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Methods of Synthesis Phthalimide Derivatives and Biological Activity-Review

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Abstract

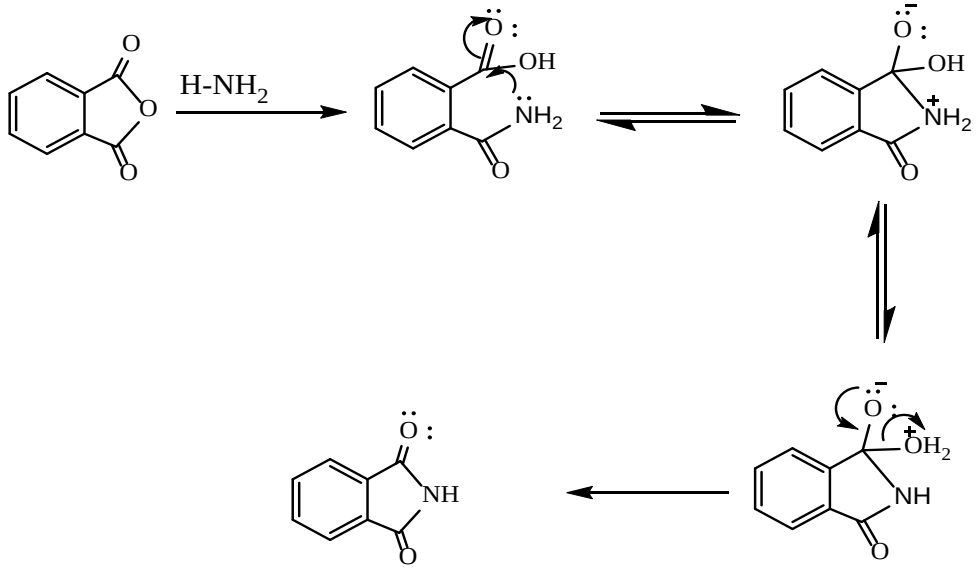
Phthalimide formation of Phthalic anhydride with various amines using microwave or without a method with the difference of the catalyst used in a prepared Phthalimide, either structure general are $C_6H_4CONRCO$ and used as starting materials in synthesis several compounds derivative phthalimides are an important compounds because spectrum wide biological activities including Antimicrobial activity, anticonvulsant activity, Anti-inflammatory activity,Analgesic activity, Anti-influenza activity and Thromboxane inhibitory activity.

Keywords: Phthalimide derivatives, biological activity

INTRODUCTION

Phthalimides is derivative of phthalic acid[(1)]and considered of bicyclic nonaromatic nitrogen heterocycles[(2)], the compounds have pharmacological activities such as analgesic, anti-inflammatory, anti-depressant etc.[(3)] because structural features for their activity are as: hydrophobic aryl ring, a hydrogen bonding domain,an electron-donor group, another distal hydrophobic site[(4)], Also enter many application industrial polymer synthesis as anticorrosion[(5)].

Mechanism of imide formation , through a nucleophilic attack of amino group to anhydride moiety, as in scheme(1) [(6)]:

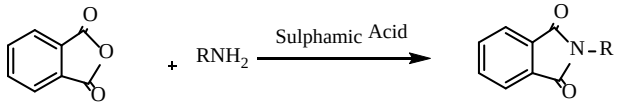


Scheme (1)

Synthesis of N- substituted phthalimide method:

1) Traditional procedure

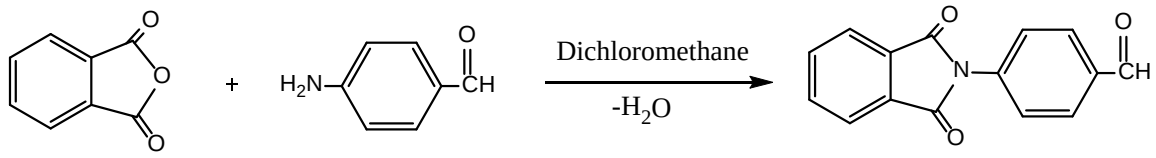
The reaction of Phthalic anhydride and primary amines in acetic acid by using (10 %) sulphamic acidcatalyst at (110 □C) give is N-substituted phthalimides 86-98%[(7)] .



R= C_6H_5,P-Cl C_6H_4,P-NO_2 C_6H_4'P-CH_3 C_6H_4'm-OH C_6H_4'$C_6H_4CH_2$'4,5 di methoxy C_6H_4'CH_2COOH,

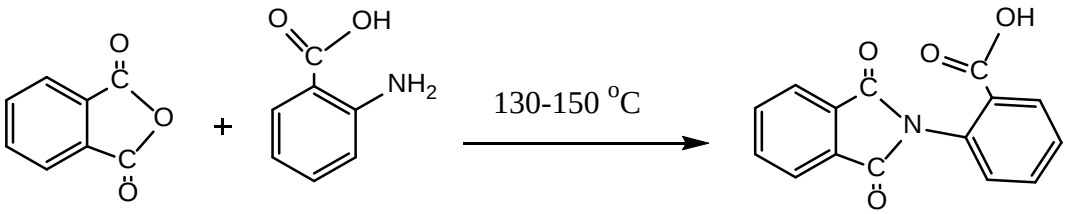
Scheme (2)

Synthesis 4-(1,3-dioxoisoindolin-2-yl)benzaldehyde: A solution of 4-aminobenzaldehyde was prepared in dichloromethane and was added dropwise of phthalic anhydride in CH_2Cl_2 was stirred for 8hr. at (15-20)^oC ,After added to mixture sodiumbicarbonat,H_2O and removed the solvent under reduced pressure to obtain a residue58%. the mixture poured in crushed ice and filter then crystallized in ether.[8]



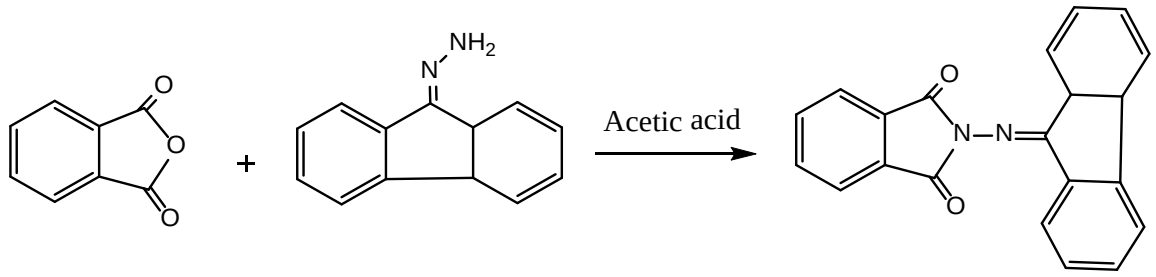
Scheme (3)

Anthranilic acid with phthalic anhydrides and heated in paraffin oil at 130°C-150°C.The resulting filtered and dried it in oven at 60°C then recrystallization was using ethanol with good yield [9].



Scheme (4)

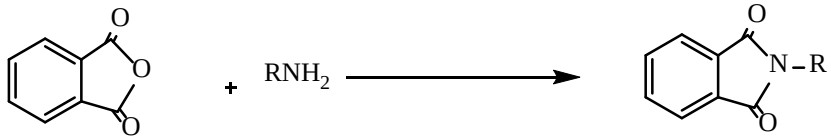
Phthalic anhydride and fluoren-9(9aH)-ylidene) hydrazine in acetic acid for 4 hour The product was hot filtered and the solvent evaporated and recrystallized from ethanol with obtained result 79%.[5]



Scheme (5)

2) Using microwave

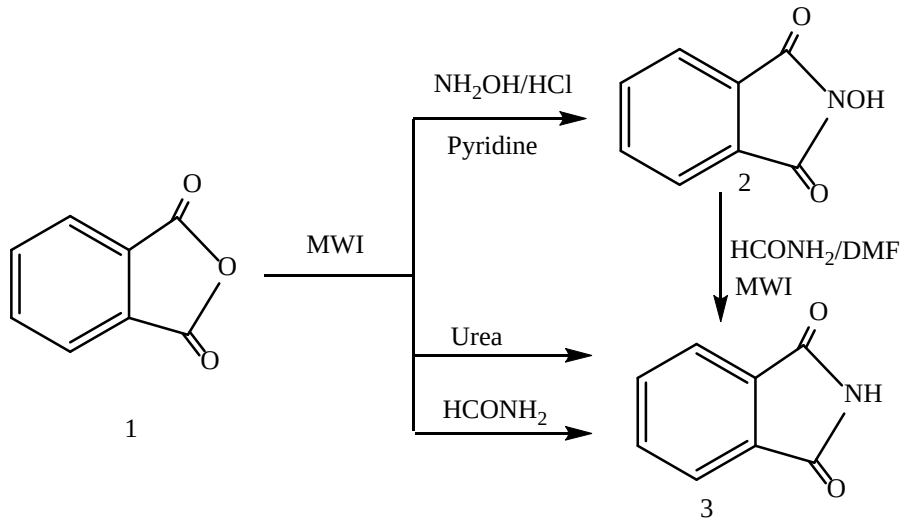
Reaction phthalic anhydride with amine in microwave with heated at 150-250 ^oC for 3-10 minutes. The product was recrystallized using Ethanol and yield (89-52%) [10].



R= C_6H_5,C_6H_{11},P-OH C_6H_4'$C_6H_4CH_2$'m-COOHC_6H_4,O-CH_3 C_6H_4'm-CH_3 C_6H_4'P-CH_3 C_6H_4,m-OCH_3 C_6H_4'C_5H_4N

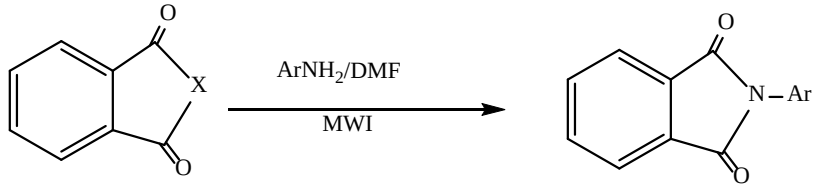
Scheme (6)

Synthesis of compounds2of phthalic anhydride and hydroxylamine hydrochloride in pyridine was MWI for 1min, After cooling solution was poured on to ice/ HCl, filtered off and recrystallized frome thanol,\While compounds 3 Phthalic anhydride and urea was fused under MWI for 5min. The product was recrystallized from water, but Synthesis of 3 from2 of N-hydroxyphthalimide and formamide in DMF were MWI for 11min, cool, was precipitate recrystallized from water.



Scheme (7)

And, reaction compounds (1or2 or 3) and aromatic amines in DMF were MWI for 3-4 min, cool , yield 48-90% ,were recrystallized from ethanol[11].



X= O,NOH, NH

Ar=Ph, p-$CH_3C_6H_4$,p-$OCH_3C_6H_4$,p-ClC_6H_4

Scheme (8)

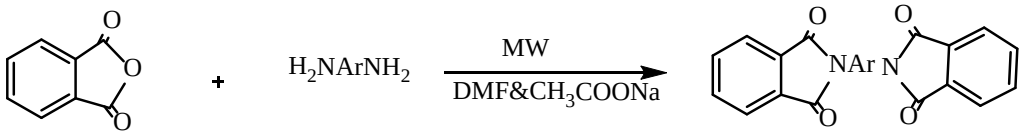
3) Synthesis phthalimide with two method :

a) Traditional method

Aryl amine in ethanol was added to a solution of phthalic anhydride and Na-acetate in acetic acid. The mixture was refluxed on water bath for about 8-10 hrs.The product was isolated by pouring in cold water, then filtered and driedthen recrystallised by ethanol.

b) Microwave method

The mixture aryl amine and phthalic anhydride was add Na-acetate in acetic acid. The mixture was then irradiated for 4-8 mins at powerlevel 600, Then the product obtain was isolated then recrystallised by ethanol[12].



Ar=-C6H4 -CH2- C6H4, -C6H4 – C6H4-,-C6H4-

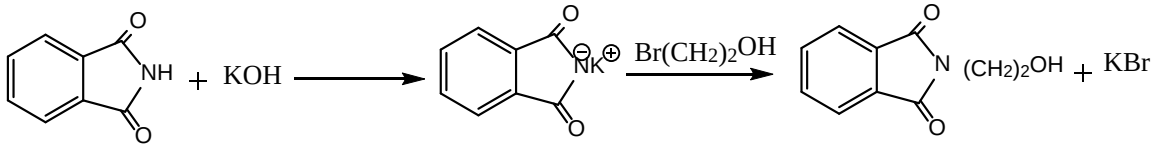
Scheme (9)

Compounds M.F.	Reaction time		Percent Yield	
	Traditional	M.W.	Traditional	M.W.
$C_{29}H_{18}O_4N_2$	8	4.5	71	82
$C_{28}H_{16}O_4N_2$	9	5	68	83
$C_{22}H_{12}O_4N_2$	8.5	5.5	71	87

Reaction of N- substituted phthalimide it is:

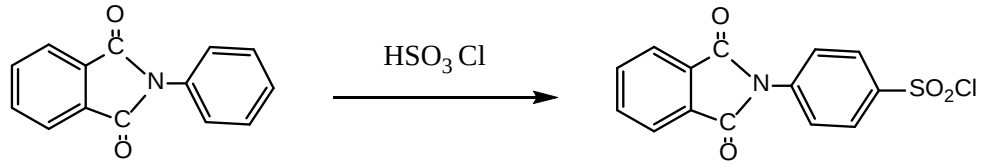
1) Traditional reaction

Reaction unsubstituted phthalimid with alkyl halides leads to produce N-substituted phthalimid[13].



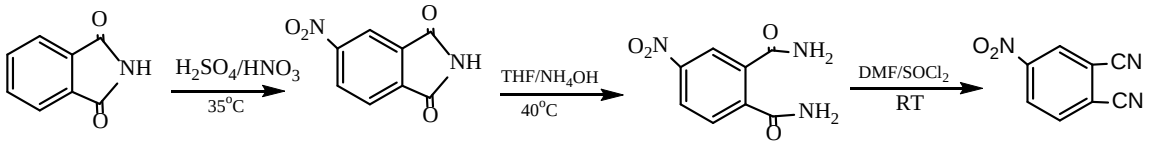
Scheme (10)

And when chlorosulfonic acid was added drop wise to N-phenyl phthalimide during two hours with stirring and keeping temperature at zero°C to give Yield 72%[14].



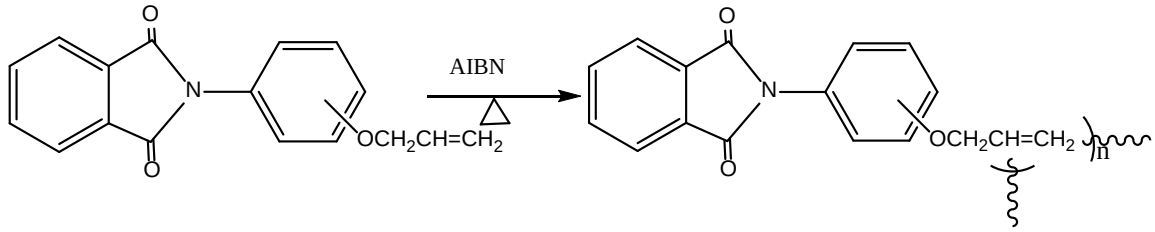
Scheme (11)

Synthesis 4-nitrophthalonitrile of 4-nitro phthalimide using THF and 4-nitro phthlimide the mixture was heated to 40°C and added (7mL) NH_4OH to the solution with stirring for 2hr and product obtain 90% [15].



Scheme (12)

Polymerization N-(allyloxy phenyl)tetrachlorophthalimides was dissolved in of THF then added of (azobisisobutyronitrile) in dry bottle was flushed with nitrogen then stoppered and maintained at(75C°) for 3hr. The solution was filtered, washed with methanol and dried, give result 62-71%[16].



Scheme (13)

2) Using microwave

The mixture of phthalimide and potassium hydroxide chloroaceticacid was added, Then added was few drops of DMF. The reaction was then irradiated under MW for up to 4.5 min at power level 600. The product obtain was then recrystallized by solvent ethanol, and yield 95 % [12].

Scheme (14)

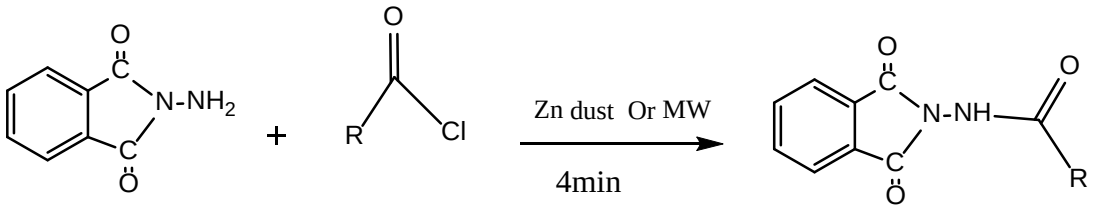
3) Reaction phthalimide with two method :

a) traditional method

N-aminophthalimide, zinc dust and acid chloride .mixture was stirred at room temperature for 4minutes, result was extracted with Chloroform was washed two times with saturated solution of sodium bicarbonate and once with water. the product was crystallized from methanol.

b) Microwave method

N-aminophthalimide and acid chloride ,The mixturewas submit to microwave irradiation at 450 wattfor 4 minutes. The result was crystallized from methanol[17]



R=C_6H_5 CHO,4-$NO_2C_6H_4$CHO

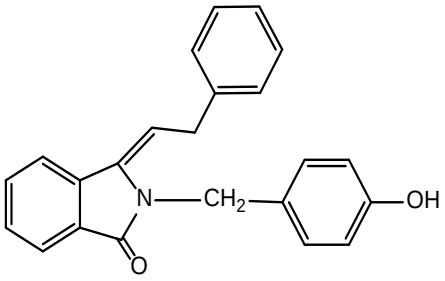
Scheme (15)

Compounds	Percent Yield	
	Traditional	M.W.
N-(1,3-dioxoisoindolin-2-yl)benzamide	30	70
N-(1,3-dioxoisoindolin-2-yl)-4-nitrobenzamide	-	20

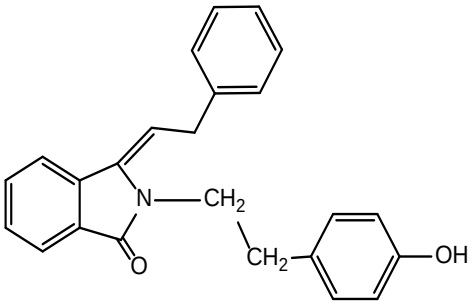
BIOLOGICAL ACTIVITY OF PTHALIMIDE DERIVATIVES

Thromboxane inhibitory activity

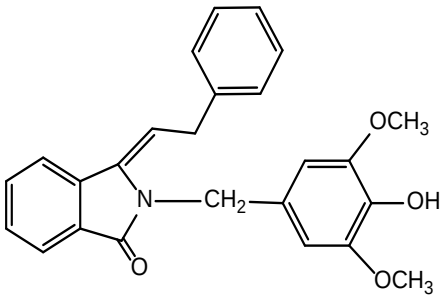
When synthesized a series of novel 1-isoindolinone derivatives p-hydroxybenzyl type and p-hydroxyphenyl-ethyl type compounds observed inhibited the contraction of pig coronary artery induced by U-46619, a thromboxane A2 analogue, were inhibitory activity[18].



[1]



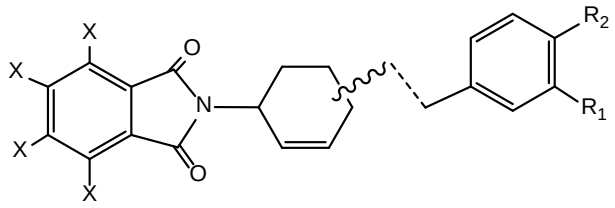
[2]



[3]

Anti- influenza activity

The synthesized phenethyl phenylphthalimide screening , anti-influenza A virus assay and the results indicated also be utilised in the screening of anti-influenza drugs[19]



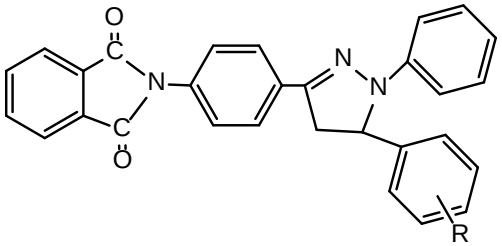
X= H, Cl

R_1, R_2 = H, OH

[4]

Anti inflammatory activity and Analgesic activity

Phthalimide derivatives is contains pyrazoline ring show active anti-inflammatoryin the carrageenin induced paw edema model also compounds give best activity in the acetic acid induced writhing model[20].



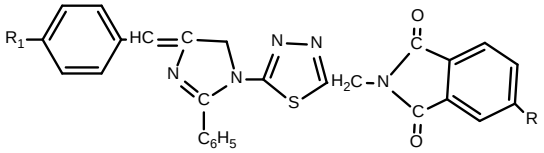
R=o-NO_2,H,m-Br

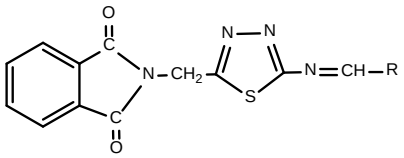
[5]

Antimicrobial activity

Antibacterial and Antifungal

The structure activity against bacterial their *E. coli*, *Pseudomonas aureus* and *Cytobacteria freundii* and four species of fungi namely *Aspergillus niger*, *Aspergillus flavus*, *Penicillium sp* and *Candida albicans.*[21]



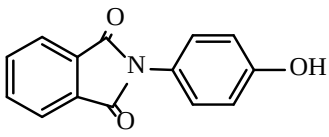


(6a-g) (7a-d)

R = H, R_1 = H =6a, R = -C_6H_5 = 7a, R = H, R_1 = 4'''-OH = 4b, R =4''-OH- C_6H_{4-} = 7b, R = H, R_1 =2'''- Cl = 6c, R =2''-Cl-C_6H_4 - =7c, R = H, R1 = (3'''-OCH_3-4'''-OH) = 6d, R_1 = (3''-OCH_3-4''-OH) -C_6H_3- = 7d, R = NO_2, R_1 = H= 6e, R = NO_2, R1 =2'''- Cl = 6f , R = NO_2, R_1 = (3'''-OCH_3-4'''-OH) =6g

Anticonvulsant activity

The synthesized compounds was screening anticonvulsant activity of evaluated in mice using PTZinducedconvulsions,and observe good anticonvulsant activity[10].



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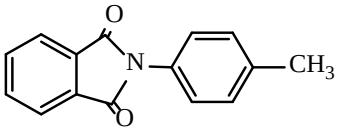

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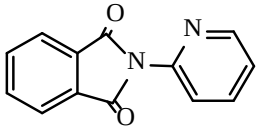

[10]

CONCLUSION

Phthalimide is formation of Phthalic anhydride with different amine either using microwave or traditional method, but microwave best method in terms of time and yield. It is of great importance because many of compounds related that biological activities.

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