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## An environmentally benign one-pot synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-one derivatives catalysed by phosphomolybdic acid

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**Abstract:** A phosphomolybdic acid catalysed novel method for the synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-one derivatives by a one-pot, three-component reaction of  $\beta$ -naphthol, aromatic aldehydes and urea in excellent yields is described.

**Keywords:** MCRs; phosphomolybdic acid; naphtho-oxazine; catalysis; aldehydes.

### INTRODUCTION

Oxazinone, benzoxazinone and their derivatives are an important class of heterocyclic compounds. These heterocyclic systems exhibit biological activities, such as HIV-1 reverse transcriptase inhibitors<sup>1</sup> (Fig. 1). Naphthalene-condensed 1,3-oxazin-2-ones have been reported to act as antibacterial agents.<sup>2</sup> They have been used as precursors in the preparation of phosphinic ligands for asymmetric catalysis.<sup>3</sup> Hitherto, only few reports for the synthesis of naphthalene-condensed oxazinone derivatives have been documented in the literature. Aromatic oxazines were first synthesized in 1944 by Holly and Cope through Mannich reactions from phenols, formaldehyde, and amines.<sup>4</sup> From the 1950s to the 1960s, many benzoxazines and naphthoxazines were synthesized by Burke and co-workers.<sup>5</sup> Fulop *et al.* reported the condensation of amino alkylnaphthols as precursors with phosgene in the presence of triethylamine giving naphthalene-condensed 1,3-oxazin-2-one derivatives in moderate yields.<sup>6</sup> Cimarelli and co-workers used carbonyl di-imidazole instead of phosgene for the synthesis of these compounds.<sup>7</sup>

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Recently, Bazgir *et al.* reported the synthesis of naphthoxazine derivatives using *p*-TSA and microwave radiation under solvent-free conditions.<sup>8</sup>

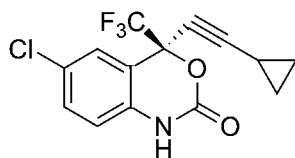


Fig. 1. Efavirenz (Sustiva™).

However, some difficulties still exist, such as unsatisfactory yields, long reaction times, strong acidic conditions, highly expensive reagents. The required solvents or the reagents used are toxic and hazardous which causes environmental pollution. Therefore, to overcome these limitations, the discovery and development of a new, simple, green, one pot and efficient protocol with a highly active catalyst for the preparation of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]-oxazin-3-one derivatives under neutral, mild and practical conditions is of prime interest.

In recent decades, considerable attention has been devoted to heterogeneous organic transformations using heteropolyacids. Due to the super acidic properties of solid heteropolyacids (HPAs), they have been employed in numerous applications as useful and versatile acid catalysts over the last three decades.<sup>9</sup> They are usually solids that are insoluble in non-polar solvents but highly soluble in polar ones. They can be used in bulk or supported forms in both homogeneous and heterogeneous systems. They are more active catalysts than conventional inorganic and organic acids for various reactions in solution;<sup>10</sup> phosphomolybdic acid as a HPA catalyst has become important in industries related to fine chemicals.<sup>11</sup> Furthermore, heteropolyacids have several advantages, such as mild reaction conditions, easy work-up procedures and high selectivity including high flexibility in the modification of the acid strength, ease of handling, environmental compatibility, non-toxicity and experimental simplicity. They are non-corrosive and environmentally benign, as they can be reused and recycled.<sup>12</sup>

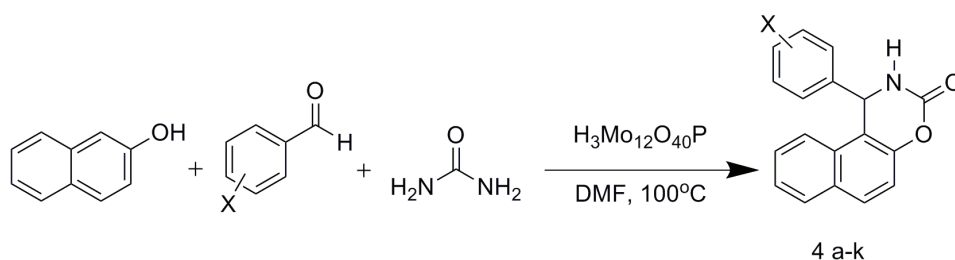
Our group has been working extensively on the development of novel methodologies under mild reaction conditions using phosphomolybdic acid.<sup>13</sup> In this study, the convenient and practical synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives *via* the simple and efficient, one-pot multi-component condensation reaction of  $\beta$ -naphthol, aldehydes and urea in the presence of a catalytic amount of phosphomolybdic acid in DMF was realised (Scheme 1). The products were synthesized in good to excellent yields and characterized by <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and mass spectroscopy, as well as by their physical constants. The physical and spectral data of known compounds are in agreement with those reported in the literature.<sup>6-8</sup>

## EXPERIMENTAL

All commercial reagents were used as received without purification and all solvents were of reagent grade. The reaction was monitored by TLC using 0.25 mm Merck silica gel 60 F254 pre-coated plates, which were visualized with UV light. The melting points were determined in open capillaries. The IR spectra were recorded on a PerkinElmer 257 spectrometer using KBr discs. The  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were recorded on a VXR-300 MHz instrument using TMS as the internal standard.

*General experimental procedure*

A mixture of  $\beta$ -naphthol (0.01 mol), aldehyde (0.01 mol), urea (0.015 mol), phosphomolybdic acid (0.001 mol) and dimethylformamide (5 mL) was heated at 100 °C for an appropriate time (see later). After completion of reaction, as monitored by TLC, the reaction mixture was poured onto crushed ice, extracted with ethyl acetate and washed with water. The ethyl acetate extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was crystallized by using 2-propanol.



Scheme 1. Synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-ones.

## RESULTS AND DISCUSSION

A preliminary experiment was performed to determine the suitable reaction conditions. The reaction of  $\beta$ -naphthol, benzaldehyde and urea in presence of phosphomolybdic acid was investigated. The best result was obtained in the presence of phosphomolybdic acid at 100 °C in DMF (Table I).

TABLE I. Effect of solvents on the preparation of 1,2-dihydro-1-phenyl-3H-naphth[1,2-e][1,3]oxazin-3-one (reaction conditions:  $\beta$ -naphthol (0.01 mol), benzaldehyde (0.01 mol), urea (0.015 mol), phosphomolybdic acid (0.001 mol), solvent (5 mL))

Entry	Solvent	$t / ^\circ\text{C}$	Time, h	Isolated yield, %
1	Ethanol	75	6.5	72
2	Methanol	55	6	75
3	Dimethylformamide	100	3	87
4	Acetonitrile	75	7	48
5	IPA	100	6.5	70
6	Chloroform	55	8	52
7	Toluene	110	7.5	48
8	Dichloromethane	38	10	40

To investigate the feasibility of this synthetic methodology for the synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives, the reaction of  $\beta$ -naphthol with a variety of aromatic aldehydes and urea in presence of a catalytic amount of phosphomolybdic acid was performed, furnishing thereby the respective 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives in high yields. The optimized results are summarized in Table II, from which it can be observed that the results were excellent in terms of yields and product purity using aromatic aldehydes carrying electron-donating as well as electron-withdrawing substituents. When the reactions were conducted without the catalyst, the product yields were only 15–20 %, therefore phosphomolybdic acid provokes a considerable enhancement in the conversion.

In this protocol, phosphomolybdic acid was used as a recyclable catalyst. After completion of the reaction, the catalyst was recovered as follows: the reaction mixture was poured into ice-cold water and extracted with ethyl acetate. The ethyl acetate layer was then washed with water, dried over sodium sulphate and evaporated under reduced pressure to obtain the product. The aqueous layer was evaporated under reduced pressure to recover the phosphomolybdic acid, which was further reused for two more processes. The average percentage yield of recovery of phosphomolybdic acid is given in Table III.

TABLE II. Synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives (reaction conditions:  $\beta$ -naphthol (0.01 mol), aldehyde (0.01 mol), urea (0.015 mol) phosphomolybdic acid (0.001 mol), dimethylformamide (5 mL),  $t = 100\text{ }^{\circ}\text{C}$ )

Entry	Product	Aldehyde (X)	Time, h	Isolated yield, %
1	<b>4a</b>	2-OH	3	85
2	<b>4b</b>	2-Cl		89
3	<b>4c</b>	4-Cl		89
4	<b>4d</b>	4-OMe		86
5	<b>4e</b>	4-Me	2.5	87
6	<b>4f</b>	4-NO <sub>2</sub>		92
7	<b>4g</b>	3-NO <sub>2</sub>		92
8	<b>4h</b>	H	3	87
9	<b>4i</b>	2,5-OH	3.5	85
10	<b>4k</b>	2-OH, 5-OMe		84

TABLE III. Recyclability of the system using phosphomolybdic acid for the preparation of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives

Run	Yield, %
1	87
2	87
3	86

*Representative spectral data*

*1,2-Dihydro-1-(4-chlorophenyl)-3H-naphth[1,2-*e*][1,3]oxazin-3-one (4c)*. M.p. 209 °C. IR (KBr,  $\text{cm}^{-1}$ ): 3224, 3146, 1734, 1600, 850, 730.  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ,  $\delta$ , ppm): 6.21(1H, *s*, CH), 7.30–8.12 (10H, *m*, Ar-H), 8.89 (1H, *s*, NH).  $^{13}\text{C-NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ,  $\delta$ , ppm): 53, 114, 117, 123, 125, 127, 128, 129, 130, 129.5, 129.6, 130.5, 133, 142, 147, 149 ppm. MS ( $m/z$ ): 309 ( $\text{M}^+$ ).

*1,2-Dihydro-1-(4-methylphenyl)-3H-naphth[1,2-*e*][1,3]oxazin-3-one (4e)*. M.p. 167 °C. IR (KBr,  $\text{cm}^{-1}$ ): 3225, 3127, 7210, 1658, 1580, 830.  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ,  $\delta$ , ppm): 2.23 (3H, *s*,  $\text{CH}_3$ ), 6.15 (1H, *d*, CH), 7.05–7.88 (10H, *m*, Ar-H), 8.78 (1H, *s*, NH).  $^{13}\text{C-NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ,  $\delta$ , ppm): 22, 52, 113, 116, 122, 126, 126, 128, 130, 129, 131, 132, 133, 137, 140, 148, 150. MS ( $m/z$ ): 290 ( $\text{M}^+$ ).

## CONCLUSIONS

In conclusion, a novel method with judicious choice of the solvent and catalyst for the synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-*e*][1,3]oxazin-3-one derivatives has been developed. This new protocol has enormous potential for the preparation of a large library of 1,3-oxazin-2-ones in an expeditious and environmentally friendly way in good to excellent yields from readily accessible starting materials. A variety of functional groups are compatible with the reaction conditions.

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## ИЗВОД

ЕКОЛОШКИ БЕНИГНА СИНТЕЗА ДЕРИВАТА 1,2-ДИГИДРО-1-АРИЛ-3H-НАФТ-[1,2-*e*][1,3]ОКСАЗИН-3-ОНА, У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ, КАТАЛИЗОВАНА ФОСФОМОЛИБДЕНСКОМ КИСЕЛИНОМ

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Описан је нов поступак за синтезу 1,2-дихидро-1-арил-3H-нафт[1,2-*e*][1,3]оксазин-3-она у једном реакционом кораку и високом приносу, реакцијом  $\beta$ -нафтола, ароматичних алдехида и урее у присуству фосфомолибденске киселине као катализатора.

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