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Efficient, three-component synthesis of 1-aryl-2, 3-dihydro-3-phenyl-1H-naphth[1,2-e][1,3] oxazines derivatives, using $LaCl_3/ClCH_2COOH$ as an environmentally benign and green catalytic system

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Green catalyst;
Lanthanum chloride.

Abstract. 1-aryl-2,3-dihydro-3-phenyl-1H-naphth[1,2-e][1,3] oxazines are synthesized in good to excellent yields in the presence of $LaCl_3/ClCH_2COOH$ as an inexpensive and environmentally benign catalytic system under solvent-free conditions.

1. Introduction

The N,O-containing heterocycles have received significant attention due to their biochemical activities [1,2]. Additionally, naphthoxazines and their derivatives possess important biological properties, including analgesic, anti-convulsant, anti-tubercular, anti-bacterial and anti-cancer [3-6], and have attracted far more interest due to their therapeutic potential for the treatment of Parkinson's disease [7,8]. The tautomeric character of 1,3-O,N-heterocycles offers a great number of synthetic possibilities [9-11]. Because of the importance of naphthoxazines, the synthesis of new derivatives of these compounds is an important and useful task in organic chemistry.

Multi-Component Reactions (MCRs) are powerful and useful synthetic tools to produce complex organic molecules due to the formation of carbon-carbon and carbon-heteroatom bonds in a one-pot process [12-14]. Therefore, the design of novel MCRs has attracted great attention from research groups working in medicinal chemistry and drug discovery.

However, the reported methods for the synthesis of 1,3-diaryl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazines involve the condensation reaction of 2-naphthol and various substituted aryl and hetero aryl aldehydes in the presence of dry methanolic ammonia, via known two-step reactions [15-17]. In this paper, we report an environmentally benign, solvent-free approach for the synthesis of new naphthoxazine derivatives via multi-component reactions in the presence of $LaCl_3/ClCH_2COOH$ (Scheme 1).

2. Experimental

2.1. Materials and methods

Chemicals were either prepared in our laboratory or purchased from Merck or Fluka chemical companies, and were used without any further purification. All

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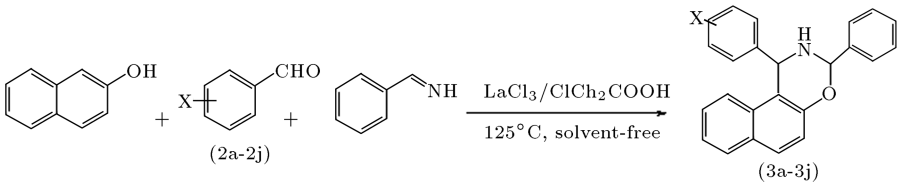


Scheme 1. The synthesis of 1-aryl-2,3-dihydro-3-phenyl-1H-naphth[1,2-e][1,3] oxazines using $LaCl_3/ClCH_2COOH$.

Table 1. The results of synthesis of 1-aryl-2, 3-dihydro-3-phenyl-1H-naphth[1,2-e][1,3] oxazines:

Entry	Aldehyde	Times (min)	Yield[a](%)	M.p. (°C)	
				Found	Reported
2a	PhCHO	55	94	143-145	146-148 [16]
2b	4-ClC_6H_4CHO	50	96	169-171	171-173 [16]
2c	4-OHC_6H_4CHO	70	94	158-160	New compound
2d	4-$O_2NC_6H_4CHO$	50	94	180-182	176-178 [16]
2e	4-$OMeC_6H_4CHO$	65	87	144-146	143-146 [16]
2f	4-MeC_6H_4CHO	70	92	158-160	155-157 [16]
2g	2-ClC_6H_4CHO	45	97	135-137	New compound
2h	2, 4-Cl, ClC_6H_3CHO	40	98	143-145	New compound
2i	3-$O_2NC_6H_4CHO$	48	95	176-178	New compound
2j	4-BrC_6H_4CHO	50	97	150-152	153-155 [16]

[a]: Isolated yields.

reactions were monitored by TLC, and petroleum-ether EtOAc, 3:1. Melting points were determined with a hot-plate microscope apparatus. IR spectra were recorded in KBr, using a BRUKER FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400-MHz spectrometer using $CDCl_3$ and TMS as the solvent and internal standard, respectively.

2.1.1. Synthesis of phenylmethanimine

A round-bottomed flask (100 ml) was charged with a 6.6 M ammonia solution in methanol (23 ml) and then benzaldehyde (1 g, 9.4 mmol) was added dropwise over time increments of 5 minutes at ambient temperature. After the addition was complete, the reaction mixture was left stirring for 24 h at 20°C. The precipitate formed was filtered and washed with hexane and, finally, dried at room temperature to give phenylmethanimine as white powder, 95% yield [18].

2.2. General procedure for the preparation of 1-aryl-2,3-dihydro-3-phenyl-1H-naphth[1,2-e][1,3] oxazine using $LaCl_3/ClCH_2COOH$ catalytic system

Typically, a mixture of 2-naphthol (0.144 g, 1 mmol), phenylmethanimine (0.116 g, 1.1 mmol), benzaldehyde (1 mmol), lanthanum (III) chloride (0.04 g, 0.16 mmol) and chloroacetic acid (0.189 g, 2.0 mmol) was heated at 125°C under stirring for the required amount of time. The progress of the reaction was checked periodically using TLC and, after completion of the reaction, the mixture was diluted with $CHCl_3/CH_3OH$ (3:1). The solvent was evaporated and the crude product was recrystallized from EtOH to afford the final product. Other substituted aromatic aldehydes also reacted well under the same conditions, giving the corresponding product with excellent yields (Table 1). All the products obtained were characterized by spectroscopic methods such as IR, ^1H NMR and ^{13}C NMR, and have been identified by comparison of the spectral data and melting point with those obtained in authentic samples.

Note: In all IR spectra of products, the OH bond disappeared and sharp signals of NH bond at about 3400 cm^{-1} were emerged.

The spectral data for some selected compounds are presented as follows:

2.2.1. Spectra data of 2,3-dihydro-1,3-diphenyl-1H-naphth[1,2-e][1,3] oxazine (3a)

Yield 94%; yellow solid, m.p. 143-145°C. IR (KBr) v (cm^{-1}): 3426(NH), 3057, 1594, 1244. ^1H NMR ($CDCl_3$, 400 MHz,): δ (ppm): 6.44 (s, 1H, CH), 6.53 (brd, 1H, NH), 6.79 (s, 1H, CH), 7.03(d, 2H, J =8 Hz, arom), 7.15 (d, 1H, J = 7 Hz, arom), 7.16 (d, 3H, J = 8 Hz, arom) 7.36-750 (m, 4H, arom), 7.50-7.72 (m, 3H, arom), 7.76-7.941 (m, 3H, arom); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 37.16 (Nph-CHAr-NH), 87.40 (O-CHAr-NH), 117.36, 118.03, 119.31, 122.71, 122.99, 123.44, 124.26, 125.47, 126.40, 126.54, 126.81, 128.27, 128.45, 128.49, 128.81, 129.02, 129.35, 130.56, 131.08, 131.48, 134.84. 143.39.

2.2.2. Spectra data of 4-(2, 3-dihydro-3-phenyl-1H-naphth[1, 2-e][1,3]oxazin-1-yl) phenol (3c)

Yield 94%; violet solid, m.p. 158-160°C. IR (KBr) v (cm^{-1}): 3471(NH), 3163, 3064 (OH), 1514, 1249 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 6.47 (s, 1H, CH), 6.53 (brd, 1H, NH), 6.72 (s, 1H, CH), 7.03-7.50 (m, 7H, arom), 7.50-7.70 (m, 3H, arom), 7.84 (d, 5H, $J = 7.5$ Hz, arom), 8.43(s, 1H, OH). ^{13} C NMR ($CDCl_3$, 100 MHz): δ (ppm): 38.04 (Nph-CHAr-NH), 87.06 (O-CHAr-NH), 117.04, 117.34, 118.03, 119.39, 122.70, 124.25, 126.39, 126.80, 128.27, 128.49, 128.81, 129.05, 129.37, 130.63, 131.07, 131.46, 141.63, 142.07, 142.42.

2.2.3. Spectra data of 1-(2-chlorophenyl)2,3-dihydro-3-phenyl-1H-naphth [1,2-e][1,3]oxazine (3g)

Yield 97%; white powder, m.p. 135-137°C. IR (KBr) v (cm^{-1}): 3354(NH), 3057, 1895, 1594, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 6.46 (s, 1H, CH), 6.52 (brd,1H, NH), 6.64 (s, 1H, CH), 7.03 (t, 1H, $J = 8.5$ Hz, arom), 7.17-7.32 (m, 4H, arom), 7.42-7.51 (m, 3H, arom), 7.54 (d, 1H, $J = 9$ Hz, arom), 7.67 (t, 3H, $J = 8$ Hz, arom), 7.8-7.98 (m, 3H, arom). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 37.66 (Nph-CHAr-NH), 89.49 (O-CHAr-NH), 117.36, 118.04, 119.31, 122.51, 123.44, 124.26, 125.44, 126,40, 126.54, 128.27, 128.45, 128.49, 128.58, 128.66, 128.81, 128.87, 129.02, 129.35, 130.56, 131.48, 134.88, 144.34.

2.2.4. Spectra data of 1-(2,4-dichlorophenyl)-2,3-dihydro-3-phenyl-1H- naphth[1,2-e][1,3]oxazine (3h)

Yield 98%; white powder, m.p. 148-150°C. IR (KBr) v (cm^{-1}): 3409 (NH), 2957, 1236, 803 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.51(s, 1H, CH), 6.79(s, 1H, NH), 6.92 (s, 1H, CH), 7.02 (t, 1H, $J = 8$ Hz, arom), 7.15 (t, 2H, $J = 7.5$ Hz, arom), 7.35-7.71 (m, 9H, arom), 7.86 (m, 2H, arom). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 38.04 (Nph-CHAr-NH), 86.37 (O-CHAr-NH), 117.48, 118.11, 122.69, 123.15, 123.24, 124.58, 126.38, 126.79, 127.07, 127.97, 128.26, 128.47, 128.85, 129.15, 130.17, 130.61, 130.93, 131.05, 131.60, 132.71, 148.73, 148.93.

2.2.5. Spectra data of 1-(3-nitrophenyl)2,3-dihydro-3-phenyl-1H-naphth [1,2-e][1,3]oxazine (3i)

Yield 95%; yellow powder, m.p. 176-178°C. IR (KBr) v (cm^{-1}): 3492(NH), 3234, 3063, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 6.53 (s, 1H, CH), 6.90 (brd, 1H, NH), 7.02(s, 1H, CH), 7.14(d, 2H, $J = 8$ Hz, arom), 7.21 (m, 2H, arom), 7.42 (m, 3H, arom), 7.51 (d, 2H, $J = 8.5$ Hz, arom), 7.53-7.73 (m, 3H, arom), 7.81 (m, 2H, arom), 7.87 (t, 1H, $J = 9$ Hz, arom). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 37.82 (Nph-CHAr-NH), 87.82 (O-CHAr-NH), 118.45, 122.86, 122.99, 123.12, 124.67, 124.81, 127.22, 127.36, 128.68, 128.90, 129.07, 129.22, 129.28, 129.35, 129.42, 129.44, 129.53, 129.93, 131.50, 149.18.

3. Results and discussion

To optimize and find the best conditions, the reaction of 2-naphthol (1 mmol), benzaldehyde (1 mmol) and phenylmethanimine (1.1 mmol), in the presence of $LaCl_3$ (0.16 mmol) was performed in different solvents, and the results are summarized in Table 2 (entries 1-5). High yield and short reaction time were obtained when the reaction was carried out in the presence of chloroacetic acid.

In another study, the condensation of 2-naphthol, 4-hydroxybenzaldehyde and phenylmethanimine was examined in the presence of different quantities of $LaCl_3$ at 125°C temperature (Figure 1). As Figure 1 indicates, reasonable results were obtained when the reaction was performed using 0.04 g of lanthanum chloride. No improvement in the reaction results was observed by increasing the amount of catalyst.

To optimize the temperature in the mentioned reaction, we have carried out a model study with benzaldehyde and 2-naphthol and phenylmethanimine using $LaCl_3/ClCH_2COOH$ at various temperatures under solvent-free conditions (Table 3). Table 3 clearly

Table 2. Investigated conditions for preparation of 2,3-dihydro-1-(4-nitrophenyl)-3-phenyl-1H-naphth[1,2-e][1,3] oxazine using LaCl3 as catalyst.

NO	Solvent	Condition	Time	Yield[a](%)
1	THF	Reflux	6h	25
2	CH_2Cl_2	Reflux	5h	Trace
3	EtOH	Reflux	3h	55%
4	$[ET_3N^+][HSO_4^-]$	125°C	3h	30%
5	$ClCH_2COOH$	125°C	45-70 min	97%

[a]: Isolated yields.

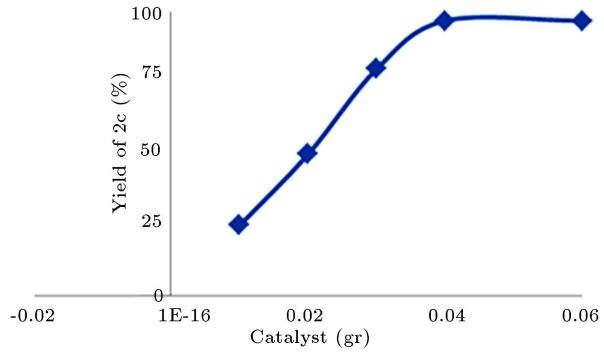
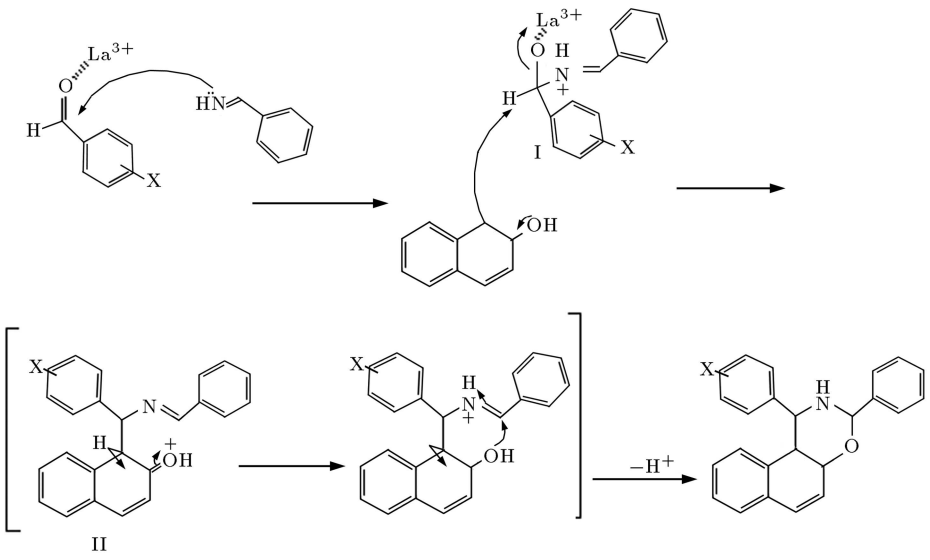


Figure 1. Optimization amount of catalyst on the reaction of 2-naphthol, benzaldehyde, and phenylmethanimine under thermal solvent-free conditions at 125°C.



Scheme 2. The proposed mechanism for synthesis 1-aryl-2,3-dihydro-3-phenyl-1H-naphth[1,2-e][1,3]oxazine.

Table 3. Optimization of temperature using $LaCl_3/ClCH_2COOH$ (0.6 mol %) as catalyst.

Entry	Temperature (°C)	Time (min)	Yield[a] (%)
1	60	180	75
2	80	125	82
3	100	90	90
4	125	55	94
5	135	50	94

[a]: Isolated yields.

demonstrates that 125°C is an effective temperature in terms of reaction time and yields.

After optimizing the conditions, the generality of this method was examined by the reaction of 2-naphthol with different kinds of aromatic aldehydes (2a-2j) and phenylmethanimine, using $LaCl_3/ClCH_2COOH$ as a catalyst under solvent-free conditions.

The proposed mechanism for synthesis of 1-aryl-2,3-dihydro-3-phenyl-1H-naphthol[1,2-e][1,3] oxazines has been shown in Scheme 2.

4. Conclusion

In summary, we have developed a practical method for preparation of new naphth[1,2-e][1,3]oxazines derivatives in the presence of $LaCl_3/ClCH_2COOH$, as an efficient, inexpensive, readily available and environmentally benign catalytic system. This green methodology has the advantages of mild reaction conditions, short reaction times, good yields, easily accessible starting materials, and easy purification of products, which makes it a useful and reliable method for the synthesis of the described compounds. In addition, it is consistent with a green chemistry approach, since no organic solvent is needed.

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References

1. Klayman, D.L., Scovill, J.P., Bartosevich, J.F. and Mason, C.J. "2-Acetylpyridine thiosemicarbazones. 2. N4,N4-disubstituted derivatives as potential antimalarial agents", *J. of Med. Chem.*, **22**(11), pp. 1367-1373 (1979).

2. Hermakens, P.H.H. and Ottenheijm, H.C. "Solid-phase organic reactions II: A review of the literature Nov 95-Nov 96", Tetrahedron, **53**(16), pp. 5643-5678 (1997). (b) Gordon, E.M., Barrett, R.W., Dower, W.J., Foder, S.P.A. and Gallop, M.A. "Applications of combinatorial technologies to drug discovery. 2. Combinatorial organic synthesis, library screening strategies, and future directions", *J. of Med. Chem.*, **37**(10), pp. 1385-1401 (1994).

3. Adib, M., Sheibani, E., Mostofi, M., Ghanbary, K. and Bijanzadeh, H.R. "Efficient highly diastereoselective synthesis of 1,8a-dihydro-7H-imidazo[2,1-b][1,3]oxazines", Tetrahedron, **62**(14), pp. 3435-3438 (2006).

4. Kurz, T. "Synthesis of novel pyrido[2,3-e][1,3] oxazines", Tetrahedron, **61**(12), pp. 3091-3096 (2005).

5. Zhang, P., Terefenko, E.A., Fensome, A., Wrobel, J., Winneker, R. and Zhang, Z. "Novel 6-aryl-1,4-dihydrobenzo[d]oxazine-2-thiones as potent, selective,

and orally active nonsteroidal progesterone receptor agonists", *Bioorg. Med. Chem. Lett.*, **13**(7), pp. 1313-1316 (2003).

6. Poel, Hv., Guilaument, G. and Viaud-Massuard, M. "Synthesis of 6,7,8,9-tetrahydropyrido[2,3-b]indolizine and 3,4-dihydro-2H-pyrido[2',3':4,5] pyrrolo[2,1-b][1,3] oxazine derivatives as new melatonin receptor ligands", Tetrahedron Lett., **43**(7), pp. 1205-1208 (2002).

7. Joyce, J.N., Presgraves, S., Renish, L., Borwege, S., Osredkar, D.H., Replogle, M., Pazsoldan, M. and Millan, M.J. "Neuroprotective effects of the novel D3/D2 receptor agonist and antiparkinson agent, S32504, in vitro against 1-methyl-4-phenylpyridinium (MPP+) and in vivo against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): a comparison to ropinirole", *Exp. Neurol.*, **184**(1), pp. 393-407 (2003).

8. Kerdesky, F.A.J. "A novel and efficient method for the conversion of a trans-hexahydronaphthoxazine to a cis-isomer using boron tribromide", *Tetrahedron Lett.*, **46**(10), pp. 1711-1712 (2005).

9. Cimarelli, C., Mazzanti, A., Palmieri, G. and Vopini, E. "Solvent-free asymmetric aminoalkylation of electron-rich aromatic compounds: stereoselective synthesis of aminoalkylnaphthols by crystallization-induced asymmetric transformation", *J. Org. Chem.*, **66**(14), pp. 4759-4765 (2001).

10. Cimarelli, C., Palmieri, G. and Vopini, E. "Ready N-alkylation of enantiopure aminophenols: synthesis of tertiary aminophenols", *Tetrahedron*, **57**(28), pp. 6089-6096 (2001).

11. Dong, Y., Sun, J., Wang, X., Xu, X., Cao, L. and Hu, Y. "Highly regioselective N-alkylation of nonracemic Betti base: A novel one-pot synthesis of chiral N-methyl-N-alkyl Betti bases", *Tetrahedron Asymmetr.*, **15**(10), pp. 1667-1672 (2004).

12. Lu, J., Baj, Y., Wang, Z., Yang, B. and Ma, H. "One-pot synthesis of 3, 4-dihydropyrimidin-2(1H)-ones using lanthanum chloride as a catalyst", *Tetrahedron Lett.*, **41**(47), pp. 9075-9078 (2000).

13. Domling, A. and Ugi, I. "Multi-component reactions with isocyanides", *Angew. Chem. Int. Ed.*, **39**(18), pp. 3168-3210 (2000).

14. Zhu, J., Bienaymé, H., *Multicomponent Reactions book*, Wiley-VCH: Weinheim (2005).

15. Smith, H.E. and Cooper, N.E. "Ring-chain tautomerism of derivatives of 1-(.alpha.-aminobenzyl)-2-naphthol with aromatic aldehydes", *J. Org. Chem.*, **35**(7), pp. 2212-2215 (1970).

16. Szatmari, I., Martinek, T.A., Lazar, L. and Fulop, F. "Substituent effects in the ring-chain tautomerism of 1,3-diaryl-2,3-dihydro-1H-naphth[1,2-e] [1,3]oxazines", *Tetrahedron.*, **59**(16), pp. 2877-2884 (2003).

17. Szatmari, I., Martinek, T.A., Lazar, L. and Fulop, F. "Stereoelectronic effects in ring-chain tautomerism of 1,3-diarylnaphth[1,2-e][1,3]oxazines and 3-Alkyl-1-arylnaphth[1,2-e][1,3]oxazines", *J. Org. Chem.*, **69**(11), pp. 3645-3653 (2004).

18. Korotaev, Y.V., Sosnovskikh, Y.V., Kutyashev, B.I., Barkov, Y.A., Matochkina, G.E. and Kodess, I.M. "A simple and convenient synthesis of 4-methyl-3-nitro-2-trihalomethyl-2H-chromenes from N-unsubstituted imines of 2-hydroxyacetophenones and trichloro(trifluoro)ethylidene nitromethanes", *Tetrahedron.*, **64**(22) pp. 5055-5060 (2008).

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