4.1 Introduction

Isocyanides belong to a rare class of organic compounds with a formally divalent carbon. For long time, isocyanides were considered as unnatural molecules with a vile odour, but the last century saw a number of natural products containing isocyanide functionality being isolated. Isocyanide chemistry underwent a facelift with the discovery of the monumental Ugi and Passerini reactions. The present chapter deals with a new multicomponent reaction (MCR) of vicinal tricarbonyl compounds with isocyanides and dimethyl acetylenedicarboxylate (DMAD). Before going to the results, a brief overview of isocyanide chemistry is presented. This is followed by a brief introduction to tricarbonyl compounds.

4.2 Isocyanides

Isocyanides are isoelectronic with carbon monoxide and is shown to be of linear geometry by electron diffraction and microwave studies.

\[
\begin{align*}
R-\tilde{N}==C : & \quad R-\tilde{N}=C & :C=O & \quad \tilde{C}=O \\
1 & \quad 1a & \quad 2 & \quad 2a
\end{align*}
\]

Figure 1

The presence of both non-bonding electrons and electron-deficient \(\pi\)-orbitals imparts a dual character to the isocyanide carbon, which is clear from its chemical properties. The reason why isocyanides were not used for a long time was neither their suspected toxicity nor their vile odour, but rather the lack of accessibility to pure isocyanides. There are various methods available for the synthesis of isocyanides and these are given below.
4.2.1 Synthesis of isocyanides

Gautier in 1867 identified isocyanides in the reaction of alkyl iodides with silver cyanide. The isocyanide-silver iodide complex formed, on treatment with potassium cyanide afforded the isocyanide (Scheme 1).

\[
R\text{I} + AgCN \rightarrow [R\text{-NC}.Ag\text{I}]^+ \rightarrow R\text{-NC}^+ + AgI^-
\]

Scheme 1

Another method for the synthesis of isocyanides is the Hofmann carbylamine reaction. This involves the reaction of primary amines with chloroform in basic conditions followed by elimination of hydrogen chloride as shown below. The reaction occurs by an initial insertion of the dichlorocarbene generated from chloroform in basic conditions into the N-H bond followed by \(\alpha\)-elimination (Scheme 2).

\[
\text{NH}_2 \quad \text{CHCl}_3 \quad \text{KOH}
\]

\[
\quad \text{HN.CHC}_2 \quad \text{N=CHCl}
\]

\[
\quad \alpha\text{-elimination} \quad \text{-HCl}
\]

\[
\quad \text{NC}
\]

Scheme 2

The most convenient method for the synthesis of isocyanides was developed by Ugi and it is based on the dehydration of N-substituted formamides with phosgene in presence of triethylamine.

Later on, several other dehydrating agents were used to replace the toxic phosgene in the synthesis of isocyanides. These include thionyl chloride, \(p\)-toluene sulfonyl chloride, phosphorus tribromide, triphenylphosphine dibromide and
chlorodimethylformiminium chloride in combination with bases like trialkylamine, pyridine, quinoline and potassium carbonate.

4.2.2 Chemistry of Isocyanides

The chemistry of isocyanides is centered mainly on its three basic properties of $\alpha$-acidity, $\alpha$-addition and propensity to form radicals as shown below (Scheme 4).

4.2.2.1 $\alpha$-Metallation

Isocyanides can undergo two types of reactions with organometallic reagents depending on their structure. If the isocyanides possess $\alpha$-hydrogen atom, $\alpha$-metallated isocyanides 13 are produced whereas if the isocyanides lack $\alpha$-hydrogen, metalloaldimines of the type 12 are obtained as shown below (Scheme 5).

Schöllkopf has shown that $\alpha$-metallated isocyanides can be used for a variety of purposes like chain extension of amines and amino acids, heterocyclic synthesis and carbonyl olefinations. A general scheme for the addition of $\alpha$-metallated isocyanides to polar double bonds such as carbonyls and imines is shown below (Scheme 6). All other relevant informations in this area are covered in the review by Hoppe.
The presence of electron-withdrawing substituent at the α-carbon of isocyanide, as in tosylmethyl isocyanide (TosMIC) 16, has a profound effect on the reactivity pattern. The synthetic utility of TosMIC has been extensively investigated by Van Leusen’s group and hence TosMIC is known as Van Leusen reagent. A variety of bases under mild conditions can be used to remove the α-hydrogen of TosMIC. Oxazolines 18 are produced by the reaction of 16 with aldehydes in protic solvents at 20 °C, whereas under reflux conditions oxazole 20 is formed by the elimination of p-toluene sulphinic acid (Scheme 7).

Similar reactions with imines led to the formation of imidazoles whereas thiazoles were formed with dithioesters or carbon disulphide.

4.2.2.2 Radical reactions

Radical species can add to isocyanides to form imidoyl radicals which are common intermediates in all isocyanide based radical reactions as shown below (Scheme 8).
Chapter 4: Synthesis of aminofurans

The imidoyl radical 21 thus formed can undergo $\beta$-scission or can add to various carbon-carbon or carbon-heteroatom double bonds or can add to other radical species to form a variety of products. A generalized representation of the fate of the imidoyl radical is given below (Scheme 9).

Fukuyama applied the intramolecular capture of the imidoyl radical by styrenic double bonds in an efficient route to 2,3-disubstituted indoles 23 starting from 2-alkenylphenyl isocyanide 22 (Scheme 10).\(^\text{13}\)

An elegant use of radical initiated cyclization reaction of isocyanides is illustrated in the synthesis of Camptothecin by Curran. The reaction of bromopyridine 24, phenyl isocyanide and hexamethylditin afforded the intermediate 25 after two radical cyclizations and an oxidative rearomatization (Scheme 11).\(^\text{14}\)
4.2.2.3 Multicomponent reactions

Isocyanides are very useful in multicomponent reactions due to the diversity of bond forming processes available for the molecule. A detailed account of isocyanide based MCRs is given in chapter 1 of this thesis and hence it will not be discussed here.

4.2.2.4 Reactions of coordinated isocyanides

The presence of non-bonding pair of electrons in sp-hybridized orbital on the terminal carbon enables isocyanides to behave as strong carbon ligand for transition metals. For example, formation of the carbodiimide 27 by the reaction of primary amines and isocyanides via the formation of the carbon co-ordinated Pd(II) complex 26 is shown below (Scheme 12).\(^{15}\)

\[
\begin{align*}
R^1\text{-NH}_2 + R\text{-NC} & \xrightarrow{\text{PdCl}_2} \text{Cl}_2\text{Pd}^{\text{II}}(\text{RNC})\text{C}_\text{NHR}^1 \xrightarrow{\text{Ag}_2\text{O}} R^1\text{N} = \text{C} = \text{NR}
\end{align*}
\]

Scheme 12

Isocyanide-nickel complexes such as 28 react with diphenyl acetylene 29 to form diiminocyclobutene derivative 30. However, in presence of Pd complexes, isocyanide reacts with diphenyl acetylene to form imino cyclopentadiene 31 by a [1+2+2] cycloaddition as shown below (Scheme 13).\(^{16}\)
4.2.2.5 Miscellaneous reactions

There are a variety of reactions of isocyanides that cannot be restricted to any one of the above categories. These include isocyanide addition to carbonyl compounds,\(^\text{17}\) addition to olefins\(^\text{18}\) and reaction with 1,3-dipoles. Activation by Lewis acids is necessary for the addition of isocyanides to carbonyl compounds while addition to olefins occurs readily to form zwitterionic species which can undergo further reactions to form various products. The reaction of 1,3-dipoles with isocyanides will be discussed here.

Isocyanides act as a one carbon synthon, which on annulation by a 1,3-dipole should furnish four membered ring systems. Nitrile ylides have been shown to produce four membered rings \(^\text{33}\) on reaction with isocyanides (Scheme 14).\(^\text{19}\)

Azomethine ylide \(^\text{35}\), generated by the thermal ring opening of aziridine \(^\text{34}\), has been successfully cyclized with isocyanides to give the 3-iminoazetidines \(^\text{36}\) (Scheme 15).\(^\text{20}\)
Nitrones have also been added to isocyanides. Moderhack and Lorke have shown that using boron trifluoride as a catalyst, dialkyl nitrones 37 are readily cyclized with isocyanides to yield 4-imino-1,2-oxazetidines 38 (Scheme 16).\(^{21}\)

\[
\text{37} + \text{R}^2-\text{NC} \xrightarrow{\text{BF}_3\text{OEt}_2, \text{Et}_3\text{N}} \text{38}
\]

Scheme 15

Isocyanides add to benzynes to generate 1,3-dipolar species which can either get protonated or add to other electrophiles present in the system. Knorr showed that the reaction of cyclohexyl isocyanide with benzenediazonium-2-carboxylate 39 as a benzyne precursor in tert-butanol produced N-cyclohexylbenzamide and isobutene, concomitant with the evolution of CO\(_2\) and N\(_2\) gases (Scheme 17).\(^{22}\)

\[
\text{39} \xrightarrow{\Delta, -\text{N}_2, -\text{CO}_2} \text{Cy-NC} \xrightarrow{\text{OH}} \text{40} + \text{41}
\]

Scheme 16

A novel class of isocyanide based MCRs were developed in our laboratory based on the reactivity of the 1:1 intermediate formed by the reaction of isocyanide with dimethyl acetylenedicarboxylate. Earlier there have been few unsuccessful attempts to trap this reactive 1,3-dipolar intermediate.\(^{23}\) Experiments in our laboratory have shown...
that the 1,3-dipole 44 generated from cyclohexyl isocyanide 42 and DMAD 43 can be trapped with a variety of aldehydes, thus constituting a novel multicomponent aminofuran synthesis (Scheme 18).²⁴

Various dipolarophiles like N-tosylimines, 1,2-dicarbonyl compounds, o- and p-quinones and quinoneimines were also reactive towards the dipole affording novel heterocyclic systems.²⁵ Recent work has also shown that activated double bonds of dicyanostyrenes can react with the dipole generated from isocyanide and DMAD to yield fully substituted cyclopentadiene derivatives as shown below (Scheme 19).²⁶

Recently, a three-component reaction involving isoquinoline, gem-diactivated olefins and isocyanides leading to the formation of dihydropyrroloisoquinoline systems 52 was reported by Mironov.²⁷ The reaction proceeds through the pentannulation of a Huisgen 1,4-dipole 51, formed from isoquinoline and olefin, by isocyanide (Scheme 20).
A three-component reaction of isocyanides, arynes and aldehydes was reported very recently by Yoshida, constituting a straightforward synthesis of benzannulated iminofurans (Scheme 21).²⁸

Apart from the above mentioned reactions, isocyanides are also known to undergo [4+1] cycloadditions with suitable dienes.²⁹ Work from our laboratory has shown that [4+1] cycloaddition reactions of isocyanides can be used for the construction of 2-imino-1,3-oxathioles and furan annulated heterocycles by reaction with o-thioquinones and heterocyclic quinonemethides respectively.³⁰ The latter are in turn generated *in situ* by the reaction of active methylene compounds and aldehydes.

As the present chapter is focused on the addition of isocyanide-DMAD zwitterion to vicinal tricarbonyl compounds, a brief discussion of the latter will be appropriate in this context.

### 4.3 Vicinal tricarbonyl compounds

Vicinal tricarbonyl compounds refer to systems in which three carbonyl groups are arranged adjacently in an array. These have been known to synthetic organic chemists ever since the first preparation of diphenyl triketone in 1890 by Pechmann et
The synthetic importance of these systems is due to the reactivity of the highly electrophilic central carbonyl group of these molecules. Recent reviews by Wasserman and Rubin cover many aspects of the chemistry and applications of these species. The vicinal tricarbonyl (VTC) system may be prepared in high purity by a variety of procedures, some of which are outlined in the following sections.

**4.3.1 Methods of preparation**

**4.3.1.1 From β-dicarbonyl compounds**

Tricarbonyl compounds can be prepared by a variety of methods from β-dicarbonyl compounds by functionalizing the central carbon of the latter followed by an oxidation. Some of these methods are illustrated below (Scheme 22).

**4.3.1.2 From monoketones**

Tatsugi and Isawa\(^{37}\) reported a one-pot bromination-oxidation sequence to convert 1- and 2-indanones 65 and 66 to ninhydrin 67 (Scheme 23).
4.3.1.3 SmI\textsubscript{2} mediated insertion of isocyanides

Reaction of alkyl bromides with isocyanides and esters\textsuperscript{38} mediated by SmI\textsubscript{2} produced diimino compounds which could be hydrolyzed to tricarbonyls (Scheme 24).

The central carbonyl group of a vicinal tricarbonyl system is a highly electrophilic site due to the inherent coulombic repulsion between the carbonyl groups. So these can participate in several bond forming reactions, some of these are illustrated in the following section.
4.3.2 Reactions of tricarbonyl compounds

4.3.2.1 Reaction with nucleophiles

Exposure to moist air is sufficient to convert highly coloured polycarbonyls to their faintly coloured hydrates. The problem of hydration is particularly acute with cyclic compounds where the carbonyl groups are forced to near coplanar conformations.

\[ R'(CO)_nR^2 + H_2O \rightleftharpoons R'(CO)_nR^2.H_2O \]

Scheme 26

A variety of procedures have been used to obtain the free carbonyl compound from its hydrate. These include heating in vacuum or sublimation, distillation, crystallization, treatment in solution with molecular sieves or chemical dehydrating agents such as phosphorus pentoxide. Azeotropic distillation with toluene or chlorobenzene followed by concentration has also been reported. However, hydration is not a major problem in chemical reactions as in solution there is always some concentration of the free tricarbonyl compound.

Tricarbonyl compounds can readily undergo reaction with various nitrogen and carbon nucleophiles. Synthesis of papaveraldine\(^{41}\) 84, an isoquinoline alkaloid, by the reaction of the trione 80 with 3,4-dimethoxy phenethylamine 79 is shown below (Scheme 27).
Scheme 27

A large number of enolizable β-dicarbonyl compounds, phenols, phosphorus ylides, enamines, alkoxy or hydroxy substituted anilines and malonic acids can react with vicinal polycarbonyls. Wasserman observed that reaction of the phosphorane, 87 with the vicinal trione 86 in ethyl acetate at 0 °C afforded the cyclopentenone, 88 (Scheme 28).42

Scheme 28
4.3.2.2 Rearrangement reactions

Benzilic acid type rearrangements of the tricarbonyl compound have been applied for the conversion of the immunosuppressant FK 506 (masked α, β-diketoamide) 89 into its rearranged product 91. Partial structures are shown in scheme 29.\textsuperscript{43}

\begin{equation}
\text{N} \text{COOR} \xrightarrow{\text{LiOH\,THF\,0°C}} \text{N} \text{COOR} \xrightarrow{\text{Pb(OAc)}_4} \text{N} \text{COOR} + \text{CO}_2
\end{equation}

\text{89} \quad \text{90} \quad \text{91}

Scheme 29

Diacylcarbinol rearrangement of diphenyl triketone 92 with phenyl magnesium bromide resulted in the formation of benzoin 94 (Scheme 30).\textsuperscript{44}

\begin{equation}
\text{Ph} \text{CO} \xrightarrow{\text{PhMgBr}} \text{Ph} \text{CO} \xrightarrow{\text{PhMgBr}} \text{Ph} \text{CO}
\end{equation}

\text{92} \quad \text{93} \quad \text{94}

Scheme 30

4.3.2.3 Thermolysis

Flash vacuum thermolysis of cyclopententrione 95 at 430 °C produced cyclobutene dione 96 in 10% yield. Trapping of the intermediate bisketene with methanol gave good yields of dimethyl succinate (Scheme 31).\textsuperscript{45}
4.3.2.4 Cycloaddition reactions

Tetrahydroindole derivative 100 has been prepared by the reaction of acylamino diene 98 with vinyl vicinal tricarbonyl 99 as shown below (Scheme 32).

Scheme 32

4.3.3 Ninhydrin

Ninhydrin (1,2,3-triketo-hydrindene hydrate) 67 has been recognized for more than hundred years as a reagent for detecting amino acids. It is widely used as a spray reagent in the identification and quantitative estimation of amino acids. All α-amino acids react with ninhydrin to give a blue coloured product, except proline and hydroxy proline which give yellow products. Intensity of the colour is proportional to the amount of amino acid present. The reaction of ninhydrin with α-amino acids is given in scheme 33.
During the mid nineteen fifties, it was discovered that ninhydrin could also be used to develop latent finger prints on paper and porous surfaces. When ninhydrin comes into contact with amino acids in fingerprint residue, the reaction yields a red to purple print. This has wide spread application in the forensic laboratories for the identification of finger prints for various purposes.

4.4 Statement of the problem

Although there are literature reports on the addition of a variety of nucleophiles to the trione unit, there have been no attempts to add zwitterionic species to it. Backed by our experience in the area of isocyanides, particularly addition of isocyanide-DMAD dipole to electrophilic carbonyl groups, we investigated the reaction of the isocyanide-DMAD zwitterion towards the vicinal tricarbonyls. Results of our investigations in this area are detailed below.

4.5 Results and Discussion

The tricarbonyl compounds selected for our studies are shown below (Figure 2).

Diphenyl triketone hydrate 92 and the diketoester hydrates (103-107) were prepared by a reported procedure involving the oxidation of the corresponding 1,3-dicarbonyl compounds with Dess-Martin periodinane 110 as shown in scheme 34. Alloxan hydrate 109 was obtained by the chromium trioxide oxidation of barbituric acid in acetic acid. Diethyl ketomalonate 108 and ninhydrin 67 are commercially available.
The 1,3-dicarbonyl compound was treated with Dess-Martin periodinane 110 in presence of pyridine in dry DCM. Processing of the reaction mixture followed by column chromatography of the crude mixture on silica gel yielded the corresponding tricarbonyl compound in moderate yields.

In a pilot experiment, a solution of the diketoester 104 and DMAD 43 in dry dichloromethane was treated with tert-butyl isocyanide 46 at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was processed, and the residue was subjected to column chromatography on silica gel to afford the fully substituted furan 111 as a colourless liquid in 56% yield (Scheme 35).

The IR spectrum of 111 displayed characteristic ester carbonyl and N-H vibrations at 1743, 1722 and 3345 cm⁻¹. In the ¹H NMR spectrum, sharp singlet at δ 1.47 was characteristic of the tert-butyl group while the methoxy protons of the ester moiety resonated at δ 3.90 and 3.76. The N-H proton was discernible as a sharp singlet at δ 6.99 and was exchangeable with D₂O. In the ¹³C NMR spectrum, the ester carbonyl carbons were discernible at δ 164.8, 163.8 and 162.2. The compound gave satisfactory mass analysis also.
Chapter 4: Synthesis of aminofuran

Figure 3 $^1$H NMR spectrum of compound 111

Figure 4 $^{13}$C NMR spectrum of compound 111
To test the generality of the reaction, a number of diketoesters were prepared and were subjected to the same reaction conditions with isocyanide and DMAD in dichloromethane as solvent. In all these cases the reaction afforded the aminofuran derivatives in moderate yields. The results are summarized in table 1.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diketoester</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103 R = Me</td>
<td>112</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>105 R = Bu</td>
<td>113</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>106 R = CH2Ph</td>
<td>114</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>107 R = CH2CH=CHPh</td>
<td>115</td>
<td>50</td>
</tr>
</tbody>
</table>

^aIsolated Yield

The reaction was also found to be variable with respect to the isocyanide component. Cyclohexyl isocyanide and DMAD reacted with the diketoesters leading to the substituted furans in moderate yields and the results are catalogued in table 2.

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diketoester</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103 R = Me</td>
<td>116</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>104 R = Et</td>
<td>117</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>105 R = Bu</td>
<td>118</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>106 R = CH2Ph</td>
<td>119</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>107 R = CH2CH=CHPh</td>
<td>120</td>
<td>45</td>
</tr>
</tbody>
</table>

^aIsolated Yield
A different kind of reaction occurred when a solution of diphenyl triketone 92 and DMAD 43 in dry dichloromethane was treated with tert-butyl isocyanide 46 at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was processed and the residue was subjected to column chromatography on silica gel to afford 121 as a viscous liquid in 42% yield. It was clear from the $^1$H NMR spectrum of the compound that it contained two isocyanide molecules per molecule of DMAD and the trione. The reaction conditions were modified accordingly using two equivalents of the isocyanide and the reaction was found to yield the same iminopyrone 121 in 83% yield. Similar reaction with cyclohexyl isocyanide afforded 122 (Scheme 36).

![Scheme 36](image)

Scheme 36

The product was characterized on the basis of spectroscopic data. The IR spectrum of 121 displayed characteristic ester and benzoyl carbonyl vibrations at 1741 and 1681 cm$^{-1}$ respectively. In the $^1$H NMR spectrum sharp singlets at $\delta$ 1.51 and 1.38 corresponded to the two tert-butyl groups and the protons of the carbomethoxy groups resonated at $\delta$ 3.87 and 3.66. The N-H proton was discernible at $\delta$ 6.79 and it was exchangeable with D$_2$O. $^{13}$C resonance signals at $\delta$ 185.6, 163.8 and 162.3 were characteristic of the benzoyl and ester carbonyl carbons respectively. Mass spectral data also agreed with the proposed structure.
Chapter 4: Synthesis of aminofurans

Figure 5 \(^1\)H NMR spectrum of compound 121

Figure 6 \(^{13}\)C NMR spectrum of compound 121
A mechanistic rationale for the reaction sequence can be outlined as shown in scheme 37. Vicinal tricarbonyl compounds in solution are known to be in equilibrium with their hydrates. Nucleophilic addition of the isocyanide-DMAD zwitterion to the central carbonyl of the trione leads to the formation of the tetrahedral intermediate I which in turn can cyclize according to path A to form the iminofuran. This is followed by the debenzoylation of the iminofuran probably by the attack of the water molecule present in the system to yield the aminofuran. The formation of the iminopyrone may be rationalized as occurring via path B. Presumably the steric effect imposed by the two benzoyl groups prevents the closure of the oxyanion in the intermediate I and allows the approach of another isocyanide molecule to participate in the reaction.

The participation of two isocyanide molecules in the reaction of diphenyl triketone 92 with isocyanide and DMAD is an example of a one-pot three-compound, pseudo four-component reaction.
The reaction of diethyl ketomalonate 108 with DMAD and isocyanide was found to be ineffective in generating the substituted furan indicating that at least one additional ketone functionality is necessary for the reaction to occur.

Subsequently, the reactivity of the zwitterion towards cyclic tricarbonyl compounds was examined. First, when we attempted the reaction of ninhydrin 67 with isocyanide and DMAD, under the same reaction conditions, only intractable mixtures could be observed. It was speculated that this is due to the high reactivity of ninhydrin in comparison to open chain tricarbonyl compounds. Therefore alloxan hydrate 109, another cyclic tricarbonyl compound with a much less reactive central carbonyl, was chosen for the study.

It was observed that alloxan hydrate 109, on reaction with DMAD and isocyanide in dry dichloromethane led to the formation of the spiroadduct 123 albeit in low yield (Scheme 38).

![Scheme 38](image)

The product 123 was characterized by spectroscopic analysis. The IR spectrum displayed characteristic ester and amide carbonyl stretchings at 1738 and 1665 cm\(^{-1}\) respectively. In the \(^1\)H NMR spectrum, the protons of the carbomethoxy group were discernible at \(\delta\) 3.77 and 3.72 while the signal due to tert-butyl protons appeared at \(\delta\) 1.43. The \(^{13}\)C resonance signals of the amide carbonyls were observed around \(\delta\) 172.0 while the ester carbonyls were discernible at \(\delta\) 165.3 and 164.8.

### 4.6 Conclusion

In conclusion, a novel reaction of tricarbonyl compounds with the isocyanide-DMAD zwitterion which led to a convenient one-pot synthesis of tetra-substituted
furans and iminopyrones was discovered. Substituted furans are useful intermediates in synthetic organic chemistry and there have been numerous approaches towards their synthesis. It is noteworthy that the reaction occurs at room temperature and allows the introduction of all functional groups in a single step. To the best of our knowledge, this is the first report of the interception of the carbonyl group of the tricarbonyl system with zwitterionic species.

4.7 Experimental Details

General information about experiments is given in section 2 of Chapter 2. Cyclohexyl isocyanide was prepared by a reported procedure. Tricarbonyl compounds were prepared by a known literature procedure given below.

Synthesis of 1,3-Dicarbonyl Compounds

The 1,3-dicarbonyls, required as starting materials, were prepared by the following procedure. To a solution of diisopropylamine (2.2 g, 0.02 mol) in dry THF at -78 °C, was added n-BuLi (1.34 g, 0.02 mol) rapidly but slowly. After complete addition, the temperature was brought to -10 °C by immersion in an ice-salt bath for 15 minutes. The mixture was re-cooled to -78 °C and the acetate (0.02 mol) was added dropwise. This is followed by the dropwise addition of benzoyl chloride in THF (1 g, 0.007 mol). The reaction mixture was allowed to warm to room temperature. After completion, it was diluted with 10% aqueous HCl and extracted with ether (3 times). Combined organic extracts was dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography. Elution with hexanes-ethyl acetate (95:5) solvent mixture afforded the 1,3-dicarbonyl compounds in good yields which were used for the next step.

Synthesis of 1,2,3-Tricarbonyl compounds

To the suspension of Dess-Martin periodinane (1 g, 3.2 mmol), (prepared freshly from IBX) in dry DCM was added pyridine (0.26 g, 3.33 mmol) and stirred till the solution becomes clear. This is followed by the addition of the 1,3-dicarbonyl compound (1 mmol) and the mixture was stirred for 12 h. After completion, the
reaction mixture was diluted and extracted with DCM (3 x 10 mL). The organic layer was washed with saturated solutions of sodium thiosulphate (10 mL), sodium bicarbonate (10 mL) and copper (II) sulphate (10 mL). Combined organic layer was finally dried over anhydrous sodium sulphate. The solvent was distilled off in a rotary evaporator and the residue was subjected to column chromatography on silica gel. Elution with hexanes-ethylacetate (85:15) solvent mixture yielded the tricarbonyl hydrates. The same procedure was followed for the preparation of diphenyl triketone and triketo esters.

Alloxan hydrate was prepared by the chromium trioxide oxidation of barbituric acid. To 2.4 g chromium trioxide in acetic acid-water mixture was added 2 g barbituric acid. The mixture was cooled to 5-10 °C and stirred for an hour. Alloxan hydrate (2 g) was filtered and washed with acetic acid and finally with ether, mp 254-255 °C.

**General Procedure for the Reaction of Diketoesters with Isocyanide and DMAD**

A solution of dimethyl acetylenedicarboxylate (114 mg, 0.80 mmol) and diketoester (0.67 mmol) in 10 mL anhydrous CH$_2$Cl$_2$ was stirred for 2 minutes. To this solution, tert-butyl or cyclohexyl isocyanide (0.80 mmol) was added via a syringe and the reaction mixture was allowed to stir at room temperature for 12 h. On completion of the reaction, solvent was distilled off using a rotary evaporator and the residue was subjected to chromatography on silica gel column using hexanes-ethylacetate solvent mixture (90:10) to afford pure products.

**3,4-Dimethyl-2-ethyl-5-(tert-butylamino) furan-2,3,4-tricarboxylate 111**

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 104 (150 mg, 0.67 mmol) was added tert-butyl isocyanide 46 (67 mg, 0.80 mmol) and stirred. Processing of the reaction mixture as described in the general procedure afforded the fully substituted furan 111 as a colourless liquid (123 mg, 56%).
IR (thin film) $\nu_{\max}$: 3345, 2969, 1743, 1722, 1614, 1537, 1459, 1322, 1262, 1217, 1094, 1052 cm$^{-1}$.

$^1$H NMR: $\delta$ 6.99 (s, 1H, D$_2$O exchangeable), 4.31-4.24 (q, 2H, $J$ = 7.20 Hz), 3.90 (s, 3H), 3.76 (s, 3H), 1.47 (s, 9H), 1.35-1.32 (t, 3H, $J$ = 4.89 Hz).

$^{13}$C NMR: $\delta$ 164.8, 163.8, 162.2, 157.3, 133.5, 130.2, 129.5, 128.4, 60.7, 53.2, 52.6, 51.3, 29.5, 14.2.

Mass spectrometric analysis (HRMS-El) m/z calcd for C$_{15}$H$_{21}$NO$_7$: 327.1316; found: 327.1333.

3,4-Dimethyl-2-methyl-5-(tert-butylamino) furan-2,3,4-tricarboxylate 112

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 103 (141 mg, 0.67 mmol) was added tert-butyl isocyanide 46 (67 mg, 0.80 mmol) and stirred. Processing of the reaction mixture as described in the general procedure afforded the fully substituted furan 112 as a colourless liquid (130 mg, 62%).

IR (thin film) $\nu_{\max}$: 3353, 2957, 1751, 1731, 1605, 1490, 1435, 1370, 1340, 1265, 1225, 1154 cm$^{-1}$.

$^1$H NMR: $\delta$ 7.01 (s, 1H, D$_2$O exchangeable), 3.92 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 1.47 (s, 9H).

$^{13}$C NMR: $\delta$ 164.2, 163.8, 162.1, 157.7, 133.5, 130.1, 128.7, 128.4, 89.1, 53.3, 52.8, 51.8, 51.4, 29.7.

Mass spectrometric analysis (HRMS-El) m/z calcd for C$_{14}$H$_{19}$NO$_7$: 313.1162; found: 313.1139.

2-Butyl-3,4-dimethyl-5-(tert-butylamino) furan-2,3,4-tricarboxylate 113

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 105 (168 mg, 0.67 mmol) in anhydrous CH$_2$Cl$_2$ was added tert-butyl isocyanide 46 (67 mg, 0.80 mmol) and stirred. The reaction mixture was processed in the usual manner to afford the fully substituted furan 113 as a colourless liquid (134 mg, 57%).
IR (thin film) $\nu_{\text{max}}$: 3348, 2958, 2927, 2871, 1748, 1727, 1614, 1531, 1449, 1435, 1372, 1325, 1269, 1217, 1135, 1049, 1063 cm$^{-1}$.

$^1$H NMR: $\delta$ 6.99 (s, 1H, D$_2$O exchangeable), 4.24-4.21 (m, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 3.62-3.61 (m, 2H), 1.68-1.64 (m, 2H), 1.48 (s, 9H), 0.98-0.93 (t, 3H, $J = 11.1$ Hz).

$^{13}$C NMR: $\delta$ 164.2, 162.2, 133.7, 130.0, 128.5, 126.1, 66.1, 64.5, 53.2, 52.6, 51.4, 30.1, 29.5, 28.4, 19.0, 13.7.

Mass spectrometric analysis (HRMS-EI) m/z calcd for C$_{17}$H$_{25}$NO$_7$: 355.1631; found: 355.1625.

2-Benzyl-3,4-dimethyl-5-(tert-butylamino) furan-2,3,4-tricarboxylate 114

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 106 (191 mg, 0.67 mmol) in anhydrous CH$_2$Cl$_2$ was added tert-butyl isocyanide 46 (67 mg, 0.80 mmol) and stirred. Usual processing of the reaction mixture afforded the fully substituted furan 114 as a colourless liquid (116 mg, 49%).

IR (thin film) $\nu_{\text{max}}$: 3353, 2933, 2850, 1748, 1727, 1609, 1496, 1367, 1264, 1212, 1135, 1094 cm$^{-1}$.

$^1$H NMR: $\delta$ 7.24-7.02 (m, 5H), 7.02 (s, 1H, D$_2$O exchangeable), 5.24-5.16 (m, 2H), 3.97 (s, 3H), 3.76 (s, 3H), 1.47 (s, 9H).

$^{13}$C NMR: $\delta$ 164.2, 163.0, 162.3, 133.5, 130.6, 129.5, 128.5, 127.6, 126.0, 113.2, 109.6, 108.8, 66.5, 53.3, 52.5, 51.4, 41.8, 29.6.

2-Cinnamyl-3,4-dimethyl-5-(tert-butylamino) furan-2,3,4-tricarboxylate 115

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 107 (210 mg, 0.67 mmol) in anhydrous CH$_2$Cl$_2$ was added tert-butyl isocyanide 46 (67 mg, 0.80 mmol) and stirred. Usual processing of the reaction mixture led to the fully substituted furan 115 as a colourless liquid (139 mg, 50%).
IR (thin film) $\nu_{\text{max}}$: 3350, 2959, 1743, 1727, 1676, 1609, 1485, 1454, 1372, 1331, 1259, 1212, 1140, 1088, 1047, 970 cm$^{-1}$.

$^1$H NMR: $\delta$ 7.44-7.26 (m, 5H), 7.03 (s, 1H, D$_2$O exchangeable), 6.72-6.66 (d, 1H, $J = 16.2$ Hz), 6.33-6.26 (m, 1H), 4.95-4.87 (m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 1.48 (s, 9H).

$^{13}$C NMR: $\delta$ 164.0, 163.8, 162.3, 141.4, 136.2, 134.1, 133.5, 130.2, 129.1, 128.7, 128.0, 126.7, 126.6, 122.8, 121.9, 66.8, 53.3, 52.7, 51.9, 39.4, 29.4.

Mass spectrometric analysis (HRMS-El) m/z calcd for C$_{22}$H$_{25}$NO$_7$: 415.1631; found: 415.1655.

3,4-Dimethyl-2-methyl-5-(cyclohexylamino) furan-2,3,4-tricarboxylate 116

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 103 (141 mg, 0.67 mmol) in anhydrous CH$_2$Cl$_2$ was added cyclohexyl isocyanide 42 (87 mg, 0.80 mmol) and stirred. Usual processing of the reaction mixture led to the fully substituted furan 116 as a colourless liquid (116 mg, 51%).

IR (thin film) $\nu_{\text{max}}$: 3350, 2953, 2851, 1750, 1731, 1669, 1480, 1434, 1352, 1264, 1243, 1146 cm$^{-1}$.

$^1$H NMR: $\delta$ 6.82 (s, 1H, D$_2$O exchangeable), 3.92 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.58 (bs, 1H), 2.93-1.96 (m, 2H), 1.76-1.63 (m, 4H), 1.55-1.25 (m, 4H).

$^{13}$C NMR: $\delta$ 163.8, 162.9, 162.5, 133.5, 130.2, 128.8, 110.7, 52.7, 51.4, 50.8, 40.2, 33.4, 32.7, 29.7, 26.1, 25.4.

Mass spectrometric analysis (HRMS-El) m/z calcd for C$_{16}$H$_{21}$NO$_7$: 339.1318; found: 339.1339.

3,4-Dimethyl-2-ethyl-5-(cyclohexylamino) furan-2,3,4-tricarboxylate 117
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To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 104 (150 mg, 0.67 mmol) in anhydrous CH₂Cl₂ was added cyclohexyl isocyanide 42 (87 mg, 0.80 mmol) and stirred. Usual processing of the reaction mixture led to the fully substituted furan 117 as a colourless liquid (137 mg, 58%).

\[
\text{IR (thin film) } \nu_{\text{max}}: 3348, 2928, 2850, 1748, 1722, 1614, 1480, 1449, 1387, 1305, 1233, 1135 \text{ cm}^{-1}.
\]

\[
\begin{align*}
\delta & \quad 6.80 (s, 1H, D_2O \text{ exchangeable}), 4.31-4.24 (q, 2H, J = 7.20 \text{ Hz}), 3.90 (s, 3H), 3.76 (s, 3H), 3.69 (s, 1H), 2.03-1.79 (m, 2H), 1.76-1.61 (m, 2H), 1.61-1.39 (m, 2H), 1.36-1.25 (m, 7H).
\end{align*}
\]

\[
\text{Mass spectrometric analysis (HRMS-EI) } m/z \text{ calcd for C}_{17}\text{H}_{23}\text{NO}_{7}: 353.1475; \text{ found: 353.1481.}
\]

2-Butyl-3,4-dimethyl-5-(cyclohexylamino) furan-2,3,4-tricarboxylate 118

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 105 (168 mg, 0.67 mmol) in anhydrous CH₂Cl₂ was added cyclohexyl isocyanide 42 (87 mg, 0.80 mmol) and stirred. Usual processing of the reaction mixture led to the fully substituted furan 118 as a colourless liquid (153 mg, 60%).

\[
\text{IR (thin film) } \nu_{\text{max}}: 3353, 2933, 2852, 1745, 1721, 1615, 1485, 1465, 1255, 1225, 1150, 1109 \text{ cm}^{-1}.
\]

\[
\begin{align*}
\delta & \quad 6.79 (s, 1H, D_2O \text{ exchangeable}), 4.22 (t, 2H, J = 12.9 \text{ Hz}), 3.89 (s, 3H), 3.76 (s, 3H), 2.03-1.99 (m, 2H), 1.74-1.61 (m, 5H), 1.45-1.25 (m, 8H), 0.98-0.90 (m, 3H).
\end{align*}
\]

\[
\begin{align*}
\text{Mass spectrometric analysis (HRMS-EI) } m/z \text{ calcd for C}_{17}\text{H}_{23}\text{NO}_{7}: 353.1475; \text{ found: 353.1481.}
\end{align*}
\]

2-Butyl-3,4-dimethyl-5-(cyclohexylamino) furan-2,3,4-tricarboxylate 118
13.7.

**Mass spectrometric analysis (HRMS-EI) m/z calcd for**
C\textsubscript{19}H\textsubscript{27}NO\textsubscript{7}: 381.1788; found: 381.1769.

2-Benzyl-3,4-Dimethyl-5-(cyclohexylamino) furan-2,3,4-tricarboxylate 119

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 106 (191 mg, 0.67 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} was added cyclohexyl isocyanide 42 (87 mg, 0.80 mmol) and stirred. Usual processing of the reaction mixture led to the fully substituted furan 119 as a colourless liquid (103 mg, 37%).

**IR (thin film) v\textsubscript{max}:** 3380, 2933, 2847, 1736, 1721, 1666, 1621, 1560, 1500, 1460 cm\textsuperscript{-1}.

**\textsuperscript{1}H NMR:** δ 7.25-7.01 (m, 5H), 6.89 (s, 1H, D\textsubscript{2}O exchangeable), 5.31-5.12 (m, 2H), 3.77 (s, 3H), 3.62 (s, 3H), 3.57 (bs, 1H), 1.93-1.77 (m, 5H), 1.45-1.25 (m, 5H).

**\textsuperscript{13}C NMR:** δ 163.4, 162.0, 161.8, 133.7, 132.1, 129.6, 128.8, 128.1, 110.1, 107.3, 68.0, 53.3, 52.8, 51.5, 48.8, 41.6, 38.6, 33.3, 32.8, 29.7, 29.4, 26.4, 26.0.

**Mass spectrometric analysis (HRMS-EI) m/z calcd for**
C\textsubscript{22}H\textsubscript{25}NO\textsubscript{7}: 415.1631; found: 415.1666.

2-Cinnamyl-3,4-Dimethyl-5-(cyclohexylamino) furan-2,3,4-tricarboxylate 120

To a solution of DMAD 43 (114 mg, 0.80 mmol) and the diketoester 107 (210 mg, 0.67 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} was added cyclohexyl isocyanide 42 (87 mg, 0.80 mmol) and stirred. Usual processing of the reaction mixture led to the fully substituted furan 120 as a colourless liquid (133 mg, 45%).
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IR (thin film) \( \nu_{\text{max}} \): 3348, 2957, 2926, 1742, 1727, 1616, 1600, 1475, 1424, 1382, 1330, 1239, 1200, 1140, 1077, 1035 cm\(^{-1}\).

\(^1\)H NMR: \( \delta \) 7.49-7.25 (m, 5H), 6.83 (s, 1H, D\(_2\)O exchangeable), 6.71-6.66 (d, 1H, \( J = 16.5 \) Hz), 6.47-6.26 (m, 1H), 4.89-4.87 (m, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 3.57 (bs, 1H), 2.00-1.63 (m, 5H), 1.45-1.17 (m, 5H).

\(^{13}\)C NMR: \( \delta \) 164.0, 162.8, 162.3, 140.4, 135.2, 134.4, 133.4, 130.3, 128.6, 126.7, 126.4, 121.7, 121.6, 66.7, 53.6, 52.8, 51.3, 48.8, 41.5, 38.6, 33.3, 32.6, 29.2, 29.3, 26.3, 26.1.

Mass spectrometric analysis (HRMS-EI) m/z calcd for \( \text{C}_{24}\text{H}_{27}\text{NO}_{7} \): 441.1788; found: 441.1797.

**General Procedure for the Reaction of Diphenyl triketone with Isocyanide and DMAD**

A solution of dimethyl acetylenedicarboxylate (114 mg, 0.80 mmol) and diphenyl triketone (171 mg, 0.67 mmol) in 10 mL anhydrous CH\(_2\)Cl\(_2\) was stirred for 2 minutes. To this solution, tert-butyl or cyclohexyl isocyanide (1.6 mmol) was added via a syringe and the reaction mixture was allowed to stir at room temperature for 12 h. On completion of the reaction, solvent was distilled off and the residue was subjected to chromatography on silica gel column using hexanes-ethylacetate solvent mixture (90:10) to afford pure products.

**Dimethyl-(2E)-6-benzoyl-3-(tert-butylamino)-2-(tert-butylimino)-2H-pyran-4,5-dicarboxylate 121**

To a solution of DMAD 43 (114 mg, 0.80 mmol) and diphenyl triketone 92 (171 mg, 0.67 mmol) in anhydrous CH\(_2\)Cl\(_2\) was added tert-butyl isocyanide 46 (133 mg, 1.60 mmol) and stirred. Processing of the reaction mixture as described above afforded the fully substituted pyran 121 as an amorphous solid (246 mg, 83%).
**IR** (thin film) \( \nu_{\text{max}} \): 3333, 2976, 1741, 1475, 1365, 1336, 1221, 1082 cm\(^{-1}\).

**\(^1\)H NMR:** \( \delta \) 7.68 (d, 1H, \( J = 7.9 \) Hz), 7.27-7.26 (m, 2H), 7.16 (t, 1H, \( J = 7.4 \) Hz), 6.90 (t, 1H, \( J = 7.6 \) Hz), 6.79 (s, 1H, \( \text{D}_2\text{O exchangeable} \)), 3.87 (s, 3H), 3.66 (s, 3H), 1.51 (s, 9H), 1.38 (s, 9H).

**\(^{13}\)C NMR:** \( \delta \) 185.6, 163.8, 162.3, 142.9, 141.3, 136.1, 132.9, 132.1, 131.2, 130.9, 129.4, 127.9, 127.1, 60.8, 55.9, 52.8, 52.3, 29.9, 28.5.

**Mass spectrometric analysis (LRMS-FAB)** [M+2H]\(^+\) calcd for C\(_{24}\)H\(_{30}\)N\(_2\)O\(_6\): 444.59; found: 444.01.

**Dimethyl-(2E)-6-benzoyl-3-(cyclohexylamino)-2-(cyclohexylimino)-2H-pyran-4,5-dicarboxylate 122**

To a solution of DMAD 43 (114 mg, 0.80 mmol) and diphenyl triketone 92 (171 mg, 0.67 mmol) in anhydrous CH\(_2\)Cl\(_2\) was added cyclohexyl isocyanide 42 (174 mg, 1.60 mmol) and stirred. Processing of the reaction mixture in the usual manner led to the fully substituted pyran 122 as a colourless liquid (182 mg, 55%).

**IR** (thin film) \( \nu_{\text{max}} \): 3350, 2928, 2856, 1722, 1681, 1439, 1352, 1305, 1264, 1202, 1120, 1022 cm\(^{-1}\).

**\(^1\)H NMR:** \( \delta \) 7.88 (d, 1H, \( J = 7.8 \) Hz), 7.39 (t, 2H, \( J = 7.4 \) Hz), 7.14 (t, 2H, \( J = 7.6 \) Hz), 6.61 (s, 1H, \( \text{D}_2\text{O exchangeable} \)), 3.84 (s, 3H), 3.78 (s, 3H), 3.58 (s, 2H), 3.53 (bs, 2H), 2.38-2.31 (m, 2H), 1.94-1.20 (m, 16H).

**\(^{13}\)C NMR:** \( \delta \) 186.8, 164.8, 162.6, 141.7, 141.5, 139.7, 138.7, 136.0, 131.1, 130.1, 127.8, 127.2, 126.8, 114.7, 93.1, 92.4, 61.0,
56.7, 52.7, 52.1, 51.4, 50.8, 33.6, 30.4, 28.9, 26.3, 25.6, 25.3, 25.0, 24.6.

Mass spectrometric analysis (LRMS-FAB) Calcd for C_{28}H_{34}N_{2}O_{6} [M+H]^{+}: 495.24; found: 495.47.

Dimethyl-(2E)-2-(tert-butylamino)-6,8,10-trioxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-3,4-dicarboxylate 123

A solution of DMAD 43 (114 mg, 0.80 mmol) and alloxan hydrate 109 (108 mg, 0.67 mmol) in 10 mL anhydrous CH_{2}Cl_{2} was stirred for 2 minutes. To this solution, tert-butyl isocyanide 46 (67 mg, 0.80 mmol) was added via a syringe and the reaction mixture was allowed to stir at room temperature for 12 h. On completion of the reaction, solvent was distilled off and the residue was subjected to chromatography on silica gel column using hexanes-ethylacetate solvent mixtures (70:30) to afford the spiro compound 123 as a colourless liquid (82 mg, 33%).

IR (thin film) \nu_{\text{max}}: 3350, 2989, 2062, 1738, 1665, 1547, 1454, 1434, 1367, 1269, 1218 cm\textsuperscript{-1}.

\[ \text{E} = \text{CO}_{2}\text{Me} \]

\[
\begin{align*}
\text{IR} & \quad \nu_{\text{max}}: 3350, 2989, 2062, 1738, 1665, 1547, 1454, 1434, 1367, 1269, 1218 \text{ cm}^{-1}. \\
\text{H NMR:} & \quad \delta 4.86-4.84 (d, 1H, J = 6.9 \text{ Hz}), 3.77 (s, 3H), 3.72 (s, 3H), 3.42-3.39 (d, 1H, J = 6.9 \text{ Hz}), 1.43 (s, 9H). \\
\text{C NMR:} & \quad \delta 172.6, 172.5, 169.7, 165.3, 164.8, 135.7, 132.5, 115.6, 110.7, 70.2, 53.1, 52.8, 29.9, 28.7, 28.4.
\end{align*}
\]

4.8 References


