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Graphical Abstract

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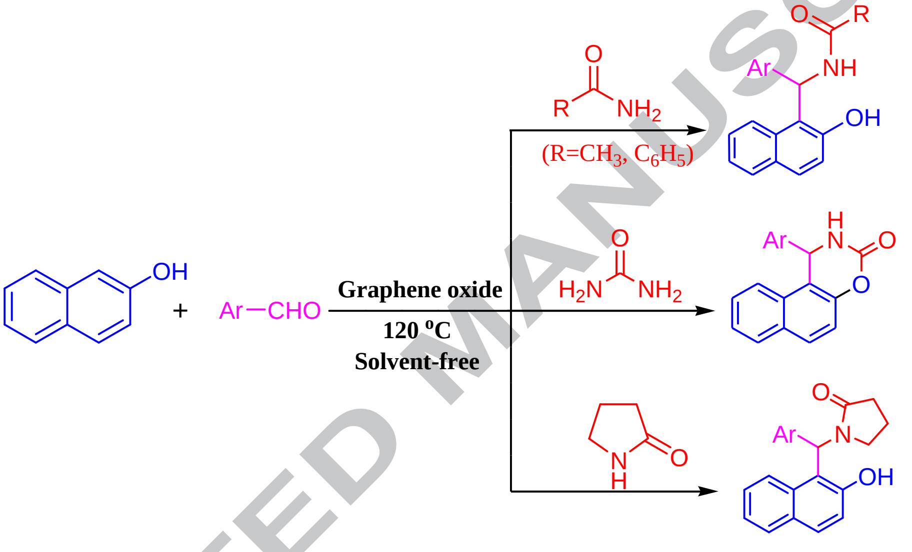
Annah Gupta, Dilpreet Kour, Vivek K. Gupta and Kamal K. Kapoor*



(Total 19 examples)

- ***High Yield***
- ***Broad Substrate Scope***
- ***Eco-friendly Catalyst***
- ***Easily Recoverable and Reusable Catalyst***

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Graphene oxide mediated solvent-free three component reaction for the synthesis of 1-amidoalkyl -2-naphthols and 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin -3-ones

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ABSTRACT

The present report describes a solvent-free synthesis of 1-amidoalkyl-2-naphthols and 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin-3-ones *via* one-pot multicomponent reaction of 2-naphthol, aryl/heteryl aldehyde and amide/urea in presence of graphene oxide as an eco- benign heterogeneous catalyst in good to excellent yields. The catalyst is easily recoverable and reusable.

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1-amidoalkyl-2-naphthols upon hydrolysis produces 1-amino alkyl-2-naphthols, known to possess depressor and bradycardiac effects.[1] 1-aminoalkyl-2-naphthols being 1,3-amino alcohol also find applications in asymmetric synthesis and catalysis as bidentate ligands.[2] Oxazinones shows a variety of biological activities such as antibacterial,[3] HIV-1 reverse transcriptase inhibitors,[4] human cytomegalovirus protease inhibitor,[5] neuropeptide Y5 antagonist.[6]

One-pot multicomponent reactions serve as a powerful tool for the synthesis of wide variety of structurally diverse molecules[7] including pharmaceuticals owing to their high atom economy, time and energy efficiency, high selectivity, low cost, simpler and environmental friendly procedures. Among the various known multicomponent reactions, the synthesis of amidoalkyl naphthol is one of the well established reactions.

1-amidoalkyl-2-naphthols and naphthoxazinone derivatives have been synthesized by the one-pot three component reaction of 2-naphthol, aldehyde and amide or urea in presence of catalysts such as iodine,[8] $FeCl_3.SiO_2$,[9] cellulose sulphuric acid,[10] p-TSA,[11] sulfanilic acid- functionalized silica coated nano-Fe_2O_3 particles,[12] montmorillonite K10,[13] cyanuric chloride,[14] $Fe(HSO_4)_3$,[15] $SnCl_4$. $5H_2O$,[16] $HClO_4–SiO_2$,[17] P_2O_5,[18] zwitter ionic salts,[19] N,N,N',N'-tetrabromobenzene-1,3-disulphonamide [TBBDA],[20] TMSCl/NaI, [21] nano- sulfated zirconia,[22] acidic ionic liquid [Hnmp]HSO_4 [23] etc.[24] Other methods for the synthesis of naphthoxazinone involve the condensation of aminoalkyl naphthol with phosgene/TEA [25] or diimidazole/DMAP.[26] However, these protocols suffer from one or more disadvantages from the green chemistry perspective such as prolonged reaction time, use of carcinogenic reagents and solvents, unsatisfactory yields, strong acidic conditions and non-recyclability of the catalyst. Therefore, it is desirable to develop clean procedures utilizing eco-benign heterogeneous catalyst for the synthesis of 1-amidoalkyl-2-naphthols and naphthoxazinone derivatives.

Graphene oxide (GO) has emerged as a promising, economical and efficient carbocatalyst[27] in organic synthesis due to its large surface area, biocompatibility, inertness, low-cost and ease in synthesis. [28] The acidic nature (pH 4.5 at 0.1 mg mL^{-1}) [29] and oxidising properties [30] of graphene oxide result from the presence of many oxygen containing functionalities such as epoxy, hydroxyl and carboxyl groups on its surface (**Figure 1**).

In our ongoing efforts to develop newer methodologies,[31] we wished to explore the role of graphene oxide in one-pot synthesis of 1-amidoalkyl-2-naphthols and 1,2-dihydro-1-arylnaphth[1,2-*e*] [1,3]oxazin -3-ones from 2-naphthol, aldehyde and amide/urea.

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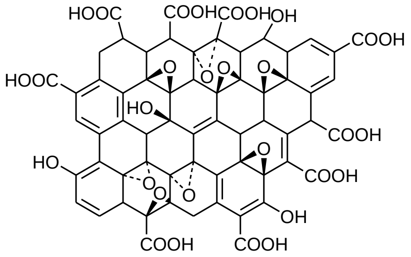
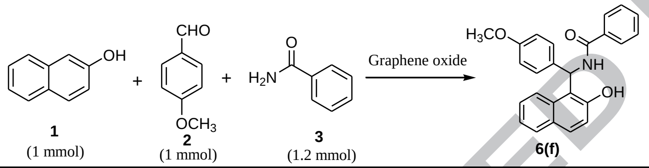


Figure 1: Structural model of graphene oxide

A reaction of 2-naphthol (1mmol), anisaldehyde (1mmol) and benzamide (1.2 mmol) in the presence of 35 wt % of graphene oxide (which was prepared by modified Hummers method[28] and was characterized by IR spectrum) in refluxing ethanol yielded the desired product N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl) benzamide *albeit* in low yield (35%). To improve the yield of the product, ethanol was replaced with various solvents, but only a marginal increase in yield was noticed (**Entry 1-8, Table 1**). Stripping away the solvent from the reaction and heating at 80 °C resulted in the improvement of yield (**Entry 9, Table 1**). However, further increasing the temperature of the reaction revealed that at 120 °C, the product was obtained in 93% yield. (**Entry 9-14, Table 1**). In order to establish the role of GO, the reaction was carried out without catalyst, but desired product was obtained in only 35% yield (**Entry 15, Table 1**). Variation in the amount of catalyst (17, 52, 70 wt %) w.r.t. one mmol of 2-naphthol didn't lead to any improvement (**Entry 16-18, Table 1**).

Table 1: Optimization of reaction conditions



Entry	Solvent	Amount of catalyst	Temp(°C)	Yield[a](%)
1	EtOH	35 wt%	Reflux	35
2	MeOH	35 wt %	Reflux	40
3	*n*-Butanol	35 wt %	Reflux	19
4	Toluene	35 wt %	Reflux	54
5	CH_3CN	35 wt %	Reflux	44
6	$CHCl_3$	35 wt %	Reflux	41
7	DCE	35 wt %	Reflux	31
8	1,4-Dioxane	35 wt %	Reflux	33
9	-	35 wt %	80	72
10	-	35 wt %	90	75
11	-	35 wt %	100	82
12	-	35 wt %	110	90
13	**-**	**35 wt %**	**120**	**93**
14	-	35 wt %	130	93
15	-	Nil	120	35
16	-	17 wt %	120	79
17	-	52 wt %	120	93
18	-	70 wt %	120	93

[a] Isolated Yield

With the optimized conditions in hand, the substrate scope of the reaction was studied and results are depicted in **Table 2**. Aldehydes bearing electron withdrawing and electron donating groups underwent reactions smoothly. It was also observed that the present reactions gave satisfactory results with acetamide as well as 2-pyrrolidone. Akin to earlier observations,[10, 11, 21] usage of urea led to the formation of cyclized product 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin-3-one **7.** When thiophene-2-carboxaldehyde was used, the corresponding crystalline product (**7g**) was obtained in 85% yield, the structure of which was further confirmed by single crystal X-ray analysis **(Figure 2)**. [32]

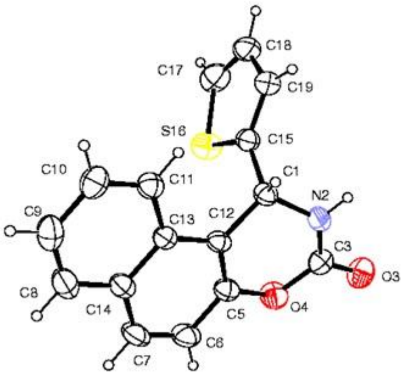


Figure 2: Single crystal X-ray structure of compound **7g**

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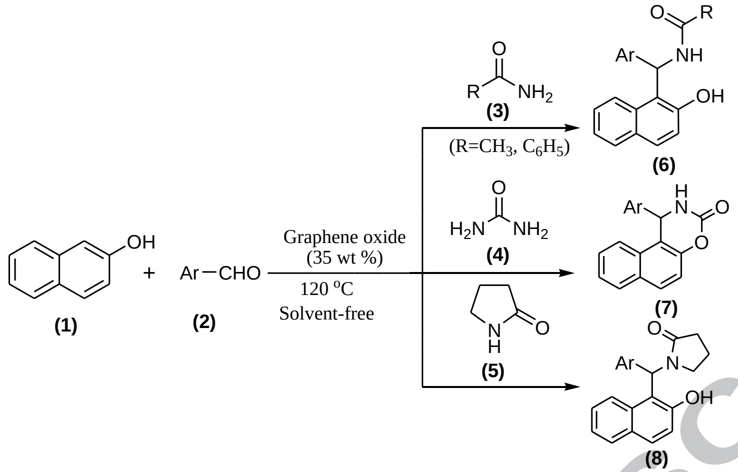
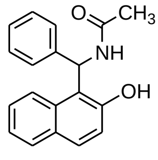
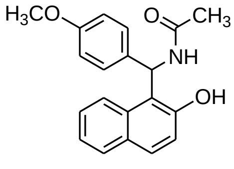
Table 2: Synthesis of 1-amidoalkyl-2-naphthols and 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3] oxazin-3-ones by the reaction of 2-naphthol, aldehyde and various amides/ urea.




(6a)
20 min, 90%


(6b)
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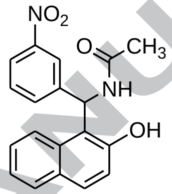
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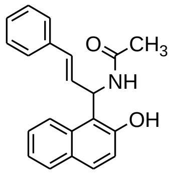
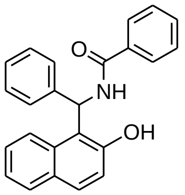

(6d)
25 min, 88%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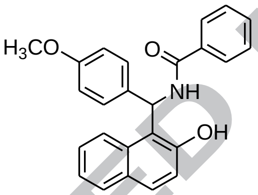
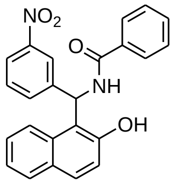

(6f)
15 min, 93%


(6g)
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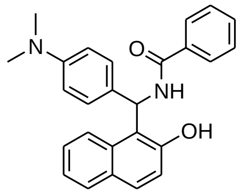
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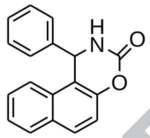
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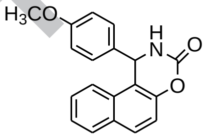
(7b)
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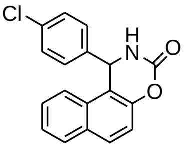
(7c)
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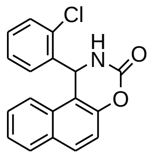
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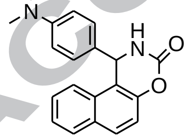
(7e)
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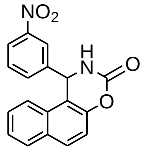
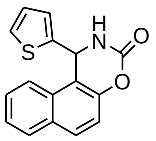

(7f)
25 min, 86%


(7g)
30 min, 85%


(8a)
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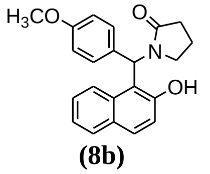
(8b)
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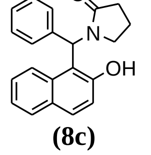
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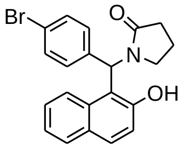
(8d)
30 min, 85%

To check the recyclability of the catalyst, GO was recovered from the reaction of 2-naphthol, anisaldehyde and benzamide and was reused, after washing with ethanol, in a series of six consecutive runs for the synthesis of N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl) methyl)benzamide and the results are depicted in **Figure 3** making it evident that catalyst is stable and recyclable up to six runs without any significant loss of activity.

In conclusion, GO has been found to be an efficient heterogeneous catalyst for the one-pot synthesis of 1-amidoalkyl-2-naphthols and 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin-3-ones from 2-naphthol, aldehyde and various amides and urea under solvent- free conditions. The present

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protocol offers several advantages such as high yields, reduced reaction time, easy work-up and handling. The method is environmentally safe and catalyst is recyclable**.**

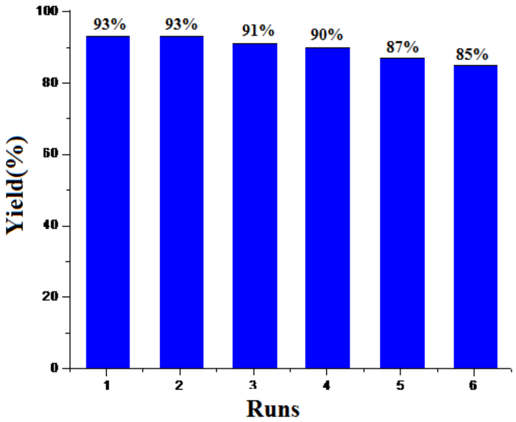

Figure 3: Recyclability of catalyst

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32. Crystal data of product **7g**: $C_{32}H_{22}N_2O_4S_2$, Formula weight=562. 64, Wavelength=0.71073 Å, Orthorhombic, P bca, a =7.8313 (6) Å, b =13.8840 (11) Å, c =24.667 (2) Å, α = 90°, β = 90°, γ= 90°, V=2682.1 (4) Å^3, Z=4, D_{Calcd}=1.393 Mg/m^3, CCDC No. 1500314.
33. **General procedure for the synthesis of 1-amidoalkyl-2-naphthols and 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3] oxazin-3-ones**: A mixture of 2-naphthol (1mmol), aldehyde (1mmol), amide/urea (1.2 mmol) and graphene oxide (35 wt %) was grounded in a pestle-mortar and was transferred to 25 ml round-bottom flask, which was heated in oil-bath maintained at 120 ^oC till the completion of reaction (TLC). After cooling the reaction, ethanol (20 ml) was added and resultant mixture was sonicated for 10 min. The catalyst was filtered and the filtrate upon concentration to 5 ml resulted in precipitation of the product. The product was isolated by filtration.

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Highlights

- This protocol offers solvent-free synthesis.
- Graphene oxide is recoverable and reusable.
- Works well with benzamide, acetamide, 2-pyrrolidone as well as with urea.
- Rapid access to a variety of products in good yields.

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