Soluble Polymer-supported Synthesis of *trans* β-Lactams with High Diastereoselectivity

Shan-Zhong Jian and Yan-Guang Wang*
Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

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A general method for the liquid-phase synthesis of *trans* β-lactams with high diastereoselectivity is described. The mechanism can be explained by a chair-like transition state involving the imine and the (*Z*)-enolate.

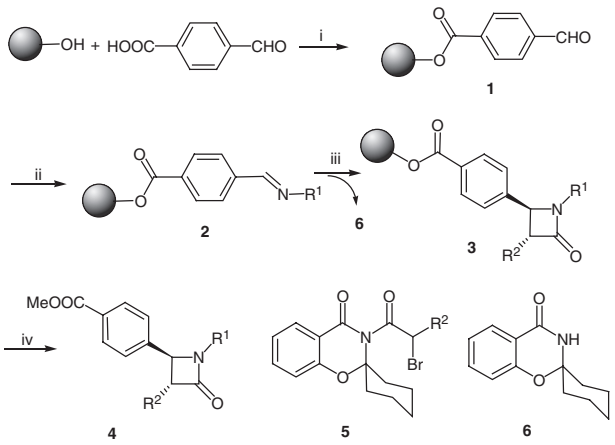
In recent years, the liquid-phase synthesis of small heterocyclic molecules has been a subject of intense research activity,[1] since it represents one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry.[2] It profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis without following the cleavage-and-check technique) and of solid-phase methods (use of excess reagents and easy isolation and purification of products). Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising.[3] This polymer is soluble in many solvents, e.g., THF, CH_2Cl_2, or H_2O at room temperature, but can be precipitated from a solution and thus purified by addition of diethyl ether, hexane, or 2-propanol. Furthermore, each reaction can be easily monitored by solution phase ^{1}H NMR of a polymer sample in $CDCl_3$.

β-Lactams are very important compounds existing widely in various antibiotics and other natural products.[4] Recent developments about the synthesis of β-lactams have mainly focused on the catalytic asymmetric and the polymer supported synthesis. Even though methods for the *cis* β-lactams preparation are well studied in both liquid and solid phase,[5] there are very limited procedures available for the synthesis of the *trans* isomers.[6] In connection with our research on the PEG-supported liquid-phase synthesis,[7] we synthesized the *trans* β-lactams on PEG support using an auxiliary. Herein we report the results of our work.

As shown in Scheme 1, the investigation began by coupling 4-formylbenzoic acid to PEG 4000 in the presence of 1,3-dicyclohexycarbodiimide (DCC) with a catalytic amount of DMAP in anhydrous CH_2Cl_2 at room temperature for 24 h to give the polymer-supported aldehyde **1**.[7] The representative imines **2** were prepared by treating **1** with aromatic amines in the presence of trimethyl orthoformate in CH_2Cl_2 at room temperature. The reaction gave the corresponding PEG-bound aldimines **2**.[7] In general, the progress of both the esterification and imines formation steps was routinely monitored by ^{1}H NMR spectroscopy.

After precipitated with ether and dried by vacuum, the polymer-bound **2** reacted with 4 equivalents of the auxiliary carboximide **5**[8] and 4.8 equivalents of zinc power in THF to afford the polymer supported *trans* β-lactams **3** with high diastereoselectivity. The *trans*/*cis* ratio was determined by ^{1}H NMR, based on the H-3/H-4 coupling constant values ($J_{trans} = 1.5$–2.5 Hz, $J_{cis} = 4.5$–6.0 Hz). Substrate cleavage was accomplished by treating **3** with Et_3N/MeOH (1/2, v/v) at 60 °C and monitored for the disappearance of the polymeric β-lactams by TLC.[9] Normally, cleavage was completed after stirring for 24 h.[10] The reaction conditions are mild enough not to alter the *trans*/*cis* ratio of β-lactams. The results are summarized in Table 1.

As shown in Table 1, when R^1 was an aryl group (Entries a–n), the reaction gave products **4** in high yields (85–96%), good



Scheme 1. i) 4 equiv. DCC, cat. DMAP, CH_2Cl_2, rt, overnight; ii) 4 equiv. NH_2R^1, 4 equiv. $HC(OCH_3)_3$, CH_2Cl_2, rt, overnight; iii) 4 equiv. **5**, 4.8 equiv. zinc power, THF, reflux, 3 h; iv) Et_3N/MeOH (1/2, v/v), 60 °C, 24 h.

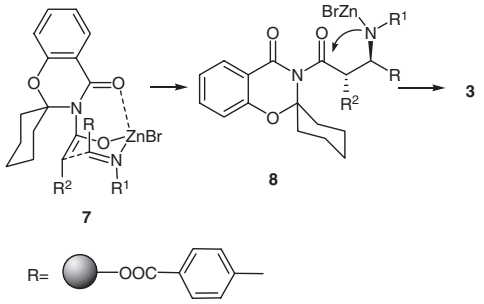
Table 1. Liquid-phase synthesis of *trans* β-lactams using PEG as support

Entry	R^1	R^2	Yield / /%[a]	Purity /%[b]	*trans*/*cis*[c]
a	C_6H_5	Me	91	85	>98:2
b	C_6H_5	Et	89	81	>98:2
c	*p*-$MeOC_6H_4$	Me	92	90	>98:2
d	*p*-$MeOC_6H_4$	Et	87	86	>98:2
e	*p*-MeC_6H_4	Me	89	93	>98:2
f	*p*-MeC_6H_4	Et	90	92	>98:2
g	*p*-FC_6H_4	Me	85[d]	89	>98:2
h	*p*-FC_6H_4	Et	88[d]	87	>98:2
i	*p*-ClC_6H_4	Me	89[d]	83	>98:2
j	*p*-ClC_6H_4	Et	89[d]	89	>98:2
k	*o*-MeC_6H_4	Me	95	90	>98:2
l	*o*-MeC_6H_4	Et	90	85	>98:2
m	3, 4-$Me_2C_6H_3$	Me	87	85	>98:2
n	3, 4-$Me_2C_6H_3$	Et	90	83	>98:2
o	$C_6H_5CH_2$	Me	—	—	—
p	C_6H_5CHMe	Me	—	—	—

[a]Yields refer to products cleaved from the resin.
[b]Purity determined by HPLC analysis of crude products. All products show satisfactory ^{1}H NMR and MS (ESI) data.
[c]Determined by ^{1}H NMR from **3** and **4**.
[d]Two times of loading are needed to insure the yield.

to excellent purities (81–93%) and high diastereoselectivity (*trans*/*cis* > 98:2). However, when R^1 was benzyl (Entry o) or phenylethyl (Entry p), the cycloaddition reaction did not take place.

The production of the *trans* β-lactams could be explained by the chair-like transition state **7** involving the imine and the (*Z*)-enolate (Scheme 2). The transition state gave the intermediate 8, which cyclized to produce the *trans* β-lactam **3**. The formation of the (*Z*)-enolate involving in the transition state may be due to the steric repulsion of the six-membered ring.



Scheme 2. Plausible mechanism for the formation of β-lactams.

In summary, we have developed a general method for the liquid-phase synthesis of *trans* β-lactams on PEG-support. The protocol gave the *trans* products in high diastereoselectivity and yields with good purity.

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9 The polymeric β-lactams exhibited fluorescence on TLC, so the disappearance of fluorescence of the polymer point on TLC could indicate the completion of cleavage reactions.

10 **Typical procedure for synthesis of *trnas* β-lactams**: The mixture of polymer-supported imine (1 mmol), carboximide (4 mmol), and zinc powder (4.8 mmol) in anhydrous THF (8 mL) was refluxed under N_2 for 15 min. After filtering through celite and washing with THF (3 × 2.5 mL), the filtrate was concentrated to the original volume. The cold Et_2O (30 mL) was added to precipitate the PEG-bound *trans* β-lactam. The precipitate was then collected on a sintered glass funnel and thoroughly washed with Et_2O (10 mL × 3). The resulting PEG-bound *trans* β-lactam was cleaved by 3-mL Et_3N in 6-mL MeOH at 60 °C for 24 h. Cold Et_2O (30 mL) was added to precipitate the detached PEG-OH. The polymer was filtered and the combined filtrate was flash passed through a short column to remove trace amount of PEG and **6**. The solvent was removed to give the corresponding crude product. Compound **3m** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.05$ (d, 1 H), 7.41 (d, 1 H), 7.17 (s, 1 H), 6.94 (d, 1 H), 6.85(m, 1 H), 4.61 (d, 1 H, $J = 1.9$ Hz), 4.47 (t, 2 H, $J =$ 4.6 Hz, PEGOCH_2**C**$\mathbf{H_2}$OCO), 3.13 (dq, 1 H, $J_1 = 7.4$ Hz, $J_2 = 1.9$ Hz), 2.18 (s, 3 H, $J = 7.4$ Hz), 2.17 (s, 3 H), 1.49 (d, 3H, $J = 7.4$ Hz). Compound **4m** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.05$ (d, 1 H), 7.41 (d, 1 H), 7.17 (s, 1 H), 6.94 (d, 1 H), 6.85(m, 1 H), 4.60 (d, 1 H, $J = 1.9$ Hz), 3.91 (s, 3 H,), 3.13 (dq, 1 H, $J_1 = 7.4$ Hz, $J_2 = 1.9$ Hz), 2.18 (s, 3 H), 2.17 (s, 3 H), 1.49 (d, 3H, $J = 7.4$ Hz) ESI-MS m/z 346 ($[M + Na]^+$) IR (film) 1751.2, 1724.1, 1278.2.

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