Chapter 3

General introduction
The nature presents organic chemists with unique opportunities to pursue new chemical entities. In the construction of six-membered ring, which is widely distributed in the nature,¹ the value of DA methodology has greatly been realized.² After the first heterocycles, accessed from electron rich diene—cyclopentadiene with electron poor dienophile—azodicarboxylate,³ there come into view a variety of dienes and dienophiles. Cyclic frameworks achieved in chemo-, regio-, diastereo- and enantioselective manner are central cores of many bio-active scaffolds.⁴ In addition, pyran, thiopyran, chromene and piperidine which these scaffolds incorporate exist in alkaloids, terpenes, pharmaceuticals, agrochemicals, pesticides and steroids.⁵ With application in bidirectional search (combined retrosynthetic and synthetic search), total synthesis and of course in medicinal chemistry, the area seems interesting to explore further.⁶ The sequential transformations,⁷ which couple two or more reactions, ease the effort further simple in the synthesis of complex heterocycles.

**Simple dienes**

Based on the location of double bond, a diene can be classified into three categories; conjugated, non-conjugated- and cumulated ones. The former in comparison with later two however is most stable due to delocalization of the electron. Open chain-, outer ring-, inner-outer ring-, across ring- and inner ring-dienes are other forms this diene exist in the natural and synthetic compounds. This simple diene consists of four carbons with two \( \pi \) bonds, which are joined in a linear fashion. Four \( \pi \) electrons are delocalized onto the four-atom system. The resonance not only makes the charge distribution feasible but provides diene with an extra stability, too. Rotation of C2—C3 bond in the molecule is therefore become tough, requires higher energy.
3.1 Heterodiens

Heterodiens is another class of dienes that contains one or more hetero atoms in place of carbon(s) in simple diene, which include nitrogen, oxygen sulphur and phosphorous. The *in situ* generation of heterodiene from a specially designed substrate, which allows its indirect use in hetero–Diels–Alder (HDA) strategy, is an interesting area of heterocyclic preparations. In the literature, there are many reports on the synthesis and application of heterodiens. Azabutadienes, oxabutadienes, thiabutadienes and phosphabutadienes are among the vastly exploited heterodiens. Examples include 1-aza-1,3-butadiene 1, 2-aza-1,3-butadiene 2, 1,2-diaza-1,3 butadienes 3, 2,3-diaza-1,3-butadienes 4, 1,3-diaza-1,3-butadienes 5, 1,4-diaza-1,3-butadienes 6 and 1,2,4-triaza-1,3-butadienes 7. Others which contain more hetero atoms include N-acyl mine 8, vinyl nitroso or nitro alkene 9, acyl nitroso 10, 1,2-diaza-4-oxa-1,3-butadiene 11, and 4-oxa-1-aza-butadiene 12.

Oxabutadiene, thiabutadiene, phosphabutdiene are examples of oxygen, sulfur and phosphorous containing hetero atoms, respectively. Heterothiabutadienes include; 1-thiabutadienes 13, 1,4-dithiabutadienes 14, 4-oxa-1-thiabutadiene 15, 1-aza-4-thiabutadiene 16, 1-thio-3-azadienes 17.

The hetero-phosphabutadienes with other heteroatoms include 1-phosphabutadienes 18, 2-phosphabutadienes 19, 1,3-diphosphabutadienes 20, 21.
1,4-diphosphabutadienes or 1,4-diphosphine \textsuperscript{21,22} 2,3-diphosphabutadienes \textsuperscript{22}, 1-aza-4-phosphabutadiene \textsuperscript{23}, 1-phospha-3-azabutadiene or 1,3,5-diazaphosphinines \textsuperscript{24,23} 1-phospha-2-azabutadiene \textsuperscript{25,24} 1,3,2-diazaphosphine \textsuperscript{26,25} 2-aza-3-phosphabutadiene or 1,2-azaphosphinines \textsuperscript{27}, 1-oxa-4-phosphabutadiene \textsuperscript{28}.

In the same way, oxabutadienes, such as 1-oxabutadienes, 1,4-dioxabutadienes and hetero-1-oxabutadienes that contain oxygen atom and/or hetero atom include 1-oxabutadienes \textsuperscript{29}, 1,4-dioxabutadiene \textsuperscript{30,26} acyl sulfines \textsuperscript{31,27} acyl sulfenes \textsuperscript{32}, and acyl thionitroso diene \textsuperscript{33}, N-sulfinyl amides \textsuperscript{34}, N-sulfonyl amides or N-sulfonyl urethanes \textsuperscript{35,28}.

These skeletons are present in both simple and complex heterocyclic systems. More on heterodienes in the heterocyclic synthesis can be highlighted below.

Fletcher \textit{et al.}\textsuperscript{29} described MW-assisted HDA reaction between azabutadienes \textsuperscript{36} and electron deficient acetylenes \textsuperscript{37}. The reactivity of a range of \(\alpha,\beta\)-unsaturated oximes and hydrazones is assessed in the synthesis of tri- and tetra-substituted pyridines \textsuperscript{38} bearing an oxygen functionality at C–3.

![Diagram of HDA reaction between azabutadienes and electron deficient acetylenes](image)

Moghaddam \textit{et al.}\textsuperscript{30} synthesized polycyclic indole derivatives from \(\alpha\)-acrylated salicylaldehyde derivatives \textsuperscript{39} and dihydroindole-2-thiones \textsuperscript{40} in
water. Reaction proceeds via intermediate 1-thiabutadienes, in situ generated by Knoevenagel condensation. Product yields were in the 65–95 % range with high regio- and stereoselectivities.

\[
\begin{align*}
39 & \quad + \quad 40 \\
& \quad \xrightarrow{\text{reflux, } H_2O} \\
& \quad 41
\end{align*}
\]

Martin et al. generated 1-phosphabutadienes 43 by thermolysis of the corresponding diallylphosphines 42, dimerize on warming in a [4+2] cycloaddition mode to give 44.\(^{31}\)

\[
\begin{align*}
42 & \quad \xrightarrow{\text{FVT}} \\
& \quad \xrightarrow{\oplus} \\
& \quad 43 \\
& \quad \xrightarrow{\text{R} = \text{Ph, 4-FPh, } \text{t-Eu}} \\
44 & \quad \xrightarrow{\oplus} \\
\end{align*}
\]

Gohier et al.\(^ {32}\) described the HDA reactions between chiral \(\beta\)-substituted N-vinyloxazolidinones 45 and oxabutadienes 46, affording cycloadducts 47 and 48 with high endo and facial selectivities. The choice of the Lewis acid proved critical, affording selectively either the endo \(\alpha\) 47 adduct using Eu(fod)\(_3\) as the catalyst or endo \(\beta\) 48 if the promotor was SnCl\(_4\).

\[
\begin{align*}
& \quad \xrightarrow{\text{Eu(fod)\(_3\), reflux, cyclohexane}} \\
& \quad \xrightarrow{\text{SnCl\(_4\), -78 °C, DCM}}
\end{align*}
\]

### 3.2 Oxabutadiene and scope of its reaction

Oxabutadiene is a heterodiene in which oxygen is one of the four atoms of simple diene. Generated via many synthetic routes, one of its common forms \(\alpha,\beta\)-unsaturated aldehyde/ketone has been widely used in the construction of heterocycles. Knoevenagel condensation,\(^ {33}\) aldol reaction,\(^ {34}\) Perkin reaction\(^ {35}\) and Claisen–Schmidt condensation\(^ {36}\) that utilize mono and 1,3-diketones are important routes to generate oxabutadiene. Any ketone that is cyclic or acyclic, heterocyclic or heteroacyclic in nature can be used. Examples of diketones include dimerone, 1,3-cyclohexanedione, 4-hydroxy coumarin, 2,4-dihydroxy quinoline, rhodamine, barbituric acid, Meldrum's acid and 1,3-cycloalkanedione, \(\beta\)-ketoesters, and 1,3-diones. Pyrazolone and isoxazolone are examples of mono
ketones. Other sources also include Mannich reaction, Horner–Wadsworth–Emmons reaction, Horner–Wittig reaction, and Peterson reaction, Meyer–Schuster rearrangement, Wittig reaction of acyl bromide, elimination of groups α or β to carbonyl, decarboxylative allylation of α-oxocarboxylates, oxidation of allylic alcohols, by insertion of carbon monoxide, by sequential aldol-type reaction and β-elimination, etc. Common structural feature of the oxabutadiene is depicted below.

**Oxabutadiene**

### 3.2.1 Oxabutadienes in *hetero*-Diels–Alder strategy

Oxabutadienes usually undergo four types of reaction; electrophilic addition, nucleophilic addition, Michael addition and Diels–Alder reaction. In the last strategy, which is commonly known as HDA approach, 1-oxa-1,3-butadiene has been widely demonstrated. Few significant examples are as follows.

Tan *et al.* synthesized pyrano[2,3-c]pyrazole derivatives by three component reaction of formaldehyde, pyrazolone and alkene under solvent-free conditions.

Seo and Kim described asymmetric organocatalytic Michael addition reaction of 2-arylacetates/acetonitriles having an EWG to α,β-unsaturated aldehydes has been established using diphenylprolinol trimethylsilyl ether as organocatalyst.

Fotiadou and Zografos demonstrated a tandem Knoevenagel/6π-electrocyclization sequence using 4-hydroxypyrid-2-one and α,β-unsaturated aldehydes to produce highly substituted pyranopyridones from moderate to high yields in a one-step reaction.
Other transformations are Nazarov cyclization\textsuperscript{50} for cyclopentenones, Rauhut—Currier reaction\textsuperscript{51} for dimerization or isomerization of \(\alpha,\beta\)-unsaturated ketone, Baylis—Hillman reaction\textsuperscript{52} for allylic alcohol, Morita—Baylis—Hillman Reaction\textsuperscript{53} for cyclopentenes, Mukaiyama—Michael addition,\textsuperscript{54} and many others.\textsuperscript{55}

### 3.2.2 Oxabutadines in Domino Knoevenagel—hetero—Diels—Alder (DKHDA) strategy

Promoted \textit{via} formation of 1-oxa-1,3-butadiene \textsuperscript{62}, DKHDA approach is among the versatile anionic—pericyclic domino reactions,\textsuperscript{57,58} affording dihydropyran\textsuperscript{63} (Fig 3.1). DKHDA reaction begins with the simple substrate, but ends with formation of a highly complex molecule.\textsuperscript{59}

According to Prof. Lutz F. Tietze, a domino reaction is the "process which involves two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step"\textsuperscript{60}. The strategy is a powerful tool to construct complex heterocycles rapidly in one-pot, offering environmental and industrial both the advantages. Cascade and tandem are other similar terms.

\begin{equation}
\begin{array}{c}
R_3 \quad \text{O} \quad R_1 \quad R_2 \\
\quad \left[ R_1 \quad R_2 \quad \text{O} \quad X \quad Y \quad R_3 \right]
\end{array}
\end{equation}

\textbf{Fig 3.1} DKHDA reaction promoted \textit{via} oxabutadiene intermediate.

Generation of oxabutadiene takes place in both the DKHDA approaches:

1. Three-component reaction between 1,3-dicarbonyl, an aldehyde and a vinyl ether.

\begin{equation}
\begin{array}{c}
\quad \text{R} \quad \text{O} \quad \text{CHO} \\
\quad \text{H} \quad \text{O} \quad \text{CO}
\end{array}
\end{equation}

\textbf{Fig 3.2} Intermolecular HDA reaction.
2. Two-component reaction: Intermolecularly formed oxabutadiene undergoes intramolecular HDA reaction.

![Diagram showing intramolecular HDA reaction.](image)

**Fig 3.3** Intramolecular HDA reaction.

As an inverse electron demand Diels–Alder reaction, HDA involves the overlap of diene LUMO with dienophile HOMO. The reaction has excellent stereoselective control. Aromatic and aliphatic α,β-unsaturated aldehydes usually give *cis*-fused products, whereas simple aliphatic aldehydes the *trans*-adduct. Chiral aldehydes, diketones and Lewis acids also help afford enantiopure products. Acetonitrile, CH₂Cl₂ and toluene are among the most appropriate solvents used in the strategy. Alcohols and water are also suitable.

### 3.2.3 Transition states (TS)

![Diagram showing four possible TS.](image)

**Fig 3.4** Four possible TS that different orientations of dienophile towards oxabutadiene results in.

The orientation of a tethered dienophile leads to four possible TS; *exo-E-anti* (1), *endo-E-syn* (2), *exo-Z-syn* (3) and *endo-Z-anti* (4). From the experiments and theoretical calculations, it showed that the most favored among them which decides stereoselective outcome of the reaction (Fig 3.4) are first and forth leading to *trans* and second and third leading to *cis*-annulated dihydropyran.
Knoevenagel reaction of 64 with 65 gives exclusively (Z)-compound 66 which isomerizes at higher temperature to (E)-form 67 and then to 68 via an endo-E-syn TS. The mechanism was observed under irradiation also which allowed the Z/E-isomerization of 67/68.64

![Chemical structure](image)

### 3.2.4 DKHDA strategy in natural products synthesis

DKHDA approach allows synthesis of heterosteroids,65 cannabinoids, deoxyloganin and secologanin,66 monoterpenoid indole alkaloids67 and preethulia coumarin.68 Tietze et al. described stereoselective trans-bonded hetero-steroids 71 (de > 98 %) from 69 and 70 or its analogs.

![Chemical structure](image)

### 3.2.5 DKHDA strategy in diversified heterocycles synthesis

Besides natural products, the DKHDA route also allowed many diversified heterocyclic preparation. Ghoshal et al. reported MW-assisted, piperidine-catalysed highly stereoselective synthesis of julolidine hybrid analogs 74 and 75 using asymmetrical and unsymmetrical 1,3-diones 73.69

![Chemical structure](image)

Ramesh et al.70 reported MW assisted, K-10 Montmorillonitile catalysed intramolecular DKHDA reaction to afford pyrano[2,3,4-kl]xanthenes 78 and 79.
Tietze et al.\textsuperscript{71} described a very short, three component DKHDA approach to 2-alkoxy-6-methyl-5-nitro-3,4-dihydro-2H-pyrans 83 with 81–95% yields.

\[
\text{O}_2\text{N} - \text{O} + \text{CHO} + \text{CHO} \xrightleftharpoons{\text{CH}_2\text{Cl}_2 \text{ reflux, 3h}} \text{O}_2\text{N - OR}
\]

Gandhi et al.\textsuperscript{72} employed one-pot DKHDA reaction using bifunctional materials 84 containing an aldehyde and an sulfonate groups with N,N-dimethylbarbituric acid 85 in water. It gave a mixture of novel pyrano[2,3-\text{d}] pyrimidine-annulated benzo-\(8\)-sultones 86 and 87 in moderate to high yields.

Majumdar et al.\textsuperscript{73} reported catalyst-free synthesis of pentacyclic benzopyran-annulated thiopyrano[2,3-\text{b}]thiochromones 90 from 4-hydroxy dithiocoumarin 88 and \textit{O}-propargylated salicylaldehyde 89 in aqueous medium.

Majumder and Bhuyan\textsuperscript{74} obtained thiopyrano[2,3-\text{b}]indoles 93 from oxindole 91 and 1,3-diketones 92 in the 62–75\% range in the presence of catalyst EDDA in MeCN.

Subba Reddy et al.\textsuperscript{75} reported angularly fused chromenes 96 from alkene-tethered chromene-3-aldehyde 94 and 1,3-cyclic diketones 95.
3.2.6 Oxabutadienes in Domino/Knoevenagel—Michael—cyclization (DKMC) reaction

Like DKHDA reaction, DKMC reaction is also an important domino strategy to afford pyran-annulated heterocycles. Oxabutadiene, a Knoevenagel condensate, obtained from two- or three-component reaction, undergoes a Michael addition step and finally Michael products a cyclization—through water removal step.

![Diagram of the reaction](image)

**Fig 3.5** Knoevenagel—Michael—cyclization reaction.

Jin et al.\(^76\) developed a highly efficient, less expensive and toxic method for 2,2'-alkylmethylene 1,8-dioxo-octahydroxanthenes 99, by grinding aldehyde 97 and dimerdone 98 in solid state using catalyst TiO\(_2\)/SO\(_4^{2-}\).

![Reaction scheme](image)

Chebanov et al.\(^77\) reported regio- and chemoselective multicomponent protocols for hexahydro-pyrazolo[3,4-b]quinolin-5-ones 103.

![Additional reactions](image)

Sakhuja et al.\(^78\) synthesized spiro[indole-pyran] 105 from one mole of isatin 104 with two mole of pyrazolone 77 in ethanol at rt, highlighting a Knoevenagel-Michael-cyclization.
Wen et al.\(^79\) successfully synthesized unusual fused tricyclic thiochromeno[2,3-\(b\)]pyridines \(108\) and \(111\) by [3+3] annulation and \(S_NAr\) of \(\beta\)-(2-chloroaroyl)thioacetanilides \(106\) in tandem with activated 4-arylidene-2-phenyloxazol-5(4\(H\))-ones \(107\) or aromatic aldehydes \(109\) and ethyl 2-cyanoacetate \(110\) under MW irradiation.

Liu et al.\(^80\) developed an enzymatic method to construct highly substituted dihydropyridinones \(115\) via a three-component reaction of aldehyde \(112\), cyanoacetamide \(113\), and 1,3-dicarboxyl compound \(114\).

Moghadam et al.\(^81\) reported an IL N,N,N,N-tetramethylguanidium triflate mediated, synthesis of 4-substituted pyrano[4,3-\(b\)]pyran-2,5-diones \(119\) by taking an 4-hydroxy-2-pyranone \(116\), Meldrum acid \(117\) and aldehyde \(118\).

### 3.3 Catalysts and ionic liquids (ILs) in domino reaction

#### 3.3.1 Catalysts used in HDA reaction

Catalyst\(^82\) has generally less influence on DA reaction rate.\(^83\) But Lewis acid greatly promotes it. Yates and Eaton reported a remarkable increase in rate of reaction between anthracene and maleic anhydride at rt and between 1,4-
benzoquinone and dimethyl fumarate catalysed by $\text{AlCl}_3$. $\text{SnCl}_4$ also promoted the reaction. Many other examples have been reported in the literature.

### 3.3.2 Lewis acids in Diels–Alder reaction

Examples of Lewis acids used in HDA reaction include $\text{ZnCl}_2$, $\text{BF}_3$, $\text{MeAlCl}_2$, and $\text{Et}_2\text{AlCl}$. Their influence on this reaction has been rationalized by applying FMO theory. Normally DA reaction involves interaction of dienophile LUMO with diene HOMO. The smaller is the HOMO–LUMO energy gap, the better is the overlap and hence more readily the occurrence of reaction. For example, activation occurs when carbonyl oxygen lone pair electrons co-ordinate to the Lewis acid. Such co-ordination decreases the LUMO and HOMO energies of the aldehyde, resulting into decrease in an energy gap HOMO–LUMO (Fig 3.6). Additionally, co-ordination of Lewis acid towards carbonyl oxygen increases magnitude of its LUMO, making it more susceptible to the diene. Polarization, therefore, may change the reaction pathway from a concerted non-synchronous mechanism to a stepwise one. Substituents on the reactants and the reaction conditions also affect the mechanism.

![FMO diagram of HDA reaction in the presence and absence of a Lewis acid.](image)

**Fig 3.6** FMO diagram of HDA reaction in the presence and absence of a Lewis acid.

![endo-selectivity in the Lewis acid catalyzed HDA reaction](image)

**Fig 3.7** The *endo*-selectivity is seen in the Lewis acid catalyzed HDA reaction as the solvated Lewis acid is *exo*, due to its size.
The orientation of dienophile towards diene in TS decides the stereochemistry of products. Lewis acid catalyzed HDA reactions are endo-selective due to the preference of the Lewis acid being exo as a result of its size (Fig 3.7). In addition, the Lewis acid and the carbonyl R group are proposed to be trans to each other. Similarly, the uncatalyzed reaction of aldehydes and a diene demonstrate endo-selectivity for the carbonyl substituent.

Lewis acids employed are chosen based on experimental trial and error. Kobayashi et al. developed a concept of Lewis acids activity with aldehydes and imines. It states that strong acids didn’t necessarily promote the reaction smoothly and that observed selectivities of aldehyde or aldime depends upon Lewis acid employed. In conjunction with Kobayashi, Cozzi et al. reported a deleterious effect stating that a decrease in diastereo- and enantioselectivity with strong Lewis acids employed in a catalytic enantio-selective addition of allyl organometallic reagents to aldehydes. However, the presence of weak Lewis acids drives the stereochemistry toward a high level of enantio- and diasterocontrol.

Many metals like Eu, Ti, Yb, Cr, Zn, Co, Cu, Al, Sc, Li, etc., and its chiral auxiliaries have been used as Lewis acids in the DA reaction. From earlier reports, it also infers that required catalyst loadings would be in 5—25 mol % range. Solvent affect the rate of the reaction. Traditionally, there were non-polar organic solvents such as aromatic hydrocarbons. However, water and other highly polar solvents, such as ethylene glycol, and formamide accelerate the DA reaction. ILs are also employed as a both solvent and catalyst.

### 3.3.3 Catalysts used in DKHDA reaction

A variety of catalysts/conditions have effectively been employed in DKHDA reaction. Examples include Lewis acids, EDDA, CuI, BiCl₃, InCl₃, LiClO₄, PPh₃.HClO₄, ZnO, D-proline, ILs, TEA in acetic acid, pyridine, ZrO₂-nanopowder (NP) in IL, water, melt reaction etc.

### 3.3.4 TBA—HS as a catalyst in organic synthesis

In the development of new synthetic methodologies that minimize the wastes generation, the PTC often improved the results.

PTC are used in small quantity, is quaternary 'onium' salt such as ammonium, phosphonium, antimonium, and tertiary sulfonium salts.
Dichlorocarbene can be generated by thermal decomposition of sodium trichloroacetate, suspending in anhydrous chloroform in the presence of quaternary salt. Requiring no vigorous conditions, it offers fast reaction, even in anhydrous condition, and involves no tedious workup procedure. TBA—HS has been widely used in the synthetic organic chemistry.

Kotta S. et al. prepared various 2,2-spirobiindane-1,3-diones 122 from 1,3-indenedione 120 and 2,3-bis(iodomethyl)buta-1,3-diene 121, which are useful precursors for unsymmetrical benzo-annulated fenestranes obtained via key steps [2+2+2] and [4+2] cycloadditions.108

![Chemical reaction](image)

TBA—HS109 was used in the reaction of 2-phenylalkanenitriles 123 with 1,1- or cis-dichloroethylene 124, which gives ethynylated 125 in good yield.

![Chemical reaction](image)

Carbamate 127110 (5-methoxy-N-acetyltryptamine-hormone produced and secreted in the pineal gland) is obtained from 126 with ethyl chloroformate in TBA—HS and NaOH in CH2Cl2.

![Chemical reaction](image)

Similarly, TBA—HS is used in alkylation,111 allylation,112 and sulfonylation.113

Also found that TBA—HS has been used to convert alkyl halides into azides. Under milder condition, heterocyclic chloroaldehyde 128 react with NaN₃ in DMSO to give azides 129 in higher yields.114
3.3.5 ILs in the organic synthesis

Rate enhancement, better yields and selectivity of a chemical reaction are key requirements of modern synthetic management.\textsuperscript{115} ILs, being best alternative to toxic and hazardous organic solvents (particularly chlorinated hydrocarbons) have received considerable attention.\textsuperscript{116} The green media has improved many synthetic routes;\textsuperscript{117} hence its demonstration is must in the chemical synthesis.

3.3.5.1 ILs, their composition and properties

As low-melting salts (i.e. below 100 °C), ILs are electrolytes consisting of cationic and anionic species. Since their properties like melting point, viscosity, density and hydrophobicity can be modified with a particular end use, they are also known as designer solvents. Immiscibility with many organic solvents is useful polar alternative for two phase system. With thermal stability allowing a wide working temperature range, they have no vapor pressure, dissolving organic, inorganic and organometallic compounds. Significant impact on the reactivities and selectivities are due to their polar and non-coordinating properties. ILs are of two categories; simple salts and binary ILs. Example of former is [Et$_3$NH]NO$_3$ and of later is mixture of AlCl$_3$ and 1,3-dialkylimidazolium. Cations in use to build up ILs include ammonium, pyrroldinium, phosphonium, sulfonium, and imidazolium. Anionic species include mononuclear [Cl$^-$, Br$^-$, NO$_3^-$, BF$_4^-$ etc.], bi- and polynuclear anions [Al$_2$Cl$_7^-$, Al$_3$Cl$_7^-$, Fe$_2$Cl$_7^-$ etc], which are sensitive to water. Sulfonamides are those ILs which contains both cationic and anionic centres in a single molecule.

Asymmetric cation confers ILs with lower melting.\textsuperscript{118} ILs may be hydrophilic and hydrophobic. Most tetra alkylammonium, alkylpyridinium, and 1,3-dialkylimidazolium ILs with perflorinated anions are hydrophobic.

3.3.5.2 Synthetic uses of ILs

Nature of ILs has great effect on the reaction. Acidic C(2) of imidazolium cation easily exchanges proton with base even in mild condition.\textsuperscript{119} Baylis–Hillman reaction\textsuperscript{120} although 100% atom economic in diazabicyclo [2.2.2] octane (DABCO), it takes more time. In [bmin][PF$_6$] however it is 33 times faster. Solubility of Knoevenagel adducts in malanonitrile in base KOH is drawback of [bmim][PF$_6$].\textsuperscript{121} Imidazolium ILs are thus suitable under basic condition for only few reactions.
3.3.5.3 ILs used in chemical reactions

Alkylation of isobutane by 2-butene in [bmim]Cl/AlCl₃ increases octane number of alkene produced. The reaction is more advantageous than the one in HF or H₂SO₄. Other examples are alkylation of benzene, indol and 2-napthol and active methylene units in C–C bond formation.

\[
\begin{align*}
\text{O} & \quad \text{R} \quad \text{X} \quad \text{TEA, [bpy][BF₄]} \quad 60-70^\circ\text{C} \\
\text{O} & \quad \text{R} \quad \text{X} \\
\end{align*}
\]

More eco-friendly alkylation of methylene units is in palladium(0) by diphenylallyl acetate in [bmim][BF₄].

Hydroformylation of higher olefins competently soluble in ILs with PF₆⁻, SbF₆⁻ and BF₄⁻ anions is industrially useful reaction.

\[
\begin{align*}
\text{CHO} \quad \text{Co/H}_{2} & \quad [\text{PdCl}_{2}(\text{PPh}_{3})] \\
[\text{bmim}]\text{Cl} & \quad \text{SnCl}_{2} \\
\end{align*}
\]

The reaction rates and selectivity are enhanced more in [emim]Cl-AlCl₃ than in conventional AlCl₃. Chloroaluminates in Knoevenagel condensation have variable Lewis acidity.

\[
\begin{align*}
\text{R} & \quad \text{CHO} \quad \text{COOEt} \quad [\text{bmim}]\text{Cl} \times \text{AlCl₃} \text{ or} \\
\text{R} & \quad \text{CHO} \quad \text{COOEt} \\
\end{align*}
\]

The Heck reaction of arylhalides and alkene in ionic liquids with catalyst Pd(OAc)₂ can be performed at rt with excellent yields. Consequently, the catalyst and ionic liquid can be recycled and reused.

\[
\begin{align*}
\text{R} & \quad \text{CHO} \quad \text{COOEt} \quad \text{Pd(OAc)}_{2} \quad \text{ionic liquid} \quad \text{base} \\
\text{R} & \quad \text{CHO} \quad \text{COOEt} \\
\end{align*}
\]

Michel addition of acetylacetone to methyl vinyl ketone in Ni(acac)₂ in IL [bmim][BF₄] provides with excellent results in terms of activity, high selectivity and recyclable catalytic system.
Stereo-controlled Wittig reaction in [bmim][BF₄]¹²⁷ involves no by-product (Ph₃PO) isolation. High yields of diaryl ethers from phenol, diaryl from aryl halide can be achieved in a base in [bmim][BF₄]-immobilized-CuCl than in DMF. ILs also promote enzyme catalyzed reactions with other transformations. It includes Z-aspartame from carboxbenzoxyl-L-aspartate and L-phenylalanine methyl ester in catalyst thermolysin in [bmim][PF₆]. The usefulness of Diels—Alder¹²⁸ reaction lies in its high yield and high stereospecificity in ILs, and examples include [bmim][BF₄], [bmim][ClO₄], [emim][CF₃SO₃],[emim][NO₃] and [emim][PF₆]. The reduction of aromatic and aliphatic aldehydes with trialkylborane generally requires higher temperature (150 °C). But in [bmim][BF₄] and [emim][PF₆] reaction rate enhances at low temperature. Other IL mediated reactions includes oxidation of aldehyde,¹²⁹ alcohol and oximes,¹³¹ oxidative carbonylation of amines,¹³² Wacker type oxidation and hydrogenation,¹³⁴ C—C bond forming Aldol reaction,¹³⁵ Suzuki,¹³⁶ Still,¹³⁷ and Negishi,¹³⁸ and Trost—Tsuji¹³⁹ type coupling reactions, Sakui,¹⁴⁰ Henry,¹⁴¹ Stetter,¹⁴² and Songashira¹⁴³ type reactions.

### 3.3.5.4 ILs used in hetero-Diels—Alder reaction

Fischer et al.¹⁴⁴ reported Diels—Alder reaction between methyl acrylate and cyclobutadiene in a number of air and moisture stable ILs; [bmim][BF₄], [bmim][ClO₄], [emim][CF₃SO₃], etc. with endo selectivity.

Yadav et al.¹⁴⁵ converted (R)-(−)-citronellal/3-methylcitronellal ¹⁴⁹ and aromatic amines ¹⁵⁰ into octahydroacridines ¹⁵¹ and ¹⁵² via intramolecular HDA reaction in IL.
Balalaie et al.\textsuperscript{146} performed DKHDA reaction of substrates \textsuperscript{153} with unactivated dienophile \textsuperscript{154} in catalyst Cul in [bmim][NO\textsubscript{3}].

![Chemical Reaction Image]

Fazila et al.\textsuperscript{147} employed ILs as a safe recyclable media, using catalyst microencapsulated Sc(SO\textsubscript{3}CF\textsubscript{3})\textsubscript{3} in aza–DA for pyridones.

### 3.4 Chromenes

Among the oxygenated heterocycles, chromenes are widely distributed in the nature. Known as benzopyrans, they are obtained from fusing benzene with six-membered pyran unit. Benzopyran exist in two isomeric forms 1-benzopyran (chromene) and 2-benzopyran (isochromene). The numbering is universally accepted, and is also supported by IUPAC system.

![Chemical Structures]

Each has more isomers depending on position of carbon whether fully saturated giving rise to 2\textsuperscript{H}-1-benzopyran (2\textsuperscript{H}-chromene) and 4\textsuperscript{H}-1-benzopyran (4\textsuperscript{H}-chromene). Former with allyl ether type unit is known as \(\alpha\)-chromene or \(\Delta^2\)-chromene. Later with vinyl ether unit is \(\gamma\)-chromene or \(\Delta^3\)-chromene.

#### 3.4.1 Physical properties

Just like most of natural products, chromenes are also derived from isoprene units and show physical properties like isolated isoprene like products. 2\textsuperscript{H}-chromene is liquid; density 1.099 g/cm\textsuperscript{3} and bp 132 °C, refractive index 1.5869 (at 297 K). The dihydro 4\textsuperscript{H}-chromene is oil with peppermint like odor; bp 215 °C, volatile in steam.

#### 3.4.2 Synthesis of chromenes

Isolated in 19\textsuperscript{th} century from natural products, syntheses of chromene were known in early 20\textsuperscript{th} century.

##### 3.4.2.1 From phenol

Resorcinol \textsuperscript{156} with acetylacetone compound in acetic acid or formic acid gave \textsuperscript{157} reported in 1923 first by Buck and Heilborn\textsuperscript{148}.
3.4.2.2 From O-hydroxybenzaldehydes

O-Hydroxybenzaldehyde gave chromenes with ketone, which is probably the commonest method. Acetone on being condensed in abnormal manner with in alkali forms 2-methyl-4-acetonyl-5,6-benzo-γ-chromene.

Salicylaldehyde gives 2-(O-hydroxyphenyl)-3-nitro-Δ^3-chromene with nitromethane.

3.4.2.3 Other methods for chromene derivatives

Youn and Eom reported chromene ring via palladium catalyzed oxidative cyclization of.

Worlikar et al. gave route to chromenes via electrophilic cyclization of by I₂, ICl in excellent yields.
Naturally occurring chromenes mollugin were synthesized via pericyclic reaction of 3-(3-methylbut-2-enyl)-naphthoquinon-2-carboxylate.\(^{155}\) Cacchi \textit{et al.}\(^{156}\) reported addition type reaction of (2-hydroxy-aryl) mercury chlorides with chalcones in a two-phase system.

### 3.4.3 Biological significance

Since a long back, chromenes have been therapeutic agents. Besides being intermediates in the synthesis of natural and medicinal products, they also resemble potassium channel activating drugs.\(^{157}\) Serving as framework of a range of tannins,\(^{158}\) are becoming increasingly important due to their health-promoting effects in vegetables, fruits, fruit juices and red wines. Chromenes are also used in treating proliferative skin disorders and microbial infections.\(^{159}\) Coutoreagenin possesses antidiabetic activity.\(^{160}\) Reported as antiproliferative,\(^{161}\) antichemo-preventive,\(^{162}\) antibacterial,\(^{163}\) antifungal,\(^{164}\) anticancer,\(^{165}\) pasmolitic, diuretic, anticoagulant, and antianaphylactic agents.

6-Substituted benzopyran are good potassium channel activators,\(^{166}\) antipicornavirus capsid-binders,\(^{167}\) selective estrogen receptor-\(\beta\) agonist,\(^{168}\) and potential antagonists of *Mycobacterium bovis* BCG.\(^{169}\) 6-Substituent contributes to receptor affinity either by a direct interaction or indirect by withdrawing electrons from the phenyl moiety of the benzopyran nucleus, optimizing charge-transfer interactions of the aromate with the receptor. In addition, chromenes are well-known for their photochromic properties.\(^{170}\)

### 3.5 Present Work

In view of significance of pyran-annulated heterocycles (introduced in present \textbf{Chapter 3}), included in \textbf{Part-II} are some improved DKHDA and DKMC reactions in ionic liquid TEAA (\textbf{Chapter 4}) and in solvent-free TBA―HS (\textbf{Chapter 5}) respectively, for the synthesis of related heterocycles. All polyheterocycles have been screened \textit{in vitro} for their antimicrobial, anti-tuberculosis and antioxidant activities.
Chapter 3

References


Chapter 3


