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Microwave-assisted synthesis of phthalimides, phthalazines and quinazolines

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Abstract : A versatile highly accelerated, efficient and environmentally friendly microwave assisted synthesis of phthalimides, phthalazines, and quinazolines is described. This method shows the advantages of good substrate, tolerance, clean and rapid conversion to these important heterocycles.

Keywords : Microwave heteaing; Phthalimides; Phthalazines; Quinazolinones.

INTRODUCTION

The development of simple and versatile synthetic routes that can be applied to a wide variety of commercially available starting materials continues to be one of the most exciting topics in organic synthesis, especially when environmentally friendly methodologies are employed. The nonconventional microwave-assisted organic synthesis has shown broad applications as a very efficient way to accelerate the course of many organic reactions, giving higher yields and better selectivity, lower quantities of side products and consequently, easier work-up and purification of the products[1]. Therefore, the growing interest in academic, research and industrial laboratories is not surprising and is reflected in an exponential increase in the production of scientific papers, books[2,3], and reviews[4,5] related to the use of this technology.

Cyclic imides are heterocyclic compounds, some of which have biological activity[6]. Moreover, they are synthetic precursors in organic synthesis,[7] and have wide application in supramolecular chemistry[8], polymer synthesis[9], new materials[10] and molecular electronic devices[11]. Quinazolinone derivatives attract a widespread interest due to the diverse biological activities[12] associated with them. They are pharmaceutically important as antituberculars[13], antibacterial,[14] antiparkinsons[15], antihelmintics[15], and they also show blood platelet anti aggregating activity[16]. Herein, we repeat part of our ancient work[17-20] to touch the advantage of this new technology.

RESULTS AND DISCUSSION

In continuation of our interest in the development efficient and simple procedures for the synthe-

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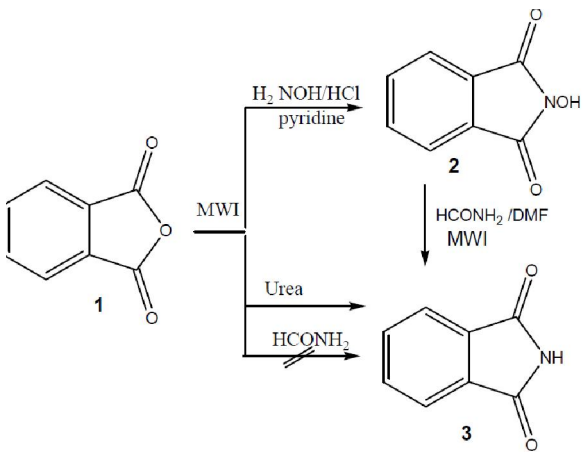
sis of heterocycles we have reported previously the synthesis of cyclic imides, phthalazines and quinazolines[19] via conventional methods. Herein, we would like to report synthesis of these heterocycles under microwave irradiation method (MWI). Thus, a solution of phthalic anhydride **(1)** and hydroxylamine hydrochloride in pyridine, was irradiated in a microwave oven of power 800 W to give N-hydroxyphthalimide**(2)** after 1 min.in74 % yield as depicted in Scheme 1. The product was isolated by treating of the crude reaction mixture with ice / HCl, followed by filtration and washing the solid obtained with water to remove the pyridenium salt. The transformation proceeded very clean, without any traces of side products. The solution of N-hydroxyphthalimide**(2)** in formamide was MWI to produce phthalimde**(3)** after 11min. with 60 % yield. Treatment of phthalic anhydride **(1)** with the formamide failed to give the expected phthalimide (**3**),however, it was produced by reaction of **1** with urea, in 5 min. under solvent free procedure (Cf. TABLE 1). Complete conversion was observed within few minutes in all cases, which leads to a serious energy saving. For comparative studies, the reactions were also carried out under traditional conditions[21]. All the products are known compounds and were identified on the basis of their IR spectra and by direct comparison of their tlc, m.p. and m.m.p. with those of authentic samples.



Scheme 1

Compounds **1-3** were microwave irradiated with aromatic amines, in DMF to afford N-aryl phthalimide derivatives **4a-d** in 3-4 min. (yield 48 – 95%) as shown in Scheme 2 and TABLE 2. Sena et al[22]. reported the reaction of aromatic amines with phthalic anhydride under solvent free procedure afforded N-aryl phthalamic acid **5** as well as, noexamplesof imide formation on solid support without the addition of strong Lewis acid have been reported so far[23]. The role of DMF can be explained as an energy transfer agent and homogenizer to increase the reaction temperature[24]. The reactions were also carried out under traditional conditions[17] and the products were proved by their tlc, mp.andm.m.p. (Cf. TABLE 2) and their IR spectra[25-28]. The IR spectra of compounds **4a-d** showed a doublet in the regions (1789 – 1764) cm^{-1} and (1715 – 1705) cm^{-1} for carbonyl group of cyclic imides.

The reaction of the imides **1,2** with hydrazine hydrate and/or phenylhydrazine under solvent free procedure afforded 1,4-phthalazinedione derivatives **6a,b** (Scheme 2, TABLE 2). However, reaction of compound **3** with phenyl hydrazineafforded N-anilinophthalimide[17]**(7)** instead of the expected N-phenyl-1,4-phthalazinedione (**6b**). The structure of compounds **6a,b** and **7** was established on the basis of their characteristic IR data and direct comparison of tlc, m.p. and m.m.p with authentic samples[29-31].

Treatment of N-(*p*-tollaylsulphonyloxy) phthalimide**(8)** with aromatic amines under microwave irradiation produced 3-aryl-1,2,3,4-tetrahydroquinazoline-2,4-diones **9a-d** (Scheme 3, TABLE 2). The formation of compounds **9a-d** can

TABLE 1 : Formation of compounds 2 and 3 under traditional and microwave heating

Product number	Traditional		MWI		mp °C	Litt. mp°C
	Time (min.)	Yield (%)	Time (min.)	Yield (%)		
2	20		1	74	230-233	230-232
3[a]	20		11	60		234-236
3[b]	20		5	89		234-236

[a] **product of MWI of compound 2 and formamid;** [b] **product of MWI of compound 1 and urea.**

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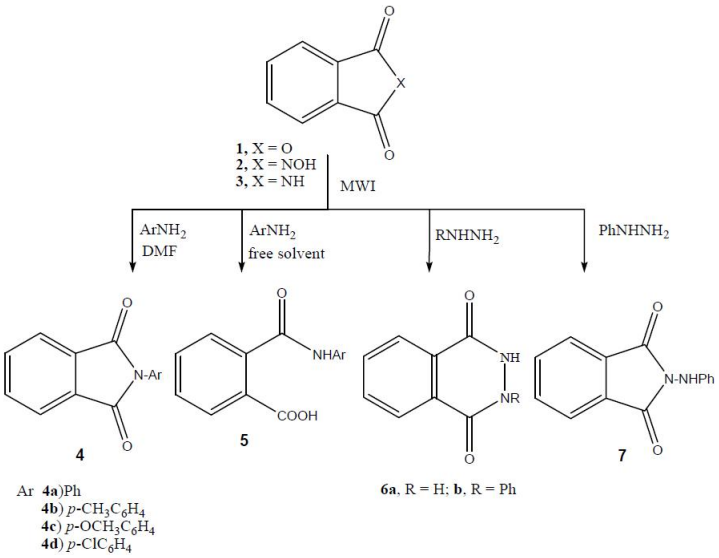

Scheme 2

TABLE 2 : Formation of compounds 4,6,7 and 3 under traditional and microwave heating

S*	Product number	Traditional		MWI		mp °C	Litt. mp°C
		Time (min.)	Yield (%)	Time (min.)	Yield (%)		
			Ar				
1	4a C_6H_5	3	85	4	88	197-198	204-205
1	4b *p*-$CH_3C_6H_4$	3	72	4	75	197-199	201-202
1	4c*p*-$OCH_3C_6H_4$	3	75	4	76	146-148	153-155
1	4d *p*-ClC_6H_4	3	75	4	80	190-192	194-195
2	4a C_6H_5	3	80	3	95	198-190	204-205
2	4b *p*-$CH_3C_6H_4$	3	79	4	83	196-198	201-202
2	4c *p*-$OCH_3C_6H_4$	3	82	4	90	148-150	153-155
2	4d *p*-ClC_6H_4	3	86	4	87	188-190	194-195
3	4a C_6H_5	3	56	3	50	199-190	204-205
3	4b *p*-$CH_3C_6H_4$	3	62	3	51	196-198	201-202
3	4c*p*-$OCH_3C_6H_4$	3	53	3	48	147-148	153-155
3	4d *p*-ClC_6H_4	3	60	3	57	190-192	194-195
			R				
1	6a H	0.5	89	1	80	>300	>300
2	6a H	0.5	80	1	60	>300	>300
3	6a H	0.5	83	1	83	>300	>300
1	6b Ph	3	70	4	46	214-215	210-212
2	6b Ph	3	79	4	35	214-215	210-212
3	7	3	70	4	85	174-175	173-175
8	9a Ph	3	60	1.5	55	288-290	287-289
8	9b *p*-$CH_3C_6H_4$	3	62	1.5	60	256-258	255-257
8	9c *p*-$OCH_3C_6H_4$	3	58	1	50	214-215	218-220
8	9d *p*-ClC_6H_4	3	49	1.5	58	>300	>300

S = number of the starting compound

be visualized on the basis of Lossen rearrangements (Cf. Scheme 4) to give anilide**A**, followed by cy-

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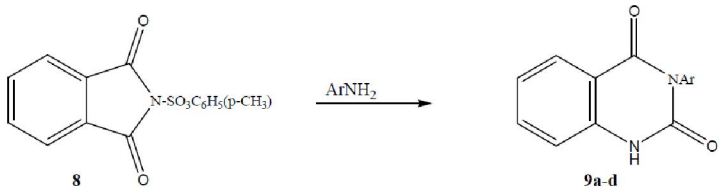
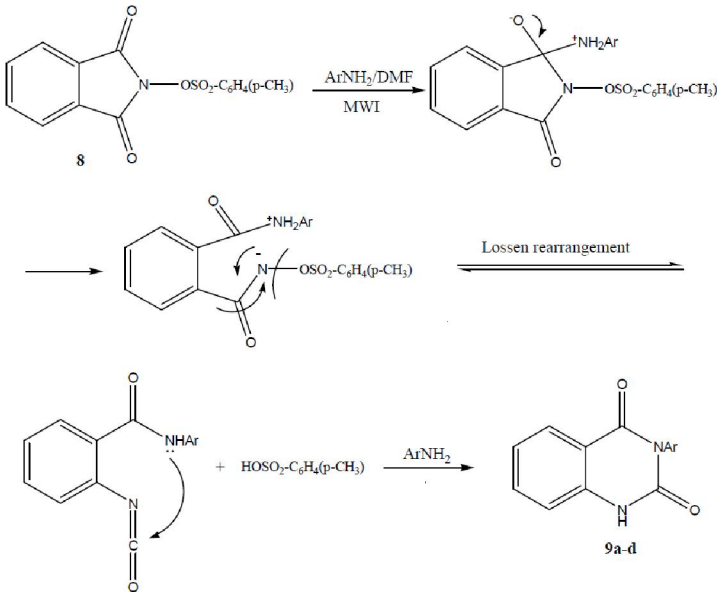


Scheme 3



Scheme 4 : Lossen rearrangement and formation of compounds 9a-d

clization via a removal an amine molecule to give quinazolinones**9a-d**. Contrary to the traditional methods[19], high yields were obtained within short reaction times as well as a reduction of one step in the formation of quinazolinone**9a-d**. The structure of compounds **9a-d** was established on the basis of their characteristic IR data that showed a doublet in the regions (1727 – 1704 cm^{-1}) and (1673 – 1656 cm^{-1}) for carbonyl group of cyclic imides and 3291 – 3206 cm^{-1} for NH group as well as direct comparison tlc, m.p. and m.m.p. with authentic samples obtained by conventional experiments[19].

CONCLUSION

Cyclic imides **2-4 and 7**;phthalazinediones**6**, and quinazolinones**9** were prepared by applying a simple, fast, and highly efficient procedure under microwave irradiation. The transformation proceeded very clean, without any traces of side products apart from the main one and starting materials. This method affords high yield of the desired products in remarkably short reaction times with serious energy saving. All the reactions were performed in domestic household oven "SHARP" R-231F, 230-240 V, 50Hz, 800W. Conventional reflux was performed in parallel with MW irradiation. The products are fully examined by their melting points, mixed melting, TLC, and IR spectroscopy with authentic samples. All yields correspond to isolated pure compounds.

EXPERIMENTAL

The melting points were determined in capillary tubes on Gallankemp melting point apparatus and were uncorrected. The infrared spectra were recorded on FTIR Maltson (infinity series) spectrometers as KBr discs. Thin layer chromatography (TLC) was carried out for the monitoring of the progress of all reactions and homogeneity of synthesized compounds. TLC was performed using TLC aluminum sheet silica gel F_{254} (Merck). The microwave irradiated reactions (MWI) were performed in domestic household oven "SHARP" R-231F, 230-240 V, 50Hz, 800W. Conventional reflux was per-

formed in parallel with MW irradiation. All yields correspond to isolated pure compounds.

General procedure

Synthesis of compounds**2, 3, 4a-d,**[17] **6a, b,**[17] **and 7,**[17] **9a-d**[19] were performed according to procedures described in the literatures.

Synthesis of 2 from phthalic anhydride

The mixture of phthalic anhydride (3 mmole) and hydroxylamine hydrochloride (3mmole) in pyridine (2 ml) was MWI for 1min. After cooling, the reaction mixture was poured onto ice / HCl, the solid product was filtered off and recrystallized from ethanol.

Synthesis of 3 from 2

N-hydroxyphthalimide (**2**) (3 mmole) andformamide (8 mmole) in DMF (2 ml) were MWI for 11min, cool, the solid product was recrystallized from water.

Synthesis of 3 from phthalicanhydride

Phthalic anhydride (3 mmole) and urea (5 mmole) was fused under MWI for 5min. The solid product was recrystallized from water.

Synthesis of N-arylphthalimide4a-d

Phthalic anhydride, (3 mmole) or N-hydroxyphthalimide, (3 mmole) or phthalimide (3 mmole) and aromatic amines (3 mmole) in DMF (2 ml) were MWI for 3-4 min, cool, the solid products were recrystallized from ethanol.

Action of hydrazines on compounds 1-3

Compounds **1**or**2** or **3** (3 mmole) and hydrazine hydrate (0.5 ml) or phenyhydrazine (0.5 ml) were MWI for 1-4 min to give compounds **6a,b** and **7**, which recrystallized from ethanol.

Synthesis of 2-aryl- 1,2,3,4-tetrahydroquinazoline-2,4-diones9a-d

A mixture of N-(*p*-tollaylsulphonyloxy) phthalimide**(8)** (3mmole)and aromatic amines (3mmol) in DMF (2ml) was MWI for 1-1.5 min., the solid product obtained after cooling was recrystalized from ethanol.

Formation of anilides 7a-h and quinazolinones 8a,b

Benzoxazine derivatives **6a-c** (3mmol) and aromatic amines(3mmol) or formamide (5mmol) in DMF (2ml) was MWI for 3-10 min.

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