



## MICROWAVE ASSISTED ONE POT DRY MEDIA SYNTHESIS OF 4H-BENZO [1, 3] OXAZIN-4-ONES FROM ISATOIC ANHYDRIDE

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### ABSTRACT

A facile one pot microwave assisted protocol has been developed for the synthesis of 4H-benzo[1, 3]oxazin-4-ones (**3a-g**) from isatoic anhydrides (**1a-g**). MW irradiation of a mixture of isatoic anhydride (**1a-g**) and acetic anhydride over the basic alumina support produced benzoxazin-one (**3a-g**) in excellent yield.

**Key words:** Microwave assisted, 4H-benzo[1, 3]oxazin-4-ones, Isatoic anhydrides.

### INTRODUCTION

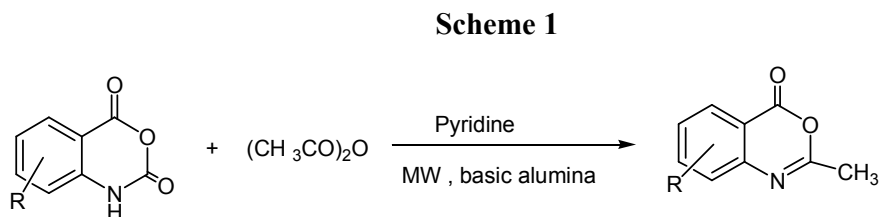
The broad spectrum of pharmacological properties<sup>1-5</sup> exhibited by benzoxazinones has placed them in an important class of medicinally potent compounds. Benzoxazinone derivatives have been recently shown to be useful as a human immuno deficiency virus (HIV) reverse transcriptase inhibitors<sup>6,7</sup> and as peroxisome proliferator activated receptor gamma (PPAR. gamma.) agonists or antagonists<sup>8</sup>. They have also found application as antiphlogistic and hypnotic drugs<sup>2, 3, 9</sup>. Anthalexine, another compound belonging to this class, finds use as an antifungal and antibacterial agent<sup>10-12</sup>. 2-(6'-Methoxy-3, 4'-dihydro<sup>-1'</sup>-naphthyl)-4H<sup>-1</sup>, 3-benzoxazin-4-one is evaluated as a new potent substrate inhibitor of human leukocyte elastase<sup>13</sup>.

One of the most recorded method for the synthesis of benzoxazinone ring involves the reaction of isatoic anhydride with acylating agents, e. g. anhydrides, acyl halides<sup>14,15</sup>. As the reaction under conventional method requires prolonged refluxing conditions and tedious work-up procedures, this calls for a need to streamline the existing procedure to

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permit faster reaction under milder conditions involving easier work-up preferably by eco-friendly procedures. Application of microwave irradiation technique is suitable in this regard. In continuation to our interest<sup>16-18</sup>, on the use of MW irradiation approach in the synthesis of nitrogen heterocycles, we describe in this paper a facile one-pot synthesis of 4H-benzo[1, 3]oxazin-4-ones (**3a-g**) from isatoic anhydrides (**1a-g**) under microwave conditions. Microwave reactions were carried out over basic alumina at 720W, generating 2450 MHz frequency under solvent free conditions to give 4H-benzo[1, 3]oxazin-4-ones (**Scheme 1**).



	<b>(1a-g)</b>		<b>(2)</b>			<b>(3a-g)</b>		
	<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>	<b>f</b>	<b>g</b>	
<b>1</b>	R	7-Cl	6, 8-Cl, Cl	6, 7- OMe, OMe	5-Me	6, 8-I, I	6-Br	6, 8-Br, Br
<b>3</b>	R	7-Cl	6, 8-Cl, Cl	6, 7- OMe, OMe	5-Me	6, 8-I, I	6-Br	6, 8-Br, Br

## EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. TLC was done on silica gel 'G' coated glass plates using benzene : methanol (9.5 : 0.5) as eluant. IR spectra in KBr were recorded on FTIR -8400S, CE (Shimadzu). <sup>1</sup>H NMR spectra were recorded on Model AC-300F (Bruker) using CDCl<sub>3</sub>/DMSO-d<sub>6</sub> as solvent and TMS as an internal standard. Microwave reactions were carried out on LG MC-808 WAR model, operating at 540 W, generating 2450 MHz frequency.

### General procedure

#### Conventional method

A solution of (**1a**)<sup>16</sup> (0.01 mol) and acetic anhydride (20.0 mL) in dry pyridine (15.0 mL) was heated in oil bath for six hours, cooled and poured on ice cold HCl. The

solid thus obtained was filtered and crystallized from ethanol to give **(3a)**, yield 54%.

### Solution phase microwave assisted method

A solution of **(1a)**<sup>16</sup> (0.01mol) and acetic anhydride (20.0 mL) in dry pyridine (15.0 mL) was taken in a 100 mL borosil flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at 20% (180 W) microwave power for 6 min, at 360W for 3 min and then at 540 W for 3 min in short intervals to avoid the excessive evaporation of solvent. The reaction mixture was cooled and poured on an ice cold HCl. The resulting solid was filtered, recrystallized with ethanol and dried to give **(3a)**, yield 63%.

### Solid phase microwave assisted method

A slurry of **(1a)**<sup>16</sup> (0.01mol) and acetic anhydride (20.0 mL) in dry pyridine (5.0 mL) and basic alumina (15 g) was prepared. The dried slurry was powdered and the free flowing powder was placed in a 100 mL borosil beaker, in an alumina bath and irradiated at 720W for 5 min. The temperature of the reaction mixture inside the alumina bath reached 115°C. (However, the temperature of the reaction mixture when alumina bath was not used reached to only 50 °C). The completion of the reaction was checked by TLC. The organic product was extracted from the inorganic solid support with ethanol (3 x 5 mL). Evaporation of the ethanol layer gave **(3a)**, yield 73%, m. p. 150°C (lit<sup>20</sup>151°C); IR;  $\nu_{\max}$  1650(C=N), 1765(C=O), 1450 and 1325(CH<sub>3</sub>), 782 cm<sup>-1</sup>(C-Cl); <sup>1</sup>H NMR;  $\delta$  : 0.90(s, 3H, -N=C-CH<sub>3</sub>), 7.5-8.1(m, 3H, ArH).

Similarly **(3b-g)** were prepared following the above procedure.

**(3b)** yield 73%, m. p. 192°C (lit<sup>21</sup>194°C); IR;  $\nu_{\max}$  1653 (C=N), 1768 (C=O), 1455 and 1330 (CH<sub>3</sub>), 784 cm<sup>-1</sup> (C-Cl); <sup>1</sup>H NMR;  $\delta$  1.00 (s, 3H, -N=C-CH<sub>3</sub>), 7.6-8.0 (m, 2H, ArH). **(3c)**- yield 71%, m. p. 201°C (lit<sup>22</sup>202°C); IR;  $\nu_{\max}$  1648 (C=N), 1763 (C=O), 1448 and 1323 (CH<sub>3</sub>), 1375 and 1460 cm<sup>-1</sup> (-OCH<sub>3</sub>); <sup>1</sup>H NMR;  $\delta$  0.80 (s, 3H, -N=C-CH<sub>3</sub>), 6.9-7.5 (m, 2H, ArH), 3.73 (s, 6H, OCH<sub>3</sub>). **(3d)**- yield 72%, m. p. 134°C (lit<sup>23</sup>133°C); IR;  $\nu_{\max}$  1645 (C=N), 1762 (C=O), 1450 and 1325 cm<sup>-1</sup> (CH<sub>3</sub>); <sup>1</sup>H NMR;  $\delta$  0.70 (s, 3H, -N=C-CH<sub>3</sub>), 7.3-7.5 (m, 3H, ArH), 2.35 (s, 3H, CH<sub>3</sub>). **(3e)**- yield 70%, m. p. 251°C (lit<sup>24</sup>250°C); IR;  $\nu_{\max}$  1648 (C=N), 1762 (C=O), 1447 and 1322 (CH<sub>3</sub>), 500 cm<sup>-1</sup> (C-I); <sup>1</sup>H NMR;  $\delta$  0.75 (s, 3H, N=C-CH<sub>3</sub>), 8.4-8.5 (m, 2H, ArH). **(3f)**- yield 70%, m. p. 181°C (lit<sup>25</sup>183°C); IR;  $\nu_{\max}$  1650 (C=N), 1763 (C=O), 1449 and 1323 (CH<sub>3</sub>), 780 cm<sup>-1</sup> (C-Br); <sup>1</sup>H NMR;  $\delta$  0.85 (s, 3H, N=C-CH<sub>3</sub>), 7.4-8.3 (m, 3H, ArH). **(3g)**- yield 71%, m. p. 255°C (lit<sup>26</sup>254°C); IR;  $\nu_{\max}$  1652

(C=N), 1767 (C=O), 1452 and 1327 (CH<sub>3</sub>), 782 cm<sup>-1</sup> (C-Br); <sup>1</sup>H NMR; δ 0.88 (s, 3H, N=C-CH<sub>3</sub>), 7.9-8.2 (m, 2H, ArH).

## RESULTS AND DISCUSSION

With a view to examine the versatility of the above green synthetic protocol, the process was carried out in presence of solvent, as well as in absence of solvent (using a solid support) under microwave conditions. Suitability of different solid supports was also examined by conducting the reaction with acidic, basic, neutral alumina and silica powder. These results are summarized in Table 1.

**Table 1: Reaction of isatoic anhydride (1a) with acetic anhydride using different solid supports at 720 W under MW conditions**

Microwave induced method (Medium)	Time (min)	Temp. <sup>a</sup> (°C)	Yield <sup>b</sup> (%)
Basic alumina	8	115	73.0
Acidic alumina	13	100	60.0
Neutral alumina	15	90	55.0
Silica powder	18	80	58.0
Neat	14	65	Nil

<sup>a</sup>Temperature was noted at the end of exposure during microwave experiment by immersing glass thermometer into the reaction mixture and it is an approximate temperature range.

<sup>b</sup>Yield of isolated products.

Further, to check the possible intervention of specific (nonthermal) MW effect, the results of the solvent assisted and solvent free MW irradiation were compared with the conventional heating. The results of these reactions are summarized in Table 2.

Our observation on this reaction reveals two features to be clearly apparent. The effect of MW was not simply thermal and secondly, the reaction under solvent free conditions required a solid support to be present for the transmission of energy. Authentic samples of **3a-g** were prepared by known methods<sup>19</sup>. Their formation under MW conditions was confirmed by mixed melting point, co-TLC and superimposable IR spectra.

**Table 2: Yield of 4H-benzo[1,3]oxazin-4-ones (3a-g) by the reaction of isatoic anhydrides (1a-g) with acetic anhydride under conventional and MW irradiation conditions**

Entry product	Reaction temp <sup>a</sup> (°C)			Time (min)			Yield <sup>b,c</sup> (%)			Found m.p./lit m.p. (°C)
	Convnt.*	MW solvent phase	MW solid phase	Convnt.*	MW solvent phase	MW solid phase	Convnt.*	MW solvent phase	MW solid phase	
<b>3a</b>	Reflux	100	115	360	12	8	54	63	73	150/151 <sup>20</sup>
<b>3b</b>	Reflux	95	113	380	12	8	52	62	73	192/194 <sup>21</sup>
<b>3c</b>	Reflux	100	115	360	13	7	54	61	71	201/202 <sup>22</sup>
<b>3d</b>	Reflux	95	111	375	14	7	55	60	72	134/133 <sup>23</sup>
<b>3e</b>	Reflux	100	114	400	12	8	54	61	70	251/250 <sup>24</sup>
<b>3f</b>	Reflux	97	112	360	12	8	53	62	70	181/183 <sup>25</sup>
<b>3g</b>	Reflux	97	113	380	13	9	52	60	71	255/254 <sup>26</sup>

<sup>a</sup>Temperature was noted at the end of exposure during microwave experiment by immersing glass thermometer into the reaction mixture and it is an approximate temperature range.

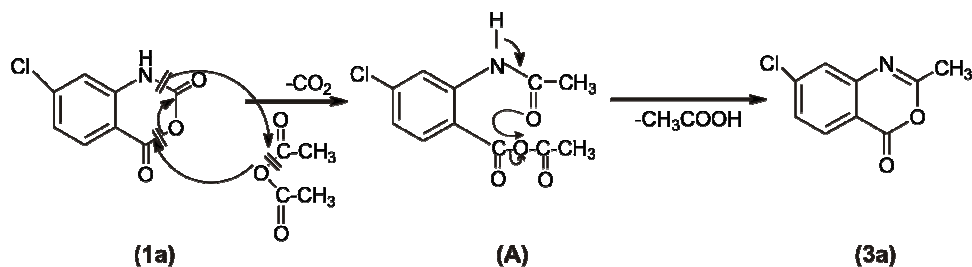
<sup>b</sup>Yield of isolated products

<sup>c</sup>To control the reaction in microwave assisted solvent phase, the irradiation was carried out in three stages, with a cooling period between each radiation ( irradiation conditions for solvent were [i] P/T 180W/6 min, [ii] P/T 360W/3 min, [iii] P/T 540W/3 min).

\*Conventional method (solvent pyridine)

We suggest that formation of 7-chloro- 2-methyl-4H- benzo[1, 3]oxazin- 4-one (**3a**) from 7-chloro-[2H-3, 1-benzoxazin-2, 4(1H)-dione] (**1a**) probably takes place following the sequence of reactions shown in **Scheme 2**. The reaction proceeds through the formation of species (**A**), which in the subsequent step undergoes ring closure to give the product (**3a**).

### Scheme 2



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