ARTICLE

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Synthesis of β-Aminocarbonyl and β-Aminonitrile Compounds Catalyzed by Water Extract of *Musa balbisiana* (Colla) *via* Aza-Michael Reaction

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ABSTRACT

A greener method for the conjugate addition of amines to conjugated alkenes *via* aza-Michael reaction under the influence of water extract of the biocatalyst derived of *Musa balbisiana* (Colla) was developed. Reaction yields was excellent at room temperature where several amines to α,β-unsaturated ketones, esters (specially Baylis-Hillman adducts) and nitriles has been carried out efficiently in water. Bio-catalysts used in the reaction can be reused for several times. *Bis*-product formation can be controlled by varying the ratio of substrates in this environmentally benign procedure, which has provided clean formation of the products with good selectivity.

KEYWORDS

β-Aminocarbonyl, β-Aminonitrile, Aza-Michael, Biocatalyst, *Musa balbisiana* (Colla).

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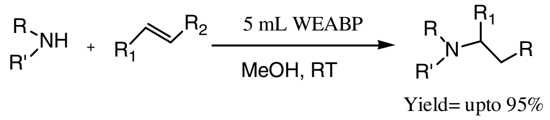
INTRODUCTION

The importance of β-aminocarbonyl as well as β-aminonitriles compounds such as β-amino alcohols, 1,2-diamines and β-lactams [1-3] are because of their use as precursor of many natural products and pharmaceutically active molecules [4-7]. Since Mannich reaction [8,9] is a method for the synthesis of β-amino carbonyl compounds, but the method is limited due to several drawbacks in the direction of time, yield and substrate variability. An alternative method for synthesizing β-aminocarbonyl compound is aza-Michael reaction [10-12]; which is a described as a modified form of Michael reaction for conjugate addition of amines to electron deficient alkenes in presence or absence of catalyst with limited substrates. Due to reasons like atom economy and high selectivity, this reaction is growing interest for preparation of different precursor for biologically active natural products as well as pharmaceutically active molecules. Literature reveals a number of catalysts such as $PdCl_2(MeCN)_2$ [13], $InCl_3$ [14], $CeCl_3 \cdot H_2O$ [15], $Yb(OTf)_3$ [16], SmI_2 [17], $Cu(OTf)_2$ [18], $Bi(NO_3)_3$ [19], $Bi(OTf)_3$ [20], $LiClO_4$ [21], $FeCl_3 \cdot 6H_2O$ [22], $SnCl_4$ [23], molecular iodine [24], bases [25-27], ionic liquids [28-31], $FeCl_3$/montmorillonite K10 [32] and others [33-35], *etc*. Ranu *et al.* [34], Kwong *et al.* [36] and Jiang *et al.* [37] reported catalyst free and solvent free protocol with a few activated alkenes and amines.

The ash obtained from peel of *Musa balbisiana* (Colla), the banana fruit commonly known as bhim koll (banana), available in North-East India, rich in potassium carbonate, potassium chloride and other bases [38] are used as food additive, salt substitute and cleansing agent among rural people. Since banana peels contain potassium, sodium, carbonate and chloride as major constituents along with a number of other trace elements and many reactions are known in literature using this eco-friendly catalyst [39-42]. In continuation of our studies on aza-Michael reaction [40,41], here we report a novel protocol using water extract of ash of banana plant (WEABP). To best of our knowledge, there is no such protocol available in literature for aza-Michael reaction (**Scheme-I**), which falls under the criteria of sustainable chemistry.



R=R'=aryl, benzyl, alkyl
R_1= PhCO, PhCH(OH), $NO_2C_6H_4CH(OH)$, $ClC_6H_4CH(OH)$, 2,4-$Cl_2C_6H_3$
R_2= COOMe, CN, Ph, WEABP = water extract of ash of banana plant

Scheme-I

In this report a primary, secondary and less reactive amine such as imidazole and less reactive α,β-unsaturated compound such as chalcone, Baylis-Hillman adducts (prepared by existing procedure) [42] are employed to get the product in good yield in a few minutes and for reactive substrates time is only reduced. An advanced improved method, free from tedious process of purification was developed; where in relatively larger scale *i.e.* more than 2g scale, pure products can be obtained after washing the crude product with water and the water part can be reused for three times after concentrating the aqueous part.

EXPERIMENTAL

All the reagents used were purchased from Sigma Aldrich and used without further purification.. IR spectra were recorded on a SHIMADZU FTIR-8400. NMR spectra for ^{1}H and ^{13}C were recorded on advance DPX 300 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal reference and $CDCl_3$ and CD_3OD as solvents. Mass spectra were recorded on ESQUIRE 3000 Mass spectrometer. Melting points were recorded with a Buchi B-540 melting point apparatus. All the reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck) and visualization of the plates were done in iodine chamber for all products and UV active materials were visualized under UV illumination at 254 nm. Further visualization was done in H_2SO_4-anisaldehyde stain.

Experimental procedure for synthesis of aza-Michael adduct: In a template reaction, a mixture of benzylamine (0.107 g, 1 mmol) and acrylonitrile (0.053 g, 1 mmol) was added in 5 mL 20 weight % of water extract of ash of banana plant (WEABP) at room temperature. To the above solution 2 mL of methanol was added and stirred. The progress of the reaction was monitored by using TLC. After completion of the reaction, solid crude product was isolated from water by filtration. In case of gummy products, ethyl acetate was used to extract the product from aqueous medium.

Spectral data of 2-(benzylaminomethyl)-3-hydroxy-3-phenylpropanoic acid methyl ester (entry 7): White solid, melting point 45 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.27 (m, 10H), 5.11 (d, *J* = 6.3 Hz, 1H), 3.8-3.7 (m, 1H), 3.75 (d, *J* = 3.9 Hz, 1H), 3.62 (s, 3H), 3.06-3.00 (m, 1H), 2.9 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.61, 141.75, 139.39, 128.54, 128.32, 124.24, 128.03, 127.63, 127.25, 74.98, 53.82, 51.76, 48.34; IR (Thin film on KBr plate) 3425, 3313, 3066, 2912, 1728, 1597, 1446, 1269,1026 cm^{-1}; MS (ESI) *m/z* 299 (M+); Elemental analysis: C, 72.22; H, 7.07; N, 4.68; found:72.10, H, 7.50; N, 4.62.

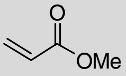
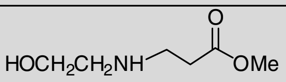
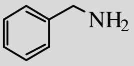
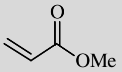
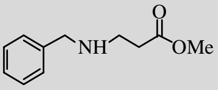
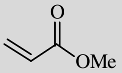
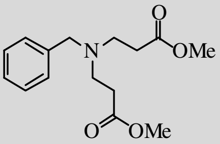
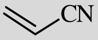
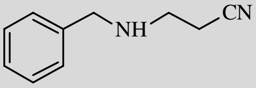
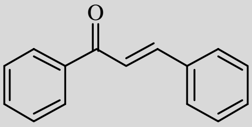
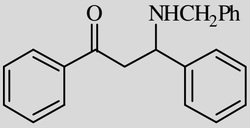
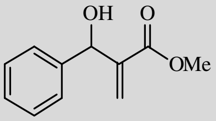
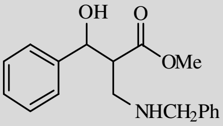
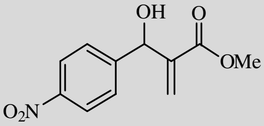
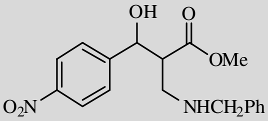
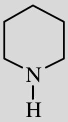
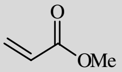
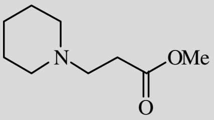
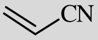
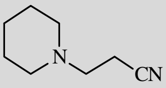
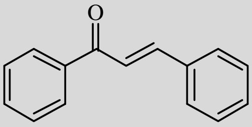
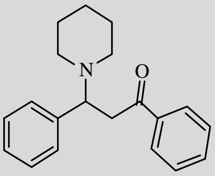
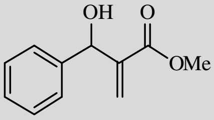
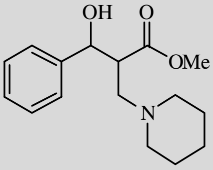
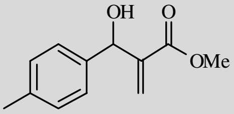
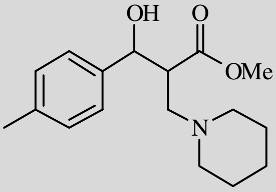
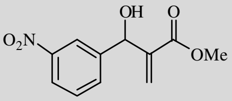
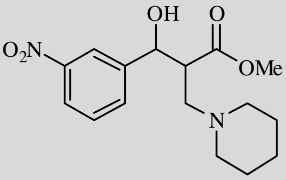
RESULTS AND DISCUSSION

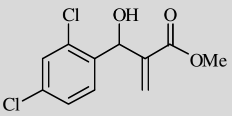
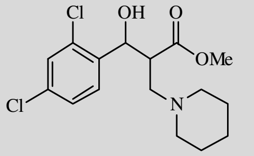
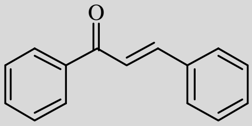
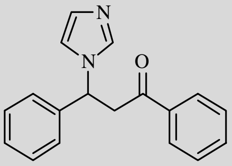
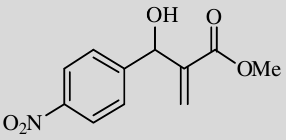
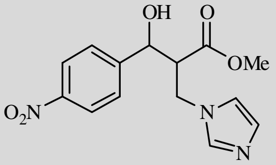
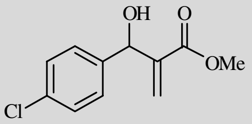
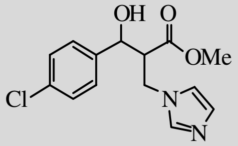
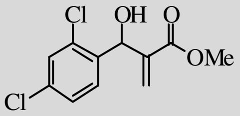
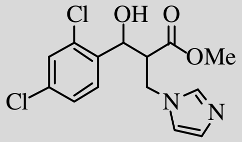
Preliminary reaction was focused to investigate the catalytic action of water extract of the ash of banana plant (WEABP) on a template reaction of benzylamine and acrylonitrile 1:1 molar ratio in methanol to get the product. Several trial and error reactions were performed to standardize the reaction condition using different catalyst loadings as well as solvents. Effect of solvent was studied using solvents like dichloromethane, tetrahydrofuran, acetonitrile, ash of banana plant (ABP) without solvent and water extract of ash of banana plant and methanol; where water extract of the ash of banana plant in methanol was the best choice for the transformation. It was observed that the water extract of 20 weight % of the catalyst was enough to catalyze the reaction.

Owing to the solubility of the amine in water, the model reaction was examined in neat water extract of the ash of the banana plant. A very clean reaction was observed with 95 % yield in 15 min. For this reaction both template substrates were taken in 1:1 molar ratio in 5 mL of water extract of the ash of banana plant and 2 mL of MeOH. It was observed that neat water extract of the ash of banana plant is more effective than ash of banana plant in catalyzing the conjugate addition both in terms of yields and time. The rate enhancement using water extract of the ash of banana plant is probably due to water forms hydrogen bond with the oxygen atom of the carbonyl group of α,β-unsaturated carbonyl compound thereby increasing the electrophilicity of β-carbon, where the nucleophilic amine attacks. On the other hand water enhances the nucleophilicity of N-atom of amine with its oxygen atom. Thus, water activates both the conjugated alkene as well as the amine and thereby greatly facilitates the addition. Besides that, the main basic component CO_3^{2-} present in the water extract also helps in accelerating the reaction more.

The scope of substrates for this reaction was studied using a wide range of nitrogen nucleophiles such as primary, secondary (both acyclic and cyclic) and aromatic amines with a number of electron deficient species including Baylis-Hillman adducts. The results are summarized in Table-1. Formation of *bis*-addition product in case of primary amines can be controlled by taking substrates (amine and alkene) in 1:1 ratio, where *bis*-product formation was observed if the ratio was 1:2. A few Baylis-Hillman adducts were used as active electrophiles successfully with a good yield. It was observed that steric effect on the substituted alkene have an important role on reaction rate. Baylis-Hillman adducts with a free methylene group and other active alkenes like acrylonitrile, methyl acrylate underwent

TABLE-1
AZA-MICHAEL REACTION OF AMINES TO α,β-UNSATURATED COMPOUNDS

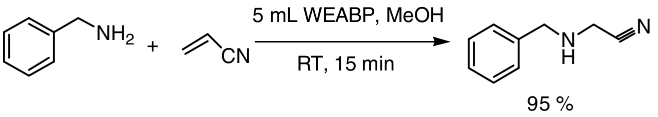
Entry	Amines (A)	α,β-unsaturated compounds (B)	Product	Time (min)	Yield^{b,c} (%)	Ref.
1	HOCH$_2$CH$_2$NH$_2$			5	87	[40]
2				15	90	[25]
3				20	90	[41]
4				10	95^{c}	44
5				25	94	[43]
6				15	90	[41]
7				10	92	[41]
8				15	90	[41]
9				10	89	[41]
10				20	90	[21]
11				15	87	[41]
12				12	90	[41]
13				15	89	[41]

14			14	90	[41]
15			30	92	[44]
16			25	89	[41]
17			35	88	[41]
18			45	89	[41]

[a]All the products were characterized by NMR, IR, mass spectrometry and CHN analysis; [b]Isolated yields; [c]Catalyst was recovered and reused for four consecutive runs in this reaction without change in the yield and purity but in a slow reaction rate.

the conjugate addition smoothly where chalcones with intact methylene group reacted slowly.

The recyclability and reusability of the catalyst was investigated by reacting benzylamine and acrylonitrile at room temperature (**Scheme-II**). After the first run, ethyl acetate was added to the reaction mixture and then filtered off and washed with a mixture of 1:1 ethyl acetate and water. The aqueous part was then concentrated to 5 mL and the reactants were added, which gave 80 % yield in 30 min and the water extract of the ash of banana plant can be used up to 4th run to get an effective yield in a slow reaction.



Scheme-II

Conclusion

An eco friendly and green method for aza-Michael reaction promoted by water extract of ash of banana plant in room temperature has been developed. The advantage of this protocol is mostly in the direction of high yield, green solvent, reusability of catalyst and easy extraction method.

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