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$Bi(NO_3)_3 \cdot 5H_2O$-catalyzed Mannich Reaction: A Potent Catalyst for Synthesis of β-Aminocarbonyl Compounds

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Abstract: Biologically active compounds containing nitrogen, natural molecules and drugs are important for organic synthesis. Mannich reaction is one of the most common methods used for the synthesis of these compounds. $Bi(NO_3)_3$ was used as an efficient catalyst for the one-pot three-component Mannich reactions of ketones with different aromatic amines and aromatic aldehydes at room temperature. It is a good method to prepare β-aminocarbonyl compounds in excellent yield. The high efficiency using simple starting materials and a catalytic amount of a reusable catalyst is especially noteworthy.

Keywords: Mannich reaction, One-pot synthesis, Bismuth(III) nitrate, β-Aminocarbonyls.

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INTRODUCTION

In recent years, β-amino ketones are compounds with significant biological effects such as antibacterial, antifungal, antitumor, antidiabetic effects (1-6). They can be easily converted into their derivatives and are often used in the field of medicine. These compounds are the most important structural units used for the synthesis of 1,3-aminoalcohol and β-amino acid forms (2). Presently, β-aminocarbonyl forms are present in many synthetic drugs available for treatment in various medical conditions (7). β-aminocarbonyl compounds are frequently used in the synthesis of various antibiotics such as neopolyoxin and nikomycin. In the synthesis and modification of β-amino acids have been recorded several methods. Mannich reaction has an important role in organic chemistry for obtaining bioactive compounds and natural products. Several methods have been reported in the literature for the synthesis of β-aminocarbonyl compounds using Brønsted acids (8), Lewis acids (9) and organocatalysts (10). However, there are also problems such as long reaction time, difficult reaction conditions, toxicity, and difficulties in separating complex molecules. Hence there is an increasing interest in developing environmentally benign reactions for the synthesis of β-aminocarbonyl compounds' syntheses. Nowadays, bismuth(III) salts (11-13) are used as catalysts in organic synthesis because of easy handling, low cost, and eco-friendly behavior. We notify a fast synthesis of β-aminocarbonyl compounds in the presence of $Bi(NO_3)_3 \bullet 5H_2O$ (BN) for it is non-toxic, stable in air, and cheaper.

The synthesized *β*-aminocarbonyl compounds (**4a-o**) were purified by crystallization and characterized by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, and MS methods. Some of these compounds were first synthesized in this study (**4g, 4j, and 4o**).

EXPERIMENTAL SECTION

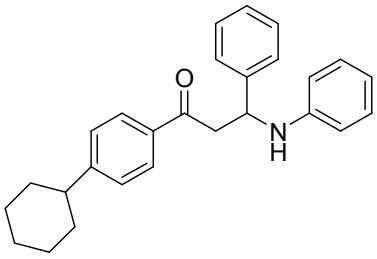
The chemicals used in this study were commercially available from Merck and Aldrich and were used without further purification. The obtained compounds were purified by crystallization. ^{1}H and ^{13}C NMR (500 and 125 MHz, respectively) spectra were recorded using Me_4Si as the internal standard in $CDCl_3$. Mass spectra were obtained on Thermo Finnigan LCQ Advantage MAX MS/MS spectrometer. FT-IR spectra were recorded on Bruker Vertex 70.

General procedure for the synthesis of *β*-amino carbonyl compounds

Ketone (2.2 mmol), aldehyde (2 mmol) and amine (2 mmol) and 10 mol% $Bi(NO_3)_3$ (11-13) were added to a one-necked round bottom flask. The reaction mixture was stirred vigorously with a magnetic stirrer at room temperature (r.t.) for the mentioned time. After reaction completion, EtOH and H_2O at the reaction-mixture were evaporated at ambient temperature. Then 60 mL of hot CH_2Cl_2 was added to dissolve the solid product. The catalyst was removed by filtration and the organic layer was washed twice with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated. The product was purified by recrystallization from an ethanol–acetone mixture (3/2, v/v) to afford the corresponding compounds.

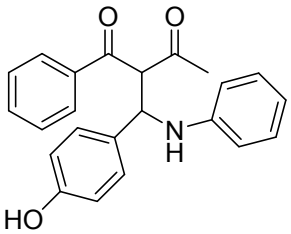
Compounds (**4a-f**, **4h-i,** and **4k-n**) are known in the literature and their results are in accordance with the literature. The analytical and spectral data of the other products (**4g**, **4j,** and **4o**) so obtained were as follows:

1-(4-Cyclohexylphenyl)-3-phenyl-3-(phenylamino)-propan-1-one (4g),



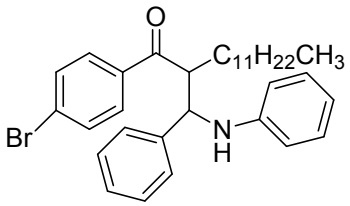
Yield, 91%; white crystals; Mp.: 157,4- 158,5 °C. IR (neat, cm^{-1}): 3384 (-NH), 3045, 3024, 2921, 2847, 1666(-CO), 1178 (C-N), 746, 690. ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 1.18 (2H, m, alicyclic -C<u>H</u>$_2$-), 1.33 (4H, m alicyclic -C<u>H</u>$_2$-), 1.69 (2H, m, alicyclic -C<u>H</u>$_2$-), 1.78 (2H, m, alicyclic -C<u>H</u>$_2$-), 2.48 (1H, m, alicyclic -C<u>H</u>-) 3.34 (1H$_a$, dd, J=16.2 ve 7.8 Hz, -C<u>H</u>$_{2a}$-CH-NH), 3.43 (1H$_b$, d, J=16.1 ve 5.2 Hz, -C<u>H</u>$_{2b}$-CH-NH), 4.91 (1H, dd, J=7.6 ve 5.2Hz, CH$_2$-C<u>H</u>-NH), 6.51 (2H, d, J=7.8 Hz, arom.-<u>C</u>H-), 6.60 (1H, t, J=7.3 Hz, arom.-<u>C</u>H-), 6.97-7.04 (2H, m, arom.-<u>C</u>H-), 7.15 (1H, t, J=7.3 Hz, arom.-<u>C</u>H-), 7.19 (2H, d, J=8.4 Hz, arom.-<u>C</u>H-), 7.24 (2H, t, J=7.6 Hz, arom.-<u>C</u>H-), 7.37 (2H, d, J=7.5 Hz, arom.-<u>C</u>H-), 7.76 (2H, d, J=8.4 Hz, arom.-<u>C</u>H-). ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 26.3 (alicyclic <u>C</u>H$_2$), 27.1 (alicyclic 2x<u>C</u>H$_2$), 34.3 (alicyclic 2x<u>C</u>H$_2$), 34.4 (alicyclic <u>C</u>H$_2$), 44.9 (-<u>C</u>HNH-), 46.2 (-CO<u>C</u>H$_2$CH-), 114.5, 126.8, 127.4 (2x<u>C</u>H), 127.6, 128.7 (4x<u>C</u>H), 129.0 (3x<u>C</u>H), 129.3 (3x<u>C</u>H), 134.7, 154.2, 197.9 (-C=O). MS (ESI+) m/z (%): 384.0 (100, $[M + H]^+$). Anal. calcd for $C_{27}H_{29}NO$ (383.22): C, 84.55; H, 7.62; N, 3.65. Found: C, 84.53; H, 7.63; N, 3.67.

1-Phenyl-2-[(4-hydroxyphenyl) (phenylamino)methyl]-butan-1,3-dione (4j),



Yield, 89%; yellow crystals; Mp.: 110,5- 111,5 °C. IR (neat, cm^{-1}): 3404 (-OH), 3291 (-NH), 3024, 3007, 2916, 2856, 1646 (-CO), 1220 (C-N), 752, 698. ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 1.50 (1H, s, -N<u>H</u>-), 2.08 (3H, s, -C<u>H</u>$_3$-), 3.70 (1H, brs, -O<u>H</u>), 4.13 (1H, d, J= 5.2 Hz, -CH-C<u>H</u>-NH), 5.34 (1H, d, J= 5.2 Hz, -C<u>H</u>-CH-NH), 7.11- 7.29 (5H, m, arom. -<u>C</u>H-), 7.30-7.39 (7H, m, arom. -<u>C</u>H-), 7.85 (2H, m, arom. -<u>C</u>H). ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 19.4 (-<u>C</u>H$_3$), 28.7 (-<u>C</u>H$_2$), 93.3 (-<u>C</u>H$_2$), 114.8, 119.8, 123.7 (2x-<u>C</u>H), 123.8, 124.5, 124.8, 126.0 (2x-<u>C</u>H), 127.2 (2x-<u>C</u>H), 128.7 (2x-<u>C</u>H), 129.7, 129.9 (-<u>C</u>H), 134.6, 139.0, 158.9 (-<u>C</u>-OH), 161.2 (-C=O), 187.7 (-C=O). MS (ESI+) m/z (%): 359.1 (100, $[M]^+$). Anal. calcd for $C_{23}H_{21}NO_3$ (359.15): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.83; H, 5.83; N, 3.82.

1-(4-Bromophenyl)-2-[phenyl(phenylamino)methyl]-tetradecan-1-one (4o),



Yield, 88%; pale yellow crystals; Mp.: 176,8-178,1 °C. IR (neat, cm^{-1}): 3406 (-NH), 3055, 3028, 2915, 2848, 1578 (-CO), 1180 (C-N), 806, 752. ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 0.81 (3H, t, J= 7.8 Hz, -C<u>H</u>$_3$), 1.14-1.31 (22 H, m, -C<u>H</u>$_2$), 2.29 (1H, m, -CH-C<u>H</u>-NH), 2.84 (1H, dd, J= 7.5 and 5.2 Hz, -C<u>H</u>-CH-NH), 6.85 (1H, s, -N<u>H</u>-), 7.00- 7.03 (5H, m, arom. -<u>C</u>H-), 7.25-7.28

(5H, m, arom.-CH-), 7.51-7.53 (2H, m, arom.-CH), 7.74 (2H, d, J= 5 Hz, arom.-CH). ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 14.0 (-CH_3), 22.9, 27.9, 28.9 (5x-CH_2), 29.2 (2x-CH_2), 31.0, 31.7, 53.4, 60.0, 116.4 (2x-CH_2), 119.6, 122.3, 127.4, 128.1 (2x-CH_2), 128.2 (2x-CH_2), 129.1 (2x-CH_2), 129.4 (2x-CH_2), 131.8 (2x-CH_2), 136.3, 140.2, 146.2, 207.2 (-C=O). MS (ESI+) m/z (%): 547.1 (100, $[M]^+$). Anal. calcd for $C_{33}H_{42}BrNO$ (547.24): C, 72.25; H, 7.72; N, 2.55: Br, 14.57. Found: C, 72.23; H, 7.70; N, 2.52; Br, 14.55.

RESULTS AND DISCUSSION

Mannich reaction of aniline, benzaldehyde, and acetophenone was selected as a model and various catalysts have been tried (Table 1). The highest yield was obtained with $Bi(NO_3)_3$ (Table 1, entry 3). Several conventional organic solvents such as acetone, ethanol, THF, toluene, and DCM were used to optimize the reaction conditions. Ethanol was found to be a more suitable solvent for the reaction. Different molar ratios of catalyst were investigated to find the best yield. The optimum value was 10 mol% of $Bi(NO_3)_3$ catalyst (Table 2).

Table 1. Mannich reaction of acetophenone, aniline and benzaldehyde in the presence of several catalysts.

Entry	Catalyst	Time(h)	Yield[a] (%)
1	No catalyst	48	No reaction
2	I_2	24	80
3	$Bi(NO_3)_3$	24	92
4	$Al(NO_3)_3.9H_2O$	24	68
7	2,4,6-Trichloro-1,3,5-triazine(TCT)	12	75
8	$AlCl_3$	20	70

[a]Isolated yield. Mannich reaction; 2.0 mmol of aldehyde, 2.0 mmol of amine and 2.2 mmol of acetophenone in 5 mL of ethanol in the presence of catalyst at room temperature.

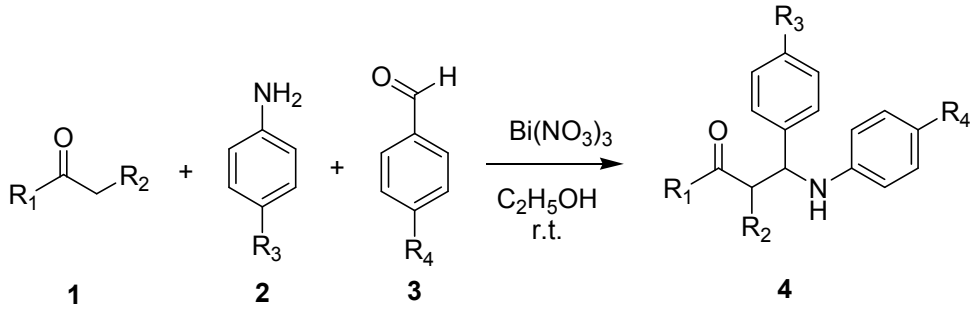
Table 2. Screening of molar ratios of $Bi(NO_3)_3$ to synthesize of **4a**.

Entry	$Bi(NO_3)_3$ %	Time (h)	Yield[a] (%)
1	2.5	24	42
2	5	24	65
3	7.5	24	70
4	10	24	92
5	15	24	86
6	20	24	84

[a]Isolated yield. Mannich reaction; acetophenone (2.2 mmol benzaldehyde (2.0 mmol), aniline (2.0 mmol) in 5 mL of ethanol by $Bi(NO_3)_3$ catalyst at r.t.

The reactions were also tried with $Bi(NO_3)_3$ under solvent-free conditions and in ethanol without catalyst, but good yields were not obtained. The optimum molar ratio of aldehyde, amine, and acetophenone was investigated. It was shown that using ethanol as the solvent, aniline/benzaldehyde/acetophenone = 2: 2: 2.2 was optimum to obtain the desired product in good yields.

To investigate the extent and universality of this method, many different ketones, aromatic aldehydes and amines were performed for their Mannich reactions in ethanol at room temperature (see Table 3). Mannich reactions occurred quite easily by reaction for the time as disclosed in Table 3 in the presence of 10 mol% of bismuth(III) nitrate to give the corresponding β-aminocarbonyl compounds in excellent yields (Table 3, entries 1–18). Numerous ketones and aromatic amines having methoxy and methyl para position and aromatic aldehydes with different substituents, such as para methyl, methoxy, hydroxyl and nitro proved to be suitable for the reactions. The effect of electron-deficient or donating bulky groups were very effective on the reaction yield. Our results are summarized in Table 3. To elucidate the structures of the synthesized compounds we used IR, NMR, MS, and elemental analysis.



Scheme 1. Direct, $Bi(NO_3)_3$-catalyzed, Mannich reaction of various ketones, aldehydes and amines.

Table 3. Results of the obtained β-amino carbonyl compounds.

Entry	Products [a]	R_1, R_2	R_3	R_4	Yield [b] (%)	Mp (°C) Found	Literature
1	**4a**	C_6H_5, H	H	H	92	165-166	166-168 (14)
2	**4b**	C_6H_5, H	CH_3	H	80	158.5-159.5	159 (15)
3	**4c**	C_6H_5, H	OCH_3	H	76	164.5-165.5	166-167 (16)
4	**4d**	C_6H_5, H	H	OH	90	195.2-196.2	181-182 (16)
5	**4e**	C_6H_5, H	H	OCH_3	88	155-156	153-156 (17)
6	**4f**	C_6H_5, H	H	NO_2	94	161.0-161.5	154-156 (18)
7	**4g**	4-Cyclo-$C_6H_{11}C_6H_4$, H	H	H	91	157.4-158.5	
8	**4h**	C_6H_5, CH_3C=O (19)	H	H	87	108-109	
9	**4i**	C_6H_5, CH_3C=O (20)	OCH_3	H	81	109-110	
10	**4j**	C_6H_5, CH_3C=O	H	OH	89	110.5-111.5	
11	**4k**	C_6H_5, CH_3C=O (19)	H	OCH_3	85	107.5-108	
12	**4l**	CH_3, C_2H_5OC=O	H	H	78	105.5-106	106-107 (21)
13	**4m**	CH_3, C_2H_5OC=O	CH_3	H	70	138.5-139.5	137-139 (22)
14	**4n**	CH_3, C_2H_5OC=O	H	OH	79	137.2-138.2	137-139 (23)
15	**4o**	4-BrC_6H_4, $CH_3(CH_2)_{11}$	H	H	88	176.8- 178.1	

[a]Mannich reaction; aldehyde and amine (2 mmol) and ketone (2.2mmol) in 5 mL of ethyl alcohol and 10% mol $Bi(NO_3)_3$ as catalyst at room temperature. [b]Isolated yield.

In conclusion, we have improved an eco-friendly and high yield reaction for three-component Mannich reactions catalyzed by bismuth(III) nitrate, which is a practical method for the synthesis of β-aminocarbonyls. This method suggests numerous advantages, including good yields of the resulting compounds.

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