

# Synthesis of $\beta$ -Amino Esters by Bismuth Triflate Catalyzed Three-Component Mannich-Type Reaction

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**Abstract:** We have developed an efficient, bismuth-catalyzed, Mannich-type three-component reaction by combining the corresponding aldehyde, amine, and silyl ketene acetal. The reaction proceeds rapidly and affords the corresponding  $\beta$ -amino esters in high yields (up to 90%).

**Key words:** amino esters, bismuth, green chemistry, Mannich-type reaction, multicomponent reactions (MCR), silyl enolates

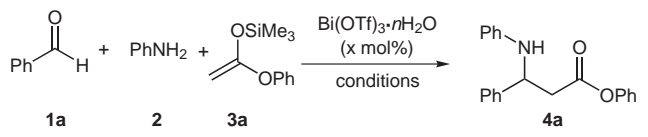
The development of new methods for the synthesis of  $\beta$ -amino carbonyl derivatives is an important area of synthetic efforts.  $\beta$ -Amino ketones and esters are extremely important compounds as biologically active molecules.<sup>1</sup> The Lewis acid-mediated reactions of imines with silyl enolates are among the most efficient for the synthesis of  $\beta$ -amino carbonyl compounds. Therefore, the development of new catalytic methods for their preparation is of first importance in organic synthesis. Catalytic Mannich-type reactions have been reported by several groups as an efficient method to prepare  $\beta$ -amino carbonyl compounds.<sup>1,2</sup> However, many imines tend to be unstable during purification by chromatography, distillation, or prolonged storage. Thus, it is desirable from a synthetic point of view that imines, formed in situ from aldehydes and amines, immediately react with silyl enolates and provide  $\beta$ -amino esters in a one-pot process.<sup>3,4</sup> Nevertheless, most Lewis acids cannot be used in this reaction because they decompose or deactivate in the presence of the amines and water produced during imine formation. Recently, synthetic methods involving rare-earth and lanthanide triflates as catalysts for Mannich-type reactions have been reported.<sup>4</sup> High catalytic activity, low toxicity, and moisture- and air-tolerance make lanthanide triflates attractive catalysts. However, the high cost of these catalysts restricts their use.

Bismuth compounds too have attracted recent attention due to their low toxicity, low cost, and good stability.<sup>5</sup> Bismuth salts have been reported as catalysts for opening of epoxides,<sup>6</sup> allylation of imines,<sup>7</sup> Mukaiyama aldol reactions,<sup>8</sup> formation and deprotection of acetals,<sup>9</sup> Friedel–Crafts reactions,<sup>10</sup> Diels–Alder reactions,<sup>11</sup> Fries rearrangement,<sup>12a</sup> Claisen rearrangement,<sup>12b</sup> and intramolecular Sakurai cyclizations.<sup>13</sup>  $\text{Bi}(\text{OTf})_3$  is particularly

attractive because it is commercially available or can be easily prepared from commercially available starting materials.<sup>14</sup>

As a part of our ongoing interest in bismuth(III)-catalyzed multicomponent reactions involving silyl nucleophiles (allyl silanes and silyl enol ethers),<sup>7,15</sup> we report herein a three-component bismuth(III)-catalyzed Mannich-type reaction of silyl ketene acetals. A major merit of the three-component reaction is indeed that many unique structures can be afforded rapidly when three or more reactants are combined in a single step to afford new compounds. We wish to disclose our results in this area: the development of an efficient, bismuth-catalyzed Mannich-type three-component reaction that combines an aldehyde, aniline, and a silyl ketene acetal to afford compounds with a  $\beta$ -amino ester core structure.  $\beta$ -Amino esters are obtained efficiently in the presence of 2 mol% of  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$  (with  $1 < n < 4$ ).

**Table 1** Optimization of the Three-Component  $\text{Bi}(\text{OTf})_3$ -Catalyzed Mannich-Type Reaction Involving Benzaldehyde, Aniline, and (1-Phenoxyvinyl)oxy)trimethylsilane<sup>a</sup>



Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield of 4a (%) <sup>b</sup>
1	1	MeCN	0	1	64 <sup>c</sup>
2	1	Et <sub>2</sub> O	-78	3.5	75
3	1	THF	-78	3.5	80
4	1	CH <sub>2</sub> Cl <sub>2</sub>	-78	1.3	66
5	1	ClCH <sub>2</sub> CH <sub>2</sub> Cl	-11	3.2	45
6	1	THF <sup>d</sup>	-78	2	65
7	1	THF <sup>e</sup>	-78	5.5	53
8	2	THF	-78	3.5	84
9	5	THF	-78	2	81

<sup>a</sup> Conditions: benzaldehyde (1.0 equiv), aniline (1.0 equiv), (1-phenoxyvinyl)oxy)trimethylsilane (**3a**, 1.2 equiv),  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ , benzaldehyde concentration = 0.50 M.

<sup>b</sup> Isolated yield.

<sup>c</sup> Conversion according to <sup>1</sup>H NMR.

<sup>d</sup> Benzaldehyde concentration = 1.0 M.

<sup>e</sup> Benzaldehyde concentration = 0.25 M.

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Initially, we screened various conditions for the one-pot Mannich-type reaction of imine derived from benzaldehyde (**1a**) and aniline (**2**) with (1-phenoxyvinyloxy)trimethylsilane (**3a**) in the presence of  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$  (Table 1). Among various polar solvents tested, acetonitrile, diethyl ether, dichloromethane, and dichloroethane gave moderate to good yields of the expected product (Table 1, entries 1, 2, 4, 5). The best solvent was found to be tetrahydrofuran. In this solvent, phenyl 3-phenyl-3-

(phenylamino)propanoate (**4a**) was obtained with the best yield [1% mol of  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ ,  $-78^\circ\text{C}$ , 3.5 h, 80% of **4a**; Table 1, entry 3]. With further optimization of the reaction conditions, we found that either a lower or a higher substrate concentration gave a decreased yield of the product due to lower conversion (Table 1, compare entries 6 and 7 with entry 3). Next, the effect of the catalyst loading was examined in the test reaction, using tetrahydrofuran at  $-78^\circ\text{C}$ . When the reaction was carried out

**Table 2** Three-Component  $\text{Bi}(\text{OTf})_3$ -Catalyzed Mannich-Type Reactions with Various Silyl Ketene Acetals<sup>a</sup>

Entry	<b>3</b>	Method <sup>b</sup>	Time (h)	<i>syn/anti</i> <sup>c</sup>	Product <b>4</b>	Yield of <b>4</b> (%) <sup>d</sup>
1		A	3.5	–	<b>4a</b>	84
2		B	3	–	<b>4a</b>	63
3		A	8	–	<b>4b</b>	67
4		B	1.5	–	<b>4b</b>	83
5		B	0.8	–	<b>4c</b>	85
6		A	2.5	78:22	<b>4d</b>	81
	<i>E/Z</i> = 78:22					
7		A	2.5	74:26	<b>4e</b>	80
8		B	2	73:27	<b>4e</b>	74
	<i>E/Z</i> = 80:20					
9		B	1.7	–	<b>4f</b>	59
10		B	1	24:76	<b>4g</b>	89
	<i>E/Z</i> = 5:95					
11		B	1.8	78:22	<b>4h</b>	83
	<i>E/Z</i> = >99:1					
12		B	1	–	<b>4i</b>	85
13		B	1	–	<b>4j</b>	90

<sup>a</sup> Conditions: benzaldehyde (1.0 equiv), aniline (1.0 equiv), silyl ketene acetal (1.2 equiv),  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$  (0.02 equiv).

<sup>b</sup> Method A: reaction performed at  $-78^\circ\text{C}$ . Method B: addition of silyl ketene acetal at  $-78^\circ\text{C}$ , then reaction mixture was allowed to reach r.t. after 0.15 h.

<sup>c</sup> The diastereoisomers were not separable by chromatography and the yield is of the mixture.

<sup>d</sup> Isolated yield.

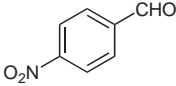
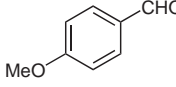
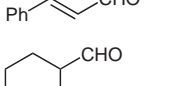
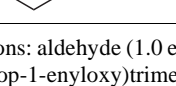
with 2 mol% of  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ , the product **4a** was obtained in better yield (Table 1, entry 8). An increased catalyst loading (5 mol%) gave decreased yields (Table 1, entry 9).

Several examples of  $\text{Bi}(\text{OTf})_3$ -catalyzed Mannich-type reactions with various silyl ketene acetals are summarized in Table 2. Silyl ketene acetals derived from various esters were reacted with an equimolar mixture of benzaldehyde (**1a**) and aniline (**2**). The corresponding  $\beta$ -amino esters **4** were obtained in good yields (Table 2). Silyl enolates derived from esters as well as thioesters reacted smoothly to give the adducts. No adducts between aldehydes and the silyl enolates were observed in any reaction according to NMR analysis of the crude reaction mixture. As for the diastereoselectivity of the reaction, good results were obtained with the following substrates. Moderate *syn* selectivity was observed with [(*E*)-1-ethoxy-2-phenylvinyl]trimethylsilane (Table 2, entry 6). [(*E*)-1-Methoxyprop-1-enyl]trimethylsilane afforded the expected product with *syn* stereoselectivity (Table 2, entries 7, 8). While the *anti* adduct was produced preferentially with [(*Z*)-1-(ethylthio)prop-1-enyl]trimethylsilane (Table 2, entry 10), the *syn* adduct was obtained with [(*E*)-1-(ethylthio)prop-1-enyl]trimethylsilane (Table 2, entry 11).

Next, other aldehydes were tested and the results are summarized in Table 3. Generally, excellent yields of  $\beta$ -amino ester were obtained with 1.2 equivalents of (1-methoxy-2-methylprop-1-enyl)trimethylsilane (**3c**) and 0.02 equivalent of  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$  at  $-78^\circ\text{C}$  in THF. Aromatic aldehydes as well as an  $\alpha,\beta$ -unsaturated aldehyde reacted smoothly to give the corresponding  $\beta$ -amino ester derivatives **4** in high yield (Table 3, entries 1–4). The reaction worked well with a variety of aldehydes including those bearing an electron-withdrawing group, and the corresponding  $\beta$ -amino ester **4** was obtained with good yields (Table 3, entry 1). Electron-rich *p*-methoxybenzaldehyde led to the desired product in moderately good yield (Table 3, entry 2). Conjugated aldehydes were good substrates as well (Table 3, entry 3). Aliphatic aldehydes do not react under such conditions probably due to enamine formation, except cyclohexane carboxaldehyde, which afforded product **4n** in poor yield (Table 3, entry 4). Product **4n** was obtained in a good crude yield, but a decreased isolated yield was obtained due to decomposition on silica gel chromatography. Interestingly, we never observed side reaction products such as aldol and deamination products.

In summary, we have found that the Mannich-type reaction of in situ prepared imines proceeds smoothly with silyl ketene acetals and a catalytic amount of  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ .<sup>16</sup> This method offers several advantages including mild reaction conditions, highly catalytic (2%) process, and no formation of by-products. Moreover, our

**Table 3** Three-Component  $\text{Bi}(\text{OTf})_3$ -Catalyzed Mannich-Type Reactions with Various Aldehydes<sup>a</sup>

Entry	Aldehyde	Time (h)	Product <b>4</b>	Yield of <b>4</b> (%) <sup>b</sup>
1		2	<b>4k</b>	82
2		2	<b>4l</b>	70
3		2.5	<b>4m</b>	61
4		1	<b>4n</b>	38

<sup>a</sup> Conditions: aldehyde (1.0 equiv), aniline (1.0 equiv), (1-methoxy-2-methylprop-1-enyl)trimethylsilane (1.2 equiv),  $\text{Bi}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$  (0.02 equiv), addition of silyl ketene acetal at  $-78^\circ\text{C}$ , then reaction mixture allowed to reach r.t. after 0.15 h.

<sup>b</sup> Isolated yield.

protocol does not require prior isolation of the imine. The  $\beta$ -amino ester is directly obtained, usually as a crystalline product, in a one-pot process. Because of its numerous benefits, this method for the one-pot synthesis of  $\beta$ -amino esters using bismuth triflate catalysis should find utility in the synthesis of biologically active compounds.

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- (16) **General Procedure for the Bismuth-Catalyzed Mannich-Type Reaction.**  
 Under an inert atmosphere of argon, the silyl ketene acetal (1.2 mmol) in 1 mL of dry THF was added dropwise to a solution of Bi(OTf)<sub>3</sub>·*n*H<sub>2</sub>O (0.02 mmol), the aldehyde (distilled, except *p*-nitrobenzaldehyde; 1 mmol), and the aniline (1 mmol) in 1 mL of dry THF at -78 °C. The mixture was stirred at -78 °C (Method A) or stirred at -78 °C for 0.15 h and then allowed to reach r.t. (Method B). The mixture was stirred until the reaction was completed as indicated by TLC. The reaction was quenched with H<sub>2</sub>O (4 mL) and extracted with Et<sub>2</sub>O (3 × 20 mL). The organic phase was washed with H<sub>2</sub>O and sat. aq NaCl, dried over MgSO<sub>4</sub>, and concentrated under vacuum (rotary evaporator). If the crude product was a solid, it was triturated with hexane (10 mL) and filtered; otherwise, it was purified by column chromatography (eluent hexane-EtOAc). The spectral data for **4b–h, j–n** match with those reported in the literature.  
**Phenyl 3-Phenyl-3-(*N*-phenylamino)propanoate (4a).**  
 Reagents: benzaldehyde (102 μL, 106 mg, 1.0 mmol), aniline (91 μL, 93 mg, 1.0 mmol), (1-phenoxyvinyl)oxy)trimethylsilane (250 mg, 1.2 mmol), and Bi(OTf)<sub>3</sub>·*n*H<sub>2</sub>O (14 mg, 0.02 mmol). The reaction was stirred for 3.5 h at -78 °C (Method A). The crude product was washed with hexane to afford 265 mg (84%) of **4a** as a white solid; mp 129–130 °C; *R*<sub>f</sub> = 0.55 (hexane-EtOAc = 4:1). IR (KBr): ν = 3401, 1735 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.44 (2 H, d, *J* = 7.6 Hz), 7.26–7.38 (5 H, m), 7.21 (1 H, tt, *J* = 7.4, 1.3 Hz), 7.12 (2 H, dd, *J* = 8.6, 7.4 Hz), 6.89–6.91 (2 H, m), 6.70 (1 H, t, *J* = 7.3 Hz), 6.61 (2 H, dd, *J* = 8.6, 1.0 Hz), 5.00 (1 H, t, *J* = 6.3 Hz), 4.59 (1 H, s), 3.07 (2 H, d, *J* = 6.6 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 170.0, 150.6, 146.9, 141.9, 129.7, 129.5, 128.00, 126.6, 126.3, 121.7, 118.3, 114.0, 55.3, 43.0. HRMS: *m/z* calcd for C<sub>21</sub>H<sub>19</sub>NO<sub>2</sub> [M<sup>+</sup>]: 317.1416; found: 317.1421.  
**(*S*)-tert-Butyl 3-Phenyl-3-(*N*-phenylamino)propanethioate (4i).**  
 Reagents: benzaldehyde (102 μL, 106 mg, 1.0 mmol), aniline (91 μL, 93 mg, 1.0 mmol), [1-(*tert*-butylthio)vinyl]oxy]trimethylsilane (245 mg, 1.2 mmol), and Bi(OTf)<sub>3</sub>·*n*H<sub>2</sub>O (14 mg, 0.02 mmol). The reaction was stirred for 0.15 h at -78 °C, then allowed to reach r.t. for 1 h (Method B). The crude product was washed with hexane to afford 265 mg (85%) of **4i** as an orange solid; mp 99–101 °C. *R*<sub>f</sub> = 0.75 (hexane-EtOAc = 4:1). IR (KBr): ν = 3391, 1664 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.29–7.38 (4 H, m), 7.24 (1 H, tt, *J* = 7.0, 2.4 Hz), 7.09 (2 H, dd, *J* = 8.4, 7.4 Hz), 6.67 (1 H, t, *J* = 7.3 Hz), 6.56 (2 H, d, *J* = 8.0 Hz), 4.79 (1 H, t, *J* = 6.7 Hz), 2.90 (2 H, d, *J* = 6.8 Hz), 1.40 (9 H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 198.3, 147.1, 142.3, 129.3, 129.0, 127.7, 126.5, 117.9, 113.9, 56.1, 52.3, 48.9, 29.9. HRMS: *m/z* calcd for C<sub>19</sub>H<sub>23</sub>NOS [M<sup>+</sup>]: 313.1500; found: 313.1508.