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PEG Mediated Eco-Friendly One Pot Synthesis of β-Amino Carbonyl Compounds under Ambient Temperature Conditions

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ABSTRACT

Various β–amino carbonyl derivatives were synthesized, by the reaction of aniline, acetophenone and aromatic aldehydes, in high yields within shorter reaction times using PEG-600 as a safer catalyst under solvent-free conditions at room temperature. This synthetic route is exceedingly easy and avoids the use of toxic catalysts.

Keywords: One pot reaction, β-amino carbonyl compounds, green synthesis, PEG-600, room temperature, solvent-free.

INTRODUCTION

The Mannich reaction is one of the most important multicomponent reactions because of its atom economy and potential application in the synthesis of biologically active molecules [1–3]. It consists in the condensation of a primary or secondary amine, a nonenolizable aldehyde and an enolizable carbonyl compound in the presence of either acidic or basic catalysts to produce β-amino carbonyl compounds which are used either as versatile synthetic intermediates for the synthesis of amino alcohols, peptides, and lactams or as precursors to optically active amino acids [4, 5]. Moreover, the Mannich bases have their greatest importance as intermediates in the synthesis of a variety of compounds otherwise difficult to synthesize or completely inaccessible by other chemical processes.

Even though a number of modified methods under improved conditions have been reported, many of them suffer from some drawbacks including long reaction times, harsh reaction conditions, and difficult separation of the product; therefore, there is still room for further searches for better conditions that could be superior to the existing ones. In this respect, we are interested to introduce a potential catalyst to overcome these limitations.

Considering the focus on green synthesis in recent years [6], poly ethylene glycol (PEG) and its monomethyl ethers have been explored as potential reaction media for a wide array of organic reactions, which is clearly evident from the numerous reports in the literature [7]. Due to its low vapor pressure, nonflammable, nonvolatile and safe character and availability in high quantities at low prices, organic synthesis in the presence of PEG under solvent-free conditions is an area of significance in modern organic synthesis [8].

MATERIALS AND METHODS

Chemistry

All products are known and were characterized by comparison of their physical and spectroscopic data with those of authentic samples. Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. IR spectra were obtained as KBr pellets with a Shimadzu FT IR-8201 PC spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX spectrometer. Chemical shifts (δ) are reported in ppm and J values in hertz (Hz).

General procedure for the synthesis of (4a-h)

A mixture of an aromatic aldehyde (1.0 mmol), aniline (1.0 mmol) and acetophenone (1.0 mmol) was stirred at room temperature in the presence of a catalytic amount of PEG-600 (10 mol%). After the completion of the reaction (monitored by TLC), the reaction mixture was poured onto crushed ice and stirred for further 10 minutes. The formed solid, was isolated by filtration and crystallized from ethanol to give the pure product **4.**

The structures of all the prepared products were clearly established on the basis of their spectral analysis (IR, ^{1}H&^{13}C NMR) and melting points.

3-(4-chlorophenyl)-1-phenyl-3-(phenyl amino)-propan-1-one (4a): Yield: 93%; mp 114-115 °C; **IR** cm^{-1}: 3372 (NH), 1670 (CO); **^{1}H NMR ($CDCl_3$)** δ: 7.88 (m, 2H),7.62 (m, 1H), 7.37-7.48 (m, 4H),7.35 (m, 2H), 7.28 (m, 1H), 7.08 (m, 2H), 6.42 (d, 2H, *J* = 7.5 Hz) , 4.90 (dd, 1H, *J* = 7.4 and 5.4 Hz), 4.50 (s, 1H) 3.52 (dd, 1H, *J* = 16.0 and 5.3 Hz), 3.40 (dd, 1H, *J* = 15.9 and 7.5 Hz); **^{13}CNMR ($CDCl_3$)** δ**:** 197.30, 147.40, 143.41, 140.30, 135.42, 130.20, 118.51, 114.30, 55.13, 46.52.

3-(4-Methylphenyl)-1-phenyl-3-(phenyl amino)-propan-1- one (4b): Yield: 90%; mp 134-135 °C; **IR** cm^{-1}: 3394.5 (NH), 1743.5 (CO); **^{1}H RMN** ($CDCl_3$) δ: 7.98 (dd, 2H, *J* = 7.0 and 1.5 Hz), 7.61 (tt, 1H, *J* = 7.2 and 1.3 Hz), 7.49 (t, 2H, *J* = 7.6 Hz), 7.41 (t, 2H, *J* = 8.1 Hz), 7.29 (s, 1H), 7.20 (dd, 2H, *J* = 6.3 Hz and 0.9 Hz), 7.15 (dd, 2H, *J* = 5.4 Hz and 1.2 Hz,), 6.73 (tt, 1H, *J* = 7.3 Hz, and 1.0 Hz), 6.65 (dd, 2H, *J* = 7.6 Hz and 1.1 Hz), 5.05 (dd, 1H, *J* = 5.5 Hz), 3.58 (dd, 1H, *J* = 3.8 Hz and 9.3 Hz), 3.46 (dd, 1H, *J* = 3.9 Hz and 8.7 Hz), 2.40 (s, 3H); **^{13}C RMN (**$CDCl_3$) δ: 198.30, 146.90, 139.91, 136.60, 133.42, 129.50, 129.10, 128.71, 128.20, 126.35, 117.80, 116.40, 113.90, 54.51, 46.30, 21.11.

3-(4-Methoxyphenyl)-1-phenyl-3-(phenylamino)-propan-1-one (4c): Yield: 70%; mp 147-148 °C; **IR** cm^{-1}: 3390.6 (NH), 1743.5 (CO);**^{1}H RMN** ($CDCl_3$) δ: 7.95 (dd, 2H, *J* =5.1 Hz and 1.5 Hz) 7.60 (tt, 1H, *J* = 6.3 Hz and 1.4 Hz), 7.47(t, 2H, *J* = 5.3 Hz), 7.40 (t, 2H, *J* = 5.0 Hz), 7.29 (s, 1H), 7.13 (dd, 2H, *J* = 6.5 Hz and 1.1 Hz), 6.88 (dd, 2H, *J* = 8.8 Hz and 2.1 Hz), 6.72 (tt, 1H, *J* = 6.3 Hz, 1.0 Hz), 6.61 (dd, 2H, *J* = 10.0 Hz and 1.1 Hz), 5.01 (dd, 1H, *J* = 5.9 Hz), 3.79 (s, 3H), 3.55 (dd, 1H, *J* = 0.9 Hz and 6.5 Hz), 3.41 (dd, 1H, *J* = 2.9 Hz and 8.9 Hz); **^{13}C RMN (**$CDCl_3$) δ: = 198.3, 158.7, 146.6, 136.6, 134.6, 133.4, 129.1, 128.6, 128.2, 127.5, 117.9, 114.1, 114.2, 55.2, 54.4, 46.2.

1, 3-diphenyl -3-(phenylamino)-propan-1-one (4d): Yield: 80%; mp 169-170 °C; IR cm^{-1}: 3384 (NH), 1668 (CO); ^{1}H NMR($CDCI_3$) δ: 7.94-7.96 (m, 2H), 7.59-7.62 (m, 1H), 7.42-7.55 (m, 4H), 7.35-7.38 (m, 2H), 7.26-7.31 (m, 1H), 7.05-7.09 (m, 2H), 6.73 (t, 1H, *J* = 6.7 and 6.7 Hz), 6.63 (d, 2H, *J* = 7.8 Hz), 5.03 (dd, 1H, *J* = 7.4 and 5.4 Hz), 4.55 (s, 1H), 3.58 (dd, 1H, *J* = 16.2 and 5.3 Hz), 3.51 (dd, 1H, *J* = 16.2 and 7.5 Hz); ^{13}C NMR ($CDCI_3$) δ: 198.29, 147.00, 142.99, 136.73, 133.42, 129.11, 128.83, 128.70, 128.21, 127.36, 117.80, 113.84, 54.83, 46.31.

3-(4-nitrophenyl)-1-phenyl-3-(phenylamino)-propan-1-one (4f): Yield: 69%; mp 104-105 °C; IR cm^{-1}: 3429 (NH), 1670 (CO); **^{1}H NMR ($CDCI_3$)** δ: 8.18 (m, 2H), 7.70 (m, 4H), 7.58 (m, 1H), 7.49 (m, 2H), 7.11 (m, 2H), 6.73 (t, 1H, *J* = 6.6 Hz), 6.70 (d, 2H, *J* = 6.6 Hz), 5.15 (dd, 1H, *J* = 7.4 and 5.39 Hz), 4.53 (s, 1H), 3.58 (dd, 1H, *J* = 16.2 and 5.2 Hz), 3.52 (dd, 1H, *J* = 16.1 and 7.5 Hz); **^{13}C NMR ($CDCI_3$)** δ: 197.17, 150.70, 147.16, 146.23, 141.48, 136.25, 133.78, 129.23, 123.80, 128.10, 127.41, 124.05, 118.44, 113.79, 54.13, 45.63.

RESULTS AND DISCUSSION

In continuation of our work for developing convenient synthetic protocols for bioactive molecules and considering the need of developing environmentally accepted protocols [9], herein we report the synthesis of Mannich β-amino carbonyl compounds in the presence of PEG-600 under solvent-free conditions at room temperature (Scheme 1) (Table **2**).

Firstly, to screen the effect of the solvent on the product yield, the Mannich reaction of 4-chlorobenzaldehyde (1.0 mmol), aniline (1.0 mmol), and acetophenone (1.0 mmol) in the presence of PEG-600 (10 mol%, regarding to the aldehyde) was carried out in different solvents (Table **1,** entries 1-4). The results summarized in Table **1**, demonstrate that the reaction proceeded best under solvent-free conditions (Table **1**, entry 5) rather than using solvents (Table **1**, entries1-4).

Secondly, the model reaction was carried out at room temperature in the absence and in the presence of different quantities of PEG-600 (Table **1**, entries 6-10). The best result was obtained with 10 mol% of PEG-600 for 1.0 mmol of 4-chloro-benzaldehyde under solvent-free conditions within 4 h (Table **1**, entry 5). Using more than 10 mol% of PEG-600 did not improve the yield of the product. As the reaction carried out in the absence of PEG-600 gave just

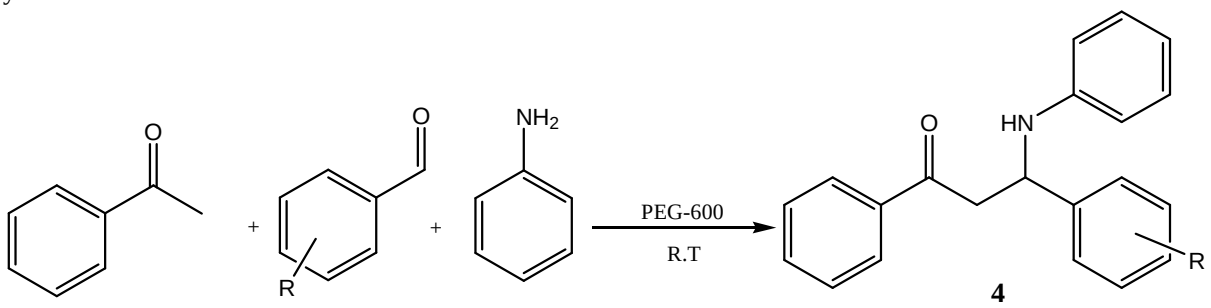
traces of the product (Table **1**, entry 6) and as only 10 mol % of PEG-600 was needed to produce the desired product in good yield (Table **1**, entry 5), PEG-600 acted as a catalyst not as a solvent in the present procedure.

Table 1. Optimizing the reaction conditions

Entry	PEG-600 (mmol%)	Solvent (ml)	Temperature	Yield (%)[b]
1	10	CH_3CN	reflux	35
2	10	THF	reflux	40
3	10	H_2O	reflux	65
4	10	EtOH	reflux	75
5	10	none	room temperature	93
6	none	none	room temperature	traces
7	5	none	room temperature	55
8	20	none	room temperature	85
9	50	none	room temperature	75
10	100	none	room temperature	75

[a]The reaction was carried out using 4-chlorobenzaldehyde (1.0 mmol), acetophenone (1.0 mmol) and aniline(1.0 mmol) at room temperature.
[b]isolated yield

Subsequently, to examine the efficiency and applicability of this protocol, the reaction was extended to other substituted aromatic aldehydes. The results summarized in Table **2** demonstrate that all the reactions proceeded smoothly and efficiently to yield the corresponding Mannich β-amino carbonyl compounds (**4a-h**) in fair to good yields.



Scheme 1: Synthesis β-amino carbonyl derivatives

Table 2: Physical data of the prepared β-amino carbonyl derivatives (4a-h) [a]

Entry	R	Time (h)	Product[b]	Yield[c] (%)	Mp (°C)	
					Found	Reported [ref]
1	4-Cl	5	**4a**	93	114 -115	112-114 [10]
2	4-CH_3	5	**4b**	90	134-135	134-135 [11]
3	4-OCH_3	5	**4c**	70	147 -148	142-143 [11]
4	H	4	**4d**	80	169-170	170-172 [10]
5	4-F	4	**4e**	55	110-111	111-112 [12]
6	4-NO_2	4	**4f**	70	104-105	102-104 [10]
7	3-NO_2	5	**4g**	75	131-132	131-132 [13]
8	4-$N(CH_3)_2$	3	**4h**	83	200-201	202-203 [13]

[a]The reaction was carried out using acetophenone (1.0 mmol), aniline (1.0 mmol) and aromatic aldehyde (1.0 mmol) in the presence of PEG-600 (10 mol %) at room temperature under solvent free-conditions.
[b]All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H-and ^{13}C-NMR spectral analysis and by direct comparison with authentic materials.
[c]Isolated yields

CONCLUSION

In conclusion, we have developed a simple, versatile and an environmentally friendly one-pot method for the synthesis of β-amino carbonyl compounds in good yields in the presence of PEG-600 as a very efficient ‘‘green’’ catalyst under solvent-free conditions at room temperature. This is a very general and environmentally benign procedure that would prove beneficial to both academic and industrial fields.

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