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Amberlyst-15: An Efficient and reusable heterogeneous catalyst for the synthesis of *β*-amino carbonyl compounds

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Abstract: A simple and efficient method has been developed for the synthesis of *β*-amino carbonyl compounds from aromatic ketones, aldehydes and amines by Mannich reaction in the presence of amberlyst-15 as a reusable heterogeneous catalyst at room temperature under solvent-free conditions. The noteworthy advantages of the present method are short reaction times, good product yields, simple procedures and use of non-toxic catalyst.

Keywords: *β*-Amino carbonyl compounds; Amberlyst-15; Mannich reaction.

1. Introduction

Synthesis of *β*-amino carbonyl compounds and their derivatives has gained considerable attention in recent years due to their wide range of biological and therapeutic properties such as plant growth regulators, analgesic, antiparkinson, neuroleptic,[1] antibacterial[2] and antitubercular. They are useful in the synthesis of *β*-peptides and *β*-lactams, which are present in different bioactive molecules such as fluoxetine (antidepressant), taxol (antitumor) SCH48461 (anti-cholesterol) and tolmetin (anti-inflammatory).[3] Further these are useful as precursors to optically active aminoalcohols.

Mannich reaction, offers robust method for formation of C-C bond in organic synthesis. A number of synthetic methods have been developed for the synthesis of *β*-amino carbonyl compounds. In this context some catalysts have been reported such as HCl,[4] Proline,[5] *p*-dodecyl benzene sulfonic acid (DBSA),[6] Polymer supported sulfonic acid (PS-SO_3H),[7] Lewis acids,[8] silica-$AlCl_3$,[9] $Yb(OiPr)_3$,[10] $InCl_3$,[11] CAN,[12] $BiCl_3$,[13] $SnCl_2$,[14] $Al(CH_3SO_3)_3.4H_2O$[15] and $Al(NO_3)_3.9H_2O$.[16] Though these are prompt with excellent yields and short reaction times, they are environment non-benevolent. Hence, the identification of environmentally benign and cost effective catalyst is of current interest for the synthetic chemists.

Recently, ion exchange resins have identified as catalysts due to their properties like open pore structure, excellent physical, thermal, chemical stability. In this view we identified Amberlyst-15[17] catalyst and used as catalyst for the preparation of *β*-amino carbonyl compounds, which serves as a source of strong acid in non-aqueous media. In previous, it is also used effectively in a wide variety of organic reactions such as Esterification[18] etherification,[19] oxidation,[20] condensation,[21] cyclization[22] and electrophilic aromatic substitution.[23] This method is operationally simple and the catalyst is also easily recoverable and reusable after reaction. So, herein we report an efficient and convenient procedure for

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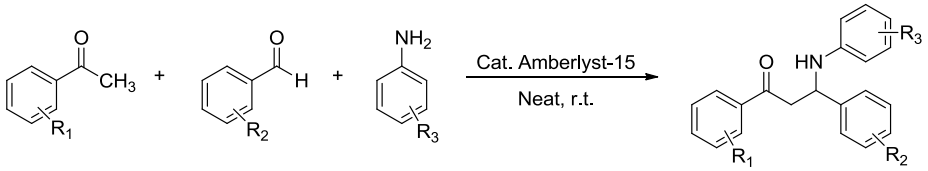
the synthesis of *β*-amino carbonyl compounds using catalytic amount of Amberlyst-15 under solvent-free condition at room temperature.

2. Results and discussion

In this Letter, we report Amberlyst-15 facilitated synthesis of *β*-amino carbonyl compounds in good to excellent yields under neat, mild reaction conditions (**Scheme 1**).



Scheme 1. Synthesis of *β*-amino carbonyl compounds **(4a-t)**

To optimize the reaction conditions, we took the model reaction of acetophenone, benzaldehyde and aniline (**4a**) was selected as a model reaction. Initially, the effect of various solvents on reaction rate as well as the yields of the product was examined in the presence of catalytic amount of amberlyst-15. Almost all solvents afforded products in relatively low yield with a longer reaction time. Further the model reaction were carried out under solvent free conditions, surprisingly the reactions occurred almost spontaneously within short reaction times and with improved yields given in **Table 1**.

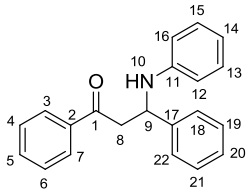
Table 1. Influence of the solvent on the synthesis of 4a[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	Ethanol	8	85
2	Toluene	12	86
3	Acetonitrile	8	80
3	THF	12	82
4	PEG 600	8	74
5	H_2O	10	60
6	Neat	4	96
7	Solvent	8	85

[a]Reaction conditions: acetophenone (4 mmol), benzaldehyde (4 mmol), aniline (4 mmol), Amberlyst-15 (0.1g) at rt. [b]Isolated yield.

Further, the effect of temperature on model reaction was also investigated. At high temperatures, the product yield was decreased because the Mannich Bases are unstable at high temperatures.[12] Hence these reactions were carried out at room temperature. These reports are presented in **Table 2**.

Table 2. Influence of the temperature on the synthesis of **4a**[a]



Entry	Temperature (°C)	Time (h)	Yield (%)[b]
1	rt	4	96
2	50	5	78
3	70	4	77
4	100	4	65

[a]Reaction conditions: acetophenone (4mmol), benzaldehyde (4 mmol), aniline (4 mmol), Amberlyst-15 (0.1g). [b]Isolated yield.

Based on these optimized conditions, we conducted the same reaction using different aromatic ketones, aromatic aldehydes and aromatic amines in the presence of catalytic amount (0.1g) of amberlyst-15 at room temperature under solvent free condition (**Scheme 1**). The results of this study are summarized in **Table 3**.

Table 3. Synthesis of various *β*-amino carbonyl compounds using amberlyst-15

Compound	R^1	R^2	R^3	Time (h)	Yield (%)[a]
4a	H	H	H	4	96
4b	H	H	4-F	6	95
4c	H	H	4-Cl	8	95
4d	H	H	4-NO_2	6	86
4e	H	H	4-CH_3	8	84
4f	H	H	4-OCH_3	10	88
4g	H	3-CH_3	H	10	91
4h	H	4-OCH_3	H	10	93
4i	H	3-NO_2	3-Cl	2	92
4j	H	3-NO_2	4-F	5	86
4k	H	3-NO_2	4-Cl	6	88
4l	H	3-NO_2	4-Br	9	92
4m	H	4-NO_2	3-Cl	5	94
4n	H	4-NO_2	4-COOH	2	96
4o	H	3-NO_2	3-Cl, 4-F	3	90
4p	H	3-NO_2	2, 4-CH_3	8	94
4q	4-CH_3	H	H	6	86
4r	4-Cl	4-CH_3	4-Cl	4	89
4s	4-OCH_3	3-NO_2	4-Cl	8	85
4t	4-CH_3	4-OCH_3	4-Cl	6	90

[a]Isolated yield

Aldehydes possessing electron-withdrawing group such as *m*-NO_2 (**4k**) afforded the corresponding *β*-amino carbonyl compounds in shorter reaction times and in higher yields. In addition to, aromatic amines bearing *p*-F (**4b**), -OMe (**4h**), -Br (**4n**), -CH_3 (**4g**) and *m*-Cl (**4d**) on the aryl rings were also favorable to the reaction. Although meta- and para-substituted aromatic amines both bearing electron withdrawing and electron donating substituents gave good results, ortho substituted aromatic amines (**4c**) give moderate yield after long reaction time because of large steric hindrance effect.[8, 9] Moreover, the catalyst can be reused without affecting the yield of the desired product (Table **3**, **4a**) and reaction time thus, making it environmentally friendly.

Table 4. Comparison of the efficiency of amberlyst-15 with other reported catalysts

Entry	Reaction Conditions	Time (h)	Yield (%)[a]
1	No Catalyst, EtOH/rt	48	NR[13]
2	$Al(NO_3)_3.9H_2O$, EtOH/rt	4	85[16]
3	$Al(CH_3SO_3)_3.4H_2O$, EtOH/rt	8	86[15]
4	CAN, PEG400/rt	10	98[12]
5	$BiCl_3$, EtOH/rt	11	95[13]
6	[PY][CF_3COO], Neat/rt	8	82[25]
7	DBSA, Water/23^oC	12	69[6]
8	Silica-$AlCl_3$, EtOH/rt	5	93[9]
9	Amberlyst-15, Neat/rt	4	96[b]

[a]Isolated yield.
[b]Present work

IR absorptions for NH group for **4a-t** appeared as broad signal in the region 3306-3437 cm^{-1} and for C=O group absorption appeared in the region 1615-1672 cm^{-1}. In the ^{1}H-NMR spectrum, all

the aromatic protons resonate as multiplets at δ 6.37-8.66. The -NH proton gave a broad signal at δ 4.12-4.91. In ^{13}C-NMR all the aromatic carbons resonated at δ 119.8-158.0. ESI-MS Spectra gave molecular ions and diagnostic daughter ion peaks at their respective expected m/z values.

Finally, we compared the catalytic activity of amberlyst-15 with other catalysts reported earlier for the synthesis of 4a and shown in **Table 4**. It was found that amberlyst-15 is convincingly superior to the reported methods with respect to reaction time and yield of product.

3. Experimental Section

All reagents were purchased from Sigma-Aldrich and were used throughout without further purification unless otherwise stated. NMR spectra were recorded on a Bruker instrument at 400 MHz for ^{1}H NMR, 100MHz for ^{13}C NMR in $CDCl_3$ solution using TMS as internal standard. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in (Hz). Mass spectra were recorded on IR spectra of samples were recorded as potassium bromide pellet on a Bruker Vector 21 FT-IR spectrophotometer. ESI mass spectra were recorded on a Micromass Quattro LC instrument. Elemental analyses were performed on a Thermo Finnegan Instrument. Melting points were determined in open capillary tubes are uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC) and spots were visualized in iodine vapor. The reactions were carried out at room temperature and all aldehydes, ketones, amines and catalysts used are commercially available.

3.1. General procedure for synthesis of a series of α- hydroxyphosphonates

A mixture of acetophenone (**1a**, 4 mmol) benzaldehyde (**2a**, 4 mmol), aniline (**3a**, 4 mmol) and catalytic amount of amberlyst-15 were stirred at room temperature under neat condition for a period of **4h**. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with acetone to separate the catalyst and reused for another reaction after 3 to 4 washings with acetone. The resulting product was purified by column chromatography using silica gel as absorbent and ethyl acetate & petroleum ether (1:4) as an eluent to yield the *β*-amino carbonyl compounds **4a-t**. The structures of all the products were confirmed by IR, ^{1}H & ^{13}C NMR and mass spectral data.

3.2. Spectral data for selected compounds

3.2.1. 1,3-Diphenyl-3-(phenylamino)propan-1-one (4a): White solid; mp: 169-170°C; IR (KBr, cm^{-1}) υ_{max}: 3306 (NH), 1620 (C=O); ^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.42 (d, J= 6.2Hz, 2H), 4.68 (t, J= 6.2 Hz, 1H), 4.83 (s, 1H), 6.52-7.85 (m, 15Ar-H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 46.5 (C-9), 52.6 (C-8), 112.6 (C-12 & C-16), 119.8 (C-14), 124.2 (C-20), 126.7 (C-18 & C-22), 128.6 (C-19 & C-21), 129.0 (C-4 & C-6), 129.4 (C-3 & C-7), 132.6 (C-13 & C-15), 136.5 (C-5), 139.4 (C-2), 142.1 (C-17), 144.2 (C-11), 198.6 (C-1); ESI-MS m/z: 301 (M^+); *Anal*. calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65; Found: C, 83.65; H, 6.32; N, 4.61.

3.2.2. 3-(4-Fluorophenylamino)-1,3-diphenylpropan-1-one (4b): White solid; mp: 161-162°C; IR (KBr, cm^{-1}) υ_{max}: 3372 (NH), 1654 (C=O); ^{1}HNMR (400MHz, $CDCl_3$) δ: 3.49 (d, J= 6.1Hz, 2H), 4.82 (t, J= 6.1 Hz, 1H), 4.91 (s, 1H), 6.78-8.06 (m, 14Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δ: 48.6 (C-9), 55.4 (C-8), 116.2 (C-13 & C-15), 117.5 (C-12 & C-16), 118.4 (C-20), 124.6 (C-18 & C-22), 125.2 (C-19 & C-21), 126.8 (C-4 & C-6), 127.2 (C-3 & C-7), 133.2 (C-5), 136.7 (C-2), 140.2 (C-17), 143.5 (C-11), 145.2 (C-14), 202.1 (C-1); ESI-MS m/z: 319 (M^+); *Anal*. calcd. for $C_{21}H_{18}FNO$: C, 78.98; H, 5.68; N, 4.39; Found: C, 78.92; H, 5.65, N, 4.36.

3.2.3. 3-(4-Chlorophenylamino)-1,3-diphenylpropan-1-one (4c): White solid; mp: 168-169°C; IR (KBr, cm^{-1}) υ_{max}: 3328 (NH), 1628 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.54 (d, J= 6.1Hz, 2H), 4.65 (t, J= 6.1 Hz, 1H), 4.82 (s, 1H), 6.64-8.52 (m, 14Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 47.6 (C-9), 54.8 (C-8), 116.3 (C-12 & C-16), 116.8 (C-14), 120.6 (C-20), 125.4 (C-18 & C-22), 126.8 (C-19 & C-21), 126.9 (C-4 & C-6), 127.4 (C-7 & C-9), 129.6 (C-13 & C-15), 133.2 (C-5), 136.8 (C-2), 142.8 (C-

17), 143.2 (C-14), 201.6 (C-1); ESI-MS m/z: 335 (M^+); *Anal*. calcd. for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17; Found: C, 75.08; H, 5.34; N, 4.14.

3.2.4. 1,3-Diphenyl-3-(p-nitrophenylamino)-1-propanone (4d): Yellow solid; mp: 182-184°C; IR (KBr, cm^{-1}) υ_{max}: 3374 (NH), 1610 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.58 (d, *J*= 6.1 Hz, 2H), 4.72 (t, *J*= 6.0 Hz, 1H), 5.29 (s, 1H), 7.32-8.15 (m, 14H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 47.4 (C-9), 52.4 (C-8), 117.5 (C-12 & C-16), 121.3 (C-20), 126.2 (C-18 & C-22), 126.5 (C-19 & C-21), 127.9 (C-4 & C-6), 128.5 (C-3 & C-7), 133.9 (C-5), 137.2 (C-14), 138.5 (C-2), 142.7 (C-17), 143.9 (C-11), 201.3 (C-5); ESI-MS m/z: 346 (M^+); *Anal*. calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09; Found: C, 72.73; H, 5.19; N, 8.05.

3.2.5. 1,3-Diphenyl-3-(p-methylphenylamino)-1-propanone (4e): White solid; mp: 169-171°C; IR (KBr, cm^{-1}) υ_{max}: 3387 (NH), 1683 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.47 (s, 3H, CH_3) 3.48 (d, *J*= 6.0 Hz, 2H), 4.82 (t, *J*= 6.2 Hz, 1H), 5.32 (s, 1H), 6.68-7.92 (14H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 29.8 (-CH_3), 42.3 (C-9), 51.8 (C-8), 114.9 (C-12 & C-16), 118.7 (C-20), 121.4 (C-18 & C-22), 125.8 (C-19 & C-21), 128.3 (C-4 & C-6), 129.8 (C-14), 130.8 (C-13 & C-15), 131.6 (C-3 & C-7), 134.6 (C-5), 136.4 (C-2), 141.7 (C-17), 142.8 (C-11), 201.7 (C-1); ESI-MS m/z: 315 (M^+); *Anal.* calcd. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44; Found: C, 83.61; H, 6.63; N, 4.39.

3.2.6. 3-(4-Methoxyphenylamino)-1,3-diphenylpropan-1-one (4f): White solid; mp: 122-123°C; IR (KBr, cm^{-1}) υ_{max}: 3312 (NH), 1615 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.38 (d, *J*=6.2Hz, 2H), 3.58 (s, 3H), 4.12 (s, 1H), 4.74 (t, *J*= 6.2 Hz, 1H), 6.58-7.97 (m, 14Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 40.1 (O-CH_3), 41.6 (C-9), 58.3 (C-8), 79.1 (C-13 & C-15), 114.6 (C-14 & C-16), 118.8 (C-20), 121.2 (C-18 & C-22), 125.4 (C-19 & C-21), 128.0 (C-4 & C-6), 129.6 (C-3 & C-7), 130.5 (C-5), 134.2 (C-2), 136.1 (C-11), 141.2 (C-17), 142.3 (C-14), 200.6 (C-1); ESI-MS m/z: 331 (M^+); *Anal*. calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23; Found: C, 79.68; H, 6.36; N, 8.05; N, 4.17.

3.2.7. 1-Phenyl-3-(phenylamino)-3-p-tolylpropan-1-one (4g): White solid; mp: 130-131°C; IR (KBr, cm^{-1}) υ_{max}: 3343 (NH), 1652 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.39 (s, 3H), 3.26 (d, *J*= 6.2 Hz, 2H), 4.48 (t, *J*=6.2 Hz, 1H), 3.82 (s, 1H), 6.68-8.14 (m, 14Ar-H); ^{13}C NMR (100MHz,$CDCl_3$) δ: 25.4 (CH_3), 46.5 (C-9), 59.6 (C-8), 72.3 (C-12 & C-16), 112.9 (C-14), 113.6 (C-22), 119.5 (C-18), 126.2 (C-20), 128.7 (C-21), 128.9 (C-4 & C-6), 129.2 (C-3 & C-7), 129.8 (C-13 & C-15), 133.2 (C-5), 136.8 (C-2), 137.4 (C-19), 147.3 (C-17), 148.3 (C-11), 202.4 (C-1); ESI-MS (m/z): 315 (M^+); Anal. calcd. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.75; H, 6.65; N, 4.41.

3.2.8. 1-Phenyl-3-(p-methoxyphenyl)-3-phenylamino-1-propanone (4h): White solid; mp: 150-152°C; IR (KBr, cm^{-1}) υ_{max}: 3379 (NH), 1670 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.37 (d, *J*= 6.2 Hz, 2H), 3.70 (s, 3H), 3.94 (s, 1H), 4.52 (t, *J*= 6.3 Hz, 1H), 6.69-8.32 (m, 14H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 29.4 (CH_3), 46.5 (C-9), 59.6 (C-8), 113.6 (C-12 & C-16), 119.5 (C-19 & C-21), 126.2 (C-14), 128.7 (C-18 & C-22), 128.9 (C-4 & C-6), 129.2 (C-3 & C-7), 129.8 (C-13 & C-15), 133.2 (C-5), 136.8 (C-17), 137.4 (C-2), 147.3 (C-11), 158.3 (C-20), 162.5, 202.4 (C-1); ESI-MS (m/z): 331 (M^+); Anal. calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23; Found: C, 79.68; H, 6.35; N, 4.17.

3.2.9. 3-(3-Chlorophenylamino)-3-(3-nitrophenyl)-1-phenylpropan-1-one (4i): Yellowish solid; mp: 114-116°C; IR (KBr, cm^{-1}) υ_{max}: 3328 (NH), 1632 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.00 (d, *J*= 6.1 Hz, 2H), 4.90 (t, *J*= 6.1Hz, 1H), 4.42 (s, 1H), 6.38-8.40 (m, 13Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.9 (C-9), 50.5 (C-8), 112.1 (C-16), 113.7 (C-12), 118.6 (C-15), 121.4 (C-18), 122.8 (C-14), 124.8 (C-20), 129.5 (C-4 & C-6), 130.0 (C-3 & C-7), 130.4 (C-22), 132.9 (C-5), 135.1 (C-13), 144.6 (C-2), 147.4 (C-17), 148.8 (C-19), 149.3 (C-11), 206.1 (C-1); ESI-MS (m/z): 380 (M^+); Anal. calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36; Found: C, 66.19; H, 4.47; N, 7.31.

3.2.10. 3-(4-Fluorophenylamino)-3-(3-nitrophenyl)-1-phenylpropan-1-one (4j): Yellowish solid; mp: 108-110°C; IR (KBr, cm^{-1}) υ_{max}: 3308 (NH), 1660 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.50 (d, *J*= 6.2 Hz, 2H), 4.88 (t, *J*= 6.2 Hz, 1H), 4.43 (s, 1H), 6.48-8.52 (m, 13Ar-H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 46.8 (C-9), 57.1 (C-8), 117.4 (C-13 & C-15), 122.5 (C-12 & C-16), 122.7 (C-18), 123.6 (C-20), 124.7 (C-4 & C-6), 124.8 (C-3 & C-7), 128.3 (C-21), 129.0 (C-22), 129.9 (C-5), 130.1 (C-2), 133.5 (C-11), 134.5 (C-17), 136.8 (C-19), 141.8 (C-14), 199.8 (C-1); ESI-MS (m/z): 364 (M^+); Anal. calcd. for $C_{21}H_{17}FN_2O_3$: C, 69.22; H, 4.70; N, 7.69; Found: C, 69.18; H, 4.64; N, 7.64.

3.2.11. 3-(4-chlorophenylamino)-3-(3-nitrophenyl)-1-phenylpropan-1-one (4k): Yellowish solid; mp: 115-117°C; IR (KBr, cm^{-1}) υ_{max}: 3314 (NH), 1664 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49 (d, *J*= 6.2 Hz, 2H), 4.87 (t, *J*= 6.2 Hz, 1H), 4.41 (s, 1H), 6.47-8.50 (m, 13Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.8 (C-9), 57.1 (C-8), 117.4 (C-12 & C-16), 122.5 (C-18), 122.7 (C-20), 123.6 (C-14), 124.7 (C-4 & C-6), 124.8 (C-3 & C-7), 128.3 (C-21), 129.0 (C-15 & C-13), 129.9 (C-22), 130.1 (C-5), 133.5 (C-2), 134.5 (C-17), 136.8 (C-11), 141.8 (C-19), 200.9 (C-1); ESI-MS (m/z): 380.5 (M^+); Anal. calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36; Found: C, 66.16; H, 4.43; N, 7.31.

3.2.12. 3-(4-bromophenylamino)-3-(3-nitrophenyl)-1-phenylpropan-1-one (4l): Yellowish solid; mp: 126-127 °C; IR (KBr, cm^{-1}) υ_{max}: 3349 (NH), 1666 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.51 (d, *J*= 6.2 Hz, 2H), 5.06 (t, *J*= 6.2 Hz, 1H), 4.76 (s, 1H), 6.39-8.29 (m, 13Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.9 (C-9), 57.2 (C-8), 110.4 (C-12 & C-16), 115.6 (C-14), 121.5 (C-18), 122.8 (C-20), 128.3 (C-4 & C-6), 129.0 (C-3 & C-7), 130.0 (C-21), 132.1 (C-5), 132.9 (C-13 & C-15), 134.0 (C-22), 136.4 (C-2), 145.1 (C-17), 145.4 (C-11), 148.9 (C-19), 202.3 (C-1); ESI-MS (m/z): 425 (M^+); Anal. calcd. for $C_{21}H_{17}BrN_2O_3$: C, 59.31; H, 4.03; N, 6.59; Found: C, 59.28; H, 4.01; N, 6.53.

3.2.13. 3-(3-Chlorophenylamino)-3-(4-nitrophenyl)-1-phenylpropan-1-one (4m): Yellow solid; IR (KBr, cm^{-1}): 3408 (NH), 1678 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$-d_6): 3.48 (*d*, *J*= 6.2 Hz, 2H), 5.12 (*t*, *J*= 6.1 Hz, 1H), 4.75 (s, 1H), 6.41-8.33 (M, 13Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.7 (C-9), 57.5 (C-8), 110.6 (C-22), 115.5 (C-18), 121.7 (C-21), 122.6 (C-20), 128.6 (C-12 & C-16), 129.2 (C-13 & C-15), 130.8 (C-4 & C-6), 132.3 (C-3 & C-7), 132.5 (C-5), 134.3 (C-19), 136.4 (C-2), 145.2 (C-14), 145.9 (C-11), 148.4 (C-17), 201.2 (C-1). MS (ESI) m/z: 380 (M+); Anal. Calcd for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.35; Found: C, 66.21; H, 4.47; N, 7.32%.

3.2.14. 3-(1-(4-nitrophenyl)-3-oxo-3-phenylpropylamino)benzoic acid (4n): White solid; mp: 186-187°C; IR (KBr, cm^{-1}) υ_{max}: 3416 (NH), 1692 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$-d_6): 11.45 (s, 1H, -COOH), 3.52 (*d*, *J*= 6.2 Hz, 2H), 5.16 (*t*, *J*= 6.1 Hz, 1H), 4.88 (s, 1H), 6.37-8.31 (m, 13Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.75(C-9), 57.7 (C-8), 110.3 (C-16), 115.7 (C-14), 121.2 (C-12), 122.7 (C-18 & C-22), 128.5 (C-19 & C-21), 129.3 (C-4 & C-6), 130.6 (C-3 & C-7), 132.5 (C-13), 132.8 (C-5), 134.7 (C-15), 136.2 (C-2), 145.4 (C-20), 145.8 (C-17), 148.5 (C-11), 165.6 (C-23), 202.4 (C-1). MS (ESI) m/z: 390 (M+); Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18; Found: C, 67.62; H, 4.61; N, 7.14;

3.2.15. 3-(3-chloro-4-fluorophenylamino)-3-(3-nitrophenyl)-1-phenylpropan-1-one (4o): Yellowish solid ; mp: 142-143 °C; IR (KBr, cm^{-1}) υ_{max}: 3414 (NH), 1649 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.43 (d, *J*= 6.1Hz, 2H), 4.92 (t, *J*= 6.2 Hz, 1H), 3.27 (s, 1H), 6.43-8.66 (m, 12Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.8 (C-9), 57.2 (C-8), 114.5 (C-15), 117.1 (C-12), 117.3 (C-16), 121.1 (C-18), 121.2 (C-13), 123.0 (C-20), 123.7 (C-4 & C-6), 124.8 (C-3 & C-7), 126.1 (C-21), 129.0 (C-22), 130.1 (C-5), 134.3 (C-2), 134.7 (C-17), 144.2 (C-11), 147.5 (C-15), 149.8 (C-19), 201.9 (C-1). ESI-MS (m/z): 399 (M^+). Anal. calcd. for $C_{21}H_{16}ClFN_2O_3$: C, 63.24; H, 4.04, N, 7.02; Found: C, 63.18; H, 4.02, N, 6.97.

3.2.16. 3-(2,4-dimethylphenylamino)-3-(3-nitrophenyl)-1-phenylpropan-1-one (4p): Yellowish solid; mp: 143-144°C; IR (KBr, cm^{-1}) υ_{max}: 3437 (NH), 1622 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 2.29 (s, 3H), 3.24 (d, *J*= 6.2 Hz, 2H), 4.72 (t, *J*= 6.2 Hz, 1H), 3.64 (s, 1H), 6.28-8.24 (m, 12 Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.5 (*o*-Me), 25.6 (*p*-Me), 41.1 (C-9), 56.8 (C-8), 115.2 (C-16), 117.1 (C-18), 123.4 (C-20), 125.4 (C-13), 127.4 (C-15), 128.9 (C-4 & C-6), 129.7 (C-3 & C-7), 131.5 (C-21), 132.8 (C-13), 134.1 (C-22), 136.7 (C-5), 138.4 (C-14), 141.4 (C-2), 143.9 (C-11), 145.6 (C-17), 148.4 (C-19), 200.5 (C-1). ESI-MS (m/z); 374 (M^+). Anal. calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.75; H, 5.88; N, 7.41.

3.2.17. 3-Phenyl-3-(phenylamino)-1-p-tolylpropan-1-one (4q): Colorless crystals; mp: 139-140°C; IR (KBr, cm^{-1}) υ_{max}: 3379, 1657, 1608, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.37 (d, *J*= 6.3 Hz, 2H), 4.89 (t, *J*= 6.2 Hz, 1H), 4.60 (s, 1H) 6.34-8.47 (14H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7 (CH_3), 46.2 (C-9), 54.9 (C-8), 113.8 (C-12 & C-16), 117.7 (C-14), 126.4 (C-20), 127.3 (C-18 & C-22), 128.4 (C-19 & C-22), 128.8 (C-3 & C-7), 129.1 (C-4 & C-6), 129.4 (C-13 & C-15), 134.2 (C-2), 143.1 (C-17), 144.4 (C-5), 147.1 (C-11), 199.9 (C-1); ESI-MS (m/z); 315 (M^+); Anal. calcd. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.62; H, 6.67; N, 4.38.

3.2.18. 1-(4-chlorophenyl)-3-(4-chlorophenylamino)-3-p-tolylpropan-1-one (4r): Paleyellow solid; mp 144-146ºC. IR (KBr, cm^{-1}) υ_{max}: 3368 (NH), 1672 (C=O). ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.28 (s, 3H), 3.39 (d, *J*= 6.2Hz, 2H), 4.89 (t, *J*= 6.2 Hz, 1H), 4.48 (s, 1H), 6.54-8.25 (m, 12Ar-H); ^{13}C-NMR (100MHz, $CDCl_3$) δ: 21.6 (CH_3), 48.2 (C-9), 57.8 (C-8), 113.8 (C-12 & C-16), 114.6 (C-18 & C-22), 120.8 (C-14), 125.6 (C-4 & C-6), 128.7 (C-19 & C-21), 128.9 (C-13 & C-15), 129.5 (C-3 & C-7), 129.9 (C-2), 130.6 (C-20), 132.5 (C-17), 136.4 (C-5), 145.5 (C-11), 199.2 (C-1); ESI-MS m/z: 383 (M^+); *Anal.* calcd. for $C_{22}H_{19}Cl_2NO$: C, 68.76; H, 4.98; N, 4.16. Found: C, 68.73; H, 4.94; N, 4.11.

3.2.19. 3-(4-chlorophenylamino)-3-(3-nitrophenyl)-(4-methoxyphenylpropan)-1-one (4s): White solid; mp: 121-122ºC; IR (KBr, cm^{-1}) υ_{max}: 3362 (NH), 1664 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.48 (d, J=6.2Hz, 2H), 3.84 (s, 3H), 4.56 (t, *J*= 6.2 Hz, 1H),4.24 (s, 1H), 6.48-8.34 (m, 12Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 44.6 (-O-CH_3), 48.2 (C-9), 52.4 (C-8), 113.8 (C-4 & C-6), 114.7 (C-12 & C-16), 115.6 (C-18), 115.9 (C-20), 126.8 (C-14), 126.9 (C-2), 128.5 (C-21), 128.9 (C-13 & C-15), 129.4 (C-3 & C-7), 129.5 (C-22), 131.4 (C-17), 133.2 (C-11), 136.7 (C-19), 141.5 (C-5), 200.8 (C-1); ESI-MS m/z: 410 (M^+); Anal. calcd. for $C_{22}H_{19}ClN_2O_4$: C, 64.29; H, 4.66; N, 3.69. Found: C, 64.25; H, 4.64; N, 3.63.

3.2.20. 3-(4-chlorophenylamino)-3-(4-methoxyphenyl)-1-p-tolylpropan-1-one (4t): White solid; mp: 130-132ºC; IR (KBr, cm^{-1}) υ_{max}: 3365 (NH), 1665 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.45 (s, 3H, CH_3), 3.48 (d, *J*= 6.2Hz, 2H), 3.56 (s, 3H, -OCH_3), 3.84 (s, 1H), 4.56 (t, *J*= 6.2 Hz, 1H), 6.48-8.34 (m, 12Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 24.8 (-CH_3), 43.5 (-O-CH_3), 48.7 (C-9), 52.9 (C-8), 112.9 (C-19 & C-21), 113.9 (C-12 & C-16), 115.4 (C-14), 115.7 (C-18 & C-22), 125.9 (C-3 & C-7), 126.5 (C-4 & C-6), 128.1 (C-13 & C-15), 129.0 (C-17), 129.5 (C-2), 131.1 (C-5), 132.9 (C-11), 141.2 (C-6), 201.5 (C-1); ESI-MS m/z: 379.5 (M^+); Anal. calcd. for $C_{23}H_{22}ClNO_2$: C, 72.72; H, 5.84; N, 3.69; Found: C, 72.67; H, 5.80; N, 3.65.

4. Conclusions

We have reported a very simple, efficient and environmentally benign procedure for the synthesis of *β*-amino carbonyl compounds from aromatic ketones, aromatic aldehydes and aromatic amines in the presence of Amberlyst-15 catalyst at room temperature under solvent-free condition. In addition, low cost, easy availability, reusability, low toxicity of the catalyst, excellent yields and short reaction time makes this methodology a valid contribution to the existing process in the field of *β*-amino carbonyl compounds synthesis.

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References

[1] Arend, M.; Westermann, B.; Risch, N. Modern variants of the mannich reaction. *Angew. Chem., Int. Ed.*, **1998**, *37*, 1044-1070.

[2] Rai, U.S.; Isloor, A.M.; Shetty, P.; Isloor, N.; Malladi, S.; Fun, H.K. Synthesis and biological evaluation of amino ketones. *Eur. J. Med. Chem*., **2010**, *45*, 6090-6094.
[3] Werder, M.; Hauser, H.; Carreira, E.M. Synthesis and in vitro evaluation of inhibitors of intestinal cholesterol absorption. *J. Med. Chem.*, **2005**, *48*, 6035-6053.
[4] Yang, D.C.; Zhang, G.L.; Yang, Y.; Zhong, Y.G. *Chem. J. Chinese U.*, **2000**, *21*, 1694-1696.
[5] Kantarn, M.L.; Rajasekhar, C.V.; Gopikrishna, G.; Reddy, K.R.; Choudary, B.M. Proline catalyzed two-component, three-component and self-asymmetric mannich reactions promoted by ultrasonic conditions. *Tetrahedron Lett*., **2006**, *47*, 5965-5967.
[6] Manabe, K.; Mori, Y.; Kobayashi, S. Three-component carbon–carbon bond-forming reactions catalyzed by a bronsted acid surfactant combined catalyst in water. *Tetrahedron*, **2001**, *57*, 2537-2544.
[7] Limura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. Mannich-type reactions in water using a hydrophobic polymer-supported sulfonic acid catalyst. *Chem. Commun*., **2003**, *2003*, 1644-1645.
[8] Wang, R.; Li. B.G.; Huang, T.K.; Shi, L; Lu, X.X. $NbCl_5$-catalyzed one-pot mannich-type reaction: three component synthesis of *β*-amino carbonyl compounds. *Tetrahedron Lett*., **2007**, *48*, 2071-2073.
[9] Li, Z.; Ma, X.L.; Liu, J.; Feng, X.; Tian, G.Q.; Zhu, A.G. Silica-supported aluminum chloride: A recyclable and reusable catalyst for one-pot three-component Mannich-type reactions. *J. Mol. Catal. A: Chem*. **2007**, *272*, 132-135.
[10] Ojan, C.T.; Gao, F.F.; Chen, R.F. Yb $(OiPr)_3$, A highly efficient catalyst for the nitro-mannich reaction. *Tetrahedron Lett*., **2001**, *42*, 4673-4675.
[11] Loh, T.P.; Chen, S.C. $InCl_3$ catalyzed three-component asymmetric mannich-type reaction in methanol. *Org. Lett*., **2002**, *4*, 3647-3650.
[12] Mazaahir, K.; Divya, B.; Neeraj, K.; Vikas, B. CAN catalyzed synthesis of β-amino carbonyl compounds via mannich reaction in PEG. *Catalysis Commun*., **2008**, *9*, 2547-2549.
[13] Hua Li.; Hong-yao, Z.; Hua-wu, S. Bismuth (III) chloride-catalyzed one-pot mannich reaction: three-component synthesis of *β*-amino carbonyl compounds. *Tetrahedron Lett*., **2009**, *50*, 6858-6860.
[14] Min, W.; Zhi-Guo, S.; Xin, W. $SnCl_2$-catalyzed three-component one-pot mannich-type reaction: efficient synthesis of *β*-amino carbonyl compounds. *Monatsh. chem*., **2009**, *140*, 1205-1208.
[15] Wang, Min.; Song, Z.G.; Jiang, H. Three-Component Mannich Reaction of Aromatic Ketones, Aldehydes and Amines Catalyzed by Reusable Aluminium Methane sulfonate. *Org. Prep. Proced. Int*. **2009**, *41*, 315-321.
[16] Min, W.; Yan, L.; Zhi-Guo, S. Aluminium nitrate as an efficient and reusable catalyst for the three components one-pot mannich reaction: synthesis of *β*-amino carbonyl compounds. *Indian J. Chem.*, **2010**, *49B*, 1653-1656.
[17] Zhang, X.; Fan, X.; Wang, J.; Li, Y.A Novel preparation of 4-phenylquinoline derivatives in ionic liquids. *Journal of the Chinese Chemical Society*, **2004**, *51*, 1339-1342.
[18] Chen, X.; Xu, Z.; Okuhara, T. Liquid phase esterification of acrylic acid with 1-butanol catalyzed by solid acid catalysts. *Appl. Catal., A*, **1999**, *180*, 261-269.
[19] Jayadeokar, S.S.; Sharma, M.M. Ion exchange resin catalysed etherification of ethylene and propylene glycols with isobutylene. *Reactive Polymers*, **1993**, *20*, 57-67.
[20] Kumari, P.; Shive M.S.; Chauhan. Efficient synthesis of 5, 10, 15-triarylcorroles using amberlyst 15 under solvent-free conditions. *J. Heterocycl. Chem.*, **2008**, *45*,779-783.
[21] Farhanullah; Ashoke, S..; Prakas, R.M.; Vishnu, J.R. Amberlyst-15 catalyzed synthesis of indole-pyrazole based tri (hetero) aryl methanes. *Tetrahedron Lett.*, **2004**, *45*, 5099-5102.
[22] Soni, A.S.; Shilpi, K.; Reena, P.K; Shrikant, P.N., Kiran, B.U.; Sujata, V.B. Amberlyst-15 catalyzed efficient cyclization of *γ*- and *δ*-unsaturated alcohols: green synthesis of oxygen heterocycles. *Synth. Commun.*, **2009**, *40*, 74-80.
[23] Rei-Sheu, H.; Jian-Long, W.; Hui-Ting, C.; You-Teng, X.; Ling-Ching, C. Amberlyst-15 catalyzed novel synthesis of quinoline derivatives in ionic liquid. *J. Chinese Chem. Soc.*, **2008**, *55*, 915-918.
[24] Shen, W.; Wang, L.M.; Tian, H. Quaternary ammonium salt gemini surfactants containing per fluoro alkyl tails catalyzed one-pot mannich reactions in aqueous media. *J. Fluorine Chem.*, **2008**, *129*, 267-273.
[25] Cai, B.Y.; Ting, F.Y.; Chuan, B.Z.; Gang, L. Mannich reaction catalyzed by a novel catalyst under solvent-free conditions. *J. Ind. Eng. Chem.*, **2009**, *15*, 653-656.