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Review IJEM

Review on the Synthesis, Reactions, Biological Importance and Application of Phthalic Anhydride

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Abstract

Phthalic anhydride (also known as IUPAC name: benzofurandione), abbreviated PA, represents a cyclic organic substance derived through the oxidative transformation of xylene or naphthalene compounds. The coexistence of the benzene and furan-1, 3-dione ring structures significantly contributes to the formation of numerous heterocycles and certain polycyclic molecules. In organic chemistry, the aromatic system within para-amino benzoic acid acts as a reactive site towards double bond-containing molecules like those featuring an olefin group, leading to the formation of polycyclic structures through various mechanisms including acylation followed by hydrolysis into esters, or amidation via coupling with amino groups derived from primary/secondary amines.

Keywords: Phthalic Anhydride, naphthalene compounds, Phthalic anhydride, methylanthraquinones

INTRODUCTION

Our evaluation entails elucidating these responses alongside identifying any relevant indicators in regards to how phthalic anhydride reacts when combined with molecules containing alkenes or proteins. Additionally, our discussion includes illustrating how P. A. reacts when exposed to o-methylquinoline; this serves as an instance demonstrating the transformation where an oxygen atom is replaced by a carbon atom in a nuclear fusion process. Conversely, our discussion will cover how PA interacts with alcohols through an esterification process and its behavior when dealing with polyhydric substances via a polymerization mechanism. In conclusion, our explanation involves demonstrating how phthalic anhydride reacts chemically with benzene or xylene compounds to produce various forms of methylanthraquinones [1]. These compounds—3,5-dihydrophthalic anhydride, its trans isomer in methanol form, and 1,4-phthalhydrazide—are readily accessible via conventional procedures outlined in existing research, utilizing phthalic anhydride initially for synthesis (Figure 1) [2].

Phthalic anhydride (PA) is used in synthesis and multiple-aspect applications. In addition, it is applied as a substrate in esterification reactions and multistep synthesis (Figure 2) [3].

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Obtaining glyphthalic resins by polycondensation process with the change of acid number during the reaction of obtaining glyphthalic resin of polyatomic alcohol of glycerol and phthalic anhydride. It is revealed that the results of acid number determination during polycondensation can be used for directed regulation of synthesis of alkyd oligomers and their subsequent curing to obtain a polymer with specified properties (Figure 3) [4].

A series of phthalimides were prepared in satisfactory yields by reaction of phthalic anhydride with amines (amino pyridine, 5-methyl aminopyridine, 4-methyl aminoquinolin,

aminobenzothiazol, 4-amino antipyrine, fluoren-9(9a*H*)-ylidene) hydrazine). These synthesized compounds were screened for their antibacterial activity against four microorganisms *Staphylococcus aureus*, *Bacillus*. *subtilis*, *Escherichia Coli* and *Klebsiella pneumonia* and they were found to exhibit good to moderate antibacterial activity, these compounds were tested to determine their ability to inhibit corrosion of mild steel in 1 mol.L^{-1} H_2SO_4 (Figure 4) [5].

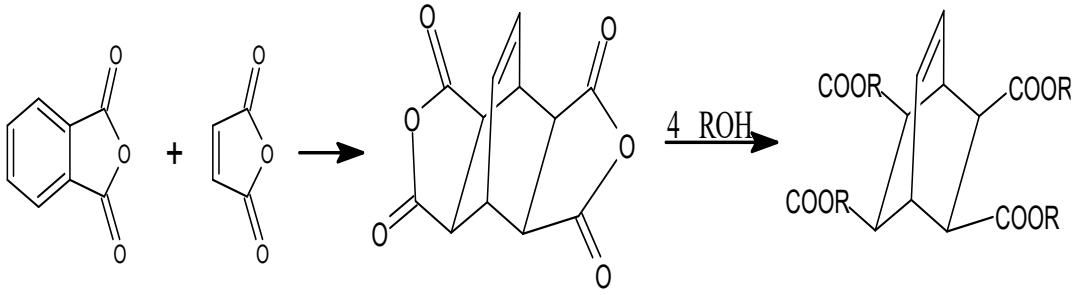

Figure 1. Polycyclic compounds synthesized from hthalic Anhydride.

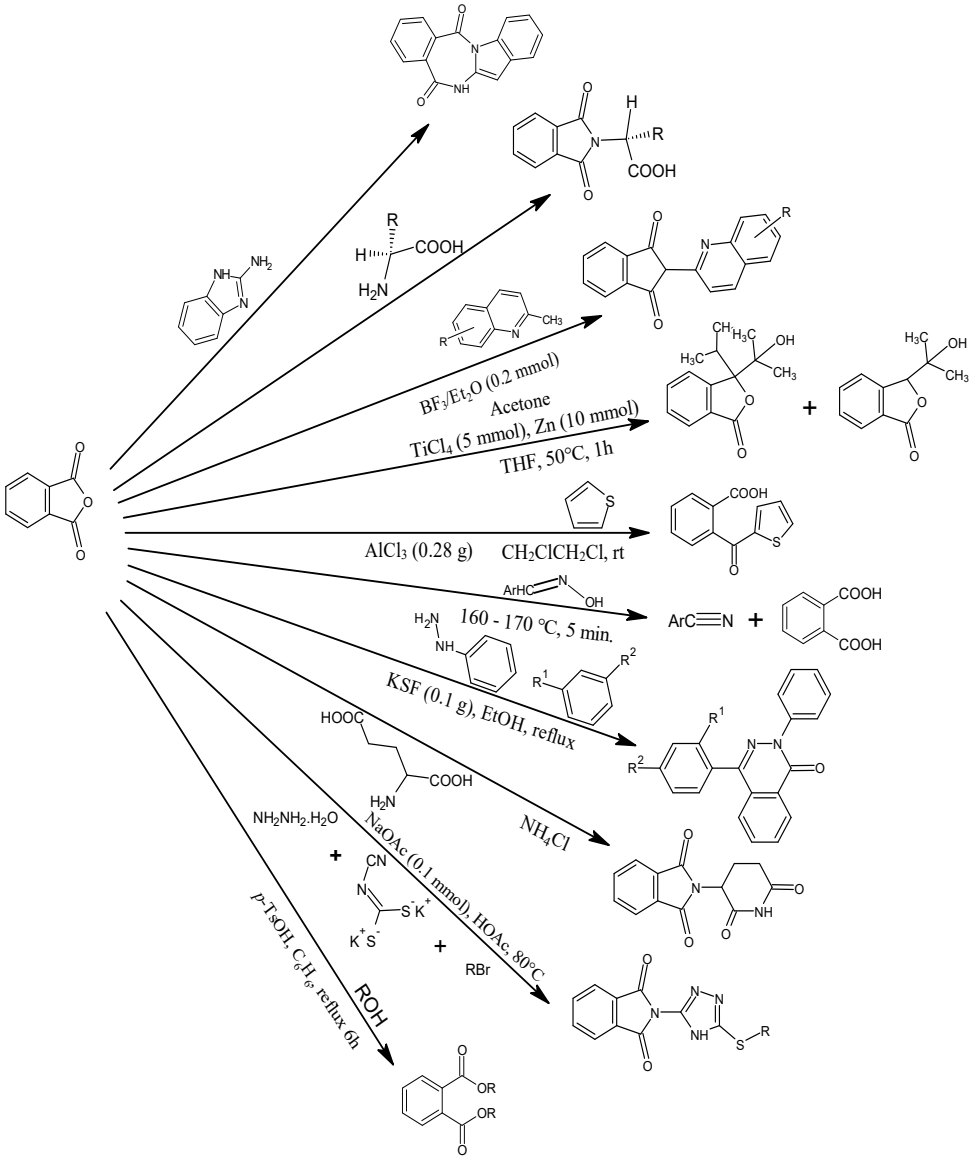

Figure 2. Use of phthalic anhydride in synthesis of various organic compounds.

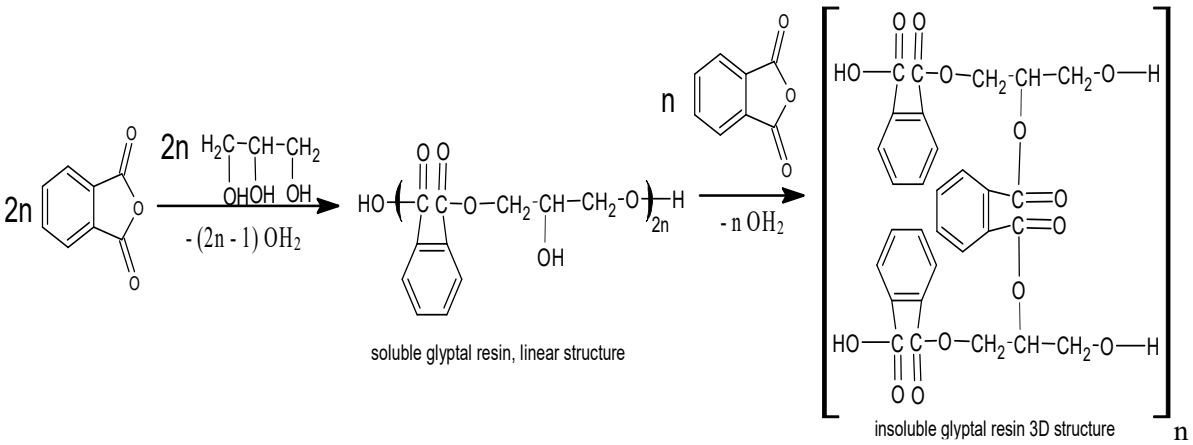

Figure 3. Glyphthalic resin production.

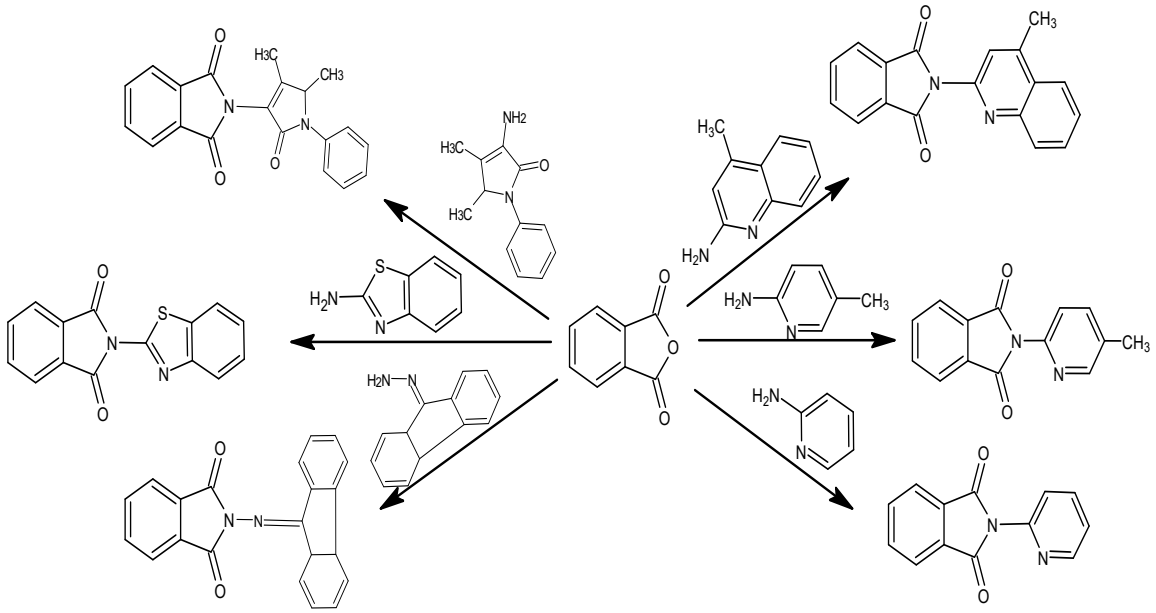

Figure 4. Reaction of phthalic anhydride with aromatic amines.

N-substituted phthalimide analogues were synthesized through reaction of phthalic anhydride with various amines (Triazolamine, Benzocaine, *p*-Nitro-aniline, pyrazinamide, Phenazone and glycine) in reflux synthesizer. The analgesic activity of the selected products was evaluated *in vivo* by ip carboxymethylcellulose (CMC) and acetic acid- induced 'writhing' test in mice. The products exhibited significant analgesic activity in hot-plate and acetic acid inducer screening test comparable to the control CMC (Carboxymethylcellulose) and aspirin (Figure 5) [6].

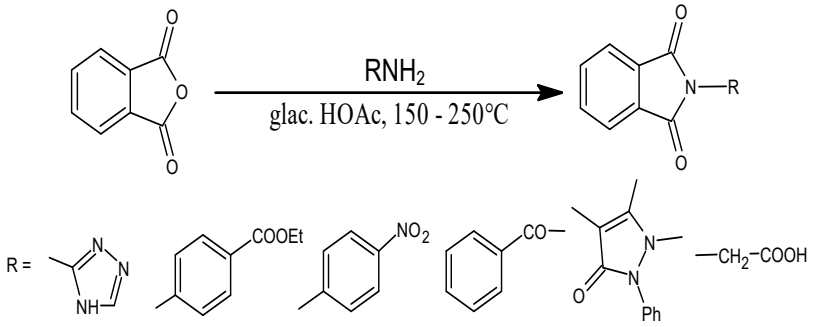

Figure 5. Synthesis of N-substituted phthalimide analogues.

Similarly, N-substituted pthalimide analogues were synthesized by reacting phthalic anhydride with various amines (aminoethanol, aminopropanol, amino ethyl morphline, amino ethyl morphline iodide) in reflux synthesizer. The antibacterial activity of the synthesized derivatives was done in comparison with phenol as standard compound, where they showed very good activity against (*S.aureus*), *Escherichia coli* (*E. Coli*) when compared with phenol. Infectious and parasitic diseases are responsible for 23% of percentage of worldwide deaths and the second ranking cause of death according to the World Health Organization (Figure 6) [7].

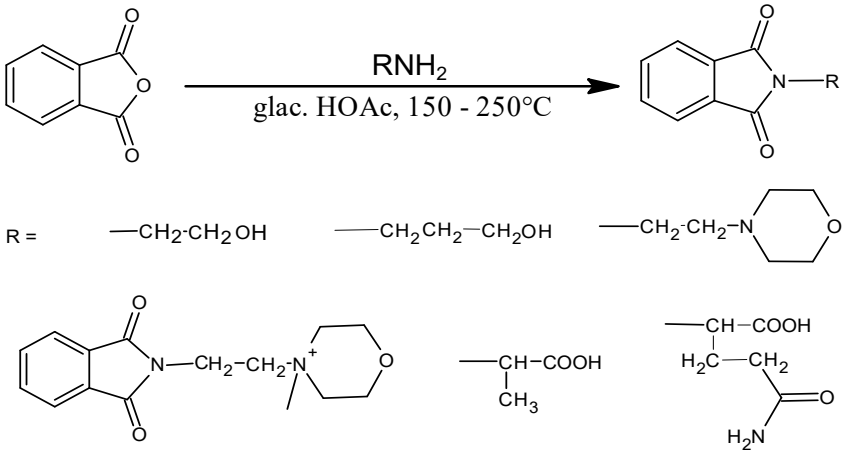

Figure 6. Reaction of phthalic anhydride with aliphatic amines.

On the other hand, N-phthalimides of amino acids were synthesized by cyclocondensation of phthalic anhydrie with amino acids like glycine, L-alanine, L-valine, L-leucine, L-phenylalanine, and L-aspartic in glacial acetic acid under an oil bath at 170-180 ºC. The products were then heated with *o*-phenylene diamine in 4N HCl for 2 hours, forming N-(1*H* benzimidazol-2-yl alkyl)phthalimide (Figure 7). These compounds were tested against four bacteria and fungi: *Streptococcus Epidermidis, Escherichia Coli, Mycobacterium Tuberculosis,* and *Candida Albicans* [8].

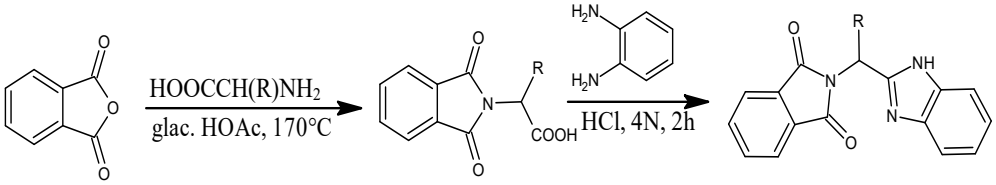

Figure 7. Synthesis of N-phthalimides of amino acids.

When phthalic anhydride reacted with urea, it formed phthalimide. This phthalimide was used to convert different amines into amides, both aliphatic and aromatic. It also reacted with alkyl halides in a basic solution to produce N-alkyl derivatives (Figure 8) [9].

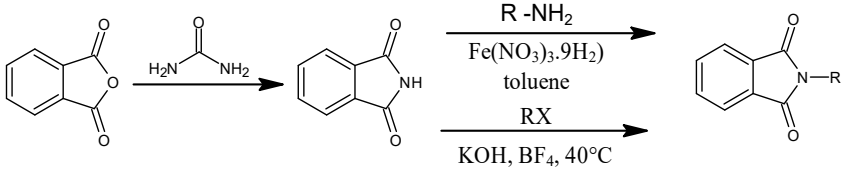

Figure 8. Reactions of Phthalic acid with urea and alkyl halides.

Isoindoline-1,3-dione compounds were synthesized by coupling phthalic anhydride with suitable aromatic amines (Figure 9). These compounds were tested against different bacteria and fungi. Their activity was measured using thr agar-dilution method. The results showed that these compounds had some antibacterial and antifungal activity [10].

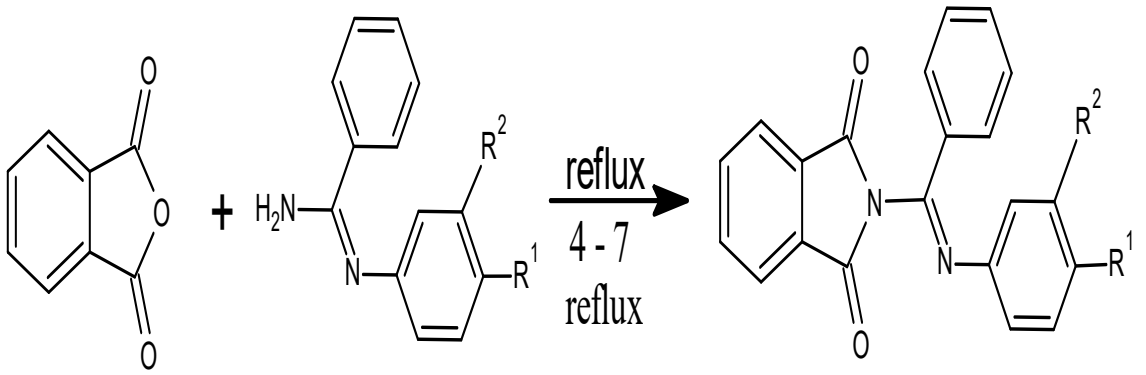

Figure 9. Coupling phthalic anhydride with aromatic amines.

Some phthalimide derivatives were synthesized using eco-friendly microwave irradiation methods with montmorillonite-KSF as a reusable catalyst (Figure 10). In green chemistry, microwaves can replace traditional heating, using electromagnetic energy to create heat in materials. Toxicity tests were done according to OECD guidelines. The compounds were tested for pain relief using aspirin as a reference. Their activity was linked to FISA, which measures how much of the surface of a molecule is exposed and can interact with other substances [11].

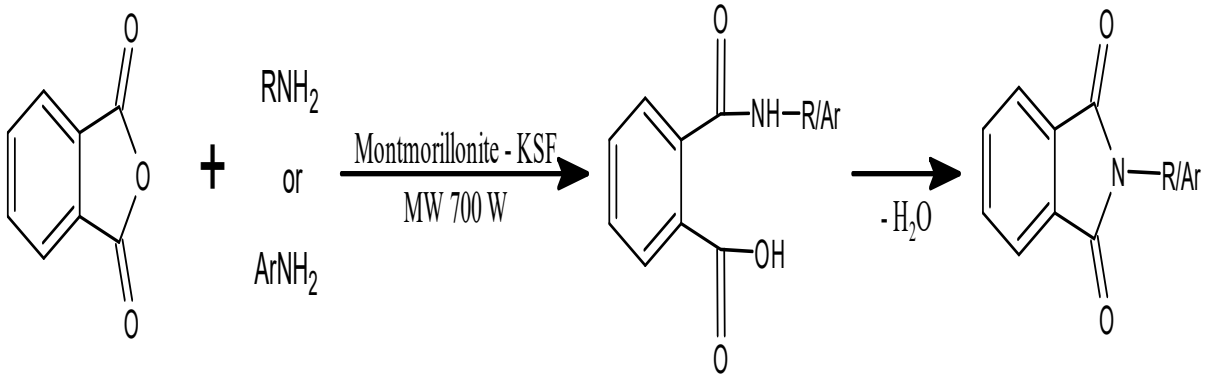

Figure 10. Synthesis of phthimides by eco-friendly microwave irradiation methods.

The chalcones 2-(4-acetyl-phenyl)-4-nitro-isoindole-1,3-dione were synthesized by heating 3-nitrophthalic anhydride with *p*-aminoacetophenone. The product was grinded with different aromatic aldehydes in sodium hydroxide without using any solvent (Figure 11) [12].

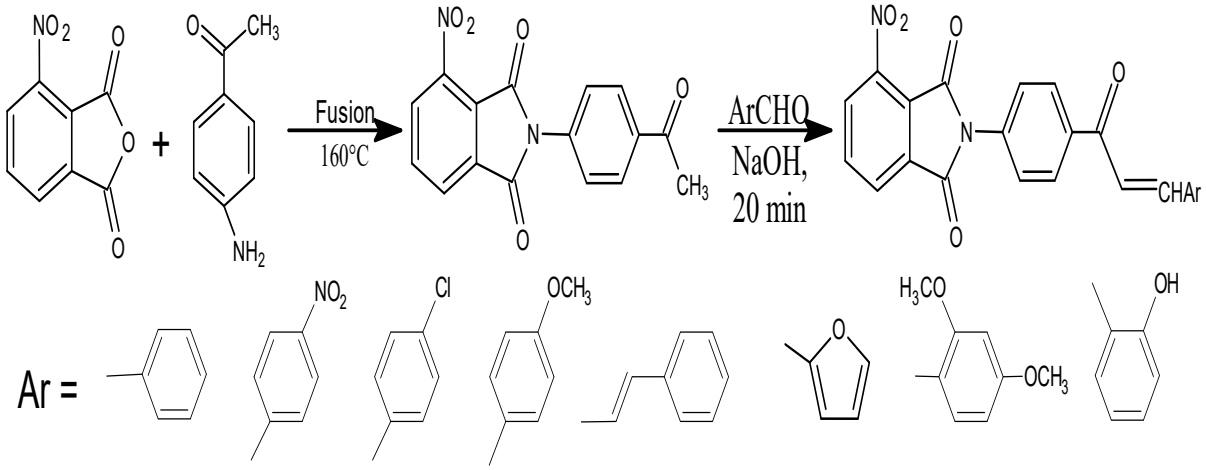

Figure 11. Synthesis of chalcones using phthalimide derivatives.

Anthranilic acid and phthalic anhydrides can form complexes with metal ions, which are useful for various purposes (Figure 12). In this study, complexes of anthranilic acid and phthalic anhydride with lead acetate ($Pb(CH_3COO)_2$), cobalt chloride ($CoCl_2$. $6H_2O$), cadmium sulfate ($CdSO_4 \cdot H_2O$), copper chloride ($CuCl_2.2H_20$), and tin chloride were made in solutions with pH values between 6 and 8 in variable ratios. These complexes were tested for antibacterial activity [13].

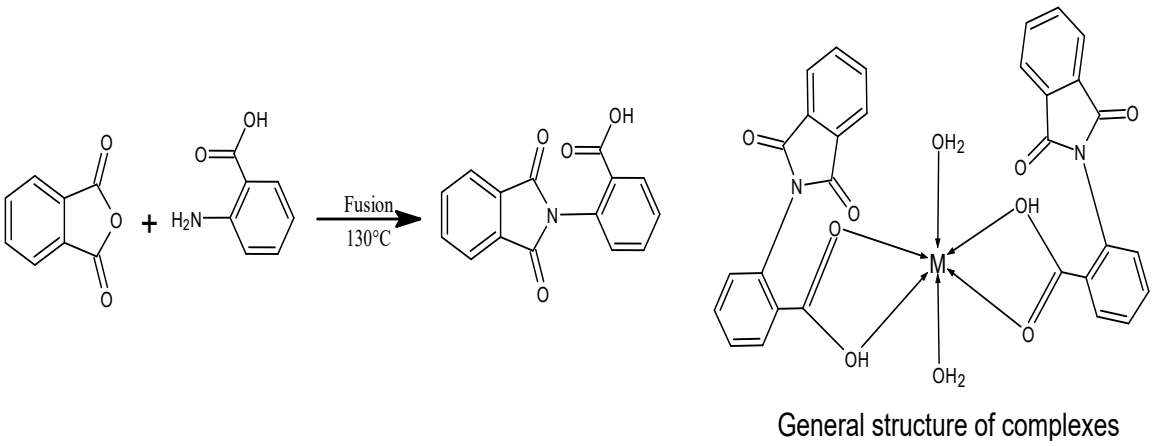

Figure 12. Complexes with phthalimide derivatives.

Phthalic anhydride was combined with benzidine in acetic acid to form biphenyl. When phthalic anhydride was reacted with different amino acids like D-glycine, D-alanine, and D-valine in hot oil bath without using a solvent, N-phthaloylamino acids were formed. These were then heated with *o*-phenylenediamine (OPDA) in dilute HCl to make benzimidazole derivatives (Figure 13). The products were tested to check antibacterial activity [14].

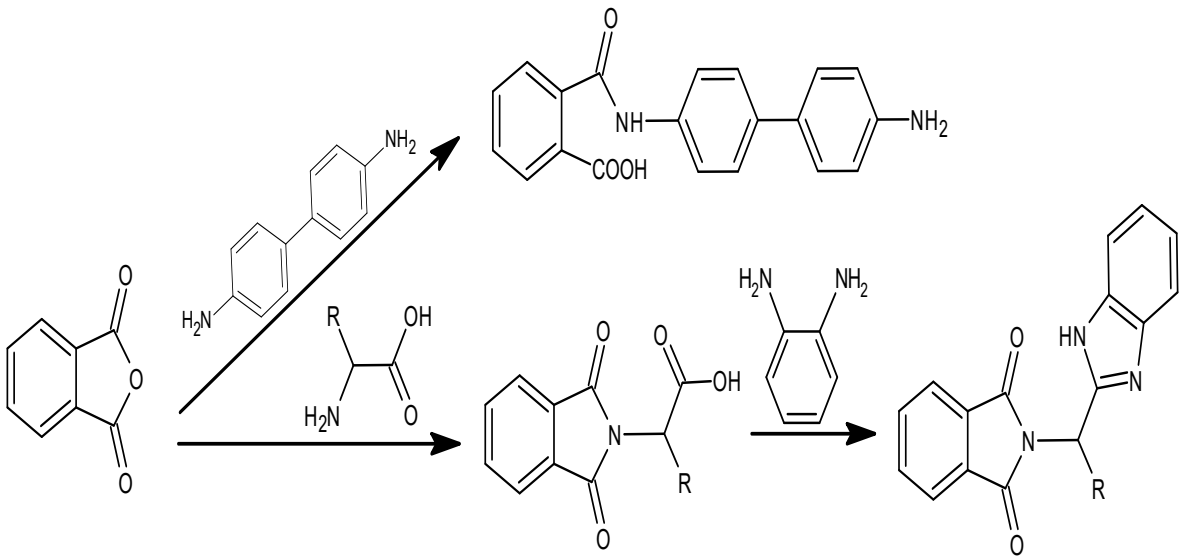

Figure 13. Biphenyl and benzimidazole phthalimide derivatives.

A simple method for make isoindoline-1,3-diones derivatives was developed by combining N-arylbenzene carboximidamides with phthalic anhydride in benzene at high temperature. If the reaction was done without heating monoacylation products like phthalic acid amides were formed (Figure 14). In silico toxicity and biological activity were tested using online programs. For some compounds, in vivo tests were also done in mice. The results from both methods were similar, showing low toxicity. One compound, 2-(phenyl(phenylimino)methyl)isoindoline-1,3-dione, had high pain-relieving activity, 1.6 times more than the drug metamizole sodium [15].

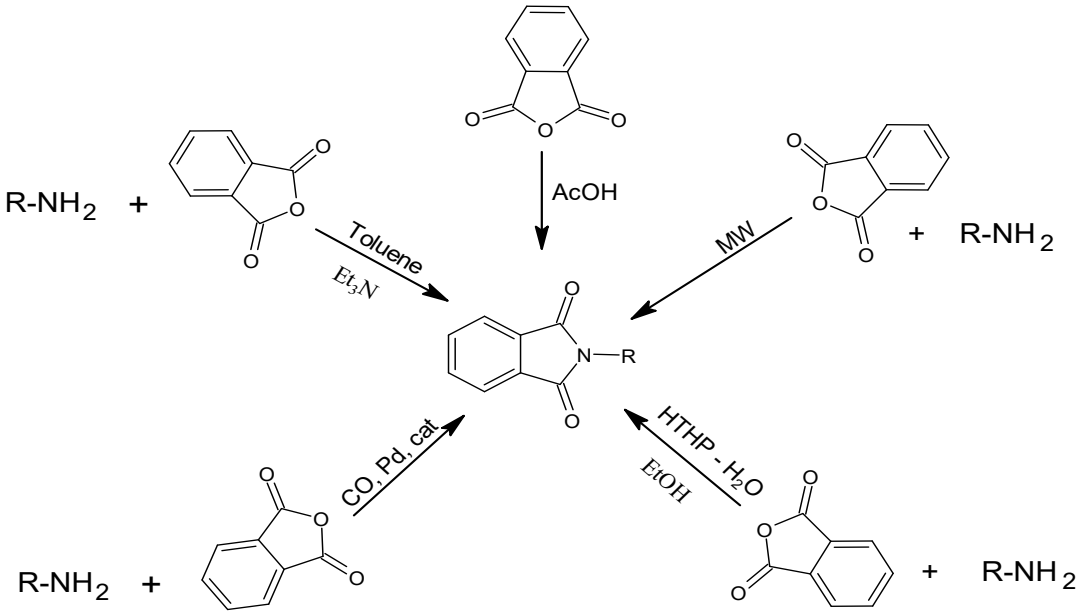

Figure 14. Known methods for making N-substituted phthalimide derivatives.

When 4-methyl aniline was mixed with phthalic anhydride, 2-[N-(4-methylphenyl)]phthalamic acid was formed. This was then reacted with dimethylsulphate in anhydrous sodium carbonate in acetone to obtain 2-[N-(4-methylphenyl)]phthalamide acetate ester. The ester was then heated with hydrazine in ethanol to the form 2-[N-(4-methylphenyl)]-phthalamic acid hydrazide. This was reacted with different aromatic aldehydes in some glacial acetic acid and ethanol to make Schiff bases. These Schiff bases were then combined with phthalic anhydride in dry benzene to obtain 1,3-oxazepines derivatives (Figure 15) [15].

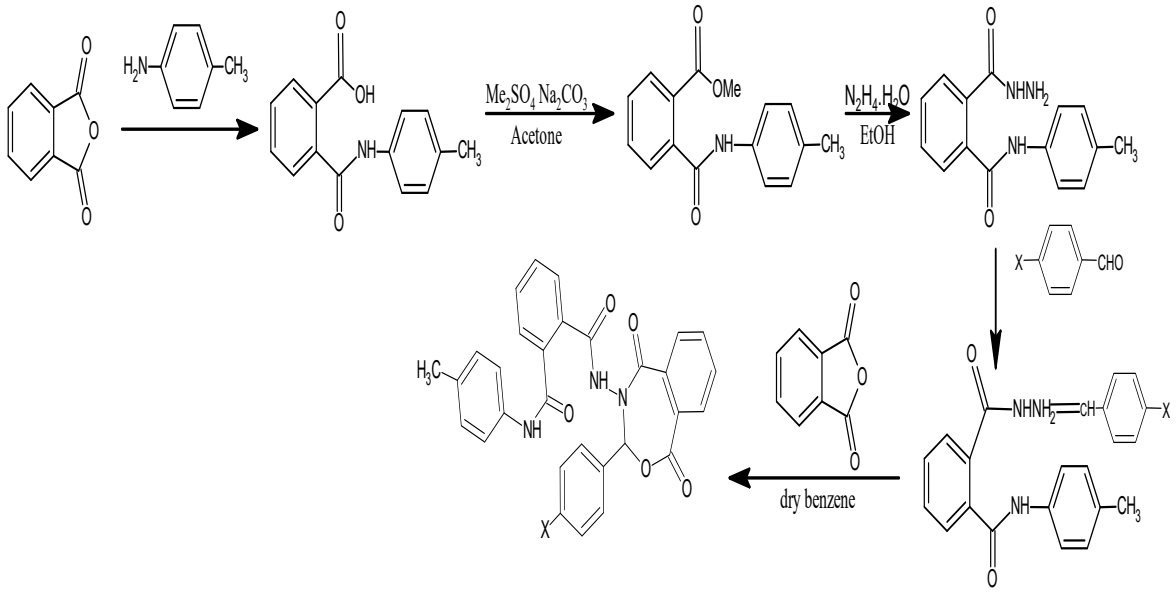

Figure 15. Multi-step synthesis of various azepine derivatives.

Researchers tried to obtain 2-methyl anthraquinone (2-MAQ) by mixing phthalic anhydride with toluene instead of using 2-methyl phthalic anhydride and benzene. This process didn't make much 1-methyl anthraquinone (1-MAQ), byproduct (Figure 16). One advantage is that toluene is less toxic than benzene, which is known to cause cancer. The 2-MAQ synthesized this way worked as well as commercially available 2- methyl anthraquinone [16].

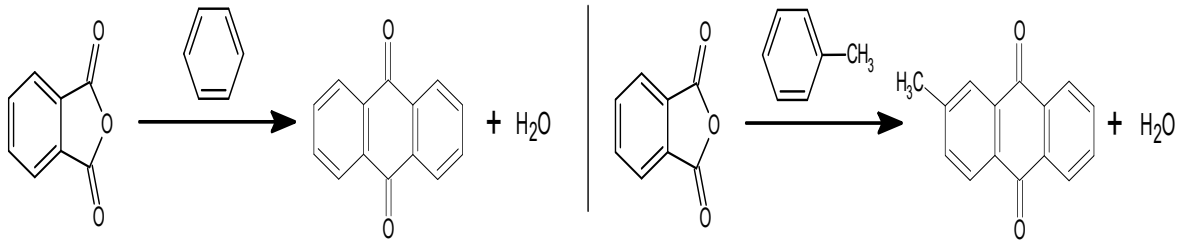

Figure 16. Synthesis of 2-Methyl anthraquinone using phthalic anhydride and toluene.

Metal Complexes of Phthalic Anhydride

Under microwave assisted solvent-free conditions, a green synthesis procedure for making metal phthalocyanines involved combination of phthalic anhydride and urea with metal chlorides,using $(NH_4)_2MoO_4$ as a catalyst (Figure 17) [17].

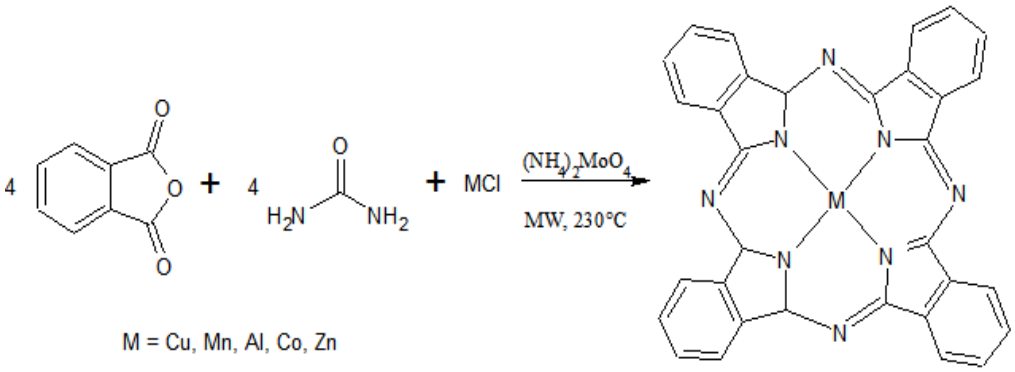

Figure 17. Synthesis of metal phthalocyanine.

Another approach involved obtaining five therapeutic drugs from sulphanilic acid-phthalic anhydride complexes (Figure 18) [18].

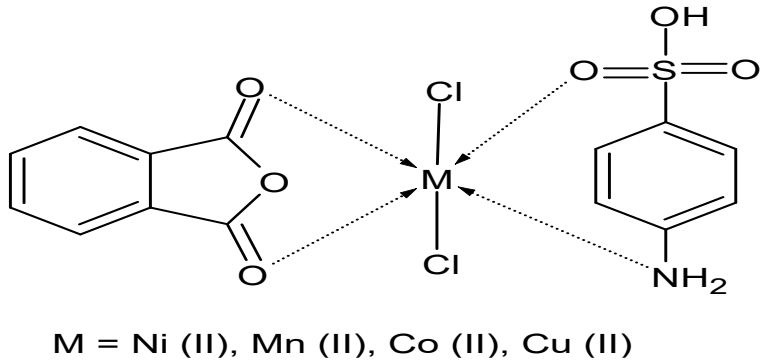

Figure 18. Metal complexes of sulphanilic acid-phthalic anhydride.

CONCLUSION

Phthalic anhydride, the important industrial chemical and the commercially available white solid is that compound necessary for the scientific progress. It is used in variety of fields:

- An easily obtained compound of comparatively low price
- In industry, its phthalate ester - a plasticizer for plastics
- In pharmacy, important in drug synthesis
- In polymer chemistry, for the Glyphthalic resin production
- A precursor for dyestuff, when reacted with phenolic compounds

- An antiviral compound
- A key initiator for synthesis of uncountable products

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