

Chemistry of carbofunctionally substituted hydrazones

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Abstract

Synthetic approaches and chemical reactivity of title compounds since 1894 to date are reported. Emphasis is placed on pinpointing old literature reports that need reinspection in light of modern techniques and recent advances in utilizing the title compounds as precursors to polyfunctional heteroaromatics.

Keywords: Tautomerism, arylhydrazones as nucleophiles, carbon Mitsunobu reaction, aryl hydrazones as precursors to polyfunctional azoles and azines, gas phase pyrolysis

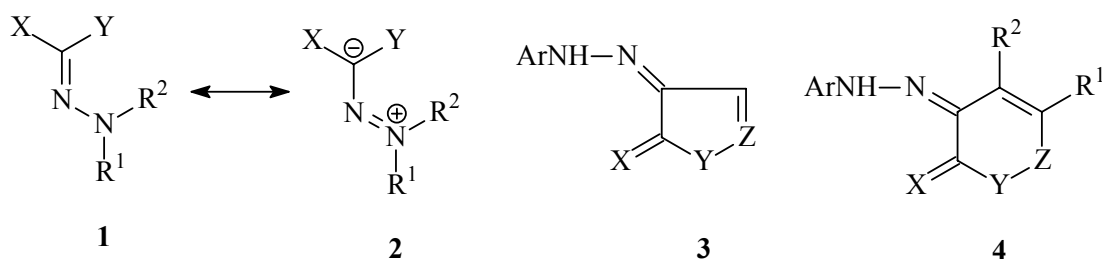
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1. Introduction

Hydrazone in which X and Y are carbon functionality as CO₂R, CN are extremely important compounds in dye industry.¹⁻³ Nitrogen lone pair resonance (cf. Scheme 1) renders hydrazone carbon atom electron rich and nucleophilicity of this carbon atom although have been noted in old literature⁴ has now been recognized and utilized extensively in synthesis. Despite their theoretical and practical importance to our knowledge, no trial to review reported chemical reactivities, structural studies and synthetic approaches to those molecules has ever been made. In the following article we review the chemistry of this class of compounds. Arylhydrazone azoles, azines and their condensed derivatives if having an α -functional group on ring nitrogen (e.g. **3** and or **4**) are not considered in this review as plenty of these derivatives have been extensively utilized as dyes and their chemistry is reviewed in specialized dye chemistry texts³. The chemistry of hydrazonyl halide X or Y = halogen and of hydrazononitriles X or Y = CN have been surveyed recently and will not be included here.



Scheme 1

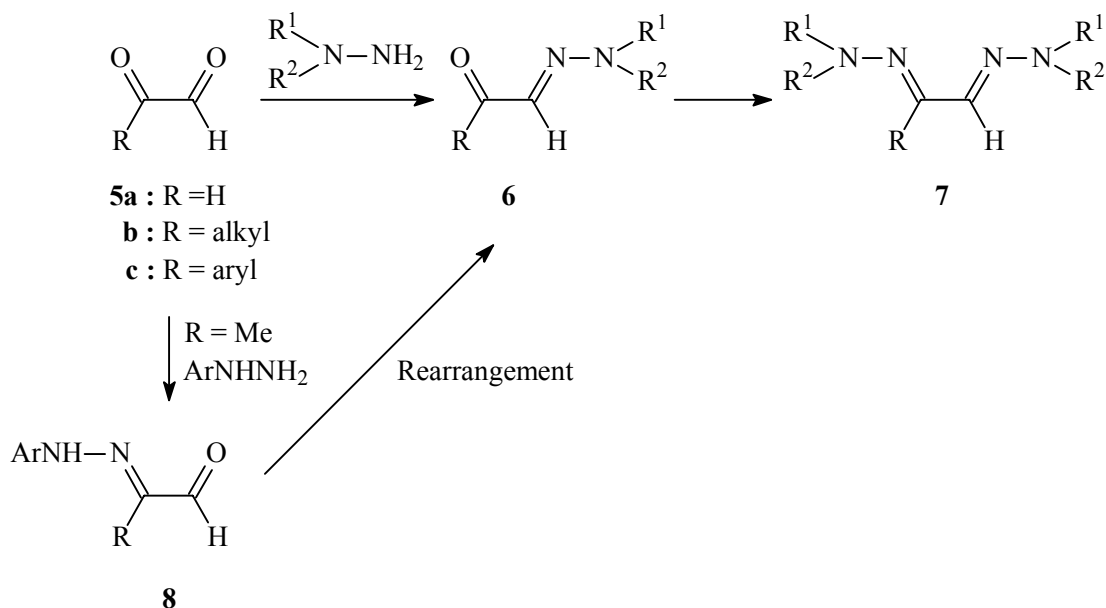
2. Synthetic Approaches to Carbofunctionally Substituted Hydrazones

2.1. Condensation of functionalized aldehydes and ketones with hydrazines

This is a most logical route provided the required α -functional aldehyde and / or ketone is easily obtainable. As functionally substituted aldehydes are generally difficult to obtain and store this route however has only relatively limited application for the synthesis of monofunctionally substituted hydrazone⁵⁻¹¹

Condensing glyoxal **5a** and substituted glyoxal **5b,c** with substituted hydrazines leads to formation of mono or bis hydrazones **6** or **7** depending on molar ratio and applied reaction

conditions⁵⁻¹¹ It has been reported that **5b** reacts with phenylhydrazine to yield initially **8** which then rearranges into the thermodynamically stable **6**; R = CH₃ (cf. Scheme 2). The mechanism of this rearrangement however had to be classified although reversibility of initial condensation reaction might be visual and that **8** is the kinetic product.

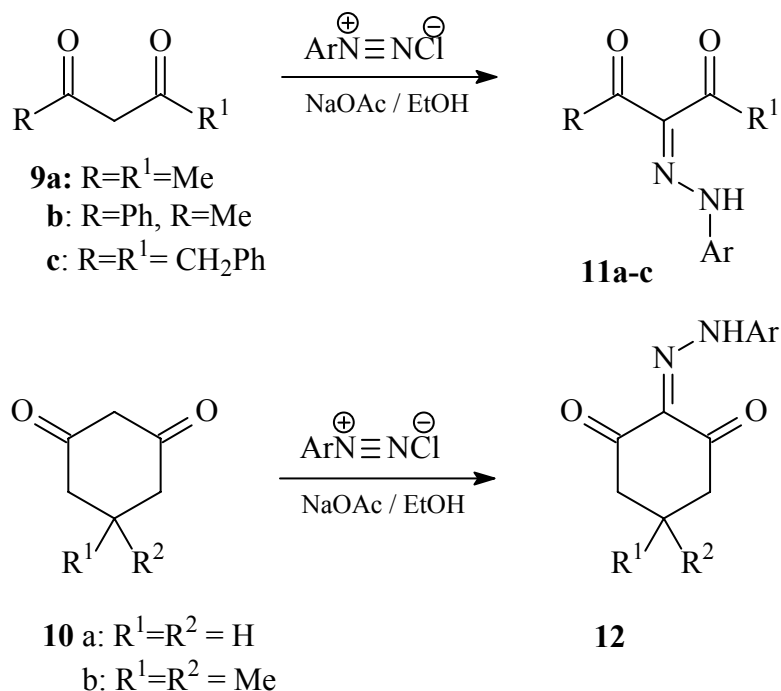


Scheme 2

2.2. Coupling active methylenes with aromatic and heteroaromatic diazonium salts

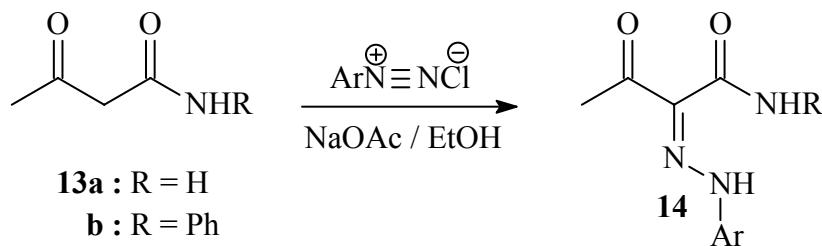
This is the most generally utilized route to **1**. The coupling reaction is generally conducted at room temperature and in protic organic solvent in presence of a base. Sodium acetate is most commonly used but coupling in presence of sodium hydroxide or in pyridine solutions has been reported.

Acetylacetone **9a**, benzoylacetone **9b**, diphenylpentanedione **9c** and other 1,3-diketones including cyclic ketones (e.g. **10a,b**) have been coupled with aromatic diazonium salts in ethanolic sodium acetate to yield corresponding coupling products **11a-c**¹²⁻²⁰ and **12a,b**^{21,22} (cf. Scheme 3).



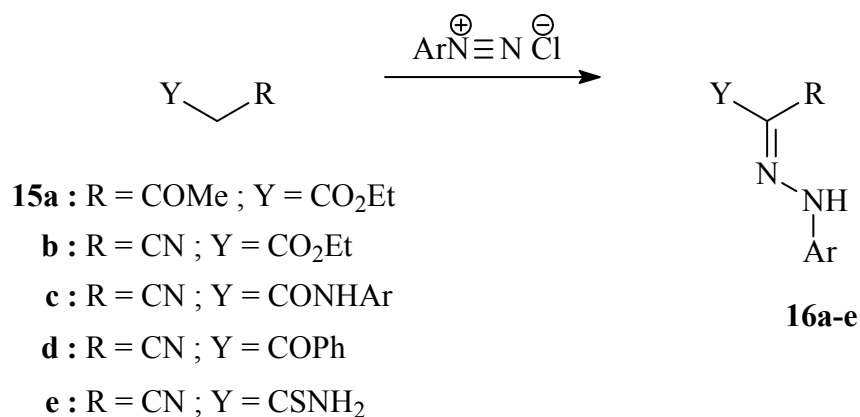
Scheme 3

Similarly, oxobutanamide **13a** and oxophenylbutanamide **13b** couple readily to yield aryl hydrazones **14a,b**²³⁻³⁴ that have been extensively used as dyes and pigments (cf. Scheme 4).



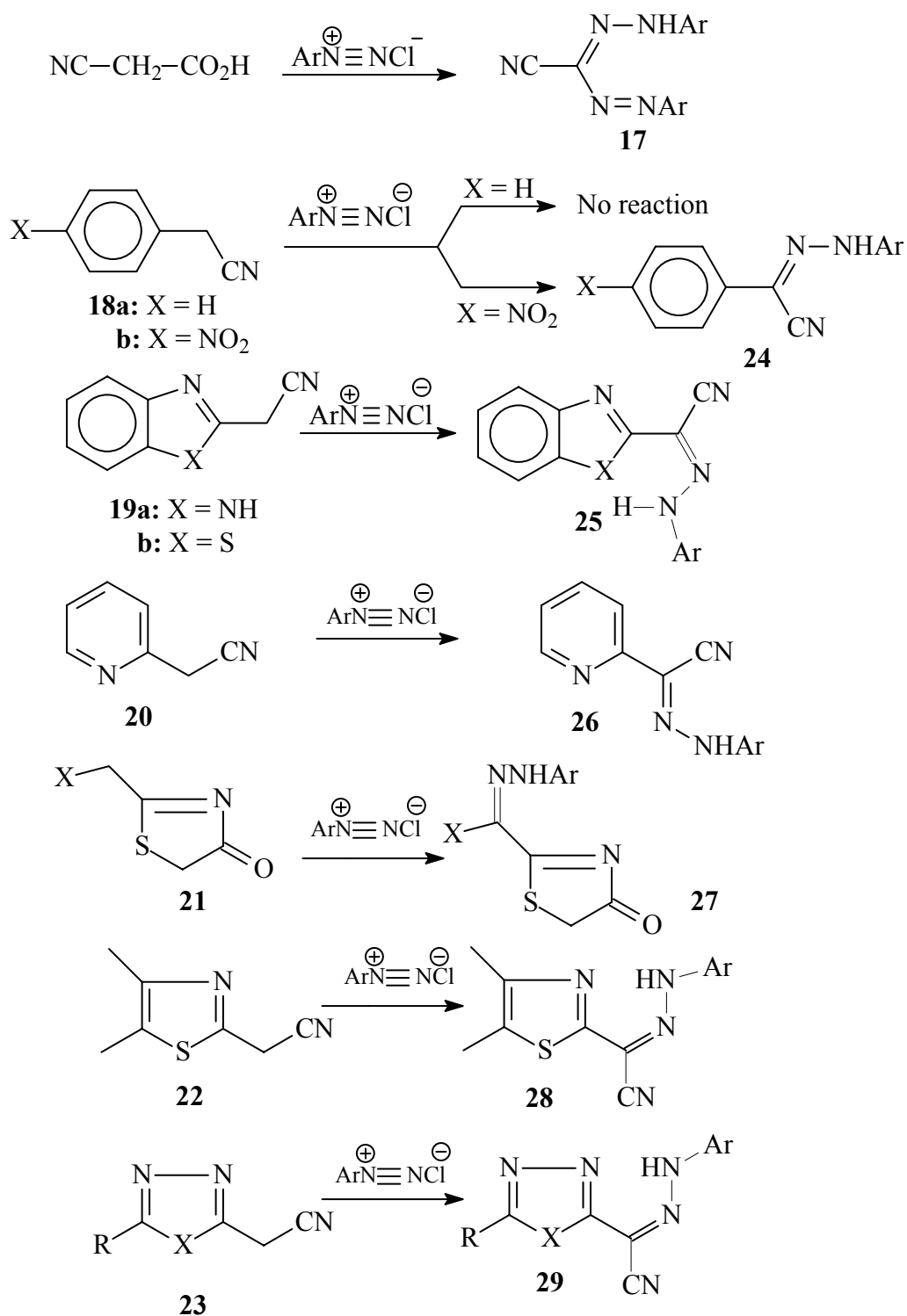
Scheme 4

Ethyl acetoacetate **15a**³⁵⁻⁵⁰ ethyl cyanoacetate **15b**,⁵¹⁻⁶⁶ cyanoanilides **15c**,⁶⁷⁻⁶⁹ benzoylacetonitrile **15d**⁷⁰ and cyanothioacetamide **15f**^{71,72} couple readily with aromatic diazonium salt in presence of sodium acetate to yield corresponding arylhydrazones whose exact geometry has only been recently established **16** (cf. Scheme 5).



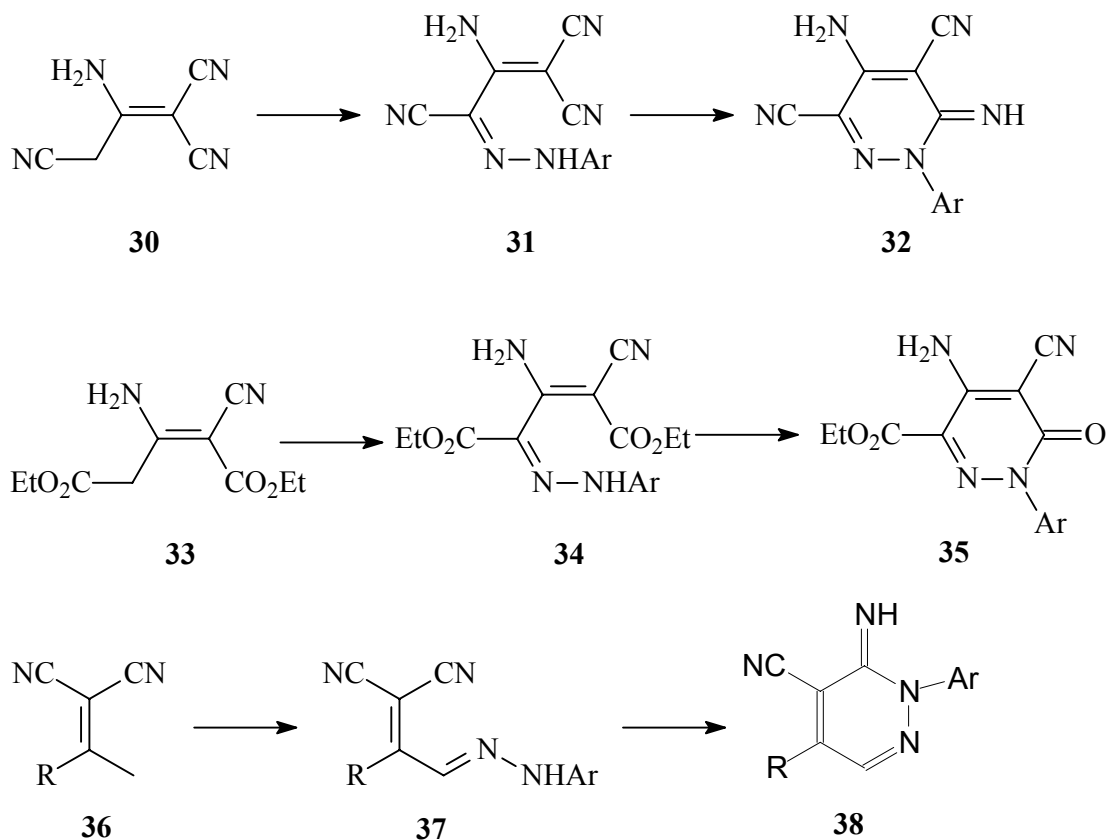
Scheme 5

The methylene functions in acetonitriles and benzyliocyanide are not sufficiently reactive toward aromatic diazonium salts attempted coupling of cyanoacetic acid with aromatic diazonium salt affords only formazans **17**.^{73,74} However acetonitrile derivatives **18-23** readily couple with aromatic diazonium salts to yield the corresponding arylhydrazones **24-29**⁷⁵⁻⁸⁶ whose configuration have not yet been defined with certainty although structures have been assumed (Scheme 6).



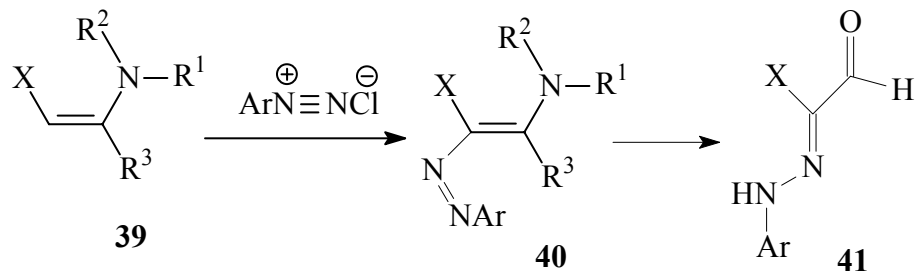
Scheme 6

The methylene group in **30**, **33** and **36** also couples with aromatic diazonium salts to yield intermediate functionally substituted arylhydrazones **31**, **34** and **37** that readily cyclize into pyridazines **32**, **35** and **38** (cf. Scheme 7).⁸⁷



Scheme 7

Enamines **39** couple with aromatic diazonium salts to yield 2-arylhydrazonoaldehyde **41**⁸⁸⁻⁹⁹ and arylhydrazonoketones in excellent yield. An intermediate derivative **40** is believed to be formed in all cases and could sometimes be isolated (Scheme 8).

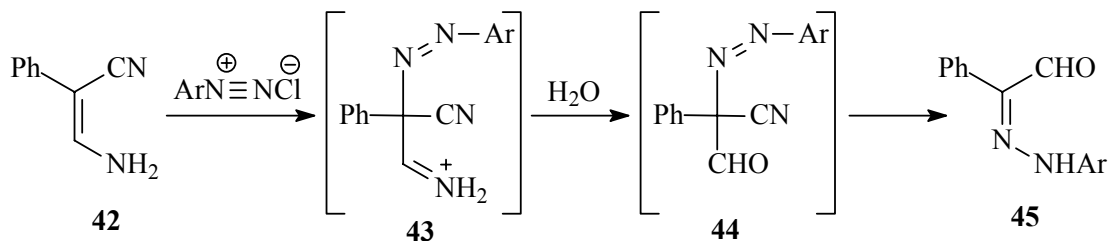


X = H ;COR⁴, CO₂Et, CHO, CN

R³ = H, Me; R¹, R² = H, alkyl

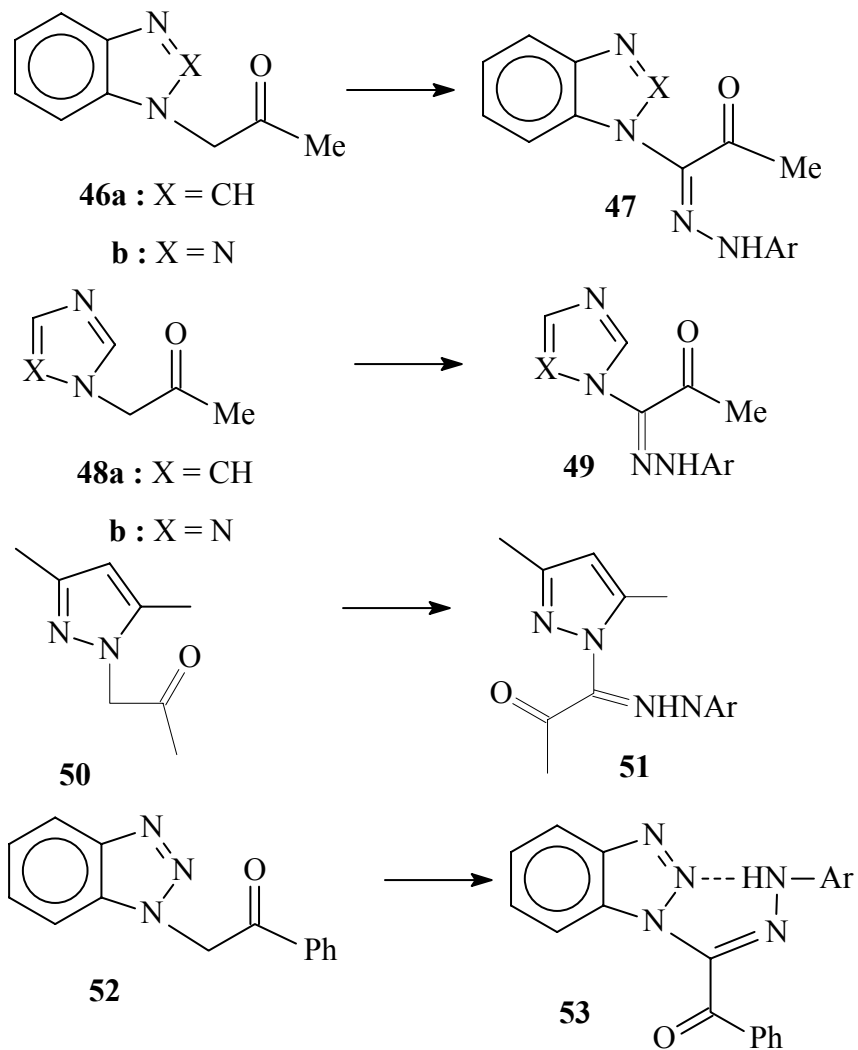
Scheme 8

It has been recently observed that **42** couples with aromatic diazonium salt to yield arylglyoxal-2-arylhydrazones **45**. Formation of intermediate iminium ion **43** is believed to hydrolyze to **44** that undergo a Japp-Klingemann cleavage to **45** (cf. Scheme 9).¹⁰⁰

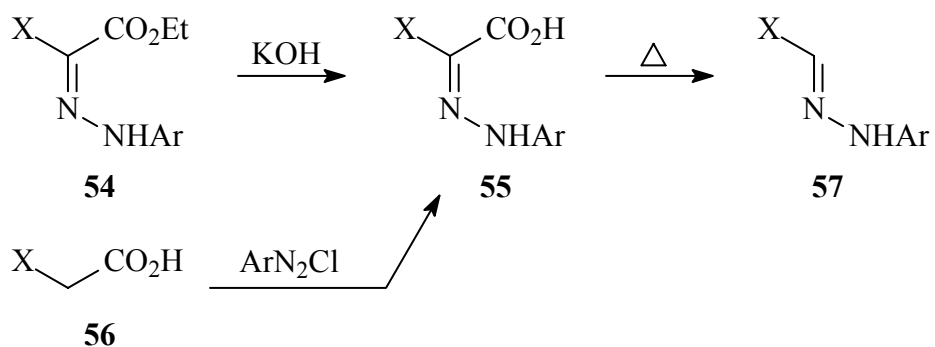


Scheme 9

Recent research at Kuwait and Cairo Universities showed that *N*-acetylazoles **46a,b**, **48**, **50** and **52** couple readily with aromatic diazonium salts to yield arylhydrazonals **47**, **49**, **51** and **53**¹⁰¹⁻¹⁰⁷ whose stereochemistry have not been defined. Phenacylbenzotriazole **52** has been coupled with aromatic diazonium salts to yield **53** that was suggested to exist in a (*Z*)-form. This form is stabilized by H-bonding with benzotriazole N-2 (cf. Scheme 10).¹⁰⁸



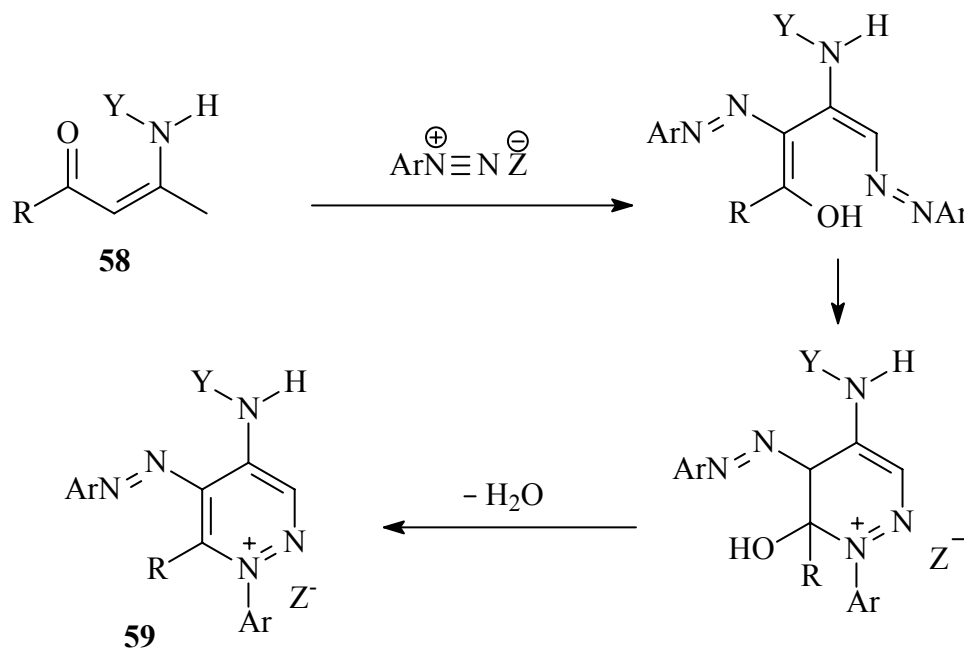
Scheme 10



Scheme 11

Functionally substituted arylhydrazones of type 1 where either X or Y = H are generally prepared from the corresponding esters **54** via conversion into the acid **55**¹⁰⁹⁻¹²⁴ and subsequent decarboxylation to give **57**.¹²⁵⁻¹³² One step synthesis from the appropriate acids **56** has also been reported (c.f. Scheme 11).^{133,134}

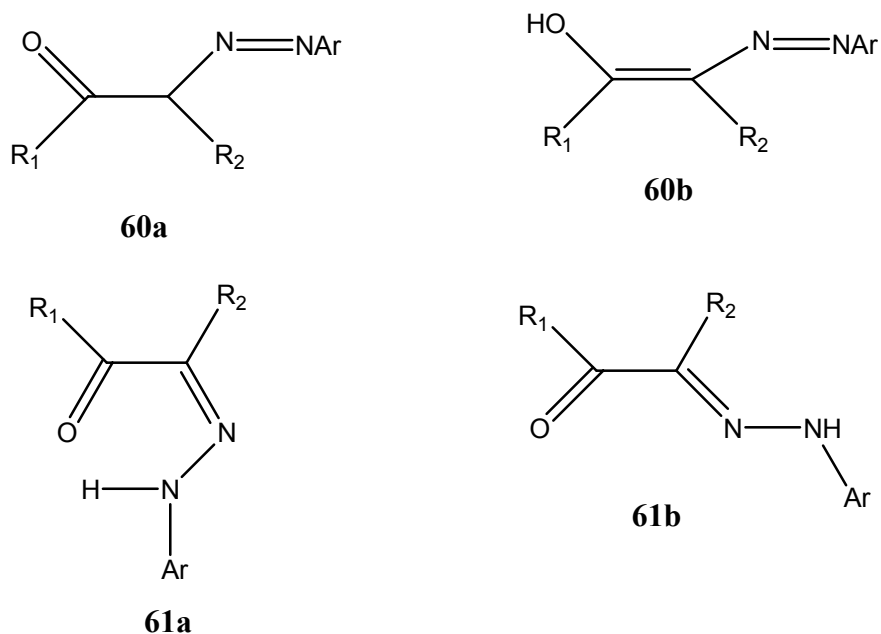
Interestingly coupling the enaminones **58** with aromatic diazonium fluoroborates have afforded **59**. The structure of this unexpected product is supported by X-ray crystallography. It is believed to be formed via intermediacy as shown in Scheme 12.^{135,136}



Scheme 12

3. Structure Investigation

α -Oxohydrazones may exist in azo form **60a**, eneazo form **60b**, (*Z*)- and (*E*)-hydrazone forms **61a** and **61b**. From time to time different methods utilizing roles variable for chemists by time presented at a supporting existence of these compounds in hydrazone form (cf. Scheme 13).



Scheme 13

Thus, it was assumed by Bamberger *et al.*¹³⁷ that (*Z*)-phenylglyoxal-2-nitrophenylhydrazones could be distinguished from the (*E*)- isomer by its relatively lower melting point, as in (*E*) recently H-bonding decrease tendency for association through intramolecular hydrogen bonding greater stability in certain solvents like benzene, deeper shade of colour and ease of crystallization.¹³⁷

Some authors believed that phenylhydrazones having a strong internal hydrogen bonding has a lower carbonyl band frequency in IR.¹³⁸ This finding was utilized to differentiate between the (*Z*) and (*E*) forms of pyruvamide phenylhydrazone.¹³⁹ The (*E*) form showed the carbonyl band at higher frequency than that of the (*Z*) form. On the other hand, IR studies¹⁴⁰ of phenylglyoxalarylhydrazones indicate that the isomeric (*Z*) and (*E*) forms of these compounds can be easily distinguished by the position of the carbonyl as well as the NH stretching bands. Tanner¹⁴¹ found that the carbonyl frequencies of both the (*Z*) and (*E*) forms of phenylglyoxal-2-nitrophenylhydrazone were almost the same (1641 and 1640 cm^{-1} , respectively) and that there was only a little difference in the NH stretching frequencies of these isomers (3128 and 3166, respectively).

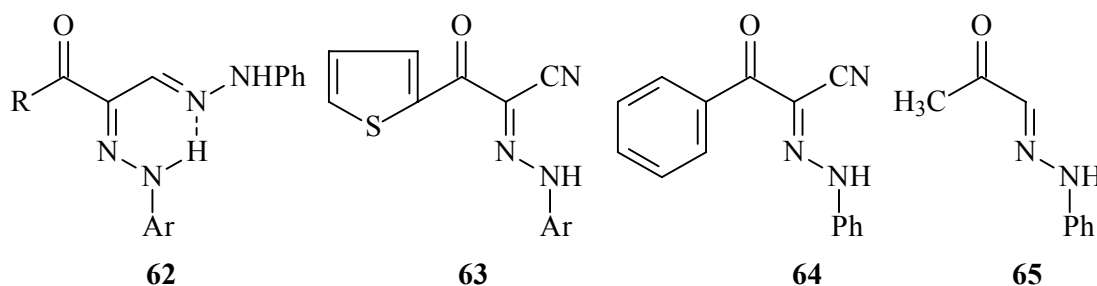
The NMR of the hydrazone NH of α -oxophenylhydrazones appears at δ 12-14 ppm. Studies of the isomeric forms in different solvents indicate that the equilibrium shifts in favor of (*E*) form in solvents that favor hydrogen bonding formation.

The structure of phenylhydrazones of four α -dicarbonyl compounds were determined from the IR and NMR spectra of the ^{14}N and ^{15}N isotopes. The compounds exist only in the phenylhydrazone tautomeric form and, except for the phenylhydrazones of phenylglyoxal in solution, primarily as the geometric isomer with the NHC_6H_5 group oriented away from the

carbonyl. The effect of solvent on the composition of the geometric isomerism equilibria was discussed.¹⁴² El-Ashry *et al.*¹⁴³ concluded that these compounds exist mainly in chelated hydrogen bonded form.

In the light of recent x-ray crystallography by Elnagdi *et al.*¹⁴⁴⁻¹⁵⁻⁴⁶ that arylhydrazone-3-oxoalkene nitriles exists in (*E*) form to make up for stereo electronic requirements previous conclusions about structure of arylhydrazone-ketones and ketoester should be rechecked (cf. structures **62-65**).

It can thus be concluded that the observed low field NH signal in ¹H-NMR is in fact due to extensive delocalization of nitrogen atom lone pair rendering hydrazone carbon atom electron rich. In support of this view ¹H-NMR of phenylazomalononitrile showed NH signal at δ 13.0 ppm. Here hydrogen bonding is not possible.



Scheme 14

4. Chemical Reactivity

4.1. Introduction

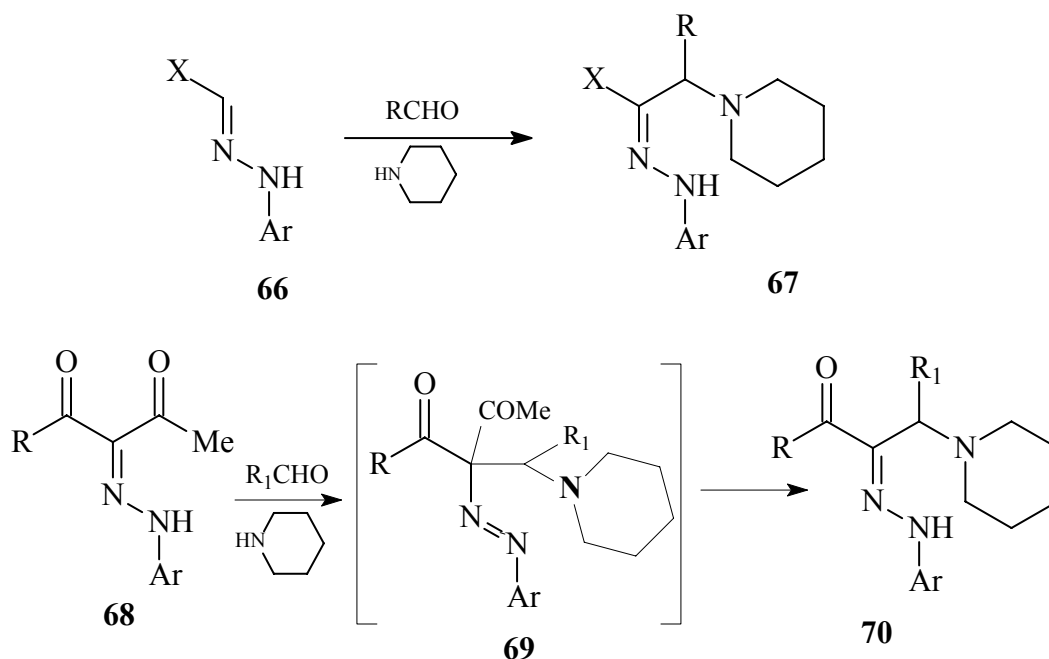
The most significant reactivity is the nucleophilicity of hydrazone carbon atom. This was noted since more than hundred years. Thus reactions like Mannich reaction, coupling reaction and halogenation have took place readily at such carbon. Recently Michael type addition was also described. Hydrazone nitrogen atom however remains the main site for attack by acylating and alkylating agents. It seemed that hard nucleophiles attack preferentially nitrogen atom, while soft ones attack preferentially at carbon atom.

The functional substituents retain their established reactivity pattern although generally become more electrophilic. Also multidentate reagents in several cases afford rings involving hydrazone moiety. In addition a variety of intramolecular cyclizations leading to cinnolines have been reported. In the following we will survey reported chemical reactivity pattern.

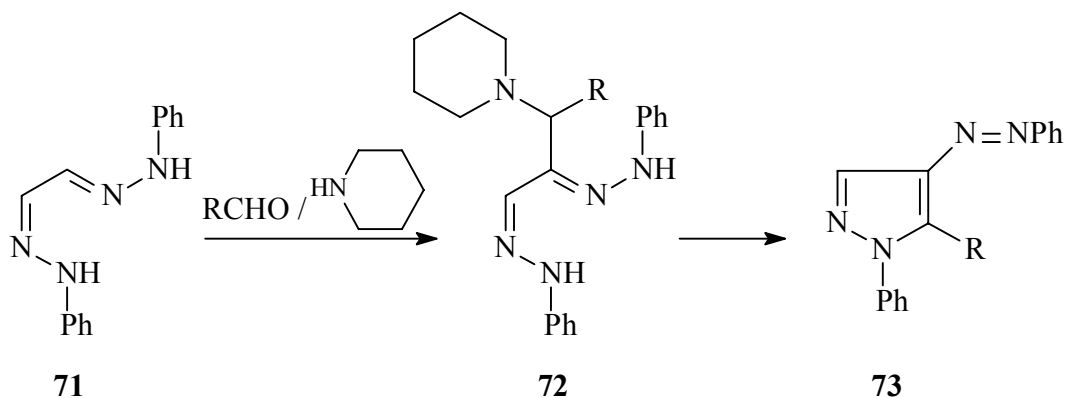
4.2. Reaction with electrophilic reagents

4.2.1. Reaction with carbon electrophiles

The reaction of α -ketohydrazones with Mannich reagents have been reported in the last century (c.f. formation of **67** from **66** is Scheme 15). Mustafa *et al.*¹⁴⁷ have shown that **68** undergo Mannich reaction at hydrazone carbon atom to yield intermediates **69** that readily undergo Japp-Klingemann cleavage yielding **70** in good yields. This reaction has recently been adopted to aromatic aldehydes.¹⁴⁷⁻¹⁵¹



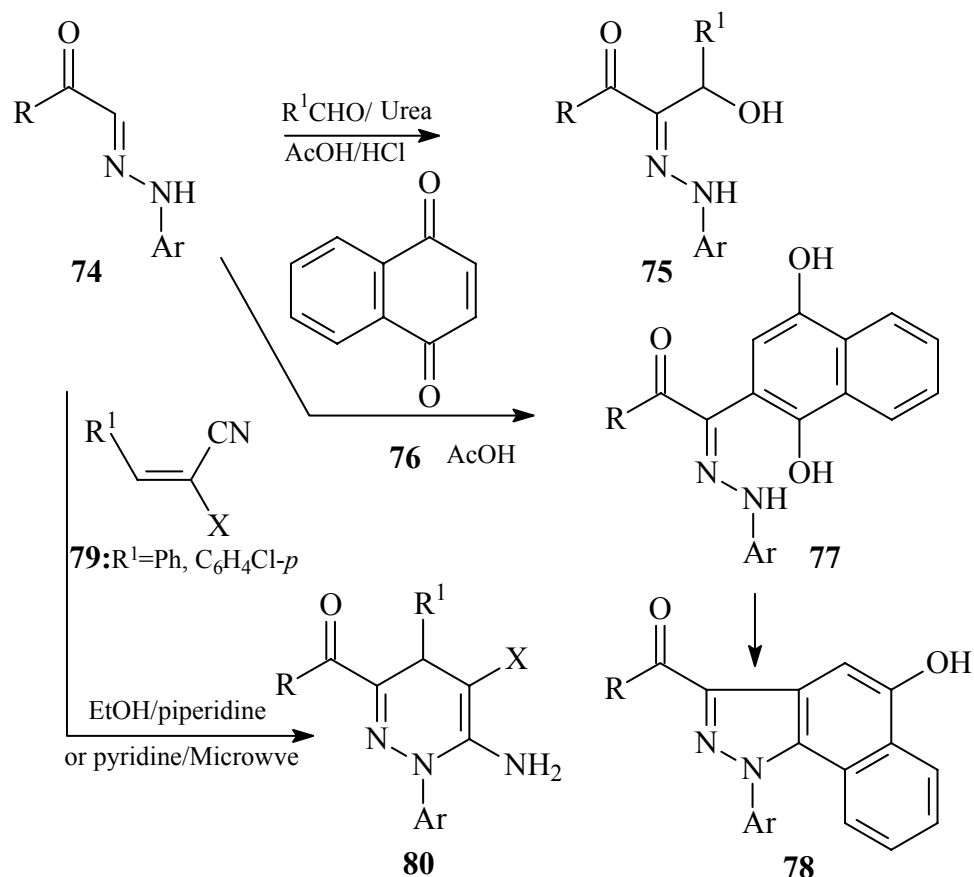
Scheme 15



Scheme 16

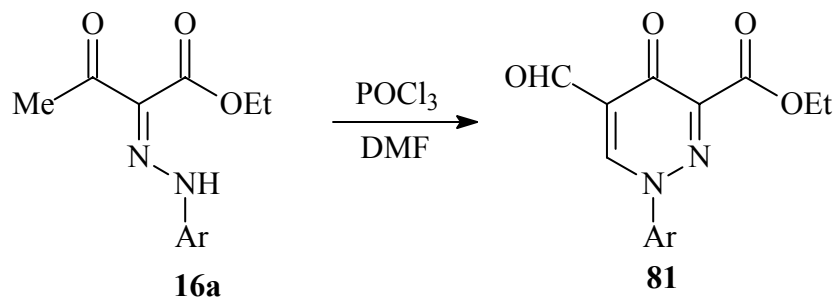
Glyoxaldiphenylhydrazone **71** also react with Mannich bases to yield either **72** or **73** depending on nature of utilized aldehyde (cf. Scheme 16).¹⁵²⁻¹⁵⁴

Aromatic aldehydes also react with **74** to yield **75**. In absence of urea the reaction does not proceed. Naphthoquinone **76** reacts with **74** to yield either **77** or **78** depending on applied reaction conditions. Cinnamionitriles **79** also reacted with **74** to yield dihydropyridazines **80** (cf. Scheme 17).¹⁵⁵



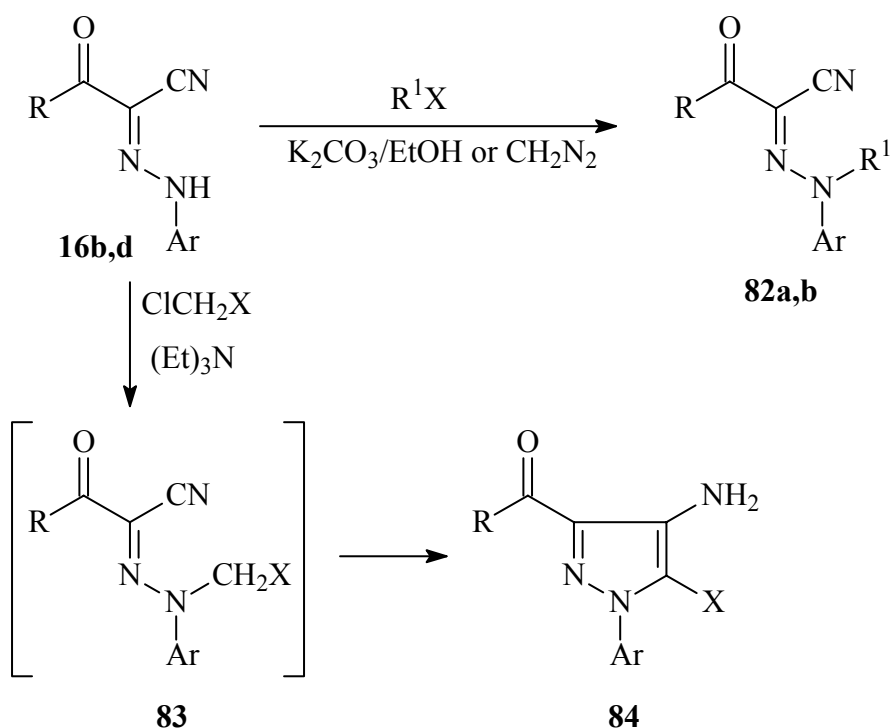
Scheme 17

Treatment of ethyl 2-phenylhydrazono-3-oxobutanoate **16a** phenylazoethyl-acetoacetate **16a** with Vilsmeier reagent affords pyridazine carboxylic esters **81** (Scheme 18).¹⁵⁶



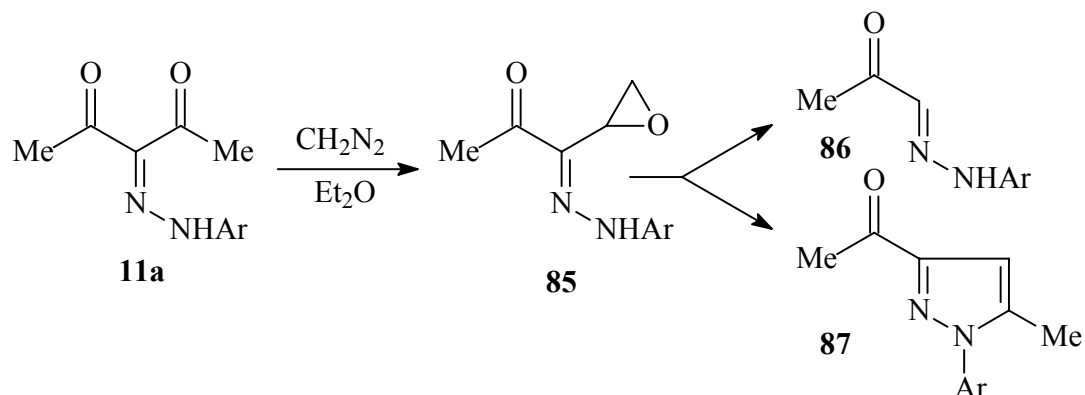
Scheme 18

In contrast to reported reactivity at carbon in this reaction, treatment of **16b,d** with alkylhalides affords N-alkyl derivatives **82a,b**¹⁵⁷⁻¹⁵⁹. The reaction of **16b,d** with chloroacetone, chloroacetonitrile or ethyl chloroacetate affords aminopyrazoles **84**, most likely, via intermediacy of non isolable acyclic **83**.¹⁶⁰



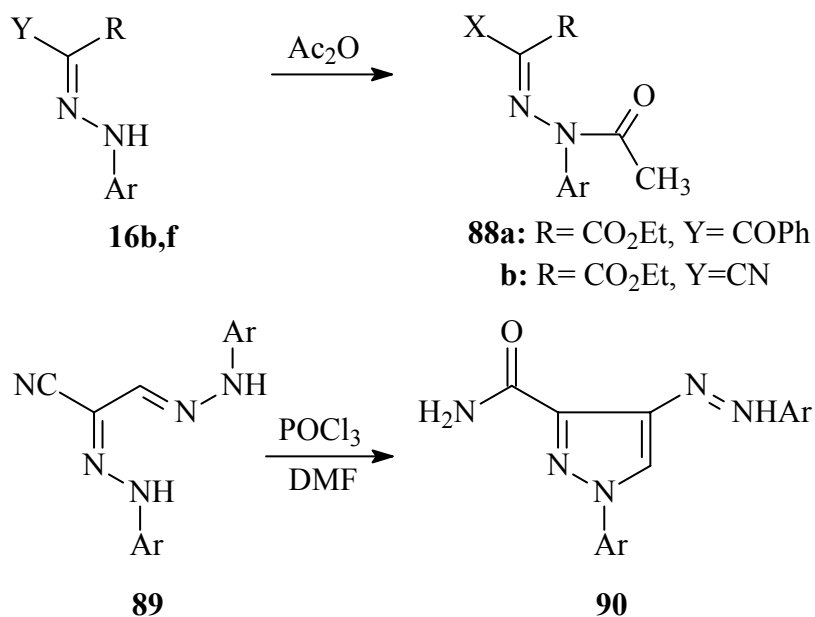
Scheme 19

The reaction of 3-(2-phenylhydrazono)pentane-2,4-dione **11a** with diazomethane afforded pyrazole **87** in addition to **85** and **86**.^{161,162} Although reaction sequence looks logical, this result should be checked again and reaction product should be characterized spectroscopically.

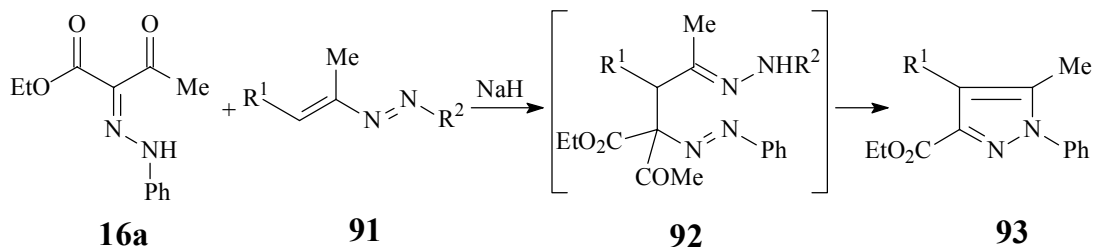


Scheme 20

Acetylation of **16b** and **16f** ($\text{R}=\text{CO}_2\text{Et}$, $\text{Y}=\text{COPh}$) give **88a,b** in good yield.^{163,164} Recently Elnagdi et al¹⁶⁵ have reported both N and C-acetylation and benzylation of glyoxal diphenylhydrazones. Successful Vilsmeier formylation of **89** followed by cyclization and hydrolysis to yield pyrazole **90** has been also recently reported.¹⁶⁶



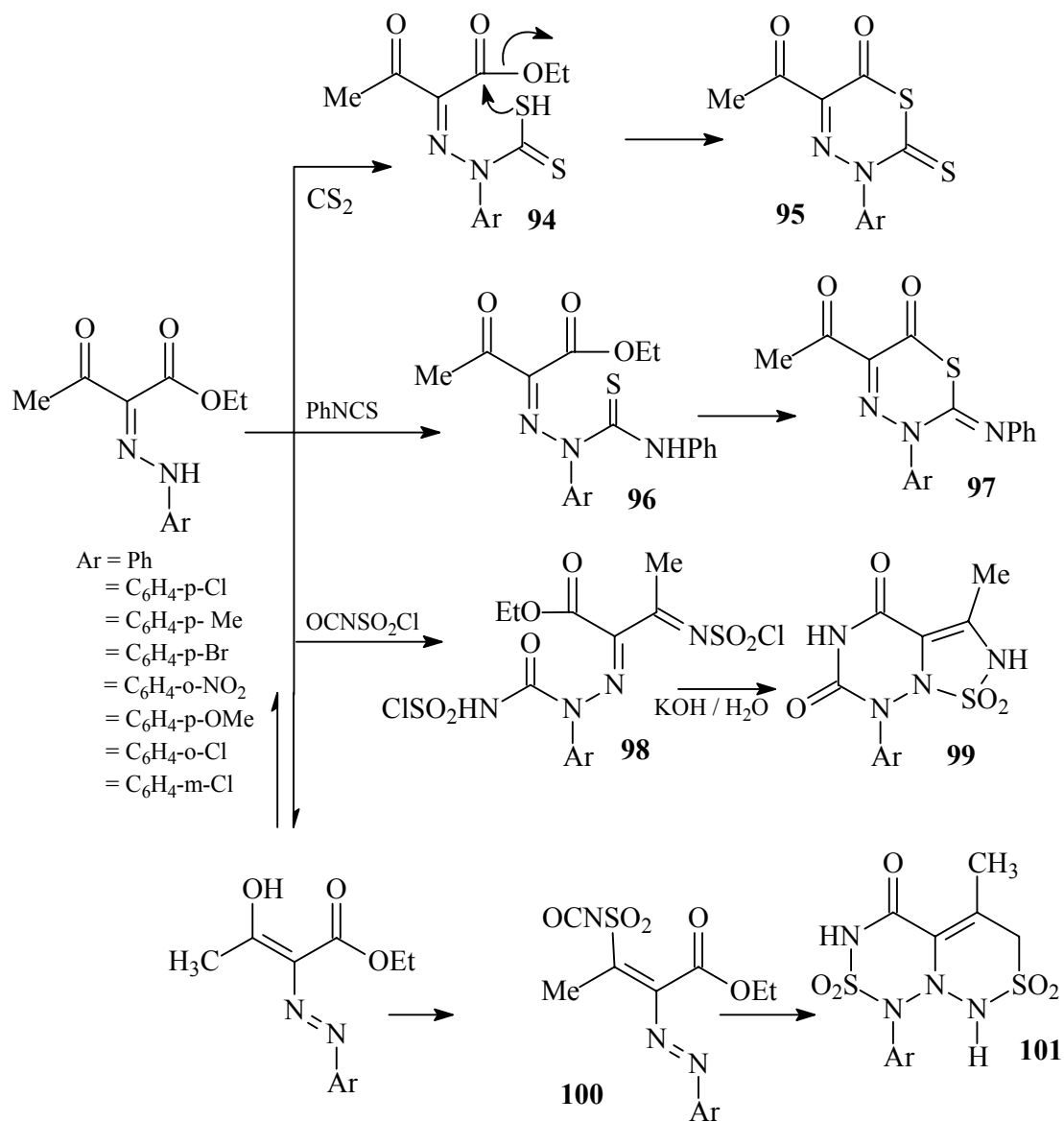
Scheme 21



Scheme 22

The azadiene **91** reacts with **16a** to yield the pyrazole **93**. Initial formation of adduct **92** is postulated.¹⁶⁷

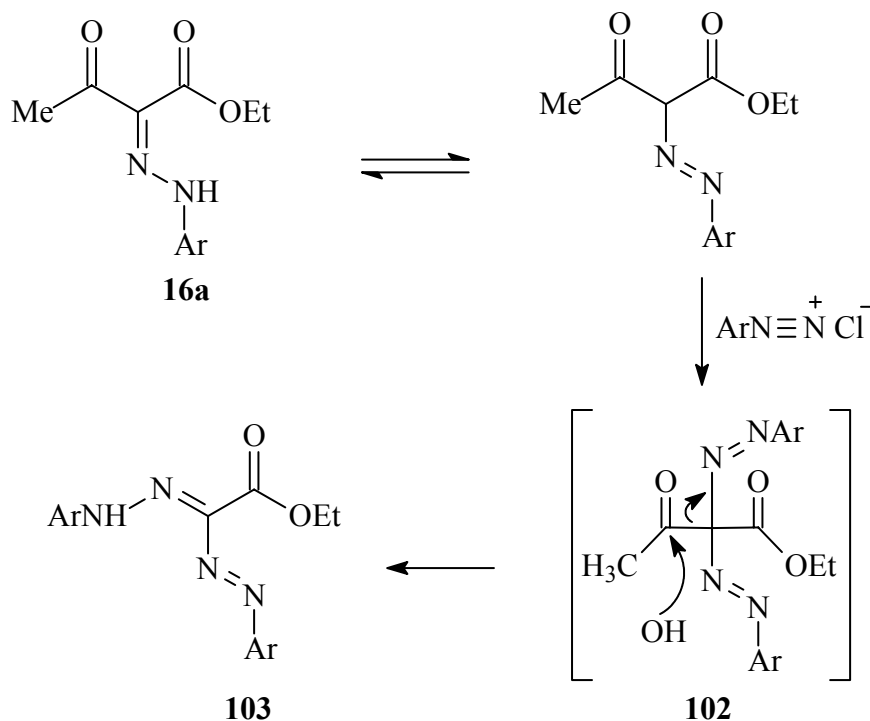
The hydrazone nitrogen atom is the preferred site of attack by electrophilic *sp* carbon atoms. Thus carbon disulphide reacts with **16** to yield **95** via intermediate **94**. Similarly phenylisothiocyanate affords **97**, most likely via intermediate **96**. The reaction of **16** with chlorosulfonylisothiocyanate affords at 0-5 °C the chlorosulphonyl derivative **98** that is readily cyclized into **99** by aqueous KOH in presence of thiophenol. At 105-110 °C however enol form of **16** affords **101** via intermediacy of **100**.^{168,169} It should be mentioned however that in absence of convincing spectral evidence supporting these structures reported conclusions seems highly unlikely. For example **97** can also cyclized to 1,2,4-triazine formation of N-N bonds or N-S bonds as well as highly strained non aromatic heterocycles seems in light of modern knowledge least likely.



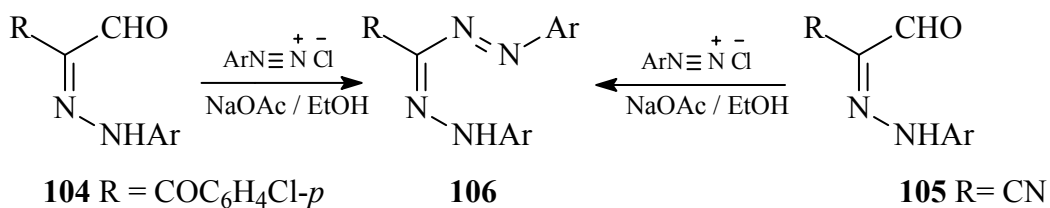
Scheme 23

4.2.2. Reaction with nitrogen electrophiles

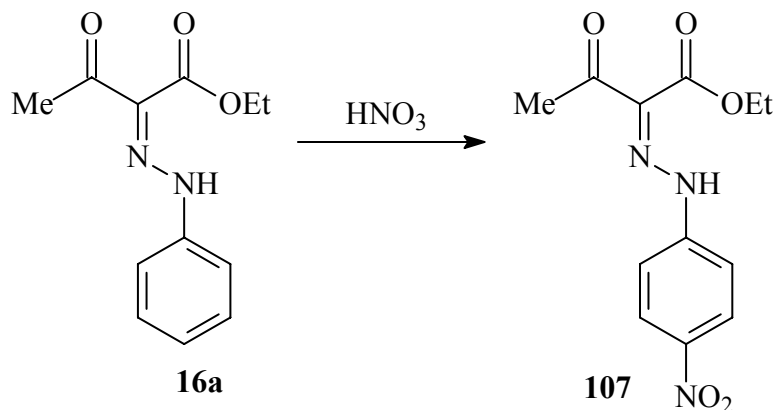
Coupling occurs at hydrazone carbon atom and formed bisazo in case of hydrazones of type **1** coupled normally undergo a Japp-Klingemann cleavage of a functional group. Thus, **16a** couple with aromatic diazonium salts to yield intermediate **102** that is directly converted into the isolable formazan **103**.¹⁷⁰

**Scheme 24**

Formation of formazan **106** has been also observed upon coupling arylhydrazonoaldehyde **104a,b** and/or **105** with aromatic diazonium salts (c.f. Scheme 25).^{171,172}

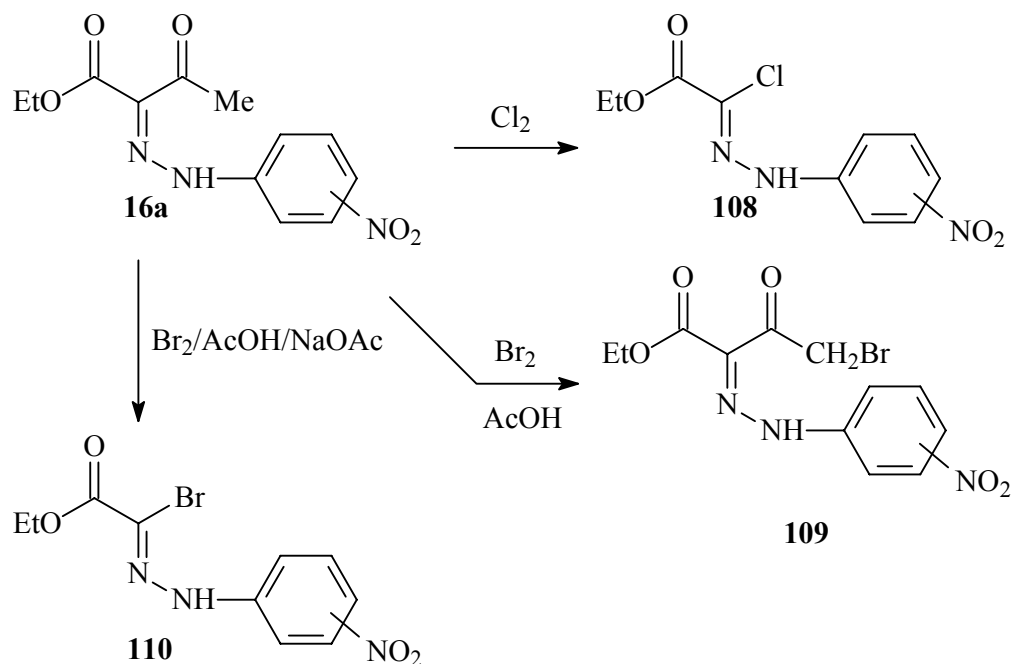
**Scheme 25**

Ethyl 2-phenylhydrazono-3-oxobutanoate **16a** is readily nitrated at phenyl moiety on treatment with nitric acid to give **107**.²⁴

**Scheme 26**

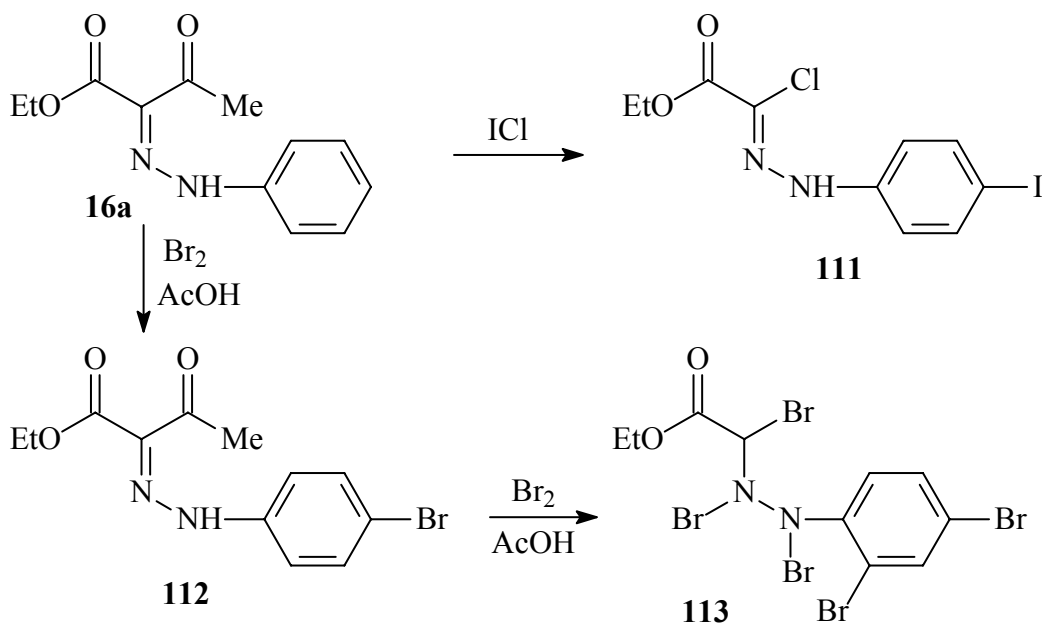
4.2.3. Reactions with halogen electrophiles

Halogenation occurs either at hydrazone carbon or at aryl or alkyl moieties depending on the nature of substituents on hydrazone moiety. Normally in acetic acid and in presence of sodium acetate halogenation occurs at hydrazone carbon and is followed by Japp-Klingemann cleavage of one of the functional groups attached to hydrazone carbon. If the hydrazone aryl moiety carry a strong electron attracting substituent (e.g. nitro function) initial halogenation occur at alkyl moieties in the molecule when they do exist. For example chlorination of **16a** (Ar = C₆H₄NO₂) with chlorine gas gives the hydrazone halides **108**.¹⁷³⁻¹⁷⁵ Bromine in acetic acid affords mono bromination products **109**. If bromination is conducted in acetic acid in the presence of sodium acetate bromination at hydrazone carbon followed by Japp-Klingemann cleavage yielding **110** occurs. We believe that under such basic conditions the reacting species is a molecule of **16** that is capable of delocalizing negative charge on hydrazone carbon making it thus sufficiently nucleophilic.¹⁷⁶⁻¹⁸⁰

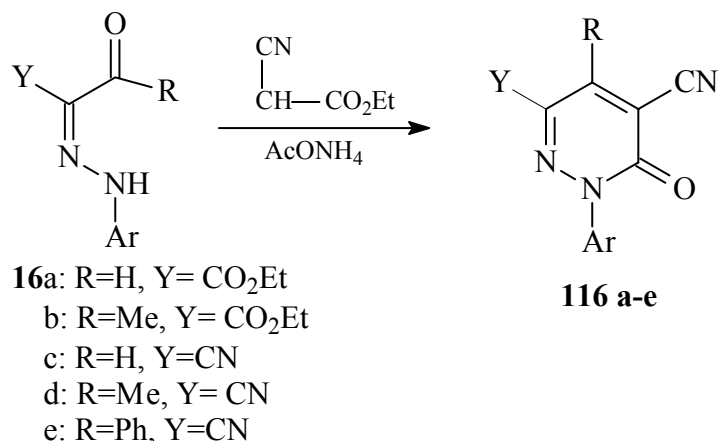


Scheme 27

It has been reported that if the arylhydrazone moiety is not substituted it can also participate in these reactions. For example chlorination of **16a** with iodine chloride gives product of attack at both hydrazone carbon and phenyl moiety yielding **111**.¹⁸¹ Bromination of **16a** gives **112**. Utility of excess of bromine is believed to yield **113**.¹⁸² Again spectroscopic evidence or X-ray crystallography is needed to support or revise these structures.

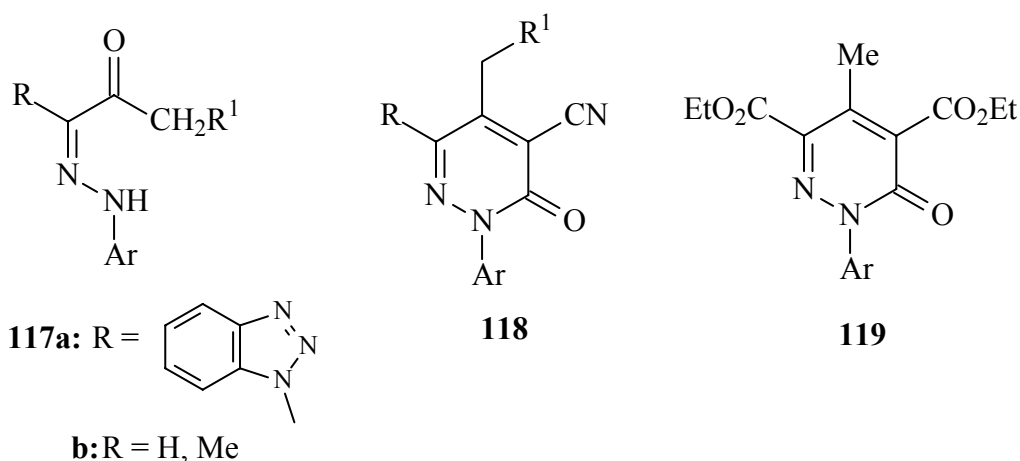


Scheme 28



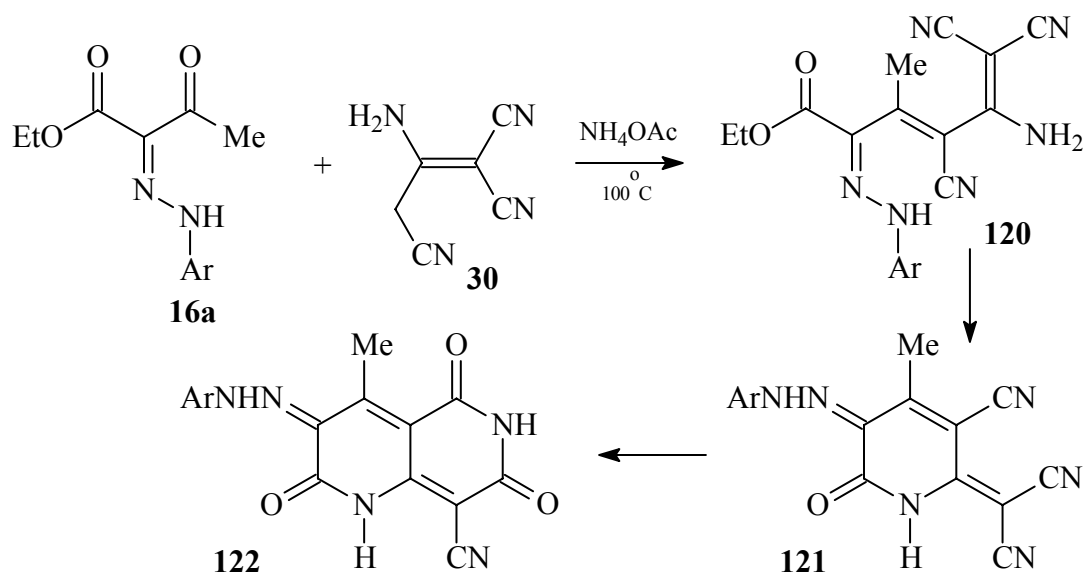
Scheme 30

Benzoylacetonitrile, cyclohexanone, cyanoacetamide and malononitrile were also condensed with arylazo derivatives to yield pyridazinones.¹⁹² The benzotriazolyl derivative **117** and the hydrazonopyruvate also condense with ethyl cyanoacetate to yield **118** and **119**, respectively.¹⁸⁶



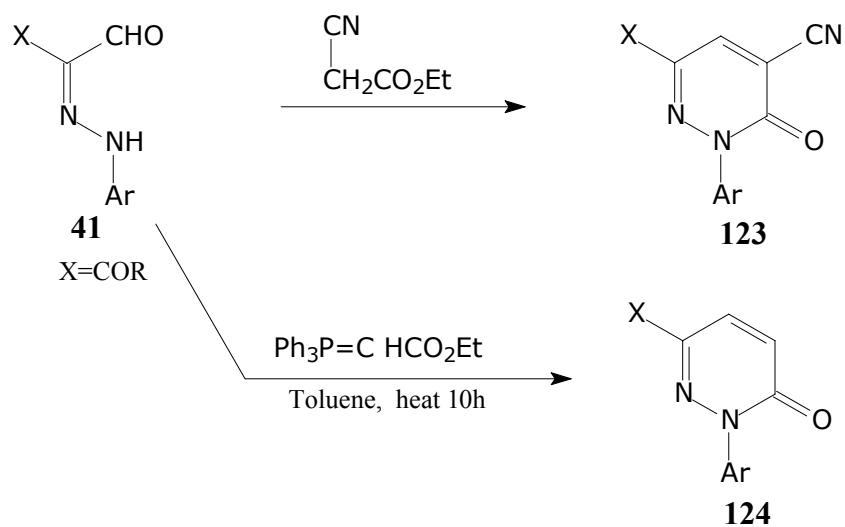
Scheme 31

Condensation of **16** with 2-aminoprop-1-ene-1,1,3-tricarbonitrile **30** gives **122** via **120** and **121**.^{193,194} Although this work has been published recently, the lack of convincing spectral evidence to support these conclusions seems quite strange as several alternate structures looks also possible.



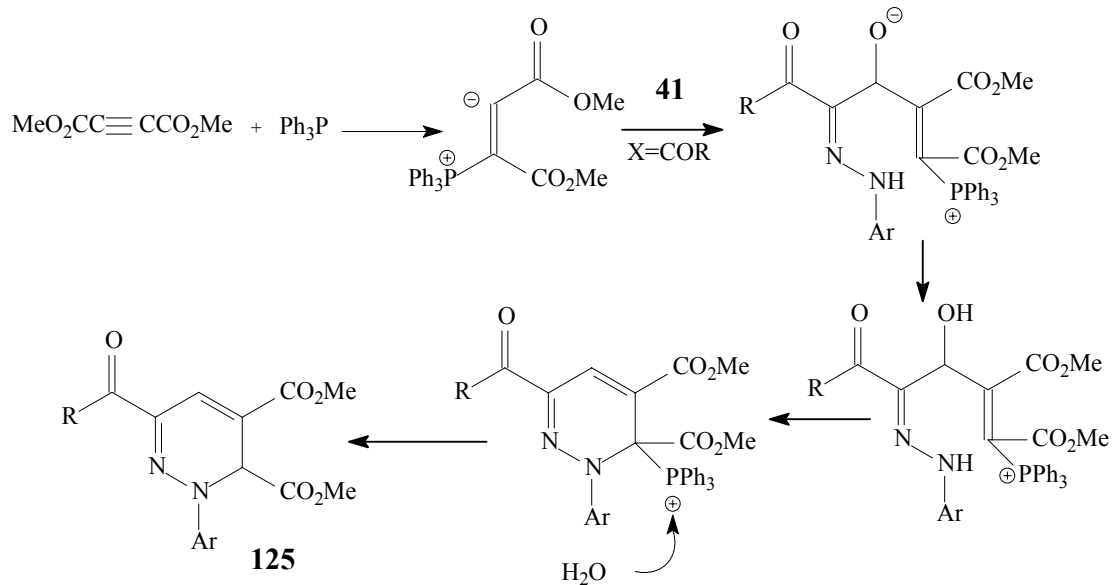
Scheme 32

The arylhydrazones **41** also reacted with ethyl cyanoacetate yielding pyridazinones **123**. Wittigs reagents also with **41** to yield the corresponding pyridazinones **124** in good to excellent yields.^{195,196}



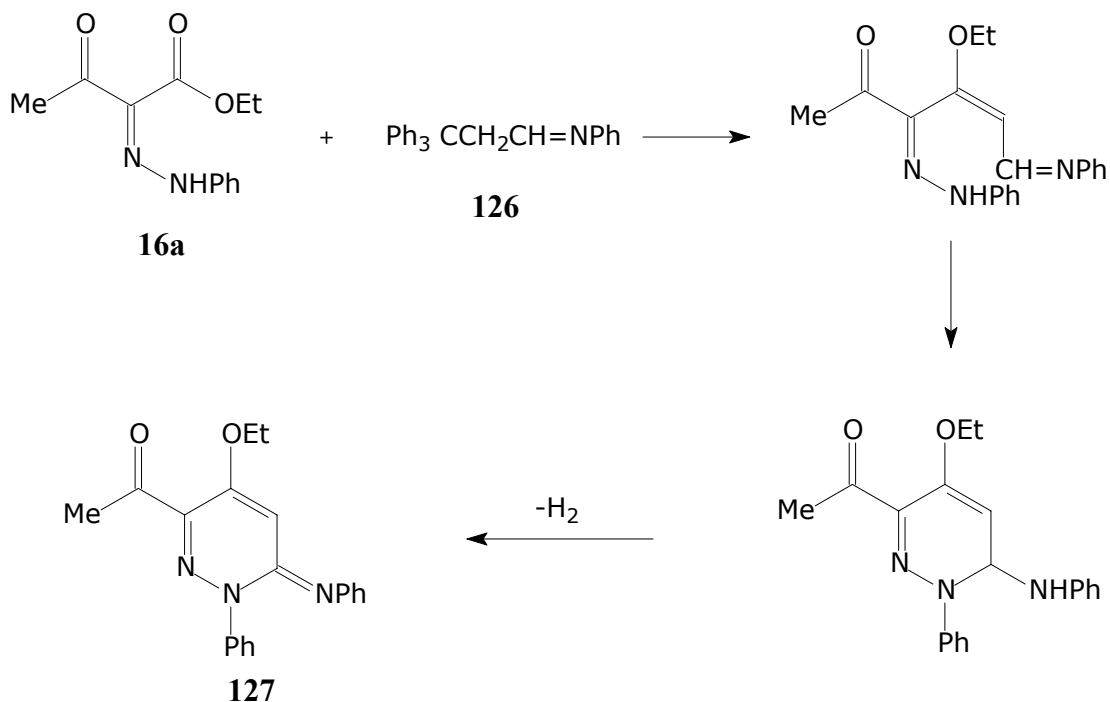
Scheme 33

A carbon Mitsunobu reaction of **41**; $\text{X} = \text{CHAr}$ (or better a Baylis-Hillman like reaction) has been reported. Thus reacting **41**; $\text{X} = \text{COAr}$ with dimethyl acetylene dicarboxylate and triphenylphosphine in methylene chloride gives the pyridazinedicarboxylates **125**. It is believed that this reaction proceeds via sequence shown in Scheme 35.^{197,198}



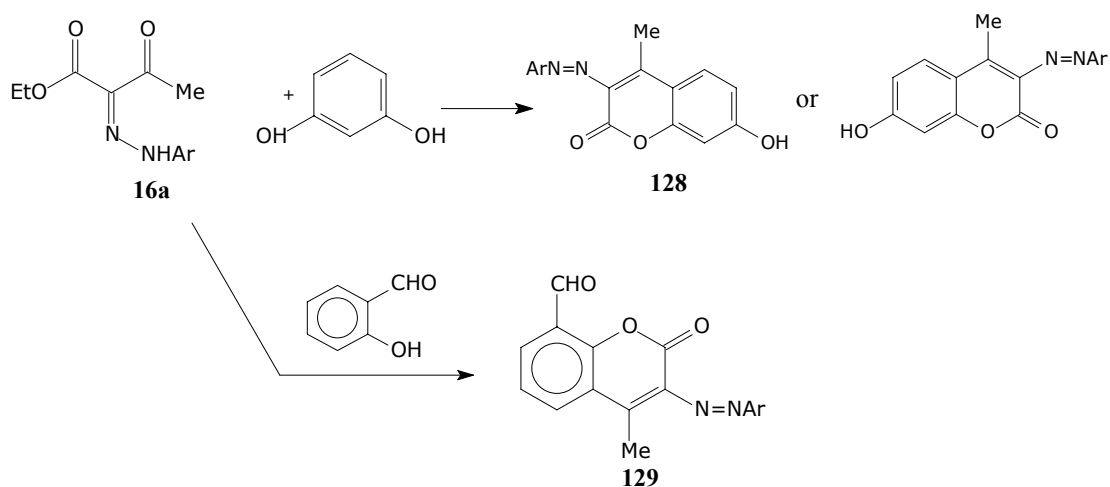
Scheme 34

The reaction of **16a** with **126** gives **127**.¹⁹⁹



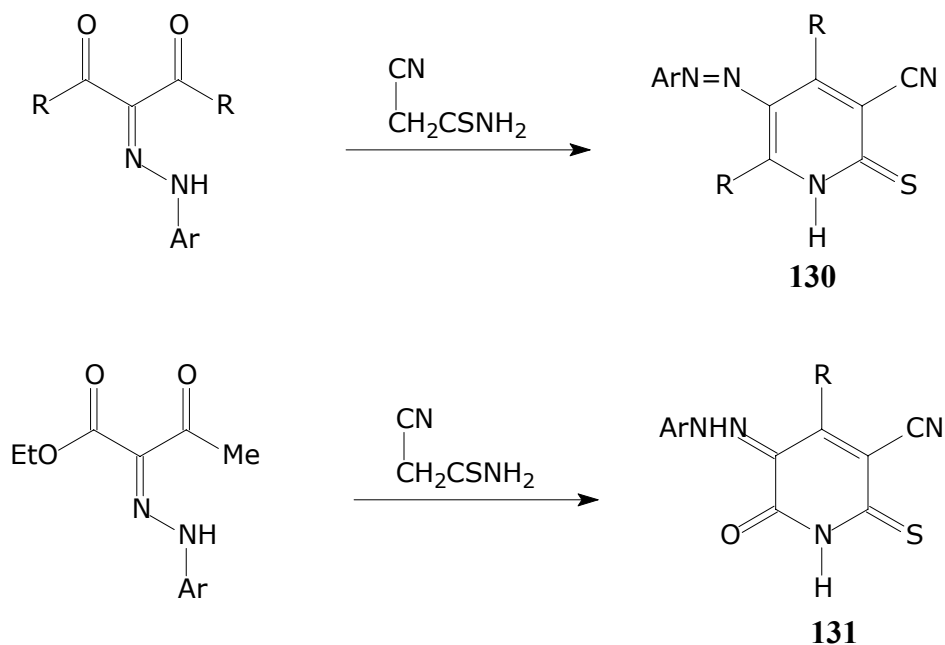
Scheme 35

Phenols condense with **16** to yield chromene derivatives. For example condensation of **16a** with resorcinol affords **128**, salicylaldehyde gives **129**.^{35,37}



Scheme 36

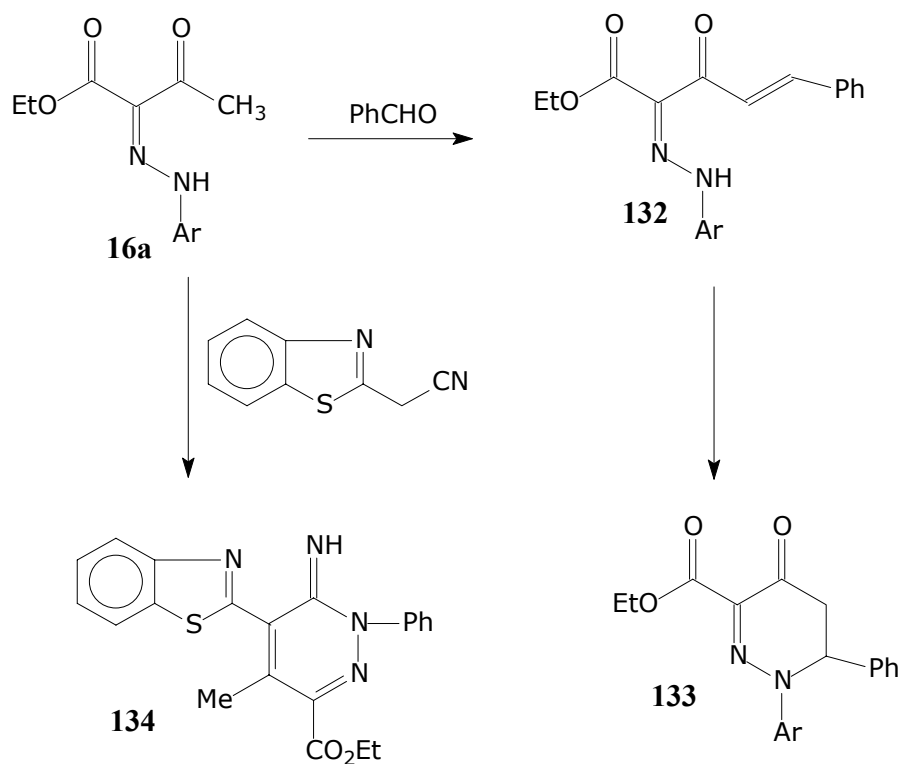
Cyanothioacetamide condensed with **16a,b** to yield **130** and **131**, respectively.¹⁶



Scheme 37

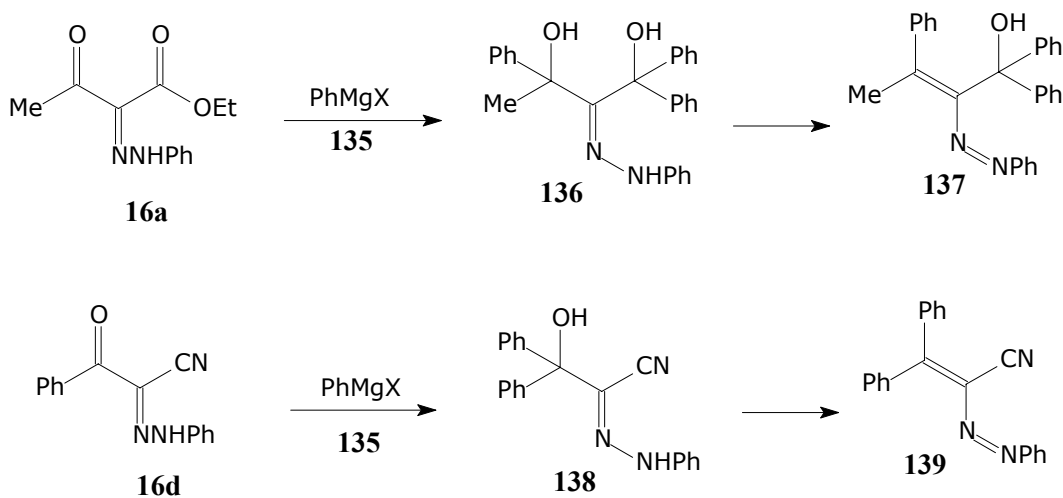
Benzaldehyde condenses with **16a** to yield pyridazinones **133**. Intermediate **132** could be isolated. Compound **133** can also exist in enol form or may also readily autooxidize into

aromatic pyridazinones. It seems that of value to reconfirm the suggested structure, condensation of benzothiazolylacetonitrile with **16** gives **134**.^{186,200,201}



Scheme 38

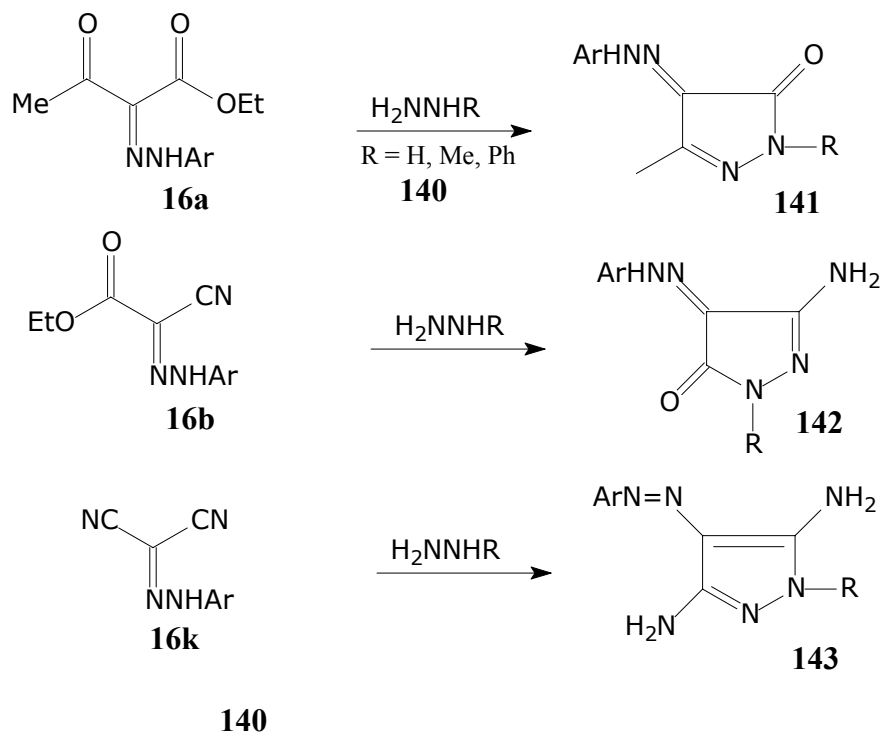
The reaction of Grignard reagent **135** with **16a,d** gives **136** and **138** which were readily dehydrated by reflux in acetic acid to yield **137** and **139**, respectively.²⁰²



Scheme 39

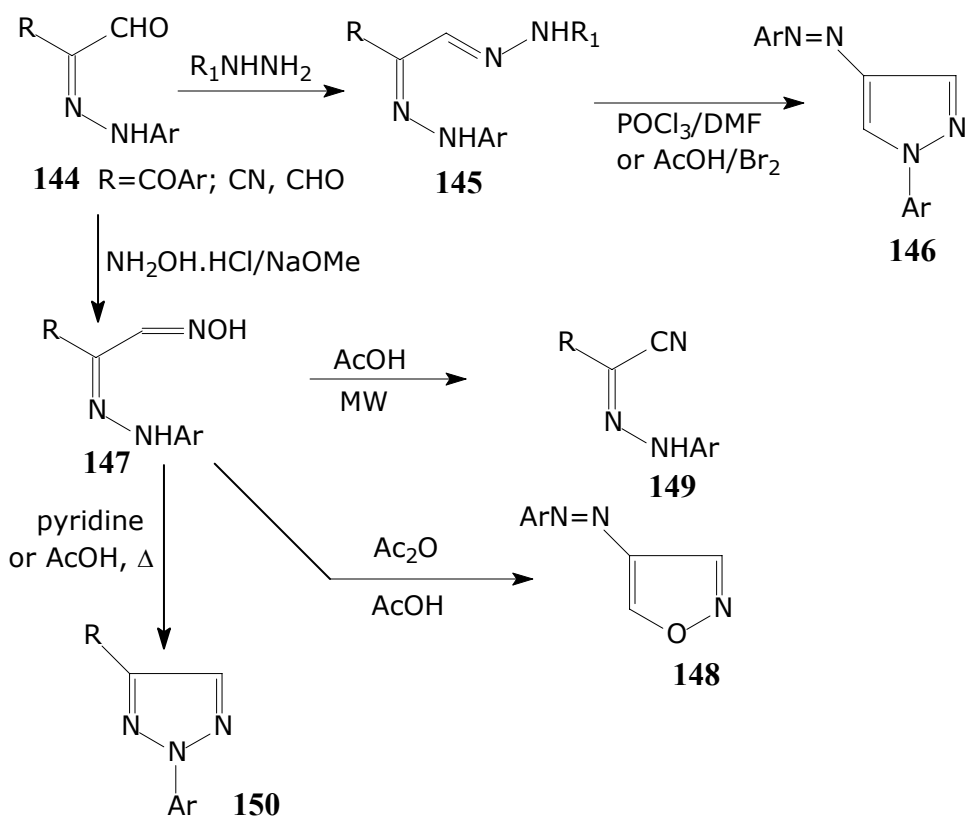
4.3.3. Reactions with nitrogen nucleophiles

These reactions have been extensively investigated in the literature because of potential utility of formed arylazo heteroaromatics in dye industry. Quite a number of arylazopyrazolones and aminoarylazopyrazoles is commercialized. It is well established that **16a,b,k** react with hydrazine derivatives **140** to yield pyrazolone **141** or arylazoaminopyrazoles **142** and **143**.²⁰³⁻²⁰⁷



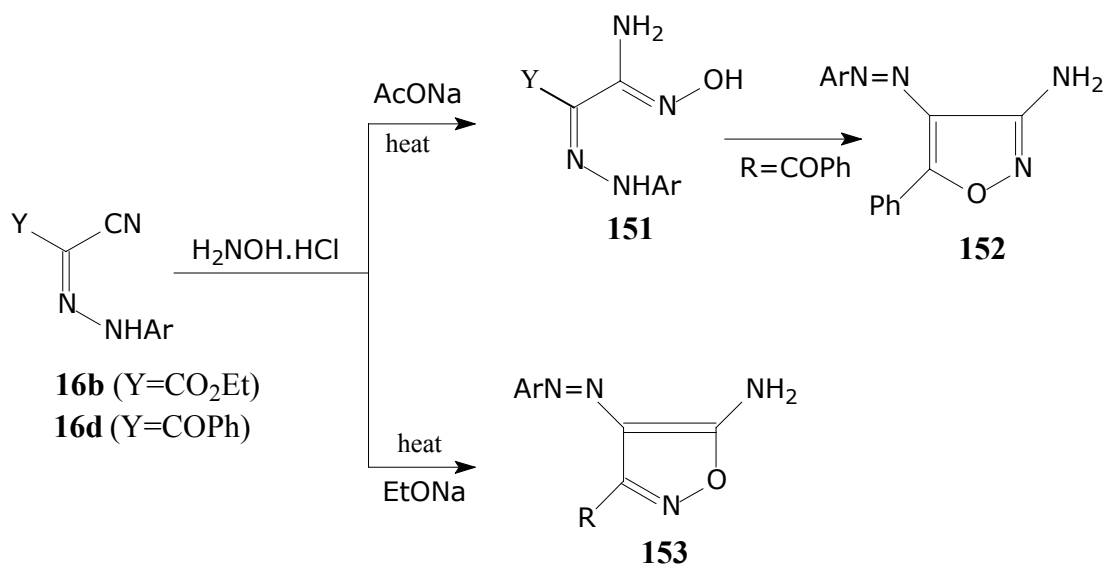
Scheme 40

Recently, however, Elnagdi *et al.*²⁰⁸ have reported that reaction of **144** with hydrazines affords the stable hydrazones **145**. These could be cyclized only under drastic conditions into pyrazoles **146**²⁰⁹⁻²¹¹. It can thus be suggested that this is beyond the stability of these hydrazones. Hydroxylamine hydrochloride reacts with **144** in basic media to yield isoxazolones **148**.^{212,213} However, again only oximes **147** were produced from reaction of **144** with hydroxylamine. The latter either cyclised into 1,2,3-triazoles **150**^{214, 215} or were converted into nitriles **149**²¹⁶ by action of acetic acid. Only upon reflux in Ac₂O isoxazoles **148** were produced.



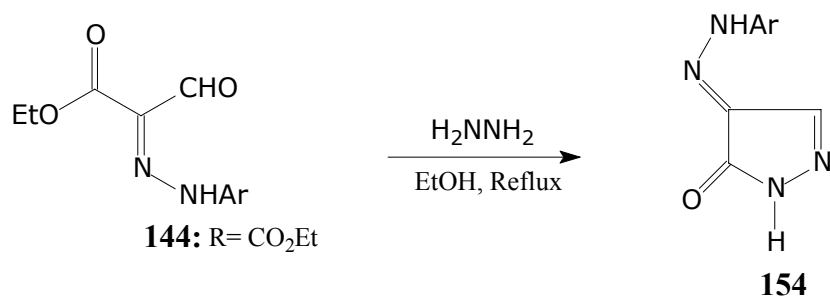
Scheme 41

The reaction of hydroxylamine hydrochloride with **16b,d** derivatives give amidoximes **151** that are converted into isoxazoles **152** upon reflux in ethanolic sodium ethoxide or treated with concentrated sulfuric acid. On the other hand when the reaction is conducted in ethanolic sodium ethoxide, isomeric 5-aminoisoxazoles **153** were produced. The dependence of the products on the applied reaction conditions is attributed to extra activation of cyano function in protic media.²¹⁷



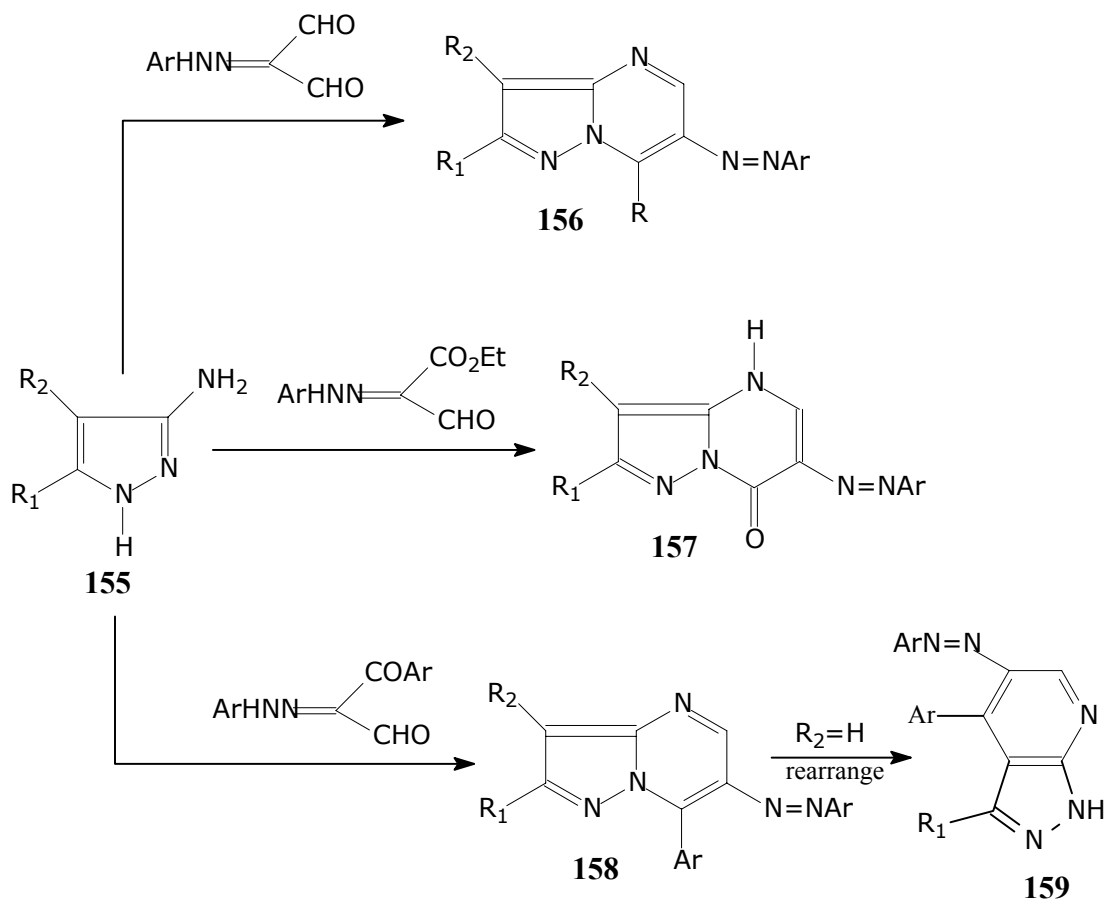
Scheme 42

The ester **144** afforded arylazopyrazoles **154** upon treatment with hydrazine hydrate in refluxing ethanol.^{218,219}



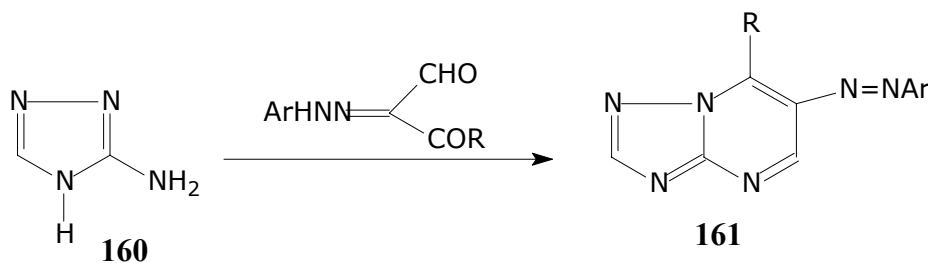
Scheme 43

Aminopyrazoles **155** condense with arylhydrazonals to yield pyrazoles[1,2-*a*] pyrimidines **156-158** that rearranged in some cases when C-4 in pyrazole is unsubstituted into pyrazoles[3,4-*b*]pyridines **159**.^{16,220}



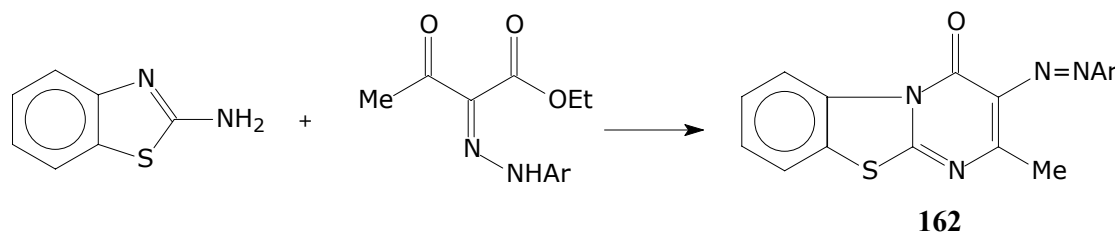
Scheme 44

In a similar way 1*H*-1,2,4-triazole-5-amine **160** reacted with arylhydrazone to yield triazolo[1,5-*a*]pyrimidines **161**. The structure of these derivatives was established by x-ray diffraction analysis.^{198,221,222}



Scheme 45

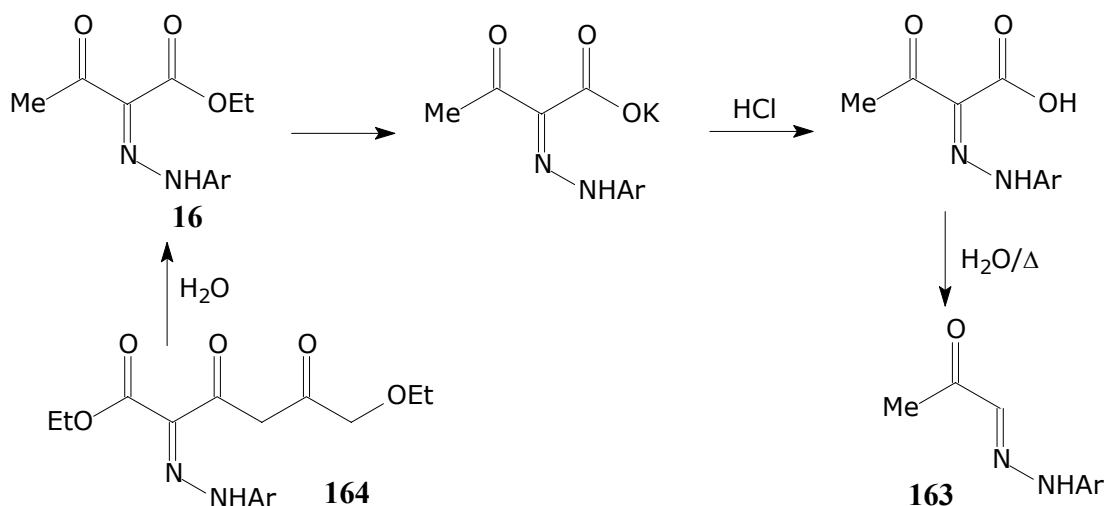
2-Aminobenzothiazole reacts with **16a** to yield **162**.²²³



Scheme 46

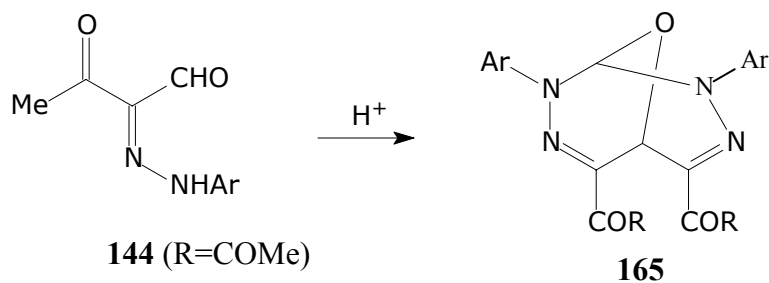
4.3.4. Reaction with oxygen nucleophiles

Hydrolysis of ester function in **16** and subsequent decarboxylation of the formed acid that readily decarboxylate into pyrovaldehyde-1-phenylhydrazone **163** by action of alcoholic or aqueous sodium hydroxide is well established route to **163**. The diester **164** is readily converted upon treatment with water into **16**.^{224,225} Again this old reaction should be rechecked as possible cyclization into pyridazin-4-one can not be overlooked.



Scheme 47

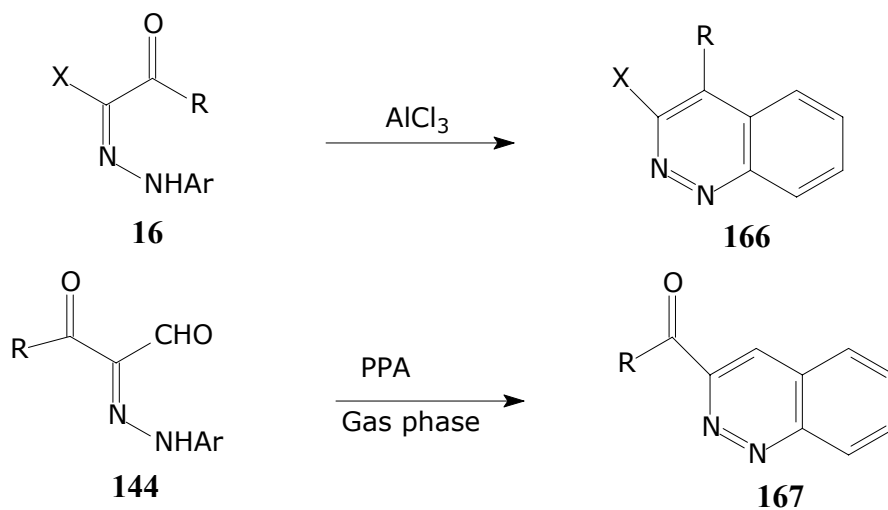
3-Oxo-2-arylhydrazonals **144** ($\text{R} = \text{COMe}$) are reported to dimerise readily upon reflux in acid media. The structure of the dimer **165** was confirmed by X-ray crystal structure determination.¹⁷⁰



Scheme 48

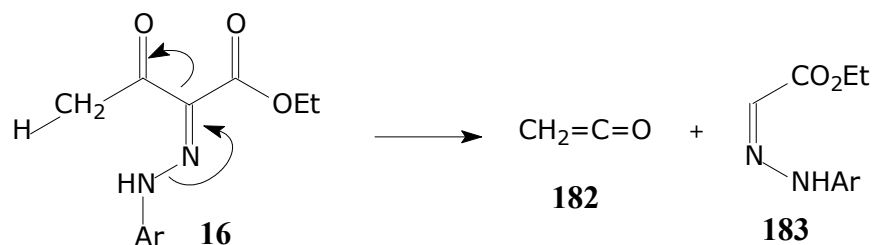
5. Intramolecular Processes

2-Oxoarylhydrazones **16** are readily cyclised in presence of Lewis acids into **166**. Similarly **144** are cyclised either by the action of polyphosphoric acid or upon pyrolysis in the gas phase into **167**.^{226,227}



Scheme 49

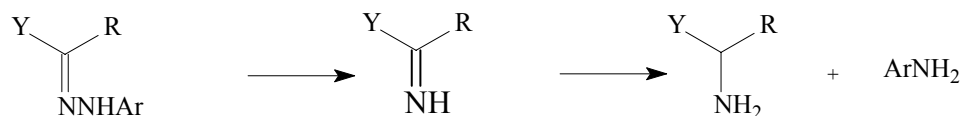
Gas-phase pyrolysis of **16** gives **168** and **169** via a six-membered transition state.^{17,228}



Scheme 50

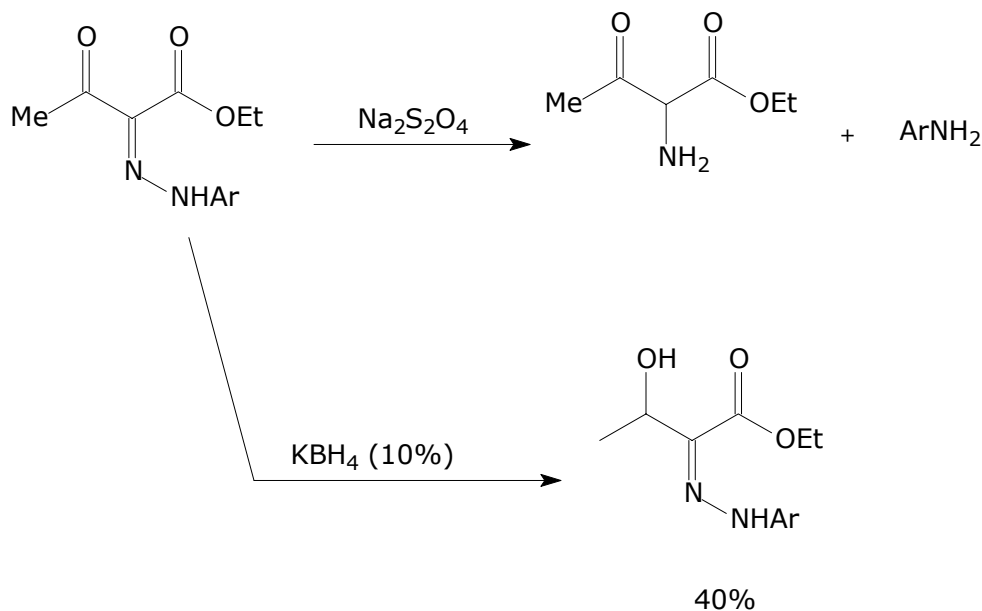
6. Reduction

Reduction of arylhydrazone **16** at dropping mercury electrode proceeds in two successive 2e processes. Initially reductive cleavage of N-N bond occurs. This is followed by 2e reduction of C=NH yielding pi-functionally substituted amines. Again we believe that these results need to be rechecked as functional amines are unstable compounds and although may be formed in solution isolated products should be carefully identified by modern tools.²²⁹



Scheme 51

The arylhydrazone moiety in **16** is reduced by sodium dithionite into aromatic amine and an α -amino ester. While in potassium borohydride (10%) reduction of carbonyl group was occurred (cf. Scheme 52).^{230,231}



Scheme 52

7. References

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