Nano-manganese hydrogen sulfate as a novel catalyst for the anti-diastereoselective Mannich reaction in water

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Abstract β -Amino carbonyl compounds are attractive targets for chemical synthesis, because they are widely used as biologically active compounds and are important synthons for a variety of pharmaceuticals. Nano-manganese hydrogen sulfate was prepared and used as a novel nano-catalyst for the named organic transformation, i.e. Mannich-type reaction of benzaldehyde, aniline, and cyclohexanone in water. Mannich products were obtained in high yields, with excellent diastereoselectivity, and short reaction time in the presence of a catalytic system comprising nano-Mn(HSO₄)₂ and a surfactant, for example sodium dodecyl sulfate. Use of mild, environmentally benign reaction conditions, low loading, and ready accessibility are the main features of this new catalyst.

Keywords $Mn(HSO_4)_2 \cdot \beta$ -Amino ketone \cdot Diastereoselective \cdot Mannich reaction \cdot Micelles \cdot SDS

Introduction

Nanoparticles have recently attracted much interest because of their many applications in a variety of disciplines, for example chemistry, materials science, and the biomedical sciences [1, 2]. Metal nanoparticles are of fundamental interest because of their unique performance in ultrasensitive chemical and biological sensors and their selectivity as catalysts in chemical and photochemical reactions [3–8]. Because of their high surface-to-volume ratio, metal nanoparticles have more active sites per unit area than traditional catalysts [9]. Hydrophilic nanoparticles with high dispersity in environmentally benign solvents are extremely important in

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biological applications [10]. These nanoparticles are soluble in water in a pH range of approximately 5–9 [11].

Diastereoselectively pure β -amino ketones, vital intermediates in the synthesis of pharmaceuticals [12, 13] and natural products [14, 15], are widely used for asymmetric synthesis of nitrogen-containing compounds [16–19]. Multicomponent Mannich reactions to produce such compounds have attracted much attention [1, 20–29].

Water as a solvent is not only inexpensive and environmentally benign, but can also lead to unique reactivity and selectivity in organic reactions, which cannot be achieved in organic solvents [18]. Nevertheless, one major disadvantage of water as a solvent is the insolubility of organic compounds in water. To solve this problem one can use a catalyst that solubilizes organic compounds [30]. In this article we report the development of a new efficient catalyst for environmentally benign Mannich transformation under mild reaction conditions with high stereoselectivity.

Experimental

General

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka, and Aldrich. All yields refer to isolated products. The reactions were monitored by thin-layer chromatography conducted on silica plates. The products were characterized by comparison of their physical or spectral properties with those of authentic samples. IR spectra were recorded on an Thermo Nicolet Avatar-370 FTIR spectrophotometer. ¹H NMR spectra were recorded on Bruker 100-MHz spectrometer in CDCl₃ as the solvent and with TMS as internal standard.

General procedure for synthesis of manganese hydrogen sulfate

MnCl₂·2H₂O (0.1 mol) was placed in a 500-mL flask and concentrated sulfuric acid (98 %, 10.8 mL, 0.2 mol) was added dropwise over a period of 30 min at r.t. HCl gas was evolved immediately. After completion of the addition of H₂SO₄, the mixture was shaken for 30 min. A pale pink solid was obtained. To eliminate H₂SO₄ contamination, the solid was washed with absolute ethanol, furnishing a white solid in 86 % yield.

Mn(HSO₄)₂ nanostructure characterization

The XRD pattern of the Mn(HSO₄)₂ was recorded in the range $2\theta = 0^{\circ}-60^{\circ}$ (Fig. 1).

The prominent peaks were used to calculate the grain size, by use of the Scherrer equation:

$$D = K\lambda/(\beta\cos\theta)$$

where λ is the wavelength ($\lambda = 1.542$ Å) (CuK α), β is the full width at half maximum (FWHM) of the line, and θ is the diffraction angle [31]. The grain size of



Fig. 1 XRD pattern of Mn(HSO₄)₂

the $Mn(HSO_4)_2$ nanostructure was 40 nm, and peaks were observed for the (9.00), (12.64), (12.86), and (13.51) planes.

Results from transmission electronic microscopy (TEM) of $Mn(HSO_4)_2$ nanoparticles is shown in Fig. 2. It is apparent the average size of nanospheres is 50 nm.

The FT-IR spectrum of $Mn(HSO_4)_2$ contained characteristic bands at 3,360 cm⁻¹ (–O–H stretching), 1,158 cm⁻¹ (S=O sulfate asymmetric stretching), and 823 cm⁻¹ (sulfate S–O stretching), and 609–625 cm⁻¹ (Mn–O stretching). The results confirmed the desired compound had been successfully synthesized.

General procedure for the Mannich reaction

The aromatic aldehyde (1 mmol), aromatic amine (1 mmol), cyclohexanone (1.2 mmol), Mn(HSO₄)₂ (10 mol%), and SDS (2.5 mol%) were added to water (0.5 mL). The reaction mixture was stirred at room temperature for the appropriate time. The progress of reaction was monitored by TLC. After completion of the reaction, the solid mixture was isolated by filtration to eliminate the catalyst, then the crude product was extracted with chloroform. The extract was dried over anhydrous Na₂SO₄ then evaporated to dryness. The residue was purified by recrystallization from ethanol.

2-((4-(Diethylamino)phenyl)(phenylamino)methyl)cyclohexanone (4)

m.p. 125 °C; IR (KBr) υ = 3335, 3047, 2969, 2930, 2851, 1705, 1601, 1520, 1497, 1275, 816, 748, 689; ¹H NMR (CDCl₃, 100 MHz, δ ppm): 1.11 (t, 6H, *J* = 7.5 Hz), 1.5–2 (m, 6H), 2.2–2.5 (m, 2H), 2.5–2.8 (m, 1H), 3.2–3.4 (q, 4H, *J* = 7.5 Hz), 4.5



Fig. 2 Results from TEM of Mn(HSO₄)₂

(d, 1H, J = 8.5 Hz, anti), 6.5–6.7 (m, 5H), 6.95–7.25 (m, 4H); EI-MS: m/z 350 [M]⁺, 349 [M–H]⁺, 257 [M–C₆H₆N]⁺, 253 [M–C₆H₉O]⁺, 239 [M–C₇H₁₀O]⁺, 93 [M–C₁₇H₂₄NO]⁺.

2-((4-Isopropylphenyl)(phenylamino)methyl)cyclohexanone (8)

m.p. 83 °C; IR (KBr) $\upsilon = 3412$, 3051, 2931, 2858, 1700, 1600, 1503, 749, 688; ¹H NMR (CDCl₃, 100 MHz, δ ppm): 1.5–2.1 (m, 6H), 2.3–2.6 (m, 2H), 2.65–2.95 (m, 1H), 4.65 (d, 0.65H, J = 7.5 Hz, anti), 4.8 (d, 0.35H, J = 5 Hz, syn), 6.5 (d, 2H, J = 10 Hz), 7.1 (d, 2H, J = 10 Hz), 7.2–7.6 (m, 5H); EI–MS: m/z 321 [M]⁺, 319 [M–2H]⁺, 229 [M–C₆H₆N], 223 [M–C₆H₈O]⁺.

Results and discussion

We have modified an efficient method for preparation of Mannich products, in water, from aldehydes, aromatic amines, and ketones under very mild conditions by using manganese hydrogen sulfate and sodium dodecylsulfate (Scheme 1).

Because one or two chiral carbon atoms are formed during the Mannich reaction, diastereoselectivity and enantioselectivity are the most important features of the reaction. Initially, the effect of different solvents was examined to achieve the best diastereoselectivity, lowest reaction time, and high yield (Table 1). Reaction in ethanol and methanol under catalyst-free conditions proceeded in moderate yield with low diastereoselectivity, reaction in water failed under the same conditions.



Scheme 1 Preparation of Mannich products in water by using manganese hydrogen sulfate and sodium dodecylsulfate



			11111	~	~9.0	
Entry	Solvent	Temp. (°C)	Anti/syn	Time (h)	Yield	
1	_	25	_	4	NR ^a	
2	_	100	-	4	NIL ^b	
3	H ₂ O	25	60/40	5	10	
4	EtOH	25	60/40	3	72	
5	MeOH	25	60/40	1	87	
6	ACN	25	_	12	NR ^a	
7	Ру	25	_	12	NR ^a	
8	CH_2Cl_2	25	_	12	NR ^a	

^a No reaction

^b Aldol condensation occurs; product not isolated

Next, the effect of manganese(II) salts as catalysts of the Mannich reaction was examined, to gain insight into diastereoselectivity, reaction time, and product yield. Manganese(II) chloride and acetate do not catalyze this reaction under aqueous conditions (Table 2, entries 1 and 2).

Mn(HSO₄)₂ was prepared, for the first time, from MnCl₂ by addition of two equivalents of H₂SO₄; the yield was 86 %. Atomic absorption analysis showed the Mn content was 22.15 %, is agreement with the formula given. The effect of using different solvent systems, for example MeOH, EtOH, CH₃CN, H₂O, and EtOH–H₂O, with manganese hydrogen sulfate as catalyst was examined. Water was found to be the most suitable solvent with regard to both diastereoselectivity (>99 % anti isomer) and environmental considerations (Table 2, entries 2–6). Eventually we chose manganese hydrogen sulfate (10 %) with SDS (2.5 %) as the best catalyst system (Table 2, entry 11). To the best of our knowledge, this is the first time Mn(HSO₄)₂ has been used as an effective and highly stereoselective catalyst for Mannich-type multicomponent one-pot synthesis of β -amino ketones.

Table 2	Optimization of the conditions used	for the Mannich r	eaction		
°	+ $($ + $($ + $($ $)$ + $($ $)$ $($ $Cata$	alyst	HN	+ U	
			Anti	2	Syn
Entry	Catalyst	Solvent	Time (h)	Yield	Anti/syn
1	MnCl ₂ (10 %)	H ₂ O	4	NIL ^a	_
2	Mn(OAc) ₂ (10 %)	H ₂ O	4	NIL ^a	-
3	Mn(HSO ₄) ₂ (10 %)	EtOH	3	87	75/25
4	Mn(HSO ₄) ₂ (10 %)	EtOH/H ₂ O	3	92	75/25
5	Mn(HSO ₄) ₂ (10 %)	MeOH	1	85	>99/<1
6	Mn(HSO ₄) ₂ (10 %)	CH ₃ CN	5	NR^{b}	-
7	Mn(HSO ₄) ₂ (10 %)	H ₂ O	5	75	>99/<1
8	Mn(HSO ₄) ₂ (5 %)	H ₂ O	5	61	>99/<1
9	Mn(HSO ₄) ₂ (15 %)	H_2O	5	77	>99/<1
10	Mn(HSO ₄) ₂ (10 %), SDS(10 %)	H ₂ O	1	90	>99/<1
11	Mn(HSO ₄) ₂ (10 %) SDS(5 %)	H_2O	1	90	>99/<1
12 ^c	Mn(HSO ₄) ₂ (10 %) SDS(2.5 %)	H ₂ O	1	89	>99/<1
13	Mn(HSO ₄) ₂ (10 %) SDS(1 %)	H_2O	4	77	>99/< 1

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^a Imine product not isolated

^b No reaction

^c Optimized conditions

Using the optimized reaction conditions, the scope of the reaction was assessed. Excellent results were obtained when different combinations of aldehydes, amines, and cyclohexanone were used. The generality of this method can be deduced from the results summarized in Table 3.

In the reaction of benzaldehyde with most aromatic amines, the anti isomer is formed exclusively. The presence of weak electron-withdrawing or electrondonating groups, for example Cl and Me, at the 4-position of benzaldehyde does not change the diastereoselectivity of the reaction (Table 3, entries 3-5 and 7-9). However, the presence of a strong electron-withdrawing group, for example NO₂, at the para or meta position of the benzaldehyde caused precipitation of the corresponding imine and prevented completion of the reaction (results not shown). When 4-*i*-propyl-substituted benzaldehyde is used, anti/syn selectivity is reduced to 65:35 (Table 3, entry 8). Furthermore, the presence of a substituent at the ortho position of benzaldehyde entirely changed the stereoselectivity, leading to the syn isomer (Table 3, entries 6 and 11). The presence of chloro or methoxy substitution at the ortho positions of benzaldehyde or aniline changed the diastereoselectivity, leading to the syn isomer (Table 3, entries 6, 11, 12). The presence of a methoxy group at the *para* position of benzaldehyde resulted in formation of the anti isomer

R ₁ ^{NH2}	+ R2	+	$\frac{\text{Mn(HSO}_4)_2 (10 \text{ mm})}{\text{SDS} (2.5 \text{ mole } 0)}$	$\xrightarrow{\text{ole \%}} \qquad \bigcirc \qquad$		+ R_2
					Anti > 99 % 1-12	Syn
Entry	R ₁	R ₂	Yield % ^a	Anti/syn ^b	Time (h)	M.p. (°C)/lit.
1	Н	Н	90	>99/<1	1	139–140/139–140 [9]
2	3-CH ₃	Н	92	>99/<1	6	115/115–116 [32]
3	Н	4-CH ₃	70	>99/<1	1	123/120–121 [33]
4	Н	$4-N(C_2H_5)_2$	72	>99/<1	4	125
5	Н	4-N(CH ₃) ₂	75	>99/<1	4	148/160–162 [30]
6	Н	2-OMe	81	<1/>99	8	128/127.8–128 [34]
7	4-Cl	4-OMe	73	>99/<1	2	128/131 [13]
8	Н	4- <i>i</i> -Pr	70	65/35	7	83
9	4-Cl	Н	82	>99/<1	8	139/137–138 [<mark>13</mark>]
10	4-Cl	4-Cl	70	>99/<1	10	136/137–138 [32]
11	Н	2-Cl	71	<1/>99	5	139/144 [13]
12	2-Cl	Н	94	45/55	6	133/136–137 [13]

Table 3 Synthesis of β -amino ketones derivatives with *anti* diastereoselectivity by use of Mn(HSO₄)₂–SDS under aqueous conditions

^a Isolated yield

^b Determined by ¹H NMR spectroscopy

whereas methoxy at the *ortho* position gave the syn isomer as major product (Table 3, entries 6 and 7).

This phenomenon can mainly be attributed to formation of micelles from the starting materials and intermediates in the presence of H_2O and SDS. In other words, the smooth progress of the reaction in the presence of alkyl or halogen substitution of the aniline or benzaldehyde is the result of the tendency to form micelles, as a result of the alkyl groups and the lipophilic properties of SDS, with the result that hydrogen bond formation by halogen and methoxy groups is disrupted. One possible reaction mechanism (Fig. 3) is that micelle formation is essential to gather all the components, i.e. ketone, amine, aldehyde, and catalyst. As expected, the presence of polar groups with nonbonding electron pairs near the center of the reaction (imine groups) leads to exit of the imine from micelle and into the aqueous phase. In such circumstances the possibility of isomerization is increased.

As we expected, only the E enolate of cyclohexanone was formed; this reacted with the more stable anti imine to produce the anti product under these reaction conditions. For *ortho*-chloro or *ortho*-methoxy-substituted aniline or benzaldehyde, the syn imine is the more stable isomer. Perhaps interaction of these hydrophilic groups with the water removes the imine from the micelles, which causes the anti-



Fig. 3 Possible mechanism of synthesis of β -amino ketones with anti diastereoselectivity by use of Mn(HSO₄)₂–SDS as catalyst system under aqueous conditions

syn isomerization possible for the imine intermediate. For *para*-substituted *i*-propylbenzaldehyde, the micelle moves to this side group and lets the imine group penetrate the water, with increased production of the syn isomer.

R ₁ NH ₂ R ₁	+ R2 +	CH ₃	Mn(HSO ₄) ₂ (10% mole) SDS (2.5% mole) H ₂ O,rt		$ \begin{array}{c} $	
Entry	R ₁	R ₂	Yield (%)	Time (h)	M.p. (°C)/Lit	
13	Н	Н	73	12	167/167–168 [35]	
14	3-CH ₃	Н	95	10	135–136/131–134 [36]	
15	Н	4-CH ₃	70	10	136–137/139–140 [37]	

 $\label{eq:stability} \begin{array}{l} \mbox{Table 4} & \mbox{Synthesis of other } \beta\mbox{-amino ketone derivatives by use of } Mn(HSO_4)_2\mbox{-SDS as catalyst system under aqueous conditions} \end{array}$

To indicate the sufficiency of our catalytic system, the reaction was performed with other ketones. The reactions were feasible but, because the keto form of acetophenone is more stable than the enol form, reaction times were increased (Table 4). The micelle droplets formed by $Mn(HSO_4)_2$, SDS, and the substrates were, however, sufficiently hydrophobic to reject water molecules, facilitating formation of the iminium ion. In these reactions, the micelle acts as a nano reactor by enabling efficient contact between the catalyst and the substrate in its interfacial area.

In conclusion, we report an environmentally benign, novel, and easy procedure for diastereoselective synthesis of Mannich products by use of nano-manganese hydrogen sulfate and SDS in water. The procedure has several advantages, for example high diastereoselectivity, high yields, mild reaction conditions, use of inexpensive reagents, low temperature, and very simple work-up procedures. Low loading and ready accessibility are the main features of the new catalyst.

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