

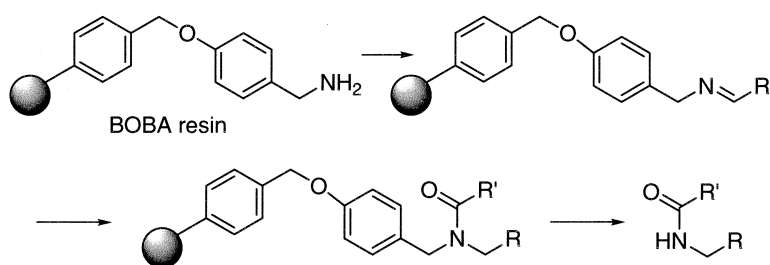
Report

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 for the Synthesis of *N*-Alkylated Amides**

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## Development of a Reductive Alkylation Method Using *p*-Benzyloxybenzylamine (BOBA) Resin for the Synthesis of N-Alkylated Amides

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Naturally occurring molecules having amide bonds, especially peptidyl amides, show various bioactivities, and it is desirable to develop a new method for the synthesis of terminally N-alkylated amides in the solid phase from the point of view of molecular diversity. N-Reductive alkylation followed by acylation was often used for the synthesis of N-alkylated amide. Although several successful studies of N-reductive alkylation have already been made in the solid phase,<sup>1–3</sup> the alkylations were achieved in almost all cases by in situ methods using excess amounts of aldehydes and reducing reagents. According to these methods, however, dialkylation cannot be avoided, especially in the reactions using sterically less hindered aldehydes. Furthermore, the yields of acylation were often low when sterically hindered aldehydes or acylating reagents were used.<sup>1a</sup> To solve these problems, we adopted a two-step N-reductive alkylation procedure using sterically less demanding *p*-benzyloxybenzylamine (BOBA) resin. In the previous paper, we have already developed a new type of polymer-supported amine, BOBA resin (**1**).<sup>4</sup> BOBA resin is readily prepared, and cleavage from the solid support can be performed under both oxidative and Lewis acidic conditions. In addition, the less hindered amino group of BOBA resin reacts with an aldehyde immediately to form an imine. We decided to use BOBA resin in the reductive alkylation for the synthesis of diverse N-alkylated amides.

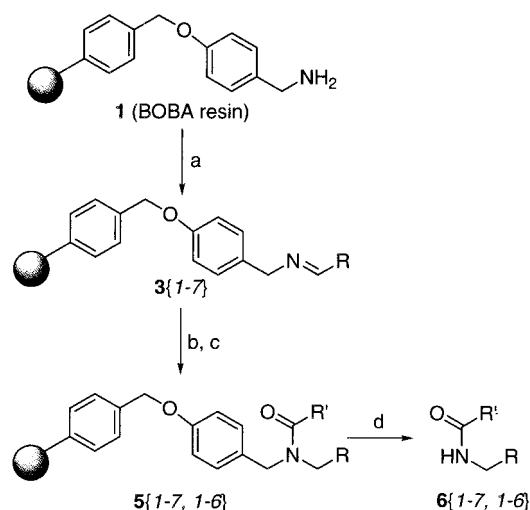
To prevent dialkylation, a two-step procedure including the first imine formation followed by the second reduction step was planned. In liquid phase reactions, aliphatic and  $\alpha,\beta$ -unsaturated imines are known to be unstable due to enamine isomerization, self-condensation, etc., which often cause lower yields. On the other hand, it was expected that such imines were stabilized in the solid phase.<sup>5</sup> We selected butanal (**2**{5}), isovaleraldehyde (**2**{6}), and (*E*)-cinnamaldehyde (**2**{7}) as models, and imine formation was tested using BOBA resin. It was found that treatment of aldehydes with BOBA resin using trimethylorthoformate (TMOF) as a solvent at room temperature (rt) for 1 h gave the best results, while other conditions using acetic acid or scandium triflate as a catalyst gave lower yields. The imine formation was successfully confirmed by <sup>13</sup>C SR-MAS NMR spectra

**Table 1.** <sup>13</sup>C SR-MAS NMR Chemical Shifts of Polymer-Supported Imines

entry	aldimine	chemical shift (ppm)
1	<b>3</b> {5}	13.84, 19.43, 37.79, 64.46, 70.09, 165.83
2 <sup>a</sup>	<b>3</b> {6}	22.64, 26.38, 64.60, 70.14, 165.49
3	<b>3</b> {7}	64.55, 70.04, 135.66, 141.98, 163.16

<sup>a</sup> The signal of  $-\text{N}=\text{CH}-\text{CH}_2-$  was not observed because of overlapping with the signal of the polystyrene matrix.

**Scheme 1<sup>a</sup>**



<b>2</b> {1–7}		
PhCHO <b>2</b> {1}	<i>p</i> -MePhCHO <b>2</b> {2}	<i>p</i> -ClPhCHO <b>2</b> {3}
<i>o</i> -C <sub>6</sub> H <sub>11</sub> CHO <b>2</b> {4}	<i>n</i> -PrCHO <b>2</b> {5}	<i>i</i> -BuCHO <b>2</b> {6}
<i>(E)</i> -PhCH=CHCHO <b>2</b> {7}		
<b>4</b> {1–6}		
PhCO <sub>2</sub> H <b>4</b> {1}	PhCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H <b>4</b> {2}	FmocGly <b>4</b> {3}
FmocPhe <b>4</b> {4}	FmocVal <b>4</b> {5}	FmocPro <b>4</b> {6}

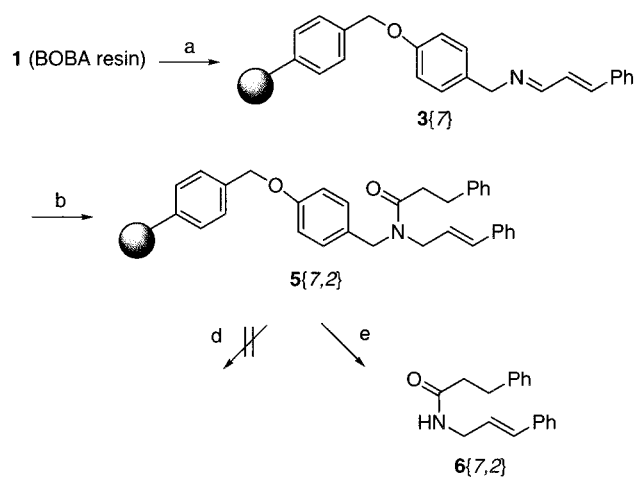
<sup>a</sup> Reagents and conditions: (a) RCHO **2**{1–7}, (5 equiv), TMOF, rt, 1 h; (b) NaBH<sub>4</sub>, DMF:EtOH = 3:1, rt, 1 h; (c) R'COOH **4**{1–6}, (3 equiv), PyBOP (3 equiv), DIEA (6 equiv), DMF, rt, 8 h; (d) CAN (5 equiv), THF: H<sub>2</sub>O = 10:1, rt, 5 h; (e) 50% TFA in CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 h.

(Table 1).<sup>6</sup> It is noted that even the imine derived from the  $\alpha,\beta$ -unsaturated aldehyde formed successfully in the solid phase and that neither starting materials nor side reaction products were observed in the <sup>13</sup>C SR-MAS NMR spectra.

We then examined the preparation of an N-alkylated amide library according to Scheme 1, and the results are summarized in Table 2. Among the reducing reagents tested (e.g., NaBH(OAc)<sub>3</sub>, NaBH<sub>3</sub>CN, borane pyridine complex, and trichlorosilane), NaBH<sub>4</sub> was found to give the best results. In all cases using aromatic and aliphatic aldehydes, the two-step N-reductive alkylation and the amide forming reactions proceeded smoothly. It should be noted that the yields were not reduced when sterically demanding aldehydes (e.g., **2**{1–4}) or carboxylic acids (e.g., **4**{1}, **4**{5–6}) were

**Table 2.** N-Alkylated Amide Library

entry	product	yield (%)	entry	product	yield (%)
1	6{1,1}	58	17	6{4,1}	67
2	6{1,2}	77	18	6{4,2}	82
3	6{1,3}	86	19	6{4,3}	41
4	6{1,4}	57	20	6{4,4}	44
5	6{1,5}	44	21	6{4,5}	79
6	6{1,6}	60	22	6{4,6}	59
7	6{2,1}	87	23	6{5,1}	67
8	6{2,2}	74	24	6{5,2}	77
9	6{2,3}	93	25	6{5,3}	53
10	6{2,4}	65	26	6{5,4}	79
11	6{2,5}	65	27	6{5,5}	65
12	6{2,6}	68	28	6{5,6}	60
13	6{3,1}	73	29	6{6,1}	69
14	6{3,2}	67	30	6{6,2}	82
15	6{3,3}	54	31	6{6,3}	93
16	6{3,4}	57	32	6{6,6}	65

**Scheme 2<sup>a</sup>**

<sup>a</sup> Reagents and conditions: (a) (*E*)-PhCH=CHCHO 2{7}, (5 equiv), TMOF, rt, 1 h; (b) NaBH<sub>4</sub>, DMF:EtOH = 3:1, rt, 1 h; (c) Ph(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H 4{2}, (3 equiv), PyBOP (3 equiv), DIEA (6 equiv), DMF, rt, 8 h; (d) CAN (5 equiv), THF:H<sub>2</sub>O = 10:1, rt, 5 h; (e) 50% TFA in CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 h.

used. Oxidative cleavage using ceric ammonium nitrate (CAN) was found to be successful in most cases. An

exception was the adduct using (*E*)-cinnamaldehyde (2{7}). In the reactions using 2{7} and carboxylic acid 4{2}, no adduct was obtained after cleavage from the support using CAN. However, the desired adduct was obtained when the cleavage was performed using 50% trifluoroacetic acid (TFA) in dichloromethane (Scheme 2).

In summary, a two-step N-reductive alkylation procedure using BOBA resin has been successfully carried out to afford diverse N-alkylated amides. Furthermore, it has been demonstrated that aliphatic and  $\alpha,\beta$ -unsaturated imines, which are known to be unstable in the liquid phase, are stable in the solid phase and readily react in the secondary reactions.

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**Supporting Information Available.** Experimental details and physical data of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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