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Ultrasound Irradiated High-Speed Classical Synthesis and Biological Studies of Various N-Substituted Phthaloyl Derivatives

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Abstract
Ultrasound irradiation high-speed and classical synthesis of various N-substituted phthaloyl derivatives as potent bactericidal agents are described. All compound show antibacterial activities when compared with standard drugs.A series of various N-substituted phthaloyl derivatives have been synthesized in a very good yield under irradiation conditions (ultrasound irradiation high-speed) and conventional heat. All compound show antibacterial activities when compared with standard drugs. All compounds have been characterized by IR, ^{1}H NMR and ^{13}C NMR.
Keywords: phthalymide, phthalimido dimer, phthalic anhydride, ultrasound irradiation, high-speed synthesis.

INTRODUCTION

Cyclic amides and their derivatives have been found to be an important moiety in creation of novel medical [(1)], polymeric [(2)], photonic [(3)], and electronic materials [(4, 5)]. Often, these cyclic imides are oxidative stable [(6)] heat retardant, solvent resistant [(7)], and have superior mechanic properties [(8)]. The specific reactivity of imides is a result of the relative acidity of the N group, a direct consequence of the presence of the two carbonyl groups [(9)].

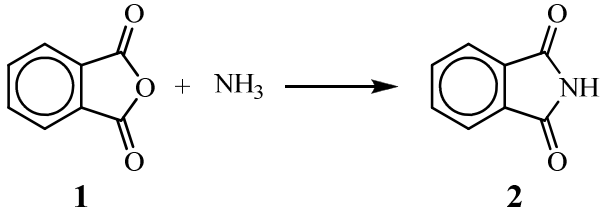
Among heterocyclic scaffolds, phthalimides are white solid aromatic imide in which two carbonyl groups bound to an amine functional moiety. It is a very important starting synthone for organic synthetic chemists for preparing diverse biologically active molecules. It alkali metal salt is generally used for Gabriel synthesis of amine [(10)]. Number of phthalimide derivatives are of particular biological interest and have been reported as herbicides, insecticides, antipsychotics and anti-inflammatory agents [(11)]. Phthalimide derivatives with phenyl acetic acid and phenyl propionic acid were found to possess anti-inflammatory and analgesic properties [(12)]. Substituted phthalimides are used predominantly as chiral building blocks in organic synthesis and can be used as key intermediates in the preparation of bio-active compounds i.e. antibacterial analgesic, antifungal, virucidal, plant growth regulator and also in dye industry [(13)]. Phthalimide an intermediate in the production of agricultural pesticides is produced almost exclusively from phthalic anhydride and ammonia, nowever, processes based on phthalic anhydride and urea or oxidative ammonolysis of *o*-oxylene are also known [( )].

In the present communication, 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

Chemicals were purchased from sigma Aldrich co. and used as received. Melting points were determined in open capillaries on Thomas Hoover apparatus. The IR spectra were recorded on SHIMADZU 8400 Fourier Transform infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ / DMSO-d_6 on a Bruker ultra shield 300 MHz spectrometer using TMS as internal reference. Incubator D-63450 (Germany) model was used for incubation samples in biological study.

Scheme 1 synthesis 4-(4-aryl)-1-(phthaloyl)buta-3en-2-one.



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Scheme 1: synthesis of phthalimide

Reaction scheme 1

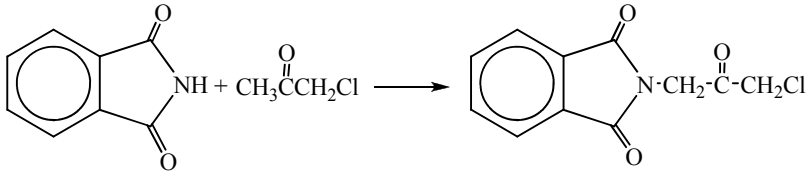
a) Conventional method

A solution of phthalic anhydride 1 (1 g, 0.00675 mole) and ammonia (1.5 ml, d 0.88) was heated directly on wire guaze 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 C_6H_6 : EtOH, 9 : 1). The crude product obtained was then recrystallized by solvent ethanol to give product 2. The yield obtained was 83 %

and m.p (233-234) ℃.

b) Ultrasound method

A solution of phthalic anhydride 1 (1 g, 0.00675 mole) and ammonia (1.5 ml, d 0.88) was placed in round bottom flask and subjected to ultrasound irradiation for 7 min. progress of reaction was monitored by TLC. After completion of reaction, the content was dumped in crushed ice and filtered. The product was recrystallized from ethanol to yield 2. yield 87 % and m.p (233-234) ℃.



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Scheme 2: synthesis of N-phthaloyl acetone

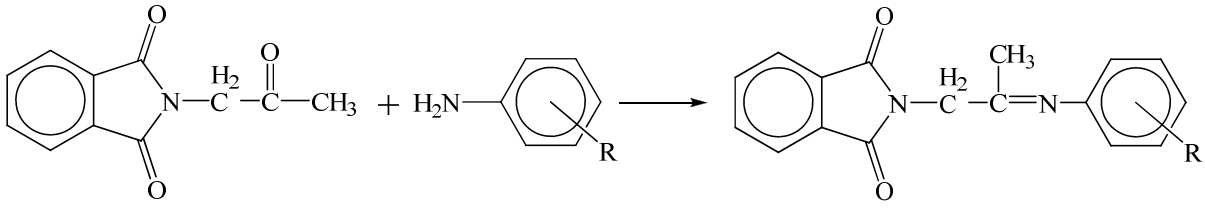
a) Conventional method (A)

Phthalimide 2 (10 g, 0.0068 mole) was dissolved in aqueous potassium hydroxide solution (3.92 g, 0.07 mole) and then in the above solution, chloroacetone was added (0.07 mole) drop wise at 0 ℃. The reaction mixture was refluxed on 2 hours. The progress of reaction was monitored by TLC (solvent system Ether : Methanol, 9 : 1). The reaction mixture was poured onto crushed ice. The solid obtained was filtered off, washed with water and recrystallized from ethanol to give compound 3, yield 58 %, m.p 225 ℃.

b) Ultrasound method (B)

The same amounts of reagents in round bottom flask and subjected to ultrasound irradiation for (7-8) min. The progress of reaction was monitored by TLC. The reaction mixture was poured onto crushed ice. The solid obtained was filtered off, washed with water and recrystallized from ethanol to yield 3, yield 68 %, m.p 225 ℃.

IR (cm^{-1}): 1783 (C=O), 2993 (CH in CH_3), 3151 (CH in CH_2), ^{1}H NMR (δ, ppm): 2.5 (s, 3H, CH_3), 4.7 (s, 2H, CH_2), 8.2-7.9 (m, 4H, ArH). ^{13}C NMR (ppm) 27 (CH_3), 47.2 (CH_2), 126-137 (aromatic carbon), 169.1 (2C=O imide), 199.8 (C=O acetone).



Where R:(4) H
(5) *p*-NO_2
(6) *p*-OCH_3
(7) *p*-OH

Scheme 3: Synthesis of Schiff bases (4-7)

Reaction step 3

a) Conventional method (A)

Compound 3 (0.01 mole),different types of arylamines (0.002 mole), sodium acetate (0.04 mole) in absolute alcohol (10 ml) were placed in round bottom flask and refluxed on water bath for 3 hours. The reaction was monitored by TLC and after completion of the reaction the content was poured onto crushed ice. The solid obtained was filtered off, washed with water and recrystallized from ethanol to give compounds (4-7).

b) Ultrasound method (B)

The same amounts of reagents in round bottom flask and subjected to ultrasound irradiation for (7-5) min. progress of reaction was monitored by TLC. After completion of reaction, the content was dumped in crushed ice and filtered. The product was recrystallized from ethanol to yield (3a-d). the spectral and analytical data were found to be similar as reported for conventional method.

Characterization data of the following compounds are listed below in table 1.

Table 1. synthesized Schiff bases (3a-d)

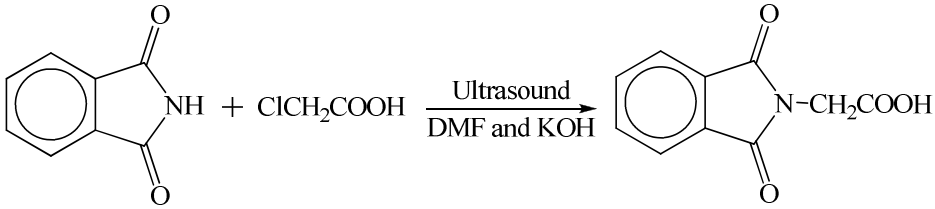
Compound No.	R	Reaction time		m.p. (℃)
		Conventional Hours	Ultrasound Min.	
4	-H	2.45	5.50	282
5	p-NO_2 *p*-OCH_3		5.00	274
6	*p*-OH	2.45	6.30	287
7		2.30	7.00	276

(4) IR (cm^{-1}): 1725 (imide C=O), 1655 (C=N). ^{1}H NMR, DMSO-d_6 (δ, ppm): 0.9 (s, 3H, CH_3), 1.31 (s, 2H, CH_2), 7.05-7.35 (m, 9H, ArH).

(5) IR (cm^{-1}): 1730 (imide C=O), 1650 (C=N), 1592-1310 (NO_2). ^{1}H NMR, DMSO-d_6 (δ, ppm): 0.94 (s, 3H, CH_3), 1.36 (s, 2H, CH_2), 7.1-7.56 (m, 8H, ArH).

(6) IR (cm^{-1}): 1737 (imide C=O), 1625 (C=N), 3091 (CH (CH_3)). ^{1}H NMR, DMSO-d_6 (δ, ppm): 0.92 (s, 3H, CH_3), 1.32 (s, 2H, CH_2), 3.9 (s, 3H, OCH_3), 7.3-7.65 (m, 8H, ArH).

(7) IR (cm^{-1}): 1735 (imide C=O), 1605 (C=N), 3253 (OH). ^{1}H NMR, DMSO-d_6 (δ, ppm): 0.98 (s, 3H, CH_3), 1.39 (s, 2H, CH_2), 7.72-8.00 (m, 8H, ArH), 13.2 (s, 1H, OH).



(8)

Scheme 4: synthesis of N-phthaloyl Glycine 4

Reaction of step 4

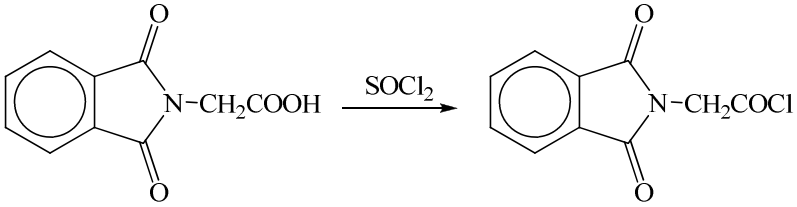
a) Conventional method (A)

Phthalimide 2 (0.0068 mole) was dissolved in aqueous potassium hydroxide solution (0.07 mole) and then in the above solution, chloroacetone was added (0.07 mole). The reaction mixture was refluxed on sand bath 3-4 hours. The progress of reaction was monitored by TLC (Ether : Methanol, 9 : 1). The reaction mixture was cooled to room temperature and acidified by dilute HCl. solid thus separate was filtered, washed with water and dried and then recrystallized by solvent ethanol to obtained product 4, yield 80 %, m.p 194 ℃.

b) Ultrasound method (B)

The same amounts of reagents in round bottom flask and subjected to ultrasound irradiation for 4 min. upon completion of the reaction (monitored by TLC). The mixture was cooled to room temperature and acidified by dilute HCl. solid thus separate was filtered, washed with water and dried and then recrystallized by solvent ethanol to obtained product 4, yield 89 %, m.p 194 ℃.

4: IR (cm^{-1}): 1744 (C=O amide), 1710 (acid C=O), 3320 (OH), ^{1}H NMR DMSO-d_6 (δ, ppm): 4.48 (s, 2H, CH_2), 8.5-8.3 (m, 4H, ArH), 13.2 (s, 1H, OH).

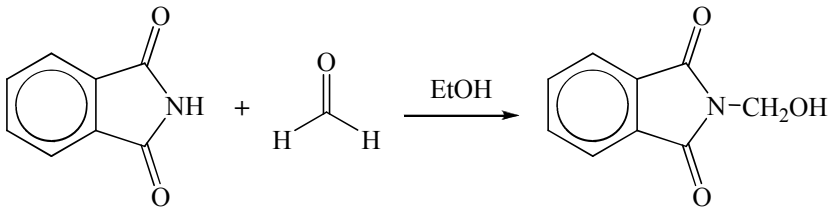


(8) (9)

Scheme 5: synthesis of N-phthalimide acetyl chloride 9

Conventional method

A mixture of N-phthaloyl glycine (5 g, 0.02 mole) and $SOCl_2$ (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, Ethanol : Methanol, 9 : 1). The crude chloride product obtain was then distilled out under vacuum at 50-55 ℃ which gives colourless product 9, yield 92 %.



(10)

Scheme 6: synthesis of N-methylhydroxylphthalimide 10

Reaction step 6

a) Conventional method (A)

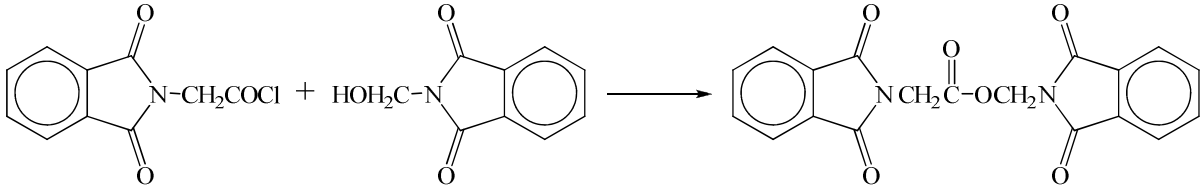
A solution of formaldehyde (0.06 mole) and phthalimide (2.5 g, 0.017 mole) in ethanol (5 ml) was refluxed on water bath for 1.5 hour, then allowed to stand at room temperature for 24 hours. The completion of reaction was monitored by TLC (solvent system Ether : Methanol, 9 : 1). The content was cooled to give solid product, which was recrystallized from water, yield 72 %, m.p 230 ℃.

b) Ultrasound method (B)

The same amounts of reagents were subjected to ultrasound irradiation for 45 min. The reaction was monitored by TLC and after completion of the reaction in a similar manner as described above. yield 86 %, m.p 230 ℃.

5: IR (cm^{-1}): 1750 (C=O amide), 3293 (OH), ^{1}H NMR DMSO-d_6 (δ, ppm): 5.1 (s, 2H, CH_2), 8.2-7.4 (m, 4H, ArH), 6.6 (, 1H, OH).

^{13}C NMR (ppm): 63 (CH_2), 128-139 (C_b-C_a), 161 (C=O amid).



(11)

Scheme 7: synthesis of methyl N,N'-bisphthalolyl acetate 11

Reaction step 7

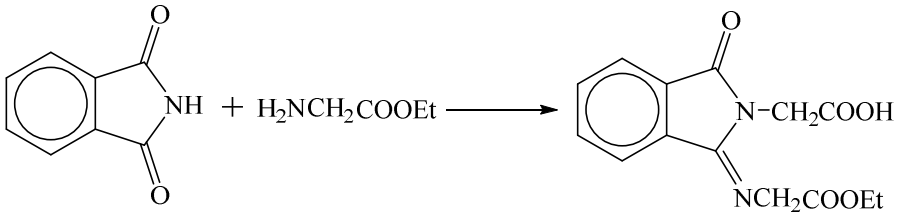
a) Conventional method (A)

A mixture of N-phthalimido methanol (0.039 mole), sodium acetate (0.473 g, 1 mole) in 15 ml DMSO added to N-phthalimido acetyl chloride (1 g, 0.0039 mole) and then it was refluxed on water bath for 4 hours. The progress and completion of reaction was monitored by TLC (solvent system, Ether : Methanol, 9 : 1). The reaction mixture was brought to room temperature and then poured into water (200 ml) and extracted with ethyl acetate (2*20 ml). The organic layer was washed two times with 50 ml water and dried over anhydrous Na_2SO_4. After evaporation of ethyl acetate the solid obtained was recrystallized in ethanol to give pure product, yield 58 %, m.p 178 ℃.

b) Ultrasound method (B)

The same amounts of reagents in round bottom flask and subjected to ultrasound irradiation for 7 min. the product was isolated in a similar manner as described above. yield 82 %, m.p 178 ℃.

IR (cm^{-1}): 1741 (C=O amide), 1705 (C=O), 2952 (CH in CH_2), 2876 (CH aromatic). ^{1}H NMR DMSO-d_6 (δ, ppm): 4.2 (s, 4H, $2CH_2$), 7.9-8.3 (m, 8H, ArH).



(12)

Scheme 8. Synthesis N-[3-isoindolinyliden-(1)]-glycine ethyl ester 12

Reaction step 8

a) Conventional method (A)

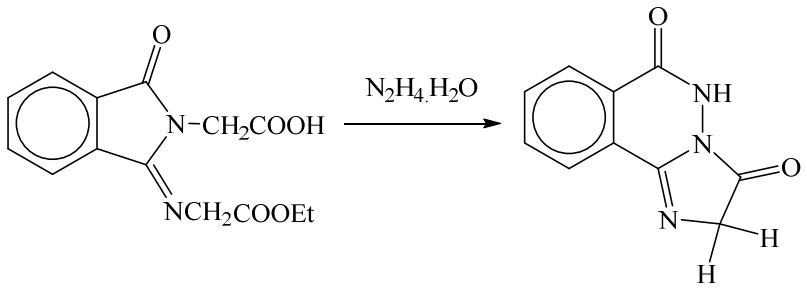
phthalimide (0.01 mole), ethyl glycine ester (0.01 mole) dissolved in methanol (20 ml) and then reaction

mixture was refluxed for 3 hours. After completion of reaction, solid crystal was obtained. The synthesized compound was analyzed by TLC with using solvent system (Ethanol : water, 7 : 3). Then the solid crystal was recrystallized from ethanol, yield 62 %, m.p 218 ℃.

b) Ultrasound method (B)

The same amounts of reagents were subjected to ultrasound irradiation for 5 min. the product was isolated in a similar manner as described above. yield 80 %, m.p 218 ℃.

IR (cm^{-1}): 1765 (C=O amide), 1685 (C=N), 3320 (NH). ^{1}H NMR DMSO-d_6 (δ, ppm): 2.05 (s, 5H, C_2H_5), 3.43 (s, 2H, CH_2), 7.76 (s, 1H, NH), 7.9-8.6 (m, 4H, ArH).



(13)

Scheme 9. Synthesis of 3,6-dioxo-2,3,5-tetrahydroimidazo[2,1-a]phthalazines

Reaction step 9

c) Conventional method (A)

A solution of 52 % hydrazine hydrate in ethanol (48 ml). The whole reaction mixture was refluxed on water bath for about 8-10 hours. The progress and completion of reaction was monitored by TLC (solvent system, Ether : Methanol, 8 : 2) in each 0.5 hour interval. The crude product was isolated by pouring the reaction mixture in cold water, then filtered and dried. The crude product obtained was then recrystallized by ethanol to give compound 9, yield 56 %, m.p 198 ℃.

d) Ultrasound method (B)

The same amounts of reagents were subjected to ultrasound irradiation for 50 min. the product was isolated and recrystallized in a similar manner as described above to give compound 9. yield 77 %, m.p 198 ℃.

IR (cm^{-1}): 1715 (C=O), 1635 (C=N), 3298 (OH). ^{1}H NMR DMSO-d_6 (δ, ppm): 5.2 (s, 2H, CH_2), 6.7 (s, 1H, OH), 7.9-8.2 (m, 4H, ArH).

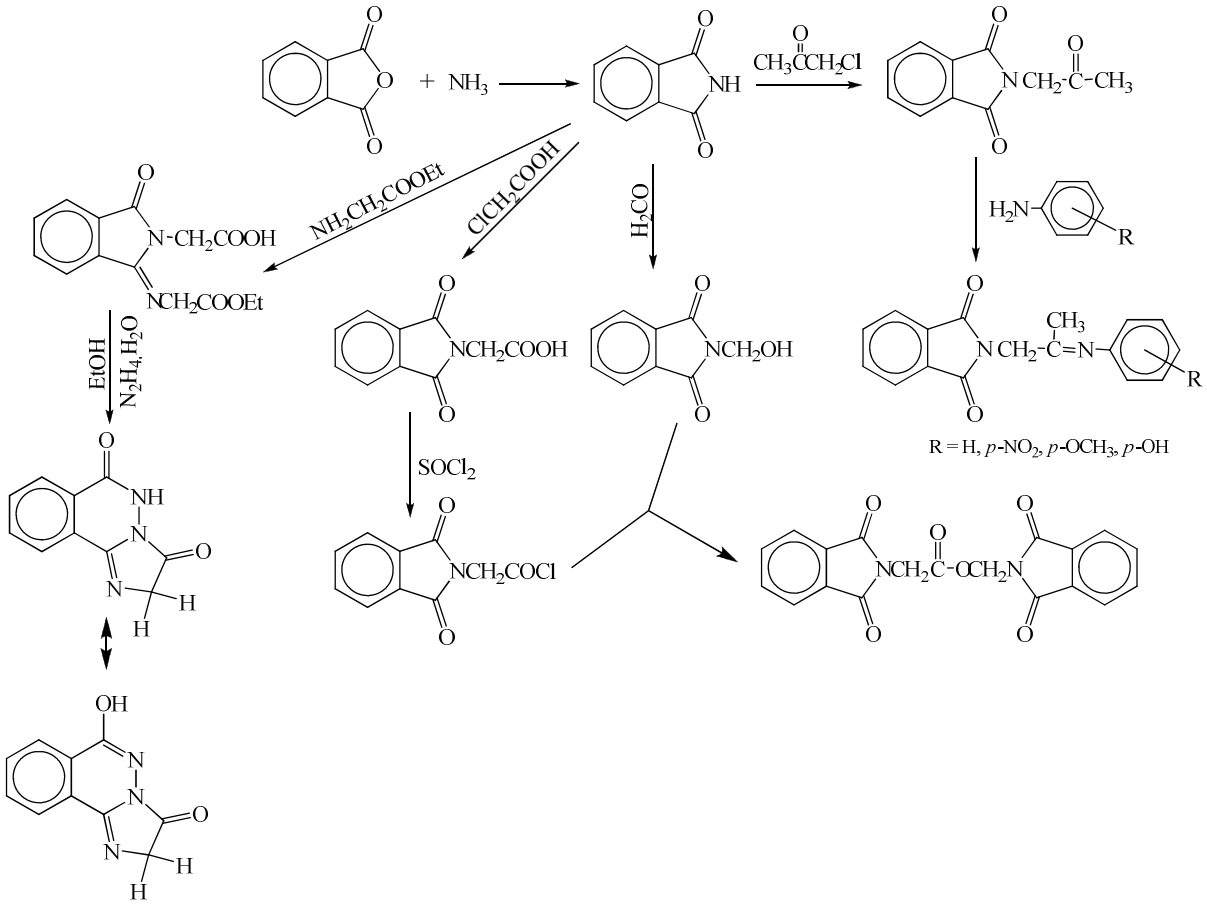
THE BIOLOGICAL ACTIVITY

The bacteria species used are listed in table (2) . All strains, were obtained from college of Medicine, Tikrit University . They were grown up to the stationary phase nutrient bath at 37C° and a sample of 0.5ml of each bacteria was spread of each bacteria was spread over a surface of a nutrient ager plate [14] .

RESULTS AND DISCUSSION

The derivative nature of chemical universe requires various green strategic path ways 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, ionic liquids at room temperature, and water as reaction media that can be combined with microwave or ultrasound irradiation.

The synthesis of phthaloyl compounds has been carried out by both classical and ultrasound methods. In classical method reaction is carried out in different solvents and it takes many hours, while under ultrasound irradiation it takes only 3-50 min. In classical method the yield is lower as compared to ultrasound irradiation. Ultrasound irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur. All these synthesized compounds as depicted in scheme (10).



Scheme (10)

ANTIMICROBIAL ASSAY

Disc of filter paper (6mm diameter) were sterilized at 140C° for 1 hr and impregnated with the germs, absolute ethanol was used as a solvent for compounds (1-14) . The same solvent was used of antibiotics, blank paper discs of absolute ethanol was used as control .The incluted plates were incubated at 37C° for 24 hr, and the inhibition zones (mm) were measured [15] , In all experiments the mean of each triplicate was measured

ANTIMICROBIAL ACTIVITY:

The antimicrobial activity was tested using the cup-plate agar different method by measuring the zone of inhibition in mm[15] . All the compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains, such as Escherichia coil, staphylococcus aureus, salmonella typhi and Pseudomonas aeruginosa. The diameter zone of inhibition was measured in mm and are represented by (+), (++) and (±) depending upon the dia meter. The antimicrobial screening data are recorded in table (2) Looking at the structure activity relation ship, compound (5) exhibit significant activity against staphylococcus aureus, compound (13) showed good activity against staphylococcus aureus, and salmonella typhi. The preliminary screening results reveral that the compounds containing (NO_2) exhibit the highest antimicrobial activity while the other compounds showed either low or no activity .

Table (2): Biological activity for compounds (3-14)

Compounds No.	Staph.aureus	E.coil	Sat.typhi	Ps.aeruginous
3	+	+	±	-
4	±	±	±	+
5	+	-	-	-
6	++	+	±	±
7	±	+	-	±
8	+	+	±	±
11	+	+	±	±
12	-	+	-	-
13	++	+	±	±

CONCLUSION

In conclusion, the ultrasound irradiation for synthesis of the title compounds offers reduction in the reaction time, operation simplicity, cleaner reaction, preclusion of toxic solvents, easy work up and improved yields. The procedure clearly highlights the advantages of ultrasound. Additionally, this protocol is adaptable to parallel synthesis and generation of combinatorial library of potentially biological active phthalimido compounds.

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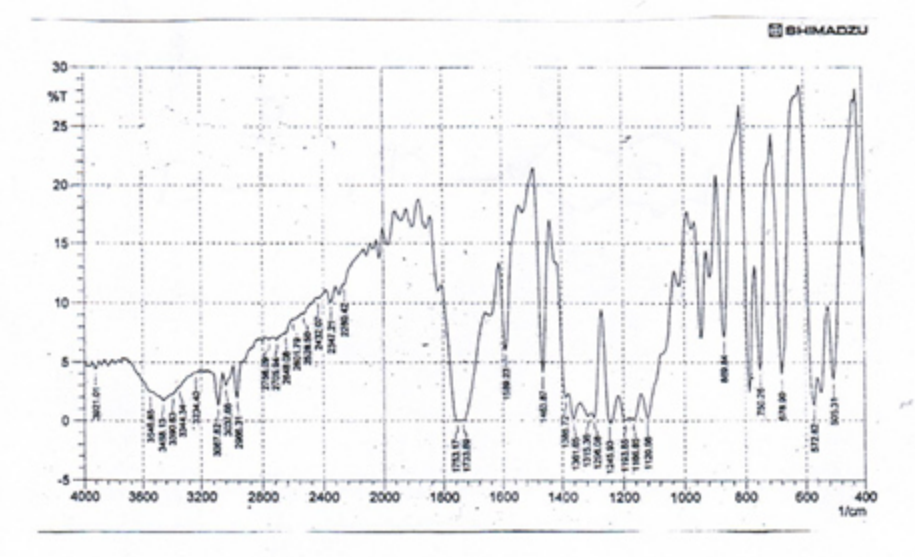
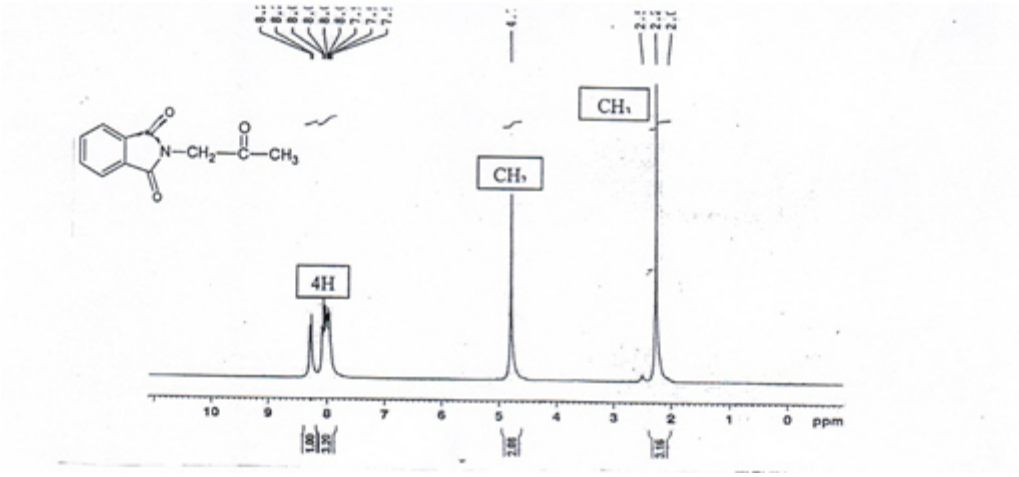
FIGURES



Fig(1) IR of compound (3)



Fig(2) H-NMR of compound (3)

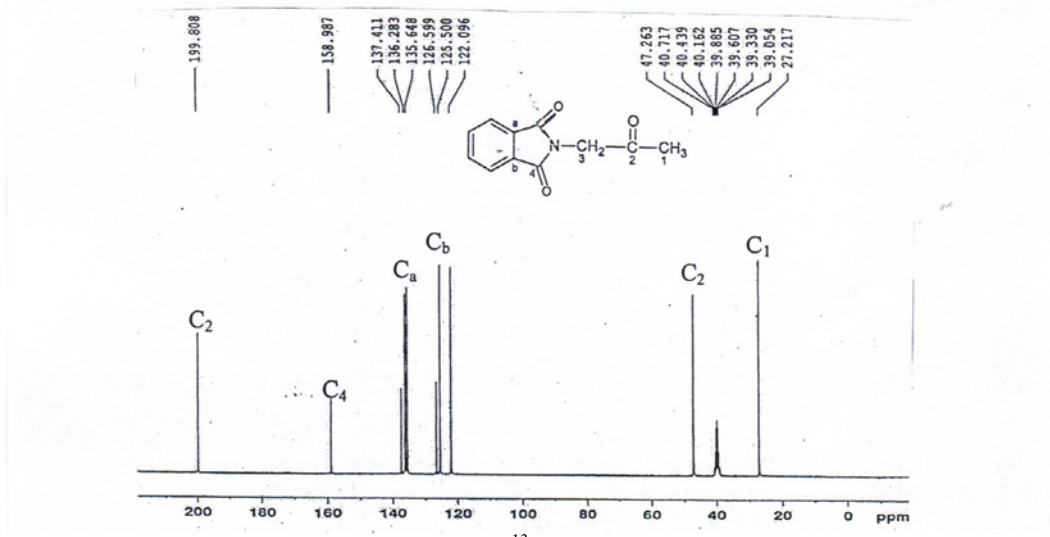
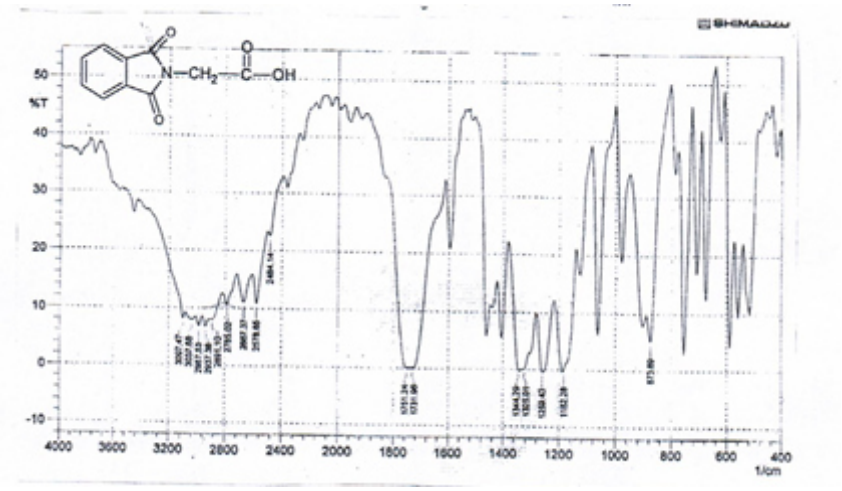
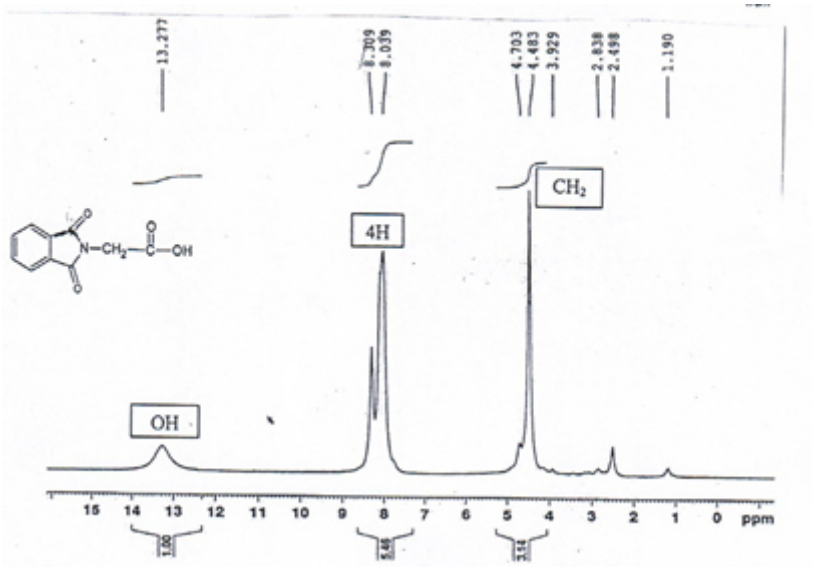


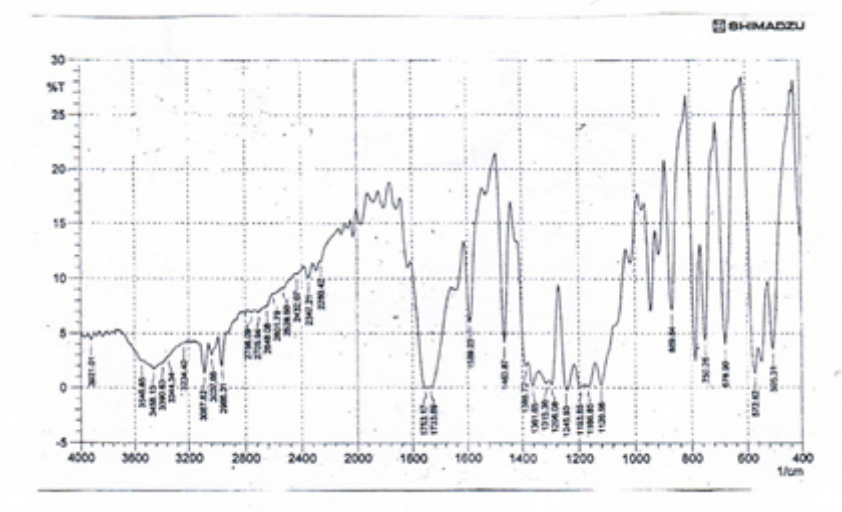
Fig (3) C^{13}NMR of compound (3)



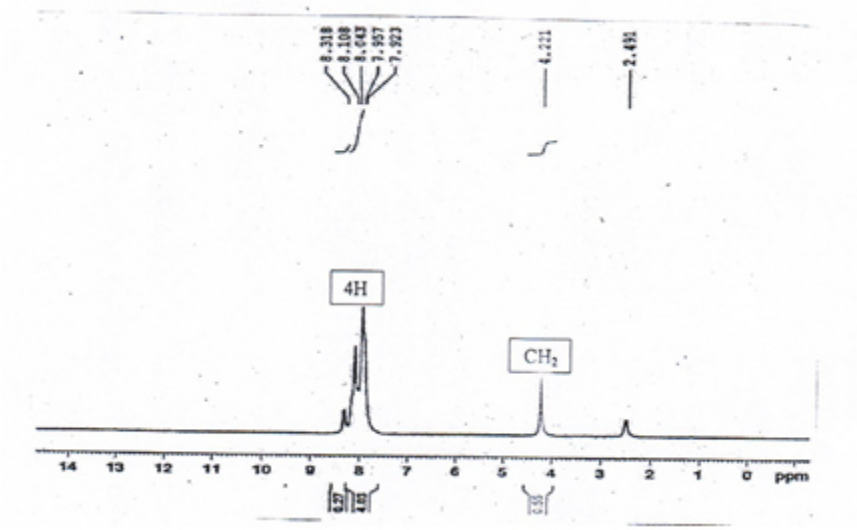
Fig(4) IR of compound (8)



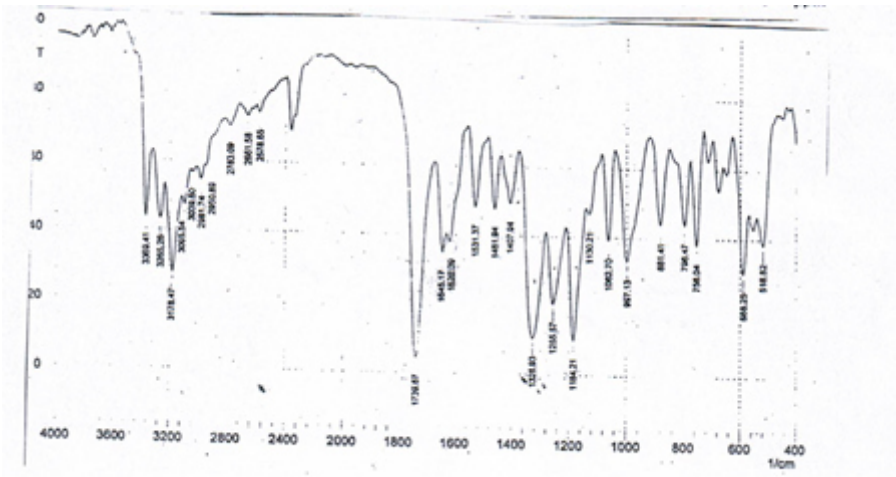
Fig(5) H-NMR of compound (8)



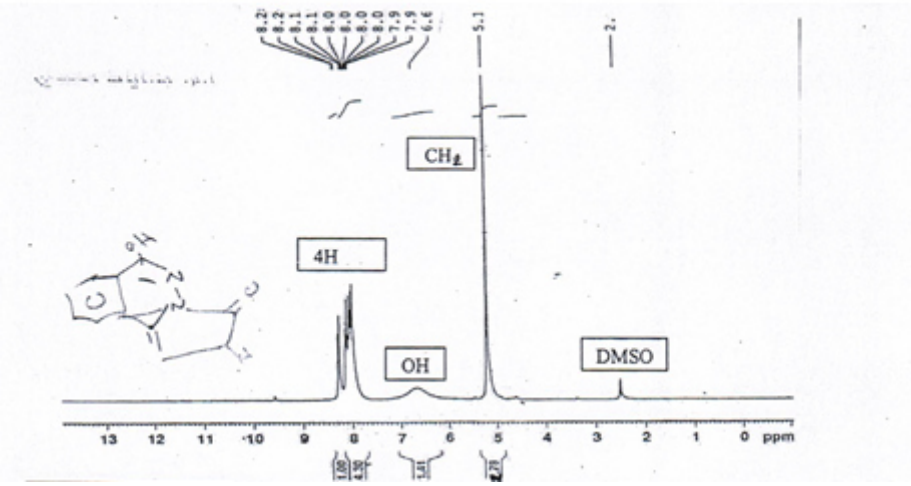
Fig(6) IR of compound (9)



Fig(7) H-NMR of compound (9)



Fig(8) IR of compound (13)



Fig(9) H-NMR of compound (13)

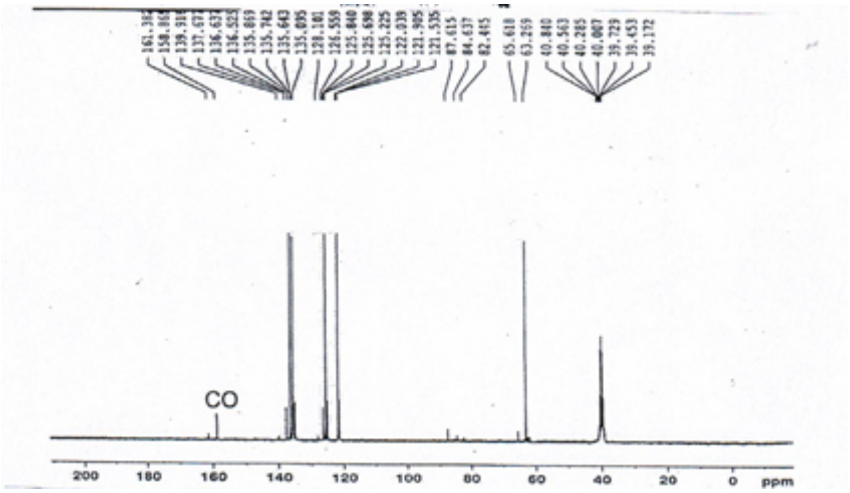


Fig (10) C^{13}NMR of compound (13)

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