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Report

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Viktor Krchk

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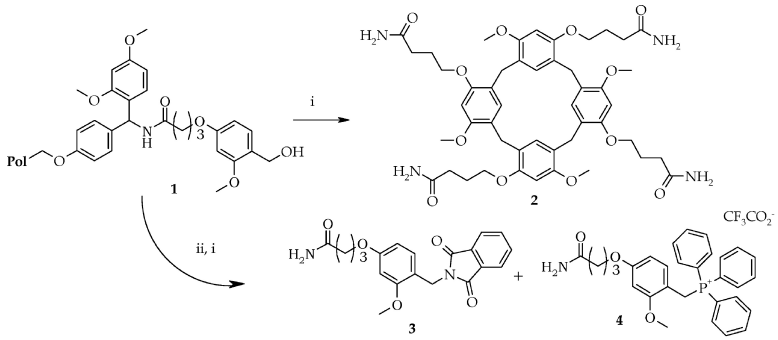

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Application of a Dual Linker with a Reference Cleavage Site in the Identification of a Side Product in the Mitsunobu Transformation of Polymer-Supported Alcohols to Amines

Viktor Krchňák

Department of Chemistry and Biochemistry, 251 Nieuwland Science Center, University of Notre Dame, Notre Dame, Indiana 46556

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The inability to purify intermediates during solid-phase synthesis requires careful optimization of reaction conditions to achieve target products of acceptable purity and yield. To accelerate the development and optimization of reaction conditions for solid-supported transformations, we have designed and used dual linkers with a reference cleavage site.[1] The key feature of dual linkers is their inherent ability to provide complete cleavage of all polymer-supported reaction components. A dual linker consists of a sequence of two linkers in series cleaved by the same reagent. The second linker is attached to the polymer-supported first linker and a reference cleavage site is formed between the first and second linkers. The second linker is always cleaved from the first linker, independent of the chemical transformations performed on the second linker. Herein, we report the use of a dual linker in the discovery of an unexpected side reaction that occurs during the Mitsunobu reaction of polymer-supported alcohols with *N*-hydroxyphthalimide.

Transformation of functional groups on solid phase is an indispensable synthetic tool.[2] Conversion of polymer-supported hydroxyl groups into amino groups was reported, via chloride intermediate, by nucleophilic displacement with potassium phthalimide.[3] An alternative route takes advantage of the Mitsunobu reaction with phthalimide or hydrazoic acid.[4] The lengthy, three-step chloride protocol and hazards associated with the nature of hydrazoic acid make the Mitsunobu phthalimide approach the method of choice. However, conversions with phthalimide under Mitsunobu conditions are not quantitative.[4] We observed only 80% conversion of the 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid (HMPB linker)[5] coupled to the aminomethyl polystyrene resin to the corresponding amine. However, we were unable to detect any side products after cleavage. This strongly suggested that decreased yields could be accounted for by side products that are still attached to the resin. To identify the side products, we performed the transformation on our dual linker with a reference cleavage site,[1] which was designed to provide complete cleavage of all the polymer-supported reaction components.

To study the Mitsunobu transformation of polymer-supported alcohol to amine, we designed the dual linker **1** with Rink linker[6] as the first linker and HMPB linker as the second linker. First, we describe the synthesis and properties of the dual linker **1**; we then report the results with the Mitsunobu reaction, using the dual linker **1**.

The dual linker **1** was synthesized by acylating polymer-supported Rink linker with the HMPB linker, using carbodiimide in the presence of *N*-hydroxybenzotriazole. Acylation was complete after 16 h, as indicated by the negative bromophenol blue test.[7] In the dual linker **1**, the HMPB linker is attached to the Rink linker via an amide bond (the reference cleavage site) that allows its cleavage by diluted trifluoroacetic acid (TFA). When treated with 50% TFA in dichloromethane (DCM), a calix[4]arene derivative (**2**) was detected as the major product (Scheme 1). Calix[4]arene **2** was easily identified on the liquid chromatography−mass spectroscopy (LC/MS) traces (molecular weight 884.485) by two signals corresponding to a singly charged species ($m/z = 885.5$, $M+H^+$) and a doubly charged species ($m/z = 443.3$, $[M+2H]^{2+}/2$). The highly symmetric calix[4]arene **2** exhibited a deceptively simple ^{1}H NMR spectrum containing singlets that corresponded to the two aromatic protons, methylene, and methyl protons. There is a literature precedent for cyclotetramerization of 2,4-dimethoxybenzyl alcohol in diluted TFA.[8] However, the formation of calix[4]arene **2** from the Rink−HMPB dual linker is contrary to the behavior of the Rink−Wang dual linker, when the Wang linker[9] is in the second linker position. The Wang linker polymerizes upon treatment with a TFA cleavage cocktail, and no single product can be detected.[1]

The dual linker resin **1** was used in the identification of a side product in the Mitsunobu reaction with phthalimide. Briefly, a solution of triphenylphosphine (PPh_3) and phthalimide in anhydrous THF was added to the preconditioned resin, followed by the addition of diisopropyl azodicarboxylate (DIAD). After 5 h at ambient temperature, the resin was washed with dimethyl formamide (DMF) and DCM before being treated with 50% TFA in DCM. The cleaved sample was analyzed by LC/MS. In addition to the expected phthalimide derivative **3** (phthalimide is not cleaved from the HMPB linker under these conditions[10]), we detected an additional component. The side-product was isolated by semipreparative high-performance liquid chromatography (HPLC). Both LC/MS ($m/z = 484.5$, $[M+H]^+$) and ^{1}H NMR analyses were consistent with benzyl triphenylphosphonium salt **4** (see Scheme 1). The transformation of the alcohol was quantitative, because no calix[4]arene derivative **2** was detected in the cleaved sample. This is a telling example of a chemical transformation yielding products that are not cleaved from the linker. When the reaction was performed on the HMPB linker directly attached to the aminomethyl polystyrene resin, neither the resin-bound triphenylphosphonium salt nor the phthalimide were cleaved and identified.

To prevent this side reaction, we studied the effects of the relative ratio of reaction components and the order of addition. If a solution of PPh_3 and phthalimide is added to

* Author to whom correspondence should be addressed. E-mail address: vkrchnak@nd.edu.

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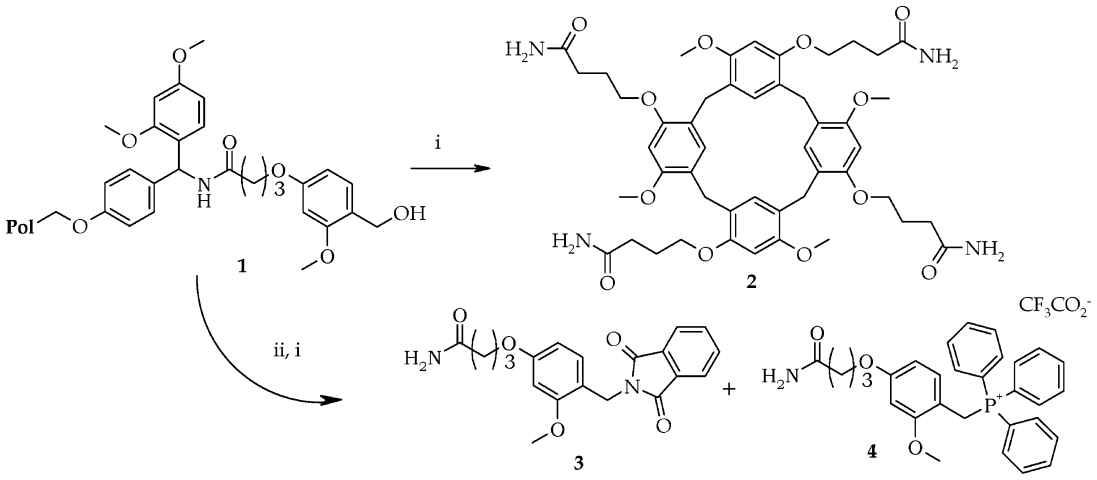
Scheme 1. Reactions of the Rink-HMPB Dual Linker.[a]



[a] Reagents: (i) 50% TFA, DCM, 30 min; and (ii) phthalimide, PPh_3, DIAD, anhydrous THF, 20 °C, 5 h.

Table 1. Amount of Side Product **4**, as a Function of Reaction Conditions

entry	procedure[a]	PhthNH concentration (M)	PPh_3 concentration (M)	DIAD concentration (M)	compound **4** yield (%)
1	A	0.25	0.25	0.25	16
2	A	0.38	0.25	0.25	24
3	A	0.25	0.20	0.25	13
4	A	0.38	0.20	0.25	15
5	B	0.25	0.25	0.25	<1

[a] Procedure A is described as follows: a solution of PPh_3 and phthalimide in anhydrous DMF was premixed with the resin, and then DIAD was added. Procedure B is described as follows: DIAD was added to a solution of PPh_3 and phthalimide in anhydrous dimethyl formamide (DMF), and then the solution was added to the resin.

the resin prior to DIAD,[4] increasing the ratio of phthalimide increases the relative amount of the side product (Table 1). Decreasing the ratio of PPh_3 reduced the amount of side product; however, the level of the side product remained too high, from a preparative point of view. In the absence of phthalimide, the reaction mixture did not produce any observable product. The triphenylphosphonium salt (**4**) was the only product when the reaction was performed in the absence of DIAD. The same phosphonium salt (**4**) was identified as the main product when phthalimide was replaced by an equimolar amount of TFA; the use of TFA for the preparation of phosphonium salts has already been reported.[11] Side-product formation was only eliminated when DIAD was added to the solution of PPh_3 and phthalimide prior to the addition of the solution to the resin. The effect of the reverse reagent addition can be explained by the formation of quaternary phosphonium salt from the reaction of triphenylphosphine and azodicarboxylate and its protonation by phthalimide.[12] Thus, phthalimide is not available for protonation of the benzyl alcohol and subsequent formation of the phosphonium salt (**4**).

Transformation of resin-bound benzyl alcohol to benzyloxyamine using an analogous reaction with *N*-hydroxyphthalimide is a general route that is used to prepare hydroxamic acids.[13−16] The formation of the phosphonium salt (**4**) was observed at a level of 10% when the Mitsunobu reaction was performed with *N*-hydroxyphthalimide on the HMPB linker. Analogously to the phthalimide reaction, the formation of **4** was eliminated by changing the order of reaction components addition.

In contrast to the electron-rich benzyl alcohol of the HMPB linker, the formation of the triphenylphosphonium salt was not observed on the resin-bound 4-hydroxymethylbenzoic acid. We detected partial conversion to the phosphonium salt only when the reaction was performed in the presence of TFA.

The aminomethyl PS/DVB resin was acylated with HMPB linker via DIC/HOBt activation, and the resulting resin was reacted with phthalimide under Mitsunobu conditions, using the optimized protocol with a solution of phthalimide, PPh_3, and DEAD added to the resin-bound alcohol. The phthalimide group was cleaved by hydrazine hydrate, and the resin-bound benzylamine reacted with Fmoc-Cl. The Fmoc group was cleaved by piperidine and the product spectrometrically quantified at 302 nm. The yields from two independent experiments was 93% and 96%, with respect to the declared resin loading.

In conclusion, we used the Rink−HMPB dual linker with a reference cleavage site to detect and isolate a side product of transformation of alcohol into an amine, using Mitsunobu reaction with phthalimide. The formation of the side product, benzyl triphenylphosphonium salt, was prevented by changing the order of reagents addition.

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Supporting Information Available. Experimental procedure, involving materials and methods (PDF). This material

is available free of charge via the Internet at http://pubs.acs.org.

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