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The Use of a Dithiane Protected Benzoin Photolabile Safety Catch Linker for Solid-Phase Synthesis.

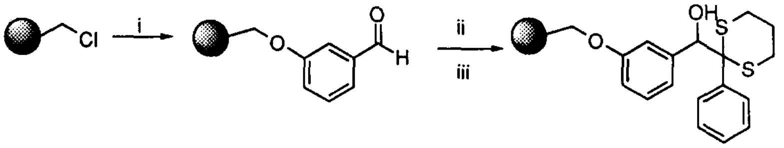
Anne Routledge, Chris Abell and Shankar Balasubramanian*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

Abstract: The dithiane protected benzoin group is shown to be a useful safety catch photolabile linker in solid-phase synthesis. Methods for the synthesis, loading, deprotection and photolysis of the linker are described. © 1997, Elsevier Science Ltd. All rights reserved.

In the construction of a library of compounds on solid-phase the linker, which connects the compounds to the resin, has a unique role. It must be stable to the increasingly diverse reaction conditions being employed on solid-phase and yet be cleaved under conditions which will not affect the attached compounds. These constraints have focused attention on photolabile linkers, in particular derivatives of the *ortho*-nitrobenzyl group.[1,2] However *ortho*-nitrobenzyl esters suffer from slow cleavage kinetics and the generation of a reactive chromogenic nitroso aldehyde on the resin support.[3] Even in derivatives where these problems have been reduced, the linkers remain sensitive to sunlight.[4]

In this Letter we describe the use of a dithiane protected 3-alkoxybenzoin **1** as a photolabile linker for solid -phase organic synthesis. Benzoin esters have been used as photolabile protecting groups for carboxylates and phosphates.[5,6,7,8] Upon irradiation at 350 nm the substituted benzoin undergoes a photosolvolytic cleavage and subsequent rearrangement to isomeric benzofurans (see Scheme 2).[6] If the carbonyl of the benzoin is protected as a dithiane and only deprotected immediately prior to photolysis it can act as a safety catch and prevent premature photolysis. Chan recently reported the use of a dithiane protected 3-alkoxy benzoin as a photolabile linker in solution.[9,10]



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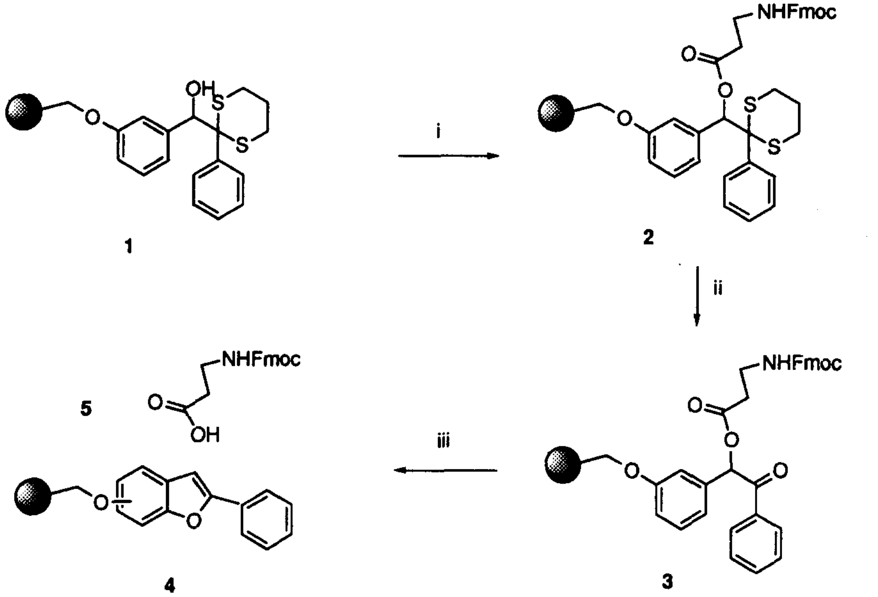
Scheme 1 (i) 3-hydroxybenzaldehyde (3 eq.), NaH(60% dispersion in oil) (3 eq.), DMF, 60 °C, 72 h, >95% yield. (ii) 2-phenyl-1,3-dithiane (3 eq.), *n*-BuLi (2.5 M in hexanes) (3 eq.), THF, -78-0 °C, 4h. (iii) 1N HCl : dioxane (1:4), ambient temperature, 5 min, 91%.

To study the utility of the dithiane protected 3'-alkoxybenzoin as a photolabile linker on solid phase the linker was assembled on the resin (Scheme 1). 3-Hydroxybenzaldehyde was attached to chloromethylpolystyrene (1 mmol / g, 2% cross-linked, Aldrich) by alkylation providing a stable ether linkage. The aldehyde was then reacted with the anion of 2-phenyl-1,3-dithiane to form **1**. The loading of the resin was determined to be 0.71 mmol / g by elemental analysis of sulphur. The modified resin **1** was characterised by gel-phase FTIR and ^{13}C NMR spectroscopy. The signals for the dithiane methylenes at δ 25.3, 27.5, 27.7 ppm provided a clear marker in the NMR spectrum.

UV analysis of the dibenzofulvene-piperidine adduct released on treatment of 9-fluorenylmethoxycarbonyl (Fmoc) protected resin-bound substrates with 20% piperidine/DMF provides a reliable and quantitative method of determining the loading of such substrates.[11] We therefore attached Fmoc-protected β-alanine **5** to the linker **1** using diisopropylcarbodiimide coupling to afford the ester **2** (Scheme 2). The extent of ester formation was determined to be 32%, measured by Fmoc-release. One important property of the dithiane protecting group is that it can be removed under a range of different conditions in solution. Deprotection on resin was performed with three reagents: (a) *bis*[(trifluoroacetoxy)iodo]benzene,[12] (b) mercury (II) perchlorate,[13] and (c) periodic acid.[14] All three procedures cleanly removed the dithiane group to form **3**. In all three samples the dithiane methylene signals completely disappeared in the gel-phase ^{13}C NMR spectrum and a new peak at ~1690 cm^{-1} was observed in the gel-phase FTIR spectrum.



Scheme 2 (i) diisopropylcarbodiimide (3 eq.), Fmoc-β-alanine (3 eq.), DIPEA (3 eq.), DMAP (cat.), HOBt (cat.), DMF, ambient temperature, 18 h. 32%. (ii) (a) *bis*[(trifluoroacetoxy)iodo]benzene, (b) mercury (II) perchlorate, or (c) periodic acid (4 eq.), THF :water (10:1) (for a and c), THF (for b), ambient temperature, 18 h. >95% conversion. (iii) *hv* (350 nm), THF:MeOH (3:1), 28 °C, 2 h.

Aliquots of the resin with deprotected linker **3**, formed by each deprotection method, were separately irradiated at 350 nm in tetrahydrofuran: methanol (3:1)[15] and the release of Fmoc-β-alanine followed by HPLC. The release profiles (Figure 1) show that release reaches a maximum after 120 minutes. The release from the mercury perchlorate deprotected resin **3** was faster and gave a higher yield of product (ca. 75%) than that deprotected by either *bis*[(trifluoroacetoxy)iodo]benzene or periodic acid (ca. 65%). The reason for this difference is unclear as all the samples appeared identical by gel-phase ^{13}C NMR and FTIR spectroscopy prior to irradiation. Under the same conditions of irradiation, less than 3% product release was observed from the protected dithiane **2**. Upon exposure to laboratory light ca. 5% of the product was released from the deprotected resin **3** after 7 days. The nature of the phenyl benzofuran photoproducts **4** remaining on the resin were not investigated

In order to generalise the use of this photolabile safety catch linker we used carbonyl-1,1-diimidazole to activate the secondary alcohol on **1**. The acyl imidazole **6** is much less sterically crowded than the secondary hydroxyl and can be derivatised in a number of ways e.g. using an amine to make an urethane or using an alcohol to make a carbonate. In the example shown in Scheme 3 the acyl imidazole was reacted with cholesterol to form carbonate 7. Treatment of 7 with mercury perchlorate followed by irradiation at 350 nm in tetrahydrofuran : methanol (3:1) for 180 minutes resulted in the release of cholesterol in 72% yield and > 95% purity as determined by HPLC.

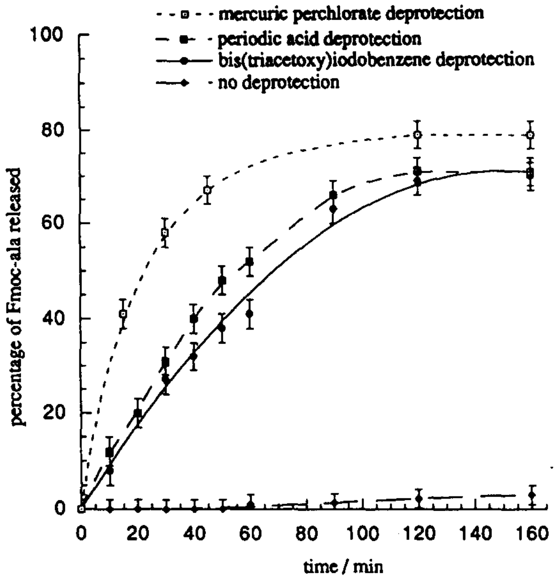
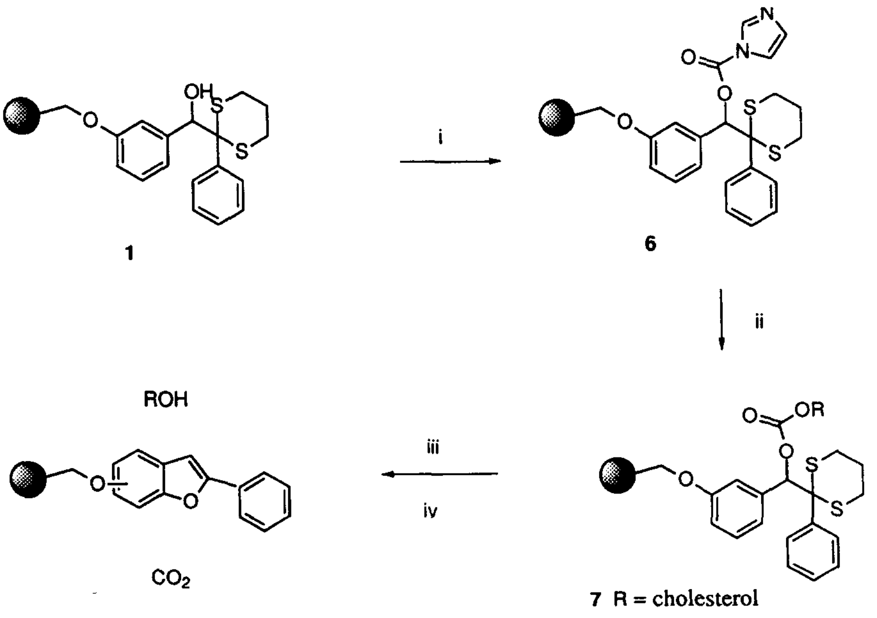


Figure 1: Time course of Fmoc-alanine release from **3** prepared by deprotection of **2** using three different protocols. The control is a sample of **2** which has not been deprotected.



Scheme 3 (i) carbonyl-1,1-diimidazole (3 eq.), pyridine (3 eq.), dichloromethane, 20 °C, 18 h 78%; (ii) cholesterol (3 eq.), DBU (6 eq.), DMF, 40°C, 18 h, 83%; (iii) mercury (II) perchlorate (4 eq.), THF:water (10:1), 20 °C; (iv) *hν* (350 nm), 28 °C, 3 h, 72%.

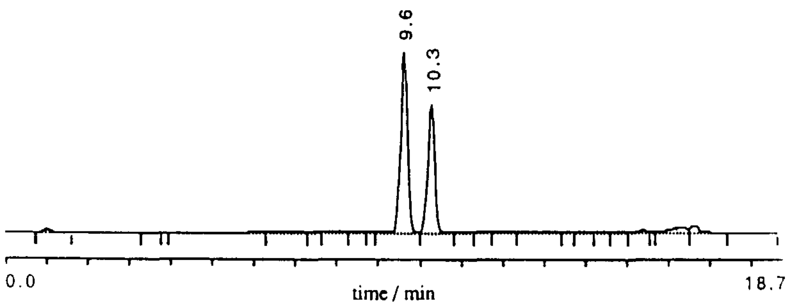


Figure 2: HPLC trace of released Fmoc-β-alanine (10.3 min) with Fmoc-serine (9.6 min) as an internal standard using a SEDEX evaporative light scattering detector.

In this Letter we have shown how the dithiane protected benzoin group can act as a linker on solid-phase. Facile protocols for each aspect of its use: attachment to the resin, coupling to the library compound, and finally photolytic cleavage, have been demonstrated. We envisage that this linker will find widespread use in solid-phase synthesis.

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15. **Procedure for the photolysis of 3**
    The resin **3** (0.1 g, 0.022 mmol of loaded Fmoc-β-alanine) was swollen in THF:MeOH (3:1, 40 ml), Fmoc-serine (8 mg) was added as an internal standard for HPLC and the solution degassed with nitrogen for 10 min. The solution was photolysed in a Pyrex vessel at 350 nm using a Rayonet photochemical reactor. Aliquots of solvent (0.5 ml) were removed at various time intervals and analysed by HPLC (UV and SEDEX evaporative light scattering detection).

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