Chapter 1
CHAPTER 1

Synthesis of 3,4-disubstituted N-arylmaleimide via β-enaminone

In this chapter, we report synthesis of several 3-aminosubstituted-N-arylmaleimide via conjugate elimination-addition-elimination pathway. Syntheses of their various 4-substituted derivatives have also been described. Introduction of secondary amino group at 3-position in N-arylmaleimide leads to the formation of enaminones, which undergo facile electrophilic substitutions at 4-position to provide highly functionalized maleimides.

This chapter is divided in three sections:

Section A: Synthesis of β-enaminone from N-arylmaleimide

Section B: Electrophilic substitution reactions of β-enaminone: Synthesis of 3,4-disubstituted N-arylmaleimide

Section C: Comparative studies on the $^1$H NMR Signals and stereochemistry of piperidine, morpholine and pyrrolidine ring in derivatives of 3-amino-N-arylmaleimides and 3-amino-4-bromo-N-arylmaleimide

1.1 Introduction

A number of natural products such as polycitrine [1], himanimide [2], antrodia camphoratimide [3], rebeccamycine and staurosporine [4] which contain maleimide as a part in their framework have been recently reported.
The S. Zacchino and group have reported that the intact maleimide ring is essential for biological activities [5]. The SAR study by Sortino and co-workers have demonstrated that, variation of substituent on 3 and 4 position of the maleimide ring influences the biological properties [6]. The maleimide molecules contain general structure $\text{CO-N(R)-CO}$, so they are hydrophobic and neutral, and can therefore penetrate biological membranes [7].

**Figure 1: Natural products containing maleimide skeleton**

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Naturally occurring as well as synthetic maleimide derivatives show various biological activities such as angiogenesis inhibition [4, 8], protein kinase inhibition [9, 10], antiproliferative [11], antibacterial, antifungal [12,13], anti stress agents [14], anti protozoal and cytotoxic [15]. Therefore, from last two decades these molecules have attracted attention of many researchers all over the globe in search of different biological activities. Libraries of symmetrical, unsymmetrical, aryl/heteroaryl and amino substituted N-aryl maleimide have been synthesised to get lead molecules for the biological applications (figure 2). So, development of efficient synthetic methods for mono- and di-substituted maleimide derivatives deserves to be explored.

Figure 2: Synthetic compounds containing maleimide skeleton with their biological activities

Therefore, developments of versatile methods to synthesized substituted maleimides attract increasing attention in current synthesis. The synthesis of mono- and di-substituted maleimides can be achieved by two main approaches, a linear synthetic sequence based
on the formation of maleimide ring in the last step of synthesis or by selective functionalization at 3-position and 4-position carbon of maleimide.

- **Concise literature updates for the synthesis of 3, 4-disubstituted N-arylmaleimide derivatives**

A) Linear synthetic sequence:

Veerendhar and group reported synthesis of natural Himanimide A through Baylis-Hillman adduct [16]. Himanimide A, was synthesized by linear synthetic sequence in 11.28% overall yield in three steps starting from the α-keto ester 1 and acrylonitrile 2 using DABCO at room temperature for 4 days to obtain 3. This Baylis-Hillman adduct 3 was treated with benzene in presence of methanesulphonic acid to afford 4, finally, which on treatment with allyl bromide and potassium carbonate gave Himanimide A 5.

![Synthetic sequence diagram](image)

Argade and co-workers reported the synthesis of natural Camphorataanhydride, Camphoratamide B and Camphoratamide C [17]. Compound 7 was obtained by reacting dimethyl bromomethylfumarate 6 as a starting material with p-
methoxyphenylmagnesium bromide followed by base-catalyzed hydrolysis. Dehydrative cyclization of 7 using acetic anhydride yielded an anhydride 8, which on NBS-mediated bromination on allylic carbon of 8 furnishes desired bromohydrate 9. Isopropylmagnesium bromide was reacted with 9 to give 2-(p-methoxyphenyl)-3-isobutylmaleic anhydride, which was then de-methylated using boron tribromide to provide 2-(p-hydroxyphenyl)-3-isobutylmaleic anhydride 10. Reaction of 10 with 3,3-dimethylallyl bromide in presence of potassium carbonate furnishes a camphorataanhydride 11 in 20% overall yield. Camphorataanhydride 11 was treated with urea and hydroxylamine hydrochloride to obtain camphorataaimide B 12 and camphorataaimide C 13 in 16 and 15% overall yield respectively.
Ruthenium catalyzed [2+2+1] cocyclization of isocyanates, alkynes and CO to polysubstituted maleimides [18] was reported by T. Mitsuda et. al. The aryl isocyanates 14 were reacted with different alkynes 16 in presence of catalytic amount of Ru$_3$(CO)$_{12}$ in mesitylene at 130 °C for 3 to 42 hours under 1 atm carbon monoxide 15 to yield corresponding di-substituted maleimide 17.

Smith and co-workers gave synthesis of 3-anilino-4-arylmaleimides [19]. Arylacacetamide on condensing with dimethyl oxalate in presence of base gave the 3-hydroxy-4-arylmaleimide 20 in 53-100% yield, which further treated with phosphorous oxychloride to provide the chlorinated derivatives 21 in 15-66% yield. Treatment of these with various aromatic amines afforded 3-anilino-4-arylmaleimides 22.

Similar to the approach reported above by Smith and co-workers synthesis of 7-azaindolyl-heteroaryl-maleimide [20] was reported by O’Neill et. al. α-keto ester
23 on treatment with amide 24 in presence of potassium t-butoxide in THF afforded 3, 4-diheteroaryl substituted maleimide 25.

![Chemical structures and reaction equation]

B) Selective functionalization at 3-/or 4-position of maleimides: To date, functionalization of maleimides at the 3,4-positions has been reported mainly by arylation or heteroarylation by the Heck reaction and Suzuki reaction [23, 24], cross-coupling reaction using indium organometallics [22] and alkylation by Sonogashira coupling reaction [21].

Deore et. al reported synthesis of natural Cacospongionolide C and Luffarin X [21] by selective functionalisation of 26. The bromomaleimide 26 was reacted with aliphatic alkynes in the presence of PdCl₂(PPh₃)₂/CuI in THF, and desired product 27 were obtained in very good yield. The selective reduction of imide using Lindlar catalyst in presence of quinoline and acetone as an solvent yielded 28. Base catalysed hydrolysis followed by the acetic anhydride induce ring-closure of 28 provided the corresponding alkylmaleic anhydride 29. The selective reduction of 29 using DIBAL-H and NaBH₄ produced Cacospongionolide C 30 and Luffarin X 31 respectively.
Sarandeses et al. reported synthesis of 3,4-disubstituted maleimides by selective cross coupling reactions using indium organometallics [22]. The double cross coupling product 34 was obtained as the major product by treating triorganoindium with 32 in presence of Pd(Ph₃P) or Pd(Ph₃P)₂Cl₂ and triorganoindium reagent, while same reaction when carried out using Pd(PhCN)₂Cl₂ and triorganoindium reagent only monocoupling product 33 was obtained regioselectively. This method is useful for the synthesis of symmetrical as well as unsymmetrical substituted maleimides.
Stewart S. G. and co-workers reported the synthesis of natural antrodia camphoratamide [23]. The alkyl maleimide 37 was obtained in 49% yield using metal mediated conjugate substitution reaction using the Negishl reaction protocol. 37 was brominated in presence of AlBr3 to give 38. Palladium catalysed Suzuki cross-coupling reaction of 38 with 39 afforded 40. Hydrolysis of the compound 40 using KOH in THF/MeOH followed by acidic workup afforded the camphoratanhydride 41. Compound 41 was reacted with urea and hydroxylamine hydrochloride to afford camphoratamide 42 and 43.

\[
\begin{align*}
\text{Br} & \quad \text{BnNH, AcOH} \\
35 & \quad 50^\circ \text{C, 16 h} \\
\text{Br} & \quad \text{Ni(PPh3)2Cl2 (5 mol%)}, \\
36 & \quad \text{'BuZnBr, THF} \\
\text{Ph} & \quad 20^\circ \text{C, 4h} \\
\text{Br} & \quad \text{AIBr3, DCM, 1h,} \\
37 & \quad 0-20^\circ \text{C} \\
\text{Br} & \quad \text{Pd2(dba)3, Cy2NMe, dioxane, 20^\circ \text{C, 3h}} \\
38 & \\
\text{Br} & \quad \text{Urea, 140^\circ \text{C, 4h for R=H}} \\
42: R=H & \quad \text{NH2OHHCl, Pyridine,} \\
43: R=OH & \quad 100^\circ \text{C, 12h, for R=OH} \\
\text{KOH, THF/MeOH} & \quad 78^\circ \text{C, 12h then HCl} \\
40 & \\
\end{align*}
\]

Dubernet et. al. reported synthesis of substituted bis(heteroaryl)maleimides [24]. The synthesis of symmetrical and unsymmetrical bis(heteroaryl)maleimide can be achieved by palladium catalysed Suzuki cross coupling reaction. The dihalomaleimide 44 on Suzuki cross coupling reaction with boronic acid 45 afforded symmetrical bis(heteroaryl)maleimide 46.
When monohalomaleimide 47 was reacted with 48 using palladium catalyzed Suzuki cross coupling reaction afforded 49. Which on further halogenation using bromination and subsequent elimination yielded 50. Compound 50 on again Suzuki cross coupling reaction with some other boronic acid 51 afforded unsymmetrical bis(heteroaryl)maleimide 52.

Literature survey reveals that maleimides are an important core for many biological as well as synthetic application. Therefore, development of a new and efficient synthetic methods for mono and di substituted maleimides deserves to be explore. The present study describes an enaminone approach for the synthesis of mono and di substituted N-arylmaleimide.
Enaminones:

Enaminones are structures consisting of an amino group linked through a C=C to a carbonyl group 57a. They are versatile synthetic intermediates that combine the ambient nucleophility of enamines with the ambient electrophility of enones. They are typical push-pull ethylenes in which the amine group pushes and carbonyl group pulls electron density 57b. The carbonyl group, conjugated to the enamine moiety, gives this system enough stability to be easily prepared, isolated and stored under atmospheric conditions at room temperature. The chemistry of the enaminone carbonyl group is potentially an area of considerable scope when one considers that there are present in this moiety three nucleophilic sites (a, c and e) and two electrophilic sites (b and d) 57c.

\[ 
\begin{align*} 
\text{57a} & \quad \text{57b} & \quad \text{57c} \\
\end{align*} 
\]

The chemistry of enaminone has numerous attractive features that have made them important building blocks in current organic trends [25, 26]. Over the decades, enaminones have been used for the synthesis of a wide variety of heterocyclic compounds [27]. They are versatile intermediates for the synthesis of many bioactive molecules such as taxol [28-30], anticonvulsant [28, 31], anti-inflammatory [28, 32], duocarmycin classes of antitumor agents [28, 33] and quinoline antibacterials [28, 34-35]. Some β-enaminones are pharmacologically active in their own right and exhibit anticonvulsant activity [36-39].
Literature updates for the synthesis of various β-enaminones

There are several methods reported in the literature for the preparation of β-enaminones. Among them, the oldest and most general method for the preparation of enaminones 56 is the direct condensation of amines 55 and dicarbonyl compounds 54 under reflux in aromatic solvent with azeotropic removal of water [40-43].

\[
\text{Acetylacetone } 57 \text{, on condensation with N-methylhydroxylamine } 58 \text{ gives enaminone } 59 \text{ [44]. Condensing } 60 \text{ with ammonia gives } 61 \text{ [45].}
\]

The β-enaminoketones 64(a-c) were obtained by reacting β-diketone 62(a-c) with ammonia or primary amines 63 on montmorillonite K-10 under ultrasound for 20 h in 40-95% yield [46].
Active methylene ketones 65 condense readily with dialkylamino dimethyl acetal to yield enaminone 66 in 47% yields were reported [47]. Use of various solvents such as aromatic hydrocarbons [48-49], ether [50], ethanol [51], toluene [52], DMF [53], under nitrogen [54] or without solvent [55, 56] were reported in literature.

\[
\begin{align*}
65 & \xrightarrow{\text{DMF DMA}} 66 \\
\end{align*}
\]

Condensation of 67 and 68(a-c) with DMF DMA in xylene afforded 69 and 70(a-c) in 73 and 82% yield respectively [57, 58].

\[
\begin{align*}
67 + \text{DMF DMA} & \xrightarrow{\Delta \text{Xylene}} 69 \\
68(a-c) + \text{DMF DMA} & \xrightarrow{\Delta \text{Xylene}} 70(a-c) \\
\text{a) } X = \text{COMe} & \text{ b) } X = \text{COPh} & \text{ c) } X = \text{CN} \\
\end{align*}
\]

Cleavage of heterocycles: The reduction of isoxazole 71 produced the enaminone 72 [48], while heating isoxazole 73 with DMF DMA afforded 74 [59]. The arylamines on reaction with oxathiolones 75 gives the enaminone derivative 76 in 33-57% yields [60].
The enantiomerically pure (S)-enamino ketone 78 were obtained from (S)-alcohol 77 of the isoxazole ring using H₂ with PtO₂ or Raney Ni to give 78 and 100 % yield respectively [61, 62].

**Literature updates for the reactions of β-enaminones**

Reactions with halogen electrophiles: The β-enaminone 79a, on reaction with benzyltrimethylammonium dichloroiodate (BTMA-ICl₂) gives the α-iodo derivatives 80, while 79b gives the α-chloro derivatives 81 [63].
The reaction of 82 with bis(pyridine)iodonium tetrafluoroborate 83 gives the α-iodo derivatives 84 in almost quantitative yields (91-93%) [64].

\[
\begin{align*}
\text{R}_4\text{C} & \quad + \quad \text{I(Py)}_2\text{BF}_4 \\
\text{82} & \quad \xrightarrow{\text{CH}_2\text{Cl}_2} \\
\text{83} & \quad \xrightarrow{} \\
\text{NR}_1\text{R}_2 & \quad \text{84}
\end{align*}
\]

Similarly, compounds 87 and 88 were obtained from 85 and 86 respectively using 83 in 91-96% yield [64].

\[
\begin{align*}
\text{O} & \quad \text{N} \quad \text{Me} \\
\text{Ph} & \quad \text{N} \quad \text{Me} \\
\text{85} & \quad \xrightarrow{\text{I(Py)}_2\text{BF}_4} \\
\text{83} & \quad \xrightarrow{} \\
\text{NR}_1\text{R}_2 & \quad \text{87}
\end{align*}
\]

Reaction of cyclic enaminone 89 with 1-[hydroxyl(tosyloxy)iodo]-2,2,2-trifluoroethane 90, gives stable iodonium tosylate 91 which further on thermolysis provides the electrophilic substitution product 92 and 2,2,2-trifluoroethyl tosylate 93 [65].

\[
\begin{align*}
\text{CF}_3\text{CH}_2(\text{OH})(\text{OTs}) & \quad + \\
\text{89} & \quad \xrightarrow{\text{CH}_2\text{Cl}_2} \\
\text{RT/\text{H}_2\text{O}} & \quad \xrightarrow{} \\
\text{CH}_2\text{CF}_3\text{OTs} & \quad \text{91}
\end{align*}
\]

\[
\begin{align*}
\text{90} & \quad \xrightarrow{\text{MeCN/Reflex}} \\
\text{92} & \quad + \\
\text{93} & \quad \text{CF}_3\text{CH}_2\text{OTs}
\end{align*}
\]

The enaminones are an important skeleton which has received considerable interest in the synthetic organic chemistry. These are the valuable intermediate for the synthesis of several interesting classes of compounds [66-68].
1.2 Present Work

The present chapter describes synthesis of 3,4-disubstituted maleimides 99 by selective functionalisation of the N-arylmaleimide. In order to functionalise N-arylmaleimide retrosynthetic analysis is outlined in scheme 1. The dibromosuccinimide derivatives 96 could be obtained by bromination of the maleimide derivatives 95, which on elimination followed by nucleophilic substitution by amine could access 98. The compound 98 could be utilized further for various electrophilic substitution reactions to obtain disubstituted maleimide derivatives.

\[ \text{Scheme 1} \]

1.3 Results and Discussion

1.3.1 Section A: Synthesis of β-enaminone from N-arylmaleimide

In present chapter we report applications of β-enaminone in synthesis of 3,4-disubstituted N-arylmaleimide. Synthetic routes to obtain desired compounds start from synthesis of N-arylmaleimide, followed by synthesis of enaminones. Synthesized enaminones was reacted with different electrophiles to obtain 3,4-disubstituted maleimides.
1.3.1.1 Synthesis of N-arylmaleimide, 100(a-c):

N-arylmaleimides 100(a-c) required for the study was prepared by the procedure developed by our group [76]. The aromatic amines was treated in acetic acid with the maleic anhydride at 25-45°C for 10-20 minutes followed by treatment with sulfuric acid at 60°C for 30 to 45 minutes to afford N-arylmaleimide 100(a-c) (scheme 2). This simple method reported here has several advantages, in particular, use of simple reagents, easy work-up, short reaction time, excellent yields.

Scheme 2

Figure 1: $^1$H NMR of N-phenylmaleimide, 100a
The bicarbonate insoluble solid was characterized by spectral and analytical methods. The $^1$H NMR (CDCl$_3$) of this solid showed singlet at $\delta$ 6.84 for olefinic protons. Multiplet at $\delta$ 7.23-7.60 appeared for five protons of phenyl ring (figure 1).

1.3.1.2. Synthesis of 3,4-dibromosuccinamides, 104(a-c):

Our efforts to synthesis trans-3, 4-dibromosuccinamide 104a as a sole product using reported method [77] with bromine in refluxing CCl$_4$ failed. $^1$H NMR spectra of the product showed it to be mixture of two compounds (Figure 2). We attributed it to the thermodynamically controlled trans-3,4-dibromosuccinamide 104a and kinetically controlled cis-3,4-dibromosuccinamide 105a. Their $R_f$ values on TLC were same for both the compounds. Therefore we explored the possibility of synthesizing the thermodynamically stable 104a under different set of conditions among which bromine in DMF at room temperature (25-27 °C) was found to give only 104a (figure 3) in 90-95% yield. $^1$H NMR spectra and physical constant matched with literature reports [77, 78].

![Scheme 3](image-url)
Figure 2: $^1$H NMR of cis/trans-3, 4-dibromosuccinamide, 104a/105a

The $^1$H NMR (CDCl$_3$) of the compound obtained by refluxing 100a with Br$_2$ in CCl$_4$ showed the three peaks at 4.8 δ for desired two protons and at 5.10 δ. Third signal at 7.20-7.60 δ with the integration for more than five aromatic protons merge in itself indicates presence of some more aromatic proton. This observation leads us to point out that there is the formation of cis and trans isomers. $^1$H NMR obtained by reaction of 100a with Br$_2$ in DMF at room temperature gives only two signals at 4.80 δ for desired two protons and second signal at 7.25-7.50 with integration for five aromatic protons.
1.3.1.3. Synthesis of 3-dialkylamino-1-aryl-maleimide (β-enaminones), 106 (a-i) and 107:

Our attempts to synthesized N-aryl-3-bromomaleimide by reacting 104(a-c) with one to two moles of piperidine as the base to bring about dehydro-halogenation to obtain the monobromo compound was fruitless instead, complex mixtures with unreacted dibromosuccinimide were obtained (tlc). However, a clean reaction was observed when three moles of piperidine was used and the sole product was characterized by all spectroscopic means to be 3-piperidylmaleimide 106a (Scheme 4). The reaction followed a base-induced elimination-conjugate addition-elimination path to provide the corresponding enaminone. This observation was generalized by reacting 104(a-c) with three equivalents...
of morpholine, pyrrolidine or N, N-dimethylamine to give the corresponding 3-dialkylaminated N-arylmaleimides 106(b–i) and 107 in high yields. The dimethylamino group in such enaminones (e.g. 107) is known to be displaced [79, 80] by other nucleophiles offering further promising pathways in synthesis.

\[ \text{Scheme 4} \]

\[ ^1H \text{ NMR of 106(a–i) and 107 showed a singlet at } \delta 4.84-5.09 \text{ attributed to the olefin proton in addition to signals at } \delta 1.70, 3.65 \text{ due to the secondary amino residue, while aromatic protons appeared at } \delta 7.20-7.65 \text{ (figure 4).} \]
1.3.2 Section B: Electrophilic substitution reactions of β-enaminone: Synthesis of 3, 4- disubstituted N-arylmaleimide:

We realized that presence of the amino functionality on C-3 position of maleimide 108 should increases the nucleophilic nature at C-4 carbon bearing hydrogen. This resulted in formation of enaminone structure (Figure 5). This electron rich C-4 position expected to show very facile electrophilic substitution reactions.

Figure 5: Nucleophilic C-4 position of Enaminone
1.3.2.1. Synthesis of 3-bromo-4-dialkylamino substituted maleimide, 109(a-i) and 110:

Herein, we explored the synthetic utility of synthesized \( \beta \)-enaminones. \( \beta \)-enaminones 106(a-i) and 107 on bromination afforded 109(a-i) and 107 respectively. As expected, bromine reacted instantaneously with 106(a–i) and 107 in DMF at 0°C to provide 109(a-i) and 110 respectively in almost quantitative yields (scheme 5).

The structures of products 109(a-i) and 110 were confirmed by the absence of \( ^1 \text{H} \) NMR (CDCl₃) signal at \( \delta \) 4.84 to 5.09 (figure 6). The mass spectrum of all of the synthesized compounds showed characteristic M⁺ and M+2 peaks due to presence of bromine.
1.3.2.2. Synthesis of 3-carbaldehyde-4-dialkylamino substituted maleimide, 111(a-c) and 112:

The enaminone nature of the 106(a-i) and 107 prompted us to carry out investigation related with further electrophilic substitution reactions. The Vilsmeier Haack formylation of 106(a-c) was resulted in formation of 111(a-c) and 112 with good yield at low temperature (0-5 °C) in 30 minutes.

\[ \text{\text{Maleyl-\text{c}}}_3 \text{O} + x \text{\text{C}_{6}H_{4}Cl} \rightarrow \text{\text{Maleyl-\text{c}}}_3 \text{O} + x \text{\text{C}_{6}H_{4}Cl} \text{C}_{6}H_{4} \text{Cl} \text{C}_{6}H_{4} \text{Cl} \text{C}_{6}H_{4} Cl} \]
The IR of I11(a-c) showed the characteristic conjugated aldehyde carbonyl stretching frequency at 1701-1706 cm\(^{-1}\) and (O=C-H) at 2777-2786 cm\(^{-1}\). The \(^1\)H NMR (CDCl\(_3\)) of
the 111a showed absence of allylic proton, aldehyde proton appeared at δ 9.80. The piperidine proton signals appeared at δ 1.70 to 2.0, 4.1 and 4.42. The aromatic signal appeared at δ 7.20-7.45 (Figure 7). The 13C NMR (CDCl3) of the compound showed aldehyde carbon peaks at δ 182.1. The maleimide ring carbons appeared at 97.8, 148.0, 163.5 and 169.4. The piperidine ring carbon appeared at δ 23.7, 27.3, 27.6, 51.0, 57.7. The aromatic ring carbons appeared at δ 127.6 (2C’s), 129.2 (2C’s), 129.6 and 133.8 (Figure 8). The mass spectra (70 eV) of 111a showed M+1 peak at 285.
1.3.2.3. **Synthesis of 3-Chlorosulfonyl-4-dimethylaminomaleimide, 113:**

Excess of the chlorosulphonic acid was treated with 107 in THF at 0°C followed by room temperature stirring for 4 hours afforded 3-Chlorosulfonyl-4-dimethylaminomaleimide 113. The most crucial step was the isolation of the final product due to basic nature of the enaminone. When starting material was consumed (tlc) the reaction mass was neutralized using triethyl amine, the solvent was removed using high vacuum. The solid residue was then purified using column chromatography.

Formation of the compound 113 was confirmed by disappearance of the olefin proton signal of 107 at δ 4.15. IR spectrum of the compound 113 showed characteristic stretching frequency at 1373, 1174 cm⁻¹ for S=O. The mass spectra (70 eV) showed peak at 315 [M+1], 315 [M+3].

1.3.2.4. **Synthesis of N-Phenyl-3-benzyl-4-dimethylaminomaleimide, 114:**

Reaction of 107 with benzyl chloride in presence of AlCl₃ as a catalyst in DCM at room temperature for 18 hours afforded 114 in 59% yield. On completion of the reaction (tlc), triethylamine was added to neutralized AlCl₃, the solvent was removed on high vacuum. The solid residue was then purified using column chromatography. The obtained solid was characterized by spectral and analytical methods.
The $^1$H NMR spectra (CDCl$_3$) of the compound showed singlet at $\delta$ 3.26 for six protons of N, N dimethyl amine. Singlet at $\delta$ 3.94 for two protons attributed to benzylic protons. The aromatic ring protons appeared as multiplet for 10 protons at $\delta$ 7.20–7.47 (Figure 9). The $^{13}$C NMR spectrum (CDCl$_3$) of the compound showed ten aromatic carbons appeared at their respective chemical shift positions in between 126.0 and 140.8. The amine carbon appeared at 42.9. The benzylic carbon appeared at $\delta$ 28.5. The maleimide ring carbon appeared at $\delta$ 100.7, 145.3, 166.7 and 171.5. Further, the mass spectrum of this solid showed the characteristic M+1 peak at 307.

Figure 9: $^1$H NMR of N-Phenyl-3-benzyl-4-dimethylaminomaleimide, 114
1.3.2.5. Synthesis of Ethyl 4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1-phenyl-1H-pyrrole-3-carboxylate, 115 and 3-acetyl/benzoyl-4-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 116:

The reactions of the enaminone 107 with ethyl chloroformate, acetyl chloride and benzoyl chloride were also examined. The enaminone 107 was reacted with ethyl chloroformate at reflux condition in presence of triethyl amine in DMF for 6 hours to afford 115 in 56% yields. Reaction of 107 with acetyl chloride and benzoyl chloride in presence of triethyl amine in DMF at 80°C for 5-8 hours afforded 116a and 116b respectively.

The IR spectra of the compound 115 showed C=O stretching frequency of amide carbonyl at 1751 and 1693 cm⁻¹. Ester carbonyl stretching frequency appeared 1730 cm⁻¹. The 'H NMR (CDCl₃) of 115 showed triplet and quartet at δ 1.45 and 4.43 respectively with J=9 Hz for ethyl group of ester. The methyl protons of N, N dimethylamine protons showed singlet at δ 3.65. The aromatic ring protons appeared at δ 7.22-7.43 as a multiplet.
The $^{13}$C NMR (CDCl$_3$) spectra of 115 showed peak for C=O of ester at $\delta$ 169.3 while ethoxy carbons appeared at $\delta$ 16.1 and 60.8. The maleimide ring carbons appeared at $\delta$ 98.1, 149.8, 162.2 and 163.4. The aromatic carbons appeared at their respective chemical shift. Mass peak appeared at 289 [M+1] (figure 10). The $^1$H NMR spectra of the compound showed singlet for methyl protons of acetyl group at $\delta$ 2.59. Methyl protons of N, N dimethyl amine appeared as two separate broad singlet at $\delta$ 3.21 and 3.65. The aromatic protons appeared as multiplet at $\delta$ 7.29–7.50 (figure 11). The $^{13}$C NMR (CDCl$_3$) signal of methyl carbon of acetyl appeared at $\delta$ 30.8. The methyl carbon of N, N dimethyl group appeared separately at $\delta$ 42.3 and 47.3. Carbonyl carbon of imide appeared at 163.9, 168.1. Acetyl group carbon appeared at 192.6 (figure 12). The mass spectra (70 eV) showed peak at 259 [M+1].
Figure 11: $^1$H NMR of 3-Acetyl-4-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 116a

Figure 12: $^{13}$C NMR of 3-Acetyl-4-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 116a
1.3.3 Section 3: Comparative studies on the $^1$H NMR Signals and stereochemistry of Piperidine, morpholine and pyrrolidine derivatives of 106(a-i) and 109(a-i):

Some interesting observations in the $^1$H NMR spectra of 106(a-i) and 109(a-i) encourages us to explore the study of $^1$H NMR signals and stereochemistry of piperidine/morpholine and pyrrolidine ring in 106(a-i) and 109(a-i).

**Observations**

- The piperidine ring in 106a shows two sets of the protons at $\delta$ 1.63 (6H, broad singlet) and $\delta$ 3.72 (4H, broad singlet) which on bromination gives 109a in which $^1$H NMR signal shifts to $\delta$ 1.89 (6H, sharp singlet) and $\delta$ 4.0 (4H, sharp singlet).

  In conclusion peak at $\delta$ 3.72 (4H, broad singlet) changes to $\delta$ 4.0 (4H, sharp singlet) and peak at $\delta$ 1.63 (6H, broad singlet) changes to $\delta$ 1.89 (6H, sharp singlet) (Figure 13).

  ![Figure 13](image)

- Morpholine ring in 106b shows only one set of protons at $\delta$ 3.68-3.73 ppm (8 H, broad peak) which on bromination yielded 109b in which $^1$H NMR signal shifts into two signals at $\delta$ 3.83 (4 H, triplet) and $\delta$ 4.05 ppm (4 H, triplet) (Figure 14).
This change in a splitting pattern of the peaks can be explained on the basis of conformation of these heterocycles:

- The conformational analysis of six-membered heterocycles is complicated by the fact that the ring inversion and pyramidal inversion [81] go side by side and often competitive (Figure 15).

- Both these inversions lead to complications in $^1$H NMR spectra of 106(a,b) therefore broad signal was observed.

- In case of 109 (a, b) the piperidine/ morpholine ring is set in more stable conformation according to Repulsive gauche type effect [81] which arises because of repulsion between non bonded p-orbital of substituents N and Br in the unit -N-C-C-Br- which restricts the pyramidal inversion in 109 (a, b) leads to sharp peaks in 1H NMR spectra instead of peak broadening (Figure 16).
Repulsive gauche type effect between p-orbital of N and Br restricts the pyramidal inversion and only ring inversion takes place.

Figure 16

Figure 17: $^1$H NMR Spectrum of 106a and 109a, showing difference in peak splitting pattern of piperidine protons.
Figure 18: $^1$H NMR of 106b and 109b, showing difference in peak splitting pattern of morpholine protons

For five membered heterocycles the more stable conformation is the half chair with heteroatom in the middle of the three atom plane [81].

Figure 19

$^1$H NMR spectra of pyrrolidine in 106c shows three sets of proton at $\delta$ 2.05 (4H, singlet), at $\delta$ 3.38 (2H, singlet) and at $\delta$ 3.98 (2H, singlet) indicating half chair
conformation of the pyrrolidine ring. Bromination of 106c gave 109c which shows only two sets of proton at $\delta$ 1.96 (4H, singlet) and at $\delta$ 4.02 (4H, singlet) which suggested envelope conformation of the pyrrolidine ring.

Figure 20

Figure 21: $^1$H NMR Spectrum of 106c and 109c, showing difference in peak splitting pattern of pyrrolidin protons
1.4 Conclusion

An efficient and convenient route was developed for the synthesis of new disubstituted maleimide derivatives by using β-enaminone approach. The β-enaminone derivatives of maleimide 106(a-i) and 107 were synthesized using simple and general base-induced elimination-conjugate addition-elimination path to obtain important key synthon. It was interesting to observe that with synthesized enaminone the first attempt for electrophilic substitution reaction i.e. bromination proceeded smoothly to yield 109(a-i) and 110. Therefore, enaminones 106 (a-i) and 107 was then reacted with various electrophiles to obtained synthetically valuable maleimide intermediates in moderate to good yield. Vilsmeier formylation of t66te'-i) and 107 at low temperature (0 to 5°C) afforded 111(a-c) and 112 in high yields. The reactions of the enaminone 106 (a-i) and 107 with chlorosulphonic acid, benzyl chloride, ethyl chloroformate, acetyl chloride and benzoyl chloride were also examined and respectively obtained the functionally rich products 113, 114, 115, 116a and 116b in good to excellent yields, opening up a broad vista for further elaboration. All the products obtained were fully characterized by $^1$H NMR, CMR, CHN analysis and mass spectrometry and are new addition to the family of heterocyclic compounds. In summary, we have demonstrated simple and general approach to potentially useful substituted maleimides synths. We feel that the present approach will be useful to design several structurally interesting and biologically important substituted maleimides. The dimethylamino group in such enaminones (e.g. 107) is known to be displaced [79, 80] by other nucleophiles offering further promising pathways in synthesis.
1.5 Experimental Section

Experiment No. 1

General Procedure for the synthesis of N-arylmaleimide, 100(a-c)

Procedure

To a solution of the substituted anilines (0.01 mol) in acetic acid (10 mL), the maleic anhydride was added. The reaction mixture was stirred for 10 min. To this suspension, sulfuric acid (0.025 mol) was added while stirring. The temperature of the reaction mixture was then maintained at 60 °C for 30-45 min. The cooled reaction mixture was poured onto crushed ice. The solid separated was collected, washed with aqueous sodium bicarbonate and then with water, and recrystallized from aqueous ethanol. Yellow solid, yield 85-90%.

1-phenyl-1H-pyrrole-2,5-dione, 100a

M.p. 90°C; IR (KBr): \( \nu = 1748, 1703, 1614 \text{ cm}^{-1} \); \(^1\text{H} \text{NMR} \ (300 \text{ MHz, CDCl}_3): \delta = 6.84 \ (s, 2H, =CH), 7.23-7.58 \ (m, 5H, Ar-H), \ MS \ (70 \text{ eV}): m/z = 174 \ [M^+].

Analysis Calculated for C\(_{10}\)H\(_7\)NO\(_2\) (173.2): Calcd: C, 69.36; H, 4.07; N, 8.09%. Found: C, 69.33; H, 4.17; N, 8.21%.

1-(4-chlorophenyl)-1H-pyrrole-2,5-dione, 100b
M.p. 115°C; IR (KBr): $\nu = 1751, 1705, 1617 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 3.82 (s, 3H, CH$_3$), 6.83 (s, 2H, =CH), 7.03 (d, 2H, $J = 8.7$ Hz, Ar-H), 7.44 (d, 2H, $J = 8.7$ Hz, Ar-H), MS (70 eV): $m/z = 208$ [M$^+$].

Analysis Calculated for C$_{10}$H$_6$CINO$_2$ (207.6): Calcd: C, 57.85; H, 2.91; N, 6.75. Found: C, 57.75; H, 2.81; N, 6.65.

1-p-toly1-1H-pyrrole-2,5-dione, 100c

M.p. 115°C; IR (KBr): $\nu = 1748, 1702, 1614 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 2.43 (s, 3H, CH$_3$), 6.84 (s, 1H, =CH)7.21 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.31 (d, 2H, $J = 8.4$ Hz, Ar-H), MS (70 eV): $m/z = 188$ [M$^+$].

Analysis Calculated for C$_{11}$H$_9$NO$_2$ (187.2): Calcd: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.60; H, 4.90; N, 7.51.

Experiment No. 2

General Procedure for the synthesis of 3, 4-dibromosuccinamide 104(a-c)

To a solution of N-arylmaleimide 100(a-c) (1 mmol) in DMF (3 mL) was added dropwise a solution of bromine (1 mmol) in DMF (2 mL) at 25°C and stirred further for 1 to 2.5 h (TLC, hexane:ethyl acetate, 4:1). The reaction mixture was poured onto crushed ice. The precipitated white solid was filtered, washed with cold water, dried and recrystallized using ethanol.

trans-3, 4-dibromo-1-phenylpyrrolidine-2,5-dione, 104a
Yield: 95%; M.p. 156-158 °C;
IR (KBr): $\nu = 1797, 1731 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 4.85$ (s, 2H), 7.20–7.60 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 41.9, 44.4, 126.0 (2C’s), 129.4 (2C’s), 130.6, 130.8, 169.2, 169.4 ppm; MS (70 eV): $m/z = 333 \ [M^+], 335 \ [M+2], 337 \ [M+4]$.  
Analysis Calculated for C$_{10}$H$_7$Br$_2$NO$_2$ (334): Calcd: C, 36.07; H, 2.12; N, 4.21%. Found: C, 36.37; H, 2.21; N, 4.29%.

**trans -3,4-Dibromo-1-(4-chlorophenyl)pyrrolidine-2,5-dione, 104b**

Yield: 94%; M.p. 158-160 °C;
IR (KBr): $\nu = 1797, 1728 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 4.95$ (s, 2H), 7.25–7.58 (m, 4H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 41.6, 44.2, 127.2 (2C’s), 129.2, 129.6 (2C’s), 135.3, 168.8, 169.1 ppm; MS (70 eV): $m/z = 367 \ [M+1], 369 \ [M+3], 365 \ [M+5]$. Analysis Calculated for C$_{10}$H$_6$Br$_2$ClNO$_2$ (365.4): Calcd: C, 32.69; H, 1.65; N, 3.81%. Found: C, 32.78; H, 1.51; N, 3.69%.

**trans -3,4-Dibromo-1-p-tolylpyrrolidine-2,5-dione, 104c**

Yield: 92%; M.p. 160-162 °C;
IR (KBr): $\nu = 1799, 1722 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 2.39 (s, 3H, CH$_3$), 4.85 (s, 2H), 7.18–7.37 (m, 4H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 21.2, 41.9, 44.4, 125.7 (2C’s), 128.1, 129.9 (2C’s), 131.8, 169.4, 169.5 ppm; MS (70 eV): $m/z = 345 \ [M^+], 347 \ [M+2], 349 \ [M+4]$. Analysis Calculated for C$_{11}$H$_8$Br$_2$NO$_2$ (345): Calcd: C, 38.07; H, 2.61; N, 4.04%. Found: C, 37.87; H, 2.51; N, 4.24%.
Experiment No. 3

General Procedure for the synthesis of 3-dialkylamino-1-aryl-maleimide (β-enaminones), 106 (a-i) and 107

To a solution of trans-3,4-dibromo-succinamide 104(a-c) (1 mmol) in DMF (5 mL) secondary amine (3 mmol) was added dropwise at 10 °C and stirred for 10 min. The reaction mixture was poured over crushed ice. The precipitated golden yellow solid was filtered, washed with cold water, dried and was purified by silica gel column chromatography (hexane:ethyl acetate, 6:4).

1-Phenyl-3-(piperydin-1-yl)-1H-pyrrol-2,5-dione, 106a

Yield: 98%; M.p. 122-124°C;

IR (KBr): $\tilde{\nu} = 1749, 1701, 1612 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.63$ (s, 6H, 2×CH$_3$), 3.72 (bs, 4H, 2×CH$_2$), 5.10 (s, 1H), 7.25–7.50 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 23.6$ (2C’s), 25.4, 48.2 (2C’s), 87.9, 127.2 (2C’s), 128.6 (2C’s), 130.4, 132.3, 149.6, 165.4, 169.0 ppm; MS (70 eV): $m/z = 257$ [M+1].

Analysis Calculated for C$_{15}$H$_{16}$N$_2$O$_2$ (256.3): Calcd: C, 70.29; H, 6.29; N, 10.93%.
Found: C, 70.45; H, 6.21; N, 10.72%. 

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3-Morpholino-1-phenyl-1H-pyrrol-2,5-dione, 106b

Yield: 96%; M.p. 118-120°C;

IR (KBr): $\tilde{\nu} = 1751, 1703, 1620$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.70$ (bs, 8H, 4×CH$_2$), 5.03 (s, 1H), 7.19–7.39 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 47.1$ (2C’s), 66.0 (2C’s), 89.8, 127.2 (2C’s), 128.8 (2C’s), 130.1, 132.8, 149.5, 165.4, 168.8 ppm; MS (70 eV): $m/z = 259$ [M+1].

Analysis Calculated for C$_{14}$H$_{14}$N$_2$O$_3$ (258.3): Calcd: C, 65.11; H, 5.46; N, 10.85%. Found: 65.25; H, 5.21; N, 10.72%.

1-Phenyl-3-(pyrrolidin-1-yl)-1H-pyrrol-2,5-dione, 106c

Yield: 97%; M.p. 128-130°C;

IR (KBr): $\tilde{\nu} = 1741, 1703, 1616$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.05$ (s, 4H, 2×CH$_2$), 3.38 (s, 2H, CH$_2$), 3.98 (s, 2H, CH$_2$), 4.92 (s, 1H), 7.31–7.49 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 23.6, 25.9, 48.7, 50.1, 85.6, 126.8$ (2C’s), 128.4 (2C’s), 130.6, 132.0, 147.8, 164.8, 169.4 ppm; MS (70 eV): $m/z = 243$ [M+1].

Analysis Calculated for C$_{14}$H$_{14}$N$_2$O$_2$ (242.3): Calcd: C, 69.41; H, 5.82; N, 11.56%. Found: C, 69.59; H, 5.71; N, 11.52%.

1-(4-Chlorophenyl)-3-(piperydin-1-yl)-1H-pyrrol-2, 5-dione, 106d

Yield: 97%; M.p. 102-104°C;

IR (KBr): $\tilde{\nu} = 1740, 1693, 1620$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.64$ (s, 6H, 3×CH$_2$), 3.55 (bs, 4H, 2×CH$_2$), 4.99 (s, 1H), 7.25–7.50 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 291$ [M+1], 293 [M+3].

Analysis Calculated for C$_{15}$H$_{15}$ClN$_2$O$_2$ (290.7): Calcd: C, 61.97; H, 5.20; N, 9.64%. Found: C, 61.72; H, 5.29; N, 9.53%.
1-(4-Chlorophenyl)-3-morpholino-1H-pyrrol-2,5-dione, 106e

Yield: 96%; M.p. 136-138°C;

IR (KBr): $\tilde{\nu} = 1757, 1701, 1612 \text{ cm}^{-1}$; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta = 3.80$ (s, 8H, 4×CH$_2$), 5.09 (s, 1H), 7.27–7.50 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 293$ [M+1], 295 [M+3].

Analysis Calculated for C$_{14}$H$_{13}$CIN$_2$O$_3$ (292.7): Calcd: C, 57.44; H, 4.48; N, 9.57%.
Found: C, 57.33; H, 4.40; N, 9.36%.

1-(4-Chlorophenyl)-3-(pyrrolidin-1-yl)-1H-pyrrol-2,5-dione, 106f

Yield: 94%; M.p. 160-162°C;

IR (KBr): $\tilde{\nu} = 1751, 1706, 1625 \text{ cm}^{-1}$; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta = 1.97$ (s, 4H, 2×CH$_2$), 3.29 (s, 2H, CH$_2$), 3.89 (s, 2H, CH$_2$), 4.84 (s, 1H), 7.31–7.35 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 277$ [M+1], 279 [M+3].

Analysis Calculated for C$_{14}$H$_{13}$CIN$_2$O$_2$ (276.7): Calcd: C, 60.77; H, 4.74; N, 10.12%.
Found: C, 60.62; H, 4.84; N, 10.25%.

3-(Piperidin-1-yl)-1-p-tolyl-1H-pyrrol-2,5-dione, 106g

Yield: 95%; M.p. 112-114°C;

IR (KBr): $\tilde{\nu} = 1741, 1693, 1608 \text{ cm}^{-1}$; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta = 1.65$ (s, 6H, 3×CH$_2$), 2.39 (s, 3H, CH$_3$), 3.72 (bs, 4H, 2×CH$_2$), 5.00 (s, 1H), 7.10–7.30 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 271$ [M+1].

Analysis Calculated for C$_{16}$H$_{18}$N$_2$O$_2$ (270.3): Calcd: C, 71.09; H, 6.71; N, 10.36%.
Found: C, 71.22; H, 6.86; N, 10.21%.

3-Morpholino-1-p-tolyl-1H-pyrrol-2,5-dione, 106h

Yield: 97%; M.p. 200-202 °C;
IR (KBr): $\bar{\nu} = 1749, 1699, 1612 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.29$ (s, 3H, CH$_3$), 3.79 (bs, 8H, 4×CH$_2$), 5.09 (s, 1H), 7.10–7.30 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 273 [M+1], 274 [M+1]$.

Analysis Calculated for C$_{13}$H$_6$N$_2$O$_3$ (272.3): Calcd: C, 66.16; H, 5.92; N, 10.29%. Found: C, 66.29; H, 5.76; N, 10.15%.

3-(Pyrrolidin-1-yl)-1-p-tolyl-1H-pyrrole-2,5-dione, 106i

Yield: 95%; M.p. 150-152 °C;

IR (KBr): $\bar{\nu} = 1741, 1703, 1616 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.00$ (s, 4H, 2×CH$_2$), 2.39 (s, 3H, CH$_3$), 3.35 (s, 2H, CH$_2$), 3.95 (s, 2H, CH$_2$), 4.85 (s, 1H), 7.18–7.30 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 257 [M+1]$.

Analysis Calculated for C$_{15}$H$_{16}$N$_2$O$_2$ (256.3): Calcd: C, 70.29; H, 6.29; N, 10.93%. Found: C, 70.12; H, 6.41; N, 10.75%.

3-(Dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 107

Yield: 94%; M.p. 142-144 °C;

IR (KBr): $\bar{\nu} = 1753, 1691, 1624 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.22$ (bs, 6H, 2×CH$_3$), 4.95 (s, 1H), 7.33–7.43 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 41.0$ (2C’s), 87.4, 126.2 (2C’s), 127.1, 128.2 (2C’s), 131.8, 150.3, 165.5, 169.4 ppm; MS (70 eV): $m/z = 217 [M+1]$.

Analysis Calculated for C$_{12}$H$_{12}$N$_2$O$_2$ (216.2): Calcd: C, 66.65; H, 5.59; N, 12.96%. Found: C, 66.42; H, 5.67; N, 12.85%.
Experiment No. 4

General Procedure for the Synthesis of 3-bromo-4-dialkylamino substituted maleimide, 109(a-i) and 110

To a solution of 3-dialkylamino-N-arylmaleimide 106(a-i) or 107 (1 mmol) in DMF (3 mL) was added drop wise a solution of bromine (1 mmol) in DMF (2 mL) at 0 °C. After addition of bromine, the reaction mixture was poured over crushed ice. The precipitated yellow solid was filtered, washed with cold water, dried and purified by silica gel column chromatography (hexane:ethyl acetate, 6:4).

3-Bromo-1-phenyl-4-(piperidine-1-yl)-1H-pyrrol-2,5-dione, 109a

Yield: 94%; M.p. 96-98 °C;

IR (KBr): $\bar{\nu} = 1760, 1701, 1608 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.89$ (s, 6H, 3×CH$_2$), 4.00 (s, 4H, 2×CH$_2$), 7.34–7.49 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 23.7, 26.5$ (2C’s), 49.7 (2C’s), 80.8, 127.0 (2C’s), 128.7 (2C’s), 130.0, 132.7, 144.1, 164.3, 165.0 ppm; MS (70 eV): $m/z = 335$ [M+1], 337 [M+3].
Analysis Calculated for C₁₅H₁₅BrN₂O₂ (335.2): Calcd: C, 53.75; H, 4.51; N, 8.36%.
Found: 53.61; H, 4.73; N, 8.55%.

3-Bromo-4-morpholino-1-phenyl-1H-pyrrole-2,5-dione, 109b

Yield: 95%; M.p. 94-96 °C;
IR (KBr): $\tilde{\nu} = 1763, 1708, 1622 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl₃): $\delta = 3.83$ (t, 4H, $J = 6$ Hz, 2×CH₂), 4.05 (t, 4H, $J = 6$ Hz, 2×CH₂), 7.26-7.39 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl₃): $\delta = 48.6$ (2C’s), 66.9 (2C’s), 83.3, 127.2 (2C’s), 129.1 (2C’s), 129.8, 133.4, 143.6, 164.6, 164.9 ppm; MS (70 eV): $m/z = 337$ [M+1], 339 [M+3].

Analysis Calculated for C₁₄H₁₄BrN₂O₃ (337.2): Calcd: C, 49.87; H, 3.89; N, 8.31%.
Found: C, 49.65; H, 3.97; N, 8.51%.

3-Bromo-1-phenyl-4-(pyrrolidin-1-yl)-1H-pyrrole-2,5-dione, 109c

Yield: 96%; M.p. 108-110 °C;
IR (KBr): $\tilde{\nu} = 1759, 1707, 1612 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl₃): $\delta = 1.96$ (s, 4H, 2×CH₂), 4.02 (s, 4H, 2×CH₂), 7.26-7.45 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl₃): $\delta = 25.1$ (2C’s), 50.9(2C’s), 84.2, 127.1 (2C’s), 128.9 (2C’s), 130.3, 133.0, 142.8, 164.0, 165.8 ppm; MS (70 eV): $m/z = 321$ [M+1], 323 [M+3].

Analysis Calculated for C₁₄H₁₃BrN₂O₃ (321.2): Calcd: C, 52.36; H, 4.08; N, 8.72%.
Found: C, 52.53; H, 4.17; N, 8.85%.

3-Bromo-1-(4-chlorophenyl)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione, 109d

Yield: 96%; M.p. 114-116 °C;
IR (KBr): $\tilde{\nu} = 1757, 1703, 1606 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl₃): $\delta = 1.66$ (s, 6H, 3×CH₂), 3.87 (s, 4H, 2×CH₂), 7.20-7.40 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 368$ [M⁺], 320 [M+1], 372 [M+4].
Analysis Calculated for C_{15}H_{14}BrClN_{2}O_{2} (369.6): Calcd: C, 48.74; H, 3.82; N, 7.58%.
Found: C, 48.46; H, 3.88; N, 7.67%.

3-Bromo-1-(4-chlorophenyl)-4-morpholino-1H-pyrrole-2,5-dione, 109e
Yield: 95%; M.p. 118-120 °C;
IR (KBr): $\overline{\nu} = 1762, 1710, 1622$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.87$ (s, 4H, 2$\times$CH$_2$), 4.04 (s, 4H, 2$\times$CH$_2$), 7.20-7.50 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 370$ [M$^+$], 372 [M+1], 374 [M+4].

Analysis Calculated for C_{14}H_{12}BrClN_{2}O_{3} (371.6): Calcd: C, 45.25; H, 3.25; N, 7.54%.
Found: C, 45.54; H, 3.36; N, 7.49%.

3-Bromo-1-(4-chlorophenyl)-4-(pyrrolidin-1-yl)-1H-pyrrole-2,5-dione, 109f
Yield: 96%; M.p. 122-124 °C;
IR (KBr): $\overline{\nu} = 1753, 1712, 1620$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.95$ (s, 2H, CH$_2$), 4.00 (s, 2H, CH$_2$), 7.19-7.55 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 354$ [M$^+$], 356 [M+1], 358 [M+4].

Analysis Calculated for C_{14}H_{12}BrClN_{2}O_{3} (355.6): Calcd: C, 47.28; H, 3.40; N, 7.88%.
Found: C, 47.57; H, 3.38; N, 7.66%.

3-Bromo-4-(pyrrolidin-1-yl)-1-p-tolyl-1H-pyrrole-2,5-dione, 109g
Yield: 94%; M.p. 118-120 °C;
IR (KBr): $\overline{\nu} = 1759, 1704, 1608$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.74$ (s, 6H, 3$\times$CH$_3$), 2.37 (s, 3H, CH$_3$), 3.95 (s, 4H, 2$\times$CH$_2$), 7.20-7.27 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 349$ [M+1], 351 [M+4].

Analysis Calculated for C_{16}H_{17}BrN_{2}O_{2} (349.2): Calcd: C, 55.03; H, 4.91; N, 8.02%.
Found: C, 55.27; H, 4.88; N, 8.22%.
3-Bromo-4-morpholino-1-p-tolyl-1H-pyrrole-2,5-dione, 109h
Yield: 93%; M.p. 136-138 °C;
IR (KBr): $\overline{\nu} = 1764, 1707, 1622$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.37$ (s, 3H, CH$_3$), 3.82 (t, 4H, $J = 6$ Hz, 2×CH$_2$), 4.03 (t, 4H, $J = 6$ Hz, 2×CH$_2$), 7.16-7.27 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 351$ [M+1], 353 [M+3].
Analysis Calculated for C$_{15}$H$_{15}$BrN$_2$O$_3$ (351.2): Calcd: C, 51.30; H, 4.31; N, 7.98%. Found: C, 51.21; H, 4.47; N, 7.82%.

3-Bromo-4-(pyrrolidin-1-yl)-1-p-tolyl-1H-pyrrole-2,5-dione, 109i
Yield: 94%; M.p. 112-114 °C;
IR (KBr): $\overline{\nu} = 1755, 1710, 1622$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.95$ (s, 4H, 2×CH$_2$), 2.39 (s, 3H, CH$_3$), 4.25 (s, 4H, 2×CH$_2$), 7.17-7.30 (m, 4H, Ar-H) ppm; MS (70 eV): $m/z = 335$ [M+1], 337 [M+3].
Analysis Calculated for C$_{15}$H$_{15}$BrN$_2$O$_3$ (335.2): Calcd: C, 53.75; H, 4.51; N, 8.36%. Found: C, 53.55; H, 4.36; N, 8.22%.

3-Bromo-4-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 110
Yield: 93%; M.p. 108-110 °C;
IR (KBr): $\overline{\nu} = 1753, 1699, 1614$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.45$ (s, 6H, 2×CH$_3$), 7.26-7.45 (m, 5H, Ar-H) ppm; MS (70 eV): $m/z = 295$ [M$^+$], 297 [M+2].
Analysis Calculated for C$_{12}$H$_{13}$BrN$_2$O$_2$ (295.1): Calcd: C, 48.84; H, 3.76; N, 9.49%. Found: C, 48.71; H, 3.626; N, 9.59%.

Experiment No. 5

General Procedure for the synthesis of of 3-carbaldehyde-4-dialkylamino substituted maleimide, 111(a-c) and 112
To a Vilsmeier Haack adduct prepared from DMF (3 mL) and POCl₃ (1.2 mmol) at 0 °C was added 106(a-c) or 107 (1 mmol) and stirred at 0–5 °C for 30 min. The reaction mixture was poured into cold water. The yellow solid was separated on neutralization with 10% NaHCO₃ solution was filtered, washed with cold water, dried and purified by column chromatography (hexane:ethyl acetate, 6:4).

2,5-Dihydro-2,5-dioxo-1-phenyl-4-(piperidin-1-yl)-1H-pyrrole-3-carbaldehyde, 111a

Yield: 88%; M.p. 162-164 °C;

IR (KBr): \( \tilde{\nu} = 2858, 2777, 1758, 1701, 1668 \text{ cm}^{-1} \); \( \delta = 1.81 \text{ (s, 6H, } 3\times \text{CH}_2), 4.12 \text{ (s, 2H, CH}_2\), 4.40 \text{ (s, 2H, CH}_2\), 7.26–7.46 \text{ (m, 5H, Ar-H), 9.78 \text{ (s, 1H, CHO ppm; } ^{13}\text{C NMR (75 MHz, CDCl}_3\): } \delta = 23.7, 27.3, 27.6, 51.0, 57.7, 97.8, 127.6 \text{ (2C’s), 129.2 \text{ (2C’s), 129.6, 133.8, 148.0, 163.5, 169.4, 182.1; MS (70 eV): } m/z = 285 [M+1].

Analysis Calculated for C₁₆H₁₆N₂O₃ (284.3): Calcd: C, 67.59; H, 5.67; N, 9.85%. Found: C, 67.44; H, 5.89; N, 9.66%.
2,5-Dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrole-3-carbaldehyde, 111b

Yield: 84%; M.p. 166-168 °C;

IR (KBr): \(\bar{\nu} = 2871, 2786, 1760, 1676 \text{ cm}^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 3.87\) (s, 4H, \(2\times\text{CH}_2\)), 4.21 (s, 2H, \(\text{CH}_2\)), 4.47 (s, 2H, \(\text{CH}_2\)), 7.27-7.50 (m, 5H, Ar-H), 9.77 (s, 1H, CHO) ppm; \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 49.9, 55.8, 67.1, 67.4, 98.0, 126.3\) (2C’s), 128.1, 128.8 (2C’s), 130.7, 147.5, 163.6, 169.2, 182.1; MS (70 eV): \(m/z = 287\) [M+1].

Analysis Calculated for C\(_{15}\)H\(_{14}\)N\(_2\)O\(_4\) (286.3): Calcd: C, 62.93; H, 4.93; N, 9.79%. Found: C, 62.60; H, 4.64; N, 9.52%.

2,5-Dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1H-pyrrole-3-carbaldehyde, 111c

Yield: 86%; M.p. 148-150 °C;

IR (KBr): \(\bar{\nu} = 2860, 2780, 1764, 1704, 1660 \text{ cm}^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.06\) (m, 4H, \(2\times\text{CH}_2\)), 4.18 (m, 4H, \(2\times\text{CH}_2\)), 7.30-7.54 (m, 5H, Ar-H), 9.83 (s, 1H, CHO) ppm; \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 21.0, 25.1, 50.8\) (2C’s), 99.9, 126.0 (2C’s), 129.1, 129.4 (2C’s), 137.4, 142.8, 164.4, 166.3, 183.0; MS (70 eV): \(m/z = 271\) [M+1].

Analysis Calculated for C\(_{15}\)H\(_{14}\)N\(_2\)O\(_3\) (270.3): Calcd: C, 66.66; H, 5.22; N, 10.36%. Found: C, 66.46; H, 5.44; N, 10.62%.

4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1-phenyl-1H-pyrrole-3-carbaldehyde, 112

Yield: 81%; M.p. 166-168 °C;

IR (KBr): \(\bar{\nu} = 2866, 2767, 1757, 1708, 1656 \text{ cm}^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 3.62\) (s, 6H, \(2\times\text{CH}_3\)), 7.32-7.45 (m, 5H, Ar-H), 9.78 (s, 1H, CHO) ppm; \(^13\)C NMR (75
MHz, CDCl₃): $\delta = 42.5, 48.3, 98.0, 126.3$ (2C’s), 127.9, 128.8 (2C’s), 130.9, 149.4, 163.3, 169.4, 182.1; MS (70 eV): $m/z = 245$ [M+1].

Analysis Calculated for $C_{13}H_{12}N_{2}O_{3}$ (244.2): Calcd: C, 63.93; H, 4.95; N, 11.47%.
Found: C, 63.77; H, 4.85; N, 11.52%.

Experiment No. 6

Synthesis of 4-(Dimethylamino)-2,5-dihydro-2,5-dioxo-1-phenyl-1H-pyrrole-3-sulfonyl chloride, 113

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{Cl} \\
107 & \quad \text{SO}_3\text{H}, \text{THF} \\
0-25 ^\circ\text{C}, 4 \text{ h} & \quad 69\% \\
\rightarrow & \\
113 & \quad \text{O} \quad \text{O} \\
\end{align*}
\]

To a solution of 3-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione (107, 0.5 g, 2.3 mmol) in dry THF (5 mL) was added chlorosulphonic acid (0.80 g, 6.9 mmol) at 0 °C and then reaction mixture was stirred to 25–27 °C for 4 h (TLC checked), triethylamine was then added slowly at 0 °C to neutralized excess chlorosulphonic acid and then solution was stirred for 10 min, THF was removed under reduced pressure, solid residue was then extracted with DCM, solvent stripped off and the yellow solid purified by column chromatography (hexane:ethyl acetate, 8:2).

Yield: 72%; M.p. 98-100 °C;
IR (KBr): $\bar{\nu} = 1760, 1701, 1629, 1373, 1174$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl₃): $\delta = 3.68$ (s, 6H, 2×CH₃), 7.58-7.68 (m, 5H, Ar-H) ppm; MS (70 eV): $m/z = 315$ [M+1], $317$ [M+3].

Analysis Calculated for $C_{12}H_{11}ClN_{2}O_{3}S$ (314.7): Calcd: C, 45.79; H, 3.52; N, 8.90%.
Found: C, 45.64; H, 3.85; N, 8.77%.
To a solution of 3-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 107, (0.5 g, 2.3 mmol) in DCM (10 mL), anhydrous AlCl₃ (0.31 g, 2.3 mmol), benzyl chloride (0.29 g, 2.3 mmol) was added and then the reaction mixture was stirred for 18 h. The solvent was removed under reduced pressure and residue was extracted with ethyl acetate and washed with water, saturated NaHCO₃ solution, brine and dried over MgSO₄, filtered and then solvent was evaporated. The obtained crude product was purified by silica gel column chromatography by using hexane:ethyl acetate (6:4) to obtain golden yellow solid.

Yield: 0.48 g, (69%), M.p. 122-124 °C;

IR (KBr): $\tilde{\nu} = 1753, 1691, 1623 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl₃): $\delta = 3.26$ (s, 6H, 2×CH₃), 3.94 (s, 2H, CH₂), 7.20–7.47 (m, 10H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl₃): $\delta = 28.5, 42.9$ (2C’s), 100.7, 126.0 (2C’s), 127.1 (2C’s), 127.8 (2C’s), 128.6, 128.8 (2C’s), 132.1, 140.8, 145.3, 166.7, 171.5; MS (70 eV): $m/z = 307$ [M+1].

Analysis Calculated for C₁₉H₁₈N₂O₂ (306.4): Calcd: C, 74.49; H, 5.92; N, 9.14%. Found: C, 74.34; H, 5.78; N, 9.01%.
General Procedure for the synthesis of 115, 116a and 116b

To a solution of 3-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 107, (1.0 mmol) in DMF (5 mL), ethyl chloroformate/acetyl chloride or benzoyl chloride (1.0 mmol) was added and to this mixture triethyl amine (3.0 mmol) was added slowly at 25–27 °C. The resulting reaction mixture was then refluxed for 5–8 h and poured over crushed ice. The yellow solid obtained was filtered, dried and purified by silica gel column chromatography (hexane:ethyl acetate, 6:4).

**Ethyl 4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1-phenyl-1H-pyrrole-3-carboxylate, 115**

Yield: 56%, M.p. 96-98 °C;

IR (KBr): $\tilde{\nu} = 1751, 1730, 1693 \text{ cm}^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.45$ (t, 3H, $J = 9$ Hz, CH$_3$), 3.65 (s, 6H, $2 \times$ CH$_3$), 4.43 (t, 2H, $J = 9$ Hz, O-CH$_2$), 7.22-7.43 (m, 5H, Ar-H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 16.1, 42.2, 48.4, 60.8, 98.1, 122.0, 128.1$ (2C’s), 130.2, 133.1 (2C’s), 149.8, 162.2, 163.4, 169.3; MS (70 eV): $m/z = 289$ [M+1].
Analysis Calculated for $\text{C}_{15}\text{H}_{16}\text{N}_{2}\text{O}_{4}$ (288.1): Calcd: C, 62.49; H, 5.59; N, 9.72%. Found: C, 62.55; H, 5.41; N, 9.58%.

**3-Acetyl-4-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 116a**

Yield: 58%, M.p. 106-108 °C;  
IR (KBr): $\tilde{\nu} = 1755, 1708, 1693 \text{ cm}^{-1}$; $^1\text{H NMR (300 MHz, CDCl}_3)$: $\delta = 2.59$ (s, 3H, CH$_3$), 3.21 (bs, 3H, CH$_3$), 3.65 (bs, 3H, CH$_3$), 7.29–7.50 (m, 5H, Ar-H) ppm; $^{13}\text{C NMR (75 MHz, CDCl}_3)$: $\delta = 30.8, 42.3, 47.3, 100.8, 126.6$ (2C’s), 127.9, 128.9 (2C’s), 131.2, 151.7, 163.9, 168.1, 192.6; MS (70 eV): $m/z$ = 259 [M+1].

Analysis Calculated for $\text{C}_{14}\text{H}_{14}\text{N}_{2}\text{O}_3$ (258.3): Calcd: C, 65.11; H, 5.46; N, 10.85%. Found: C, 65.33; H, 5.41; N, 10.48%.

**3-Benzoyl-4-(dimethylamino)-1-phenyl-1H-pyrrole-2,5-dione, 116b**

Yield: 60%, M.p. 112-114 °C;  
IR (KBr): $\tilde{\nu} = 1753, 1712, 1685 \text{ cm}^{-1}$; $^1\text{H NMR (300 MHz, CDCl}_3)$: $\delta = 3.10$ (s, 6H, 2×CH$_3$), 7.22–7.38 (m, 5H, Ar-H); 7.42–7.63 (m, 5H, Ar-H) ppm; MS (70 eV): $m/z$ = 321 [M+1].

Analysis Calculated for $\text{C}_{19}\text{H}_{16}\text{N}_{2}\text{O}_3$ (320.3): Calcd: C, 71.24; H, 5.03; N, 8.74%. Found: C, 71.01; H, 5.25; N, 8.83%. 
1.6 References


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