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Straightforward and General Method for Coupling Alcohols to Solid Supports

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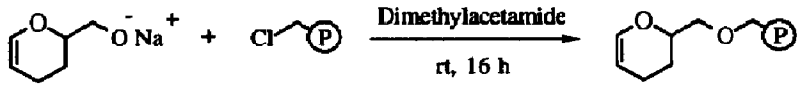
Abstract: *A new method for attaching alcohols to solid supports has been developed employing dihydropyran-functionalized resin. High loading levels are obtained for primary and secondary as well as functionalized alcohols. The attachment functionality is stable to both strongly basic and nucleophilic reagents. However, the alcohols can readily be cleaved from the support with PPTS in 1:1 butanol/1,2-dichloroethane.*

Solid-phase synthesis has become increasingly important for the construction of biopolymers,[1] polymer-supported reagents and catalysts,[2] and most recently, organic compound libraries.[3] Central to the success of any solid-phase synthesis strategy is a straightforward and general method for coupling the initial starting materials onto the solid support. Attachment to the solid support through alcohol functionality provides one of the most versatile strategies. Accordingly, a number of methods have been developed to couple alcohols through ester,[4] silyl ether[5] and trityl ether[6] functionality. While these methods have been very useful for the synthesis of biopolymers, their utility in the solid-phase synthesis of many organic compound libraries is limited by the lability of the attachment functionality to nucleophilic or basic reagents, and/or difficulties in obtaining useful loading levels, particularly for secondary alcohols. Herein, we report a dihydropyran-functionalized support which provides a general and straightforward method for alcohol attachment through the base-stable tetrahydropyranyl (THP) ether linkage.

The THP protecting group has been employed extensively in organic synthesis. Even hindered alcohols can be coupled to dihydropyran in high yield under very mild conditions, and the THP ether product is stable to most basic reagents. In solution-based organic synthesis, the addition of the THP group to a molecule introduces a stereocenter, which for chiral molecules, results in diastereomers that often complicate chromatographic purification and NMR evaluation. However, on solid support these complications do not occur with a tetrahydropyranyl-based linkage agent since product isolation is accomplished simply by washing away excess reagent from the support-bound material, and analytical evaluation predominately is performed on compounds after cleavage of the compounds from the solid support.[7]

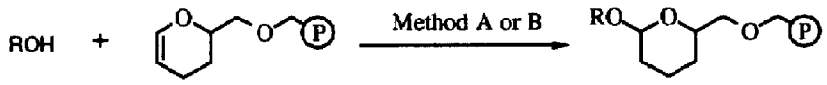
The dihydropyran-functionalized support is synthesized in a single step as shown in eq 1. Merrifield resin (chloromethylpolystyrene-1%-divinylbenzene) is treated with the sodium salt of (6-hydroxymethyl)3,4-dihydro-2*H*-pyran (**1**)[8] in dry N,N-dimethylacetamide at rt for 16 h. The resin is then rinsed with CH_2Cl_2 (1x), 1:1 DMF/H_2O (4x), DMF (3x), and CH_2Cl_2 (3x) and dried *in vacuo*. In this form the functionalized resin is stable indefinitely.



(1)

1 **2**

Alcohols are attached to the resin employing PPTS in 1,2-dichloroethane at 80 °C for 16 h (method A).[9] Alternatively, the alcohol can be coupled to the support employing anhydrous p-TsOH at 0 °C for 16 h (method B).[10] The reactions conditions were chosen to ensure complete coupling of the alcohol to the support, although for most alcohols shorter reaction times or lower temperatures can be employed. Loading levels are determined by cleaving the alcohol from the resin employing PPTS in 1:1 butanol/1,2-dichloroethane at 60 °C.[11] Treatment of the resin with 95:5 trifluoroacetic acid/H_2O for 15 min also results in complete cleavage of the material from the resin, and provides a particularly effective strategy for the concomitant removal of standard acid labile protecting groups employed in solid-phase peptide synthesis. As shown in Table 1, both primary and secondary alcohols can be coupled to the solid support with high efficiency. In addition, no decomposition of the functionalized alcohols epiandosterone (**5**) and the 4-hydroxyproline derivative **7** was observed in the coupling or cleavage steps. Tertiary alcohols, however, show very poor loading efficiencies



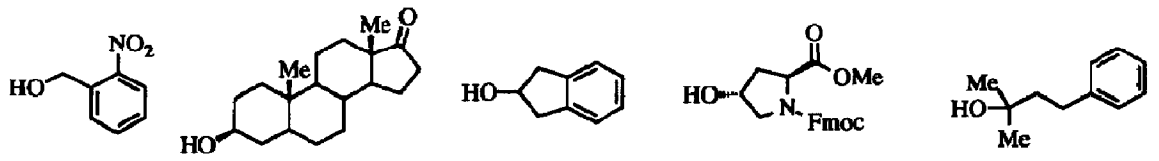
(2)

2 **3**

Table 1. Coupling alcohols to the solid support **2** (eq 2).

Entry	Alcohol	Rxn Method[1]	Loading Level	Yield[2]
A	**4**	A	0.49 mequiv/g	79%
B	**5**	A	0.51 mequiv/g	84%
C	**5**	B	0.51 mequiv/g	84%
D	**6**	A	0.50 mequiv/g	77%
E	**6**	A[3]	0.43 mequiv/g	66%
F	**7**	A	0.54 mequiv/g	95%
G	**8**	A	0.07 mequiv/g	10%

(1) In method A, the resin is stirred with 2 equiv of PPTS and 5 equiv of alcohol at a 0.4 M concentration at 80 °C for 16 h. In method B, the resin is stirred with 1 equiv of p-TsOH and 5 equiv of alcohol at a 0.4 M concentration at 0 °C for 16 h. (2) The yield is based on the initial chloride loading level of the Merrifield resin (0.77 mequiv/g). (3) Only 2 equiv of 2-indanol were employed in this experiment.



4 5 6 7 8

Fig. 1. Alcohols that are coupled to the solid support (see Table 1).

as demonstrated for alcohol **8** in entry G, and define a limit to the coupling strategy. In most of the coupling experiments, five equivalents of the starting alcohol were employed relative to the theoretical number of sites on the resin. However, for expensive alcohols as little as two equivalents of alcohol can be employed to obtain useful loading levels as observed for coupling 2-indanol (**6**) to the support (entry E).

The reported method to attach alcohols to the solid support has successfully been employed to attach a number of alcohols to solid-supports and is currently being utilized in the construction of several organic compound libraries.

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7 Complete reactions on solid support should be observed even if the diastereomeric tetrahydropyranyl derivatives react at different rates since excess reagents are inherently employed to drive reactions to completion.

8. (6-Hydroxymethyl)3,4-dihydro-2*H*-pyran is prepared by $LiAlH_4$ reduction of commercially available (3,4-dihydro-2*H*-pyran-2-ylmethyl)3,4-dihydro-2*H*-pyran-2-carboxylate (Fluka) followed by distillation under reduced pressure. In the coupling reaction, three equiv of sodium salt **1** (0.2 M in N,N-dimethylacetamide) are employed relative to chloromethyl sites on the Merrifield resin. After the alkoxide displacement, no chloride remained on the resin as determined by elemental analysis.

9. General conditions for method A. Resin **2** (1.05 g, 0.780 mequiv) is solvated in 7.8 mL of 1,2-dichloroethane. The alcohol (3.9 mmol) and PPTS (0.39 g, 1.6 mmol) are added. The mixture is stirred at 80 °C for 16 h. The resin is then washed with CH_2Cl_2 (1x), 1:1 DMF/H_2O (4x), DMF (3x), and CH_2Cl_2 (3x) and dried *in vacuo*.

10. General conditions for method B. Resin **2** (1.05 g, 0.780 mmol) is solvated in 7.8 mL of CH_2Cl_2 at rt for 15 min. The alcohol (3.9 mmol) is then added and the mixture is chilled to 0 °C followed by addition of *p*-TsOH (134 mg, 0.780 mmol) in one portion. The resulting slurry is stirred at 0 °C for 16 h. The resin is then washed with CH_2Cl_2 (1x), 1:1 DMF/H_2O (4x), DMF (3x), and CH_2Cl_2 (3x) and dried *in vacuo*.

11. General conditions for cleaving alcohols from the solid support. Alcohol derivatized support (1.0 g, 0.74 mmol) is solvated in 20 mL of 1:1 *n*-butanol/1,2-dichloroethane, and PPTS (370 mg, 1.48 mmol) is then added. The flask is stoppered and heated to 60 °C for 16 h. The solution is isolated by filtration and concentrated *in vacuo*. The resulting material can be separated from the PPTS either by extraction or flash chromatography.

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