

# Articles

## Resins with Identical Specifications Are Not Identical. Identifying a Useful Solid-Phase Resin

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The quality of the most commonly used support for solid-phase syntheses, polystyrene resin cross-linked with 1% of divinylbenzene, differs considerably even among different lots of resin from the same source. Determination of the swelling capacity of resins before carrying out solid-phase syntheses represents a very simple means of nondestructive presynthetic resin characterization.

### Introduction

Successful solid-phase organic syntheses (SPOS) are well-known to largely depend on the properties and quality of the relevant solid support.<sup>1,2</sup> The original Merrifield resin, based on polystyrene (PS) cross-linked with divinylbenzene (DVB), is the solid support of choice for most SPOS applications and versions of this fundamental resin are available from numerous vendors. Because they are functionalized copolymers, analysis of the quality and application reproducibility of individual resin batches is problematic. Practitioners of solid-phase syntheses are thus faced with a problem of obtaining a resin that provides reliable, reproducible, and satisfactory outcomes of polymer-supported transformations. Although resins from different and the same sources may have identical specifications (descriptive/nominal parameters, typically cross-linking, substitution, bead size), they often behave differently in solid-phase syntheses. As pointed out more than fifteen years ago by Pugh and co-workers “The advertised cross-linking, mesh-size, and substitution of commercially available polystyrene resins are rarely correct”.<sup>1</sup> Although resin quality has improved, in general, over the years, our experience with currently available resins indicated that the quality and batch to batch reproducibility is still a relevant issue of concern. To address the inequality of “equal” resins, we carried out model transformations on several supposedly “identical” resins and arrived at a simple test to address the suitability of a resin for SPOS.

Our aim was to compare performance of the most commonly used support for solid-phase syntheses, polystyrene resin cross-linked with 1% of divinylbenzene, from

different lots and suppliers. Unlike numerous reports that compared various kinds of solid supports to identify resin parameters relevant for particular and sometimes diverse synthetic needs,<sup>3–7</sup> we compared resins that had identical specifications but were either provided by different suppliers or originated from different lots.

### Results and Discussion

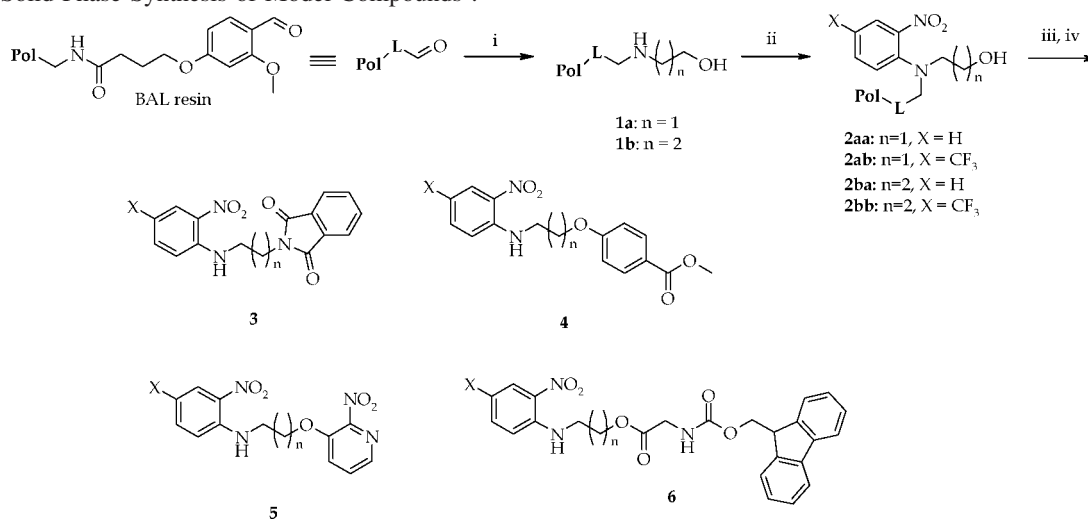
To compare resins, we carried out a synthetic sequence developed for traceless solid-phase syntheses of nitrogen-containing heterocycles.<sup>8,9</sup> The first two steps, portrayed in Scheme 1, included reductive amination of the backbone amide linker (BAL) resin, followed by reaction with aryl fluorides. To expand the diversity of compounds made, we included amino alcohols in representative reductive amination reactions. In the next step, we transformed the individual alcohols to the corresponding amines, ethers, and esters by Mitsunobu reactions with phthalimide, phenols, and acids, respectively. Typically, these reactions were complete within 1 h. When performing the reactions using a new batch of resin obtained from the same vendor, we observed incomplete conversion.<sup>10</sup>

To determine whether the observed reactivity differences were not just the result of resin variation from a single source, we acquired two additional resins from different sources (Table 1) and carried out a set of model reactions using identical polymer-supported intermediates prepared from all four resins. Using reported procedures,<sup>10</sup> we prepared four different resin-bound intermediates **2** that differed by the length of side-chain bearing the hydroxyl group and electronic properties of the aromatic ring. Polymer-supported alcohols **2** were reacted with phthalimide, methyl 4-hydroxybenzoate, 3-hydroxy-2-nitropyridine, and Fmoc-Gly-OH under Mitsunobu conditions.

After each reaction, a sample of resin was treated with TFA in DCM to release the resin-bound components gener-

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**Scheme 1.** Solid-Phase Synthesis of Model Compounds<sup>a</sup>.

<sup>a</sup> Reagents and conditions: (i) amine, 10% AcOH/DMF, overnight, then NaBH(OAc)<sub>3</sub>, 5 h; (ii) 1-fluoro-2-nitrobenzenes, DIEA, DMSO, overnight, 80 °C for compounds **2aa** and **2ba**, ambient temperature for **2ab** and **2bb**; (iii) for reaction conditions see experimental part; (iv) 50% TFA in DCM, 1 h.

**Table 1.** Specifications of Aminomethyl Polystyrene–1% Divinylbenzene Resins

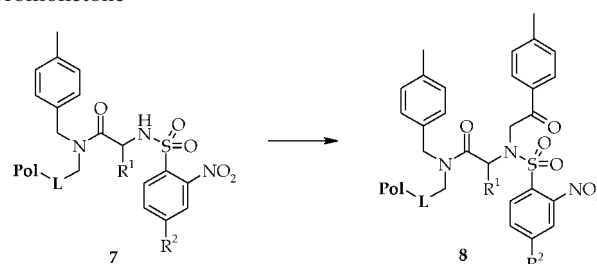
resin	loading [mmol/g]	bead size [mesh]	swelling in DCM [mL/g]
<b>A</b>	0.78	100–200	5.5
<b>B</b>	0.88	100–200	7.8
<b>C</b>	0.90	100–200	8.1
<b>D</b>	1.28	200–400	12.5

**Table 2.** Conversion of Resin-Bound Alcohols **2** with Model Substrates

resin	<b>3aa</b>	<b>3ab</b>	<b>4aa</b>	<b>4ab</b>	<b>5ba</b>	<b>6aa</b>	<b>6ab</b>	<b>3ba</b>
<b>A</b>	63%	45%	77%	63%	60%	59%	53%	76%
<b>B</b>	85%	93%	97%	88%	95%	90%	89%	93%
<b>C</b>	95%	95%	97%	93%	NT	98%	96%	96%
<b>D</b>	86%	92%	97%	90%	NT	97%	96%	97%

ated. Conversion to products **3** to **6** was determined by LCMS analyses of cleaved samples. The presence of the 2-nitroaniline moiety in all of the compounds provided an internal calibration that allowed simple quantification by integration of LC traces at 440 nm. The results are summarized in Table 2. Data indicated that in reactions using resins that swelled to less than 7 mL/g of dry resin, a substantial amount of starting material **2** was recovered. On the other hand, bead size and loading did not exhibit any significant effect on reaction rate. The Mitsunobu reaction with resin-bound alcohol **2** synthesized on resin **A** was not complete even after overnight reaction.

Unrelated chemical transformations that also showed substantially reduced reaction rates with resin **A** included alkylation of nitrobenzenesulfonamides **7** with bromoketones

**Scheme 2.** Alkylation of Nitrobenzenesulfonamides with a Bromoketone<sup>a</sup>

<sup>a</sup> Reagents and conditions: 0.5 M 2-bromo-4'-methylacetophenone, 1 M DIEA in DMF, overnight.

(Scheme 2). Table 3 compares conversion of resin-bound sulfonamides **7** to alkylated species **8** using resins **A** and **B**.

In all model experiments, the polymer-supported intermediates prepared from resin **A** provided unsatisfactory transformation to products. Interestingly enough, resins **A** and **B** originated from the same vendor, they differed just by lot number. We were obviously interested in finding an easily observable parameter that would indicate differences between resin **A** and the other resins. Our experiments have shown that transformation of model reactions correlated with resin swelling. We measured resin swelling in DCM, and the results are listed in Table 1. Swelling differed considerably even among different lots of resin from the same source.

The effect of resin swelling has been reviewed<sup>2</sup> and efficient swelling of 1%-DVB cross-linked PS resins is known to be essential for reactivity, and reportedly, significantly diminished swelling caused synthetic problems in peptide coupling.<sup>11–14</sup> We suspect that the low swelling

**Table 3.** Comparison of Resins **A** and **B** in Alkylation Reaction

resin	swelling DCM	loading [mmol/g]	compound	temperature	R <sup>1</sup>	R <sup>2</sup>	conversion [%]	purity [%]
<b>A</b>	5.5	0.78	<b>8ab</b>	RT	H	NO <sub>2</sub>	75	70
<b>A</b>	5.5	0.78	<b>8bb</b>	RT	CH <sub>3</sub>	NO <sub>2</sub>	70	70
<b>B</b>	7.8	0.88	<b>8ab</b>	RT	H	NO <sub>2</sub>	99	97
<b>B</b>	7.8	0.88	<b>8bb</b>	RT	CH <sub>3</sub>	NO <sub>2</sub>	99	97
<b>A</b>	5.5	0.78	<b>8aa</b>	RT	H	H	20	ND
<b>A</b>	5.5	0.78	<b>8aa</b>	40 °C	H	H	95	ND
<b>B</b>	7.8	0.88	<b>8aa</b>	RT	H	H	96	ND

capacity of a particular resin is caused by higher level of cross-linking.<sup>1</sup> Higher cross-linking is known to increase the half-lives of polymer-supported reactions.<sup>15</sup> Unfortunately, resin suppliers typically do not provide the swelling capacity of resins.

To conclude our observations, determination of the swelling capacity of resins before carrying out solid-phase synthesis represents a very simple means of nondestructive presynthetic resin characterization. Our results indicated that swelling in DCM greater than 7 mL/1 g of dry resin provided satisfactory conversion to products in all model reactions. Lower swelling substantially reduced the conversion rate. Resin suppliers are encouraged to include swelling capacity as one of the specification parameters that characterizes each batch of resin.

### Experimental Section

Aminomethyl polystyrene–1% divinylbenzene resins were obtained from NovaBiochem (San Diego, CA, www.emd-biosciences.com), Advanced ChemTech (Louisville, KY, www.peptide.com), and TCI (Portland, OR, www.tci-america.com/). Resins **A** and **B** were obtained from one vendor, and they differed by a lot number. Resins **C** and **D** were obtained from two other vendors. Resin-bound intermediates **2** and **7** were prepared according to the reported protocols.<sup>10,16</sup>

**Compounds 3, 4, and 6.** Resin-bound intermediates **2** prepared from resins **A**, **B**, **C**, and **D**, 50 mg, were washed with dry NMP. A solution of phthalimide (for compounds **3**), methyl 4-hydroxybenzoate (for compounds **4**), and Fmoc-Gly-OH (for compounds **6**) (0.25 mmol), and PPh<sub>3</sub> (0.25 mmol, 66 mg) in 1 mL of dry NMP was prepared, and diisopropylazodicarboxylate (DIAD, 0.25 mmol, 49  $\mu$ L) was added. The solution was added to the resin, and the resin slurry was shaken for 30 min at ambient temperature.

**Compounds 5.** Resin-bound intermediates **2ba** prepared from resins **A** and **B**, 500 mg, were washed with dry THF. A solution of 3-hydroxy-2-nitropyridine (2.5 mmol, 350 mg) and PPh<sub>3</sub> (2.5 mmol, 656 mg) in 5 mL of dry THF was chilled, and DIAD (2.5 mmol, 484  $\mu$ L) was added. The solution was added to the resin, and the resin slurry was shaken overnight at ambient temperature.

**Compounds 8.** Resin-bound intermediates **7** prepared from resins **A** and **B**, 20 mg, were washed 3 times with DCM and 3 times with DMF. A 0.5 M solution of bromoketone

and 1 M DIEA in 2 mL of DMF were added. The resin slurry was shaken overnight at ambient temperature.

**Analysis of Reaction Mixtures.** After it was washed with the reaction solvent and DCM, a sample of resin was treated with 50% TFA in DCM for 1 h, and the cleavage cocktail was evaporated with a stream of nitrogen. The crude reaction mixture was extracted with methanol, and the reaction mixture components were identified (MS) and quantified (LC) by LCMS.

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