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Facile Synthesis of a o-Nitrobenzyl Photolabile Linker for Combinatorial Chemistry.

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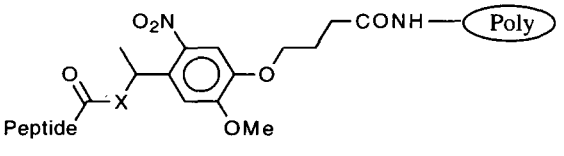
Abstract: Two facile syntheses are described of the o-nitrobenzyl alcohol photolabile linker (**5**). This compound is a valuable intermediate in the preparation of combinatorial libraries, where it allows release from the solid support to give libraries of acids. Copyright © 1996 Elsevier Science Ltd

The use of photolabile linkers[1] has become widespread in the generation of combinatorial libraries of small organic molecules[2] for lead discovery and multiple parallel synthesis around hit structures. The use of photolabile linkers allows for release of the library under neutral conditions. One advantage of this technique is that it makes it possible to release the library ready formatted in microtitre assay plates. In order that libraries of acids could be prepared a suitable synthesis of the linker (1) (Scheme 1) was sought.

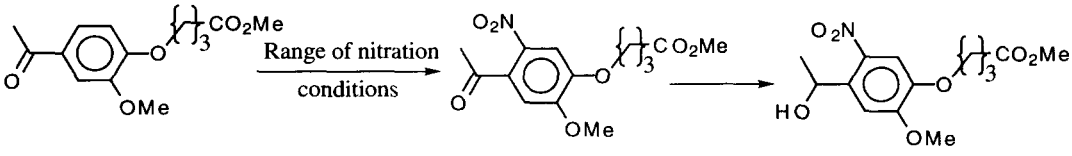
Scheme 1.



(1) X=O —hν→ Peptide acid
(2) X=NH —hν→ Peptide amide

Although a useful 5 step route for the synthesis of the amino linker (2), X=NH, has recently been published[3], problems were encountered when attempting a synthesis of the oxy analogue (1) by an analogous route. Nitration of (3) (Scheme 2) under a variety of reaction conditions resulted in the production of the required compound (4)[4] contaminated with substantial quantities of the product of ipso substitution of the acetyl group[5] together with a range of more minor products. After extensive chromatographic purification, reduction of (4) with sodium borohydride gave the required material (5).

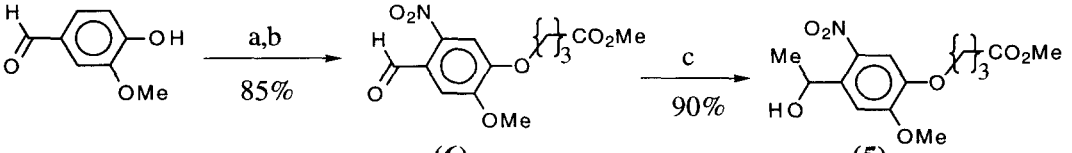
Scheme 2.



(3) **(4)** **(5)**

Examination of the literature[6] and consideration of the lower propensity of the formyl group to undergo ipso substitution resulted in the development of an improved synthetic route (Scheme 3).

Scheme 3.



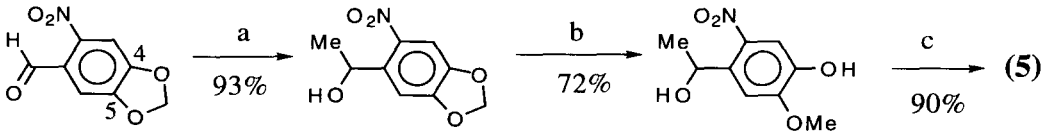
(6) **(5)**

Reagents: a) Methyl 4-Bromobutyrate, DMF, K_2CO_3, 100°C b) $cHNO_3$, CH_2Cl_2, -20°C c) 2.2 Equiv. Me_3Al, CH_2Cl_2, 25°C.

Alkylation of vanillin with methyl 4-bromobutyrate followed by low temperature nitration with fuming nitric acid gave (6). Ipso substitution was only observed if the reaction mixture was allowed to warm above -10°C. It was anticipated that addition of a methyl group to the aldehyde using the lithium or Grignard reagent in the presence of a nitro group would be troublesome, so a range of other organometallic reagents was examined. Although $(iPrO)_3TiMe$ was effective[7] it proved more convenient to use the commercially available reagent Me_3Al at room temperature to give (5), which can be crystallised directly from the crude, three step reaction mixture. The material obtained proved to be suitable for the subsequent transformations. The entire sequence can be performed on a 10g scale[8] without recourse to chromatography, making this photolinker readily accessible. Hydrolysis and coupling of (5) to aminomethyl polystyrene resin gave the materials required for the generation of combinatorial libraries.

It is also proved possible to synthesise the required linker from the commercially available compound (7) (Scheme 4).

Scheme 4



(7) (8) (9)

Reagents: a) 2.2 Equiv. Me_3Al, CH_2Cl_2, 25°C. b) MeOH, Na, DMSO, 100°C. c) Methyl 4-Bromobutyrate, DMF, K_2CO_3, 25°C.

When aromatic nucleophilic displacement with methoxide[9] was carried out on (7) the reaction lacks the required regioselectivity, giving approximately 15% of the product from displacement at the 4-position and 85% at the required 5-position. However, if the same reaction is carried out upon (8), the diplacement is completely regioselective. The secondary alcohol present in the starting material does not compete with the methoxide, presumably because of a combination of steric effects and its lower pKa. It proved possible to effect this transformation at 80°C rather than 150°C as previously suggested. Only one equivalent of sodium metal is required and the product is essentially homogeneous except for a small quantity of dark baseline material[10]. The synthesis of (5) is completed by regioselective alkylation of the diol (9). This sequence allows for the incorporation of a number of alcohols into the linker nucleus and thus makes possible the construction of a range of bifunctional linkers[11] with orthogonal cleavage protocols.

Photolabile linkers will continue to be valuable in the field of polymer supported organic synthesis where mild methods of compound release are crucial. Work to further exploit these methods for library synthesis is ongoing in our laboratories.

Acknowledgement: I wish to acknowledge the contribution of Dr. M. Bradley of the University of Southampton in bringing the current limitations of photolinkers to our attention and for a stimulating interchange of ideas during the course of this work.

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2. Terrett, N. K., Gardner, M., Gordon, D. W., Kobylecki, R. J. and Steele, J., *Tetrahedron* (**1995**), 51(30), 8135-8173.

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7. a) Weidmann, B. and Seebach, D. *Angew. Chem. Int. Ed. Engl.* (**1983**), 22, 31-45. b) Fürstner, A., Jumbam, D. N. and Seidel, G. *Chem. Ber.*, (**1994**), 127(6), 1125-1130.

8. **Experimental procedure:**
Potassium carbonate (10g, 72 mmol) was added to a solution of vanillin (10g, 66 mmol) and methyl 4-bromobutyrate (12g, 66 mmol) in DMF (80ml). The mixture was heated at 100°C for 1.5hrs. then poured into water (700ml), and extracted with ether. The extracts were washed with water, aq. hydrochloric acid, dried and evaporated to give a white solid. The crude product in methylene chloride (600ml) at -20°C was treated with fuming nitric acid (80ml). Upon completion (approx. 3hrs) the yellow mixture was poured into water (700ml) and extracted with methylene chloride. The extracts were washed with aq. sodium bicarbonate, dried and evaporated to give a yellow solid. The crude product was dissolved in dry methylene chloride (600ml) and treated dropwise at room temperature with trimethyl aluminium in hexanes (2M, 74 ml). Upon completion the reaction was poured into a beaker of ice cold aq. hydrochloric acid (700ml) **[caution, foaming and methane evolved.]** Extraction with methylene chloride, drying and evaporation gave a yellow solid which could be purified by crystallisation from 30% ethyl acetate in hexanes (approx 200ml).

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10. **Experimental procedure:**
Sodium metal (1.2g, 52 mmol) was added in small portions to a dry degassed (N_2) solution of (**8**) (10g, 47 mmol) in DMSO (60ml) and methanol (30ml) at a rate sufficient to maintain reflux. **[Caution hydrogen gas evolved]**. Once the initial reaction had subsided the reaction was warmed at 80°C until complete (Tlc. 1:1 Ethyl acetate-hexanes). The excess methanol was evaporated at reduced pressure and the mixture poured into aq. hydrochloric acid (2M, 800ml). Extraction with ethyl acetate, drying and evaporation gave the required compound (**9**) as a brown solid (7.3g).

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