SYNTHESIS OF 2-AROYLISOINDOLINE-1, 3-DIONE FROM PHTHALIMIDE.

M. Sc THESIS

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THESIS TITLE: SYNTHESIS OF 2-AROYLISOINDOLINE-1, 3-DIONE FROM PHTHALIMIDE.

Abstract

Phthalimide(Isoindoline-1, 3-dione) derivatives have received attention due to their antibacterial, antifungal, analgesic, antitumour, anxiolytic and anti HIV-1 activities. Isoindoline 1,3-dione derivatives can be used as promising and effective drugs for the treatment of different diseases such as AIDS, tumour, diabetes, multiple myeloma, convulsion, inflammation, pain, bacterial infection.

A convenient, general and facile method for the synthesis of aroylsubstituted isoindoline-1, 3-dione(7-11) from Phthalimide has been developed. The reactions of Phthalimide (1) with aroylchlorides (2-6) were performed in the presence of Lewis acid (AlCl₃) and also in absence of acid in different solvents under mild conditions in good yield %.

Scheme-1:

1) 1, 4-dioxane r. t, 16-18 h or 2) 1, 4-dioxane with AlCl₃ r. t, 6-7 h

- 2, 7 R= C₆H₄CH₃ (p)
- 3, 8 R= C₆H₄Cl (p)
- 4, 9 R= C₆H₅
- 5, 10 R= CH₃
All the synthesized compounds were characterized by IR, $^1$H-NMR and $^{13}$C-NMR spectra and Elemental Analysis to establish the structure.
LIST OF ABBREVIATIONS

Aq  Aqueous
Ar  Aromatic
b. p.  Boiling point
d  Doublet
DMF  N, N-dimethyl formamide
Et  Ethyl
Et-OH  Ethanol
EtOAc  Ethyl acetate
h  hour
hv  light
Hz  Hertz
IR  Infrared
J  coupling constant
m  multiple or medium
min  minutes
mmolmili mole
mol  mole
mol %  mole percent
M. p.  melting point
NMR  nuclear magnetic resonance
OAc  Acetate
Ph  Phenyl
PhH  Benzene
ppm  parts per million
quin  Quintet
r. t. Room temperature
s singlet/ strong/ second
t triplet
T temperature
TLC thin layer chromatography
TMS trimethylsilane
UV ultra-violet
Δ heat/ reflux
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1. Introduction

Isoindole 1 is isomeric with indole 2 which comprises a benzene ring fused with a pyrrole nucleus. The parent compound and the 2-unsubstituted derivatives can tautomerize with the 1H isomer, i.e. isoindolenine or (1H-isoindole). Isoindole is much more unstable compared with indole and undergoes rapid oxidation in air to form polymers. Isoindole is thermodynamically more stable than its isoindolenine isomer at room temperature. The next stable reduction state of isoindole is isoindoline 4. Isoindolinone (phthalimidine) 5 is the more stable derivative of isoindole.

(Phthalimide) 1,3-dihydro-2H-isoindole-1,3-dione
To generate isoindole, phthalimidine ring requires nucleophilic addition or reduction at the carbonyl group followed by elimination of water. The chemical instability of isoindole is well documented which prevented its isolation and detailed characterization until 1972. The preparation of the first isoindole derivative, i.e. N-methylisoindole in 1951 and the unsubstituted parent isoindole in 1972 demonstrated that the ring system was stable enough for isolation.

2. Structure of isoindole

Isoindole is a bicyclic 10π electron array and complies with the Hueckel (4n + 2) rule for aromatic stabilization. There have been several calculations of the electronic structure of isoindoles. The distribution of charge density around the isoindole nucleus was calculated based on the LACO-MO method or the 'frontier electron concept', and the relatively high electron density found at position-1. Therefore, the expectation is that electrophilic substitution on carbon will occur most readily at this position. The semi empirical calculations of Dewar, and Polansky et al. estimate a substantial degree of resonance stabilization for isoindole with a value of about 56 kcal mol⁻¹ which is significantly larger than the value of pyrrole and is close to that ascribed for indole. Isoindole should be favored over its tautomer, isoindolenine by about 8 kcal mol⁻¹ according to a molecular orbital calculation of Veber and Lwowski et al. Theoretical studies by Dewar et al. are consistent with structure.

3. Naturally occurring isoindole and isoindolinone (phthalimidine) derivatives

The first isoindolobenzazepine alkaloid (+)-chilenine has been found in Berberis empetrifalia Lam. (Berberidaceae) by Fajardo et al. Valuencia et al. isolated nuevamine, the first known isoindoloisoquinoline alkaloid and lennox amine, an isoindolobenzazepine structurally related to (+)-chilenine from Berberis darwinii Hook (Berberidaceae).
Valencia et al.\textsuperscript{13} also isolated a series of novel isoindolobenzazepines including (\(\pm\))-Bdeoxychilenine 10, pictonamine 11, chileninone 12, (\(\pm\))-chilenamine 13, and (\(\pm\))-palmanine 14 from three Chilean Berberis species, namely, B. Aclinacanlha Mart. ex. Schult, B. darwinii Hook and B. va/diviana Phil. The isolation of the first known isoindolobenzazocine alkaloid magallanesine 15 from Berberis darwinii Hook was also achieved by Valencia et al.\textsuperscript{14}. Staurosporine 16 containing an isoindolinone moiety was isolated from Saccharothrix Sp. AM 2282\textsuperscript{15}, and has very interesting biological activities, such as antimicrobial\textsuperscript{16a}. Hypotensive\textsuperscript{16b} cytotoxic activities. It is also an inhibitor of protein kinase\textsuperscript{16c}, and platelet aggregation\textsuperscript{16d}. The naturally occurring isoindole 17 was isolated from sponge Reniera Sp.\textsuperscript{17}
A series of cytostatically active metabolites have been isolated from microorganisms in which a highly substituted hydrogenated isoindolone unit is fused to an 11-to 14-membered macrocycle.
The isolation of the first two substances (cytochalasin B 18 and cytochalasin D 19) of the cytochalasin series was achieved by Rothweiler\textsuperscript{18} and Aldridge \textit{et al.}\textsuperscript{19}. The cytochalasins are group of about two dozen structurally related fungal metabolites having a wide range of biological activities\textsuperscript{20a,b}.

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{cytochalasin_b_d}
\caption{Cytochalasin B and Cytochalasin D}
\end{figure}

4. Isoindole compound with 3-D structure

Isoindoline is a heterocyclic organic compound with the molecular formula $C_8H_9N$. The parent compound has a bicyclic structure, consisting of a six-membered benzene ring fused to a five membered nitrogen-containing ring. The compound's structure is similar to indoline except that the nitrogen atom is in the 2 position instead of the 1 position of the five-membered ring. Isoindoline itself is not commonly encountered, but several derivatives are found in nature and some synthetic derivatives are commercially valuable drugs, e.g. pazinaclone\textsuperscript{22}.

1-Substituted isoindolines and isoindolinones are chiral. Isoindolylcarboxylic acid and 1,3-disubstituted isoindolines are constituents of some pharmaceuticals and natural products.
Isoindolines can be prepared by 1,2-addition of a nucleophile onto a bifunctional ε-benzoiminoenoates followed by intramolecular aza-Michael reaction. Another route involves [3+2] cycloaddition of the azomethine ylides (e.g. (CH₂)₂NR) to quinone in the presence of suitable catalysts. These methods have also been adapted to give chiral derivatives²³,²⁴.

5. Synthesis of Isoindolinone derivative by heating

Phthalimide can be prepared by heating phthalic anhydride with aqueous ammonia giving 95-97% yield. Alternatively, it may be prepared by treating the phthalic anhydride with ammonium carbonate or urea. It can also be produced by ammonoxidation of ortho-xylene. Phthalimide is used as a precursor to anthranilic acid, a precursor to azo dyes and saccharin²⁵.

![1,3-dioxoisoiindoline](image)

1,3-dioxoisoiindoline

Alkyl phthalimides are useful precursors to amines in chemical synthesis, especially in peptide synthesis where they are used "to block both hydrogens and avoid racemization of the substrates"²⁶.

Alkyl halides can be converted to the N-alkylphthalimide:

C₆H₄(CO)₂NH + RX + NaOH → C₆H₄(CO)₂N-R + NaX + H₂O
The amine is commonly liberated using hydrazine:

\[ \text{C}_6\text{H}_4(\text{CO})_2\text{NR} + \text{N}_2\text{H}_4 \rightarrow \text{C}_6\text{H}_4(\text{CO})_2\text{N}_2\text{H}_2 + \text{RNH}_2 \]

Dimethylamine can also be used\(^{27}\).

Some examples of phthalimide drugs include thalidomide, taltrimide and talmetoprim salts upon treatment with bases such as sodium hydroxide. The high acidity of the imido N-H is the result of the pair of flanking electrophilic carbonyl groups. Potassium phthalimide, made by reacting phthalimide with potassium carbonate in water at 100 °C or with potassium in absolute ethanol is used in the Gabriel synthesis of primary amines, such as glycine\(^{28}\).

6. Synthesis of Isoindolinone derivatives from phthalimides

A highly efficient transamidation of several primary, secondary, and tertiary amides with aliphatic and aromatic amines (primary and secondary) is performed in the presence of a 5 mol % concentration of different hydrated salts of Fe(III). The methodology was also applied to urea and phthalimide to demonstrate its versatility and wide substrate scope. A plausible mechanism explains the crucial role of water\(^{29}\).

A convenient, efficient, and selective N-Alkylation of N-acidic heterocyclic compounds with alkyl halides is accomplished in ionic liquids in the presence of potassium hydroxide as a base. In this manner, phthalimide, indole, benzimidazole, and succinimide can be successfully alkylated\(^{30}\). 

![Chemical reaction diagram]
7. Synthesis of Isoindolinone derivatives by the N-alkylation of aromatic cyclic imides reactions.

An efficient and simple method enables the N-alkylation of aromatic cyclic imides using cesium carbonate as the base in anhydrous N,N-dimethylformamide at low temperatures (20-70°C). The employment of microwave irradiation presents noteworthy advantages over conventional heating. The method is compatible with base labile functional groups\textsuperscript{31}.

8. Synthesis of Isoindolinone derivatives by Transition-metal-free multicomponent reactions

Transition-metal-free multicomponent reactions involving arynes, isocyanides, and CO\textsubscript{2} as the third component resulted in the formation of N-substituted phthalimides in good yields, whereas the use of water as the third component furnished benzamide derivatives in good yields.
These reactions took place under mild conditions with broad scope\textsuperscript{33}.

\begin{center}
\includegraphics[width=\textwidth]{reaction_diagram.png}
\end{center}

9. Chemistry of isoindole natural products

Isoindole (2H-isoiindole, 1), known since more than a century, consists of a fused benzopyrrole ring system and constitutes the regioisomer of the abundant 1H-indole heterocycle. The fully reduced member of the isoindole family is termed isoindoline (2, 3-dihydro 1H-isoiindole, 2). Formal oxidation to the 10π-system leads to isoindole (1), which is usually only stable when the labile ortho-quinoid structure is embedded in a π-system\textsuperscript{34}. Incorporation of additional oxygen gives the isoindolinone (1, 3-dihydro-2 H-isoiindole-1-one, 3) and phthalimide (1, 3-dihydro-2 H-isoiindole-1, 3-dione, 4) substitution pattern.

The isoindole structure has attracted scientists for decades and can be found in several natural and pharmaceutical compounds\textsuperscript{35, 36}. A number of structures were explored over the years and promising drug conjugates such as 5 – 11 could be developed (Figure 1).
Figure 1: a) Structural features and b) selected examples of non-natural congeners.
Compared to the synthesis of indoles, where a number of named-reactions have been reported, only conventional methods are used for the related isoindole motif. For the construction of this rare skeleton inter- and intramolecular Diels–Alder reactions are one of the most powerful methods. This was also exemplified by medicinal chemists from AstraZeneca in the manufacturing route to an mGluR2 positive allosteric modulator\textsuperscript{37}.

In 2012, a programmable enantioselective one-pot synthesis of isoindolines was reported by Waldmann\textsuperscript{38}. Several other strategies were pursued for the synthesis of isoindoline-type structures and the synthesis, chemical and spectroscopic properties of this substance class were reviewed elsewhere\textsuperscript{39,40}.

In the late 1950s, thalidomide (8), a phthalimide-based drug used by pregnant women against morning sickness, became the most infamous drug in history and caused thousands of fatal casualties as well as numerous severe birth defects. Modification of the phthalimide core led to the approval of lenalidomide (9)\textsuperscript{41} in 2004 and pomalidomide (10) in 2013 by the Food and Drug Administration (FDA) as drugs against multiple myeloma. The phosphodiesterase 4 (PDE4) inhibitor apremilast (11), which lacks the glutarimide is currently in phase III clinical trials.

The first naturally occurring isoindole, 6-methoxy-2,5-dimethyl-2 H-isoindole-4,7-dione (18), was isolated from the sponge Reniera sp. in 1982\textsuperscript{42}. The postulated structure was elucidated through extensive NMR studies and unambiguously confirmed by a four-step synthesis. In 1991, a more concise and elegant route to this antimicrobial metabolite was established by Schubert-Zsilavecz et al.\textsuperscript{43}.

**A. Synthesis of isoindole by heating paraformaldehyde and sarcosine:**

The reaction was initiated by heating paraformaldehyde (13) and sarcosine (14) in the presence of benzoquinone 16. This transformation proceeds via a 1,3-dipolar cycloaddition between the in situ formed azomethinylide 15 and the benzoquinone 16 to directly give 17 (Scheme 1). Spontaneous oxidation of the so-obtained cyclization adduct generates isoindole 18.
Scheme 1: Synthesis of isoindole 18.

Isoindoles have also found application as dyes. Pigment yellow 139 (12), which is sold by BASF as Paliotol Yellow K 1841 belongs to the class of highly resistant and effective 1, 3-disubstituted isoindoline dyes. Recently, the use of isoindoles as red to near-infrared fluorophores was reported. Another interesting isoindole-based dye, 25, arises from the condensation of primary amines with o-diacylbenzene 19 (Scheme 2). After initial formation of 20, isomerization to 21 and 22 can occur through a sequential dehydration–hydration process. Dimerization of 21 and 22 generates 23, the substrate for a formal retro-Aldol reaction. Loss of formaldehyde gives 24, which is spontaneously oxidized to the intensive blue-violet pigment 25. This reaction sequence is characterized by its high sensitivity and has found application as a marker in analytical chemistry (e.g. staining of primary amines).
Scheme 2: Staining amines with 1,4-diketone 19 (R = H).

10. Synthesis of Isoindolinone through Gabriel procedure

The Gabriel synthesis is a chemical reaction that transforms primary alkyl halides into primary amines. Traditionally, the reaction uses potassium phthalimide\textsuperscript{48,49,50}. The reaction is named after the German chemist Siegmund Gabriel\textsuperscript{51}. The Gabriel reaction has been generalized to include the alkylation of sulfonamides and imides, followed by deprotection, to obtain amines (see Alternative Gabriel reagents)\textsuperscript{52,53}.

The alkylation of ammonia is often an unselective and inefficient route to amines. In the Gabriel method, phthalimide anion is employed as a surrogate of H\textsubscript{2}N\textsuperscript{−}.

In this method, the sodium or potassium salt of phthalimide is N-alkylated with a primary alkyl halide to give the corresponding N-alkylphthalimide\textsuperscript{54,55}. The reaction fails with most secondary alkyl halides: Upon workup by acidic hydrolysis the primary amine is liberated as the amine salt\textsuperscript{57}. 
Scheme: Synthesis of Isoindolinone through Gabriel procedure.

Ing–Manske procedure, involving reaction with hydrazine. This method produces a precipitate of phthalhydrazide ($C_6H_4(CO)_2N_2H_4$) along with the primary amine:

$$C_6H_4(CO)_2NR + N_2H_4 \rightarrow C_6H_4(CO)_2N_2H_2 + RNH_2$$

The first technique often produces low yields or side products. Separation of phthalhydrazide can be challenging. For these reasons, other methods for liberating the amine from the phthalimide have been developed.$^{58}$

11. Recent Advances and Future Prospects of isoindoline Derivatives

Phthalimides possess a structural feature $–CO-N(R)-CO–$ and an imide ring which help them to be biologically active and pharmaceutically useful. Phthalimides have received attention due to their androgen receptor antagonists (Sharma et al., 2012)$^{59}$, anticonvulsant (Kathuria and Pathak, 2012)$^{60}$, antimicrobial (Khidre et al., 2011)$^{61}$, hypoglycaemic (Mbarki and Elhallaoui, 2012)$^{62}$, anti-inflammatory (Lima et al., 2002)$^{63}$, antitumour (Noguchi et al., 2005)$^{64}$, anxiolytic (Yosuva and Sabastiyan, 2012)$^{65}$, and anti HIV-1 activities (Sharma et al., 2010)$^{66}$. Several reports demonstrated the antimicrobial potential of phthalimide derivatives (Santos et al., 2009)$^{67}$.

Phthalimide derivatives of amino acid analogues possess anthelmintic activity (Srinivasan et al., 2010)$^{68}$. There is a growing interest in the usefulness of phthalimides and its derivatives. They have found relevance as inhibitors of tumor necrosis factor production.
Phthalimides have served as starting materials and intermediates for the synthesis of many types of alkaloids and pharmacophores.

Phthalimide is an imido derivative of phthalic acid. In organic chemistry, imide is a functional group consisting of two carbonyl groups bound to nitrogen. They are hydrophobic and neutral, and can therefore cross biological membranes in vivo. These compounds are structurally related to acid anhydrides (Azzawi and Razzak, 2011).

In N-Benzyl phthalimide the benzene and imide groups are planar and make a dihedral angle of 74.2 (1)° with one another. There are three weak C-HO hydrogen bonds, forming a two-dimensional network structure. Most of the imides are cyclic compounds derived from dicarboxylic acids and their names reflect the parent acid. Examples are succinimide derived from succinic acid and phthalimide derived from phthalic acid. As imide has the formula NH, being highly polar, imides exhibit good solubility in polar media. The N-H centre for imides derived from ammonia is acidic and can participate in hydrogen bonding.

11A. Effect of neighboring carbonyl groups on acidity of N-Bond

Imides such as phthalimide readily dissolve in aqueous NaOH as water-soluble salts. Imides are more acidic than amides. The order of acidity N- bond given in figure 1:

\[
\begin{align*}
    \text{amine} & \quad \text{amide} & \quad \text{imide} \\
    \text{pK}_a = 38 & < & \text{pK}_a = 15 - 17 & < & \text{pK}_a = 8 - 10
\end{align*}
\]

Fig. 1: increasing order of N-H acidity.
Phthalimide is highly acidic in nature due to it easily donate the proton and form water soluble salts with stronger bases. Reaction for salt formation is given in figure 2:

![Phthalimide salt formation with strong base.](image1)

Imides are more acidic than amides because:

1. The electron-withdrawing inductive of the two adjacent C=O groups weakens the N-H bond

2. More resonance delocalization of the negative charge. Phthalimide have resonance stabilized structures which are shown in figure 3:

![A Resonance-stabilized anion.](image2)

Phthalimides are oxidative stable, heat retardant, solvent resistant, and have superior mechanical properties. The specific reactivity of imides is a result of the relative acidity of the NH group, a direct consequence of the presence of the two carbonyl groups. It is also observed that the metal complexes are more active than the free organic ligand. Chelation reduces the polarity
of the metal ion and enhances the lipophilicity or hydrophobicity of metal chelate which favours its permeation through microbial cell wall. The metal chelates may also disturb the respiration process of the microbial cells and thus protein synthesis and further growth of the microorganism is hindered. Though the co-ordination of aliphatic tertiary amino nitrogen is not sterically favored, the high electron density available on the tertiary amino nitrogen favors its coordination to a metal ion where there is a possibility for chelation (Ramesh and Sabastiyan, 2012)\(^7\).

The phthalimide moiety serves as a ‘protected’ form of ammonia. The phthalimide carbonyls increase the acidity of the nitrogen (thus allowing formation of its conjugate base). Most importantly, the phthalimide carbonyls protect the nitrogen from ‘over alkylation’ thus preventing the formation of quaternary ammonium salts. N-benzoyl phthalimide resembles both classical benzodiazepines and barbituric acid structure. It consists of tricyclic hydrophobic structure comparable to that of benzodiazepines and possesses a conjugated ureid functional group as can be found in barbiturates. Size and tridimensional structure of benzodiazepines and phthalimide backbones are similar (Hassanzadeh et al., 2011)\(^7\).

Phthalimide and N-substituted phthalimides are an important class of compounds because they possess important biological activities the identifiable structural features for their activity are as: hydrophobic aryl ring, a hydrogen bonding domain, an electron-donor group, another distal hydrophobic site Bhat and Al-Omar (2011)\(^7\). \(4\)-(Phthalimide)-substituted phenoxy propanolamines also possessed cardioselective \(\beta\)-adrenergic receptor binding affinity (Jindal et al., 2005)\(^7\). Some marketed pharmaceutical products of phthalimide derivatives are reported in table 1.

<table>
<thead>
<tr>
<th>S. N.</th>
<th>Structure</th>
<th>Name</th>
<th>Use</th>
</tr>
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<td>Name</td>
<td>Reference</td>
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<td>---</td>
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<td>2</td>
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<tr>
<td>3</td>
<td><img src="image2" alt="Thalidomide" /></td>
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<td>Wu et al., (2005)</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<td>Schett et al., (2010)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image5" alt="LASSBio-468" /></td>
<td>LASSBio-468</td>
<td>Barbosa et al., (2012)</td>
</tr>
</tbody>
</table>
B. Preparation of phthalimide moiety

synthetic reactions for preparation of phthalimide moiety summarized in scheme 1:

Scheme. 1: Reactions for preparation of phthalimide moiety.
C. Mathews Reaction

The Mathews’ reaction, a ‘dry’ hydrolysis procedure of nitriles by phthalic acid or amides by phthalic anhydride to give the corresponding carboxylic acid and phthalimide. Mathews’ reaction is given in scheme 2:

Scheme. 2: Synthesis of phthalimide by Mathews’ reaction.

11D. Synthesis of imides in the presence of formamide as reagent.

A general and interesting synthetic pathway for the synthesis of imides by direct condensation using cyclic anhydrides or their corresponding dicarboxylic acids and form amide which is a simple affordable reagent. This approach has the advantage that this specific reagent
can also serve as solvent, especially for aliphatic imides. For aromatic cyclic imides with lower solubility in formamide, another appropriate solvent can be supplementary used in order to maintain a homogeneous reaction medium and to allow the main product to be obtained in high yields. Synthesis of phthalimide in presence of formamide reagent given in scheme 3:

Scheme. 3: Synthesis of imides in the presence of formamide as reagent.

**11E. Preparation and mechanism of Phthalimide by Condensation reaction**

Chiriac et al., (2007)\(^7\) reported that aromatic or aliphatic cyclic imides and their derivatives are obtained by the reaction of dicarboxylic acids or their corresponding anhydrides with reagents bearing a reactive amino (–NH\(_2\)) functional group, through a nucleophilic attack of amino group to a anhydride moiety, by mechanism presented in figure 4:
12. Biological Activity of Pthalimide Derivatives Along with Structure Activity Relationship study

A. Cytotoxic Activity

Stanton et al., (2008) demonstrated that presence of benzothiazole unit attached to nitrogen of phthalimide, exhibits cytotoxic activity (compound 1) carried out ‘one pot’ condensation reaction for the synthesis of phthalic imide derivative (benzothiazole containing phthalimide), exhibiting in vitro cytotoxic potential on human cancer cell lines. They further reported that both caspase dependent and independent pathways were involved in the induction
of apoptosis in cancer cells. Khokra et al., (2011) synthesized some benzothiazole containing phthalimide derivatives were found to exhibit in-vitro cytotoxic potential on human cancer cell lines.

Singh et al., (2011) designed and evaluated anticancer activity of some novel isoindoline-1, 3-dione derivatives. It may act due to multiple events or apoptosis inducer. The compounds 2 and 3 showed significant anticancer activity. It may be due to chloro-phenyl ring attached to the isoindoline-1, 3-dione with ethyl groups respectively or the compound 2 at 2, 4 positions di-chloro-substitution and in compound 3 chloro-substitution at 4 positions of phenyl ring. From the structural point of view, the chloro group which has the electron withdrawing property may be the crucial for tumor weight inhibition and tumor cell inhibition.

![Leo.png](https://example.com/Leo.png)

The isoindoline-1, 3-dione derivatives were evaluated for in vivo anticancer activity against the Ehrlich Ascites Carcinoma bearing mice model. Male Swiss albino mice were used as test animals. The synthesized compounds were administered intraperitoneally at a dose of 20-25 mg/kg body wt. per day for seven days after 24 hrs of tumor inoculation in mice. The standard drug used was 5-Fluorouracil (20 mg/kg, b. wt.). Compounds treated (III-VII) groups were found to reduce the body weight, tumor volume, packed cell volume, viable cell count and increase the tumor weight (%) inhibition, ascites cells (%) inhibition and non-viable cell count and Increase in life span (% ILS). Compound 2 showed the highest inhibition of cancerous cell growth compared to compound 3. From the present study, it can be concluded that isoindoline-1, 3-dione derivatives might have potent anti-proliferative activity.
Yang et al., (2010) designed and synthesized a series of structurally diverse heterocycle substituted phthalimide derivatives including furan, imidazo-[1,2-a]-pyridine, 1,3,4-thiadiazine, imidazo-[2,1-b][1,3,4]-thiadiazine, pyrazole, thiazole, thiazoline, etc by the reactions of α-bromoketone intermediate with various nucleophiles containing oxygen, nitrogen and sulfur atom. Their cytotoxic activities were also evaluated against five human cancer cell lines in vitro and were found to be potent. The researchers concluded that a large number of structurally diverse phthalimide derivatives for drug development can be synthesized by this method.
Selvum et al., (2013)\textsuperscript{80} reported some new N-substituted phthalimide derivatives (compound 6 and 7) been synthesized by condensation of phthalic anhydride and primary amines. Synthesized compounds were screened for antiviral activity against HIV-1 and -2 replication in MT-4 cells. Cytotoxicity was also investigated in uninfected MT-4 cells. All the synthesized compounds exhibited cytotoxicity in MT-4 cells (CC50: 84-125 μg/ml).

![N-substituted phthalimide derivatives](image)

Chan et al., (2008)\textsuperscript{81} carried out ‘one pot’ condensation reaction for the synthesis and potent antiproliferative inhibition of a phthalimide based ketones. One of the molecule, 2-Phthalimide-1-(4-fluoro-phenyl) ethanone, had the best growth inhibition on human MDAMB-231 breast carcinoma and SKHep-1 hepatoma cell lines. The bioactivity of the molecule was
reported to be due to the presence of strong electronegative fluorine group at the para-position of the aryl ring (compound 8).

\[ \text{X} = \text{CH}_2, \text{CH(CH}_3)\]
\[ \text{Ar}= \text{Ph}, 4-\text{F-Ph} \]

B. Antimicrobial activity

Pawar et al., (2012) synthesized and investigated structural modifications of phthalimide to various N-alkyl (compound 9) and N-alkyloxy derivatives (compound 10) have been reported to result in modification of biological activity. N-alkyl and N-alkyloxy produce potent fungicidal action due to which they are extensively used as pesticides, preservatives as well as pharmaceuticals.

\[ \text{Ar} = -\text{C}_6\text{H}_5, -\text{p-CH}_3\text{-C}_6\text{H}_4, -\text{p-OCH}_3\text{-C}_6\text{H}_4, -\text{o-OCH}_3\text{-C}_6\text{H}_4, -\text{p-NO}_2\text{-C}_6\text{H}_4, -\text{C}_{10}\text{H}_7 \]

Atukuri et al., (2011) demonstrated that 1, 2, 4-triazolinone derivatives of phthalimide (compound 11) possess anti tubercular activity.
Bhambhi et al., (2009) reported that alkoxy derivative of phthalimide (compound 12 and 13) possess potent fungicidal, trypanocidal, they inhibit the growth of Plasmodium falciparum. The synthesized compounds were tested for their biological activity against bacteria and fungi.

Santos et al., (2009) synthesized a series of phthalimide derivatives. All compounds were evaluated against Mycobacterium tuberculosis H37Rv using Alamar Blue susceptibility. They suggested that the lead compounds have the potency in the treatment of tuberculosis and multi-drug resistant tuberculosis.

It has been shown that hybridization of both phthalimide (Thalidomide) and sulfonamide (Dapsone) moiety leads to compounds with activity against M. leprae. In this sense, the design
of new products such as anti-TB agents is interesting. SAR study of a series of derivatives (compound 14) showed that if the pyrimidine ring is substituted in any position or changed by an isosteric, this decreases activity on M. tuberculosis. Amino group substitutions by another phthalimide ring also lead to a decrease in anti-TB activity. Modifications in the pyridine ring decrease anti-TB activity. Introduction of a phthalimide group by molecular hybridization did not produce compounds with an activity similar to isoniazid (INH).

C. Anticonvulsant activity

Bhat et al., (2010) synthesized and demonstrated a series of novel 1, 3, 4-oxadiazole derivatives of phthalimide and evaluated their anticonvulsant and neurotoxicity studies. Compound having methoxy substitution at para position of the distal aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity. The presence of methoxy group in ring B causes more lipophilic character of the molecule. Distal hydrophobic center alters the bioavailability of compounds. It was established fact that there are at least four parameters for anticonvulsant drugs: lipophilic domain, distal aryl ring (hydrophobic centre) whose size effects
pharmacokinetic properties, (-CONH) acts as hydrogen donor, an electron donor (C=N) system is also present.

Phthalimide derivatives of 1, 3, 4-oxadiazole (compounds 15 a-j) were screened for anticonvulsant activity. All the compounds were active in MES test, making them useful for broad spectrum of seizure type.

Bhat et al., (2011) synthesized and investigated Schiff bases (compound 16) with phthalimide pharmacophore and evaluated for anticonvulsant and neurotoxic properties.

Anticonvulsant screening was performed using MES test. All the Schiff bases of phthalimides were active in the MES test indicative of their ability to prevent seizure spread. All the compounds...
were less neurotoxic than phenytoin. The evaluation of compounds indicated the importance of
the size of the group at the carbimino carbon atom. Replacement of the hydrogen atom on the
carbimino carbon atom by methyl group is leading to an increase in the size at this position of
the molecule and has shown a change in activity. This modification may increase the
anticonvulsant activity because of additional vander walls bonding or alternately steric
impedance to alignment at the binding site causing lower activity or its loss. The attachment of
distal aryl ring to the proximal aryl ring increases the vander Walls bonding at the binding site
and increases potency. The distal aryl ring at carbimino terminal (benzylidene ring) is
essential for the pharmacokinetic properties of compounds since the variation in the substitution at the
distal.

Aryl ring was found to affect biological activity. During metabolism, the distal aryl ring is expected
to be p-hydroxylated. Introduction of nitro substitution showed more protection at as compared
to methyl, chloro and hydroxy substitution at distal aryl ring. Compound with nitro substitution
at ortho-position of distal aryl ring have emerged as the most promising anticonvulsant agent
with low neurotoxicity.

Arti et al., (2011) synthesized and reported that substituted 4-Pthalamido-N-Phenyl-
benzene sulphonamide 17 (a-e) derivatives possessed anticonvulsant activity which was
evaluated by MES (maximal electric shock-induced seizure) method. In substituted phthalimido
sulphonamide series aniline derivative showed least anti-convulsant activity (i.e., R=H), but 4-
nitro derivatives (R=NO2) were found to be effective than chloro derivatives (R= Cl). Electron
withdrawing nitro derivatives were found to be effective than electron donating aniline

![Substituted 4-Pthalamido-N-Phenylbenzenesulphonamide](image)

17a: H 17b: 4-NO2 17c: 4-Br 17d: 4-Cl 17e: 2-Cl
derivative which were found to be ineffective. Sulphonamide (compound 17a-e) derivatives possessed anticonvulsant activity which was evaluated by MES (maximal electric shock-induced seizure) method. In substituted phthalimido sulphonamide series aniline derivative showed least anti-convulsant activity (i.e., R=H), but 4-nitro derivatives (R=NO₂) were found to be effective than chloro derivatives (R= Cl). Electron withdrawing nitro derivatives were found to be effective than electron donating aniline derivative which were found to be ineffective.

Wieck et al., (2009) synthesized two series of phthalimides one that possessed an N-phenoxyalkyl moiety substituted at position 3 or 4 of the phenyl ring and a series of N-alkenyl or alkinyl phthalimides (compound 18). They evaluated their anticonvulsant activity and estimated their lipophilicity in silico using computer programs.

The anticonvulsant activity of phthalimides containing an unsaturated substituent at the phthalimide nitrogen was superior to that of the N-phenoxyalkyl phthalimides.

![Phthalimide structure](image-url)
Khan et al., (2009) synthesized and evaluated a series of 4-(5-bromo-1,3-dioxo-1,3-dihydro-2H-isooindol-2-yl)-butyrI N-(substituted phenyl) amides (compound 19) for their anticonvulsant activity in MES test according to the protocols of Antiepileptic Drug Development (ADD) programme of National Institutes of Health (NIH, Bethesda, USA). The studies revealed that the alkyl substitution at the aromatic ring was essential for activity being lipophilic in nature.

D. Anxiolytic activity

Hassanzadeh et al., (2007) synthesized and evaluated N-Benzoyl phthalimide and N-Benzyolphthalimide for their anxiolytic activity and demonstrated that N-Benzoyl Phthalimide possesses excellent anxiolytic activity. N-Benzoyl-3-nitrophthalimide (compound 21) showed a lower activity compare to that of diazepam and N-benzoil phthalimide (compound 20). An
electron withdrawing group (Cl, NO$_2$) on C$_7$ of benzodiazepines is essential for sedative and anxiolytic activities of classic benzodiazepine agonists. Substitution of Cl or NO$_2$ on other positions of the aromatic ring (6, 8, and 9) of benzodiazepines dramatically reduce activity. Reduction in activity of N-benzoyl 3-nitro-phthalimide might be due to the improper accommodation of electron withdrawing group (NO$_2$) in the benzodiazepine active site. Substitution of an electron donating group (CH$_3$) on the C ring of the parent compound in N-(4’-methylbenzoyl)-phthalimide (compound 22) and N-(4’-methylbenzoyl)-3-nitro-phthalimide (compound 23) were also in favor for anxiolytic activity, this also has been seen in benzodiazepine series. Substitution at the 4’-(para)-position of the phenyl ring of benzodiazepines is unfavorable for N-Benzyl Phthalimide (ortho)-substituents are not detrimental to agonist activity.

N-Benzyl 3-nitro-phthalimide (compound 25) distorted from planarity due to the change of C=O group of N-benzoyl phthalimide to CH$_2$ group. This distortion probably prevents the accommodation of the compound with its receptor and makes the compound ineffective as an anxiolytic agent. In benzodiazepines, the phenyl ring is attached directly to the ring B and its relationship to the ring a planarity may be important for agonist activity.

**E. α-Glucosidase inhibitory activity**

Ibrahim Ali et al., (2009)$^{92}$ demonstrated that N-Phenyl-3, 4, 5, 6-tetrachlorophthalimide and N-(4-phenylbutyl)-3, 4, 5, 6-tetrachloro-phthalimide (compound 26) showed very potent α-Glucosidase inhibitory activity. Potency of tricyclic Phthalimide derivatives could be achieved by
increasing the overall lipophilicity of the molecules and by incorporating halogen substituents in the benzylic aromatic ring attached to the phthalimido nitrogen atom.

Pascale et al., (2010)\textsuperscript{93} synthesized and investigated alpha glucose inhibitors, bearing a phthalimide moiety connected to a variously substituted phenoxy ring by an alkyl chain that inhibited alpha glucosidase which is the key enzyme which catalyzes the final step in the digestive process of carbohydrates in mammalians. Hence, alpha glucosidase inhibitors can retard the liberation of D-glucose of oligosaccharides and disaccharides from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial plasma glucose levels and suppressed postprandial hyperglycaemia.

In particular, basing on pharmacological studies involving thalidomide, it was found that phenyl alkyl tetrachlorophthalimide derivatives exhibited potent $\alpha$-glucosidase inhibition. The structure activity relationship studies revealed the importance of the distance between the Phthalimide ring and the phenyl moiety and the positive influence of electron withdrawing groups attached to the Phthalimide moiety. Although tetrachlorophthalimide skeleton is a useful non-sugar type sugar mimic pharmacophore, the above mentioned compounds are characterized by high lipophilic.

The which could influence their pharmacokinetic properties and biological activity. A large series of phenoxyalkyl derivatives (compound 27), bearing a non-substituted phthalimide moiety, were prepared in order to investigate structure activity relationships and improve $\alpha$-Glucosidase
inhibitory activity. In particular, the effects of substitutions at the aryloxy moiety

and the length of the methylene spacer between the phthalimide group and the phenoxy moiety were investigated.

The length of the methylene spacer seems to be critical for enzyme inhibition. The potency of the α-glucosidase inhibitory activity increased as the length of the methylene spacer increased to \( n = 10 \). Introduction of a chlorine atom at the para-position \((R_2 = \text{Cl})\), caused the enhancement of the activity, which seemed to be further increased by the introduction of one or two additional methyl groups at the ortho-positions \((R_1 = R_2 = \text{CH}_3)\).

N-(phenoxydecyl) phthalimide derivatives (compound \(28\)), presence of an electron withdrawing group \((\text{NO}_2, \text{CF}_3\text{ etc.})\) at the 4-position \((R_3)\) were more potent than the corresponding 4-methyl derivative. Introduction of a nitro group at the ortho position \((R_1)\) of markedly enhanced the activity giving the most potent compound. However presence of two strong electron-withdrawing groups at the phenoxy ring simultaneously did not increase the activity.
F. Anti inflammatory activity

Qaisi Jinan et al., (2011) evaluated amino acetylenic isoindoline derivative (compound 29) for anti-inflammatory activity.

![Aminoacetylenic isoindoline derivatives.](image)

Stewart et al., (2010) demonstrated that thalidomide analogues (compound 30, 31) containing either a phenyl or alkyne using Sonogashira and Suzuki cross coupling reactions from their aryl halogenated precursors. All the thalidomide analogues were evaluated for their ability to inhibit the expression of the proinflammatory cytokine Tumor Necrosis Factor (TNF).

Orzeszko et al., (2010) Compounds containing an aryl-isobutyl or aryl isopropoxy groups were reported to be several times more active than thalidomide in inhibiting TNF expression and apoptotic response.

Shakir *et al.*, (2007) synthesized aminoacetylenic isoindoline-1, 3-dione (compound 33) and showed their anti-inflammatory activities by reducing carrageenan-induced rat paw edema and modulating proinflammatory and anti-inflammatory cytokines.
G. Anti viral activity and Anti HIV activity

Bansal et al., (2007) demonstrated that increased HIV-1 inhibitory potency of tricyclic phthalimide derivatives could be achieved by increasing the overall lipophilicity of the molecules and by incorporating halogen substituents in the benzylic aromatic ring attached to the phthalimido nitrogen atom. Molecular flexibility and hydrophobicity predominantly govern the integrase inhibitory activity of phthalimides.

Molecular flexibility increases with the number of flexible bonds in the molecule and the importance associated with flexible bond might be owing to the fact that they play an important role in the orientation of pharmacophoric groups in the active site of the enzyme. Hydrophobic substituents in the molecule might influence enzyme-drug affinity through non-specific interactions with hydrophobic region in the active site of the enzyme. Furthermore, it appears that the halogen substitution in the phenyl ring plays a significant role molecule enzyme affinity, a fact reflected in increased integrase inhibitory potency exhibited by molecules with halogen substituents (compound 34) Presence of bulky groups and electronegative atoms in the molecule disfavors the HIV-1 integrase inhibitory affinity of the title compounds.
H. Anti-influenza activity

Yuma et al., (2010)\textsuperscript{100} identified potential and novel anti-influenza agents by screening the synthesized phenethyl phenyl phthalimide analogues (compound 36) on PA endonuclease inhibition assay and anti-influenza A virus assay. The four analogs were found to inhibit PA endonuclease and retard the growth of influenza A. The results also indicated that PA endonuclease assay may also be utilised in the screening of anti-influenza drugs and is useful for future strategies to develop novel anti-influenza A drugs and for mapping the function of the influenza A RNA polymerase subunit.

\[
\text{X} = \text{H, Cl} \\
\text{R1, R2} = \text{H, OH}
\]

i) Anti-Angiogenesis Activity

Noguchi et al., (2005)\textsuperscript{101} revealed that 5-Hydroxy-2-(2, 6-diisopropylphenyl)-1H-isoindole-1, 3-dione (compound 37), obtained from structural development studies on thalidomide, was found
to possess potent anti-angiogenic activity in a human umbilical vein endothelial cell (HUVEC) assay. Thalidomide and its metabolite, 5-hydroxythalidomide (compound 38) showed weak or moderate activity in the same assay.

Nagarajan et al., (2013) synthesized benzothiazole and benzimidazole containing phthalimide derivatives (39, 40, 41 & 42) and their anti-angiogenic activity was evaluated using ex vivo egg yolk angiogenesis model.
J. Histone deacetylase (HDAC) inhibitors

Chihiro et al., (2007)\textsuperscript{103} designed and synthesized several hydroxamic acid derivatives with a substituted phthalimide group (compound 43) as histone deacetylase (HDAC) inhibitors.

Further, with SAR studies they concluded that the distance between the N-hydroxyl group and the cap structure are important for HDAC-inhibitory activity.

K. Thromboxanee inhibitory activity

Yoshiaki et al., (1999)\textsuperscript{104} synthesized a series of novel 1-isoindolinone derivatives, which inhibited the contraction of pig coronary artery induced by U-46619, a thromboxane A2 analogue. The activities of p-hydroxybenzyl type and p-hydroxyphenyl-ethyl type compounds 44, 45 and 46 were inhibitory activity.
2. Present work: Synthesis & characterization of 5, 6- Disubstitutedaroylisoindoline-1, 3-dione

2.1 Rationale for present work:

Heterocyclic compounds containing the isoindolinone skeleton have generated considerable interest in recent years as reflected by recent articles dealing with their synthesis and emphasizing their biological and medicinal properties. Isoindoline-1, 3-dione was structural feature -CO-N(R)-CO- and an amide ring which help them to be biologically active and pharmaceutically useful. Our interest in, isoindolinones stemmed from their fascinating chemistry, pharmaceutical and medicinal properties.

Recent Advances and Future Prospects of isoindoline Derivatives, a) Effect of neighboring carbonyl groups on acidity of N-Bond, b) Preparation of phthalamide moiety, c) Mathews Reaction, d) Synthesis of imides in the presence of formamide as reagent, e) Preparation and mechanism of phthalamide by Condensation reaction. Naturally occurring and synthetic isoindolin-1,3-diones have a range of biological activities including, a) Cytotoxic Activity, b) Antimicrobial activity, c) Anticonvulsant activity, d) Anxiolytic activity, e) α-Glucosidase inhibitory activity, f) Anti inflammatory activity, g) Anti viral activity & Anti HIV activity, h)Anti- influenza activity, i) Anti-Angiogenesis Activity, j) Histone deacetylase (HDAC) inhibitors, k) Thromboxane inhibitory activity.

In view of the extensive natural occurrence and biological importance of isoindolin-1,3-dione derivatives to develop a general and facile method for the synthesis of isoindoline-1,3-dione. We became interested in the synthesis of isoindoline-1,3-dione from phthalamide.
2. 2 Results and discussion:

2. 2. 1: Synthesis of 5, 6- Disubstitutedaroylisouindoline-1, 3-dione 7- 11.

The compounds 7- 11 were synthesized by treating Phthalimide with different aroylchlorides in the Presence of solvent 1, 4-dioxane at room temperature for 16- 18 hours or 1, 4-dioxane with AlCl₃ at room temperature for 6-7 hours as shown in Scheme-1, Scheme-2 and Table-1.

Scheme-1:

- 2, 7 R= C₆H₄CH₃ (p)
- 3, 8 R= C₆H₄Cl (p)
- 4, 9 R= C₆H₅
- 5, 10 R= CH₃

Scheme-2:

- 6, 11 R= SO₂C₆H₄CH₃ (p)
<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Substrate</th>
<th>Reagents and conditions</th>
<th>Products</th>
<th>m. p (^\circ)C</th>
<th>Yield (%)</th>
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</thead>
<tbody>
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<td>1.</td>
<td>p-CH(_3)C(_6)H(_4)COCl</td>
<td>1, 4-dioxane r. t, 16-18 h or 1, 4-dioxane with AlCl(_3), r. t, 6-7</td>
<td><img src="image1.png" alt="Image" /></td>
<td>168-170</td>
<td>92</td>
</tr>
<tr>
<td>2.</td>
<td>p-ClC(_6)H(_4)COCl</td>
<td>1, 4-dioxane r. t, 16-18 h or 1, 4-dioxane with AlCl(_3), r. t, 6-7</td>
<td><img src="image2.png" alt="Image" /></td>
<td>217-118</td>
<td>90</td>
</tr>
<tr>
<td>3.</td>
<td>C(_6)H(_5)COCl</td>
<td>1, 4-dioxane r. t, 16-18 h or 1, 4-dioxane with AlCl(_3), r. t, 6-7 h</td>
<td><img src="image3.png" alt="Image" /></td>
<td>230-232</td>
<td>92</td>
</tr>
<tr>
<td>4.</td>
<td>CH(_3)COCl</td>
<td>1, 4-dioxane r. t, 16-18 h or 1, 4-dioxane with AlCl(_3), r. t, 6-7</td>
<td><img src="image4.png" alt="Image" /></td>
<td>138-140</td>
<td>90</td>
</tr>
</tbody>
</table>
The reaction between Phthalimide and aroylchloride was performed basic medium such as KOH in ethanol, Et$_3$N in acetone, K$_2$CO$_3$ in acetone and in pyridine but no desired product was obtained. The reaction also carried out in neutral medium in different solvents such as 1, 4-dioxane, Benzene, DMF, DMSO, THF and acetone at room temperature to allevated temperature (25-80 °C) for 6-24 h. The satisfactory results were obtained in case of 1, 4-dioxane at room temperature for 16-18 h. The coupling reaction between Phthalimide and aroylchloride was done by using AlCl$_3$ as Lewis acid in 1, 4-dioxane at room temperature for 6-7 h and desired products were obtained in good yields. The reactions of Phthalimide and different aroylchloride were used in the reaction and ratio 1:3 (Phthalimide to aroylchloride) was found to be best reaction to obtain the complete reaction.

Therefore, the best reaction condition was obtained by using 1, 4-dioxane at room temperature for 16-18 h.

2.3.1: Characterization of 5, 6-di-p-methylbenzoyl isoindoline-1, 3-dione 7

The compound 7 was synthesized from phthalimidine (Isoindoline 1, 3-dione) with the reaction of p-methyl benzoyl chloride by stirring at room temperature for 16-18 hours in the presence of solvent 1, 4-dioxane or stirring at room temperature for 6-7 hours in the presence of solvent 1, 4-dioxane with AlCl$_3$. 
The structure of the compound was established by various spectral data.

In IR spectrum of the compound 7, the absorption band was found at 3050 cm\(^{-1}\) due to the C-H (aromatic) absorption, whereas a broad band at 3197.12 cm\(^{-1}\) Stretching absorption represents the N-H aliphatic group. Absorption band at 1750 cm\(^{-1}\) display keto group. Stretching absorption 1053.85 cm\(^{-1}\), 1285.53 cm\(^{-1}\) stretching bands indicated the presence of C-N. Stretching absorption 1419.66 cm\(^{-1}\) and 1375 cm\(^{-1}\) stretching bands indicated the presence of C-C (aromatic) and C-H respectfully.

In \(^1\)H NMR spectrum of compound 7, the chemical shift at \(\delta_H\) 2.45 (s, 2 x 3H, Ar-CH\(_3\)) was found as a singlet for the hydrogen atom in two CH\(_3\) groups. Chemical shift at \(\delta_H\) 7.89 (d, 2 x 2H, Ar-H, \(J=6.4\) Hz) showed a doublet for atomic protons of H-2', H-6' carbon of two phenyl rings and \(\delta_H\) 7.30 (d, 2x2H, Ar-H, \(J=6.4\) Hz) showed another doublet for similar protons of H-3', H-5' carbon of two phenyl rings and \(\delta_H\) 8.52 (s, 2x1H,Ar-H) showed singlet for protons of H-4, H-7. The chemical shift at \(\delta_H\) 10.43 (s, H ) showed singlet for protons of N-H.

In the \(^{13}\)C NMR spectral data of compound 7, the chemical shift at \(\delta\) 21.72 indicated the presence of two identical carbons in two methyl groups (Ar-CH\(_3\)). The chemical shift at \(\delta\) 123.64 was found for the C-4, C-7 of phenyl rings. The peak at \(\delta\) 126.66 represents the aromatic carbon of C-3', C-5'. The chemical shift at \(\delta\) 129.20 was obtained for the carbons C-2', C-6'. The chemical shift at \(\delta\) 130.26 was obtained for the carbons C-8, C-9 and the chemical shift at \(\delta\) 132.68 was obtained for the carbons C-5, C-6. The chemical shift \(\delta\) 134.34 was obtained for the carbons C-1'. The chemical shift \(\delta\) 144.60 was obtained for the carbons C-4' and the chemical shift \(\delta\) 168.49 was obtained for the carbons C-1, C-3. The chemical shift at \(\delta\) 172.16 was obtained for the carbonyl ketones in the carbons of C-10.
2.3.2: Characterization of 5, 6-di-p-chlorobenzoyl isoindoline-1, 3-dione 8

The compound 8 was synthesized from phthalimidine ( Isoindoline 1, 3-dione ) with the reaction of p-chlorobenzoyl chloride by stirring at room temperature for 16-18 hours in the presence of solvent 1, 4-dioxane or stirring at room temperature for 6-7 hours in the presence of solvent 1, 4-dioxane with AlCl₃.

The structure of the compound was established by various spectral data.

In IR spectrum of the compound 8, the absorption band was found at 3050 cm⁻¹ due to the C-H (aromatic) absorption, whereas a broad band at 3198 cm⁻¹ Stretching absorption represents the N-H aliphatic group. Absorption band at 1700 cm⁻¹ display keto group. Stretching absorption 1098 cm⁻¹, 1176.62 cm⁻¹ stretching bands indicated the presence of C-N. Stretching absorption 1432.44 cm⁻¹ and 1600 cm⁻¹ stretching bands indicated the presence of C=C (aromatic) and 548.77 cm⁻¹ and 714.65 cm⁻¹ indicated the presence of C-Cl respectfully.

In ¹H NMR spectrum of compound 8, the chemical shift at δ_H 7.80 (d, 2 x H, Ar-H, J=8.4) showed a doublet for atomic protons of H-2', H-6' carbon of two phenyl rings and δ_H 7.53 (d, 2x2H, Ar-H, J=8.4) showed another doublet for similar protons of H-3', H-5' carbon of two phenyl rings and δ_H 7.93 (s, 2x1H, Ar-H) showed singlet for protons of H-4, H-7. The chemical shift at δ_H 11.30 (s, H) showed singlet for protons of N-H.
In the $^{13}$C NMR spectral data of compound 8, the chemical shift at δ 123.35 was found for the C-4, C-7 of phenyl rings. The peak at δ 129.14 represents the aromatic carbon of C-3', C-5'. The chemical shift at δ 130.09 was obtained for the carbons C-2', C-6'. The chemical shift at δ 131.57 was obtained for the carbons C-8, C-9 and the chemical shift at δ 133.05 was obtained for the carbons C-5, C-6. The chemical shift δ 134.72 was obtained for the carbons C-1'. The chemical shift δ 138.26 was obtained for the carbons C-4' and the chemical shift δ 166.92 was obtained for the carbons C-1, C-3. The chemical shift at δ 169.67 was obtained for the carbonyl ketones in the carbons of C-10.

![Chemical structure of compound 8](image)

### 2.3.3: Characterization of 5, 6-dibenzoyl isoindoline-1, 3-dione 9

The compound 9 was synthesized from phthalimidine (Isoindoline 1, 3-dione) with the reaction of benzoyl chloride by stirring at room temperature for 16-18 hours in the presence of solvent 1, 4-dioxane or stirring at room temperature for 6-7 hours in the presence of solvent 1, 4-dioxane with AlCl$_3$.

The structure of the compound was established by various spectral data.

In IR spectrum of the compound 9, the absorption band was found at 3050 cm$^{-1}$ due to the C-H (aromatic) absorption, whereas a broad band at 3210.76 cm$^{-1}$ Stretching absorption represents the N-H aliphatic group. Absorption band at 1748 cm$^{-1}$ display keto group. Stretching absorption 1050.17 cm$^{-1}$, 1140.93 cm$^{-1}$ and 1185.30 cm$^{-1}$ stetching bands indicated the presence of C-N. Stetching absorption 1468.84 cm$^{-1}$ and 1600 cm$^{-1}$ stetching bands indicated the presence of C=C (aromatic) respectfully.
In $^1\text{H}$ NMR spectrum of compound 9, the chemical shift at $\delta_{\text{H}}$ 7.94 (d, 2x2H, Ar-H, $J$=6.8 Hz) showed a doublet for atomic protons of H-2', H-6' carbon of two phenyl rings and $\delta_{\text{H}}$ 7.50 (d, 2x2H, Ar-H, $J$=6.8 Hz) showed another doublet for similar protons of H-3', H-5' carbon of two phenyl rings, $\delta_{\text{H}}$ 7.60 (d, 2x2H, Ar-H, $J$=6.4 Hz) showed another doublet for protons of H-4' carbon of two phenyl rings and $\delta_{\text{H}}$ 7.81 (s, 2xH,Ar-H) showed singlet for protons of H-4, C-7. The chemical shift at $\delta_{\text{H}}$ 11.33 (s, H) showed singlet for protons of N-H.

In the $^{13}\text{C}$ NMR spectral data of compound 9, the chemical shift at $\delta$ 123.36 was found for the C-4, C-7 of phenyl rings. The peak at $\delta$ 128.99 represents the aromatic carbon of C-3', C-5'. The chemical shift at $\delta$ 129.69 was obtained for the carbons C-2', C-6'. The chemical shift at $\delta$ 131.16 was obtained for the carbons C-4'. The chemical shift at $\delta$ 132.99 was obtained for the carbons C-8, C-9 and the chemical shift at $\delta$ 133.29 was obtained for the carbons C-5, C-6. The chemical shift $\delta$ 134.75 was obtained for the carbons C-1'. The chemical shift $\delta$ 167.82 was obtained for the carbons C-1, C-3. The chemical shift at $\delta$ 169.71 was obtained for the carbonyl ketones in the carbons of C-10.

![Chemical Structure](image)

2.3.4: Characterization of 5, 6-di-acetyl isoindoline-1, 3-dione 10

The compound 10 was synthesized from phthalimidine (Isoindoline 1, 3-dione) with the reaction of acetylchloride by stirring at room temperature for 16-18 hours in the presence of solvent 1, 4-dioxane or stirring at room temperature for 6-7 hours in the presence of solvent 1, 4-dioxane with $\text{AlCl}_3$.

The structure of the compound was established by various spectral data.
In IR spectrum of the compound 10, the absorption band was found at 3050 cm\(^{-1}\) due to the C-H (aromatic) absorption. The absorption band was found at 1375 cm\(^{-1}\) due to the C-H (CH\(_3\)) absorption, whereas a broad band at 3200 cm\(^{-1}\) Stretching absorption represents the N-H aliphatic group. Absorption band at 1750 cm\(^{-1}\) display keto group. Stretching absorption 1089.82 cm\(^{-1}\), 1140.93 cm\(^{-1}\) and 1184.33 cm\(^{-1}\) stretching bands indicated the presence of C-N. Stretching absorption 1604.83 cm\(^{-1}\), 1419.66 cm\(^{-1}\) and 1375 cm\(^{-1}\) stretching bands indicated the presence C=C, C-C (aromatic) and C-H respectfully.

In \(^1\)H NMR spectrum of compound 10, the chemical shift at \(\delta_H\) 3.42 (s, 2 x 3H, C-CH\(_3\)) was found as a singlet for the hydrogen atom in two CH\(_3\) groups. Chemical shift at \(\delta_H\) 7.81 (s, 2xH, Ar-H) showed singlet for protons of H-4, H-7. The chemical shift at \(\delta_H\) 11.32 ( s, H ) showed singlet for protons of N-H.

In the \(^{13}\)C NMR spectral data of compound 10, the chemical shift at \(\delta\) 21.72 indicated the presence of two identical carbons in two methyl groups. The chemical shift at \(\delta\) 123.64 was found for the C-4, C-7 of phenyl rings. The chemical shift at \(\delta\) 130.68 was obtained for the carbons C-8, C-9 and the chemical shift at \(\delta\) 132.26 was obtained for the carbons C-5, C-6. The chemical shift \(\delta\) 168.49 was obtained for the carbons C-1, C-3. The chemical shift at \(\delta\) 172.16 was obtained for the carbonyl ketones in the carbons of C-10.

![Chemical Structure](image)

2.3.5: Characterization of di-p-tolyl-1, 3-dioxoisoindoline-5, 6-disulfinate 11

The compound 11 was synthesized from phthalimidine (Isoindoline 1, 3-dione ) with the reaction of p-tolyl sulfonylchloride by stirring at room temperature for 16- 18 hours in the presence of solvent 1, 4-dioxane or stirring at room temperature for 6-7 hours in the presence of solvent 1, 4-dioxane with AlCl\(_3\).
The structure of the compound was established by various spectral data.

In IR spectrum of the compound 11, the absorption band was found at 3060 cm\(^{-1}\) due to the C-H (aromatic) absorption, whereas a broad band at 3200 cm\(^{-1}\) Stretching absorption represents the N-H aliphatic group. Absorption band at 1742 cm\(^{-1}\) display keto group. Stetching absorption 1089.20 cm\(^{-1}\), 1140.93 cm\(^{-1}\) and 1185.30 cm\(^{-1}\) stetching bands indicated the presence of C-N. Stetching absorption 1468.84 cm\(^{-1}\) and 1593 cm\(^{-1}\) stetching bands were indicated the presence of C=C respectfully. Stetching absorption 1053 cm\(^{-1}\) stetching bands were indicated the presence of S=O respectfully.

In \(^1\)H NMR spectrum of compound 11, the chemical shift at δ\(_H\) 2.27 (s, 2 x 3H, Ar-CH\(_3\)) was found as a singlet for the hydrogen atom in two CH\(_3\) groups. Chemical shift at δ\(_H\) 7.12 (d, 2x2H, Ar-H, \(J=12\)) showed a doublet for atomic protons of H-2', H-6' carbon of two phenyl rings and δ\(_H\) 7.47 (d, 2x2H, Ar-H, \(J=8\)) showed another doublet for similar protons of H-3', H-5' carbon of two phenyl rings and δ\(_H\) 7.81 (s, 2xH,Ar-H) showed singlet for protons of H-4, H-7. The chemical shift at δ\(_H\) 11.34 ( s, H ) showed singlet for protons of N-H.

In the \(^{13}\)C NMR spectral data of compound 11, the chemical shift at δ 21.72 indicated the presence of two identical carbons in two methyl groups (Ar-CH\(_3\)). The chemical shift at δ 123.64 was found for the C-4, C-7 of phenyl rings. The peak at δ 126.66 represents the aromatic carbon of C-3', C-5'. The chemical shift at δ 129.20 was obtained for the carbons C-2', C-6'. The chemical shift at δ
130.26 was obtained for the carbons C-8, C-9 and the chemical shift at δ 132.68 was obtained for the carbons C-5, C-6. The chemical shift δ 134.34 was obtained for the carbons C-1’. The chemical shift δ 144.60 was obtained for the carbons C-4’ and the chemical shift δ 168.49 was obtained for the carbons C-1, C-3.

2. 3. 6: Computational methods for the reaction between Phthalimide and aroylchlorides.

All calculations were carried out using the Gaussian 09 program package (Gaussian Inc., Wallingford, CT, USA). The equilibrium geometry of phthalimide and p-methyl benzoyl chloride were optimized at the b3lyp/6-311+g(d, p) level of theory. Electrostatic potential surfaces and Frontier molecular orbitals were generated (color, red to blue) from optimized structure using webmo demo version (www.wbmo.net).

1. Equilibrium geometries

<table>
<thead>
<tr>
<th>Compound</th>
<th>Phthalimide</th>
<th>p-Methyl benzoyl Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td># opt b3lyp/6-311+g(d, p) # opt b3lyp/6-311+g(d, p)</td>
<td></td>
</tr>
<tr>
<td>Symmetry</td>
<td>C2</td>
<td>C1</td>
</tr>
<tr>
<td>Dipole Moment</td>
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<td>5.0235</td>
</tr>
<tr>
<td>(Debye)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RB3LYP Energy</td>
<td>-513.23729904</td>
<td>-844.63680829</td>
</tr>
<tr>
<td>(Hartree)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. HOMO and LUMO combinations:

This study discloses that the molecular orbitals for both reactants and estimate the energy difference between the two possible HOMO-LUMO combinations. The HOMO of the Phthalimide and the LUMO of the Aroylchlorides (p-methylbenzoyl chloride) interact with each other to form the product.

<table>
<thead>
<tr>
<th>Orbital\Compound</th>
<th>Phthalimide</th>
<th>p-Methyl benzoyl Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMO</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>HOMO</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>

3. Electrostatic Potential Map:

The following illustration shows the mapped electrostatic potential surface red (-0.212 Hartee) to blue (0.212 Hartee) for two reactants were considering
The electrostatic potential has a large negative value in the region of C5 and C6 in Phthalimide and the the region of carbon atom in Aroylchlorides (p-methylbenzoyl chloride) has a positive electrostatic potential. This visualization allows us to easily identify the bonding orientation for the two molecules.

4. α –Deuterated and β –deuterated Phathalimide intermediate:

For Phthalimide, the intermediate involving the β-carbon has a significantly lower energy than the one involving the α-carbon.*The following table represents the total energy:

<table>
<thead>
<tr>
<th>Stoichiometry</th>
<th>C₈H₆NO₂(1+), α -Deuterated</th>
<th>C₈H₆NO₂(1+), β -Deuterated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetry</td>
<td>C1</td>
<td>C1</td>
</tr>
<tr>
<td>Route</td>
<td># opt b3lyp/6-311+g(d, p)</td>
<td># opt b3lyp/6-311+g(d, p)</td>
</tr>
<tr>
<td>Dipole Moment (Debye)</td>
<td>7.0205</td>
<td>7.7120</td>
</tr>
<tr>
<td>RB3LYP Energy (Hartree)</td>
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<td>-513.51390439</td>
</tr>
<tr>
<td>Energy Difference (Hartree)</td>
<td>0.00120730</td>
<td></td>
</tr>
<tr>
<td>**Energy Difference (kJ/mol))</td>
<td>3.13898</td>
<td></td>
</tr>
</tbody>
</table>
**1 hartee = 2600 kJ/mol

5. Equilibrium geometries

<table>
<thead>
<tr>
<th>Stoichiometry</th>
<th>C_{24}H_{17}NO_{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetry</td>
<td>C1</td>
</tr>
<tr>
<td>Route</td>
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</tr>
<tr>
<td>Dipole Moment (Debye)</td>
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</tr>
<tr>
<td>RB3LYP Energy (Hartree)</td>
<td>-1280.56312267</td>
</tr>
</tbody>
</table>

2. 3. 7: Mechanism of reaction between Phthalimide and aroylchloride:

It can be perceived that the reactions proceed according to Scheme-1. It was observed that the reaction was completed without Lewis acid at room temperature in 1, 4-dioxane and also the reaction was occurred in the presence of Lewis acid (AlCl₃) at lower time. The key steps of the possible mechanism were based on the following observations.

In presence of Lewis acid:

- The acylium in (A) generated from the reaction between aroylchlorides (2-5) and AlCl₃.
- The acylium ion (A), acting as an electrophile reacts with Phthalimide (1) to form the arenium ion (B).
• A proton is removed from the arenium ion forming the aryl ketones (7-10).

In absence of Lewis acid:

• Phthalimide (1) reacts with aroylchlorides (2-5) to form complex (C).
• A proton is removed from the complex (C) forming the products (7-10)

Mechanism:
2.3.8: CONCLUSION:

1. A convenient, general and facile method for the synthesis of 5, 6-Disubstitutedaroylisoindoline-1, 3-dione from Phthalimide has been developed first time.
2. Dioxane was found to be the good solvent for this reaction.
3. The reaction was performed in the presence of Lewis acid (AlCl₃) and also in absence of acid.
4. The most important features of the synthesis are that the reading available starting material are used under relatively mild reaction conditions at room temperature.
5. No toxic and hazardous compounds are produced by this procedure.
6. A variety of aroyl groups can be introduced at the 5 and 6-positions of the isoindoline-1, 3-dione moiety by this procedure.
3.1: Experimental Data

Unless otherwise noted, all reagents were reagent grade and were used without purification. 1,4-Dioxane was used as reaction solvent. These solvents were purchased from Aldrich and used as received. The melting point of the synthesized compound were determined by open capillary tubes by a melting point apparatus (Model BUCHI, B-540). The IR spectra were taken on a Shimadzu FTIR 8400S Fourier transform. Infrared Spectrophotometer (400-4000 cm$^{-1}$) with KBr pellets. $^1$H-NMR and $^{13}$C-NMR spectra were at 400 MHz and 100 MHz respectfully, on a JEOL AL 300/BZ instrument. Chemical shifts were given relative to TMS. Analytical thin layer chromatography (TLC) were Merck silica gel 60 F254 coated on 25 TCC aluminium sheets (20-20 cm). All reagents were purchased from Sigma Aldrich and were directly used without further purification.

3.1.1: Synthesis of 5, 6-di-p-methylbenzoyl isoindoline-1, 3-dione 7

A mixture of 0.5 g (0.0034015 mol) of phthalimidine and 1.58 g (0.010205 mol) of p-methyl benzoyl chloride was added in 5 mL solvent of 1, 4-dioxane or 1, 4-dioxane with AlCl$_3$ and the reaction mixture was stirred at room temperature for around 6-7 hours in a 250 ml round bottomed flask. The progress of the reaction was monitored carefully. The mixture was turned into a clear solution at the beginning and gradually it turned into white precipitate. After 6 to 7 hours, the reaction was stopped by adding cold distilled water. After a while it was filtered under suction on a Buchner funnel and precipitate was separated. These white precipitates was washed with sufficient distilled water. Finally, the product was crystallized by using ethyl acetate and the derived compound was obtained as white crystalline solid.
MF: C\textsubscript{24}H\textsubscript{17}NO\textsubscript{4}

MW: 383.39608

Physical analysis: White crystalline solid, m. p: 168-170 °C, odorless and 92 % of yield.

Analytical analysis:

IR (KBr): \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3050 (C-H aro.), 3197.12 (N-H), 1750 (C=O), 1053.85 and 1285.53 (C-N), 1419.66 (C=C aro.), 1375 (C-H in CH\textsubscript{3}).

\(^1\text{H NMR:}\) \(\delta_H\) 2.45 (s, 2 x 3H, Ar-CH\textsubscript{3}), 7.89 (d, 2 x 2H, Ar-H, \(J=6.4\) Hz, H-2', H-6'); 7.30 (d, 2x2H, Ar-H, \(J=6.4\) Hz, H-3', H-5'); 8.52 (s, 2xH, Ar-H, H-4, H-7); 10.43 ( s, 1xH, N-H).

\(^{13}\text{C NMR:}\) \(\delta_c\) 21.72 (Ar-CH3). \(\delta_c\) 123.64 (C-4, C-7); \(\delta_c\) 126.66 ( C-3', C-5' of phenyl ring); \(\delta_c\) 129.20 (C-2', C-6'); \(\delta_c\) 130.26 (C-8, C-9); \(\delta_c\) 132.68 (C-5, C-6); \(\delta_c\) 134.34 (C-1'); \(\delta_c\) 144.60 ( C-4'); \(\delta_c\) 168.49 ( C-1, C-3); \(\delta_c\) 172.16 (C-10 of keto group).

Analytical Calculated for C\textsubscript{24}H\textsubscript{17}NO\textsubscript{4}: (%) C, 75.19; H, 4.47; N, 3.65.
3.1.2: Synthesis of 5, 6-di-p-chlorobenzoyl isoindoline-1, 3-dione 8

The compound 8 was obtained through the reaction of 0.5 g (0.0034015 mol) of phthalimidine and 1.79 g (0.010205 mol) of p-chloro benzoyl chloride was added in 5 mL solvent of 1, 4-dioxane or 1, 4-dioxane with AlCl₃ by following the previous procedure.

**Formula:** C₂₂H₁₁NCl₂O₄

**Molecular Weight:** 424.23304

**Physical analysis:** White crystalline solid, m. p: 217-218 °C, odorless and 90 % of yield.

**Analytical analysis:**

**IR (KBr):** ν max (cm⁻¹) 3050 (C-H aro.), 3198 (N-H), 1700 (C=O), 1098 & 1176.62 (C-N), 1432.44 (C=C aro.), 548.77 and 714.65 (C-Cl).

**1H NMR:** δH 7.80 (d, 2 x 2H, Ar-H, J=8.4 Hz, H-2', H-6'); 7.53 (d, 2x2H, Ar-H, J=8.4 Hz, H-3', H-5'); 7.93 (s, 2xH, Ar-H, H-4, H-7); 11.30 (s, 1xH, N-H).

**13C NMR:** δc 123.35 (C-4, C-7 of phenyl ring); δc 129.14 ppm (C-3', C-5'); δc 130.09 ppm (C-2', C-6'); δc 131.57 ppm (C-8, C-9); δc 133.05 ppm (C-5, C-6); δc 134.72 ppm (C-1'); δc 138.26 ppm (C-4'); δc 166.92 ppm (C-1, C-3); δc 169.67 ppm (C-10 of keto group).

**Analytical Calculated for C₂₂H₁₁NCl₂O₄: (%)** C, 62.29; H, 2.61; N, 3.30. Found: C, 60.54; H, 3.266; N, 2.85.
3.1.3: Synthesis of 5, 6-dibenzoyl isoindoline-1, 3-dione 9

The compound 9 was obtained through the reaction of 0.5 g (0.0034015 mol) of phthalimidine and 1.43 g (0.010205 mol) of benzoyl chloride was added in 5 mL solvent of 1, 4-dioxane or 1, 4-dioxane with AlCl₃ by following the previous procedure.

\[
\text{MF: } C_{22}H_{13}NO_{4} \\
\text{MW: } 355.34292 \\
\text{Physical analysis: } \text{White crystalline solid, m.p: 230-232 ℃, odorless and 92 % of yield.} \\
\text{Analytical analysis:} \\
\text{IR (KBr): } v_{\text{max}} \text{ (cm}^{-1}) 3050 \text{ (C-H aro.), 3210.76 (N-H), 1748 (C=O), 1050.17,1140.93 and 1185.30 (C-N), 1468.84 (C=C aro.).} \\
\text{1H NMR: } \delta_H 7.94 \text{ (d, 2 x 2H, Ar-H, } J=6.8 \text{ Hz, H-2', H-6'}); 7.50 \text{ (d, 2x2H, Ar-H, } J=6.8 \text{ Hz, H-3', H-5'}); 7.60 \text{ (d, 2xH, Ar-H, H-4', } J= 6.4 \text{ Hz); 7.81 \text{ (s, 2xH, Ar-H, H-4, H-7); 11.33 ( s, 1xH, N-H).} \\
\text{13C NMR: } \delta_c 123.36 \text{ ppm (C-4, C-7); } \delta_c 128.99 \text{ ppm ( C-3', C-5'); } \delta_c 129.69 \text{ ppm (C-2', C-6'); } \delta_c 132.99 \text{ ppm (C-8, C-9); } \delta_c 133.29 \text{ ppm (C-5, C-6); } \delta_c 134.75 \text{ ppm (C-1'); } \delta_c 131.16 \text{ ppm ( C-4'); } \delta_c 167.82 \text{ ppm ( C-1, C-3); } \delta_c 169.71 \text{ ppm (C-10 of keto group).} \\
\text{Analytical Calculated for } C_{22}H_{13}NO_{4}: (\%) \text{ C, 74.36; H, 3.69; N, 3.94.}
### 3.1.4: Synthesis of 5, 6-di-acetyl isoindoline-1, 3-dione 10

The compound 10 was obtained through the reaction of 0.5 g (0.0034015 mol) of phthalimidine and 0.80 g (0.010205 mol) of acetyl chloride was added in 5 mL solvent of 1, 4-dioxane or 1, 4-dioxane with AlCl₃ by following the previous procedure.

![Reaction Scheme](image)

**MF:** C₁₂H₉NO₄

**MW:** 231.20416

**Physical analysis:** White crystalline solid, m.p: 138-140 °C, odorless and 90 % of yield.

**Analytical analysis:**

**IR (KBr):** \( \nu_{\text{max}} \) (cm⁻¹) 3050 (C-H aro.), 3200 (N-H), 1750 (C=O), 1375 (C-H of CH₃), 1089.82, 1140.93 and 1184.33 (C-N), 1419.66 (C=C, aro.).

**1H NMR:** \( \delta_H \) 3.42 (s, 2 x 3H, C-CH₃), 7.81 (s, 2xH, Ar-H, H-4, H-7); 11.32 (s, 1xH, N-H).

**13C NMR:** \( \delta_C \) 21.72 (Ar-CH₃), 123.64 (C-4, C-7 of phenyl ring); 130.68 (C-8, C-9); 132.26 (C-5, C-6); 168.49 (C-1, C-3); 172.16 (C-10 of keto group).

**Analytical Calculated for C₁₂H₉NO₄:** (%) C, 62.34; H, 3.92; N, 6.06. Found: C, 64.12; H, 3.32; N, 9.036
3.1.5: Synthesis of di-p-tolyl-1, 3-dioxoisoindoline-5, 6-disulfinate 11

The compound 11 was obtained through the reaction of 0.5 g (0.0034015 mol) of phthalimidine and 1.94 g (0.010205 mol) of p-tolyl sulfonylchloride was added in 5 mL solvent of 1, 4-dioxane or 1, 4-dioxane with AlCl₃ by following the previous procedure.

**MF:** C₂₀H₁₃S₂NO₆

**MW:** 427.45032

**Physical analysis:** White crystalline solid, m.p: 170-172 °C, odorless and 92 % of yield.

**Analytical analysis:**

**IR (KBr):** νmax (cm⁻¹) 3060 (C-H aro.), 3200 (N-H), 1742 (C=O), 1089.20, 1140.93 and 1185.30 (C-N), 1468.84 and 1593 (C=C aro.), 1053 (S=O).

**1H NMR:** δH 2.27 (s, 2 x 3H, Ar-CH₃), 7.89 (d, 2 x 2H, Ar-H, J=12 Hz, H-2', H-6'); 7.47 (d, 2x2H, Ar-H, J=8 Hz, H-3', H-5'); 7.81 (s, 2xH, Ar-H, H-4, H-7); 11.34 (s, 1xH, N-H).

**13C NMR:** δc 21.72 (Ar-CH₃). δc 123.64 (C-4, C-7 of phenyl ring); δc 126.66 (C-3', C-5'); δc 129.20 (C-2', C-6'); δc 130.26 (C-8, C-9); δc 132.68 (C-5, C-6); δc 134.34 (C-1'); δc 144.60 (C-4'); δc 168.49 (C-1, C-3).

**Analytical Calculated for C₂₀H₁₃S₂NO₆:** (%): C, 56.20; H, 3.07; N, 3.28; S, 15.00.
When Benzene reacts with an alkyl chloride or aroylchlorides in the Presence of Lewis acid (anhydrous AlCl₃) as catalyst, one of the hydrogen atoms of the ring is substituted by the alkyl or aroyl group. But without Lewis acid Benzene does not give the coupling or substituted by the alkyl or aroyl group.
IR spectra of 5,6-di-p-methylbenzoyl isoindoline-1,3-dione 7
H NMR spectra of 5,6-di-p-methylbenzoyl isoindoline-1,3-dione
C NMR spectra of 5,6-di-p-methylbenzoyl isoindoline-1,3-dione
IR Spectra of 5,6-di-p-chlorobenzoyl isoindoline-1,3-dione 8
$^1$H NMR spectra of 5,6-di-p-chlorobenzoxyloisoindoline-1,3-dione 8
$^{13}$C NMR spectra of 5,6-di-p-chlorobenzoyl isoindoline-1,3-dione 8
IR spectra of 5,6-dibenzoyl isoindoline-1,3-dione 9
$^1$H NMR spectra of 5,6-dibenzoxy isoindoline-1,3-dione 9
C NMR spectra of 5,6-dibenzoyl isoindoline-1,3-dione 9
IR spectra of 5,6-di-acetyl isoindoline-1,3-dione 10
$^1$H NMR spectra of 5,6-di-acetyl isoindoline-1,3-dione 10
$^{13}$C NMR spectra of 5,6-di-acetyl isoindoline-1,3-dione 10
IR Spectra of di-p-tolyl-1,3-dioxoisooindoline-5,6-disulfinate 11
$^1$H NMR of di-p-tolyl-1,3-dioxoisooindoline-5,6-disulfinate 11
$^{13}$C NMR of di-$p$-tolyl-1,3-dioxoisoindoline-5,6-disulfinate 11
References:


23. A Facile Access to Enantioenriched Isoindolines via One-Pot Sequential Cu(I)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition/Aromatization.

24. Asymmetric organocatalytic formal double-arylation of azomethines for the synthesis of highly enantiomerically enriched isoindolines.


