

Exploring Potential, Synthetic Methods and General Chemistry of Pyridazine and Pyridazinone: A Brief Introduction

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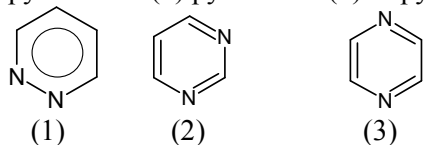
ABSTRACT: Pyridazin-3-one, a saturated or unsaturated form of pyridazine with carbonyl group on third carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. Present article is sincere attempt to review chemistry, synthesis, spectral studies and applications of pyridazinone.

Key words: Pyridazinone, pyridazine, biological activities.

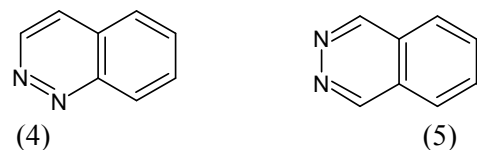
INTRODUCTION

Pyridazine are diazine. The diazines are a group of compounds formally derived from benzene by the replacement of two of the ring carbon atom by nitrogen.

Three isomeric diazines are possible with the nitrogen atoms in 1-2, 1-3, or 1-4 relationship, giving rise to the pyridazines (1) pyrimidine (2) & pyrazine (3) respectively.



Pyridazine (1,2-diazine) (1) & its benzo analogs cinnoline (1,2-diazanaphthalene) or benzo (C) pyridazine (4) & phthalazine benzo (d) pyridazine (5) have been known since the nineteen century. Although the basic synthetic principles and reactivity were investigated in the early years, interest in these compounds revived only during the past 35 years, when many of their derivatives found application as a result of their biological activities.



But interest in there compounds were not very intense, compare with pyrimidines, pyrazines & their bicyclic analogs.¹⁻⁴

Pyridazinones are the derivatives of pyridazine which belong to an important group of heterocyclic compounds containing two nitrogen atoms at 1 and 2 positions in a six member ring. A lot of research work on pyridazinones

has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. Numbers of methods for synthesis by using various agents are available in the references.

An assessment of various literatures one can collect information about the different structure form of pyridazinone that has been utilized as a part of a large number of complex compounds & these compounds exhibits diversified pharmacological activities due to presence of pyridazinone moieties⁵⁻¹³. In recent years a substantial number of 6-aryl-3-(2*H*)-pyridazinones have been reported to possess antimicrobial¹⁴⁻¹⁸, potent analgesic¹⁹⁻²⁵, anti-inflammatory and analgesic²⁶⁻³⁹, COX inhibitor^{26,40}, antifeedant⁴¹, antidiabetic⁴², herbicidal⁴³, antihypertensive⁴⁴⁻⁴⁶ and antiplatelet activities⁴⁷⁻⁵⁰, anticancer effects⁵¹⁻⁵³, antitubercular¹⁶, antifungal^{16,54,55} and other anticipated biological⁵⁶ and pharmacological properties^{57,58}. In particular, a large number of pyridazinone derivatives are well known as intermediates for drugs and agrochemicals^{43,54}, antipyretics, neurological disorders^{59,60}, blood platelet aggregation inhibitors^{49,61-63}, cardiotoxic and antihypertensive agents^{45,49,61-82}, myocardial imaging agent⁸³, anticonvulsant^{84,85}, bronchial asthma and allergy⁸⁶⁻⁸⁸, antidepressant and anxiolytic⁸⁹⁻⁹¹ and Inhibition of linolenic acid in wheat roots⁹². As part of our program, we reported different compounds containing the different moiety or substituents as starting materials for the synthesis of pyridazine and pyridazinone derivatives and their interesting biological activities.

Physical properties of pyridazine

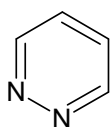
Pyridazine is colourless liquid b. p. 207°C & is miscible with water as well as benzene. The lone electron pair on nitrogen atom are involved in H-bond formation with protic solvents and benzene. It is weakly basic (pka-2.3). Electron donating groups augment basicities, thus 4-methyl pyridazine has pka of 2.93. It possesses a high dipole moment (4D) value¹⁻⁴.

S. No.	Physical properties of pyridazine	
1	Melting point	-8°C
2	Boiling point	208°C (760 mm)
3	Density	1.1054
4	Index refraction	15231
5	Salts (a) Hydrochlorides (b) Monopicrate	Yellow solid m. p. 161-163°C Yellow solid m. p. 161-163°C

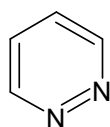
Chemistry of Pyridazine and pyridazinone:

Pyridazine is one of the three possible isomeric diazines. In pyridazine (1) two nitrogen atoms are present adjacent to each other. This ring system does not form a part of any natural product and thus has been less extensively investigated than other diazine. It was obtained as early as 1886 by Fischer & was first synthesized by Tauber in 1895. Because of the natural proximity of the nitrogen atoms pyridazine displays properties different from the other isomeric diazine.

Pyridazine is assumed to be a planer six membered ring & is represented as a resonance hybrid of two structure (1a) & (1b) with a greater contribution from the canonical structure (1a).



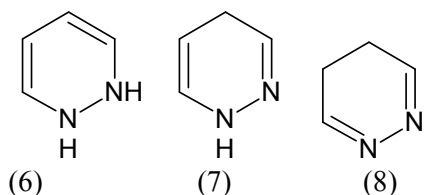
(1-a)



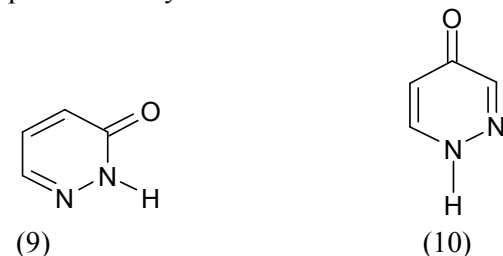
(1-b)

This is supported by the result of electron diffraction, microwave spectroscopy data & X-ray crystallographic analysis, which all indicate that the N-N bond has single bond character. Bond length and bond angle have been also calculated by electron diffraction, microwave spectroscopy.

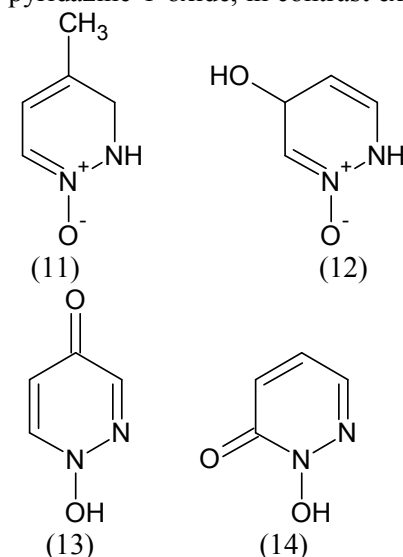
Six possible reduced pyridazines, 1,2(6), 1,4(7) and 4,5(8) dihydropyridazines are known.



Appropriately substituted pyridazines exhibits tautomerism. This 3 & 4- hydroxyl pyridazines (9) and (10) exist predominantly in the oxo form¹⁻⁴.



Though 3 and 5-hydroxy pyridazine-1-oxides exist in the hydroxyl N-oxide form (11) & (12). The 4 & 6-hydroxy pyridazine-1-oxide, in contrast exist predominantly in the hydroxyl pyridazinone forms (13) & (14)

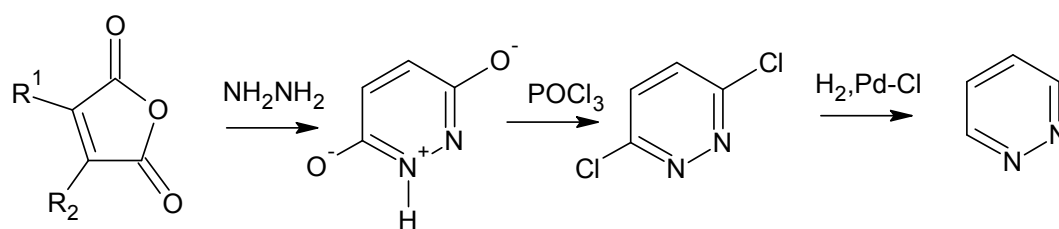
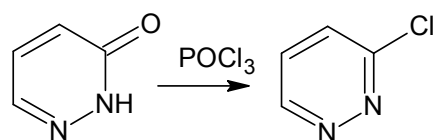


3-pyridazinones are derivatives of pyridazine with a carbonyl group at the 3 position. A detail study of tautomerism in 6-(2-pyrrolyl)pyridazin-3-one and 6-(2-pyrrolyl)pyridazin-3-thione has been done by R. Alan Jones and Alexander Whitmore, regioisomers study of different 3-pyridazinones and chiral resolution and absolute configuration of the enantiomers of 5-acetyl-2-methyl-4-methylsulfinyl-6-phenyl-3(2H)-pyridazinone has been done^{55,93}.

Synthetic method of pyridazine and pyridazinone

Several methods for syntheses are available in literatures which involve conventional synthesis methods. Most synthesis of pyridazine is based on the addition of hydrazine or its derivative to an appropriately 1, 4-disubstituted carbon chain. As part of our program aimed at utilizing β -aroylpropionic acid derivatives containing the different aromatic moiety as starting materials react with different hydrazine derivatives for the synthesis of pyridazine and pyridazinone derivatives, these reports of interesting biological activities prompted us to synthesize a new series of pyridazinones containing different other moieties to give the corresponding pyridazinones^{1-4,11,26,39,43,46,49,54,58,70,71,96,97,98,99,100}.

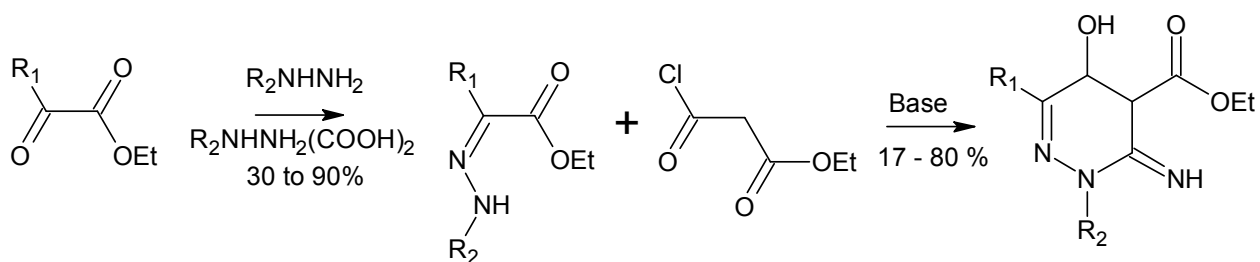
From maleic Anhydride- The condensation of hydrazine or it's derivatives with maleic anhydride derivatives, 1,4-dicarbonyl ethenes, butenolides or dihydrofuran derivatives result in the formation of pyridazine rings.



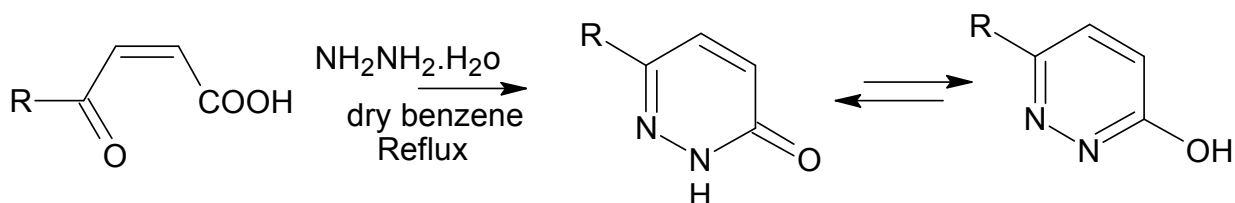
R_1 and R_2 = Alkyl group, same or different.

From diketones

To a solution of the corresponding diketone in DMF was added, at 80°C , a solution of cyanoacetoamide in DMF. The mixture was heated at 100°C until the reaction was completed (TLC). Then the solution was concentrated under vacuum. The residue was purified by recrystallization from the appropriate solvent or by column chromatography using the appropriate eluents^{52,99}.



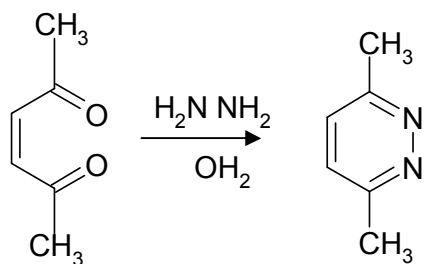
R_1 = aryl, alkyl R_2 = alkyl



R = aryl

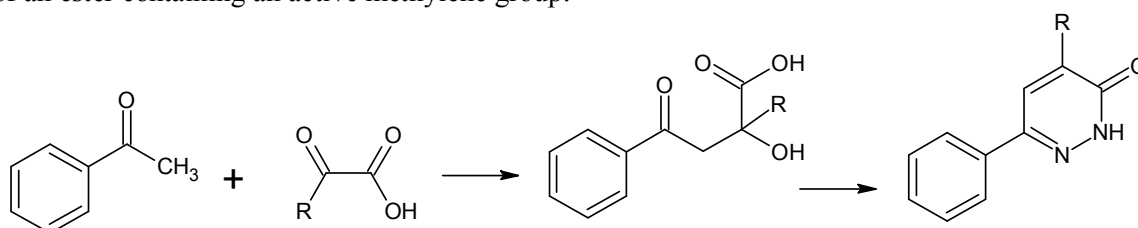
From 1,4-dicarbonyl compounds

The most common method for the preparation of alkyl or acyl- substituted pyridazine consists of the direct one step cyclization from an unsaturated diketone & hydrazine.



From 1-2,diketone compounds

It is a useful synthesis of 3(H) pyridazine involve the reaction of ketones with hydrazine derivatives in the presence of an ester containing an active methylene group.



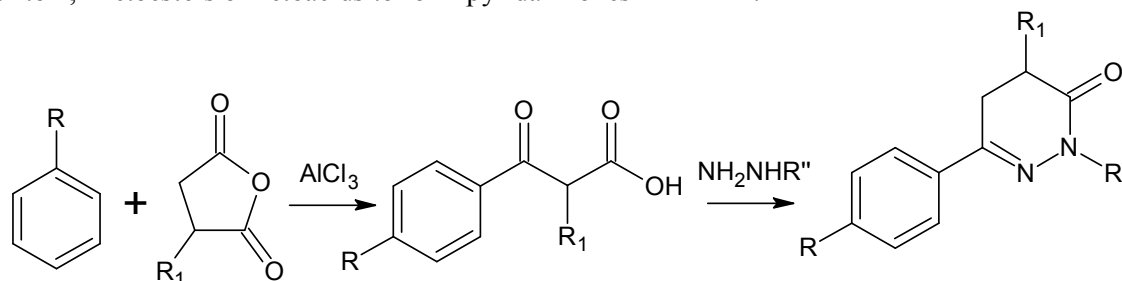
(i) KOH, 4°C, 96h; (ii) NH₂NH₂, 100°C.

From succinic anhydride or its derivatives

A mixture of substituted phenyl/appropriate hydrocarbon and succinic anhydride/methyl succinic anhydride/itaconic anhydride, was added to a stirred solution of aluminum chloride in purified carbon disulphide. Acidification of the filtrate with concentrated hydrochloric acid gave a precipitated. Then hydrazine hydrate/hydrazine derivative was added to a stirred and refluxing solution of β- 4-substituted benzoyl propionic acid/4-(4-substitutedphenyl)-4-oxobutyric acid/β- 4-substituted benzoyl-2-methylene propionic acid (I). The crystals obtained, washed with cold ethanol, dried and recrystallized from ethanol^{16,54,67,70}.

From 1,4 ketoesters or ketoacids (commercially available starting materials):

A common method for formation of the pyridazine ring involves addition of a hydrazine molecule to an anhydride or to 1,4 ketoesters or ketoacids to form pyridazinones^{60,62,91,94,100}.



R= Different substituted aryl derivatives, R₁= H, CH₃ and R'' = H, Phenyl, substituted phenyl, different heterocyclic groups.

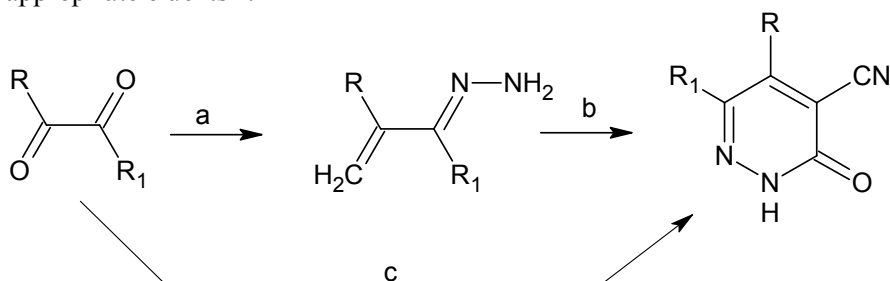
Formation of the 6-(4-substitutedphenyl)-2-substituted-4,5-dihydropyridazin-3(2H)-ones.

Synthesis from monohydrazones and diethylmalonate derivatives

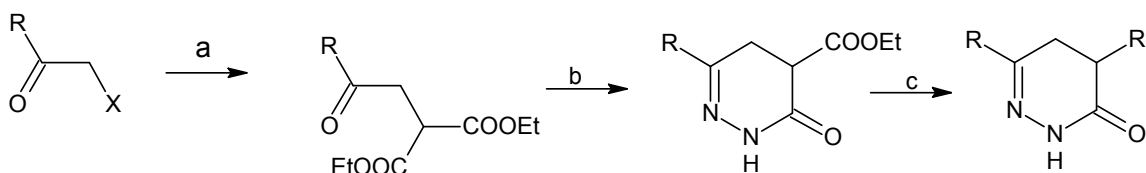
General Procedure for the Preparation of Monohydrazones

The method utilized for the synthesis of pyridazines derivative is outlined in Scheme. The necessary 1,2-dicarbonyl compounds were commercially available or easily prepared following previously described methods.

A suspension of the corresponding diketone in absolute EtOH containing an excess of $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ was heated at reflux temperature until the reaction was completed. After the solution was cooled, the formed solid was isolated by filtration and purified by recrystallization from the appropriate solvent or by column chromatography using the appropriate eluents⁵².



Reagents: (a) NH_2NH_2 , EtOH; (b) (i) Na, EtOH, ethyl cyanoacetate; (ii) 1 N HCl; (c) cyanoacetohydrazide, EtOH, or DMF.

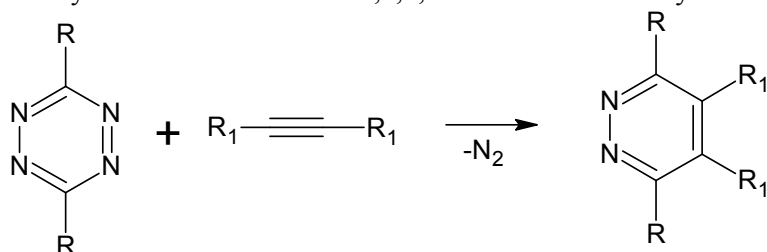


X= Cl, Br

(a) diethyl malonate, K_2CO_3 , KI; (b) NH_2NH_2 , EtOH; (c) Br_2 , AcOH

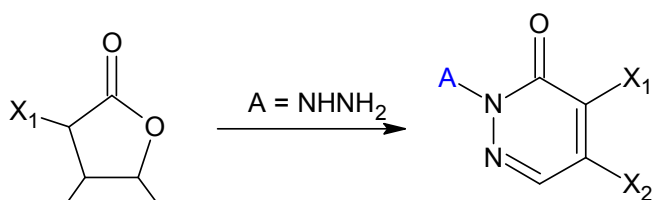
From 1,2,4,5-Tetrazines:

The cycloaddition reaction of 1,2,4,5-tetrazines with acetylenes or alkenes result in the formation of pyridazines.



Direct ring synthesis

Most preparation of the pyridazinone derivatives depend on the nucleophilic substitution of the starting material of these derivatives, prepared from mucochloric acids. 4,5-dihalo-3(2H)-pyridazinone derivatives were prepared by different reaction such as direct ring synthesis, alkylation, and halogen- exchange reaction.

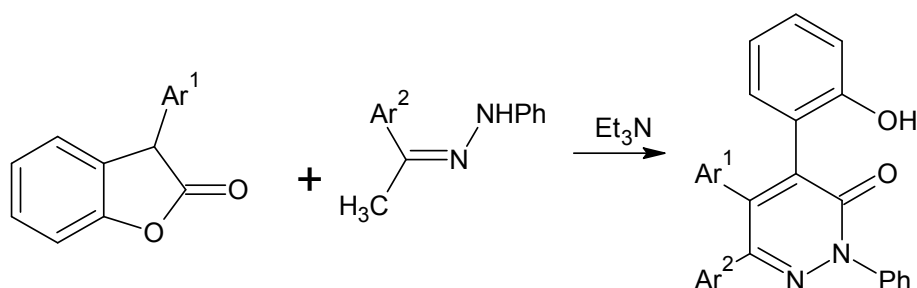


A= H, Ph, Py, Bu

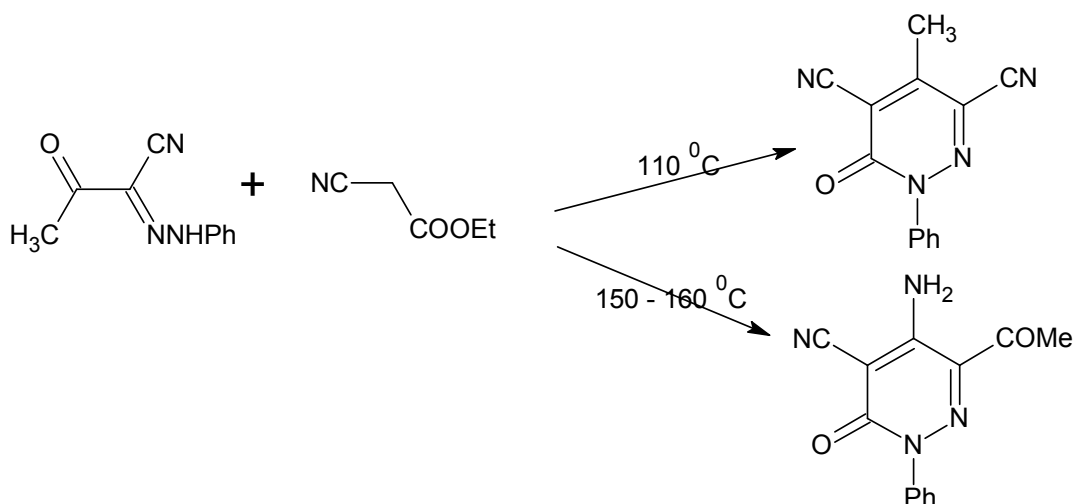
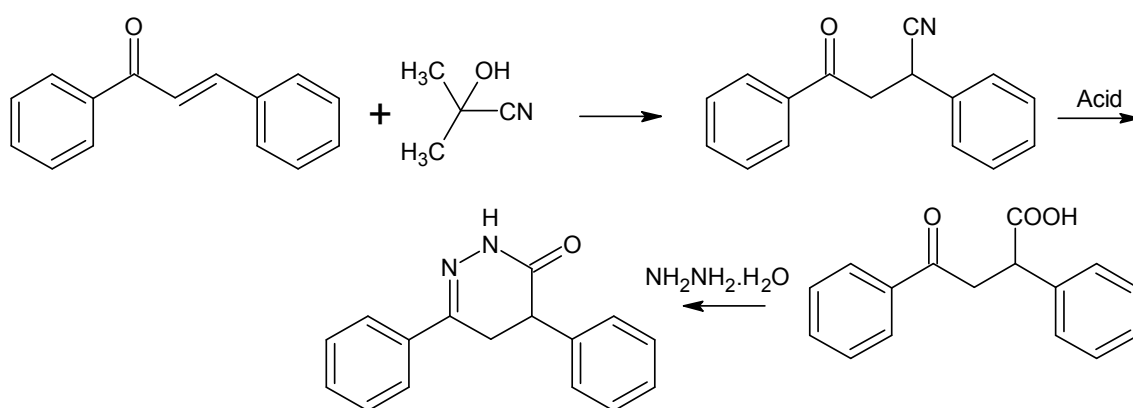
X1= X2= Cl, Br

Miscellaneous methods

From 3-oxo-2-phenylhydrazonobutyronitriles and reactive methylene compounds, various substituted pyridazines have been prepared. The reaction with ethyl cyanoacetate at 110 °C gave A, whereas at 150- 160°C B was obtained.



In a simple new method, 4-(o-hydroxyphenyl)-3-(2H)-pyridazinones can be prepared by 1,3-dipolar cycloaddition of the in situ prepared diarylnitrilimines and 3-arylidine-2(3H) benzofuranones^{5,36}.



All these compounds were prepared by the reaction of mucohalo acid with the corresponding hydrazine.

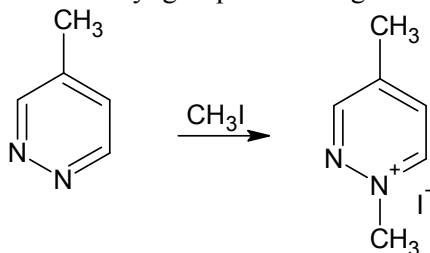
Chemical reactions:

Reaction with acid:

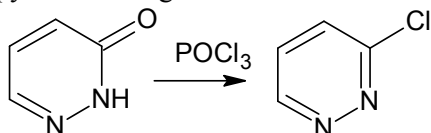
Pyridazine is a weak base & thus form salt with mineral acid. Pyridazines and pyridazinones derivatives give different type reactions. The protonation of second nitrogen atom is difficult because of the high energy required to generate two positive charges on adjacent atom^{8,18,93-95}.

Quaternization: -

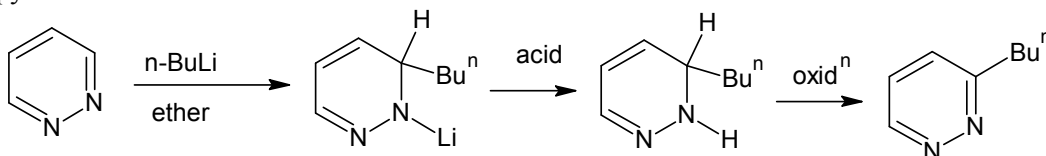
The pyridazine ring reacts with alkyl halide or di alkyl sulphate in the presence of base to furnish monoquaternary salts though less readily than pyridine. The position of the mono alkylation on the ring is determined by the presence of alkyl group on the ring.


Electrophillic Substitution: -

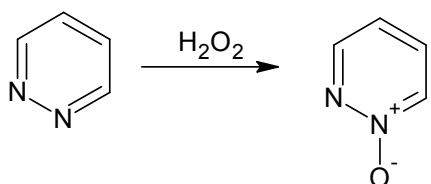
The 3,4,5, & 6 positions in pyridazine nuclear are electron deficient due to the inductive effects of nitrogen atoms. Pyridazine itself is very resistant to electrophillic substitution & can under go reaction only under drastic condition. No sulphonation or nitration of pyridazine has been reported. When suitable activating groups are present on the pyridazine ring nitration becomes feasible¹⁰³.


Reaction with Nucleophilic Reagents: -

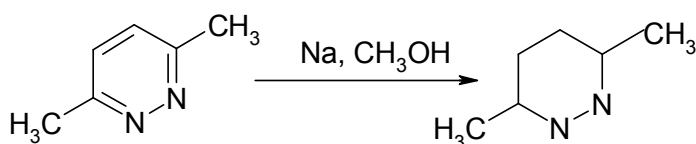
The diazines, in general, are very susceptible to the action of nucleophilic reagents. The effect of the presence of the second nitrogen atom is to make the carbon atoms of the ring even more electron deficient than they are in pyridazine¹⁰².


Reaction with oxidizing and reducing agents: -

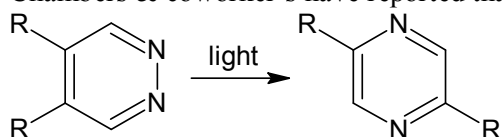
Pyridazine is also resistant to the attack of the oxidizing agents because of electron deficiency in the ring with hydrogen peroxide. However the N-oxide formation takes place but no di-N-oxide is obtained.



Diazines are readily reduced. The ring in situ can be easily cleaved when the two nitrogen are adjacent. The ring can be completely reduced with Na/CH₃OH

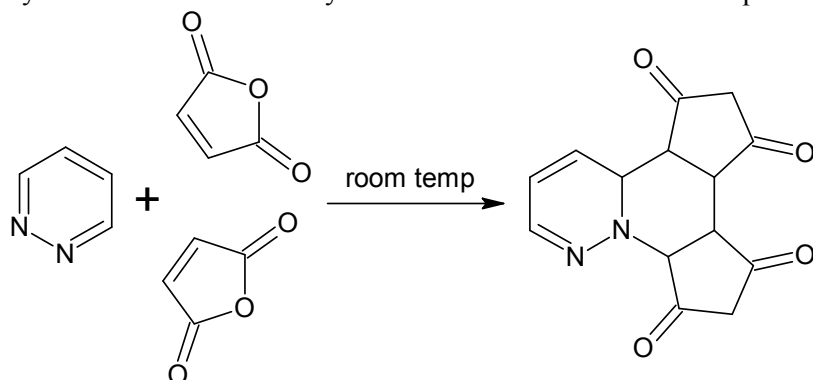

Photo chemical reaction:

Chambers & coworker's have reported that pyridazine is rearranged to pyrazine on irradiation.



Cycloaddition reaction:

Pyridazine with malice anhydride form 1:2 adduct at room temperature.



Spectral analysis

Compounds were structurally confirmed on the basis of NMR, IR and mass spectral data, IR and NMR spectroscopy were used for structural assignment. NMR data is readily available in papers treating the synthesis and chemical transformations of pyridazinones. The IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). ¹H-NMR spectra were recorded on a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO-d₆/CDCl₃ and mass spectra under electron impact conditions (EI) were recorded at 70eV ionizing voltage with a VG Prospec instrument and are presented as m/z. Mass spectrometry has been used only for determining the molecular mass, as no studies on the fragmentation mechanisms of pyrrolopyridazine derivatives have been performed to this date^{16,44,54,70}.

Infrared Spectra

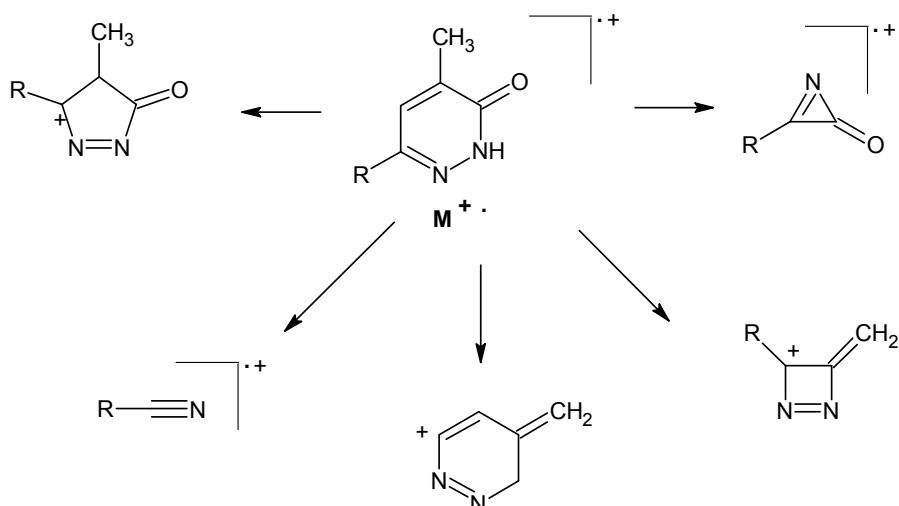
The infrared spectra of pyridazine and pyridazinones are helpful in determining the structure of the compounds. IR: (KBr, cm⁻¹): 3206 (NH), 1678 (C=O).

NMR spectra

Both ¹H and ¹³C NMR are important so as to confirm the structure of the derivatives and are also useful in regioselective synthesis of isomers. Some articles describe ¹H-NMR spectroscopic study as a method to distinguish between the intramolecular and intermolecular hydrogen bonding. A series of substituted 4-thiazolidinones in CDCl₃ were synthesized the chemical shift and C, H spin coupling constants are given. 2.45 (t, 2H, CH₂), 2.93 (t, 2H, CH₃), 7.41 (m, 3H, H-3'-H-5'), 7.74 (d, 2H, H-2'-H-6'), 10.94 (s, 1H, CONH)

Mass Spectra

The molecular ion peaks in the mass spectra of 6-phenyl-2,3,4,5-tetrahydro pyridazinone have been assigned. Various substituted pyridazinones were synthesized and characterized. In which the parent peaks usually are the base peak. Substituted pyridazinones were synthesized and possible fragmentation patterns of these compounds by electron impact mass spectrometry were reported. All compounds have shown the same base peak at m/z. 6-Phenyl-2,3,4,5-tetrahydropyridazin-3-one: MS (m/z): 174 (M⁺), 159, 147, 130, 115, 109.



Mass spectral fragmentation of 6-substituted-4- methyl pyridazinone derivatives on a jeol SX 102/DA 6000 mass spectrometer.

Spectral characterization of some substituted pyridazinones

6-phenyl 2,3,4,5-tetrahydro-3- pyridazinones:

IR: (KBr, cm-1): 1667(C=O), 3220 (NH), 1426(C=N) (DMSO-d₆, δ,ppm): 2.6 (2H,m,CH₂), 2.9(2H,m,CH₂), 7.5(3H,m,H-3',4',5'), 7.8(2H,m,H-2',6'), 2(NH,s), MS (m/z): 174 (M⁺), 159, 147, 130, 115, 109.

6-p-tolyl-2,3,4,5-tetrahydro-3pyridazinones:

IR:(KBr,cm-1):1658.8(C=O), 3217.4(NH),1510.8(C=N), 1HNMR (DMSO-d₆,δ,ppm): 2.38(s,3H,CH₃), 2.60 (m,2H,), 2.97 (t,2H,J=8.1Hz), 7.26(t,2H,J=9Hz,H3',5'), 7.63 (d,2H,H2',6'),8.79(s,NH).

6-p-anisyl2,3,4,5-tetrahydro-3-pyridazinones:

IR:(KBr,cm-1):1665.9(C=O),3208.7(NH),1613.5(C=N),1HNMR(DMSO-d₆,δ,ppm):2.59 (t,2H,J=8Hz),2.96(t,2H,J=8Hz),3.86(OCH₃),6.94(d,2H,H3',5'),7.68(m,2H,H2',6'),8.81(s,NH).

6-p-ethylphenyl2,3,4,5-tetrahydro-3-pyridazinones:

IR:(KBr,cm-1):1665.8(C=O),3427.7(NH),1595.3(C=N).1HNMR(DMSO-d₆,δ,ppm):1.25 (t,3H,J=7Hz),1.59(s),2.64(m,2H),3.01(m,2H),7.26(d,2H,J=8.1HzH3',5')7.65(d,2H,J=8.1Hz,H2',6'), 8.54(s,NH).

6-(3,4-dimethylphenyl)-2,3,4,5-tetrahydro-3-pyridazinones:

IR:(KBr,cm-1): 1666.8(C=O), 3218.0(NH), 1507.9(C=N), 1HNMR (DMSO-d₆, δ,ppm): 2.38(t,3H), 2.63(m,2H), 3.01(m,2H,), 7.44(d,H5'), 7.66(d,H6'),7.52(s,H2'), 8.69(s,NH).

*6-phenyl-2,3,4,5-tetrahydro-3-thiopyridazinones:*IR:(KBr, cm-1): 3398(NH), 1600(C=N), 1287(C=S) IR: 1HNMR (DMSO-d₆, δ,ppm): 7.49(m,3H,H3',4',5'),7.829m,2H,H2',6'),

6-p-tolyl-2,3,4,5-tetrahydro-3-thiopyridazinones:

IR:(KBr,cm-1):1289.6(C=S),1598.2(C=N),3412.6(NH).1HNMR(DMSO-d₆,δ,ppm):2.41(s,3H),3.42(s,H,ArSH), 7.28(t,2H,H3',5'), 7.74 (m,2H,H2',6').

6-p-anisyl-2,3,4,5-tetrahydro-3-thiopyridazinones:

IR:(KBr,cm-1): 1605.7(C=N), 3401.8(NH), 1259.9(C=S).1HNMR (DMSO-d₆,δ,ppm):2.764(m,2H), 2.276 (m,2H), 7.47(d,2H,H3',5'), 7.77(m,2H,H2',6').

6-p-ethylphenyl-2,3,4,5-tetrahydro-3-thiopyridazinones:

IR:(KBr,cm-1): 1285.2(C=S), 1598.2(C=N),3429.7(NH),2917.9 1HNMR (DMSO-d₆, δ,ppm):1.27 (t,3H), 2.72(m,2H), 3.80(m,2H), 7.52 (d,2H,H2',6'), 7.77(m,5H), 7.33 (d,2H,H3',5'), 3.5(m,ArSH).

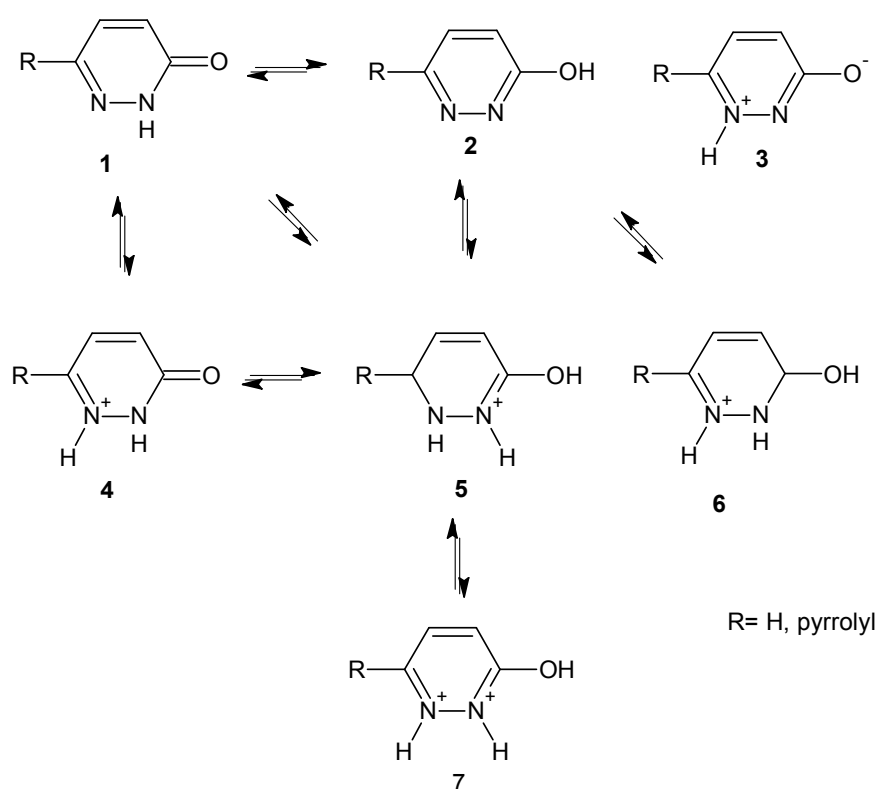
6-(3,4-dimethylphenyl)-2,3,4,5-tetrahydro-3-thiopyridazinones:

IR:(KBr,cm-1): 1605.1 (C=N), 3429.4(NH),1259.5(C=S).1HNMR(DMSO-d₆,δ,ppm): 2.32(m,2H), 2.76(m,2H), 2.55(s,3H),3.50(ArSH),7.60(s,1H,H2'),7.33(d,1H,H5'),7.28(d,1H,H6')

Tautomeric study of some pyridazinones

The pyrrolyl substituent enhances the electron densities on the pyridazine ring and has the effect of shifting the positions of the tautomeric equilibrium for **1** \rightleftharpoons **2**, which exist predominantly as the pyridazin-3-one form, towards the hydroxyl structure, compared with those of those for the parent unsubstituted systems.

Protonation of the potentially tautomeric pyridazine systems **1** \rightleftharpoons **2** can lead to three monocationic species: a common N-protonated species **5**, which would be formed from both tautomers and two other monocations **4** and **6**, which would be produced specifically from **1** and **2**, respectively. Thus, the observed pKa values for the conjugated acids of the tautomeric systems **1** \rightleftharpoons **2** would be expected to reflect not only the tautomeric equilibrium constants but also the ratio-averaged values for the ionisation of the appropriate monoprotinated conjugate acid pairs **4** \rightleftharpoons **5** and **5** \rightleftharpoons **6**. A third tautomeric (zwitterionic) form **3**, which on protonation would give rise to **4** or **6**, is also possible, but is excluded from this study on the basis of AM1 MO calculations for the three tautomeric forms, which indicate that **3** would contribute less than 0.1% to the tautomeric equilibria. Subsequent protonation of the each of the monocationic species, **4**, **5** and **6**, produces only the single dication **7**. Not unexpectedly, evidence has been provided indicating that the parent tautomeric systems **1** \rightleftharpoons **2** exist predominantly as the oxo forms and cursory studies indicating similar tautomeric equilibrium positions for substituted derivatives have also been reported.¹⁰¹



CONCLUSION

The literature reveals that pyridazinone has diverse biological potential, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. The review of synthetic methods of substituted pyridazinones and this new class of substituted pyridazinone has shown a wide spectrum of biological activities. The biological profile of these new generations of pyridazinones presents much progress with regards to the old compounds.

The anti-inflammatory, analgesic, antibacterial, antifungal activities are the most reported activities on pyridazinone compounds. Also the research in anticonvulsant, antitubercular, antimalarial, platelet inhibitory activity, anticancer and anti HIV has given positive results. The anticancer, cardiovascular and anti HIV activities are the most encouraging activities for the pharmacists. By the present scenario it can be concluded that pyridazinone have a great potential which remain to be disclosed till date.

Therefore, the synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemists in recent years. For this purpose, various compounds incorporating a 3(2H)-pyridazinone ring have been synthesized and their pharmacological activities have been reported. Recently, it has been reported that a considerable number of 3(2H)-pyridazinone derivatives bear different biological activities. Among these compounds, emorfazone (4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone) is an analgesic and anti-inflammatory compound marketed as pentoil and nandron. Rohet et al. reported that most 4,6-diphenyl-2-[3-(4-

arylpiperazin-1-yl)propyl]-3(2H)-pyridazinone derivatives, which were synthesized by inspiration from Trazodone (an antidepressant compound), were more potent than acetaminophen and noramidopyrine in a *p*-benzoquinone-induced writhing test. In addition, Santagati et al. claimed that 2-substituted 4,5-dihalo-3(2H)-pyridazinone derivatives had high analgesic activity. Vetmedin (pimobendan) 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazole-5-yl]-5-methyl-3(2H)-pyridazinone, is a benzimidazole-pyridazinone derivative, is a nonsympathomimetic, non-glycoside inotropic drug with vasodilative properties. Pimobendan exerts a stimulatory myocardial effect by a dual mechanism of action consisting of an increase in calcium sensitivity of cardiac myofilaments and inhibition of phosphodiesterase (Type III). Pimobendan exhibits vasodilating activity by inhibiting phosphodiesterase III activity. Pyridazine derivatives show various biological activities such as antimicrobial activity, enzyme inhibition, herbicides, etc. Research on the biological action of pyridazines intensified four decades, with many papers and patents on this subject are available.

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