# Preparation of Reusable Dihydropyran-Functionalized Resins Cross-Linked with Tetrahydrofuran

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**Abstract:** The novel dihydropyranyl-functionalized resins, referred to as "JJ-DHP", prepared from JandaJel-Cl resin, have been developed. We have also clarified that JJ-DHP has shown a good swelling property in common organic solvents and reusable ability in solid-phase organic synthesis.

**Keywords:** Dihydropyran, resin, reusable solid-phase organic synthesis, swelling property.

## INTRODUCTION

In recent years, solid-phase organic synthesis (SPOS) has evolved into a widely used synthetic tool for the construction of biopolymers, catalysts, and more complicated organic compound libraries [1]. The main advantages of SPOS are that its reactions can be driven to completion by the use of a large molar excess of reagents, and that desired products can be isolated easily by simple filtration and removed from chemically inert insoluble polymers (resins). Moreover, SPOS enables the automation of all steps in a synthesis protocol: the addition of reagents, agitation, filtration, and washing. Despite these advantages, this technique presents some drawbacks: the physicochemical parameters of the resin, such as loading capacity, bead size, and swelling properties, can influence the reaction kinetics. Side reactions with the polymer support itself may occur. We focused on *J*anda*J*el (JJ) polystyrene resins [2], which are cross-linked with a polytetrahydrofuranic structure because they exhibit excellent swelling characteristics when evaluated against commercially available Merrifield resins, which are cross-linked with divinylbenzene [3]. JJ resins can swell well in common organic solvents (even in lower polar solvents such as benzene and toluene). Among commercially available JJ resins, those with a chloromethyl group (JJ-Cl), an aminomethyl group (JJ-$NH_2$), a hydroxymethyl group (JJ-OH), or a (4-hydroxymethyl)phenoxymethyl group (JJ-Wang-OH) are known as versatile JJ resins. In recent years, JJ resins with a triphenylphosphine group (JJ-TPP) have also been developed as a reusable organocatalyst [4].

In the course of our research toward the development of novel chemical tools for the construction of our chemical libraries, we needed novel resins with good swelling properties, reactivity to an alcohol functional group, and reusability. The resins with a dihydropyranyl group (DHP) are attractive because they can satisfy these requirements. However, only a few reports regarding the preparation and swelling properties of DHP-functionalized resins have published, though most such resins were prepared from Merrifield resins, SynPhase [5] Lanterns, or linear polystyrene-supported polymers [6]. Therefore, we speculated that JJ resins with a DHP group (JJ-DHP) should become a valuable asset for solid-phase organic synthesis.

In this paper, we report the preparation and properties of JJ-DHP. Its application to solid-phase organic synthesis and its reusability are also discussed.

## RESULTS AND DISCUSSION

The preparation of JJ-DHP is shown in Scheme **1**. The commercially available JJ-Cl, with a loading level of 0.96 mmol/g, was shaken with sodium salt of 3,4-dihydro-2*H*-pyran-2-methanol, which was prepared by treatment with sodium hydride, in dry *N*,*N*-dimethylformamide (DMF) at room temperature for 18 h. The resulting reddish-brown resins were then washed with DMF, dichloromethane, and methanol, and then dried *in vacuo* for 48 h to give JJ-DHP [7]. The loading level of JJ-DHP was determined to be 0.469 mmol/g by FMOC release assay [8]. The resulting JJ-DHP was thermally stable and was also mechanically stable against magnetic stirring during a 48 h period.

Next, the swelling property of JJ-DHP was estimated in several common solvents [9]. The Merrifield resins with a DHP group (MR-DHP) were also prepared to compare the relative importance of cross-linkers in resins: a cross-linker with a polytetrahydrofuranic structure for JJ resins and a cross-linker with divinylbenzene for MR resins (Scheme **1**). The results are summarized in Table **1**.

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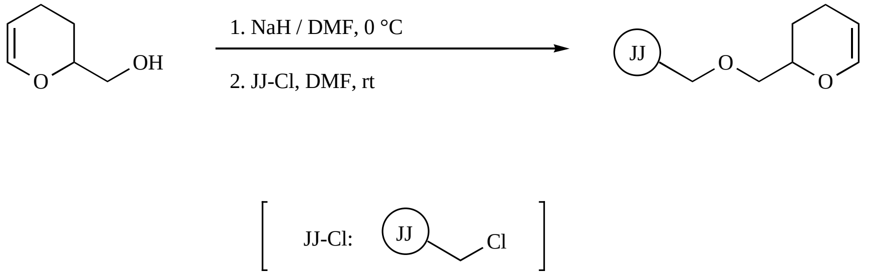


**Scheme 1.** Preparation of JJ-DHP and MR-DHP.

**Table 1. Swollen Volume (mL/g) of Various Resins.** [a]

| Entry | Resins | DMF | $CH_2Cl_2$ | 1,2-DCE [b] | MeOH | THF | $CH_3CN$ |
|---|---|---|---|---|---|---|---|
| **1** | **JJ-DHP** | **7.0** | **10.0** | **8.6** | **1.2** | **10.8** | **2.0** |
| 2 | MR- DHP | 5.2 | 8.3 | 7.5 | 1.1 | 8.6 | 1.5 |
| 3 | JJ-Cl [c] | 5.4 | 7.8 | 7.4 | 0.89 | 8.3 | 1.3 |
| 4 | MR-Cl [c] | 4.0 | 5.9 | 4.7 | 0.80 | 5.5 | 1.1 |

[a]Volumes were measured in syringes equipped with a sintered frit after equilibrating for 24h. [b]1,2-dichloroethane. [c]These resins were purchased from Aldrich Chemical Co. Inc., and used as received.

JJ-DHP was found to have superior swollen volumes compared to the corresponding MR-DHP in all solvents tested (Entries 1 and 2). The distinctive advantage of the swelling property of JJ-Cl over that of MR-Cl is consistent with the theoretical explanation (Entries 3 and 4). It is also noteworthy that the chemical transformation to the DHP group from the chloro group leads to higher swollen volumes of the resins prepared in this study (Entries 1 and 2 (for entries 3 and 4, respectively)). These findings indicate that the increased hydrophilic character of a resin significantly affects its swelling properties. Ether group, which was connected with a resin backbone and a DHP group, may also play an important role in increased swollen volumes. Preparation of JJ resins with greater hydrophilicity should lead to the development of novel JJ resins with better swelling ability.

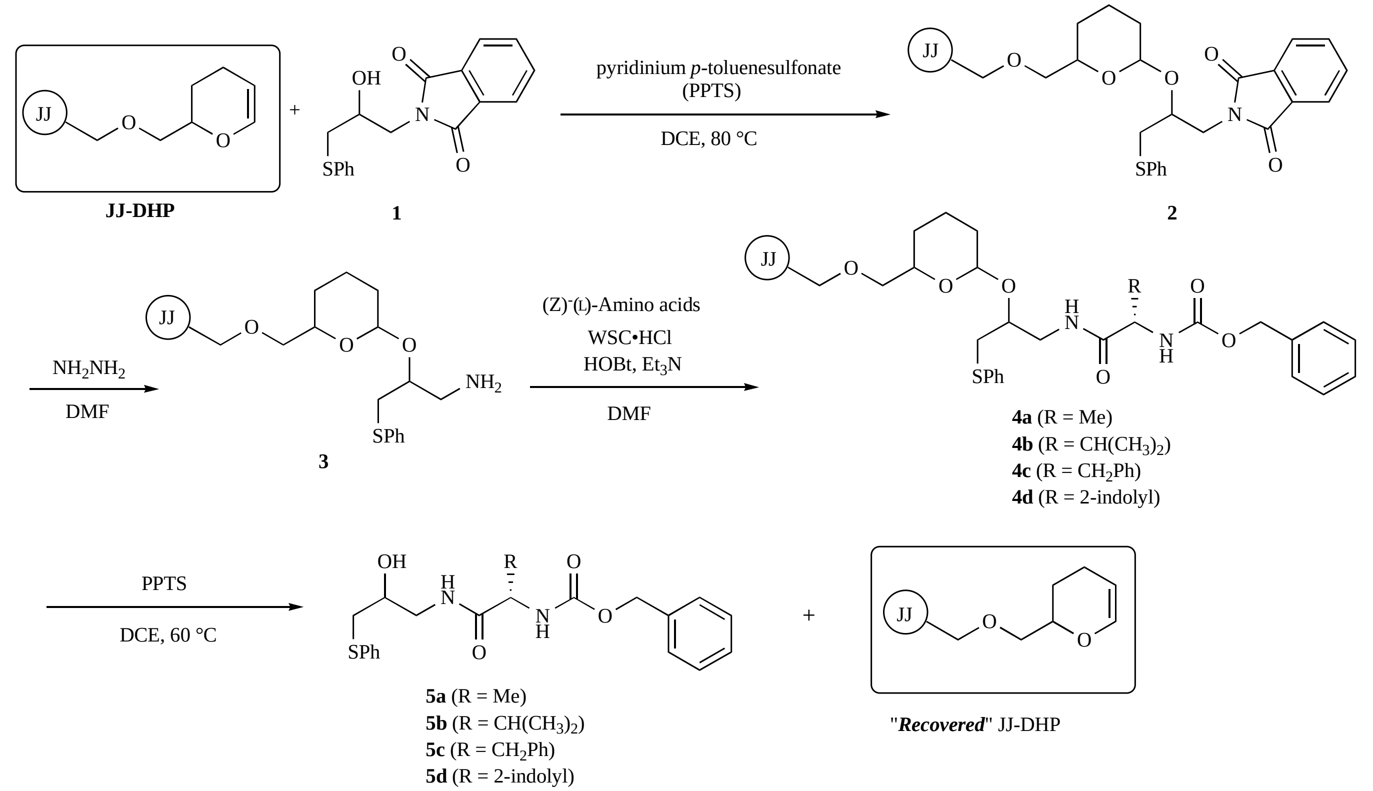
To investigate the application of JJ-DHP in organic synthesis, we used it for the synthesis of amino acid-functionalized alcohol derivatives (**5a-d**), which we needed for another project regarding chemical library of peptidomimetics. The reaction scheme is outlined in Scheme **2**.

Alcohol derivative **1** was attached to JJ-DHP employing pyridinium *p*-toluenesulfonate (PPTS) in 1,2-dichloroethane (DCE) at 80 °C, and then tetrahydrofuranyl-functionalized JJ resins **2** was obtained. The coupling reaction of four ($_L$)-amino acid derivatives (alanine, valine, phenylalanine, and tryptophane) with amine-functionalized resins **3**, obtained by treatment of **2** with hydrazine, in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSC-HCl) and 1-hydroxybenzotriazole (HOBt) proceeded at room temperature smoothly to give resins **4a-d**, respectively. These coupling reactions were monitored by Kaiser Test. Cleavage of **4a-d** with PPTS in DCE at 60 °C gave amino acid-functionalized alcohol derivatives **5a-d**, accompanied by the recovery of JJ-DHP [10]. Compounds **5a-d** were identified by comparison with spectral data of compounds **5a-d** obtained by conventional solution-phase organic synthesis. The overall isolated yields of **5a-d** were determined to be 17% (for **5a**), 20% (for **5b**), 19% (for **5c**), and 21% (for **5d**) yields, based on the initial loading level of JJ-DHP, respectively. The lower yield may be attributed to a lower loading rate in the steps of synthesis of **2** and the cleavage of **4a-d**, because Kaiser Test allowed us to thoroughly monitor the synthetic steps from **2** to **4**.

Finally, we investigated the reusability of "recovered JJ-DHP" as a by-product in this study. The loading level of "recovered JJ-DHP" was determined to be 0.330 mmol/g by the FMOC release assay mentioned above. Therefore, it was clarified that the "recovered JJ-DHP" had a loading level of about 70% that of the original JJ-DHP. Moreover, the loading level of "recovered JJ-DHP (2nd generation)", obtained from SPOS in scheme 2 by using "recovered JJ-DHP" as a starting resin, was determined to be 0.234 mmol/g. This indicates that even the "recovered JJ-DHP (2nd generation)" has a loading level of about 50% that of the original JJ-DHP. Therefore, JJ-DHP should become a versatile resin for solid-phase organic synthesis.

## CONCLUSIONS

We have succeeded in synthesizing the novel dihydropyranyl-functionalized JJ resin (JJ-DHP) with good swelling property in common organic solvents. We have also demonstrated JJ-DHP's usefulness for reacting with an alcohol derivative in solid-phase organic synthesis, and as well as its great ability as a reusable resin. Further studies on the scope and limitation of JJ-DHP in organic synthesis are in pro-



**Scheme 2.** SPOS of amino acid-functionalized alcohol derivatives (**5**) by using JJ-DHP.

gress, and the construction of a chemical library by using JJ-DHP will be described elsewhere.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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