CHAPTER 4

STUDIES ON THE MICROWAVE ASSISTED REACTIONS OF
ISATOIC ANHYDRIDE AND SCHIFF BASES

4.1. INTRODUCTION

Microwave ovens have been used in chemical laboratories for moisture analysis and wet washing procedures of biological and geological materials for a number of years.\textsuperscript{151-157} The rapid capability of the microwave oven has been exploited to heat mixtures of ore samples and acid in sealed vessels, leading to considerable savings in dissolution times. The microwave technology also finds application in catalytic hydrogenation of alkenes, hydrocracking of bitumen from tar sands and degradation of polychlorinated hydrocarbons. Applications concern reactions in solution, as the acceleration of nucleophilic substitution reactions or the preparation of short-lived radiopharmaceuticals; solid-liquid reaction in the dissolution of geological samples, or reaction of solids in the synthesis of inorganic compounds and in the reticulations of polymers.\textsuperscript{158-170}

The inherent hazard of violent explosion due to the high pressure and temperature developed in a closed vessel under microwave irradiation has limited the scale at which these rapid microwave reactions can be carried out to less than 1 g. A continuous flow reaction process has been devised by which preparative scale samples (> 20 g) may be synthesized safely. The potential reaction hazard of closed-vessel microwave heating can be avoided by using a continuous flow process. The use of ion-exchange resins as catalysts for the conversion of sucrose to glucose and fructose under microwave irradiation may be able to compete with the industrial
operation currently achieved by immobilized enzyme process. Continuous flow microwave irradiation has been shown to be an inexpensive process for the conversion of unwanted optical enantiomers into their racemic mixtures for enrichment and recovery of useful enantiomers.\textsuperscript{171-176}

Chemical reactions brought about by microwave irradiation gathered momentum in recent years.\textsuperscript{177-180} The elegance of the reaction, high yield, short time, simplified work-up procedure and eco-friendly conditions are the main advantages of the method. Although microwave reactions were begun in domestic microwave ovens, it is replaced by more sophisticated chemical microwave ovens now a days.\textsuperscript{181} The existence of "Hot Spots", inhomogeneity of the microwave field on the heating spot, handicap in measuring the temperature of reaction, possibility of explosion are some of the main defects of the microwave oven reactions.\textsuperscript{182-188} However, rotating the reaction platform that averages the field can decrease the inhomogeneity of the field. The temperature can be measured by taking out the sample at once outside. The reproducibility of the result can also be checked by repeating the experiment several times. We used the domestic oven, as we are unable to use chemical ovens at present.

Bari \textit{et al.} noticed that the Diels - Alder reaction of anthracene \textsuperscript{149} and maleic anhydride \textsuperscript{150}, in \textit{p}-xylene under microwave irradiation requires only a time interval of 3 min (Scheme \textsuperscript{98}).\textsuperscript{189}
Adduct 151 was obtained in 92% yield.

The above reaction when carried out thermally requires a reflux time of 10 min and the yield of the adduct 151 obtained was 90%.190

Under microwave conditions dimethyl fumarate 152 in p- xylene, cyclises with anthracene 149 to give 87% adduct 153 within 10 min (Scheme 99).189

Thermal reaction between dimethyl fumarate 152 and anthracene 149 in p-xylene, requires a reflux time of 4 h. The yield of adduct 153 was only 67%.191

1,4-diphenyl-1,3- butadiene 154 was found to react with diethyl acetylene dicarboxylate 155 to give 55% of adduct 156, under microwave conditions, in 12 min (Scheme 100).189
The above reaction when repeated thermally requires a reflux period of 5 h.\textsuperscript{192}

66\% of the adduct 159 was obtained by the microwave reaction of furan 157 with diethyl acetylene dicarboxylate 155. The reaction took 10 min for completion (Scheme 101).\textsuperscript{189}

Thermal investigation of the above reaction required 4 h for completion.\textsuperscript{193}

The above discussions convincingly demonstrate that the use of microwave oven technique can lead to substantial savings in time for many laboratory syntheses.\textsuperscript{194-217}
4.2. RESULTS AND DISCUSSION

4.2.1. Reaction of isatoic anhydride under microwave conditions with Schiff bases

It has been found that the study of the reaction of anthranilic acid – thionyl chloride or 2-(sulfinylamino) benzoyl chloride in closed microwave oven environment is hazardous. Therefore a similar substrate isatoic anhydride, which can safely and conveniently give rise to iminoketene, is subjected to microwave heating with azomethines under solvent free conditions.

An equimolar mixture of isatoic anhydride 12 (3.64 mmol) and Schiff bases 117a-d was ground together in a mortar. The mixture was then irradiated under microwave conditions in a 50 mL beaker without solvent for 2 min. The reaction mixture was extracted with dichloromethane and cooled. Removal of solvent and recrystallisation from appropriate solvents yielded dihydroquinazolin-4(1H)-ones 118a-d in 70.88 – 90.10% yield (Scheme 102).

![Scheme 102](image)

<table>
<thead>
<tr>
<th>117a</th>
<th>117b</th>
<th>117c</th>
<th>117d</th>
</tr>
</thead>
<tbody>
<tr>
<td>118a</td>
<td>118b</td>
<td>118c</td>
<td>118d</td>
</tr>
</tbody>
</table>

1) μW, in absence of solvent

Scheme 102
4.2.1.1. Reaction of isatoic anhydride under microwave conditions with \(N\)-benzylideneaniline

A mixture of 3.64 mmol of isatoic anhydride 12 and 3.64 mmol of \(N\)-benzylideneaniline 117a was irradiated in a microwave oven for 2 min. The reaction mixture was extracted with dichloromethane (20 mL), filtered to remove intractable material. The clear solution was concentrated and the compound, 2,3-diphenyl-2,3-dihydroquinazolin-4(1H)-one 118a (90.10%), was recrystallised from dichloromethane. Its mp was found to be \(210^\circ C\) (Scheme 103).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
12 & \quad 117a
\end{align*}
\]

1)\(\mu W, 2\) \(\text{min}, 90.10\%\)

Scheme 103

The structure of the product was established by spectroscopic methods earlier.

4.2.1.2. Reaction of isatoic anhydride under microwave conditions with \(N\)-benzylidene-\(p\)-chloroaniline

\(N\)-Benzylidene-\(p\)-chloroaniline 117b (3.64 mmol) on treatment with isatoic anhydride 12 (3.64 mmol) yielded a product in 90.10% yield on microwave irradiation for 2 min. The reaction mixture was extracted with 20 mL of dichloromethane, filtered to remove intractable materials. The clear solution was concentrated and cooled and the solid obtained was recrystallised from
dichloromethane. This solid on spectral analysis was found to be identical to 3-(4'-chlorophenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one 118b (Scheme 104).

![Reaction Scheme](image)

1) μW, 2 min, 90.10%

Scheme 104

The compound 118b melted at 481 °C.

4.2.1.3. Reaction of isatoic anhydride under microwave conditions with N-benzylidene-p-toluidine

3-(4'-methylphenyl)-2-phenyl-2,3 dihydroquinazolin-4(1H)-one 118c was obtained in 90.10% yield, on microwave irradiation of a mixture of N-benzylidene-p-toluidine 117c (3.64 mmol) with isatoic anhydride 12 (3.64 mmol) for 2 min. The reaction mixture was extracted with 20 mL dichloromethane, filtered to remove intractable materials. The clear solution was concentrated and cooled and the solid obtained was recrystallised from dichloromethane. This solid melted at 480 °C (Scheme 105).
The structure of the product was established by spectroscopic methods.

4.2.1.4. Reaction of isatoic anhydride under microwave conditions with \(N\)-benzylidene-\(o\)-methoxyaniline

\(N\)-Benzylidene-\(o\)-methoxyaniline 117d on treatment with isatoic anhydride 12, gave a product in 70.88% yield under microwave irradiation for 2 min. The reaction mixture was extracted with 20 mL dichloromethane, filtered to remove all intractable materials. The clear solution was concentrated and cooled and the solid obtained was recrystallised from dichloromethane. This solid which melted at \(140^\circ\text{C}\) was found to be identical to 3-(2-methoxyphenyl)-2-phenyl 2,3-dihydroquinazolin-4(1H)-one 118d, from IR, \(^1\text{H} \text{NMR}, \(^{13}\text{C} \text{NMR}, \text{EIMS and elemental analysis data (Scheme 106).}

![Scheme 105](image-url)
4.2.1.5. Reaction of isatoic anhydride under microwave conditions

3.64 mmol of isatoic anhydride 12 was irradiated under microwave condition for 3 min. The residue was dissolved in 20 mL CHCl₃ which was washed with 10% NaHCO₃ solution, dried over anhydrous MgSO₄ and chromatographed over silica gel using a mixture of petroleum ether-benzene (1:1 v/v) as solvent. Evaporation of solvent afforded a lemon yellow product, which was recrystallised from benzene. The compound melted at 166 °C. This compound was found to be identical with dibenzo[b,f] [1,5] diazocine-6,12-(5H,11H)-dione 118 by the spectral analysis (Scheme 107).
The results of reaction of isatoic anhydride with Schiff base in solvent free and microwave conditions are tabulated in Table 4.1.

Table 4.1. Summary of the results of reactions of isatoic anhydride 12 with Schiff bases

<table>
<thead>
<tr>
<th>Mass of isatoic anhydride (mg)</th>
<th>Dienophile used</th>
<th>Mass of dienophile used (mg)</th>
<th>Dihydroquinazolin-4(1H)-ones isolated</th>
<th>Mass of yield of dihydroquinazolin-4(1H)-ones mg/ (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>593.3</td>
<td>N-benzylideneaniline 117a</td>
<td>658.84</td>
<td>2,3-diphenyl-2,3-dihydroquinazolin-4(1H)-one 118a</td>
<td>983.67/ 90.10</td>
</tr>
<tr>
<td>593.3</td>
<td>N-benzylidene-p-chloroaniline 117b</td>
<td>784.42</td>
<td>3-(4'-chlorophenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one 118b</td>
<td>1096.83/ 90.10</td>
</tr>
<tr>
<td>593.3</td>
<td>N-benzylidene-p-toluidine 117c</td>
<td>709.80</td>
<td>3-(4'-methylphenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one 118c</td>
<td>1029.05/ 90.10</td>
</tr>
<tr>
<td>593.3</td>
<td>N-benzylidene-o-methoxyaniline 117d</td>
<td>768.04</td>
<td>3-(2'-methoxyphenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one 118d</td>
<td>851.14/ 70.88</td>
</tr>
</tbody>
</table>

*isolated yield

4.3. MECHANISM

A plausible mechanism is depicted in Scheme 108.
The formation of dihydroquinazolin-4(1H)-ones 118a-d from isatoic anhydride 12 can be explained by a plausible mechanism. It can be visualized that isatoic anhydride first decomposes to a dipolar ion 139c which can add on to Schiff bases to give 139d. 139d undergoes elimination of carbon dioxide to give dihydroquinazolin-4(1H)-one 118a-d (Scheme 108).
It is very interesting to note that even trace amount of dibenzo-[bj] [1,5]-diazocene-6,12-(5H,11H)-dione 118, dimer of iminoketene 10 was not isolated in any of these isatoic anhydride- Schiff base reactions under microwave conditions.

This illustrates a dipolar ion mechanism as proposed in route a, while an iminoketene intermediate is proposed in route b in the absence of other dipolarophiles.

4.4. EXPERIMENTAL

General: The details are described in Chapter 2 (vide supra).

Microwave oven reactions were performed in KENSTAR domestic, multimode, without on and off mode, microwave oven, with rotating platform tray, with power source 230 V, 50 Hz, with microwave energy output 800W, with microwave input power 1200W and with microwave frequency 2450 MHz.

The temperature of the reaction mixture at the time of reaction in microwave oven, was measured by microwave irradiation of the same mass of reactants taken in a BOROSIL open test tube of 7.0 cm length, 0.9 cm diameter and 3.5 mL capacity. The test tube was kept in a 100 mL beaker and then microwave irradiated for 2 min. The test tube was taken out and the temperature of the molten material was noted immediately with a thermometer and was found to be \( 60^\circ C \). Every reaction was repeated three times to ensure repeatability.
4.5. Experimental Procedures

4.5.1. Reaction of isatoic anhydride under microwave conditions with \(N\)-benzylideneaniline

Isatoic anhydride 12 (593.3 mg, 3.64 mmol) and \(N\)-benzylideneaniline 117a (658.84 mg, 3.64 mmol) were ground together in a mortar and transferred into a 50 mL beaker. The reaction mixture was placed on the rotating platform tray and then microwave irradiated for 2 min. The temperature was noted and was found to be 60 °C (Scheme 103). After cooling to room temperature, the reaction mixture was extracted with dichloromethane (20 mL) and filtered to remove intractable material (30 mg). The clear solution was concentrated and cooled. The 2,3-diphenyl-2,3-dihydroquinazolin-4(1H)-one 118a (983.67 mg, 3.28 mmol, 90.10%), was recrystallised from dichloromethane to afford cream coloured crystalline platelets. mp 210 °C. (lit. mp 211 °C (271,30)).

4.5.2. Reaction of isatoic anhydride under microwave conditions with \(N\)-benzylidene-\(p\)-chloroaniline

\(N\)-Benzyldiene-\(p\)-chloroaniline 117b (784.42 mg, 3.64 mmol) and isatoic anhydride 12 (593.3 mg, 3.64 mmol) were ground together in a mortar and transferred into a 50 mL beaker. Microwave irradiation of the reaction mixture was carried out without solvent for 2 min at a temperature of 60 °C (Scheme 104). After cooling to room temperature, the reaction mixture was extracted with dichloromethane (20 mL) and filtered to remove intractable material (30 mg). The clear solution is concentrated and cooled. The 3-(4'-chlorophenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one 118b (1096.83 mg, 3.28 mmol, 90.10%) was recrystallised from dichloromethane, to afford a cream coloured solid. mp 221 °C. (lit. mp 221 °C).
4.5.3. Reaction of isatoic anhydride under microwave conditions with *N*-benzylidene-*p*-toluidine

Isatoic anhydride 12 (593.3 mg, 3.64 mmol) and *N*-benzylidene-*p*-toluidine 117c (709.8 mg, 3.64 mmol) were ground together in a mortar and transferred into a 50 mL beaker. The reaction mixture was then microwave irradiated without solvent for 2 min at a temperature of 60°C (Scheme 105). After cooling to room temperature, the reaction mixture was extracted with dichloromethane (20 mL) and filtered to remove intractable material (35 mg). The clear solution is concentrated and cooled. The 3-(4-methylphenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one 118c (1029.05 mg, 3.28 mmol, 90.10%), was recrystallised from dichloromethane, to afford a pale yellow solid. mp 188°C.

4.5.4. Reaction of isatoic anhydride under microwave conditions with *N*-benzylidene-*o*-methoxyaniline

*N*-Benzyldiene-*o*-methoxyaniline 117d (768.04 mg, 3.64 mmol) and isatoic anhydride 12 (593.3 mg, 3.64 mmol) were ground together in a mortar and transferred into a 50 mL beaker. Microwave irradiation of the reaction mixture was carried out without solvent for 2 min at a temperature of 60°C (Scheme 106). After cooling to room temperature, the reaction mixture was extracted with dichloromethane (20 mL) and filtered to remove intractable material (70 mg). The clear solution is concentrated and cooled. The 3-(2-methoxyphenyl)-2-phenyl 2,3-dihydroquinazolin-4(1H)-one 118d (851.14 mg, 2.58 mmol, 70.88%), was recrystallised from dichloromethane, to get a lemon yellow solid mp 190°C.
4.5.5. Reaction of isatoic anhydride under microwave conditions

Powdered isatoic anhydride 12 (593.3 mg, 3.64 mmol) was taken in a 50 mL beaker. Microwave irradiation of isatoic anhydride was carried out without solvent for 3 min at a temperature of 60 °C (Scheme 107). After cooling to room temperature, the residue was dissolved in CHCl₃ (20 mL), which was washed with 10% NaHCO₃ solution (3 x 10 mL), water (3 x 10 mL), dried over anhydrous MgSO₄ and chromatographed over silica gel using petroleum ether–C₆H₆ mixture (1:1 v/v) as solvent. The solvent on evaporation afforded a lemon yellow product which was found to be identical with dibenzo[b,f][1,5]-diazocine-6,12-(5H,11H)-dione 118 (349 mg, 1.47 mmol, 80.63%) m.p 166 °C.

Final elution using CH₃OH afforded only intractable material (70 mg).