

## Synthesis of Structurally Diverse 2-Azetidinones via Staudinger Reaction on a Solid Support

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Trimellitic anhydride was attached to Merrifield resin and a ketene was generated from polymer-bound phthaloylglycine. Then this polymer reacted with imines in the presence of Vilsmeier reagent and triethylamine to afford the solid-phase-tethered  $\beta$ -lactam products. Selective cleavage of supported  $\beta$ -lactams by trifluoroacetic acid and methylhydrazine gave 4-carboxyphthalimido- and 3-amino- $\beta$ -lactams, respectively. The *trans*-stereochemistry was found in all products.

The  $\beta$ -lactam unit is the key structural element of the most widely employed family of  $\beta$ -lactam antibiotics and is responsible for the observed biological activity. These miracle drugs have improved the health and life expectancy of humans.<sup>1</sup> In addition to their well-recognized properties as antibiotics,  $\beta$ -lactams have been recently shown to possess other relevant biological activities.<sup>2</sup> On the other hand, the use of 2-azetidinones as building blocks in organic synthesis and semi-synthesis of Taxol derivatives is now well established.<sup>3</sup>

Building of the  $\beta$ -lactam (2-azetidinone) ring is a crucial step in the synthesis of new  $\beta$ -lactam antibiotics, and development of new preparative approaches toward  $\beta$ -lactam cycles is highly important.<sup>4</sup> Among several methods for the synthesis of  $\beta$ -lactams,<sup>5</sup> the [2 + 2] cycloaddition reaction of Schiff bases with ketenes (Staudinger reaction)<sup>6</sup> is mostly applied.<sup>7</sup>

The use of polymeric supports in organic synthesis has become a common practice, especially following the rapid development of combinatorial chemistry.<sup>8</sup> Primarily, the uses of polymers in synthesis have fallen into one of two areas: (A) the use of the polymer as a support for reactants or (B) the use of the polymer as support for reagents and catalysts during a reaction.<sup>9</sup> IR spectroscopy is a fast and simple method for the qualitative detection of certain functional groups on insoluble supports.<sup>10</sup>

Interest in solid-phase heterocyclic chemistry originated mainly in the pharmaceutical industry. Several review articles have appeared covering the synthesis of heterocycles on insoluble supports for the production of compound libraries for drug discovery.<sup>11</sup> One of the support types most frequently used for solid-phase organic synthesis are styrene–divinylbenzene copolymers (crosslinked polystyrene).<sup>12</sup> Chloromethyl polystyrene (Merrifield resin)<sup>13</sup> has been used widely in the polymer-supported synthesis of organic compounds.<sup>12</sup> It is commercially available and also has been prepared by several methods.<sup>14</sup>

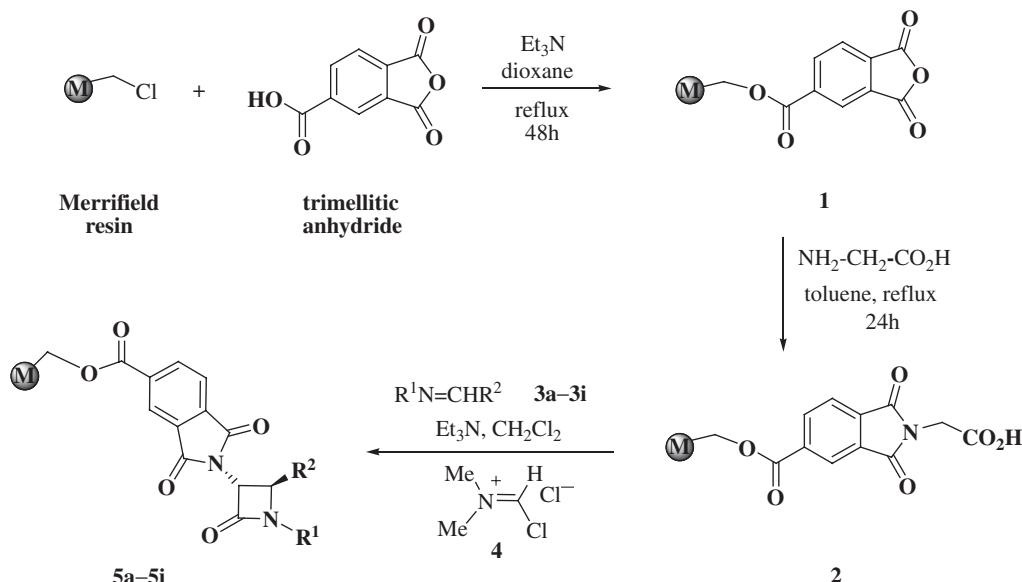
The application of combinatorial and related methodologies to the chemistry of the  $\beta$ -lactam ring is a very attractive challenge to modern medicinal chemistry, a fact that has been recognized by different research groups around the world.<sup>15</sup> In the polymer-supported synthesis of  $\beta$ -lactams, the methods reported in Ref. 5 have been used whereas one of the reactants or reagent has been supported on soluble or insoluble polymer.<sup>16</sup>

Herein, we summarize our efforts directed toward the development of a new method for the synthesis of  $\beta$ -lactams via ketene–imine cycloaddition using polymer-supported ketene. This paper further deals with the methods for deprotection of products from polymer.

Trimellitic anhydride was easily linked to Merrifield resin via a classical synthetic method using triethylamine as a base to give the polymer-supported trimellitic anhydride **1**. The chemical reaction was monitored by IR spectroscopy which showed definitely the ester and anhydride functional groups. Then the Merrifield resin-bound anhydride **1** reacted with glycine in refluxing toluene for 24 h to afford polymer-supported phthaloylglycine **2** (Scheme 1). The appearance of carbonyl and hydroxy groups of COOH in the IR spectrum confirmed the structure of **2**.

The Staudinger reaction was used for the generation of the  $\beta$ -lactam ring. The [2 + 2] cycloaddition was performed by adding imines **3a–3i**, (chloromethylene)dimethylammonium chloride (Vilsmeier reagent) (**4**), and triethylamine in excess to a suspension of **2** in dry  $\text{CH}_2\text{Cl}_2$  at room temperature to afford polymer-supported  $\beta$ -lactams **5a–5i**. In all cases the IR spectra of polymer-supported  $\beta$ -lactams **5a–5i** definitely showed the carbonyl group of the 2-azetidinone ring at  $1775\text{--}1781\text{ cm}^{-1}$ .

In the next step, the polymer-supported  $\beta$ -lactams **5a–5i** were cleaved by two methods, ester-bond cleavage and dephthalation. The libraries of  $\beta$ -lactam compounds have been developed using this solid-phase strategy (Table 1 and Table 2). Overall yields ranged from good to very good for the four-step synthetic sequence and exclusive formation of the



Scheme 1.

**Table 1.** Cleavage of the Resin-Bound  $\beta$ -Lactams **5a–5i** with TFA or  $\text{AlCl}_3$ 

Product	$\text{R}^1$	$\text{R}^2$	Yield/% <sup>a)</sup>	
			TFA	$\text{AlCl}_3$
<b>6a</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-MeC <sub>6</sub> H <sub>4</sub>	68	49
<b>6b</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	71	46
<b>6c</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	66	45
<b>6d</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	78	46
<b>6e</b>	C <sub>6</sub> H <sub>5</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	73	53
<b>6f</b>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	64	50
<b>6g</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	75	55
<b>6h</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	72	51
<b>6i</b>	4-(C <sub>6</sub> H <sub>5</sub> N=N)C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	70	48

a) Overall isolated yield (based on the initial loading level of Merrifield resin).

*trans*-isomer was detected in all cases. Different  $\beta$ -lactam derivatives with various substituents at positions 1 and 4 were obtained including many potential intermediates for the synthesis of active compounds. For instance *p*-ethoxyphenyl, *p*-methoxyphenyl, *p*-chlorophenyl, *p*-nitrophenyl, and carboxyl group undergo facile functional group transformations, and free amino group at C-3 allows the introduction of amide side chain, present in most of the  $\beta$ -lactam antibiotics.

Cleavage of resins **5a–5i** using trifluoroacetic acid (TFA) or aluminum chloride ( $\text{AlCl}_3$ ) resulted in the *trans*-4-carboxyphthalimido- $\beta$ -lactams **6a–6i** (Scheme 2 and Table 1). While treatment with  $\text{AlCl}_3$  gave 45–55% overall yield, use of 10% TFA in  $\text{CH}_2\text{Cl}_2$  was found to be the most effective method for the cleavage, affording  $\beta$ -lactams **6a–6i** in 64–78% overall isolated yield (based on the loading of starting Merrifield resin). The presence of H-3, H-4, hydroxy group in <sup>1</sup>H NMR spectra and carboxyl group in IR spectra definitely confirmed the structure of  $\beta$ -lactams **6a–6i**.

*trans*-Stereochemistry was deduced from H-3 and H-4 coupling constants in <sup>1</sup>H NMR ( $J \leq 2.5$  Hz). It is noteworthy

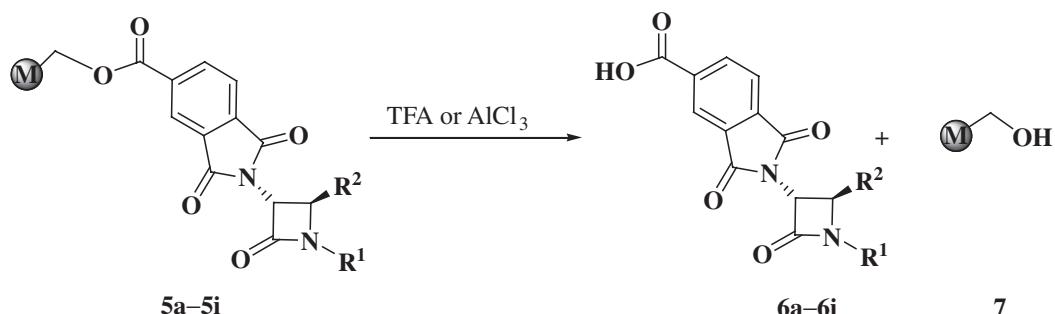
**Table 2.** Dephthalation of the Resin-Bound  $\beta$ -Lactams **5a–5i** with MeNNHNH<sub>2</sub>

Product	$\text{R}^1$	$\text{R}^2$	Yield/% <sup>a)</sup>
<b>8a</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-MeC <sub>6</sub> H <sub>4</sub>	58
<b>8b</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	61
<b>8c</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	53
<b>8d</b>	4-EtOC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	56
<b>8e</b>	C <sub>6</sub> H <sub>5</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	58
<b>8f</b>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	50
<b>8g</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	51
<b>8h</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	55
<b>8i</b>	4-(C <sub>6</sub> H <sub>5</sub> N=N)C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	53

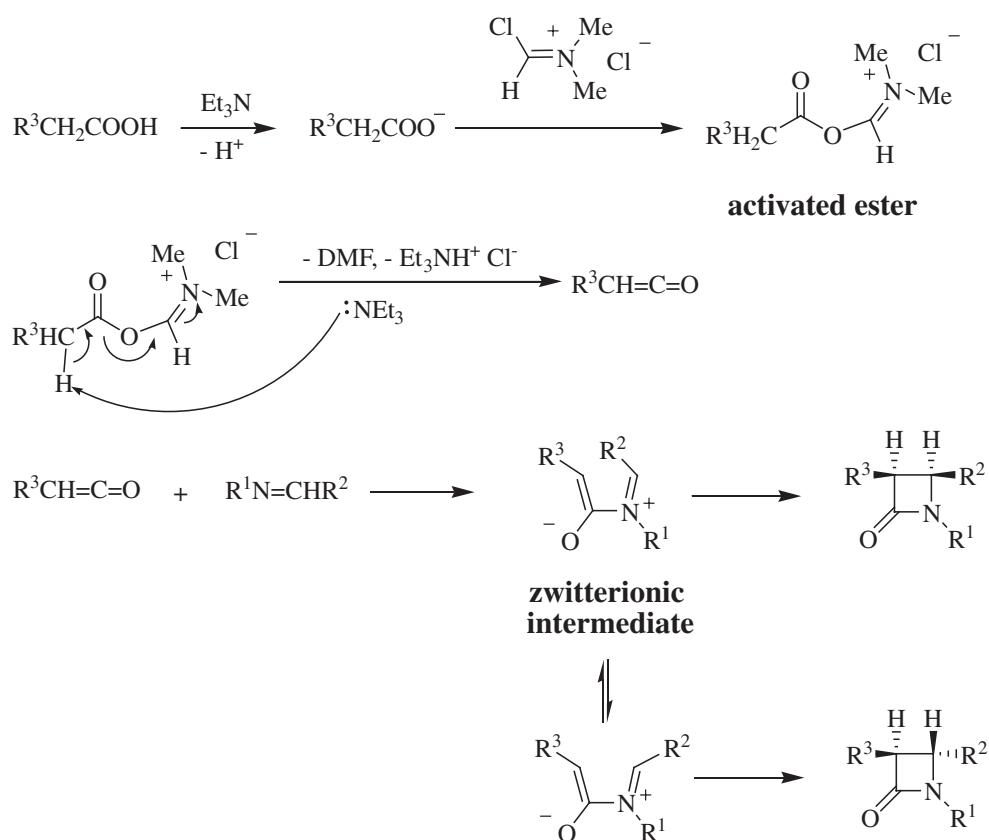
a) Overall isolated yield (based on the initial loading level of Merrifield resin).

that the preparation of the  $\beta$ -lactam ring via classical ketene-imine cycloaddition reaction leads to  $\beta$ -lactams with *cis*-selectivity<sup>17</sup> although *trans*- $\beta$ -lactams have been obtained by other methods,<sup>18</sup> refluxing in toluene<sup>19</sup> and catalytic asymmetric Staudinger reaction.<sup>20</sup> The stereochemistry is mainly dominated by electronic effects and steric hindrance of ketene and imine substituents.<sup>21</sup> The *cis*-3-phthalimido- $\beta$ -lactams have been previously synthesized via cycloaddition of imines and activated acetic acid derivatives<sup>22</sup> while the stereochemistry is all *trans* in this solid-supported method. The mechanism is perhaps similar to our previously reported mechanism for the Staudinger reaction from acetic acid derivatives and imines using methoxymethylene-*N,N*-dimethyliminium salt (Scheme 3).<sup>23</sup>

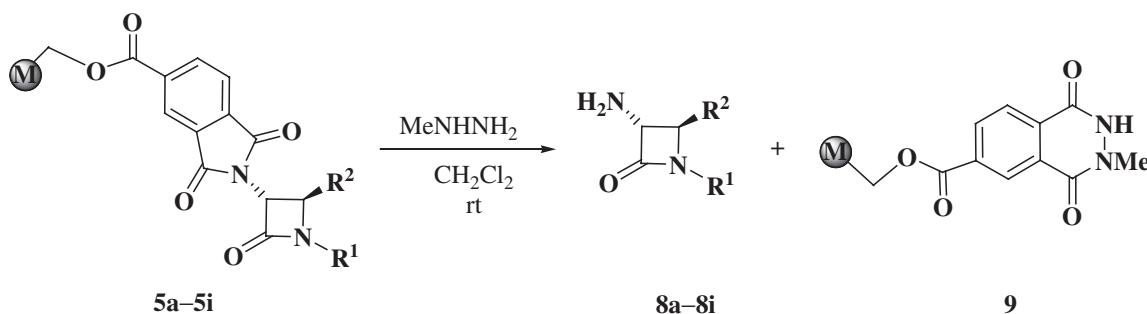
In another way, the polymer-supported  $\beta$ -lactams **5a–5i** were treated with methylhydrazine to give 3-amino- $\beta$ -lactams **8a–8i** (Scheme 4 and Table 2). The appearance of NH<sub>2</sub> peaks in IR and <sup>1</sup>H NMR spectra confirmed the synthesis of 3-amino- $\beta$ -lactams **8a–8i**. The polymer-supported 2-methylphthalazine-1,4(2H,3H)-dione **9** was cleaved by trifluoroacetic acid to hydroxymethyl resin **7**.



Scheme 2.



Scheme 3.



Scheme 4.









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