CONDENSATION OF CARBONYL ORGANIC COMPOUNDS AND MONOSACCHARIDES IN BIOACTIVE HETEROCYCLES IN HOMOGENEOUS AND HETEROGENEOUS LIQUID SYSTEMS

Yosra Snoussi & Néji Besbes

Laboratoire Matériaux Composites et Minéraux Argileux, Centre National de Recherches en Sciences des Matériaux, Technopole Borj Cédria, Soliman 8027, Tunisie
Faculté des Sciences Mathématiques, Physiques et Naturelles de tunis

E-mail: yosrasnoussi2016@gmail.com ; besbesneji@yahoo.fr

Yosra Snoussi born Aout 2, 1994 in Nabeul Tunisia. I am a PhD Student in the 2nd year Doctoral Thesis in Chemistry at the Faculty of Sciences of Tunis - Tunis El Manar University under the direction of Professor Néji BESBES Head of the Group of Green and Applied Organic Chemistry which is part of the Laboratory of Composite Materials and Clay Minerals at the National Center for Research in Materials Science (CNRS) - Borj Cedria Technopole. 2 articles in organic chemistry communication published in Rhazes. 2 oral communications, 3 communications posters. Participation in 2 international congresses CMCH and TJAAST in juin and novembre 2019 and participation in the 5th forum of young chemical researchers at the Palais des Sciences in Monsatir in decembre 2019.

Néji Besbes born June 1, 1957 in Monastir - Tunisia. Professor at the National Center for Research in Materials Science, Specialty: Synthesis, Reactivity and Chemical Kinetics of Heterocycles by Catalysts in Homogeneous and Heterogeneous Media, Application of Theoretical Studies in Organic Synthesis.Professor at the National Center for Research in Materials Science, Founder and President of STCHA. President 2 Congresses, Co-President 3 Congresses. Supervision 9 Masters, 8 Doctorates, 3 Univeristy Habilitations. Authors 30 Books, 71 Articles, 35 Proceedings, 42 Conferences, 42 Orals, 75 Posters. Jury Member 7 University Authorizations, 43 Doctorates, 12 Masters.
Abstract

Heterocycles are ubiquitous in nature and occupy a unique place in organic chemistry because they are part of the DNA and hemoglobin that make life possible. The chemistry of heterocycles covers an introduction to the subject. Three, four or five-membered heterocycles are abundantly present in various natural and synthetic products of pharmacological importance. This article review describes the synthesis, chemical reactivity in homogeneous and heterogeneous liquid systems and their medicinal importance. This class of compounds is present in the form of substructures in penicillin and cytotoxic taxol. Finally, we did a little research on the synthesis, chemical reactivity and pharmacological importance of monosaccharides in the synthesis of heterocycles.

Introduction

Nitrogen, oxygen, and sulfur are the most common heteroatoms present either alone or together in a cyclic system. In fact, five- and six-membered heterocyclic compounds are widely present as isolated form or part of the fused ring systems of natural and synthetic origin. However, heterocycles with other heteroatoms such as As, Ag, Bi, Sb, Se, Te, Pb, B, etc. are also known but not very common. Of more than 21 million registered organic compounds, more than half are heterocycles either from synthetic or natural product origin. The stability and reactivity of the heterocycles depend on the ring strain as well as a degree of unsaturation of the ring system. The electronic configuration of the heteroatom and ring strain in a heterocyclic system plays a significant role in their physical, chemical, and biological properties. Numerous mono-, di-, and polycyclic heterocycles in the form of isolated and fused ring systems are reported in the literature from natural and nonnatural resources. A large number of heterocyclic compounds such as alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin, hormones, and synthetic drugs and dyes are essential to life. Nucleic acids are among those heterocycles known for carrying genetic information controlling inheritance. These nucleic acids are long chains of pyrimidine and purine bases held together by other types of materials. Numerous, naturally occurring pigments, fungicides, pesticides, herbicides, dyes, and plastics are heterocyclic compounds. More than 70% of the pharmaceuticals in clinical use belong to heterocyclic systems. Insertion of heteroatoms in a carbocyclic framework enhances the bioavailability of the molecule due to higher electronegativity of the heteroatom compared to carbon, and thereby displays significant increased biodynamic properties. Nitrogen heterocycles are abundantly distributed in nature and many of them are also present as subunits in various natural products and display diverse pharmacological activities. The significant contributions of heterocycles as agrochemicals, pharmaceuticals, imaging agents, pheromones, catalysts, and polymers have made them popular among other classes of organic compounds and play a pivotal role in taking the initiative for further investigation to obtain molecules of great significance for humankind and industry.

In this perspective, the Research Topic “Green Synthesis of Heterocycles” encompasses a collection of research and review articles focusing on heterocyclic compounds synthetized according to Green Chemistry principles. The focal point was to build on efficient catalytic methodologies aiming at high process performances by means of non-toxic/green and...
biodegradable chemicals. Industrial applications, process developments, and future perspectives of the so-synthetized heterocyclic compounds have also been addressed.

**A. Three-Membered Ring Heterocycles**

The first review focuses on the synthesis of Three-Membered Ring Heterocycles: Insertion of a heteroatom such as nitrogen, oxygen, sulfur, phosphorus, etc. in the cyclopropane and cyclopropane ring, replacing one of the carbons, produced a variety of three-membered saturated heterocycles such as aziridine, oxirane, thiirane, phosphirane, and their unsaturated counterparts azirine, oxirene, thiirene, phosphirene, etc. This change greatly affects the physical and chemical properties of the new molecules due to distortion in the bond angles and ring strain.

![Three membered saturated heterocycles](image)

**1. Importance in Natural products, Medicine, and Materials Activité biologique**

**Aziridine**

Aziridine alkaloids comprise a rare group of natural products, mainly isolated from either microorganisms, plants, or certain marine species. Fused-ring aziridines have significant importance in the synthesis of complex natural products. These fused-ring aziridines have great potential in being transformed to other nitrogen-containing heterocycles under very mild conditions with a wide functional group of diverse pharmacological properties. Various purified alkaloids are found to display potent antitumor, antibacterial, antimicrobial, and other activities. The polymerized products of simple aziridine (ethylenimine), their polymerizable homologs, as well as substitution products are found useful as disinfectants and preservatives for textiles, leather, skins, meat, glands, blood, glue, casein, starch, and vegetables. The azirimycin, 3-methyl-2H-azirine-2-carboxylic acid (1a), isolated from a strain of Streptomyces aureus and its methyl ester (1b) exhibited broad-spectrum antibiotic activity in vitro against both Gram-positive and Gram-negative bacteria [1,2] and is most active against Staphylococcus aureus followed by Proteus vulgaris, Bacillus subtilis, and Streptococcus faecalis. Some synthetic analogous (2,4) have been used for the treatment of multiple
sclerosis.7a Leacadine (2), an aziridine derivative, was synthesized as a neoplasm inhibitor and used in the treatment of multiple sclerosis [3a]. Methyl aziridine-2-carboxylate (3) and 2-methylaziridine hydrazide (4) showed antitumor activity against mammary gland tumor [3b]. Some of the natural products, aziridine derivatives, FR-900482 (5) and FR66979 (6), are found to display potent antitumor antibiotics [4].

![Chemical structures](image)

**Oxirane**

Oxirane also known as ethylene oxide, is used for the manufacture of products such as polysorbate 20 and polyethylene glycol that are often more effective and less toxic than alternative materials. It is also a useful material for making detergents, thickeners, solvents, plastics, resins, and various organic chemicals such as ethylene glycol, ethanolamines, simple and complex glycols, polyglycol ethers, and other compounds. Pure ethylene oxide is a disinfectant and is widely used in hospitals for sterilizing medical equipment, replacing steam for heat-sensitive tools and equipment, such as disposable plastic syringes [5].

**Thiiranes**

are immensely present in nature. 3,4-Epithiobutanenitrile is present in cruciferous plants and is a weak alkylating agent. Acanthifolicin (I), a polyether carboxylic acid isolated from the marine sponge, has protein phosphatase inhibitory properties. Cephalosporines (II) are synthetic thiirane derivatives known for broad-spectrum antibacterial activity.

![Chemical structure](image)
Various thiiranes and fused thiiranes are reported to exhibit cytotoxic properties. The vapors of simple thiirane have better disinfecting properties than oxirane and are capable of destroying *Bacterium globigii* even at lower concentrations, iriranes are also used as insecticides and fungicides. Chlorocyclopropane sulfide, a thiirane derivative, is used as a nematocide [6].

Thiiranes are found as valuable synthetic building blocks for the construction of a variety of compounds with industrial potential for the preparation of polymers, liquid crystals [7] and adhesives [8]. In addition, thiiranes are pharmacologically active as selective gelatinase inhibitors [9]. A1 adenosine receptor agonists [10] potential topoisomerase I inhibitors [11] and estrogen synthetase inhibitors [12].

1. **Tree-Membred Mononitrogen heterocycles**

A new approach for the synthesis of aziridines is also reported [13] from the reaction of electron-rich azides and electron-poor olefins in the presence of triflic acid in cold acetonitrile.

\[
\text{RN}_3 + R\overset{\text{TfOH}}{\longrightarrow} \text{R} \overset{\text{MeCN}, 0^\circ C, 12h}{\longrightarrow} R_N\overset{\text{R}}{\longrightarrow}
\]

**Scheme 1.** Synthesis of aziridines from the reaction of electron-rich azides and electron-poor olefins in the presence of triflic acid.

A stereoselective synthesis of aziridines is reported [14] from the reaction of ethyl diazoacetate with imine using montmorillonite K-10 as solid catalyst at room temperature.

\[
\text{Ar} = \overset{\text{N}}{\text{Ar}_1} + \overset{\text{N}_2}{\text{COOEt}} \overset{\text{Montmorillonite K-10, Neat, r.t.}}{\longrightarrow} \text{Ar} \overset{\text{Ar}}{\longrightarrow} \text{Ar_1} \overset{\text{COOEt}}{\longrightarrow}
\]

**Scheme 2.** Synthesis of aziridines is reported from the reaction of ethyl diazoacetate with imine using montmorillonite K-10.

Cyclic and acyclic ketones are important substrates for the synthesis of 3,3-disubstituted diazirines.
The synthesis of 3,3-disubstituted diazirines using cyclic and acyclic ketones.

The first step is the synthesis of diaziridines from the reaction of carbonyl compounds and hydroxylamine using pyridine as a base followed by tosylation (or mesylation) and treatment with ammonia [15]. The second step is the oxidation of diaziridine to diazirine by using different oxidizing agents.

2. Three-Membred Monooxygen heterocycles

A reaction of α-haloester with a carbonyl compound in the presence of sodium ethoxide produced 2-(ethoxycarbonyl) oxirane. The first step in the reaction was the formation of carbanion from ethyl chloroacetate using sodium ethoxide and the second step was the addition of carbanion to the carbonyl group followed by cyclization with elimination of halogen [16].

Industrial oxirane is prepared [17] by oxidation of ethylene in air or oxygen in the presence of metallic silver deposited on various matrices, including silica gel, pumice aluminum silicates, alumina, and silicon carbide, activated by certain additives like Sb, Bi, barium peroxide, etc. at elevated temperatures of 220–280°C and a pressure of 3 MPa.

3. Tree-Membred Mono soufré heterocycles
Diastereoselective synthesis of thiiranes is reported in excellent yield by microwave irradiation of a mixture of α-haloketones, O,O-diethyl hydrogen phosphorodithioate, and aluminum-supported sodium borohydride in solvent-free conditions [18].

\[
\begin{align*}
R COOH + SHOEt & \xrightarrow{\text{NaBH}_4 \cdot \text{Al}_2\text{O}_3, \text{MW} (600\text{W})} R S R_1 \quad \text{(Scheme 6)}
\end{align*}
\]

**Scheme 6.** Synthesis of thiiranes by a mixture of cyclic carbonate obtainable from 1,2-diol with alkali thiocyanate at high temperature.

A mixture of cyclic carbonate obtainable from 1,2-diol with alkali thiocyanate at high temperature produced thiiranes.

**Scheme 7.** Synthesis of thiiranes by a mixture of cyclic carbonate obtainable from 1,2-diol with alkali thiocyanate at high temperature.

The synthesis of N-sulfonyloxaziridines was first reported in 1970 [19] by m-CPBA oxidation of N-sulfonyl imines in the presence of phase transfer catalyst, benzyltrimethylammonium chloride. The methodology improved yield further by using Oxone as an oxidizing agent, [20].

**Scheme 8.** The synthesis of N-sulfonyloxaziridines by m-CPBA oxidation of N-sulfonyl imines in the presence of phase transfer catalyst.

**B. Four-Membered Ring Heterocycles**

The second review is centered on the synthesis of Four-Membered Ring Heterocycles Replacement of one or more carbons from cyclobutane, cyclobutene, or cyclobutadiene by one or more heteroatoms such as nitrogen, oxygen, sulfur, phosphorus, etc. generates a variety of four-membered saturated and unsaturated heterocycles. Some of these
heterocycles are azetidines, azetines, azetes, 1,2-diazetidines, 1,3-diazetidines, oxetanes, oxetanones, oxetenes, thietanes, thietanones, 1,2-dithietanes, etc. Due to different physical and chemical properties of heteroatoms from carbon, four-membered heterocycles behave differently from carbocycles.

\[ \text{NH} \quad \text{O} \quad \text{S} \]

1. Importance in Natural products, Medicine, and Materials
Four-membered heterocycles are present as isolates or substructures in various molecules of medicinal and material importance. **Penicillin V**, one of the four-membered fused N-heterocycles, is an antibiotic and belongs to the penicillin group of drugs. Penicillin V is used to treat various bacteria caused by different types of infections.

![Penicillin core structure]

Oxetanes are found only in a few natural products; many of them are terpenoids. Oxetanocin A that inhibits the reverse transcriptase of HIV by mimicking adenosine was first isolated from the soil bacterium *Bacillus megaterium* NK840218.

![Oxetanocin A]

Various mono- and dialkyl thietanes of biological importance have been detected in anal gland secretions of small mammals (ferrets, polecats, stoats, minks, weasels, kiores, voles, etc.). A thietane-based sweetening agent, L-\(\alpha\)-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide, with the trade name Alitame, has been developed by Pfizer and commercialized in different countries, and is 2000 times sweeter than sugar.
2. *Four-Membered Mononitrogen heterocycles* (Azetidine)

[2+2] cycloaddition of imine and ketene under thermal conditions yielded azetidin-2-one.

Scheme 9. Cycloaddition of imine and ketene under thermal conditions yielded azetidin-2-one.

Two-step synthesis of a wide range of 3-methylene-1,2-diazetidines has been carried out by using a Cu(I)-catalyzed 4-exo ring closure of allyl hydrazine [21].

Scheme 10. Synthesis of 3-methylene-1,2-diazetidines by using a Cu(I)-catalyzed 4-exo ring closure of allyl hydrazine.

A reaction of alkene with chlorosulfonyl isocyanate generated in situ from the reaction of chlorocyanogen and sulfur trioxide provided 1-chlorosulfonylazetidin-2-ones. Removal of the sulfonyl chloride group by reaction with thiophenol afforded azetidin-2-ones. This reaction is stereospecific because cis-azetidin-2-one is obtained only from a Z-alkene.

Scheme 11. A reaction of alkene with chlorosulfonyl isocyanate provide 1-chlorosulfonylazetidin-2-ones.

3. *Four-Membered Monoxygen heterocycles* (Oxetane)
Photochemical [2+2] cycloaddition of carbonyl compounds and alkenes afforded highly substituted oxetanes. This reaction is known as the Paterno-Buchi reaction [22]. During the first step of the reaction, carbonyl compound absorbs a quantum of light and undergoes an electronically excited state ($n \rightarrow \pi^*$ transition), and the spin moment of electrons in $n$ and $\pi^*$ orbitals is antiparallel. This intermediate underwent conversion of lower energy to the triplet state. The cycloaddition of the alkene is directed by Woodward-Hoffmann rules and the reaction occur stereospecifically.


α,β-Unsaturated carbonyl compounds are photochemically cyclized to oxetene and its structure was established by hydrogenation over 5% palladium on calcium carbonate, which gave oxetane as a major reduced product [23].

Scheme 13. Synthesis of oxetane by cyclisation of α,β-Unsaturated carbonyl compounds.

4. Synthesis of 1,2 thiazetidines

In the next step, 1,2-thiazetidines were synthesized by cycloaddition of imine and sulfonyl chloride. The nature of the substituent on sulfonyl chloride decided the stereoselectivity. If sulfonyl chloride contains a weak electron-donating or -withdrawing group it provides a mixture of cis and trans products. If the group is strong electron donating then nucleophilicity of imine decides the stereoselectivity [24].

Scheme 14. Synthesis of 1,2-thiazetidines by cycloaddition of imine and sulfonyl chloride.

C. Five-Membered Ring Heterocycles

The third review is centered on the synthesis of Five-Membered Ring Heterocycles: Compounds derived by replacing one of the carbon atoms of five-membered carbocyclic compounds such as cyclopentane or cyclopentadiene by an atom other than carbon are
designated as five-membered heterocycles with monoheteroatoms. Commonly, N, O, S, P, Se, etc. are used as heteroatoms. Broadly, these heterocycles are classified mainly into two categories: one in which the ring is saturated such as pyrrolidine, tetrahydrofuran (THF), tetrahydrothiophene, etc. and the other in which the ring system is unsaturated such as pyrrole, furan, thiophene, etc. In other words, these compounds are comprised of four carbon atoms and one heteroatom. The simplest members of this class of compounds are pyrrole, furan, and thiophene. The saturated five-membered heterocycles behave like aliphatic compounds, while unsaturated molecules show their heteroaromatic character, because these meet the criteria of delocalized odd numbers of pairs of $\pi$ electrons essential for aromaticity.

1. Importance in Natural products, Medicine, and Materials
Heterocyclic compounds are widely distributed in nature and play a vital role in the metabolism of all living cells. Numerous heterocyclic compounds both natural and synthetic are pharmacologically active and are in clinical use. Heterocyclic compounds have a wide range of applications as pharmaceuticals, [25] agrochemicals, and veterinary products. They are also useful as antioxidants, developers, sensitizers, corrosion inhibitors, and copolymer dyes [26]. They have been used as precursors in the synthesis of important natural products. Tryptophan, an important amino acid-containing indole ring, has been found in most proteins, and is used by the body to produce some important compounds, including the neurotransmitter serotonin and the B-complex vitamin niacin.

Skatole, a degradation product of tryptophan, has been isolated and characterized as 3-methylindole with a strong odor of mammalian feces. It is a powerful attractant of males of various species of orchid bees. It also attracts mosquitoes in both field and laboratory conditions. Another important indole derivative, (indole-3-yl) acetic acid, known as a plant hormone, is widely used as a plant growth regulator.
The simple member of oxygen heterocycles is furan and its reduced derivative THF is used as a solvent in the production of adipic acid and hexamethylenediamine, and as a raw material for nylon-6,6. The other industrially important derivative of furan is maleic anhydride and phthalic anhydride, which are constituents of resins and plastics. Furan-2-aldehyde is another furan derivative, which is industrially used as a solvent in the manufacturing of plastics and other furan derivatives.

Aflatoxin B1 is a polycyclic carcinogenic oxygen heterocycle produced by the fungus Aspergillus niger.

1,3-Dioxolane is a five-membered, nonplanar, fully saturated oxygen heterocycle with two oxygen atoms at the 1,3-positions of the cyclic system. It closely resembles THF because the methylene group at position 3 is replaced by an oxygen atom. In other words, it is a five-membered cyclic acetal.
1,3-Dioxolane derivatives are recognized as important motifs for the construction of numerous pharmacologically active molecules as antiviral, antifungal, anti-HIV, and adrenoreceptor antagonists. Some of the important drugs of this ring system in clinical use are depicted in the following scheme.

Thiophene is a five-membered, fully unsaturated, coplanar, sulfur heterocycle comprised of four carbon atoms and one sulfur atom, formed by replacement of the methylene group of 1,3-cyclopentadiene by sulfur. It was discovered by Victor Meyer in 1882 as a contaminant of commercial benzene. The development of the blue color from commercial benzene on heating with isatin and concentrated sulfuric acid was considered to be due to the formation of “indophenine,” a blue dye from thiophene present as an impurity. This mystery was resolved when pure benzene obtained by the decarboxylation of benzoic acid failed to give a blue-colored dye and also by isolation of a blue indophenine dye from commercial benzene.
Various thiophene derivatives either isolated or with fused ring systems have displayed diverse pharmacological activities and have been used as drugs in the treatment of various ailments. A number of thiophene derivatives are mentioned in the following scheme.

Drugs in Clinical Use

Tienilic acid (Diuretic)  Methapyrilene (Antihistaminic)  Tiaprofenic acid (NSAID)

Suprofen (NSAID)  Zileuton (Antiasthmatic)  OSI-930 (Anticancer)

Olanzapine (Antipsychotic)  1-(2,5-Dimethylthiophen-3-yl)
ethoxy)-3-(5-methyl-1H-imidazole-4-yl)prop-1-ene (Antialzheimer)
2. Five-Membered Mononitrogen heterocycles (pyrrole)

A new protocol for the synthesis of N-acyl pyrroles has been reported through condensation of carboxylic acids with 2,4,4-trimethoxybutan-1-amine followed by acid-mediated cyclization synthesis.

![Scheme 15](image)

Scheme 15. Synthesis of N-acyl pyrroles followed by acid-mediated cyclization.

A general synthesis of 3-substituted pyrroles has been reported [27] in good yields by two subsequent Pd-catalyzed monoallylations of amine with allylic alcohols. Ru-catalyzed ring-closing metathesis performed on the diallylated amines yielded pyrrolines in excellent yields, which on selective aromatization by FeCl₃ gave the desired product.

![Scheme 16](image)


An iron-catalyzed intramolecular C–H amination reaction of methyl 2-azido-3-phenylacrylate with commercially available iron(II) triflate as catalyst has been used for the construction of indole derivatives [28].

Scheme 17. An iron-catalyzed intramolecular C–H amination reaction of methyl 2-azido-3-phenylacrylate.

Rh(III)-catalyzed reaction of arylated amidines with α-diazo-β-ketoesters via C–H activation offered N-unprotected indoles [29].

Scheme 18. Rh(III)-catalyzed reaction of arylated amidines with α-diazo-β-ketoesters.

A cyclization of α-amino carbonyl compounds and aldehydes catalyzed by I2 produced [30] 1,3,4-triarylpyrroles. This reaction proceeds smoothly in good yields and tolerates various functional groups.

Scheme 19. A cyclization of α-amino carbonyl compounds and aldehydes catalyzed by I2.

3. Four-Membred Monooxygen heterocycles (Furrane)
Furan is economically and commercially prepared from inexpensive starting materials aldopentose or ketopentose by acid-catalyzed dehydration that yielded α-ketoaldehyde as an intermediate, which intramolecularly cyclized to give furfural. Deformylation of furfural in the presence of copper in quinoline at 400 °C furnished furan.

Scheme 20. preparation of furan from an aldopentose or ketopentose by acid catalyzed dehydration.
An efficient and convenient synthesis of trisubstituted furans has been reported by a gold-catalyzed coupling reaction of phenyl glyoxals, secondary amines, and terminal alkynes [31].

\[ \text{Ar} \begin{array}{cc} \text{O} & \text{HN} \\
\text{O} & \text{R'} \\
\end{array} + \begin{array}{cc} \text{Ar} & \text{R'} \\
\end{array} \rightarrow \begin{array}{cc} \text{N} & \text{R} \\
\end{array} \] \quad \text{5 mol\% AuBr}_3 \quad \text{MeOH, 60°C}

**Scheme 21.** Synthesis of trisubstituted furans by a gold-catalyzed coupling reaction of phenyl glyoxals.

Polysubstituted furans have been synthesized by a copper(I) salt-catalyzed reaction from readily available aryl methyl ketone and electron-deficient alkynes through direct C(sp^3)–H functionalization in the presence of di-tert-butylperoxide (DTBP) as an external oxidant [32].

\[ \text{ArCHO} + \begin{array}{cc} \text{COOEt} & \text{COOEt} \\
\end{array} \rightarrow \begin{array}{cc} \text{Ar} & \text{COOEt} \\
\text{COOEt} & \end{array} \] \quad \text{0.2 eq. CuBr, SMe}_3 \quad \text{0.3 eq. bipy, 3eq. DTBP, DCE, 75°C, 5-8h}

**Scheme 22.** Polysubstituted furans have been synthesized by a copper(I) salt-catalyzed reaction.

Copper-mediated addition of enolate derived from ketone to nitrostyrene followed by cyclization produced trisubstituted furans in good yields [33].

\[ \text{Ar} \begin{array}{cc} \text{O} & \text{HN} \\
\text{O} & \text{R'} \\
\end{array} + \begin{array}{cc} \text{O}_2 & \text{Ar'} \\
\end{array} \rightarrow \begin{array}{cc} \text{Ar} & \text{O}_2 \\
\text{Ar'} & \end{array} \] \quad \text{1eq. CuBrMe}_2\text{S, 1eq. TBHP, Ar, DMF, 120°C, 24h}

**Scheme 23.** Copper-mediated addition of enolate derived from ketone to nitrostyrene followed by cyclization.

4. **Five-Membered dioxygen heterocycles (1,3-dioxolane)**

The parent 1,3-dioxolane has been obtained through condensation of ethylene glycol with formaldehyde in toluene using p-toluenesulfonic acid as catalyst. The same has also been obtained by the reaction of ethylene oxide with formaldehyde using SnCl\(_4\) or tetraethylammonium bromide as catalyst.

\[ \begin{array}{cc} \text{O} & \text{HCHO} \\
\end{array} \rightarrow \begin{array}{cc} \text{O} & \text{O} \\
\end{array} \] \quad \text{P-TsOH} \quad \text{HCHO} + \begin{array}{cc} \text{CH}_2\text{OH} & \text{CH}_2\text{OH} \\
\end{array}

**Scheme 24.** condensation of ethylene glycol with formaldehyde in toluene using p-toluenesulfonic acid as catalyst.
Acetalization or ketalization of aldehyde and ketones with ethylene glycol in the presence of $p$-toluenesulfonic acid forms mono- and disubstituted 1,3-dioxolanes separately [34].

Scheme 25. Acetalization or ketalization of aldehyde and ketones with ethylene glycol in the presence of $p$-toluenesulfonic acid.

A new approach for acetalization and ketolization have been developed by the reaction of aldehyde or ketone with ethylene glycol in the presence of trialkyl orthoformate with a catalytic amount of tetrabutylammonium tribromide in absolute ethanol.

Scheme 26. The reaction of aldehyde or ketone with ethylene glycol in the presence of trialkyl orthoformate.

Various hydroxyacetophenones are conveniently transformed to their respective ketals [35] under mild reaction conditions on reaction with ethylene glycol using cerium(III) triflate as a catalyst in the presence tri(isopropyl) orthoformate in hexane at 25 °C.

Scheme 27. Reaction of aromatic ketone with ethylene glycol using cerium (III) triflate.

Aliphatic and aromatic ketones are efficiently ketalized to corresponding $\alpha$-chloroalkylcyclic ketal using iodobenzene dichloride in ethylene glycol in the presence of molecular sieves at room temperature in very good yields [36].

Scheme 28. Aliphatic and aromatic ketones are efficiently ketalized to corresponding $\alpha$-chloroalkylcyclic ketal using iodobenzene dichloride.
2-Vinylxyethoxymagnesium bromide prepared in situ from the reaction of 2-bromomethyl-1,3-dioxolane with magnesium in THF underwent addition reaction with different aldehydes in the presence of 10 mol% Sc(OTf)$_3$ and gave a protected aldol product [37].

Scheme 29. 2-Vinylxyethoxymagnesium bromide prepared in situ from the reaction of 2-bromomethyl-1,3-dioxolane with magnesium in THF.

Synthesis of 2-methyl-1,3-dioxolane has been reported by heating vinyl ether with KOH [37].

Scheme 30. Synthesis of 2-methyl-1,3-dioxolane has been reported by heating vinyl ether with KOH.

Dintzner et al have demonstrated the utility of montmorillonitic clays in the Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene with ortho-bromobenzaldehyde. The desired product is obtained with a good yield and a high conversion (68%) [38].

Scheme 31. The utility of montmorillonitic clays in the Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene with ortho-bromobenzaldehyde.

Reactions have been made using Smectite as an effective catalyst. We can cite the transesterification of β-ketoesters with carbohydrate derivatives at 110 °C for 48 hours and the dehydration of glucose in furfural under mild conditions [39].
Scheme 32. The dehydration of glucose in furfural under mild conditions and using smectite as an effective catalyst.

A highly efficient catalytic system such as silica supporting magnesium bisulphate Mg (HSO₄)₂ / SiO₂ has been developed to synthesize a variety of dioxolanes [40]. The reactions were carried out under mild conditions allowing the expected products to be obtained with good yields (87-98%).

\[
\text{R= Me, OMe, Cl, NO}_2
\]

Scheme 33. A highly efficient catalytic system such as silica supporting magnesium bisulphate Mg (HSO₄) / SiO₂ has been developed to synthesize a variety of dioxolane. A simple and clean synthesis of dioxolanes has also been reported in the presence of Tunisian clay. The acid treatment of this clay gives rise to Brönsted acid sites which promote synthesis [41]. The surface acidity of clay is considered to be a determining factor in its catalytic activity. This strategy presents an interesting alternative for conventional acetalization reactions. In addition, a range of carbonyl compounds have been considered via acetalization in the presence of silica and alumina [42].

\[
\text{R = Ph-CH=CH}_2, \text{p-OMe-C}_6\text{H}_4, \text{p-NO}_2\text{-C}_6\text{H}_4
\]

Scheme 34. A synthesis of dioxolanes reported in the presence of Tunisian clay.

Reusable and non-polluting catalysts such as titanium-bridged clays (Mont-Ti⁴⁺) are effectively used for the selective acetalization of a variety of carbonyl compounds with ethylene glycol [43].

\[
\text{Toluène, reflux, 1h}
\]

Scheme 35. Acetalization of a variety of carbonyl compounds with ethylene glycol in the presence of catalysts such as titanium-bridged clays (Mont-Ti⁴⁺).
Previous work has been done to improve the catalytic activity of Tunisian clays. In this context, clays bridged by metals such as zirconium, cerium and aluminum or a mixture of these metals have also shown great selectivity in the synthesis of 2,2-dimethyl-1,3-dioxolane with yields satisfactory which depend on the nature and the acidity of the clays used and the reaction time [44].

\[
\begin{align*}
\text{OH} + \text{Me} & \rightarrow \text{Me} \\
\text{Me} & \rightarrow \text{Me}
\end{align*}
\]

Scheme 36. Synthesis 2,2-dimethyl-1,3-dioxolane using as catalyst clays bridged by metals such as zirconium, cerium and aluminum.

5. Four-Membered Monosoufre heterocycles (thiophène)

This reaction is a cyclocondensation of \( \alpha \)-methylene carbonyl compounds with alkyl cyanoacetate or malononitrile and sulfur in the presence of an organic base such as morpholine or piperidine in ethanol to deliver 2-aminothiophenes [45].

Scheme 37. A cyclocondensation of \( \alpha \)-methylene carbonyl compounds with alkyl cyanoacetate or malononitrile and sulfur in the presence of an organic base such as morpholine.

Under analogous conditions, cyclocondensation of cyclic ketones such as cyclohexanone or cyclopentanone with malononitrile or cyanoacetate and sulfur afforded bicyclic thiophene in high yields.

Scheme 38. Cyclocondensation of cyclic ketones such as cyclohexanone or cyclopentanone with malononitrile.

Various methyl 2-amino-4-substituted thiophene-3-carboxylates have been synthesized by nucleophilic addition to the cyanoacetic acid ester followed by intramolecular cyclocondensation in high yields [46].
Scheme 39. Nucleophilic addition to the cyanoacetic acid ester followed by intramolecular cyclcondensation.

Benzothiophene has been prepared by intramolecular cyclization of various aryl sulfides in the presence of different catalysts under different reaction conditions.

(i) Benzo[b]thiophene has been prepared by oxidation-cyclization of 2-phenylthioethanol in the presence of Pd/Al as catalyst at high temperature [47].
(ii) Arylmercapto acetals have also been used as a precursor for the construction of benzo[b]thiophene through gas phase reaction using ZnCl₂-impregnated montmorillonite as catalyst [48].
(iii) Arylmercapto acetals are also cyclized using Amberlyst A-15 as catalyst in boiling toluene as shown in the foregoing scheme.
(iv) Arylthioacetic acid obtainable from the reaction of thiophenol and chloroacetic acid in refluxing alcohol followed by cyclization in acetic anhydride gave 3-hydroxybenzo[b]thiophene, which on dehydroxylataion afforded benzo[b]thiophene [49].

Scheme 40. Intramolecular cyclization of various aryl sulfides in the presence of different catalysts under different reaction conditions.

D. Importance of Monosaccharides in the synthesis of five-membered heterocycles

1. Preparation of glycosyl azide dipoles
The preparation of glycosyl azide dipoles Carbohydrates \((C_nH_{2n}O)_n\), or carbohydrates, saccharides, or more commonly "sugars", constitute a class of essential organic compounds, both by the roles they play in biological reactions (metabolism, labeling, recognition), only by their importance as chiral auxiliaries in asymmetric synthesis of biologically active compounds. Carbohydrates are thus found in fundamental natural substances, such as nucleosides, glycoproteins, glycosyl-\(\alpha\)-amino acids, tannins, etc. The chemistry of monosaccharides (or oses) calls for specific methods of selective protection / deprotection of hydroxyl functions. Armed with this knowledge, we undertook the synthesis of functionalized glycosyl azides in different positions. The starting sugars used are (D) -ribose, (D) -galactose and (D) -glucose, in the form of furanose and pyranose respectively, the key stage being the nitrogenization stage. A synoptic reminder on this last reaction is proposed in Diagram 14. Thus, the fixation of the azide in primary position (C-6 for hexoses, C-5 for pentoses) requires the prior protection of the secondary hydroxyl groups, then the tosylation of the primary alcohol, before introduction of the azide group (Route 1, Diagram 14). Furthermore, the fixing of the azide in the anomeric position (C-1) requires protection of all the hydroxyl functions in the form of acetates, then a regio- / chemoselective activation with a Lewis acid (SnCl₄) of the acetate. Anomeric.

Scheme 41. Preparation of glycosyl azide dipoles.

2. Synthesis of Imidazoles derivative from D-glucose

Like other five-membered N-heterocycles, substituted imidazoles occur in natural products bearing broad-spectrum biological activities, and are target-oriented in the preparation of functional molecules such as ionic liquids or N-heterocyclic carbenes (NHCs) [50-52]. Industrially, simple imidazoles are synthesized from the condensation of 1,2-dicarboxyls with ammonia and aldehydes via the Radziszewski reaction [53]. In the presence of basic catalysts (e.g., CuCO\(_3\)/Cu(OH)\(_2\)), 4-hydroxymethyl imidazole is obtained by thermal treatment of formaldehyde and concentrated ammonia with fructose or glucose that underwent retro-aldol fission to in situ release of dihydroxyacetone and glyceraldehydes [54]. If hexose sugar (e.g., fructose) is heated in a pressure vessel with formamidinium acetate and liquid ammonia, the retro-aldol fission is remarkably inhibited and instead affords 4-tetrahydroxy-butyl imidazole \(A\) as the dominant product [55].

![Scheme 42. Synthesis of Imidazoles derivative from D-glucose.](image)

3. **Synthesis of furylthiazole derivative from bio-based furfural**

Furfural, as one of five-membered oxygen-containing heterocycles, could be readily produced from xylose [56]. Through condensation of cysteine with 2-cyanofuran that is pre-synthesized from furfural, aqueous ammonia and iodine over basic K\(_2\)CO\(_3\) in a mixture of methanol/water at 60 °C, 4-carboxy-2-furylthiazoline could be obtained, followed by alkylation with MeI over K\(_2\)CO\(_3\) in \(N,N\)-dimethylformamide (DMF) to produce furylthiazoline in a three-step overall yield of 63% [57]. Finally, 2-furylthiazole (97% yield) is formed by activated carbon-promoted the thermal aromatization of the thiazoline ring of in an oxygen atmosphere (1 bar, O\(_2\) balloon) at 100 °C in toluene.
Scheme 43. Synthesis of furylthiazole derivative from bio-based furfural.

4. Synthesis of pyrazole derivative from D-glucose and phenylhyrazine

are a class of structural motifs prevalent in biologically active agents and medicines, notably, Lexiscan, Xalkori, Celebrex, and Viagra,[58] and these motifs are also present in dyes and they are utilized as ligands for metal catalysts [59,60].

Scheme 43. Synthesis of pyrazole derivative from D-glucose and phenylhyrazine.

The synthesis of pyrazole derivative from acetic anhydride reacting with glucose phenylosazone which is readily derivable from glucose and phenylhydrazine in the presence of acetic acid was first reported by El Khadem et al. [61] Under microwave irradiation, cyclic addition of glucose phenylosazone goes to completion in 5 min, affording the pyrazole derivative in good yields (86%) [64]. The microwave-assisted reaction system [61-63] is applicable to synthesis of pyrazoles (up to 96% yield) from respective osazones derived from galactose, arabinose, and xylose, and although comparable yields of pyrazoles are obtained using conventional heating modes, more than 1 h is required.

Conclusion

Heterocycles encompass an amazingly diverse family of compounds containing at least one heteroatom. Most of them, especially those containing oxygen, nitrogen or sulfur or any combination of them, arise from natural products and often exhibit useful and interesting biological properties. For these reasons, they are often the main component of drugs and thus still drive medicinal chemistry. More recently, heterocycles have been used as building or component units for materials as well as for surface modification in material sciences. Due to their wide interest, numerous methods have been developed for their synthesis since at least the mid-XIXth century. These old but reliable synthetic routes often rely on stoichiometric
processes with far from green reagents, leading to large amounts of wastes. Besides these classical syntheses, the use of catalysts has become during the last decades a more efficient way to produce heterocycles. Among others, the most preeminent catalysts are those exhibiting good π-Lewis acidity, i.e. palladium, copper, and more recently silver and gold salts or complexes. Unfortunately, these methods rely on homogeneous catalysts, leading to some new drawbacks, such as metal contamination and the non-recovery or recyclability of catalysts. One way to solve these problems would be to apply heterogeneous catalysis to heterocycle synthesis. Successfully and extensively applied in petrochemistry and bulk chemical production, zeolites Amberlyste-15, Montmorillonite, Acid Activate clay, Silice, Alumine…… are more and more applied to added value chemicals, such as those derived from biomass, with a clear trend towards high added value compounds such as drugs, phytochemicals, etc. For conciseness, only the latter aspect will be covered in the present survey.

References

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