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ADVANCES IN THE SYNTHESIS AND CHEMISTRY OF ARYLHYDRAZONALS DERIVATIVES AS KEY PLAYERS IN MEDICINAL CHEMISTRY AND BIOLOGICAL SCIENCE

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Abstract

This review analyses the chemical characteristics of arylhydrazonals in depth, with a particular emphasis on their critical function in heterocyclic synthesis. Arylhydrazonals are bidentate electrophilic substances that exhibit tridentate properties under certain functional group configurations. This review thoroughly examines the production processes and reactivity of these chemicals. The importance of arylhydrazonals in a variety of fields such as pharmaceuticals, agriculture, materials research, and catalysis are emphasized. Arylhydrazones emerge as essential intermediates in heterocyclic synthesis, exhibiting versatility in cyclization reactions as well as susceptibility to both nucleophilic and electrophilic processes. The review gets into the technical intricacies of arylhydrazonal preparation methods, with a particular emphasis on their synthesis from aldehydes, ketones, esters, enaminones, hydrazones, and hydroxymethyl derivatives. The adaptability of arylhydrazonals in nucleophilic addition processes is enhanced, allowing for the rapid synthesis of complex molecular structures. Because of their electrophilic reactivity, arylhydrazonals are useful in medicines, materials science, and catalysis. Furthermore, the review goes into arylhydrazonal potential for the synthesis of five and six-membered ring heterocycles such as 1,2,3-triazoles, pyrazoles, and pyridazines. The malleability of arylhydrazonals as intermediates finds a compromise between simplicity and complexity, opening the door to a broad range of heterocyclic compounds. Finally, thorough investigation of the chemistry of arylhydrazonals establishes them as flexible building blocks in the synthesis of varied heterocyclic structures, contributing to advances in a variety of scientific and industrial sectors.

Keywords: Arylhydrazonals; Synthesis; Biological activity, hydrazones, enaminones.

Introduction

Arylhydrazonals represent a fascinating class of compounds that has garnered significant attention in the realm of organic chemistry. These compounds are characterized by the presence of aryl groups on both ends of a hydrazone moiety, creating a distinctive structural arrangement. The hydrazone functional group, featuring a nitrogen-nitrogen double bond, imparts unique properties and reactivity to Arylhydrazonals, making them versatile building blocks in the synthesis of various organic molecules [1].

The synthesis and exploration of Arylhydrazonals have been particularly intriguing due to their potential applications in medicinal chemistry, material science, and catalysis. Researchers have been keenly investigating their diverse reactivity, seeking to harness their capabilities for the creation of novel compounds with valuable properties. Additionally, the incorporation of aryl groups adds an extra layer of complexity and tunability to these compounds, enhancing their utility in a range of synthetic methodologies [2]. In medicinal chemistry, arylhydrazonals have emerged as promising candidates for drug development, owing to their potential pharmacological activities. Researchers have explored their antimicrobial, anticancer, and anti-inflammatory properties, among others, opening avenues for the design and synthesis of novel therapeutic agents. Additionally, the ability of aryl hydrazones to undergo facile transformations makes them valuable tools for the construction of molecular architectures with specific biological activities [3]. Furthermore, the significance of aryl hydrazonals extends to materials science, where their electronic and optical properties have been harnessed for applications in sensors, organic electronics, and photoresponsive materials. The tunability of their structures allows for the fine-tuning of material properties, enabling the development of advanced materials with tailored functionalities.

Herein, we aim to provide an overview of Aryl hydrazonals, touching upon their structural characteristics, synthetic strategies, and the manifold applications that make them a subject of continuous interest in contemporary organic chemistry. As we delve deeper into the exploration of Aryl hydrazonals, their potential to contribute to the advancement of various scientific disciplines becomes increasingly apparent [4].

1. Structural investigations of arylhydrazonals

There are two main categories of arylhydrazonals based on their binding capabilities. Firstly, arylhydrazonals **1** are classified as bidentate electrophilic compounds when the substituted groups R=aryl. Secondly, arylhydrazonals **2a-d** exhibit tridentate behavior when the substituent X= represents functional groups such as CN, CHO, COR, or ester, as illustrated in **Figure 1**. These functional groups are strategically positioned to serve as precursors for unique five and six-membered heterocycles [1]. This review focuses on detailing the synthesis pathways of these compounds and elucidating their reactivity. Additionally, the reactivity of **2a-d** towards nitrogen nucleophiles is documented [4]

1, R= aryl **2a-d**

a, X= COR; **b**, X= CN
c, X= CO_2Et; **d**, X= CHO

Figure 1. Structures of compounds incorporated arylhydrazonal moiety.

While 3-Oxo-2-arylhydrazonals exhibit the potential to exist in multiple tautomeric forms denoted as **A-D**. It is postulated that the preeminent tautomeric state is the anti-hydrazone form **A**, with form **B** representing the keto tautomer and forms **C** and **D** representing potential enol forms, as shown in **Figure 2**.

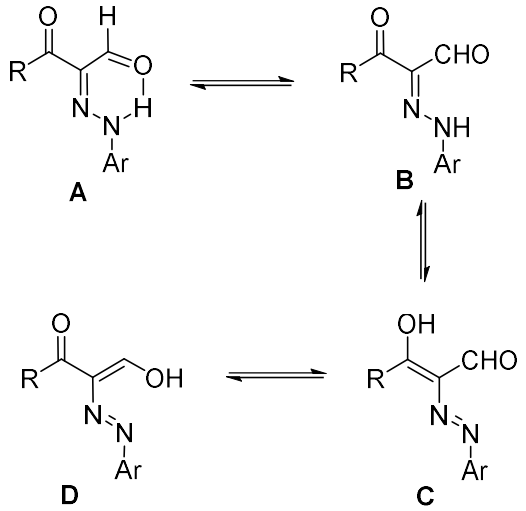


Figure 2. Possible tautomeric structures of arylhydrazonals

However, when X-ray crystallographic analysis was conducted, it was found that these substances do not engage in intramolecular hydrogen bonding, as initially assumed. Instead, it was observed that an equilibrium exists between two tautomeric forms, arylhydrazonals **A** and **E**, in dimethyl sulfoxide (DMSO). The composition of this equilibrium mixture is influenced by the nature of the substituent, **Figure 3** [5].

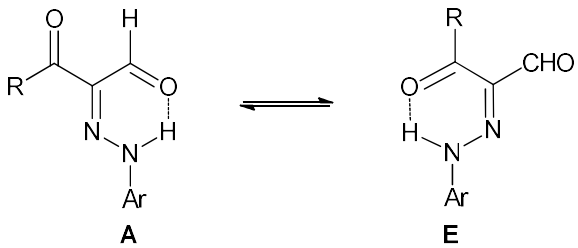


Figure 3. Tautomeric structures of arylhydrazonals

2. Heterocyclic Compounds and Arylhydrazonals: Driving Innovation and Molecular Design

Heterocyclic compounds, featuring non-carbon atoms within at least one ring, are pivotal across disciplines due to their diverse structures and reactivity. They've transformed pharmaceuticals by providing intricate frameworks for effective drug discovery, enhancing therapeutic impact in antibiotics, antivirals, and anticancer agents. In agriculture, they bolster crop protection and yield [6]. Heterocycles drive tailored materials, propelling organic electronics and photonics, seen in advanced displays and efficient lighting. Their catalytic prowess drives chemical manufacturing, synthesizing fuels, plastics, and pharmaceutical building blocks. These compounds influence sensory experiences through distinct atomic arrangements in flavors and fragrances, while their integration in polymers tailor's mechanical, thermal, and chemical properties [7].

A specific subset of heterocyclic compounds, Arylhydrazonals, has become invaluable in the synthesis of heterocyclic compounds. Their versatility in cyclization procedures, combined with their propensity for nucleophilic and electrophilic reactions, makes them indispensable for designing complex heterocyclic compounds with specialized features in a variety of scientific and industrial fields [8]. Arylhydrazonals, a fascinating and versatile class of compounds, occupy a crucial role in heterocyclic synthesis by virtue of their diverse applications and the multitude of opportunities they offer for molecular manipulation. These compounds serve as versatile building blocks for the creation of various heterocyclic structures, making them pivotal in the realm of chemical synthesis. One of the primary functions of arylhydrazones lies in their involvement in nucleophilic addition reactions. This property allows them to act as precursors for forming a wide range of heterocyclic compounds. By carefully selecting the appropriate reagents and reaction conditions, arylhydrazonals can undergo cyclization reactions that result in the formation of heterocyclic rings of varying sizes, including five- to seven-membered rings and even larger structures [9]. This unique capability empowers chemists to diversify their synthetic toolkit and efficiently construct complex molecular architectures. Moreover, arylhydrazones exhibit great flexibility in cyclization reactions, enabling the rapid and efficient assembly of intricate molecular structures with tailored functionalities. This adaptability is a boon to synthetic chemists, as it provides a means to create a wide array of heterocyclic compounds efficiently, thereby fostering innovation in the field. Additionally, arylhydrazones are reactive in electrophilic reactions, which facilitates the controlled introduction of functional groups and substituents at specific positions within the heterocyclic framework. This feature is particularly valuable for designing molecules with desired electronic properties and enhancing bioactivity, extending the applicability of arylhydrazones across a broad spectrum of fields [10]. The versatility of arylhydrazones transcends the laboratory setting, finding application in pharmaceuticals, materials science, and catalysis. Their unique ability to fine-tune heterocyclic structures equips researchers with the means to create compounds with precisely tailored properties. This adaptability drives innovation and advancements in industries critical to human progress [11]. As intermediates, arylhydrazones play a pivotal role in bridging the gap between simple starting materials and complex heterocyclic targets. Their adaptability in both nucleophilic and electrophilic processes empowers synthetic

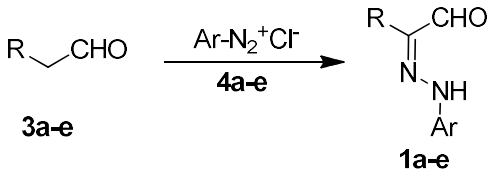
chemists to access a broad spectrum of heterocyclic compounds, facilitating molecular design and fostering innovation [9]. In sum, the versatility and adaptability of arylhydrazones are indispensable assets in advancing the field of heterocyclic synthesis and molecular design.

3. Synthesis of arylhydrazonals

The synthesis of arylhydrazonals involves the condensation reaction between an aryl aldehyde and a hydrazine derivative. This reaction is typically carried out in the presence of a suitable catalyst or under acidic conditions. The arylhydrazonals product is formed along with the liberation of water as a byproduct. To purify the product, common methods include filtration and column chromatography. Arylhydrazonals find utility in various fields including medicinal chemistry and materials science due to their diverse chemical and biological properties [12].

3.1. Synthesis from aldehydes, ketones and esters

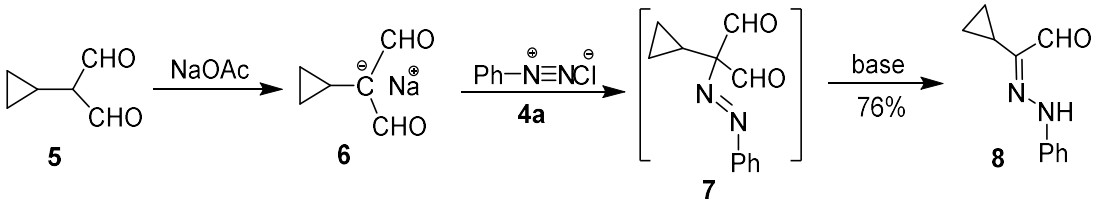
Arylhydrazonals **1a-e** were obtained in moderate yields *via* coupling of aldehydes **3a-e** containing active methylene moiety with arenediazonium salts **4a-e** (**Scheme 1**) [13, 14].



1a: R= 1-CH_3-3,5-$(NO_2)_2$-1*H*-pyrazol-4-yl, Ar= C_6H_5 (73%)
b: R= 4-ClC_6H_4CO, Ar= 2-$MeO_2CC_6H_4$ (80%)
c: R= 2,4,6-$(NO_2)_3$-C_6H_2, Ar= C_6H_5 (79%)
d: R= C_6H_5, Ar= 2-CO_2H-C_6H_4 (75%)
e: R= CHO, Ar= 4-CH_3-C_6H_4 (42%)

Scheme 1. Synthesis of arylhydrazonals.

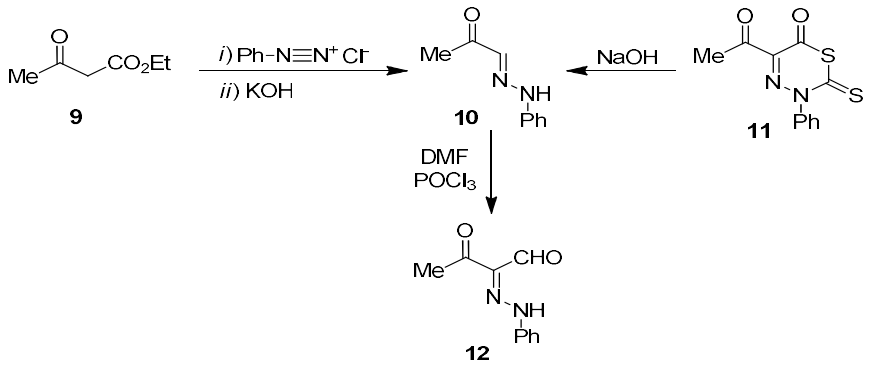
In a similar manner, diazocoupling of 2-cyclopropylmalonaldehyde sodium salt **6** [obtained from 2-cyclopropylmalonaldehyde (**5**)] with phenyl diazonium chloride **4a** gave 2-cyclopropyl-2-(2-phenylhydrazono) acetaldehyde **8** *via* the formation of intermediate **7**, as illustrated in **Scheme 2** [15].



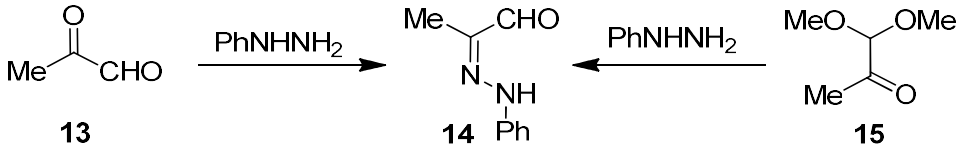
Scheme 2. Synthesis of cyclopropyl derivative.

Hydrazone **10** was obtained from either the reaction of ethyl acetoacetate **9** with phenyldiazonium chloride **4a** followed by hydrolysis and decarboxylation or by treatment of **11** with NaOH. Formylation of hydrazone **10** yielded the respective arylhydrazonal **12** under

Vilsmeier-Haack conditions (**Scheme 3**) [16]. Treatment of pyruvaldehyde **13** and its acetal **15** with phenylhydrazine produced the phenyl hydrazonal **14**, **Scheme 4** [14].

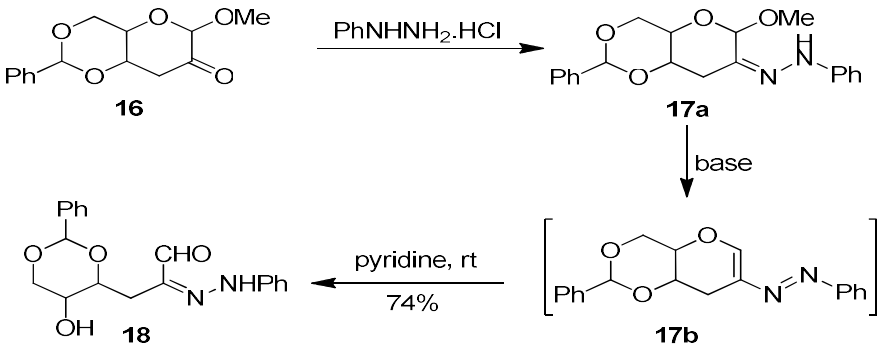


Scheme 3. Synthesis of 3-oxo-2-(2-phenylhydrazono)butanal.



Scheme 4. Synthesis of 2-(2-phenylhydrazono)propanal.

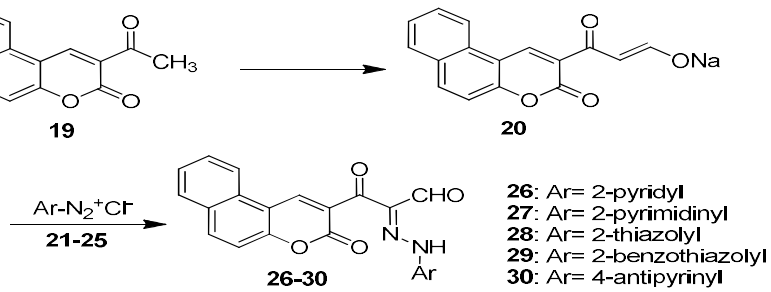
In a similar fashion, treatment of glycopyranosidulose **16** with phenyl hydrazine hydrochloride gave the phenyl hydrazone **17a**. Base-catalyzed elimination of methanol from **17a** gave a rise to the intermediate enolic ether **17b** which readily followed hydrolysis in pyridine at room temperature to give hexosulose phenyl hydrazone **18, Scheme 5** [17].



Scheme 5. Synthesis of 3-(5-hydroxy-2-phenyl-1,3-dioxan-4-yl)-2-(2-phenyl-hydrazono)propanal.

2-(3-Hydroxyacryloyl)-3*H*-benzo[*f*]chromen-3-one sodium salt **20** was obtained from reaction of 2-acetyl-3*H*-benzo[*f*]chromen-3-one **19** with ethylformate in dry ether containing sodium methoxide [18]. Heteroaryl hydrazonals **26-30** were obtained from reaction of **20** with various diazotized heterocyclic amines **21-25** through diazocoupling reaction in ethanol containing

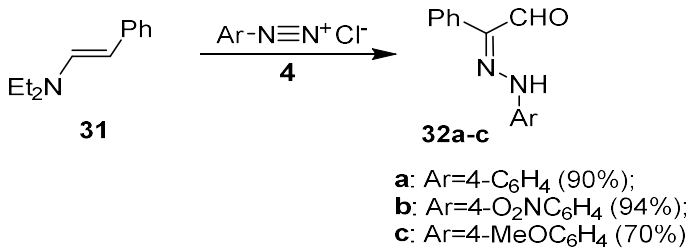
sodium acetate. Arylhydrazonals **28** and **29** were prepared using sulfuric acid in diazocoupling step, while **27** and **30** were prepared using hydrochloric acid solution, **Scheme 6** [19].



Scheme 6. Synthesis of arylhydrazonals of benzo[*f*]chromen-3-one.

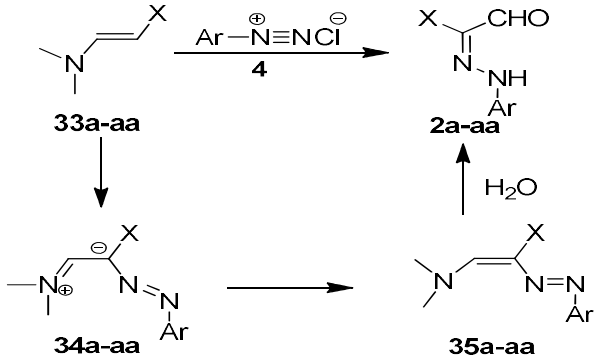
3.2. Synthesis from enaminones

The most extensively utilized route for the synthesis of 2-arylhydrazonals involves coupling of enamines with aromatic diazonium salts. For example, the synthesis of arylhydrazonals **32** *via* reaction of enamine **31** with aromatic diazonium salts **4**, as illustrated in **Scheme 7** [20].



Scheme 7. Synthesis of arylhydrazonals **32a-c**.

The synthesis of arylhydrazonals **2a-aa** was achieved by coupling of enamines **33a-aa** with aryldiazonium salt **4**. The mechanistic pathway is thought to involve coupling of the enamine **33a-aa** with diazonium ion to form the zwitter ionic intermediate **34a-aa**, which underwent hydrolysis to produce the arylhydrazonal **2a-aa**, as illustrated in **Scheme 8** and **Table 1** [23].



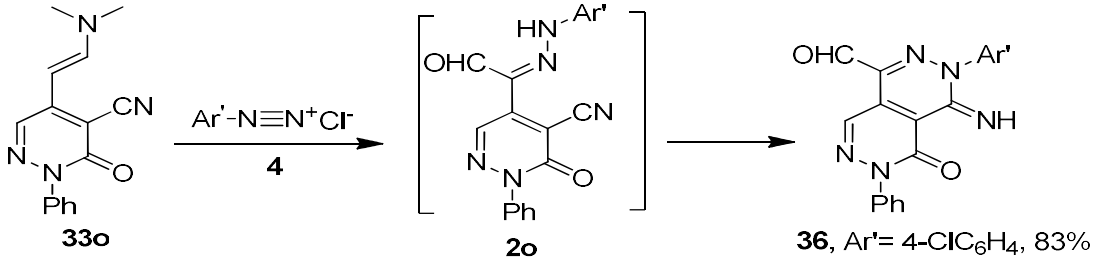
Scheme 8. Preparation of arylhydrazonals from the respective enamines.

Table 1. Substituents of compound **2a-aa** with their corresponding yields in percentage [21, 22].

Compound 2	X	Ar	Yield (%)
a	CHO	4-ClC_6H_4	70
b	CO_2Et	4-ClC_6H_4	62
c	C_6H_5CO	Ph	73-78
		4-NCC_6H_4	62
		2-NCC_6H_4	80
d	4-ClC_6H_4CO	Ph	74
		4-ClC_6H_4	70
e	4-$O_2NC_6H_4CO$	Ph	80-82
		4-BrC_6H_4	76
f	4-BrC_6H_4CO	Ph	84
g	4-MeC_6H_4CO	4-$MeOC_6H_4$	70
h	4-$MeOC_6H_4CO$	Ph	70
i	4-$O_2NC_6H_4CO$	Ph	80
		4-ClC_6H_4	70
		4-BrC_6H_4	60
		4-NCC_6H_4	70
j	CN	4-$MeOC_6H_4$	73
		2-$CO_2MeC_6H_4$	68
		4-ClC_6H_4	78
k	Me	4-n-$PrOC_6H_4$	20
l	Et	Ph	--
m	CO_2Et	Ph	70
n	COCH=CHPh	Ph	80
o	4-cyano-3-oxo-2-phenyl-2,3-dihydropyridazin-5-yl	4-ClC_6H_4	Intermediate
p	4-CO-2-furyl	Ph	86
	4-CO-2-thienyl	2-$MeOC_6H_4$	63
	4-CO-2-pyroyl		
q	4-CO-3-methoxy-5,6-diphenylpyridazine	Ph	76
r	3-quinoxalin-2(1*H*)-one	Ph	--
s	3-CO-4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline	4-$O_2NC_6H_4$	75
t	CO-CH_2-1,3-dioxoisoindolin-2-yl	Ph	73
u	1-(4-ClC_6H_4)-3-CO-4-CN-1*H*-pyrazole	4-ClC_6H_4	82

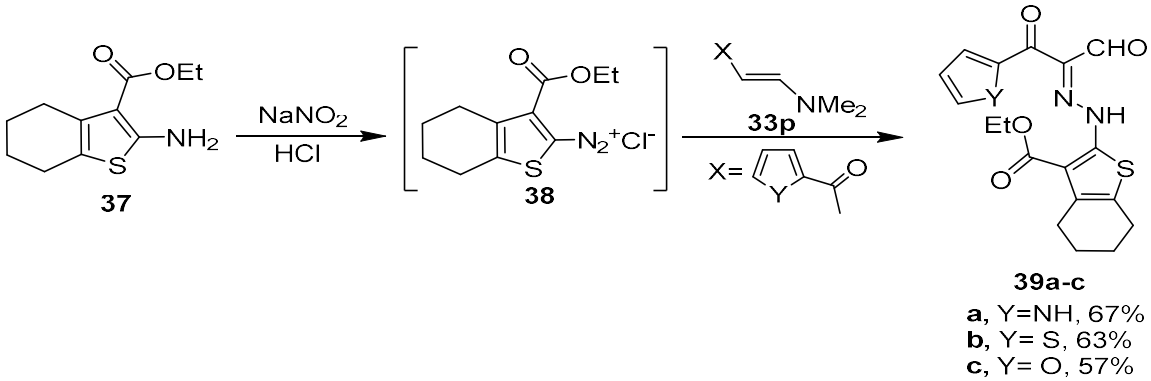
v	5-CO-4,6-dimethoxybenzofuran	4-$O_2NC_6H_4$	75
w	3-CO-2-oxo-2*H*-chromene	4-$O_2NC_6H_4$ Ph	45 60
x	3-CN-2-oxo-2*H*-chromen-3-yl	Ph	71
y	2-CO-3-CH_3-6-phenylimidazo[2,1-*b*]thiazole	Ph	77
z	1-CH_3-2-oxo-3-CN-1,2-dihydropyridin-4-yl	Ph	59
aa	2-(4-chlorophenyl)-5-CH=CH-2*H*-tetrazole	4-ClC_6H_4	52

In support of this proposal, Elnagdi *et al*, successfully isolated the enamine hydrazone intermediate **35** (X = CN and Ar = 2-NCC_6H_4), which converted to product **2j** when treated with water (X= CN) [24]. However, the enamine **33o** reacted with aryldiazonium chloride **4** to afford **2o** which readily cyclized to produce the structurally complex heterocycle **36**, **Scheme 9** [25].



Scheme 9. Synthesis of 3,4,5,6-tetrahydropyridazino[4,5-*d*]pyridazine.

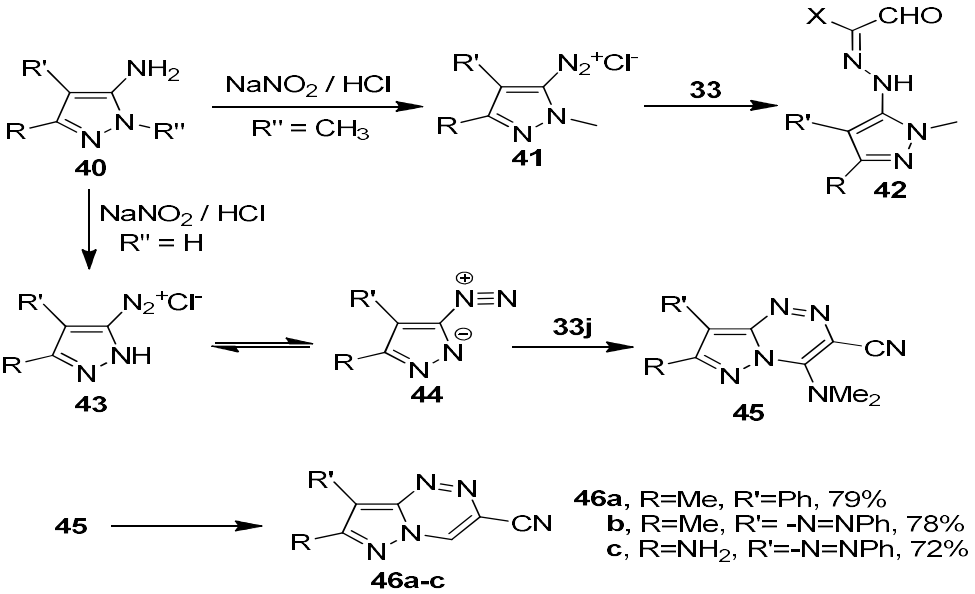
Compound **37** underwent diazotation, leading to the generation of heteroaromatic diazonium salts **38** which underwent coupling reaction with enamines **33p** to yield heteroaromatic hydrazonals **39a-c,** as showed in **Scheme 10** [26].



Scheme 10. Synthesis of arylhydrazonal of tetrahydrobenzo[*b*]thiophene.

In addition, diazocoupling of pyrazole diazonium chloride **41** with enamine **33** afforded arylhydrazonals **42** [27]. However, attempts to couple diazonium salt **43** with enaminonitrile **33j**

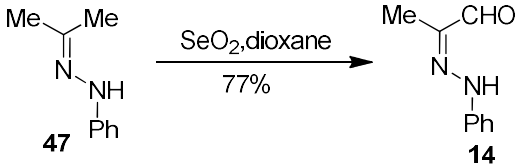
resulted in the formation of the pyrazolo[5,7-*c*]-1,2,4-triazine **45** [28]. In this reaction, the pyrazolyl intermediate **44** is added to **33j** forming cycloadduct **45**, which then loses dimethylamine to generate **46, Scheme 11**.



Scheme 11. Synthesis of pyrazolo[5,1-*c*][1,2,4]triazines.

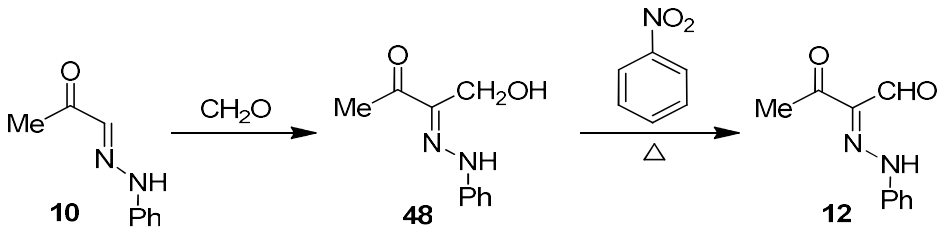
3.3. Synthesis from hydrazones

Arylhydrazone methyl ketones **47** were readily oxidized to form the respective aldehydes **14** upon treatment with selenium dioxide in dioxane, **Scheme 12** [20].



Scheme 12. Synthesis of 2-(2-phenylhydrazono)propanal.

The reaction of **10** with formaldehyde yielded the respective hydroxymethyl hydrazone **48** which on oxidation by refluxing in nitrobenzene produced the 3-oxo-2-(2-phenylhydrazono)butanal **12**, **Scheme 13** [29].

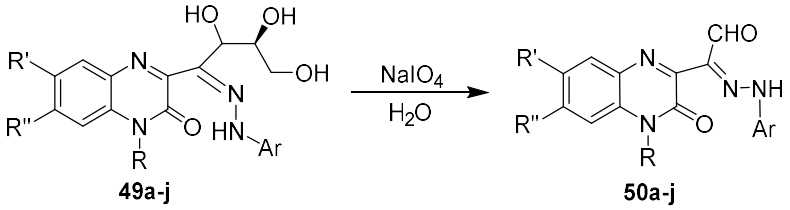


Scheme 13. Synthesis of 3-oxo-2-(2-phenylhydrazono) butanal.

3.4. Synthesis from hydroxymethyl derivatives

Periodate oxidation of **49a-j**, either in alcoholic solutions or as water suspensions, afforded the respective 3-[1-(arylhydrazono)glyoxal-1-yl]-2-quinoxalinones **50a-j**. Higher yields were

obtained when the oxidation were performed under microwave irradiation conditions, **Scheme 14** and **Table 2** [14, 15].



Scheme 14. Synthesis of 3,4-dihydroquinoxalinone arylhydrazonals.

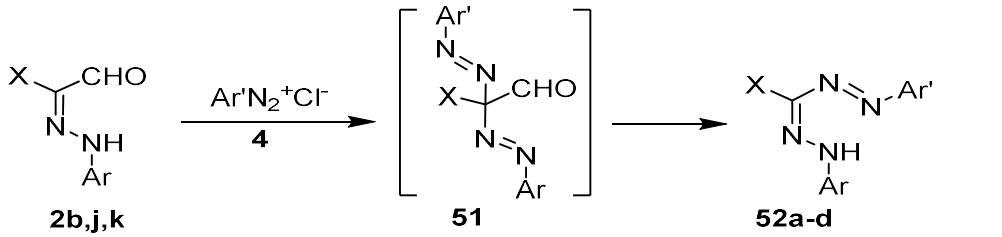
Table 2. Substituents of compound **50a-j** with their corresponding yields in percentage [20, 21].

Compound 50	R, R', R"	Ar	Yield (%)
a	H, H, H	C_6H_5	92
b	H, H, H	2,4,6-$(Cl)_3C_6H_2$	79
c	H, H, H	2-naphthyl	96
d	H, H, H	4-FC_6H_4	87
e	H, H, H	4-MeC_6H_4	85
f	H, H, H	2-MeC_6H_4	78
g	H, H, H	4-ClC_6H_4	89
h	H, Me, Me	C_6H_5	85
i	H, Cl, H	4-BrC_6H_4	61
j	Me, H, H	C_6H_5	90

4. Reactivity of Arylhydrazonals

4.1. Formation of formazans

The C-2 position of arylhydrazonals **2b,j,k** is quite nucleophilic and, as a result, these substances converted readily with aromatic diazonium salts into amidrazones **52a-d**. It was believed that initially formed adducts **51** underwent Japp-Klingmann-type cleavage to **52a-d**, **Scheme 15** [30, 31].

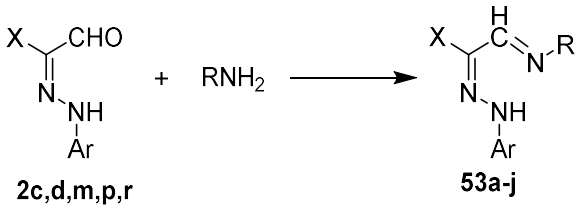


52a, Ar= 4-ClC_6H_4, Ar'= 4-ClC_6H_4, X=CO_2Et
b, Ar= 4-ClC_6H_4, Ar'= 4-ClC_6H_4, X= CN
c, Ar= 4-ClC_6H_4, Ar'= 4-BrC_6H_4, X= CN
d, Ar= C_6H_5, Ar'= 4-MeC_6H_4, X= Me

Scheme 15. Synthesis of 3-substituted-1,5-diarylformazan.

4.2. Condensation reactions

Arylhydrazonals **2c,d,m,p,r** reacted with amines, hydrazines and hydroxylamine to give the corresponding condensation products **53a-j**, **Scheme 16** and **Table 3**.



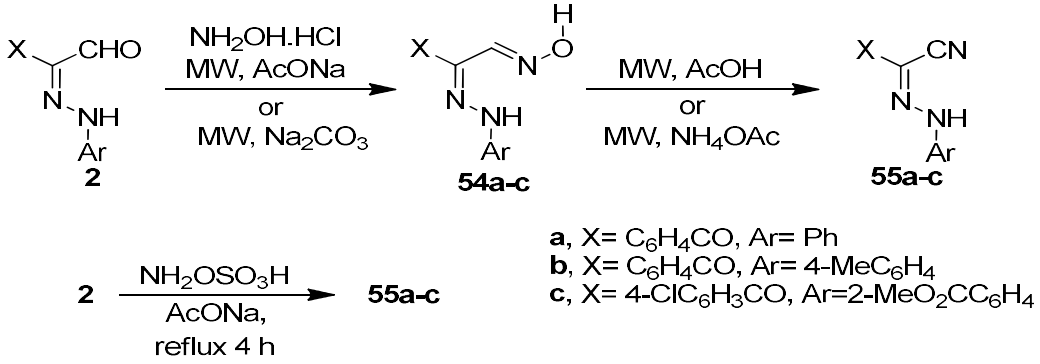
2c,d,m,p,r **53a-j**

Scheme 16. Synthesis of hydrazone derivatives.

Table 3. Substituents of hydrazone derivatives **53a-j** with their corresponding yields in percentage [21, 22].

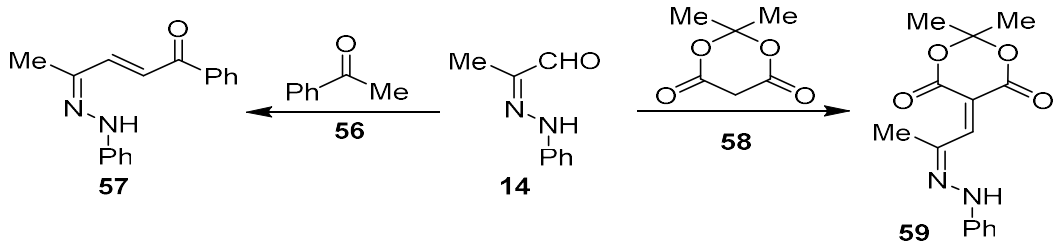
Compound 53	X	Ar	R	Yield (%), Refs.
a	COEt	Ph	PhNH	70
b	C_6H_5CO	Ph	OH or OSO_3H	80-90
c	COMe	Ph	PhNH	69
d	Me	Ph	2,6-$(CH_3)_2C_6H_3$	82
e	CO-2-furyl	2-NCC_6H_4	Ethyl 4,5,6,7-tetrahydrobenzo[*b*] thiophen-2-yl-3-carboxylate	95
f	quinoxalin-3-yl-2(1*H*)-one	4-FC_6H_4 4-BrC_6H_4	OH BnNH	89 90
g	6-Cl-quinoxalin-3-yl-2(1*H*)-one	4-IC_6H_4	C_6H_4NH	--
h	*N*-CH_3-quinoxalin-3-yl-2(1*H*)-one	Ph	OH	70
i	CO-*n*-Pr	Ph	3-CN-4,5-dimethyl-1*H*-pyrrol-2-yl	50
j	CO-2-thienyl	Ph 2-NCC_6H_4	NH_2 OH	85 81

As mentioned above in **Scheme 16**, the reaction of arylhydrazonal **2c,d** with hydroxylamine hydrochloride in the presence of sodium acetate or sodium carbonate, under microwave irradiation and conventional heating conditions, afforded oxime **54**, which in the presence of ammonium acetate or AcOH under microwave irradiation yielded 3-oxoalkanonitrile **55**. Also, hydrazonoyl cyanides **55a-c** were directly formed by reaction of **2c,d** with hydroxylamine *o*-sulphonic acid, **Scheme 17** [32, 33].



Scheme 17. Synthesis of hydrazonoyl cyanides.

(Z)-2-(2-phenylhydrazineylidene)propanal **14** underwent facile condensation reactions with active acetophenone **56** and Meldrum's acid **58** to yield the condensation adducts **57** and **59**, respectively, **Scheme 18** [34].

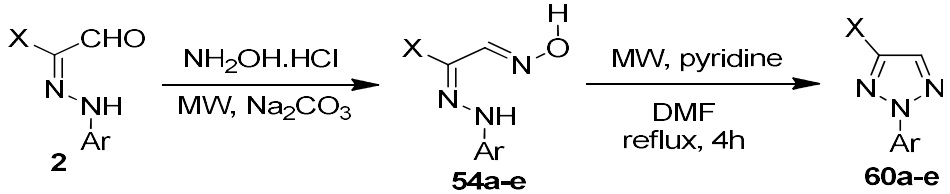


Scheme 18. Reactions of hydrazonopropanal with active methylenes.

4.3. Synthesis of five membered ring systems

4.3.1. Synthesis of 1,2,3-triazoles

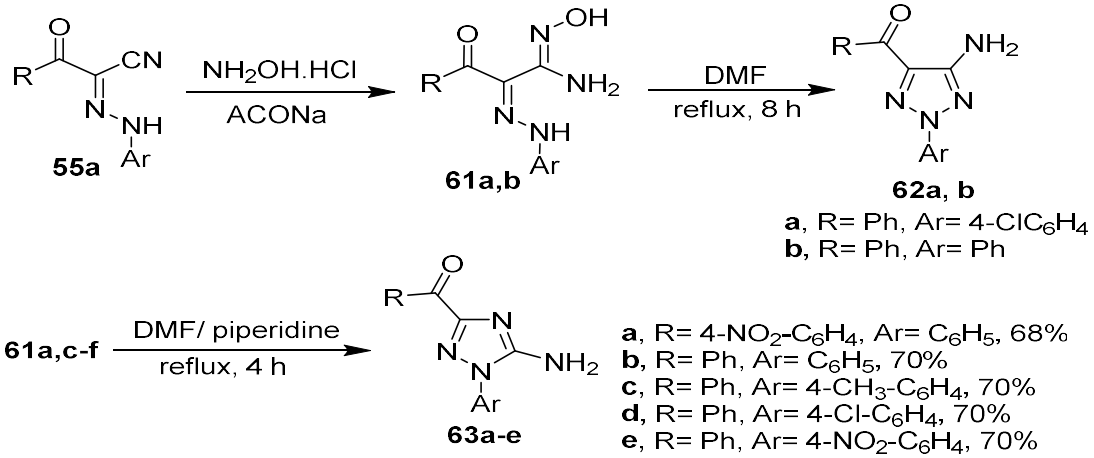
Refluxing of oxime derivative **54a-e** in DMF or pyridine under microwave irradiation afforded the corresponding triazole **60a-e**, **Scheme 19** [35].



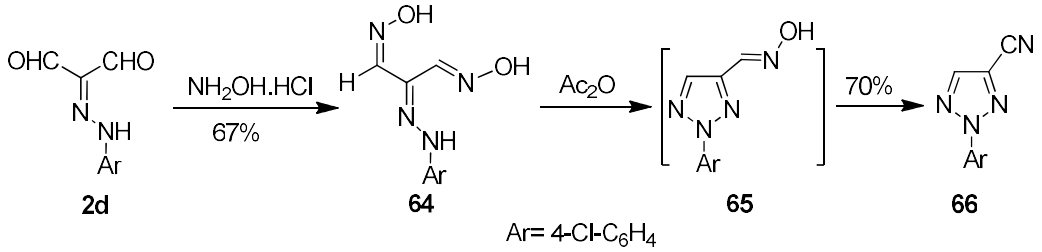
a, X= 2-acetylfuran, Ar=2-MeO$_2$CC$_6$H$_4$; **b**, X= 4-ClC$_6$H$_4$CO, Ar= 2-MeO$_2$CC$_6$H$_4$; **c**, X=EtO, Ar= 4-ClC$_6$H$_4$; **d**, X= C$_6$H$_4$CO, Ar= C$_6$H$_5$; **e**, X= C$_6$H$_4$CO, Ar= 4-MeC$_6$H$_4$

Scheme 19. Synthesis of 4-substituted-2-aryl-2*H*-1,2,3-triazoles.

The reaction of arylhydrazononitriles **55a** with hydroxylamine afforded amidoxime **61** which underwent intramolecular cyclization when treated with pipridine in refluxing DMF to furnish 1,2,3-triazoles **62a**, **b**. Also, amidoxime **61a,c-f** cyclized to generate 1,2,4-triazoles **63a-e** upon treatment with pipridine in DMF, **Scheme 20** [36].



Scheme 20. Synthesis of aminotriazoles.

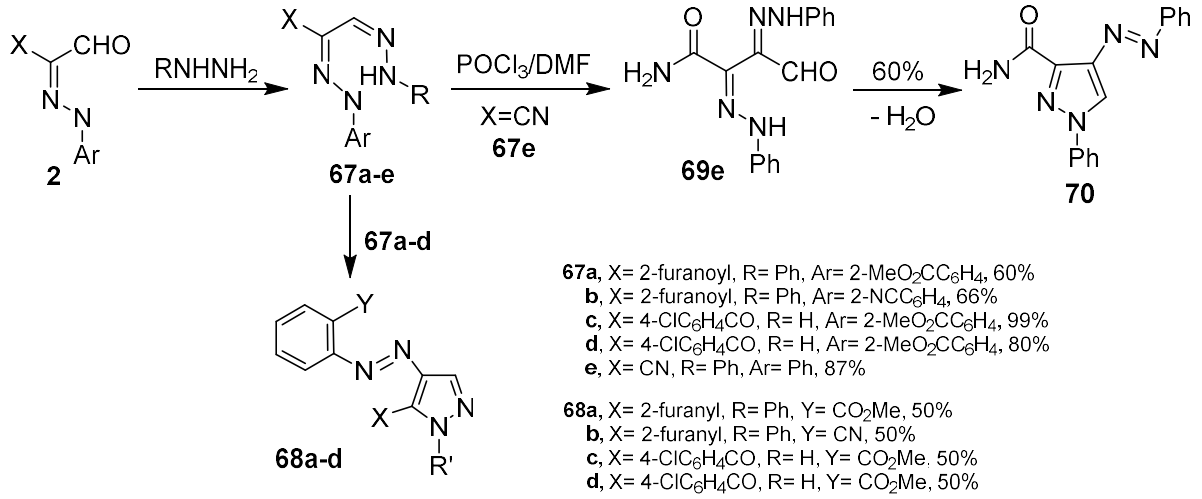


Scheme 21. Synthesis of 2-aryl-2*H*-4-cyano-1,2,3-triazole.

Treatment of **2d** with excess of hydroxylamine hydrochloride in ethanolic sodium acetate yielded the respective dioxime **64** in 67% yield. Treatment of dioxime **64** with acetic anhydride afforded 1,2,3-triazole-4-carbonitrile **66** in 70% yield, **Scheme 21** [15, 37].

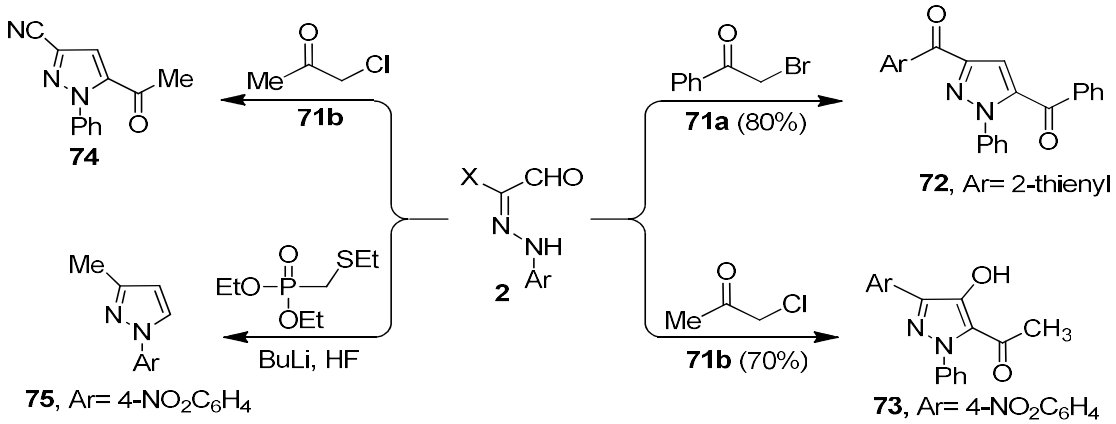
4.3.2. Synthesis of pyrazoles

Reactions of arylhydrazonals with bidentate reagents have been extensively utilized in the synthesis of five and six membered ring heterocycles. One example is the reactions of arylhydrazonal **2** with hydrazine hydrate and phenyl hydrazine afforded the bishydrazones **67a–d** under both conventional heating and microwave irradiation conditions. Treatment of **67a–d** with pyridine using conventional heating yielded pyrazoles **68a-d** [38], as sole products. However, the reaction of arylhydrazonal **2** (X= CN, Ar= Ph) with phenyl hydrazine, which gave phenyl hydrazone **67e** in 87% yield. The products of these reactions were readily formylated to give the corresponding aldehydes **69** that underwent intramolecular cyclization to produce pyrazoles **70**, **Scheme 22** [39].



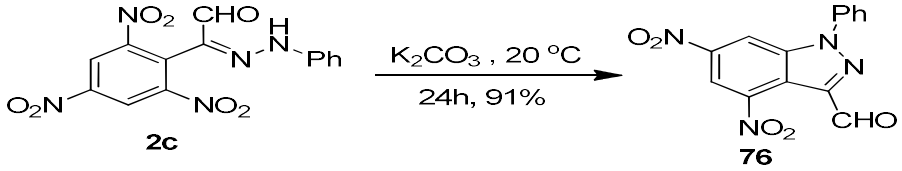
Scheme 22. Synthesis of arylazopyrazoles.

Arylhydrazonals **2** also attack phenacyl bromide **71a** and chloroacetone **71b** to produce pyrazoles **72–74** [14], formed most likely *via* alkylation of **2** and subsequent cyclization. The anion, formed by treatment of diethyl ethylthiomethylphosphonate with *n*-butyllithium in tetrahydrofuran at -78°C, underwent reaction with arylhydrazone **2** at 60°C to directly generate the cyclized product **75** (**Scheme 23**) [40].



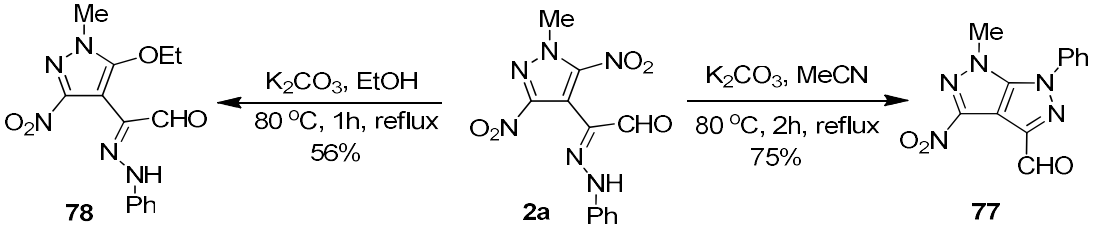
Scheme 23. Synthesis of substituted pyrazoles.

The arylhydrazonal **2c** underwent intramolecular substitution of an ortho-nitro group when treated with base to produce *N*-arylindazole **76** (**Scheme 24**) [15].



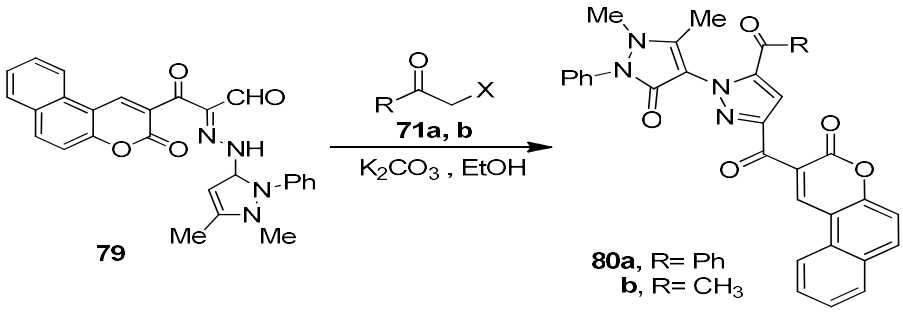
Scheme 24. Synthesis of 3-formyl-4,6-dinitro-1-phenyl-1*H*-indazole.

Pyrazolo[3,4-*c*]pyrazole **77** was obtained from the reaction of hydrazone **2a** with K_2CO_3 in acetonitrile. In contrast, heating of hydrazone **2a** with K_2CO_3 in ethanol resulted in replacement of the 5-nitro group by an ethoxy function to give **78, Scheme 25** [41, 42]



Scheme 25. Synthesis of pyrazole and its fused derivative.

The reaction of **79** with phenacylbromide **71a** and chloroacetone **71b** in ethanol containing K_2CO_3 at room temperature afforded the corresponding pyrazole derivatives **80a** and **80b**, respectively, **Scheme 26** [43, 44]

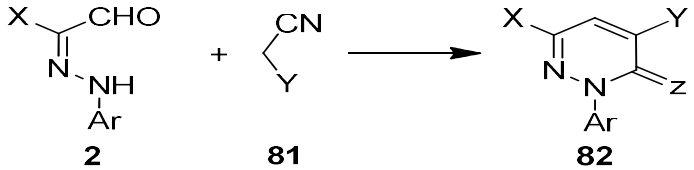


Scheme 26. Synthesis of binary pyrazole system.

4.4. Synthesis of six membered ring systems

4.4.1. Synthesis of pyridazines

Active methylene reagents **81** readily condensed with arylhydrazonals **2** to afford condensation product that typically underwent cyclization to generate pyridazines **82a-o**, as illustrated in **Scheme 27** and **Table 4**. Moreover, the treatment of **2j** with hippuric acid in refluxing acetic anhydride, pyradazinone **84** was formed *via* the formation of an intermediate **83, Scheme 28** [45]. In addition, arylhydrazonal **2pi** also reacts with the benzotriazolylacetonitrile derivative **85a** and ethyl benzotriazolylacetate **85b** to form the respective benzotriazolylpyridazines **86a**, **b, Scheme 29** [46]. Also, the reaction of 3-oxo-2-arylhydrazonal **2** and some active methylene compounds, such as *p*-nitrophenylacetic acid **87a**, *o*-nitrophenyacetic acid **87b** and cyanoacetic acid **87c** in acetic anhydride, the corresponding pyradazin-3-one derivatives **88a-l** were formed as sole isolable products in an excellent yield. The structure of the pyradazin-3-one **88** was established based on their spectroscopic analysis and X-ray crystallographic analysis, **Scheme 30** [47].

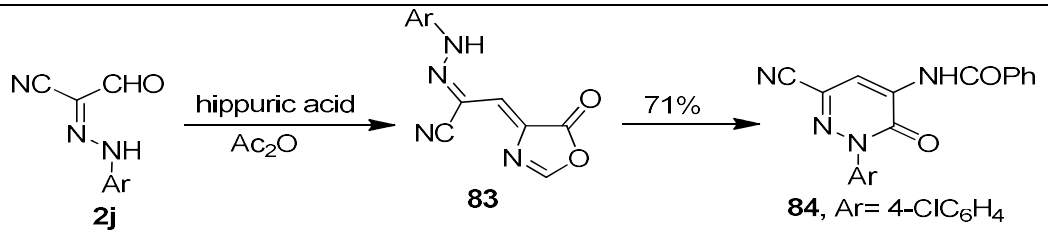


Scheme 27. Synthesis of 1,6-dihydropyridazines.

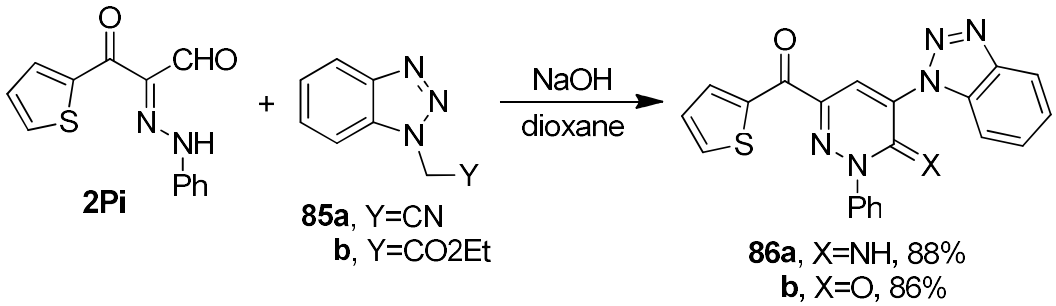
Table 4. Substituents of 1,6-dihydropyridazines derivatives **82a-o** with their corresponding yields in percentage [21, 22].

Compound 82	X	Ar	Y	Z	Yield (%), Refs.
a	Me	C_6H_5	CO_2Me	O	89
b	CO-thien-2-yl	C_6H_5	CO_2Et	O	--
c	4-ClC_6H_4CO	C_6H_5	CO_2Et	O	--
		4-C_6H_4Me	CO_2Et	O	--
		4-C_6H_4OMe	CO_2Et	O	--
		2,3-$(CH_3)2$-C_6H_3	CO_2Et	O	--
		C_6H_5	$CONH_2$	O	--
d	C_6H_5CO	2-$MeO_2CC_6H_4$	CN	O	70
		4-$O_2NC_6H_4$	CN	NH	69
		C_6H_5	$CONHNH_2$	O	98
		C_6H_5	$CONH_2$	O	95
		C_6H_5	Indole-2-carbonyl	O	80
		C_6H_5	2-benzothazolyl	O	95
e	4-$NO_2C_6H_4$	4-ClC_6H_4	CN	NH	70
f	5-CO-4,6-$(OMe)_2$benzofuran	4-$NO_2C_6H_4$	CN	NH	73
g	4-CO-3-MeO-5,6-$(Ph)_2$pyridazine	C_6H_5	CO_2Et	O	72
h	quinoxalin-3-yl-2(1*H*)-one	C_6H_5	CN	NH	69
i	3-CO-4-OH-1-methylquinolin-2(1*H*)-one	4-$O_2NC_6H_4$	CN	NH	55
j	2-$(COCH_2)$isoindoline-1,3-dione	C_6H_5	CN	NH	65
k	CO-thien-2-yl	4-$MeOC_6H_4$	2-benzoimidazolyl	NH	75
		C_6H_5	$CONHNH_2$	O	95

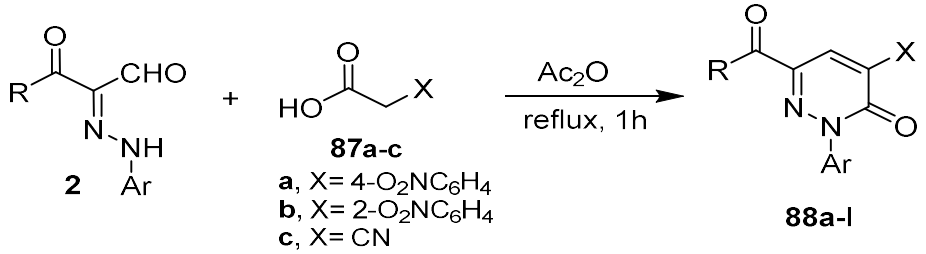
l	2-oxo-3-CN-2*H*-chromen-4-yl	C_6H_5	CN	O	67
m	2-CO-3-Me-6-Ph-imidazo[2,1-*b*]thiazole	C_6H_5-	CN	N H	74
n	2-CO-3*H*-benzo[*f*]chromen-3-one	1,5-Me_2-2-Ph-2,3-dihydro-1H-pyrazol-3-yl	$CONH_2$ COPh	O	--
o	4-$H_3CC_6H_4CO$	C_6H_5	CN, CO_2Et $CONH_2$	O O	-- --



Scheme 28. Synthesis of (2,3-dihydropyridazin-4-yl)benzamide.

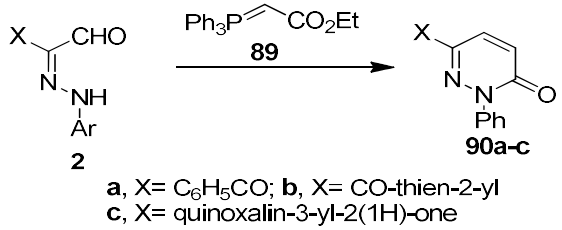


Scheme 29. Synthesis of binary heterocycles of 1,6-dihydropyridazines.



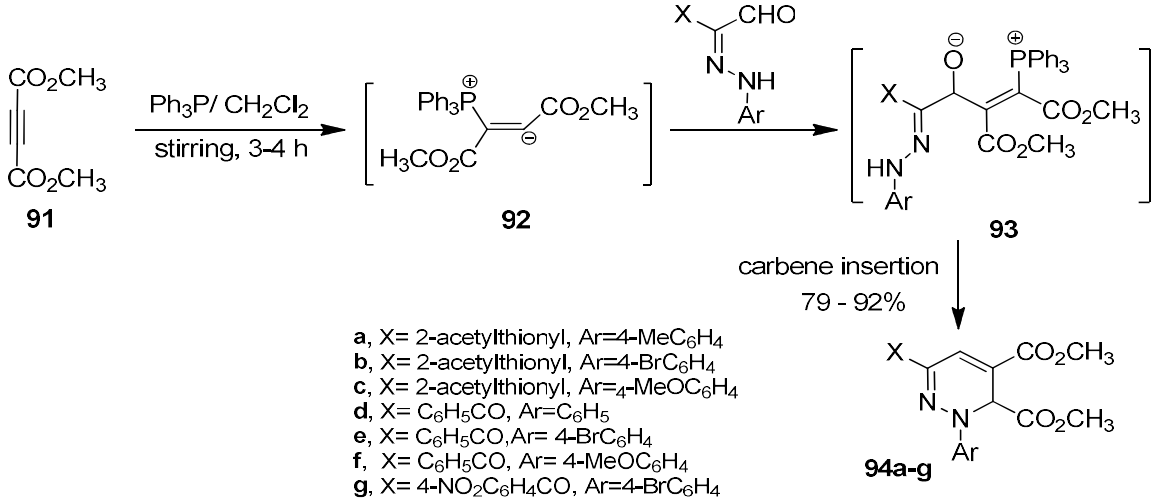
a, R= ph, Ar= ph, X= 4-$O_2NC_6H_4$;
b, R= ph, Ar= 4-$MeOC_6H_4$, X= 4-$O_2NC_6H_4$
c, R= ph, Ar= 4-ClC_6H_4, X= 4-$O_2NC_6H_4$;
d, R= 4-FC_6H_4, Ar= Ph, X= 4-$O_2NC_6H_4$
e, R= 4-FC_6H_4, Ar= 4-ClC_6H_4, X= 4-$O_2NC_6H_4$;
f, R= 4-ClC_6H_4, Ar= 4-ClC_6H_4, X= 4-$O_2NC_6H_4$
g, R= 4-BrC_6H_4, Ar= 4-Cl-3-$O_2NC_6H_3$, X=4-$O_2NC_6H_4$;
h, R= 4-BrC_6H_4, Ar= 4-Cl-3-$O_2NC_6H_3$, X=2-$O_2NC_6H_4$
i, R= 4-BrC_6H_4, Ar= 4-Cl-3-$O_2NC_6H_3$, X=CN;
j, R= 4-ClC_6H_4, Ar= 4-ClC_6H_4, X=CN
k, R= Ph, Ar= 4-$MeOC_6H_4$, X=CN;
l, R= CH_3, Ar= Ph, X=4-$O_2NC_6H_4$

Scheme 30. Synthesis of pyridazin-3(2*H*)-ones.

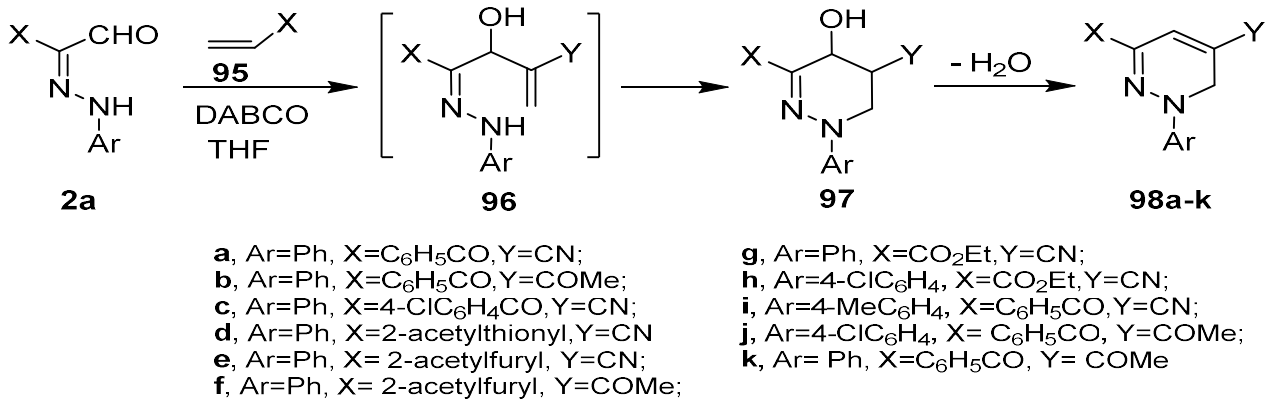


Scheme 31. Synthesis of 2-phenylpyridazin-3(2*H*)-ones.

The reactions of arylhydrazonals **2** with Wittig reagents **89** afforded pyridazinones **90, Scheme 31** [48]. On the other hand, Al-Awadi *et al* [21, 22] have reported an efficient reaction of **2a** with dimethylacetylenedicarboxylate (DMAD) in presence of Ph_3P to yield pyradazin-5,6-dicarboxylate **94a-g, Scheme 32** [49].



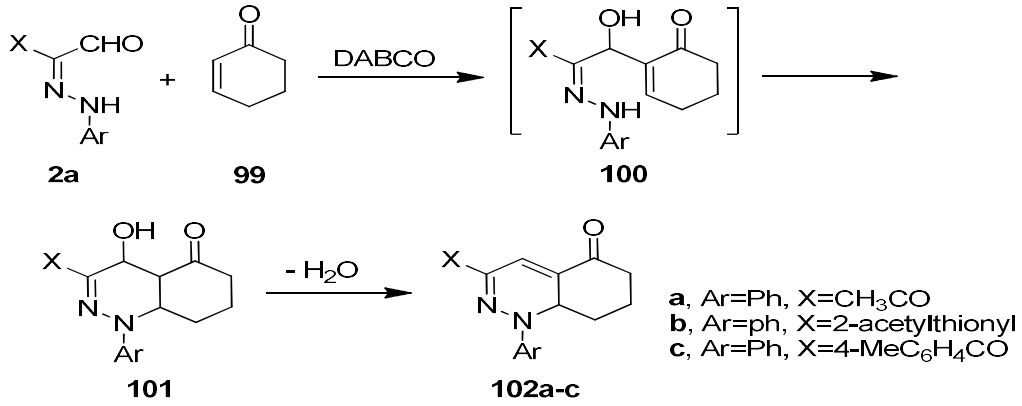
Scheme 32. Synthesis of 2,3-dihydropyridazines.



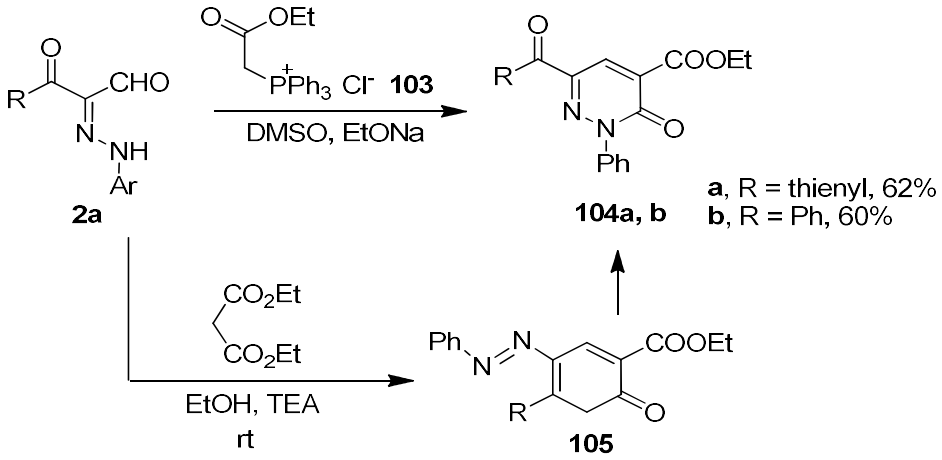
Scheme 33. Synthesis of 1,6-dihydropyridazines.

A novel synthetic route of pyridazine has been reported by Al-wadai *et al*. [50]. Hydrazonals serve as aldehyde components in Baylis-Hillman reactions, which led to the formation of 1,6-dihydropyridazines. Thus, addition of aryl hydrazonals **2a** to acrylonitrile or methyl vinyl ketone in the presence of DABCO or benzotriazole, utilizing microwave irradiation

conditions, results in the formation of the Baylis-Hillman intermediates **96** that cyclize under the reaction conditions followed by water elimination to yield dihydropyridazines **98**. The alcoholic intermediates **97** can be isolated in some cases, **Scheme 33** [51]. Arylhydrazonals also attack 2-cyclohexenone **98** to assemble tetrahydrocinnolin-5(1*H*)-one derivatives **102**, which were formed *via* the non-isolable intermediates **100** and **101, Scheme 34** [52].

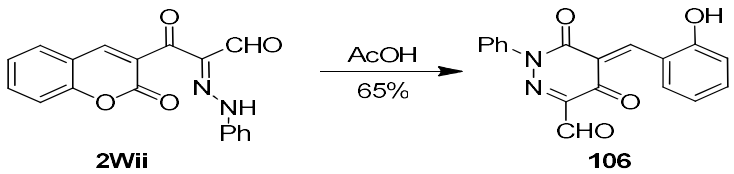


Scheme 34. Synthesis of 6,7,8,8a-tetrahydrocinnolin-5(1*H*)-ones.



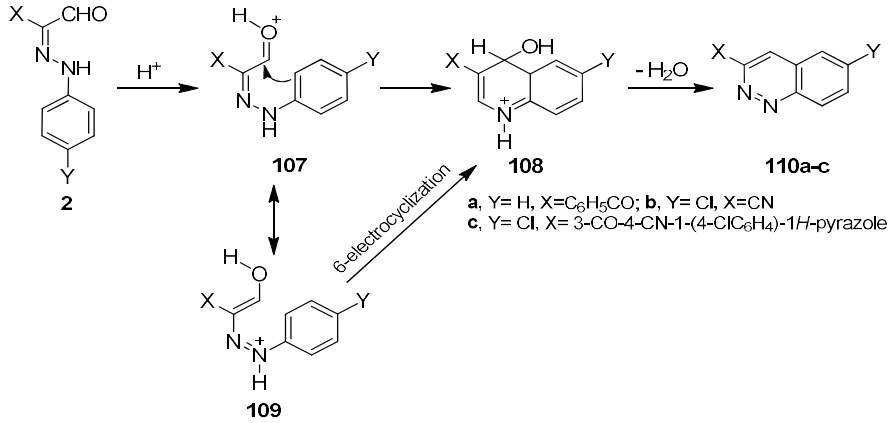
Scheme 35. Synthesis of ethyl 2,3-dihydropyridazine-4-carboxylates.

Treatment of arylhydrazonals with carbethoxymethyl triphenyl-phosphonium chloride **103** in dimethylsulfoxide in the presence of sodium ethoxide results in the formation of pyridazinones **104** [53]. These products were obtained by condensation reactions of hydrazonals **2** with diethylmalonate in ethanol at room temperature in the presence of diethylamine. In these processes the initially formed arylpyran-2-ones **105** isomerize to form **104** in refluxing sodium ethoxide solutions, **Scheme 35** [54]. Treatment of 3-oxo-3-(2-oxo-2*H*-chromen-3-yl)-2-(2-phenylhydrazono) propanal (**2wii**) with acetic acid afforded 1,4,5,6-tetrahydropyridazine-3-carbaldehyde **106** in 65%, **Scheme 36** [55].



Scheme 36. Synthesis of 1,4,5,6-tetrahydropyridazine-3-carbaldehyde.

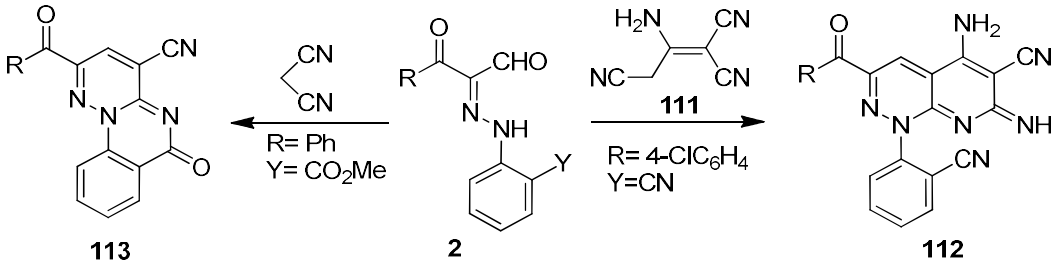
Heating of arylhydrazonals **2** in sulfuric acid promotes the formation of 3-aroylcinnolines **110**. Two mechanistic pathways could be suggested for this process. The first involved nucleophilic addition of the aromatic ring of the hydrazone moiety to the aldehyde carbonyl carbon to afford **108** followed by elimination of water. Alternatively, initial isomerization of **107** could occurred to generate **109**, a substance which then underwent 6 π -electrocyclization to yield **110**, **Scheme 37** [56].



Scheme 37. Synthesis of 3,6-disubstitutedcinnolines.

4.4.2. Synthesis of fused pyridazines

Condensation of arylhydrazonal **2** (R= 4-Cl-C_6H_4, Y= CN) with 2-amino-1,1,3-tricyanopropene **111** yielded pyridopyridazine **112**. On the other hand, reaction of the related phenone derivative **2** (R=Ph,Y=CO_2Me) with malononitrile gave pyridazinoquinoxaline **113, Scheme 38** [57].

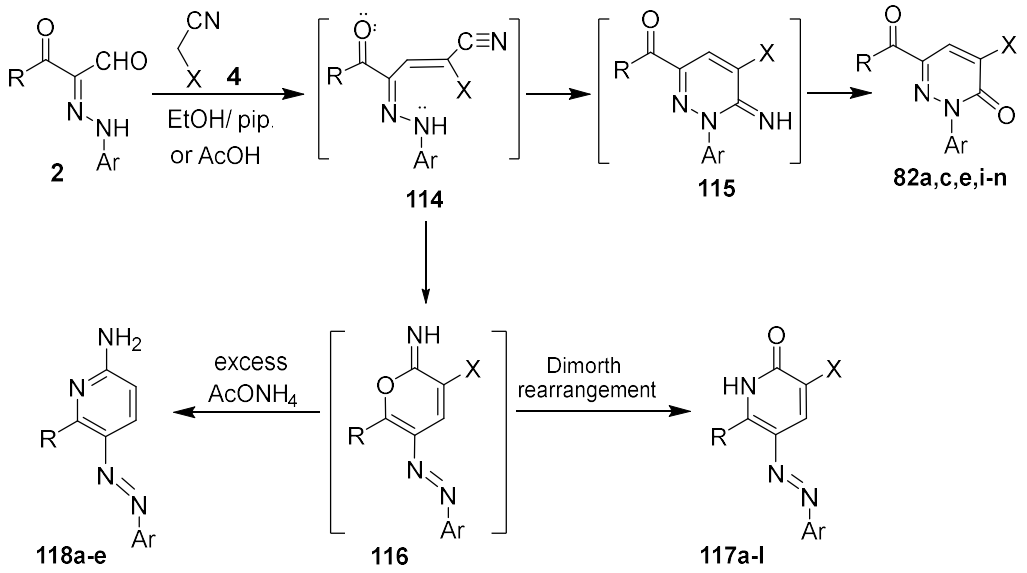


Scheme 38. Synthesis of pyridopyridazine and pyridazino[1,6-*a*]quinazoline.

4.4.3. Synthesis of nicotinates and fused pyridines

The product of reaction of **2** with active methylene reagent has been subject to some depute that only selected recently. Condensation of **2a** with ethylcyanoacetate and malononitrile has been proposed to yield pyradazine-6-imine **115** [58]. The product of reaction of **2** with active methylene reagent has been subject to some depute that only selected recently. Condensation of **2a** with

ethylcyanoacetate and malononitrile has been proposed to yield pyradazine-6-imine **115**. However, taking in consideration that heterocyclic imine are highly unstable, Elnagdi *et al* have reinvestigated this reaction discovering that the reaction in fact produce either pyridazinones **82** or pyridines **117**, **118**, as illustrated in **Scheme 39** and **Tables 5,6**. A detailed investigation on the effect of structure and reaction conditions on nature of the final product has been published by Elnagdi *et al* [59].



Scheme 39. Synthesis of pyridazin-3(2*H*)-ones and arylazo pyridines.

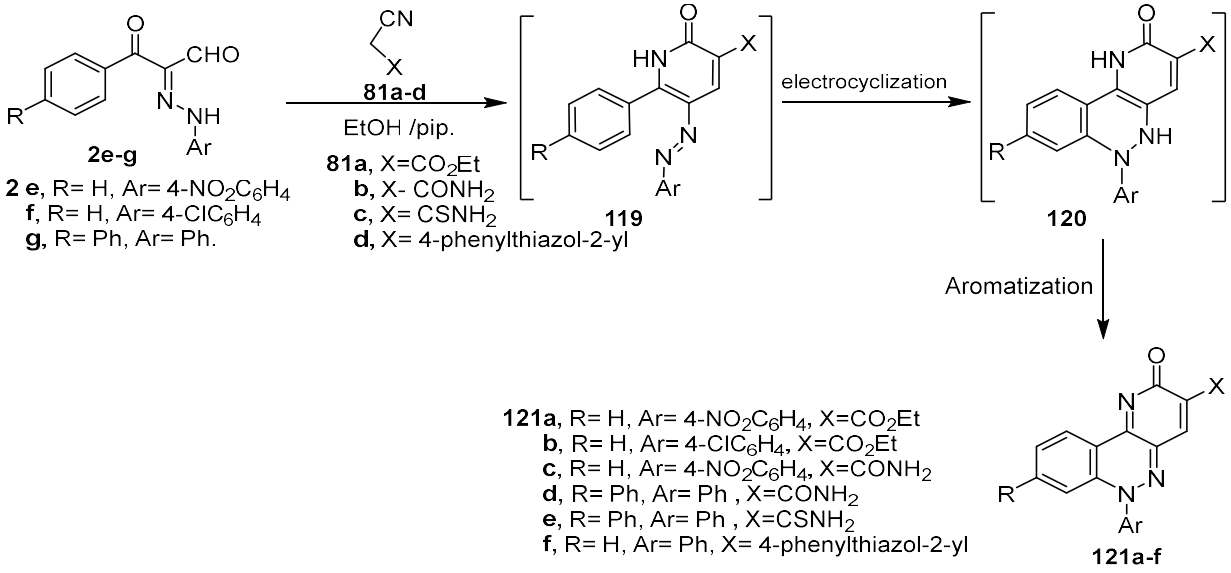
Table 5. Substituents of arylazo pyridines **117a-o** with their corresponding yields in percentage [21, 22, 60].

Compound 117	R	Ar	X
a	C_6H_5	C_6H_5	CN, $CSNH_2$ $CONH_2$, CO_2Et Thiazol-2-yl-4(5*H*)-one
b	4-PhC_6H_4	C_6H_5	CN, $CONHNH_2$
c	2-thionyl	C_6H_5	benzo[*d*]thiazol-2-yl
d	2-furyl	C_6H_5	CN
e	C_6H_5	4-$CH_3C_6H_4$	$CONH_2$, CO_2Et, $CSNH_2$
f	C_6H_5	4-BrC_6H_4	CO_2Et
g	4-$CH_3C_6H_4$	C_6H_5	$CSNH_2$
h	4-$OCH_3C_6H_4$	C_6H_5	CO_2Et
i	4-$NO_2C_6H_4$	C_6H_5	CN
j	4-ClC_6H_4	C_6H_5	CO_2Et
k	CH_3	C_6H_5	$CONH_2$, CO_2Et
l	*1H*-pyrrol-2-yl	C_6H_5	CO_2Et

Table 6. Substituents of arylazo pyridines **118a-e** with their corresponding yields in percentage [21, 22, 60].

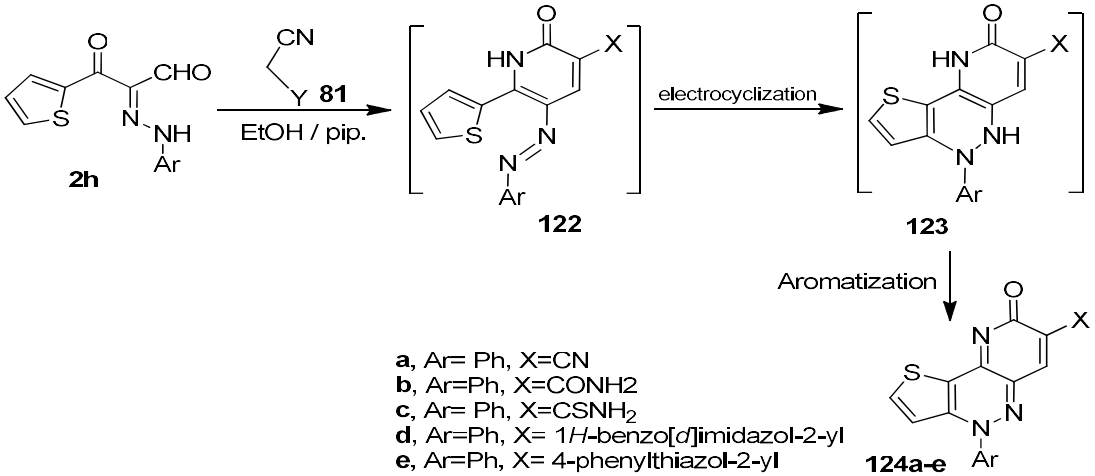
Compound 118	R	Ar	X
a	C_6H_5	4-$CH_3C_6H_4$ 4-ClC_6H_4 4-$NO_2C_6H_4$ 5-(SCH_3)-1*H*-1,2,4-triazol-3-yl	CO_2Et
b	4-$NO_2C_6H_4$	C_6H_5, 4-ClC_6H_4	CO_2Et
c	Napthalene-2-yl	4-ClC_6H_4	CO_2Et
d	4-ClC_6H_4	4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-ClC_6H_4, 3-BrC_6H_4, 2-$NO_2C_6H_4$, 2-Cl-5-NO_2-C_6H_3	CO_2Et, CN
e	4-BrC_6H_4	3-NO_2-4-ClC_6H_3	CO_2Et, CN

Behbehani *et al* suggested that if the aryl group in the arylazo moiety was substituted with an electron withdrawing group, the final product will be pyradazinone **82**. While electron donating groups on arylhydrazonal increase pyradazine imine that readily hydrolyze in media to pyranimine **116** followed by Dimorth rearrangement. Subsequently, Al-Moussawi *et al*, have found that if the reaction tested in excess of ammonium acetate major product is amino arylazonicotinates, **Scheme 39** [58, 60]. An unexpected condensation of arylhydrazonal **2e-g** with some active methylene nitriles **81a-d** afford products corresponding to condensation *via* water and hydrogen molecule elimination. It has assumed that the initial formed arylazonicotinate has underwent 6 π-electrocyclization that then aromatized to the final product **121, Scheme 40** [61].



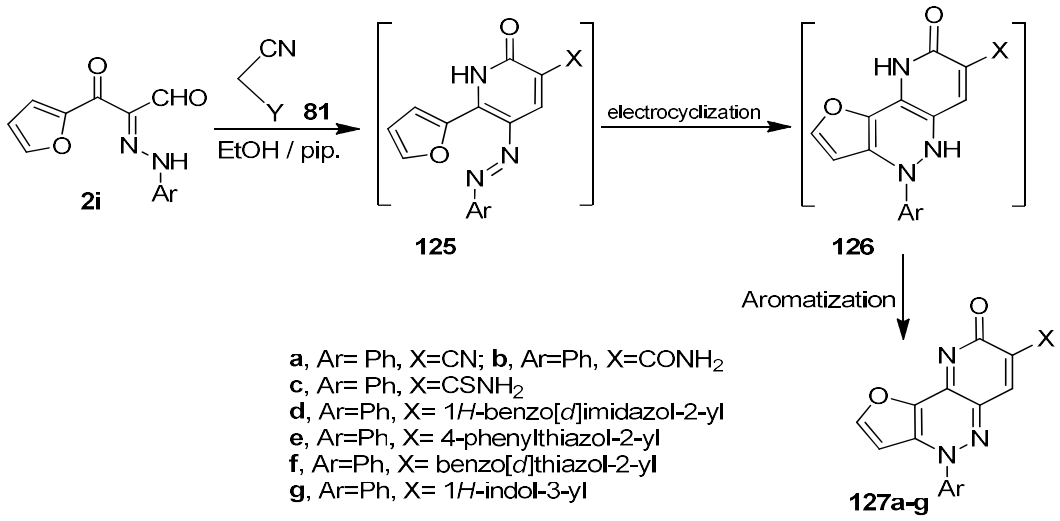
Scheme 40. Synthesis of pyrido[3,2-*c*]cinnolin-2(6*H*)-ones.

Elnagdi *et al* have suggested that the decreased aromaticity of the thiophene ring as compared to benzene is behind this electrocyclization, and in support of this conclusion it was found that **2h** afforded **124** upon reaction with **81**; again, the initially formed derivative of **122** underwent electrocyclization to **123** and then aromatized to yield **124a-e** (**Scheme 41**) [62].



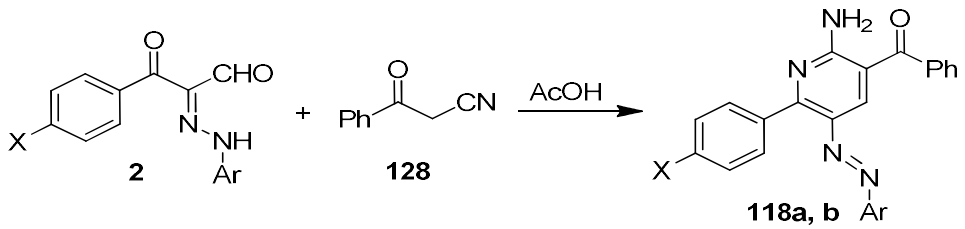
Scheme 41. Synthesis of pyrido[3,2-*c*]thieno[2,3-*e*]pyridazin-8(4*H*)-ones.

Similar to this behavior compound **2i** reacted with **81** to afford compounds **127a-g** under the same reaction conditions (**Scheme 42**) [62].



Scheme 42. Synthesis of furo[3,2-*c*]pyrido[2,3-*e*]pyridazin-8(4*H*)-ones.

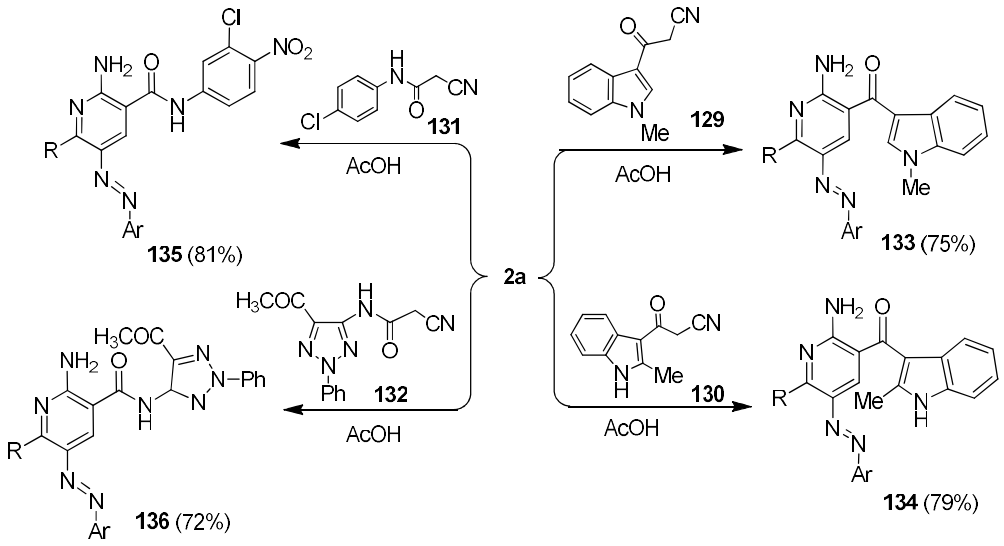
Recently, 2-amino-6-arylazo-3-benzoylpyridines **118** were formed as the sole isolable products from reaction of 3-oxo-3-phenylpropionitrile **128** and 3-oxo-2-arylhydrazonal **2** containing electron poor arylhydrazone groups as substrates, possessing two electron-withdrawing nitro and Cl groups on the aryl ring of the moiety, **Scheme 43** [63]



a, X= Br, Ar= 3-NO_2-4-ClC_6H_3; **b**, X= Cl, Ar= 3-NO_2-4-ClC_6H_3

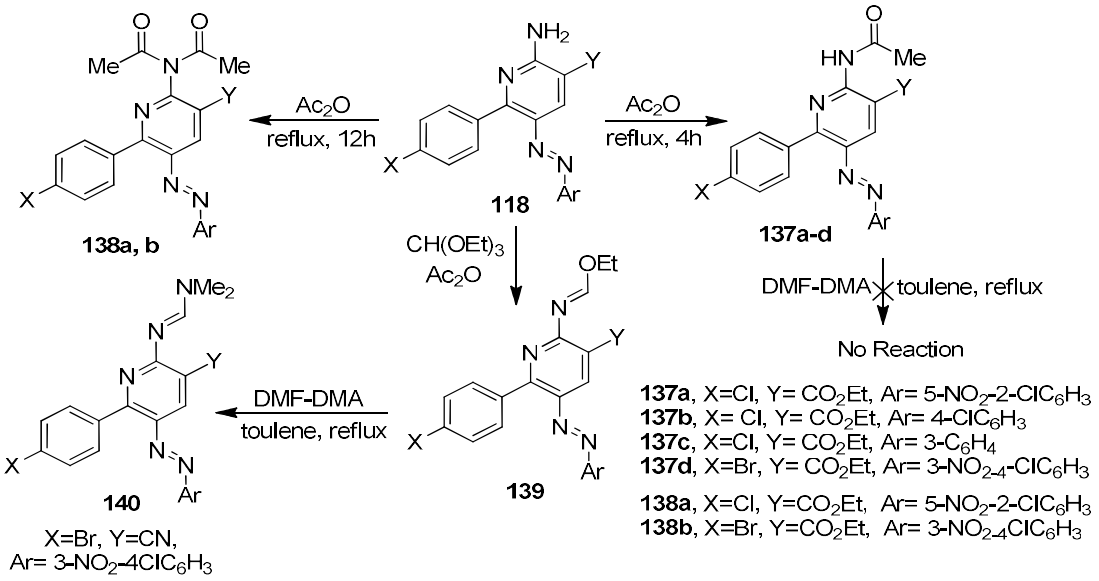
Scheme 43. Synthesis of arylazopyridines.

The reaction between 3-oxo-2-arylhydrazonal **2a** with miscellaneous active methylene compounds like cyanoacetylindoles **129**, **130** and different cyanoacetamides **131, 132** to afford respective 2-aminopyridine derivatives **133-136, Scheme 44** [64].

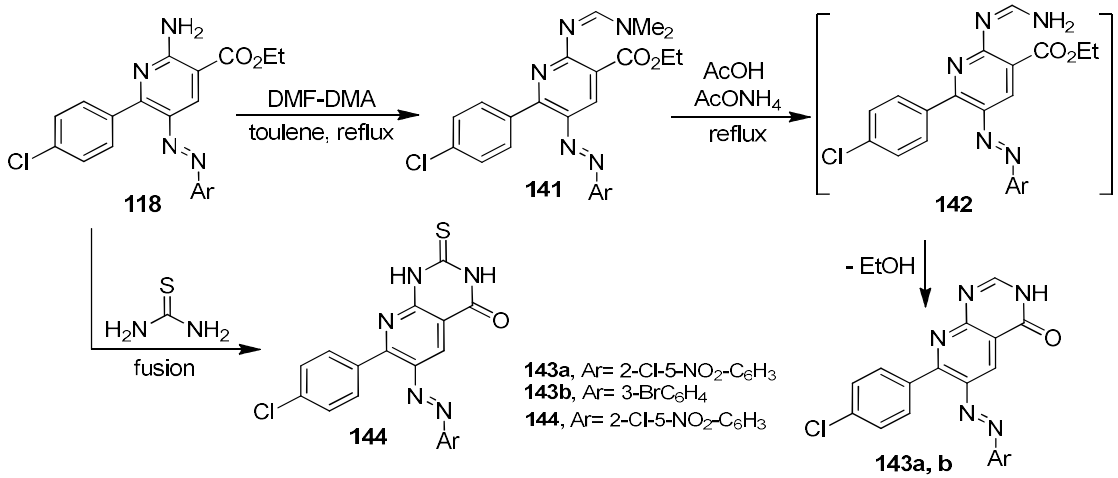


Scheme 44. Synthesis of 5-arylazopyridin-3-yl derivatives.

Recently, Bahbehani *et al* [21, 22], have suggested that the obtained amino-nicotinates **118** are interesting precursors for synthesis of a variety of a novel arylazoheterocycles that may possess interesting biological activities. Reaction of the 2-amino-5-arylazonicotinates **118** with acetic anhydride afforded the mono- and di- acetylated products **137** and **138** respectively, depending upon the reaction time. Also, the 2-amino-5-arylazonicotinates **118** undergoes reaction with triethylor- thoformate to yield the ethyl formamidine derivative **139**, which on treatment with MF-DMA afforded the pyrazolo[3,4-*c*]pyridine **140, Scheme 45** [63].



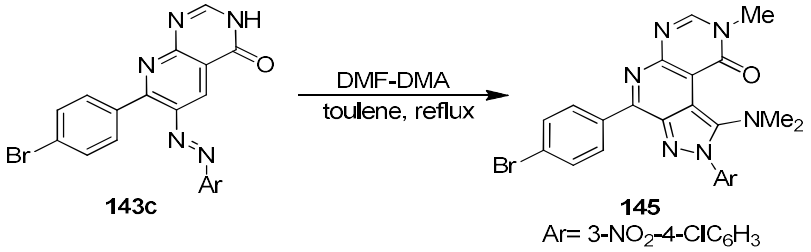
Scheme 45. Synthesis of arylazopyridines.



Scheme 46. Synthesis of arylazopyridines.

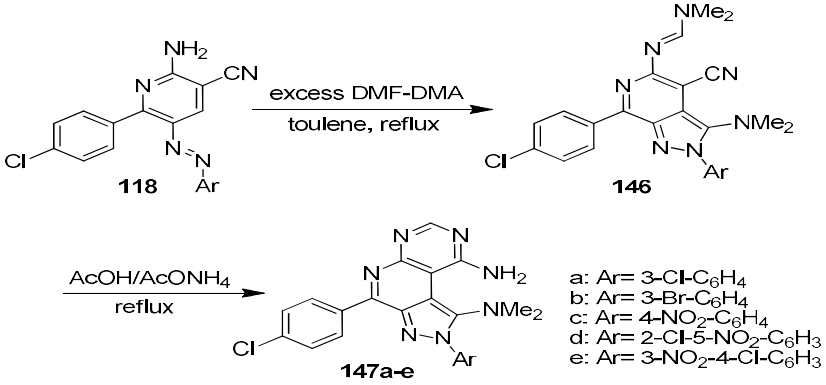
Moreover, the 2-amino-5-arylazonicotinates **118** reacted with DMF-DMA to yield the corresponding amidines **141**. The amidines **141a,b** reacted with ammonium acetate in refluxing acetic acid to yield the corresponding pyrido[2,3-*d*]pyrimidine **143a,b** . Furthermore, fusion of the azonicotinates **118c** with thiourea afforded the corresponding pyrido[2,3-*d*]pyrimidine derivatives **144, Scheme 46** [63].

The pyrido[2,3-*d*]pyrimidines **143c** was found to undergo non-concerned nucleophilic [4+1] cycloaddition reactions with DMF-DMA to produce the novel pyrazolo[4',3':4,5]pyrido[2,3-d]pyrimidine derivative **145, Scheme 47** [65].



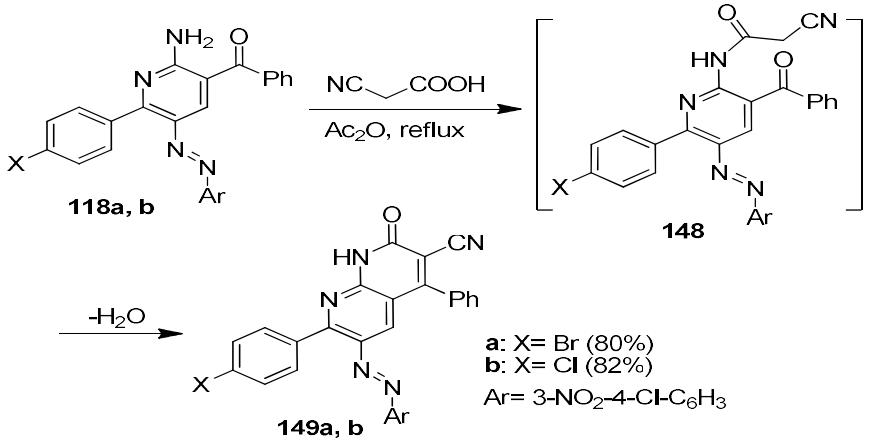
Scheme 47. Synthesis of pyrazolo[4',3':4,5]pyrido[2,3-*d*]pyrimidin-9(8*H*)-one.

Similarly, Bahbehani *et al* , have studied the reaction of 2-amino-5-arylazonicotinates **118** (X=CN) with excess of DMF-DMA in refluxing toluene to give pyrazolo[3,4-*c*]pyridine amidine **146** which react with ammonia in refluxing acetic acid to yield the corresponding fused tricyclic pyrazolo [4',3':4,5]pyrido[2,3-*d*]pyrimidine derivative **147, Scheme 48** [66].



Scheme 48. Synthesis of pyrazolopyrido[2,3-*d*]pyrimidine-1,9-diamines.

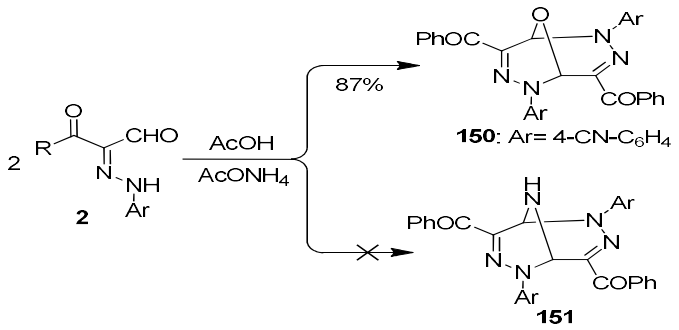
The reaction of 2-aminopyridine derivatives **118a, b** with cyanoacetic acid in the presence of acetic anhydride smoothly afforded the desired 1,8-naphthyridinecarbonitrile derivatives **149a, b.** The reaction proceeded most likely *via* the intermediacy of **148, Scheme 49** [67].



Scheme 49. Synthesis of 1,8-naphthyridine-3-carbonitriles.

4.5. Dimerization reactions

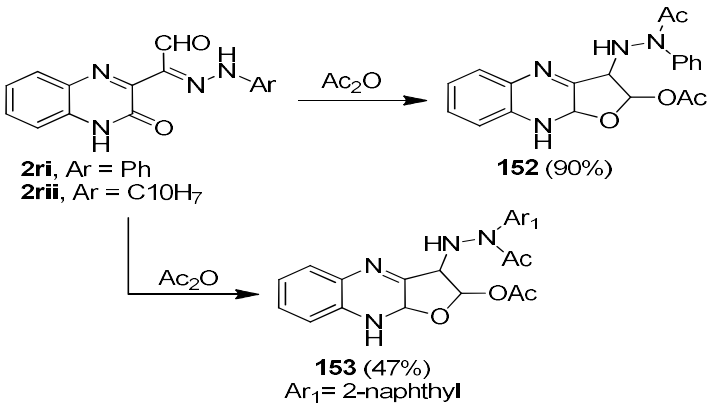
When solutions of arylhydrazonals **2** in acetic acid and ammonium acetate are stirred at reflux, the reaction affords dimers **150** rather than **151** (**Scheme 50**) [68].



Scheme 50. Synthesis of tetraazabicyclo[3.3.1]nona-3,7-diene.

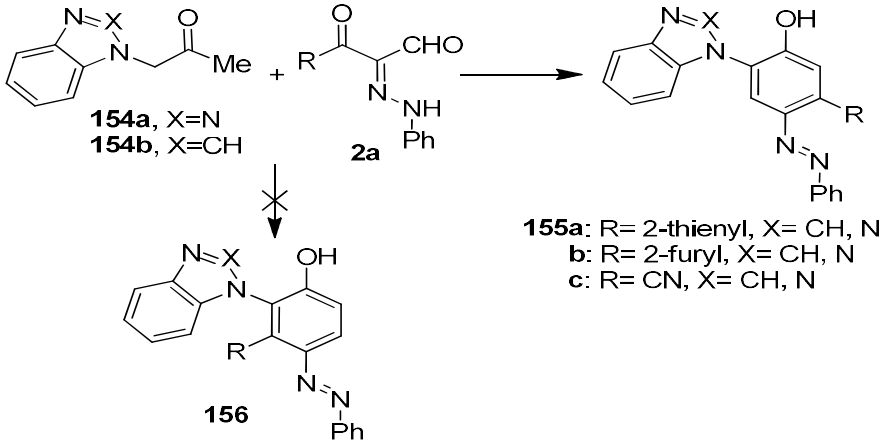
4.6. Miscellaneous reactions

Heating hydrazonals **2r** and **2ii** in acetic anhydride leads to the formation of *N*-acetyl-*N*-arylazotetrahydrofuro[3,2-*b*]quinoxalines **152** and **153**, respectively, **Scheme 51** [69].



Scheme 51. Synthesis of furo[2,3-*b*]quinoxalines.

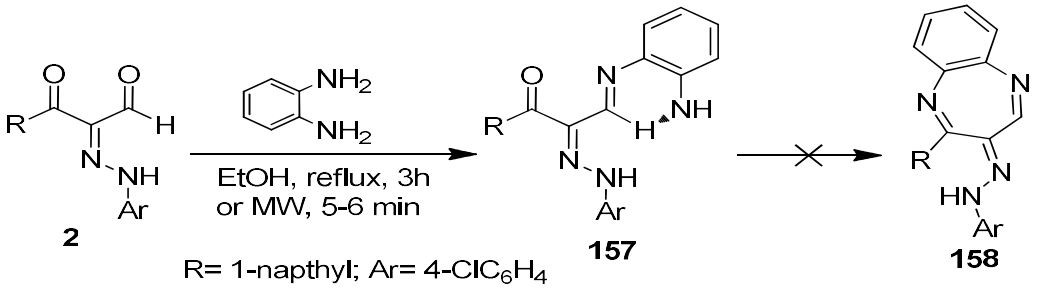
Moreover, it has been observed that **154a,b** convert arylhydrazonals **2a** into products that may be formulated as **155** or their positional isomers **156, Scheme 52** [70].



Scheme 52. Synthesis of benzotriazolyl and benzoimidazolyl-benzonitriles.

o-Phenylenediamine also reacted with arylhydrazonal **2** (R=1-napthyl, Ar= 4-ClC_6H_4) in ethanol (under microwave irradiation for 5-6 min. or reflux for 3 hours) to give a mono Schiff's base as the uncyclized product **157**, and this compound could not be cyclized to yield

benzodiazepines **158** [21], indicating that most likely this product adopted the hydrogen bonded form, **Scheme 53** [8].



Scheme 53. Reaction of arylhydrazonal with *o*-phenylenediamine.

5. Applications of Arylhydrazonals: Versatility and Impact

Arylhydrazonals, formed by the reaction of aryl aldehydes/ketones with hydrazine derivatives, exhibit versatile properties that significantly impact diverse scientific realms [63]. This review succinctly highlights their key applications: In pharmaceuticals, arylhydrazonals serve as intermediates in drug synthesis, aiding the creation of bioactive heterocyclic structures, structural optimization, and prodrug design. In materials science, incorporation into polymers provides tailor-made electronic, optical, and mechanical properties for applications in flexible electronics, photovoltaics, and sensors. In catalysis, arylhydrazones catalyze complex reactions, offering innovative synthetic pathways and reactivity beyond traditional catalysts. In organic synthesis, they streamline heterocyclic synthesis, enabling efficient creation of intricate compounds with controlled regio- and stereoselectivity. In biological studies, arylhydrazones facilitate biomolecule visualization and exploration of cellular processes in live systems [63]. Conjugated arylhydrazones contribute to photonic devices like OLEDs, enhancing optoelectronic advancements. Modified arylhydrazones yield versatile colorants for textiles, paints, and inks, broadening application options. Non-covalent interactions form supramolecular assemblies useful in molecular recognition and drug delivery. Designed as chemical sensors, arylhydrazones offer a simple method for pollutant detection, aiding environmental monitoring. The reactivity of arylhydrazones aids both education and research by allowing exploration of synthetic strategies and mechanisms [71]. In short, arylhydrazones' adaptability across various fields underscores their role in advancing science, technology, and innovation.

6. Recent Advances: Novel Synthesis Methodologies

Recent years have witnessed groundbreaking developments in arylhydrazone synthesis, introducing innovative methodologies that enhance efficiency and diversity. These methods include metal-free C-H activation, enabling direct arylhydrazone synthesis from arenes without the need for transition metal catalysts for sustainability. Visible-light photoredox catalysis utilizes visible light to directly produce arylhydrazones from aryl halides and hydrazines, expanding synthetic capabilities. Catalyst-free synthesis methods streamline arylhydrazone formation from

aldehydes/ketones and hydrazines, reducing reaction steps and complexity [8]. Flow platforms enhance arylhydrazone synthesis control, enabling continuous production and offering automation and efficiency improvements. Multicomponent reactions (MCRs) use arylhydrazones as intermediates to swiftly construct diverse heterocyclic structures. Microwave-assisted synthesis methods expedite arylhydrazone formation, accelerating reactions and improving yields [8]. Click chemistry principles facilitate the modular assembly of arylhydrazone-containing molecules, vital for functional materials and bioconjugates. Cascade strategies efficiently synthesize complex architectures in a single reaction by orchestrating sequential transformations. Enantioselective methodologies yield chiral arylhydrazones with high optical purity, valuable for bioactive compounds. Boronic acids enable mild arylhydrazone synthesis, accommodating boron-containing functional groups [72, 73]

7. Conclusion

This study investigates the reactivity of arylhydrazonals, which are versatile four-atom building blocks in heterocyclic synthesis. The aldehyde carbonyl is highly electrophilic, while the hydrazone NH and C-2 positions are nucleophilic. The nucleophilic character of C-2 is due to delocalization of lone-pair electrons from nitrogen to this position. The study covers structural investigations, synthetic methods, and reactions of arylhydrazonals, including synthesis from aldehydes, ketones, esters, enaminones, hydrazones, and hydroxymethyl derivatives. It also discusses the synthesis of monocyclic and fused cyclic systems, 1,2,3-triazoles, pyrrazole derivatives, and pyridazines. The reactions mechanisms of the investigated arylhydrazonal derivatives are discussed, along with their synthetic importance. The study also discusses the synthesis of pyridazines through the reaction of arylhydrazonals with active methylene compounds in basic medium or in the presence of acetic anhydride.

8. Future Directions

Arylhydrazone chemistry presents promising opportunities for exploration in future directions. Enantioselective methodologies could enable the creation of optically active compounds, while bioconjugation strategies could offer targeted drug delivery. Integrating arylhydrazones into materials design could lead to responsive applications in sensing and electronics. Novel catalytic systems, sustainable synthesis routes, and mechanistic studies could enhance efficiency and insights. Interdisciplinary collaborations and data-driven approaches could catalyze transformative discoveries. Unexplored areas include exploring new reaction pathways and radical chemistry, investigating remote functionalization and redox-active properties, and harnessing photoredox transformations and chiral catalysts for unconventional bond formations and asymmetric synthesis. Integrating arylhydrazones into synthetic routes offers advantages like accelerated cyclization, late-stage diversification, bioorthogonal modulation, efficient scaffold variation, dynamic cascade reactions, and clickable functionalization [74-100].

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Competing interests

The authors declare that there are no competing interests.

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