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Efficient Multicomponent Reaction for the Synthesis of Piperidine Derivatives: $Yb(OTf)_3$/AgOTf Cocatalyzed Preparation of Trimethyl 3,5,5-Piperidonetricarboxylate

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Efficient Multicomponent Reaction for the Synthesis of Piperidine Derivatives: $Yb(OTf)_3$/AgOTf Cocatalyzed Preparation of Trimethyl 3,5,5-Piperidonetricarboxylate

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Abstract: A novel and convenient one-pot synthesis of trimethyl 3,5,5-piperidonetricarboxylate was reported. Cocatalyzed by $Yb(OTf)_3$ and AgOTf under mild conditions, a piperidone containing a β-amino acid template was synthesized from dimethyl malonate and formaldehyde *O*-benzyl oxime in high yield. It could be a useful building block for the synthesis of multisubstituted piperidine derivatives.

Keywords: Cocatalyst, multicomponent reaction, piperidine derivatives

Multisubstituted piperidines are key building blocks for the synthesis of bioactive compounds or natural products (e.g., agonists of human GABA-A receptors,[1] farnesyl-protein transferase inhibitors,[2] and optically active indole alkaloids[3]). Consequently, stereoselective construction of piperidine derivatives is of great interest.[4] Among these compounds, as show in Scheme 1, 3,5-*cis*-piperidine-dicarboxylates (**A**) are common intermediates for the preparation of biologically important compounds, for example, conformational constrained cyclic β,γ′-diamino acid units (**B**), which serve as inducing factors of the peptidomimetic secondary structures[5], and *N*-(indol-3-ylglyoxylyl) 3,5-*cis*-piperidinedicarboxylate (**C**), which was reported to be a high-affinity agonist of human GABA-A receptors.[1] Usually, structure-related compound **A** is

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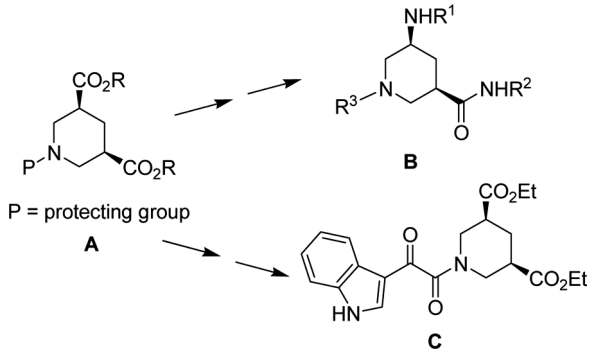
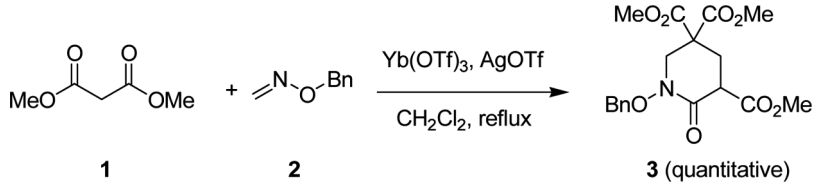


Scheme 1. Examples of bioactive piperidine derivatives.

synthesized by hydrogenation of corresponding pyridine derivatives under strict reaction conditions in medium yield.

In our continuous study of asymmetric synthesis of β-amino acids, an efficient multicomponent synthesis of 3,5,5-piperidonetricarboxylate **3**[6] (which can be easily transferred to the key intermediate 3,5-piperidinedicarboxylate **A**, followed literature methods[7,8]), from dimethyl malonate **1** and formaldehyde *O*-benzyl oxime **2** was found accidentally. In the present work, we describe our preliminary results on this Lewis acid and metal triflate cocatalyzed, one-pot, multicomponent reaction.

Initially, we predicted a simple Mannich base product from the reaction of dimethyl malonate **1** to oxime **2**. To our surprise, a multisubstituted piperidone **3** was obtained in almost quantitative yield (Scheme 2). The structure of piperidone **3** has been characterized by a detailed analysis by NMR spectroscopy, including ^{1}H NMR, ^{13}C NMR, distortionless enhancement by polarization transfer (DEPT 135), H-H correlation spectroscopy (COSY), and heteronuclear multiple-quantum coherence (HMQC) spectra. Three singlet methoxy group signals (δ 3.80, 3.76, and 3.75 ppm) and four carbonyl group signals (δ 169.3, 168.5, 168.1, and 162.5 ppm) are indicated in ^{1}H and ^{13}C NMR spectra. DEPT 135 spectrum proves that the product possesses one quaternary carbon at δ



Scheme 2. Synthesis of piperidone derivative **3**.

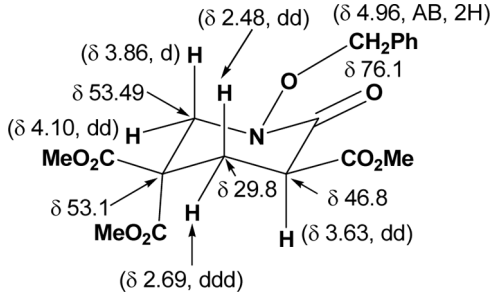
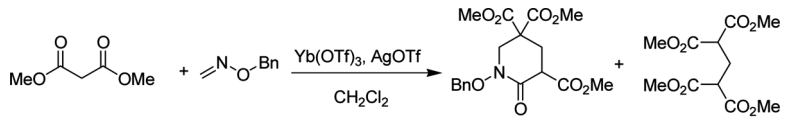


Figure 1. Characterization of ^{1}H NMR and ^{13}C NMR signals of compound **3**. The chemical shifts of ^{1}H NMR are in parenthesis.

53.1 ppm, one tertiary carbon at δ 46.8 ppm (which is related to the dd signal of δ 3.63 presented in ^{1}H NMR spectrum), and other three secondary carbons of δ 76.1, 53.49, and 29.8 ppm (attributed by benzyloxy methylene and two methylenes of the piperidine ring, respectively). The characterization of the signals of ^{1}H and ^{13}C NMR spectra are indicated in Fig. 1.

Further studies revealed that both $Yb(OTf)_3$ and AgOTf are essential to this multicomponent reaction. The results are shown in Table 1. No reaction happened without either of the catalysts (entries 2 and 3). When

Table 1. Reaction of dimethyl malonate **1** and oxime **2** cocatalyzed by silver triflate and ytterbium triflate

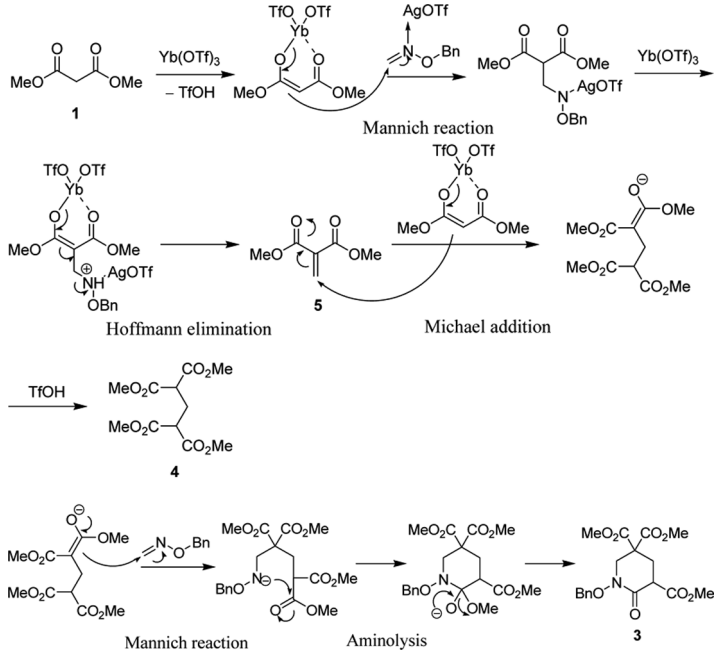


1 2 3 4

Entry	**1**/**2**/$Yb(OTf)_3$/AgOTf	Conc. of Substrate **2**	Conditions	Isolated yield (%)	
				3	**4**
1	1.1/1/0.3/0.2	0.5 M	Reflux, 17 h	Quantitative	
2	1.1/1/0.3/—	0.5 M	Reflux, 17 h	No reaction (NR)	
3	1.1/1/—/0.2	0.5 M	Reflux, 5.5 h	NR	
4	1.1/1/0.3/0.05	0.5 M	Reflux, 17 h	NR	
5	1.1/1/0.3/0.2	0.5 M	rt 23 h	NR	
6	1.1/1/0.3/0.2	0.05 M	Reflux, 17 h	19	18
7	2.1/1/0.3/0.2	0.5 M	Reflux, 17 h	11	72
8	1/1.8/0.3/0.4	0.5 M	Reflux, 17 h	Quantitative	

the loading amount of AgOTf was too low (0.05 equiv.), the reaction did not happen (entry 4). The reaction temperature and concentration were found among other prominent effects to the reaction. At room temperature, no reaction was detected (entry 5). When the concentration of the reaction mixture was as low as 0.05 M, the yield of **3** dropped dramatically to 19%. Simultaneously, 18% of tetramethyl propane-1,1,3,3-tetracarboxylate **4**[9] was produced (entry 6). To make a conjecture about the reaction mechanism, we examined the reactions carried out at different ratios of malonate **1** to oxime **2**. The results showed that the ratio of the two reactants is very important to the population of the two products. When the ratio of **1** to **2** was 2.1:1, the yield of **3** decreased to 11% while the yield of **4** increased to 72% (entry 7). When the oxime **2** was more then 1.8 equiv of that of malonate **1**, compound **3** was quantitatively produced, just like the result of the reaction of equal equivalents of the two reactants (cf. entry 8 and entry 1).

A possible mechanism of this reaction is presented in Scheme 3. The formation of compounds **3** and **4** could constitute the process of the following domino reactions. Dimethyl malonate **1**, activated by Lewis acid $Yb(OTf)_3$, undergoes nucleophilic addition to oxime **2**, which is



Scheme 3. Possible reaction mechanism.

combined with AgOTf through the Mannich reaction. Then, followed by the Hoffmann elimination, the Michael acceptor **5** is obtained. Another molecular of activated dimethyl malonate plays the role of the Michael donor; a 1,4-addition reaction with this Michael acceptor **5** produces the product **4**. The compound **4** can react with another equivalent of oxime **2** to construct the Mannich base with a quaternary carbon center. Following intramolecular aminolysis, this crowd builds six-membered ring piperidone derivative **3**. If not enough oxime **2** exists, the reaction would be favored to stop at compound **4** (Table 1, entry 7).

In conclusion, we developed a novel $Yb(OTf)_3$ and AgOTf cocatalyzed multicomponent reaction for synthesis of trimethyl 3,5,5-piperidonetricarboxylate. A domino-sequence mechanism was put forward to explain this one-pot synthesis.

EXPERIMENTAL

All the starting materials are commercial available. Formaldehyde *O*-benzyl oxime **2** was prepared according to the reported process.[10] CH_2Cl_2 was used directly without pretreatment. Flash-column chromatography was performed on Qing Dao Hai Yang silica gel 60 (230–400 mesh ASTM) using ethyl acetate/*n*-hexane as eluting solvents. NMR spectra were recorded on a Jeol ECA-400 or Bruker DMX-400. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low-resolution and high-resolution mass spectra (LRMS and HRMS).

Typical Procedure for $Yb(OTf)_3$ and AgOTf Cocatalyzed Reaction Between Dimethyl Malonate (1) and Formaldehyde *O*-Benzyl Oxime (2)

Formaldehyde *O*-benzyl oxime **2** (68 mg, 0.5 mmol) and dimethyl malonate **1** (60 μL, 0.55 mmol) was dissolved in CH_2Cl_2 (1 mL); AgOTf (26 mg, 0.1 mmol) and $Yb(OTf)_3$ (91 mg, 0.15 mmol) were added subsequently. The reaction was warmed up to reflux. After 17 h, the reaction was quenched by water (1 mL). The mixture was extracted by CH_2Cl_2 (2 mL × 2). The aqueous layer was combined and dried with anhydrous Na_2SO_4. After concentration, the residue was purified by flash-column chromatography to get **3** (105 mg, quantitative).

Trimethyl 1-(Benzyloxy)-piperidone-3,5,5-tricarboxylate (3)

Yellow oil; EtOAc–*n*-hexane=1:2, R_f=0.54; ^{1}H NMR (400 HMz, $CDCl_3$) δ 7.44–7.26 (m, 5H, Ph), 4.96 (AB, J_{AB}=10.2 Hz, 2H, OCH_2), 4.10 (dd,

J=11.7, 2.0 Hz, 1H, *e*-bond NCH_2), 3.86 (d, *J*=12.2 Hz, 1H, *a*-bond NCH_2), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.63 (dd, *J*=12.0, 6.4 Hz, 1H, C*H*), 2.69 (ddd, *J*=13.7, 6.4, 2.0 Hz, 1H, *e*-bond CH_2), 2.48 (dd, *J*=13.7, 11.2 Hz, 1H, *a*-bond CH_2); ^{13}C NMR (100 HMz, $CDCl_3$) δ 169.3 (*C*=O), 168.5 (*C*=O), 168.1 (*C*=O), 162.5 (*C*=O), 134.8 (*C*), 129.6 (*C*H), 128.8 (*C*H), 128.5 (*C*H), 76.1 (OCH_2), 53.6 (OCH_3), 53.51 (OCH_3), 53.49 (NCH_2), 53.1 (*C*), 52.8 (OCH_3), 46.8 (*C*H), 29.8 (*C*H_2); LRMS (EI) *m/z* 214 ($M^+ + 1$–CO_2Me–OBn, 100); HRMS (EI) for $C_{18}H_{21}NO_8$ (M^+): calcd. 379.1267, found 379.1286.

Tetramethyl Propane-1,1,3,3-tetracarboxylate (4)[9]

Colorless oil; EtOAc–*n*-hexane=1:2, R_f=0.37; ^{1}H NMR (400 HMz, $CDCl_3$) δ 3.75 (s, 12H, 4OCH_3), 3.52 (t, *J*=7.5 Hz, 2H, 2C*H*), 2.50 (t, *J*=7.5 Hz, 2H, CH_2); ^{13}C NMR (100 HMz, $CDCl_3$) δ 168.9 (*C*=O), 52.7 (OCH_3), 49.0 (*C*H), 27.4 (*C*H_2). Its data were identical to those reported in the literature.

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