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Catalyst-free, visible light irradiation promoted synthesis of spiroacenaphthylenes and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones in aqueous ethyl lactate

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ABSTRACT

Catalyst-free three-component tandem approach can synthesize spiroacenaphthylenes and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones *by* Knoevenagel-Michael cyclocondensation *via* visible light irradiation in aqueous ethyl lactate at room temperature. The significant advantages of the present protocol include energy-effectiveness, catalyst-free, excellent yields, operational simplicity, high atom-economy, commercially accessible, inexpensive preliminary substances, so it meets some features of sustainablility and green chemistry.

1. Introduction

Given the increased requests for influential, sustainable, and eco-friendly synthesis methods in catalyst-free, green chemistry use was very useful for preparing the organic mixtures over the last years due to low expense, easy workup, low pollution, and precluding the catalyst effect on substrates. Also, visible light irradiation has been a reliable approach for green chemists because of its plentiful reserves of the energy, low cost and its renewable source of energy in the eco-friendly synthesis of organic compounds [1,2]. In general, we employed light emitting diodes and compact fluorescent lights as the sources of visible light for various transformations.

We report spiropyrans and pyrazolophthalazines with various pharmacological features as (Fig. 1) anticancer [3], fungicidal [4], anti HIV [5], antimalarial [6], antitubercular [7], in addition these spirocycles are MDM2 inhibitor [8] and progesterone receptor modulator [9], anti-inflammatory [10], anti micrbiological [11], vasorelaxant [12], cardiotonic [13] and anticonvulsant [14].

Many approaches are accessible such as Et_3N [15], [BDDMA]Cl [16], DABCO [17], DBU [18], Fe_2O_3 [19], $NiFe_2O_4$@SiO_2@Melamine [20], Isinglass [21], SBA-Pr-SO_3H [22], $InCl_3$ [23], $NiCl_2.6H_2O$ [24], [Bmim]OH [25], Ultrasound-assisted [26], *P*-TSA [27], STA [28], CuI nanoparticles [29], PTSA/[Bmim]Br [30], TBBAD [31], $Cu(OAc)_2.H_2O$ [32], K_2CO_3 [33], β-cyclodextrin [34], $[Bu_3NH][HSO_4]$ [35], CuO nanoparticles [36], NZF@HAP-Cs [37], theophylline [38], carboxymethyl cellulose [39] and STA-Amine-Si-Magnetite [40].

The reported procedures may result in several cases. Some of synthetic policies include restrictions regarding metal catalyst, the expensive reagents, intense reaction conditions, uniform training process, environmental hazard, long reaction time.

Searching for simple, effective, and eco-safe strategies, which, under green circumstances, can increase organic reactions have fascinated many researchers due to the mentioned difficulties and our considerations for an environmentally benign protocols [41]. Therefore, we report the catalyst-free synthesis of spiroacenaphthylenes and 1*H*-pyrazolo[1,2-b]phthalazine-5,10-diones with the CFL irradiation at room temperature as green endorsing media in aqueous ethyl lactate *via* tandem Knoevenagel-Michael cyclocondensation which can provide short reaction times and the anticipated products in excellent yields to overcome some expense problems in industry.

2. Experimental

2.1. General

Using a 9100 electro-thermal device, the melting points of all compounds were found. In addition, the nuclear magnetic resonance recording, the spectrum (^{1}H NMR) was performed on a Bruker (DRX-400) instruments using DMSO-d_6 as solvent. All reagents were purchased from the chemical companies called Fluka, Merck, and Acros and used without additional treatment.

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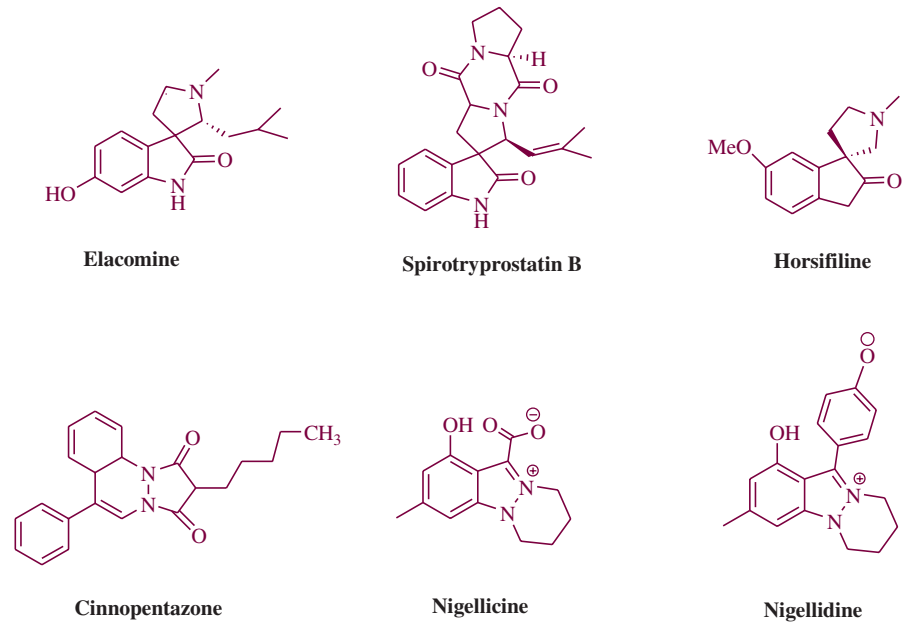
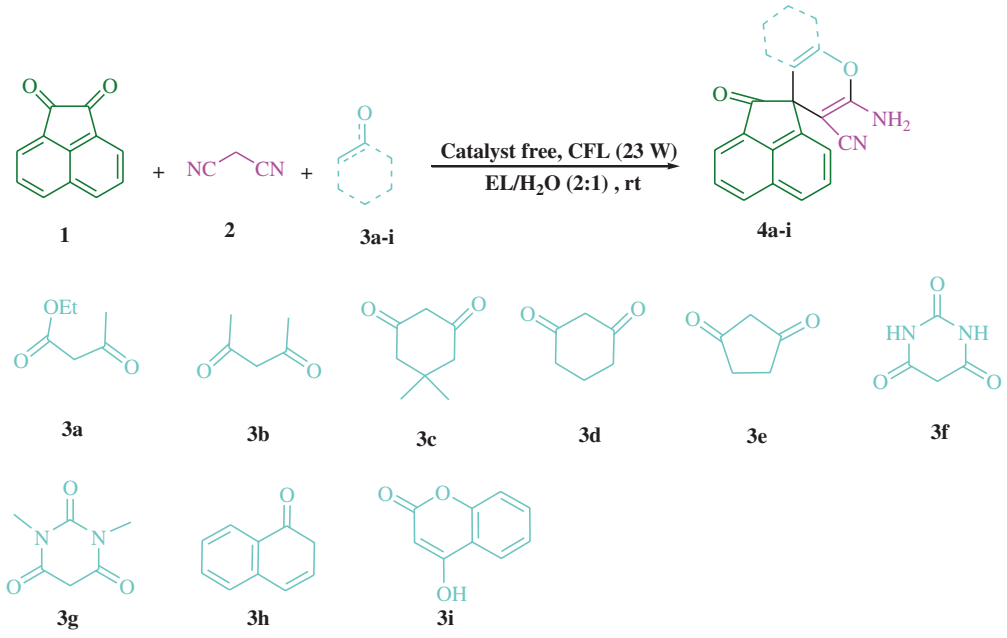


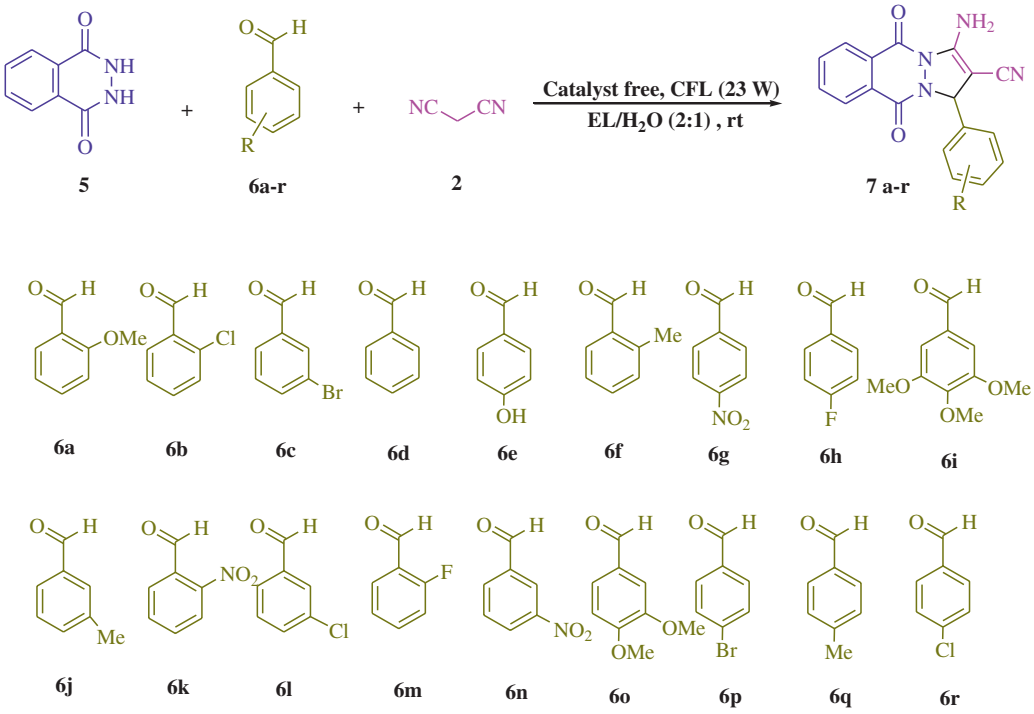
Fig. 1. Some alkaloids containing biologically active compounds and heterocyclic spirooxindoles unit with two ring junction nitrogen atoms.



Scheme 1. Synthesis of spiroacenaphthylenes.

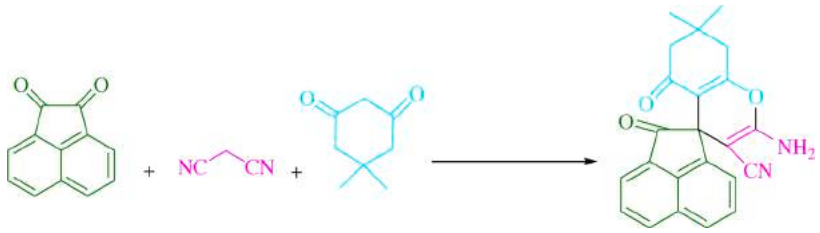
2.2. *The overall process of preparing (**4a-i**)*

Multifarious reagents including acenaphthequinone (**1**, 1.0 mmol), malononitrile (**2**, 1.0 mmol) and various reagents including a-methyl-encarbonylcompounds/enols (**3a-i**, 1.0 mmol) were reacted opposed to CFL (23 W) irradiation at room temperature in aqueous ethyl lactate (2:1, 3 mL) (Scheme 1). This was observed by TLC that employed (ethyl acetate/*n*-hexane (1:3)). Afterwards, the filtering of the acquired solid was conducted, then the solid was rinsed water (2 × 3 mL) and ethanol (2 × 3 mL) and solid composition became recrystallized by EtOH. The products were classified after the comparison of spectroscopic information (^{1}H NMR). Support for this manuscript can be found in the online version.



Scheme 2. Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones.

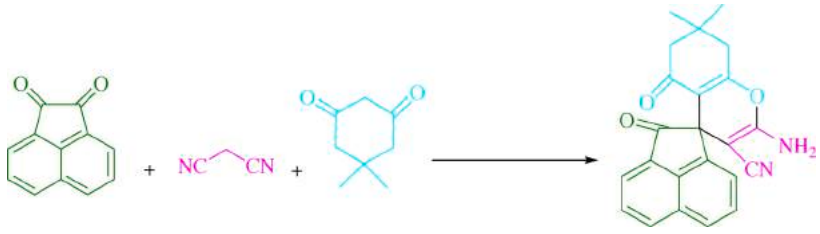
Table 1
Solvent optimization in synthesis of **4c**[a].



Isolated Yields (%)	Time (h)	Solvent (3 mL)	Entry
trace	14	H_2O	1
43	10	EL	2
31	10	EtOH	3
22	10	H_2O/EtOH (1:1)	4
trace	14	EtOAc	5
trace	8	Solvent free	6
74	5.5	EL/H_2O (1:1)	7
91	**5**	**EL/H_2O (2:1)**	**8**
91	5	EL/H_2O (3:1)	9
24	14	CH_3CN	10
45	14	DMSO	11
60	14	DMF	12
63	14	THF	13
38	12	MeOH	14
trace	14	$CHCl_3$	15
trace	14	DCM	16

[a] Reaction conditions: acenaphthequinone (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in the presence of CFL (23 W) irradiation under catalyst-free circumstances at rt.

Table 2
CFL optimization in synthesis of **4c**[a].



Isolated Yields (%)	Time (h)	Reaction conditions	Entry
76	5	CFL (18 W)	1
81	5	CFL (20 W)	2
84	5	CFL (22 W)	3
91	**5**	**CFL (23 W)**	**4**
91	5	CFL (32 W)	5

[a] Reaction conditions: acenaphthequinone (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in the presence of CFL irradiation under catalyst-free conditions in EL/H_2O (2:1) at rt.

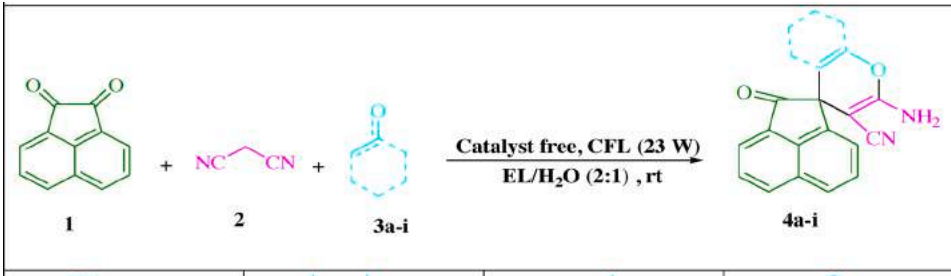
2.3. The overall process of preparing (7a-r)

Multifarious reagents including phthalhydrazide (**5**, 1.0 mmol), malononitrile (**2**, 1.0 mmol) and aromatic aldehydes (**6a-r**, 1.0 mmol) were reacted opposed to CFL (23 W) irradiation at room temperature in aqueous ethyl lactate (2:1, 3 mL) (Scheme 2). This was observed by TLC that employed (ethyl acetate/*n*-hexane (1:3)). Afterwards, the filtering of the acquired solid was conducted, then the solid was rinsed water (2 × 3 mL) and ethanol (2 × 3 mL) and solid composition became recrystallized by EtOH. The products were classified after the comparison of spectroscopic information (^{1}H NMR). Support for this manuscript can be found in the online version.

3. Results and discussion

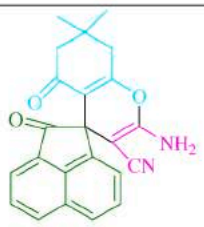
At first, Table 1 shows the results of the reaction between acenaphthequinone (1.0 mmol), malononitrile (1.0 mmol) and dimedone (1 mmol) (**4c**) in different solvents under catalyst-free conditions opposite compact floating lamp radiation (CFL (23 W)) at room temperature. Accordingly, a small amount of H_2O, EL, EtOH, H_2O/EtOH (1:1), EtOAc, CH_3CN, DMSO, DMF, THF, MeOH, $CHCl_3$, DCM and solvent-free products were found. Extraordinary improvements were clear under EL/H_2O as a solvent (Table 1, entries 7–9). Using CFL (23 W) irradiation without further catalyst, an ultra-91 % yield was established under EL/H_2O (2:1) as a solvent (Table 1, entry 8). Also, by changing the intensity of CFL (18 W, 20 W, 22 W, 23 W and 32 W) irradiation, the optimized conditions were defined. According to Table 2, the best results were opposite the compact fluorescent lamp (CFL) (23 W) irradiation (Table 2, entry 4).

Table 3
Catalyst-free synthesis of spiroacenaphthylenes.

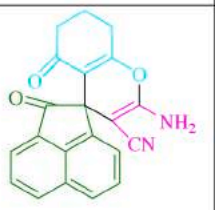


4a (5 h, 93%)
Mp. Mp>300 °C
Lit. Mp>300 °C [15]

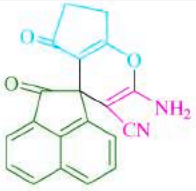
4b (4.5 h, 89%)
Mp. Mp>300 °C
Lit. Mp>300 °C [15]



4c (5 h, 91%)
Mp. 265-267 °C
Lit. 263-265 °C [21]



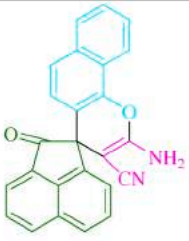
4d (4 h, 94%)
Mp. 241-243 °C
Lit. 242-244 °C [16]



4e (4 h, 92%)
Mp. 299-301 °C
Lit.. 302-303 °C [21]

4f (5 h, 87%)
Mp. 281-283 °C
Lit. 283-285 °C [20]

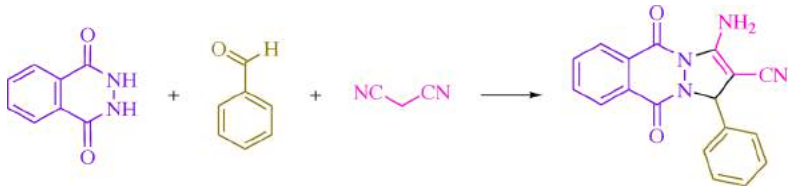
4g (5.5 h, 90%)
Mp. 277-279 °C
Lit. 276-278 °C [20]



4h (6 h, 85%)
Mp. Mp>300 °C
Lit. Mp>300 °C [15]

4i (6.5 h, 88%)
Mp. Mp>300 °C
Lit.. Mp>300 °C [16]

Table 4
Solvent optimization in synthesis of **7d**[a].



Isolated Yields (%)	Time (h)	Solvent (3 mL)	Entry
trace	10	H_2O	1
52	8	EL	2
44	8	EtOH	3
35	8	H_2O/EtOH (1:1)	4
trace	10	EtOAc	5
trace	8	Solvent free	6
78	4	EL/H_2O (1:1)	7
93	**4**	**EL/H_2O (2:1)**	**8**
94	4	EL/H_2O (3:1)	9
29	10	CH_3CN	10
51	12	DMSO	11
64	10	DMF	12
59	10	THF	13
41	8	MeOH	14
trace	10	$CHCl_3$	15
trace	10	DCM	16

[a] Reaction conditions: phthalhydrazide (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) in the presence of CFL (23 W) irradiation under catalyst-free circumstances at rt.

Table 5
CFL optimization in synthesis of **7d**[a].

Isolated Yields (%)	Time (h)	Reaction conditions	Entry
73	4	CFL (18 W)	1
82	4	CFL (20 W)	2
89	4	CFL (22 W)	3
93	**4**	**CFL (23 W)**	**4**
93	4	CFL (32 W)	5

[a] Reaction conditions: phthalhydrazide (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) in the presence of CFL irradiation under catalyst-free in EL/H_2O (2:1) conditions at rt.

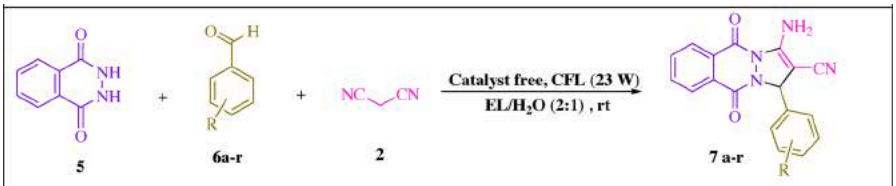
Table 3 and Scheme 1, shows that its functionality with different substrates.

Also in continuation, Table 4 shows the results of the reaction between phthalhydrazide (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) (**7d**) in different solvents under catalyst-free conditions opposite compact floating lamp radiation (CFL (23 W)) at room temperature. Accordingly, a small amount of H_2O, EL, EtOH, H_2O/EtOH (1:1), EtOAc, CH_3CN, DMSO, DMF, THF, MeOH, $CHCl_3$, DCM and solvent-free products were found. Extraordinary improvements were clear under EL/H_2O as a solvent (Table 4, entries 7–9). Using CFL (23 W) irradiation without further catalyst, an ultra-93 % yield was established under EL/H_2O (2:1) as a solvent (Table 4, entry 8). Also, by changing the intensity of CFL (18 W, 20 W, 22 W, 23 W and 32 W) irradiation, the optimized conditions were defined. According to Table 5, the best results were opposite the compact fluorescent lamp (CFL) (23 W) irradiation (Table 5, entry 4). Table 6 and Scheme 2, shows that its functionality with different substrates.

The scheme 3 indicates the proposed procedure for the synthesis of **4c**. At first, the active methylene compound **2** was formed by tautomering malononitrile irradiated with visible light in EL/H_2O. The combination of activated methylene **2** and acenaphthequinone **1** was subjected to a Knoevenagel condensation in solution to give a cyanoolefin **A** by removing water. Then, visible light activated the cyanoolefin to form a free radical **B**. The intermediate **B** abstracted a methylene hydrogen from malononitrile, and produced a malononitrile radical, which in turn summarizes a hydrogen from dimedone **3** to form the intermediate **E**. Therefore, intermediate **B** also becomes intermediate **C**. Subsequently, the intermediate **E** reacted further with the intermediate **C** by Michael's additive, resulting in the intermediate **F** of shape, followed by the intra-molecular cycle to produce the desired product **4c**.

The proposed mechanism for the synthesis of (**7a-r**) is indicated by the Scheme 4. The intermediate ylidenemalononitrile (cyano olefin) **H** was willingly formed at the site of Knoevenagel concentration between arylaldehyde **6** and active methylene compound **2** opposite the visible light irradiation in the solvent (EL/H_2O) which can be responded to by the sterile effects of arylaldehydes on efficacy (Table 6). Then, visible light could activate the mediator to form a free radical Intermediate **I**. Intermediate **I** absorbs a hydrogen from methylene malononitrile **2**, and

Table 6
Catalyst-free synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones.

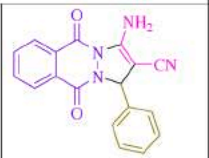


5 6a-r 2 7 a-r

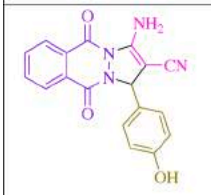
7a (4 h, 91%)
Mp. 151-153 °C
Lit. 153-155 °C [37]

7b (4.5 h, 88%)
Mp. 258-260 °C
Lit. 257-259 °C [28]

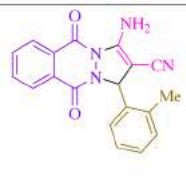
7c (5 h, 85%)
Mp. 268-270 °C
Lit. 270-272 °C [22]



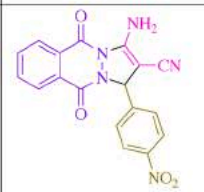
7d (4 h, 93%)
Mp. 269-271 °C
Lit. 270-272 °C [29]



7e (5 h, 84%)
Mp. 272-274 °C
Lit. 270-272 °C [23]

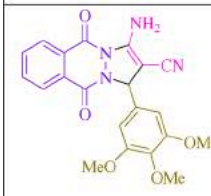


7f (2.5 h, 93%)
Mp. 249-251 °C
Lit. 248-250 °C [29]

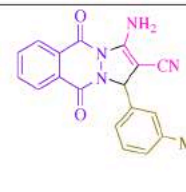


7g (3 h, 90%)
Mp. 227-229 °C
Lit. 228-229 °C [28]

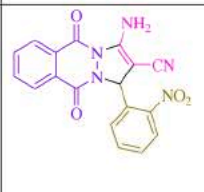
7h (2.5 h, 94%)
Mp. 264-266 °C
Lit. 263-265 °C [22]



7i (5 h, 87%)
Mp. 252-254 °C
Lit. 253-255 °C [23]



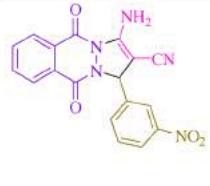
7j (3 h, 90%)
Mp. 250-252 °C
Lit. 250-252 °C [29]



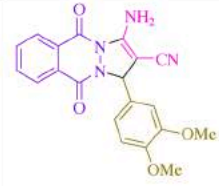
7k (2.5 h, 94%)
Mp. 266-268 °C
Lit. 265-266 °C [22]

7l (4.5 h, 85%)
Mp. 264-266 °C
Lit. 266-267 °C [22]

7m (2 h, 93%)
Mp. 269-271 °C
Lit. 268-270 °C [23]

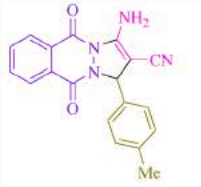


7n (3 h, 93%)
Mp. 267-269 °C
Lit. 269-271 °C [30]

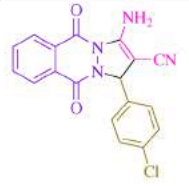


7o (5 h, 84%)
Mp. 233-235 °C
Lit. 233-237°C [28]

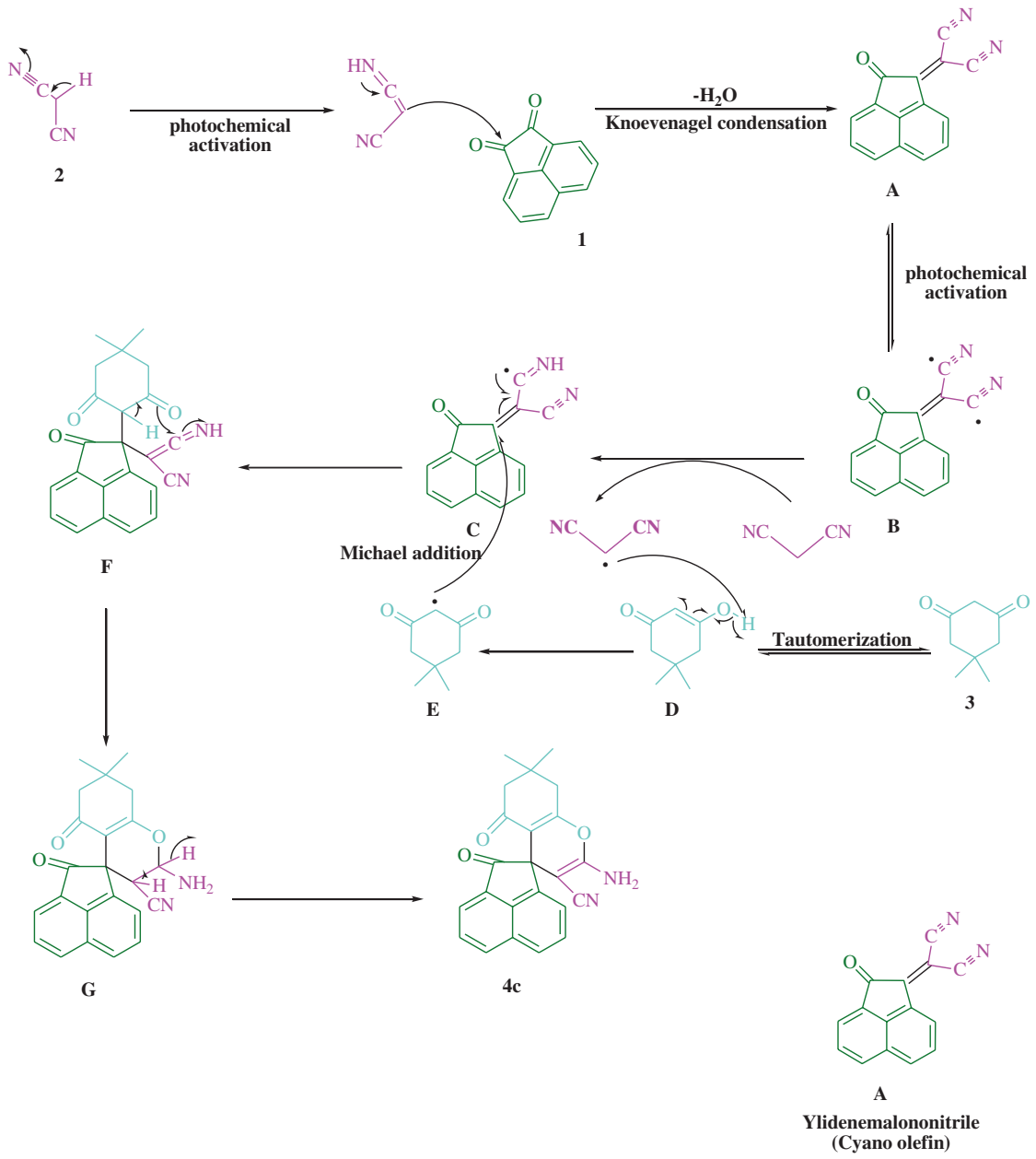
7p (5 h, 83%)
Mp. 266-268 °C
Lit. 265-267 °C [22]



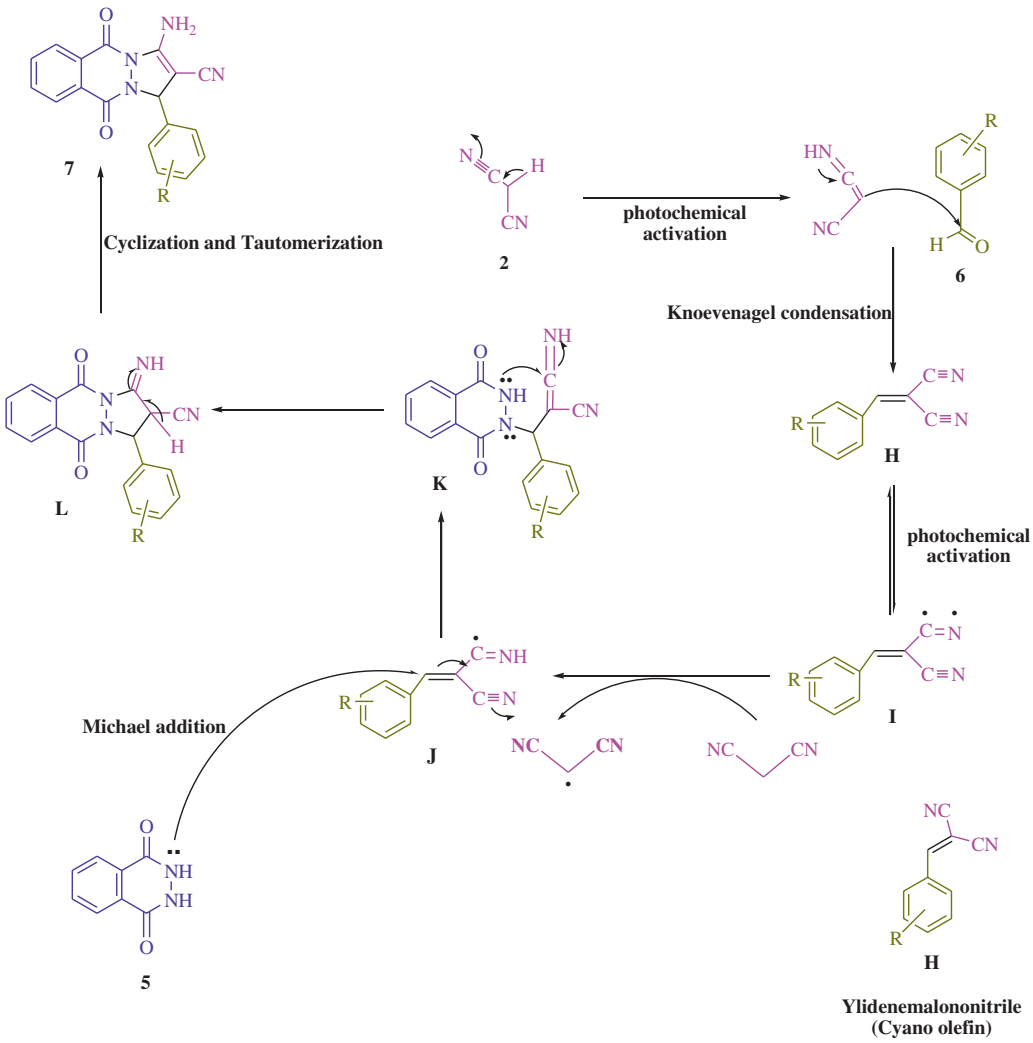
7q (3 h, 92%)
Mp. 252-254 °C
Lit. 253-255 °C [29]



7r (5 h, 86%)
Mp. 272-274 °C
Lit. 270-272 °C [30]



Scheme 3. Recommended mechanistic path for synthesizing spiroacenaphthylenes.



Scheme 4. Recommended mechanistic path for synthesizing 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives.

thus converts malononitrile to radical malononitrile, thus, it is composed of intermediate J which suffers from Michael addition of phthalhydrazide **5** to the C═C bond of J forms iminomethylene derivative intermediate **K**. Finally, the mentioned compounds (**7a-r**) were created by intra-molecular cyclization and cooperation with tautomerization of Michael's additive **K**.

4. Conclusion

The study indicated a catalyst-free preparation of spiroacenaphthylenes and 1H-pyrazolo[1,2-b]phthalazine-5,10-diones -a biologically significant scaffold- *via* visible light irradiation as a low-cost and green promoter in aqueous ethyl lactate at room temperature according to the principles of green chemistry. The important points in the current study include the use of non-hazardous reaction circumstances, application of cheap initiating substances, operational simplicity, catalyst-free, separation of the pure product by easy filtration thus avoids the need for column chromatography, efficient features of the reaction, excellent yields, metal-free, one key characteristic of the existing work is to use CFL irradiation as green endorsing media sufficiently remarking the rising potential of CFL irradiation in organic synthesis.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jphotochem.2020.113041.

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