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Sulfated zirconia (SO_4/ZrO_2) as a reusable solid acid catalyst for the Mannich-type reaction between ketene silyl acetals and aldimines

Sainan Wang, Shuichi Matsumura and Kazunobu Toshima*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

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Abstract—Sulfated zirconia (SO_4/ZrO_2) catalyzed Mannich-type reactions of ketene silyl acetals and aldimines proceeded smoothly at room temperature to afford β-amino esters in good to high yields. In addition, the heterogeneous solid acid catalyst SO_4/ZrO_2 was easily recovered from the reaction mixture and then reused without significant loss of effectiveness.

Carbon–carbon bond forming reactions continue to be the central focus of research in synthetic organic chemistry. Among them, the Mannich-type reaction of ketene silyl acetals and aldimines giving β-amino esters in a single step is of considerable importance for synthesizing biologically attractive molecules containing nitrogen atom.[1] While several Lewis or Brønsted acids have been reported as effective in promoting nucleophilic addition of ketene silyl acetals to aldimines, the possibility of developing an environmentally benign simple synthetic method has recently attracted much attention.[2] In this context, pioneering work by Onaka et al.[3] and Akiyama et al.[4] on the Mannich-type reaction demonstrated the use of heterogeneous solid acids such as Fe–Montmorillonite and Montmorillonite K10, but did not show the reusability of those solid acids. Here, we report a Mannich-type reaction between ketene silyl acetals and aldimines effected by a heterogeneous solid acid, sulfated zirconia (SO_4/ZrO_2), under mild conditions to give β-amino esters in good to high yields. We also found that the SO_4/ZrO_2 catalyst could be recovered easily from the reaction mixture and then directly reused without significant loss of activity.

With the aim of investigating a novel heterogeneous solid acid for the Mannich-type reaction between ketene silyl acetals and aldimines, we examined sulfated zirconia (SO_4/ZrO_2), which is known to function as both Lewis and Brønsted acids as shown in Figure 1.[5] We previously reported several stereoselective glycosylation reactions using SO_4/ZrO_2 as the catalyst.[6] Based on the mechanism of generation of the Brønsted acidic site of SO_4/ZrO_2 by the coordination of water with the Zr in SO_4/ZrO_2, we expected that recycling of SO_4/ZrO_2 would be easily achieved for the Mannich-type reaction between ketene silyl acetals and aldimines. With this expectation, we first examined the Mannich-type reaction of the aldimine **1** and the ketene silyl acetal **2** under several conditions. These results are summarized in Table 1. We found that the reaction using 50 or 100 wt % SO_4/ZrO_2[7] in MeCN at room temperature (25 °C) proceeded smoothly to give the β-amino ester **3** in high yield (entries 1 and 2 in Table 1). Furthermore,

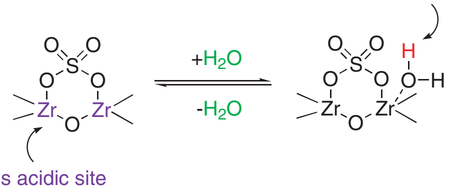

Figure 1.

Keywords: Sulfated zirconia; Solid acid; Mannich-type reaction; Ketene silyl acetal; Aldimine.

* Corresponding author. Tel./fax: +81 45 566 1576; e-mail: toshima@applc.keio.ac.jp

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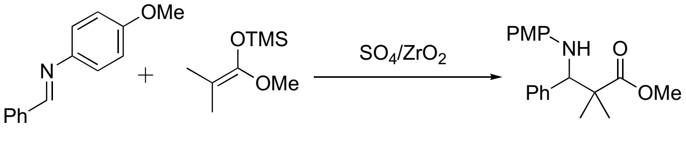
Table 1. Mannich-type reaction of aldimine **1** and ketene silyl acetal **2** using SO_4/ZrO_2 under different conditions[a]



1 **2** **3**

Entry	wt % of SO_4/ZrO_2	Solvent	Time (h)	Yield (%)
1	100	MeCN	20	92
2	50	MeCN	20	83
3	100	EtOH	20	72
4	100	PhMe	20	77
5	150	MeCN	5	99

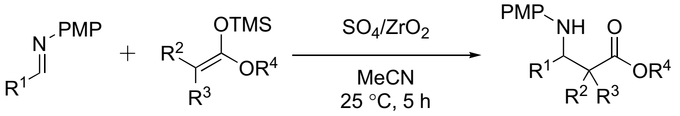
[a] 2.0 equiv of **2** was used.

MeCN was superior to other solvents such as EtOH[8] and PhMe (entry 1 vs entries 3 and 4 in Table 1). In addition, the use of 150 wt % SO_4/ZrO_2 shortened the reaction time and offered a quite satisfactory result (entry 5 in Table 1). Thus, the reaction of **1** and **2** using 150 wt % SO_4/ZrO_2 in MeCN at room temperature for 5 h provided the β-amino ester **3** in 99% yield.

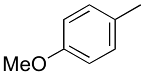
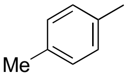
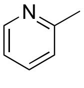
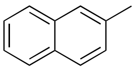
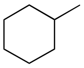
After achieving this favorable result, we next examined the Mannich-type reaction of the ketene silyl acetal **2** with a range of aldimines. The results in Table 2 showed that aldimines **4–8** derived from aliphatic aldehyde as well as aromatic aldehyde gave the corresponding β-amino esters **9–13** in good to high yields (entries 2–6 in Table 2). In the case of **8**, the yield was relatively low due to its instability (entry 6 in Table 2). Furthermore, the Mannich-type reaction of the aldimine **1** with the ketene silyl acetals **14** and **15** also proceeded smoothly to provide the β-amino esters **16** and **17**, respectively, in high yields (entries 7 and 8 in Table 2). These results showed the high versatility of using SO_4/ZrO_2.

Our attention next turned to the effect of the water content of SO_4/ZrO_2 on the efficiency of the Mannich-type reaction. If the Brønsted acidic site of SO_4/ZrO_2,

Table 2. Mannich-type reaction of aldimines and ketene silyl acetals using SO_4/ZrO_2[a]



1, **4-8** **2**, **14**, **15** **3**, **9-13**, **16**, **17**

Entry	Aldimine	Ketene silyl acetal	β-Amino ester	Yield (%)
1	**1**: $R^1 = Ph$	**2**: $R^2 = R^3 = R^4 = Me$	**3**	99
2	**4**: $R^1 =$  MeO	**2**	**9**	100
3	**5**: $R^1 =$  Me	**2**	**10**	100
4	**6**: $R^1 =$  N	**2**	**11**	97
5	**7**: $R^1 =$ 	**2**	**12**	100
6	**8**: $R^1 =$ 	**2**	**13**	65
7	**1**	**14**: $R^2 = Me$, $R^3 = H$, $R^4 = Et$ ($E/Z = 36:64$)	**16** (*syn*/*anti*[b] = 84:16)	93
8	**1**	**15**: $R^2 = Ph$, $R^3 = H$, $R^4 = Me$ ($E/Z = 32:68$)	**17** (*syn*/*anti*[b] = 63:37)	100

[a] 2.0 equiv of ketene silyl acetal and 150 wt % SO_4/ZrO_2 were used.

[b] The ratio of *syn*/*anti* was determined by the procedure described in Ref. 3.

generated by the coordination of water with Zr, significantly affected the reaction, the efficiency of the reaction would be highly dependent on the water content of SO_4/ZrO_2 used. To confirm this hypothesis, we prepared sulfated zirconia containing three differing water contents—68,755, 31,364, and 17,815 ppm—by drying wet-SO_4/ZrO_2 under 2 mmHg at room temperature.[9] We then examined the Mannich-type reaction of aldimine **1** and ketene silyl acetal **2** using the three sulfated zirconias with differing water contents in MeCN at room temperature for 5 h, as shown in Table 3. It was found that the sulfated zirconias containing 68,755 and 31,364 ppm water gave the β-amino ester **3** in high yield (entries 1 and 3 in Table 3), while the yield of **3** significantly decreased when SO_4/ZrO_2 containing 17,815 ppm water was used (entry 4 in Table 3). It was also confirmed that the SO_4/ZrO_2 used in Tables 1 and 2 contained 32,215 ppm water (entry 2 in Table 3). These results clearly indicated that the reactivity of SO_4/ZrO_2 for the Mannich-type reaction is highly dependent on its water content, as we expected, and satisfactory results were obtained when SO_4/ZrO_2 containing over about 30,000 ppm water was employed. In addition, it was found that a mixture of MeCN and H_2O (10:1) could also be used as the effective solvent.

Based on these findings, we finally examined the recovery of the used SO_4/ZrO_2 from the reaction mixture for its effective recycling, and finally found the following concise protocol. After the Mannich-type reaction was completed, a mixture of water and EtOAc (1:1) was added to the reaction mixture, and then the resulting mixture was extracted with EtOAc. The extracts were combined and concentrated in vacuo. Purification of the residue by silica-gel column chromatography gave β-amino ester. During this process, we found that the used SO_4/ZrO_2 could be completely collected in the aqueous layer due to its high affinity with water. Then, evaporation of only the water in the aqueous layer provided SO_4/ZrO_2 containing 65,000–70,000 ppm water in almost quantitative yield. The SO_4/ZrO_2 thus recovered could be directly reused for the Mannich-type reaction with only slight loss in efficiency, providing high yields over many reuses, as summarized in Table 4.

In conclusion, we have developed Mannich-type reactions of ketene silyl acetals and aldimines using a heterogeneous solid acid, sulfated zirconia (SO_4/ZrO_2). The reaction proceeded smoothly under mild conditions to give several types of β-amino esters in good to high yields, and we clarified that the water content of SO_4/ZrO_2 is very important for promoting the Mannich-type reaction. In addition, the heterogeneous solid acid SO_4/ZrO_2 could be easily recovered from the reaction mixture and then directly reused without significant loss of activity.

Table 3. The effect of the water content of SO_4/ZrO_2 on the Mannich-type reaction of **1** and **2**[a]

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{MeCN, } 25\,^{\circ}\text{C, 5 h}]{SO_4/ZrO_2} \mathbf{3}$$

Entry	Water amount of SO_4/ZrO_2/ppm	Yield (%)
1	68,775	99
2	32,215	99
3	31,364	97
4	17,815	52

[a] 2.0 equiv of **2** and 150 wt % SO_4/ZrO_2 were used.

Table 4. Recycling of SO_4/ZrO_2 for the Mannich-type reaction of **1** and **2**[a]

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{MeCN, } 25\,^{\circ}\text{C, 5 h}]{SO_4/ZrO_2} \mathbf{3}$$

	First run	1st reuse	2nd reuse	3rd reuse
Yield of **3**	99	99	97	90

[a] 2.0 equiv of **2** and 150 wt % SO_4/ZrO_2 were used.

General experimental procedure for the Mannich-type reactions of ketene silyl acetals and aldimines using sulfated zirconia (SO_4/ZrO_2): To a mixture of ketene silyl acetal (0.2 mmol) and aldimine (0.1 mmol) in MeCN (0.1 M for aldimine) was added sulfated zirconia (SO_4/ZrO_2) (150 wt % for aldimine, water content: >30,000 ppm) at 25 °C. After stirring at 25 °C for 5 h, a mixture of water and EtOAc (1:1) was added to the reaction mixture, and the resulting mixture was extracted with EtOAc. The extracts were combined, then dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica-gel column chromatography gave β-amino ester, while evaporation of the water in the aqueous layer provided SO_4/ZrO_2 (water content: 65,000–70,000 ppm), which could be directly reused for further reactions.

Acknowledgments

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7. SO_4/ZrO_2 was purchased from Wako Pure Chemical Industries, Ltd and used without further purification.
8. It was confirmed that MeOH and *i*-PrOH were also less effective than MeCN as the solvent.
9. Wet-SO_4/ZrO_2 (containing ~70,000 ppm water) was prepared by exposure of the purchased SO_4/ZrO_2[7] with water for 10 min followed by evaporation. Water amount of SO_4/ZrO_2 was measured using Karl Fischer moisture meter (756 KF Coulometer, Metrohm Ltd).