

# Synthesis of $\beta$ -Amino Esters by Regioselective Amination of Allyl Bromides with Aryl and Alkyl Amines

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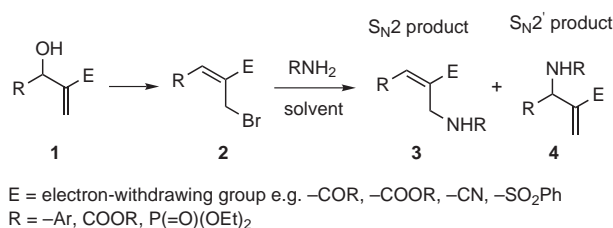
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**Abstract:** One of the two possible regioisomers can be exclusively formed by combining a suitable solvent and a specific amount of triethylamine as a base during the amination of allyl bromide **5**. The  $S_N2'$  product **7** was produced using dichloromethane as a solvent and triethylamine (7 equiv) as base;  $S_N2$  product **6** was predominantly generated in hexane with 0.5 equivalents of triethylamine. Furthermore, a new reaction condition for the efficient cyclization of **7** to yield  $\alpha$ -methylene  $\beta$ -lactam **8** using  $\text{Sn}[\text{N}(\text{TMS})_2]_2$  as a reagent, is disclosed.

**Key words:**  $\beta$ -amino ester, amination, regioselectivity,  $\alpha$ -methylene  $\beta$ -lactam, allyl bromide

$\beta$ -Amino acid is a non-proteinogenic amino acid and an important moiety in many biologically active compounds.<sup>1</sup> It is an important precursor in the synthesis of  $\beta$ -lactams.<sup>2</sup>  $\beta$ -Lactams themselves are important antibiotics and clinically important molecules,<sup>3</sup> so numerous synthetic methods have been developed to construct  $\beta$ -amino acids and  $\beta$ -lactam skeletons. For instance, the Mannich reaction,<sup>4</sup> Michael addition (nitrogen nucleophiles),<sup>5</sup> base-catalyzed ring-opening of  $\beta$ -lactams,<sup>6</sup> epoxide ring-opening by nitrogen nucleophiles,<sup>7</sup> aziridine ring-opening<sup>8</sup> and Sharpless aminohydroxylation<sup>9</sup> are some of the methods used to synthesize  $\beta$ -amino acids. Despite the impressive range of synthetic methods, newer and simpler methods by which chemists can control the regio- and stereoselectivity of the synthesis of  $\beta$ -amino esters are highly desirable. Scheme 1 presents one such simple method in which a nitrogen nucleophile attacks allyl bromide intermediate **2**, obtained from Baylis–Hillman adduct **1**, to yield  $S_N2$   $\beta$ -amino acid **3** and  $S_N2'$  product **4** (for  $\text{E} = \text{COOR}$ , Scheme 1).<sup>2b</sup> However, the nucleophilic attack by nitrogen at the allyl bromide  $\alpha,\beta$ -unsaturated system commonly leads to the formation of a mixture of  $S_N2$  and  $S_N2'$  products.<sup>2b,10–12</sup> This work reports the regioselective amination of allyl bromo  $\alpha,\beta$ -unsaturated compounds by controlling the solvent and the base.

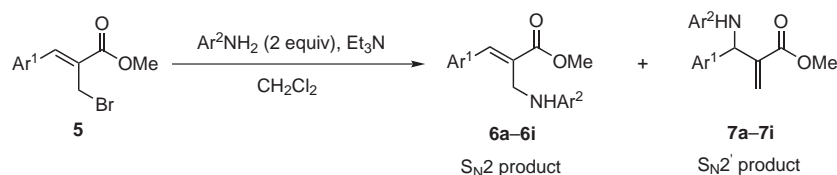
In earlier investigations of the amination of allyl bromides **2** (Scheme 1), where the substituents at the C-2 positions were nitrile,<sup>10</sup> sulfonyl,<sup>11</sup> ketone<sup>12</sup> or ester,<sup>2b,12a,13</sup> the product formation depended on the steric bulk and



Scheme 1

basicity of the nitrogen nucleophile, on the polarity of the solvent used in the reaction, and on the substituent at C-2 position of the allyl bromide **2**. The addition of amine to the allyl bromide **2** with ester substituent at the C-2 position has been reported to yield a mixture of **3** and **4**.<sup>2b,12a</sup> The thermodynamically more stable product **3** was produced by the  $S_N2$  replacement of the bromide with amine, and the kinetic product **4** was formed by either N-allylic rearrangement or the  $S_N2'$  replacement of allyl bromide with amine.<sup>10–13</sup> In this work the polarity of the solvent, the basicity of the nucleophilic amines and amount of base strongly affected the regioselective addition of allylic bromides with arylamines.

As shown in Table 1, the reaction time was shortened from four days to under 12 hours, and the regioselectivity was improved from that of two regioisomers in a ratio of 1:1 to that of an exclusive product **7** using excess base (7 equiv, entries 1–4). When the reaction procedure was modified by initially stirring triethylamine and allyl-bromide **5** for 30 minutes and then adding the arylamines (entries 2–4), **7a** was formed exclusively with very little change in yields over a range of reaction times. The use of aryl amines as nucleophiles caused only a very slight change in the yield (entries 5–10). Notably, alkyl amines (allylamine, *n*-butylamine, morpholine and diethylamine) failed to give any clean isolable products under the same reaction conditions.<sup>14</sup> Entries 5–12 (Table 1) show the effect of the substituent at the C-3 position of allyl bromide and arylamines.<sup>15</sup> Good yields of exclusively formed **7b–i** were obtained in these cases, indicating that the regioselectivity of the addition reactions of allylic bromides with arylamines was only weakly affected by the substituents at the C-3 position of allyl bromide and arylamines, except in the case of entry 12.

**Table 1** Amination of Allyl Bromide **5** in CH<sub>2</sub>Cl<sub>2</sub>

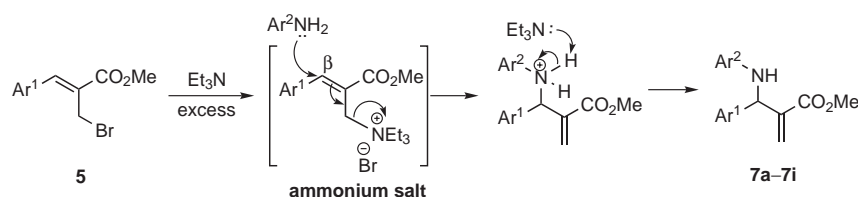
Entry	Ar <sup>1</sup>	Ar <sup>2</sup>	Et <sub>3</sub> N (equiv)	Time (h)	Yield (%)	Ratio <b>6</b> : <b>7</b>	Product
1	Ph	Ph	–	96	61	1:1	<b>6a</b> : <b>7a</b>
2	Ph	Ph	7	3	91	0:1 <sup>a</sup>	<b>7a</b>
3	Ph	Ph	7	6	93	0:1 <sup>a</sup>	<b>7a</b>
4	Ph	Ph	7	12	94	0:1 <sup>a</sup>	<b>7a</b>
5	Ph	<i>p</i> -MeOPh	7	6	86	0:1 <sup>a</sup>	<b>7b</b>
6	Ph	2,4-Me <sub>2</sub> Ph	7	6	90	0:1 <sup>a</sup>	<b>7c</b>
7	<i>m</i> -BrPh	<i>p</i> -MeOPh	7	6	89	0:1 <sup>a</sup>	<b>7d</b>
8	<i>m</i> -BrPh	Ph	7	6	95	0:1 <sup>a</sup>	<b>7e</b>
9	<i>p</i> -MeOPh	Ph	7	6	87	0:1 <sup>a</sup>	<b>7f</b>
10		Ph	7	24	91	0:1 <sup>a</sup>	<b>7g</b>
11		Ph	7	24	81	0:1 <sup>a</sup>	<b>7h</b>
12		Ph	7	24	20	0:1 <sup>a</sup>	<b>7i</b>

<sup>a</sup> Reaction was performed by stirring **5** with Et<sub>3</sub>N for 30 min and adding the amine, whereas in other entries all the reactants were added together and stirred for the indicated time.

Based on the facts reported herein and other reports,<sup>12,13</sup> a speculative reaction mechanism, presented in Scheme 2, is proposed to explain the exclusive formation of **7**. Allyl bromide **5** initially reacts with the added base triethylamine to yield ammonium salt, which then undergoes S<sub>N</sub>2' attack at the C-3 carbon by amine nucleophile to produce an intermediate with the release of bromotriethylamine salt. The abstraction of a proton from nitrogen on the intermediate by the base yields **7**, which is known to be able to rearrange to **6** in the presence of ammonium halide or a base.<sup>12</sup>

Non-polar solvent promoted S<sub>N</sub>2 substitution in ester-substituted allyl bromide **2**.<sup>12a</sup> Therefore, an attempt was made to change the reaction product from **7** to **6** by chang-

ing the reaction solvent to hexane. Initially, when allyl bromide **5** and aniline were stirred together in hexane at room temperature for five days (entry 1, Table 2), a mixture of products **6a** and **7a** in a 2:1 ratio was obtained with a 66% yield. When triethylamine (0.3 equiv of **5**) was added as a base, the reaction time was shortened to 10 hours and the regioselectivity markedly improved with a five-fold increase in the product yield (entry 2). Further increasing the amount of base (0.5 equiv) further increased regioselectivity (entry 3), which then decreased as the amount of base was increased to one equivalent or seven equivalents. (entries 4 and 5). Thus, 0.5 equivalents of triethylamine were used in the following reactions. Entries 6–10 show the effect of the substituent at the C-3 position

**Scheme 2**

of allyl bromide and arylamines. In all of the examples, product **6** was the major product. Notably, naphthalenyl-substituted allyl bromide had the best regioselectivity (entry 8, **6l:7l** >99:1), and other substituents on allyl bromide afforded less regioselectivity than that of phenyl substituents. Other aryl and allyl amines such as *para*-methoxyaniline and allylamine, also displayed  $S_N2$  favored selectivity (entries 11 and 12). However, when more basic alkyl amines such as *n*-butylamine, diethylamine and morpholine were used, the trend was reversed, and regioisomer **7** was formed as the dominant product (entries 13–15).

The ability to access  $\beta$ -aminoesters **7** exclusively was exploited and its cyclization to  $\alpha$ -methylene  $\beta$ -lactam **8** (Table 3), which is a valuable precursor in the synthesis of substituted  $\beta$ -lactams, was investigated.<sup>16</sup> Conventional


bases such as ethyl magnesium bromide, *n*-butyllithium, potassium *tert*-butoxide, lithium hydroxide and potassium hydroxide, which were reported earlier to have been used in such cyclizations, failed to cyclize **7** to  $\beta$ -lactam (entries 1–5). Thus, another reagent,  $\text{Sn}[\text{N}(\text{TMS})_2]_2$ , which has been previously used in the cyclization of  $\beta$ -aminoesters,<sup>2a</sup> was examined. The reaction solvent and temperature importantly affected the cyclization of **7a**, as shown in entries 6–11. The optimal cyclization conditions were found to involve 1.5 equivalents of  $\text{Sn}[\text{N}(\text{TMS})_2]_2$  in toluene under reflux.

In conclusion, reaction conditions are disclosed in which one of two possible regioisomeric reaction products can be obtained using a properly chosen solvent and base. Moreover,  $\text{Sn}[\text{N}(\text{TMS})_2]_2$  was found to be a good reagent in the cyclization of product **7** to  $\beta$ -lactam.

**Table 2** Amination of Allyl Bromide **5** in Hexane

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <math>\text{Ar}^3\text{-CH=CH-CH}_2\text{-Br}</math>  <b>5</b> </div> <div> <math>\xrightarrow[\text{hexane}]{\text{R}^1\text{R}^2\text{NH}_2 \text{ (2 equiv), Et}_3\text{N}}</math> </div> <div style="text-align: center;"> <math>\text{Ar}^3\text{-CH=CH-CH}_2\text{-NR}^1\text{R}^2</math>  <b>6j-6s</b>  <math>S_N2</math> product         </div> <div>+</div> <div style="text-align: center;"> <math>\text{Ar}^3\text{-CH=CH-CH(R}^1\text{R}^2\text{N)-CO}_2\text{Me}</math>  <b>7j-7s</b>  <math>S_N2'</math> product         </div> </div>							
Entry	Ar <sup>3</sup>	R <sup>1</sup> R <sup>2</sup> NH	Et <sub>3</sub> N (equiv)	Time (h)	Yield (%)	Ratio <sup>a</sup> <b>6:7</b>	Product
1	Ph	PhNH <sub>2</sub>	–	120	66	2:1	<b>6a:7a</b>
2	Ph	PhNH <sub>2</sub>	0.3	10	89	10:1	<b>6a:7a</b>
3	Ph	PhNH <sub>2</sub>	0.5	10	93	30:1	<b>6a:7a</b>
4	Ph	PhNH <sub>2</sub>	1	10	91	17:1	<b>6a:7a</b>
5	Ph	PhNH <sub>2</sub>	7	10	87	6:1	<b>6a:7a</b>
6	<i>p</i> -MeOPh	PhNH <sub>2</sub>	0.5	10	88	19:1	<b>6j:7j</b>
7	<i>m</i> -BrPh	PhNH <sub>2</sub>	0.5	10	80	16:1	<b>6k:7k</b>
8		PhNH <sub>2</sub>	0.5	10	77	>99:1	<b>6l:7l</b>
9		PhNH <sub>2</sub>	0.5	10	82	24:1	<b>6m:7m</b>
10		PhNH <sub>2</sub>	0.5	10	71	16:1	<b>6n:7n</b>
11	Ph	<i>p</i> -MeOPhNH <sub>2</sub>	0.5	10	75	6:1	<b>6o:7o</b>
12	Ph	allylamine	0.5	10	89	4:1	<b>6p:7p</b>
13	Ph	<i>n</i> -BuNH <sub>2</sub>	0.5	10	99	1:2	<b>6q:7q</b>
14	Ph	Et <sub>2</sub> NH	0.5	10	92	1:3	<b>6r:7r</b>
15	Ph	morpholine	0.5	10	90	1:3	<b>6s:7s</b>

<sup>a</sup> The ratios of **6:7** were determined after chromatographic purification.

**Table 3** Cyclization of  $\beta$ -Aminoesters **7** to  $\alpha$ -Methylene  $\beta$ -Lactam **8**


Entry	Reagents/Conditions	Product yield
1	EtMgBr (2.0 equiv), THF, 0 °C to r.t., 2 d	n.r.
2	<i>n</i> -BuLi (1.2 equiv), THF, 0 °C to r.t., 2 d	n.r.
3	<i>t</i> -BuOK (1.5 equiv), THF, 0 °C to r.t., 30 min	mess
4	LiOH (2.0 equiv), H <sub>2</sub> O–dioxane, reflux, 1.5 h	mess
5	KOH (2.0 equiv), MeOH, r.t., 2 d	mess
6	Sn[N(TMS) <sub>2</sub> ] <sub>2</sub> (1.2 equiv), THF, r.t., 48 h	n.r.
7	Sn[N(TMS) <sub>2</sub> ] <sub>2</sub> (1.2 equiv), THF, reflux, 48 h	5% <sup>a</sup>
8	Sn[N(TMS) <sub>2</sub> ] <sub>2</sub> (2.0 equiv), THF, reflux, 96 h	29% <sup>b</sup>
9	Sn[N(TMS) <sub>2</sub> ] <sub>2</sub> (1.5 equiv), toluene, reflux, 6 h	83%
10	Sn[N(TMS) <sub>2</sub> ] <sub>2</sub> (2.5 equiv), toluene, reflux, 6 h	83%

<sup>a</sup> Starting material (80%) was recovered.<sup>b</sup> Starting material (60%) was recovered.**Synthesis of  $\beta$ -Aminoester **7** ( $S_N2'$  Product)**

To a solution of compound **5** (1.0 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was added Et<sub>3</sub>N (1 mL) and the reaction mixture was stirred at r.t. for 30 min. Aniline (2.0 mmol) was added at r.t. when the solution became a suspension. After the reaction was complete (monitored by TLC), aq HCl (2 M, 10 mL) was added. The mixture was extracted with Et<sub>2</sub>O (3 × 20 mL) and the organic layer was washed with brine (40 mL), dried (MgSO<sub>4</sub>), filtered and concentrated.

**Synthesis of  $\beta$ -Aminoester **6** ( $S_N2$  Product)**

To a solution of compound **5** (1.0 mmol) in 5 mL hexane was added Et<sub>3</sub>N (0.5 mmol) and aniline (2.0 mmol) at r.t. The reaction mixture was stirred at r.t. for 10 h and then H<sub>2</sub>O (10 mL) was added. The mixture was extracted with Et<sub>2</sub>O (3 × 20 mL) and the organic layer was dried with MgSO<sub>4</sub>, filtered and concentrated. Purification was achieved by silica gel flash chromatograph and eluted with EtOAc–hexane.

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