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# Note

## Facile chemoselective synthesis of novel 6-aryl-12*H*-indolo[2,3-*e*][1,4]benzodiazocine derivatives by the reaction of 3-aroylmethylene-2*H*-indol-2-ones with *o*-phenylenediamine

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Syntheses of 6-aryl-12*H*-indolo[2,3-*e*][1,4]benzodiazocine derivatives **8** have been achieved for the first time by the reaction of 3-aroylmethylene-2*H*-indol-2-ones **4** with *o*-phenylenediamine **5** While the analogous reaction of **4** with ethylene diamine **9** resulted in exclusive formation of Schiff base derivatives *viz*. 1,3-dihydro-3-[2- (2-aminoethylimino)-2-aryl-ethylidene]indol-2-ones **12**. The structures are assigned with the help of analytical and $^{1}$H, $^{13}$C NMR, DEPT, IR and mass spectral studies.

**Keywords**: 6-aryl-12*H*-indolo[2,3-*e*][1,4]benzodiazocine, 1,3-dihydro-3-[2-(2-aminoethyl-imino)-2-aryl-ethylidene]indol-2-one, 3-aroylmethylene-2*H*-indol-2-one, microwave irradiation, sonication

The indole ring system has become an important structural component in many pharmaceutical agents. Indole containing heterocyclic compounds are interesting as potential biologically active substances[1-3]. Isatin **1** has important applications in synthetic organic chemistry[4]. Some of its derivatives show a wide range of antibacterial, antifungal and anti HIV activities[5]. A recent trend in the indole chemistry is to incorporate seven or eight membered rings into the indole moiety to yield novel compounds which may lead to the development of pharmacologically active compounds[6]. A perusal of literature reveals that some work on the synthesis of 1,5-benzodiazocine[7], 6-aryl-1,5-benzodiazocine[8] and indolo[2,1-*d*][1,5]benzodiazocine[6] derivatives have been reported. But no work has been reported on indolo[2,3-*e*][1,4]benzodiazocine derivatives. Some of the [1,4]diazocino indole derivatives are used as antipsychotic and antiobesity agents[9].

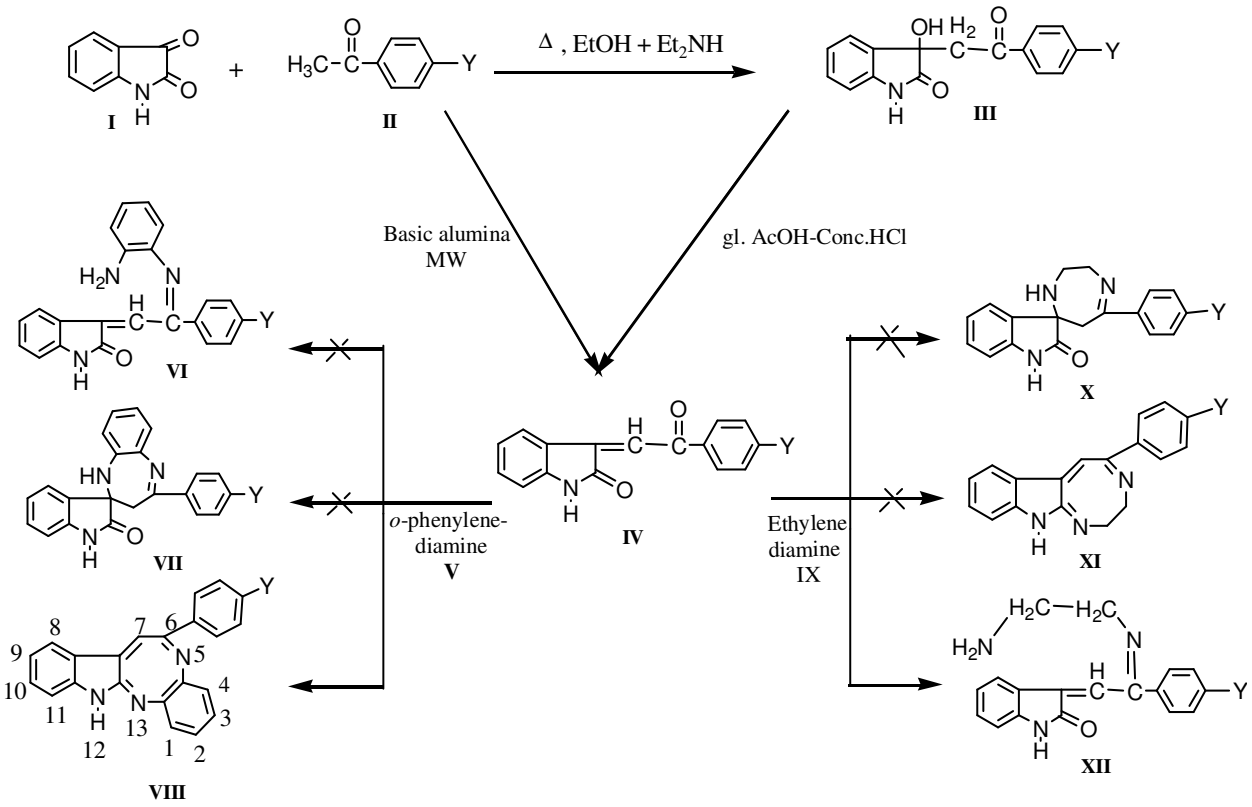
The 3-aroylmethylene-2*H*-indol-2-ones **4** have been proved as potential building block for the synthesis of various heterocyclic systems and have shown wide variety of biological activities[10,11]. The investigation of the reaction of **4** with *o*-phenylenediamine led to the formation of 6-aryl-12*H*-indolo-[2,3-*e*][1,4]benzodiazocine **8**, an eight membered condensed novel heterocyclic compound instead of the expected formation of compounds **6** and **7** on account of availability of different reaction sites in the key intermediate **4**, as have already been reported with several other nitrogen containing nucleophiles[12-14]. While the analogous reaction with ethylene diamine resulted in exclusive formation of Schiff base derivatives *viz* 1,3-dihydro-3-[2-(2-aminoethyl-imino)-2-aryl-ethylidene]indol-2-one **12** in place of products **10** and **11**.

The application of microwaves[15] and ultrasonic irradiations[16], as non-conventional energy source for reaction activation, has now become a very popular and useful technology in organic chemistry. The above reactions were studied under different reaction conditions e.g. conventional, microwaves and sonication to find out the best method giving the product in higher yield with operational simplicity. It was noticed that the best results were obtained under sonication.

### Results and Discussion

In the present investigation the intermediates **4a-c** were obtained in quantitative yields in 4-6 min, by the reaction of isatin **1** with substituted acetophenones **2** using basic alumina as inorganic solid support under microwaves[14]. Alternatively these were also synthesized conventionally by two step procedure[17].

The reaction of appropriate 3-aroylmethylene-2*H*-indol-2-ones **4** with *o*-phenylenediamine **5** in ethanol at room temperature for 20 hr resulted in the exclusive formation of the products **8** as white crystals (**Scheme I**). However, the absence of >C=O absorption peaks in their IR and carbonyl carbon in $^{13}$C NMR spectra ruled out the possibility of formation of expected products **6** and **7**. Absence of $CH_2$ group in the DEPT 135 spectrum further ruled out the possibility of formation of product **7** in the reaction. The mass spectra of the products **8a** and **8b** did not exhibit recognizable molecular ion peaks but base peaks at *m/z* 237 and 207 were observed due to the loss of $C_8H_4N$ moiety respectively. Thus product **8**




**a** : Y = -$OCH_3$, **b**: Y= -H, **c** : Y=-$CH_3$

**Scheme I**

was decisively identified as 6-aryl-12*H*-indolo[2,3-*e*][1,4]benzodiazocine on the basis of its IR, $^1$H, $^{13}$C NMR, DEPT and MS spectral studies.

This reaction has been studied extensively for the first time using different modes of reaction activation e.g. conventional, microwaves and sonication for the synthesis of 6-(4-methoxyphenyl)-12*H*-indolo[2,3-*e*][1,4]benzodiazocine **8a**. The best results were obtained by conducting reaction under sonication (**Table I**).

The similar reaction of appropriate 3-aryl-methylene-2*H*-indol-2-ones **4** with ethylene diamine **9** led to the exclusive formation of Schiff bases **12** instead of **10** and **11** in all reaction conditions (**Table II**). The structures of compounds **12a-c** were ascertained by their detailed spectral studies. The IR spectra of the products **12a-c** showed intense carbonyl absorption bands around 1650 $cm^{-1}$ further ruling out possibility of product **11**. In the mass spectra of **12a** and **12b** molecular ion peaks were recognizable along with base peaks at *m/z* 320 and 290 respectively. Presence of two $CH_2$ groups concluded by their DEPT 135 specta. Compounds **12a-e** were identified as 1,3-dihydro- 3-[2-(2-aminoethyl-imino)- 2- aryl-ethylidene]-indol-2-ones. This reaction has also been studied extensively using different modes of reaction activation and the best yield of the product **12a** was obtained under sonication.

**Table I** — Comparative results for the synthesis of 6-(4-methoxyphenyl)-12*H*-indolo[2,3-*e*][1,4]benzodiazocine, **8a**

| S.No. | Reaction conditions | Method | Time | Yield (%) |
|---|---|---|---|---|
| 1 | Ethanol | RT | 24 hr | 42 |
| 2 | Ethanol | Thermal | 6 hr | 48 |
| 3 | Neat + ε DMF | MW (400 W) | 5 min | 45 |
| 4 | Ethanol | MW (300 W) | 4-5 min | 52 |
| 5 | Ethanol | US (RT) | 2 hr | 55 |

## Experimental Section

Melting points were determined in soft glass capillaries in an electrothermal melting point apparatus and are uncorrected. Qualitative and quantitative TLC were conducted on TLC aluminium sheets Kieselgel 60 $F_{254}$ [E. Merck]. IR spectra (KBr) were recorded on a Shimadzu FTIR-8400S spectrometer and $^1$H, $^{13}$C NMR and DEPT spectra were

recorded on JEOL AL 300 MHz FT NMR instrument using $CDCl_3$ as solvent. Mass spectra (FAB MS) were generated on a JEOL SX 102/DA-6000 mass spectrometer. All compounds were homogeneous on TLC in various solvent systems. Microwave assisted reactions were carried out on a BPL BMO Model, operating at 700 W, generating 2450 MHz frequency. Ultrasonic-reactions were carried out in ultrasonic bath (Bandelin Sonorex) operating at room temperature.

**Synthesis of 1,3-dihydro-3-[2(4-methoxyphenyl)-2-oxoethylidene]indol-2(1*H*)-one, 4a**

It was prepared under microwaves involving a one step procedure. Isatin **1** (0.01 mole) and 4-methoxy acetophenone **2** (0.01 mole) were adsorbed separately on basic alumina (20% by weight of the reactants) *via* a solution in acetone. These were mixed thoroughly and irradiated in a domestic oven (700 W, generating 2450 MHz frequency) at an emitted power of 640 W for 5-6 min at 128°C (monitored by TLC). The product was extracted by eluting with ethanol. Excess solvent was evaporated on water-bath to give orange crystals of the chalcone **4a**, m.p. 195-97°C, yield 94%.

Likewise **4b** and **4c** were obtained as orange crystals, m.p. 190-92°C, yield 96% and orange needles, m.p. 166-68°C, yield 98% respectively by the same procedure.

**Synthesis of 6-(4-methoxyphenyl)-12*H*-indolo[2,3-*e*][1,4]benzodiazocine 8a**: It was synthesized by four methods. The percentage yields and reaction time varied in each case.

**(A) At room temperature**

The *o*-phenylene diamine **5** (0.5 mmole) was added to the solution of 1,3-dihydro-3-[2-(4-methoxy-phenyl)-2-oxoethylidine]indol-2(1*H*)-one **4a** (0.5 mmole) in absolute ethanol. Progress of reaction was monitored on TLC plate. After 20 hr colour of reaction-mixture changed from orange to yellow, which indicated completion of the reaction. A white coloured compound separated out which was filtered, washed with cold petroleum ether and recrystallized from ethanol.

**(B) Conventional method**

Equimolar mixture of **4a** and **5** (0.5 mmole each) in 20 mL ethanol was refluxed for 6 hrs. Reaction-mixture was cooled and kept for crystallization at RT. White coloured compound was separated out which was recrystallized from ethanol.

**(C) Microwave irradiation Method**: The reaction was studied under different conditions to optimize the best process.

**(i) Neat + few drops of DMF**

An Equimolar mixture of **4a** and **5** (1 mmole each) with few drops of dimethylformamide in an open vessel was mixed thoroughly with a glass rod. The mixture was then irradiated in microwave oven for a period of 5 min at 450 W. Progress of the reaction was monitored by TLC. It was purified by preparative TLC using benzene as eluant.

**(ii) Using ethanol**

Equimolar mixture of **4a** and **5** (1 mmole each) was placed in a conical flask and the minimum quantity of ethanol was added. The mixture was placed in the MW oven and irradiated at power output of 300 W for 4-5 min intermittently. Progress of the reaction was monitored by TLC. Reaction-mixture was cooled and kept for crystallization. White coloured crystalline product was separated out which were recrystallized from ethanol.

**(D) Ultrasonic irradiation**

An equimolar quantity of **4a** and **5** (1 mmole each) were added in a conical flask and dissolved in ethanol. The reaction-mixture was placed under ultrasonic waves using ultrasonic-bath (operating at 230 V generating 33 KHz output frequencies) for 2 hr (TLC) at RT. Reaction-mixture was kept for crystallization. White coloured product separated out which was recrystallized from ethanol.

The identity of products formed under different reaction conditions was ascertained by TLC, mixed m.p. and spectral studies. The best results were obtained under sonication, hence remaining two compounds **8b** and **7c** were synthesized by sonication.

**Synthesis of 1,3-dihydro-3-[2-[2-aminoethyl-imino]-2-(4-methoxyphenyl)-ethylidene]indol-2-one, 12a**

It was synthesized by the reaction of ethylene diamine **9** (1 mmole) with 1,3-dihydro-3-[2-(4-methoxy-phenyl)-2-oxoethylidene)indol-2(1*H*)-one **4a** (1 mmole) in 20 mL ethanol at RT. After 20 hrs reaction-mixture was worked out by preparative TLC using benzene-ethyl acetate (9:1) mixture. A bright

**Table II—** Comparative results for the synthesis of 1,3-dihydro-3-[2-[2-aminoethylimino]-2-(4-methoxy-phenyl)-ethylidene]indol-2-one, **12a**

| S.No. | Reaction conditions | Method | Time | Yield (%) |
|---|---|---|---|---|
| 1 | Ethanol | RT | 20 hr | 63 |
| 2 | Ethanol | Thermal | 8 hr | 65 |
| 3 | Ethanol | MW (300 W) | 4-5 min | 70 |
| 4 | Ethanol | US (RT) | 2 hr | 76 |

orange crystalline product separated out which was recrystallized from ethanol.

Alternatively this reaction was also studied under conventional method, microwave irradiation and ultrasonic irradiation. Same product was obtained in each case. The identity of products obtained under different conditions was checked by TLC, mixed m.p. and spectral studies. The percentage yields and reaction time varied in each case as illustrated in **Table II**.

The best result was obtained under sonication so rest of the two compounds **12b,c** were synthesized by sonication.

## Physical and analytical data

### 6-(4-Methoxyphenyl)-12*H*-indolo[2,3-*e*][1,4]benzodiazocine, 8a

White needles, yield: 55%, m.p. 100-102°C; (Found: C, 78.42; H, 4.61; N, 12.01. $C_{23}H_{17}N_3O$, requires C, 78.63; H, 4.84; N, 11.97%); IR (KBr): 3175 (NH), 3005-2900 (C-H), 1610 and 1575 (C=N), 1550-1430 $cm^{-1}$ (C=C); $^1H$ NMR (300 MHz; $CDCl_3$; $Me_4Si$): δ 9.29 (s, 1H, NH), 8.18 (m, 5H, ArH and =CH), 7.78 (m, 4H, ArH), 7.07 (m, 4H, ArH), 3.93 (s, 3H, $OCH_3$); $^{13}C$ NMR (75.45 MHz; $CDCl_3$; $Me_4Si$): δ 55.41($OCH_3$), 114.56, 128.95, 129.04, 129.24, 129.37, 130.16, 141.17, 142.29, 143.04 (aromatic carbons), 151.39 (C=N), 161.44 (C=N). FAB-MS: *m/z* 237 $[M-C_8H_4N]^+$ (100), 236 $[237-H]^+$(60).

### 6-Phenyl-12*H*-indolo[2,3-*e*][1,4]benzodiazocine, 8b

White needles, yield: 72%, m.p. 75-77°C; (Found: C, 82.57; H, 4.50; N, 13.33. $C_{22}H_{15}N_3$, requires C, 82.24; H, 4.67; N, 13.08%); IR (KBr): 3100 (NH), 1610 and 1580 (C=N), 1550-1430 $cm^{-1}$ (C=C); $^1H$ NMR (300 MHz; $CDCl_3$; $Me_4Si$): δ 9.33 (s, 1H, NH), 8.17 (m, 6H, ArH and =CH), 7.80 (m, 4H, ArH), 7.53 (m, 4H, ArH); $^{13}C$ NMR (75.45 MHz; $CDCl_3$; $Me_4Si$): δ 127.46, 129.06, 129.45, 129.53, 130.10, 130.20, 136.65, 141.46, 142.19, 143.27 (aromatic carbons), 143.48, 151.72 (C=N); ESI-MS: *m/z* 207 $[M-C_8H_4N]^+$ (100).

### 6-(4-Methyl-phenyl)-12*H*-indolo[2,3-*e*][1,4]benzodiazocine, 8c

White crystals, yield: 62%, m.p. 76-79°C; (Found: C, 82.01; H, 4.98; N, 12.71. $C_{23}H_{17}N_3$ requires C, 82.39; H, 5.07; N, 12.54%); IR (KBr): 3100 (NH), 3010-2900 (C-H), 1620 and 1580 (C=N), 1550-1420 $cm^{-1}$ (C=C); $^1H$ NMR (300 MHz; $CDCl_3$; $Me_4Si$): δ 9.31 (s, 1H, NH), 8.13 (m, 5H, ArH and =CH), 7.77 (m, 4H, ArH), 7.36 (m, 4H, ArH), 2.43 (s, 3H, $CH_3$); $^{13}C$ NMR (75.45 MHz; $CDCl_3$; $Me_4Si$): δ 21.43 (-$CH_3$), 127.42, 129.07, 129.30, 129.52, 129.90, 130.20, 133.94, 140.50, 141.40, 142.30 (aromatic carbons), 143.29 (C=N), 151.81 (C=N).

### 1,3-Dihydro-3-[2-[2-aminoethyl-imino]-2-(4-methoxyphenyl)-ethylidene]indol-2-one, 12a

Orange red crystals, yield: 76%, m.p. 210-13°C, (Found: C, 70.87; H, 5.44; N, 13.42. $C_{19}H_{19}N_3O_2$, requires C, 71.02; H, 5.92; N, 13.08%); IR (KBr): 3100-3250 (br, $NH_2$, and NH), 1650 (C=O), 1600 (C=N), 1400-1550 $cm^{-1}$ (C=C); $^1H$ NMR (300 MHz; $CDCl_3$, $Me_4Si$): 10.81 (s, 2H, $NH_2$) 9.03 (s, 1H, NH), 7.74 (m, 3H, ArH), 6.87 (m, 3H, ArH), 6.85 (s, 1H, =CH-), 6.48 (m, 1H, ArH), 6.03 (d, 1H, *J* = 7.89, ArH), 3.82 (t, 2H, *J* = 5.31, -$CH_2$-), 3.77 (s, 3H, -$OCH_3$), 3.40 (t, 2H, *J* = 5.31, -$CH_2$-); $^{13}C$ NMR (75.45 MHz; $CDCl_3$; $Me_4Si$): δ 37.30 ($CH_2$), 48.71 ($CH_2$), 55.39(-$OCH_3$), 109.01, 114.36, 120.58, 122.13, 122.77, 123.32, 129.41, 129.90, 135.36, 143.24, 145.13 (aromatic carbons), 163.60 (C=N), 172.79 (C=O); ESI-MS: *m/z* 321 $[M]^+$ (25) ($C_{19}H_{19}N_3O_2$), 320 $[M-H]^+$(100), 319 (98).

### 1,3-Dihydro-3-[2-[2-aminoethyl-imino]-2-phenyl-ethylidene]indol-2-one, 12b

Orange crystals, yield: 79%, m.p. 210-12°C; (Found: C, 74.45; H, 5.80; N, 14.03. $C_{18}H_{17}N_3O$, requires C, 74.23; H, 5.84; N, 14.43%); IR (KBr): 3100-3250 (br, $NH_2$, NH), 1650 (C=O), 1600 (C=N), 1550-1450 $cm^{-1}$ (C=C); $^1H$ NMR (300 MHz; $CDCl_3$; $Me_4Si$): δ 10.85 (s, 2H, $NH_2$), 8.77 (s, 1H, NH), 7.81 (m, 2H, ArH), 7.36 (m, 3H, ArH), 7.33 (s, 1H, =CH-), 6.85 (m, 2H, ArH), 6.45 (m, 1H, ArH), 5.92 (d, 1H, *J* = 8.07, ArH), 3.94 (t, 2H, *J* = 5.49, -$CH_2$-), 3.41 (t, 2H, *J* = 5.49, -$CH_2$-); $^{13}C$ NMR (75.45 MHz; $CDCl_3$; $Me_4Si$): δ 37.08 ($CH_2$), 48.92 ($CH_2$), 108.93, 120.43,

121.96, 122.69, 123.44, 127.79, 129.02, 130.70, 135.29, 137.31, 144.62 (aromatic carbons), 164.39 (C=N), 172.68 (C=O); ESI-MS: *m/z* 291 $[M]^+$ (20) ($C_{18}H_{17}N_3O$), 290 $[M-H]^+$(100).

### 1,3-Dihydro-3-[2-[2-aminoethyl-imino]-2-(4-methyl-phenyl)-ethylidene]indol-2-one, 12c

Orange red crystals, yield: 96%, m.p. 240-44°C; (Found: C, 74.52; H, 6.45; N, 13.51. $C_{19}H_{19}N_3O$, requires C, 74.75; H, 6.22; N, 13.77%); IR (KBr): 3100-3250 (br, $NH_2$ and NH) 2900-3005 (C-H), 1650 (C=O), 1600 (C=N), 1400-1550 $cm^{-1}$ (C=C); $^1H$ NMR (300 MHz; $CDCl_3$; $Me_4Si$): δ 10.83 (s, 2H, $NH_2$), 8.04 (s, 1H, NH), 7.68 (d, $J$ = 8.04, 2H, ArH), 7.28(s, 1H, =CH-), 7.15 (d, 1H, $J$ = 8.07, ArH), 6.83 (m, 2H, ArH), 6.47 (m, 2H, ArH), 5.98 (d, 1H, $J$ = 8.04, ArH), 3.91 (t, 2H, $J$ = 5.31, -$CH_2$-), 3.38 (t, 2H, $J$ = 5.31, -$CH_2$-), 2.30 (s, 3H, -$CH_3$); $^{13}C$ NMR (75.45 MHz; $CDCl_3$; $Me_4Si$): δ 21.46 ($CH_3$), 37.19 ($CH_2$), 48.83 (-$CH_2$), 108.89, 120.41, 122.10, 122.81, 123.33, 127.69, 129.71, 134.57, 135.26, 141.02, 144.97 (aromatic carbons), 164.24 (C=N), 172.65 (C=O); ESI-MS: *m/z* 305 $[M]^+$ ($C_{19}H_{19}N_3O$).

## Conclusion

A facile chemoselective synthesis of a novel eight membered ring system *viz* 6-aryl-12*H*-indolo[2,3-*e*][1,4]benzodiazocine derivatives **8** by the reaction of 3-aroylmethylene-2*H*-indol-2-ones **4** with *o*-phenyl-enediamine **5** in the absence of any catalyst.

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