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Aluminium Phosphate Mediated Three-Component Mannich-Type Reaction

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Aluminium phosphate efficiently catalyzed the one-pot, three-component Mannich-type reaction of acetophenones with aromatic aldehydes and aromatic amines under solvent-free conditions at ambient temperature and afforded the corresponding β-amino carbonyl compounds in good to excellent yields. The present methodology offers several advantages such as mild reaction conditions, shorter reaction times and simple workup procedure.

Key Words: Mannich reaction, Aluminium phosphate, β-Amino ketones, One-pot synthesis, Shorter reaction times.

INTRODUCTION

β-Amino carbonyl compounds are attractive targets for chemical synthesis because of their wide use as biological active molecules[1]. Therefore, the development of new synthetic methods leading to β-amino carbonyl compounds or their derivatives has attracted much attention in organic synthesis. The Manninch reaction is a classified method for the preparation of β-amino ketones and aldehydes[2,3] and has been one of the most important basic reactions in organic chemistry for its use in natural product and pharmaceutical synthesis. However, due to drastic reaction conditions and the long reaction times, the classical intermolecular Manninch reaction is plagued by a number of serious disadvantages. However, catalytic Manninch reactions have been reported by several groups as an efficient method to prepare β-amino carbonyl compounds[4-15].

In continuation of our work on the application of heterogeneous catalysts for the development of useful synthetic methodologies, we now describe a mild, convenient and simple procedure for effecting the one-pot, three-component reaction of an aldehyde, aniline and acetophenone for the preparation of β-amino carbonyl compounds under mild and solvent-free conditions in the presence of aluminium phosphate ($AlPO_4$: Heterogeneous catalyst).

Heterogeneous catalysts have gained interesting attraction in recent years due to economic and environmental considerations. The catalyst is generally inexpensive and can conveniently be handled and removed from the reaction mixture, thus making the experimental procedure simple and eco-friendly.

EXPERIMENTAL

All yields refer to isolated products. NMR spectra were recorded on a Varian 200 MHz or Bruker 300 MHz. IR spectra were run on a Perkin-Elmer bio-spectrometer. The purity of the substances and the progress of the reactions were monitored by TLC on silica gel.

Typical procedure: To a stirred mixture of $AlPO_4$ (20 mg) in aniline (2.5 mL) added an aldehyde (106 mg) and acetophenone (120 mg). The reaction mixture was stirred at room temperature for 4-7 h. The mixture was filtered to remove the catalyst and the filtrate was poured into ice-cold water. The precipitated solid was filtered, washed with petroleum ether (60-80 ºC) to remove any residual starting material and dried. All products were characterized by their physical constants and spectral data.

Compound 4a: IR (KBr, cm^{-1}) 3385, 3020, 2915, 2875, 1670; ^1H NMR (200 MHz, $CDCl_3$): δ 3.30-3.52 (dd, 2H, J = 4.20 & 7.24 Hz,-CH_2), 4.85-5.05 (m, 1H, -CHN-), 6.50-7.85 (m, 15H, Ar-H).

Compound 4b: IR (KBr, cm^{-1}) 3400, 1665; ^1H NMR (200 MHz, $CDCl_3$): δ 3.35-3.47 (d, 2H, J = 4.25 & 7.20 Hz, -CH_2-), 4.83-4.95 (m, 1H, -CHN-), 6.40-8.40 (m, 14H, Ar-H).

Compound 4c: IR (KBr, cm^{-1}) 3400, 1665; ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, 6H, $2CH_3$), 2.68-2.84 (m, 1H, -CH-),

3.26-3.50 (dd, 2H, *J* = 4.22 & 7.20 Hz, -CH_2-), 4.78- 4.82 (m, 1H, -CHN-), 6.42-7.95 (m, 13H, Ar-H).

Compound 4d: IR (KBr, cm^{-1}) 1675, 3410; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (d, 6H, $2CH_3$), 2.79-3.00 (m, 1H, -CH-), 3.30-3.50 (dd, 2H, *J* = 4.25 & 7.20 Hz, -CH_2-), 4.80- 4.92 (m, 1H, -CHN-), 6.40- 8.42 (m, 13H, Ar-H).

Compound 4e: IR (KBr, cm^{-1}) 3385,1675; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10-1.17 (d, 6H, *J* = 5.5 Hz, $2CH_3$), 2.69-2.80 (m, 1H, -CH-), 3.30-3.50 (dd, 2H, *J* = 4.25 & 7.25 Hz, -CH_2-), 4.87- 4.90 (m, 1H, -CHN-), 6.39-7.90 (m, 14H, Ar-H).

Compound 4f: IR (KBr, cm^{-1}) 3388,1665; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30-3.46 (dd, 2H, *J* = 4.20 & 7.25 Hz, -CH_2-), 4.86- 4.95 (m, 1H, -CHN-), 6.40-8.40 (m, 14H, Ar-H).

Compound 4g: IR (KBr, cm^{-1}) 3400, 1670; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (d, 6H, $2CH_3$), 2.16-2.82 (m, 1H, -CH-), 3.35-3.50 (dd, 2H, *J* = 4.22 & 7.20 Hz, -CH_2-), 4.80-4.90 (m, 1H, -CHN-), 6.40- 7.90 (m, 13H, Ar-H).

Compound 4h: IR (KBr, cm^{-1}) 3380, 1675; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.28-3.53 (dd, 2H, *J* = 4.26 & 7.25 Hz, -CH_2-), 3.80 (s, 3H, -OCH_3), 4.78-4.89 (m, 1H, -CHN-), 6.36-7.92 (m, 14H, Ar-H).

Compound 4i: IR (KBr, cm^{-1}) 3385, 1670; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (d, 6H, $2CH_3$), 2.60-2.80 (m, 1H,-CH-), 3.25-3.50 (dd, 2H, *J* = 4.25 & 7.24 Hz, -CH_2-), 3.75 (s, 3H, -OCH_3), 4.80- 4.90 (m, 1H, -CHN-), 6.38-7.90 (m, 13H, Ar-H).

Compound 4j: IR (KBr, cm^{-1}) 3405, 1685; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20-3.25 (dd, 2H, *J* = 4.20 & 7.20 Hz, -CH_2-), 5.00- 5.12 (m, 1H, -CHN-), 6.20-8.25 (m, 14H, Ar-H).

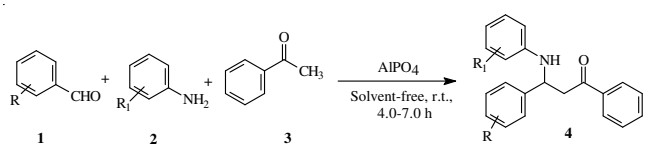
Compound 4k: IR (KBr, cm^{-1}) 3385,1670; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15-3.25 (dd, 2H, *J* = 4.15 & 7.20 Hz, -CH_2-), 4.80-4.85 (m, 1H, -CHN-), 6.40-8.15 (m, 14H, Ar-H).

Compound 4l: IR (KBr, cm^{-1}) 3375,1670; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30-3.46 (dd, 2H, *J* = 4.24 & 7.20 Hz, -CH_2-), 4.90- 4.96 (m, 1H, -CHN-), 6.45-7.80 (m, 14H, Ar-H).

Compound 4m: IR (KBr, cm^{-1}) 3380,1665; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H, -CH_3), 3.24-3.50 (dd, 2H, *J* = 4.22 & 7.24 Hz, -CH_2-), 4.85- 4.50 (m, 1H, -CHN-), 6.40-8.40 (m, 14H, Ar-H).

RESULTS AND DISCUSSION

Initially, *p*-chlorobenzaldehyde was selected as a representative aldehyde along with aniline, acetophenone and $AlPO_4$ in order to optimize the reaction conditions. As can be seen from Table-1, it was found that the reaction in the presence of 20 mg of $AlPO_4$ needs shorter reaction time than that without any catalyst at room temperature (Table-1, entry 1). So the best condition was that the reaction was catalyzed by 20 mg of $AlPO_4$ at room temperature (Table-1, entry 5).

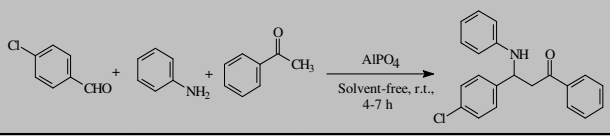


Scheme-I

Using the best conditions reported in Table-1 (entry 5), we continued to investigate the reaction at room temperature under solvent free media with 20 mg of $AlPO_4$ and the desired product was obtained in satisfactory yields. Encouraged by these results, we then continued to study the reaction using various aldehydes, anilines and acetophenones in the presence of 20 mg of $AlPO_4$. The results are summarized in Table-2 indicating that various aromatic aldehydes underwent smooth reaction with an aniline and acetophenone to give high yields of products. Clearly, the effect of the nature of the substituent on the aromatic ring showed no obvious effect on this conversion.

In conclusion, this paper describes a convenient and efficient process for the synthesis of β-amino ketones through the three-component coupling of various aromatic aldehydes,

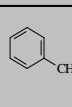
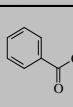
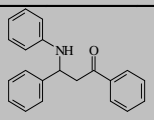
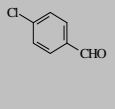
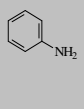
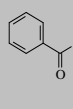
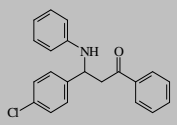
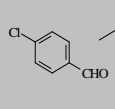
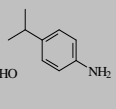
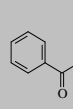
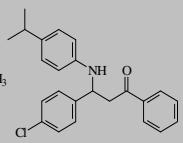
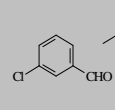
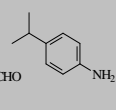
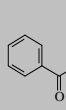
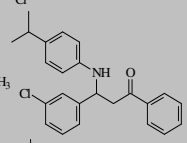
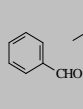
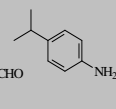
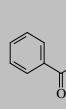
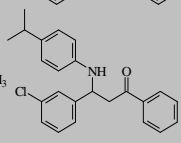
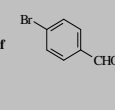
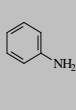
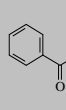
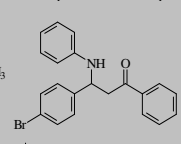
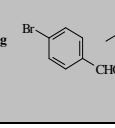
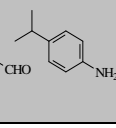
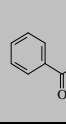
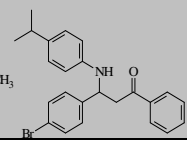
TABLE-1
OPTIMIZING THE REACTION CONDITIONS*
AT ROOM TEMPERATURE

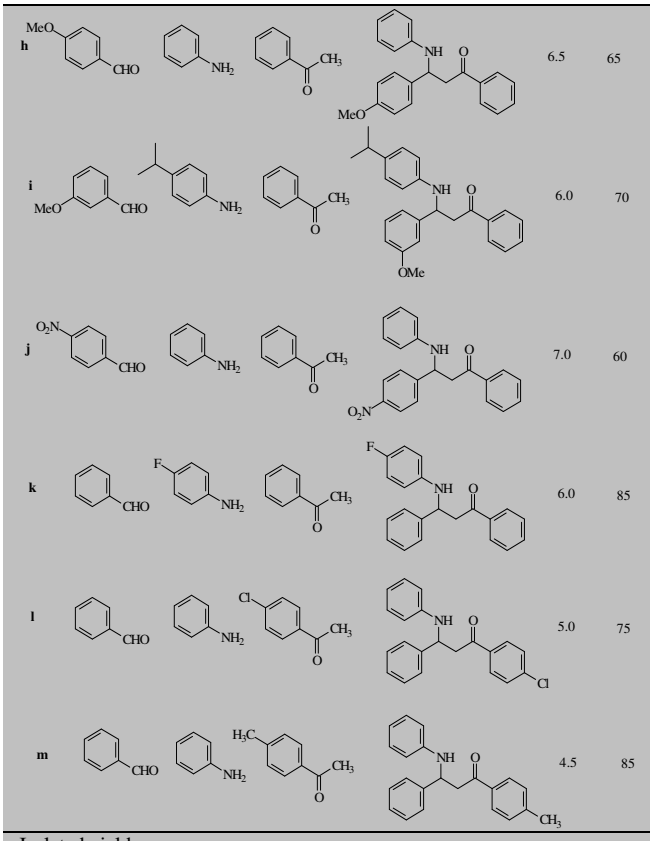


Entry	$AlPO_4$ (mg)	Time (h)	Yield (%)**
1	0	8	9
2	5	4	50
3	10	4	70
4	15	4	80
5	20	4	92
6	25	4	92
7	30	4	94

**p*-Chlorobenzaldehyde/aniline/acetophenone = 1:1:1
**Isolated yields.

TABLE-2
$ALPO_4$ CATALYZED THREE-COMPONENT MANNICH REACTION

Entry	Aldehyde	Aniline	Acetophenone	Product	Time (h)	Yield (%)*
a					4.5	75
b					4.0	92
c					4.0	85
d					4.0	72
e					4.5	70
f					4.5	70
g					6.0	72



Isolated yields.

anilines and acetophenones using $AlPO_4$ as a heterogeneous recyclable catalyst at room temperature. Present methodology offers very attractive features such as simple experimental procedure, reduced reaction times, higher yields, the catalyst can easily be removed by filtration and economic viability, when compared with conventional method as well as with other catalysts and will have wide scope in organic synthesis.

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