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Microwave Mediated Synthesis of Biologically Active Various *N*-Substituted Phthaloyl Derivatives

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ABSTRACT

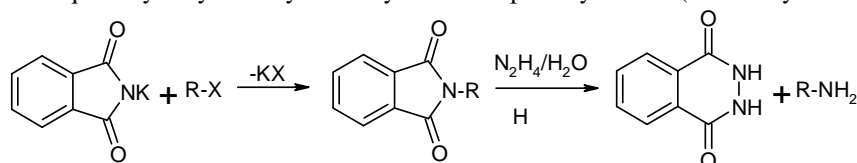
Microwave-induced Organic Reaction Enhancement (MORE) Chemistry has received considerable attention due to several advantages. Thus keeping in view the utility of MORE chemistry, various *N*-substituted phthalimide compounds have been synthesized by microwave irradiation as well as conventional method.

Key Words: Microwave irradiation, Phthalimide, Dimer, Phthalhydrazine and mixed phthalimido dimer

INTRODUCTION

Imide group is an interesting functionality, due to its wide presence in the natural products and in the pharmacologically active compounds. Compounds containing phthalimide moiety are distinguished by their potent fungicidal action[1-3]. The well known products namely, capton [N-(trichloromethyl-thio) tetrahydrophthalimide], folpet [N-(trichloro methyl)-phthalimide has industrial importance as the starting material for producing anthranilic acid by Hoffmann degradation and a large number of primary amines can be produced by the Gabriel synthesis. Phthalimide, an intermediate in the production of agricultural pesticides is produced almost exclusively from phthalic anhydride and ammonia, however, processes based on phthalic anhydride and urea or oxidative ammonolysis of *o*-xylene are also known.

With bases phthalimide forms water-soluble salts and also reacts with halogens to form the corresponding *N*-chloro, *N*-bromo or *N*-iodo compounds. These *N*-halo compounds are also obtained if alkali-metal phthalimides are reacted with hypochlorous or hypobromous acid. When *N*-halo compounds are heated, anthranilic acid (*O*-amino benzoic acid) is formed in Hoffmann degradation. The reaction of alkali-metal phthalimides with alkyl halides gives *N*-alkyl phthalimides and subsequent hydrolysis or hydrazinolysis affords primary amines (Gabriel synthesis)[4].



Phthalimides are important synthetic intermediates to prepare primary amines, agricultural pesticides and also used in preservatives, pigments and pharmaceuticals[5-10]. The phthaloyl group is a well-established protective group for

primary amines[11] in various types of compounds, particularly peptides[12], aminoglycosides[13] and β -lactum antibiotics[14].

Keeping in view the importance of phthalimides not only as fungicides in crop protection but also equally as protective group for primary amines, H_2NR , we have reported a simple and efficient method for the preparation of various *N*-substituted phthaloyl derivatives in higher yields with higher purity under mild reaction conditions.

Experimental work

Various aryl amines, chloroacetic acid, phthalimide, sodium acetate, potassium hydroxide, hydrazine hydrate, phenyl hydrazine, 2,4-dinitro phenyl hydrazine, p-nitro phenyl hydrazine, hydroxyl amine and solvents were synthetic grade commercial products [s.d. fine chemicals, Qualigens etc] solvents were distilled before use. The completion of reaction of phthalimide derivatives checked by Thin Layer Chromatography technique. The synthesized products were also characterized by physical constants and spectroscopic methods like IR and NMR.

Scheme-1 Synthesis of N-Aryl phthalimides



Where Ar-

- a) o- NO_2 - C_6H_4
- b) p- $COOH$ - C_6H_4
- c) C_6H_5
- d) p- Cl - C_6H_4
- e) p- Br - C_6H_4
- f) α - $C_{10}H_7$
- g) m- OH - C_6H_4
- h) m- NO_2 - C_6H_4
- i) p- CH_3 - C_6H_4
- j) p- OH - C_6H_4
- k) 3, 4-Dichloro- C_6H_3

Reaction scheme-1

a) Conventional method

A solution of aryl amine IIc (0.6283 gm, 0.006 mole) in ethanol (10 ml) was added to a solution of phthalic anhydride I (1 gm, 0.0067 mole) and sodium acetate (0.473 gm, 1 mole) in acetic acid (15 ml). Then the reaction mixture was refluxed on water bath for near about 4-5 hrs. The completion of the reaction was monitored by TLC [Solvent system, Pet. Ether: Methanol (9:1)]. The reaction mixture was then cooled to obtain solid product, washed with water several times. The crude product was recrystallised with ethanol to give compound IIIc.

b) Microwave method

Aryl amine IIc (0.6283 gm, 0.006 moles) was added to a mixture of phthalic anhydride I (1 gm, 0.0067 mole) and sodium acetate (0.473 gm, 1 mole) in DMF solvent (1-2 ml). The reaction mixture was then irradiated in microwave oven for 4-5 mins at 800 power level. The completion of the reaction was monitored by TLC. Then it was cooled to obtain solid product, washed with water several times. The crude product obtained was recrystallised by ethanol to obtain compound IIIc. The spectral and analytical data were found to be similar as reported for conventional method.

Similarly, the compounds IIIa-k were synthesized by conventional as well as microwave method, using different types of aryl amines. Spectral data of the following compounds are listed below in Table-1.

Table – 1: Synthesized N-aryl phthalimides

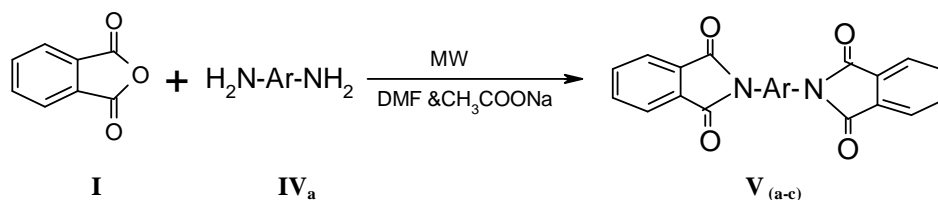
Compounds	M.F.	Reaction time		Percent Yield		M.P. [15,16] °C
		Conventional (Hrs.)	M.W. (Mins.)	Conventional (Hrs.)	M.W. (Mins.)	
III _a	C ₁₄ H ₈ O ₄ N ₂	6	4.5	81	92	70
III _b	C ₁₅ H ₉ O ₂ N	2	4	77	83	282
III _c	C ₁₄ H ₉ O ₂ N	4	4.5	77	92	206
III _d	C ₁₄ H ₈ O ₂ NCl	4	4	79	92	185
III _e	C ₁₄ H ₈ O ₂ NBr	5	5	78	96	215
III _f	C ₁₄ H ₁₁ O ₂ N	4	3	70	96	178
III _g	C ₁₄ H ₉ O ₃ N	4	4	70	91	222
III _h	C ₁₄ H ₈ O ₄ N ₂	2	3	62	93	288
III _i	C ₁₅ H ₁₁ O ₂ N	4.5	4.5	61	89	236
III _j	C ₁₄ H ₉ O ₃ N	5	4.5	72	85	274-76
III _k	C ₁₄ H ₇ O ₂ NCl ₂	4	4.5	68	95	190

Characterization data: ¹H-NMR DATA

III_f: δ_{ppm} 7.4-7.8 (m, Ar-H), 7.9-8.02(m, Ar-H).

III_i: δ_{ppm} 4.09(s, 2H, -CH₂-), 7.35-7.45(m, 4H, Ar-H), 7.89-7.95(m, Ar-H)

III_j: δ_{ppm} 2.41 (s, 3H, -CH₃), 7.26 (d, 4H, Ar-H), 7.78 (dd, Ar-H), 7.95 (dd, Ar-H).

Scheme-2 Synthesis of N,N'-p-phenylene bis phthalimides

Where Ar-

- a) -C₆H₄-CH₂-C₆H₄
- b) -C₆H₄-C₆H₄-
- c) -C₆H₄-

Reaction scheme-2**a) Conventional method**

A solution of aryl amine **IV_a** (1.33 gm, 0.006 moles), in ethanol (10ml) was added to a solution of phthalic anhydride **I** (2 gm, 0.012 mole) and Na-acetate (0.473 gm, 1 mole) in acetic acid. The whole reaction mixture was refluxed on water bath for about 8-10 hrs. The progress and completion of reaction was monitored by TLC [solvent system Pet. Ether: Methanol (8:2)] in each 0.5 hrs interval.

The crude product was isolated by pouring the reaction mixture in cold water, then filtered and dried. The crude product obtained was then recrystallised by ethanol to give compound **V_a**. Yield 70.60 %, M.P. 98 °C. Similarly compound **V_{b-c}** prepared.

b) Microwave method

An aryl amine **IV_a** (1.33 gm, 0.006 moles), was added to a mixture of phthalic anhydride **I** (2 gm, 0.012 mole) and Na-acetate (0.473 gm, 1 mole) in acetic acid. The whole reaction mixture was then irradiated for 4-8 mins at power level 600.

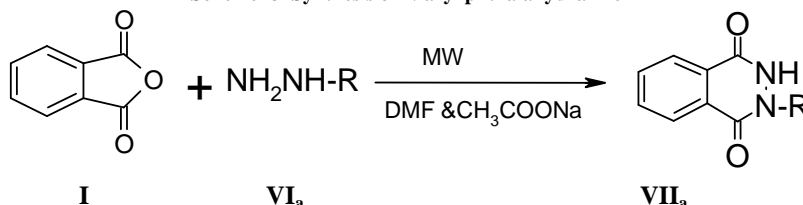
Then the crude product obtained was isolated then recrystallised by ethanol to give compound **V_a**. Yield obtained is 82 % having M.P. 90 °C.

Table 2. Synthesized dimers of N-Aryl phthalimides

Compounds	M.F.	Reaction time		Percent Yield		M.P. [15,16] °C
		Conventional (Hrs.)	M.W. (Mins.)	Conventional (Hrs.)	M.W. (Mins.)	
V _a	C ₂₉ H ₁₈ O ₄ N ₂	8	4.5	71	82	98
V _b	C ₂₈ H ₁₆ O ₄ N ₂	9	5	68	83	300
V _c	C ₂₂ H ₁₂ O ₄ N ₂	8.5	5.5	71	87	305

Compound IIIa: IR data: 2924.51, 1459.49, 1377.55, 1094.68, 887.58, 814.88, 712.86, 532.56

Scheme -3 Synthesis of N-aryl phthalahydrazine



Where

- R- a) -H
 b) -Ph
 c) -p- NO₂-C₆H₄-
 d) 2, 4-Dinitro- C₆H₃

Reaction scheme-3

a) Conventional method

A solution of hydrazine VI_a (0.21 gm, 0.0067 moles) in DMF (10 ml) was added to a solution of phthalic anhydride I (1gm, 0.0067 moles) and Na-acetate (0.473 gm, 1mole) in acetic acid (15 ml) and the reaction mixture was refluxed on water bath for about 8-10 hrs. The completion of the reaction was monitored by TLC (System system Pet.Ether:Methanol, 9:1). Then the crude product obtained was isolated and recrystallised by ethanol to give compound VII_a. Yields obtain 80 %, M.P.343⁰C. Similarly the compounds VII (b-d) were synthesized using same procedure.

b) Microwave method

Hydrazine VI_a (0.21 gm, 0.0067 mole) was added to a mixture of phthalic anhydride I, (1 gm, 0.0067 mole) and Na-acetate (0.473 gm, 1mole). Then in the above mixture few drops of solvent DMF were added. The reaction mixture was then irradiated under MW for up to 4-7 mins at power level 300. The progress and completion of reaction was monitored by TLC (solvent system Pet.Ether:Methanol, 9:1).

Finally, the product obtained is poured in to ice cold water and it becomes isolated. The crude product obtained was then recrystallised by ethanol to give compound VII_a. Similarly compound VII_(b-d) were synthesized by MW method. The yield obtain by this method are good.

The characterization data of synthesized compounds VII_(a-d) were formulated in Table 3.

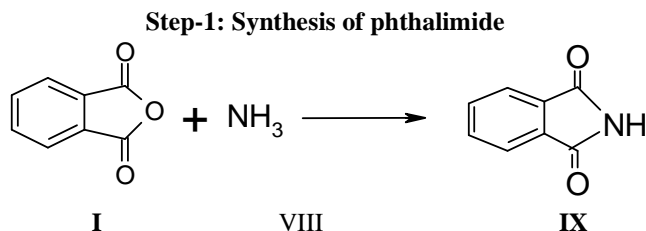
Table 3: Synthesized N-aryl phthalahydrazine

Compounds	M.F.	Reaction time		Percent Yield		M.P. [15] °C
		Conventional (Hrs.)	M.W. (Mins.)	Conventional	M.W.	
VII _a	C ₈ H ₆ O ₂ N ₂	6	4.5	80	96	343
VII _b	C ₁₄ H ₁₀ O ₂ N ₂	8	6	70	98	211
VII _c	C ₁₄ H ₉ O ₄ N ₃	6	4.2	65	85	345
VII _d	C ₁₄ H ₈ O ₆ N ₄	5	4	72	95	312

Characterization data

Compound IV_a: 3372cm⁻¹(-N-Stretching), 2924(-C-H stretching), 1666 (-NH-C=O stretching), 1667-1590 (C=C-H aromatic stretching), 1464 - 89 (NO₂ stretching).

Scheme -4 Synthesis of N,N'-bis phthalolyl glycyloxy compound



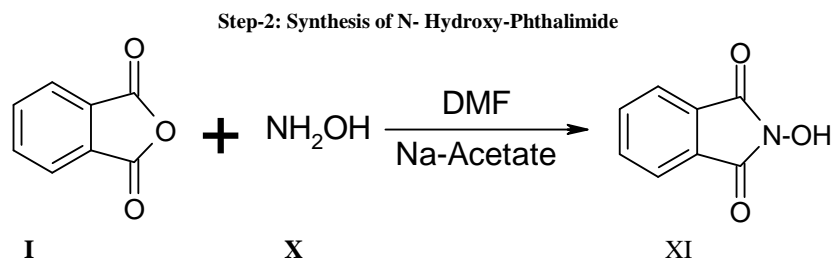
Reaction scheme-4

a) Conventional method

A solution of phthalic anhydride **I** (1gm, 0.00675 moles) and ammonia (1.5 ml, d 0.88) was heated directly on wire gauze by attaching air condenser for about 1.5-2 hours. Then poured this mixture in porcelain dish and cooled. The completion of reaction was monitored by TLC (System used C₆H₆: EtOH, 9:1). The crude product obtained was then recrystallised by solvent ethanol to give product **V**. The yield obtained was 85 % and M.P. 233-234 °C.

b) Microwave method

A solution of Phthalic anhydride **I** (1 gm, 0.00675 moles) and ammonia (1.5 ml, d 0.88) was irradiated under microwave irradiation for about 1-1.5 mins at power level 200. The crude product **IX** obtained was then recrystallised by using solvent ethanol. Yield 90% and M.P. 233 °C.



Reaction scheme-5

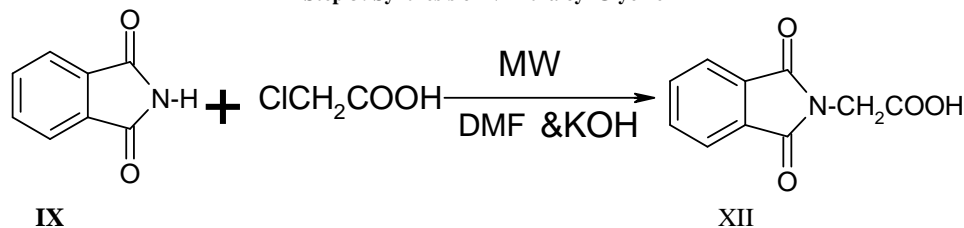
a) Conventional method

A solution of Hydroxyl amine (0.5 gm, 0.0067 moles) in ethanol (10 ml) and phthalic anhydride **I** (1gm, 0.0067 moles) and Na-acetate (0.473 gm, 1mole) in acetic acid (10 ml) was refluxed on water bath for about 4 hrs. The content was cooled to give solid product, which was recrystallised from water, Yield 80 %, M.P. 230 °C.

b) Microwave method

Hydroxyl amine hydrochloride (0.5 gm, 0.0067 moles) was added to a solution of phthalic anhydride **I** (1gm, 0.0067 moles) and Na-acetate (0.473 gm, 1mole) in which few drops of DMF was added. The reaction mixture was then irradiated under MW for up to 4-8 mins. The completion of reaction was monitored by TLC. The crude product obtained was then recrystallised by solvent ethanol to obtain product **VI**.

Step-3: Synthesis of N-Phthaloyl Glycine



Reaction scheme-6

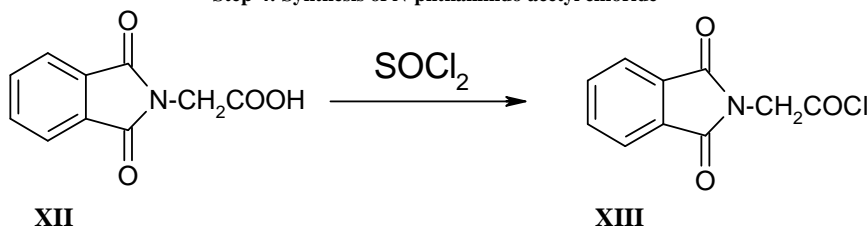
a) Conventional method

Phthalimide **IX** (10 gm, 0.068 moles) was dissolved in aqueous potassium hydroxide solution (3.92 gm, 0.07 moles) and then in the above solution, Chloroacetic acid was added (6.67 gm, 0.07 moles). The reaction mixture was refluxed on sand bath for 3 to 4 hours. The progress of reaction was monitored by TLC (Solvent system Pet. Ether: Methanol, 9:1). The reaction mixture was cooled to room temperature and acidified by dilute HCl. Solid thus separated was filtered, washed with water and dried and then recrystallised by solvent ethanol to obtained product **VII** M.P. 194°C, Yield 80 %.

b) Microwave method

In the mixture of phthalimide **IX** (10 gm, 0.068 moles) and potassium hydroxide (3.92 gm, 0.07 moles), chloroacetic acid was added (6.67 gm, 0.07 moles). Then in the above reaction mixture few drops of DMF was added. The reaction mixture was then irradiated under MW for up to 4.5 mins at power level 600. The completion of reaction was monitored by TLC. The crude product obtain was then recrystallised by solvent ethanol to obtained product **XII**. Yield 95 % and M.P. 194 °C.

Step-4: Synthesis of N-phthalimido acetyl chloride

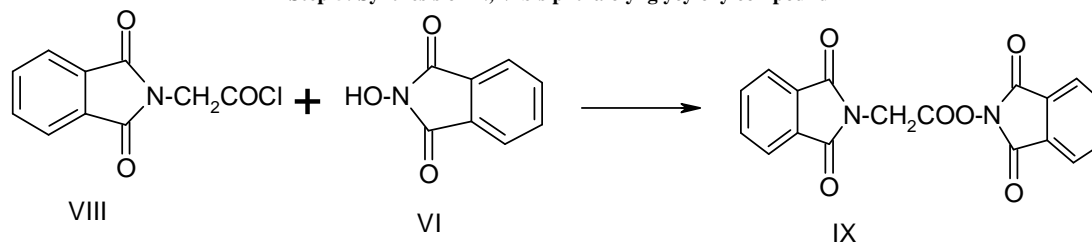


Reaction scheme-7

Conventional method

A mixture of N- phthaloyl glycine **XII** (5.0 gm, 0.02 mole) and SOCl₂ (6 ml, 0.048 mole) refluxed for 30 to 40 min. on water bath under anhydrous condition. The completion of reaction was monitored by TLC (Solvent system Pet.Ether: Methanol, 9:1). The crude chloride product obtain was then distilled out under vacuum at 50-55 °C, which gives colourless product **XIII**. Yield 95 %.

Step-5: Synthesis of N,N'-bis phthaloyl glycyloxy compound



Reaction scheme-8

a) Conventional method

A mixture of N-hydroxy phthalimide **XI** (0.6357 gm, 0.0039 mole), sodium acetate (0.473gm, 1 mole) in 15 ml DMSO added to N-phthalimido acetyl chloride **XIII** (1 gm, 0.0039mole) and then it was refluxed on water bath for

4 hrs. The progress and completion of reaction was monitored by TLC (solvent system: Methanol, 9:1). The reaction mixture was brought to room temperature, and then poured into water (200ml) and extracted with ethyl acetate (2×20 ml). The organic layer was washed 2 times with 50 ml 10 % NaOH solution, followed by 2 times 50 ml water and dried over anhydrous Na₂SO₄.

After evaporation of ethyl acetate the solid obtain was recrystallised in ethanol to give pure product **XIV**.

b) Microwave method

A mixture of N-hydroxy phthalimide **XI** (0.6357 gm, 0.0039 mole), sodium acetate (0.473gm, 1mole) in 15 ml DMSO added to N-phthalimido acetyl chloride **XIII** (1 gm, 0.0039 mole) and was exposed to MW irradiation for 1 min at 300 power level. On completion of the reaction followed by TLC examination (Chloroform: Methanol, 9:1) and the product obtained was isolated by same procedure as used for conventional method. Yield 82 %, M.P. 178 °C[16].

RESULTS AND DISCUSSION

The diverse nature of chemical universe requires various green strategic pathways in our quest towards attaining sustainability. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. One of the thrust area achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformation with minimized by products or waste as well as eliminating the use of conventional organic solvents, wherever possible. Consequently, several newer strategies have appeared such as solvent free (dry media), solid supported[17-20] and solid/solid reactions (grinding), the use of room temperature ionic liquids[21], supercritical carbon dioxide, and water[22] as reaction media that can be combined with microwave or ultrasonic irradiation. Indeed, the best solvent is 'no solvent,' but in such cases the problem of handling of materials and heat-and mass-transfer aspects need to be addressed in close cooperation with chemical engineers.

The synthesis of phthaloyl compounds was reported several existing procedures. Which involves harsh reaction conditions and yields are moderate to good. Further some of the procedure requires use of more stoichiometric amounts of reagents, longer reaction time and separation of product from catalysts.

In the present investigation, a reaction mixture consisting of phthalic anhydride, substituted anilines or various hydrazine hydrates was exposed to microwave intermittently for 30 sec. [Table – 1, 2 and 3]. The homogenous mixture quickly turned solid at room temperature and led to the isolation of pure phthaloyl compounds in good yield with shorter reaction period.

Under the similar condition, aromatic amines bearing electron withdrawing and donating groups afforded the corresponding phthaloyl compounds in high yields and purity. [Table – 1, 2 and 3]

In order to study the generality of this protocol, various hydrazines were used in place of substituted aryl amines. Further more, in case of synthesized mixed phthalimido dimer product, does not influence the outcome of the reaction significantly.

CONCLUSION

The conclusion of simple, efficient and cost effective method is described for the synthesis of phthalimido compounds. This simple, facile and environmentally benign safe procedure is advantageous in terms of experimentation, yield of product, short reaction time, and preclusion of toxic solvents. Additionally, this protocol is adaptable to parallel synthesis and generation of combinatorial library of potentially biological active phthalimido compounds.

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