ORGANIC LETTERS

2012
Vol. 14, No. 12
3092–3095

A Highly Diastereoselective Decarboxylative Mannich Reaction of β-Keto Acids with Optically Active *N*-Sulfinyl α-Imino Esters

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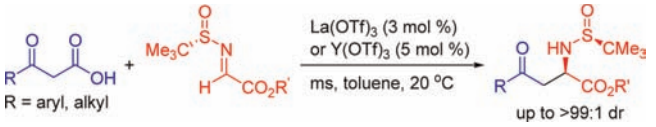
Received May 1, 2012

ABSTRACT



A range of protected γ-oxo-α-amino esters have been prepared in a highly regio- and stereoselective manner through the decarboxylative Mannich reaction of β-keto acids with optically active *N*-*tert*-butanesulfinyl α-imino esters in the presence of 3 mol % La(OTf)$_3$ or 5 mol % Y(OTf)$_3$ at 20 °C. Preliminary mechanistic studies indicate that the reaction proceeds through imine addition followed by decarboxylation.

The asymmetric Mannich reaction of α-imino esters constitutes a facile synthetic route to optically active functionalized α-amino acid derivatives that are widely employed in the construction of biologically important compounds.[1] Although enolizable ketones can serve as the carbon nucleophiles, the reaction suffers from insufficient reactivity with many simple ketones and unsatisfactory regioselectivity with unsymmetrical dialkyl ketones.[2] Employment of silyl enol ethers as surrogates of ketones significantly improves the reactivity, but control of the regioselectivity still remains problematic with silyl enol ethers derived from unsymmetrical dialkyl ketones.[3] In this context, it seemed interesting and rewarding to explore whether reactive and readily accessible surrogates of ketones would undergo asymmetric additions to α-imino esters in a highly regio- and stereoselective manner. Herein, we report that β-keto acids do undergo a diastereoselective

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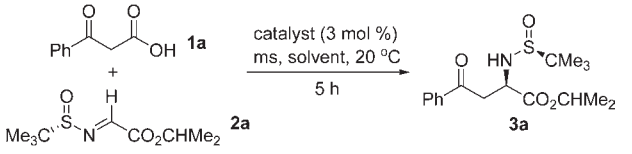
10.1021/ol301180z
Published on Web 05/31/2012

decarboxylative Mannich reaction with optically active *N*-*tert*-butanesulfinyl α-imino esters at 20 °C to give a range of functionalized α-amino acid derivatives in high dr.

Whereas *β*-keto acids are unstable to heat, acids, and bases, it has been reported that they can undergo decarboxylative carbon−carbon bond-forming reactions under appropriate conditions with carbon electrophiles such as aldehydes,[4] ketones,[5] 1-pyrroline/zinc iodide,[6] electron-deficient alkenes,[7] allylic electrophiles,[8] and *N*-benzylic sulfonamides.[9] These biomimetic reactions have demonstrated that *β*-keto acids can serve as attractive surrogates of ketones in the formation of carbon−carbon bonds due to their higher reactivity and regioselectivity. We therefore envisioned that it would be possible to develop a decarboxylative Mannich reaction of *β*-keto acids with α-imino esters under appropriate acidic conditions through extrusion of carbon dioxide. Nevertheless, it is a formidable challenge to fine-tune reaction conditions that allow one to execute imine addition prior to decarboxylation.

Due to their stability and easy accessibility, optically active *N*-*tert*-butanesulfinyl α-imino esters were selected as the carbon electrophiles in our proposed asymmetric Mannich reaction.[10] Initially, we took advantage of the acidity of *β*-keto acids to activate *N*-*tert*-butanesulfinyl α-imino esters and found that *β*-keto acid **1a** underwent a decarboxylative Mannich reaction with chiral imine **2a** in dioxane at 20 °C to give *γ*-oxo-α-amino ester **3a** in 12% yield and with 70:30 dr (Table 1, entry 1). Addition of 5 Å molecular sieves (ms) to the reaction mixture dramatically improved the yield and dr to 47% and 96:4, respectively (Table 1, entry 2). Reasoning that an external acid might activate the *β*-keto acid and the chiral imine in a synergistic manner,[11] we examined a range of metal triflates and found that the employment of 3 mol % $La(OTf)_3$ led to the formation of product **3a** in 79% yield and with 98:2 dr (Table 1, entry 9). Further investigation revealed that toluene was the solvent of choice, and the reaction performed in toluene gave the desired product in 89% yield and with >99:1 dr (Table 1, entry 10).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]	dr[c]
1[d]	none	dioxane	12	70:30
2	none	dioxane	47	96:4
3	TfOH	dioxane	38	94:6
4	$Cu(OTf)_2$	dioxane	51	61:39
5	$Zn(OTf)_2$	dioxane	71	84:16
6	$Fe(OTf)_3$	dioxane	46	93:7
7	$Bi(OTf)_3$	dioxane	52	87:13
8	$Y(OTf)_3$	dioxane	67	75:25
9	$La(OTf)_3$	dioxane	79	98:2
10	$La(OTf)_3$	toluene	89	>99:1
11	$La(OTf)_3$	dichloromethane	61	98:2
12	$La(OTf)_3$	chloroform	70	98:2
13	$La(OTf)_3$	ether	55	97:3
14	$La(OTf)_3$	ethyl acetate	71	96:4
15	$La(OTf)_3$	acetonitrile	83	97:3
16	$La(OTf)_3$	nitromethane	76	98:2

[a] Reaction conditions: *β*-keto acid **1a** (0.24 mmol), imine **2a** (0.20 mmol), catalyst (if any, 3 mol %), 5 Å molecular sieves (40 mg), solvent (0.40 mL), 20 °C, 5 h. [b] Isolated yield. [c] Determined by HPLC analysis as described in the Supporting Information. [d] Without molecular sieves.

In the presence of 3 mol % $La(OTf)_3$, a range of *β*-keto acids smoothly underwent a decarboxylative Mannich reaction with optically active *N*-*tert*-butanesulfinyl α-imino esters at 20 °C to give structurally diverse protected *γ*-oxo-α-amino esters in good yields and with excellent diastereoselectivity (Table 2, entries 1−12). The R^1 group in the *β*-keto acid could be an aryl or a heteroaryl group, and the reaction tolerated electron-rich and electron-poor aromatic moieties. However, such reaction conditions failed to afford excellent diastereoselectivity when the R^1 group in the *β*-keto acid was an alkyl group. Gratifyingly, alternative employment of $Y(OTf)_3$ (5 mol %) as the catalyst led to excellent diastereoselectivity with regard to such substrates (Table 2, entries 13−17), and importantly, no regioisomeric product was obtained from the reaction with *β*-keto acids **1k**−**n** (Table 2, entries 13−16).

The optically active *γ*-oxo-α-amino esters we obtained could undergo a range of chemical transformations under appropriate conditions. For example, when *γ*-oxo-α-amino ester **3a** was treated with hydrogen chloride in dioxane under reflux, *γ*-oxo-α-amino acid **4a** (HCl salt) was formed in 94% yield (Scheme 1). In contrast,

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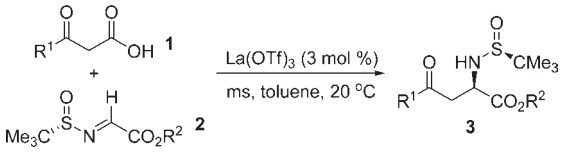
Table 2. Decarboxylative Mannich Reaction of β-Keto Acids with Optically Active *N*-Sulfinyl α-Imino Esters[a]

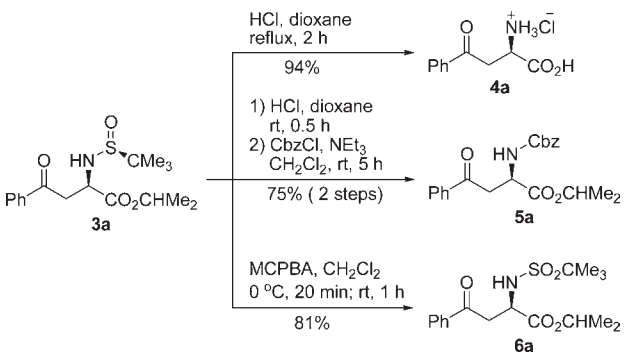


entry	**1**, R^1	**2**, R^2	**3**	time (h)	yield (%)[b]	dr[c]
1	**1a**, Ph	**2a**, $CHMe_2$	**3a**	5	89	>99:1
2	**1a**, Ph	**2b**, Et	**3b**	5	89	99:1
3	**1a**, Ph	**2c**, CH_2Ph	**3c**	8	67	96:4
4	**1b**,4-$MeOC_6H_4$	**2a**, $CHMe_2$	**3d**	5	71	>99:1
5	**1c**, 4-FC_6H_4	**2a**, $CHMe_2$	**3e**	10	85	99:1
6	**1d**,4-ClC_6H_4	**2a**, $CHMe_2$	**3f**	11	75	99:1
7	**1e**, 4-BrC_6H_4	**2a**, $CHMe_2$	**3g**	10	81	99:1
8	**1f**, 4-$O_2NC_6H_4$	**2a**, $CHMe_2$	**3h**	10	71	97:3
9	**1g**, 3-$O_2NC_6H_4$	**2a**, $CHMe_2$	**3i**	12	61	99:1
10	**1h**,2-ClC_6H_4	**2a**, $CHMe_2$	**3j**	24	66	94:6
11	**1i**, 2-furyl	**2a**, $CHMe_2$	**3k**	5	79	98:2
12	**1j**, 2-thienyl	**2a**, $CHMe_2$	**3l**	5	87	99:1
13[d]	**1k**, $PhCH_2$	**2a**, $CHMe_2$	**3m**	12	82	99:1
14[d]	**1l**, $MeCH_2CH_2$	**2a**, $CHMe_2$	**3n**	10	77	98:2
15[d]	**1m**, $Me(CH_2)_{10}$	**2a**, $CHMe_2$	**3o**	14	69	97:3
16[d]	**1n**, Me_2CH	**2a**, $CHMe_2$	**3p**	10	80	97:3
17[d]	**1o**, Me_3C	**2a**, $CHMe_2$	**3q**	10	70	>99:1

[a] Reaction conditions: β-keto acid **1** (0.24 mmol), imine **2** (0.20 mmol), $La(OTf)_3$ (3 mol %), 5 Å molecular sieves (40 mg), toluene (0.40 mL), 20 °C. [b] Isolated yield. [c] Determined by HPLC analysis as described in the Supporting Information. [d] $La(OTf)_3$ was replaced with $Y(OTf)_3$ (5 mol %), and 1.0 mL of toluene was used.

treatment of compound **3a** with hydrogen chloride at room temperature just removed the *N*-*tert*-butanesulfinyl group, and when the resulting mixture was treated with benzyl chloroformate (CbzCl) and triethylamine, it gave Cbz-protected γ-oxo-α-amino ester **5a** in 75% yield (two steps). It is noteworthy that no epimerization took place at the α-chiral center. In addition, compound **3a** was oxidized with *meta*-chloroperoxybenzoic acid (MCPBA) to give *N*-sulfonyl γ-oxo-α-amino ester **6a** in 81% yield. The absolute configuration of compound **6a** was assigned to be *R* by single-crystal X-ray analysis.

Scheme 1. Transformations of Compound **3a**



ESI-mass spectroscopic analysis of the mixture of β-keto acid **1a** and imine **2a** allowed us to identify intermediate **7a** (Figure 1) according to the high resolution mass data [HRMS (ESI) calcd for $C_{18}H_{26}NO_6S^+$ ($M + H^+$) 384.14753, found 384.14781]. Nevertheless, isolation of β-keto acid **7a** was not successful by chromatography on silica gel due to rapid decomposition. Although acetophenone was detected in a significant amount in the reaction mixture, it could not react with imine **2a** under our standard conditions. These observations clearly indicate that the imine addition step occurs prior to the decarboxylation step in the asymmetric decarboxylative Mannich reaction.

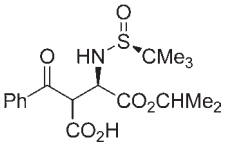
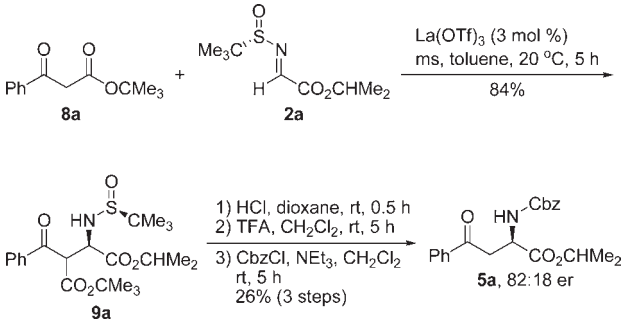


Figure 1. Structure of intermediate **7a**.

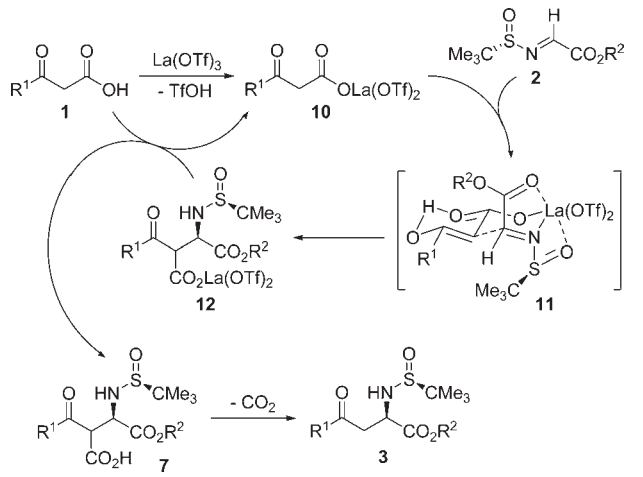
For comparison, we further examined the reactivity of β-keto esters under our standard conditions. Although the reaction of β-keto ester **8a** with imine **2a** smoothly proceeded in the presence of 3 mol % $La(OTf)_3$ to give adduct **9a** in 84% yield, the product was transformed in three steps into Cbz-protected γ-oxo-α-amino ester **5a** with only 82:18 er (Scheme 2). These experiments clearly show that the reaction with β-keto ester **8a** is much less diastereoselective than that with β-keto acid **1a** (> 99:1 dr, Table 2, entry 1) and indicate that the carboxylic acid group in the β-keto acid plays a crucial role for the asymmetric decarboxylative Mannich reaction to proceed with excellent diastereoselectivity.

Scheme 2. Reaction of β-Keto Ester **8a** with Imine **2a**



Based on our experimental results, we propose the following reaction pathway for the asymmetric decarboxylative Mannich reaction of β-keto acids with *N*-sulfinyl α-imino esters (Scheme 3). Displacement of $La(OTf)_3$ catalyst by β-keto acid **1** results in the formation of salt **10**, which undergoes addition to *N*-sulfinyl α-imino ester **2** to

Scheme 3. Proposed Mechanism



give salt **12**. Displacement of salt **12** by β-keto acid **1** gives β-keto acid **7** and regenerates salt **10**. Decarboxylation of β-keto acid **7** leads to the formation of product **3**. Such an imine addition/decarboxylation sequence should account for the extremely high regioselectivity observed in the reaction (Table 2, entries 13−16). The excellent diastereoselectivity probably originates in the imine addition step. The coordination of salt **10** with *N*-sulfinyl α-imino ester **2** might form a chairlike transition state, **11**, in which the β-keto acid moiety sits far away from the *N*-sulfinyl group due to steric repulsion.

In summary, we have developed, for the first time, a highly diastereoselective decarboxylative Mannich reaction of β-keto acids with optically active *N*-*tert*-butanesulfinyl α-imino esters. In the presence of 3 mol % $La(OTf)_3$ or 5 mol % $Y(OTf)_3$, a variety of β-keto acids smoothly undergo a decarboxylative Mannich reaction with *N*-*tert*-butanesulfinyl α-imino esters at 20 °C to give structurally diverse protected γ-oxo-α-amino esters in good yields and with extremely high regioselectivity and excellent diastereoselectivity. Preliminary mechanistic studies indicate that the reaction proceeds through imine addition followed by decarboxylation.

Acknowledgment. We are grateful for the financial support from the National Natural Science Foundation of China (21172206, 20972147, and J1030412), the National Basic Research Program of China (973 Program 2010CB833300), and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1189).

Supporting Information Available. Experimental procedures; characterization data; copies of ^{1}H NMR, ^{13}C NMR, and HPLC spectra for products; and crystal data of compound **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.