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An Improved Synthesis and Selective Coupling of a Hydroxy Based Photolabile Linker for Solid Phase Organic Synthesis

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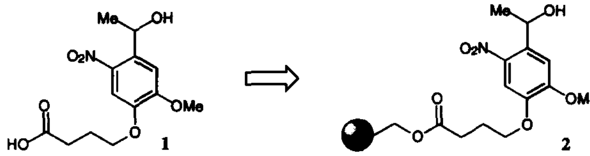
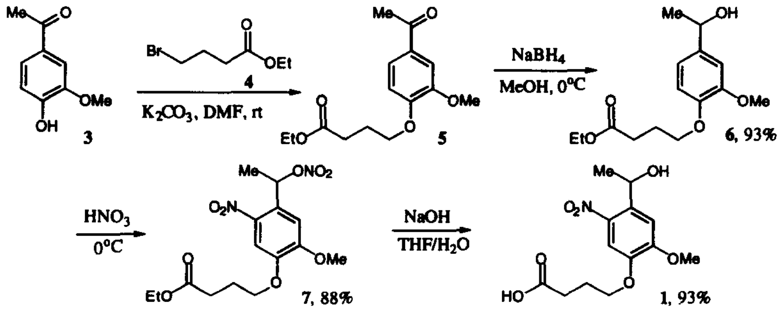
Abstract: Photolabile linkers have become an important orthogonal technique for substrate cleavage off the resin in solid-phase organic synthesis. Herein, we report an improved synthesis and selective coupling of a hydroxy based photolinker to a hydroxy based solid-phase resin, thereby removing the necessity for protection or on-resin manipulation. © 1997 Elsevier Science Ltd.

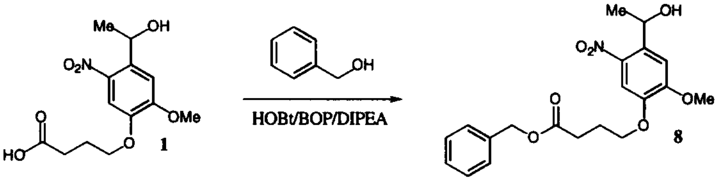
Since their first description,[1] photolabile linkers have become an important option for orthogonal substrate cleavage in solid phase organic synthesis.[2] Holmes et al.[3] and Greenberg et al.[4] have reported the synthesis of vanillin-based photolabile linkers with improved cleavage properties. While an amino-resin bound version of the Holmes photolabile linker **1** has been commercially available for some time,[5] the synthesis of this molecule has only recently been reported.[6] Furthermore, the coupling of this compound to a hydroxy-based resin, to form **2**, has never been reported. For our work, we required a photolabile support without acidic protons. Since neither the synthesis nor coupling of compound **1** had been reported, at that time, we undertook the synthesis and investigated the selective coupling of the hydroxy acid photolinker to the hydroxy based Wang resin[7] to avoid the acidic N-H proton of the amide based linker.



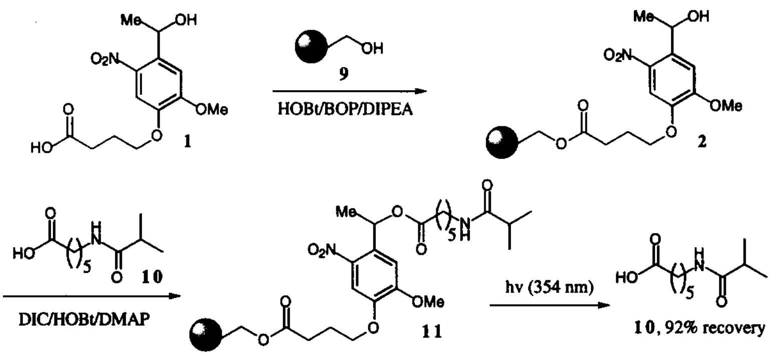
Starting with acetovanillone **3**, the phenol was alkylated with ethyl 4-bromobutanoate **4** in the presence of potassium carbonate in dimethyl formamide (DMF). Reduction to the alcohol **6** with sodium borohydride was followed by treatment with nitric acid to yield nitro nitrate **7**. When the nitration was performed on ketone **5**, lower yields were observed, which is consistent with the Holmes synthesis.[6] The nitrate ester of **7** was then displaced by heating to reflux in a THF/NaOH solution with concomitant ester hydrolysis to yield the desired photolinker **1** in 76% overall yield from acetovanillone **3**.



To determine the optimal conditions for resin-esterification, the coupling reaction of the photolinker **1** with benzyl alcohol was carried out under a variety of standard peptide coupling conditions.[8] Self condensation side-product was observed when **1** was treated with either 1,1-carbonyl diimidazole (CDI) or diisopropylcarbodiimide (DIC)/dimethylaminopyridine (DMAP) as coupling reagents. However, when treated with benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP),[9] 1-hydroxybenzotriazole (HOBt), and diisopropylethylamine (DIPEA) in methylene chloride, photolinker **1** could be coupled to benzyl alcohol to give **8** without any observable self coupled product.



These conditions were then employed to couple the photolinker to a solid phase resin. Wang[7] resin **9** was treated with **1** in the presence of BOP, HOBt, and DIPEA in methylene chloride to give the photolabile support **2**.[10]



To examine the stability and compare photolysis to the amide-linked photolinker,[6] we coupled a functionalized aminocaproic acid **10** to yield solid support **11**. Photolysis of **11** at 354 nm lead to a 92% recovery of acid **10**, based on initial resin loading. No nitroso-ketone was observed in the resultant solution, indicating that no photolinker dimer had been formed on the resin. The selective coupling of this photolabile linker, without the need for protection or on-bead reduction, should prove very useful in solid phase synthesis.

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(10) Photolinker **1** (2.0 eq.), BOP (2.0 eq.), HOBt (2.0 eq.), DIPEA (3.0 eq.) were added consecutively to a suspension of Wang resin (1.0 eq.) in methylene chloride (10 mL per gram resin). The resultant mixture was rotated at room temperature for 24 hours, filtered, and washed to yield the photolinker resin **2**.

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