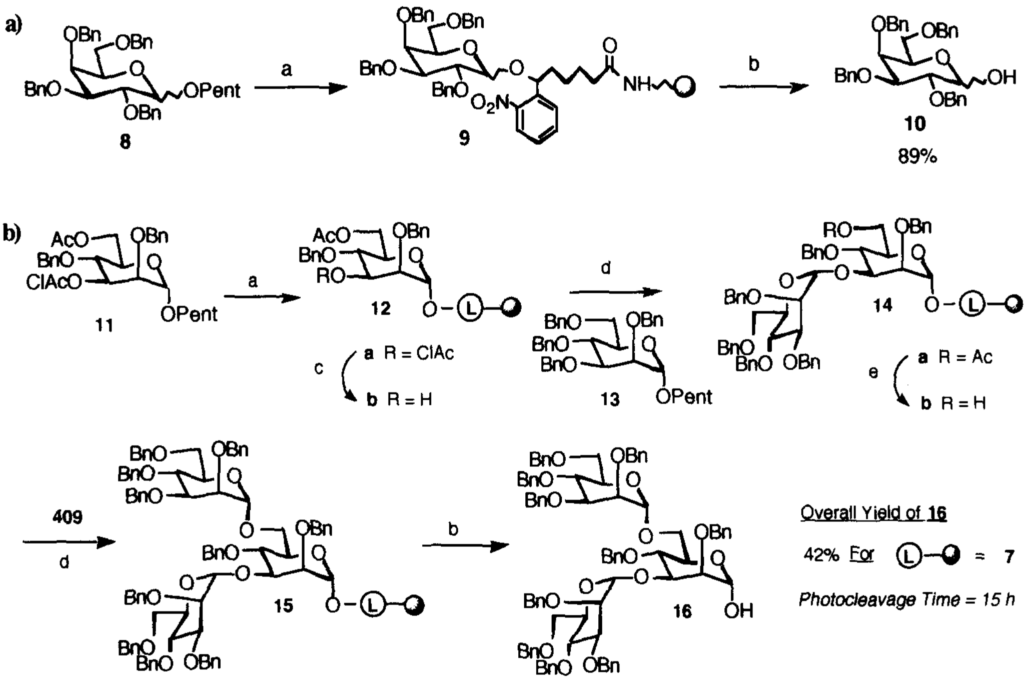
As a test of the general utility of **7** as a linking agent, a comparative time course study of the photolysis of polymer supports **1b**, **2**, **3**, and **7** was conducted by monitoring the formation of **8** (X = NH_2 or OH) from the corresponding polymer-bound amide or ester. The intensity of the mass spectral signal for the parent ion was used as a gauge.[10] Other investigators have reported that measuring the intensity of an MH^+ signal in a mass spectrum is a viable method for quantifying analyte in solution.[11,12]

As shown in Figure 1, photocleavage was extremely efficient for the production of either Fmoc-Arg(Tos)-NH_2 (MH^+ = 550.2) or Fmoc-Arg(Tos)-OH (MH^+ = 551.2) from linkers **2**, **3**, and **7**. The amine

Figure 1 - Comparative Study of Photolinkers



Scheme 2



(a) 7, NIS, TESOTf, CH_2Cl_2, 2h; (b) hυ, THF. (c) thiourea, methoxyethanol, 80 °C, 6h; (d) NIS, TESOTf, CH_2Cl_2 (e) NaOMe / MeOH in THF.

linkers (**2** and **3**) produced the desired amide in a total yield of 82% and 96% after 23 h, respectively. The main difference between these two linkers seemed to be the fact that **3** underwent the cleavage process at a faster rate than did **2**.

It was gratifying to see that the new alcohol linker **7** afforded the carboxylic acid product in nearly the same yield (87% after 23 h) as **3**. Furthermore, the reaction kinetics were quite similar, the desired compound being produced at an almost identical rate as that from the ANP linker, **3**. In order to validate these results, samples of Fmoc-Arg(Tos) derivatized **1b** were irradiated. As revealed in Figure 1, the slow cleavage of the desired product is evident, with only 42% yield of the desired Fmoc-Arg(Tos)-OH after 23 h.

Since linker **7** had proven to be an excellent agent for the cleavage of a carboxylic acid, it was anticipated that this linker would be useful in the cleavage of sugars from polymer supports. In the initial experiment, the pentenyl galactosyl donor **8** was coupled to **7** with the aid of *N*-iodosuccinimide (NIS) and triethylsilyl trifluoromethanesulfonate (TESOTf) to give **9** (Scheme 2a). Irradiation of this polymer intermediate overnight in degassed THF produced hemiacetal **10** in 89% yield.[13]

With these encouraging results, the construction of the branched trimannan **15** was then undertaken with the aid of polymer support **7** (Scheme 2b). This demanding target required that a chemoselective deprotection be carried out upon the resin-bound saccharide at the branching point. In order to facilitate this deprotection, pentenyl glycoside **11**, which contained a chloroacetate at C-3 and an acetate at C-6, was chosen as the precursor. Coupling of **11** to the photolabile resin **7** proceeded smoothly to give the bound monosaccharide **12a** which underwent dechloroacetylation with thiourea to give **12b**. Glycosidation of the hindered secondary alcohol at the C-3 position with perbenzylated mannoside **13**[14] afforded disaccharide **14a**. Subsequent deprotection of the C-6 acetate with NaOMe and coupling with the same donor, **13**, proceeded to give resin bound trisaccharide **15**. Irradiation polymer **15** for 15 h in THF at 365 nm afforded the branched trimannan **16**[15] in an overall yield of 42%, representing an average yield of 87% per step.[13]

The new photolabile linker reported herein represents an excellent alternative for the cleavage of carboxylic acids and reducing oligosaccharides from polymer supports. Further investigations into the utility of **7** and its analogs in solid phase synthesis will be reported in due course.

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References and Notes

‡ Taken from the Ph.D. Thesis of R.R., Duke University, 1997.
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10. Equal amounts (0.6 mg) of the arginine derivatized analogs of **2**, **3**, **7**, and **1b** in Eppendorf tubes were irradiated for various times in degassed THF:H_2O (3:1) before dilution and analysis. Electrospray ionization (ESI) mass spectra were collected with the mass spectrometer in the positive mode. A standard solution of Fmoc-Arg(Tos)-NH_2 or Fmoc-Arg(Tos)-OH was used to normalize the intensity of the MH^+ signals and to determine the percentage cleaved from the various resins.
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15. Selected data for **16**: $[\alpha]_D^{21} = +22.9°$ (c = 1.78, $CHCl_3$), ^{1}H NMR (300MHz, $CDCl_3$); δ 7.22-7.53 (m, 50H, Ph), 5.40 (s, 1H, H-1), 5.22 (s, 1H, H-1), 5.15 (s, 1H, H-1), 4.98-5.06 (m, 2H, $C\underline{H}_2$Ph), 4.53-4.80 (m, 18H, $C\underline{H}_2$Ph), 4.31-4.40 (m, 1H), 3.75-4.10 (m, 17H), 3.19 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$); δ 99.98 (C-1), 98.70 (C-1), 92.17 (C-1); MS (FAB) *m/e* 1403.5 MH^+, 1427 $(M+Na)^+$.

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