POLYCYCLIC AROMATIC COMPOUNDS
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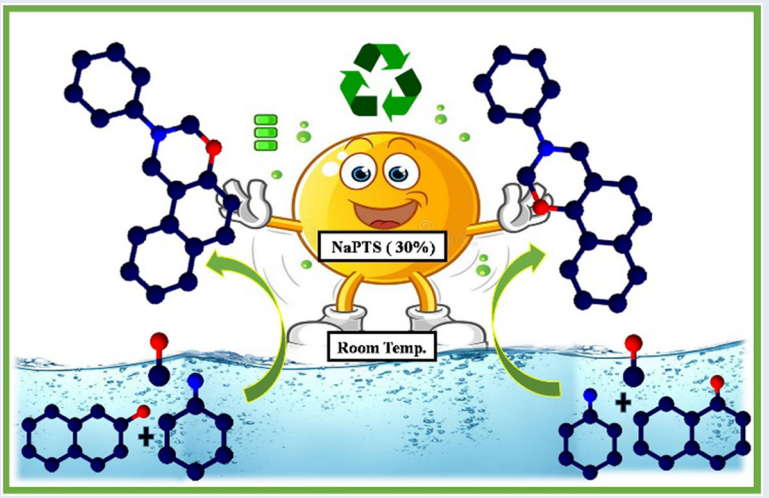
Clean and Green Approach for Synthesis of Various Derivatives of [1,3]Oxazine in Sustainable Aqueous Hydrotropic Medium

Aboli Sapkal, Suraj Attar, Avdhut Kadam, Pramod Gaikwad, and Santosh Kamble

Department of Chemistry, Yashavantrao Chavan Institute of Science, Satara, India

ABSTRACT

An efficient and sustainable synthesis of 2,3-dihydro-2-phenyl-*1H*-naphtho[1,2-e] [1,3]Oxazine and 3,4-dihydro-3-phenyl-*2H*-naphtho[2,1-e][1,3]oxazine derivatives has been achieved by the one-pot, multicomponent condensation of α- or β-naphthol (1 mmol), an aniline (1 mmol) and formaldehyde (2 mmol) using aq. 30% NaPTS hydrotropic solution at room temperature. The aqueous hydrotropic medium is nontoxic, reusable, inexpensive, and easily available. This improved strategy allows the very comfortable preparation of a wide variety of substituted [1,3]Oxazine derivatives under mild reaction conditions with a maximum yield of up to 92%, easy isolation of purified compounds, and an eco-friendly approach under sustainable development. This organic transformation shows a clean and green protocol for the synthesis of 2,3-dihydro-2-phenyl-*1H*-naphtho[1,2-e] [1,3]oxazine and 3,4-dihydro-3-phenyl-*2H*-naphtho[2,1-e][1,3]oxazine derivatives.



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Introduction

In multicomponent reactions (MCRs), three or more different starting materials react to form a final product. The MCRs are assembled products as per a cascade of elementary chemical

CONTACT Santosh Kamble santosh.san143@gmail.com Department of Chemistry, Yashavantrao Chavan Institute of Science, Satara, India

reactions.[1] These reactions, which favor covalent bonds between the reacting molecules, have been of considerable importance in the field of synthetic organic chemistry. In particular, MCRs allow the molecular complexity and diversity to develop importance of synthetic chemistry in a one-pot transformation, and this class of reactions has found widespread applications in synthetic organic and medicinal chemistry.[2] The combination of MCRs and heterocyclic chemistry is a very important concept in organic synthesis. The efficiency of MCRs is evident in the synthesis of a series of heterocyclic scaffolds. Therefore, the development of multicomponent reactions has become an active and challenging topic in the modern era of organic chemistry, which provides better atom-economic access to a wide spectrum of compounds.[3–5] MCRs are better routes for those reactions that transform simple and readily available substrates into complex molecules in a single one-pot reaction, which is a major task in organic synthesis. According to this, MCRs noticeably show simplicity, reactivity, and atom-economy. The main advantages of MCRs are fully automated synthesis, that is, there is no need to separate intermediate forms in reaction. Reaction proceeds in only one vessel, which avoids the use of complex equipments.[6,7] The varieties of nitrogenous compounds are built up by the Mannich reaction, and it has been widely used to introduce oxazine into a variety of organic compounds.[8–10] Because of their important biochemical properties, heterocyclic compounds containing N=O-atoms have received a lot of attention.[11] The naphthoxazine and its derivatives have anti-cancer, anti-tubercular, anti-bacterial, anti-convulsant, and analgesic properties.[12] These compounds have attracted far more interest due to their therapeutic potential for the treatment of Parkinson's disease.[13] The non-nucleoside reverse transcriptase inhibitor[14] trifluoromethyl 1,3-oxazine-2-one, shows high activity against a variety of HIV-1 mutant strains.[15] Therefore, Figure 1 shows the structures of some biologically active [1,3]oxazines such as anti-tumour, anti-Parkinson and potent non-steroidal progesterone receptor agonists.

For the synthesis of 1,3-Oxazine, various catalysts were used, including palladium-phosphine,[16] Zeolite Erbos-4,[17] chiral Lewis base ((S)-BINAPO) with trichlorosilane[18] Lewis acids,[19] $H_3PW_{12}O_{40}$,[20] alum,[21] SiO2. NaCl[22] and several methods for this transformation have been reported, including the use of solvent free,[23] carboxylic acids,[24] aldehydes,[25] N-thioacyl 1,3-amino alcohols,[26] K_2CO_3 or $Cs_2CO_3$27 as well as some ionic liquids, 1-benzyl-3-methyl imidazolium hydrogen sulfate [bnmim] [HSO_4],[28] 1-butyl-3-Methyl imidazolium hydrogen sulfate [bmim]HSO4-ionic liquid with a phase transfer catalyst (PTC) such as tridecyl trimethyl amonium bromide (TDTMAB),[29] ultrasonicated with BF_3-SiO_2.[30]

Chemical synthesis via green chemistry addresses our future challenges in working with chemical processes by inventing novel reactions that can maximize the desired products and minimize

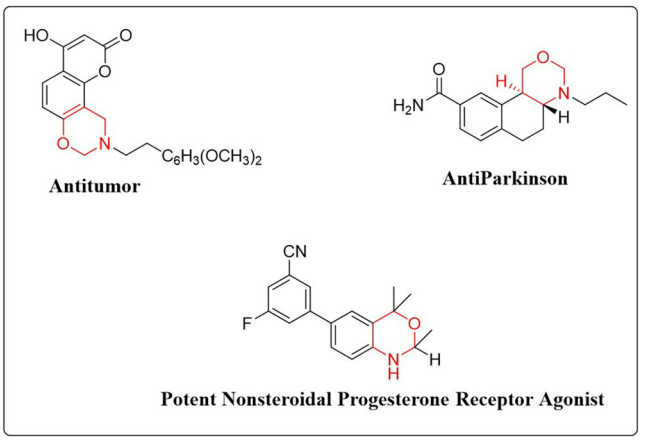


Figure 1. Structures of some biologically active [1,3]oxazines.

by-products; designing new synthetic schemes that can simplify operations in chemical production; and seeking greener solvents that are inherently environmentally and ecologically benign. The development of simple and sustainable synthetic methodologies and the use of readily available reagents is one of the main objectives of organic synthesis. Aqueous solutions of hydrotropes represent the unique properties of an alternative reaction medium for organic synthesis. In our efforts devoted to green chemistry, we have established the compatibility of aqueous hydrotropic solutions as a safer solvent for organic synthesis.[31–33] In continuation with our efforts to tap the barely exploited potential of hydrotropes in organic synthesis, we report here the sustainable synthesis of 2,3-dihydro-2-phenyl-*1H*-naphtho[1,2-e][1,3]Oxazine and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e] [1,3]Oxazines in an aqueous hydrotropic medium at ambient temperature.

Experimental

Melting points of products were determined on electrical melting point apparatus EQ 730 A-EQUIPTRONICS and are uncorrected. Infrared spectra were recorded on a lamda FTIR 750 spectrometer. The samples were examined as KBr disks ~5% w/w. ^{1}H NMR,^{13}C NMR and DEPT spectra were recorded on a Bruker Ascend 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal reference. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companie and used without further purification. NaBS, NaXS, and NaPTS were synthesized by the following procedures reported in the literature.[34]

General procedure for synthesis of [1,3]oxazine derivatives

A mixture of Aniline (1 mmol), α-Naphthol or β-Naphthol (1 mmol) and formaldehyde (2 mmol) in 5 ml of 30% aqueous hydrotropic solution was stirred at room temperature. The completion of the reaction as monitored by thin layer chromatography. After completion of the reaction product was filtered and recrystalized in ethyl acetate.

Spectral data of synthesized compounds

3,4-Dihydro-3-phenyl-2H-naphtho[2,1-e][1,3]oxazine (Entry-1)

IR (neat, thin film): $\upsilon = 1606, 1580, 1214, 1028\ cm^{-1}$.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.70 (s, 2H, Ar-CH_2-N), 5.82 (S, 2H, N-CH_2-O), 6.88-8.20 (m, 11H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.6, 93.4, 113.4, 114.3, 119.6, 121.9, 122.9, 124.6, 125.2, 125.5, 127.1, 129.6, 149.6; DEPT of two –CH_2 carbon appeared at 59.6 and 93.4 resp (Table 2).

3,4-Dihydro-3-(4-chlorophenyl)-2H-naphtho[2,1-e][1,3]oxazine (Entry-3)

IR (neat, thin film): $\upsilon = 1610, 1585, 1460, 1208, 1032, 788\ cm^{-1}$.

^{1}HNMR(400 MHz, $CDCl_3$, δ ppm): δ 4.72 (s, 2H, Ar-CH_2-N), 6.00 (S, 2H, N-CH_2-O), 6.88-8.28 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.8, 93.4, 113.4, 115.7, 119.6, 122.9, 124.6, 125.2, 125.5, 127.1, 127.2, 129.7, 132.5, 147.7, 149.0; DEPT of two –CH_2 carbon appeared at 59.8 and 93.4 resp (Table 2).

3,4-Dihydro-3-(4-nitrophenyl)-2H-naphtho[2,1-e][1,3]oxazine (Entry-6)

IR (neat, thin film): $\upsilon = 1617, 1590, 1454, 1555, 1365, 1215, 1025\ cm^{-1}$.

^{1}HNMR(400 MHz, $CDCl_3$, δ ppm): δ 4.72 (s, 2H, Ar-CH_2-N), 6.00 (S, 2H, N-CH_2-O), 6.88-8.28 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 59.8, 93.4, 112.3, 113.4, 119.6, 122.9, 124.6, 124.8, 125.2, 125.5, 127.1, 132.5, 137.4, 149.0,155.7; DEPT of two –CH_2 carbon appeared at 59.8 and 93.4 resp (Table 2).

2,3-Dihydro-2-phenyl-1H-naphtho[1,2-e][1,3]oxazine (Entry-8)

IR (neat, thin film): $\upsilon = 1615, 1585, 1456, 1212, 1032\,cm^{-1}$.

^{1}HNMR(400 MHz, $CDCl_3$, δ ppm): δ 5.04 (s, 2H, Ar-CH_2-N), 6.12 (S, 2H, N-CH_2-O), 6.90-7.91 (m, 11H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 53.7, 83.0, 111.5, 114.3, 118.4, 120.8, 121.9, 123.4, 126.3, 128.0, 128.3, 128.8,129.6, 131.7, 149.6, 151.7; DEPT of two –CH_2 carbon appeared at 53.7 and 83.0 resp (Table 2).

2,3-Dihydro-2-(p-tolyl)-1H-naphtho[1,2-e][1,3]oxazine (Entry-14)

IR (neat, thin film): $\upsilon = 1614, 1588, 1454, 1218, 1038\,cm^{-1}$.

^{1}HNMR(400 MHz, $CDCl_3$, δ ppm): δ 2.32 (s, 3H, -CH_3), 5.05 (s, 2H, Ar-CH_2-N), 6.10 (S, 2H, N-CH_2-O), 6.90-7.91 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 21.3, 57.7, 93.0, 111.5, 112.8, 118.4, 120.8, 123.4, 126.3, 128.0, 128.3, 128.8, 129.9, 130.7, 131.7, 146.6, 151.7; DEPT of two –CH_2 carbon appeared at 57.7 and 93.0 resp (Table 2).

2,3-Dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine (Entry-15)

IR (neat, thin film): $\upsilon = 1626, 1436, 1228, 1037, 793\,cm^{-1}$.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 3.78 (s, 3H, -OCH_3), 4.92 (s, 2H, Ar-CH_2-N), 5.38 (S, 2H, N-CH_2-O), 6.84-7.80 (m, 10H, Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm):48.7, 55.5, 80.8, 112,5, 114.5, 118.8, 120.9, 121.1, 123.6, 126.6, 128.2, 128.7, 129.0, 131.2, 142.7, 152.3, 155.1; DEPT of two –CH_2 carbon appeared at 48.7 and 80.8 resp (Table 2).

2,3-Dihydro-2-(4-bromophenyl)-1H-naphtho[1,2-e][1,3]oxazine (Entry-16)

IR(neat, thin film): $\upsilon = 1597, 1479, 1199, 801\,cm^{-1}$.

^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): δ 4.95 (s, 2H,Ar-CH2-N), 5.41 (s,2H,N-CH2-O), 7.06-7.80 (m 10H,Ar-H).

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 48.2, 79.3, 112.1, 114.06, 118.71, 120.27, 120.81, 123.7, 126.8, 128.4, 128.7, 129.0, 131.1, 132.1, 147.8, 152.1; DEPT of two –CH_2 carbon appeared at 48.2 and 79.3 resp (Table 2).

Result and discussion

The selection of hydrotropes plays a significant role in the synthetic transformation involving aromatic amine, formaldehyde withα-Naphthol or β-Naphthol in to 3-dihydro-2-phenyl-1H-naphtho[1,2-e][1,3]Oxazine and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e] [1,3]Oxazines in aqueous medium. The amphiphilic character and hydrophobic region favor the solubility of organic reactants in aqueous media and thus differ from classical surfactants. The nature of hydrotrope used

Table 1. Comparative various synthetic methods for synthesis of [1,3]Oxazines derivatives.

Entry	Reagents and condition	Time (m/h)	Yield (%)	References
1	(S)-BINAPO chiral lewis base with $HSiCl_3$ in DCM	10–11 h	77	[13]
2	$KAl(SO_4)_2$ _$12H_2O$ (alum) in H_2O	15 min	75	[16]
3	Solid-support catalyst, SiO_2.NaCl at room temperature	5–10 min	78	[18]
4	1-benzyl-3-methyl imidazolium hydrogen sulfate i.e. [bnmim] $[HSO_4]$, room temperature and stirring	1 min	77	[24]
5	1-butyl-3-Methyl imidazolium hydrogen sulfate [bmim]HSO_4 Ionic liquid and PTC such as tridecyl trimethyl ammonium bromide (TDTMAB) at 60 °C.	30 min	90	[25]
6	BF_3–SiO_2 Ultrasonicated room temperature	10 min	90	[26]
7	*Sodium p*-Toluene Sulfonate (NaPTS) at room temperature	10 min	94	Present work

Table 2. Screening of various hydrotropes for synthesis of [1,3]Oxazines derivatives.

Entry	Hydrotrope	Time (Min.)	Yield (%)[a]
1	*p*-Toluene Sulfonate (NaPTS)	10	94
2	*p*-Xylene Sulfonate (NaXS)	50	70
3	Benzene Sulfonate (NaBS)	120	40

Reaction at room temperature.
[a]Isolated yield.

as a reaction medium and its minimum hydrotropic concentration (MHC) above which there is maximum solubility of reactants.[35] As hydrotropes increase the solubility of compounds by many folds excess, this effect is attributed to a direct interaction between the reactants, which are practically insoluble in water. A wide number of synthetic methodologies were reported for these transformations.

According to a survey of previous studies for the synthesis of [1,3]Oxazine derivatives, the novelty of the present protocol is to overcome the problem of solubility of organic compounds in an aqueous medium. Due to the poor or insolubility of organic moiety, they are not interacting with each other. The hydrotropic aqueous medium is one of the best alternatives for hazardous organic solvents that solubilize insoluble organic compounds in an aqueous medium. Hydrotropes are not only recyclable but also nontoxic in nature. Hydrotrope is cheap in cost as well as can be synthesized in the laboratory, which makes it an environmentally and economically efficient protocol.[36,37]

Here, we represent the comparative table of previous and present study (Table 1). The different hydrotropes such as sodium benzene sulfonate (NaBS), sodium p-xylene sulfonate (NaXS) and sodium p-toluene sulfonate (NaPTS) were selected for this synthetic transformation. As an evident from the results in Table 2, NaPTS was found to be better alternative as compared to NaBS and NaXS. NaPTS in aqueous solution shows better outcome for this synthetic transformation.

We opted to use 30% (w/v) aqueous solutions of selected hydrotropes as a solvent. This concentration was suitable for the maximum solubilization of organic compounds. As excellent results were obtained for NaPTS, we employed this particular hydrotrope for subsequent studies. We have also studied the effect of concentration of aq. NaPTS. The efficiency of model reaction varied dramatically with respect to concentration of hydrotrope and was maximum when 30% of

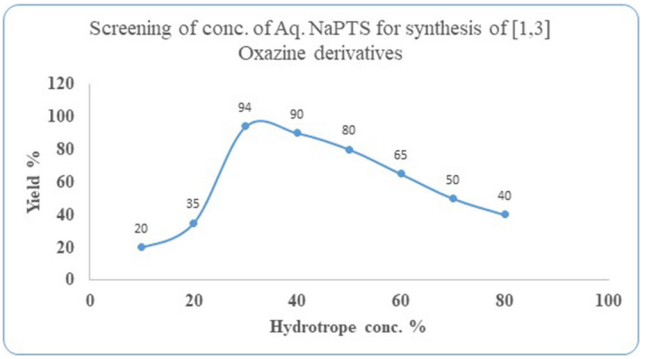
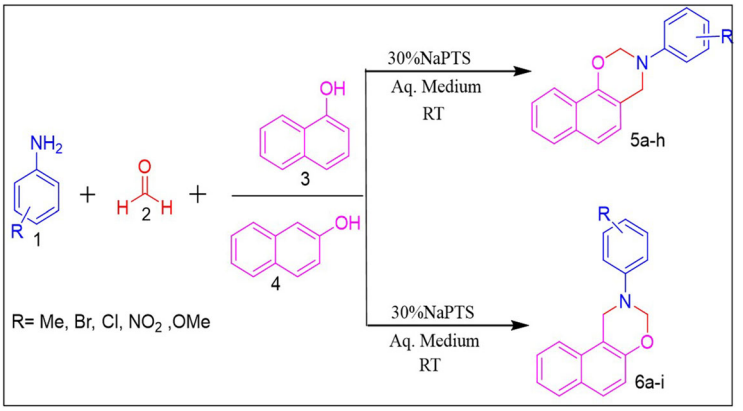


Figure 2. Screening of Conc. of Aq. NaPTS for synthesis of [1,3]oxazines derivatives.



Scheme 1. Synthesis of [1,3]Oxazine derivatives in 30% Aq. Hydrotropic medium.

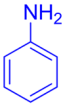
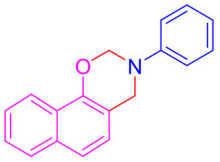
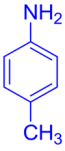
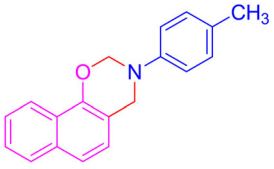
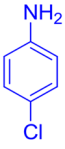
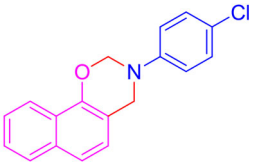
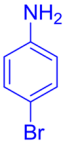
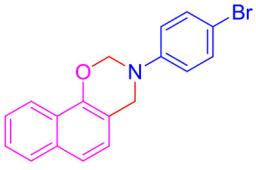
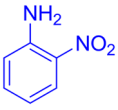
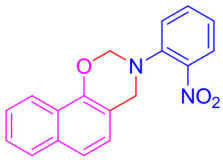
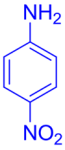
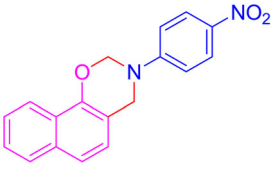
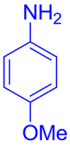
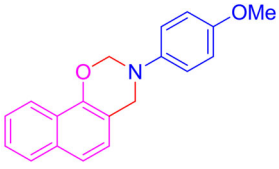
aq. NaPTS was used as a reaction medium (Figure 2). Enhance the solubility of reactant molecule at 30% conc. of NaPTS.

Our next task was to assess the efficiency of the aqueous hydrotropic solutions for this organic transformation. Accordingly, a model reaction between aniline and formaldehyde with β-Naphthol/α-Naphthol in 30% of aq. NaBS, NaXS, and NaPTS was carried out at ambient temperature (Scheme 1). On the completion of the reaction as monitored by thin layer chromatography (TLC) using n-hexane/ethyl acetate (8:2) as the solvent system, the reaction mixture was diluted with cold water during which the product separated. The filtration of the reaction mixture followed by recrystallization afforded the corresponding product of high purity. In all cases, the reactions proceeded smoothly, affording the corresponding products in high yields (Table 3) and which gave correct IR, ^{1}H NMR, ^{13}C NMR and DEPT spectral analysis. The plausible mechanism of the product formation for the synthesis of [1,3]Oxazine derivatives is conceptualized in Figure 3.

Recyclability of hydrotrope

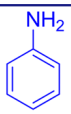
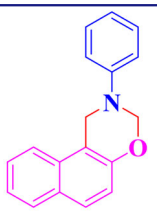
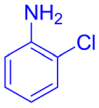
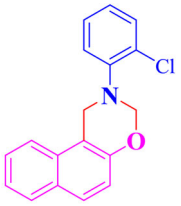
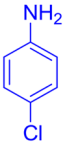
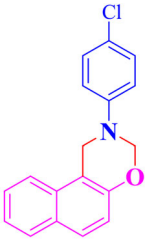
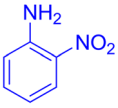
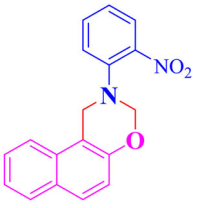
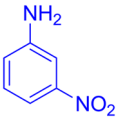
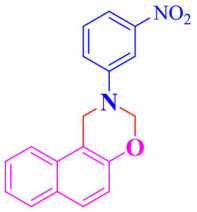
In organic synthesis, reusability and recovery of hydrotropic medium are very vital from the point of view of environmental effects and economy. Therefore, we first recovered the hydrotropes after completion of the reaction. The reaction mixture was filtered, the product was washed with water, and both the product and all the aqueous medium were collected. Then the aqueous medium was kept for evaporation to remove water, and finally we recollected the

Table 3. Synthesis of [1,3]oxazine derivatives in 30% aq. NaPTS solution.[a]

Entry	Aniline	Product	Time (min)	Yield %[b]	M.P.°C Lit. [16,23]
1.		 5a	30	90	110–111 [23]
2.		 5b	30	90	196–198 [23]
3.		 5c	40	90	80–82
4.		 5d	20	90	115–117 [23]
5.		 5e	45	85	85–87
6.		 5f	10	94	114–116
7.		 5g	10	92	298–300 [23]

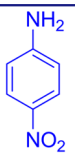
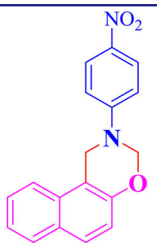
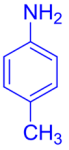
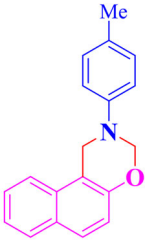
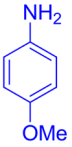
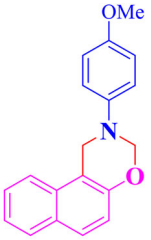
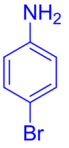
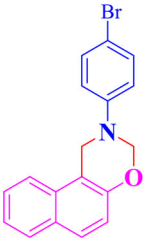
(*continued*)

Table 3. Continued.

Entry	Aniline	Product	Time (min)	Yield %[b]	M.P.°C Lit. [16,23]
8.		 6a	30	90	47–49 [23]
9.		 6b	40	84	146–148
10.		 6c	30	88	221–223
11.		 6d	40	84	132–134 [23]
12.		 6e	45	80	140–142 [24]

(*continued*)

Table 3. Continued.

Entry	Aniline	Product	Time (min)	Yield %[b]	M.P.°C Lit. [16,23]
13.		 6f	10	94	171–173 [23]
14.		 6g	20	88	88–90 [23]
15.		 6h	20	92	78–80 [16]
16.		 6i	20	90	117–119

[a]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and DEPT spectroscopy.
[b]Isolated yields after recrystallization.

hydrotrope. The reusability of that hydrotropic solution was studied four times, including the use of freshly prepared solution for the respective synthesis. We got good results with a small amount of loss of yield, as shown in Figure 4.

Conclusion

In conclusion, we have developed an environmentally benign, efficient and green methodology for the synthesis of [1,3]Oxazine derivatives by one-pot multi-component reaction of aniline,

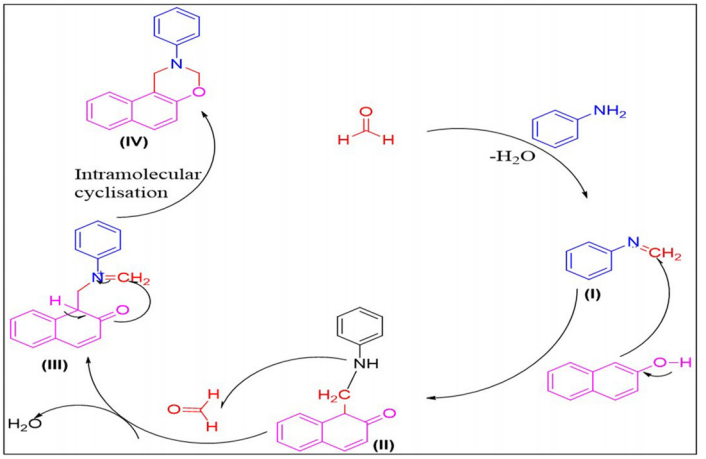


Figure 3. A Plausible reaction mechanism for synthesis of [1,3]oxazine derivatvies.

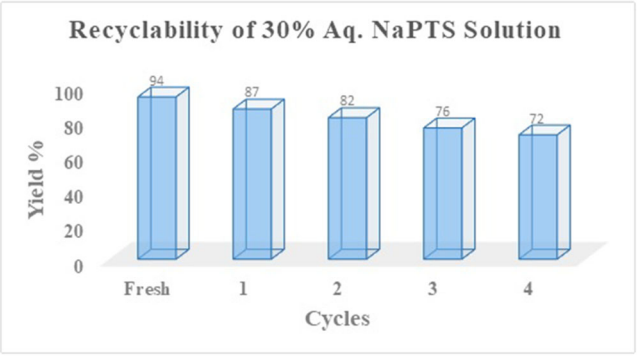


Figure 4. Recyclability of 30% aq. NaPTS solution.

α-Naphthol or β-Naphthol and formaldehyde in 30% aq. NaPTS solution. The aqueous hydrotropic solution of sodium paratoulene sulfonate can be recycled after a simple work-up and reused up to four times with good efficiency of product yield. Therefore, attractive and notable features of the present work are: shorter reaction time with high yield; environmentally friendly reaction medium; reusability of hydrotropic medium; absence of harmful organic solvents; and easy workup procedure. As a result, the current protocol plays an important role in organic synthesis by adhering to green chemistry principles.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Aboli Sapkal http://orcid.org/0000-0002-4838-1266
Suraj Attar http://orcid.org/0000-0002-1596-9696
Avdhut Kadam http://orcid.org/0000-0002-1270-5687
Pramod Gaikwad http://orcid.org/0000-0002-0486-5197

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