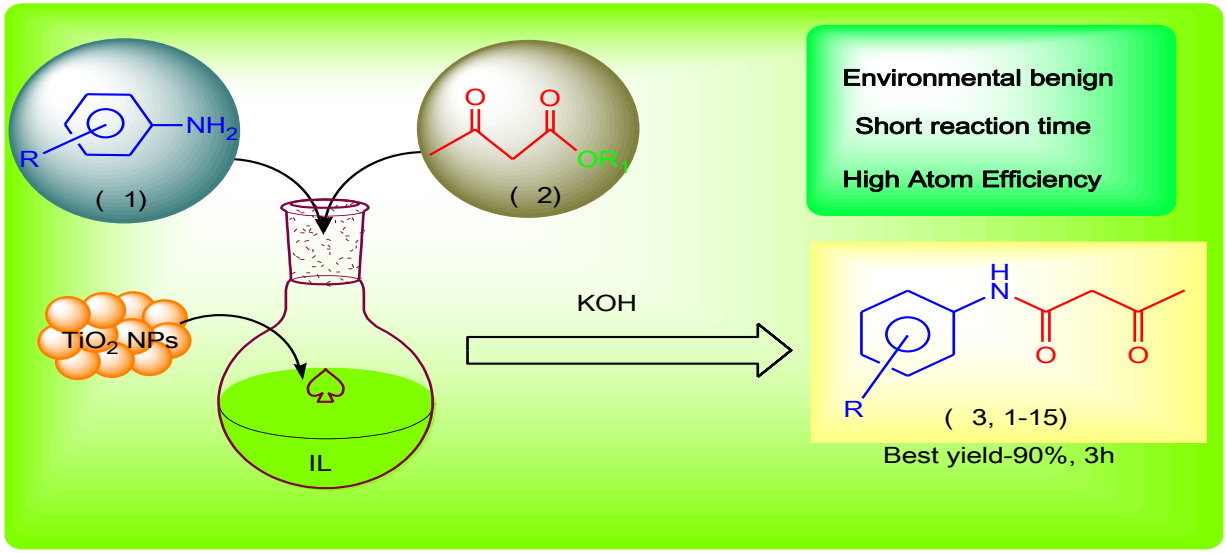
TiO_2 nanoparticles supported synthesis of acetoacetanilide derivatives in green media

Goswami P.G., Dhadda S.*, Yadav K., Jangid D.K., Guleria A. and Khandelwal C.L.
Department of Chemistry, Faculty of Science, University of Rajasthan, Jaipur, INDIA
*surbhidhadda@gmail.com

Abstract
An environment benign one pot synthesis involving reaction between β-ketoesters and substituted anilines to synthesize acetoacetanilide derivatives using ionic liquid {[MIM-NO_2]$C(NO_2)_3$} as green solvent and TiO_2 nanoparticles (NPs) as catalyst has been reported. The synthetic route provides clean, safe and eco-friendly alternative which does not involve any hydrocarbon solvent. A comparison between use of different solvents and optimization of mol% of NPs was also done. Result shows high %yield of product in a short reaction time under milder reaction conditions. The structures of synthesized compounds were confirmed by spectral and elemental analysis.

Keywords: Acetoacetanilides, green solvent, ionic liquid, one pot synthesis, TiO_2 NPs.



Graphical Abstract

Introduction

Acetoacetanilides are key intermediates and valuable synthones for the synthesis of many dyes, pigments,[1] and pharmacologically active heterocycles such as pyrimidines, piperidines, oxazoles and pyramidones derivatives.[2-5] These heterocycles are the building blocks of many biologically active drugs and a novel class of antimicrobial agents. Therefore, important efforts were devoted to the synthesis of acetoacetanilide in recent years. Traditionally many protocols for the synthesis of substituted acetoacetanilides were reported. Virsodia and co-workers[6] have reported synthesis by aniline and β-ketoester in toluene.

Suri and co-workers[7] synthesized acetocetanilide derivatives using microwave irradiation, silver(I)-catalyzed tandem approach to β- Oxo Amides was given by Nandavasi and co-workers[8]. Sridharan and co-workers[9] reported mild and high-yielding synthesis of β-keto esters and β-ketoamides.

All the reported methods involve either one or another drawback like long reaction time, harsh reaction condition, difficulties in purification of products, and use of hazardous volatile organic solvent.[10,11] Consequently, the development of more advance methods, use of proper reagents, solvent and catalyst are still in demand to make the available synthetic procedures more convenient, simple and environmentally benign.

In recent years, in organic synthesis ionic liquids have been used to overcome these problems successfully as efficient, environmentally benign reaction media and green catalyst due to their excellent properties like negligible volatility, thermal stability, recovery and reusability.[12,13] Ionic liquid can be recovered after the completion of the reaction through centrifugation or filtration and reused for the next reaction.[14]

On the other hand, use of heterogeneous solid catalyst such as nanoparticles in organic synthesis has drawn the attention of chemists because of their several advantages such as high stability, eco- friendly, safe, operational simplicity, large surface area and reusability.[15]

In many organic multicomponent reactions, TiO_2 nanoparticles have been used as a green heterogeneous catalyst to form nitrogen containing heterocyclic system such as pyridine and pyrimidine derivatives.[16,17] It displays very high catalytic activity and chemical selectivity under mild reaction conditions.

Currently we are focusing our efforts on the removal of environmental polluting solvent in such synthesis by using ionic liquid as reaction media and the use of TiO_2 NPs as an efficient solid heterogeneous catalyst to enhance the rate of reaction and to prevent the formation of side product enamino ester by masking more reactive keto-carbonyl group (Scheme 1).

Material and Methods

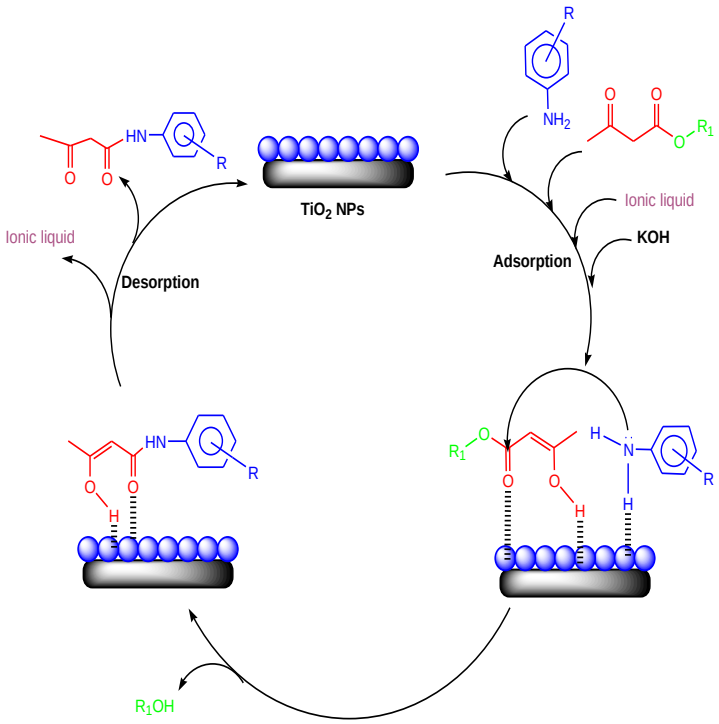
General: All the required chemicals were purchased from Sigma Aldrich, Alpha Aesar and used without further purification. The melting points were determined in open capillary tubes in melting point apparatus and are uncorrected. The completion of the reaction was checked on TLC plates coated with silica gel-G in the n-Hexane-EtOAc (v/v = 8:2) and visualised by exposure in UV chamber. The IR spectra were recorded on Shimadzu IR-435 spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL RESONANCE Spectrometer at 400.0 and 100.0 MHz respectively (δ in ppm) using TMS as an internal standard.

The elemental analysis (C, H and N) was performed using vario-III analyser. The XRD patterns were recorded on Panalyticalmake X'Pert PRO MPD diffractometer (model 3040). The wavelength of X-ray was 0.154 nm (Cu K-a). SEM was performed on Carl-Zeiss (30 keV) make and model EVO. IR spectra [4000-400 cm^{-1}] were recorded as dry KBr pellets on a Shimadzu FT-IR 8400 spectrometer.

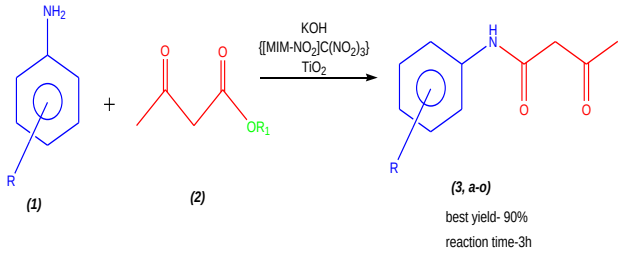
General procedure for the synthesis of ionic liquid {[MIM-NO_2]$C(NO_2)_3$}: The ionic liquid {[MIM-NO_2]$C(NO_2)_3$} was prepared by the reaction of 1-methyl imidazole and tetranitromethanide according to reported literature.[21]

General procedure for the synthesis of TiO_2 NPs: TiO_2 NPs were prepared by sol–gel method[18] using titanium(IV) isopropoxide. For the synthesis of TiO_2 NPs, [Ti{OPr^i}$_4$] (1.75g) was dissolved in dry isopropanol (~ 35 ml). To this clear solution 2-3 drops of 1:1 water-isopropanol mixture was added and stirred for 2 h. Sol formation occurred immediately. Excess of water ~ 10 ml {stoichiometric amount (0.22g)} was added in small lots with continuous stirring for ~ 4 h to ensure complete hydrolysis. The mixture was further stirred for 1 hour, till a gel is formed. The gel was dried in a preheated oven (100˚C) and then washed thoroughly with acetone. An off-white powder was obtained. This powder was sintered at 600˚C for 4 h to yield a white powder which was characterized as pure TiO_2.

General procedure for the synthesis of acetoacetanilide derivatives: The mixture of substituted aniline 1 (0.01 mol), β-ketoester **2** (0.01 mol), KOH (10 mol%) TiO_2 NPs (5 mol%) as catalyst and ionic liquid {[MIM-NO_2]$C(NO_2)_3$} as green solvent was refluxed at 90˚C for 3-5 hours. The progress of reaction was monitored by TLC after the completion of reaction ionic liquid and TiO_2 NPs were recovered. Then IL was reused for four times without loss of considerable activity. The residue was crystallized from ethanol (Scheme 2).



Scheme 1: Proposed mechanism of TiO_2 NPs supported Acetoacetanilide Synthesis



Scheme 2: Synthesis of Acetoacetanilide derivatives

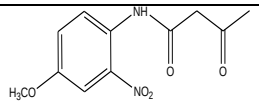
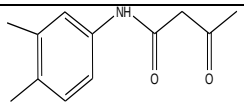
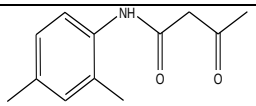
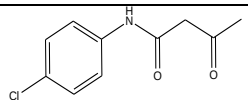
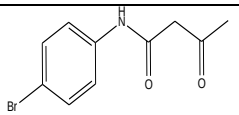
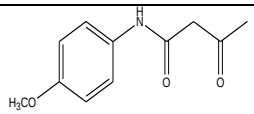
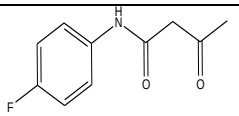
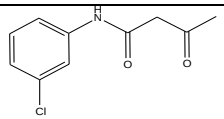
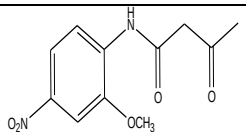
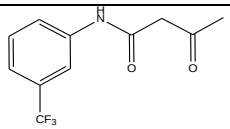
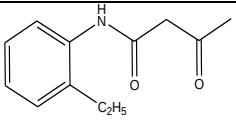
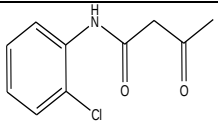
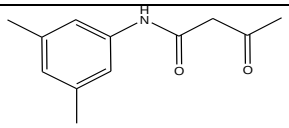
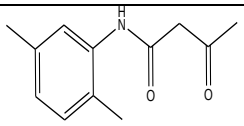
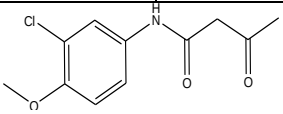
Spectral details of N-(4-Chloro-phenyl)-3-oxobutyramide (3d): MP: 130-132 °C, IR (KBr): ν 3283(NH), 1713, 1665 (CO str.), 1315 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.63 (bs, 1H, NH), 7.56-7.07 (m, 4H, Ar-H), 3.56 (s, 2H, $-CH_2-$), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 175.21, 168.99, 156.72, 146.78, 139.62, 138.63, 137.53, 129.48, 55.83, 22.27 "Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62; Found: C, 56.78; H, 4.73; N, 6.62".

Results and Discussion

Characterization of TiO_2 NPs: The catalyst was synthesized by sol-gel method and characterized by different techniques like FT-IR, and Scanning Electron Microscopy (SEM).

The SEM image of this titaniumoxide is displayed in figure 1. The scales that is shown in figure 1 is of 2 µm give an idea to designate creation of agglomerates granular morphology constituted by nano-sized crystals.

Table 1
Synthesis of various substituted acetoacetanilides using TiO_2 catalyst in ionic liquid solvent.

Compound Code/ time (h)/ yield (%)	
 3a, 6h, 80%	 3b, 6h, 85%
 3c, 4h, 84%	 3d, 3h, 90%
 3e, 5h, 75%	 3f, 4.5h, 87%
 3g, 5h, 70%	 3h, 6h, 76%
 3i, 5.2h, 80%	 3j, 4.5h, 89%
 3k, 6h, 82%	 3l, 6h, 86%
 3n, 4h, 78%	 3m, 3.5h, 81%
 3o, 4.5h, 83%	

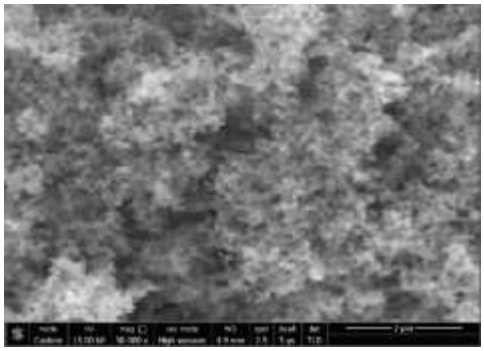


Figure 1: The SEM image of the TiO_2 NPs

FT-IR spectra of TiO_2 NPs are shown in figure 2. The absorbance bands at around 3230–3470 cm^{-1} were certified to the adsorbed water and hydroxyl group in nano sized TiO_2 (Figure 2). The band absorbed at 718 cm^{-1} is due to Ti-O-Ti while absorbance bands at 459 cm^{-1} show stretching vibration of Ti-O, which is consistent with the reported IR spectra for nano TiO_2.[18-20]

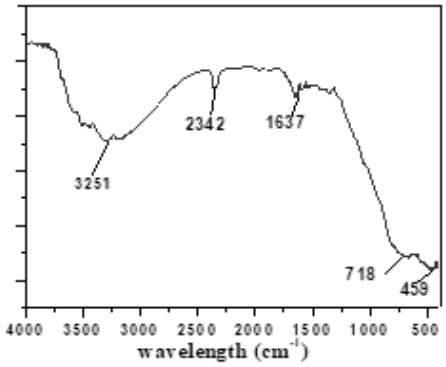


Figure 2: The FT-IR spectra of TiO_2 NPs

Characterization of synthesized compounds: A series of acetoacetanilide derivatives were synthesized by the reaction of substituted aniline with β-ketoester in ionic liquid using TiO_2 NPs as catalyst. The structures of synthesized compounds were confirmed by spectral analysis. The carbonyl group of -NH-CO (amide) was observed at 1660-1690cm^{-1} and CO bond of ketonic group was observed at 1710-1720cm^{-1} in IR spectra. In ^1H NMR spectra, amide (-NH-CO) proton was observed at 8-10ppm. The proton attached to methylene (-CH_2-) was observed at 3-4ppm. The proton of (-CH_3) group attached to carbonyl was observed at 2.21-2.35ppm and the protons of phenyl ring were observed at 7.01-8.50ppm. In ^{13}C NMR spectra, carbonyl carbon appears at 165-205ppm. The six carbon of the phenyl ring observed at the range of 125-160 ppm.

In mass spectra, molecular ion peaks were observed according to their molecular weights. The elemental analysis was found to match the calculated elemental composition within the permissible error limits. A thorough study was done including effects of solvent, catalyst and substitution pattern of reactants. In order to study effects of solvent and catalyst we have selected the synthesis of compound (3d) as model reaction.

Effect of solvent: We observed the solvent effect on the rate of the reaction and %yield of the product by performing reaction in various solvents. The best results were obtained in using ionic liquid as solvent (Table 2).

Effect of catalyst: Further we have observed that on increasing amount of catalyst TiO_2 NPs the rate of reaction and yield of product first increased to an extent and then decreased. The best results were obtained with 5 mol% of catalyst (Table 3).

Table 2
Effect of solvents on the synthesis of acetoacetanilide derivatives

Entry	Solvent	Catalyst	Time (h)	%Yield
1.	DMF	TiO_2 (5 mol%)	11	14
2.	Methanol	TiO_2 (5 mol%)	10	15
3.	Ethanol	TiO_2 (5 mol%)	9.5	21
4.	Isopropyl aclcohol	TiO_2 (5 mol%)	8	22
5.	Acetone	TiO_2 (5 mol%)	7	24
6.	CH_3CN	TiO_2 (5 mol%)	6	55
7.	Hexane	TiO_2 (5 mol%)	5	70
8.	Benzene	TiO_2 (5 mol%)	5.5	75
9.	Toluene	TiO_2 (5 mol%)	4.5	78
10.	**{[MIM-NO_2]C(NO_2)$_3$}**	**TiO_2 (5 mol%)**	**3**	**90**

Effect of substitution on substrate: To study the effect of substitution on substrate, we used various substituted aniline which were allowed to react with β-ketoester in optimized reaction conditions (TiO_2, 5 mol% in ionic liquid, Table 1). It was shown by results that the presence of electron releasing groups in aniline favoured the reaction by making it more nucleophilic towards the electronically deficient centre whereas the presence of electron withdrawing group did not favour the reaction. Further we used different β-keto ester but we observed that the structure of ester did not affect the reaction significantly.

Recovery of ionic liquid: The ionic liquid was recovered after the completion of the reaction through the centrifugation or filtration and to be further reused for next reaction without losing their catalytic activity. Ionic liquid was obtained in good yield after each cycle of recovery[21] (Figure 3).

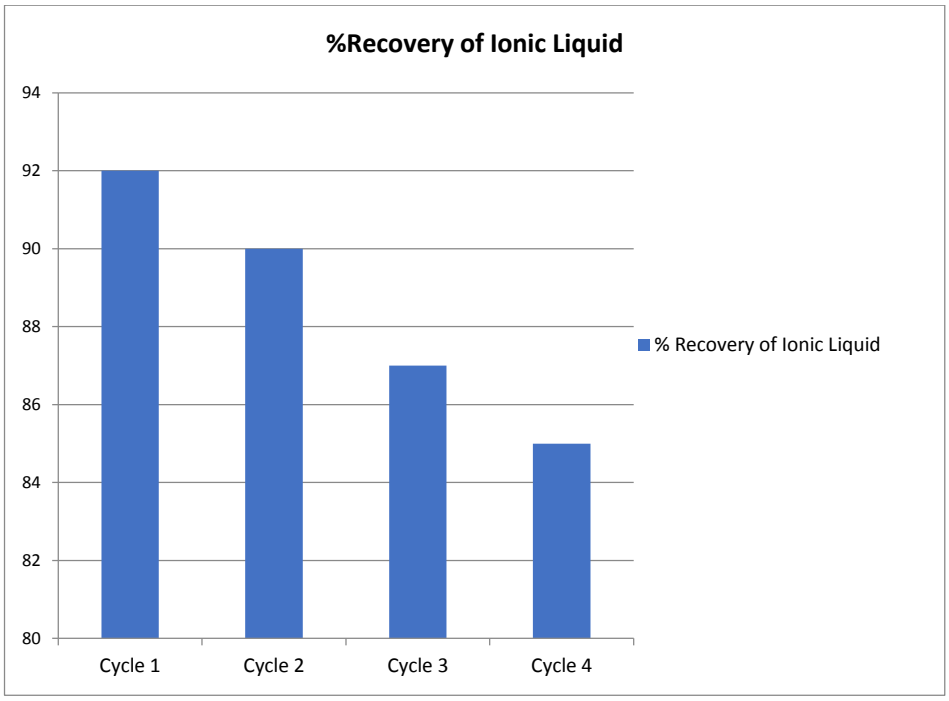


Figure 3: Recovery of ionic liquid.

Table 3
Optimization of the amount of TiO_2 NPs in the synthesis of various acetoacetanilide derivatives.

Entry	Catalyst (mol%)	Solvent	Time(h)	%Yield
1.	0	{[MIM-NO_2]C(NO_2)$_3$}	18	65
2.	1	{[MIM-NO_2]C(NO_2)$_3$}	15	72
3.	2	{[MIM-NO_2]C(NO_2)$_3$}	12	76
4.	3	{[MIM-NO_2]C(NO_2)$_3$}	10	80
5.	4	{[MIM-NO_2]C(NO_2)$_3$}	7	84
6.	**5**	**{[MIM-NO_2]C(NO_2)$_3$}**	**3**	**90**
7.	6	{[MIM-NO_2]C(NO_2)$_3$}	3.5	87
8.	7	{[MIM-NO_2]C(NO_2)$_3$}	4.0	80

Supplementary Material

Spectral studies of synthesized compounds

1. N-(4-Methoxy-2-nitro-phenyl)-3-oxobutyramide (3a): MP: 116-118 °C, IR (KBr): ν 3275(NH), 1713, 1695 (CO str.) 1274 (C-N str.) cm^{-1}; ^{1}H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.97 (bs, 1H, NH), 8.43-7.77 (m, 3H, Ar-H), 3.95 (s, 3H, OCH_3),3.59 (s, 2H, -CH_2-), 2.17 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 204.05, 166.08, 149.30, 142.72, 133.65, 119.08, 117.52, 105.32, 56.25, 52.01, 29.22 "Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11; Found: C, 52.35; H, 4.79; N, 11.13".

2. N-(3,4-Dimethyl-phenyl)-3-oxobutyramide (3b): Sticky liquid, IR (KBr): ν 3162(NH), 1733, 1630 (CO str.), 1304 (C-N str.) cm^{-1}; ^{1}H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.12 (bs, 1H, NH), 7.29-7.02 (m, 3H, Ar-H), 3.55 (s, 2H, -CH_2-), 2.34 (s, 3H, CH_3); 2.20 (s, 6H, Ar-CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 204.01, 162.45, 136.52, 135.01, 133.63, 123.25, 121.36, 116.84, 56.55, 30.66, 18.56, 18.22 "Anal. Calcd for

$C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; Found: C, 70.25; H, 7.34; N, 6.83".

3. N-(2.4-Dimethyl-phenyl)-3-oxobutyramide (3c): MP: 225-227 °C, IR (KBr): ν 3248(NH), 1719, 1644 (CO str.), 1265 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.19 (bs, 1H, NH), 7.30-7.08 (m, 3H, Ar-H), 3.58 (s, 2H, -CH_2-), 2.39 (s, 3H, CH_3); 2.22 (s, 6H, Ar-CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 204.11, 163.20, 136.80, 135.95, 133.72, 123.05, 121.85, 117.82, 56.52, 30.25, 19.58, 18.55 "Anal. Calcd for$C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; Found: C, 70.25; H, 7.33; N, 6.85".

4. N-(4-Chloro-phenyl)-3-oxobutyramide (3d): MP: 130-132 °C, IR (KBr): ν 3283(NH), 1713, 1665 (CO str.), 1315 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.63 (bs, 1H, NH), 7.56-7.07 (m, 4H, Ar-H), 3.56 (s, 2H, -CH_2-), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 175.21, 168.99, 156.72, 146.78, 139.62, 138.63, 137.53, 129.48, 55.83, 22.27 "Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62; Found: C, 56.78; H, 4.73; N, 6.62".

5. N-(4-Bromo-phenyl)-3-oxobutyramide (3e): MP: 136-138 °C, IR (KBr): ν 3289(NH), 1715, 1655 (CO str.), 1239 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.27 (bs, 1H, NH), 7.54-7.42 (m, 4H, Ar-H),3.56 (s, 2H, -CH_2-),2.30 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 205.01, 163.40, 137.19, 131.00, 122.01, 117.60, 49.70, 32.09 "Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; N, 5.47; Found: C, 46.94; H, 3.94; N, 5.45".

6. N-(4-Methoxyphenyl)-3-oxobutanamide (3f): MP: 113-115 °C, IR (KBr): ν 3289(NH), 1715, 1655 (CO str.), 1239 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 8.96 (bs, 1H, NH), 7.54-6.80 (m, 4H, Ar-H), 3.74 (s, 3H,-OCH_3)3.56 (s, 2H, -CH_2-),2.30 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 204.33, 163.50, 156.19, 131.00, 122.01, 114.60, 53.12, 49.70, 32.09 "Anal. Calcd for $C_{11}H_{12}NO_3$: C, 63.76; H, 6.32; N, 6.76; Found: C, 63.77; H, 6.31; N, 6.74".

7. N-(4-Floro-phenyl)-3-oxobutyramide (3g): MP: 97-99 °C, IR (KBr): ν 3253(NH), 1721, 1669 (CO str.) 1235 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.15 (bs, 1H, NH), 7.56-7.45 (m, 4H, Ar-H), 3.57 (s, 2H, -CH_2-), 2.31 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 205.44, 163.50, 157.22, 134.05, 133.23, 122.60, 121.33, 115.09, 49.35, 31.85 "Anal. Calcd for $C_{10}H_{10}FNO_2$: C, 61.83; H, 5.16; N, 7.18; Found: C, 61.85; H, 5.15; N, 7.20".

8. N-(3-Chloro-phenyl)-3-oxobutyramide (3h): MP: 107-109 °C, IR (KBr): ν 3242(NH), 1721, 1665(CO str.), 1239 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 10.22 (bs, 1H, NH), 7.68-7.15 (m, 4H, Ar-H), 3.56 (s, 2H, -CH_2-), 2.18 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 177.36, 166.19, 156.00, 144.34, 139.14, 137.63, 137.55, 128.11, 54.88, 21.30 "Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62; Found: C, 56.77; H, 4.78; N, 6.60".

9. N-(3-Trifluoromethylphenyl)-3-oxobutanamide (3i): MP: 107-110 °C, IR (KBr): ν 3326 (NH), 1718, 1666 (CO str.), 1309 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.46 (bs, 1H, NH), 7.80-7.29 (m, 4H, Ar-H), 3.59 (s, 2H, -CH_2-), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 205.51, 164.23, 138.74, 130.05, 129.15, 125.45, 123.37, 121.91, 116.21, 46.09, 30.75 "Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71; Found: C, 53.90; H, 4.15; N, 5.68".

10. N-(2-Methoxy-4-nitro-phenyl)-3-oxobutyramide (3j): MP: 112-114 °C, IR (KBr): ν 3272 (NH), 1711, 1688 (CO str.), 1276 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.96 (bs, 1H, NH), 8.42-7.80 (m, 3H, Ar-H),3.95 (s, 3H, OCH_3) 3.52 (s, 2H, -CH_2-), 2.18 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 203.04, 167.27, 148.50, 143.23, 134.01, 121.70, 116.07, 105.75, 56.33, 51.91, 30.56 "Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11; Found: C, 52.35; H, 4.80; N, 11.09".

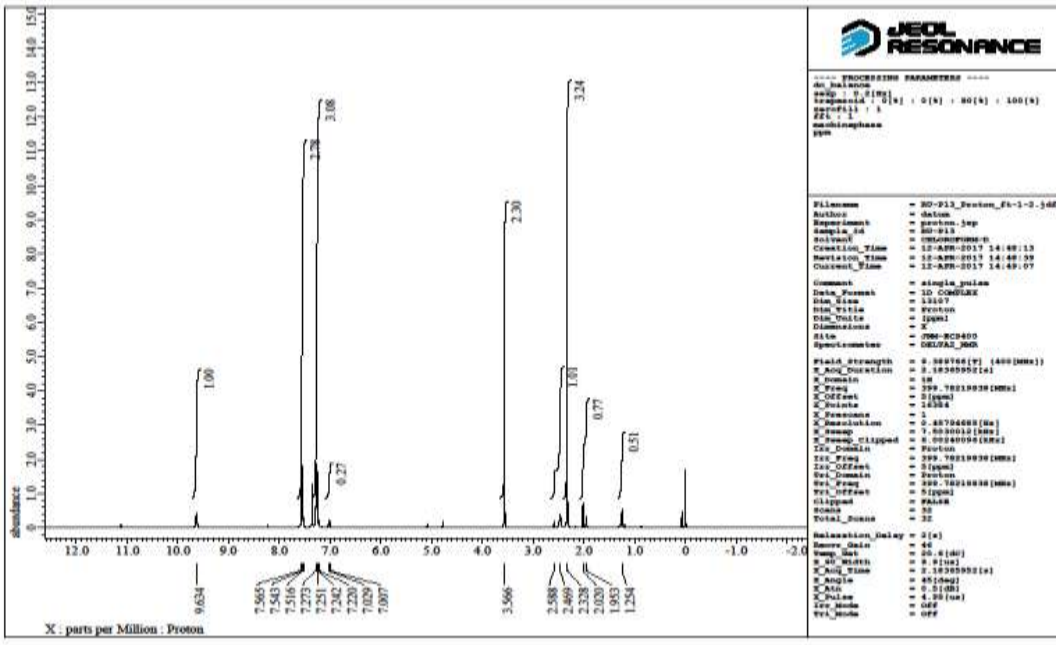
11. N-(2-Ethyl-phenyl)-3-oxo-butyramide (3k): MP: 96-99 °C, IR (KBr): ν 3230 (NH), 1742, 1666 (CO str.), 1252 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.26 (bs, 1H, NH), 7.91-7.06 (m, 4H, Ar-H), 3.65 (s, 2H, -CH_2-), 2.63 (q, 2H,-CH_2-CH3), 2.34 (s, 3H, CH3), 1.24 (t,-3H, -CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ205.04, 163.27, 134.06, 134.01, 128.41, 126.80, 124.07, 122.86, 48.71, 31.76, 24.08, 15.04 "Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; Found: C, 70.26; H, 7.39; N, 6.85".

12. N-(2-Chloro-phenyl)-3-oxo-butyramide (3l): MP: 104-107 °C, IR (KBr): ν 3285 (NH), 1717, 1669 (CO str.), 1325 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.62 (bs, 1H, NH), 8.36-7.06 (m, 4H, Ar-H), 3.68 (s, 2H, -CH_2-), 2.35 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 176.44, 167.99, 154.58, 144.25, 138.54, 137.25, 137.15, 129.58, 53.23, 21.29 "Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62; Found: C, 56.72; H, 4.74; N, 6.60".

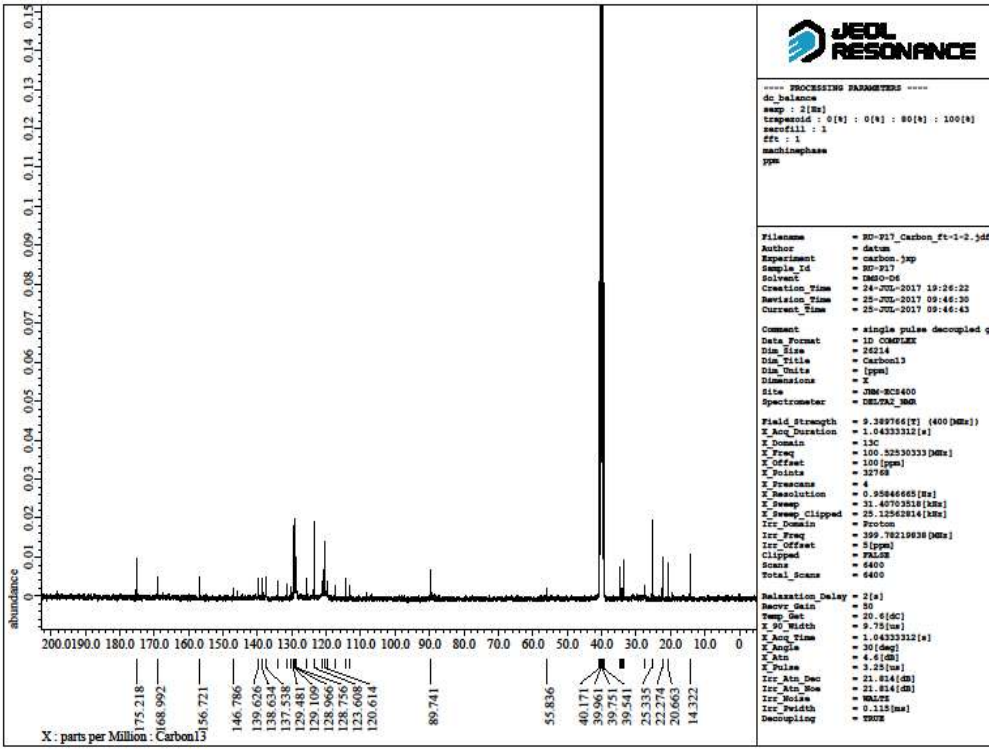
13. N-(3,5-Dimethyl-phenyl)-3-oxobutyramide (3m): MP: 136-138 °C, IR (KBr): ν 3113(NH), 1738, 1639 (CO str.), 1317 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.07 (bs, 1H, NH), 7.30-7.02 (m, 3H, Ar-H), 3.52 (s, 2H, -CH_2-), 2.41 (s, 3H, CH_3); 2.25 (s, 6H, Ar-CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 204.53, 164.15, 135.50, 134.95, 133.11, 124.05, 121.00, 116.52, 54.52, 29.25, 19.25, 17.58 "Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.72; H, 17.37; N, 15.59; Found: C, 70.75; H, 17.35; N, 15.58".

14. N-(2,5-Dimethyl-phenyl)-3-oxobutyramide (3n): MP: 92-94 °C, IR (KBr): ν 3229(NH), 1725, 1630 (CO str.), 1337 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.29 (bs, 1H, NH), 7.40-7.10 (m, 3H, Ar-H), 3.55 (s, 2H, -CH_2-), 2.31 (s, 3H, CH_3); 2.28 (s, 6H, Ar-CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 204.99, 164.20, 136.55, 134.15, 132.52, 121.085, 120.25, 116.47, 56.00, 29.14, 17.18, 16.23 "Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; Found: C, 70.19; H, 7.40; N, 6.81".

15. N-(3-Chloro-4-methoxyphenyl)-3-oxobutanamide (3o): MP: 105-107 °C, IR (KBr): ν 3284 (NH), 1719, 1662, (CO str.), 1260 (C-N str.) cm^{-1}; ^1H NMR spectral data (400 MHz, Chloroform-D, δ ppm from TMS): δ 9.12 (bs, 1H, NH), 7.62-6.70 (m, 3H, Ar-H), 3.89 (s, 3H, OCH_3), 3.52 (s, 2H, -CH_2-), 2.31 (s, 3H, CH_3); ^{13}C NMR (100.0 MHz, DMSO-d_6, ppm) δ 204.21, 164.59, 154.10, 133.55, 123.22, 122.00, 119.77, 112.65, 55.21, 49.11, 32.16 "Anal. Calcd for $C_{11}H_{12}NO_3Cl$: C, 54.60; H, 5.00; N, 5.80 Found: C, 54.62; H, 5.02; N, 5.84".



^1H NMR spectra of compound (3d)



^{13}C NMR spectra of compound (3d)

Conclusion

We have reported an efficient, environmentally benign and one pot procedure for the synthesis of acetoacetanilide derivatives using ionic liquid (1-methyl imidazolium trinitromethanide) as solvent and TiO_2 NPs as catalyst. The advantages of presented synthetic route are the removal of hazardous solvent, high productivity, short reaction time and reusability of catalyst and solvent. The ionic liquid and catalyst TiO_2 NPs can be reused several times without significant loss of their activities.

As the synthesized scaffold is found in a number of pharmacologically active agents, thus the reported compounds can be used for the synthesis of future possible anti-tubercular, antibacterial and antimycobacterial agents.[22]

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