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Abstract: Three-component Mannich-type reaction of aldehydes, aromatic amines, and silyl enolate proceeded smoothly to afford β -amino carbonyl compounds with good yields in the presence of a catalytic amount of HBF₄-SiO₂.

Keywords: aldehyde, amine, HBF₄-SiO₂, Mannich reaction, silyl enolate

The Mannich reaction is one of the important fundamental reactions in organic chemistry. It is a classical method in the routes for the synthesis of various β -amino carbonyl compounds, which are versatile synthetic building blocks for the preparation of many nitrogen-containing biological compounds.^[11] Therefore, it has found applications in the synthesis of numerous pharmaceuticals and natural products.

Because of the drastic reaction conditions and long reaction times, the classical intermolecular Mannich reaction is plagued by a number of serious disadvantages. The Lewis acid–catalyzed condensation of silyl enol ethers

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or silyl ketene acetals to imines is an excellent variant of the classical Mannich reaction. However, this Lewis acid–catalyzed one-pot Mannich reaction quite often had to be carried out under strict anhydrous conditions because many of the imines are unstable in the presence of water.^[2] In addition, an equimolar amount of Lewis acid was required as a promoter because of the stronger basicity of nitrogen. At the same time, many Lewis acids could not be used in a one-pot reaction because of the presence of free amines and water produced in the imine formation.

Thus, the development of Mannich reaction methods is always in high demand. By now, several novel catalytic systems have been reported and applied to the Mannich-type reaction.^[3] Under those reaction conditions, imines could be activated effectively, and the Mannich reaction could proceed smoothly to afford β -amino carbonyl compounds in good yields. However, many of those methods involved the use of expensive reagents, extended reaction times, and harsh conditions, and also required tedious aqueous workup, leading to the generation of a large amount of toxic waste.

Obviously, there is an urgent need to develop safe, practical, and environmentally friendly processes. Among the many methods, the use of solid acid catalysts such as clay, ion-exchange resins, and zeolites has received considerable attention in organic synthesis.^[4] In recent years, solidsupported catalysts, in which the catalysts are adsorbed onto an insoluble inorganic or organic support (e.g., silica, alumina, clay or charcoal), have been applied widely in organic chemistry.^[5] As the effective surface area of the catalysts dispersed on a support could be increased significantly, the activity and selectivity of the catalysts could be improved. Meanwhile, the use of solid-supported catalysts could offer ease of workup and opportunities for recycling and makes a great contribution to green chemistry.

Recently, Akiyama and coworkers have found that Mannich-type reaction of aldehydes, amines, and silyl enolate could proceed smoothly in the presence of a catalytic amount of HBF_4 (aq.).^[6] To explore an alternative environmentally benign condition for this reaction, we attempted to examine this reaction in the presence of HBF_4 –SiO₂, which could act as a weak protic acid and might be a useful and inexpensive catalyst for the Mannich-type reaction under mild conditions.

In a model study, the reaction of benzaldehyde (0.3 mmol), 4-fluoroaniline (0.3 mmol), and [(1-methoxy-2-methyl-1-propenyl)oxy]trimethylsilane (0.45 mmol) was carried out in the presence of HBF₄–SiO₂ (30 mol%) under various conditions. The best yield (84%) was obtained when the reaction was tested at room temperature under solvent-free conditions. Lower yields were obtained when the reactions were carried out in organic solvents such as dichloromethane (DCM), MeCN, THF, MeOH, and toluene. Meanwhile, the catalyst could be successfully recycled three times by diluting the reaction mixture with diethyl ether, filtering, and reusing it without significant reduction of acitivity compared to its initial use. The

PhCHO + R_1NH_2 + OTMS HBF ₄ / SiO ₂ OCH ₃ solvent-free Ph OCH ₃ 1a 2a-f 3 4a-f				
Entry	R ₁	Product	Yield (%)	
1	$4\text{-FC}_6\text{H}_4$	4a	84	
2	$4-ClC_6H_4$	4b	86	
3	$4-BrC_6H_4$	4 c	89	
4	C_6H_5	4d	78	
5	4-MeOC ₆ H ₄	4 e	80	
6	C ₆ H ₅ CH ₂	4 f	0	

Table 1. Results of Mannich-type reaction of benzaldehyde, aromatic amines, and 3 catalyzed by HBF_4-SiO_2

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required product could be obtained in low yield (34%) using SiO_2 as the catalyst under the same reaction conditions.

Under the optimized reaction conditions, structurally diverse amines were subjected to the Mannich-type reaction in the presence of HBF_4-SiO_2 under solvent-free conditions. The results are summarized in Table 1. For the present reaction condition, all of the desired products could be obtained in moderate to good yields, whereas an aldimine derived from aliphatic amine did not work well (Table 1, entry 6). In addition, the structure of **4a** was further confirmed by single-crystal X-ray crystallography (Fig. 1). All of this evidence showed that HBF_4 was a driving force for the Mannich-type reaction, and it played a very essential role in this methodology.

To explore generality and scope, the potential of HBF_4 -SiO₂ was further investigated as a catalyst for the Mannich-type reaction of a range of aromatic and aliphatic aldehydes.



Figure 1. Molecular structure of product 4a.

Mannich-Type Reaction

As shown in Table 2, these reactions proceeded smoothly to afford the desired products in moderate to high yields under solvent-free conditions. Furthermore, this protocol could work with both aromatic and aliphatic aldehydes.

In summary, a convenient solvent-free procedure for performing imino-aldol coupling, using HBF₄-SiO₂ solid acid support, has been developed, which could afford the β -amino ester smoothly. This method is endowed with several merits, such as simplicity in operation, mild reaction conditions, wide applicability, cost efficiency, and recyclability of catalyst, which make it a convenient, economic, and user-friendly process. Further investigations on asymmetric Mannich-type reaction catalyzed by HBF₄-SiO₂ are in progress.

EXPERIMENTAL

Apparatus and Analysis

Proton nuclear magnetic resonance spectra (¹H NMR) and carbon nuclear magnetic resonance spectra (¹³C NMR) were obtained for solution in CDCl₃ with Me₄Si as internal standard on a Bruker Avance DPX 300 spectrometer. IR spectra were obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elemental analyses were performed with a Carlo-Erba-1110 analyzer. The X-ray diffraction was performed on a Rigaku Mercury CCD X-ray diffractometer.

Table 2. Results of Mannich-type reaction of aldehydes, aniline, and 3 catalyzed by HBF₄-SiO₂

NHPh O

$R_{2}CHO + PhNH_{2} + OTMS HBF_{4} / SiO_{2} + OCH_{3} solvent-free R_{2} + OCH_{3}$				
Entry	R ₂	Product	Yield (%)	
1	4-MeOC ₆ H ₄	4g	81	
2	$4-ClC_6H_4$	4h	84	
3	$4-O_2NC_6H_4$	4i	80	
4	$2,4-Cl_2C_6H_3$	4j	89	
5	c-C ₆ H ₁₃	4k	76	
6	$C_6H_5CH_2CH_2$	41	75	
7	C ₆ H ₅ CH=CH	4m	82	
8	3,4-(OCH ₂ O)C ₆ H ₃	4n	85	
9	2-Furyl	40	86	
10	2-Thiophene	4 p	80	

General Procedure

Benzaldehyde **1a** (30 μ L, 0.3 mmol), 4-fluoroaniline **2a** (29 μ L, 0.3 mmol), [(1-methoxy-2-methyl-1-propenyl)oxy] trimethylsilane **3** (96 μ L, 0.45 mmol), and HBF₄-SiO₂ (0.18 g, 0.5 mmol HBF₄ g⁻¹) were added to a bottle in quick succession. The mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with diethyl ether. After the evaporation of solvent, the residue was purified by column chromatography on silica gel (EtOAc-PE = 1:8) to give the product **4a** in 84% yield.

Spectral Data for Selected Products

3-(4-Fluoro-phenylamino)-2,2-dimethyl-3-phenyl-propionic Acid Methyl Ester (**4a**)

IR (KBr): ν 2924, 2852, 1714, 1510, 1136 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 1.15 (s, 3H), 1.26 (s, 3H), 3.66 (s, 3H), 4.42 (d, J = 7.71 Hz, 1H), 4.66 (d, J = 7.53 Hz, 1H), 6.39–6.44 (m, 2H), 6.71–6.77 (m, 2H), 7.23–7.31 (m, 5H). ¹³C NMR (CDCl₃, 75 MHz): δ 20.5, 24.6, 47.0, 52.1, 65.1, 114.2, 114.3, 115.3, 115.6, 127.5, 128.0, 128.3, 138.9, 143.3, 177.0. Anal. calcd. for C₁₈H₂₀FNO₂: C, 71.74; H, 6.69; N, 4.65. Found: C, 71.72; H, 6.71; N, 4.62.

3-(4-Bromo-phenylamino)-2,2-dimethyl-3-phenyl-propionic Acid Methyl Ester (**4c**)

IR (KBr): ν 2954, 2889, 1714, 1610, 1176 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 1.15 (s, 3H), 1.28 (s, 3H), 3.65 (s, 3H), 4.41 (d, J = 7.74 Hz, 1H), 4.89 (d, J = 7.26 Hz, 1H), 6.36 (d, J = 8.88 Hz, 2H), 7.10 (d, J = 8.85 Hz, 2H), 7.21–7.28 (m, 5H). ¹³C NMR (CDCl₃, 75 MHz): δ 20.74, 24.69, 46.92, 52.16, 64.53, 108.96, 115.00, 127.67, 128.12, 128.22, 131.74, 138.71, 145.92, 162.03, 176.95. Anal. calcd. for C₁₈H₂₀BrNO₂: C, 59.68; H, 5.56; N, 3.87. Found: C, 59.70; H, 5.61; N, 3.85.

3-(4-Methoxy-phenylamino)-2,2-dimethyl-3-phenyl-propionic Acid Methyl Ester (**4e**)

IR (KBr): ν 2931, 2847, 1724, 1606, 1510, 1176 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 1.16 (s, 3H), 1.24 (s, 3H), 3.66 (s, 6H), 4.45 (s, 2H), 6.45 (d, J = 8.70 Hz, 2H), 6.63 (d, J = 9.00 Hz, 2H), 7.21–7.29 (m, 5H). ¹³C NMR (CDCl₃, 75 MHz): δ 20.38, 24.43, 47.07, 51.99, 55.58, 65.13, 114.61, 114.67, 127.34, 127.92, 128.31, 139.31, 141.17, 151.87, 177.07. Anal. calcd. for C₁₉H₂₃NO₃: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.80; H, 7.35; N, 4.52.

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3-Benzo[1,3]dioxol-5-yl-2,2-dimethyl-3-phenylamino-propionic Acid Methyl Ester (**4n**)

IR (KBr): ν 2936, 2878, 1688, 1141, 1083 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 1.17 (s, 3H), 1.27 (s, 3H), 3.66 (s, 3H), 4.38 (d, J = 3.78 Hz, 1H), 4.73 (d, J = 3.24 Hz, 1H), 5.91 (d, J = 8.28 Hz, 2H), 6.51 (d, J = 5.79 Hz, 2H), 6.59–6.63 (m, 1H), 6.71–6.75 (m, 3H), 6.76–7.08 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 20.82, 24.52, 47.02, 52.08, 64.13, 100.94, 107.71, 108.29, 113.37, 117.30, 121.78, 128.99, 133.21, 146.84, 147.53, 176.98. Anal. calcd. for C₁₉H₂₁NO₄: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.80; H, 6.45; N, 4.24.

Crystal Data for 4a

C₁₈H₂₀FNO₂, F.W. 301.35, colorless crystal, triclinic, space group P-1, a = 8.002 (2), b = 9.963 (2), c = 10.808 (3) Å, $\alpha = 73.953$ (13)°, $\beta = 84.084$ (15)°, $\gamma = 76.047$ (14)°, V = 803.0 (3) Å ³, Z = 2, $Dc = 1.246 \text{ mg m}^{-3}$, T = 153(2) K, Mo Ka ($\lambda = 0.71070$ Å), $\mu = 0.072 \text{ mm}^{-1}$, F(000) = 352, R = 0.0454, wR = 0.1062, largest diff. peak and hole: 253 and $-71 \text{ e} \cdot \text{nm}^{-3}$. CCDC reference number 604093.

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