



# MICROWAVE ASSISTED FACILE ONE - POT SYNTHESIS OF SUBSTITUTED ISATOIC ANHYDRIDES FROM CORRESPONDING CARBOXYLIC ACID ANHYDRIDES

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## ABSTRACT

An efficient microwave assisted protocol for the exclusive one-pot synthesis of isatoic anhydrides (**3**, **5a-c**, **7** and **9**) by the heterocyclisation of carboxylic anhydrides (**1**, **4a-c**, **6** and **8**) with trimethylsilyl azide (**2**) is described.

**Key words** : Microwave assisted, Isatoic anhydrides, Carboxylic acid anhydrides

## INTRODUCTION

The use of microwave irradiation for carrying out organic reactions has been well established and have recently been reviewed<sup>1</sup>. The use of dry media in synthesis under microwave irradiation especially the use of supported reagents on mineral oxides has been a promising alternative to environmentally unacceptable usage of solvents in thermal procedures. The application of the solvent free technology coupled with the recyclability of mineral support has led to the development of many reaction procedures, which are environment friendly, falling in the domain of Green Chemistry<sup>2</sup>.

Isatoic anhydrides have shown immense potentiality as versatile synthons in the synthesis of wide variety of heterocyclic compounds<sup>3</sup>. Several methods are known in the literature for the synthesis of isatoic anhydrides. The potentiality of organic azides to act as 1, 3-dipolarophiles towards a wide variety of olefinic and polar unsaturated linkages have been well documented in the literature<sup>4,5</sup>. Organometallic azides of tin and silicon appear to behave similarly. It has been shown recently that pyridine- 2, 3-dicarboxylic anhydride (**1**) reacts with trimethylsilyl azide to induce a facile insertion of nitrogen in the anhydride ring

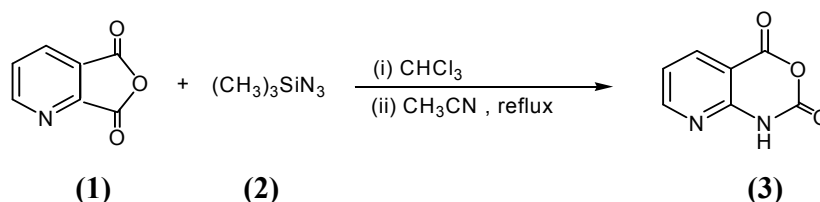
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to give 3-azaisatoic anhdride (**3**)<sup>6</sup>.

In continuation to our aim to streamline the synthesis under microwave irradiation conditions<sup>7, 8</sup>, we found it very convenient to apply the above procedure on carboxylic anhydrides (**1**, **4a-c**, **6** and **8**) with trimethylsilyl azide (**2**) to obtain the difficultly accessible isatoic anhydrides (**3**, **5a-c**, **7** and **9**). (Scheme 1)

**Scheme 1**



## 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 eluent of the reactions. IR spectra on KBr were recorded on FTIR- 8400S, CE (Shimadzu). <sup>1</sup>H NMR spectra were recorded on model AC-300F (Bruker) using  $\text{CDCl}_3/\text{DMSO-d}_6$  as solvent and TMS as an internal standard. Basic alumina used is aluminium oxide, basic, mesh size (100-300) Min. 90%, pH = 10. Microwave reactions were carried out on LG MC-808 WAR model, operating at 540 W, generating 2450 MHz frequency.

### General procedure

#### Conventional method

A mixture of (**4a**) (4.63 g, 10 m moles) and trimethylsilyl azide (2.64 mL, 20 m moles) was heated cautiously to 70-90°C for 2 hr. The process consisted of gently heating the reactants until a moderate gas evolution occurred. After evolution of nitrogen has ceased, the reaction mixture was cooled to room temperature and then diluted with benzene (4 mL). The resulting solid was filtered, recrystallized with ethanol and dried to give (**5a**), yield 57%, m. p. 353°C (lit<sup>10</sup> 354°C).

#### Solution phase microwave assisted method

A solution of (**4a**) (4.63 g, 10 m moles) and trimethylsilyl azide (2.64 mL, 20 m moles) 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 4 min and then at 360W for 5 min with short interval of 1 min to avoid the excessive evaporation of solvent. Overheating of the solution was avoided. The reaction mixture was cooled, diluted with benzene (4 mL) and the resulting solid was filtered, recrystallized with ethanol and dried to give **(5a)**, yield 63%, m. p. 353°C (lit<sup>10</sup> 354°C).

### Solid phase microwave assisted method

MW irradiation of the mixture of carboxylic anhydrides (**1**, **4a-c**, **6** and **8**) and trimethylsilyl azide over the basic alumina support produced isatoic anhydrides (**3**, **5a-c**, **7** and **9**) in excellent yields.

In a typical run, a slurry of carboxylic anhydride (**4a**) (4.63 g, 10 m moles), trimethylsilyl azide (2.64 mL, 20 m moles) and basic alumina (5 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 540 W for 5 min. The temperature of the reaction mixture inside the alumina bath reached 105°C. (However, the temperature of the reaction mixture when alumina bath was not used reached to only 40°C.) The completion of the reaction was checked by TLC. The organic product was extracted from the inorganic solid support with chloroform (3 x 5 mL). Evaporation of the chloroform layer gave **(5a)**.

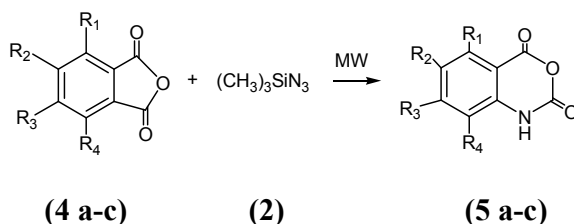
**(5a)** (75%), m. p. 353°C (lit<sup>10</sup> 354°C);  $\nu_{\max}$  3180 (NH), 1761 (CO), 1720 (CONH), 780  $\text{cm}^{-1}$  (C-Br); <sup>1</sup>H NMR  $\delta$  :8.2 (1H, s, NH); **(5b)** (74%), m. p. 332.0°C (lit<sup>11</sup> 334.0°C);  $\nu_{\max}$  3181 (NH), 1760 (CO), 1721 (CONH), 780  $\text{cm}^{-1}$  (C-Cl); <sup>1</sup>H NMR  $\delta$  :8.2 (1H, s, NH); **(5c)** (71%), m. p. 347.0°C (lit<sup>12</sup> 348.0°C);  $\nu_{\max}$  3178 (NH), 1760 (CO), 1718 (CONH), 3350 (OH); <sup>1</sup>H NMR  $\delta$  :8.1 (1H, s, NH), 8.08-8.72 (1H, s, ArH<sup>3</sup>), 11.0 (1H, s, OH); **(3)** (72.0%), m. p. 195°C (lit<sup>6</sup> 196.0);  $\nu_{\max}$  3181 (NH), 1760 (CO), 1721 (CONH); <sup>1</sup>H NMR  $\delta$  :8.0 (1H, s, NH), 8.28 (1H, s, ArH<sup>5</sup>), 7.75 (1H, s, ArH<sup>7</sup>) 7.8 (1H, s, ArH<sup>8</sup>); **(7)** (72%), m. p. >350.0°C (lit<sup>13</sup> 432.0°C);  $\nu_{\max}$  3178 (NH), 1760 (CO), 1719 (CONH); <sup>1</sup>H NMR  $\delta$  : 8.2 (1H, s, NH), 7.99-8.55 (6H, m, ArH); **(9)** (69%), m. p. >350°C (lit<sup>14</sup> 470.0°C);  $\nu_{\max}$  3181 (NH), 1762 (CO), 1722 (CONH); <sup>1</sup>H NMR  $\delta$  : 8.0 (1H, s, NH), 8.28 (1H, s, ArH<sup>5</sup>), 7.75 (2H, s, ArH<sup>7-8</sup>).

## RESULTS AND DISCUSSION

The microwave irradiation technique has been shown to score over the conventional ones in terms of safety, simplicity and eco-friendliness. To our knowledge, there has been no report on the synthesis of isatoic anhydrides from carboxylic anhydrides using trimethylsilyl azide on a solid support under MW conditions and therefore, an

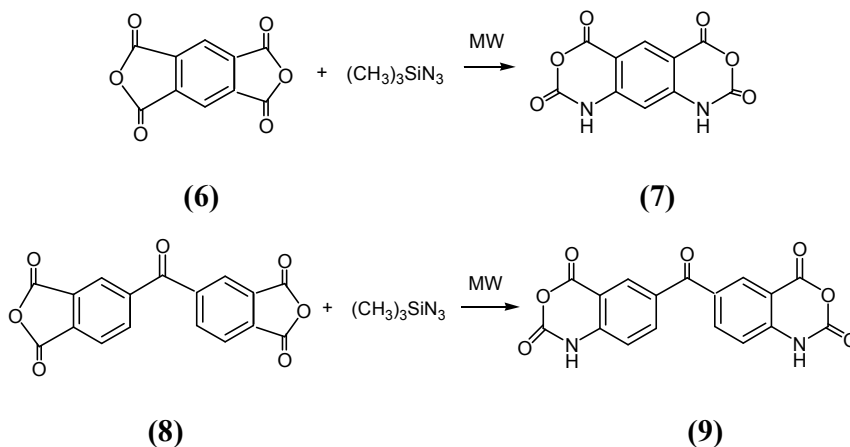
efficient microwave assisted protocol for the exclusive one-pot synthesis of isatoic anhydrides (**3**, **5a-c**, **7** and **9**) by the heterocyclisation of carboxylic anhydrides (**1**, **4a-c**, **6** and **8**) with trimethylsilyl azide (**2**) has been developed (**Scheme 2**) and is described in this paper.

In order to check the possible intervention of specific (non-thermal) MW effect, the results of the MW irradiation were compared with the conventional heating (Table 2). The power levels 540 W of MW for 10 minutes gave the best results. Suitability of different solid support was also examined by conducting the reaction with acidic, basic, neutral alumina and silica powder. The results of this study are summarized in Table – 1. The results indicate that basic alumina formed a better choice in giving good results.

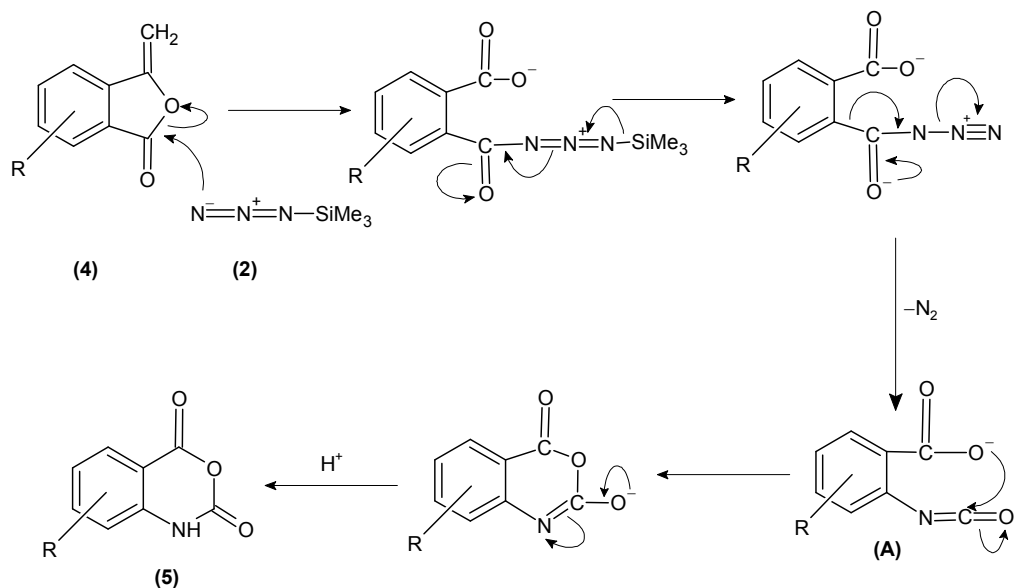


	<b>A</b>	<b>B</b>	<b>C</b>
<b>4</b>	R <sub>1</sub> = Br, R <sub>2</sub> = Br, R <sub>3</sub> = Br, R <sub>4</sub> = Br	R <sub>1</sub> = Cl, R <sub>2</sub> = Cl, R <sub>3</sub> = Cl, R <sub>4</sub> = Cl	R <sub>1</sub> = H, R <sub>2</sub> = H, R <sub>3</sub> = -COOH, R <sub>4</sub> = H
<b>5</b>	R <sub>1</sub> = Br, R <sub>2</sub> = Br, R <sub>3</sub> = Br, R <sub>4</sub> = Br	R <sub>1</sub> = Cl, R <sub>2</sub> = Cl, R <sub>3</sub> = Cl, R <sub>4</sub> = Cl	R <sub>1</sub> = H, R <sub>2</sub> = H, R <sub>3</sub> = -COOH, R <sub>4</sub> = H

**Scheme 2**



## Scheme 3



**Table 1 : Reaction of carboxylic anhydride (4a) with trimethylsilyl azide using different solid supports under MW conditions at 540 Watts.**

Microwave induced method (Medium)	Time (min)	Temp <sup>a</sup> (°C)	Yield <sup>b</sup> (%)
Basic alumina	5	115.0	75
Acidic alumina	7	90.0	60
Neutral alumina	8	90.0	55
Silica powder	6	90.0	58
Neat	15	65.0	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.

**Table 2: Yield of isatoic anhydrides (3, 5a-c, 7 and 9) by the reaction of carboxylic anhydrides (1, 4a-c, 6 and 8) with trimethylsilyl azide 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>3</b>	Reflux	105	112	240	10	5	55	61.7	72	195.0/ 196.0 <sup>6</sup>
<b>5a</b>	Reflux	102	115	240	10	5	57	63	75	353.0/ 354.0 <sup>10</sup>
<b>5b</b>	Reflux	100	112	250	11	6	55.7	60	74	332.0/ 334.0 <sup>11</sup>
<b>5c</b>	Reflux	105	115	220	10	5	55	63.4	71	347.0/ 348.0 <sup>12</sup>
<b>7</b>	Reflux	102	117	260	12	4	52.3	61.6	72	>350/ 432.0 <sup>13</sup>
<b>9</b>	Reflux	102	110	275	10	5	58	62	70	>350/ 470.0 <sup>14</sup>

<sup>a</sup>To control the reaction in microwave assisted solvent phase, the irradiation was carried out in two stages, with a cooling period between each radiation (irradiation conditions for solvent were [i] P/T 180W/5 min, [ii] P/T 360W/5 min)

\*Conventional method (solvent dichloromethane)

Authentic samples of (**3**, **5a-c**, **7** and **9**) were prepared by known methods<sup>6</sup>. Their formation under MW conditions was confirmed by mixed melting point, co-TLC and superimposable IR spectra. We believe that the reaction probably takes place by the intervention of the species A (**Scheme 3**) that undergoes concomitant ring closure to generate<sup>5</sup>.

### ACKNOWLEDGEMENT

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