Peptides: Chemistry, Structure and Biology
Pravin T.P. Kaumaya and Robert S. Hodges (Eds.)
Mayflower Scientific Ltd., 1996

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Use of Solid Phase Mitsunobu and Wittig Reactions for Construction of Peptide and Non-peptide Libraries

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Introduction

To increase the structural diversity of combinatorial libraries, we have extended the repertoire of organic reactions that can be performed in the solid phase mode, and used these reactions for the design and synthesis of peptide and non-peptide libraries. Polymer-supported chemistries include formation of ethers by the Mitsunobu reaction [1], and carbon-carbon bond formation by the Wittig reaction [2]. These solid-phase reactions can be used individually or in tandem, and combined with standard reactions for solid phase amide bond formation, to access an array of organic structures.

Results and Discussion

We selected Mitsunobu ether formation as a suitable reaction for combinatorial chemistry based on several criteria: (i) yields and purities of products; (ii) variety of available building blocks; (iii) compatibility with other chemistries; and (iv) "user friendly" reaction conditions. Out of two possible etherification modes we have studied the reaction of polymer-supported phenol with alcohol in solution. Model reactions (Figure 1) were carried out with N-acetylated tyrosine esterified to a graft copolymer, poly(ethylene glycol)-polystyrene-1% divinylbenzene, TentaGel S OH (TG). A typical procedure involved prewash of Ac-Tyr-O-TG with dry THF, followed by slurrying of the resin with a THF solution of PPh_3 and alcohol, chilling the slurry, and initiation of the reaction by addition of diethyl azodicarboxylate (DEAD). Products were cleaved from the resin by alkaline hydrolysis and analyzed by MS, HPLC, and NMR.

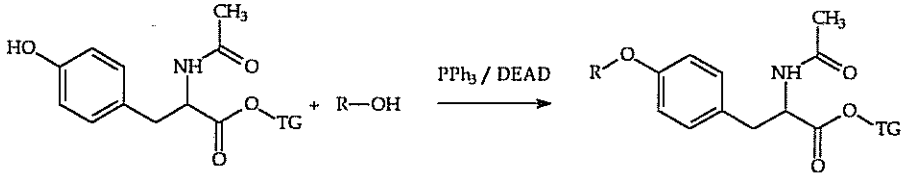

Figure 1. *Reaction scheme for polymer-supported Mitsunobu etherification.*

Figure 2. *Reaction scheme for polymer-supported Wittig reaction.*

Polymer-supported Mitsunobu ether formation can be applied in the design and synthesis of combinatorial libraries in many different ways. We incorporated this reaction into the one-bead-one-compound combinatorial library strategy [3], using the split-mix method for synthesis. Our model library involved three randomization steps: (i) N-protected amino acid attachment to the polymeric support *via* ester linkage, (ii) coupling of aromatic hydroxy acids, and (iii) Mitsunobu ether formation using a set of alcohols.

Polymer-supported carbon-carbon bond formation was performed by the Wittig reaction (Figure 2). We used TentaGel-NH_2 resin functionalized with acidolyzable handles (*e.g.*, PAL) and a chromophoric marker (*e.g.*, *p*-nitro-Phe). Carbonyl functions were introduced in three different ways: (i) oxidation of alcohols; (ii) deprotection of acetals; and (iii) direct coupling of carboxy aldehydes and ketones.

Different carbonyl functionalities were treated with ylides to form alkenes. Stabilized phosphoranes quantitatively transformed aliphatic and aromatic aldehydes to provide E-alkenes, as verified by NMR and HPLC analyses of products released by acidolysis. However, these reactions did not occur when ketone substrates were used in place of aldehydes.

Ylides derived from more reactive phosphonates smoothly transformed aldehydes to alkenes. When triethyl phosphonoacetate was used, E-alkenes formed predominantly. Polymer-supported ketones reacted sluggishly, at first, but conversion was achieved by addition of a strong base: DBU (in the presence of LiBr) or potassium hexamethyldisilazane. To avoid base-catalyzed side reactions, application of a tertiary amine (*e.g.*, DIEA in the presence of LiBr) represented a good compromise for successful reactions of sensitive substrates.

References

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