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First preparation of a novel polyol resin for purifying arylboronic acids

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Abstract

A novel polystyrene-supported triol resin was first prepared by reaction of the Merrifield resin with trometamol. Using this resin, arylboronic acids were efficiently isolated and purified through a "capture-release" procedure in organic solvents. However, in basic aqueous solvents arylboronic acids were immobilized on the resin only with low yield.

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Boronic acids have become an extremely important reagents in organic chemistry and medicinal chemistry. They are widely used in organic synthesis with the developments in Miyaura–Suzuki couplings, copper-catalyzed arylboronic acid–heteroatom coupling and the Petasis reactions [1–3]. They are also used as biologically active agents such as protease enzyme inhibitors, boron neutron capture agents for brain tumors, carbohydrate sensors[4–6]. However, boronic acids are difficultly isolated and purified by conventionals methods due to their polarity and unstability [7]. Arylboronic acids could form five or six-membered cyclic boronic esters with *cis*-diol or catechol, especially in anhydrous organic solvents [8]. Accordingly, many diol-based insoluble resins have been used to isolate boronic acids, such as the *N*,*N*-diethanolaminomethyl polystyrene resin (DEAM-PS), and catechol polystyrene resin [9,10]. A patent on DEAM-PS resin has been applied because of the excellent property in isolating boronic acids [11]. Boronic acids could be immobilized on these resins quantitatively or with satisfying yield in anhydrous solvents, particularly in THF. However, these resins were not efficient for the immobilization of boronic acids in water or water–organic mixed solvents. Matteson reported a useful generalization on the process of the thermodynamic hydrolysis of boronic esters in 1 mol/L aqueous sodium hydroxide (shown in Fig. 1) [12]. It was indicated that the major species present was the bicyclic anion **1** by the ¹H NMR spectrum. In the present study, we aim to synthesis a novel triol-based resin to investigate its immobilization effect of arylboronic acids in the organic and basic aqueous solutions.

The Merrifield resin (chloromethyl polystyrene resin) is one of the most popular resin in solid-phase synthesis. Treatment of the Merrifield resin (loading 1.2 mmol/g, 200-400 mesh) with trometamol in the presence of

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Fig. 1. Hydrolysis of phenylboronic esters.



Scheme 1. Preparation of the triol resin.

diisopropylethylamine (DIPEA) in alcohol gave the desired triol resin (Scheme 1). The loading degree was determined to be about 1.1 mmol/g by elemental analysis of the resin (anal. found C 85.57, H 7.81, N 1.53, Cl 0.05).

This triol resin was found to be efficient in immobilizing arylboronic acids in many organic solvents at room temperature, which was slightly less efficient than reported DEAM-PS resin (Table 1, entries 1-3). The electron donating or withdrawing group on phenyl ring had no obvious influence on the immobilizing effect (entries 4, 5). Cleavage of the boronic acids from the resin was carried out in a THF/water/acetic acid (90/5/5) mixture solvent and gave the pure products which were characterized by their ¹H NMR spectra. The resin could be recycled with no apparent loss of efficiency after neutralization with base washings (for example, triethylamine/THF 1/8) (entries 6, 7).

Moreover, the immobilization effect of arylboronic acids in aqueous solutions had been investigated (Table 2). The resin had none effect in neutral aqueous solution (entry 1). Although the bicyclic anion 1 was the major species present, the resin was not enough efficient in basic aqueous solutions due to the poor swelling of the resin in water perhaps. The yield in 1 mol/L sodium hydroxide water solution was only 17%, and in the mixture of 4 mol/L sodium

Table 1

The immobilization of boronic acid in organic solvents^a.



Entry	R (equiv.)	Solvent	Yield (%)
1	$4-\text{Me-C}_6\text{H}_4$ (0.8)	THF	89
2	$4-\text{Me-C}_6\text{H}_4$ (0.8)	DCM	75
3	$4-\text{Me-C}_6\text{H}_4$ (0.8)	EAC	83
4	C_6H_4 (0.8)	THF	84
5	$3-NO_2-C_6H_4$ (0.8)	THF	90
6 ^b	$4-\text{Me-C}_6\text{H}_4$ (0.8)	THF	84
7 ^c	$4-Me-C_6H_4$ (0.8)	THF	87

^a Immobilization was carried out by shaking a slight excess of resin $\mathbf{1}$ (1.0 g) with the boronic acid (0.88 mmol, 0.8 equiv.) in the given solvent (10 mL) at room temperature for 12 h. Release was carried out by shaking the resin-bound boronic acid for 2 h in a THF/H₂O/AcOH mixture (90/5/5).

^b The resin had been used for the second time.

^c The resin had been used for the third time.

Table 2 The immobilization of boronic acid in basic aqueous solutions^a.



Entry	R (equiv.)	Solvent	Yield (%)
1	$4-\text{Me-C}_6\text{H}_4\ (0.8)$	H ₂ O/MeOH (1/3)	<5
2	$4-\text{Me-C}_6\text{H}_4$ (0.8)	1 N NaOH	17
3	$4-\text{Me-C}_6\text{H}_4$ (0.8)	4 mol/L NaOH/MeOH (1/3)	35
4	C_6H_4 (0.8)	4 mol/L NaOH/MeOH (1/3)	33
5	$3-NO_2-C_6H_4$ (0.8)	4 mol/L NaOH/MeOH (1/3)	44
6	$4-\text{Me-C}_6\text{H}_4$ (0.8)	1 mol/L NaOH in MeOH	68

^a Immobilization was carried out by shaking a slight excess of resin $\mathbf{1}$ (1.0 g) with the boronic acid (0.88 mmol, 0.8 equiv.) in the given solvent (10 mL) at room temperature for 24 h. Release was carried out by shaking the resin-bound boronic acid for 2 h in a THF/H₂O/AcOH mixture (90/5/5).

hydroxide water solution and methanol (1/3) was not satisfying also (entries 2, 3). The yields were 14% and 22%, respectively using DEAM-PS resin under the same conditions. The yield of 3-nitrophenylboronic acid was higher due to the stronger acidity perhaps (entry 5). Boronic acid was obtained with 68% yield in basic methanol solution (entry 6), but was obtained with 41% yield using DEAM-PS resin.

In conclusion, a polystyrene-supported triol resin was first prepared conveniently. The resin could fish out the desired arylboronic acid in organic solvents with satisfying yield. Unluckily, the resin had poor efficiency in aqueous solutions. The efficiency of the resin was slightly less than DEAM-PS resin in organic solvents, but was slightly higher in basic conditions. Further work on expanding the use of the resin is under way.

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