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An improved microwave irradiation method for synthesis of some new N-alkyl and N-alkyloxy phthalimides

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ABSTRACT

Synthesized compounds of N-alkyl and N-alkyloxy phthalimides by Neat Reaction Technology that is if neat reactants subjected to microwave irradiation gave the required products more quickly and with better yield in comparison to the traditional methodologies.

Key words: Neat Reaction Technology, N-alkyl phthalimide, N-alkyloxy phthalimide, MW, TBAB, etc.

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-(tri chloro methyl-thio) tetra hydro phthalimide], Folpet [N-(tri chloro 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.(4) Phthalimides are important synthetic intermediates to prepare primary amines, agricultural pesticides and also used in preservatives, pigments and pharmaceuticals.(5-7) The phthaloyl group is a well-established protective group for primary amines(8) in various types of compounds, particularly peptides(9), aminoglycosides(10,11) and β-lactum antibiotics.(12)

The structural modifications of phthalimide to various N-alkyl and N-alkyloxy derivatives have been reported to result in modification of biological activity.(13,14) Due to the medicinal properties of substituted acetanilides and bioactive phthalimide moiety promoted us to undertake the synthesis of N-alkyl and N-alkyloxy compounds by microwave irradiation.

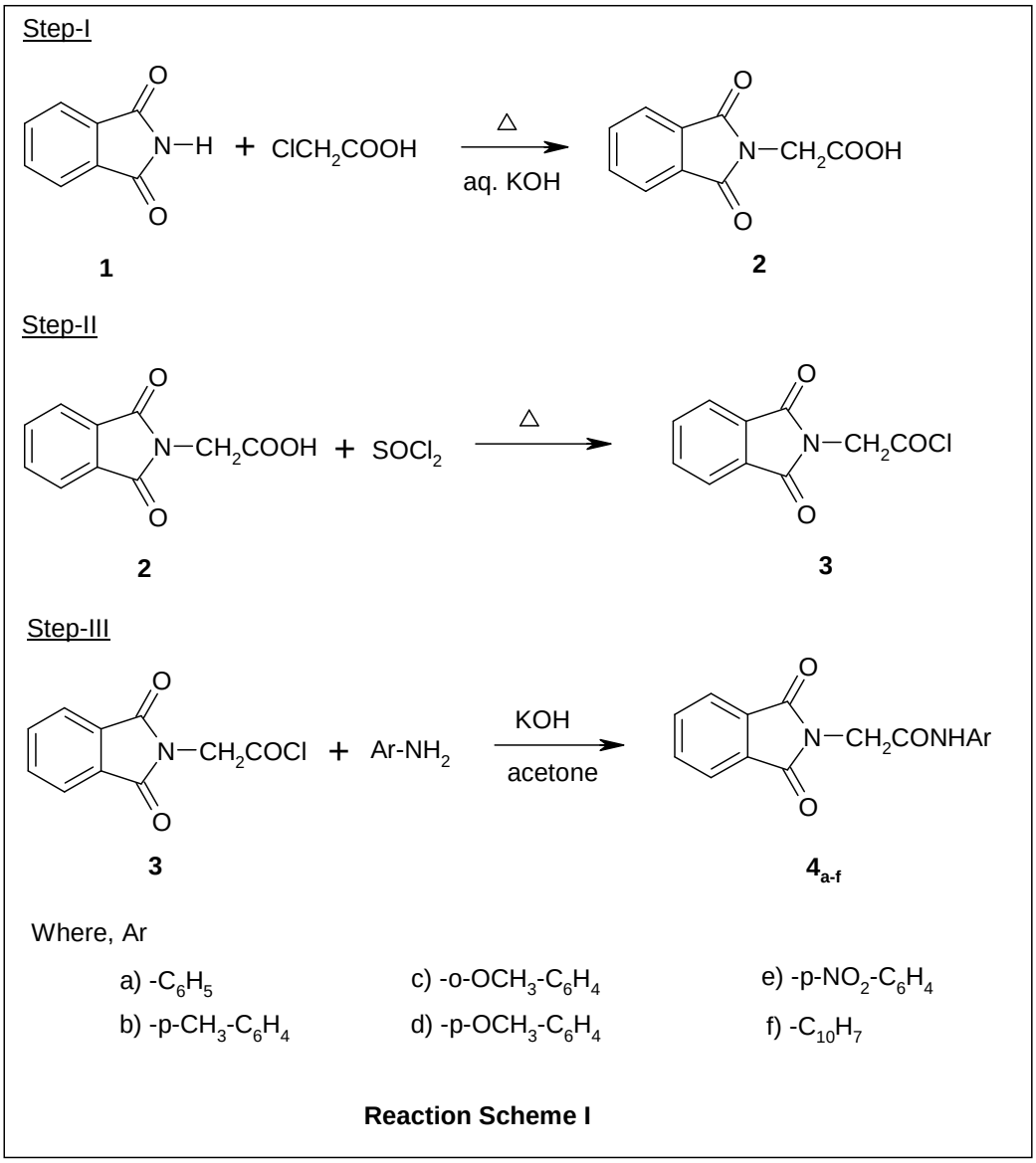
MATERIALS AND METHODS

Experimental section

Various aromatic amines (aniline, *p*-toludine, *o*-anisidine, *p*-anisidine, *p*-nitro aniline and 1-naphthyl amine), chloro acetyl chloride, phthalimide, *N*-hydroxy phthalimide, potassium carbonate, sodium acetate, potassium hydroxide, tetra butyl ammonium bromide (TBAB) and solvents were synthetic grade commercial products [s. d. fine chemicals, Qualigens, etc.] and distilled before use.

Melting points were determined using open capillary method in the paraffin liquid and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin Elmer RX1 FTIR spectrophotometer. ^1H NMR spectra were recorded on a Bruker DRX-300 MHz, FT NMR spectrometer (Chemical shift in δ, ppm) and Elemental analyses were performed on a Perkin Elmer Series II CHNS Analyzer 2400. A Samsung (Model no: 0M 9925 E) Microwave oven (2450 MHz, 800 W) was used for all experiments. The purity of compounds was checked by TLC.

Synthesis of N-Alkyl Phthalimides (By Route-I)



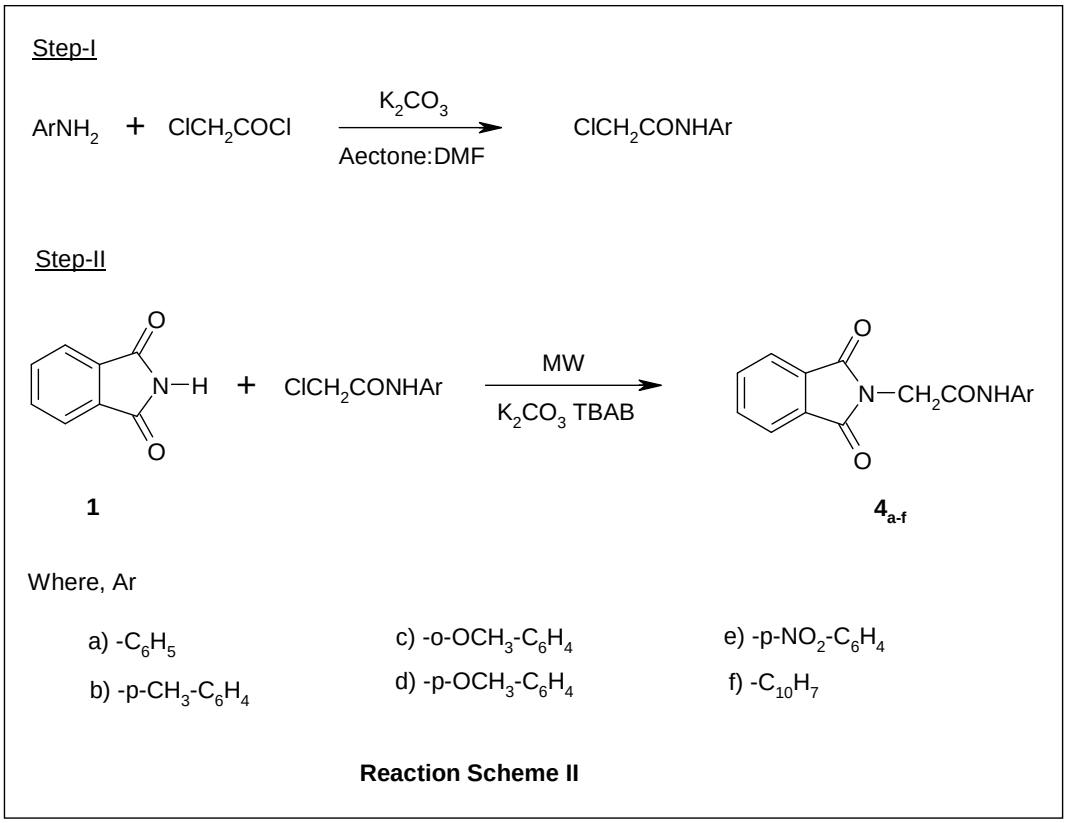
Reaction Scheme I

Procedure:

Step-I: Synthesis of N-Phthaloyl Glycine. Phthalimide **1** (10 gm, 0.068 moles) was dissolved in aqueous potassium hydroxide (3.92 gm, 0.07 moles) then add chloro acetic acid (6.67 gm, 0.07 moles). The reaction mixture heated on sand bath for 4 hrs. TLC monitored the progress of reaction in pet ether:ethanol (9:1) as a solvent. The reaction mixture was cooled to room temperature and acidified with dilute HCl. Solid thus separated was filtered, washed with water and dried. m. p. = 194 ^{0}C, Yield 80 %.

Step-II: Synthsis of N-phthaloyl glycinoyl chloride. N-phthaloyl glycinoyl chloride **3** was prepared by reacting the corresponding N-phthaloyl glycine **2** (5 gm, 0.02 mole) with excess of thionyl chloride and heating on a water bath till evolution of hydrogen chloride gas ceased. An excess of thionyl chloride was distilled off under reduced pressure using vacuum pump and the acid chloride left behind as a residue was used in a next reaction without further purification.

Synthesis of N-Alkyl Phthalimides (By Route II)



Reaction Scheme II

Step-III: Synthesis of N-Alkyl Phthalimides. In above reaction mixture solution of potassium hydroxide (3.78 gm, 0.02 mole) and substituted aryl amines (0.02 mole) in acetone, added drop wise with constant stirring for 1 to 2 hrs and the progress of reaction was monitored by TLC system, pet ether:ethanol (8:2). The reaction condition was maintained by ice-salt mixture. After complition of reaction an excess of $SOCl_2$ and solvent acetone was removed under vacuum, further mixture was taken in ether layer wash with 10 % $NaHCO_3$ followed by water twice. Then ether layer was dried over anhydrous sodium sulfate to gave the products **4$_{a-f}$**.

In the first way of synthesis, practical yield was less, more time required, difficult isolation procedure and also obtained product requires purification by column chromatography or either

by preparative TLC. Due to all these problems, we have been synthesized same compounds using MW technique.

Procedure:

Step-I: Synthesis of N-chloro acetyl aryl amines (α–chloro acetanilides). Add potassium carbonate (5.87gm 0.0425 mole) in substituted aryl amines (0.0425 mole) which was dissolved in 30 ml solvent, Acetone: DMF (9:1), then, drop wise addition of chloro acetyl chloride (4.765 gm, 0.0425 mole) with constant stirring. The reaction condition (0-5 ^{0}C) was maintain by ice-salt mixture; further reflux it for 2-3 hrs depending upon the aryl amines. Then, pour the reaction mixture into cold water to obtained crude product. Solid was filtered, dried and recrystallized in ethanol and identified by comparing their spectral data with reported values in the literature [7,8] or their melting points.

Step-II: Synthesis of N-Alkyl Phthalimides. Phthalimide **1** (2 gm, 0.013 mole) was dissolved in DMF (2 ml) containing potassium carbonate (1.794 gm, 0.013 mole) and 1 mole % tetra butyl ammonium bromide (TBAB) added as a catalyst. In this reaction mixture, substituted chloro acetanilides was introduced in an Erlenmeyer flask. This was subjected to microwave irradiation for sufficient interval of time using resting intervals of 1 min after every 30 s of irradiation at 300 power level and progress of reaction was monitored by TLC (pet ether:ethanol, 9:1), the product was poured in cold water and solid was separated out, dried it and recrystallized in ethanol to obtain a pure form of products.

Table I: Microwave synthesis of N-alkyl Phthalimides

Entry*	Ar	Molecular formula	Reaction Time (min)	m. p. (^{0}C)	Yield# (%)
4a	-C_6H_5	$C_{16}H_{12}N_2O_3$	1.5	195	89
4b	—*p*-$CH_3C_6H_4$	$C_{17}H_{14}N_2O_3$	1.0	Limpid	87
4c	—*o*-$OCH_3C_6H_4$	$C_{17}H_{14}N_2O_4$	2.0	118	85
4d	—*p*-$OCH_3C_6H_4$	$C_{17}H_{14}N_2O_4$	2.0	87	90
4e	—*p*-$NO_2C_6H_4$	$C_{16}H_{11}N_3O_5$	1.0	137	87
4f	—$C_{10}H_7$	$C_{20}H_{14}N_2O_3$	1.5	136-140	88

****** All products were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature, # Isolated yields*

Entry 4a. IR νmax (cm^{-1}): 3239 (N-H stretching), 2900 (-CH_2- stretching), 1764 (>C=O stretching of cyclic five membered ring), 1661 (C=O stretching of amides), 1357 (C-N stretching), 755-765 (mono sustituted aromatic). ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 7.94 (1H, s, N-H), δ 7.32 to 7.70 (9H, m, Ar-H), δ 4.40 (2H, s, -CH_2-). Elemental analysis: C, 68.56%, H, 4.32%, N, 9.99%; calcd for $C_{16}H_{12}N_2O_3$: C, 68.21%, H, 4.29%, N, 9.71%.

Entry 4b. IR νmax (cm^{-1}): 3201 (N-H stretching), 2927 (-CH_2- stretching), 1765 (>C=O stretching of cyclic five membered ring), 1654 (C=O stretching of amides), 1350 (C-N stretching), 864 (p-disustituted aromatic). ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.10 (1H, s, N-H), δ 7.40 to 7.60 (8H, m, Ar-H), δ 4.50 (2H, s, -CH_2-), δ 2.30 (3H, s, -CH_3-). Elemental analysis: C, 69.38%, H, 4.79%, N, 9.52%; calcd for $C_{17}H_{14}$ N_2O_3: C, 69.34%, H, 4.64%, N, 9.49%.

Entry 4c. IR νmax (cm^{-1}): 3235 (N-H stretching), 2907 (-CH_2- stretching), 1768 (>C=O stretching of cyclic five membered ring), 1670 (C=O stretching of amides), 1343 (C-N stretching), 1240 (C-O-C asymmetric streching), 1170 (C-O-C symmetric streching). ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.40 (1H, s, N-H), δ 7.26 to 7.73 (8H, m, Ar-H), δ 4.57 (2H,

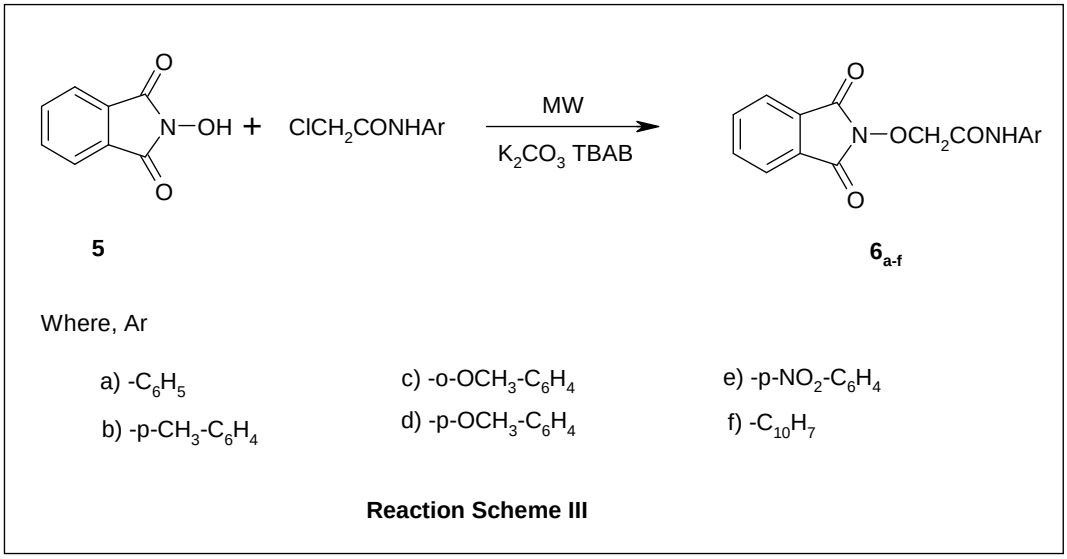
s, -CH_2-), δ 3.99 (3H, s, -OCH_3-). Elemental analysis: C, 65.80%, H, 4.55%, N, 9.03%; calcd for $C_{17}H_{14}N_2O_4$: C, 65.64%, H, 4.38%, N, 8.94%.

Entry 4d. IR νmax (cm^{-1}): 3232 (N-H stretching), 2936 (-CH_2- stretching), 1768 (C=O stretching of amides), 1344 (C-N stretching), 1254 (C-O-C streching). ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.0 (1H, s, N-H), δ 7.39 to 7.91 (8H, m, Ar-H), δ 4.4 (2H, s, -CH_2-), δ 3.75 (3H, s, -O-CH_3). Elemental analysis: C, 65.80%, H, 4.55%, N, 9.03%; calcd for $C_{17}H_{14}N_2O_4$: C, 65.56%, H, 4.49%, N, 8.72%.

Entry 4e. IR νmax (cm^{-1}): 3271 (N-H stretching), 2923 (-CH_2- stretching), 1673 (C=O stretching of amides), 1463, 1450 (due to conjugated –NO_2). ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 7.9 (1H, s, N-H), δ 7.69 to 8.17 (8 H, m, Ar-H) δ 4.57 (2H, s, -CH_2-). Elemental analysis: C, 59.08%, H, 3.41%, N, 12.92%; calcd for $C_{16}H_{11}N_3O_5$: C, 58.84%, H, 3.39%, N, 12.77%.

Entry 4f. IR νmax (cm^{-1}): 3268 (N-H stretching), 2921 (-CH_2- stretching), 1760 (>C=O stretching of cyclic five membered ring), 1678 (C=O stretching of amides), 1364 (C-N stretching). ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 7.90 (1H, s, N-H), δ 7.10 to 7.77 (11H, m, Ar-H), δ 4.34 (2H, s, -CH_2-). Elemental analysis: C, 72.72%, H, 4.27%, N, 8.48%; calcd for $C_{20}H_{14}N_2O_3$: C, 72.68%, H, 4.02%, N, 8.34%.

Synthesis of N-Alkyloxy Phthalimides (By Route II)



Reaction Scheme III

Procedure:

N-hydroxy phthalimide **5** (2 gm, 0.012 moles) dissolved in DMSO (4 ml). Add potassium carbonate (1.6 gm, 0.01 moles), in which substituted chloro acetanilides (0.01 moles) was added and then subjected to MW irradiation of 30 s each with cooling and mixing intervals of 30 s at 300 power level. The progress of reaction was monitored by TLC (pet ether:chloroform, 8:2). The product was poured in cold water and solid filtered, washed with water and dried and upon recrystallization from ethanol afforded the pure products. [Table II]

Entry 6a. ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.12 (1H, s, N-H), δ 7.18 to 7.74 (9H, m, Ar-H), δ 4.33 (2H, s, -CH_2-). Elemental analysis: C, 64.86%, H, 4.08%, N, 9.46%; calcd for $C_{16}H_{12}N_2O_4$: C, 64.59%, H, 3.84%, N, 9.26%.

Entry 6b. ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 7.90 (1H, s, N-H), δ 7.10 to 7.50 (8H, m, Ar-H), δ 4.76 (2H, s, -CH_2-), δ 2.25 (3H, s, -CH_3). Elemental analysis: C, 65.80%, H, 4.55%, N, 9.03%; calcd for $C_{17}H_{14}N_2O_4$: C, 65.67%, H, 4.41%, N, 8.83%.

Table II: Synthesis of N-alkyloxy phthalimides

Entry*	Ar	Molecular formula	Reaction Time (min)	m. p. (^{0}C)	Yield# (%)
6a	-C_6H_5	$C_{16}H_{12}N_2O_4$	0.50	84	91
6b	—*p*-$CH_3C_6H_4$	$C_{17}H_{14}N_2O_4$	4.20	128	87
6c	—*o*-$OCH_3C_6H_4$	$C_{17}H_{14}N_2O_5$	3.00	88-90	88
6d	—*p*-$OCH_3C_6H_4$	$C_{17}H_{14}N_2O_5$	4.20	125-130	89
6e	—*p*-$NO_2C_6H_4$	$C_{16}H_{11}N_3O_6$	1.00	147-150	90
6f	—$C_{10}H_7$	$C_{20}H_{14}N_2O_4$	0.40	Semi solid	93

****** All products were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature, # Isolated yields*

Entry 6c. ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.20 (1H, s, N-H), δ 6.90 to 7.30 (8H, m, Ar-H), δ 4.41 (2H, s, -CH_2-), δ 3.90 (3H, s, -OCH_3). Elemental analysis: C, 62.57%, H, 4.32%, N, 8.59%; calcd for $C_{17}H_{14}N_2O_5$: C, 62.46%, H, 4.25%, N, 8.44%.

Entry 6d. ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.01 (1H, s, N-H), δ 7.10 to 7.68 (8H, m, Ar-H), δ 4.47 (2H, s, -CH_2-), δ 3.74 (3H, s, -OCH_3). Elemental analysis: C, 62.57%, H, 4.32%, N, 8.59%; calcd for $C_{17}H_{14}N_2O_5$: C, 62.52%, H, 4.28%, N, 8.51%.

Entry 6e. ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 8.0 (1H, s, N-H), δ 7.9 to 8.1 (8H, m, Ar-H), δ 4.8 (2H, s, -CH_2-). Elemental analysis: C, 56.31%, H, 3.25%, N, 12.31%; calcd for $C_{16}H_{11}N_3O_6$: C, 56.25%, H, 3.23%, N, 12.22%.

Entry 6f. ^{1}H NMR spectral data ($CDCl_3$, 300 MHz): δ 7.88 (1H, s, N-H), δ 7.12 to 7.62 (11H, m, Ar-H), δ 4.34 (2H, s, -CH_2-). Elemental analysis: C, 69.36%, H, 4.07%, N, 8.09%; calcd for $C_{20}H_{14}N_2O_4$: C, 69.31%, H, 3.93%, N, 7.96%.

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(15-18) and solid/solid reactions (grinding), the use of room temperature ionic liquids(19), supercritical carbon dioxide, and water(20) 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.

The acceleration of synthesis processes by microwave irradiation to shorten the reaction time and elimination or minimization of side product formation is already finding acceptance in pharmaceutical industry (combinatorial chemistry) and polymer synthesis may pave the way towards the greener and more sustainable approach to chemical synthesis.

In the present investigation, a reaction mixture consisting of phthalimide or N-hydroxy phthalimide, various substituted N-chloro acetyl aryl amines dissolves in very small amount of DMF as a solvent was exposed to microwave intermittently for 30 sec. [Table – I and II]. 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.

Synthesized compounds of N-alkyl and N-alkyloxy phthalimides by Route-II that is if neat reactants subjected to microwave irradiation gave the required products more quickly and with better yield in comparison to the traditional methodologies such as Route I.

Thus, Neat Reaction Technology is a step forward in the direction of solvent free reactions and an alternative approach that eliminates the use of a solid support as well as solvent from the reaction. Solid supported reactions do not entirely meet the definition of no solvent as the usage as a solvent is only eliminated at the primary reaction stage, whereas an appreciable amount of solvent is still required for the adsorption of reactants and elution of products at the pre and post reaction stages respectively.

Under the similar condition, aromatic amines bearing electron withdrawing and donating groups afforded the corresponding phthaloyl compounds in high yields and purity. [Table – I and II]
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 and such a structural modification from parent aniline to N-chloro acetyl aryl amines and then coupling with phthalimides $\mathbf{4_{a-f}}$ and N-hydroxy phthalimide $\mathbf{6_{a-f}}$ will be beneficial in the field of pest management for designing the active molecules.

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