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$NbCl_5$-Catalyzed one-pot Mannich-type reaction: three component synthesis of β-amino carbonyl compounds

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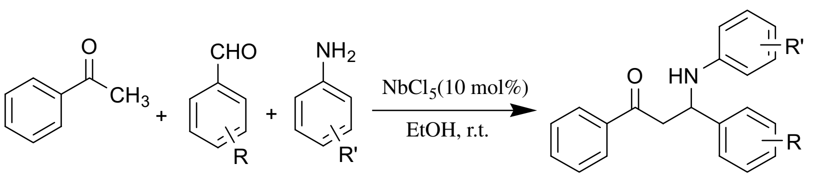
Abstract—Three-component Mannich-type reaction of acetophenone, aromatic aldehydes and aromatic amines was catalyzed by $NbCl_5$ at ambient temperature to give various β-amino ketones in high yields.

1. Introduction

The Mannich-type reactions are very important carbon–carbon bond-forming reactions in organic synthesis and one of the most widely utilized chemical transformations for constructing β-amino ketones and other β-amino carbonyl compounds, which in turn are important synthetic intermediates for various pharmaceuticals and natural products.[1,2] Mannich reactions have gained popularity in synthetic chemistry over the past decades. Recently, direct Mannich reactions of aldehydes, ketones and aryl amines have been realized via Lewis acids,[3] lanthanides,[4] transition metal salt catalysis[5] and organocatalytic[6] approaches. Most of these methods suffer from severe drawbacks including the use of a large amount of catalysts, expensive reagents or catalysts, sometimes long reaction times and low yield, etc. Hence, there is high interest in developing convenient methods for the synthesis of β-amino ketones. Some of the recent achievements in the efficient construction of this nucleus include the development of Lewis acid catalysts, however, few useful Lewis acid catalysts are developed in the past few years.[7]

Recently, $NbCl_5$ has emerged as an efficient Lewis acid in promoting various organic transformation, such as Diels–Alder reaction, ring-opening of epoxides, Mukaiyama aldol reaction, Biginelli reaction, dealkylation of alkyl aryl ethers and C–H insertion reaction.[8] The versatility of this reagent encourage us to study its utility for the three-component Mannich-type reaction. To our knowledge, direct Mannich-type reactions catalyzed by $NbCl_5$ have not been reported. Herein, we report an $NbCl_5$-catalyzed three-component Mannich-type reaction of acetophenone, aromatic aldehydes and aromatic amines, which led to the efficient synthesis of β-amino ketones under mild conditions (Scheme 1).

In the initial experiments, we screened different common Lewis acids for their ability to catalyze the three-component Mannich type reaction. To study the feasibility of the different common Lewis acids-catalyzed Mannich-type reactions, the reaction of acetophenone, benzaldehyde and aniline was selected as model. The common Lewis acids such as $ZnCl_2$, $CuCl_2$, $AlCl_3$, $FeCl_3$ $LaCl_3$ and $InCl_3$ did not furnish the desired products (Table 1, entries 2–7). However, among the common Lewis



Scheme 1.

Keywords: $NbCl_5$; Mannich-type reaction; β-Amino carbonyl compound; One-pot reaction.

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Table 1. Catalytic activity of solid acid and Lewis acid in Mannich reaction[a]

Entry	Catalyst (10 mol %)	Time (h)	Yield[b] (%)
1	No cat.	48	NR
2	$ZnCl_2$	24	NR
3	$CuCl_2$	24	NR
4	$AlCl_3$	24	NR
5	$FeCl_3$	24	NR
6	$LaCl_3$	24	NR
7	$InCl_3$	24	NR
8	$NbCl_5$	12	95

[a] Reaction conditions: benzaldehyde (1.0 mmol), acetophenone (1.0 mmol), aniline (1.0 mmol), catalyst (0.1 mmol), EtOH (1 mL), room temperature.

[b] Isolated yield.

acids studied for this reaction, $NbCl_5$ was found to be the most effective catalyst for this transformation since it resulted in the highest conversion to the desired product (Table 1, entry 8). In conclusion, $NbCl_5$ was an effective catalyst for the Mannich reaction between acetophenone, benzaldehyde and aniline. The controlled three-component reaction conducted under identical conditions and devoid of Lewis acid gave no coupled product, despite prolonged reaction times (Table 1, entry 1).

Table 2. Synthesis of β-amino ketone under different conditions[a]

Entry	$PhCOCH_3$ (mmol)	$PhNH_2$ (mmol)	$NbCl_5$ (mmol)	Yield[b] (%)
1	1.0	1.0	0.05	52
2	1.0	1.0	0.10	95
3	1.0	1.0	0.20	91
4	1.0	1.1	0.10	92
5	1.0	1.2	0.10	85
6	1.0	1.5	0.10	82
7	1.2	1.0	0.10	94
8	1.5	1.0	0.10	93
9	2.5	1.0	0.10	83
10	5.0	1.0	0.10	82

[a] Reaction conditions: benzaldehyde (1.0 mmol), EtOH (1 mL), room temperature 12 h.

[b] Isolated yield.

In a systematic study (Table 2), acetophenone was added to a solution of benzaldehyde, aniline and $NbCl_5$ in ethanol and the reaction mixture was stirred for 12 h at room temperature. Our initial experiments focused on the optimization of the amount of $NbCl_5$ by using 1 equiv of benzaldehyde, 1 equiv of acetophenone, 1 equiv of aniline and variable amount of $NbCl_5$. We observed that 10 mol % of $NbCl_5$ (based on benzaldehyde) could effectively catalyze the reaction and increasing the amount of $NbCl_5$ to 20 mol % showed no substantial improvement in the yield (Table 2, entry 3). Thereafter the reaction was carried out by varying the amount of acetophenone and aniline. The optimum ratio of benzaldehyde, acetophenone, aniline and $NbCl_5$ was found to be 1:1:1:0.1 (Table 2, entry 2).

In an effort to obtain improved yields, various solvents were screened in the three-component reaction of

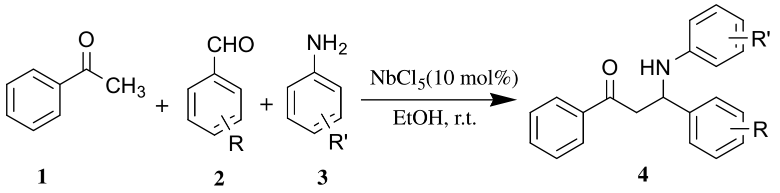
Table 3. $NbCl_5$-Catalyzed three-component Mannich-type reactions of benzaldehyde, aniline and acetophenone in different solvents[a]

Entry	Solvent	Yield[b] (%)
1	EtOH	95
2	CH_3CN	94
3	DCE	61
4	Toluene	32
5	THF	Trace
6	1,4-Dioxane	Trace

[a] Reaction conditions: benzaldehyde (1.0 mmol), aniline (1.0 mmol), acetophenone (1.0 mmol), $NbCl_5$ (0.1 mmol), room temperature 12 h.

[b] Isolated yield.

Table 4. $NbCl_5$-Catalyzed direct Mannich reaction of various aryl aldehydes and aromatic amines[a]



Entry	R	R′	Yield (%) (product)[b]	Mp (°C)
1	H	H	95 (**4a**)	169–170
2	H	4-CH_3	96 (**4b**)	167–168
3	H	2-CH_3	—(**4c**)	—
4	H	3,4-$(CH_3)_2$	92 (**4d**)	145–146
5	H	4-Cl	92 (**4e**)	169–170
6	H	3-Cl	86 (**4f**)	131–132
7	H	4-MeO	85 (**4g**)	161–162
8	H	4-NO_2	96 (**4h**)	185–186
9	H	2-NO_2	—(**4i**)	—
10	H	4-HOOC	80 (**4j**)	160–161
11	H	3-HOOC	76 (**4k**)	161–162
12	4-CH_3	H	95 (**4l**)	129–130
13	4-NO_2	H	78 (**4m**)	105–106

[a] Reaction conditions: aromatic aldehydes (1.0 mmol), acetophenone (1.0 mmol), aromatic amines (1.0 mmol), $NbCl_5$ (0.1 mmol), EtOH (1 mL), room temperature 12 h.

[b] Isolated yield; products were confirmed by ^1H NMR.

benzaldehyde, acetophenone and aniline at room temperature and the results are summarized in Table 3. Acetonitrile and ethanol provided excellent yields and proved to be the solvent of choice, whereas dichloromethane afforded lower yields. The reaction in toluene afforded very poor yields whilst the use of THF and 1,4-dioxane could not effectively catalyze the reaction.

Next, we examined the scope of the reaction by using various aromatic amines and aryl aldehydes. The results are summarized in Table 4. In general, high yields of β-amino ketones were obtained with 10 mol % of $NbCl_5$ at room temperature in ethanol for 12 h. However, when aryl aldehyde bearing electron-withdrawing substituent was subjected to the reaction under standard conditions, there was a lower yield of the desired adducts formed (Table 4, entry 13). Substrates bearing various functional groups such as CH_3, OMe, Cl, NO_2 and OH all reacted to produce the corresponding β-amino ketones. Although, *meta*- and *para*-substituted aromatic amines gave good results, *ortho*-substituted aromatic amines such as 2-methylaniline and 2-nitroaniline (Table 4, entries 3 and 9) failed to yield any product because of the steric effects.

In conclusion, a concise, high-yielding three-component Mannich reaction has been described. The method reported here is not only simple to operate but also efficient. This approach could make a valuable contribution to the existing processes in the field of β-amino ketones synthesis.

2. Experimental

Typical procedure for the synthesis of **4**: To a mixture of acetophenone (1.0 mmol), aromatic aldehydes (1.0 mmol) and aromatic amines (1.0 mmol) in anhydrous ethanol (1 mL) was added $NbCl_5$ (10 mol %). The mixture was stirred at room temperature for 12 h. After the reaction was completed, saturated $NaHCO_3$ solution (5 mL) was added, and the precipitated solid was collected by filtration, washed with ethanol. The crude product was purified via recrystalization from ethanol to give the corresponding compounds.

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