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Stereoselective synthesis of *syn*-β-amino esters using the $TiCl_4/R_3N$ reagent system

Mariappan Periasamy,* Surisetti Suresh and Subramaniapillai Selva Ganesan

School of Chemistry, University of Hyderabad, Central University PO, Hyderabad 500 046, India

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Dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday

Abstract—The reactions of benzaldehyde imines and esters with the $TiCl_4/R_3N$ reagent system give *syn*-β-amino esters as the major products in 38–87% yields.

β-Amino acid moieties are present in several biologically important compounds[1] and they are useful as building blocks for β-lactams[2] and β-peptides[3] that are present in several drugs.[4] Hence, there is interest in developing convenient methods for the synthesis of β-amino esters. In recent years, the Mannich reaction[5] and its variants have been used in key steps in the synthesis of several biologically and pharmacologically important compounds.[6] Mannich-type reactions have also been used in the synthesis of β-amino esters. For example, the Lewis acid promoted additions of silyl ester enolates[7] and lithium ester enolates[8] are widely used for the synthesis of β-amino esters. Previously, ester enolates of titanium, prepared using the corresponding silyl[9] or lithium[10] enolates, were used in Mannich reactions with aldimines. A few reports describe the Mannich reactions of titanium enolates, prepared directly from esters and amides using $TiCl_4/NR_3$, with imines. In these cases, the corresponding *anti*-β-amino carbonyl compounds were obtained as the major products and the substrates contained an additional coordinating moiety.[11] During investigations on synthetic applications of the $TiCl_4/R_3N$ reagent system,[12,13] we observed *syn* selectivity in the formation of β-amino esters from benzaldehyde imines and simple esters not containing any additional coordinating groups. These results are described herein.

We have observed that esters and imines react with the $TiCl_4$/tertiary amine reagent system to give the corresponding *syn*-β-amino esters in good yields. Initially, the experiments were carried out using methyl butyrate **1a**, *N*-benzylidene benzylamine **2a** and $TiCl_4$ in combination with different tertiary amines such as Et_3N, *i*-Pr_2NEt, *n*-Bu_3N and TMEDA. The titanium ester enolate was prepared in situ by adding $TiCl_4$ to the ester at −45 °C followed by the addition of the 3° amine. It was observed that the $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino ester **3a** in excellent yields (Eq. 1). Interestingly, only one of the possible diastereomers was formed as the major product.

We then examined this transformation with different esters and imines (Eq. 2, Table 1).

In the reaction of methyl butyrate and imines derived from alkylamines and benzaldehyde the selectivities as well as the yields were high (entries 1–3), whereas the imine derived from aniline and benzaldehyde gave a poor yield (38% entry 4). In the reaction of the imine prepared from (*R*)-α-methylbenzylamine and benzaldehyde with methyl butyrate, the chiral β-amino ester **3c** was obtained in 82% yield. An X-ray single crystal structure analysis of the corresponding 3,5-dinitrobenzamide derivative **5** (Eq. 3) revealed that the major isomer possesses *syn* stereochemistry (Fig. 1).[14] Furthermore, the absolute configurations of the newly formed chiral centres were assigned as *S*,*S* based on the X-ray data.

Keywords: β-Amino esters; Titanium ester enolates; Imines and Mannich reaction.
* Corresponding author. Tel.: +91 40 23134814; fax: +91 40 23012460; e-mail: mpsc@uohyd.ernet.in

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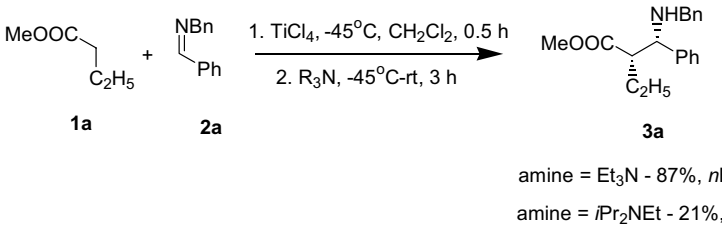
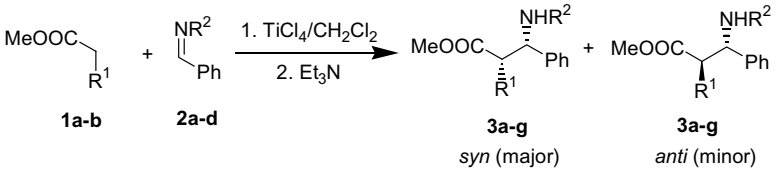


(1)

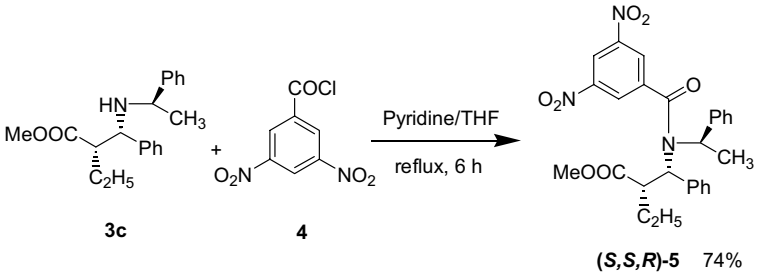


(2)

Table 1. Reactions of esters and imines with the $TiCl_4/Et_3N$ reagent system

Entry	R^1	R^2	Temperature (°C)	% Yield of **3**[a]	*syn*/*anti*
1	Et	Bn	−45	(**3a**) 87	100:0[d,e]
2	Et	*n*-Bu	−45	(**3b**) 78	95:5[d,e]
3	Et	$CH(Ph)CH_3$	−45	(**3c**) 82[b,c]	92:8[e]
4	Et	Ph	−45	(**3d**) 38	55:45[d,e]
5	Ph	Bn	0	(**3e**) 78[b]	73:27[g]
6	Ph	*n*-Bu	0	(**3f**) 80	66:34[f,g]
7	Ph	Ph	0	(**3g**) 41	67:33[e,f]

[a] The structures of the products were confirmed by spectral data (IR, ^1H NMR and ^{13}C NMR) and mass and elemental analyses (see Supplementary data). Yields are for isolated products.
[b] The *syn* stereochemistry was assigned to the major diastereomers of the products **3c** and **3e** based on the crystal structures of their derivatives **5** and **6**, respectively.
[c] This imine was prepared from (*R*)-α-methylbenzylamine and benzaldehyde. The stereochemistry of the new chiral centres was assigned (*S*,*S*) on the basis of crystal structure analysis of the derivative **5** prepared using **3c**.
[d] The stereochemistry of the major products **3a**,**b** and **3d** was assigned as *syn* by comparison of ^1H NMR data with those of **3c**.
[e] The *syn*/*anti* ratio was determined by ^{13}C NMR (50 MHz) data.
[f] The stereochemistry of the major products **3f** and **3g** was assigned as *syn* by comparison of ^1H NMR data with those of **3e**.
[g] The *syn*/*anti* ratio is the ratio of the diastereomers separated using column chromatography.



(3)

The stereochemistries of the major products **3a**,**b** and **3d** were assigned as *syn* by comparison of their ^1H NMR data with those of compound **3c**.

In the cases of β-amino esters prepared from methyl phenylacetate, the diastereomers were separable by column chromatography. We observed that the imines pre-

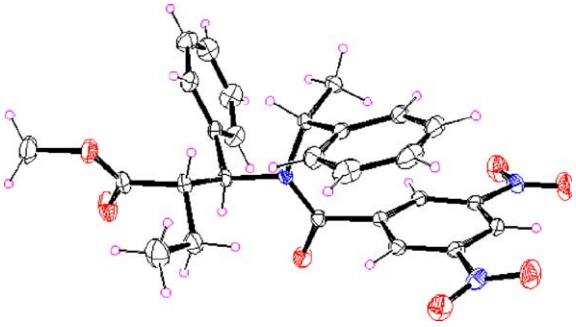


Figure 1. ORTEP representation of the crystal structure of compound **5** (thermal ellipsoids are drawn at 20% probability).

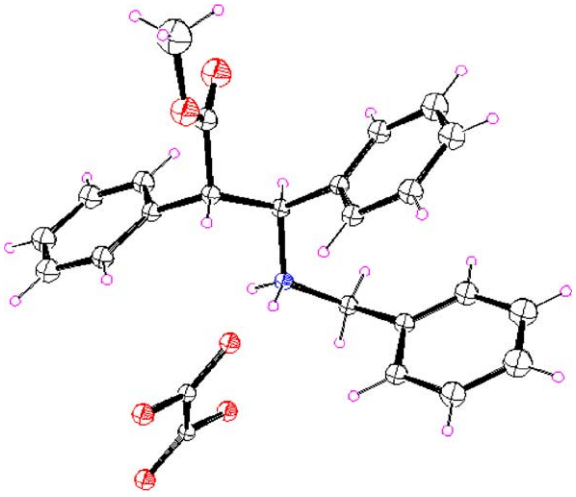


Figure 2. ORTEP representation of the crystal structure of the complex of **3e** with oxalic acid (thermal ellipsoids are drawn at 20% probability).

pared from alkyl amines and benzaldehyde gave good yields (entries 5 and 6) and that the imine prepared from aniline and benzaldehyde gave a poor yield (41% entry 7). An X-ray analysis of the complex **6** prepared from the major isomer of β-aminoester **3e** and oxalic acid revealed that the product had the *syn* stereochemistry (Fig. 2).[15]

The stereochemistries of the major isomers of products **3f** and **3g** were assigned as *syn* by comparison of ^{1}H NMR data with those of compound **3e**. The *syn* stereoselectivity for the products can be tentatively explained on the basis of the stereochemical argument is shown in Figure 3. The configuration of the imine is expected to be *E*.[16] The results can be explained considering that the *E*-titanium ester enolate would be in equilibrium with the *Z*-titanium ester enolate. The reaction of the *E*-titanium ester enolate would give a low energy transition state **TS-1** leading to the major *syn* product, whereas the *Z*-titanium ester enolate would result in a high energy transition state **TS-2** leading to the minor *anti* product.

β-Amino acid moieties are present in several biologically important compounds such as dolastins, astins, onchidin, jasplakinolide and motuporin.[1] Also, it is noteworthy that certain biologically active molecules like taxol, bestatin, kynostatins, scytonemyn A and microginin contain *syn* configured β-amino acid moieties.[1] Hence, the method described here for the synthesis of *syn*-β-amino esters using the $TiCl_4/R_3N$ reagent system has good synthetic potential.

Acknowledgements

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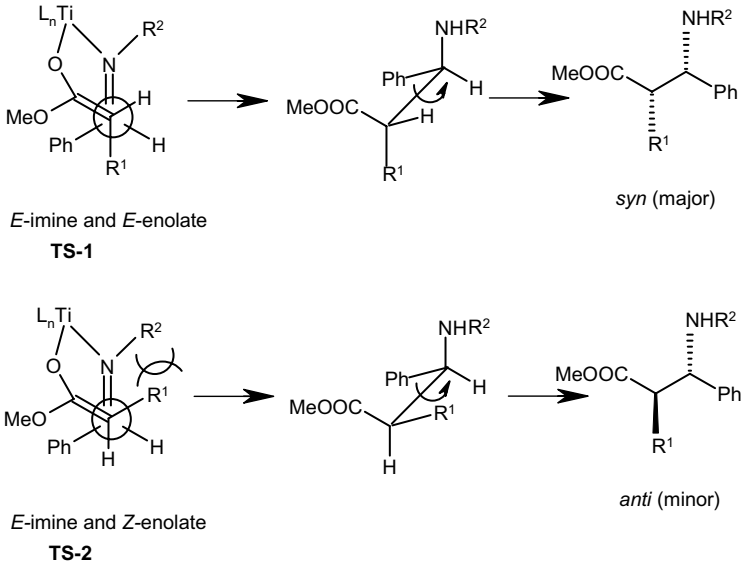

Figure 3. Stereochemical models.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.06.048.

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14. *Crystal Data*: For compound **5**: molecular formula: $C_{27}H_{27}N_3O_7$, MW = 505.52, monoclinic, space group: $P2(1)$, a = 11.3587(8) Å, b = 6.7522(5) Å, c = 17.6162(12) Å, β = 107.5420(10)°, V = 1288.26(16) Å^3, Z = 2, ρ_c = 1.303 mg m^{-3}, μ = 0.09 mm^{-1}, T = 293(2) K. Of the 5792 reflections collected, 3877 were unique (R_{int} = 0.0000). Refinement on all data converged at R_1 = 0.0490, wR_2 = 0.0830. (Deposition number CCDC 265595.)
15. The major isomer of the β-amino ester **3e** (3 mmol) and oxalic acid (3 mmol) were dissolved in dry acetone (8 mL) and the solution was stirred for 6 h. The precipitate was filtered off and crystallized from acetonitrile to obtain crystals suitable for X-ray analysis.
    Crystal Data: Complex of the amino ester **3e** and oxalic acid: molecular formula: $C_{25}H_{25}NO_6$, MW = 438.48, monoclinic, space group: $P2(1)/n$, a = 6.0118(6) Å, b = 15.7611(16) Å, c = 21.550(2) Å, β = 96.979(2)°, V = 2026.8(3) Å^3, Z = 4, ρ_c = 1.437 mg m^{-3}, μ = 0.103 mm^{-1}, T = 293(2) K. Of the 4878 reflections collected, 2855 were unique (R_{int} = 0.0000). Refinement on all data converged at R_1 = 0.0517, wR_2 = 0.1085. (Deposition number CCDC 265594.)
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