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A green alternative approach for synthesis of 2-substituted-5,6-dihydro-4*H*-1, 3-oxazines catalyzed by NBS: Ultra Sonication

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ABSTRACT

Commercially available N-Bromosuccenamide (NBS)is reported as an extremely efficient catalyst for the synthesis of 2-aryl/hetero aryl-5, 6-dihydro-4H-1,3-oxazines by ultrasound irradiation of 3-aminopropanol with different aryl/ heteroaryl aldehydes took place in one pot under aqueous medium at 70 ^{o}C, gives high yields in shorter reaction times. The reactions proceeded with extremely high efficiency under mild conditions and gave good yields. The proposed methods were found to be suitable and accurate for rapid synthesis of substituted 5, 6-dihydro-4H-1,3-oxazines derivatives available. All the newly synthesized compounds were characterized by IR, ^{1}H and ^{13}C NMR.

Keywords: 3-Amino propanol, Aldehyde, N-Bromosuccenamide (NBS), Ultra sound irradiation, 1,3-Oxazines.

INTRODUCTION

1,3-Oxazines are unique and useful in bio-active functions like antibiotics[1-4], antitumor[5-7], analgesics[8,9], anticonvulsants[10], and hepatoprotectants[11]. Recently various methodologies have been developed for the synthesis 1,3-Oxazines by using nitriles[12], carboxylic acids[13], aldehydes[14], 3-amino propanol[12,13], *N*-thioacyl 1,3-amino alcohols[15], 1,3-hyroxy azide and 2,3-allenamides[16] as substrates. Different catalysts were used like zeolite, Ersorb-4[13], Lewis acids[14], palladium-phosphine[17], nano-SiO_2, trichlorosilane[18], $H_3PW_{12}O_{40}$[19], alum[20] and some ionic liquids, 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim] [H_2SO_4] [21]. However, still there remains a need to develop a more efficient method, particularly keeping in view the disadvantages associated with some of the reported procedures such as the requirement of solvent, additional reagents, heating, long time, costly and moisture sensitive catalysts, special apparatus, etc., and also work up process to remove catalyst after the reaction by using the above catalysts is difficult and hazardous.

In such consequence we have developed a new protocol for the preparation of 1,3-Oxazines in aqueous media with short times and high yields. In our present work, we unzip our results for

preparation of 1,3-Oxazines in aqueous medium under the aspect of environmentally benign process with high yields which is superior to above methods. In order to avoid the above disadvantages we used the aqueous medium under ultra sound irradiation in presence of NBS to accomplish good results. NBS is trouble-free for work up process which is simply soluble in water medium.

METERIALS AND METHODS

Chemicals were procured from Sigma–Aldrich and Merck were used as such without further purification. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods [22]. Melting points (m.p) were determined using a calibrated thermometer by Guna Digital Melting Point apparatus. They expressed in degrees centigrade (^{o} C) and are uncorrected. Infrared Spectra (IR) were obtained on a Perkin-Elmer Model 281-B spectrophotometer. Samples were analyzed as potassium bromide (KBr) disks. Absorptions were reported in wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The ^{1}H and ^{13}C chemical shifts were expressed in parts per million (ppm) with reference to tetramethylsilane (TMS). LC-MS mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer. Ultra sonication was performed using BANDELIN SONOREX® (Germany) 4D ultrasound cleaner with a frequency of 50 KHz and an output power of 480 W.

General procedure for synthesis of 1,3-oxazines:
Sonication Method
4-Chlorobenzaldehyde **1** (0.140 g, 0. 001 mol), 3-amino propanol **2** (0.091 mL, 0. 0012 mol) were taken in water (10 mL) and irradiated by ultrasound for 3 min at room temparature. After formation of Schiff's base, NBS (0.213 g, 0. 0012 mol) is added and raised the temperature to 70 ^{o}C and irradiated until the completion of starting compounds. The reaction progress was monitored by thin layer chromatography (TLC), ethyl acetate: hexane (3:2). After completion of the reaction, 20% NaOH solution was added and extracted with ethyl acetate. Solvent was removed in a rota-evaporator to afford the title compound, 2-(3-chlorophenyl)-5,6-dihydro-4H-1,3-oxazine (**3a**). The same experimental procedure was adopted for the preparation of the remaining title compounds **3b-r**.

Conventional Method
To a stirred solution of 4-Chlorobenzaldehyde **1** (0.140 g, 0.100 mmol) solution, 3-amino propanol **2** (0.091 mL, 0.120 mmol) was added in water (10 mL) and stirred for 20 min at room temperature to this NBS (0.213 g, 0.120 mmol) is added and raised the temperature to 80^{o}C and refluxed until the completion of starting compounds. The reaction progress was monitored by thin layer chromatography (TLC), ethyl acetate: hexane (3:2). After completion of the reaction, 20% NaOH solution was added and extracted with ethyl acetate. Solvent was removed in a rota-evaporator and was purified by silica gel column chromatography eluting with ethyl acetate: hexane (2:3) mixture to afford the title compound, 2-(3-chlorophenyl)-5,6-dihydro-4H-1,3-oxazine (**3a**). The same experimental procedure was adopted for the preparation of the remaining title compounds **3b-r**.

Spectral data for selected compounds.
2-(4-Chlorophenyl)-5,6-dihydro-4H-1,3-oxazine **3b**: Colorless oil. IR (KBr) $\bar{\nu}$: 1091, 1235, 1660 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92 (quint, J = 5.8 Hz, 2H), 3.55 (t, J = 5.5 Hz, 2H), 4.52 (t, J = 5.6 Hz, 2H), 7.32–7.37 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ22.2, 42.4, 65.8, 126.5, 129.2, 131.2, 136.9, 152.4.

2-(4-Bromophenyl)-5,6-dihydro-4H-1,3-oxazine **3d**: Colorless oil. IR (KBr) $\bar{\nu}$: 1074, 1229, 1657 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.82 (quint, J = 5.8 Hz, 2H), 3.52 (t, J = 5.5 Hz, 2H), 4.49 (t, J = 5.6 Hz, 2H) 7.41–7.45 (m, 2H), 7.58 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ23.1, 41.5, 67.2, 127.2, 129.3, 130.9, 132.8, 153.4.

2-(4-Pyridyl)-5,6-dihydro-4H-1,3-oxazine **3h**: Yellow oil. IR (KBr) $\bar{\nu}$: 1044, 1276, 1652 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.65 (quint, J = 5.6 Hz, 2H), 3.62 (t, J = 6.6 Hz, 2H), 4.50 (t, J = 5.4 Hz, 2H), 8.08 (m, 2H), 8.95 (d, J = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ22.6, 43.4, 62.8, 125.2, 146.2, 150.2, 158.2.

2-(5-Bromo-2-nitrophenyl)-5,6-dihydro-4H-1,3-oxazine **3j**: Yellow oil, IR (KBr) $\bar{\nu}$:1069, 1270, 1620 cm^{-1}. ^1H NMR (400 MHz, DMSO-*d6*): δ 1.88 (p, J = 5.7 Hz, 2H), 3.59 (t, J = 6.0 Hz, 2H), 5.55 (t, J = 5.4 Hz, 2H), 7.41 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.8, 43.1, 56.2, 125.8, 128.6, 130.8, 135.4, 136.2, 147.7, 158.2;

2-(2,4-Dichlorophenyl)-5,6-dihydro-4H-1,3-oxazine **3l**: Brown solid, mp. 53-55 ^oC, IR (KBr) $\bar{\nu}$: 1074, 1263, 1642 cm^{-1}. ^1H NMR (400 MHz, DMSO-*d6*): δ 1.81 (quint, J = 5.1 Hz, 2H), 3.60 (t, J = 5.7 Hz, 2H), 5.62 (t, J = 5.4 Hz, 2H), 7.47 (d, J = 7.1 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.1, 42.5, 57.1, 128.1, 128.9, 130.5, 133.5, 136.3, 136.9, 157.9;

4-(5,6-Dihydro-4H-1,3-oxazin-2-yl)-N,N-dimethylaniline **3m**: Reddish brown oil, IR (KBr) $\bar{\nu}$: 1050, 1270, 1640 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.92 (quint, J = 5.7 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 3.99 (s, 6H), 5.67 (t, J = 5.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.1,39.3, 42.6, 65.1, 113.3, 123.4, 126.8, 155.3, 161.4;

2-(5-Bromothiophen-2-yl)-5,6-dihydro-4H-1,3-oxazine **3o**: Brown oil, IR (KBr) $\bar{\nu}$: 1072, 1242, 1520, 1615cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.3 (quint., J = 5.7 Hz, 2H), 4.08 (t, J = 5.8 Hz, 2H), 4.66 (t, J = 5.5, 2H), 7.18 (d, J = 5.0 Hz, 1H), 7.45 (d, J= 3.7 Hz, 1H), ppm . ^{13}C NMR (100 MHz, $CDCl_3$): δ22.4, 42.2, 64.8, 116.3, 125.6, 130.7, 131.4, 155.1.

2-(1H-Pyrrol-2-yl)-5,6-dihydro-4H-1,3-oxazine **3p**: IR (KBr) $\bar{\nu}$: 1066, 1252, 1631cm^{-1}. ^1H NMR (400 MHz, DMSO-*d6*): δ 1.32 (quint, J = 5.6 Hz, 2H), 3.9 (t, J = 5.7 Hz, 2H), 4.3 (t, J = 5.5 Hz, 2H), 6.25 (dd, 1H), 6.61(m, J = 7.2 Hz, 1H), 7.11 (m, 1H), 9.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.6, 43.1, 57.2, 110.4, 114.9, 118.7, 121.4, 156.9;

2-(2-Chloro-6-fluorophenyl)-5,6-dihydro-4H-1,3-oxazine **3q**: Yellow oil, IR (KBr) $\bar{\nu}$: 1071, 1263, 1638 cm^{-1}. ^1H NMR (400 MHz, DMSO-*d6*): δ 1.91 (quint, J = 5.7 Hz, 2H), 3.41 (t, J = 6.1 Hz, 2H), 5.41 (t, J = 5.7 Hz, 2H), 7.35 (m, 1H), 7.38 (m, 1H), 7.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.5, 43.5, 59.6, 116.4, 125.7, 126.2, 135.2, 135.9, 163.5, 157.6;

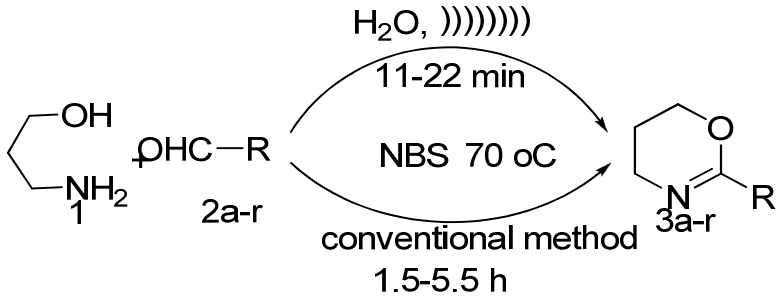
RESULTS AND DISCUSSION

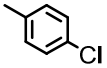
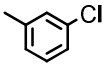
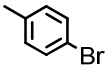
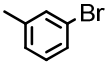
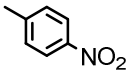
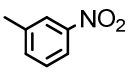
In continuation of our work to develop new and eco-friendly synthetic methodologies [23], we herein report an efficient, green and facile protocol for the synthesis of 2-substituted-5,6-dihydro-4H-1,3-oxazines (3**a-r**) catalyzed by NBS under ultrasound irradiation at 70 °C in 13-25 min (Scheme 1) and also conventional method. Among these two methods Sonication was found to be better method giving high yields in less reaction time. Ultra sound will increase the collisions between the molecules and causes to form radicals very fast. So the rate of the reaction

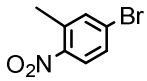
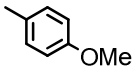
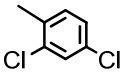
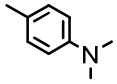
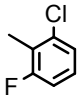
was increased. Here the solvent is water which is very effective solvent for the oxidation of C-N bond for NBS and is also gracious to environment.

By using various aldehydes we had found that, aldehydes having electron withdrawing group at ortho and para positions (**2b**, **2d**, **2f**, **2j**, **2l** & **2q**) will undergo fast reaction and gives the high yields when compared with the meta position (**2c**, **2e** & **2g**) and electron donating groups (**2k & 2m**). Due to the presence of withdrawing group at ortho or para positions of aldehyde, the attraction of radical electron from oxygen and the removal of hydrogen radical were took place easily.

All compounds were characterized by IR, ^{1}H and ^{13}C NMR spectra. The IR band was not observed in the region of 3200-3600 cm^{-1}, which is characteristic to hydroxyl group, indicating that the OH group had reacted. Characteristic absorption bands for C-O-C and C=N stretching vibrations were observed in the regions 1044-1074 and 1640-1660 respectively [24]. The chemical shifts of ^{1}H NMR spectra observed in the regions δ 1.62-1.98, 3.51-3.65, 4.45-5.20 were indicating CH_2-$C\underline{H}_2$-CH_2, O-CH_2, N-CH_2 respectively [14]. When we perceive the ^{13}C NMR the chemical shifts in the regions δ 21.9-22.6, 41.5-45.6, and 62.2-67.5 stand for CH_2-$\underline{C}H_2$-CH_2, N-$\underline{C}H_2$ and O-$\underline{C}H_2$ respectively.Based on the above spectral data, we confirm the 2-substituted-5,6-dihydro-4H-1,3-oxazine structures [12].



Entry	R	Product	Sonication Method	Conventional Method
			Time(min)/Yield(%)	Time(h)/Yield(%)
1		**3a**	15/95	4/82
2		**3b**	14/93	2.3/78
3		**3c**	16/84	3.2/70
4		**3d**	18/90	2.5/76
5		**3e**	21/89	3/72
6		**3f**	16/88	4/75
7		**3g**	19/80	5.5/70
8		**3h**	22/90	4/80
9		**3i**	18/82	2/77

10		**3j**	14/93	2.4/72
11		**3k**	19/85	4/71
12		**3l**	12/94	1.5/81
13		**3m**	17/89	2.5/70
14		**3n**	18/90	2/70
15		**3o**	16/90	2/74
16		**3p**	20/91	5/78
17		**3q**	11/93	2.2/79
18		**3r**	16/89	3.3/71

Sheme 1. ***Synthesis of 2-substituted-5,6-dihydro-4H-1,3-oxazines*** **(3a-r).**

CONCLUSION

In conclusion, we have developed an eco-friendly method for the synthesis of 1,3-oxazines by the reaction of aldehydes and 3-aminopropanol using NBS catalyst in aqueous medium to afford good yields. Some of the major advantages of this protocol are the ambient conditions, very high yields, short reaction times, simple work-up procedure. Usage of water as a solvent for chemical reactions will diminishes the cost, safe and environmental friendly. These advantages not only make this methodology as an alternative platform to the preparation of 2-substituted-5,6-dihydro-4H-1,3-oxazines and is significant under the umbrella of greener and safer processes.

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