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ORIGINAL PAPER

A facile eco-friendly approach for the one-pot synthesis of 3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-diones using glycerol as a green media

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Abstract 1,3-Oxazines have a wide variety of biological activities. Naphthoquinone scaffolds also exhibit several biological responses such as antithrombotic, apoptosis and lipoxygenase inhibitors. There is, therefore, a need to develop efficient green methodologies for hybridizing the two scaffolds in a single entity. Herein, we report a novel protocol for the synthesis of 3-aryl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-diones by one-pot three-component condensation of 2-hydroxy-1,4-naphthoquinone, aromatic amines and formaldehyde in glycerol at 50 °C. After separation of products, the glycerol–water layer was extracted using ethyl acetate and the dried glycerol layer was successfully reused several times. The products were obtained in 85–95 % yields in 5–10 min. This environmentally benign protocol holds advantages of high yields, operational simplicity and easy workup over our earlier report.

Abbreviations

CDCl$_3$	Deuterated chloroform
^{1}H-NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C-NMR	Carbon nuclear magnetic resonance spectroscopy
TLC	Thin-layer chromatography
IR	Infrared spectroscopy
FTIR	Fourier transform infrared spectroscopy
ESI-HRMS	Electrospray ionization-high-resolution mass spectrometry

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Introduction

1,3-Oxazine is present in numerous biodynamic heterocycles as the core structure. It provides a focal intermediate for variety of functional group interconversions (Meyers and Smith 1972; Meyers and Malone 1974). 1,3-Oxazine scaffolds exhibit potential biological and pharmacological activities such as anti-tumour (Kuehne and Konopke 1962; Chylinska and Urbanski 1963; Hsu and Lin 1996), antibacterial (Chylinska et al. 1971; Latif et al. 1982), anti-HIV (Pedersen and Pedersen 2000; Cocuzza et al. 2001), analgesic (Kurtz 2005), antihypertensive (Kajino et al. 1991), antithrombotic (Buckman et al. 1998) and antiulcer (Katsura et al. 1991). Moreover, 6-arylbenzoxazines and naphthoxazines possess therapeutic potential for treatment of Parkinson's disease and as non-steroidal progesterone receptor agonists, respectively (Zhang et al. 2002; Joyce et al. 2003). Some of the biologically active oxazine scaffolds are shown in Fig. 1.

Multicomponent reaction is an efficient economic methodology which allows multiple bond formation between simple starting materials generating highly complex and diverse substrates in a single step. It results in high atom economy and avoids purification processes for the intermediates (Domling and Ugi 2000; Ruijter et al. 2011). Therefore, this approach is advantageous over conventional linear type synthesis.

Glycerol has promising physical and chemical properties, which allows its use in many organic reactions that employ various homogeneous and heterogeneous chemo-

Antitumor

AntiParkinson

Potent Nonsteroidal Progesterone Receptor Agonists
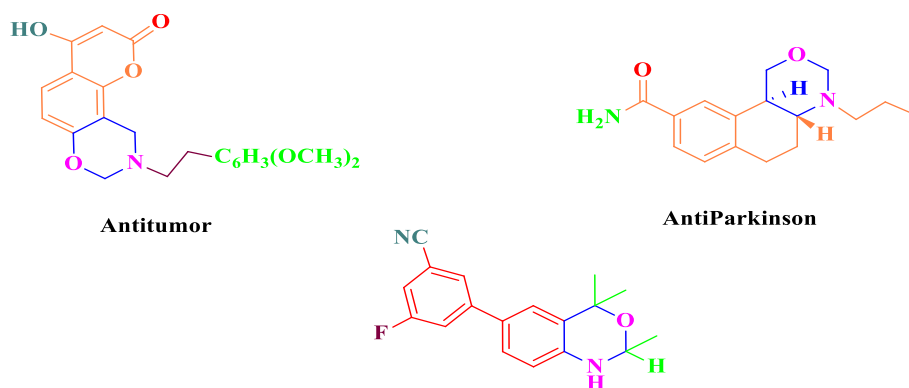
and biocatalysts (Wolfson et al. 2006, 2007, 2009). It has high boiling point, negligible vapour pressure, low toxicity, high polarity, biodegradability and also compatibility with most organic and inorganic compounds. Its manufacture from renewable sources makes it a promising solvent. In addition to this, glycerol also allows isolation of products by simple filtration, extraction and distillation processes. Glycerol has emerged as a green solvent for numerous organic reactions including Pd-catalysed Heck and Suzuki cross-couplings, Cu-catalysed cross-coupling of diaryl diselenides with aryl boronic acids, base- and acid-promoted condensations, catalytic hydrogenation, transfer hydrogenation and asymmetrical reduction (Gu and Jerome 2010; Diaz-Alvarez et al. 2011).

Our group has recently reported the synthesis of novel 3-aryl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-diones using ionic liquid [Bmim]BF$_4$ as the reaction media (Khanna et al. 2015). However, the use of ionic liquid has several disadvantages such as toxicity because of possible release into the soil or water courses and thus posing a threat to the environment and also high costs make them somewhat impractical for larger industrial applications. Keeping in consideration the need of developing a greener protocol involving environmentally benign, catalyst-free reaction conditions, we investigated the synthesis of 3-aryl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-diones from 2-hydroxy-1,4-naphthoquinone (1.0 mmol), aromatic amines (1.0 mmol) and formaldehyde (2.0 mmol) with different hydroxylic solvents.

Experimental

All the chemicals were commercial and purchased from Sigma-Aldrich or Merck and used as received. Thin-layer chromatography (GF254) was used to monitor reaction progress. Melting points were measured on Buchi M-560 melting point apparatus and are uncorrected. IR (KBr)

spectra were recorded on a Perkin Elmer FTIR spectrophotometer, and the values are expressed as ν_{max} cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 and 100 MHz, respectively, using trimethylsilane as internal standard. The chemical shift values are recorded on δ scale, and the coupling constants (J) are in Hz. Mass spectral data were recorded on Agilent 6520 QT of (ESI-HRMS) mass spectrometer.

General procedure for the synthesis of 3-aryl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-diones (IVa–n) (using IVa as an example)

A mixture of 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol), 4-fluoroaniline (111.12 mg, 1.0 mmol), formalin (60.06 mg, 37 %, w/v, 2.0 mmol) and glycerol (2 mL) was taken in a 50-mL round-bottomed flask. The contents were stirred magnetically in an oil bath maintained at 50 °C for appropriate time as indicated in Table 2. The progress of the reaction was monitored by TLC using ethyl acetate/petroleum ether (30: 70, v/v) as eluent. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and diluted with water (5 mL). The solid separated was collected by filtration at pump and washed with water followed by 2–3 mL of ethanol. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Spectral data

3-(4-Fluorophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (IVa) Khanna et al. (2015) Yellow solid; m.p. 191–193 °C (Lit. 194–197 °C); IR (ν_{max} cm^{-1}) (KBr): 1676, 1212, 1061; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 8.08–8.02 (m, 2H, ArH), 7.72–7.65 (m, 2H, ArH), 7.09–7.06 (m, 2H, ArH), 6.97–6.92 (m, 2H, ArH), 5.44 (s, 2H, CH$_2$), 4.42 (s, 2H, CH$_2$).

3-(4-Methoxyphenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVb**) Khanna et al. (2015) Yellow solid; m.p. 159–161 °C (Lit. 163–164 °C); IR (ν_{max} cm^{-1}) (KBr): 1681, 1214, 1037; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.08$–8.01 (m, 2H, ArH), 7.69–7.66 (m, 2H, ArH), 7.07 (d, 2H, ArH, $J = 9.2$ Hz), 6.80 (d, 2H, ArH, $J = 8.4$ Hz), 5.44 (s, 2H, CH$_2$), 4.40 (s, 2H, CH$_2$), 3.73 (s, 3H, OCH$_3$).

3-(3,5-Dichlorophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVc**) Yellow solid; m.p. 150–152 °C; IR (ν_{max} cm^{-1}) (KBr): 1681, 1214, 1037; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.10$–8.04 (m, 2H, ArH), 7.74–7.67 (m, 2H, ArH), 6.97–6.95 (m, 3H, ArH), 5.43 (s, 2H, CH$_2$), 4.46 (s, 2H, CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) $\delta = 183.10$, 178.67, 155.42, 149.15, 135.82, 134.40, 133.57, 131.43, 130.68, 126.66, 126.56, 126.16, 120.04, 116.63, 79.86, 46.10. HRMS (ESI) m/z calcd. for calcd. for C$_{18}$H$_{11}$Cl$_2$NO$_3$: 360.0191, found: 359.0116 [M + H]$^+$.

3-(2-Bromo-4-methylphenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVd**) Yellow solid; m.p. 192–194 °C; IR (ν_{max} cm^{-1}) (KBr): 1682, 1218, 1060; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.10$–8.02 (m, 2H, ArH), 7.71–7.68 (m, 2H, ArH), 7.39 (s, 1H, ArH), 7.20–7.18 (m, 1H, ArH), 6.99–6.97 (m, 1H, ArH), 5.38 (s, 2H, CH$_2$), 4.35 (s, 2H, CH$_2$), 2.44 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) $\delta = 183.20$, 179.07, 155.26, 144.08, 136.44, 134.26, 133.33, 131.62, 130.74, 129.01, 126.19, 126.07, 122.44, 119.93, 119.22, 83.11, 46.36, 20.36. HRMS (ESI) m/z calcd. for calcd. for C$_{11}$H$_7$O$_3$: 187.0395, found: 187.0392.

3-(3-Chlorophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVe**) Khanna et al. (2015) Yellow solid; m.p. 173–175 °C (Lit. 173–175 °C); IR (ν_{max} cm^{-1}) (KBr): 1678, 1209, 1052; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.12$–8.05 (m, 2H, ArH), 7.74–7.68 (m, 2H, ArH), 7.22–7.18 (m, 1H, ArH), 7.12–7.11 (m, 1H, ArH), 7.02–6.95 (m, 2H, ArH), 5.49 (s, 2H, CH$_2$), 4.49 (s, 2H, CH$_2$).

3-(4-Chlorophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVf**) Khanna et al. (2015) Yellow solid; m.p. 180–182 °C (Lit. 183–184 °C); IR (ν_{max} cm^{-1}) (KBr): 1676, 1212, 1061; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.09$–8.03 (m, 2H, ArH), 7.73–7.67 (m, 2H, ArH), 7.25–7.22 (m, 2H, ArH), 7.06–7.04 (m, 2H, ArH), 5.47 (s, 2H, CH$_2$), 4.46 (s, 2H, CH$_2$).

3-(4-Bromophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVg**) Khanna et al. (2015) Yellow solid; m.p. 190–192 °C (Lit. 196–198 °C); IR (ν_{max} cm^{-1}) (Film): 1678, 1213, 1058; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.09$–8.03 (m, 2H, ArH), 7.73–7.67 (m, 2H, ArH), 7.25–7.22 (m, 2H, ArH), 7.06–7.04 (m, 2H, ArH), 5.47 (s, 2H, CH$_2$), 4.46 (s, 2H, CH$_2$).

3-(3-Acetylphenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVh**) Khanna et al. (2015) Yellow solid; m.p. 179–181 °C (Lit. 183–184 °C); IR (ν_{max} cm^{-1}) (KBr): 1681, 1206, 1061; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.07$–8.02 (m, 2H, ArH), 7.70–7.67 (m, 3H, ArH), 7.54–7.52 (m, 1H, ArH), 7.38–7.29 (m, 2H, ArH), 5.52 (s, 2H, CH$_2$), 4.52 (s, 2H, CH$_2$), 2.56 (s, 3H, CH$_3$).

3-(4-Iodophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVi**) Yellow solid; m.p. 140–142 °C; IR (ν_{max} cm^{-1}) (KBr): 1682, 1218, 1060; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.07$–8.02 (m, 2H, ArH), 7.72–7.67 (m, 2H, ArH), 7.54 (d, 2H, ArH, $J = 8.4$ Hz), 6.88 (d, 1H, ArH, $J = 8.4$ Hz), 5.45 (s, 2H, CH$_2$), 4.45 (s, 2H, CH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) $\delta = 183.20$, 178.79, 155.45, 147.15, 138.29, 134.29, 133.43, 131.49, 130.71, 126.57, 126.08, 120.60, 120.08, 85.28, 46.10. HRMS (ESI) m/z calcd. for calcd. for C$_{18}$H$_{11}$Cl$_2$NO$_3$: 417.9940, found: 417.9935 [M + H]$^+$.

3-(3-Chloro-4-fluorophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVj**) Khanna et al. (2015) Yellow solid; m.p. 162–164 °C (Lit. 162–164 °C); IR (ν_{max} cm^{-1}) (KBr): 1682, 1216, 1062; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.09$–8.03 (m, 2H, ArH), 7.73–7.66 (m, 2H, ArH), 7.16–7.14 (m, 1H, ArH), 7.05–6.95 (m, 2H, ArH), 5.42 (s, 2H, CH$_2$), 4.42 (s, 2H, CH$_2$).

3-(4-Chloro-3-nitrophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVk**) Khanna et al. (2015) Yellow solid; m.p. 204–206 °C (Lit. 208–211 °C); IR (ν_{max} cm^{-1}) (Film): 1681, 1212, 1058; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.11$–8.06 (m, 2H, ArH), 7.76–7.69 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.45–7.42 (m, 1H, ArH), 7.26–7.25 (m, 1H, ArH), 5.50 (s, 2H, CH$_2$), 4.52 (s, 2H, CH$_2$).

3-(4-Nitrophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVl**) Khanna et al. (2015) Yellow solid; m.p. 216–218 °C (Lit. 216–218 °C); IR (ν_{max} cm^{-1}) (Film): 1679, 1213, 1060; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.19$–8.16 (m, 2H, ArH), 8.10–8.05 (m, 2H, ArH), 7.75–7.68 (m, 2H, ArH), 7.14–7.12 (m, 2H, ArH), 5.54 (s, 2H, CH$_2$), 4.59 (s, 2H, CH$_2$).

3-(3-Bromophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione (**IVm**) Khanna et al. (2015) Yellow solid; m.p. 170–173 °C (Lit. 170–173 °C); IR (ν_{max} cm^{-1}) (Film): 1678, 1212, 1060; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 8.08$–8.03 (m, 2H, ArH), 7.72–7.66 (m, 2H, ArH), 7.25 (s, 1H, ArH), 7.14–7.01 (m, 3H, ArH), 5.46 (s, 2H, CH$_2$), 4.47 (s, 2H, CH$_2$).

3-(2-Methylphenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]ox-
azine-5,10-dione (**IVn**) Khanna et al. (2015) Yellow
solid; m.p. 160–162 °C (Lit. 160–162 °C); IR (ν$_{max}$ cm^{-1})
(KBr): 1680, 1222, 1066; ^{1}H NMR (400 MHz, CDCl$_3$)
δ = 8.11–8.01 (m, 2H, ArH), 7.71–7.65 (m, 2H, ArH),
7.22–7.17 (m, 2H, ArH), 7.09–7.01 (m, 2H, ArH), 5.37 (s,
2H, CH$_2$), 4.24 (s, 2H, CH$_2$), 2.37 (s, 3H, CH$_3$).

Results and discussion

We report herein a facile and efficient one-pot synthesis of
3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione
derivatives by one-pot three-component condensation of
2-hydroxy-1,4-naphthoquinone, aromatic amines and
formaldehyde in glycerol at 50 °C. The optimum reaction
conditions were established using 2-hydroxy-1,4-naphtho-
quinone (**I**) (1.0 mmol), 4-fluoroaniline (**IIa**) (1.0 mmol)
and formaldehyde (**III**) (2.0 mmol), as standard compo-
nents. The model reactions were performed in various
hydroxylic solvents such as MeOH, EtOH, water, ethylene
glycol, PEG-400, PEG-600 and glycerol under catalyst-free
conditions at varying temperatures. Initially, the reaction
was attempted in MeOH under reflux which was complete
in 10 min and afforded 52 % of the desired 3-(4-fluo-
rophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-
5,10-dione as confirmed by spectral analysis (Table 1,
entry 1). The reaction in EtOH under reflux was also
complete in 10 min and afforded 54 % of the desired
product (Table 1, entry 2). The product formation was also
observed when the reaction was carried out in EtOH–water
and MeOH–water (1:1, v/v) at reflux, though with inferior
yields of 40 and 51 %, respectively (Table 1, entries 3–4).

Table 1 Optimization of reaction conditions for the synthesis of
3-(4-fluorophenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-
dione (**IVa**)

Entry	Solvent	Time (min)	Temp (°C)	Yield (%)
1.	MeOH	10	Reflux	52
2.	EtOH	10	Reflux	54
3.	EtOH–H$_2$O (1:1)	5	Reflux	40
4.	MeOH–H$_2$O (1:1)	5	Reflux	51
5.	Ethylene glycol	15	60	83
6.	Ethylene glycol	10	80	85
7.	Ethylene glycol	10	100	88
8.	PEG-400	8 h	50	–[a]
9.	PEG-600	8 h	50	–[a]
10.	Glycerol	5	50	91

Reaction carried out using 2-hydroxy-1,4-naphthoquinone (1.0
mmol), 4-fluoroaniline (1.0 mmol) and formaldehyde (2.0 mmol)

[a] Mixture of products

Reaction attempted in ethylene glycol at 60 °C gave the
desired naphtho[2,3-e][1,3]oxazine-5,10-dione in higher
yield (83 %) (Table 1, entry 5). Reaction in ethylene glycol
at higher temperatures (80 and 100 °C) did not have much
influence on the reaction yield and time (Table 1, entries
6–7). The above reaction when performed in PEG-400 and
PEG-600 resulted in a mixture of products even after 8 h as
observed by TLC using ethyl acetate/petroleum ether (30:
70, v/v) as eluent (Table 1, entries 8–9). The same reaction
was then attempted using glycerol as the solvent which
yielded 91 % of the desired 3-(4-fluorophenyl)-3,4-dihy-
dro-2H-naphtho[2,3-e][1,3]oxazine-5,10-dione in just
5 min (Table 1, entry 10).

Therefore, Table 1 clearly shows that the best optimized
reaction condition for the one-pot catalyst-free synthesis of
naphtho[2,3-e][1,3]oxazine-5,10-diones was using glycerol
as the solvent at 50 °C. To realize the generality of this
protocol, a series of naphtho[2,3-e][1,3]oxazine-5,10-dione
derivatives were synthesized by one-pot condensation of
2-hydroxy-1,4-naphthoquinone, various aromatic amines
and formaldehyde in glycerol at 50 °C. Both electron-
withdrawing and electron-releasing aromatic amines were
employed under the optimized reaction conditions to yield
the desired products in good yields (Fig. 2; Table 2).

All our attempts to prepare bis-derivatives from o- and
p-phenylene diamines were unsuccessful.

A study regarding the recovery and reuse of glycerol
was also performed. The products were separated by sim-
ple filtration from the mixture of glycerol and water. The
filtrate so obtained was then extracted with ethyl acetate.
Ethyl acetate layer was separated and the solvent was
removed. The glycerol–water layer was dried at 90 °C
under vacuum and then directly reused for reaction. Mar-
ginal loss in the yield (90 and 88 %) of **IVa** was observed
in the second and third cycles. However, the yields
decreased gradually in fourth and fifth cycle (85 and 82 %).

A probable mechanism involved in the formation of
products is outlined in Fig. 3. Initial condensation of
formaldehyde and aromatic amine (ArNH$_2$) gives an imine
intermediate 'A' which further reacts with 2-hydroxy-1,4-
naphthoquinone to form 'B'. Lastly, condensation of 'B'
with formaldehyde gives 'C' with loss of H$_2$O that
undergoes cyclization to give the final product **IV**.

Conclusion

In conclusion, we have developed an eco-friendly catalyst-
free methodology for the synthesis of 3-aryl-3,4-dihydro-
2H-naphtho[2,3-e][1,3]oxazine-5,10-diones from 2-hy-
droxy-1,4-naphthoquinone, aromatic amines and
formaldehyde in glycerol at 50 °C. Inexpensive,
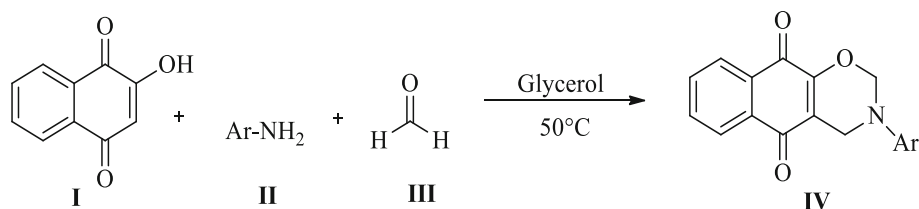
Fig. 2 One-pot multicomponent synthesis of 3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-diones. Reaction conditions: 2-hydroxy-1,4-naphthoquinone (1.0 mmol), aromatic amines (1.0 mmol) and formaldehyde (2.0 mmol) in glycerol at 50 °C

Table 2 Synthesis of 3-aryl-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-dione (**IVa–n**)

Entry	Ar	Product IV	Time (min)		Yield (%)	
			Lit. (Khanna et al.)	Obs.	Lit. (Khanna et al.)	Obs.
1.	4-FC$_6$H$_4$	**IVa**	15	5	85	91
2.	4-(OCH$_3$)C$_6$H$_4$	**IVb**	15	10	89	87
3.	3,5-Cl$_2$C$_6$H$_3$	**IVc**	–	5	–	88
4.	2-Br,4-(CH$_3$)C$_6$H$_3$	**IVd**	–	5	–	87
5.	3-ClC$_6$H$_4$	**IVe**	20	7	90	96
6.	4-ClC$_6$H$_4$	**IVf**	15	8	88	90
7.	4-BrC$_6$H$_4$	**IVg**	15	7	88	85
8.	3-(COCH$_3$)C$_6$H$_4$	**IVh**	15	5	91	99
9.	4-IC$_6$H$_4$	**IVi**	–	5	–	98
1.	3-Cl,4-FC$_6$H$_3$	**IVj**	20	7	90	89
11.	4-Cl,3-(NO$_2$)C$_6$H$_3$	**IVk**	20	10	88	92
12.	4-(NO$_2$)C$_6$H$_4$	**IVl**	20	5	89	97
13.	3-BrC$_6$H$_4$	**IVm**	15	5	90	90
14.	2-(CH$_3$)C$_6$H$_4$	**IVn**	20	5	87	86

High yields and shorter reaction times are the noticeable features
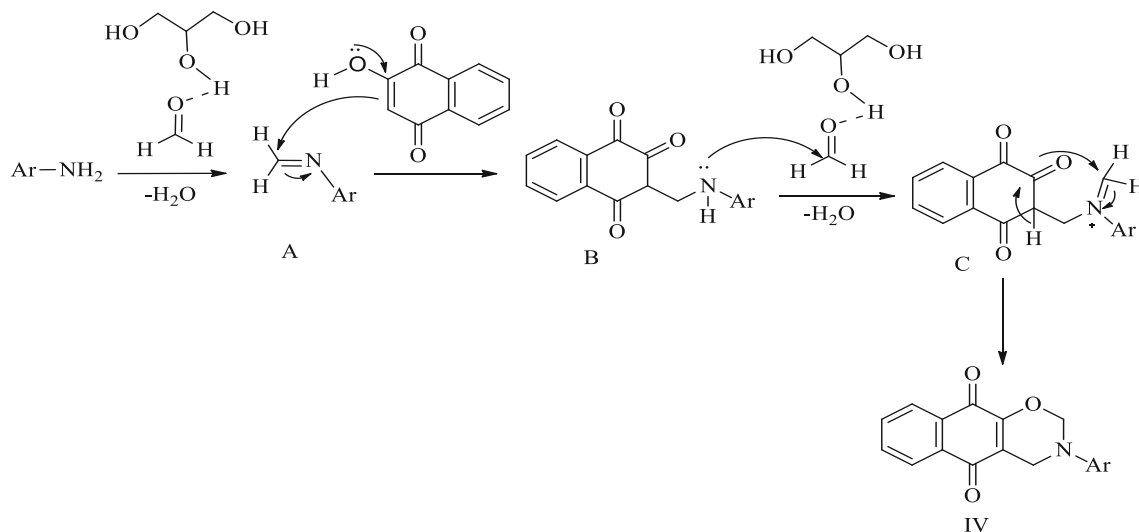
Fig. 3 Probable mechanism of the reaction. Glycerol polarizes formaldehyde for attack of aromatic amine leading to imine formation giving **A** which reacts with 2-hydroxy-1,4-naphthoquinone, and finally, condensation with another mole of formaldehyde gives final product **IV** with loss of water

environmentally benign reaction media is the advantage of this protocol.

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