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LED LIGHT ENHANCED SYNTHESIS OF 1,2-DIHYDRO-1-PHENYLNAPHTHO[1,2-E] [1,3]OXAZINE-3-ONE DERIVATIVES

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ABSTRACT

Herein, a novel, mild, and efficient intermolecular cyclization of 2-naphthol, benzaldehydes, and urea was developed for the single-pot reaction of 1,2-dihydro-1-phenylnaphtho[1,2-*e*][1,3]oxazine-3-one analogs through the formation of carbon-carbon, carbon-nitrogen, and carbon-oxygen new bonds. The main advantage of the protocol reported here is the utilization of visible (18W white LED bulb) light, which is an inexpensive and eco-sustainable catalyst.

Keywords: LED Light, Visible Light, Oxazines, Oxazinones, One-Pot Synthesis, Multicomponent Synthesis.
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INTRODUCTION

The goal of modern organic synthesis is to develop a clean, environmentally friendly synthetic profile. Visible light, such as LED, is exploited in the area of organic synthesis as a source of energy. The advantages are inexpensive, non-toxic, non-polluting, non-flammable, and renewable characteristics. Oxazine derivatives have shown diverse biological effects like antibacterial and herpes virus protease inhibition.[1- 2] Also, a few of them function as 5-HT ligands[3] and they have been employed as synthons in the asymmetric catalysis process in the synthesis of phosphine ligands.[4] Other applications for oxazine compounds include laser dyes, quantum counters, wavelength shifters, and fluorescent solar concentrators.[5–6] The photophysical characteristics of oxazine derivatives provide great opportunities for singlet oxygen photosensitization and dye laser applications.[7] There have been numerous reported ways to obtain oxazines during the past few decades. Among them, the classical approach involves 1) phenols, formaldehyde, and amines,[8] 2) salicylaldehyde/2-hydroxyacetophenone and ureas/semicarbazides,[9] 3) condensation of aldehydes, urea, and 2-naphthol.[10] However, in this era, when green methods are warranted, many of these protocols are unsatisfactory as they involve the use of costly and toxic catalysts, tedious workup protocols and harsh reaction conditions, which hampers their applications and provides room for further upgradation. To date, no protocol by any means has illustrated the synthesis of 4(a-p) analogs under LED light. LED light intensity has been found to be a very useful source in the synthesis of amino alcohols, 10 1,2,4-triazolines, 1,2,4-triazoles,[11] alkylheteroarylation of alkenes,[12] dihydropyridines,[13] and oxidation of alcohol. [14] It is crucial to remember that LED light never generates heat.

EXPERIMENTAL

Material and Methods

Without additional purification, the materials were purchased at analytical quality grade. H^1 NMR (400 MHz), ^{13}C NMR (100 MHz) (Bruker 400 MHz), and HRMS (Waters Model: Synapt G2) were used to evaluate each molecule. DMSO-d_6 was used to note the NMR spectra. The references are indicated in ppm. Melting temperatures were determined in an open capillary tube by an electric device and a mercury thermometer. Our study commenced by optimizing the reaction condition using 2-naphthol (1), benzaldehyde (2p), and urea (3) as model substrates. Oxazinone (4p) was collected with a 47% yield. When the model reaction was run in CH_2Cl_2 for 12 hours at a visible light intensity (LED, 14W) (Table 1, entry 8). In the lack of visible light intensity, no response was seen. Examining the function of solvents and the amount of visible light exposure was the next requirement (Table 1) on the model reaction. Solvents like water, DMSO, dichloromethane, and DMF led to poor yields. The yield obtained was superior when the reaction was conducted in ethanol. Moreover, we found that the yields were affected by the intensities of

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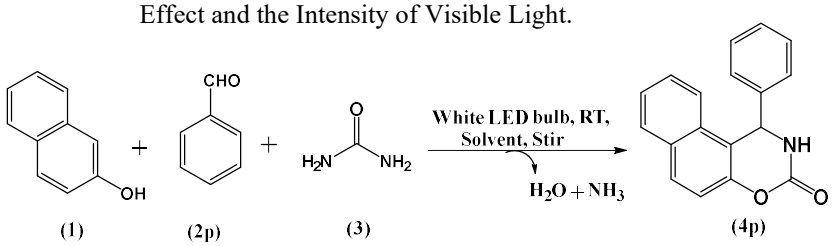
visible light. It was found that 18W visible light intensity was sufficient enough to afford (4p) with a 91% yield (Table 2, entry 16) at ambient conditions. The reaction mixture's temperature was recorded both in the dark and in the light (a shining LED bulb). It doesn't change.

Table-1: Examination of the Reaction[a] between 2-naphthol, Benzaldehyde, and Urea is Affected by the Solvent Effect and the Intensity of Visible Light.



Entry	Solvent	Visible Light Intensity (W)	Yield (%)	Time (h)
1	Toluene	14	58	11.7
2	Acetonitrile	14	68	11.7
3	Water	14	10	12.0
4	Dioxane	14	74	8.1
5	DMF	14	50	8.0
6	Methanol	14	71	10.0
7	THE	14	60	9.3
8	CH_2Cl_2	14	47	12.0
9	DMSO	14	42	10.1
10	Ethanol	14	77	7.0
11	Ethanol	9	42	8.2
12	Ethanol	12	75	7.3
13	Ethanol	18	91	6.0
14	Ethanol	26	91	6.0

[a]Experimental conditions: 2-napthol (1mmol), benzaldehyde (1mmol) and urea (1mmol) in 10ml of solvent under ambient conditions.

To explore the generality of 4(a-p) analog preparation, particularly concerning library construction, we carried out the reaction of diverse benzaldehydes under standard circumstances. Outcomes are provided (Table 2). Benzaldehydes having electron-releasing categories like methoxy, hydroxyl, methyl, and ethoxy were reacted with urea and 2-naphthol under optimum circumstances to afford high yields. Benzaldehydes with groups that take away electrons, like cyano and nitro, were also reacted with urea and 2-naphthol under standardized conditions to give excellent yields (entries 1, 2 Table 2). Halogen atoms like chloro, bromo, and fluoro also produced good yields under these conditions.

Based on the aforementioned findings as well as the literature reports,[15-20] we have suggested a possible reaction pathway (Scheme-1) to account for the process. The reaction proceeds through the ortho-quinone methides intermediates or acylimine intermediates; the subsequent addition of the urea to the ortho-quinone methides or the addition of the 2-naphthol to the acylimines, after the cyclization, forms 4(a-p) analogs. The yield of (4p) was inhibited in the presence of radical scavengers such as hydroquinone,[21] indicating that a free radical route is participating.

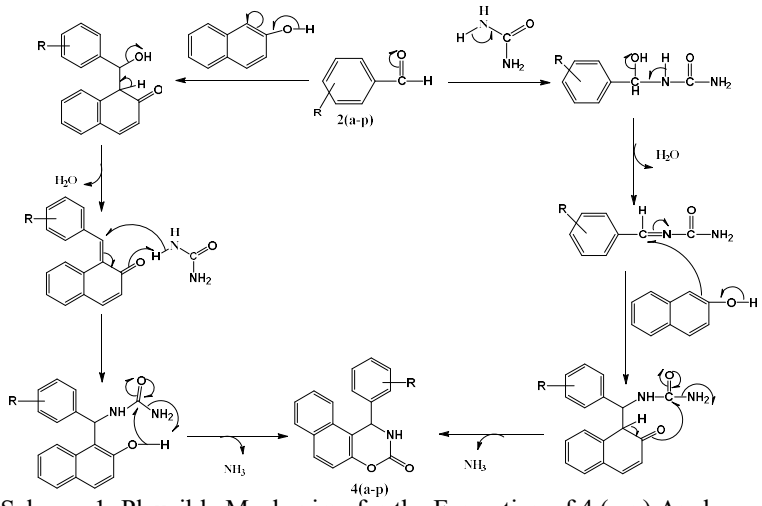
Standard protocol for 1,2-dihydro-1-phenylaphtho[1,2-e]1,3] oxazine-3-one synthesis 4(a-p)

A glowing LED bulb (18W) was put inside the 500 ml beaker just 2 cm above the surface of a mixture of benzaldehydes (1 mmol), 2-naphthol (1 mmol), and urea (1 mmol) in solvent ethanol

(10 ml) was stirred for the appropriate time (eluent: EtOAc and n-hexane monitored by TLC) under ambient conditions. To acquire the product, the solvent was extracted using a vacuum. The recrystallization is done using ethanol to produce desired 4 (a-p) analogs.

Table-2: Scope of Visible Light Enhanced Preparation of 4(a-p) Derivative

Entry	R	Product	Time (h)	Yield (%)
1	4-CN	4a	6.0	91
2	4-NO_2	4b	6.2	86
3	3,4-OCH_3	4c	8.0	89
4	3-Br	4d	7.0	91
5	4-OH	4e	7.5	96
6	3-Cl,4-F	4f	7.2	92
7	4-F	4g	7.4	91
8	4-Br	4h	7.1	90
9	4-CH_3	4i	7.4	89
10	3-Br,4-F	4j	7.5	92
11	2-Cl	4k	7.3	92
12	3-Br,4-OCH_3	4l	7.8	91
13	3-OC_2H_5	4m	8.0	90
14	3-Cl	4n	7.2	90
15	4-Cl	4o	6.9	88
16	H	4p	6.7	91



Scheme-1: Plausible Mechanism for the Formation of 4 (a-p) Analogs

RESULTS AND DISCUSSION

Spectral Details of (4a)

310.2530 mg (91% yield). Mp 178-180 °C. 1H NMR: δ 6.23 (s, 1H, CH), 6.93-7.80 (Ar-H, m, 10H), 11.19 (NH, s, 1H) ppm. 13C NMR: δ 57.1, 90.2, 100.8, 110.5, 111.9, 115.9, 116.3, 116.8, 123.3, 124.8, 125.3, 126.8, 130.8, 133.2, 133.8, 148.7, 151.1, 158.9, 169.1 ppm. HRMS for $C_{19}H_{12}N_2O_2$: M/Z = 300.0040.

Spectral Details of (4b)

300.2530 mg (86% yield). Mp 187-189 °C. 1H NMR: δ 6.44 (s, 1H, CH), 7.34-7.97 (10H, m, Ar-H), 12.30 (NH, s, 1H) ppm. 13C NMR: δ 59.9, 103.5, 115.6, 119.4, 123.4, 124.0, 124.9, 126.6,

127.7, 128.5, 129.1, 129.3, 129.4, 131.1, 141.6, 152.4, 154.9, 166.9 ppm. HRMS for $C_{18}H_{12}N_2O_4$: M/Z = 320.9020.

Spectral Details of (4c)
298.2530 mg (89% yield). Mp 185-187°C. 1H NMR: δ 3.65 ($2OCH_3$, s, 6H), 6.2 (CH, s, 1H), 6.91-7.82 (Ar-H, m, 9H) 12.13 (NH, s, 1H) ppm. 13C NMR: δ 50.3, 50.7, 61.2, 101.2, 110.5, 112.0, 116.0, 116.3, 116.9, 123.3, 125.0, 125.3, 126.8, 130.8, 133.1, 133.8, 148.6, 151.1, 158.9, 163.5 ppm. HRMS for $C_{20}H_{17}NO_4$: M/Z = 336.1300.

Spectral Details of (4d)
321.2346 mg (91% yield). Mp 233-235 °C. 1H NMR: δ 6.32 (CH, s, 1H), 7.06-7.77 (10H, m, Ar-H), 12.10 (NH, s, 1H) ppm. 13C NMR: δ 57.9, 101.2, 110.5, 111.8, 115.9, 116.3, 116.7, 123.3, 124.8, 125.3, 126.8, 130.8, 133.2, 133.8, 148.6, 151.1, 158.8, 166.9 ppm. HRMS for $C_{18}H_{12}BrNO_2$: M/Z = 354.0140.

Spectral Details of (4e)
279.4424 mg (96% yield). Mp 181-183°C. 1H NMR: δ 6.31 (CH, s, 1H), 7.22-7.83 (Ar-H, m, 10H), 11.27 (OH, s, 1H), 12.0 (s, 1H, NH) ppm. 13C NMR: δ 61.2, 104.0, 155.5, 119.5, 123.5, 124.0, 124.9, 126.6, 127.7, 128.5, 129.2, 129.3, 129.4, 131.0, 141.7, 152.4, 155.6, 166.9 ppm. HRMS for $C_{18}H_{13}NO_3$: M/Z = 292.0990.

Spectral Details of (4f)
300.8825 mg (92% yield). Mp 241-243°C. 1H NMR: δ 6.29 (CH, s, 1H), 7.06-7.83 (Ar-H, m, 9H), 12.10 (NH, s, 1H) ppm. 13C NMR: δ 59.3, 101.2, 110.5, 112.0, 116.0, 116.4, 116.8, 123.3, 124.9, 125.3, 126.9, 130.8, 133.2, 133.8, 148.6, 151.1, 158.9, 163.6 ppm. HRMS for $C_{18}H_{11}ClFNO_2$: M/Z = 328.0840.

Spectral Details of (4g)
266.7075 mg (91% yield). Mp 199-201 °C. 1H NMR: δ 6.34 (CH, s, 1H), 7.33-7.93 (Ar-H, m, 10H), 12.43 (NH, s, 1H) ppm. 13C NMR: δ 59.8, 103.6, 155.7, 119.4, 123.5, 124.0, 124.8, 126.6, 127.7, 128.6, 129.1, 129.3, 129.4, 131.1, 141.6, 152.4, 155.6, 167.0 ppm. HRMS for $C_{18}H_{12}FNO_2$: M/Z = 294.0940.

Spectral Details of (4h)
317.7045 mg (90% yield). Mp 220-222 °C. 1H NMR: δ 6.21 (CH, s, 1H), 6.55-7.82 (Ar-H, m, 10H), 12.38 (s, 1H, NH) ppm. 13C NMR: δ 55.9, 101.8, 107.6, 110.5, 112.3, 116.0, 117.5, 117.6, 119.8, 123.3, 125.3, 126.9, 130.7, 146.9, 148.4, 149.4, 150.0, 163.0 ppm. HRMS for $C_{18}H_{12}BrNO_2$: M/Z = 353.0300.

Spectral Details of (4i)
275.3081 mg (89% yield). Mp 169-171 °C. 1H NMR: δ 2.21 (CH_3, s, 3H), 6.22 (s, CH, 1H), 6.94-7.88 (10H, m, Ar-H), 11.22 (NH, s, 1H) ppm. 13C NMR: δ 36.0, 59.7, 103.5, 155.6, 119.4, 123.1, 124.0, 124.9, 126.7, 127.7, 128.5, 128.9, 129.2, 129.4, 131.0, 141.6, 152.4, 155.7, 167.1 ppm. HRMS for $C_{19}H_{15}NO_2$: M/Z = 290.1190.

Spectral Details of (4j)
284.3312 mg (92% yield). Mp 256-258 °C. 1H NMR: δ 6.54 (CH, s, 1H), 7.33-7.98 (Ar-H, m, 9H), 12.35 (NH, s, 1H) ppm. 13C NMR: δ 57.0, 101.1, 110.5, 112.0, 116.0, 116.3, 116.8, 123.3, 125.0, 125.3, 126.8, 130.8, 133.2, 133.8, 148.6, 151.5, 158.9, 166.9 ppm. HRMS for $C_{18}H_{11}BrFNO_2$: M/Z = 372.0070.

Spectral Details of (4k)
284.3312 mg (92% yield). Mp 252-254 °C. 1H NMR: δ 6.44 (CH, s, 1H), 7.33-7.97 (Ar-H, m, 10H), 12.39 (1H, s, NH) ppm. 13C NMR: δ 60.0, 104.1, 114.4, 120.0, 123.0, 124.0, 125.0, 126.6,

127.7, 128.4, 128.9, 129.2, 129.4, 130.0, 139.9, 152.4, 155.6, 167.1 ppm. HRMS for $C_{18}H_{12}ClNO_2$: M/Z = 310.0420.

Spectral Details of (4l)
348.5442 mg (91% yield). Mp 201-203 °C. 1H NMR: δ 3.76 (3H, s, OCH_3), 6.23 (s, CH, 1H), 6.93-7.82 (Ar-H, m, 9H), 12.22 (NH, s, 1H) ppm. 13C NMR: δ 36.0, 59.6, 103.5, 115.5, 119.3, 123.0, 124.1, 125.0, 126.5, 127.7, 128.4, 129.0, 129.2, 129.4, 131.0, 141.6, 152.4, 155.6, 166.0 ppm. HRMS for $C_{19}H_{14}BrNO_3$: M/Z = 384.3000.

Spectral Details of (4m)
411.000 mg (90% yield). Mp 245-247 °C. 1H NMR: δ 1.24 (t, CH_3, 3H), 3.66 (q, CH_2, 2H), 6.22 (s, CH, 1H), 6.90-7.84 (m, 10H, Ar-H), 12.42 (NH, s, 1H) ppm. 13C NMR: δ 20.3, 59.2, 101.1, 110.5, 112.0, 116.0, 116.3, 116.8, 123.3, 125.0, 125.3, 126.8 (2C), 130.8, 133.2, 133.8, 148.6, 151.1, 158.9, 163.5 ppm. HRMS for $C_{20}H_{17}NO_3$: M/Z = 320.1300.

Spectral Details of (4n)
278.1510 mg (90% yield). Mp 212-214 oC. 1H NMR: δ 6.45 (s, 1H, CH), 7.35-7.97 (Ar-H, m, 10H), 12.30 (s, 1H, NH) ppm. 13C NMR: δ 55.8, 100.8, 107.7, 110.5, 112.3, 116.0, 117.5, 117.7, 119.8, 123.3, 125.3, 126.8, 130.7, 147.3, 148.4, 149.4, 150.0, 163.1 ppm. HRMS for $C_{18}H_{12}ClNO_2$: M/Z = 310.0660.

Spectral Details of (4o)
271.9690 mg (88% yield). Mp 207-209 °C. 1H NMR: δ 6.34 (s, 1H, CH), 7.22-7.81 (m, 10H, Ar-H), 12.44 (1H, s, NH) ppm. 13C NMR: δ 57.0, 100.8, 110.5, 111.9, 115.9, 116.3, 116.8, 123.3, 124.8, 125.3, 126.8, 130.8, 133.2, 133.8, 148.6, 151.1, 158.9, 167.1 ppm. HRMS for $C_{18}H_{12}ClNO_2$: M/Z = 310.0650.

Spectral Details of (4p)
258.5889 mg (91% yield). Mp 218-220 °C. 1H NMR: δ 6.31 (1H, s, CH), 7.07-7.77 (Ar-H, m, 11H), 12.65 (s, 1H, NH) ppm. 13C NMR: δ 59.6, 103.5, 155.5, 119.4, 123.0, 124.0, 124.9, 126.6, 127.7, 128.4, 129.0, 129.2, 129.4, 131.0, 141.6, 152.4, 155.6, 167.0 ppm. HRMS for $C_{18}H_{13}NO_2$: M/Z = 276.1000.

CONCLUSION

In conclusion, our team developed an effective and single-pot approach for the production of 1,2-dihydro-1-phenylnaphtho[1,2-e][1,3]oxazine-3-one analogs by a three-component condensation of urea, benzaldehydes with 2-napthol, with the help of white LED light. Simple operation, inexpensive visible light, and mild reaction conditions make this method efficient and also practical.

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CONFLICT OF INTERESTS

There is no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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