Boric acid: mild and efficient catalyst for the synthesis of 2,3-Dihydro-2-Phenyl-1*H*-Naphtho-[1,2-e][1,3] oxazine

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Abstract : Boric acid has been used as a mild and efficient catalyst reaction promoter for the cyclocondensation of β-naphthol, formalin and aromatic amines to afford respective 2,3-dihydro-2-phenyl-1*H*-naphtho-[1,2-*e*] [1,3] oxazine derivatives. The remarkable advantages offered by this method are inexpensive and readily available catalyst, simple procedure, faster reactions, involved the nonchromatographic and high yield of products.

Keywords::Boric acid, [1,3] Oxazine derivatives, One-pot reaction, Cyclocondensation.

I. INTRODUCTION

Multicomponent reactions (MCRs), defined as one pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry.1-2 Heterocyclic compounds occur very widely in nature and are essential to the human life. Among a large variety of heterocyclic compounds, 1,3-oxazine containing moiety possesses wide synthetic utility as a useful intermediate for the variety of functional group interconversions.3-4.
Investigation of the 1,3-oxazine heterocycles has shown that they possess varied biological properties such as analgesic, anticonvulsant, antitubercular, antibacterial and anticancer activity [5, 6]. Particular attention has been paid to these βββsince the discovery of the non-nucleoside reverse transcriptase inhibitor trifluoromethyl-1,3-oxazine-2-one, which shows high activity against a variety of HIV-1 mutant strains [7]. In addition, naphthoxazine derivatives have exhibited therapeutic potential for the treatment of Parkinson's disease [8-9]. Realizing the importance of 1,3-oxazine derivatives as an intermediates as well as in the synthesis of various drug sources, reported in a few classical methods using $Cu(OAc)_2/ZnCl_2$,10 under basic condition,11 2-azadienes with alkynes,12 dry methanolic ammonia,13 Bu4NF/EtI,14 Au(I) complex,15 ammonium acetate,16 , *p*-TsCl, DMAP/CH2Cl2.17(1-butyl-3-methyl imidazolium hydrogen sulphate [bmim]HSO4) [18], alum [19]. BF3–SiO2 [20] pyridinium-based ionic liquid [21],Ammonium metavanadate [22], and potassium dihydrogen phosphate (23). All these experimental results show several procedures which are available for synthesis of several oxazine derivatives; nevertheless, expensive reagents and special conditions are required.Therefore, we have further investigated this molecule of interest using greener approaches and in search of better alternatives over reported methods. Boric acid has invoked enormous interest as a green and potential catalyst to construct carbon-carbon and carbon.heteroatom bonds in various organic transformation such as aza-Michael reaction**[24]**, transesterification of ethyl acetoacetate**[25]**, oxidation of sulfides**[26]**, Biginelli reaction**[27]**, Mannich reaction**[28]** tetrahydrobenzo[α]xanthene-11-ones (29) and β-enaminones (30) .

II. EXPERIMENTAL

III.

Apparatus and reagents

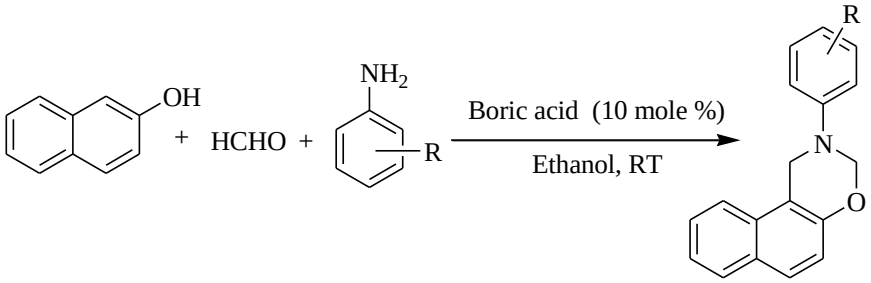
All aldehydes were obtained from freshly opened container and used without further purification with the exception of benzaldehyde and 2- furaldehyde which were distilled prior to use melting point was determined in open capillary tubes and is uncorrected.IR spectra were recorded on Perkin Elmer FTIR spectrophotometer in KBr disc, ^{1}HNMR spectra were recorded on variant 500MHZ spectrophotometer in $CDCl_3$ using TMS as internal standard.The chemical shifts have been expressed in δ-ppm scale the melting points and other data were recorded in TABLE 2 General procedure for Synthesis
of 2, 3-dihydro-2-phenyl-1*H*-naphtho-[1, 2-e] [1,3]oxazine derivative

General procedure for the synthesis 2, 3-dihydro-2-phenyl-1H-naphtho-[1,2-e] [1,3] Oxazine derivatives

Amixture of formalin (1mmol), aromatic amine (1mmol), 2-naphthol and boric acid (10 mol %) in ethanol (5 ml) was stirred at room temperature for 90-180min. The progress of the reaction was monitored by TLC.After completion of reaction conversion, the reaction mixture was poured on crushed ice. The obtained crude solid product was filtered, dried and crystallized from ethanol.Our search for an efficient catalyst and the best experimental reaction conditions in the preparation of 2,3-dihydro-2-phenyl-1*H*-naphtho-[1,2-*e*] [1,3] oxazine.

III.RESULT AND DISCUSSION

In continuation of our research devoted novel synthetic methodologies, herein, we report a simple, efficient, and rapid method for the synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho-[1,2-e] [1,3]oxazine derivatives catalyzed by boric acid. (Scheme 1).



1 **2** **3(a-k)** **4(a-k)**

The reaction of an 4-methyl aniline 3a as a representative aromatic amine, 2-naphthol and formalin in the presence of boric acid has been considered as a standard model reaction for the optimization of reaction condition. To evaluate the effect of solvent, we have screened different solvents such as tetrahydrofuran, dichloromethane, acetonitrile, methanol, water, water : ethanol (1:1) and ethanol at room temperature. Ethanol stand out as the solvent of choice among the solvents tested because of the rapid conversion and excellent yield (91%) of desired product, where as the product formed in lower yields (15-72%) by using other solvents (TABLE 1, Entry 1-6).

To determine the optimum concentration of catalyst, we have investigated the model reaction at 2.5, 5, 7.5, 10 and 12.5mol%of boric acid in ethanol at room temperature. The product was obtained in 51, 67, 80, 91 and 91 % yield respectively.This indicates that the use of 10mol%of boric acid is sufficient to promote the reaction forward (TABLE 2)

To study the generality of this process, variety of examples were illustrated for the synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho-[1,2-e] [1,3]oxazine and results are summarized in TABLE 3. The reaction is compatible for various substituents such as -CH_3, -NO_2, -OH,-OCH_3, -Cl and -Br. The formation of desired product has been confirmed by ^{1}H NMR and IR spectroscopic analysis technique and compared with the corresponding literature data.

Table 1 : Screening of solventsa

Entry	Solvent	Yield
1	Tetrahydrofuran	31
2	Dichloromethane	26
3	Acetonitrile	40
4	Methanol	75
5	Water	15
6	Water : ethanol (1:1)	45
7	Ethanol	91

Table 2 : Effect of concentration of boric acida

Entry	*Concentration (mol %)*	Yield
1	2.5	51
2	5	67
3	7.5	80
4	10	91
5	12.5	91

TABLE 3 : Boric acid catalyzed synthesis of 2,3-dihydro-2-phenyl-1*H*-naphtho-[1,2-e] [1,3]oxazine

Entry	Compound	Ar -NH_2	Time(min)	Yield (%)	Melting point (°C)
1	4a	2CH_3- C_6H_4	110	91	56-58
2	4b	3CH_3- C_6H_4	135	89	69-71
3	4c	C_6H_5	125	90	48-50
4	4d	4CH_3- C_6H_4	90	91	88-91
5	4e	2OC_2H_5-C_6H_4	140	86	100-101

6	4f	$3OCH_3$-C_6H_4	145	86	65-67
7	4g	$4OCH_3$-C_6H_4	135	75	78-80
8	4h	$2NO_2$- C_6H_4	180	89	110-112
9	4i	$3NO_2$- C_6H_4	165	86	127-129
10	4j	$4NO_2$- C_6H_4	155	88	164-166
11	4k	4F-C_6H_4	170	90	135-137

Spectral data of the the principal products:
2,3-dihydro-2- (4-methoxyphenyl)-1*H*naphtho[1,2-e][1,3]oxazine (4g): 1HNMR (DMSO) δ ppm 3.6 (s, 3H, Ar-OCH_3), 4.8 (s, 2H, N-CH_2),5.4 (s, 2H, O-CH_2-N), 6.7-7.8 (m, 10H, Ar-H).MS m/z 292 (M+).

IV. CONCLUSION

In conclusion, we have described a general and highly efficient procedure for the preparation of 2,3- dihydro-2-phenyl-1*H*-naphtho-[1,2-e] [1,3]oxazine derivatives using commercially available inexpensive boric acid in ethanol. The remarkable advantage of this protocol is mild reaction conditions, excellent yields of product, operational and experimental simplicity.We believe that, this methodology will be a valuable addition to the existing methods of the synthesis of 2,3-dihydro-2-phenyl- 1*H*-naphtho [1,2-e] [1,3]oxazine.

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