4.1: Introduction

Synthesis of new chemical entities is major bottleneck in drug discovery. Conventional methods for various chemical synthesis is very well documented and practiced (William *et al.* 1998). The methods for synthesis (Heating process) of organic compounds has continuously modified from the decade. In 1855, Robert Bunsen invented the burner which acts as energy source for heating a reaction vessel, this was latter superseded by isomental, oil bath or hot plate, but the drawback of heating, though method remain the same. Microwave Assisted Organic Synthesis (MAOS), which has developed in recent years, has been considered superior to traditional heating.

Microwave assisted organic synthesis (Jignasa *et al.* 2010;Kappe 2004;Kappe and Dallinger 2006;Nagariya *et al.* 2011) (MAOS) has emerged as a new "lead" in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of the product. Now a day's technique is considered as an important approach toward green chemistry, because this technique is more environmentally friendly. This technology is still under used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/ reagents lead to environmental pollution. This growth of green chemistry holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve much organic synthesis.

Clays are widespread, easily available and low-cost chemical substances. Both in their native state and in numerous modified forms, clays are versatile materials that catalyze a variety of chemical reactions. Just as they can be molded into any shape, their microstructure can be changed to suit chemists' needs to promote diverse chemical reactions. It is convincingly argued that clays initiated, supported and sustained the process of formation of small molecules on the earth millions of years ago, which gradually developed into more complex molecules. In the course of time, there emerged from the latter the self replicating assemblies that evolved into simple life forms and progressed to the present elaborate living world of plants and animals (Saladino *et al.* 2004;Stern and Jedrzejas 2008). Clays have a long history of use as catalysts and as supports in organic reactions (Vogels *et al.* 2005). Several excellent reviews on clay catalyzed organic reactions have appeared in the recent past (Chun-Hui Clayton 2010;Dasgupta and Török 2008;Ranu and Chattopadhyay 2009;Varma 2002) has briefly summarized the emerging trends in synthetic clay based materials. Actually, clays have been intercalated with a variety of inorganic and organic ions, metal complexes, and organic compounds. These have brought about radical changes in the performance of clays in terms of increasing the rates of reactions, yields, product selectivity, and stereoselectivity including enantioselectivity.

The condensation between isatin and 1, 2- diaminobenzene can, depending on the solvent, give rise to four different products (**Figure 4.1.1**) (Bergman *et al.* 2003;Ivashchenko *et al.* 1984;Niume *et al.* 1982).

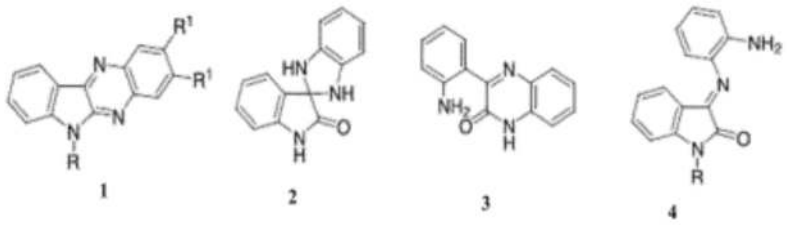


Figure 4.1.1: Condensation reaction products of isatin with 1, 2- diaminobenzene

The condensation of isatin with 1, 2- diaminobenzene in refluxing methanol has been reported (Niume *et al.* 1982) to produce a mixture of **1** (39%), **3**(30%) and only traces of the spiro compound **2**. In acidic solvents, like acetic acid, the linear

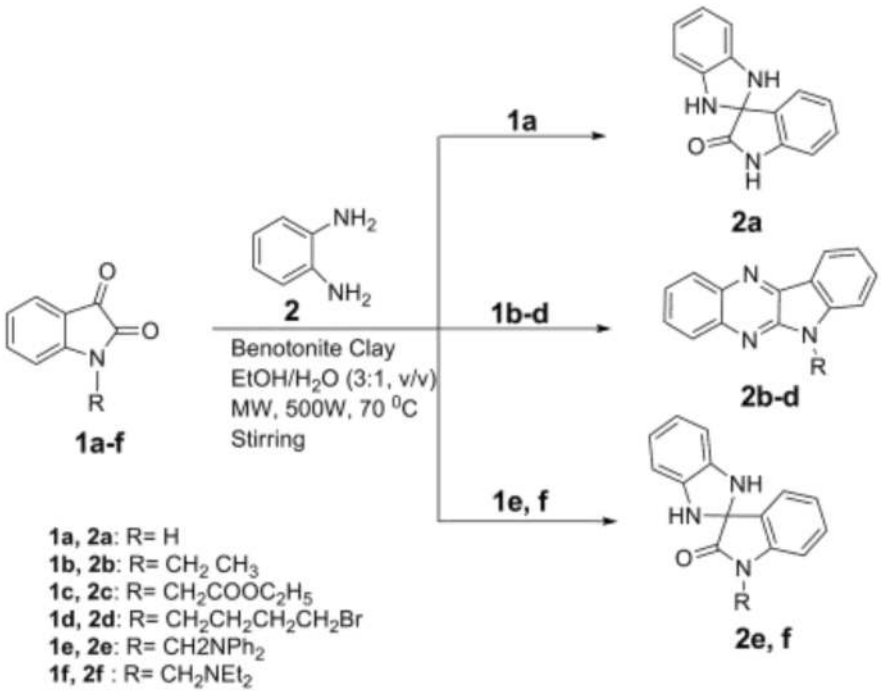
product **1** is the dominating product. The spiro compound **2** has been obtained in a high yield when the reaction was performed in *N*-methyl-2-pyrrolidone, where as the ring-opened quinoxalinone **3** was the major product when THF or benzene was used as solvent. In some papers (Bergman *et al.* 2003;Niume *et al.* 1982)compound **3**, with a carbonyl absorption at 1670 cm^{-1} in the IR spectrum (Ivashchenko *et al.* 1984), incorrectly has been assigned the structure of **4**, with a carbonyl band expected around 1715 cm^{-1}. It is uncertain if **4** has ever been described, although *N*-methyl derivative of **4** seems to have been correctly assigned (υ_{CO}= 1720 cm^{-1}) (Ivashchenko *et al.* 1984).

In view of the above it was thought worthwhile to investigate the condensation reaction of isatin derivatives with 1, 2- diaminobenzene in ethanol/water solvent system under microwave irradiation by using bentonite clay as a catalyst.

4.2: Results and discussion

In view of the emerging importance of the use of solid clay as environmentally friendly and reusable catalyst, we herein describe a simple and efficient protocol for the condensation reaction of isatin derivatives with 1, 2-diaminobenzene using bentonite clay catalyst in EtOH/H_2O solvent system under both conventional method and microwave irradiation.

Isatin derivatives **1a-f** readily undergo the condensation reaction with 1, 2-diaminobenzene **2** in the presence of catalytic amount of bentonite clay in EtOH/H_2O solvent system under both conventional method and microwave irradiation (**Scheme 4.2.1**).



Scheme 4.2.1

The microwave method was found to be better than conventional method in terms of reaction time, yield and relatively simple method to perform synthesis (**Table 4.2.1**).

Table 4.2.1: Results of comparative study for synthesized compounds **2a-f** under both conventional method and microwave irradiation

Entry	**Conventional Method**		**Microwave Method (Power: 500W)**	
	Time (h)	**% yield**	**Time (min)**	**% yield**
2a	2	80	3	92
2b	3.5	75	5	89
2c	2	81	3	91
2d	3	78	5	94
2e	2	77	3	88
2f	2	74	3	86

In our case, the reaction of **1a** with **2** gave a spiro-indole derivative **2a** as sole product by using bentonite clay in EtOH/H_2O solvent system, under both conventional method and microwave irradiation. When **1b-d** was reacted with **2**, the sole product formed was quinoxaline derivatives **2b-d**. However, when **1e & 1f** was reacted with **2**, the expected analogue to quinoxaline derivatives was not formed. Instead the spiro-indole derivatives **2e** & **2f** was the sole product. The structures of isolated products were fully confirmed by elemental analysis and spectroscopic methods (IR &^{1}H-NMR).

In order to optimize the reaction condition, the reaction of **1a** with **2** was examined under different ratio of solvent system (**Table 4.2.2**). As a result, EtOH/H_2O (3/1, v/v) was found to be the best ratio of solvent system for the generation of the desired product with maximum yield.

Table 4.2.2: The influence of different ratio of solvent system on the yield of the product **2a**

Entry	Solvent (20ml)	Time(min)	%Yield
1	H_2O	5	64
2	EtOH	5	75
3	EtOH/H_2O (1/1, v/v)	3	79
4	EtOH/H_2O (2/1, v/v)	3	85
5	**EtOH/H_2O (3/1, v/v)**	**3**	**92**
6	EtOH/H_2O (4/1, v/v)	3	86
7	EtOH/H_2O (1/2, v/v)	5	70

In another study, the amount of the catalyst (mol %) was optimized by taking the same reaction (**Table 4.2.3**). The result of this study showed that maximum yield of the product was observed with 20 mol % of the catalyst (**Entry 2**).

Table4.2.3: Effect of catalyst amount on the yield of product **2a**

Entry	Amount of catalyst (mol %)	%Yield
1	10	65
2	20	92
3	**30**	**90**
4	40	88

One of the most advantages of our method is the recycling of the catalyst. Bentonite clay can be reused several times without any appreciable loss in activity, which confirms the recyclability & reusability of the catalyst. For the reaction of **1a** with **2** no significant loss of product yield was observed when bentonite clay was used after 4 times recycling (**Table 4.2.4**).

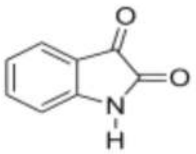
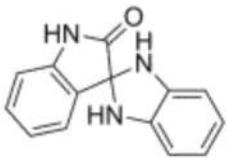
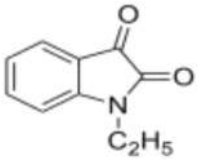
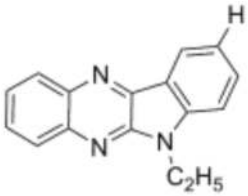
Table 4.2.4: Effect of the recycled bentonite clay on the yield of the product **2a**

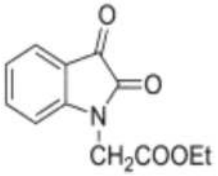
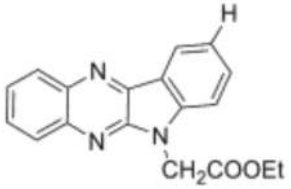
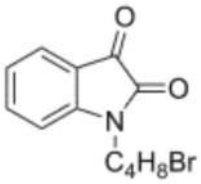
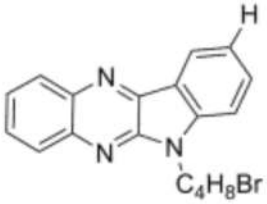
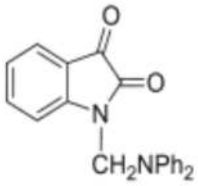
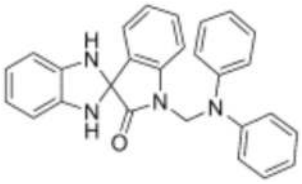
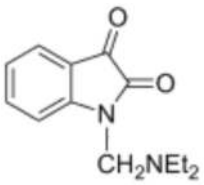
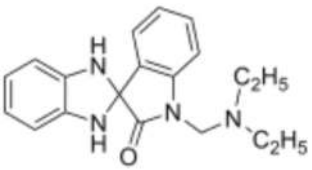
Entry	Cycle	Time(min)	%Yield
1	-	3	92
2	1	3	90
3	2	3	91
4	3	3	91
5	4	3	88

Under the optimized set of conditions, a number of isatin derivatives **1**, *viz.* Isatin (**1a**), *N*-ethylisatin (**1b**), *N*-ethylacetateisatin (**1c**), *N*-bromobutylisatin (**1d**), *N*-(diphenylamino)methylisatin (**1e**) and *N*-(diethylamino)methylisatin (**1e**) were allowed to react with 1, 2- diaminobenzene **2** in the presence of catalytic amount of bentonite clay in EtOH/H_2O (3/1, v/v) under microwave irradiation as well as

conventional method. The completion of the reaction was monitored by TLC. The catalyst was filtered, washed with ethyl acetate and dried. The resulting filtrate was evaporated under reduced pressure, dried, and recrystallized with ethanol to yield pure products **2,** *viz.*1,3-dihydrospiro[benzo[d]imidazole-2,3'-indolin]-2'-one(**2a**), 6-ethyl-6*H*-indolo[2,3-b]quinoxaline(**2b**), ethyl 2-(6*H*-indolo[2,3-b] quinoxalin-6-yl)acetate(**2c**), 6-(4-Bromobutyl)-6*H*-indolo[2,3-b]quinoxaline (**2d**) , 1'-[(diphenylamino)methyl]-1,3-dihydrospiro[benzo[d]imidazole-2,3'-indolin]-2 one(**2e**), 1'-[(diethylamino)methyl]-1,3-dihydrospiro[benzo[d]imidazole-2,3'-indolin]-2'-one(**2f**). The results are given in the table **5.2.5.**

Table 4.2.5: Condensation reaction of isatin derivatives with 1, 2-diaminobenzene

Entry	Isatin derivative	Product	% Yield	Mp (^{0}C)
1	 **1a**	 **2a**	92	232
2	 **1b**	 **2b**	98	180

3	 **1c**	 **2c**	91	160
4	 **1d**	 **2d**	94	184
5	 **1e**	 **2e**	88	228
6	 **1f**	 **2f**	86	246

4.3: Experimental

4.3.1: General procedure for the synthesis of compounds 2a-e

Conventional Method

1, 2-diaminobenzene (0.001 mol) was added to a rection mixture of isatin or *N*-substituted isatins [(**1a-1f**) (0.001 mol)], bentonite clay (20 mol%) and EtOH/H_2O (3/1, v/v, 20 ml). The resulting reaction mixture was stirred at 70^0C for 2-3.5h. The completion of the reaction was monitored by TLC. The catalyst was filtered, washed with ethyl acetate and dried. The resulting filtrate was evaporated under reduced pressure, dried, and recrystallized in ethanol.

Microwave Irradiation Method

1, 2-diaminobenzene (0.001 mol) was added to a rection mixture of isatin or N-substituted isatins[(**1a-1f**) (0.001 mol)], bentonite clay (20 mol%) and EtOH/H_2O (3/1, v/v, 20 ml.). The resulting reaction mixture was stirred at 70^0C for 3-5 min. The completion of the reaction was monitored by TLC. The catalyst was filtered, washed with ethyl acetate and dried. The resulting filtrate was evaporated under reduced pressure, dried, and recrystallized in ethanol.

1, 3-Dihydrospiro[benzo[d]imidazole-2, 3'-indolin]-2'-one (2a)

Brown-yellow solid, **IR (KBr) υ**: 3192, 3090, 3019, 1703, 1614, 1598, 1484, 1339, 718, 671 cm^{-1}. **^{1}H NMR (300 MHz, DMSO)** δ: 6.43 [s, 1H (D_2O Exchangeable), NH- Spiro system], 8.35-6.53 (m, 8H, Ar-H), 12.02 (s, 1H, NH) ppm. Anal. Calcd. For $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; O, 6.74. Found: C, 70.85; H, 4.68; N, 17.72; O, 6.74.

6-Ethyl-6*H*-indolo[2,3-b]quinoxaline (2b)

Yellow solid, **IR (KBr) υ**: 2962, 2853, 1660, 1611, 1567, 1482, 1427, 1378, 1331, 757, 738 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$)** δ: 1.52 (t, 3H, *J*=6.9 Hz, CH_3), 4.56 (q, 2H, *J*=7.2 Hz, CH_2), 8.49-7.35 (m, 8H, Ar-H) ppm. Anal. Calcd. For $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99 (%). Found: C, 77.73; H, 5.29; N, 16.98 (%).

Ethyl 2-(6*H*-indolo[2,3-b]quinoxalin-6-yl)acetate (2c)

Yellow solid, **IR (KBr) υ**: 2976. 2927, 1734, 1663, 1606, 1565, 1474, 1375, 1203, 760, 743 cm^{-1}.**^{1}H NMR (300 MHz, $CDCl_3$)** δ: 1.28 (t, 3H, *J*=7.2 Hz, CH_3), 4.24 (q, 2H, *J*=7.2 Hz, CH_2), 5.24 (s, 2H, CH_2), 8.50-7.34 (m, 8H, Ar-H) ppm. Anal. Calcd. For $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76; O, 10.48 (%). Found: C, 70.80; H, 4.96; N, 13.75; O, 10.49 (%).

6-(4-Bromobutyl)-6*H*-indolo[2,3-b]quinoxaline (2d)

Yellow solid, **IR (KBr) υ**: 3050, 2930, 1660, 1493, 1485, 1450, 1400, 1330, 1192, 1130, 751, 741 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$)** δ: 1.82 (m, 2H, CH_2), 2.02 (m, 2H, CH_2), 3.38 (t, 2H, *J*=7.2 Hz, CH_2), 4.42 (t, 2H, *J*=7.5 Hz, CH_2), 8.53-7.38 (m, 8H, Ar-H) ppm. Anal. Calcd. For $C_{18}H_{16}BrN_3$: C, 61.03; H, 4.55; Br, 22.56; N, 11.86 (%). Found: C, 61.01; H, 4.57; Br, 22.57; N, 11.85 (%).

1'-[(Diphenylamino)methyl]-1,3-dihydrospiro[benzo[d]imidazole-2,3'-indolin]-2one (2e)

Brown solid, **IR (KBr) υ**: 3090, 2980, 2850, 1703, 1614, 1567, 1483, 1350, 744, 752 cm^{-1}. **^{1}H NMR (300 MHz, DMSO)** δ: 5.21 (s, 2H, CH_2), 6.45 [s, (D_2O Exchangeable), NH-Spirosystem], 8.35-6.56 (m, 18H, Ar-H) ppm. Anal. Calcd. For $C_{27}H_{22}N_4O$: C, 77.49; H, 5.30; N, 13.39; O, 3.82 (%). Found: C, 77.50; H, 5.30; N, 13.38; O, 3.82 (%).

1'-[(Diethylamino)methyl]-1, 3-dihydrospiro[benzo[d]imidazole-2,3'-indolin]-2'-one (2f)

Yellow solid, **IR (KBr) υ**: 3384, 2850, 1703, 1613, 1598, 1483, 1322, 759, 743 cm^{-1}. **^{1}H NMR (300 MHz, DMSO) δ:** 1.63 (t, 6H, *J*=6.9 Hz, CH_3), 2.89 (q, 4H, *J*=7.0 Hz, CH_2), 4.72 (s, 2H, CH_2), 6.42 [s, (D_2O Exchangeable), NH-spirosystem], 8.07-6.53 (m, 8H, Ar-H) ppm. Anal.Calcd. For $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38; O, 4.96(%). Found: C, 70.75; H, 6.89; N, 17.41; O, 4.95 (%).

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