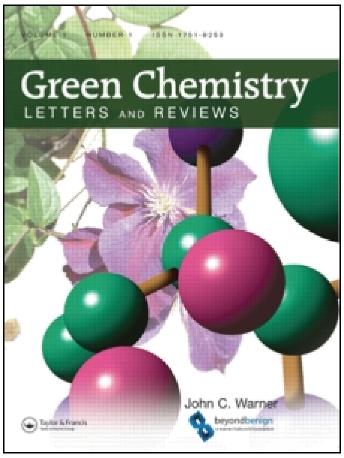

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RESEARCH LETTER

Water mediated synthesis of various [1,3]oxazine compounds using alum as a catalyst

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A simple, efficient, and practical procedure for the synthesis of various substituted 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazines and 3,4-dihydro-3-phenyl-2*H*-naphtho[2,1-e][1,3]oxazines using $KAl(SO_4)_2 \cdot 12H_2O$ (alum) as a non-toxic, reusable, inexpensive, and easily available catalyst is described using water as a solvent. These improved reaction conditions allow the preparation of a wide variety of substituted [1,3]oxazines in high yields and purity under mild reaction conditions.

Keywords: [1,3]oxazine; water; β-napthol/α-naphthol; formaldehyde; aromatic amine

Introduction

The application of greener approaches in organic synthesis using readily available reagents and reactants is one of the main objective (*1–3*). The 1, 3-oxazine nucleus features prominently in many biologically important natural products and other bioactive molecules (*4–7*). 1,3-*O,N* heterocycles having a great number of synthetic possibilities, e.g. they can be used as intermediates in the synthesis of *N*-substituted amino alcohols or nitrogen-bridged heterocyclic systems and they serve as aldehyde sources in carbon transfer reactions (*8*). In addition, naphthoxazine derivatives have therapeutic potential in the treatment of Parkinson's diseases (*9,10*). Investigations and studies of such 1,3-oxazines have been done since the 19th century. Burke *et al.* worked on such systems in 1952 through the condensation of primary aliphatic and alicyclic amines with formaldehyde and substituted phenols (*11*). This process yielded several types of well-defined monomeric products depending on the particular amine, temperature, nature, and the position of the substituents on phenol. Similar work was reported by Hardman (*12*) and Bruson (*13*). The present investigation is in relation to the reaction of representative primary aromatic amines with formaldehyde and β-naphthol as well as α-naphthol. The primary aromatic amines are of particular interest in such studies since their chemical behavior can be modified significantly by ring substitution and they are capable of undergoing nuclear condensation with formaldehyde.

Previously reported methods for synthesis of various 2,3-dihydro-2-phenyl-1*H*-naphth[1,2-e] [1,3] oxazines have required strong basic conditions and prolonged reaction times (*11*).

Literature research for the synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazine provides only few previous reports on such moiety where the synthesis of above mentioned compound was performed using formaldehyde, a primary aromatic amine, and β-naphthol (*11–14*).

Therefore, we have further investigated this molecule of interest using greener approaches and in search of better alternatives over reported methods. Alum ($KAl(SO_4)_2 \cdot 12H_2O$) has been found to be effective in the synthesis of cis-isoquinolic acids (*15*), mono and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones (*16*), dihydropyrimidines *via* Biginelli reaction (*15*), coumarins (*17*), 1,3,4-oxadiazoles (*18*), dibenzoxanthenes (*19*), 1,5-benzodiazepines (*20*), trisubstituted imidazoles (*21*), 2-arylbenzothiazoles and 2-arylbenzoxazoles (*22*), bis(indolyl)methanes (*23*), and Knoevenagel reaction (*24*). We report for the first time the use of alum as a catalyst for the synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e] [1,3]oxazine and 3,4-dihydro-3-phenyl-2*H*-naphtho [2,1-e][1,3]oxazine.

Seeleing to develop green protocols for the synthesis of biologically active heterocyclic molecules (*25–28*), we synthesized various 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazines and 3,4-dihydro-3-phenyl-2*H*-naphtho[2,1-e][1,3]oxazines using green, cost-effective, and mild methods (Scheme 1).

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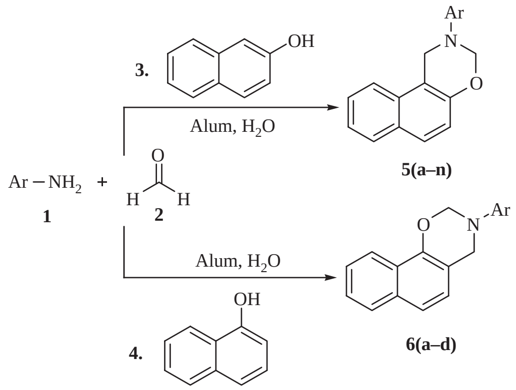

Scheme 1. Synthesis of various substituted 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazine (5) and 3,4-dihydro-3-phenyl-2*H*-naphtho[2,1-e][1,3] oxazine (6).

For the preparation of such compounds we chose alum as a catalyst and water as medium in consideration of previously reported disadvantages and problems. Initially, we carried out the condensation of formaldehyde, aniline as aromatic amine, β-naphthol (1:2:1) in solvent, and catalyst-free conditions at room temperature. The reaction time was about 4 hours with negligible yield (35%). Hence, to improve the reaction rate as well as yield, we carried out the same reaction with various catalysts. Firstly, we ran the reaction with Lewis acids such as $ZnCl_2$, $CaCl_2$, and $MgCl_2$ (20 mol%). However, these catalysts were found to not have good catalytic activity with respect to reaction time and yield (Table 1, entries 2–4).

Hence, in search of better catalysts, we moved toward heterogeneous catalysts such as silica (SiO_2), montmorillonite, and alumina (acidic, basic, and neutral) (20 mol%). We found that the reaction with SiO_2 requires longer reaction times (three hours) with low yield 40% and similarly montmorillonite also did not yield better results (Table 1, entries 5 and 6). We performed the same condensation reaction with various alumina and we found that in neutral alumina the reaction was complete in two hours with 45% yield, whereas in basic alumina the product was obtained with 55% yield in one hour. The acidic alumina catalyzed product was obtained in 20 min with good yield 70% (Table 1, entries 7–9).

The obtained results were not satisfactory, therefore, we chose alum (20 mol%) as a catalyst to perform the reaction and surprisingly we found better results over other catalysts at room temperature without solvent (reaction time 15 min and yield 75%) (Table 1, entry 10).

The reaction was then performed with various solvents to evaluate the solvent effect. For that, we have screened the reaction using various solvents such as water (H_2O), ethanol (EtOH), tetrahydrofuran (THF), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), and acetonitrile (CH_3CN) (Table 2). We found that the catalyst alum gives excellent yield 85% with shorter reaction time (10 min) at ambient temperature in aqueous conditions (Table 2, entry 6).

Table 1. Comparison data of various catalyst in the synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazine (**5a**) using formaldehyde, aniline, and β-naphthol at 20 mol% of catalysts.

Entry	Catalyst	Time (min)	Yield[a] (%)
1	–	240	35
2	$ZnCl_2$	135	55
3	$CaCl_2$	150	45
4	$MgCl_2$	160	40
5	SiO_2	180	55
6	Montmorillonite	175	55
7	Alumina (neutral)	120	45
8	Alumina (basic)	60	55
9	Alumina (acidic)	20	70
10	Alum	15	75

[a] Yields were obtained by column chromatographic separation technique.

To check the efficiency of the catalyst, we performed the same reaction with various concentrations of the catalyst and found that 20 mol% catalyst was sufficient to perform the reaction (Table 3).

Then we performed the reaction using α-naphthol, aniline, and formaldehyde (1:1:2) and found similar results for the reaction (Table 4, entries 15–18). Therefore, the reaction was then carried out for various derivatives with optimized reaction condition (Table 4).

One interesting observation was noted when the reaction was performed with electron donating (EDG) as well as electron withdrawing groups (EWG) on aromatic amines; the reaction proceeded very rapidly with EDG in comparison to EWGs. The

Table 2. Comparison data of various solvents in the synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3] oxazine (**5a**) using formaldehyde, aniline, and β-naphthol at 20 mol% of alum.

Entry	Solvent	Time (min)	Yield[a] (%)
1	CH_3CN	15	50
2	CH_2Cl_2	15	53
3	THF	15	55
4	$CHCl_3$	15	58
5	EtOH	15	65
6	H_2O	10	85

[a] Yields were obtained by column chromatographic separation technique.

Table 3. Effect of various concentrations of alum in the synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3] oxazine (**5a**) in aqueous medium.

Entry	Alum (mol%)	Time (min)	Yield[a] (%)
1	5	25	60
2	10	20	66
3	15	15	73

[a]Yields were obtained by column chromatographic separation technique.

EWGs present on aromatic ring retard the rate of reaction due to involvement of lone pair of electrons on $-NH_2$ group in resonance with EWG. Conversely, EDG accelerates the rate of reaction since it makes $-NH_2$ group more electrons rich.

In summary, we have reported a novel general and efficient method for the synthesis of various 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazines and 3,4-dihydro-3-phenyl-2*H*-naphtho[2,1-e][1,3]oxazines.

Experimental

All the reagents and aromatic aldehydes were obtained from commercial suppliers and used as such. Melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded on FT/IR-410 type (A) spectrophotometer in KBr. ^{1}HNMR spectra were measured in DMSO-d_6 solution on a Bruker spectrophotometer at 400 MHz. Electronspray ionization mass spectra (ES-MS) were recorded on a Water-micromass Quattro-II spectrometer.

General procedure

A mixture of formaldehyde (2 mmol), aromatic amine (1mmol), β-naphthol/α-naphthol (1 mmol), and alum (20 mol%) was stirred in water magnetically at ambient temperature for the appropriate amount of time. Upon the completion of reaction (monitored by TLC), 20 ml ice cold water was added to the reaction mixture and the product was extracted by ethyl acetate (2 × 20 ml). The organic layer was washed with brine (2 × 20 ml) and dried over anhydrous sodium sulphate. The solvent was distilled out under reduced pressure to afford the solid or viscous products. The solid products were charged in a column (hexane:ethyl acetate) to offer the pure form of the product 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazine and 3,4-dihydro-3-phenyl-2*H*-naphtho[2,1-e][1,3]oxazine. All collected solvents were again redistilled and reused for further reactions. Identification and confirmation of all compounds were performed to compare their physical constants with reported literature values. Representative data: (5a) IR (KBr, cm^{-1}): 3420, 2500, 2290, 1730, etc.; ^{1}H NMR (400 MHz, DMSO-d_6) Δ: 4.40 (s, 2H), 5.30 (s, 2H), 6.45 (t, 1H, 7.8 Hz, 8 Hz), 6.78 (d, 2H, 8 Hz), 6.98 (d, 1H, 8 Hz), 7.07 (d, 2H, 8 Hz), 7.35(t, 1H, 7.2 Hz, 8 Hz), 7.50 (t, 1H, 7.2 Hz, 8 Hz), 7.60 (d, 1H,

Table 4. Characterization data of synthesis of substituted 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazine (5) and 3,4-dihydro-3-phenyl-2*H*-naphtho[2,1-e][1,3]oxazine (6).

Entry	Compound	Amine	Time (min)	Yield[a] (%)	MP (°C) (ref)
1	**5a**	H	10	85	46–48 (*11*)
2	**5b**	2-Me	15	80	58–60 (*11*)
3	**5c**	3-Me	15	79	72–74
4	**5d**	4-Me	15	81	87–89 (*11*)
5	**5e**	2-NO_2	20	75	109–110 (*11*)
6	**5f**	3-NO_2	20	76	132–134 (*11*)
7	**5g**	4-NO_2	20	76	168–170 (*11*)
8	**5h**	4-Br	20	74	118–120 (*11*)
9	**5i**	2,4,6-tri bromo	25	72	98–100 (*11*)
10	**5j**	3-MeO	10	90	68–70
11	**5k**	4-MeO	10	88	76–78
12	**5l**	2-EtO	10	90	102–104
13	**5m**	4-EtO	10	89	68–70
14	**5n**	4-F	20	76	136–138
15	**6a**	H	10	88	108–110
16	**6b**	2-Me	15	85	86–88
17	**6c**	4-MeO	15	88	300(d)
18	**6d**	4-F	20	79	118–120

[a]Entries **5a–n** for β-naphthol and entries **6a–d** for α-naphthol.

8 Hz), 7.75 (d, 1H, 8 Hz), 7.80 (d, 1H, 8 Hz); ES-MS E/Z 262 (M^+).

Conclusion

Alum is an easily available, inexpensive, and efficient catalyst for the synthesis of substituted 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazine derivatives from various aryl amines. The remarkable advantages offered by this method are the use of safer catalyst, solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of substituted 2,3-dihydro-2-phenyl-1*H*-naphtho[1,2-e][1,3]oxazines and 3,4-dihydro-3-phenyl-2*H*-naphtho[2,1-e][1,3]oxazines.

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