HBF_4 Catalyzed Mannich-Type Reaction in Aqueous Media

Takahiko Akiyama,* Jun Takaya, Hirotaka Kagoshima

Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1, Mejiro, Toshima-ku, Tokyo 171-8588, Japan

Fax+81-3-5992-1029; E-mail: takahiko.akiyama@gakushuin.ac.jp

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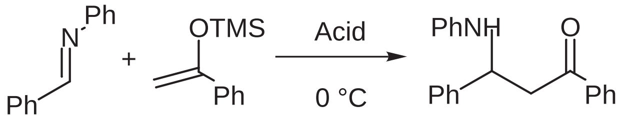
Abstract: HBF_4 catalyzed Mannich-type reaction took place smoothly in aqueous media to afford β-amino carbonyl compounds in high yields. One-pot synthesis of β-amino carbonyl compounds from aldehyde and amine also worked well.

Key words: Mannich-type reaction, aqueous reaction, HBF_4, imino aldol, aldimine

Lewis acid promoted addition of silyl enolates to imine, Mannich-type reaction, is an efficient method for the preparation of β-amino ketone or β-amino esters.[1] It is one of the most important basic reaction types in organic chemistry. Nevertheless, because imines are generally less reactive than ketone moiety, addition to imines have been less extensively studied.[2] Furthermore, equimolar amount of Lewis acid was required quite often as a promoter due to stronger basicity of nitrogen. Several novel types of activator for the imine moiety have been reported recently and have been applied to Mannich-type reaction. For example, Kobayashi and co-workers found that scandium and lanthanide triflates,[3] which are water tolerant Lewis acids, activate aldimines highly effectively and Mannich-type reaction proceeded smoothly to afford β-amino carbonyl compounds in high yields.[4,5] Asymmetric Mannich-type reaction employing Zr(IV),[5] transition metal catalyst,[6] and chiral acyl chloride have been reported.[7]

On the other hand, modern organic reactions are frequently promoted by Lewis acid in anhydrous organic solvent.[8] Restraint on the use of organic solvents, in particular halogenated solvents, is desired from the environmental point of view. Aqueous media thus have attracted considerable attention in the fields of synthetic organic chemistry.[9,10] Except lanthanide triflate,[3] common Lewis acids are not compatible with aqueous media, and hence Brønsted acid is a logical candidate as an activator in aqueous media. Along the line, HCl catalyzed allylation of carbonyl compounds with allyltin has been reported.[11]

We wish to report herein that catalytic amount of HBF_4 efficiently activate aldimines and addition of silyl enolate to aldimine took place smoothly in aqueous media.[12,13] Furthermore, one-pot synthesis of β-amino ketone and β-amino ester from aldehyde, amine, and a silyl enolate has been achieved.



1 **2**

Table 1 Effect of acid

Entry	Acid	Amount	Solvent	Reaction time	Yield/%
1	HBF_4	0.1	$CH_3OH–H_2O$ (30/1)	30 min	96
2	HBF_4	0.1	$CH_3CN–H_2O$ (30/1)	30 min	84
3	HBF_4	0.1	$CH_3OH–H_2O$ (4/1)	2 h	79
4	HCl	0.5	$CH_3CN–H_2O$ (30/1)	30 min	54
5	HF	0.2	$CH_3CN–H_2O$ (30/1)	48 h	16
6	*p*-TsOH	0.1	$CH_3OH–H_2O$ (30/1)	30 min	89

a) 1.0 equiv of **1** was employed.

At the outset, benzylideneaniline and a trimethylsilyl enol ether of acetophenone (**1**) (1.0 equiv) were allowed to react with Brønsted acid in aqueous media and the results are shown in Table 1. Simple addition of diluted aqueous HBF_4 to the solution of the aldimine and **1** in methanol at 0 °C furnished a β-amino ketone (**2**) in 96% yield (Entry 1). Catalytic amount of HBF_4 (10 mol%) promoted the Mannich-type reaction smoothly. It is noted that present addition reaction took place smoothly even in the presence of large amount of water (Entry 3). Aqueous HCl and *p*-TsOH also worked well.

Selected examples of the HBF_4 catalyzed Mannich-type reaction in aqueous media are shown in Table 2. Aldimines derived from aromatic aldehyde and aniline underwent addition reaction with **1** to afford β-amino ketones in high yields (Entries 1, 2, and 4). An α,β-unsaturated aldimine afforded exclusively 1,2-adduct and 1,4-adduct was not observed (Entry 5). For the present addition reaction, aldimine derived from aromatic amine must be employed and an aldimine derived from aliphatic amine was not effective (Entry 3). Other silyl enol ethers worked well to afford the corresponding β-amino ketones in high yields though the stereoselectivity was modest (Entries 6 and 7). Ketene silyl acetals were found to be effective as nucleophile if the reactions were run at lower temperature (Entries 8, 9, and 10). An aldimine derived from glyoxylate also worked well to give the corresponding adduct, which is an amino acid derivative, in a high yield (Entry 11).

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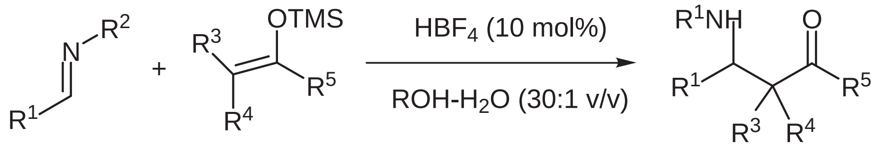
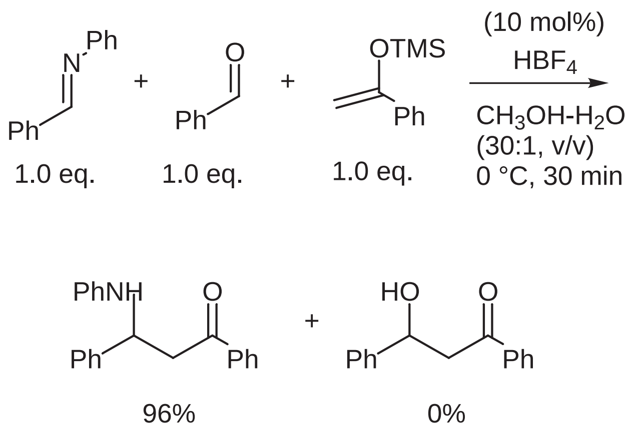


Table 2 HBF_4 catalyzed Mannich-type reaction

Entry	R^1	R^2	R^3	R^4	R^5	Solvent	Conditions	Yield/%
1	Ph	Ph	H	H	Ph	CH_3OH	0 °C, 30 min	96
2	Ph	p-$CH_3OC_6H_4$	H	H	Ph	CH_3OH	0 °C, 1 h	88
3	Ph	$PhCH_2$	H	H	Ph	CH_3OH	0 °C, 3.5 h	0
4	p-$CH_3C_6H_4$	Ph	H	H	Ph	CH_3OH	0 °C, 30 min	85
5	PhCH=CH	Ph	H	H	Ph	*i*-PrOH	0 °C, 3 h	69
6	Ph	Ph	Me[a)]	H	Ph	CH_3OH	0 °C, 3 h	83[d)]
7	Ph	Ph	H	-$(CH_2)_4$-		CH_3OH	0 °C, 1 h	94[e)]
8	Ph	Ph	Me	Me	OMe	*i*-PrOH	–40 °C, 1 h	91
9	Ph	Ph	H	Ph[b)]	OMe	CH_3OH	–20 °C, 1.5 h	98[f)]
10	Ph	Ph	H	Me[c)]	OEt	*i*-PrOH	–40 °C, 30 min	91[g)]
11	EtOCO	p-$CH_3OC_6H_4$	H	H	Ph	*i*-PrOH	0 °C, 1 h	89

a) E:Z=3:97. b) E:Z= 76:24. c) E:Z=88:12. d) syn: anti= 63:37. e) syn:anti = 50:50. f) syn:anti= 52:48. g) syn:anti =54:46. h) The amount of silyl enolate follows; 1.0 equiv for entry 1, 1.5 equiv fo entries 2–7, 11. 3.0 equiv for entries 8–10.



Scheme 1

Another characteristic feature of the present addition reaction is high chemoselectivity toward aldimine in the presence of aldehyde as shown in Scheme 1. It was found recently that selective activation of imine could be achieved under the influence of lanthanide triflates[14,15] or transition metal catalysis[16] though common Lewis acids activate aldehyde preferentially. Aldol reaction toward aldehyde did not proceed by means of HBF_4. High chemoselectivity is rationalized by considering the higher basicity of nitrogen over oxygen.

Since imines, in particular aliphatic aldimines, are not stable and are difficult to purify, it would be synthetically quite useful if imines, generated in situ from aldehyde and amine, react with silyl enolates to afford β-amino carbonyl compounds in one vessel. Judging from the high chemoselectivity of the present reaction towards aldimine in the presence of aldehyde, we expected that three-component synthesis of β-amino ketone could be achieved. Results of the one-pot Mannich-type reaction is shown in Table 3. Aliphatic aldimines as well as aromatic aldimine underwent Mannich-type reaction smoothly to afford the corresponding adducts in good to high yields.[17] It is noting that imines were formed even in the presence of water quickly[4a,18] and silyl enolates were stable enough to react under the present reaction conditions. Phenylglyoxal monohydrate, which possesses water of crystallization, afforded the addition product in 91% yield (entry 12). As

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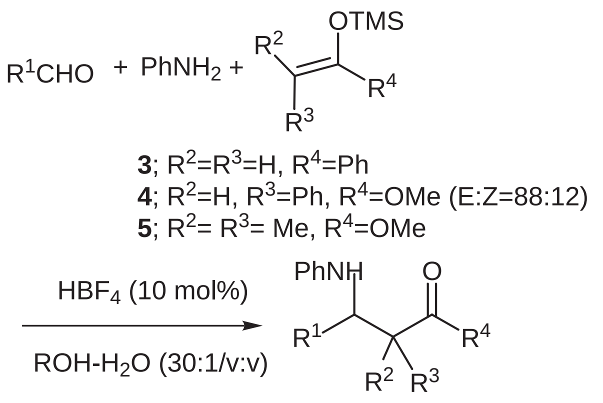

Table 3 Three-Component Synthesis[a)]

Entry	R^1	Silyl enolate	Solvent	Conditions	Yield/%
1	Ph	**3**	CH_3OH	0 °C, 1.5 h	90
2	p-$CH_3C_6H_4$	**3**	CH_3OH	0 °C, 1.5 h	84
3	p-$NO_2C_6H_4$	**3**	CH_3CN	0 °C, 2 h	89
4	PhCH=CH	**3**	*i*-PrOH	0 °C, 3 h	69
5	c-C_6H_{11}	**3**	CH_3CN	0 °C, 1 h	79
6	$PhCH_2CH_2$	**3**	*i*-PrOH	0 °C, 6 h	60
7	$PhCH_2OCH_2$	**3**	*i*-PrOH	0 °C, 2 h	70
8	PhCO	**3**	*i*-PrOH	0 °C, 3.5 h	91
9	EtOCO	**3**	*i*-PrOH	0 °C, 1.5 h	55
10	$PhCH_2CH_2$	**4**	*i*-PrOH	–20 °C, 1 h	81[b)]
11	Ph	**5**	*i*-PrOH	–40 °C, 1 h	99
12	c-C_6H_{11}	**5**	CH_3CN	–40 °C, 1 h	89
13	$PhCH_2CH_2$	**5**	*i*-PrOH	–40 °C, 1 h	80
14	$PhCH_2OCH_2$	**5**	*i*-PrOH	–40 °C, 1 h	82

a) The molar ratio of aldehyde, amine, and silyl enolate is 1.0:1.0:1.5 for entries 1–9,1.0:1.0:3.0 for entries 10–14. b) syn:anti=73:27.

a nucleophile, not only silyl enol ether as well as ketene silyl acetal were found to be quite effective if the reactions were carried out at lower temperature.

In summary, we found the first Brønsted acid promoted Mannich-type reaction in aqueous media. Salient features of the present reactions are; 1) aqueous HBF$_4$, which is a cheap Brønsted acid, could be used, 2) aldimine may be formed in situ in the presence of water, 3) aldimine derived from aliphatic aldehyde worked pretty well, 4) thus the operation is very simple, 5) use of halogenated solvent is avoided and environmentally-conscious.

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(17) A typical experimental procedure for Entry 10 of Table 3. A solution of aniline (15.0 μL, 0.165 mM) and benzaldehyde (17.0 μL, 0.167 mM) in *i*-PrOH (1.0 mL) was stirred at –40 °C for 30 min. To the solution was added a silyl ketene acetal (**3**) (0.1 mL, 0.492 mmol) and 4.3 wt% solution HBF_4 in water (34.0 μL, 0.167 mM) at that temperature. After being stirred at that temperature for 45 min, the reaction was quenched by addition of water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the crude mixture by preparative TLC (SiO_2, hexane:ethyl acetate = 5:1, v/v) gave a β-amino ester (42.7 mg, 0.166 mM) in a quantitative yield.

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