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Report

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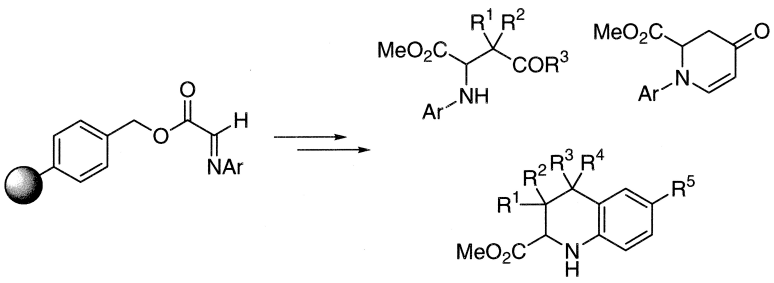


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# Polymer-Supported α-Imino Acetates. Versatile Reagents for the Synthesis of α-Amino Acid Libraries

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α-Imino acetates are useful building blocks for the synthesis of nitrogen-containing biologically important compounds such as α-amino acids,[1] β-amino alcohols,[2] etc. However, these acetates are often unstable to isolate at room temperature due to rapid decomposition and hydrolysis, and they have to be prepared just before use.[3] It was expected that these unstable compounds would be stabilized when immobilized on polymer supports. Indeed, in our previous work, we immobilized normally unstable silyl enol ethers on resins and successfully used them in several carbon−carbon bond-forming reactions.[4] In this paper, we report the synthesis of novel polymer-supported α-imino acetates and their use for the preparation of α-amino acid derivatives.

Polymer-supported α-imino acetates were prepared according to Scheme 1. Sodium diethoxyacetate, which was readily prepared from commercially available ethyl diethoxyacetate by hydrolysis, was treated with chloromethylated resin at 80 °C for 12 h in DMF. Diethoxyacetate resin (**1**) thus obtained was then treated with acetyl chloride in a hydrogen chloride dioxane solution at room temperature for 12 h, to afford an active intermediate, 2-chloro-2-ethoxyacetate resin **2**.[5,6] The loadings of **1** and **2** were determined by

**Scheme 1.** Synthesis of Polymer-Supported α-Imino Acetates

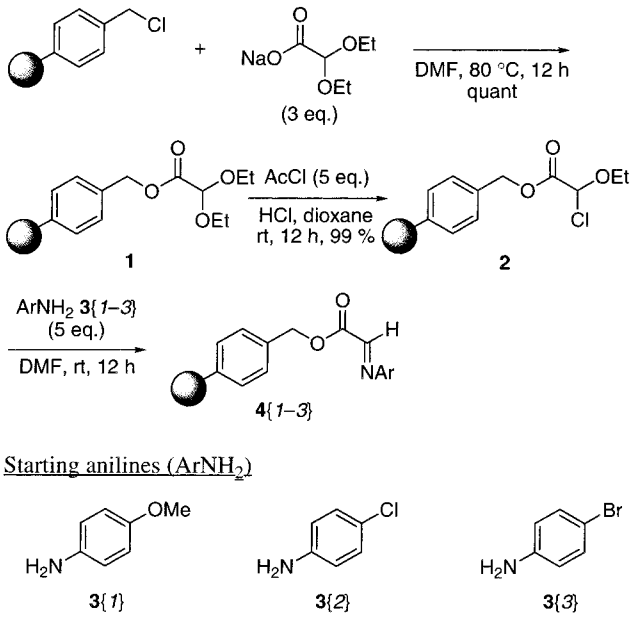
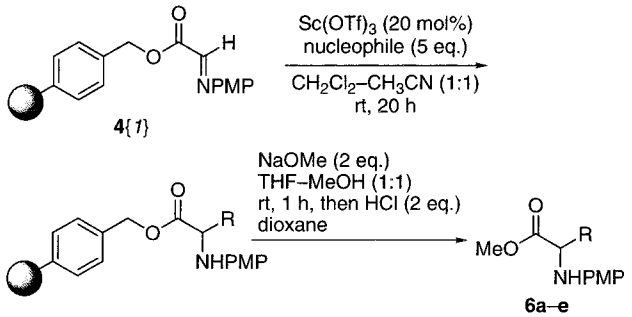
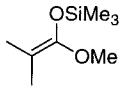
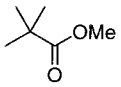
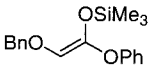
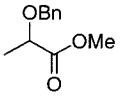
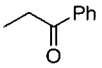
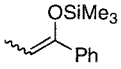
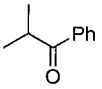
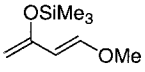
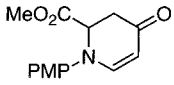



**Table 1.** Synthesis of α-amino acid derivatives[a]




| Entry | Nucleophile | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  | **6a**: R =  | 76 |
| 2 |  | **6b**: R =  | 94[c] |
| 3 |  | **6c**: R =  | 71[d] |
| 4 |  | **6d**: R =  | 65[d,e] |
| 5 |  | **6e**  | 69[f] |

[a] PMP = *p*-methoxyphenyl. [b] Based on **4**{*1*}. [c] Diastereomer ratio = 60:40. [d] $Sc(OTf)_3$ (40 mol %) was used. [e] Diastereomer ratio was not determined. [f] The reaction was performed at −5 °C.

chlorine titrations (Volhard's method).[7] The reaction of **2** with *p*-anisidine (**3**{*1*}) was performed at room temperature in DMF to give 2-(4′-methoxyphenyl)iminoacetae **4**{*1*}. The loading of **4**{*1*} was determined after converting to 2-(4′-methoxyphenyl)aminoethanol (**5**{*1*}) using lithium borohydride. All the solid-phase transformations were monitored by swollen-resin magic angle spinning NMR (SR-MAS NMR)[4e,8] and IR spectra.

Polymer-supported α-imino acetate **4**{*1*} thus prepared was first used in Mannich-type reactions with silyl nucleophiles.[9] In the presence of 20 mol % $Sc(OTf)_3$, **4**{*1*} was treated with the silyl enolate derived from methyl isobutyrate at room temperature for 20 h in dichloromethane−acetonitrile (1:1). The resulting resin was treated with NaOMe at room temperature for 1 h in THF−methanol (1:1) to afford γ-oxo α-amino acid derivatives **6a** in 76% yield. Other examples of the Mannich-type reactions in the solid phase are shown in Table 1. The silyl enolates derived from esters as well as ketones reacted smoothly to afford γ-oxo α-amino acid derivatives (**6a**−**d**), which are an interesting class of biologi-

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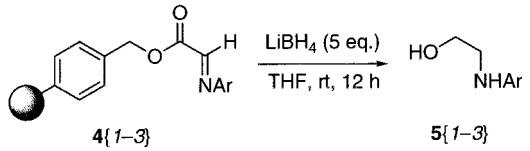
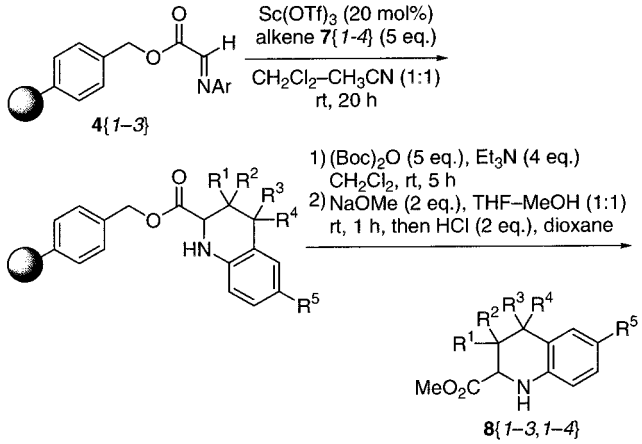
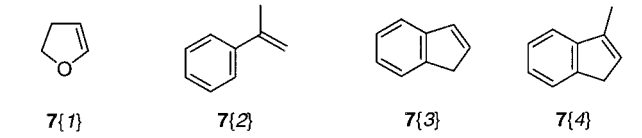
**Scheme 2.** Reductive Cleavage of **4**



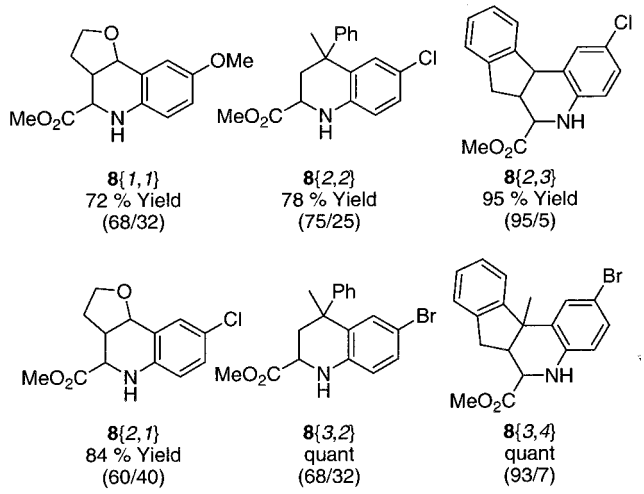

**Scheme 3.** Synthesis of Tetrahydroquinoline Derivatives




Starting alkenes




Products




cally important compounds.[10] When Danishefsky's diene[11] was used as a nucleophile (entry 5), 2-methoxycarbonyl-1-(4′-methoxyphenyl)-1,2,3,4-tetrahydro-pyridin-2-one (**6e**) was obtained in 69% yield.

α-Imino acetates **4** were also successfully used for the preparation of tetrahydroquinoline derivatives.[12] In the presence of a catalytic amount of $Sc(OTf)_3$, **4**{*1*} reacted with dihydrofuran (**7**{*1*}) at room temperature for 20 h in dichloromethane−acetonitrile (1:1) to give 2-methoxycarbonyltetrahydroquinoline derivative (**8**{*1,1*}) in 72% yield after cleavage from the polymer support. Other examples are shown in Scheme 2. In all cases, the desired reactions proceeded smoothly in the solid phase to afford the corresponding tetrahydroquinoline derivatives in good to excellent yields (Scheme 3). It should be noted that halogen substitutions on aryl groups assist further transformations.

In summary, novel polymer-supported α-imino acetates (**4**) have been successfully prepared from chloromethylated resin, and they have been used in several useful synthetic reactions. $Sc(OTf)_3$ was found to be an excellent catalyst in these syntheses. It should be noted that unstable α-imino acetates in the liquid phase were stabilized by immobilizing in the solid phase and that biologically important α-amino acid derivatives were prepared in high yields using **4**. Further investigations to perform biological tests of the α-amino acid derivatives synthesized as well as to use **4** in other synthetic reactions are now in progress.

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**Supporting Information Available.** Experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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