CHAPTER 4

MULTICOMPONENT REACTIONS OF N-HETEROCYCLIC CARBENES (NHCs) WITH DIMETHYL ACETYLENEDICARBOXYLATE AND AROMATIC ALDEHYDES

4.1 Introduction

Ever since the isolation and characterization of a stable crystalline diaminocarbene by Arduengo in 1991, there has been growing interest in the exploration of the structure and chemical reactivities of N-heterocyclic carbenes.\(^1\) The history of NHCs can be traced to the work of Wanzlick in the 1960s.\(^2\) He had recognized earlier that electron rich imidazole nucleus can stabilize a carbene center at the 2-position between two nitrogens, and he tried to prepare the 1,3-diphenyl imidazolin-2-ylidene from 1 by the thermal elimination of chloroform. At that time he could not isolate any carbene, but isolated a dimeric electron rich olefin 3 (Scheme 1).

![Scheme 1](image)

Although Wanzlick was unsuccessful in isolating aminocarbenes, he demonstrated that imidazolium salts such as 4 could be deprotonated by
potassium tertiary butoxide to afford the corresponding imidazol-2-ylidenes which were subsequently trapped with electrophiles such as isocyanates and isothiocyanates, thereby proving the intermediacy of aminocarbenes in these reactions (Scheme 2).3

\[ \text{PhO} \text{R}^{+} \text{ClO}_4^- \xrightarrow{\text{BuOK}} \text{5} \xrightarrow{\text{Ph-NCS}} \text{6} \]

Scheme 2

A major breakthrough in this area occurred when Arduengo isolated a stable crystalline diaminocarbene in 1991. When \( \text{bis} \) \( \text{(1-adamantyl)} \) imidazolium chloride 7 was deprotonated with sodium hydride in tetrahydrofuran in the presence of a catalytic amount of dimethyl sulfoxide anion, the carbene 8 precipitated as a colorless crystalline and thermally stable compound (Scheme 3).1

\[ \text{Ad} \text{OCI NaH} \xrightarrow{\text{DMSO (cat.)} 25\degree \text{C}} \text{Ad} \]

Scheme 3

In the \( ^{13}\text{C} \) NMR spectrum, the low field position of the signal for the carbene carbon (\( \delta = 211.4 \)) was diagnostic, and single crystal X-ray analysis unequivocally confirmed the structure of 8. The unusual stability of 8 was explained on the basis of a number of factors \( \text{viz.} \), the large singlet-triplet energy gap in imidazol-2-ylidene (~80 kcal/mol), \( \pi \)-interactions in the imidazole ring, and electronegativity effects from the nitrogen. In addition to the electronic factors, it was believed initially that steric effects also play a
major role in stabilizing the carbene 8. Later Arduengo has demonstrated that stable carbenes of the type 10 could be prepared by the deprotonation of imidazolium salts bearing less bulky substituents in the 1 and 3 positions (Scheme 4).4

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{NaH} & \quad \text{BuOK (cat.)} \\
\text{25 °C} & \quad \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

Scheme 4

Since then a wide variety of aminocarbenes have been synthesized, including the first air stable carbene in 1997. A solid sample of the stable carbene 13 exposed to air did not show any decomposition even after two days (Scheme 5).5

\[
\begin{align*}
\text{N} & \quad \text{Mes} \\
\text{Mes} & \quad \text{Mes} \\
\text{NaH} & \quad \text{DMSO (cat.)} \\
\text{25 °C} & \quad \\
\text{Mes} & \quad \text{Mes} \\
\text{Mes} & \quad \text{Mes}
\end{align*}
\]

Scheme 5

The synthesis of a tris carbene, in which the imidazolylidene units are attached to a benzene ring, has also been reported. The carbene 15 was synthesized by deprotonation of the corresponding imidazolium chloride with sodium hydride in presence of a catalytic amount of potassium tertiary butoxide (Scheme 6).6
Similarly, a stable *bis* carbene 17 was also prepared by employing the same strategy (Scheme 7). Enders and coworkers have reported the synthesis of the stable triazolylidene 19 by the thermal elimination of methanol from 5-methoxy-1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazole 18 (Scheme 8).

As described above, the general method for the synthesis of aminocarbenes involves the deprotonation of the corresponding azolium salts by a suitable base. Later Kuhn and coworkers have developed a novel and versatile method for the synthesis of alkyl substituted *N*-heterocyclic carbenes using a completely different strategy. In this method the carbene 23 is generated by the reaction of imidazole-2(3H)-thiones 22 obtained from aldo 20 and thiourea with potassium in THF (Scheme 9).
generated by the reaction of imidazole-2(3H)-thiones 22 obtained from aldol 20 and thiourea with potassium in THF (Scheme 9).\(^9\)

\[
\begin{align*}
\text{Me} &\quad \text{OH} & \quad \text{HN} &\quad \text{S} \\
\text{Me} &\quad \text{OH} & \quad \text{HN} &\quad \text{S} \\
\text{R} &\quad & \quad &\quad \\
\text{R} &\quad & \quad &\quad \\
\end{align*}
\]

Scheme 9

Later, Arduengo and coworkers have reported the synthesis of imidazolin-2-ylidenes by the deprotonation of bis-(mesityl) imidazolinium chloride 24 with potassium hydride. The X-ray structure of 25 has confirmed the monomeric nature of the molecule (Scheme 10).\(^{10}\)

\[
\begin{align*}
\text{Mes} &\quad \text{N} &\quad \text{Cl} \\
\text{Mes} &\quad \text{N} &\quad \text{Cl} \\
\end{align*}
\]

Scheme 10

The synthesis of stable acyclic diaminocarbenes was reported by Alder in 1998; this was followed by the isolation of stable alkoxyamino and aminothiocarbenes.\(^{11}\) The aminocarbenes were prepared by the deprotonation of the corresponding amidinium salts with lithium amide bases, and these carbenes were found to undergo slow dimerization at ambient temperatures (Scheme 11).
3.2 Reactivity Patterns of \( N \)-Heterocyclic Carbenes

By virtue of their strong \( \sigma \)-donating ability, \( N \)-heterocyclic carbenes have found impressive use as ligands in the preparation of catalysts in organometallic chemistry. It is worthy of note that the aminocarbene incorporated ruthenium alkylidene catalysts were found to be more versatile than the conventional Grubbs' catalyst in olefin metathesis reactions.\(^{13}\) The application of NHCs in organometallic chemistry is treated only superficially.
here, since it is only of peripheral relevance to the present work and excellent reviews on the subject are available in the literature.\textsuperscript{14}

Following the Brønsted-Lowry concept, Alder and coworkers have determined the nucleophilicity and basicity of various aminocarbenes. They have reported the $pK_a$ of 1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene as 24 in DMSO-$d_6$ and found that it is a much stronger base than DBN, DBU and proton sponge but weaker than phosphazene bases.\textsuperscript{15} Recently Streitweiser has calculated the $pK_a$ of 1,3-ditertiary butyl imidazole-2-ylidene in THF as 20 which is much less than that of the dimesityl derivative reported by Alder.\textsuperscript{16}

As early as 1958, Breslow recognized the role of $N$-heterocyclic carbenes as nucleophilic catalysts in enzymatic reactions. He has shown that the vitamin B$_1$ enzyme cofactor thiamin 34, a naturally occurring thiazolium salt, plays a key role in biochemical transformations (Figure 1).\textsuperscript{17}

As thiamine diphosphate, it catalyzes the decarboxylation of pyruvic acid to active acetaldehyde as well as the benzoin condensation of aromatic aldehydes. The active species involved in this reaction was found to be the thiazolylidene 35 (Scheme 13).
Upon addition of a ylidene catalyst such as imidazolium, thiazolium or triazolium salts, aliphatic aldehydes are also reported to undergo benzoin type condensation known as Stetter reaction. When α,β-unsaturated ketones are employed, the reaction is called Michael-Stetter reaction; a typical reaction involving an imidazolium salt, an α,β-unsaturated ketone and an aldehyde is shown in Scheme 14.\(^{18}\)

The formoin condensation under ylidene catalysis affords carbohydrates (Scheme 15).\(^{19}\)
Asymmetric versions of Michael-Stetter reactions employing chiral azolium salts have also been reported (Scheme 16).\(^{20}\)

In a recent study, the asymmetric intramolecular Michael-Stetter reaction using another chiral triazolium salt 48 has been reported with improved yields and enantioselectivity (Scheme 17).\(^{21}\)

The addition of stable imidazole-2-ylidenes and triazolylidenes to heterocumulenes such as carbon dioxide, carbon disulfide and phenyl isothiocyanate afforded the corresponding betaines (Scheme 18).\(^{22}\)
The reaction of triazolylidene 19 with excess phenyl isocyanate led to the formation of the spirop compound 54, presumably via a $[3+2]$ cycloaddition with the intermediate betaine 53 (Scheme 19).\textsuperscript{22}

\textbf{Scheme 19}

The reaction of 1,3-dimesityl imidazole-2-ylidene with diazo compounds such as diazofluorene and diphenyl diazomethane afforded the corresponding azines as the addition products, while the reaction of the carbene with azido trimethylsilane furnished the imine 58 (Scheme 20).\textsuperscript{23}

\textbf{Scheme 20}

Insertion of stable aminocarbenes such as triazolylidene into strongly polar X-H bonds has been reported to afford the corresponding 1,1-addition.
products in quantitative yields. However, the insertion of such species into unpolarised C-H bonds is not reported so far (Scheme 21).²

Scheme 21

Imidazolin-2-ylidene 25 has been reported to react with methyl iodide and methylene chloride to afford the olefins 61 and 64 along with the corresponding imidazolinium salts (Scheme 22).³

Scheme 22

The reaction of imidazol-2-ylidene 10 with pentafluoro pyridine afforded the corresponding substituted product 66 in good yield (Scheme 23).²⁴
Similarly the addition of carbene 67 to trimethylsilyl iodide afforded the corresponding addition product. However no reaction was observed with trimethylsilyl chloride (Scheme 24).25

![Scheme 24]

The reactivity of stable diaminocarbenes towards C-C multiple bonds has also been studied by Enders and coworkers, who have shown that unlike other singlet carbenes, the triazolylidene 19 did not furnish any cyclopropane derivative with dimethyl fumarate; instead it afforded the methylene triazoline derivative 72. According to these workers, the initial event in this reaction is the [2+1] cycloaddition of the carbene with the alkene to form the cyclopropane derivative 70 which undergoes rapid ring opening to afford the zwitterionic intermediate 71. This zwitterion on subsequent [1,2] hydrogen shift affords the methylene triazoline derivative 72 (Scheme 25).8

![Scheme 25]

Recently, the N-heterocyclic carbene 12 was reported to form stable crystalline compounds with organic acids such as phenols (Scheme 26).26
A number of imidazolium salts have found widespread use as ionic liquids. Afonso and coworkers have reported the beneficial properties of imidazolium salts as ionic liquids in Baylis Hillmann reaction. However, in a recent study, it was shown that the use of imidazolium salts as ionic liquids in Baylis Hillman reaction results in low yields of products due to side reactions of the carbene generated with aldehydes as shown in Scheme 27. Thus the study has demonstrated that the deprotonation of imidazolium salts requires only mild bases such as DABCO and 3-hydroxyquinuclidine.

The reactivity of stable diaminocarbenes towards water, oxygen and hydrogen has also been investigated. The imidazolin-2-ylidene 78 was found to undergo instant hydrolysis on exposure to moist THF while the aromatic congener 80 took days to get hydrolysed to the corresponding aldehyde (Scheme 28).
The carbenes 78 and 80 were found to be inert towards oxygen and hydrogen, but in the presence of a platinum or palladium catalyst, they underwent slow hydrogenation (Scheme 29).29

Scheme 28

Rigby has shown that the reaction of N-heterocyclic carbenes with vinyl isocyanates and vinyl ketenes led to functionalized hydroindolone and cyclopentenone derivatives (Scheme 30).30

Scheme 29

Our studies commenced by exposing 3-methylpropanaldehyde to DMAD and 1,3-dimesitylimidazol-2-ylidene with simultaneous heating at 20°C and 10°C, respectively, in THF under argon. A facile reaction leading to the formation of 2-oxoindolyl derivative 89 occurred (Scheme 31).
4.3 The Present Work

The literature survey has revealed that although the chemistry of N-heterocyclic carbenes has been explored in some detail most of the studies were focused on the coordination behavior of these species as strong σ-donor ligands. Against this literature background, and in the context of our general interest in devising novel multicomponent reactions based on nucleophilic carbenes (see Chapter 2), it was of interest to examine the reactivity pattern of N-heterocyclic carbenes in multicomponent reactions. The NHCs covered in the present study are 1,3-dimesityl-imidazolin-2-ylidene and 1,3-dimesityl-imidazol-2-ylidene and the electrophiles of our choice include a variety of aromatic aldehydes and dimethyl acetylenedicarboxylate (DMAD). The results of our explorations in this avenue are presented in the following section.

4.4 Results and Discussion

Our studies commenced by exposing 3-nitrobenzaldehyde to DMAD and 1,3-dimesityl imidazolin-2-ylidene, generated in situ by the reaction of 1,3-dimesityl-imidazolinium chloride with sodium hydride in THF under argon atmosphere. A facile reaction leading to the formation of 2-oxymaleate derivative 89 occurred (Scheme 31).
Scheme 31

The structure of the product 89 was established by spectroscopic analysis. The IR spectrum showed strong carbonyl absorption peaks at 1742 and 1730 cm\(^{-1}\) corresponding to two ester carbonyls. In the \(^1\)H NMR spectrum, the peaks corresponding to protons of the aryl methyl groups were discernible as singlets at \(\delta\) 2.01, \(\delta\) 2.21 and \(\delta\) 2.38. The carbomethoxy protons resonated as singlets at \(\delta\) 3.48 and \(\delta\) 3.69 while the methylene protons of the dihydro imidazole displayed two triplets centered at \(\delta\) 3.75 and \(\delta\) 3.89. The peak corresponding to the olefinic proton was discernible as a singlet at \(\delta\) 4.75 while the aromatic protons afforded signals between \(\delta\) 6.46 and \(\delta\) 7.36. In the \(^{13}\)C NMR spectrum, the two ester carbonyls were found to resonate at \(\delta\) 165.8 and \(\delta\) 163.5. The olefinic carbons C-3 and C-6 showed peaks at \(\delta\) 97.9 and \(\delta\) 117.3. All the other signals were in good agreement with the assigned structure. The HRMS data of the compound was also found to be satisfactory. Final proof for the structure assigned for 89 was derived from single crystal X-ray analysis (Figure 2).
The reaction was found to be applicable to a number of substituted aromatic aldehydes; reasonable yields of the products were obtained in all cases (Table 1).

Table 1

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<tr>
<td>3</td>
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</table>

Figure 2  X-Ray Crystal Structure of 89

Figure 3  $^1$H NMR Spectrum of 89

Figure 4  $^{13}$C NMR Spectrum of 89
The reaction was found to be applicable to a number of substituted aromatic aldehydes; reasonable yields of maleate derivatives were obtained in all cases (Table 1).

Table 1

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Reaction conditions: NaH, THF, Ar, r.t, 3 h.
* = isolated yield
The reaction takes place in solvents such as benzene and toluene also, but the products were obtained in much higher yields when the reaction was carried out in THF. Similarly the rate of the reaction was found to be accelerated at higher temperatures, but in some cases the reaction afforded intractable mixtures. Also the use of alkynes other than DMAD did not afford any maleate derivatives. In these cases, the only isolable product was 101 derived from the hydrolysis of the carbene (Scheme 32).

Scheme 32

A mechanistic rationale for this reaction is given in Scheme 33. Presumably, unlike in the case of nucleophiles such as isocyanides and dimethoxycarbene, the initial event in this reaction is the addition of diaminocarbene to the aldehyde to form an electron rich enaminol intermediate 102. The latter, due to steric reasons, undergoes a conjugate addition to the activated alkyne through the harder oxygen atom, followed by proton abstraction to furnish the product. It is conceivable that the addition of diaminocarbene to DMAD is reversible at r.t. and the thermodynamic stability of 102 drives the reaction towards product formation.
The reaction was found to be sensitive to the nature of the carbene employed. When the less nucleophilic 1,3-dimesityl imidazol-2-ylidene is employed, the reaction followed a different but interesting pathway leading to the furanone derivative 103 in good yield (Scheme 34).

Scheme 33

The structure of the product 103 was elucidated by spectroscopic analysis. The IR spectrum showed a peak at 1694 cm⁻¹ corresponding to the lactone and the carbomethoxy groups. In the ¹H NMR spectrum, the peaks corresponding to the aryl methyl groups were discernible as singlets at δ 2.19, and δ 2.30. The protons of the carbomethoxy group resonated as a singlet at δ 3.37 while the aromatic protons afforded two separate multiplets in the region δ 6.93-6.12 and δ 7.36-7.29. In the ¹³C NMR spectrum, signals due to the aryl methyl carbons were visible at δ 18.6 and δ 21.1 while signals at δ 71.2 and δ 111.1 were assigned to the C-3, C-14 and C-15 carbons. The signals due to
the ester and lactone carbonyls were seen at δ 164.1 and δ 165.3. All the other signals were also in good agreement with the proposed structure; the HRMS data of the compound was also found to be satisfactory. Final proof for the structure assigned for 103 was derived from single crystal X-ray analysis (Figure 5).

A plausible mechanism for this reaction is given in the following scheme (Scheme 35).

Figure 5 X-Ray Crystal Structure of 103

It is conceivable that the addition is initiated by the formation of the
zwitterion 104, from the carbene and DMAD, which adds to the aldehyde to form another zwitterionic species 105. This ion, presumably for steric reasons, adds to the ester carbonyl of DMAD in preference to the iminium ion to afford 106, which subsequently eliminates a proton to furnish the furanone derivative 103. The reaction was found to be applicable to a number of substituted aromatic aldehydes and the results are summarized in Table 2.

Table 2

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Reaction conditions: NaH, THF, Ar, r.t. 12 h.

* = isolated yield
In conclusion, we have unraveled some interesting reactivity profiles of the N-heterocyclic carbenes 25 and 12 thus constituting novel multicomponent reactions which offer a simple and efficient route to the one pot synthesis of highly functionalized 2-oxymaleate and furanone derivatives. It is worthy of mention that a wide range of biologically active molecules contain dihydridomazadole and furanone moieties as the central core.

4.5 Experimental

General information about the experiments is given in Section 2.6 of Chapter 2. The carbene precursors 1,3-dimesityl-imidazolinium chloride and 1,3-dimesityl-imidazolium chlorides were prepared by a known literature procedure.32 Gravity column was performed using basic alumina and mixtures of hexane-ethylacetate were used for elution.

**Dimethyl 2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene]-1-nitrophenyl methoxy]-2-butenedioate 89**

NaH (16 mg, 0.66 mmol) was added to a suspension of the carbene precursor 24 (226 mg, 0.66 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (69 mg, 0.49 mmol) and the aldehyde 88 (50 mg, 0.33 mmol) and the resulting solution was stirred for 30 minutes. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 89 (136 mg, 69%) as a red crystalline solid (recrystallized from hexane-CH$_2$Cl$_2$ solvent mixture), m.p. 149-150 °C.
IR (KBr) \( \nu_{\text{max}} \): 3015, 2942, 2850, 1742, 1730, 1620, 1592, 1472, 1351, 1283, 1052, 845, 737 cm\(^{-1}\).

\(^1\)H NMR: \( \delta \) 7.36 (d, \( J = 7.9 \), 1H), 7.25 (s, 1H), 7.08 (d, \( J = 7.9 \), 1H), 6.95 (t, \( J = 7.9 \), 1H), 6.84 (s, 2H), 6.46 (s, 2H), 4.75 (s, 1H), 3.89 (t, \( J = 7.7 \), 2H), 3.75 (t, \( J = 7.9 \), 2H), 3.69 (s, 3H), 3.48 (s, 3H), 2.38 (s, 6H), 2.21 (s, 9H), 2.01 (s, 3H).

\(^{13}\)C NMR: \( \delta \) 165.8, 163.5, 157.8, 147.2, 146.8, 137.9, 137.5, 136.9, 136.3, 136.1, 134.1, 129.8, 129.5, 128.3, 127.7, 119.7, 117.3, 97.9, 52.1, 51.3, 51.1, 49.8, 20.9, 20.0, 18.7, 18.3.

HRMS (EI) Calculated for C\(_{34}\)H\(_{37}\)N\(_3\)O\(_7\): 599.2631 Found: 599.2591.

Crystal data for 89: C\(_{34}\)H\(_{37}\)N\(_3\)O\(_7\), FW = 599.67, the crystal used for the X-ray study has the dimensions of 0.40 x 0.22 x 0.10 mm\(^3\). Monoclinic, space group P2\(_1\)/c. Unit cell dimensions: \( a = 8.3507(2) \) Å, \( \alpha = 90^\circ \); \( b = 16.5312(3) \) Å, \( \beta = 94.2560(10)^\circ \); \( c = 22.7552(5) \) Å, \( \gamma = 90^\circ \); \( \text{Vol} = 3132.63(12) \) Å\(^3\). Density (calcd.) = 1.271 mg/mm\(^3\). Absorption coefficient = 0.089 mm\(^{-1}\). R indices R1 = 0.1555, wR2 = 0.1439

Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene](phenyl)methoxy]-2-butenedioate 94

NaH (22 mg, 0.94 mmol) was added to a suspension of the carbene precursor 24 (322 mg, 0.94 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (99 mg, 0.70 mmol) and the aldehyde 36 (50 mg, 0.47 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite\(^\circ\). After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate mixture to afford 94 (205 mg,
53%) as a yellow crystalline solid (recrystallized from hexane-CH$_2$Cl$_2$ solvent mixture), m.p. 150-151 °C.

**IR (KBr) $\nu_{\text{max}}$:** 3013, 2948, 2854, 1742, 1721, 1627, 1592, 1485, 1352, 1283, 1135, 1040, 858, 690 cm$^{-1}$.

**$^1$H NMR:** $\delta$ 6.82-6.74 (m, 6H), 6.62-6.57 (m, 1H), 6.49 (s, 2H), 4.76 (s, 1H), 3.81-3.68 (m, 4H), 3.65 (s, 3H), 3.45 (s, 3H), 2.38 (s, 6H), 2.03 (s, 3H), 2.21 (s, 9H).

**$^{13}$C NMR:** $\delta$ 165.9, 163.2, 158.3, 145.1, 138.6, 136.2, 135.1, 134.1, 134.1, 129.6, 126.6, 124.9, 123.3, 111.1, 97.4, 51.7, 51.3, 50.8, 49.8, 20.8, 20.5, 18.5, 18.2.

**HRMS (EI) Calculated for C$_{34}$H$_{38}$N$_2$O$_5$:** 554.2780, Found: 554.2791

**Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (3-chlorophenyl) methoxy]-2-butenedioate 95**

NaH (22 mg, 0.64 mmol) was added to a suspension of the carbene precursor 24 (239 mg, 0.70 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (99 mg, 0.53 mmol) and the aldehyde 90 (50 mg, 0.35 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite$^\circledR$. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethy acetate solvent mixture to afford 95 (164 mg, 80%) as a yellow crystalline solid (recrystallized from hexane-CH$_2$Cl$_2$ solvent mixture), m.p. 135-136 °C.
solid (recrystallized from hexane-CH2Cl2)
removal of the solvent, the residue was subjected to chromatography on a basic
aluminum column using 80:20 hexane-ethyl acetate solvnet mixture to afford 96
solvent mixture). m.p. 170-171°C.
164 MHz, 62%), as a yellow crystalline solid (recrystallized from hexane-CH2Cl2)
96
19 mL, 0.32 mmol) and the resulting solution was stirred for 3 h. The
reaction mixture was then passed through a short pad of Celite. After the
reaction mixture was added to a suspension of the

N4H2 (27 mL, 0.64 mmol) was added to a suspension of the carbene

HREMS (EI) Calculated for C34H37N2O5Cl: 588.2394; Found: 588.2388
20.9, 20.6, 18.6, 18.3, 18.2, 12.1, 27, 12.9, 12.7, 12.5, 12.2, 11.2, 11.0, 9.7, 1.4, 5.1, 4.6, 9.3
13C NMR: δ 216.9, 163.2, 158.1, 145.3, 134.0, 130.3, 126.9, 126.3, 125.4, 124.6, 120.4

H NMR: δ 6.90-6.99 (m, 1H), 4.74 (s, 2H), 3.69 (s, 2H), 3.44 (t, 2H), 3.27-3.47 (m, 3H), 1.75-2.06

IR (KBr) Vmax.: 3012, 2948, 2860, 1742, 1627,
**IR (KBr) v<sub>max</sub>:** 3010, 2955, 2860, 1744, 1717, 1627, 1485, 1371, 1290, 1135, 1047, 791, 765 cm<sup>-1</sup>.

**1H NMR:** δ 8.07 (d, J = 8.2, 1H), 7.47 (d, J = 7.7, 1H), 7.32-7.21 (m, 4H), 7.11 (d, J = 7, 1H), 5.05 (s, 1H), 3.80-3.65 (m, 4H), 3.52 (s, 3H), 3.40 (s, 3H), 2.51 (s, 6H), 2.19 (s, 9H), 1.81 (s, 3H).

**13C NMR:** δ 166.1, 162.9, 158.4, 146.2, 138.7, 136.5, 134.9, 133.5, 132.3, 131.7, 129.6, 128.7, 128.1, 127.7, 126.5, 126.2, 124.8, 124.3, 109.3, 97.9, 50.8, 50.7, 50.6, 50.2, 20.9, 20.3, 18.4.

**Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (4-chlorophenyl)methoxy]-2-butenedioate 97**

NaH (22 mg, 0.70 mmol) was added to a suspension of the carbene precursor 24 (239 mg, 0.70 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (99 mg, 0.53 mmol) and the aldehyde 92 (50 mg, 0.35 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 97 (124 mg, 60%) as a yellow crystalline solid (recrystallized from hexane-CH<sub>2</sub>Cl<sub>2</sub> solvent mixture), m.p. 135-136 °C.
IR (KBr) \( \nu_{\text{max}} \): 3012, 2942, 2845, 1742, 1627, 1485, 1438, 1290, 1209, 1135, 1054, 845, 757 cm\(^{-1}\).

\(^1\)H NMR: \( \delta \) 6.95-6.51 (m, 8H), 4.72 (s, 1H), 3.84-3.68 (m, 4H), 3.65 (s, 3H), 3.45 (s, 3H), 2.32 (s, 6H), 2.23 (s, 9H), 2.20 (s, 3H).

\(^13\)C NMR: \( \delta \) 165.7, 163.0, 158.0, 145.6, 143.3, 138.4, 138.3, 136.9, 136.1, 135.7, 134.2, 132.9, 129.6, 129.2, 128.5, 126.7, 126.0, 97.8, 51.6, 51.2, 50.7, 49.8, 20.7, 20.4, 18.3, 18.1.

HRMS (EI) Calculated for C\(_{34}H_{37}N_2O_{5}C\(_1\): 588.2391, Found: 588.2362.

Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (4-trifluoromethylphenyl)methoxy]-2-butenedioate 98

NaH (13 mg, 0.56 mmol) was added to a suspension of the carbene precursor 24 (191 mg, 0.56 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (61 mg, 0.43 mmol) and the aldehyde 93 (50 mg, 0.28 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite\(^\circledR\). After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 98 (104 mg, 60%) as a yellow crystalline solid (recrystallized from hexane-CH\(_2\)Cl\(_2\) solvent mixture), m.p. 138-139 °C.
IR (KBr) \( \nu_{\text{max}} \): 3010, 2962, 2845, 1728, 1634, 1438, 1256, 1128, 1027, 798 cm\(^{-1}\).

\(^1\)H NMR: \( \delta \) 6.93-6.54 (m, 8H), 4.73 (s, 1H), 3.83-3.68 (m, 4H), 3.68 (s, 3H), 3.47 (s, 3H), 2.30 (s, 6H), 2.21 (s, 9H), 2.19 (s, 3H).

\(^{13}\)C NMR: \( \delta \) 165.8, 163.0, 158.2, 145.6, 143.3, 138.1, 136.7, 136.2, 136.1, 135.7, 134.0, 129.8, 129.4, 128.5, 126.7, 126.0, 123.8, 123.6, 123.5, 97.6, 52.0, 51.3, 51.0, 49.9, 20.9, 20.3, 18.5, 18.2.

Methyl-2-(3-chlorophenyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 103

NaH (17 mg, 0.71 mmol) was added to a suspension of the carbene precursor 11 (241 mg, 0.71 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (74 mg, 0.53 mmol) and the aldehyde 90 (50 mg, 0.35 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite.\(^{\circledR}\) After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 103 (126 mg, 65%) as a yellow crystalline solid (recrystallized from hexane-CH\(_2\)Cl\(_2\)), m.p. 279-280 °C.

IR (KBr) \( \nu_{\text{max}} \): 3010, 2962, 2850, 1694, 1600, 1533, 1479, 1371, 1216, 1047, 906, 852, 798, 730 cm\(^{-1}\).

\(^1\)H NMR: \( \delta \) 7.36-7.29 (m, 2H), 6.93-6.12 (m, 8H), 3.37 (s, 3H), 2.30 (s, 6H), 2.19 (s, 12H).

\(^{13}\)C NMR: \( \delta \) 165.3, 164.1, 148.4, 140.2, 139.3, 135.3, 133.5, 132.8, 132.3, 130.5, 129.7, 129.3, 128.7, 127.2, 126.6, 125.2, 120.9, 111.1, 71.2, 50.5, 21.1, 18.6.
HRMS (EI) Calculated for C$_{33}$H$_{31}$N$_{2}$O$_{4}$Cl: 554.1972, Found: 554.1946.

**Crystal data for 103:** C$_{33}$H$_{31}$N$_{2}$O$_{4}$Cl FW = 555.05, the crystal used for the X-ray study has the dimensions of 0.40 x 0.33 x 0.24 mm$^3$. Orthorhombic, space group P2$_1$2$_1$2$_1$. Unit cell dimensions: a = 11.05750 (10) Å, $\alpha = 90^\circ$; b = 15.0539 (2) Å, $\beta = 90^\circ$; c = 17.5750 (5) Å, $\gamma = 90^\circ$; Vol = 2925.51(6) Å$^3$. Density (calcd.) = 1.260 mg/mm$^3$. Absorption coefficient = 0.170 mm$^{-1}$. R indices R1 = 0.0639, wR2 = 0.0971.

**Methyl-2-(phenyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 110**

NaH (23 mg, 0.94 mmol) was added to a suspension of the carbene precursor 11 (319 mg, 0.94 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (100 mg, 0.70 mmol) and the aldehyde 36 (50 mg, 0.47 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite$^\circledR$. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 110 (139 mg, 57%) as a yellow crystalline solid (recrystallized from hexane-CH$_2$Cl$_2$), m.p. 295-296 °C.

**IR (KBr) $\nu_{\text{max}}$:** 3010, 2962, 2842, 1688, 1607, 1539, 1485, 1378, 1303, 1070, 1040, 906, 865, 750 cm$^{-1}$.

**$^1$H NMR: $\delta$** 7.38-7.36 (m, 2H), 7.19-7.07 (m, 3H), 6.91-6.93 (m, 6H), 3.33 (s, 3H), 2.29 (s, 6H), 2.20 (s, 12H).

**$^{13}$C NMR: $\delta$** 165.5, 164.4, 148.3, 142.1, 139.1, 130.9, 129.6, 127.5, 127.3, 126.9, 111.1, 71.2, 50.5, 23.6, 21.1, 18.6.

HRMS (EI) Calculated for C$_{33}$H$_{32}$N$_{2}$O$_{4}$: 520.2362, Found: 520.2355.
Methyl-2-(3-nitrophenyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 111

NaH (16 mg, 0.66 mmol) was added to a suspension of the carbene precursor 11 (224 mg, 0.66 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (71 mg, 0.49 mmol) and the aldehyde 88 (50 mg, 0.33 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 111 (187 mg, 79%) as a yellow crystalline solid (recrystallized from hexane-CH$_2$Cl$_2$), m.p. 250-251 °C.

IR (KBr) $\nu_{\text{max}}$: 3018, 2935, 2852, 1701, 1607, 1526, 1321, 1229, 1040, 906, 852, 747 cm$^{-1}$.

$^1$H NMR: $\delta$ 8.30 (s, 1H), 7.91 (d, $J = 7.4$, 1H), 7.77 (d, $J = 7.4$, 1H), 7.34 (t, $J = 8$, 1H), 7.03 (s, 3H), 6.96 (s, 3 H), 3.46 (s, 3H), 2.29 (s, 6H), 2.21 (s, 12H).

$^{13}$C NMR: $\delta$ 165.1, 163.8, 147.9, 139.5, 138.5, 132.4, 129.7, 128.6, 121.6, 121.1, 120.7, 118.6, 113.7, 113.1, 77.2, 50.9, 21.2, 18.6.

HRMS (EI) Calculated for C$_{33}$H$_{31}$N$_3$O$_6$: 565.2212, Found: 565.2197.

Methyl-2-(4-methyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 112

NaH (20 mg, 0.84 mmol) was added to a suspension of the carbene precursor 11 (285 mg, 0.84 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (88 mg, 0.62 mmol) and the aldehyde 107 (50 mg, 0.42 mmol), and the resulting solution was stirred for 12 h. The
reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 112 (94 mg, 45%) as a yellow crystalline solid (recrystallized from hexane-CH₂Cl₂), m.p. 255-256 °C.

**IR (KBr) ν<sub>max</sub>:** 3018, 2962, 2854, 1686, 1533, 1371, 1229, 1303, 1162, 1074, 1034, 912, 854 cm⁻¹.

**¹H NMR:** δ 7.26 (d, J = 8.3, 2H), 6.98-6.91 (m, 8H), 3.32 (s, 3H), 2.28 (s, 6H), 2.19 (s, 3H), 2.07 (s, 9H).

**¹³C NMR:** δ 165.4, 164.3, 148.2, 142.5, 138.94, 136.5, 135.1, 132.2, 130.1, 129.5, 128.1, 127.3, 120.6, 110.4, 70.9, 50.3, 21.2, 21.0, 18.5.


**Methyl-2-(1-furyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 113**

NaH (25 mg, 1.04 mmol) was added to a suspension of the carbene precursor 11 (353 mg, 1.04 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (111 mg, 0.78 mmol) and the aldehyde 108 (50 mg, 0.52 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 113 (113 mg, 42%) as a yellow crystalline solid (recrystallized from hexane-CH₂Cl₂), m.p. 268-269 °C.
Methyl-2-(4-methoxy)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 114

NaH (17 mg, 0.72 mmol) was added to a suspension of the carbene precursor 11 (217 mg, 0.72 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (78 mg, 0.55 mmol) and the aldehyde 109 (50 mg, 0.36 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford 114 (49 mg, 25%) as a yellow crystalline solid (recrystallized from hexane-CH₂Cl₂), m.p. 189-190 °C.
4.6 References:


A general introduction to carbenes, carbenoids and nucleophilic carbenes is presented in Chapter 1. A brief introduction to multicomponent reactions and the definition of the present work is also provided in this chapter.

The second chapter describes the addition of the 1:1 zwitterionic intermediate of dimethoxycarbene, generated in situ by the thermolysis of 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline and DMAD, to various carbonyl compounds such as aldehydes, ketones and α,β-unsaturated carbonyl compounds. The addition of the zwitterionic intermediate to p-tolualdehyde affording the corresponding dihydrofuran derivative in 81% yield is illustrative (Scheme 1).

Scheme 1

The addition of the zwitterionic intermediate to ketones such as p-nitroacetophenone afforded the dihydrofuran derivative in excellent yield (Scheme 2).