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FULL PAPER

Potassium Dihydrogen Phosphate as an 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:

Potassium dihydrogen Phosphate catalyzed one-pot synthesis of 2,3-Dihydro-2-Phenyl-1H-Naphtho-[1,2-e] [1,3] Oxazine, from 2-naphthol, formalin and aromatic amine was grind by pestle and mortar without any solvent at room temperature for specified period of time. The attractive features of this process are inexpensive, efficient, as well as user friendly.

Keywords: multi-component reaction; one-pot; potassium dihydrogen phosphate; solvent free

1. Introduction

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. The large numbers of biologically active molecules that contain the oxazine nucleus has play important roles in the drug discovery process and exhibit various biological activities [1, 2]. Investigation of the 1,3-oxazine heterocycles has shown that they possess varied biological properties such as analgesic, anticonvulsant, antitubercular, antibacterial and anticancer activity [3, 4]. Particular attention has been paid to these compounds since 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 [5]. In addition, naphthoxazine derivatives have exhibited therapeutic potential for the treatment of Parkinson's disease [6-7].

The synthesis of 2,3-dihydro- 1*H*-naphtho[1,2-e]-, 3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazines involves one-pot condensation cyclization reaction of naphthols with formaldehyde and primary amines. Various methods have been reported in the literature which includes BF_3–SiO_2 [8], (1-butyl-3-methyl imidazolium hydrogen sulphate [bmim]HSO_4) [9], Ammonium metavanadate [10], pyridinium-based ionic liquid [11], ionic liquid [12] and alum [13].

Solid-state syntheses have recently received much attention. These processes have many advantages such as high efficiency and selectivity, easy separation, purification and mild reaction conditions [14]. They are not only environmentally benign, but also economically beneficial because toxic wastes can be minimized or eliminated. The grinding mode for the solid-state reactions has earlier been employed for Grignard reaction, [15], Reformatsky reaction[16], aldol condensation [17], Dieckmann condensation [18], Knoevenagel condensation[19], reduction [20] and other reactions [21].

As per our interest to develop better protocols for the synthesis of biologically active heterocyclic molecules, we would like to report the synthesis of a series of new 3,4-dihydro-3-substituted-2*H*-naphtho[2,1-*e*][1,3] oxazine derivatives using 2-

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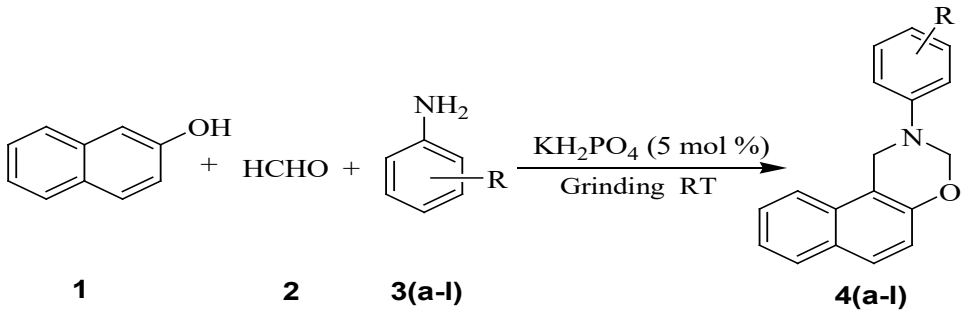
naphthol, formalin and various anilines as substrates in presence of Potassium Dihydrogen Phosphate catalyst. To the best of our knowledge there is no report on the one-pot synthesis of 3, 4-dihydro-3-substituted-2*H*-naphtho[2,1-*e*][1,3]oxazines using Potassium Dihydrogen Phosphate as a catalyst.

2. Results and Discussion

Herein, we wish to report the synthesis of 3, 4-dihydro-3-substituted-2*H*-naphtho [2,1-*e*][1,3] oxazine derivatives promoted by potassium dihydrogen phosphate as a catalyst (Scheme 1). We have considered the reaction of 2-naphthol (1 mmol), formalin (2 mmol) and aromatic aniline (1 mmol) grinding at room temperature condition as the model reaction.

To optimize the reaction conditions in order to evaluate the effect of potassium dihydrogen phosphate as catalyst screened for the model reaction (Table 1). The results indicate that Potassium Dihydrogen Phosphate catalyst gave the good result to form the desired product in 91 % yield within 7 min (Table 1, entry 2).



Scheme 1. synthesis of Substituted 2, 3-dihydro-2-phenyl-1H-naphtho-[1,2-e] [1,3] oxazine.

To study the concentration of catalyst loading for model reaction, the procedure was optimized using different molar concentrations of potassium dihydrogen phosphate under room temperature stirring condition. High yield of product 4a was observed using 5 mol% of catalyst. From these results, it was evident that, the concentration of catalyst plays a crucial role to improve the result to greater extent. It was also observed that, there is no greater change in yields of product greater than 5 mol% of catalyst.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and yield of product. The proposed mechanism for the KH_2PO_4 catalyzed substituted 2,3-dihydro-2-phenyl-1H-naphtho-[1,2-e] [1,3] oxazine is occurs *via* a tandem sequence of reaction as depicted in Figure 1. In the first step, formation of the Schiff base in reaction between amine and formalin. In formation of Schiff base (i.e product A) involves the activation of the carbonyl oxygen by the bond between oxygen of carbonyl and hydrogen of KH_2PO_4 The π electron of 2-naphthol is attack on >C=N- to give intermediate B. Intermediate B is reacts with anther formaldehyde to gives intermediate C which undergo cyclization to give final products (D).

Table 1. Effect of catalyst concentration[a].

Entry	Concentration (mol %)	Yield (%)[b]
1	2.5	65
2	5	91
3	7.5	91
4	10	91

[a]Reaction condition: 1 (1 mmol), 2 (1.2 mmol), 3a (1 mmol), potassium dihydrogen phosphate (5mol%) at room temperature. [b]Isolated yield

In order to show the merit of KH_2PO_4 in comparison with the other catalyst used for the similar reaction, a side by side comparison was run with some of the more common catalysts used for this chemistry. The results are presented in Table 2. It is evident from the results that KH_2PO_4 was an effective catalyst for the synthesis of substituted 2, 3-dihydro-2-phenyl-*1H*-naphtho-

[1,2-e] [1,3] oxazine.

To generalize this methodology, we subjected a series of other amine having electron-donating as well as electron withdrawing substituent to obtain the corresponding [1,3] Oxazine derivatives under the optimized reaction conditions. As Table 3 shows yields are good to excellent in most cases.

Table 2. Effect of different catalysts for the synthesis of 2, 3-dihydro-2-phenyl-*1H*-naphtho-[1,2-e] [1,3] oxazine from the mixture of 2-naphthol, formalin , aniline and Potassium Dihydrogen Phosphate.

Entry	Catalyst	Catalyst Conc.	Solvent/ Medium	Temp (ºC)	Time (min)	Yield (%)	Reference
1	Ionic liquid	5 mol%	-	60 ºC	30	90	09
2	Ammonium metavanadate	10 mol %	Ethanol	Room temp.	60	93	10
3	Ionic liquid	40 mol %	--	Room temp	1	77	12
4	Alum	20 mol%	Water	Room temp	10	85	13
5	KH_2PO_4	5 mol%	-	Room temp.	6	91	Present method

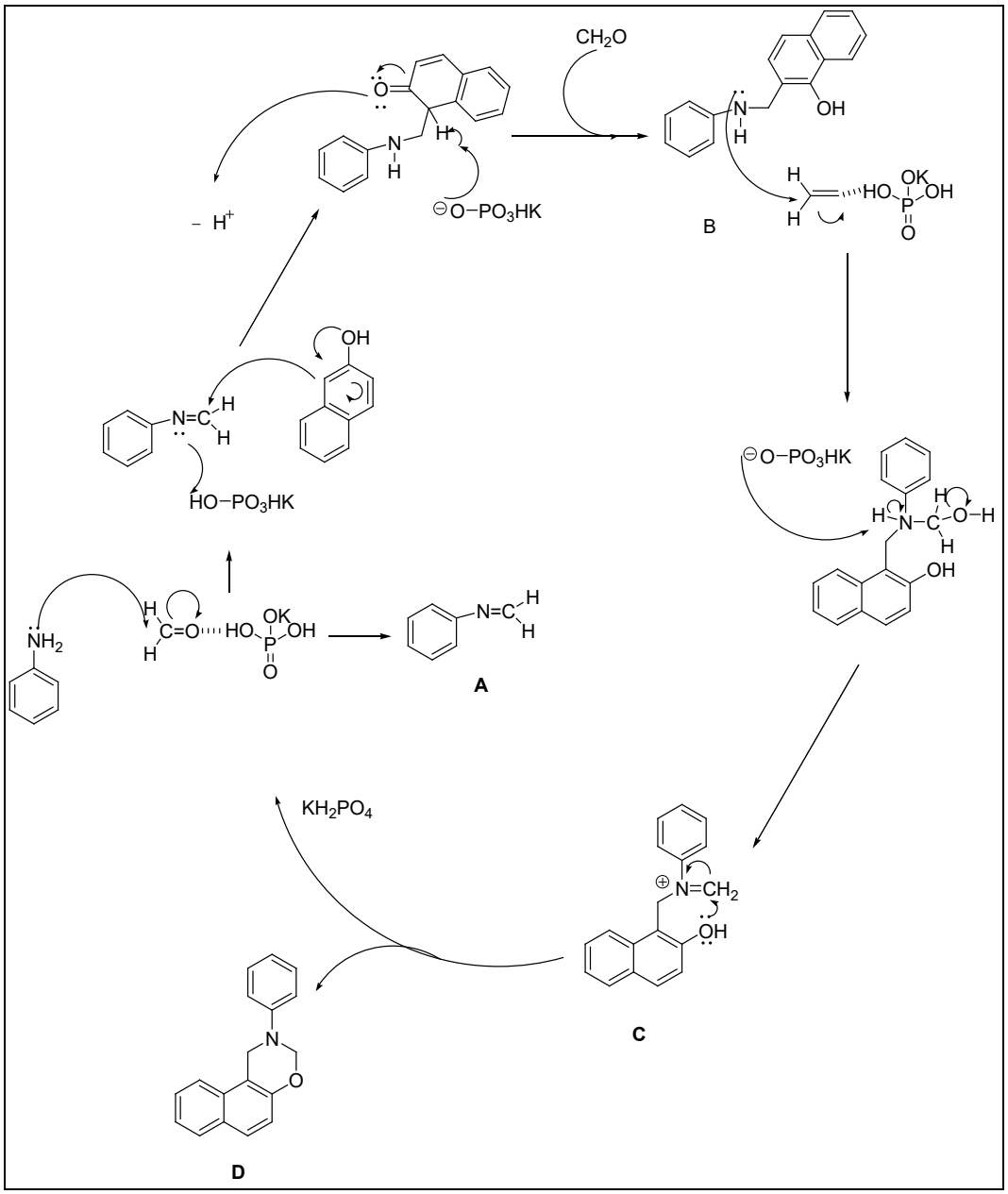


Figure 1.

Table 3. Synthesis of 2, 3-dihydro-2-Phenyl-1*H*-Naphtho-[1,2-e] [1,3] oxazin using potassium dihydrogen phosphate.[a]

Entry	Ar-NH_2	Product	Time (min)	Yield[b] (%)	M.P °C
1	C_6H_5-	4a	6	91	46-48
2	2-Me-C_6H_4	4b	8	89	58-60
3	2-NO_2-C_6H_4	4c	10	87	109-110
4	3-Me-C_6H_4	4d	9	90	70-72
5	3-OMe-C_6H_4	4e	6	91	76-78
6	3-NO_2-C_6H_4	4f	9	88	132-134
7	4-Me-C_6H_4	4g	7	91	87-89
8	4-OMe-C_6H_4	4h	5	93	78-80
9	4-NO_2-C_6H_4	4i	8	84	168-170
10	4-Br-C_6H_4	4j	8	87	114-116
11	4-F-C_6H_4	4k	9	86	136-138
12	4-OEt-C_6H_4	4l	6	90	69-71

[a]Reaction condition: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol), potassium dihydrogen phosphate (5mol%) at room temperature. [b]Isolated yield

3. Material and Methods

The chemicals used aldehydes *β*-naphthol, formaldehyde and aromatic amine were of analytical reagent grade and methods used for synthesis of 2, 3-dihydro-2-phenyl-1*H*-naphtho-[1,2-e] [1,3] oxazine and their derivatives. Melting points were determined in open capillary tube in a paraffin bath. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography). IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H nuclear magnetic resonance (NMR) (400 MHz) with tetramethylsilane as internal standard and dimethyl sulfoxide DMSO-d_6 as solvent and chemical shift values are recorded in units δ (ppm) relative to TMS as an internal standard.

General Procedure for the synthesis Substituted 2, 3-dihydro-2-phenyl-1H-naphtho-[1,2-e] [1,3] oxazine (4a-l);

A mixture of 2-naphthol (1 mmol), formalin (2 mmol), aromatic amine (1 mmol) and Potassium Dihydrogen Phosphate (5mol%) as catalyst was grind by pestle and mortar at room temperature for specified period of time as mentioned in Table 2. After completion of reaction, as monitored by TLC, the reaction mixture was poured on crushed ice. The solid thus obtained was filtered, dried, and crystallized in ethanol to get pure product.

Spectroscopic data of synthesized some principal compounds

3,4-Dihydro-3-phenyl-2H-naphtho[2,1-e][1,3]oxazine (4a): IR (KBr, ν_{max}/cm^{-1}): 1012 (sym. C-O-C), 1234 (asym. C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 4.58 (s, 2H, -Ar-CH_2-N-), 5.46 (s, 2H, -O-CH_2-N-), 6.42-7.86 (m, 11H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 49.4, 72.1, 114.7, 116.3, 117.5, 118.4, 120.5, 123.2, 125.3, 125.4, 126.4, 127.3, 130.2, 131.9, 144.5, 149.3.

3,4-Dihydro-3-o-tolyl-2H-naphtho[2,1-e][1,3]oxazine (4b): IR (KBr, ν_{max}/cm^{-1}): 1022 (sym. C-O-C), 1244 (asym. C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 2.1 (q, 3H, CH_3), 4.71 (s, 2H, -Ar-CH_2-N-), 5.52 (s, 2H, -O-CH_2-N-), 6.71-7.82 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 21.7, 51.2, 80.1, 114.4, 117.2, 118.7, 119.7, 121.5, 125.7, 125.8, 126.2, 126.9, 128.9, 129.7, 130.4, 148.2, 149.4, 149.9, 150.4.

3,4-Dihydro-3-(3-methoxyphenyl)-2H-naphtho[2,1-e][1,3] oxazine (4e): IR (KBr, ν_{max}/cm^{-1}): 1032 (sym. C-O-C), 1222 (asym. C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.61 (s, 3H, OMe), 4.70 (s, 2H, -Ar-CH_2-N-), 5.50 (s, 2H, -O-CH_2- N-), 6.22-7.77 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 50.1, 54.4, 80.2, 111.1, 114.3, 115.8, 117.7, 118.2, 121.9, 124.7, 125.8, 125.9, 126.5, 128.5, 131.3, 133.1, 148.7, 149.9, 151.2.

3,4-Dihydro-3-(4-methoxyphenyl)-2H-naphtho[2,1-e][1,3] oxazine (4h): IR (KBr, ν_{max}/cm^{-1}): 1028 (sym. C-O-C), 1244 (asym. C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.52 (s, 3H, OMe), 4.81 (s, 2H, -Ar-CH_2-N-), 5.41 (s, 2H, -O-CH_2- N-), 6.77-7.82 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6,75 MHz, δppm): 49.5, 56.5, 81.1, 111.5, 115.6, 118.5, 120.5, 122.7, 124.2, 125.7, 125.9, 126.3, 127.2, 130.4, 132.5, 146.8, 149.6.

3-(4-Fluorophenyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazine (4k):IR (KBr, ν_{max}/cm^{-1}): 1034 (sym. C-O-C), 1247 (asym. C-O-C);^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 4.84 (s, 2H, -Ar-CH_2-N-), 5.62 (s, 2H, -O-CH_2-N-), 6.80-7.80 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 50.2, 79.8, 113.3, 116.7, 116.7, 117.8, 119.4, 122.4, 123.6, 125.3, 125.5, 125.9, 127.3, 128.4, 132.4, 150.2.

3,4-Dihydro-3-(4-methoxyphenyl)-2H-naphtho[2,1-e][1,3] oxazine (4l): IR (KBr, vmax/cm^{-1}): 1021 (sym. C-O-C), 1229 (asym. C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.64 (s, 3H, OMe), 4.89 (s, 2H, -Ar-CH_2-N-), 5.41 (s, 2H, -O-CH_2- N-), 6.82-7.90(m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6,75 MHz, δ ppm): 49.2, 56.2, 84.1, 112.2, 116.6, 118.4, 119.2, 122.2, 124.2, 125.7, 125.9, 126.8, 127.5, 130.5, 133.7, 147.8, 149.6.

4. Conclusions

Potassium dihydrogen phosphate 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-1H-naphtho[1,2-e][1,3]oxazines and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e][1,3]oxazines

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