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Visible Light Mediated Organophotoredox-Catalyzed One-Pot Domino Synthesis of Novel 6,7 Disubstituted 1*H*-Pyrroles

Santhosh Govindaraju[1] · **Sumaiya Tabassum**[2]

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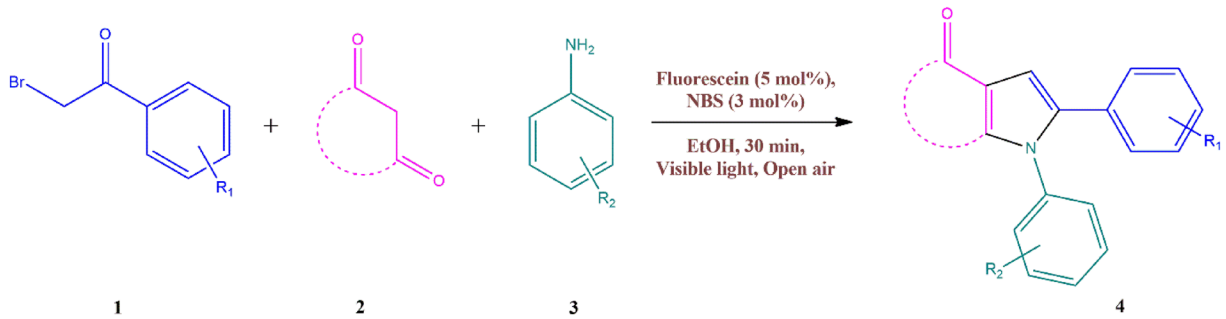
Abstract

The development of environmentally benign protocols to synthesize novel *N*-heterocycles is vital in the field of synthetic organic chemistry. We herein report a successful one-pot domino synthesis of novel 6,7 disubstituted 1*H*-pyrroles using substituted phenacyl bromide, barbituric acid/Meldrums acid, aromatic amines catalysed by 5 mol% Fluorescein in presence of visible light. This procedure is a useful and adaptable method for the synthesis of pyrroles since it is compatible with a wide range of sensitive functional groups, does not require column chromatography purification. During the reaction, Fluorescein may catalyse the formation of enamine leading to amino alcohol which subsequently undergoes dehydration to give 6,7 disubstituted 1*H*-pyrroles. All the synthesized derivatives were obtained in 90–95% yields and were characterized by ^{1}H, ^{13}C NMR and HRMS (ESI) analysis.

Graphical Abstract



Keywords 6,7 disubstituted 1H-pyrrole · Fluorescein · Organophotocatalyst · Visible light · Ethanol · Four-component reaction

1 Introduction

Pyrrole and its derivatives belong to the class of biologically active scaffold and are well known to exhibit diverse and distinct physiological properties [1–3]. The electron-rich pyrrole ring is less basic and possesses a dipole moment of 1.5–1.9 D exactly contrary to other members of the same family such as thiofuran, furan, and azine. Pyrrole derivatives act as antihypertensive [4], antidepressant [5], analgesic [6], anti-inflammatory [7], anticancer [8, 9], fungicidal [10], insecticidal [11, 12] and plant growth regulators [13]. They are well known to inhibit HIV-1 integrase [14], CYP1

✉ Sumaiya Tabassum
sumaiya87org@gmail.com

[1] Department of Sciences and Humanities, School of Engineering and Technology, CHRIST (Deemed To Be University), Kumbalagodu, Mysore Road, Bengaluru 560074, India

[2] Department of Chemistry, Surana College, South End Road, Basavanagudi, Bengaluru 560004, India

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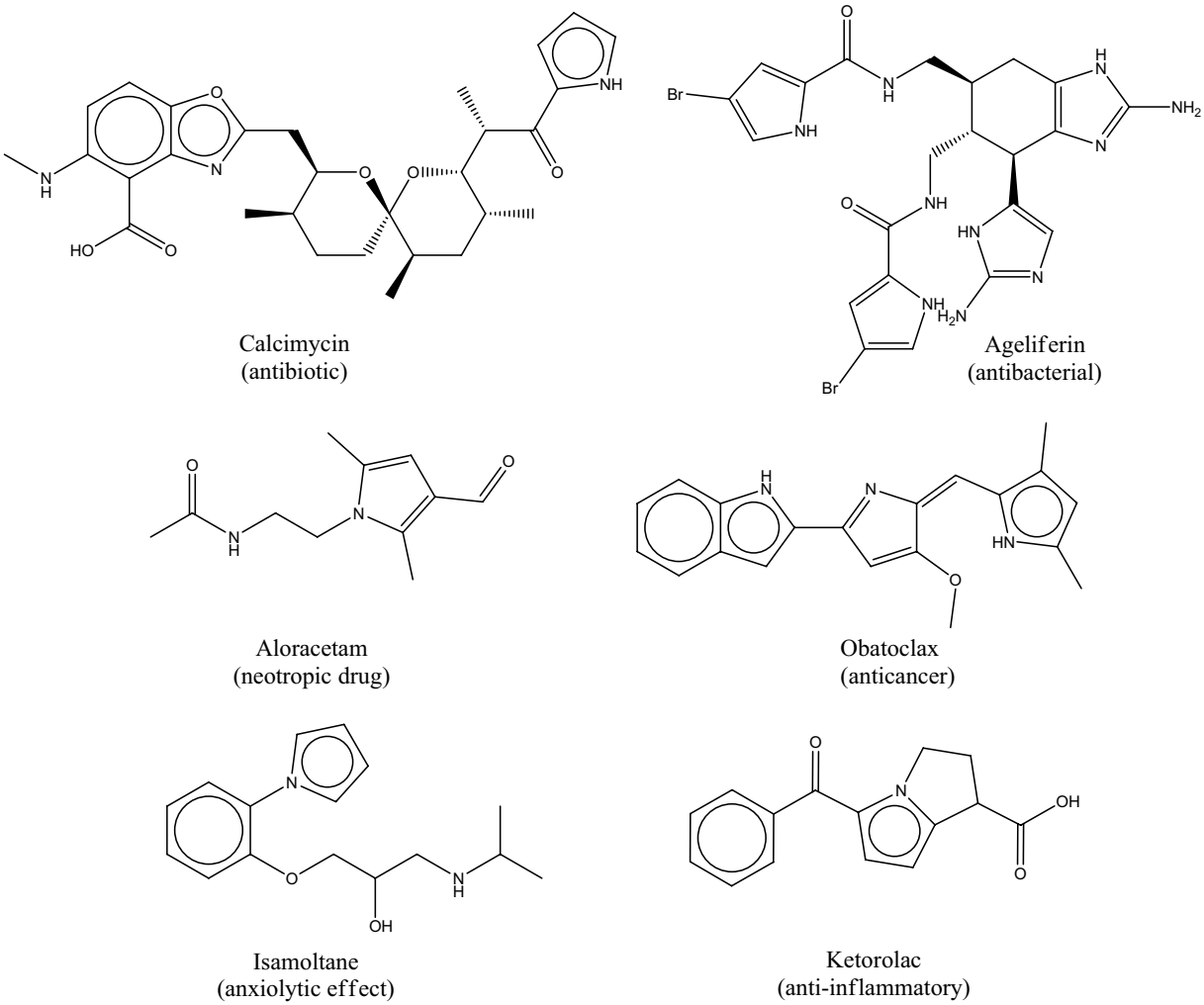


Fig. 1 Some representative drugs containing pyrrole ring

[15], DNA/RNA polymerase [16] and FMS kinase [17] enzymes present in several mammalian and microbial cells.

Substituted pyrroles behave as corrosion prohibitors [18], preservatives [19], precursors [20], form the building block for pigments such as chlorophyll and haemoglobin. They are present in the natural extracts of several alkaloids [21] and form the heart of vitamin B12, haematoidin, biliverdin, bacteriochlorin, porphobilinogen and proline. Several commercially available drugs such as calcimycin, ageliferin, aloracetam, isamoltane, obatoclax, ketorolac consist of pyrrole scaffold (Fig. 1).

The synthesis of polyfunctional pyrrole rings and the study of their medicinal properties stand out as a zone of the immense scope of research in organic chemistry. Nevertheless, synthesizing pyrroles entailing multiple substituents and functional groups are challenging for chemists, and consequently, new methodologies [22–32] following the principles of green chemistry are in demand and highly profitable.

As a result, synthetic chemists have paid intense attention to the construction of such frameworks and several reactions involving the use of condensation [33], cascade [34], cyclization [35], decarboxylation [36], 1,3 dipolar addition [37], catalytic dehydrogenation [38] reactions are reported. However, they are associated with several liabilities such as longer reaction duration, use of catalyst, lesser yield, multiple steps and column chromatography method of purification.

Multicomponent reactions (MCRs), which combine three or more substrates to generate a highly complex and divergent [39] product in a single-step manner have experienced a rapid increase in applications in all domains of organic synthesis [40, 41]. They have obvious advantages over conventional multistep processes, including high reaction efficiency [42], atom economy [43], waste reduction, and energy savings [44]. These characteristics are in line with the green chemistry principles, making MCRs a suitable synthetic strategy in combinatorial chemistry and diversity-oriented

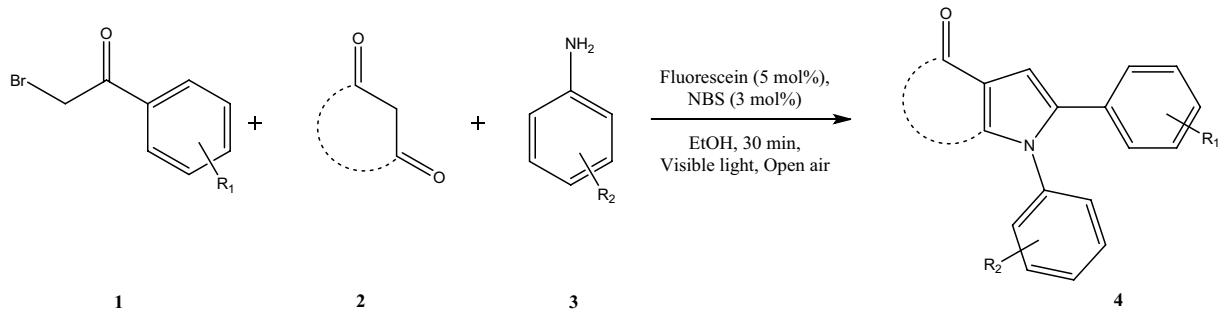


Fig. 2 Synthesis of novel 6,7 disubstituted 1*H*-pyrroles

synthesis [45]. Indeed, they have been frequently employed in the pharmaceutical industry to generate enormous libraries of small substrates that can be exploited to find lead compounds in a shorter period saving manpower. MCRs generally employ easily accessible substrates under cleaner and efficient energy transfer conditions to investigate the dimensions of the reaction to generate excellent product yields.

In this regard, visible light-mediated MCRs [46] have caught the attraction of synthetic organic chemists as they stimulate the synthesis of heterocycles under significantly moderate conditions generating the target molecules in excellent yields. Most of the photoinduced reactions work in presence of visible light [47], blue light [48], green light [49] and hence providing a cleaner and efficient pathway leading to the goal of sustainable synthesis. In a photochemical process, one of the starting materials is converted to a reactive intermediate which then subsequently interacts with other substrates generating product in a one-pot manner. The efficiency of the visible light catalyzed MCR can be further enhanced by the use of a suitable photocatalyst which can generate the radical intermediate in a shorter duration. Photocatalyzed MCRs have proven to be successful in the synthesis of polyhydroquinolines [50], 3-arylacetals, trisubstituted hydroxylamines [51], α-amino amides [52], secondary amine [53], indole [54], imidazole [55] and several others.

Contemplating these facts and in our continuous pursuit in synthesizing heterocycles [56] through cleaner reaction profiles following green chemistry principles [57] we herein successfully report a visible light-mediated, fluorescein catalyzed one-pot sustainable approach for the synthesis of twelve novel 6,7 disubstituted 1*H*-pyrroles in excellent yields (Fig. 2).

2 Materials and Methodology

2.1 Experimental Section

Reagents and solvents of commercial-grade were purchased from Sigma-Aldrich and TCI Chemicals (India) Pvt. Ltd. and were used without further purification except for aldehydes which were distilled before use. The progress of the reactions and the purity of products was assessed by TLC [analytical silica gel plates (Merck60 F_{254})]. Melting points were determined on a RAAGA, an Indian make apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Avance Bruker instrument operating at 400 MHz and 100 MHz in DMSO-d_6 respectively. Chemical shifts are reported in δ ppm. HRMS data were obtained on a Varian IonSpec QFT-MS spectrometer with the technique of electrospray ionization.

2.2 General Procedure for the Synthesis of Novel 6,7 Disubstituted 1H-Pyrroles 4(a-l)

In a 50 mL round-bottomed flask, a mixture of substituted 2-bromo-1-(phenyl)ethanone (1 mmol), barbituric acid/Meldrum's acid (1 mmol), aryl amine (1 mmol), EtOH (3 mL), Fluorescein (5% mol) along NBS (3% mol) was taken and stirred at room temperature using a magnetic stirrer for 30 min. The setup was irradiated using white light generated by a 22 W white LED. The reactions were monitored by thin-layer chromatography (TLC) using hexane: ethyl acetate (7:3) as eluent. After completion of the reaction (TLC), the reaction mixture was quenched with ice and the precipitate formed was filtered, washed, dried and recrystallized from ethanol to yield the pure product. The structures of all the products were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analysis.

2.3 Spectral Data

2.3.1 7-(4-Chlorophenyl)-6-(p-tolyl)-1H-pyrrolo[2,3-d] pyrimidine-2,4(3H,7H)-dione (4a)

Yellow solid, mp: 218 – 219 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.38 (s, 1H, -NH), 9.29 (s, 1H, -NH), 7.86 – 7.22 (m, 8H, Ar–H), 6.53 (s, 1H, Ar–H), 2.56 (s, 3H, –CH_3) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 148.9, 142.8, 138.2, 136.2, 134.9, 133.6, 131.7, 127.9, 126.1, 124.4, 122.1, 106.0, 98.4, 23.5 ppm;

HRMS (ESI) calcd for $C_{19}H_{15}ClN_3O_2$ $[M+H]^+$: 352.0853, found 352.0847.

2.3.2 7-(4-Nitrophenyl)-6-(p-tolyl)-1H-pyrrolo[2,3-d] pyrimidine-2,4(3H,7H)-dione (4b)

Daek Yellow solid, mp: 261 – 262 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H, –NH), 9.72 (s, 1H, –NH), 8.27 – 7.25 (m, 8H, Ar–H), 6.73 (s, 1H, Ar–H), 2.27 (s, 3H, -CH_3) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 149.7, 147.5, 142.7, 138.7, 136.7, 134.8, 131.6, 126.4, 125.2, 123.7, 119.4, 105.5, 99.7, 23.1 ppm;

HRMS (ESI) calcd for $C_{19}H_{15}N_4O_4$ $[M+H]^+$: 363.1093, found 363.1086.

2.3.3 7-(4-Chlorophenyl)-2,2-dimethyl-6-(p-tolyl)-[1,3] dioxino[4,5-b]pyrrol-4(7H)-one (4c)

Dark Yellow solid, mp: 233 – 234 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 – 7.23 (m, 8H, Ar–H), 6.62 (s, 1H, Ar–H), 2.22 (s, 3H, -CH_3), 1.46 (s, 3H, -CH_3), 1.25 (s, 3H, -CH_3) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 143.6, 139.7, 138.2, 136.6, 132.1, 130.6, 128.8, 125.7, 123.7, 120.3, 110.5, 109.0, 106.2, 26.5, 23.0 ppm;

HRMS (ESI) calcd for $C_{21}H_{19}ClNO_3$ $[M+H]^+$: 368.1053, found 368.1047.

2.3.4 2,2-Dimethyl-7-(4-nitrophenyl)-6-(p-tolyl)-[1,3] dioxino[4,5-b]pyrrol-4(7H)-one (4d)

Yellow solid, mp: 220 – 221 °C;

^{1}H NMR (400 MHz, DMSO-d_6): 8.26 – 7.25 (m, 8H, Ar–H), 6.56 (s, 1H, Ar–H), 2.28 (s, 3H, –CH_3), 1.47 (s, 3H, -CH_3), 1.23 (s, 3H, -CH_3) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 146.5, 144.6, 142.8, 139.1, 137.3, 131.8, 125.9, 125.2, 123.9, 121.9, 111.6, 110.2, 106.1, 26.5, 24.2 ppm;

HRMS (ESI) calcd for $C_{21}H_{19}N_2O_5$ $[M+H]^+$: 379.1294, found 379.1288.

2.3.5 7-(4-Chlorophenyl)-6-(4-methoxyphenyl)-1H-pyrrolo-[2,3-d]pyrimidine-2,4(3H,7H)-dione (4e)

Dark Yellow solid, mp: 226 – 227 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H, –NH), 9.54 (s, 1H, –NH), 7.83 – 7.02 (m, 8H, Ar–H), 6.63 (s, 1H, Ar–H), 3.69 (s, 3H, -OCH_3) ppm;14.

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.4, 158.5, 149.7, 142.7, 137.6, 134.5, 133.6, 131.6, 129.1, 127.6, 121.9, 118.3, 105.6, 99.5, 57.0 ppm;

HRMS (ESI) calcd for $C_{19}H_{15}ClN_3O_3$ $[M+H]^+$: 368.0802, found 368.0795.

2.3.6 6-(4-Methoxyphenyl)-7-(4-nitrophenyl)-1H-pyrrolo[2, 3-d]pyrimidine-2,4(3H,7H)-dione (4f)

Yellow solid, mp: 227 – 228 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H, -NH), 9.16 (s, 1H, -NH), 8.26 – 7.03 (m, 8H, Ar–H), 6.65 (s, 1H, Ar–H), 3.79 (s, 3H, -OCH_3) ppm; 14.

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.6, 157.9, 149.7, 147.4, 142.8, 136.1, 132.8, 131.4, 130.3, 126.6, 120.6, 119.8, 104.5, 100.1, 56.6 ppm;

HRMS (ESI) calcd for $C_{19}H_{15}N_4O_5$ $[M+H]^+$: 379.1042, found 379.1036.

2.3.7 7-(4-Chlorophenyl)-6-(4-methoxyphenyl)-2,2-dimethyl-[1,3]dioxino[4,5-b]pyrrol-4(7H)-one (4 g)

Yellow solid, mp: 255 – 256 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 – 6.99 (m, 8H, Ar–H), 6.68 (s, 1H, Ar–H), 3.67 (s, 3H, –OCH_3), 1.52 (s, 3H, -CH_3), 1.28 (s, 3H, -CH_3) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 159.4, 142.7, 140.3, 136.1, 132.2, 131.4, 130.1, 129.0, 120.6, 118.4, 111.7, 110.4, 105.6, 39.4, 25.5, 23.2 ppm;

HRMS (ESI) calcd for $C_{21}H_{19}ClNO_4$ $[M+H]^+$: 384.1003, found 384.0096.

2.3.8 6-(4-Methoxyphenyl)-2,2-dimethyl-7-(4-nitrophenyl)-[1,3]dioxino[4,5-b]pyrrol-4(7H)-one (4 h)

Yellow solid, mp: 239 – 240 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 – 7.04 (m, 8H, Ar–H), 6.67 (s, 1H, Ar–H), 3.78 (s, 3H, –OCH_3), 1.46 (s, 3H, -CH_3), 1.25 (s, 3H, -CH_3) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 158.5, 146.6, 144.8, 142.7, 136.9, 133.2, 130.4, 125.2, 121.6, 119.4, 112.5, 110.2, 107.3, 25.9, 23.1 ppm;

HRMS (ESI) calcd for $C_{21}H_{19}N_2O_6$ $[M+H]^+$: 395.1243, found 395.1236.

2.3.9 6-(4-Bromophenyl)-7-(4-chlorophenyl)-1H-pyrrolo[2, 3-d]pyrimidine-2,4(3H,7H)-dione (4i)

Yellow solid, mp: 231 – 232 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H, –NH), 9.52 (s, 1H, –NH), 7.92 – 7.37 (m, 8H, Ar–H), 6.67 (s, 1H, Ar–H) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 149.3, 147.2, 143.4, 139.5, 131.2, 129.3, 127.5, 126.9, 125.6, 121.4, 120.3, 107.4, 98.5 ppm;

HRMS (ESI) calcd for $C_{18}H_{12}BrClN_3O_2$ $[M+H]^+$: 415.9801, found 415.9794.

2.3.10 6-(4-Bromophenyl)-7-(4-nitrophenyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (4j)

Dark Yellow solid, mp: 249 – 250 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.69 (s, 1H, –NH), 9.21 (s, 1H, –NH), 8.27 – 7.57 (m, 8H, Ar–H), 6.75 (s, 1H, Ar–H) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.6, 150.2, 142.5, 139.4, 137.4, 135.4, 133.5, 132.2, 127.9, 127.4, 122.0, 121.2, 106.9, 100.8 ppm;

HRMS (ESI) calcd for $C_{18}H_{12}BrN_4O_4$ $[M+H]^+$: 427.0042, found 427.0036.

2.3.11 6-(4-Bromophenyl)-7-(4-chlorophenyl)-2,2-dimethyl-[1,3]dioxino[4,5-b]pyrrol-4(7H)-one (4 k)

Yellow solid, mp: 259 – 260 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 – 7.49 (m, 8H, Ar–H), 6.68 (s, 1H, Ar–H), 1.55 (s, 3H, $–CH_3$) 1.33 (s, 3H, $–CH_3$) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 167.5, 145.3, 139.9, 139.1, 136.3, 132.8, 130.1, 129.4, 126.4, 121.3, 120.2, 111.4, 109.2, 105.4, 26.1 ppm;

HRMS (ESI) calcd for $C_{20}H_{16}BrClNO_3$ $[M+H]^+$: 432.0002, found 431.9995.

2.3.12 6-(4-Bromophenyl)-2,2-dimethyl-7-(4-nitrophenyl)-[1,3]dioxino[4,5-b]pyrrol-4(7H)-one (4 l)

Yellow solid, mp: 246 – 247 °C;

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 – 7.34 (m, 8H, Ar–H), 6.52 (s, 1H, Ar–H), 1.54 (s, 3H, $-CH_3$) 1.31 (s, 3H, $-CH_3$) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.9, 150.1, 146.6, 142.7, 139.3, 136.4, 134.9, 131.6, 128.6, 125.3, 122.0, 120.2, 106.0, 99.4, 26.5 ppm;

HRMS (ESI) calcd for $C_{20}H_{16}BrN_2O_5$ $[M+H]^+$: 443.0243, found 443.0240.

3 Results and Discussion

We initiated the investigation on optimizing the reaction conditions and diversification of the methodology by selecting 2-bromo-1-(*p*-tolyl)ethenone, barbituric acid, 4-chloroaniline in 1 mmol quantity and subjecting them to divergent catalysts, solvents and additives.

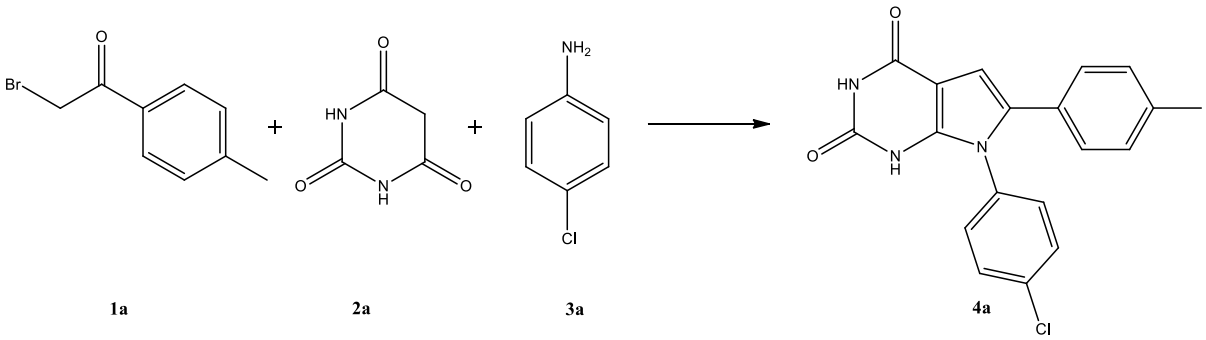
The substrates selected for the synthesis of 4a are initially exposed to visible light in presence of various solvents to conjecture their effects. The visible light-mediated model reaction was then performed in non-polar solvents such as *n*-pentane, benzene, diethyl ether, *o*-xylene and from Table 1, Entries 1 – 4, it was observed that the formation of 4a is not detected even after stirring for 600 min. The presence of polar aprotic solvents such as dioxane, acetone, acetonitrile and DMF generated a maximum of 20% yield of 4a (Table 1, Entries 5 – 8). To our amuse, the presence of polar solvents diethylene glycol, glycerol, acetic acid, H_2O, MeOH progressively increased the yield upto 40% (Table 1, Entries 9 – 13). The reaction was then conducted in EtOH:H_2O (1:1), and EtOH which generated a yield of 60% in 600 min (Table 1, Entries 14 – 15). Hence it was decided to use EtOH as a reaction medium for further studies.

To increase the yield of 4a we then exposed the substrates to varied photocatalysts such as tris(2-phenylpyridine)iridium(III) ($Ir(ppy)_3$), dimanganese decacarbonyl [$Mn_2(CO)_{10}$], titanium dioxide (TiO_2), red acid 52, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), [Acr^+-Mes][ClO_4^-], eosin B, eosin Y and fluorescein in 10 mol% concentration and it was observed that the reaction yield significantly increased from trace to 90% (Table 1, Entries 16 – 23).

To ascertain the effect of visible light in the synthesis of 4a, the reaction was performed in 10 mol% Fluorescein in ethanol in absence of visible light, and only a trace quantity of yield was obtained (Table 1, Entry 25). Its seen that when the model reaction was specifically exposed to 30 W Blue LED, 24 W Green LED to uncover their effect, a maximum of 45% yield was obtained (Table 1, Entries 26 – 27).

To reduce the reaction duration, the effect of additives was then studied. Surprisingly, when the reaction was exposed to various additives such as $AlCl_3$, $ZnBr_2$, *N*-bromosuccinimide (NBS) in a 5 mol% quantity the reaction duration was considerably reduced to 30 min yielding 95% of 4a (Table 1, Entries 28 – 30). It was also noticed from the model reaction that the right quantity of fluorescein

Table 1 Optimization of reaction conditions for the synthesis of 4a



1a **2a** **3a** **4a**

Entry	Catalyst (mol %)	Additive (mol%)	Light	Solvent	Time (min)	Yield[b]
1	–	–	Visible light	*n*-pentane	600	ND
2	–	–	Visible light	benzene	600	ND
3	–	–	Visible light	diethyl ether	600	ND
4	–	–	Visible light	*o*-xylene	600	ND
5	–	–	Visible light	dioxane	600	10
6	–	–	Visible light	acetone	600	10
7	–	–	Visible light	acetonitrile	600	10
8	–	–	Visible light	DMF	600	20
9	–	–	Visible light	diethylene glycol	600	15
10	–	–	Visible light	glycerol	600	15
11	–	–	Visible light	acetic acid	600	30
12	–	–	Visible light	H_2O	600	40
13	–	–	Visible light	MeOH	600	40
14	–	–	Visible light	EtOH:H_2O (1:1)	600	45
15	–	–	Visible light	EtOH	600	60
16	$Ir(ppy)_3$ (10%)	–	Visible light	EtOH	600	Trace
17	$Mn_2(CO)_{10}$ (10%)	–	Visible light	EtOH	600	10
18	TiO_2 (10%)	–	Visible light	EtOH	600	15
19	red acid 52 (10%)	–	Visible light	EtOH	600	20
20	DDQ (10%)	–	Visible light	EtOH	600	20
21	$[Acr^+\text{-Mes}][ClO_4^-]$ (10%)	–	Visible light	EtOH	600	45
22	Eosin B (10%)	–	Visible light	EtOH	600	50
23	Eosin Y (10%)	–	Visible light	EtOH	600	55
24	Fluorescein (10%)	–	Visible light	EtOH	600	90
25	Fluorescein (10%)	–	Dark	EtOH	600	Trace
26	Fluorescein (10%)	–	Blue light	EtOH	600	40
27	Fluorescein (10%)	–	Green light	EtOH	600	45
28	Fluorescein (10%)	$AlCl_3$ (5%)	Visible light	EtOH	30	50
29	Fluorescein (10%)	$ZnBr_2$ (5%)	Visible light	EtOH	30	55
30	Fluorescein (10%)	NBS (5%)	Visible light	EtOH	30	95
31	Fluorescein (7%)	NBS (5%)	Visible light	EtOH	30	95
32	Fluorescein (5%)	NBS (3%)	Visible light	EtOH	30	95
33	Fluorescein (3%)	NBS (5%)	Visible light	EtOH	30	90
34	–	NBS (5%)	Visible light	EtOH	30	15
35	Fluorescein (5%)	NBS (5%)	Visible light	EtOH	60	95[e]

Reaction conditions: 2-bromo-1-(*p*-tolyl)ethanone (1 mmol), barbituric acid (1 mmol), 4-chloroaniline (1 mmol), catalyst, solvent (3 mL), 22 W LED (350 – 800 nm)

ND Not detected

[b]Isolated yields

[c]30 W Blue LED (410 – 500 nm)

[d]24 W Green LED (510 – 550 nm)

[e]5 mmol scale

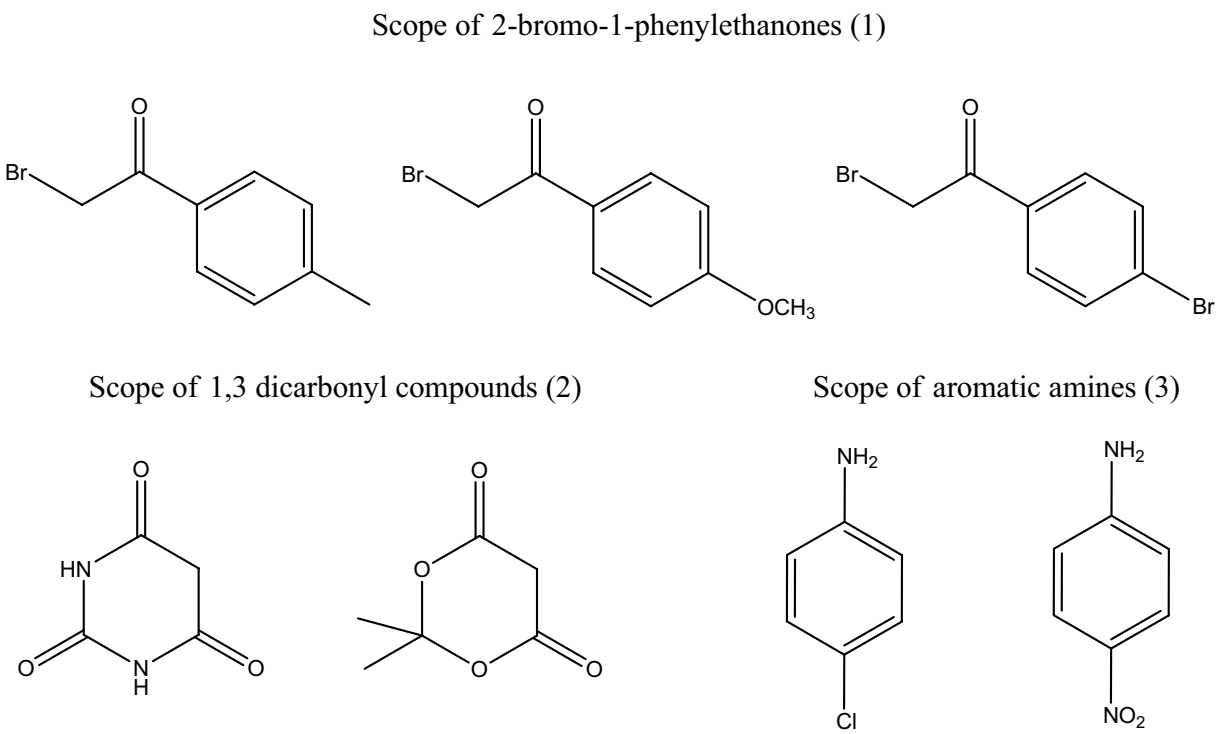


Fig. 3 Diversity of starting materials

and NBS was 5 mol% and 3 mol% respectively (Table 1, Entry 32). Further reduction in the amount of fluorescein to 3% generated less yield (Table 1, Entry 33). The reaction was also performed in presence of NBS and in the absence of fluorescein as a catalyst to divulge the importance of Fluorescein. To our dismay, the reaction performed in the absence of fluorescein generated a yield of 15% reiterating the role of catalyst in the synthesis of 4a. Hence, visible light along with 5 mol% of fluorescein as a catalyst, 3 mol% NBS as an additive in EtOH was chosen as a valid condition in the synthesis of 6,7 disubstituted 1*H*-pyrroles. The scope of optimized conditions was later applied to the gram-scale synthesis of 4a and it proved to be rewarding as a yield of 95% was obtained within 60 min.

The optimized conditions of reaction were then enforced on a reaction constituting three substituted 2-bromo-1-phenylethanones, two 1,3 dicarbonyl compounds and anilines (Fig. 3) as starting materials and a series of corresponding twelve novel 6,7 disubstituted 1*H*-pyrroles were synthesized in excellent yield (Fig. 4). The designated protocol tolerates a variety of substituents which are electron-withdrawing or donating on both 2-bromo-1-phenylethanone and aniline.

To confirm and establish the radical-mediated pathway, the designated model substrates were exposed to benzyl acrylate and 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) as radical scavengers to the optimized condition of the reaction. The presence of benzyl acrylate and TEMPO drastically reduced the yield of the expected product to 10% and 5% respectively (Fig. 5).

The control experiments were further performed to decipher the order of the combination of the reactants. As observed from Fig. 6, the addition of 2-bromo-1-(*p*-tolyl) ethanone, barbituric acid generated an intermediate 5. The reaction also generated another intermediate 6 when barbituric acid, 4-chloroaniline were exposed to the standardized conditions. However, when 2-bromo-1-(*p*-tolyl)ethanone and

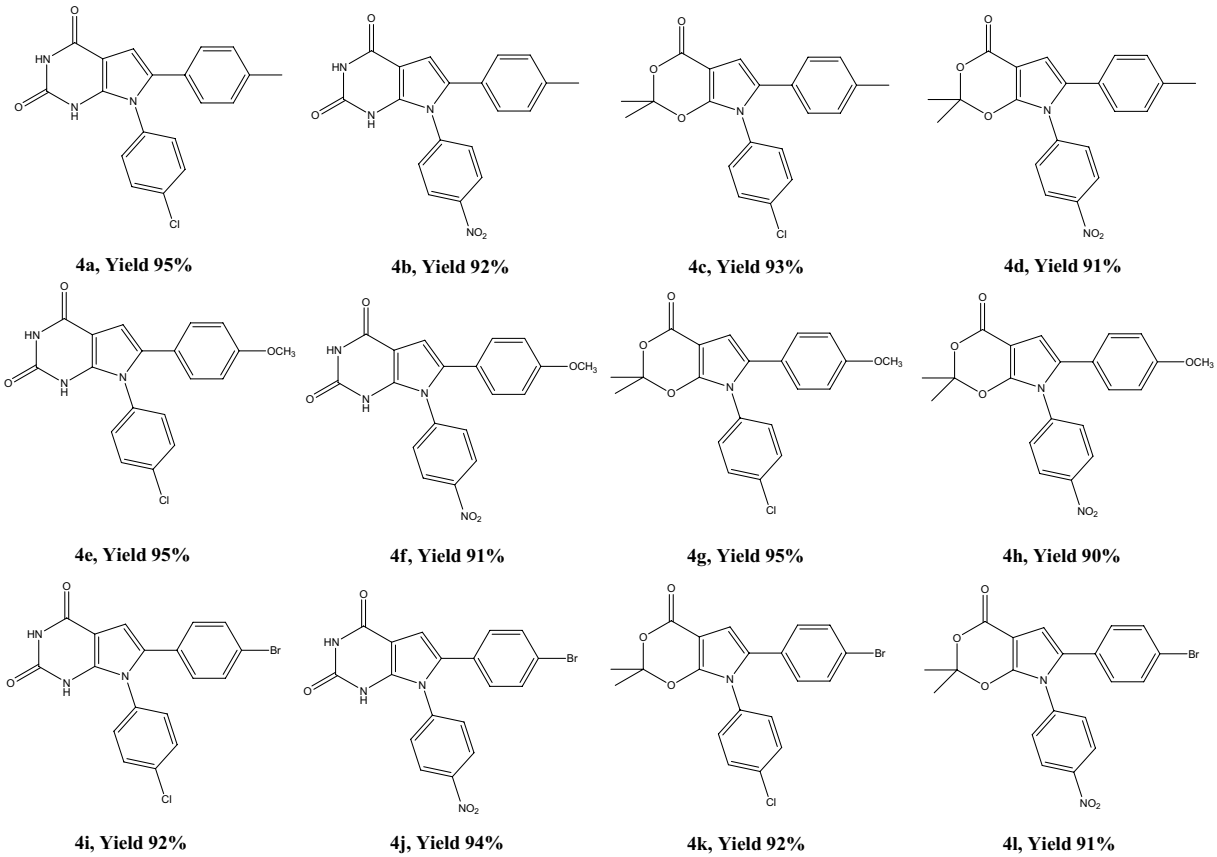


Fig. 4 Diversity of synthesized 6,7 disubstituted 1*H*-pyrroles

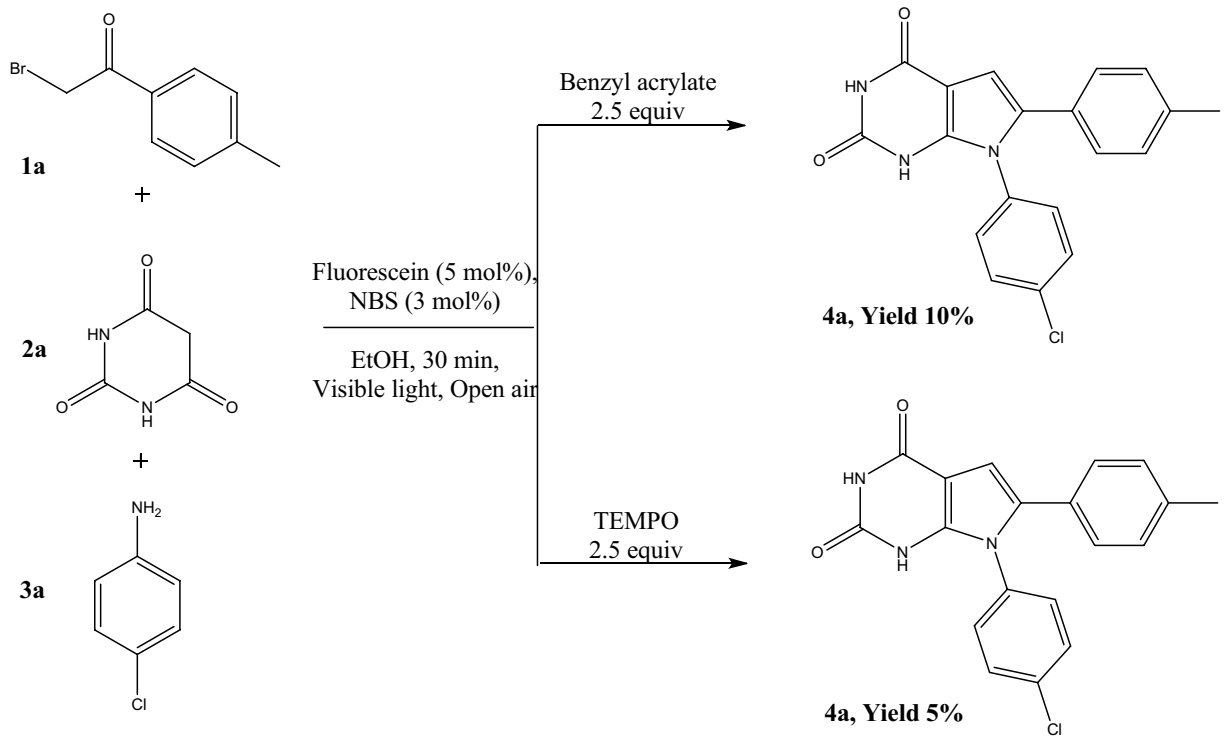


Fig. 5 Effect of radical scavengers on the synthesis of 4a

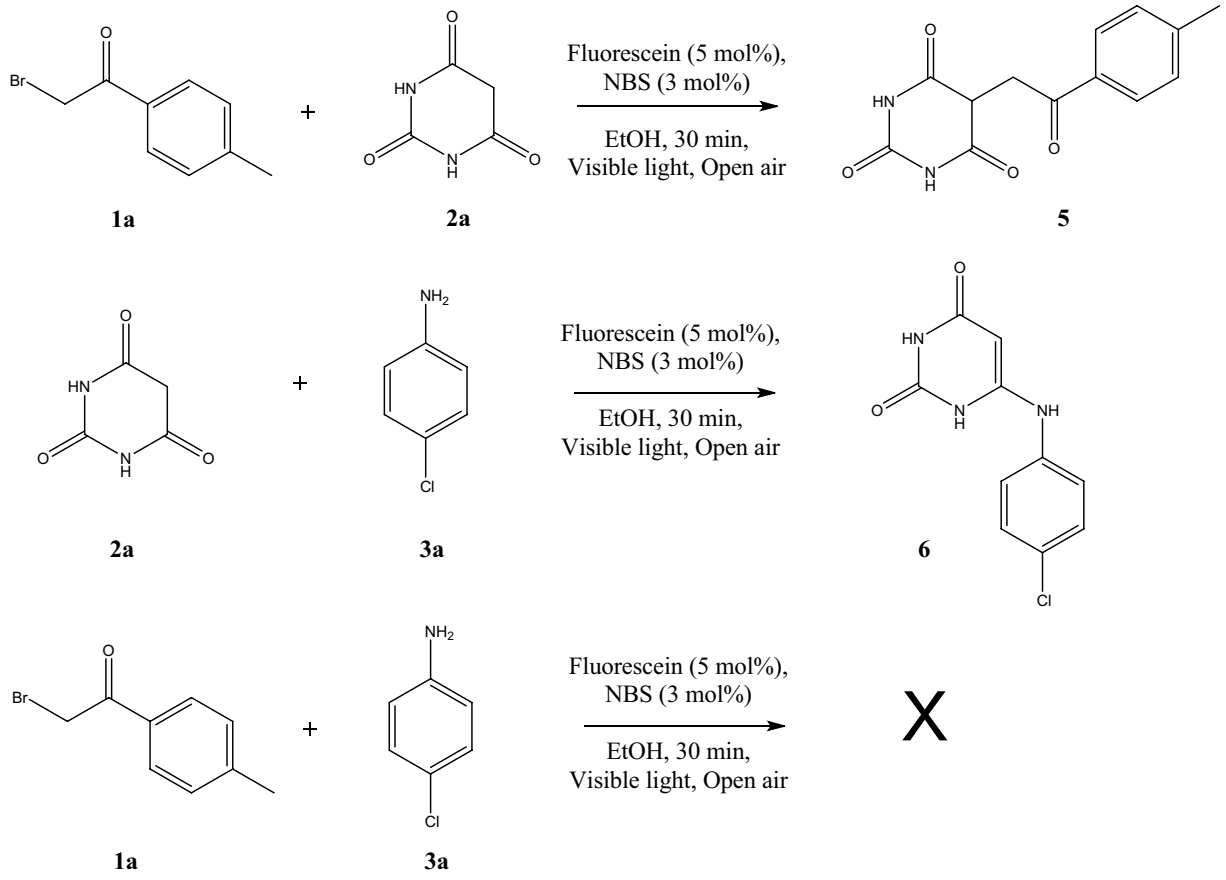


Fig. 6 Control experiments

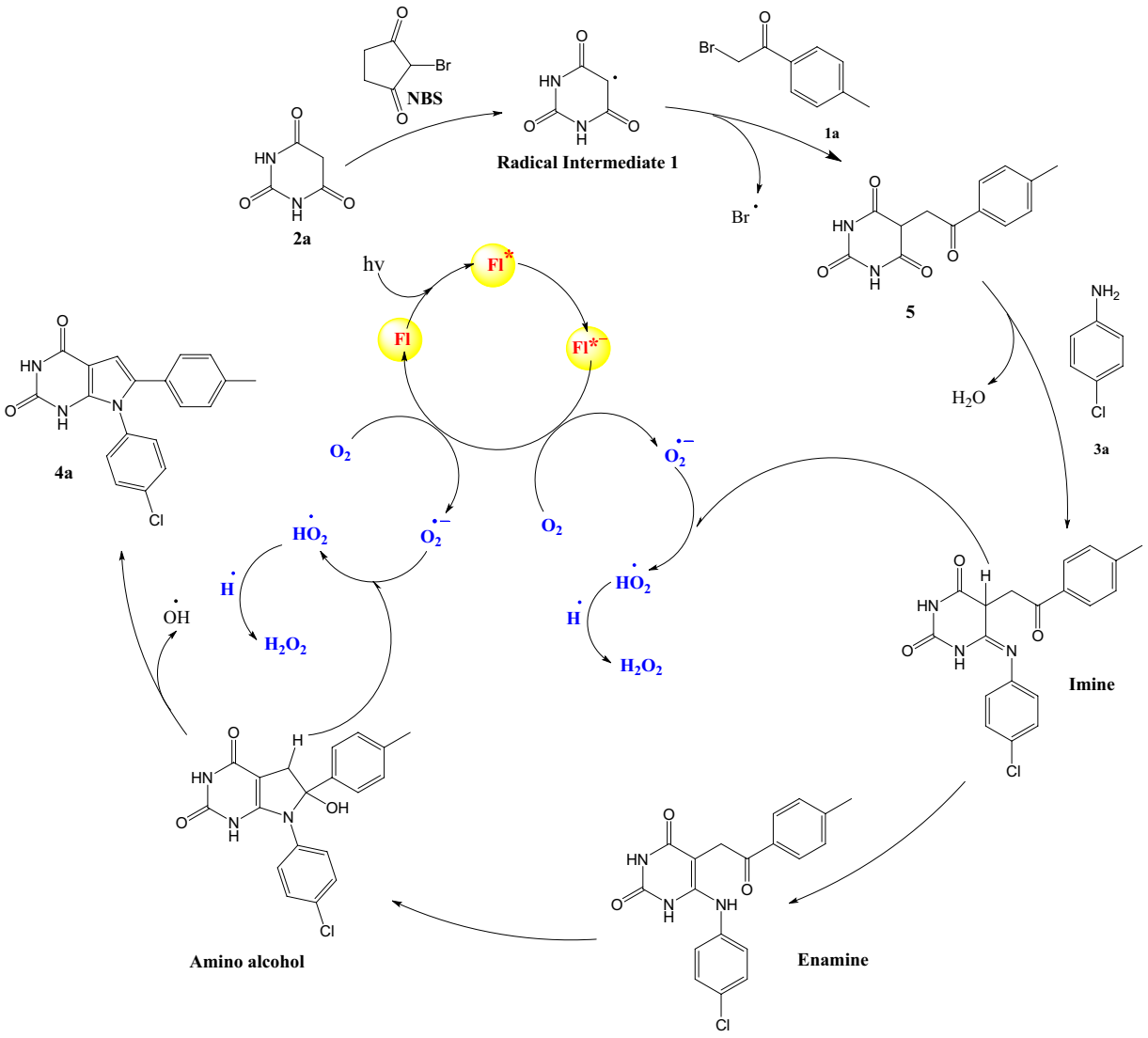


Fig. 7 A plausible mechanism for the formation of 4a

4-chloroaniline were taken as substrates no intermediates were generated. Thus it can be concluded that the reaction proceeds via the reaction of barbituric acid or intermediate 6 with 2-bromo-1-(*p*-tolyl)ethanone.

The probable mechanism based on the studies conducted is presented in Fig. 7. It is equitable to assume that NBS may initiate the formation of radical intermediate 1 from barbituric acid which reacts with 2-bromo-1-(*p*-tolyl)ethanone to generate 5. The condensation of 5 with 4-chloroaniline removes a molecule of water giving an imine which gets may get converted to a more stable enamine. The presence of Fluorescein may catalyse the formation of enamine which further leads to amino alcohol and its dehydration to give the target molecule 4a.

The structures of all synthesized 6,7 disubstituted 1*H*-pyrroles were characterized using ^{1}H NMR and ^{13}C NMR, and HRMS (ESI) spectral techniques. The ^{1}H NMR spectrum of molecule 4a shows two singlets at 10.38 and 9.29 ppm confirming the presence of -NH groups. The presence of eight protons of two aromatic rings is seen as multiplet in the range of 7.86 – 7.22 ppm. The proton of the pyrrole ring is seen as a characteristic peak at 6.53 ppm. The –CH_3 group shows a singlet at 2.56 ppm. The ^{13}C NMR spectrum shows a peak at 23.5 ppm which can be assigned to the carbon of –CH_3 group. The other peaks in the range of 98.4–142.8 ppm are due to carbon atoms of the aromatic ring. The characteristic peak at 148.9 and 162.2 is due to carbonyl groups on carbon. The HRMS (ESI) spectrum showed a $[M+H]^+$ peak at 352.0847 affirming the formation of 4a.

4 Conclusions

For the first time, a combination of multi-component approach and photocatalyst was applied for the synthesis of twelve 6,7 disubstituted 1*H*-pyrroles in excellent yield using 2-bromo-1-(phenyl)ethanone, barbituric acid/Meldrum's acid, aromatic amines in EtOH with Fluorescein as catalyst, NBS as an additive. The protocol is novel, benign, is formidable in terms of reaction time, diversity of products and follows the positive aspects of MCRs following the principles of green chemistry.

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Declarations

Conflict of interest We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

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