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ARTICLE

Ultrasound Assisted Cu(I) Catalyzed Aza-Michael Reactions in Water

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ABSTRACT

The β-amino compounds were synthesized from α,β-unsaturated esters, nitriles and amine using water as a solvent in the presence of 10 mol % Cu(I) catalyst in high yields within 2-5 min under ultrasound irradiation at room temperature. The reaction rate was enhanced tremendously under ultrasound irradiation as compared to conventional methods with improved yields have been recorded.

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KEYWORDS

Cu(I) catalyst, Aza-Michael reactions, Ultrasound irradiation, Amine, α,β-Unsaturated compounds.

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INTRODUCTION

Ultrasound technique is widely used in organic synthesis. The ultrasonic irradiation technique is used to reduce the time of reaction. Simple experimental procedure, high yield, more selectivity and clean reactions are the more important aspects of ultrasonic irradiation. Natural products are important intermediates in the synthesis of amino acids and β-lactam antibiotics [1]. The new synthetic routes have been established in organic synthesis. Conjugate addition reactions are quite easy, economic and these reactions require either basic catalyst or acidic catalyst and Lewis acid catalysts [2-4]. In past few years, a number of alternative procedures have been developed to overcome some of these limitations using a variety of catalysts such as palladium [4], $InCl_3$ [5], supported $CeCl_3{\cdot}7H_2O$-NaI [6], $Yb(OTF)_2$ [7], $Bi(NO_3)_2$ [8], $Bi(OTF)_2$ [9], $Cu(OTF)_2$ [10, 11], $LiClO_4$ [12], clay [13], silica gel [14], $FeCl_3$ [15] and KF/alumina [16]. The number of new methods are reported for this reaction such as $ZrCl_4$ [17], cinchona alkaloid [18], hexafluoroisopropyl alcohol [19], silica gel supported over perchloric acid [20], $LaCl_3$ [21], triethylammonium acetate [22], alkaline Al_2O_3 [23], polystyrenesulfonic acid [24], Amberlyst-15 [25], *p*-toluenesulfonic acid under high pressure [26], ionic liquid [27], organocatalyst [28], enzyme [29], tetrabutylammonium bromide [30] and Mg, THF, NH_4Cl [31-33]. However, all the above listed protocols suffers from one or more drawbacks such as prolonged reaction time, use of organic solvents, strong acid or base catalysts, expensive catalysts and harsh reaction conditions. Aza-Michael addition of amine with α,β-unsaturated compounds has been reported in water with boric acid [8,34,36]. But these methods suffer from drawback such as longer reaction time. In green chemistry and pseudo neutral catalysis chemistry, water was used as solvent and substrates [36].

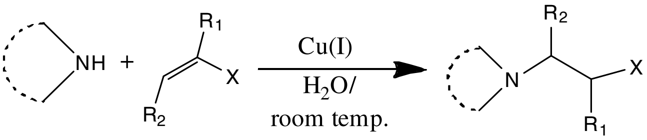
Thus, development of new environmental friendly more effective procedure for the synthesis of β-amino compounds using amine and α,β-unsaturated compounds in water and nitrato*bis*(triphenyl phosphine)copper (I) [$Cu(PPh_3)_2NO_3$] as a catalyst at room temperature.

EXPERIMENTAL

The boiling points of the compounds were determined are uncorrected. The synthesized products were monitored on silica gel G plates by using petroleum ether:ethyl acetate (7:3) as mobile phase. FT-IR spectra were recorded on a Shimadzu Miracle 10 ATR spectrometer. ^{1}H NMR spectra were recorded on a Bruker 500 MHz spectrometer with $CDCl_3$ as solvent and TMS as the internal reference. ^{13}C NMR spectra were recorded on Bruker 125 MHz spectrometer with $CDCl_3$ as solvent. All the compounds were purified by column chromatography using silica gel (70-230 mesh) and solvents peteroleum-ether:ethyl acetate as 7:3. Ultrasonic cleaner was used for ultrasound irradiation with frequency of 33 KHz and a output power of 250 W. Elemental analysis carried out using CHN elemental analyzer. The reaction flask was placed in the maximum energy area of the cleaner.

Synthesis of nitrato*bis*(triphenyl phosphine)copper(I): Triphenyl phosphine (10.5 g, 0.04 mol) and $Cu(NO_3)_2·2H_2O$ (0.01 mol, 2.45 g) was added to 100 mL hot methanol. Immediately, Cu(II) dissolves and white suspension formed. This suspension was refluxed for 10 min and cooled to ambient temperature. Then, solution was filtered, washed with ether, ethanol and dried. Recrystallization from methanol gave colourless solid. m.p.: 232 ºC, soluble in common organic solvents. IR (KBr, ν_{max}, cm^{-1}): 3047, 2924, 1538, 1479, 1464, 1384, 1295, 1096, 810, 741, 693.

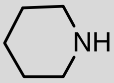
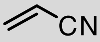
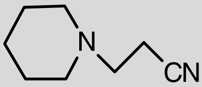
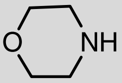
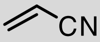
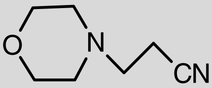
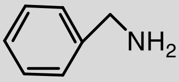
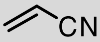
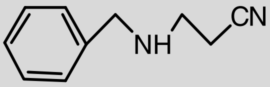
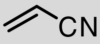
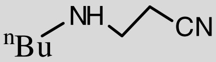
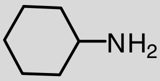
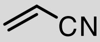
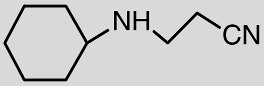
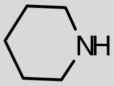
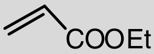
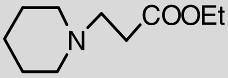
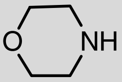
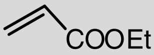
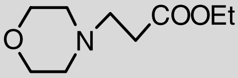
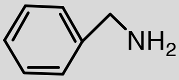
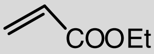
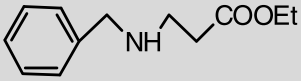
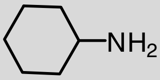
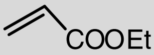
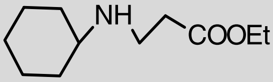
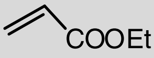
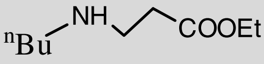
General experimental procedure: Nitratobis(triphenyl phosphine)copper(I) (10 mol % *i.e.* 31 mg) was added in 10 mL of water followed by the addition of amine (10 mmol) and α,β-unsaturated compound (10 mmol) and the whole mixture was irradiated in the water bath of an ultrasonic cleaner at room temperature for the period as shown in Table-1. After completion of the reaction, mixture was extracted with dichloromethane and dried over Na_2SO_4. The extract was then concentrated and the crude product was purified using column chromatography (silica gel 70 % petroleum ether/30 % EtOAc) to afford pure compound (**Scheme-I**). Products are easily identified by comparison of their spectroscopic data.



R_1, R_2 = H; X = CO_2Et, CN

Scheme-I: Michael addition of amines to α,β-unsaturated compound

TABLE-1
Cu(I) CATALYZED CONJUGATE ADDITION OF AMINES TO α, β-UNSATURATED COMPOUND IN WATER AT ROOM TEMPERATURE

Entry	Amine	α,β-Enone	Product	Time (min)	Yield (%)	Ref.
a				2	98	[35]
b				2	97	[8]
c				3	92	[35]
d	*n*-BuNH$_2$			4	93	[35]
e				3	90	–
f				2	98	–
g				2	98	–
h				3	92	–
i				3	90	–
j	*n*-BuNH$_2$			4	93	–

Spectral data

3-(Cyclohexylamino)propane nitrile (e): Colourless liquid, IR(KBr, ν_{max}, cm^{-1}): 3298, 2915, 2230, 1710, 1222; ^{1}H NMR δ ppm: 1.21-2.57 (m, 11H), 2.1 (s, 1H), 2.92 (t, *J* = 7Hz, 2H), 3.03 (t, *J* = 7Hz, 2H); ^{13}C NMR δ ppm: 19.6 (1C), 25.1(2C), 25.7(1C), 34.3(2C), 42.6(1C), 59.3(1C), 119.0 (1C); Anal. calcd. (found) % for $C_9H_{16}N_2$: C, 71.01 (71.05); H, 10.59 (10.45); N, 18.40 (18.43).

Ethyl 3-(piperidin-1-yl)propanoate (f): Colourless liquid, IR (KBr, ν_{max}, cm^{-1}): 3275, 2889, 1737, 1680, 1190, 1140; ^{1}H NMR δ ppm: 1.29 (t, *J* = 7 Hz, 3H), 4.13 (q, *J* = 7 Hz, 2H), 2.49 (t, *J* = 7 Hz, 2H), 3.76 (t, *J* = 7 Hz, 2H); 1.53-2.45 (m, 10H); ^{13}C NMR δ ppm: 14.1(1C), 24.5(1C), 25.9(2C), 32.3 (1C), 52.8(1C), 56.8(2C), 61.3(1C); 171.1(1C); Anal. calcd. (found) % for $C_{10}H_{19}NO_2$: C, 64.83 (64.81); H, 10.34 (10.37); N, 7.56 (7.52); O, 17.27 (17.31).

Ethyl 3-morpholinopropanoate (g): Colourless liquid, IR (KBr, ν_{max}, cm^{-1}): 3290, 2895, 1740, 1682, 1195, 1135; ^{1}H NMR δ ppm: 1.29 (t, *J* = 7 Hz, 3H), 4.13 (q, *J* = 7 Hz, 2H), 2.49 (t, *J* = 7 Hz, 2H), 3.76 (t, *J* = 7 Hz, 2H); 2.36-3.65 (m, 8H); ^{13}C NMR δ ppm: 14.1(1C), 32.3(1C), 52.8(1C), 55.8(2C), 61.3 (1C), 66.7(2C), 171.2(1C); Anal. calcd. (found) % for $C_9H_{17}NO_3$: C, 57.73 (57.65); H, 9.15 (9.20); N, 7.48 (7.5); O, 25.64 (25.60).

Ethyl 3-(benzylamino)propanoate (h): Colourless liquid, IR (KBr, ν_{max}, cm^{-1}): 3311, 2887, 1745, 1550, 1187, 1134; ^{1}H NMR δ ppm:1.29 (t, *J* = 7 Hz, 3H), 4.13 (q, *J* = 7 Hz, 2H), 2.2 (s, 1H), 2.51 (t, *J* = 7 Hz, 2H), 2.94 (t, *J* = 7 Hz, 2H), 3.76 (s, 2H), 7.23-7.33 (m, 5H); ^{13}C NMR δ ppm: 14.1(1C), 36.1(1C), 48.5 (1C), 52.3(1C), 61.3(1C), 127.0(1C), 127.9(2C), 128.5(2C), 140.2(1C), 171.3(1C); Anal. calcd. (found) % for $C_{12}H_{17}NO_2$: C, 69.54 (69.50); H, 8.27 (8.25); N, 6.76 (6.70); O, 15.44 (15.41).

Ethyl 3-(cyclohexylamino)propanoate (i): Colourless liquid, IR (KBr, ν_{max}, cm^{-1}): 3307, 2910, 1742, 1695, 1190, 1132; ^{1}H NMR δ ppm: 1.29 (t, *J* = 7 Hz, 3H), 4.13 (q, *J* = 7 Hz, 2H), 2.51 (t, *J* = 7 Hz, 2H), 2.94 (t, *J* = 7 Hz, 2H); 2.1 (s, 1H), 1.21-2.57 (m, 11H); ^{13}C NMR δ ppm: 14.1(1C), 25.1(2C), 25.7(1C), 34.3(2C), 36.4(1C), 46.7(1C), 59.8(1C), 61.8(1C), 171.3(1C); Anal. calcd. (found) % for $C_{11}H_{21}NO_2$: C, 66.29 (66.30); H, 10.62 (10.65); N, 7.03 (7.01); O, 16.06 (16.09).

Ethyl 3-(butylamino)propanoate (j): Colourless liquid, IR (KBr, ν_{max}, cm^{-1}): 3310, 2905, 1742, 1192, 1097; ^{1}H NMR δ ppm: 1.29 (t, *J* = 7 Hz, 3H), 4.13 (q, *J* = 7 Hz, 2H), 2.51 (t, *J* = 7 Hz, 2H), 2.94 (t, *J* = 7 Hz, 2H); 2.1(s, 1H), 2.55 (t, *J* = 7 Hz, 2H), 1.38 (q, *J* = 7 Hz, 2H), 1.31 (s, *J* = 7 Hz, 2H), 0.90 (t, *J* = 7 Hz, 3H); ^{13}C NMR δ ppm: 13.8(1C), 14.1(1C), 20.1(1C), 32.7(1C), 36.1(1C), 48.9(1C), 49.3(1C), 61.3(1C), 171.2(1C); Anal. calcd. (found) % for $C_9H_{19}NO_2$: C, 62.39 (62.35); H, 11.05 (11.07); N, 8.08 (8.05); O, 18.47 (18.50).

RESULTS AND DISCUSSION

The effect of reaction conditions on the formation of 1,4-additions under ultrasound irradiation is summarized in Table-2.

The reaction was initiated by the nucleophilic addition of amine to α,β-unsaturated compounds resulting in the formation of 1,4-addition product. Inspired by this result, a variety of reaction conditions were explored in order to optimize the catalytic process.

TABLE-2
SCREENING OF SOLVENT FOR SYNTHESIS OF
A UNDER ULTRASOUND IRRADIATION

Entry	Catalyst	Solvent	Time (min)	Yield (%)
1	$Cu(PPh_3)_2NO_3$	Tetrahydrofuran	50	40
2	$Cu(PPh_3)_2NO_3$	Ethanol	50	58
3	$Cu(PPh_3)_2NO_3$	Methanol	50	45
4	$Cu(PPh_3)_2NO_3$	Dichloromethane	50	35
5	$Cu(PPh_3)_2NO_3$	Acetone	50	45
6	$Cu(PPh_3)_2NO_3$	Acetonitrile	50	48
7	Catalyst free	Water	10	80
8	$Cu(PPh_3)_2NO_3$	Water	2	98

The effect of different solvents with 10 mmol piperidine and 10 mmol acrylonitrile in 10 mL water and 10 mol % Cu(I) catalyst was evaluated. Moderate yields of the products were obtained when tetrahydrofuran, dichloromethane, acetone, ethanol, methanol, acetonitrile were used as solvent under ultrasound irradiation for 50 min in the presence of Cu(I) catalyst (entries 1-6, Table-2). A desired product was isolated in 98 % within 2 min in the presence of water and Cu(I) catalyst. Same reaction was carried out in water without catalyst, 80 % yield was obtained. A controlled experiment confirmed that nitrato*bis*-(triphenyl phosphine)copper (I) [$Cu(PPh_3)_2NO_3$] catalyst was essential for the formation of β-amino compounds because Cu(I) catalyst decrease the reaction time and increases the yield of products. When reaction was performed at room temperature Cu(I) catalyst forms complex with negatively charge oxygen or nitrogen, so that rate of abstraction of proton increases due to delocalization of negative charge and hence rate of reaction increases.

α,β-Unsaturated compound such as ethyl acrylate and acrylonitrile undergo 1,4-addition with wide range of aliphatic amines in the presence of 10 mol % Cu(I) catalyst at room temperature to give the corresponding β-amino compounds in high yields with short reaction time. In general, secondary amines gave higher yields than primary amines. In order to investigate the aza-Michael condensations involving aromatic amines, a product was not detected.

Conclusion

In the present investigation, a series of novel β-amino derivatives have been synthesized by using nitrato*bis*(triphenyl phosphine)copper (I) [$Cu(PPh_3)_2NO_3$] as a catalyst under ultrasound irradiation. The short reaction time, easy workup and high yields made this protocol efficient.

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