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Photochemical synthesis of benzoxazolo[3,2-*b*]isoquinolin-11-one and isoquinolino[3,2-*b*][1,3]benzoxazin-11-one under basic conditions

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Abstract—Irradiation of *N*-phenyl substituted isoquinolines in acetonitrile containing 1 M NaOH in a multilamp reactor (MLR) furnished benzoxazolo[3,2-*b*]isoquinolin-11-ones. In contrast, irradiation of the *N*-benzyl substituted isoquinoline derivative under the same conditions afforded the hydrolysed *N*-benzylbenzamide derivative. The isoquinolinobenzoxazine was obtained by irradiating the *N*-benzyl substituted isoquinoline derivative at higher basic conditions. The required isoquinolines were synthesized under solvent-free, solid supported microwave conditions.

1. Introduction

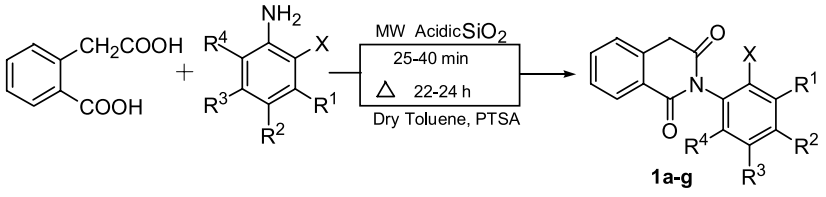
Isoquinoline fused alkaloids play an important role in the field of medicine as antihypertensive agents and antidepressant agents.[1,2] Tetrahydroisoquinolines are the building blocks for the syntheses of various isoquinolinoalkaloids.[3,4] Oxazoles and oxazines are known to exhibit a broad spectrum of biological activities.[5,6] Recently, the synthesis of benzoxazoles[7] and benzoxazines[8] has been reported. Microwave-assisted organic synthesis is a new and growing area in synthetic organic chemistry. The combination of supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short times with high conversions, without the need for solvents.[9]

In continuation of our interest on the photochemistry of heterocycles, we have reported the photochemical synthesis of benzothiazoles,[10,11] triazolobenzothiazoles,[12] and triazolobenzothiazines.[13,14] In a preliminary communication,[15] we have reported the first photochemical synthesis of isoquinoline-fused benzoxazole and benzoxazine derivatives. In this paper, we wish to report the systematic study on the thermal and microwave assisted synthesis of tetrahydroisoquinolines and their photolysis under base-mediated conditions.

2. Results and discussion

2.1. Synthesis of isoquinolines

The isoquinolines were synthesized by a direct one-step process under thermal and solvent-free, solid supported microwave conditions. In the thermal conditions, refluxing a mixture of homophthalic acid (1 equiv), substituted aniline (1 equiv) and *p*-toluenesulfonic acid (catalytic amount) in dry toluene using a Dean–Stark apparatus for 22–24 h furnished the corresponding tetrahydroisoquinoline-1,3-dione **1a–g** (Scheme 1) in good yield in one-step. In the



Scheme 1.

Keywords: Isoquinolines; Cyclization; Benzoxazoles; Benzoxazine.
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Table 1. Synthesis of tetrahyroisoquinoline-1,3-dione **1a–g** under thermal and microwave condition

1	X	R^1	R^2	R^3	R^4	Microwave condition		Thermal condition	
						Time (min)	Yield (%)	Time (h)	Yield (%)
1a	Cl	H	H	H	H	25	67	22	70
1b	Cl	Cl	H	H	H	25	73	24	68
1c	Cl	H	Cl	H	H	30	58	23	62
1d	Cl	H	H	Cl	H	30	62	24	66
1e	Cl	H	H	H	Cl	40	65	24	70
1f	Br	H	CH_3	H	H	30	78	24	75
1g	Br	H	H	H	H	35	69	24	72

microwave conditions, the synthetic procedure generally involved impregnating the solid support with homophthalic acid with the substituted anilines in methylene chloride solution, evaporating the solvent, and heating the solid residue in a microwave oven. Preliminary optimization of reaction conditions was carried out using solid supports like neutral alumina, anhydrous sodium sulfate, anhydrous magnesium sulfate and acidic silica gel. Among different supports tested, the expected isoquinolines **1a–g** were formed in higher yields when acidic silica gel was used (Scheme 1). Optimal conditions for the synthesis were found to be 25–40 min reaction time, with a cut-off of the MW irradiation after every 5 min (to monitor the progress of the reaction), using microwave irradiation power of 800 W. No reaction was observed in the absence of MW irradiation or when the solid support was omitted from the reaction mixture.

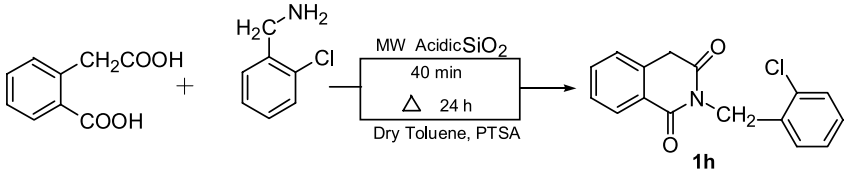
Under classical thermal conditions using high boiling solvent such as toluene in the presence of *p*-toluenesulfonic acid (PTSA), a much longer reaction time (22–24 h) was required. In contrast, with microwave irradiation, the time did not exceed 40 min for completion of the reaction. The comparative data is shown in Table 1. Likewise, the reaction of homophthalic acid with 2-chlorobenzylamine in the presence of *p*-toluenesulfonic acid required 24 h under thermal condition, but only 40 min for the solid-supported MW irradiation condition, to afford the *N*-(2-chlorobenzyl)-tetrahydroisoquinoline-1,3-dione **1h** (Scheme 2).

The products **1a–h** were characterized by spectral and analytical data. The IR spectra of compounds **1a–h** showed the C_3-carbonyl group around 1700 cm^{-1} and the C_1-carbonyl group around 1600 cm^{-1}. In the ^1H NMR spectra of compounds **1b** and **1g**, geminal coupling was observed for C_4-CH_2 protons with $J=22.5$ Hz around δ 4, while for compounds **1a**,**c**,**d**,**f** the J value could not be determined, because the splitting pattern was not resolved. In the case of compound **1e**, due to the symmetrical substituents in the *N*-aryl ring, no geminal coupling of C_4-CH_2 protons was observed. The C_8-ArH of compounds **1a–h** showed doublet around δ 8 due to the deshielding effect of the C_1-carbonyl group. The structure of the compounds **1b**,**f**,**h** were further confirmed by XRD analysis.[16]

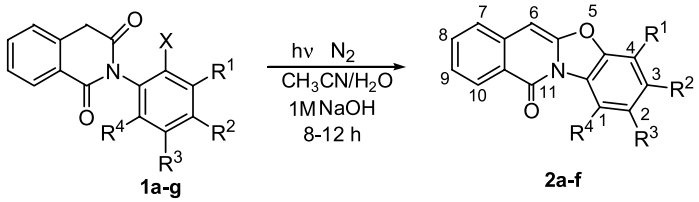
2.2. Irradiation studies

An acetonitrile solution (150 mL) of the isoquinoline **1a** (0.3 g, 1.1 mmol), containing 30 mL of aqueous 1 M NaOH, was flushed with nitrogen for 1 h and irradiated at 254 nm in an Applied Photophysics multilamp reactor (MLR) for 12 h. Usual work-up and chromatographic purification furnished the benzoxazolo[3,2-*b*]isoquinolin-11-one **2a** in 41% yield (Scheme 3). Similarly, irradiation of compounds **1b–f**, in acetonitrile containing 1 M NaOH in a multilamp reactor for 8–12 h, furnished the corresponding substituted benzoxazolo[3,2-*b*]isoquinolin-11-ones **2b–f** (Table 2). Photolysis of the bromo analogue **1g** also afforded **2a**, which was confirmed by mp, mixture mp and superimposable IR spectrum with that obtained under the same conditions from **1a**.

The photosubstitution reaction described here has to involve replacement of the halogen atom present in the *N*-phenyl moiety of the isoquinoline-1,3-diones **1a–g** by the carbonyl oxygen (C_3-CO) intramolecularly. A dark experiment



Scheme 2.



Scheme 3.

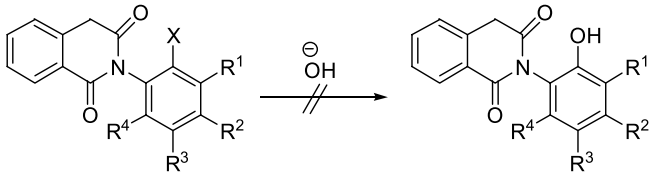
Table 2. Photolysis of isoquinoline **1a–g** to benzoxazolo isoquinoline **2a–f**

1	X	R^1	R^2	R^3	R^4	Irradiation time (h)	2	Yield of **2** (%)
1a	Cl	H	H	H	H	12	**2a**	41
1b	Cl	Cl	H	H	H	7	**2b**	43
1c	Cl	H	Cl	H	H	8	**2c**	48
1d	Cl	H	H	Cl	H	9	**2d**	46
1e	Cl	H	H	H	Cl	10	**2e**	40
1f	Br	H	CH_3	H	H	7	**2f**	52
1g	Br	H	H	H	H	8	**2a**	50

(without irradiation) of **1a** for 30 h did not produce any product. Thus the formation of benzoxazolo[3,2-*b*]isoquinolin-11-one is not due to the thermal reaction, but due to the photoinduced substitution reaction.

In presence of base such as NaOH, the UV–Vis absorption (λ_{max}) behavior of the isoquinoline **1a** in acetonitrile was changed from 247 to 314 nm. The species at 314 nm is believed to be the enolate. Thus anionic species are probably formed in solution, which induces the photosubstitution. One possible explanation is that the enolate oxygen intramolecularly displaces the halogen of the haloarene in the singlet excited state (S_N2Ar^*).[17] Another possibility is that a radical anion intramolecularly substitutes the halogen of the haloarene ($S_N(ET)Ar^*$).[17]

The photosubstitution reactivity depends on the leaving ability of the halide ion. Bromoanalogue **1g** is more reactive, which is reflected in the formation of the photosubstituted product **2a** in higher yield and in a shorter reaction time compared to the chloro analogue **1a** (Table 2). Thus the rate-determining step of the reaction is the leaving halide anion. Moreover, if the S_N2Ar^* mechanism is operative, a phenolic-type product could be formed from intermolecular substitution of the halide ion with the hydroxyl group (Scheme 4). Such a product was not detected in the reaction conditions. From these results, it is viewed that the photosubstitution reaction is more likely occurring by the intramolecular $S_N(ET)Ar^*$ mechanism and not the S_N2Ar^*mechanism.

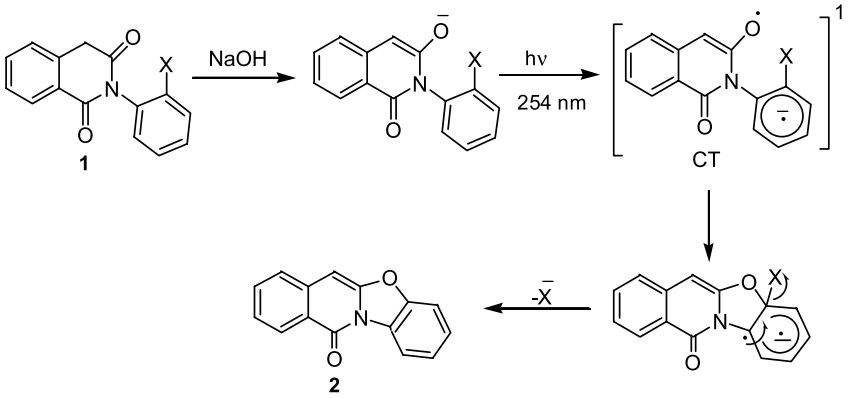


Scheme 4.

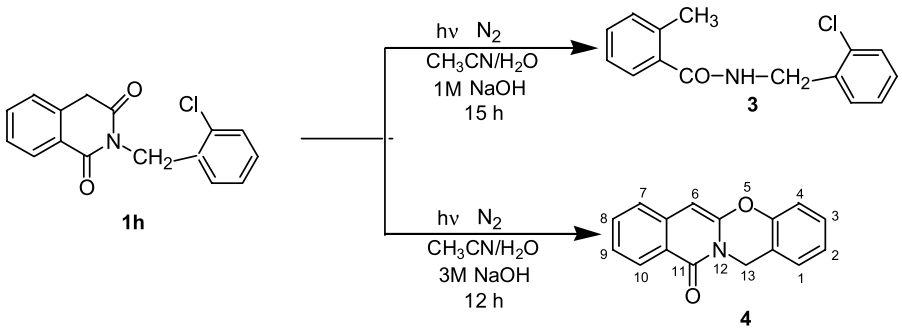
The probable mechanistic pathway is described in Scheme 5. The light absorption of enolate anion populates the intramolecular charge transfer (CT) singlet excited state, which produces a cyclohexadienyl anion radical by intramolecular addition of the oxygen radical of the enolate to the anionic halophenyl moiety in the charge transfer excited state, which in turn yields the benzoxazolo[3,2-*b*]isoquinoline **2** by the ejection of the halide ion.

A similar intramolecular electron-transfer mechanism has been proposed for 2-(pyridinyl)benzoxazoles.[18] The intramolecular electron transfer mechanism for the formation of benzothiazoles from the photoreaction of *o*-halothioacetanilide, by observing the $Cl_2^{\bullet-}$ anion radical at $\lambda_{max} \sim 345$ nm in laser flash and steady state experiments has been proposed for the first time from our laboratory.[12]

The structure of photoproducts **2a–f** were consistent with the spectroscopic data. The IR spectra showed the disappearance of the C_3-CO group of isoquinoline **1a–g** around 1700 cm^{-1}. It showed the C_{11}-CO group around 1650 cm^{-1}. The ^1H NMR spectra showed the C_6-CH proton of **2a–f** around δ 6.5, which indicates the disappearance of the C_4–CH_2 proton of isoquinolines **1a–g**. The ^{13}C NMR spectra also confirmed the presence of C_6-CH carbon and C_{11}-CO carbon, which appear around δ 82 and δ 159, respectively. Furthermore, the structure of compound **2c** was confirmed by XRD.[19]



Scheme 5.



Scheme 6.

2.3. Irradiation of the isoquinoline 1h

The irradiation of isoquinoline-1,3-dione **1h** (1.0 mmol) for 15 h in acetonitrile containing 1 M NaOH (30 mL) was carried out (after flushing with nitrogen for 1 h) in a multilamp reactor (254 nm). After completion of the reaction, usual work-up and chromatographic separation afforded the hydrolysed *N*-(2-chlorobenzyl)-2-methylbenzamide **3** (Scheme 6) instead of the expected isoquinolinobenzoxazine.

The hydrolysis product **3** was confirmed by spectroscopic and analytical data. The IR spectrum of compound **3** showed –NH peak at 3296 cm^{-1} and carbonyl peak at 1641 cm^{-1}. The ^1H NMR spectrum showed the $-CH_3$ protons at δ 2.41, $-CH_2$ protons at δ 4.68 as a doublet with coupling constant $J=6$ Hz and –NH proton at δ 6.25 as a broad singlet. The ^{13}C NMR of the compound **3** indicated the presence of $-CH_3$ carbon at δ 19.7, $-CH_2$ carbon at δ 41.8 and CO carbon at δ 169.8. Furthermore, the compound **3** was confirmed by mp, mixture mp and superimposable IR spectra with the authentic sample prepared from 2-methyl benzoylchloride and 2-chlorobenzylamine in dry benzene.

The formation of hydrolysis product is probably due to ineffective population of the enolate of **1h** in 1 M NaOH and the molecular flexibility of the *N*-benzyl substituent, which causes the base mediated hydrolysis followed by photodecarboxylation of **1h** to **3**. Light induced decarboxylation of (*o*-acylphenyl)acetic acids has been reported.[20]

In order to effect the photosubstitution reaction, we carried out the photolysis of **1h** under higher basic conditions. Hence, irradiation of **1h** (1.0 mmol) in acetonitrile containing 3 M NaOH (30 mL) was carried out for 12 h (after flushing with nitrogen for 1 h) in a multilamp reactor. The expected product isoquinolino[3,2-*b*][1,3]benzoxazin-11-one **4** was isolated.

The compound **4** was confirmed by spectroscopic and analytical data. The IR spectrum of **4** shows the disappearance of C_3-CO group of **1h** and shows the C_{11}-CO group at 1689 cm^{-1}. The ^1H NMR spectrum of **4** showed the C_{13}-CH_2 proton at δ 5.16, the C_6-CH proton at δ 6.21 and the C_4-aromatic proton at δ 8.33 as a doublet with coupling constant $J=7.8$ Hz. The remaining seven aromatic protons appeared as a multiplet at δ 7.12–7.60. The ^{13}C NMR also indicated the C_{13}-CH_2 carbon at δ 40.7, the C_6-CH carbon at δ 87.8 and the C_{11}-CO carbon at δ 161.9.

3. Conclusions

The tetrahydroisoquinoline-1,3-diones **1a–h** were synthesized in comparable yield, under solid supported solvent-free microwave conditions in shorter reaction time (<1 h) compared to the classical thermal conditions. Irradiation of tetrahydroisoquinoline **1a–g** under base mediated conditions (CH_3CN/1 M NaOH) in a multilamp reactor (MLR) afforded the respective benzoxazolo[3,2-*b*]isoquinolin-11-one **2a–f** in good yield. Photolysis of isoquinoline **1h** in CH_3CN/1 M NaOH using a multilamp reactor furnished the hydrolysed *N*-(2-chlorobenzyl)-2-methylbenzamide **3**, whereas irradiation at higher basic conditions such as acetonitile containing 3 M NaOH afforded the expected product isoquinolino[3,2-*b*][1,3]-benzoxazin-11-one **4**.

4. Experimental

4.1. General

All the melting points are uncorrected. UV spectra were recorded with Shimadzu 1601 spectrophotometer. IR spectra were recorded on Shimadzu FTIR-8300 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with Brucker-DPX 200 (200 MHz) and Jeol-GSX 400 (400 MHz) instruments with TMS as internal standard (chemical shift in δ ppm). The mass spectra were recorded with Jeol-JMS-DX 303 HF (EI, 70 eV) and GCMS QP 5000 Shimadzu instruments. Chromatographic separations were done using silica gel (ACME sample). Thin layer chromatography (TLC) was performed using glass plates coated with silica gel (ACME sample) of 0.25 mm thickness. Spots were visualized using iodine vapour. The photochemical reactions were carried out in quartz vessel of different capacity in Applied Photophysics multilamp reactor (254 nm, 12 lamps). Microwave reactions were carried out in Kenstar-India microwave oven (800 W).

4.2. General procedure for the synthesis of substituted tetrahydroisoquinoline-1,3-diones 1a–h

The tetrahydroisoquinolines were synthesized from the corresponding homophthalic acid and substituted anilines and benzylamine by a direct one-step procedure under thermal and solvent-free solid supported microwave conditions.

(i) *Thermal conditions*. A mixture of homophthalic acid (1 equiv), substituted amine (1 equiv) and *p*-toluenesulfonic acid (catalytic amount) was refluxed in dry toluene using a Dean–Stark apparatus for 22–24 h. After completion of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature, extracted with ethyl acetate and the organic layer washed with H_2O, dil. HCl and dil. $NaHCO_3$. The ethyl acetate layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid obtained was filtered and recrystallized from ethyl acetate–hexane mixture, to furnish the corresponding tetrahydroisoquinoline-1,3-dione **1a**–**h** in good yield.

(ii) *Microwave conditions*. A thoroughly ground mixture of homophthalic acid (1 equiv) and acidic silica gel (3–5 g) was mixed with a methylene chloride solution of substituted amine (1 equiv). The solvent was removed under reduced pressure; the solid residue was placed in a (Kenstar-India) microwave oven (800 W), irradiated for 5 min, cooled, and again irradiated for 5 min. The procedure was continued for a total MW irradiation time of 25–40 min. After completion of the reaction, checked by TLC, it was cooled to room temperature. The mixture was extracted with ethyl acetate and filtered. The filtrate was washed with water, dil. HCl, and dil. $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The solid obtained was filtered and recrystallized from ethyl acetate–hexane mixture. The isoquinolines thus formed were compared by mp, mixture mp and superimposable IR spectra with **1a**–**h** obtained under thermal conditions.

4.2.1. *N*-(2-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1a. A mixture of homophthalic acid (1 g, 5.0 mmol), *o*-chloroaniline (0.7 g, 5.0 mmol) and *p*-toluenesulfonic acid (catalytic amount) in toluene (50 mL) was refluxed using a Dean–Stark apparatus for 22 h. After completion of the reaction, usual work-up as mentioned above furnished **1a**. Yield: 1.05 g (70%); mp 110–112 °C; UV 246 nm (CH_3CN); IR (KBr): 1720 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.28 (bs, 2H, C_4-CH_2), 7.23–7.67 (m, 7H, Ar–H), 8.24 (d, $J=7.7$ Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.8, 125.1, 127.5, 127.8, 127.9, 129.5, 130.2, 130.4, 132.7, 133.2, 134.1, 134.2, 164.3 (C_1-CO), 169.1 (C_3-CO). MS: *m*/*z* (%): (271 (M^+), 273-trace), 236 (100), 235 (3), 208 (38), 180 (5), 179 (4), 118 (12), 117 (6), 104 (6), 90 (37), 89 (32), 63 (12). Anal. Calcd for $C_{15}H_{10}NO_2Cl$ (271.698): C, 66.30; H, 3.70; N, 5.15; Found: C, 66.52; H, 3.51; N, 5.40.

A mixture of homophthalic acid (0.3 g, 1.6 mmol), *o*-chloroaniline (0.21 g, 1.6 mmol) and acidic silica gel (3 g) was irradiated in the microwave oven for 25 min. After completion of the reaction, usual work up as mentioned above afforded **1a** (yield=67%). Refluxing a mixture of homophthalic anhydride (1 g, 6.2 mmol), *o*-chloroaniline (0.78 g, 6.2 mmol) and *p*-toluenesulfonic acid in dry toluene (100 mL) using a Dean–Stark apparatus for 24 h, followed by usual work up, afforded **1a** (yield=0.33 g, 20%).

4.2.2. *N*-(2,3-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1b. Following the general procedure, a mixture of homophthalic acid (2.5 g, 13.8 mmol), 2,3-dichloroaniline (2.25 g, 13.8 mmol) and *p*-toluenesulfonic acid in dry toluene (120 mL) was refluxed for 24 h. After completion of the reaction, usual work-up furnished **1b**. Yield: 2.87 g (68%); mp 198–200 °C; UV: 242 nm (CH_3CN); IR (KBr): 1728 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.20 (d, $J=22.5$ Hz, 1H, C_4-H_a), 4.28 (d, $J=22.5$ Hz, 1H, C_4-H_b), 7.18–7.68 (m, 6H, Ar–H), 8.24 (d, $J=7.8$ Hz, 1H, C_8-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.8, 124.9, 127.4, 127.7, 127.9, 128.6, 129.5, 131.0, 131.7, 134.1, 134.1, 134.3, 134.8, 164.1 (C_1-CO), 168.9 (C_3-CO). MS: *m*/*z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 269 (2), 242 (46) [244 (15)], 214 [216], 213 [215], 152 [154], 118 (15), 117 (4), 104 (2), 90 (58), 89 (58), 63 (16).The structure of the compound was further confirmed by XRD.[16]

A mixture of homophthalic acid (0.3 g, 1.6 mmol), 2,3-dichloroaniline (0.27 g, 1.6 mmol) and acidic silica gel (3 g) was heated in the microwave oven for 25 min. Usual work-up afforded **1b** (yield=73%).

4.2.3. *N*-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1c. A mixture of homophthalic acid (4 g, 22.2 mmol), 2,4-dichloroaniline (3.6 g, 22.2 mmol) and *p*-toluenesulfonic acid in dry toluene (150 mL) was refluxed for 23 h; the usual work-up afforded **1c**. Yield: 4.21 g (62%); mp 160–162 °C; UV: 240 nm (CH_3CN); IR (KBr): 1732 (C_3-CO), 1678 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.20 (bs, 2H, C_4-CH_2), 7.16−7.68 (m, 6H, Ar–H), 8.22 (d, $J=7.8$ Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.8, 124.9, 127.5, 128.0, 128.1, 129.5, 130.2, 131.3, 131.9, 133.6, 134.2, 134.3, 135.5, 164.1 (C_1-CO), 169.0 (C_3-CO). MS: *m*/*z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 269 (2), 242 (46) [244 (14)], 214 [216], 213 [215], 152 [154], 118 (14), 117 (5), 104 (4), 90 (60), 89 (60), 63 (20). Anal. Calcd for $C_{15}H_9NO_2Cl_2$ (306.143): C, 58.84; H, 2.96; N, 4.57. Found: C, 58.62; H, 3.11; N, 4.72.

Microwave irradiation of a mixture of homophthalic acid (0.4 g, 2.2 mmol), 2,4-dichloroaniline (0.36 g, 2.2 mmol) and acidic silica gel (4 g) for 30 min furnished **1c** (yield=58%), after usual work-up.

4.2.4. *N*-(2,5-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1d. Refluxing a mixture of homophthalic acid (4 g, 22.2 mmol), 2,5-dichloroaniline (3.6 g, 22.2 mmol) and *p*-toluenesulfonic acid in dry toluene (150 mL) for 24 h, followed by usual work-up furnished **1d**. Yield: 4.48 g (66%); mp 158–160 °C; UV: 240 nm (CH_3CN); IR (KBr): 1728 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.23 (bs, 2H, C_4-CH_2), 7.27–7.70 (m, 6H, Ar–H), 8.23 (dd, $J=7.8$, 1.1 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.2, 125.3, 127.9, 128.5, 130.0, 130.5, 130.8, 131.1, 131.4, 131.7, 133.6, 134.6, 134.8, 164.5 (C_1-CO), 169.3 (C_3-CO). MS: *m*/*z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 269 (2), 242 (32) [244 (10)], 214 [216], 213 [215], 152 [154], 118 (9), 117 (6), 104 (2), 90 (30), 89 (28), 63 (8). Anal. Calcd for $C_{15}H_9NO_2Cl_2$ (306.143): C, 58.84; H, 2.96; N, 4.57. Found: C, 58.63; H, 3.13; N, 4.68.

A mixture of homophthalic acid (0.3 g, 1.6 mmol), 2,5-dichloroaniline (0.27 g, 1.6 mmol) and acidic silica gel (3 g)

was heated in the microwave oven for 30 min. After completion of the reaction, usual work-up afforded **1d** (yield = 62%).

4.2.5. *N*-(2,6-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1e. A toluene (150 mL) solution of homophthalic acid (4 g, 22.2 mmol), 2,6-dichloro aniline (3.6 g, 22.2 mmol) and *p*-toluenesulfonic acid was refluxed for 24 h; usual work-up afforded **1e**. Yield: 4.75 g (70%); mp 170–172 °C; UV: 244 nm (CH_3CN); IR (KBr): 1720 (C_3-CO), 1674 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.24 (s, 2H, C_4-CH_2), 7.27–7.68 (m, 6H, Ar–H), 8.26 (d, J = 7.8 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.2, 125.3, 128.0, 128.4, 129.0, 130.0, 130.6, 131.0, 134.8, 135.0, 134.8, 164.5 (C_1-CO), 168.8 (C_3-CO). MS: *m/z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 242 (38) 213 [215], 152 [154], 118 (25), 117 (4), 104 (2), 90 (68), 63 (30). Anal. Calcd for $C_{15}H_9NO_2Cl_2$ (306.14): C, 58.84; H, 2.96; N, 4.57. Found: C, 58.72; H, 3.17; N, 4.77.

A mixture of homophthalic acid (0.4 g, 2.2 mmol), 2,3-dichloroaniline (0.36 g, 2.2 mmol) and acidic silica gel (4 g) was heated in the microwave oven for 40 min; usual work-up afforded **1e** (yield = 65%).

4.2.6. *N*-(2-Bromo-4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1f. Following the general procedure, a mixture of homophthalic acid (4 g, 22.2 mmol), 2-bromo-4-methylaniline (4.13 g, 22.2 mmol) and *p*-toluenesulfonic acid in dry toluene (150 mL) was refluxed for 24 h. After completion of the reaction, usual work-up furnished **1f**. Yield: 5.47 g (75%); mp 162–164 °C; UV: 245 nm (CH_3CN); IR (KBr): 1722 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.36 (bs, 3H, CH_3), 4.18 (s, 2H, C_4-CH_2), 7.09–7.63 (m,6H, Ar–H), 8.21 (d, J = 7.7 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.5, 37.4, 123.0, 125.7, 128.0, 128.3, 129.8, 129.9, 130.4, 132.6, 134.3, 134.6, 134.8, 141.4, 164.8 (C_1-CO), 169.7 (C_3-CO). MS: *m/z* (%): (329 (M^+), 331-trace), 250 (100), 249 (2), 222 (42), 194 (2), 193 (2), 132 (10), 118 (8), 117 (3), 104 (5), 90 (40), 89 (39), 63 (12). Anal. Calcd for $C_{16}H_{12}NO_2Br$ (330.176): C, 58.20; H, 3.66; N, 4.24. Found: C, 58.46; H, 3.57; N, 4.42. Further the structure was confirmed by XRD.[16]

Heating a mixture of homophthalic acid (0.5 g, 2.7 mmol), 2-bromo-4-methylaniline (0.52 g, 2.7 mmol) and acidic silica gel (5 g) in microwave oven for 30 min, followed by usual work-up furnished **1f** (yield = 78%).

4.2.7. *N*-(2-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1g. A mixture of homophthalic acid (3 g, 16.6 mmol), 2-bromoaniline (2.86 g, 16.6 mmol) and *p*-toluenesulfonic acid in dry toluene (120 mL) was refluxed for 24 h. After completion of the reaction, usual work-up afforded **1g**. Yield: 3.76 g (72%); mp 126–128 °C; UV: 242 nm (CH_3CN); IR (KBr): 1712 (C_3-CO), 1676 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.19 (d, J = 22.5 Hz, 1H, C_4-H_a), 4.28 (d, J = 22.5 Hz, 1H, C_4-H_b), 7.25 − 7.73 (m, 7H, Ar–H), 8.24 (d, J = 7.3 Hz,1H,C_8-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.8, 122.8, 125.1, 127.4, 127.9, 128.4, 129.5, 130.3, 130.4, 133.3, 134.1, 134.2, 134.8, 164.2 (C_1-CO), 169.1 (C_3-CO). MS: *m/z* (%): (315 (M^+), 317-trace), 236 (100), 235 (2), 208 (48), 180 (6), 179 (4), 118 (12), 117 (2), 104 (8), 90 (38), 89 (33), 63 (10). Anal. Calcd for $C_{15}H_{10}NO_2Br$ (316.15): C, 56.98; H, 3.18; N, 4.43. Found: C, 56.77; H, 3.29; N, 4.58.

Microwave irradiation of a mixture of homophthalic acid (0.4 g, 2.2 mmol) and 2-bromoaniline (0.38 g, 2.2 mmol) in acidic silica gel (4 g) for 35 min, furnished **1g** (yield = 69%).

4.2.8. *N*-(2-Chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1h. Following the general procedure, a mixture of homophthalic acid (3 g, 16.6 mmol), 2-chlorobenzylamine (2.35 g, 16.6 mmol) and *p*-toluenesulfonic acid was refluxed in dry toluene (120 mL) for 24 h. After completion of the reaction, usual work- up furnished **1h**. Yield: 3.36 g (71%); mp 122–124 °C; UV: 244 nm (CH_3CN); IR (KBr): 1718 (C_3-CO), 1670 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.18 (s, 2H, C_4-CH_2), 5.28 (s, 2H, N–CH_2), 7.02–7.64 (m, 7H, Ar–H), 8.20 (d, J = 7.7 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.5, 41.3, 125.1, 126.8, 127.2, 127.3, 127.9, 128.3, 129.4, 129.6, 133.0, 133.9, 134.0, 134.1, 164.7 (C_1-CO), 169.8 (C_3-CO). MS: *m/z* (%): (285 (M^+), 287-trace), 250 (100), 249 (1), 222 (13), 194 (2), 166 (4), 132 (2), 125 (6), 118 (12), 104 (3), 90 (20), 89 (22), 63 (2). Anal. Calcd for $C_{16}H_{12}NO_2Cl$ (285.725): C, 67.25; H, 4.23; N, 4.90. Found: C, 67.17; H, 4.42; N, 5.12. Further the compound was confirmed by XRD.[16]

Heating a mixture of homophthalic acid (0.5 g, 2.7 mmol), 2-chlorobenzylamine (0.38 g, 2.7 mmol) and acidic silica gel (5 g) in microwave oven for 40 min, followed by usual work-up furnished **1h** (yield = 65%).

4.3. Irradiation of the tetrahydroisoquinolines 1a–g

4.3.1. Benzoxazolo[3,2-*b*]isoquinolin-11-one 2a. An acetonitrile solution (150 mL) of *N*-(2-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1a** (0.3 g, 1.1 mmol) containing 30 mL of aqueous 1 M NaOH was flushed with nitrogen for 1 h and irradiated at 254 nm in an Applied Photophysics multilamp reactor for 12 h. The reaction was monitored by TLC until the disappearance of the starting material. After completion of the reaction, the solvent was evaporated under reduced pressure from the two-phase mixture and it was extracted with ethyl acetate. The ethyl acetate layer was separated, the aqueous layer was neutralized with dil. HCl, and then was extracted with ethyl acetate. The ethyl acetate portions were combined together, dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed over a column of silica gel; elution with ethyl acetate-petroleum ether (15:85) furnished the respective benzoxazolo[3.2-*b*]isoquinolin-11-one **2a**. It was recrystallized from ethyl acetate-hexane mixture. Yield: 0.106 g (41%); mp 200–202 °C (lit.[21] mp 204–206 °C); UV: 234 nm (CH_3OH); IR (KBr): 1685, 1625, 1606, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.45 (s, 1H, C_6-CH), 7.19–7.51 (m, 4H, ArH), 7.51–7.85 (m, 2H, ArH), 8.29–8.75 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 81.9 (C_6-CH), 109.9, 116.4, 119.6, 121.5, 124.2, 124.3, 125.9, 126.2, 127.8, 132.8, 137.7, 147.2, 149.9, 159.3 (C_{11}-CO). MS: *m/z* (%): 235 (M^+, 100), 234

(12), 207 (6), 206 (5), 179 (2), 178 (6), 177 (2), 151 (5), 125 (2), 117.5 (M^{++}), 115 (2), 101 (2), 89 (12).

Irradiation of *N*-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1g** (0.3 g, 3.1 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 8 h, using multilamp reactor (MLR), followed by usual work-up and chromatographic separation, afforded **2a** (yield = 50%), which was confirmed by mp, mixture mp and superimposable IR with that obtained under the same conditions from **1a**.

4.3.2. 4-Chlorobenzoxazolo[3,2-*b*]isoquinolin-11-one 2b. Irradiation of *N*-(2,3-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1b** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 7 h, using multilamp reactor, followed by usual work-up as mentioned above and chromatographic separation, furnished **2b**.Yield: 0.113 g (43%); mp 188–190 °C; UV: 242 nm (CH_3OH); IR (KBr): 1678, 1642, 1604, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.54 (s, 1H, C_6-CH), 7.26–7.88 (m, 5H, ArH), 8.42–8.50 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.6 (C_6-CH), 114.7, 115.4, 122.2, 124.9, 125.1, 126.5, 128.5, 129.1, 130.1, 133.2, 137.4, 146.1, 149.5, 159.2 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 30), 241 (15) [243 (6)], 234 (9), 213 (5) [215 (2)], 206 (22), 178 (30), 177 (17), 151 (8), 134.5 (M^{++}, 5), 125 (3), 115 (9), 101 (5), 89 (15). Anal. Calcd for $C_{15}H_8NO_2Cl$ (269.68): C, 66.80; H, 2.98; N, 5.19. Found: C, 66.67; H, 3.21; N, 5.37.

4.3.3. 3-Chlorobenzoxazolo [3,2-*b*] isoquinolin-11-one 2c. The compound **2c** was obtained on irradiation of *N*-(2,4-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1c** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 8 h, using multilamp reactor. Yield: 0.126 g (48%); mp 205–207 °C; UV: 243 nm (CH_3OH); IR (KBr): 1683, 1643, 1606, 1475 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.47 (s, 1H, C_6-CH), 7.32–7.69 (m, 5H, ArH), 8.44 (d, J = 8.3 Hz, 1H, C_1-ArH), 8.48 (d, J = 8.3 Hz, 1H, C_2-ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.3 (C_6-CH), 110.8, 116.7, 121.9, 124.4, 124.8, 126.1, 126.8, 127.8, 131.9, 133.0, 137.8, 147.8, 150.0, 159.5 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 36), 241 (8) [243 (3)], 234 (9), 213 (6) [215 (2)], 206 (22), 178 (16), 177 (8), 151 (8), 134.5 (M^{++}, 8), 125 (2), 115 (3), 101 (8), 89 (10). The structure of the compound was further confirmed by XRD.[19]

4.3.4. 2-Chlorobenzoxazolo [3,2-*b*] isoquinolin-11-one 2d. Irradiation of an acetonitrile (150 mL) solution of *N*-(2,5-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1d** (0.3 g, 1.0 mmol) containing 1 M NaOH (30 mL) using multilamp reactor for 9 h, followed by usual work-up and chromatographic separation, afforded **2d**.Yield: 0.121 g (46%); mp 213–215 °C (lit.[21] mp 211–212 °C); UV: 242 nm (CH_3OH); IR (KBr): 1684, 1632, 1608, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.41 (s, 1H, C_6-CH), 7.24–7.66 (m, 5H, ArH), 8.44 (d, J = 8.8 Hz, 1H, C_4-ArH), 8.51 (d, J = 2.0 Hz, 1H, C_1-ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.5 (C_6-CH), 110.8, 116.9, 121.6, 125.0, 126.3, 128.1, 128.9, 129.8, 133.3, 137.8, 146.0, 150.2, 159.3 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 34), 241 (12) [243 (4)], 234 (4), 213 (6) [215 (2)], 206 (20), 178 (30), 177 (16), 151 (14), 134.5 (M^{++}, 6), 125 (6), 115 (5), 101 (6), 89 (24).

4.3.5. 1-Chlorobenzoxazolo [3,2-*b*] isoquinolin-11-one 2e. The irradiation of *N*-(2,6-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1e** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 10 h, using multilamp reactor, followed by usual work-up as mentioned above and chromatographic separation, furnished **2e**.Yield: 0.108 g (40%); mp 183–185 °C; UV: 240 nm (CH_3OH); IR (KBr): 1680, 1641, 1600, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.37 (s, 1H, C_6-CH), 7.26–7.67 (m, 4H, ArH), 7.82–8.00 (m, 2H, ArH), 8.46–8.54 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 81.6 (C_6-CH), 108.6, 124.1, 124.7, 125.3, 126.9, 127.5, 128.5, 128.6, 131.5, 133.1, 134.6, 137.0, 150.0, 159.9 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 33), 241 (16) [243 (6)], 234 (25), 213 (5) [215 (2)], 206 (18), 178 (25), 177 (16), 151 (10), 134.5 (M^{++}, 6), 125 (3), 115 (4), 101 (8), 89 (28). Anal. Calcd for $C_{15}H_8NO_2Cl$ (269.68): C, 66.80; H, 2.98; N, 5.19. Found: C, 66.57; H, 3.17; N, 5.39.

4.3.6. 3-Methylbenzoxazolo[3,2-*b*]isoquinolin-11-one 2f. The compound **2f** was obtained on irradiation of *N*-(2-bromo-4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1f** (0.3 g, 0.9 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 7 h. Yield: 0.12 g (52%); mp 200–202 °C; UV: 236 nm (CH_3OH); IR (KBr): 1687, 1641, 1601, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.43 (s, 3H, CH_3), 6.38 (s, 1H, C_6-CH), 7.08–7.64 (m, 5H, ArH), 8.34 (d, J = 8 Hz, 1H, C_2-ArH), 8.45 (d, J = 8 Hz, 1H, C_1-ArH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.1 (CH_3), 82.2 (C_6-CH), 110.8, 116.3, 121.9, 124.7, 125.1, 126.3, 128.1, 133.0, 137.1, 138.1, 147.8, 150.5, 159.5 (C_{11}-CO). MS: *m/z* (%): 249 (M^+, 100), 221 (8), 220 (9), 193 (7), 192 (12), 178 (3), 177 (2), 165 (8), 151 (13), 125 (5), 124.5 (M^{++}), 115 (6), 101 (4), 89 (13). Anal. Calcd for $C_{16}H_{11}NO_2$ (249.26): C, 77.09; H, 4.44; N, 5.61. Found: C, 76.92; H, 4.33; N, 5.82.

4.4. Irradiation of *N*-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1h

4.4.1. *N*-(2-Chlorobenzyl)-2-methylbenzamide 3. The irradiation of **1h** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) was carried out (after flushing with nitrogen for 1 h) for 15 h in a multilamp reactor (254 nm). The completion of the reaction was checked by TLC; usual work-up and chromatographic separation using ethyl acetate-hexane mixture (1:9) afforded *N*-(2-chlorobenzyl)-2-methylbenzamide **3** (yield: 0.18 g, 69%; mp 100–102 °C).

Further, the compound **3** was confirmed with the authentic sample by mp, mixture mp and superimposable IR. The authentic sample was prepared by the addition of a benzene solution of 2-methylbenzoyl chloride (1.5 g, 9.7 mmol) to 2-chlorobenzyl amine (1.37 g, 9.7 mmol) in benzene (40 mL) containing a few drops of pyridine (yield = 1.6 g, 67%).

4.4.2. Isoquinolino[3,2-*b*[[1,3]benzoxazin-11-one 4. Irradiation of 0.3 g (1.0 mmol) of **1h** in acetonitrile containing 3 M NaOH (30 mL) was carried out for 12 h (after flushing with nitrogen for 1 h) in a multlamp reactor. After completion of the reaction (checked by TLC),

followed by usual work-up, the column chromatographic separation using petroleum ether-ethyl acetate (4:1) as eluant, afforded **4** (yield: 0.12 g, 47%; mp 210–212 °C). The spectral data of compounds **3** and **4** were reported earlier.[13]

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