Chapter I

Chemistry of Thiophenes, Triazoles, Oxadiazoles and Thienopyrimidines
Chapter I

**Thiophenes**

Victor Mayer discovered thiophene in 1882 during his ingenious experiments on the investigation of aromatic compounds. Following Meyer’s pioneering work, Steinkopf and his collaborators established similar to the parent aromatic system, benzene. Thiophenes occur in coal tar and a large number of thiophene derivatives occur in plants and animal metabolism. Thiophene responds to indophenine test.

Thiophene is a liquid (b.p. 80°C), resembles benzene in most of the features, even in smell as well as boiling point. The microwave spectroscopy has revealed that thiophene molecule is planar and their molecular dimensions are known with a great accuracy. The bond lengths, except C—S bond, in thiophene are intermediate between that of C—C and C=C bonds. However, the results of microwave studies indicate a surprisingly high degree of double bond character of the C—S bond, also not easily evident from the usual kekule structure. The molecule can be expressed as a resonance hybrid of the following contributing structures:

![Resonance Structures]

The resonance energy and aromaticity of thiophene has been a subject of considerable debate and has been found to be in the range of 29-34 Kcal/mole. This large value also indicates that there is considerable conjugation in thiophene. The magnitude of resonance energy of thiophene is higher than that of pyrrole and furan. This is in agreement with the fact that sulfur atom is less electronegative than oxygen and nitrogen (O > N > S) and as a consequence it can release electrons into the ring to form a π-sextet of electrons required for aromaticity. Thiophene is therefore aromatic and also π-electron excessive. From the molecular orbital viewpoint, thiophene is planar molecule with \( sp^2 \) hybridised carbon atoms.
Further evidence that the aromatic character for thiophene is greatest compared to the pyrrole and furan has been obtained from NMR studies. The chemical shifts of the α- and β-hydrogens of thiophene have been determined through a study of deuterated thiophenes. The fact that the resonance of β-hydrogens occurs at lower fields than that of α-hydrogens in these heterocycles has been attributed to lower electron density at the α-hydrogens.

The electrophilic attack on the thiophene takes place preferably at the 2- and 5- positions (α-positions). The π-electron density and localization energy have been calculated for thiophene and as in the case of furan, the electrophilic attack is governed by the latter parameter. The dipole moment of thiophene is calculated to be 0.51D. Pyrrole is a weak base, while furan is extremely weak and thiophene, in contrast, seems to be devoid of basic properties. The C-H stretching frequencies in thiophene are 3110 and 3063 cm\(^{-1}\) while in NMR the ring protons resonate at δ 7.18 and 6.99 for α- and β- protons respectively.

Organic semiconductors have been studied since the late 1940s, but organic materials had not been considered as the active semiconductor layer until 1986, when Kozuoka and coworkers demonstrated a polythiophene-based field-effect transistor. Thiophene derivatives have been widely studied due to their attractive electronic and optical properties. An interesting application is the use of these materials as the active semiconducting layer in organic field effect transistors (OFETs) where solution processability can be exploited in the fabrication of large area, low cost, flexible devices.

Lukas., et al. have reported the four-step synthesis of methyl 3-aminoo-4,5,6,7-tetrahydro-benzo[b]thiophene-2-carboxylate (1) as shown below.
Rosa., et al. synthesized thermally stable heterocyclic chromophores (2–6) based on an (oligo)thiophene π-conjugated bridge and an imidazo-phenanthroline moiety in moderate to excellent yields by condensation of 5,6-phenanthroline-dione with formyl (oligo)thiophenes in the presence of ammonium acetate in glacial acetic acid. They have reported the OLED application of these molecules.

\[ \text{AcONa/AcOH/Refux} \]

\[ 2, n = 1 \]
\[ 3, n = 2 \]

\[ 4 R_1 = R_3 = \text{phenanthroline}, R_2 = H \]
\[ 5 R_1 = N,N\text{-dialkyamine}, R_2 = \text{phenanthroline}, R_3 = H \]
\[ 6 R_1 = \text{alkoxy}, R_2 = R_3 = \text{phenanthroline}, \]

The versatility of 2-amino-3-cyanothiophenes for the synthesis of thieno[2,3-\(d\)]-pyrimidines has been the subject of numerous publications. As a background information, herein we have given a brief note on Gewald reaction in synthesizing useful precursor 2-aminothiophenes with desired groups at 3-position which are being used as building blocks in construction of various heterocycles in general and thienopyrimidines in particular.

Many methods for synthesis of 2-aminothiophenes have been published in last 30 years. 2-aminothiophenes attract special attention because of their applications in pharmaceuticals, agriculture, pesticides and dyes. A series of reviews have been published dealing with the latest accomplishments of 2-aminothiophenes. The chemistry of 2-aminothiophenes has received much attention because of its convenient availability through the most versatile, synthetic method developed by Gewald. The various other routes involve difficult preparation of starting materials and multistep synthesis. These routes do not
always produce good yields and high purity. The key intermediates for the synthesis of 2-aminothiophenes by other routes are generally expensive. Sabnis et al\textsuperscript{14} have described the various synthetic approaches in the Gewald reaction. However tremendous work, particularly their applications to pharmaceuticals and dyestuffs have been reported in the last decade.

**Synthesis of 2-aminothiophenes by the Gewald reaction:**

Gewald et al\textsuperscript{7} have devised the most facile and promising set of synthetic routes leading to 2-aminothiophenes (7) with electron withdrawing substituents such as cyano, carbethoxy and carboxamido etc. in the 3-positions and alkyl, aryl, cycloalkyl and heteroaryl groups in the 4- and 5-positions. This method offers considerable improvements over all other existing synthetic methods for 2-aminothiophenes. The three major variations of this reaction are described below in detail.

**Version 1.**

\[
\begin{align*}
\text{R}^1\text{CO} & + \text{X} \xrightarrow{\text{Sulphur}} \text{NH}_2 \\
\text{R}^2\text{SH} & \quad \text{Amine}
\end{align*}
\]

In this version\textsuperscript{15,16} of Gewald reaction, α-mercaptoaldehyde or α-mercaptop ketone is treated with an activated nitrile bearing electron withdrawing groups (X) such as methyl cyanoacetate, malononitrile, benzylacetonitrile or p-nitrobenzyl cyanide in solvents such as ethanol, dimethylformamide, dioxane or water in presence of basic catalyst such as triethyl amine or piperidine at 50°C. The α-mercaptoaldehyde or α-mercaptop ketone is often generated \textit{in situ} by reaction of alkali sulfides with corresponding α-halocarbonyl compounds. This particular version of the Gewald reaction has few drawbacks such as it utilizes starting compounds which are unstable and difficult to prepare.
Version 2.

\[
\begin{align*}
R^1 & + X & \xrightarrow{\text{Sulphur, Amine}} & R^2 & \text{NH}_2
\end{align*}
\]

This is the most elegant and simpler version of the Gewald reaction. The second version\(^7,17-23\) consists of a one-pot procedure, which can be extensively used for the synthesis of numerous 2-aminothiophenes. This convenient technique includes the condensation of aldehydes, ketones or 1,3-dicarbonyl compounds with activated nitriles such as malononitrile, cyanoacetic esters, cyanoacetamide and its N-substituted derivatives, heteroarylacetonitriles or \(\alpha\)-cyanoketones and sulfur in the presence of amine at room temperature. Ethanol, dimethyl formamide and dioxane are preferred solvents and amines like diethylamine, morpholine or triethylamine have been employed. The yields (8) are much higher in second version.

Version 3:

\[
\begin{align*}
R^1 & , X & \xrightarrow{\text{Sulphur, Amine}} & \text{NH}_2
\end{align*}
\]

In third version\(^7,18,21,22,24-27\) of the Gewald reaction, a two-step procedure is preferred. An \(\alpha,\beta\)-unsaturated nitrile is first prepared by a Knoevenagel-Cope condensation and then treated with sulfur and amine. The third two-step version of the Gewald reaction gives higher yields. Alkyl aryl ketones do not give thiophenes in one-pot modification, but gives acceptable yields (9) in the two-step technique.
Mechanism; Version 1:

![Mechanism Diagram](image1)

Mechanism; Version 2 and 3:

![Mechanism Diagram](image2)

The scope, synthetic utility and variations of Gewald reaction has been demonstrated in the review article "2-aminothiophens by Gewald reaction" by Sabnis and associates. The Gewald reaction goes more readily with cyclic ketones. More complex cyclic ketones and steroids also undergo Gewald reaction. The yields are excellent with high purity. Reaction time is short, which generally involves only one step. These observations are clearly observed in our present work as well. The method generates very active species such as 2-amino-3-substituted-thiophenes, which not only has enormous application in the organic reactions but also in the several applied fields. It produces 2-aminothiophenes. The method incorporates electron-withdrawing groups such as -COOMe, -COOEt, -CN, -CONH₂ or -COPh in thiophene ring, which are key intermediates for the synthesis of fused heterocycles. All these facts reveal that Gewald reaction is a very useful and elegant method in the synthesis of thiophene derivatives. This method will undoubtedly remain a very stimulating field of research for organic chemist in the years to come.
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Triazoles

Parent 1,2,4-triazole (1H-form) is in tautomeric equilibrium with 1,3,4-triazole (4H-form). 1,2,4-triazoles are cyclic hydrazidines with hydrogen atom (or substituent) on either hydrazide nitrogen 11 or on amide 12.

![](image)

The interconversion of two tautomeric forms occurs rapidly and their separation is difficult, however, 1,2,4-triazole tautomer is preferred over 1,3,4-triazole (less symmetrical 1-H-form is favored over symmetrical 4-H form).

![](image)

Acidity - Basicity

1,2,4-triazole is less acidic (pKa = 10.04 for proton loss), but more basic (pKa = 2.45 for proton addition) than 1,2,3-triazole. The basicity of 1,2,4-triazole is attributed to the mesomeric stabilization of the imidazolium type cation formed on protonation. Moreover, the maximum separation of 3-protonated nitrogens (N1 and N4 rather than N1 and N2) makes the cation most stable.

![](image)
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Structural parameters of 1,2,4-triazole

Bond Lengths (Å)

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
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<tbody>
<tr>
<td>N1-N2</td>
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<tr>
<td>N2-C3</td>
<td>1.323</td>
</tr>
<tr>
<td>C3-N4</td>
<td>1.359</td>
</tr>
<tr>
<td>N4-C5</td>
<td>1.324</td>
</tr>
<tr>
<td>N1-C5</td>
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<tr>
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<td>0.930</td>
</tr>
<tr>
<td>C3-H</td>
<td>0.930</td>
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</table>

Bond Angles (°)

<table>
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<tr>
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<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5-N1-N2</td>
<td>110.2</td>
</tr>
<tr>
<td>N1-N2-C3</td>
<td>102.1</td>
</tr>
<tr>
<td>N2-C3-N4</td>
<td>114.6</td>
</tr>
<tr>
<td>C3-N4-C5</td>
<td>103.0</td>
</tr>
<tr>
<td>N4-C5-N1</td>
<td>110.1</td>
</tr>
</tbody>
</table>

Reaction with electrophiles

Electrophilic attack at Nitrogen.

Alkylation of N-unsubstituted 1,2,4-triazoles generally occurs at N-1 rather than at N-4. If there is choice of alkylation between N-1 and N-2 due to the nature of substituents at the positions 3 and 5-, the alkylation occurs at both the positions (N-1 and N-2) with the formation of both N-alkylation products in the ratio depending on the alkylation agent. However, alkylation of 3-halo-1,2,4-triazoles with dimethyl sulfate in the absence of a base occurs at N-1, N-2 and N-4.

Reaction with nucleophilie

1,2,4-triazoles substituted with halo-group at position 3- or 5- undergo nucleophilic substitution reactions. The ease of nucleophilic displacement is
increased with the quaternization of nitrogen or by the presence of an additional electron-withdrawing substituent on the ring carbon atom (13, 14).

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{N} \\
\text{H}_3\text{C} & & \quad \text{N} & \quad \text{H}_3\text{C} & \quad \text{R} & \quad \text{NHNH}_2 \\
\end{align*}
\]

13

14

Synthesis

Synthesis of 1,2,3-triazole involves the use of (i) hydrazine, (ii) acylhydrazine, (iii) amidrazone or (IV) acylmidrazone and represented schematically in scheme.

(i) Hydrazine

(ii) Acylhydrazine

(iii) Amidrazone

(R^2)_2N\text{O} + R^2\text{CONH}_2 + R^1\text{NHNH}_2

\[
\begin{align*}
\text{R}^2 & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{R}^3 \\
\text{R}^2 & \quad \text{NH}_2 & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{R}^3 \\
\text{R}^2 & \quad \text{CONH}_2 & & & & \quad \text{R}^1 & \quad \text{NHNH}_2 \\
\end{align*}
\]

15

Acylamidrazone

R^1\text{NH} + R^3\text{COCl} + R^2\text{NH}_2

(R^2)_2N\text{O} + R^2\text{CONH}_2 + R^1\text{NHNH}_2
This reaction involves the condensation of diacylamines with monosubstituted hydrazines in the presence of a weak acid and proceeds via an amidrazone intermediate. If N-acylthioamide is used instead of diacylamines, the acylamidrazone formation occurs on the thione group.\(^{29}\)

\[
\begin{align*}
\text{Ar}-\text{CONH} & \quad \text{Ar-CONHNHNH}_2 \\
\text{X=O,S} \quad \text{H}^+ & \quad \text{Ar-CONHNHAr} \quad \text{Ar-CONHNHNH}_2 \\
\end{align*}
\]

**Reactions**

**Electrophilic attack at carbon**

1,2,4-triazole and its C-monoalkyl derivatives fail to undergo nitration. If 1,2,4-triazole is substituted with an aryl group on carbon, nitrogen occurs on the benzene ring. But in 3-(p-nitrophenyl)-1,2,4-triazole in which benzene ring is deactivated by nitro group, the nitration results in C-nitro derivatives via N-nitro derivatives.

Halogenation of 1,2,4-triazole is considered to proceed via N-halo-1,2,4-triazole with formation of 3-halo-1,2,4-triazole.
Jiang., et al²² synthesized 1-monosubstituted aryl 1,2,3-triazoles (20) in good yields using calcium carbide as a source of acetylene. The copper-catalyzed 1,3-dipolar cycloaddition reactions were carried out without nitrogen protection and in a MeCN-H₂O mixture.

\[
\text{Ar}-\text{N}_3 + \text{CaC}_3 \xrightarrow{\text{CuI, Na ascorbate, MeCN/H}_2\text{O r.t, 2-20 h}} \text{Ar}-\text{N}^\equiv\text{N}
\]

20

Barluenga., et al studied Pd-catalyzed synthesis of 1H-triazoles (21) from alkenyl halides and sodium azide which represents a completely new reactivity pattern in the context of Pd chemistry³³.

\[
\text{Ar}^\equiv\text{Br} + \text{NaN}_3 \xrightarrow{1 \text{ Mol} \% \text{ Pd}_2 \text{ dba}_3 \text{ N}^\equiv\text{N}, 4 \text{ Mol} \% \text{xantphos, dioxane, 90°C, 14h}} \text{Ar}\text{N}^\equiv\text{N}\text{NH}
\]

21

W. Zhang., et al³⁴ have reported the synthesis of 4-aryl-1H-1,2,3-triazoles (22a-b) anti-3-aryl-2,3-dibromopropanoic acids and sodium azide by a one-pot method using \(\text{N,N-dimethylformamide}\) as solvent in the presence of \(\text{Pd}_2(\text{dba})_3\) and Xantphos.

\[
\text{Ar}^\equiv\text{Br}^\equiv\text{COOH} + \text{NaN}_3 \xrightarrow{1 \text{ mol} \% \text{ Pd}_2(\text{dba})_3 \text{ Xantphos, DMF, 110°C, 36h}} \text{Ar}\text{N}^\equiv\text{N} + \text{Xantphas}
\]

22a 22b

L. Wu., et al have reported 1-substituted-1,2,3-triazoles (23) can be conveniently synthesized from the corresponding aromatic and aliphatic azides in the presence of acetylene gas using mild, copper(I)-catalyzed click chemistry.³⁵
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F. Himo., et al synthesized cycloadditions of copper(I) acetylides to azides and nitrile oxides provide ready access to 1,4-disubstituted 1,2,3-triazoles and 3,4-disubstituted isoxazoles (24). The process is highly reliable and exhibits an unusually wide scope with respect to both components. Computational studies revealed a nonconcerted mechanism involving unprecedented metallacycle intermediates.36

B. Boren., et al reported that Cp*RuCl(PPh3)2 or Cp*RuCl(COD) can be used as catalyst, when primary and secondary azides react with a broad range of terminal alkynes containing a range of functionalities selectively producing 1,5-disubstituted 1,2,3-triazoles (25). Both these complexes also promote the cycloaddition reactions of organic azides with internal alkynes, providing access to fully-substituted 1,2,3-triazoles.37
Z. Yan., et al\textsuperscript{38} studied copper(I)-catalyzed three-component reaction of amines, propargyl halides and azides forms 1-substituted-1\textH1,2,3-triazol-4-ylmethyl)-dialkyl amines (26) in water.

\[
\begin{align*}
R^2NH + Br\equiv + N_2-R^1Et_3N, Cul (5:1 \text{ eq}) & \rightarrow H_2O, r.t, 7-16h \\
R^2NH + Br\equiv + N_2-R^1Et_3N, Cul (5:1 \text{ eq}) & \rightarrow H_2O, r.t, 7-16h \\
R^2NH + Br\equiv + N_2-R^1Et_3N, Cul (5:1 \text{ eq}) & \rightarrow H_2O, r.t, 7-16h \\
\end{align*}
\]

\[R : \text{Alkyl}\]

\[R^1 : \text{Ar, alkyl, benzyl}\]

26

Y. Wu., et al\textsuperscript{39} developed a method for the regiospecific synthesis of 1,4,5-trisubstituted-1,2,3-triazole (27) catalyzed by copper(I) iodide. This is regiospecific synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazole, which can be further elaborated to a range of 1,4,5-trisubstituted-1,2,3-triazole derivatives.

\[
\begin{align*}
RN_3 + R^1& \rightarrow CuI, ICl, NEt_3 \\
RN_3 + R^1& \rightarrow CuI, ICl, NEt_3 \\
RN_3 + R^1& \rightarrow CuI, ICl, NEt_3 \\
\end{align*}
\]

27

D. Luvino., et al\textsuperscript{40} studied reliable and operationally simple one-pot reaction for a one-carbon homologation of various aldehydes followed by Cu-catalyzed azide-alkyne click chemistry giving 1,4-disubstituted 1,2,3-triazoles (28) in good yields without the need for isolation of the alkyne intermediates.

\[
\begin{align*}
O H & \rightarrow K_2CO_3, MeOH/\text{THF} r.t. 2-24h \\
O H & \rightarrow K_2CO_3, MeOH/\text{THF} r.t. 2-24h \\
O H & \rightarrow K_2CO_3, MeOH/\text{THF} r.t. 2-24h \\
\end{align*}
\]

28

D. Rogue., et al\textsuperscript{41} have reported the synthesis of 1,2,3-triazoles by cycloaddition of alkyl azides onto enol ethers under solventless conditions. The
reaction can access ring-fused triazoles that are unavailable by azide-alkyne cycloadditions and is easily scalable. The 1,2,3-triazole products bear functionality that may be readily derivatized (29).

\[
R-N_3 + \overset{\text{MeO-}}{\text{R'}} \xrightarrow{\text{Heat}} \overset{280^\circ\text{C}}{\text{6h}} \overset{\text{R}}{\text{N}} \overset{\text{N}}{\text{N}} \overset{\text{R}}{\text{R'}}
\]

29

D. Amantini, et al. synthesized TBAF-catalyzed [3 + 2] cycloadditions of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes with TMSN₃ under solvent free conditions which allows the preparation of 4-aryl-5-cyano- or 4-aryl-5-carbethoxy-1H-1,2,3-triazoles (30) under mild reaction conditions with good to excellent yields.

\[
\text{Ar-} \overset{\text{NO}_2}{\text{=}} \overset{\text{TBAF 3H₂O, TMSN₃}}{\text{Solvent free, }30^\circ\text{C} \ 15\text{min}-3\text{h}} \overset{\text{Ar}}{\text{N}} \overset{\text{N}}{\text{NH}}
\]

30

D. Liu, et al synthesized triazole-based monophosphine ligands (31) via efficient cycloadditions. Palladium complexes derived from these ligands are highly active catalysts for Suzuki-Miyaura coupling and amination reactions of aryl chlorides.

\[
\text{Ph} \overset{\text{EtMgBr, THF, }50^\circ\text{C} \ 15\text{min}}{\text{PhN₃ r.t (30 min-1hr)}} \overset{\text{NH₄Cl}}{\text{NH₃}}
\]

31

L. Ackermann, et al have reported nontoxic polyethylene glycol (PEG) as solvent and MeSCO₂H as cocatalyst enabled user-friendly palladium (0)-catalyzed
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C-H bond functionalizations under air in the absence of phosphine ligands. Direct arylation of 1,2,3-triazoles (32) gave substituted triazoles in good yields. Recycling of the catalytic system led to a slight decrease of activity.44

\[
\begin{align*}
\text{R} - \text{N} - \text{N} - \text{N} - \text{R}^1 + \text{Br} - \text{Ar} & \xrightarrow{\text{Pd(OAc)}_2 , \text{MeCOOH}, \text{K}_2 \text{CO}_3, \text{PEG-20000}, 120^\circ \text{C}, 24 \text{h}} \text{R} - \text{N} - \text{N} - \text{N} - \text{Ar} - \text{R}^1 \\
\text{R}: & \text{Ar, Bn} \\
\text{R}^1: & \text{alkyl, H, Ph}
\end{align*}
\]

32

B. Liegault., et al45 have reported the palladium-catalyzed direct arylation of a wide range of heterocycles with aryl bromides employing a stoichiometric ratio of both coupling partners, as well as a substoichiometric quantity of pivalic acid, which results in significantly faster reactions. An evaluation of the influence of the nature of the aryl halide has also been carried out (33).

\[
\begin{align*}
\text{R} - \text{N} - \text{N} - \text{N} - \text{R}^1 + \text{Ar} - \text{Br} & \xrightarrow{\text{Pd(OAc)}_2, \text{Pcy}_3 + \text{HBF}_4, \text{K}_2 \text{CO}_3, \text{PhOH, DMA} 100^\circ \text{C} 6-24 \text{h}} \text{R} - \text{N} - \text{N} - \text{N} - \text{Ar} - \text{R}^1 \\
\end{align*}
\]

33

F. Shi., et al46 have reported [3 + 2] cycloaddition of azides to benzynes affording a rapid and easy entry to a variety of substituted, functionalized benzotriazoles (34) under mild conditions.

\[
\begin{align*}
\text{R} - \text{N} - \text{N} - \text{SiMe}_3 + \text{N}_3 - \text{R}^1 & \xrightarrow{1 \text{ eq CsF}, \text{MeCN}, \text{r.t} 18-24 \text{h}} \text{R} - \text{N} - \text{N} - \text{N} - \text{R}^1 \\
\end{align*}
\]

34
1,3,4-Oxadiazoles

Compounds having a five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles or in the older literature furadiazoles A-D was reported by the Belgian workers who made the thermally unstable 1,2,4-oxadiazole (A), Four types of oxadiazole are known namely 1,2,4-, 1,2,5-, 1,3,4- and 1,2,3- oxadiazoles.

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. The electrophillic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic \( sp^3 \) carbon atom. 1,3,4-oxadiazoles are found to be most potent biologically. Much attention has been paid to 1,3,4-oxadiazole derivatives in recent years, because of their anti-inflammatory, hypoglycemic, anticonvulsant, antimicrobial and other activities.\(^{48,49}\)
1,3,4 oxadiazole ring is symmetrical and planar with the following structural parameters.

<table>
<thead>
<tr>
<th>Bond Lengths (Å)</th>
<th>Bond Angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₃-N₄ = 1.399</td>
<td>C₂-O-C₅ = 102.0</td>
</tr>
<tr>
<td>C₂-N₃ = 1.297</td>
<td>O-C₂-N₃ = 113.4</td>
</tr>
<tr>
<td>N₄-C₅ = 1.297</td>
<td>C₂-N₃-N₄ = 105.6</td>
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<tr>
<td>O-C₂ = 1.348</td>
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<tr>
<td>O-C₅ = 1.348</td>
<td>O-C₅-N₄ = 113.4</td>
</tr>
</tbody>
</table>

Reactions with electrophiles

Because of very low π electron density on the carbon atoms, the attack of electrophiles preferentially occurs at nitrogen. Alkylation of 1,3,4-oxadiazoles occurs at the position-3 with the formation of 1,3,4-oxadiazolium salts (35).

However, the alkylation of 2-alkoxy-1,3,4-oxadiazoles with alkyl halides produces labile oxadiazolium salts which undergo O-dealkylation to provide 4-alkyloxadiazolin-5-ones (36).
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Reaction with nucleophiles

The carbon atoms of 1,3,4-oxadiazole ring are relatively with low \( \pi \) electron density on the carbon atoms and therefore attack of nucleophiles occurs at the carbon atoms. The reaction proceeds either with nucleophilic substitutions or with ring cleavage (37).

\[
\begin{align*}
N'N & - O'X + \text{Nu} \\
\rightarrow & \\
N'N N'N & \text{NuR O} \\
\end{align*}
\]

Nucleophilic Substitution reactions

1,3,4-Oxadiazoles substituted with chloro or sulfonyl group at the 2-position undergo nucleophilic substitution reactions. The reaction of 2-chloro-1,3,4-oxadiazoles (\( X=Cl \)) with nucleophiles such as amines, thiourea or azides ion proceeds with the substitution of chloro group by nucleophilic and results in the corresponding 2-substitued 1,3,4-oxadiazoles (38).

\[
\begin{align*}
R-n-n
\text{O} + \text{NHR} & \\
\rightarrow & \\
\end{align*}
\]

18
Nucleophilic attack with ring cleavage

The reaction of alkyl- or aryl-1,3,4-oxadiazoles with nucleophiles involves the cleavage of 1,3,4-oxadizole ring with the formation of hydrazine derivatives which may recyclize to provide 1,2,4-triazoles.

\[ \text{N-N} \quad \text{C-X} \quad \text{RNH}_2, \text{H} \quad \text{R}_2 \quad \text{R} \quad \text{S} \quad \text{Sn} = \text{c} \quad \text{X 'NHR} \quad \text{O} \quad \text{N-N} \quad \text{R}_1 \quad \text{K.} \quad \text{X-R}_2 \quad \text{N} \quad \text{H} \quad \text{R}_3 \]

S. Dolman, et al\textsuperscript{50} reported the preparation of 2-amino-1,3,4-oxadiazoles relies on a tosylchloride/pyridine-mediated cyclization of thiosemicarbazides that consistently out performs the analogous semicarbazide cyclizations. Various 5-alkyl- and 5-aryl-2-amino-1,3,4-oxadiazoles (40) have been prepared in good yields.

\[ \text{X} \quad \text{H} \quad ^\text{\textcopyright} \quad \text{RN-NH-C—N} \quad \text{H} \quad \text{u} \quad \text{TsCl, Pyridine (1.2 : 2.1 eq) THF,65-70 °C ,20h} \]

\[ \text{R-iVN'R}_1 \quad \text{N-N} \quad 40 \]

M. Adib, et al\textsuperscript{51} have reported that N-isocyaniminitriphenylphosphorane, aldehydes, and benzoic acids undergo a one-pot, three-component reaction under mild conditions to afford 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles (41) in good yields.

\[ \text{Ar^OH} + \text{phP=N-NC} + \text{R} \quad \text{O} \quad \text{X, DCM} \quad \text{r.t 24h} \]

\[ \text{R = alkyl, Ar} \]

\[ 41 \]
Y. Park., et al\textsuperscript{52} have reported the synthesis of symmetric and unsymmetric 1,3,4-oxadiazoles in situ from hydrazine hydrate and the corresponding 2-acyl-4,5-dichloro-pyridazin-3-ones as acylating agent in polyphosphoric acid (PPA) or BF$_3$·OEt$_2$ in excellent yields (42).

Ramazani., et al\textsuperscript{53} have developed procedure for the synthesis of fully substituted 1,3,4-oxadiazole derivatives (43) using (N-isocyanimino) triphenylphosphorane, a secondary amine, a carboxylic acid, and an aromatic aldehyde.

Khan., et al\textsuperscript{54} have reported the synthesis 2, 5-disubstituted-1,3,4-oxadiazoles (44) under microwave irradiation.

Z Xu., et al\textsuperscript{55} reported series of iridium complexes with 2, 5-diaryl-[1,3,4]-oxadiazole ligands (45) and their electrochemical, photophysical, and electroluminescent (EL) properties were also reported.

\[ \text{Ar–COOC}_2\text{H}_5 + \text{NH}_2\text{NH}_2 + \text{H}_2\text{O} \xrightarrow{\text{C}_2\text{H}_5\text{OH, reflux, 17h}} \text{Ar–CONNH}_2 \]

\[ \text{Ar–CONHNH}_2 + \text{Ar}^1\text{–COOH} \xrightarrow{\text{POCl}_3, \text{reflux, 5h}} \text{Ar}^1\text{–CONNH}_2 \]
Thienopyrimidines

Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily, due to a very wide spectrum of biological activities. This is evident, in particular, from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles, such as purines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines, and pyrrolopyrimidines.

Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annulated five-membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of the chemistry and biology of isomeric thienopyrimidines have been reviewed.

Since thiophene derivatives are resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. Compounds containing the thienopyrimidine nucleus have been prepared by several workers because of their diverse biological properties. For instance, a number of thienopyrimidines are known to possess antimalarial, antiallergic, hypocholesterolemic, analgesic, anti-inflammatory, diuretic, CNS depressant and antiviral activities. Literature survey also reveals that 1,2,4-triazoles and N-bridged heterocycles fused with them possess diverse pharmacological activities.

Synthesis of Thienopyrimidines

Synthetic approaches to the construction of thienopyrimidines are sufficiently well developed. Three possible types of annulation of thiophene to the pyrimidine ring and, correspondingly, three isomeric thienopyrimidines are known: thieno[2,3-d]pyrimidine (46), thieno[3,2-d] pyrimidine (47), and thieno[3,4-c]pyrimidine (48). The structures and the conventional numbering of these heterocyclic systems are shown below.
The known approaches to the synthesis of thienopyrimidines can be divided into two main groups:

2. Thiophene ring closure in pyrimidine derivatives.

**Synthesis of thienopyrimidines by pyrimidine ring closure**

 Appropriately substituted aminothiophenes, accessible by various methods\textsuperscript{65,66} serve as the main starting compounds for the preparation of thienopyrimidines with this approach. Syntheses involving pyrimidine ring closure starting from both 2- and 3-aminothiophenes proceed under similar conditions and invoerally the same reaction sequences, due to which all three types of thienopyrimidines become accessible. Hence, it is reasonable to classify the reactions leading to these compounds according to the type of substitution in the pyrimidine rings formed. One of the most popular approaches to the synthesis of thienopyrimidinediones (50) is based on the pyrimidine ring closure in thienylureas (49).

Here in after, (46) is the thiophene ring bearing substituents at positions 2 and 3 or 3 and 4; thienopyrimidine structure (50) is thiophene analogously annulated to the pyrimidine ring the ester group is most widely used as the COX group.
A one-pot procedure was developed for the synthesis of (2-alkylthio-4-oxothieno [3,2-d]pyrimidine-3-yl) acetonitriles (51) based on the treatment of methyl 3-aminothio-phene-2-carboxylate successively with CSCI₂, NH₂CH₂CN, and alkyl halides.

The reaction of carbondisulfide with amino derivatives of thienopyridine (52) was used for the synthesis of pyridothienopyrimidinedithione (53) using basic media.

3-Cyano-2-thioureidothiophenes (55), which are prepared by the reactions of aminocyanothiophenes (54) with isothiocyanates or by reactions successively with CSCI₂ and amines, undergo intramolecular cyclization in the presence of bases at room temperature to give 3-thioxothieno[2,3-d]pyrimidine-1-imines. The latter reaction requires thorough control over the temperature to prevent the possible rearrangement (such as the Dimroth rearrangement) into aminothienopyrimidine thiones. Attempts to isolate the corresponding cyclization products of cyanoureia failed apparently due to the rapid rearrangement into aminothienopyrimidinones.
Synthesis of thienopyrimidines by thiophene ring closure

As earlier, procedures for the synthesis of thienopyrimidines by thiophene ring closure starting from the available pyrimidine are used much more rarely than the pyrimidine ring closure, because the appropriately substituted pyrimidines are less readily accessible. In this section, data is systematized according to the types of reactions giving rise to the thiophene ring. Generally, the synthesis of thienopyrimidines using the Claisen, Thorpe-Ziegler, and Friedlender condensations can be represented by the following scheme:

In the case of $Y = \text{CO}_2\text{Et}$, the reaction affords 5-hydroxythienopyrimidines, which exist predominantly as the oxo form (58). Pyrimidines (57) starting compounds can be prepared by two methods. One of them involves substitution of the mercaptoacetic acid residue for the chlorine atom in 4-chloro-5-ethoxycarbonylpyrimidines$^{70}$ (56). Pyrimidines (70) are then cyclized in the presence of bases to thieno[2,3-d]pyrimidin-5-ones (58).
A. Nucleophilic Substitution

In the chemistry of thienopyrimidinones and thienopyrimidinediones, the replacement of an oxygen atom with a chlorine atom is used rather often. Earlier, it was found\textsuperscript{71} that this reaction with thienopyrimidinediones proceeds on heating with either POCl\textsubscript{3} (an excess of POCl\textsubscript{3}, pyridine, or N,N-dimethylaniline is used as the solvent) or SOCl\textsubscript{2}. The reaction is accompanied by the formation of the corresponding dichlorothienopyrimidines. In recent years, such reactions in a series of thienopyrimidinones were most often carried out with POCl\textsubscript{3} in pyridine or N,N-dimethylaniline to prepare chlorothienopyrimidines.\textsuperscript{72,73} Thienopyrimidinones \textsuperscript{72} react analogously to afford chlorothienopyrimidines (59).

\[
\begin{array}{c}
\text{R}^1 \\
\text{N} \\
\text{A} \\
\text{H} \\
\text{N} \\
\text{R}^2 \\
\text{56} \\
\end{array}
\xrightarrow{\text{POCl}_3} \xrightarrow{\Delta} \begin{array}{c}
\text{R} \\
\text{N} \\
\text{A} \\
\text{Cl} \\
\text{N} \\
\text{R}^2 \\
\text{59} \\
\end{array}
\]

Compounds containing the thioxo group undergo the same transformations.\textsuperscript{74} Under the action of POCl\textsubscript{3}, thienopyrimidinethiones (60) are converted into chlorothienopyrimidines (61).

\[
\begin{array}{c}
\text{R}^1 \\
\text{N} \\
\text{S} \\
\text{S} \\
\text{R}^2 \\
\text{NH} \\
\text{60} \\
\end{array}
\xrightarrow{\text{POCl}_3, \text{PhNMMe}_2} \xrightarrow{\Delta} \begin{array}{c}
\text{R}^1 \\
\text{N} \\
\text{S} \\
\text{S} \\
\text{Cl} \\
\text{R}^2 \\
\text{61} \\
\end{array}
\]

Tetrahydrocycloheptathiathieno-1,2,4-triazolopyrimidine (63) was constructed starting from 2-amino-3-cyanotetrahydropyrimidine (62) in four steps.\textsuperscript{75}
D. Briel., et al reported the 2-aminothiopen derivatives (64) as GluR6-antagonists.76

\[ R^4 = NH, \text{NH}_2\text{COOEt, N=NCN, NCS, NHCOCH}_2\text{NHCH}_2\text{Ph} \]
Chapter I

Reference


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