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# APPLICATION OF MICROWAVE INDUCED DELEPINE REACTION TO THE FACILE ONE POT SYNTHESIS OF 7-SUBSTITUTED 1, 3-DIHYDRO-2*H*-[1, 4]-BENZODIAZEPIN-2-ONE-5-METHYL CARBOXYLATES FROM THE CORRESPONDING 1- CHLOROACETYL ISATINS

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## ABSTRACT

Application of microwave induced Delepine reaction to the facile one pot synthesis of 7-(fluoro, chloro, bromo, iodo, methyl, methoxy, nitro) and 5, 7- dimethyl substituted, 1, 3- dihydro-2H-[1, 4] -benzodiazepin-2-one-5-methyl carboxylate derivatives **3(a-i)** from the corresponding 1- chloroacetyl isatin **2(a-i)** has been described. The mechanism involved in the microwave assisted Delepine reaction in the transformation of **2** to **3** has been disscussed.

**Key words**: 1-Chloroacetyl isatin, 5-Carbomethoxy-1, 3-Dihydro-2H [1,4]-Benzodiazepin-2-one, Psychopharmacological agents, Anti-HIV agents.

## INTRODUCTION

The recent discovery that 5- substituted 1, 4- benzo (and pyrido)-diazepines such as the 5-pyrrolo substituted 1, 4 –benzodiazepine[1, 2] **4**, TIBO[3] **5** and nevirapine[4] **6** can serve as potential agents for the control and treatment of AIDS[5-10] has triggered the development of a variety of methods for their synthesis and has led to an impressive armoury of synthetic strategies to be devised in the literature for their preparation[10-13].

Our interest[14] in the chemistry of **4** has called upon to explore the possibilities of the formation of other derivatives of **4**, which carried at $C_5$, such heterocyclic scaffolds as oxadiazole, imidazole, pyrazole, isoxazole etc. and which also contained a variety of

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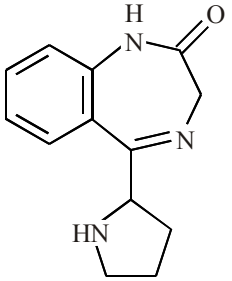
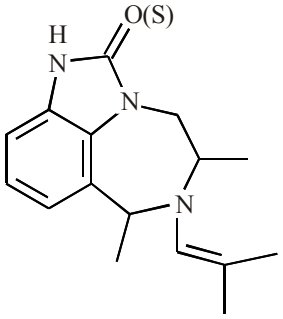
halogen atoms and other groups at $C_7$ and $C_9$. In the quest to develop, suitable strategies for their preparation, it was sought to streamline the synthetic routes, which could possibily, generate these through the straight forward procedures. We envisioned that these rings could easily be-generated[14] from the corresponding 5-carbomethoxy substituted derivative, which could then be elaborated in accordance to the literature procedure[15] to afford these at $C_5$ of 1, 4-benzodiazepine nucleus. To meet this goal, an easy, simple, practical and straight forward route is required for the synthesis of 5-carbomethoxy substituted 1, 4-benzodiazepin-2-one derivatives, which carried such atoms or groups as F, Cl, Br, I, OMe, $NO_2$, Me at $C_7$ and two methyl groups at $C_7$ and $C_9$ positions in their molecules.




**4**

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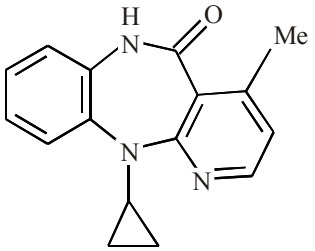
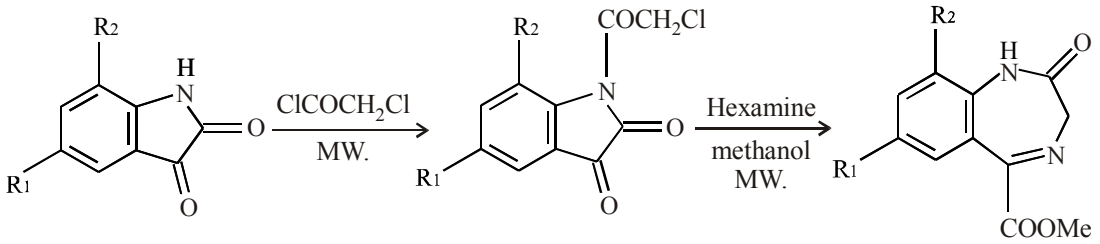



**6**

Consideration of factors on reactivity of the starting materials and simplicity in the operational procedure led us to favour the use of isatin for their synthesis. Isatin has been known to offer unprecedented opportunities in the synthesis of a variety of heterocyclic compounds. It is known to exist completely in the dicarbonyl from with its 3-carbonyl group being more reactive than 2-carbonyl group towards nucleophilic reagents. This variation in reactivity of two carbonyl groups of isatin molecule coupled with the observed facile opening of the ring under the influence of hydroxylic nucleophilic reagents offers additional advantages towards accomplishing the desired synthetic goals using isatin. Ogata and Motsumoto[16] very elegantly used these characteristics of isatin to develop a highly innovative technique for the synthesis 5-carbomethoxy substituted 1, 4-benzodiazepine-2-ones and its 7-chloro derivatives from the corresponding 1-chloroacetyl isatins. Their procedure consisted of treating 1-chloroacetyl isatin with methanolic solution of hexamine. Under these conditions, isatin underwent the cleavage of the ring, followed by the cyclocondensation of the ring-opened product, to give the desired 1, 4-benzodiazepine-2-one-5-carboxylate derivative, in a single step. An attractive feature of this reaction was, that it provided a very convenient one pot synthetic entry to the 1, 4-benzodiazepine nucleus from 1-chloroacetyl isatin. But its application in synthesis of 1, 4-benzodiazepine suffered from two serious drawbacks. Firstly, the reaction required a fairly long time (8-10 hrs.) of

heating and secondly, the yield of the product was enormously low (36-42% only), which was very discouraging. This was perhaps the reason, for its infrequent use in literature, in the synthesis of 1, 4-benzodiazepines. Clearly, a refinement of this methodology and adoption of a better technique, which allowed the reaction to take place in lesser time and in good yields, was required. Our efforts to circumvent this problem by the use of microwave induced, Delepine reaction on **2** have been highly encouraging. Recently, the use of microwave in the acceleration of organic reactions has found a widespread application in synthesis. Delepine reaction has been frequently used in the literature to provide an easy access to the amine from the activated alkyl halides through reaction with hexamine. The application of the microwave-assisted protocol of Delepine reaction on **2** with hexamine in methanol has resulted **3** in fairly high yield (70-82%) in only 8-10 min. time.

**Scheme 1**




**1(a-i)** **2(a-i)** **3(a-i)**

| **1, 2 and 3 (a-i)** |
|---|
| **a.** $R_1 = R_2 = H$ |
| **b.** $R_1 = F, R_2 = H$ |
| **c**. $R_1 = Cl, R_2 = H$ |
| **d.** $R_1 = Br, R_2 = H$ |
| **e.** $R_1 = I, R_2 = H$ |
| **f.** $R_1 = Me, R_2 = H$ |
| **g.** $R_1 = OMe, R_2 = H$ |
| **h.** $R_1 = NO_2, R_2 = H$ |
| **i.** $R_1 = Me, R_2 = Me$ |

## EXPERIMENTAL

All the melting points are taken in open capillaries and are uncorrected. The purity of all the compounds were checked by TLC using the solvent systems (benzene : methanol,

9 : 1 v/v) and silica gel G as adsorbent. IR spectra were recorded on Shimadzu FTIR-8400 infrared spectrometer using KBr, $^1$H NMR on Bruker AC 300F in $CDCl_3$+DMSO-$d_6$ (with chemical shifts expressed in δ, ppm) and mass spectra on Jeol-JMS-D-300 mass spectrometer. Reagents, 5-fluoro, 5-chloro, 5-bromo, 5-iodo, 5-methyl, 5-methoxy, 5-nitro and 5, 7-dimethyl isatins required in synthesis were obtained from commercial suppliers and used in the reaction without further purifications.

**General method for the preparation of 2(a-i) from 1(a-i)**

**Conventional method**

Isatin (**1a**, 0.068 mole) was vigorously refluxed with chloroacetyl chloride (0.090 mole) for 5 hr and the mixture was cooled for 2 hr in an icebath. The precipitate was filtered, washed with 20 mL portion of ether, then air-dried and was recrystallised from ethyl acetate to give **2a**, yield: 40%, m.p. 210-212°C[8c]. Other compounds **2(b-i)** were prepared from **1(b-i)** following the same procedure.

**Solution phase microwave assisted method**

A solution of isatin (**1a**, 0.068 mole) and chloroacetyl chloride (0.090 mole) was taken in a borosil conical flask fitted with a funnel as a loose top. The reaction mixture was irradiated in a domestic microwave oven at 180ºC for 10 min. (completion of reaction was checked by TLC) with short interval of 30s to avoid the excessive evaporation of reactant. After the completion of reaction, the mixture was cooled for 2 hr in an icebath. The precipitate was filtered, washed with 20 mL of portion of ether, then air-dried and was recrystallised with ethyl acetate to give **2a**, yield: 95%, m.p. 210-212°C[13]. Other compounds **2(b-i)** were prepared from **1(b-i)** following the same procedure.

**Solid phase microwave assisted method**

Microwave irradiation of the mixture of isatin **1(a-i)** and chloroacetyl chloride over the basic alumina support produced chloroacetyl isatins **2(a-i)** in excellent yields.

In a typical run, a slurry of isatins (0.068 mole) and chloroacetyl chloride (0.090 mole) and basic alumina (2 g) was prepared. The dried slurry was powdered and the free flowing powder was placed in a 100 mL borosil conical flask, in an alumina bath and irradiated at 180ºC for 10 min. The completion of the reaction was checked by TLC. The organic product was extracted from the inorganic solid support with chloroform and evaporation of chloroform gave **2(a-i)**. Melting points and yields of compounds are given in Table 1.

**Table 1: Yields of compounds 2(a-i) and 3(a-i) under conventional and MW conditions**

| Compound | Convt. | Reaction Temp. (ºC) | | Convt. | Time (minutes) | | Convt. | Yield (%) | | M. P. (ºC) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | MW Solvent phase | MW Solid phase | | MW Solvent phase | MW Solid phase | | MW Solvent phase | MW Solid phase | |
| **2a** | Reflux | 180 | 190 | 300 | 8.00 | 9.00 | 40 | 95 | 97 | 210-12 |
| **2b** | Reflux | 180 | 190 | 300 | 7.00 | 8.30 | 42 | 98 | 99 | 165-66 |
| **2c** | Reflux | 180 | 195 | 325 | 7.00 | 8.00 | 45 | 96 | 98 | 153-55 |
| **2d** | Reflux | 180 | 190 | 320 | 8.20 | 9.00 | 39 | 96 | 97 | 178-79 |
| **2e** | Reflux | 180 | 190 | 310 | 7.30 | 8.00 | 43 | 95 | 97 | 206-07 |
| **2f** | Reflux | 180 | 195 | 300 | 10.00 | 10.40 | 47 | 96 | 98 | 185-06 |
| **2g** | Reflux | 180 | 200 | 345 | 9.00 | 9.40 | 44 | 95 | 97 | 223-25 |
| **2h** | Reflux | 180 | 190 | 330 | 9.30 | 10.00 | 38 | 96 | 98 | 130-32 |
| **2i** | Reflux | 180 | 200 | 300 | 10.00 | 10.30 | 45 | 95 | 97 | 168-70 |
| **3a** | Reflux | 180 | 190 | 600 | 8.30 | 10.00 | 36 | 69 | 72 | 172-75 |
| **3b** | Reflux | 180 | 190 | 630 | 9.00 | 9.30 | 42 | 64 | 70 | 198-200 |
| **3c** | Reflux | 180 | 195 | 645 | 8.30 | 9.00 | 37 | 63 | 73 | 176-78 |
| **3d** | Reflux | 180 | 190 | 625 | 8.30 | 9.00 | 36 | 65 | 70 | 243-45 |
| **3e** | Reflux | 180 | 190 | 635 | 7.00 | 8.00 | 36 | 60 | 75 | 187-88 |
| **3f** | Reflux | 180 | 190 | 610 | 10.00 | 11.30 | 36 | 75 | 82 | 205-06 |
| **3g** | Reflux | 180 | 200 | 700 | 9.40 | 10.40 | 36 | 77 | 82 | 182-85 |
| **3h** | Reflux | 180 | 190 | 720 | 11.20 | 12.00 | 42 | 76 | 80 | 202-05 |
| **3i** | Reflux | 180 | 200 | 745 | 11.30 | 12.30 | 38 | 68 | 74 | 215-17 |

## General method for the preparation of 3(a-i) from 2(a-i)

## Conventional method

*N*-Chloroacetyl isatin (**2a**, 0.001 mole) and hexamethylenetetramine (hexamine) (0.01 mole) in dry methanol (20 mL) were refluxed for 10-11 hr. Progress of reaction was checked through TLC. After completion of reaction, solvent was removed under reduced

pressure and the solid was chromatographed over alumina (neutral) in $C_6H_6$ : MeOH (9.5 : 0.5) as the eluant. The product obtained was recrystallized from benzene to give **3a**, yield: 36%; m.p.-172-74°C[13]. Other compounds **3(b-i)** were prepared from **2(a-i)** following the same procedure.

**Solution phase microwave assisted method**

The mixture of *N*-chloroacetyl isatins (**2a**, 0.001 mole) and hexamethylenetetramine (hexamine) (0.01 mole) in dry methanol (20 mL) was taken in a borosil conical flask fitted with a funnel as a loose top. The reaction mixture was irradiated in a domestic microwave oven at 180ºC for 8 min. with short interval of 30s to avoid the excessive evaporation of solvent (completion of reaction was checked by TLC). After completion of reaction, solvent was removed under reduced pressure and the solid was chromatographed over alumina (neutral) in $C_6H_6$ : MeOH (9.5 : 0.5) as the eluant. The product obtained was recrystallised from benzene to give **3a**; yield: 69%; mp.172-74°C[13c]. The compounds **3(b-i)** were prepared from **2(b-i)** by adopting the same procedure at different reaction times (Table 1).

**Solid phase microwave assisted method**

Microwave irradiation of the mixture of chloroacetyl isatins **2(a-i)** and hexamethylenetetramine (hexamine) over the basic alumina support produced **3(a-i)** in an excellent yields.

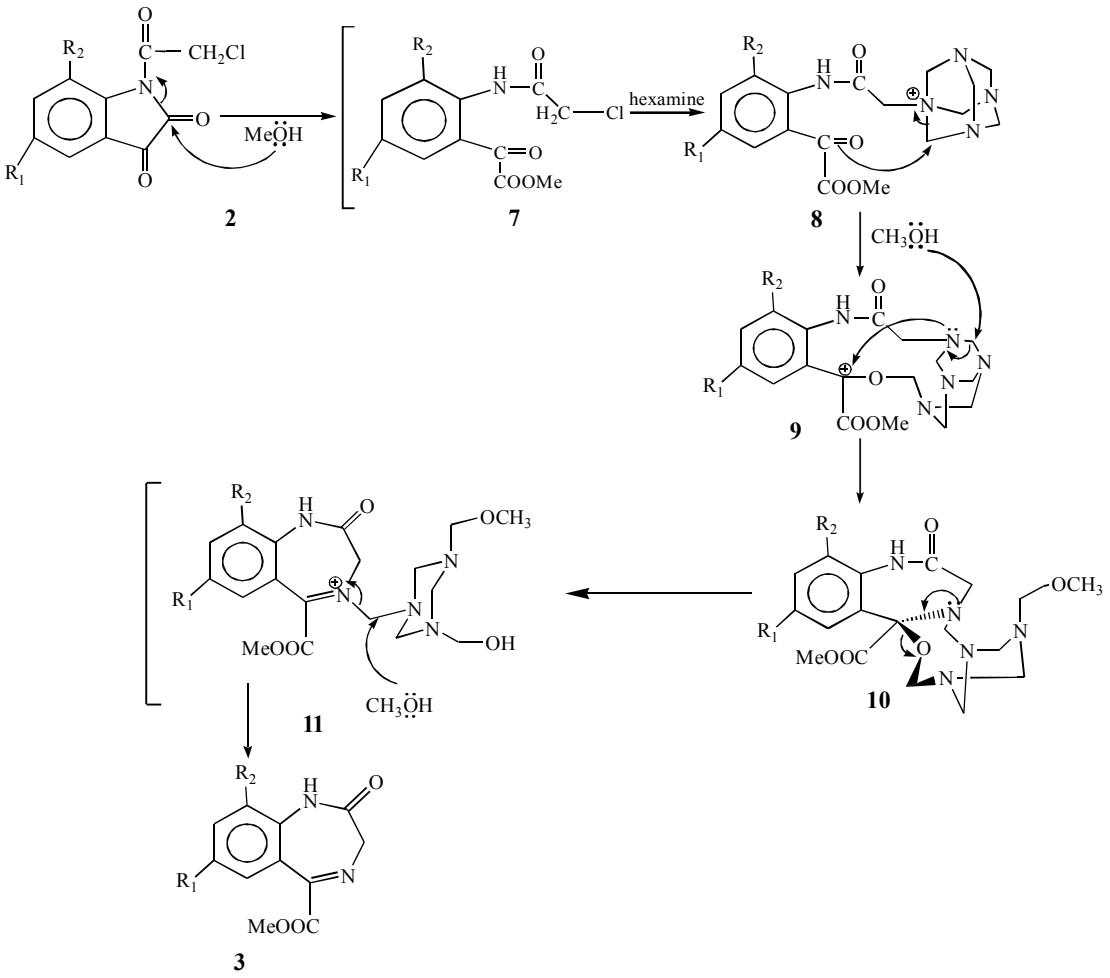
## RESULTS AND DISCUSSION

Potentiality of isatin in synthesis to give the products with expansion of the ring is well established in the literature. The highly labile nature of its lactum function allows the cleavage of the ring to take place with the nucleophilic reagents to give the ring opened products, which in appropriately substituted isatins undergo concurrent cyclocondensation leading to ring enlargement to give six or seven membered heterocyclic rings. We believe that the presence of an external carbonyl function at nitrogen in 1-chloroacetyl isatin **2** provides an extraordinary facility for the instantaneous cleavage of the ring to take place to give in succession the ring opened products **7** and **8 (Scheme 2)**. It is this property of **2**, which has formed the basis of the synthetic strategy envisaged in the present work to use this material as a synthetic tool in the preparation of **3**.

The microwave-assisted reaction of **1(a-i)** with chloroacetyl chloride gave the quantitative yields of **2(a-i)**. Treatment of **2(a-i)** with methanolic solution of hexamine under

microwave conditions produced **3(a-i)** in excellent yields. Both the reaction were carried out under microwave conditions in liquid phase, as well as in the dry media, on the basic alumina solid support. Authentic samples of the **2(a-i)** and **3(a-i)** were obtained for comparison using the conventional procedure[13]. The results of these reactions are summarized in Table 1.

**Scheme 2**




The conversion of the 1-chloroacetyl isatin **2** to 1, 4-benzodiazepine derivative **3** with methanolic hexamine is believed to take place in two steps. The first step proceeds via the cleavage of lactum function of the isatin ring to give in succession the postulated intermediates **8**, **9**, **10** and **11 (Scheme 2)**. In the subsequent step, the hexaminium salt **11**

undergoes solvolysis with MeOH to generate the imine species **3**. Delepine reaction has been known in the literature to afford the formation of an amine from activated alkyl halide from its reaction with hexamine. This reaction has been shown to proceed via the initial formation of a hexaminium salt from alkyl halide and hexamine, followed by the hydrolysis to give the amine. The mechanism of reaction suggested in **Scheme 2** is based on the earlier precedence, which exists in the literature in the formation of amine from alkyl halide from Delepine reaction. We believe that irradiation of the reaction mixture with microwave facilitates the formation of **2(a-i)** from **1(a-i)** and **3(a-i)** from **2(a-i)** to take place instantaneously is less time.

**Table 2: Spectral and analytical data of compound (2a-i)**

| Comp. | Mol. formula (Mol.wt.) | Elemental analysis Found (Cald.) | | IR (KBr) $cm^{-1}$ | $^1H$ NMR (δ ppm) |
|---|---|---|---|---|---|
| | | N | X (Cl, Br) | | |
| **2a** | $C_{10}H_{11}NO_2$ (177) | 7.90 (7.94) | ---- | 1755, 1700, 1725 | 7.83-7.19 (4H, m, ArH) 4.32 (2H, d $CH_2$) |
| **2b** | $C_{10}H_{10}FNO_2$ (195) | 7.18 (7.24) | ---- | 1735, 1680, 1675 | 7.81-7.23 (3H, m, ArH) 4.32 (2H, d, $CH_2$) |
| **2c** | $C_{10}H_{10}ClNO_2$ (211) | 6.62 (6.78) | 16.75 (16.80) | 1785, 1740, 1720 | 7.77-7.53 (3H, m, ArH) 4.32 (2H, d, $CH_2$) |
| **2d** | $C_{10}H_{10}BrNO_2$ (255) | 5.47 (5.57) | 31.20 (31.15) | 1780, 1735, 1710 | 7.96-7.69 (3H, m, ArH) 4.32 (2H, d, $CH_2$) |
| **2e** | $C_{10}H_{10}INO_2$ (303) | 4.62 (5.00) | ---- | 1770, 1725, 1690 | 8.17-7.60 (3H, m, ArH) 4.32 (2H, d, $CH_2$) |
| **2f** | $C_{11}H_{13}NO_2$ (191) | 7.32 (7.60) | ---- | 1775, 1730, 1708 | 8.33-6.81 (3H, m, ArH) 4.82 (2H, s, $CH_2$) 2.85 (3H, s, $CH_3$) |
| **2g** | $C_{11}H_{13}NO_3$ (207) | 6.76 (6.89) | ---- | 1780, 1740, 1705 | 7.72-7.03 (3H, m, ArH) 4.32 (2H, s, $CH_2$) 3.73 (3H, s, $OCH_3$) |
| **2h** | $C_{10}H_{10}N_2O_4$ (222) | 12.61 (12.92) | ---- | 1730, 1685, 1655 | 8.72-8.09(3H, m, ArH) 4.32 (2H, s, $CH_2$) |
| **2i** | $C_{12}H_{15}NO_2$ (205) | 6.82 (6.89) | ---- | 1740, 1700, 1685 | 7.40-7.12(2H, m, ArH) 4.32 (2H, s, $CH_2$) 2.35 (6H, d, $CH_3$) |

**Table 3: Spectral and analytical data of compounds 3(a-i)**

| Comp. | Mol. Formula (Mol.wt.) | Elemental analysis Found (Cald.) N | Elemental analysis Found (Cald.) X (Cl, Br) | IR (KBr) $cm^{-1}$ | $^1$H NMR (δ ppm) | MS : m/z |
|---|---|---|---|---|---|---|
| **3a** | $C_{11}H_{10}N_2O_3$ (218) | 12.84 (12.89) | --- | 743, 1200, 1540, 1608, 1690, 3050, 3180 | 8.0 (1H, s, NH)7.67-7.03 (4H, m, ArH) 4.49 (2H, d, $CH_2$) 3.69(3H, s, $CH_3$) | 218 ($M^+$) 160 (base peak) |
| **3b** | $C_{11}H_9N_2O_3F$ (236) | 11.86 (11.82) | --- | 880, 1105, 1170, 1570, 1610, 1680 2850, 3210 | 8.0 (1H, s, NH)7.31-6.98 (3H, m, ArH) 4.49 (2H, d, $CH_2$) 3.67(3H, s, $CH_3$) | 236 ($M^+$) 178 (base peak) |
| **3c** | $C_{11}H_9N_2O_3Cl$ (252) | 17.09 (17.15) | 14.03 (14.07) | 667, 790, 1250, 1610,1780,2270 2908, 3310 | 8.0 (1H, s, NH) 7.61-7.28 (3H, m, ArH) 4.49 (2H, d, $CH_2$) 3.67 (3H, s, $CH_3$) | 252 ($M^+$) **1**94 (base peak) |
| **3d** | $C_{11}H_9N_2O_3Br$ (296) | 9.43 (9.47) | 26.89 (26.85) | 570, 630, 1120, 1470, 1800,2100, 2810, 3320 | 8.0 (1H, s, NH)7.77-7.44 (3H, m, ArH)4.49 (2H, d, $CH_2$) 3.67(3H, s, $CH_3$) | 296 ($M^+$) 238 (base peak) |
| **3e** | $C_{11}H_9N_2O_3I$ (344) | 8.14 (8.19) | --- | 630, 785, 1040, 1430, 1680,1720, 2790, 3450 | 8.0 (1H, s, NH) 7.98-7.44 (3H, m, ArH)4.49 (2H, d, $CH_2$)3.67(3H, s, $CH_3$) | 344 ($M^+$) 286 (base peak) |
| **3f** | $C_{12}H_{12}N_2O_3$ (232) | 12.06 (12.12) | --- | 710, 1290, 1620, 1690, 1760,3190, 3290 | 8.0 (1H, s, NH)7.55-7.07 (3H, m, ArH)4.49 (2H, d, $CH_2$)3.67(3H, s, $CH_3$) 2.35(3H, d, $CH_3$) | 232 ($M^+$) 174 (base peak) |
| **3g** | $C_{12}H_{11}N_2O_4$ (248) | 11.29 (11.32) | --- | 730, 1130, 1550, 1690, 1730,2830, 3200 | 8.0 (1H, s, NH)7.56-6.98 (3H, m, ArH) 4.49 (2H, d, $CH_2$) 3.73(3H, s, $OCH_3$) 3.67 (3H, s, $CH_3$) | 248 ($M^+$) 190 (base peak) |
| **3h** | $C_{11}H_9N_3O_5$ (263) | 15.96 (15.93) | --- | 720, 1280, 1640, 1735, 2350,2980, 3380 | 8.0 (1H, s, NH)8.53-7.93 (3H, m, ArH)4.49 (2H, d, $CH_2$)3.67(3H, s, $CH_3$) | 263 ($M^+$) 205 (base peak) |
| **3i** | $C_{13}H_{14}N_2O_3$ (246) | 11.38 (11.42) | --- | 750, 1220, 1580, 1710, 2250,3110, 3240 | 8.0 (1H, s, NH)7.21-6.87 (3H, m, ArH)4.49 (2H, d, $CH_2$) 3.67(3H, s, $CH_3$) 2.32 (6H, d, $(CH_3)_2$) | 246 ($M^+$) 185 (base peak) |

In a typical run, slurry of chloroacetyl isatin (**2a**, 0.001 mole) and hexamethylenetetramine (hexamine) (0.01 mole) in dry methanol and basic alumina (2 g) was prepared. The dried slurry was powdered and the free flowing powder was placed in a 100 mL borosil conical flask, in an alumina bath and irradiated in a domestic microwave oven at 180ºC for 10 min. The completion of reaction was checked by TLC. The organic product was extracted from the inorganic solid support with chloroform and evaporation of chloroform layer gave **3(a-i)**. Melting points and yields of all the compounds are given in Table 1.

## CONCLUSION

A simple and efficient methodology for the facile one pot synthesis of 7-fluoro, chloro, bromo, iodo, methyl, methoxy, nitro and 5, 7-dimethyl substituted, 1, 3-dihydro-2*H* [1, 4]benzodiazepine-2-one-5-methyl carboxylate **3(a-i)** has been setup in the present work making use of the MW assisted Delepine reaction on the corresponding 1-chloroacetyl isatins **2(a-i)**.

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