

Reactions of nitrilimines with heterocyclic amines and enamines. Convenient methodology for synthesis and annulation of heterocycles

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Abstract

This review summarizes the reactions of nitrilimines, generated *in situ* by base-catalyzed dehydrohalogenation of the respective hydrazoneyl halides, with aminoazoles, aminoazines and various types of enamines. It also presents the highlights of recent developments in the utility of such reactions for synthesis of a variety of heterocycles which are not obtainable by other synthetic means. Such reactions provide convenient strategies for synthesis and annulation of heterocycles. It covers the literature from 1985 to mid 2006.

Keywords: Aminoazoles, aminoazines, 1,3-dipolar cycloadditions, hydrazoneyl halides

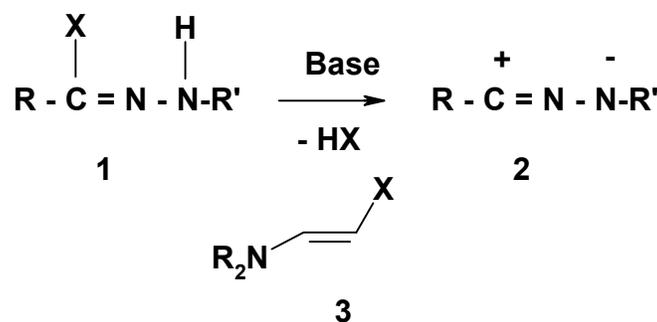
Contents

1. Introduction
2. Reactions with aminoazoles
 - 2.1 Aminopyrazoles
 - 2.2 Aminoimidazoles
 - 2.3 Amino isoxazoles
 - 2.4 Aminothiazoles
 - 2.5 Aminotriazoles
 - 2.6 Aminotetrazoles
3. Reactions with aminoazines
 - 3.1 Aminopyridines
 - 3.2 Aminopyrimidines
 - 3.3 Aminopyrazines
 - 3.4 Aminotriazines
4. Reactions with enamines

- 4.1 Acyclic enamines
 - 4.2 Endocyclic enamines
 - 4.3 Exocyclic enamines
 - 4.4 Heterocyclic enamines
 - 4.5 Ketene aminated
- 5. Conclusions
 - 6. References

1. Introduction

Ever since the first identification of nitrilimines **2**, their chemistry has developed dramatically during the past 40 years. Their ease of generation from different precursors coupled with the highly regio- and stereoselective nature of their cycloaddition reactions has resulted in extensive use as key synthons in many heterocyclic syntheses. Furthermore, hydrazonoyl halides **1** are the most commonly used precursors of nitrilimines due to their stability and their easy accessibility from different precursors. Conversion of **1** into **2** is usually accomplished by treatment of the former **1** with a suitable base such as triethylamine. The mechanism of such a conversion has been reported by Shawali et al.¹⁻³ At present, a huge variety of hydrazonoyl halides have been described and several aspects of their chemistry have been reviewed by Shawali et al.⁴⁻⁹ In addition, enamines **3** have proved to be versatile synthetic precursors for synthesis of heterocycles and natural products. Several review articles covering their chemistry have appeared in literature.¹⁰⁻¹⁷ A survey of these reviews together with those dealing with the chemistry of nitrilimines and their hydrazonoyl halides precursors reveals that little focus, if any, has been made hitherto on reactions of nitrilimines with enamines and heterocyclic amines. Our intention in this review is to remedy this situation through presenting the highlights of such reactions that have been reported from our laboratory and from others within the period from 1985 to mid 2006 and contained in Chemical Abstracts. Reactions already reported before 1985 will not be included in this review unless required for the sake of congruity. Also, reactions of heterocyclic amines that lead to the formation of arylazoheterocycles will not be covered here as such reactions have been surveyed in a recent authoritative review by Shawali et al in 2003.⁹ The usefulness of the reactions to be reviewed herein arises from their versatility and remarkable utility in annulation and ring transformations of various heterocycles (Scheme 1).

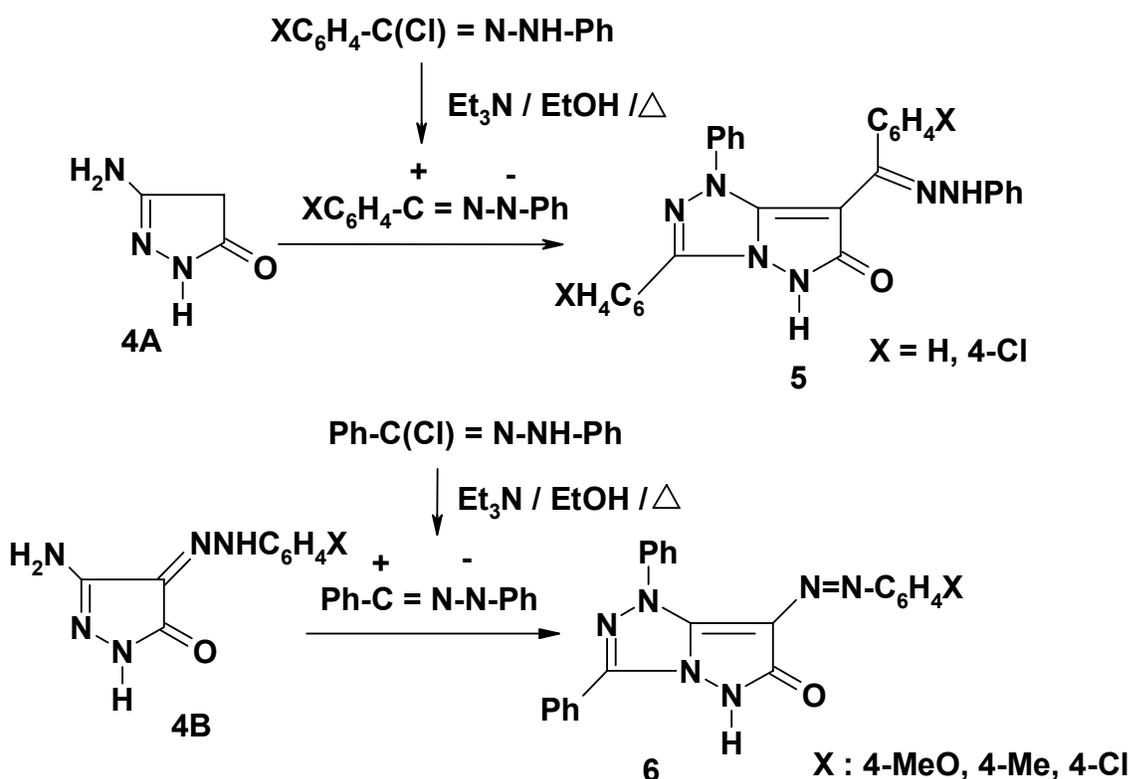


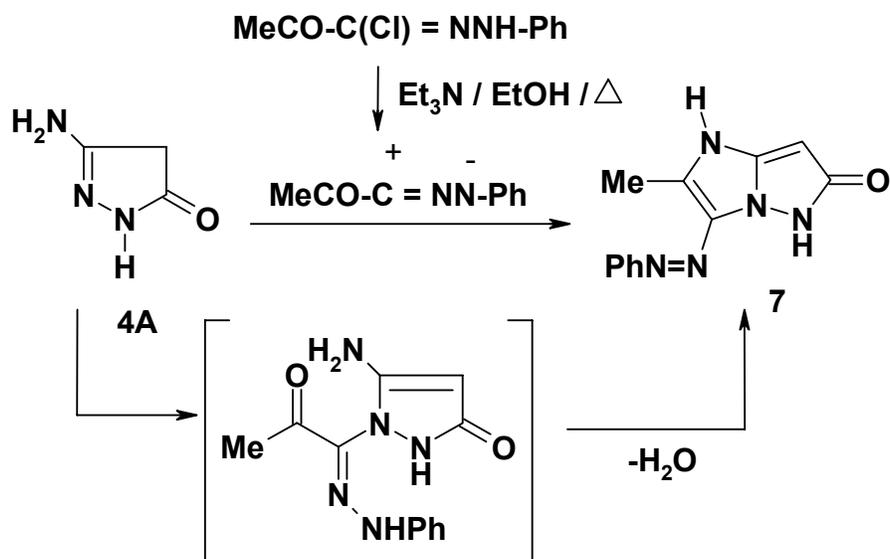
Scheme 1

2. Reactions with aminoazoles

2.1 Aminopyrazoles

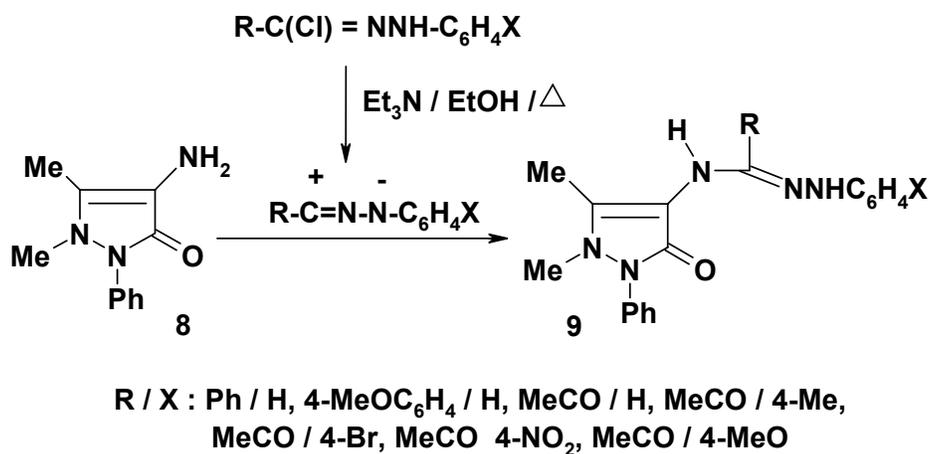
Reactions of 3-aminopyrazole derivatives **4A**^{18,19} and **4B**²⁰ with *C,N*-diarylnitrilimines were reported to give the respective pyrazolo[5,1-*c*][1,2,4]triazoles (**5**) in 24-50% yield and (**6**) in 70-85% yield. However, reaction of **4A** with *N*-phenyl-*C*-acetylnitrilimine was reported to yield the phenylazo derivative **7** in 82% yield (Scheme 2).¹⁸





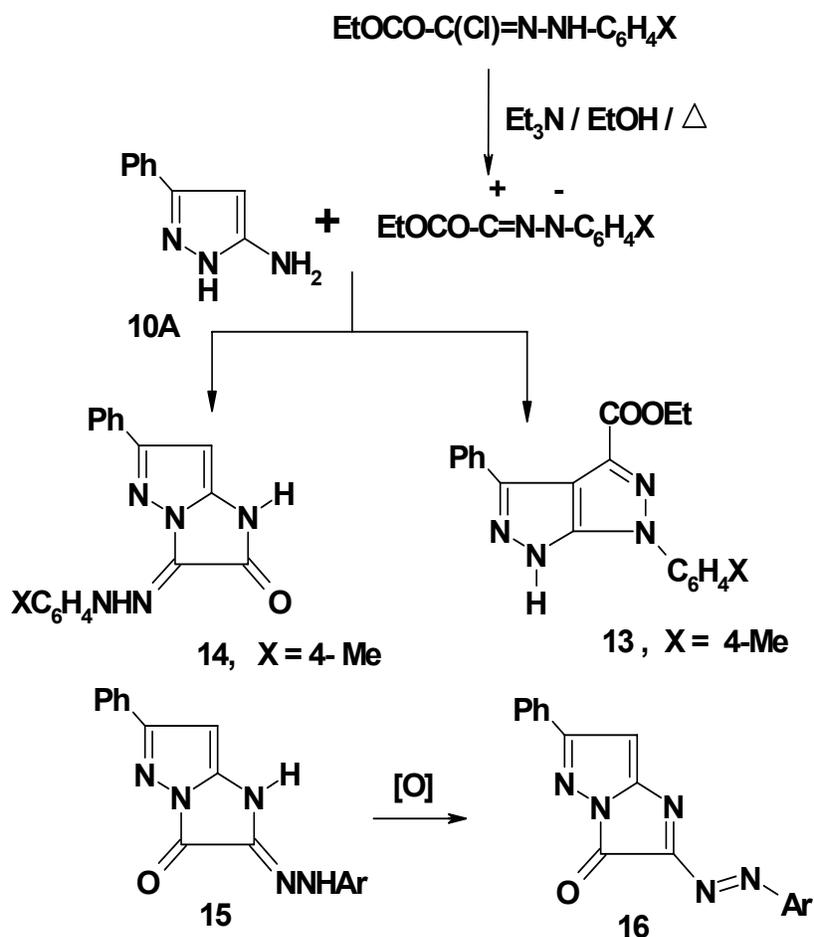
Scheme 2

Similar reaction of 4-amino-2,3-dimethyl-1-phenyl-5(2*H*)-pyrazolone **8** with each of *C,N*-diarylnitrilimines and *C*-acetyl-*N*-arylnitrilimines was reported to give the respective amidrazones **9** in 60-80% yields (Scheme 3).^{19, 21, 22}



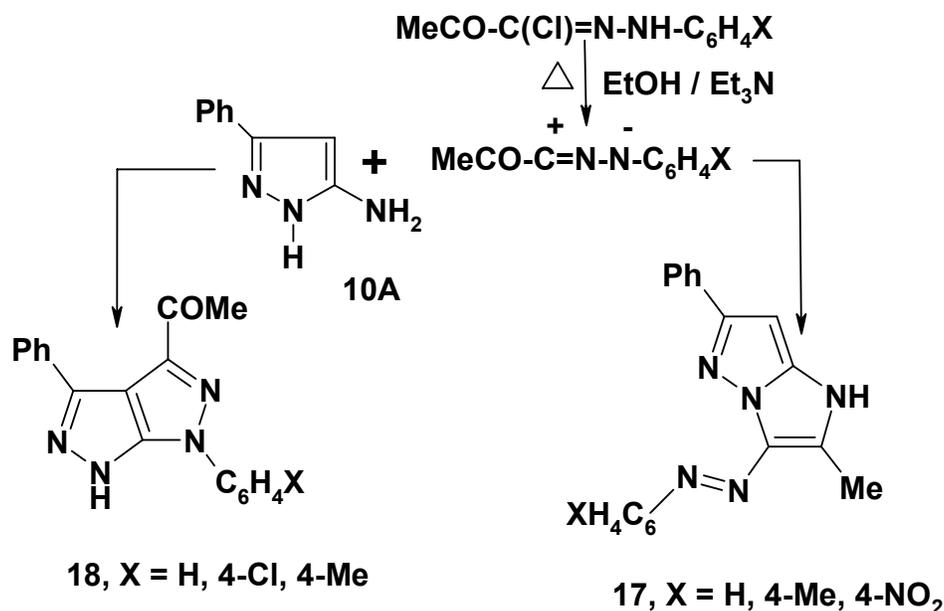
Scheme 3

Reactions of *C,N*-diarylnitrilimines with 5-amino-3-substituted-pyrazoles **10** were reported to yield the pyrazolo[5,1-*c*][1,2,4]triazole derivatives **11** *via* elimination of ammonia from the initially formed amidrazone intermediate^{19, 22} The latter products were also produced by the reaction of the same nitrilimines with the respective 3-substituted-4,5-dihydropyrazol-5-one **12** (Scheme 4).²²



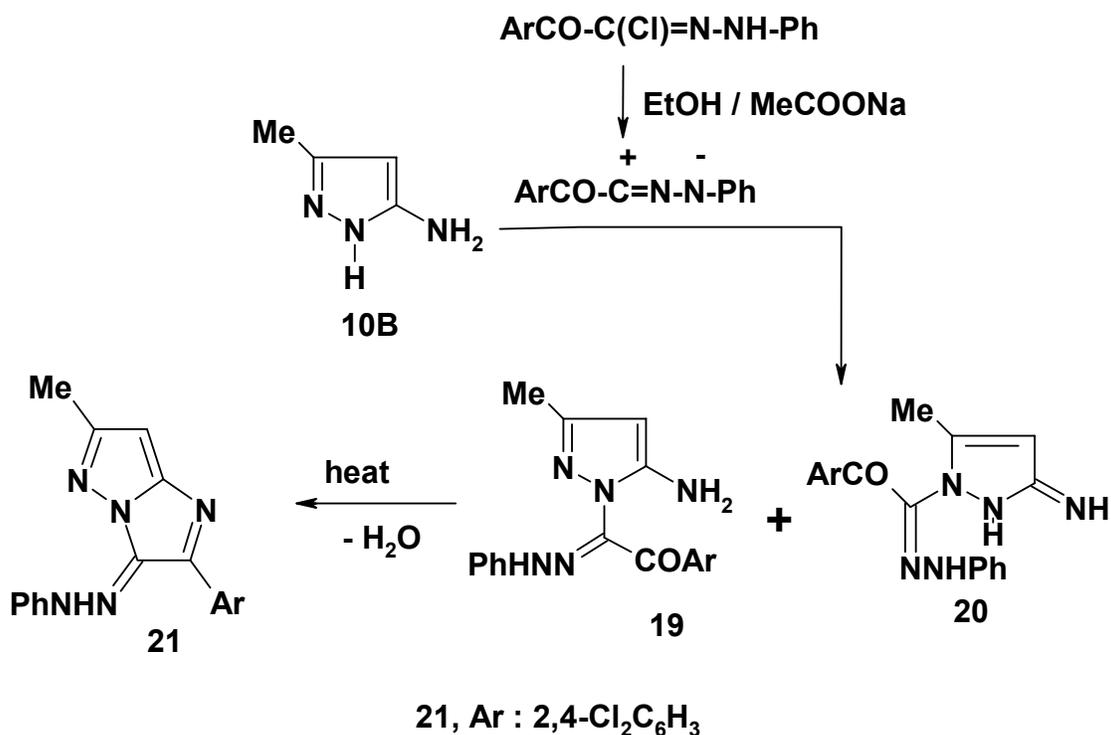
Scheme 5

Also, different results were reported for reactions of 3-phenyl-5-aminopyrazole **10A** with *C*-acetyl-*N*-aryl-nitrilimines. Thus, in three reports^{19, 22, 24} it was indicated that such a reaction afforded the respective imidazo[1,2-*b*]pyrazoles **17**. In another report²⁸ this reaction was reported to yield the respective pyrazolo[3,4-*c*]pyrazole derivatives **18** (Scheme 6).



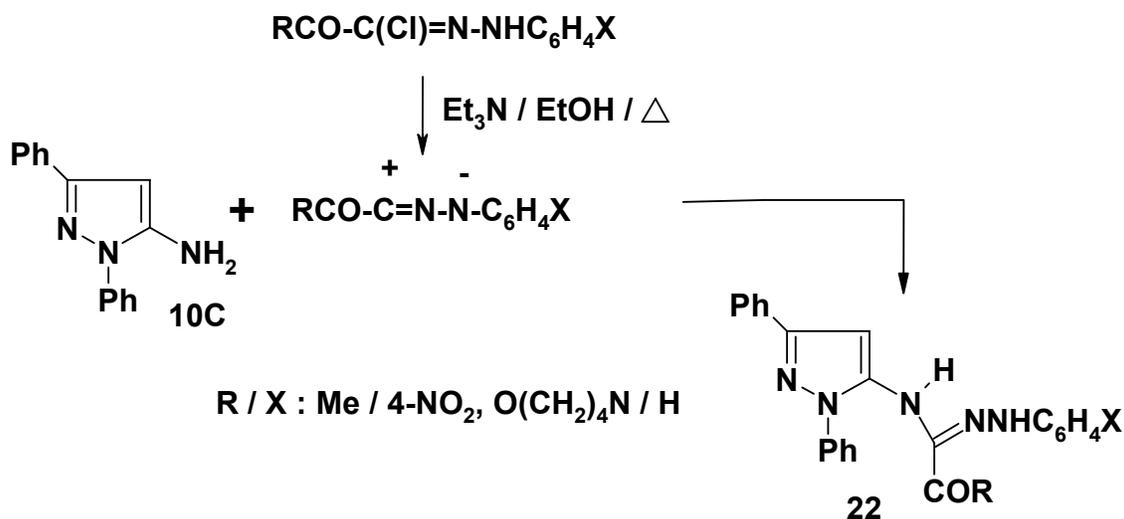
Scheme 6

Reaction of *C*-aroyl-*N*-phenylnitrilimine with 5-amino-3-methylpyrazole (**10B**) afforded a mixture of the 1,3-adducts **19** and **20**.²⁹ Heating **19** in ethanol in the presence of anhydrous sodium acetate afforded **21** in 52% yield (Scheme 7).²⁹



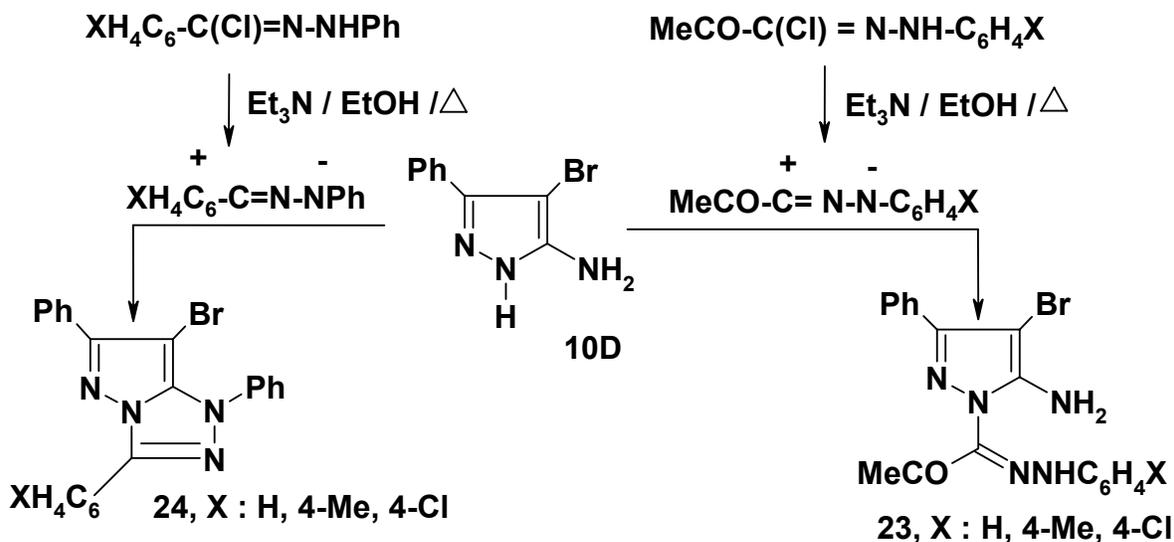
Scheme 7

Reactions of 5-amino-1,3-diphenylpyrazole (**10C**) with *C*-acyl-*N*-arylnitrilimines were reported to give the respective amidrazones **22** (Scheme 8).^{19, 22, 28}



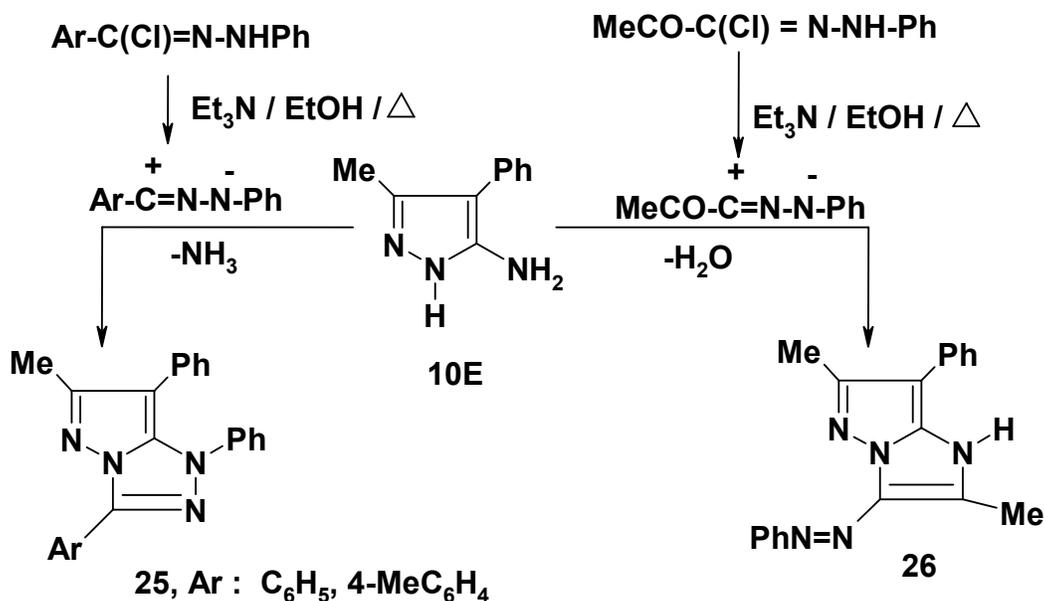
Scheme 8

Analogous reactions of 5-amino-3,4-disubstituted pyrazoles with nitrilimines gave products that depend on the type of the substituents present as well as the type of nitrilimine used. For example, *C*-acetyl-*N*-arylnitrilimines^{18, 21} were reported to react with 5-amino-4-bromo-3-phenylpyrazole **10D** to give the respective amidrazones **23** as end products in 50-90% yields.^{18, 21} Similar reaction of **10D** with *C,N*-diarylnitrilimines afforded **24** in 28 – 60% yields (Scheme 9).^{18, 19}



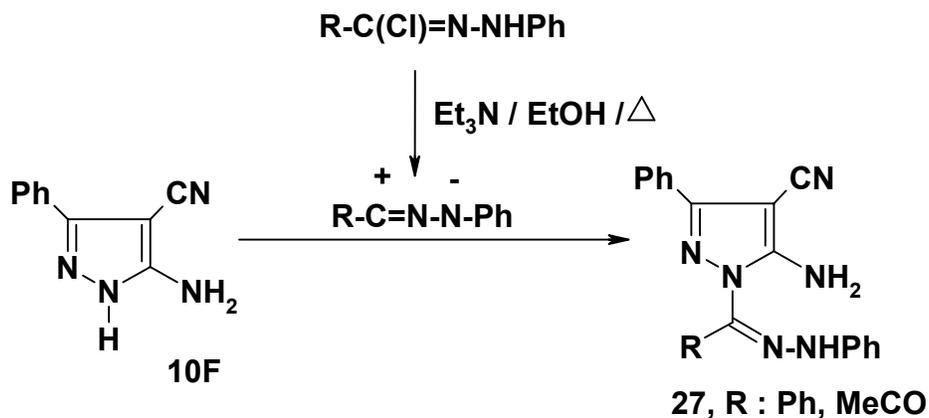
Scheme 9

Also, the reactions of 5-amino-3-methyl-4-phenylpyrazole **10E** with *C,N*-diaryl- and *C*-acetyl-*N*-phenylnitrilimines were reported to give the pyrazolo[1,5-*c*][1,2,4]triazoles **25** in 74-80% yield^{18,19} and imidazo[1,5-*b*]pyrazole derivatives **26** in 90% yield, respectively (Scheme 10).¹⁸



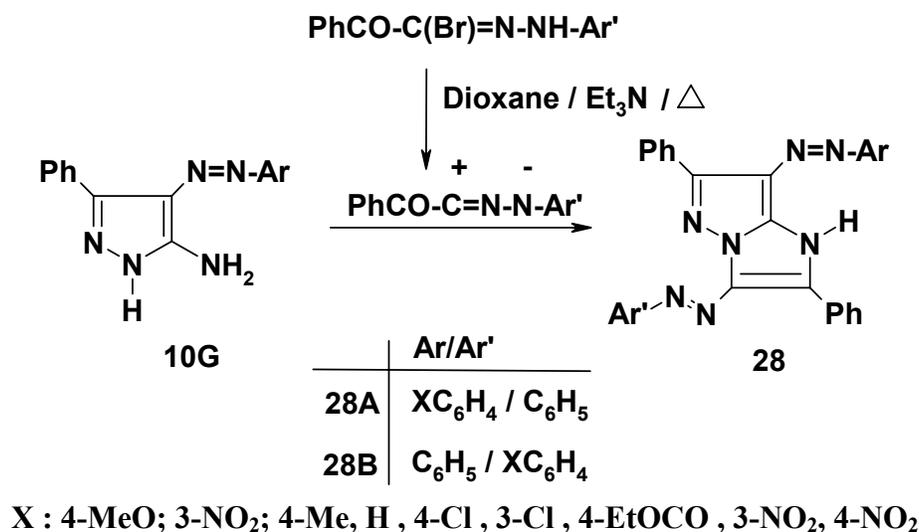
Scheme 10

However, reaction of 5-amino-4-cyano-3-phenylpyrazole **10F** with both types of the foregoing nitrilimines yielded in both cases the respective 1,3-adducts namely the amidrazones **27** in 85-88% yield (Scheme 11).¹⁸



Scheme 11

The reactions of *C*-aroyl-*N*-arylnitrilimines with 5-amino-3-phenyl-4-arylazopyrazoles **10G** were reported to give 3,7-bis(arylazo)-2,6-diphenyl-1H-imidazo[1,2-*b*]pyrazole derivatives **28** in 70-90% yields.³⁰ Although, four possible tautomeric structures **A-D** can be written for each of the compounds **28** (Figure 1), they were found to exist predominantly in the indicated tautomeric form **28A**. This structural assignment was based on the similarity of their electronic absorption spectra with those reported for the azo chromophore³¹⁻³³ and the results of the correlations of their acid dissociation constants with the Hammett equation (Scheme 12).³⁰



Scheme 12

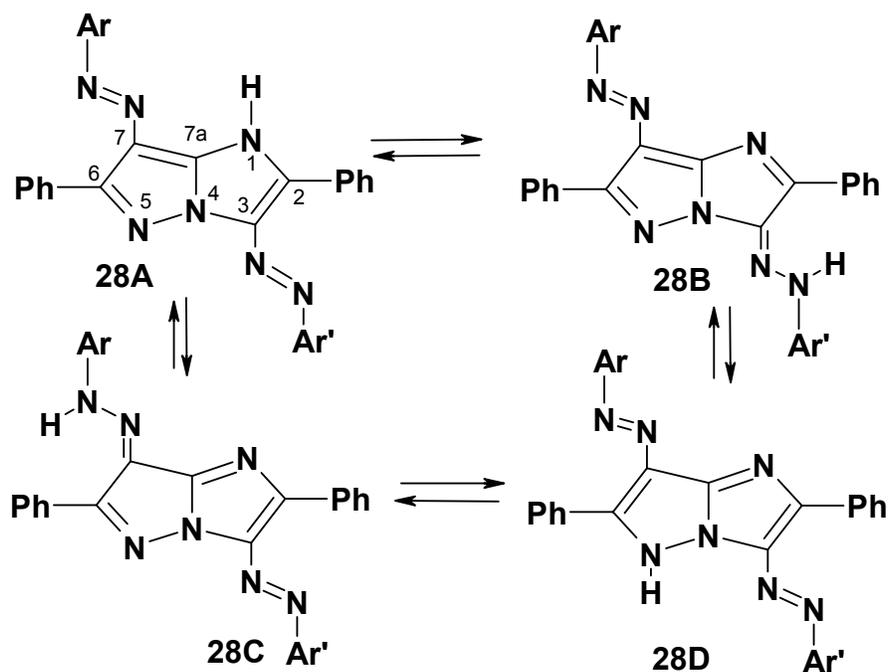
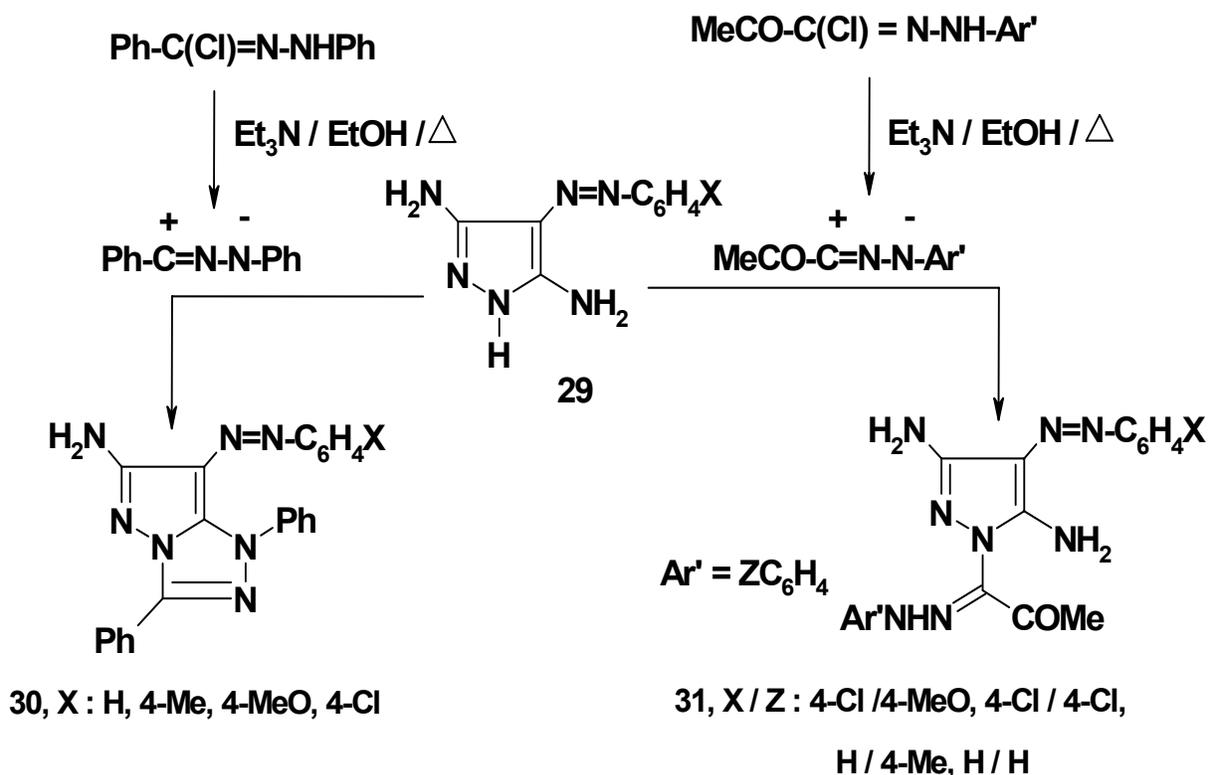


Figure 1

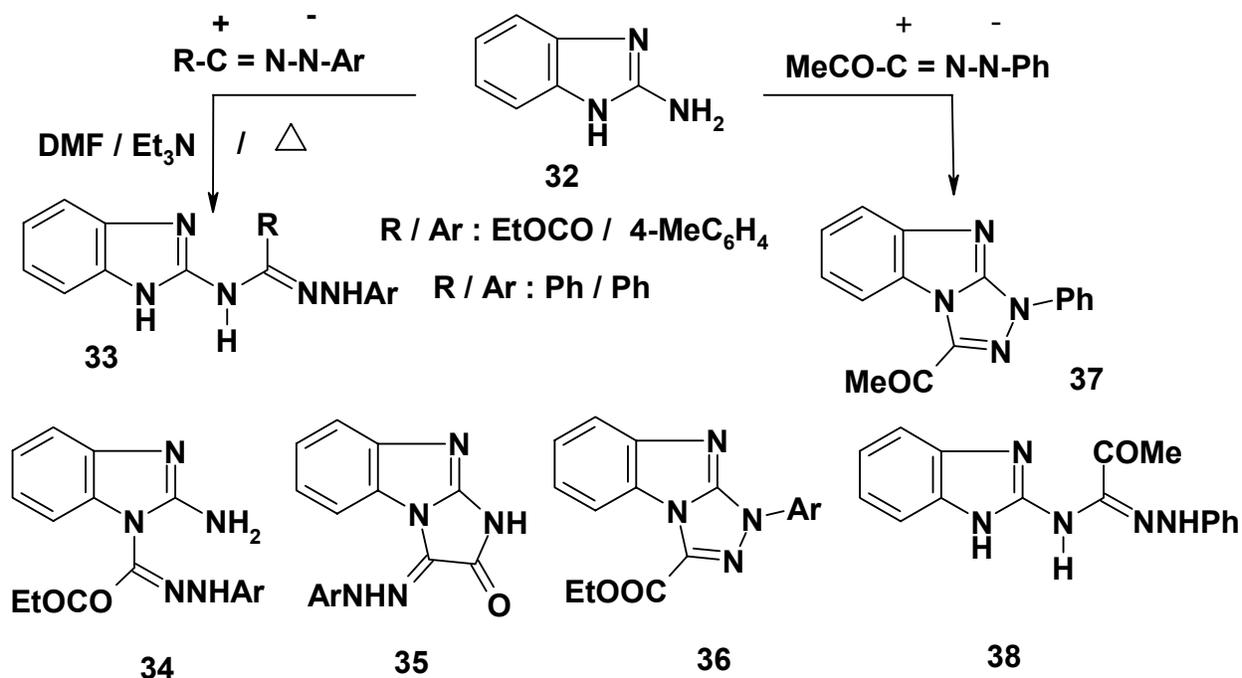
Reaction of C,N-diphenylnitrilimine with 3,5-diamino-4-arylazopyrazoles **29** was reported to give the respective pyrazolo[1,5-c][1,2,4]triazoles **30** in 60-85% yields.³⁴ Similar reaction of **29** with C-acetyl-N-arylnitrilimines yielded the 1,3- adducts **31** in 80-92% yields (Scheme 13).^{18, 19, 21, 28}



Scheme 13

2.2 Aminoimidazoles

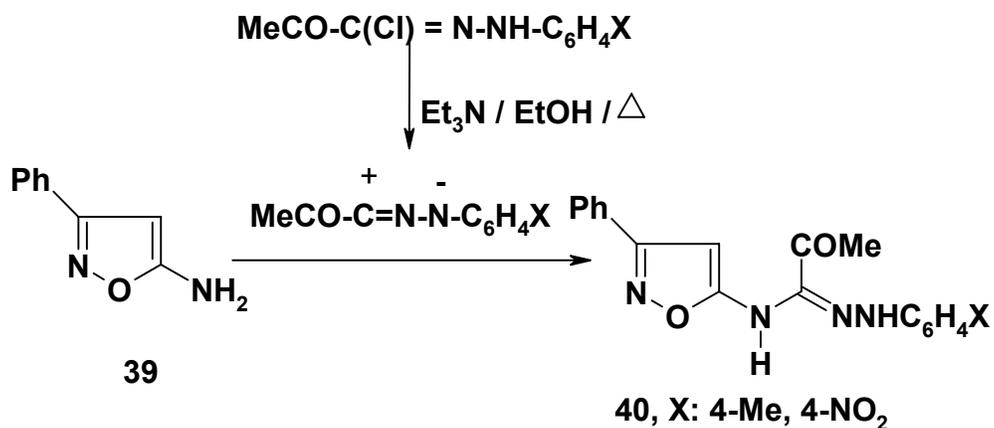
Reaction of 2-aminobenzimidazole **32** with C-phenyl- and C-ethoxycarbonyl-N-arylnitrilimines yielded the respective amidrazones **33a,b** in 55% yields.^{22, 23} The other possible isomeric structure **34** was discarded on the basis that if it were formed, it will be cyclized to give either **35** or **36**.²³ On the other hand, reaction of 2-aminobenzimidazole **32** with C-acetyl-N-phenylnitrilimine gave 1-phenyl-3-acetyl-1,2,4-triazolo[4,3-a]benzimidazole **37**.²² Recently, it was reported, however, that reaction of C-acetyl-N-(p-chlorophenyl)nitrilimine with 2-aminobenzimidazole yielded the amidrazone adduct **38** (Scheme 14).³⁵



Scheme 14

2.3 Aminoisoxazoles

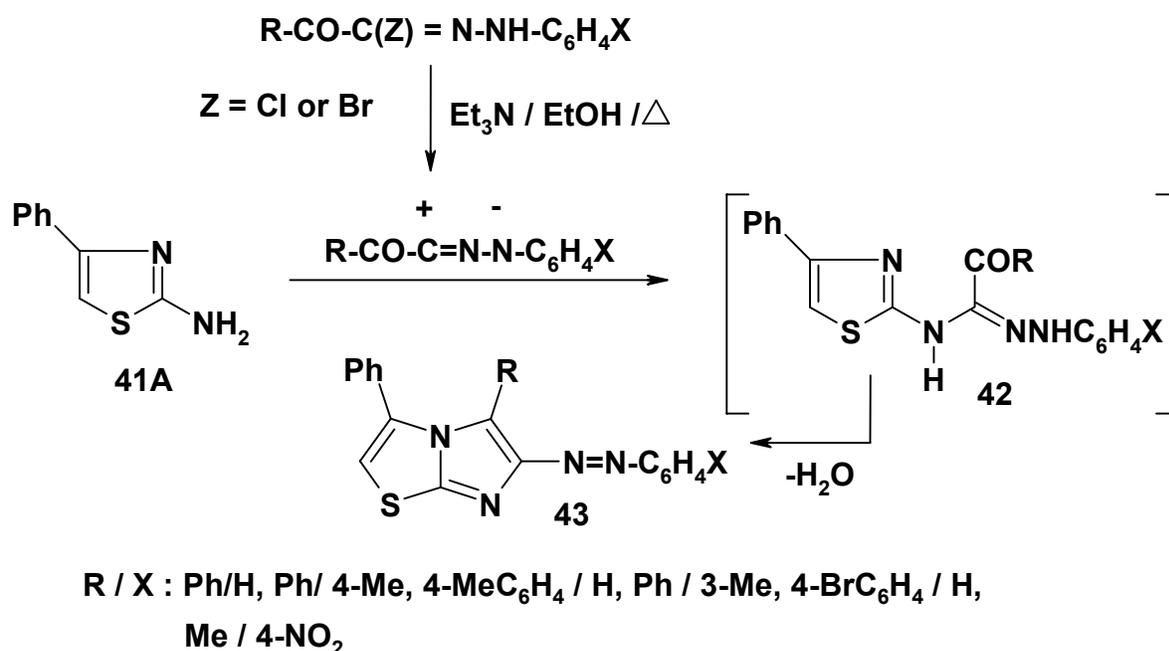
5-Amino-3-phenylisoxazole 39 was reported to react similarly with *C*-acetyl-*N*-arylnitrilimines to give the amidrazones 40 in 40-50% yields (Scheme 15).^{19, 22}



Scheme 15

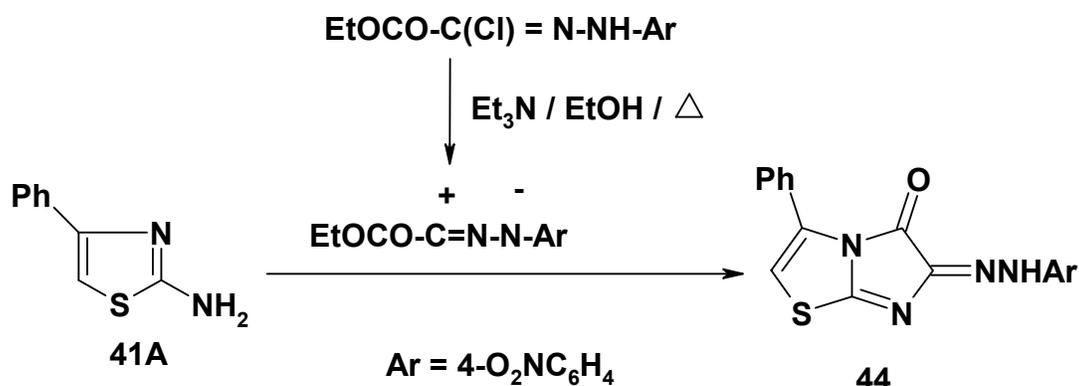
2.4 Aminothiazoles

C-Acyl-*N*-arylnitrilimines reacted with 2-amino-4-phenylthiazole (**41A**) and gave the respective imidazo[2,1-*b*]thiazole derivatives **43** in 80% yield. This reaction was supposed to proceed *via* initial formation of the amidrazones **42** followed by dehydrative cyclization of the latter to give **42** as end products (Scheme 16).²⁴



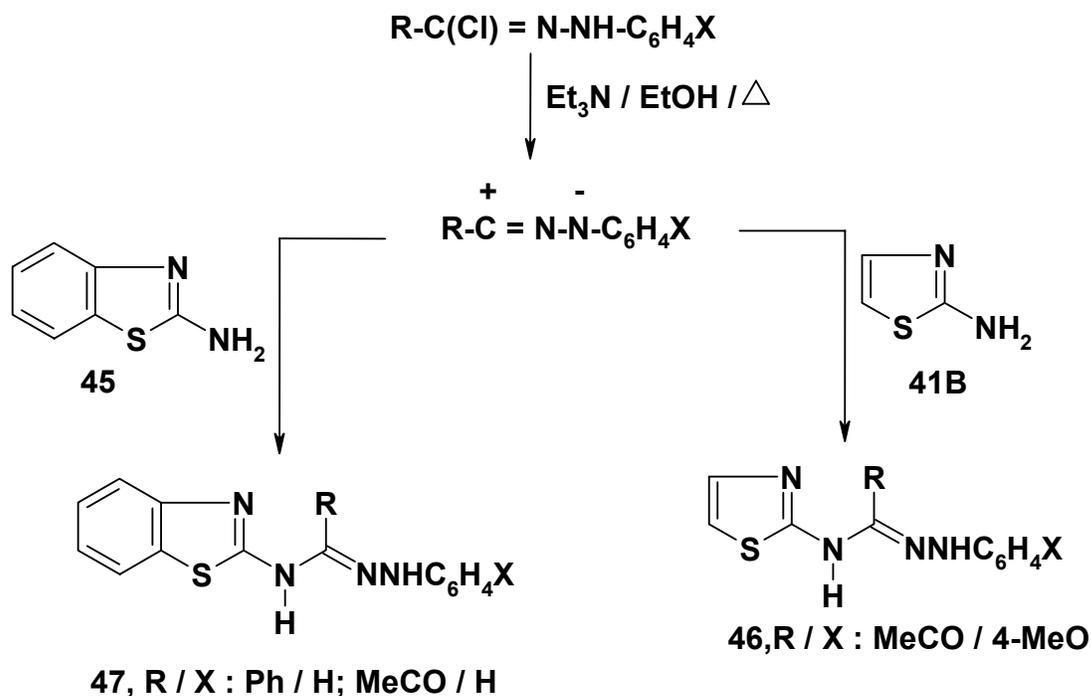
Scheme 16

Similarly, *C*-ethoxycarbonyl-*N*-phenylnitrilimine reacted with 2-amino-4-phenylthiazole **41A** and yielded 6-arylhydrazone-5-oxo-3-phenylimidazo[2,1-*b*]thiazoles **44** (Scheme 17).²⁴



Scheme 17

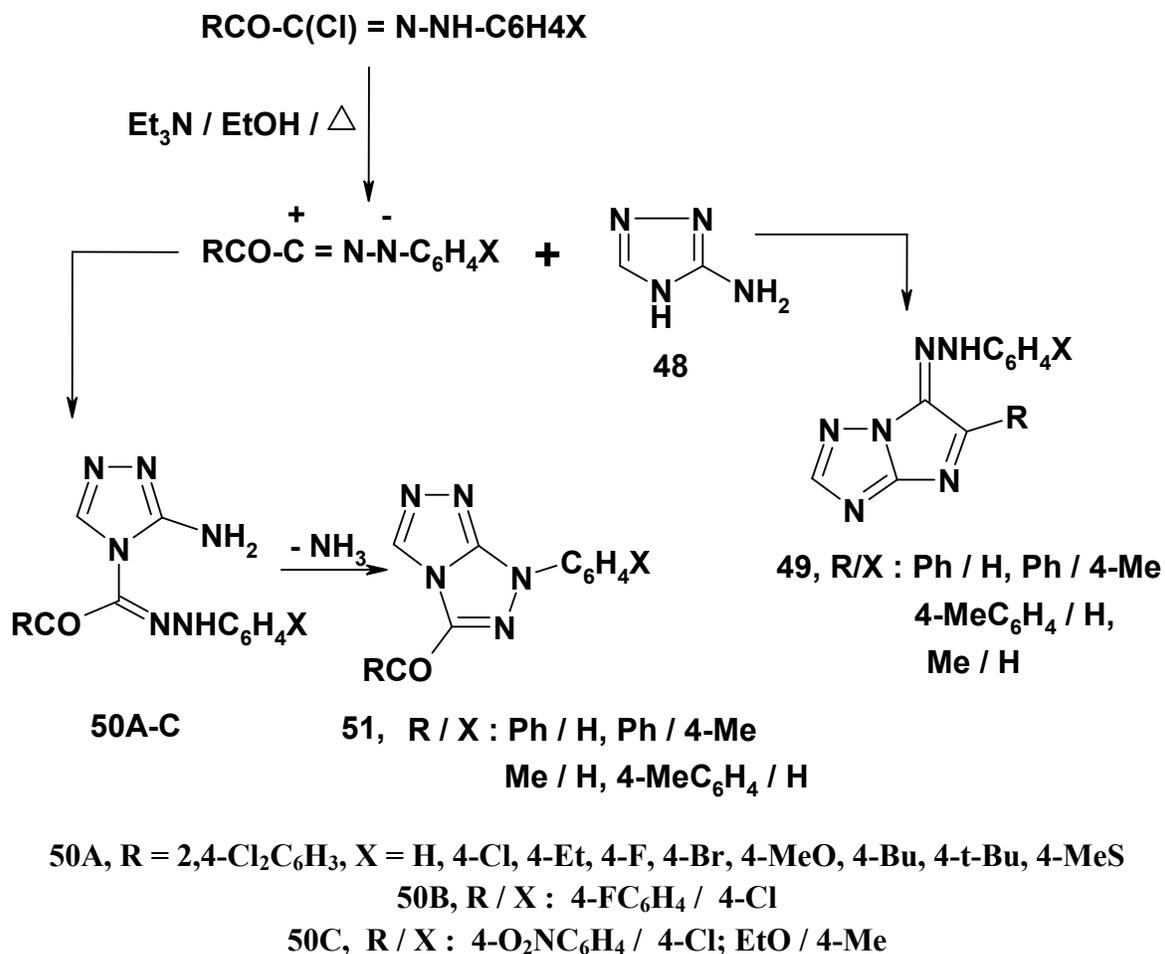
The amidrazones **46** were obtained in 88% yield from the reaction of 2-aminothiazole **41B** with *C*-acetyl-*N*-phenylnitrilimine.²¹ Similar reactions of 2-aminobenzothiazole **45** with *C,N*-diphenylnitrilimine and *C*-acetyl-*N*-phenylnitrilimine afforded the respective amidrazones **47** (Scheme 18).^{18,21}



Scheme 18

2.5 Amino-1,2,4-triazoles

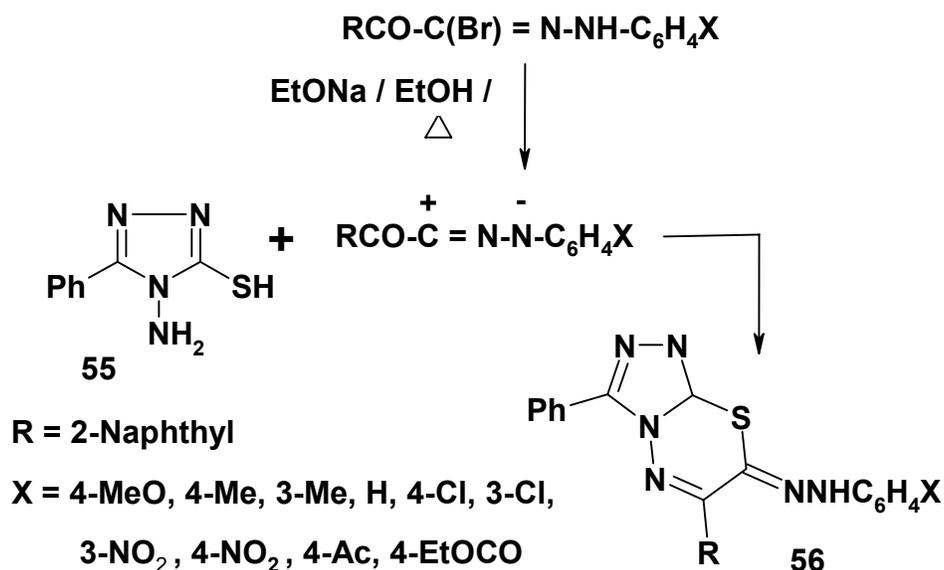
The reaction of 3-amino-1,2,4-triazole **48** with different *C*-acyl-*N*-arylnitrilimines afforded the respective 5-arylhydrazono-imidazo[1,2-*b*][1,2,4]triazole derivatives **49**.²⁴ In another report,²⁹ it was indicated that similar reaction of **48** with *C*-aroyl-*N*-arylnitrilimines yielded initially the amidrazones **50** in 39-57 % yields which underwent deaminative cyclization to give 1-aryl-3-acyl-1,2,4-triazolo[3,4-*c*][1,2,4]triazoles **51** (Scheme 19).^{23,29}



Scheme 19

Analogous reactions of **48** with each of *C,N*-diarylnitrilimines^{19, 22} and *C*-acetyl-*N*-arylnitrilimines¹⁹ were reported to be site selective and gave in both cases the respective 1,3-adducts namely the amidrazones **52** in 40-60 % yields (Scheme 20).

Reaction of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol **55** with C-acyl-N-arylnitrilimines afforded 7-arylhydrazono[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **56**.³⁶ The acid dissociation constants pK and pK^* , in the ground and excited states, respectively were correlated by Hammett equation. The pK data together with the spectral data indicate that the compounds **56** exist predominantly in the indicated hydrazone tautomeric form (Scheme 22).³⁶

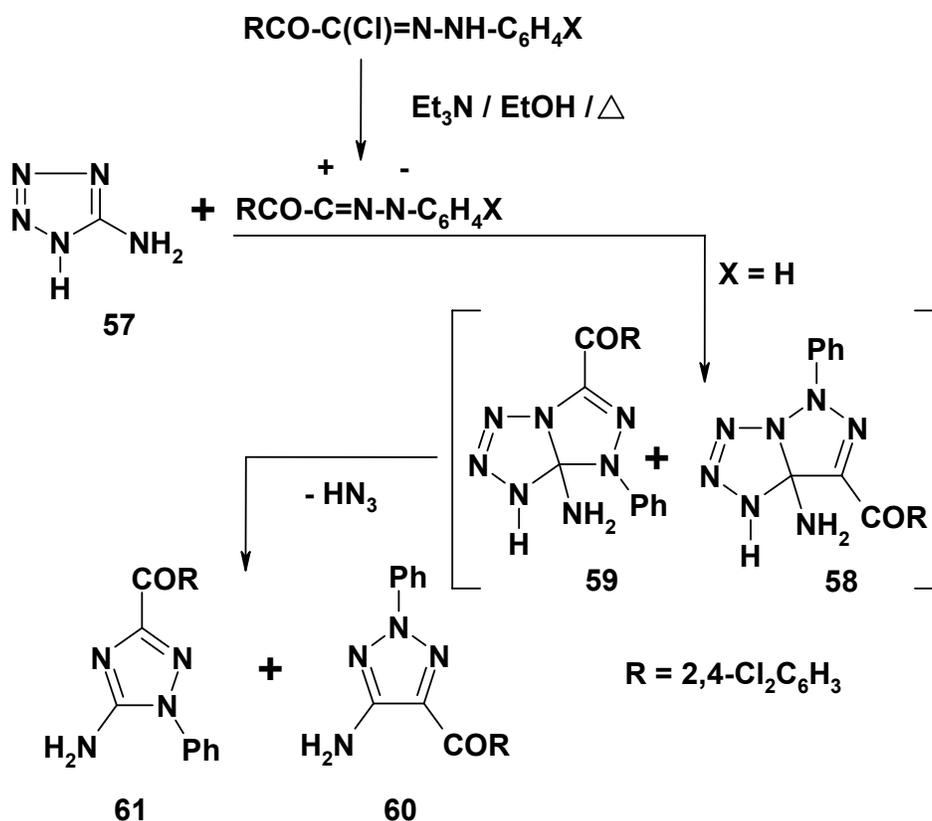


Scheme 22

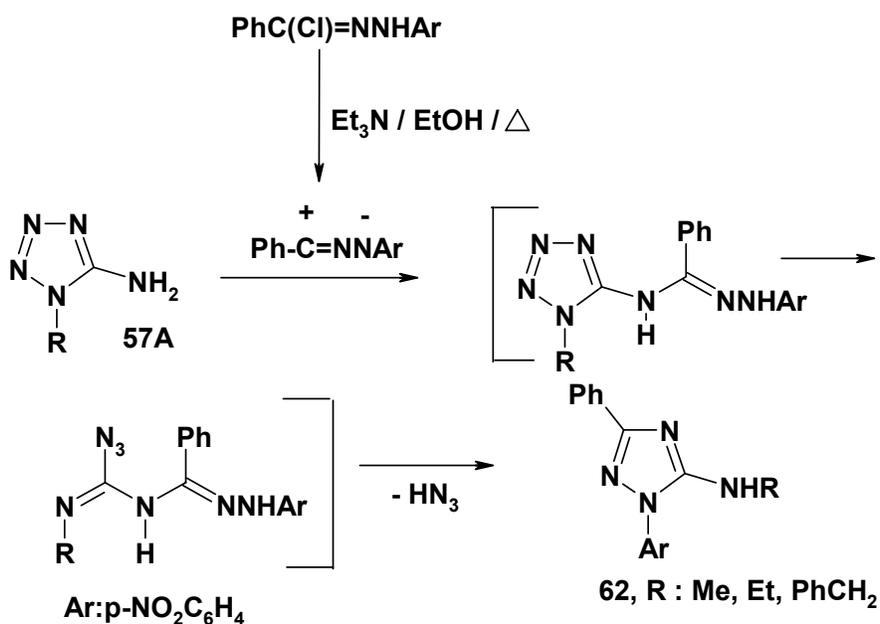
2.6 Aminotetrazoles

Reactions of C-acyl-N-arylnitrilimines with 5-aminotetrazoles **57** gave a mixture of the aminotriazoles **60** and **61** *via* elimination of hydrazoic acid from the initially formed regioisomeric cycloadducts **58** and **59**, respectively (Scheme 23).²⁹

On the other hand, reaction of 5-amino-1-substituted-tetrazoles **57A** with C-phenyl-N-(4-nitrophenyl)nitrilimine was reported to give 1,3,5-trisubstituted-1,2,4-triazoles **62** in 41-50% yields (Scheme 24).³⁷



Scheme 23

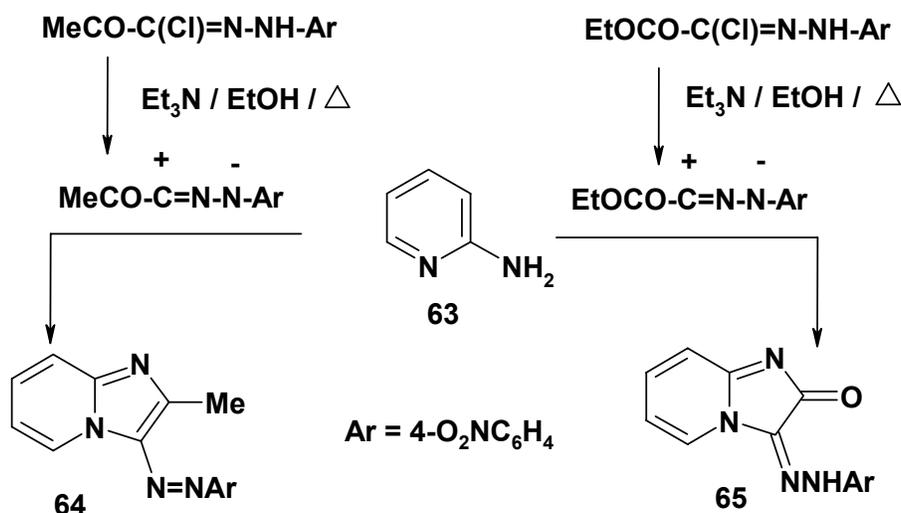


Scheme 2

3. Reactions with aminoazines

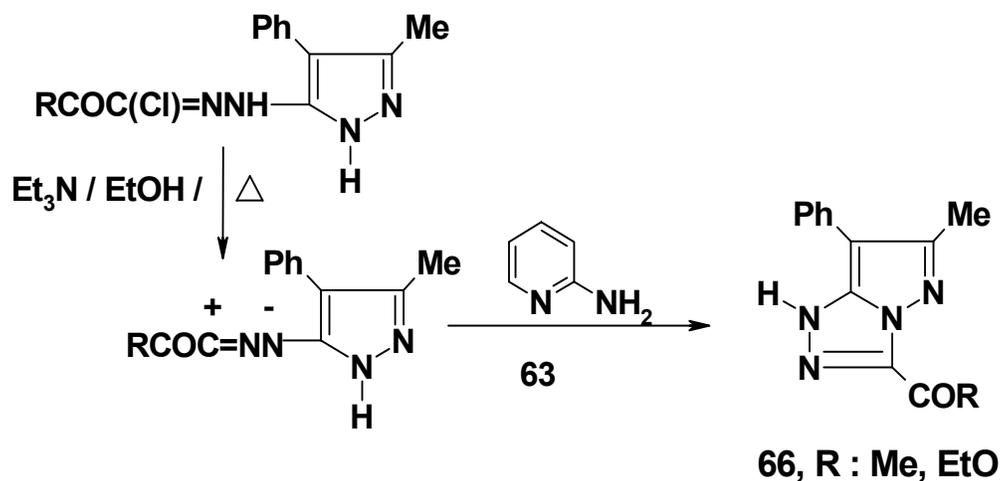
3.1 Aminopyridines

Reaction of 2-aminopyridine **63** with *N*-phenyl-2-oxopropanehydrazonoyl chloride in refluxing ethanol gave one product in 70% yield that was identified as 2-methyl-3-arylazo imidazo[1,2-*a*]pyridine **64**.²⁴ Similar reaction of 2-aminopyridine **63** with ethyl *N*-phenylhydrazonochloroacetate yielded **65** (Scheme 25).²⁴



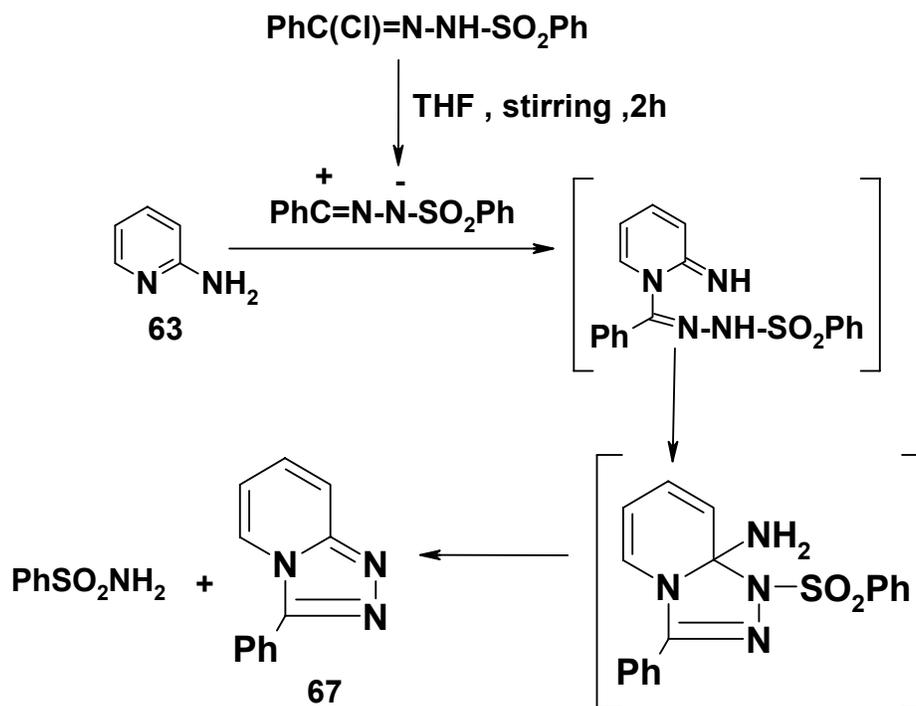
Scheme 25

However, the reaction of **63** with the nitrilimines, derived from *N*-(pyrazol-5-yl) 2-oxohydrazonoyl halides in refluxing ethanol in the presence of triethylamine or piperidine, was found to give **66** in 80% yield. The formation of the latter seems to result *via* intramolecular addition of the generated nitrilimines.^{38,39} In this case, 2-aminopyridine acted as a base catalyst. (Scheme 26).



Scheme 26

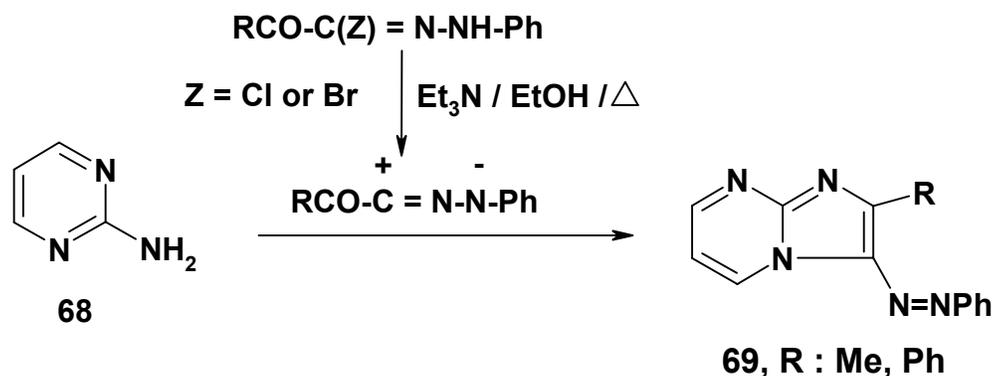
In an earlier report⁴⁰, it was indicated however that reaction of 2-aminopyridine **63** with *C*-phenyl-*N*-benzenesulfonylnitrilimine yields 3-phenyl 1,2,4-triazolo[4,3-*a*]pyridine **67** in 54% yield (Scheme 27).



Scheme 27

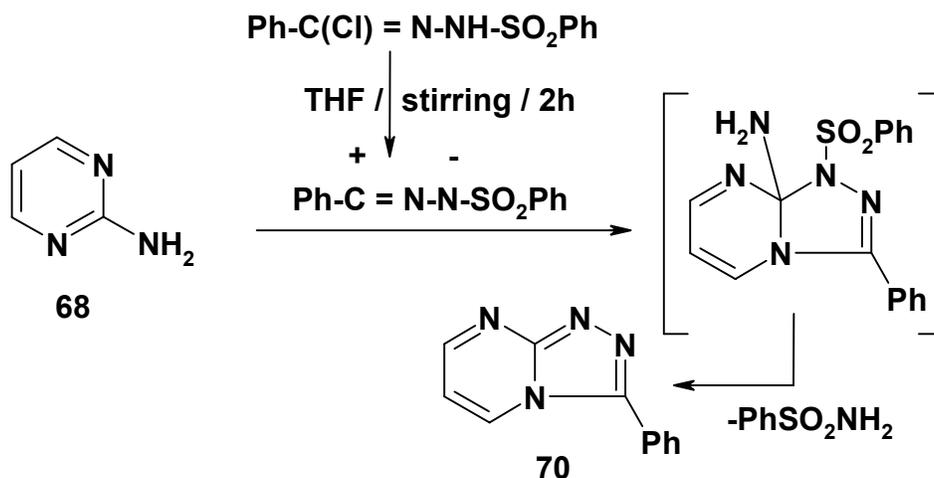
3.2 Aminopyrimidines

The reaction of 2-aminopyrimidine **68** with *C*-acyl-*N*-phenylhydrazonoyl halides was reported to give the corresponding 2-substituted-3-phenylazo-imidazo[1,2-*a*]pyrimidines **69** (Scheme 28).²⁴



Scheme 28

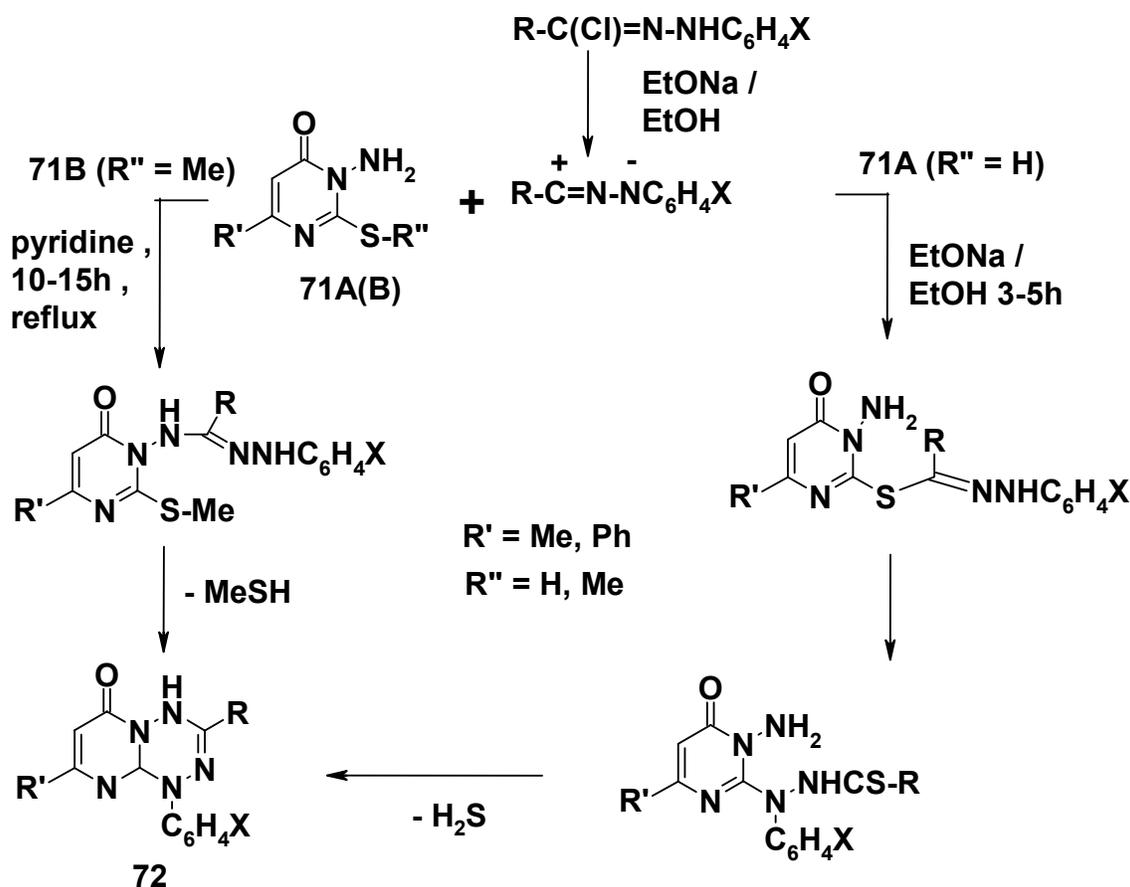
However, the reaction of 2-aminopyrimidine **68** with *C*-phenyl-*N*-phenylsulfonylnitrilimine yielded 3-phenyl-5-triazolo[4,3-*a*]pyrimidine **70** in 42% yield (Scheme 29).⁴⁰



Scheme 29

Recently it was reported that reaction of nitrilimines with 3-amino-6-methyl-4-oxo-2 (3*H*)-pyrimidinethione **71A** in boiling ethanol in presence of triethylamine, furnished pyrimido[1,2-*b*][1,2,4,5]tetrazines **72** in 35-66% yields.⁴¹ Analogous reaction of the same nitrilimines with 3-

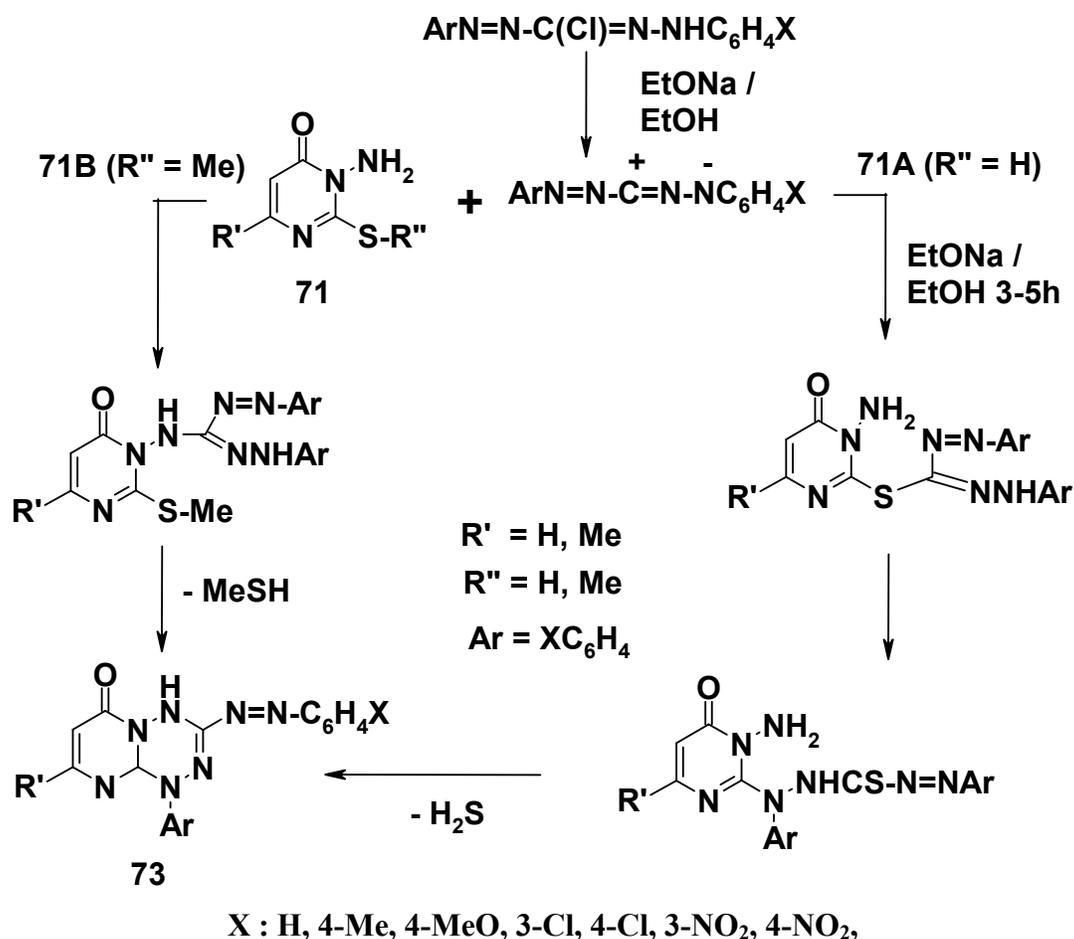
amino-6-phenyl-2-methylthio-4(3*H*)-pyrimidinone **71B** in refluxing ethanol in the presence of triethylamine afforded also **72** (Scheme 30).^{41, 42}



$\text{R} / \text{X} : \text{EtOCO} / \text{H}, \text{PhNHCO} / \text{H}, \text{MeCO} / 4\text{-Me}, \text{PhCO} / \text{H}, 2\text{-naphthoyl} / \text{H}, \text{Ph} / \text{H}, \text{Me} / 4\text{-NO}_2, \text{PhCH=CH} / \text{H}, 2\text{-thenoyl} / \text{H}, \text{ArN=N} / \text{XC}_6\text{H}_4$

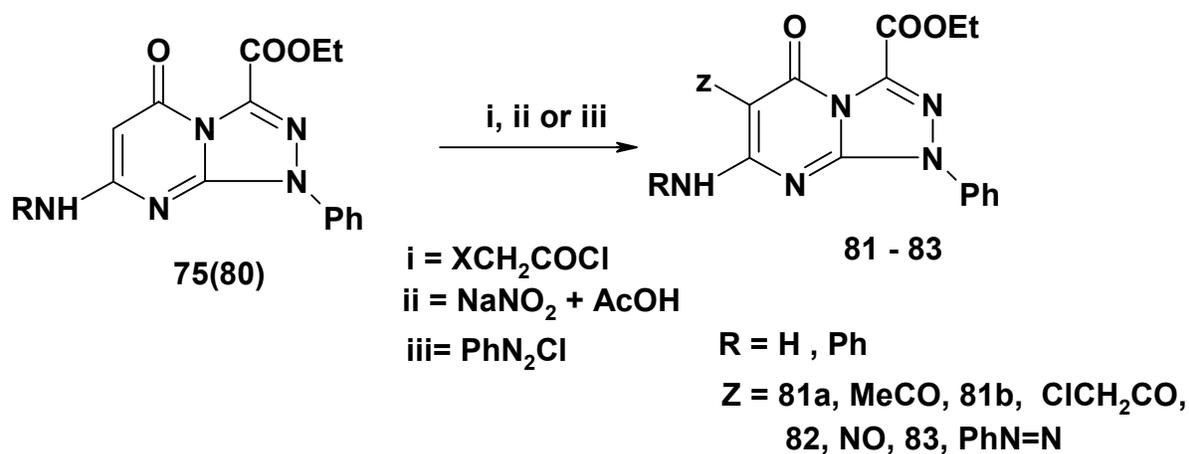
Scheme 30

Similarly, 3-arylazo-1,4-dihydro-1,8-disubstituted-6*H*-pyrimido[1,2-*b*][1,2,4,5]-tetrazin-6-ones **73** were recently reported to be obtained in good yields by reaction of *C*-arylazo-*N*-phenylnitrilimines, derived from the respective 3-chloro-1,5-diarylformazans, with 3-amino-6-substituted-2-thiouracils **71A** or their 2-methylthio analogs **71B** (Scheme 31).⁴³

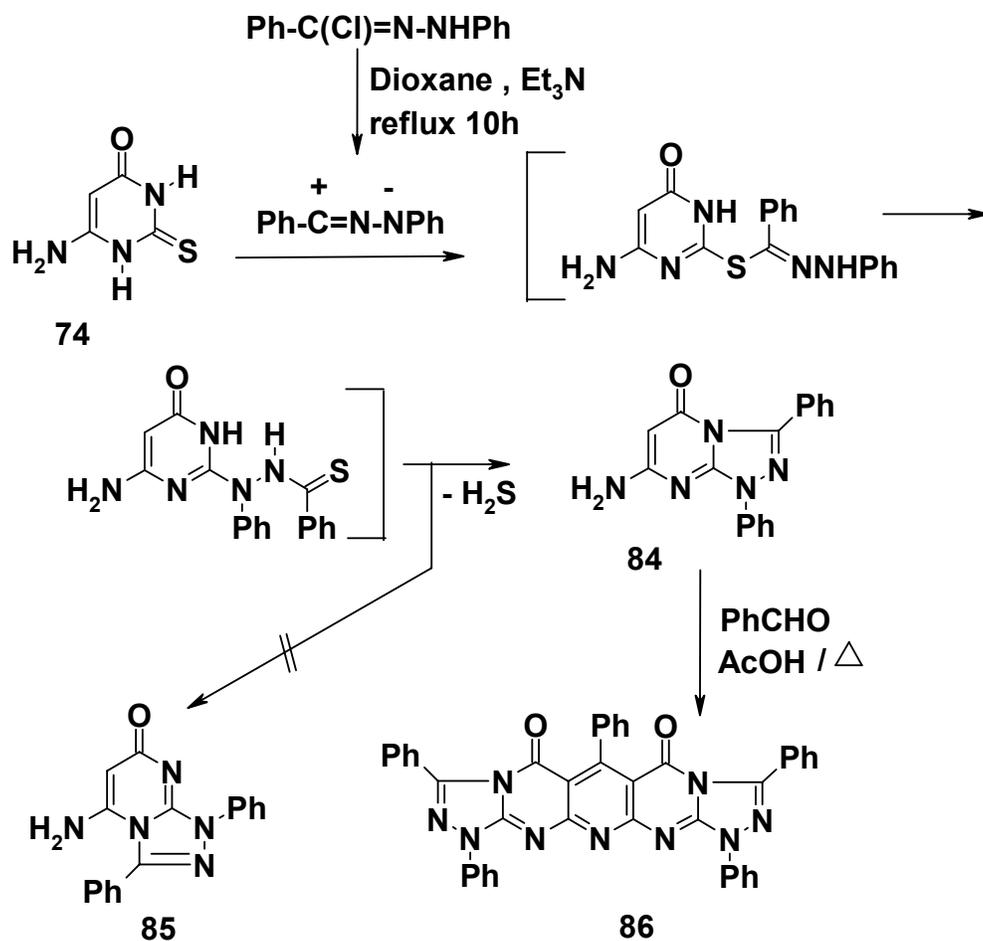


Scheme 31

Reaction of nitrilimines with 6-amino-2-thiouracil **74** in refluxing dioxane afforded regioselectively 7-amino-1,3-disubstituted-1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one **75**.^{44, 45} The product **75** was used as precursor for synthesis of pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-5,6(1*H*,9*H*)-diones **78** in 65-82% yields by its treatment with (*Z*)-2-benzylamino-3-dimethylaminopropenoate **76** in refluxing acetic acid to give **77** which was next cyclized by the action of sodium ethoxide in ethanol to give **78** (Scheme 32).⁴⁵

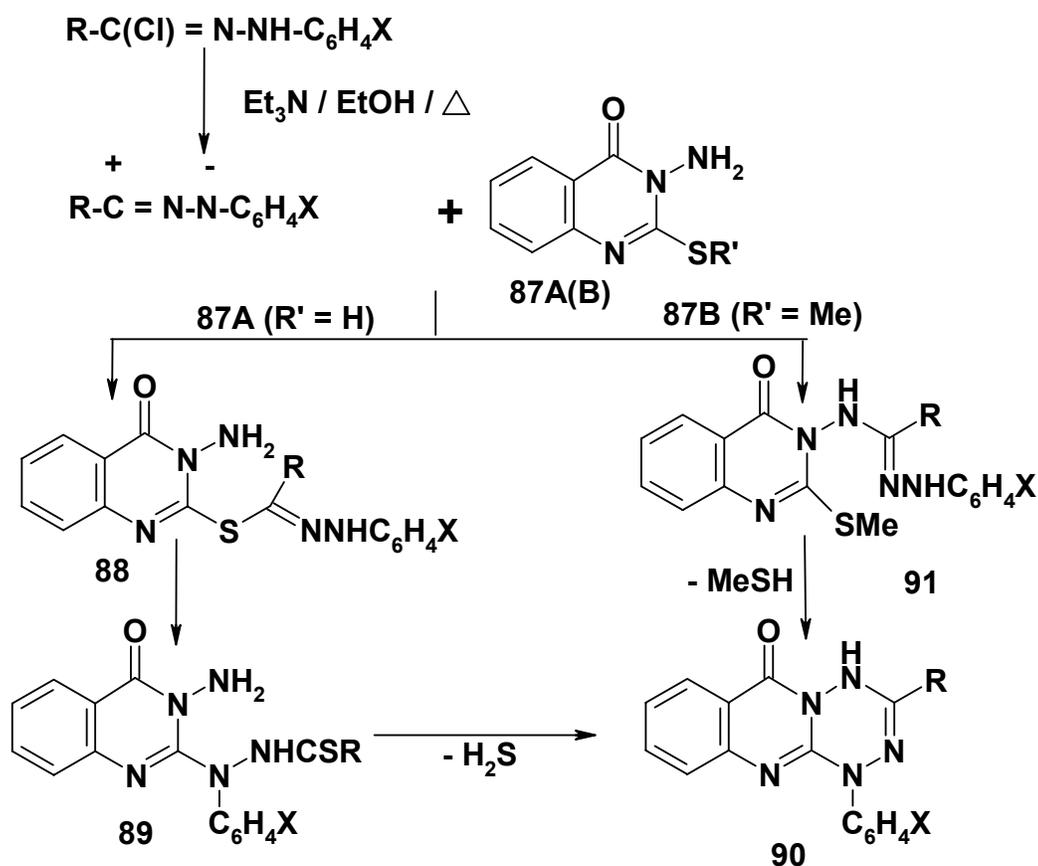


Reaction of 6-amino-2-thiouracil **74** with *C,N*-diphenylnitrilimine in dioxane under reflux yielded **84**. The other isomeric structure **85** was discarded on the basis of the IR and ¹³C-NMR evidence.⁴⁶ When compound **84** was refluxed with benzaldehyde in acetic acid, it yielded **86** in 80% yield (Scheme 34).



Scheme 34

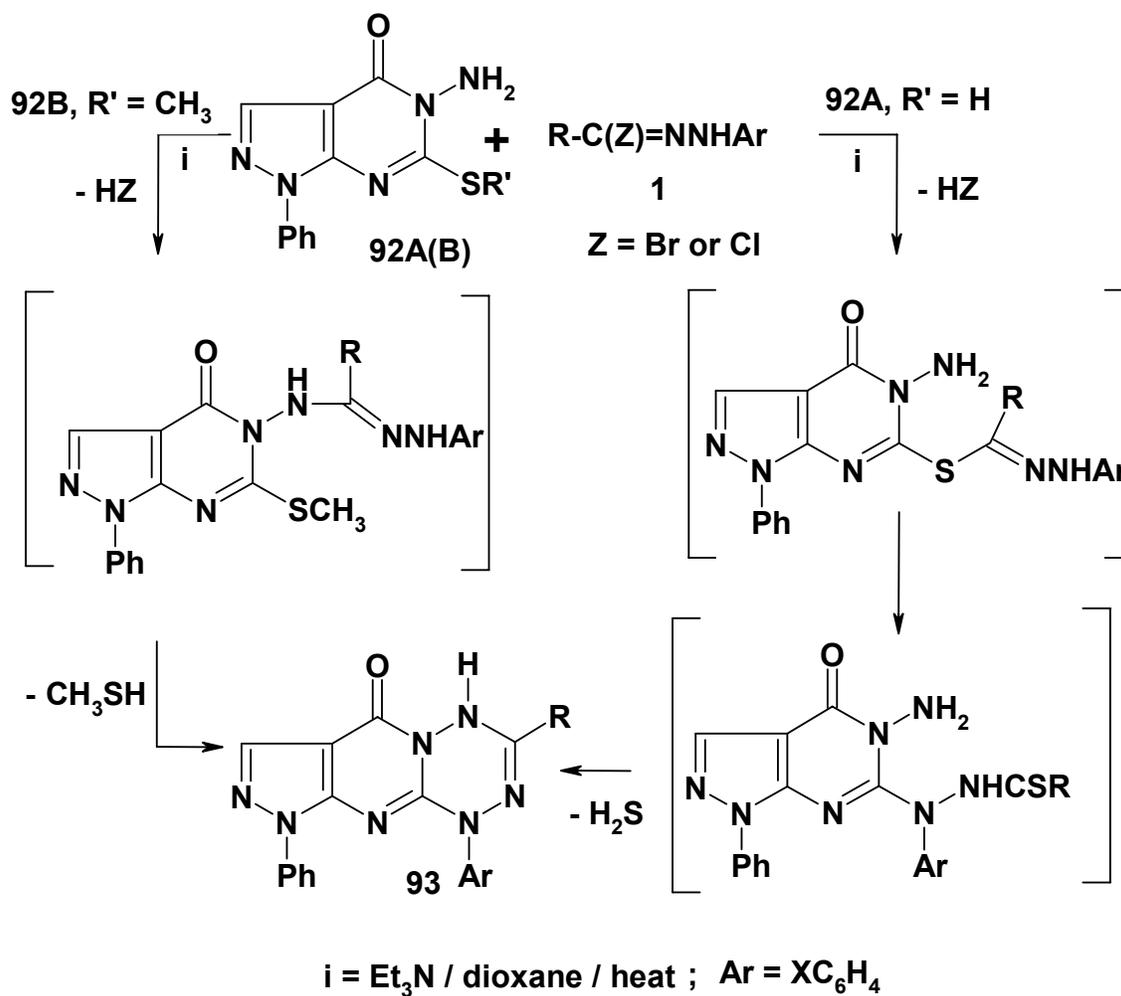
Reactions of various nitrilimines with 3-amino-4-oxo-2(3*H*)-quinazolinethione **87A** in ethanol were reported to yield the respective 6*H*-1,2,4,5-tetrazino[3,2-*b*]quinazolines **90** in 70-92% yields as end products. The latter were shown to be formed *via* the initial formation of the thiohydrazonates **88** which underwent tandem Smiles rearrangement to give **89** and cyclocondensation to give **90** as end products.⁴⁷ When the 2-methylthio derivative **87B** was used in place of **87A** in these reactions, the products **90** were also obtained.⁴⁷ In this case, the reaction was assumed to proceed through the hydrazidine intermediate **91** which in turn cyclized to give **90** (Scheme 35).⁴⁷



R / X : Ph / H, PhNHCO / H, PhNHCO / 4-Me, PhOCO / H, PhOCO / 4-Me, PhOCO / 4-Cl,

Scheme 35

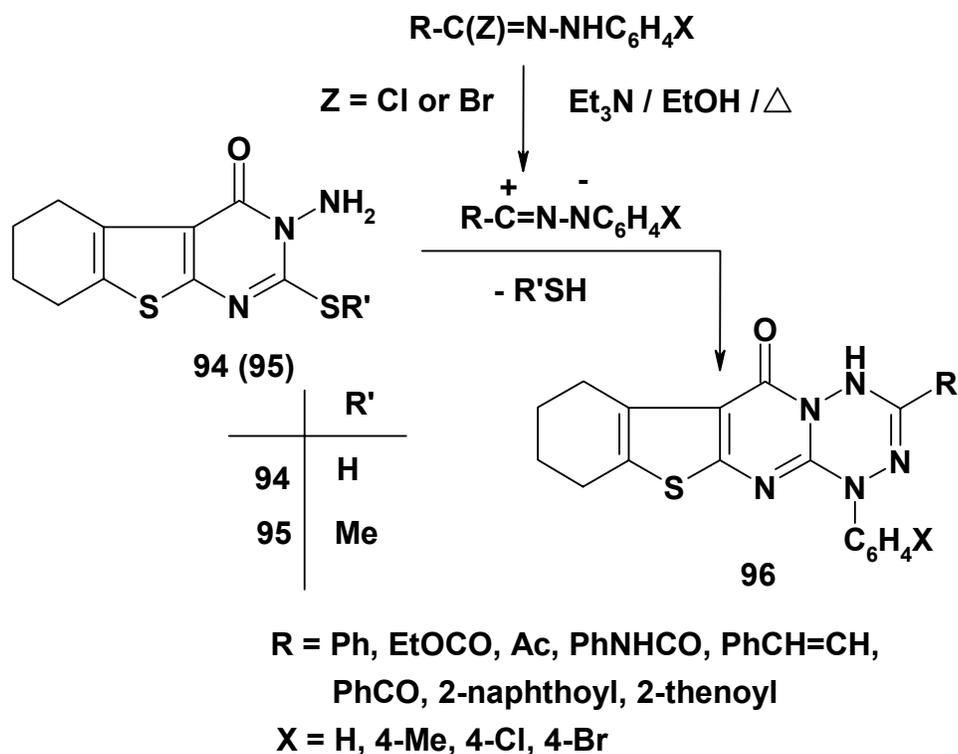
Very recently, it was reported that reaction of 92A with nitrilimines, generated in situ from the hydrazonoyl halides in dioxane in the presence of triethylamine at reflux, resulted in the formation of the respective pyrazolo[3,4-*d*]pyrimido[1,2-*b*][1,2,4,5]tetrazine **93**.⁴⁸ The latter products were also obtained by reaction of 2-methylthio derivative 92B with the same nitrilimines (Scheme 36).



R / X , a, Ph / H; b, Ph / 4-NO₂; c, Ac / H; d, Ac / 4-NO₂;
 e, Ac / 4-Me; f, Ac / 4-Cl; g, Ac / 4-MeO; h, EtOCO / H;
 i, EtOCO / 4-NO₂; j, EtOCO / 4-Me; k, EtOCO / 4-Cl;
 l, PhNHCO / H; m, PhNHCO / 4-Me; n, PhNHCO / 4-Cl;
 o, PhCO / H; q, PhCO / 4-Me; u, PhCO / 4-Cl

Scheme 36

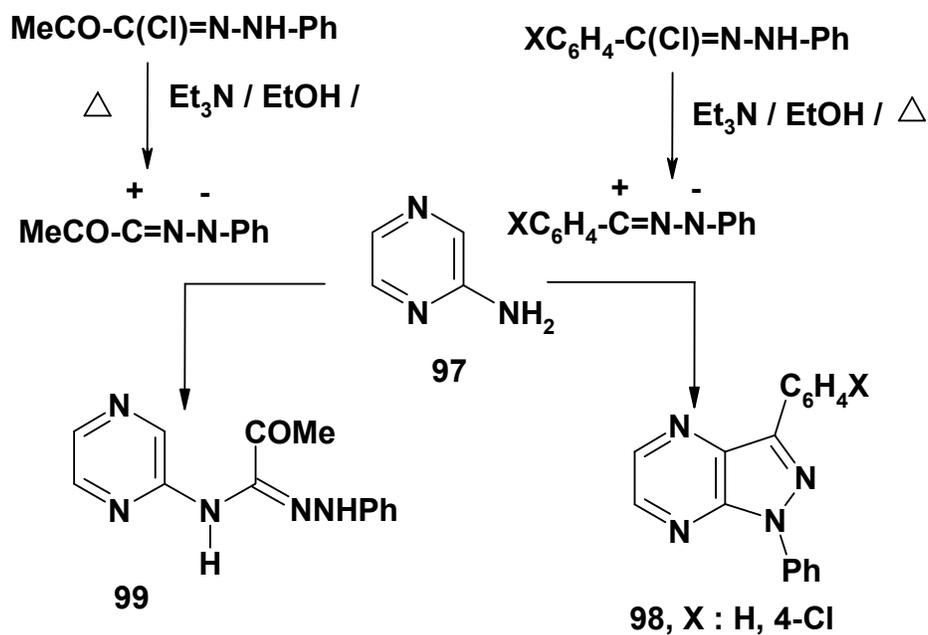
Similarly, reaction of 3-amino-2,3,5,6,7,8-hexahydro-2-thioxobenzo [4,5]thieno[2,3-d]pyrimidin-4(1H)-ones 94 and its 2-methylthio derivative 95 with nitrilimines in refluxing ethanol afforded the fused tetrazine derivatives 96 in 64-90% yields as end products (Scheme 37).⁴⁹



Scheme 37

3.3 Aminopyrazines

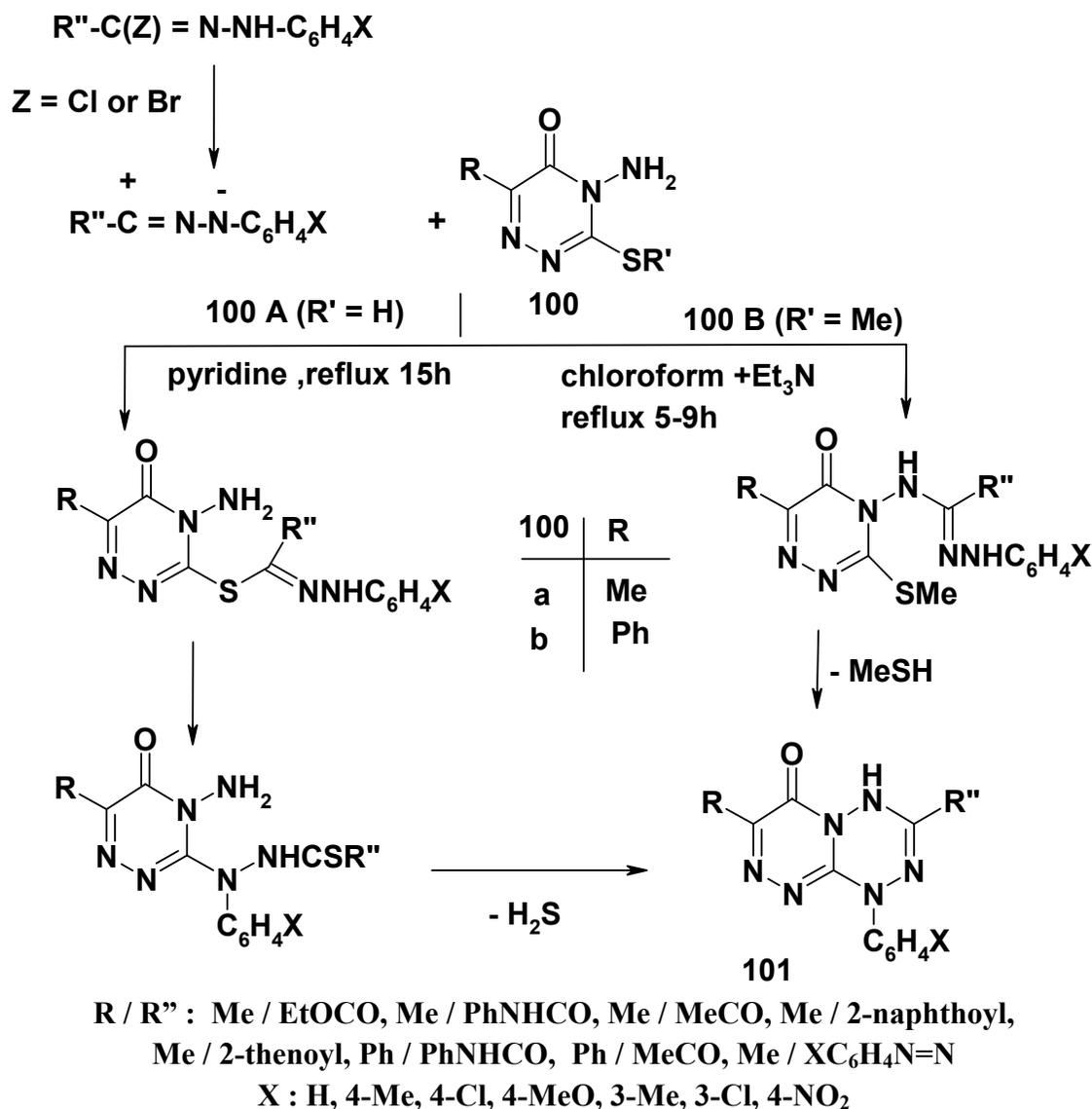
2-Aminopyrazine **97** reacted with *C,N*-diphenylnitrilimines and yielded pyrazolo[3,4-*b*]pyrazine derivatives **98** in 35-60% yields *via* elimination of ammonia from the initially formed cycloadduct.^{18,19} However, similar reaction of 2-aminopyrazine **97** with *C*-acetyl-*N*-phenylnitrilimine was reported to give the respective amidrazone **99** as end product (Scheme 38).¹⁸



Scheme 38

3.4 Amino-1, 2,4-triazines

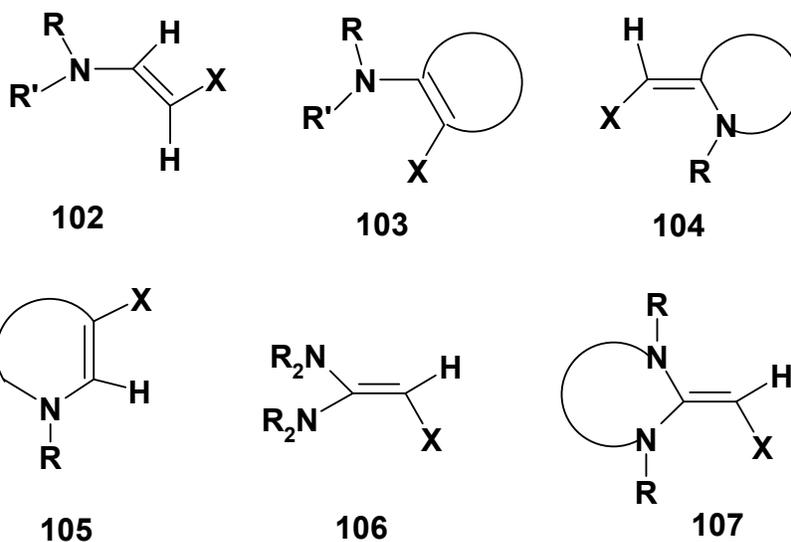
Very recently Shawali et al.^{43, 50} reported that reaction of nitrilimines with either 4-amino-2,3-dihydro-6-substituted-3-thioxo-[1,2,4]triazin-5(4*H*)-ones **100A** or 4-amino-2,3-dihydro-3-methylthio-6-substituted-[1,2,4]triazin-5(4*H*)-ones **100B** gave the respective [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine derivatives **101** in 40-95% yield (Scheme 39).



Scheme 39

4. Reactions with enamines

There are four types of enamines, namely the acyclic enamines **102**, endocyclic enamines **103**, exocyclic enamines **104** and heterocyclic enamines **105** (Chart 1). The substituent X is usually an electron-withdrawing group such as CN, RCO, ROCO, and NO₂. According to the nature of such a substituent, enamines are classified into further groups. For example, when X is CN, acyl and COOR, such enamines are referred to as enamionitriles, enamionones and enaminoesters. If the alpha hydrogen of acyclic enamine is substituted by a substituted amino group, such enamines are referred to as ketene aminals **106** and **107** (Chart 1).



R = R' = alkyl group = Me, Et

R-R' = -(CH₂)_n -; n = 4, 5, 6

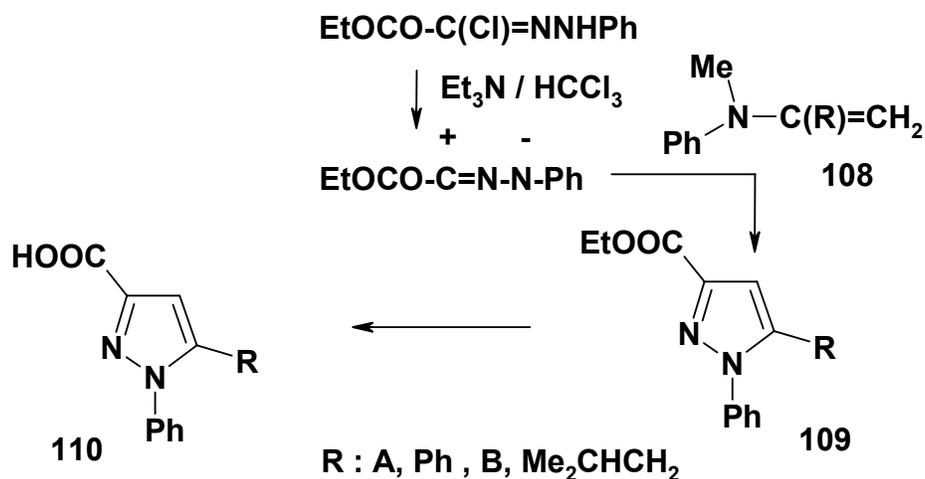
X = CN; ArCO; ROCO

Chart 1

4.1 Acyclic enamines

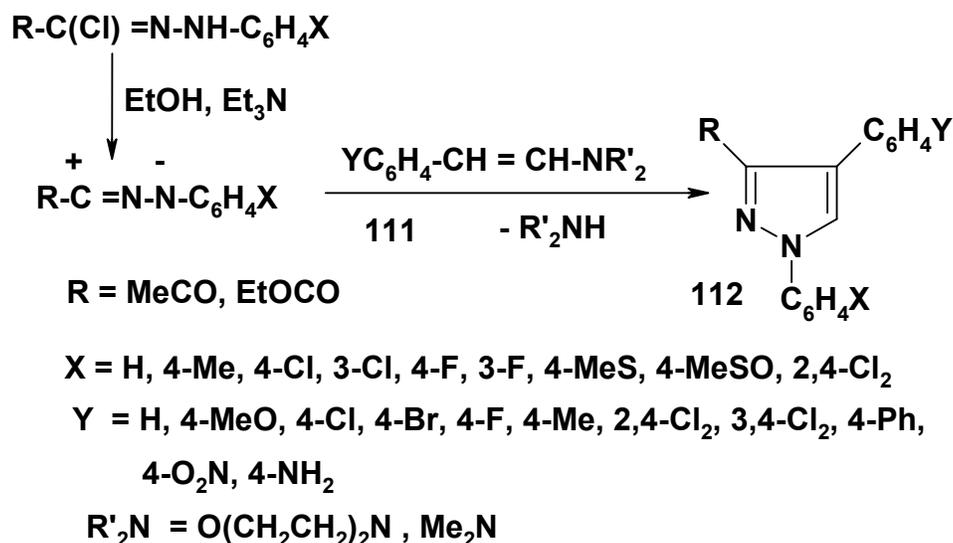
4.1.1 Enamines

Reactions of *C*-ethoxycarbonyl-*N*-phenylnitrilimine, derived from ethyl *N*-phenyl hydrazonochloroacetate, with 2-[(*N*-methyl-*N*-phenylamino)]-1-butene **108A** and α -[(*N*-methyl-*N*-phenylamino)]styrene **108B** were reported to give the respective 5-substituted pyrazole derivatives **109A** and **109B**, which upon hydrolysis afforded the respective acids **110A** and **110B**, respectively (Scheme 40).⁵¹



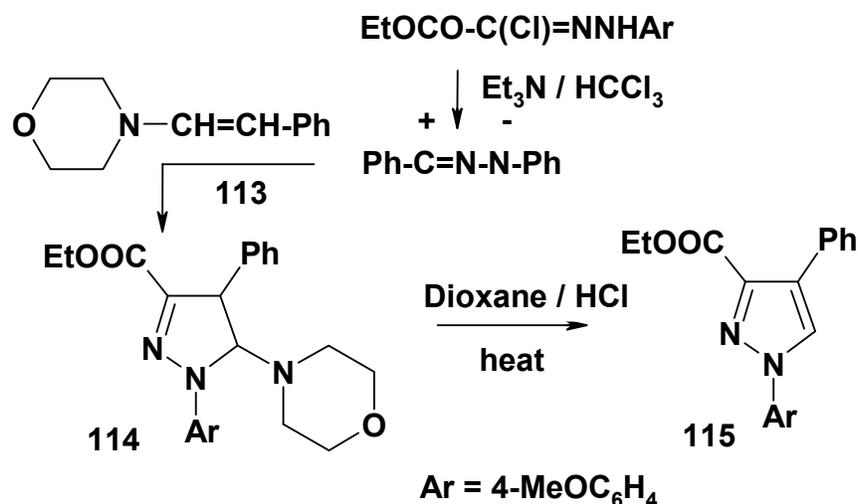
Scheme 40

Other 1,3,4-trisubstituted-pyrazoles **112** were also prepared in 55-73% yields by reactions of enamines **111** with various nitrilimines (Scheme 41).^{52,53}



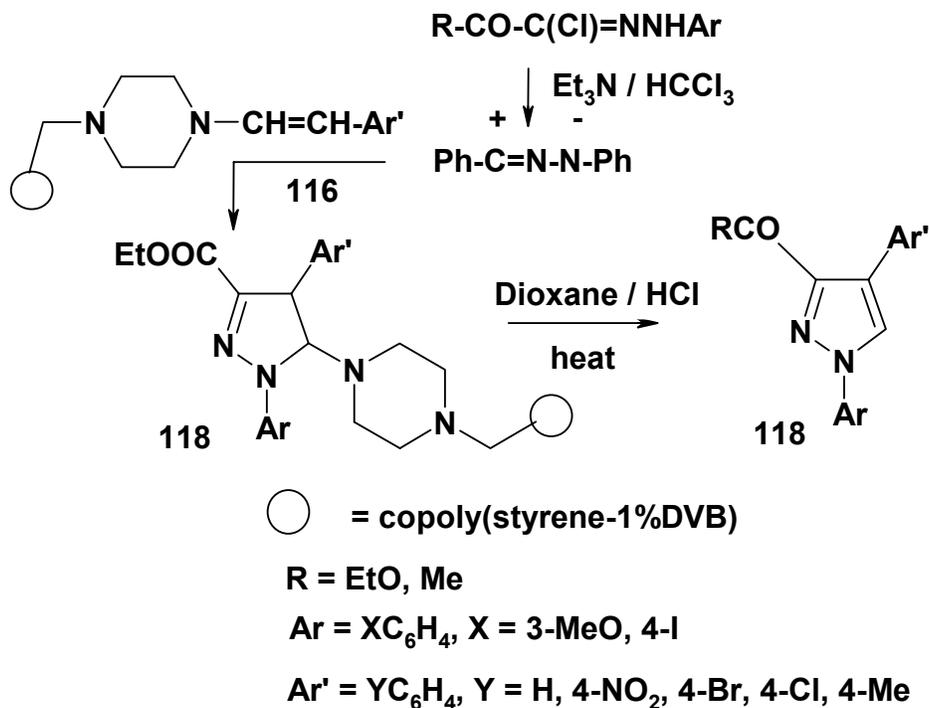
Scheme 41

The 1,3-dipolar cycloaddition of *N*-aryl-*C*-ethoxycarbonylnitrilimine with enamine **113** was reported to give the pyrazoline cycloadduct **114**, which underwent deamination when heated in dioxane in the presence of hydrochloric acid to give **115** as end product (Scheme 42).⁵⁴



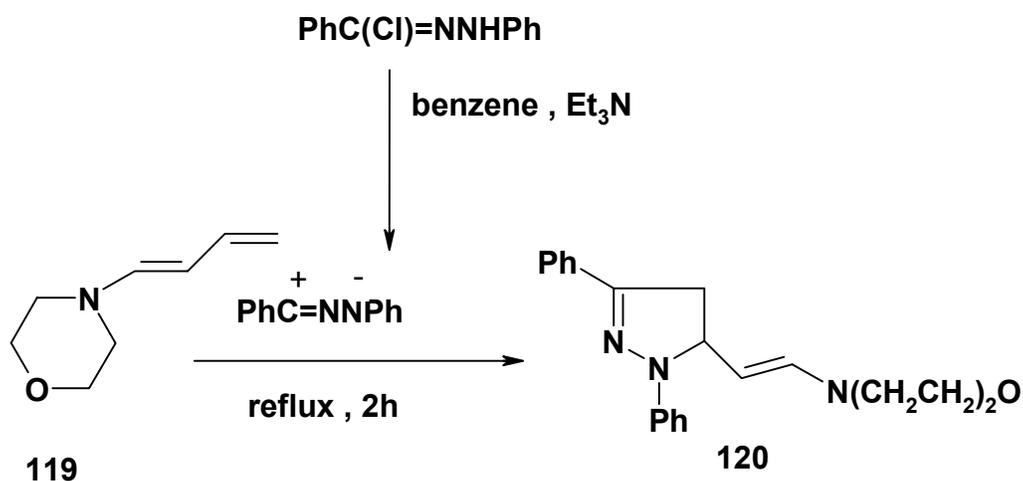
Scheme 42

Other 1,4-diarylpyrazole derivatives **118** were prepared in 90-95% yield *via* reaction of nitrilimines with resinbound piperazine enamines **116** followed by cleavage of the initially formed resin-bound pyrazoline cycloadducts **117** by heating them in DCM containing 3% trifluoroacetic acid. During this treatment, piperazine is eliminated to give **118** as end products (Scheme 43).⁵⁵



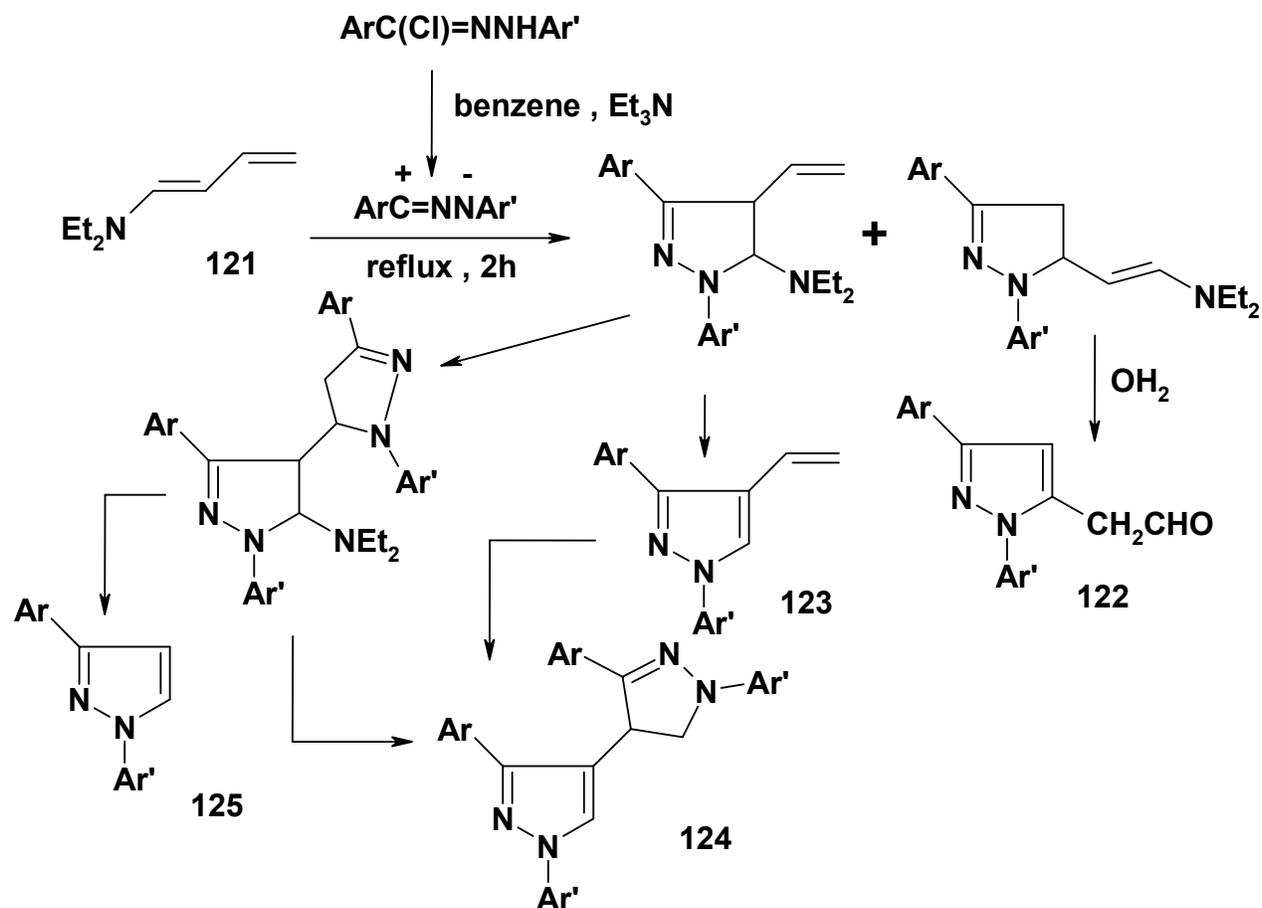
Scheme 43

The reaction of β -vinylenamine **119** with diphenylnitrilimine was reported to be site-selective as it occurred at the unsubstituted C=C double bond to give only **120** in 39 % yield (Scheme 44).⁵⁶



Scheme 44

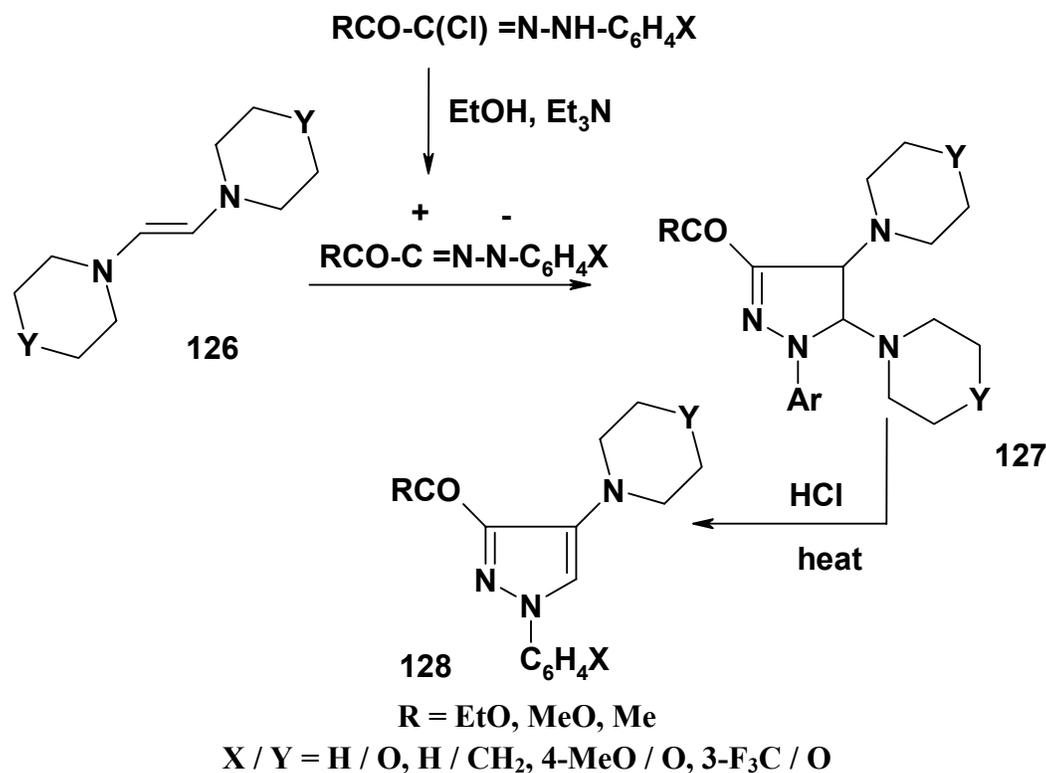
In another report, it was indicated, however, that the reaction of the enamine **121** with *C,N*-diarylnitrilimines in benzene at room temperature gave a mixture of four products namely **122-125** in 12-53% yields.⁵⁴ When this reaction was conducted at 80°C only the products **124** and **125** were produced (Scheme 45).⁵⁴



$\text{Ar} / \text{Ar}' = \text{Ph} / \text{Ph}, \text{Ph} / 4\text{-ClC}_6\text{H}_4, \text{Ph} / 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4 / \text{Ph}$

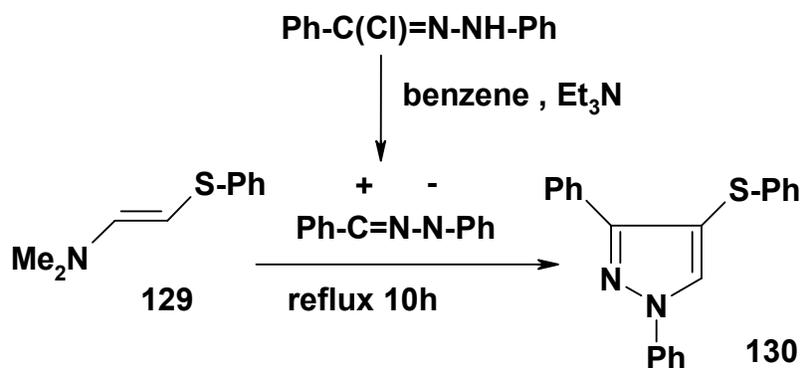
Scheme 45

The reactions of *C*-acyl-*N*-arylnitrilimines with the enamines **126** in benzene yielded the pyrazole derivatives **127** in 45-65% yields.⁵⁷ The latter products underwent deamination upon heating in ethanol in the presence of hydrochloric acid to afford the aminopyrazole derivative **128** in 85-96% yields (Scheme 46).⁵⁷



Scheme 46

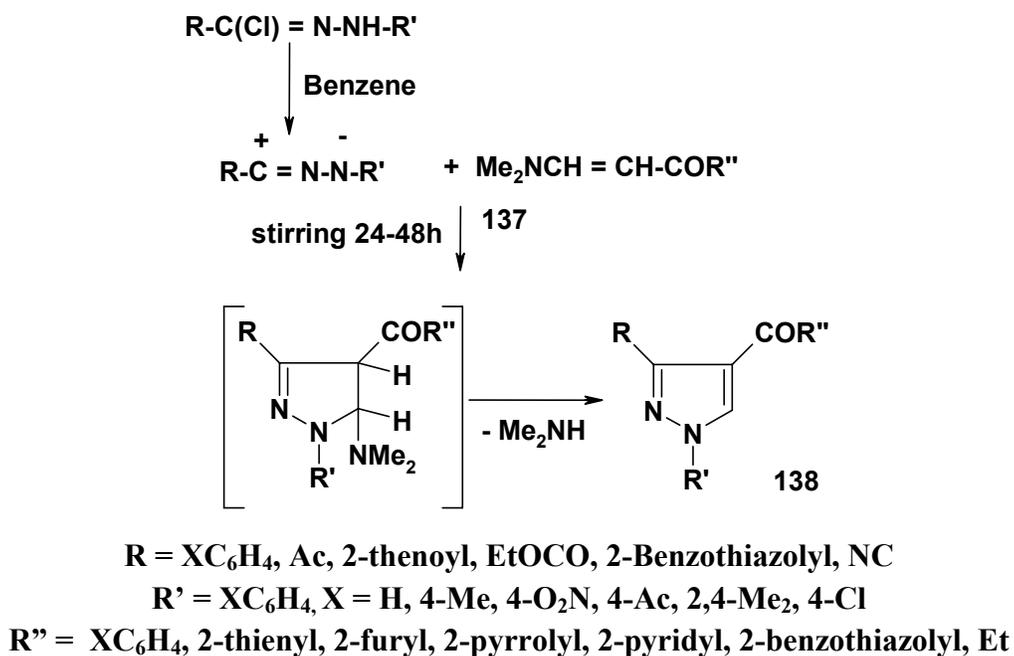
Reaction of 2-phenylthioenamine **129** with *C,N*-diphenylnitrilimine yielded 4-phenylthio-1,3-diphenylpyrazole **130** in 40 % yield (Scheme 47).⁵⁸



Scheme 47

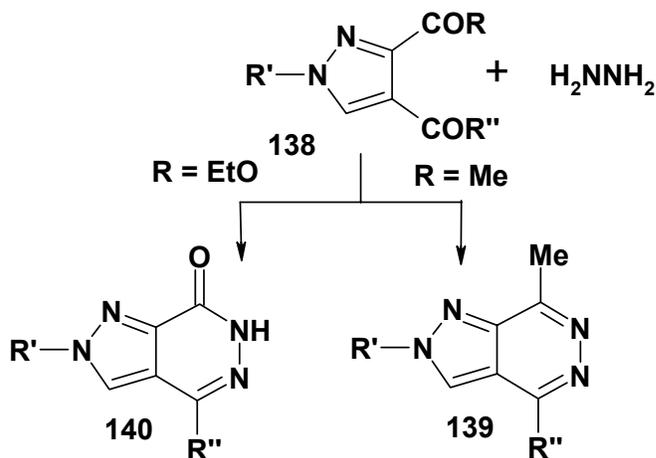
Reactions of *C,N*-diaryl nitrilimines with each of the enamines **131A** and **131B** yielded pyrazolines **132** and **133** in 70 % and 80 % yields, respectively. Heating each of the latter products in ethanol in presence of hydrochloric acid afforded in both cases the the respective pyrazole derivatives **134** in 90% yield (Scheme 48).⁵⁹

respective hydrazoneyl halides, proved to be regioselective and afforded the corresponding 1-aryl-3,4-disubstituted-pyrazoles **138** in 2-90 % yields (Scheme 50).⁶¹⁻⁶⁶



Scheme 50

Treatment of each of the products **138** having 3,4-diacyl and 3-ethoxycarbonyl-4-acyl groups each with hydrazine hydrate afforded the respective pyrazolo[3,4-*d*]pyridazines **139** and **140** in 78-96% yields (Scheme 51).^{62-64, 66}

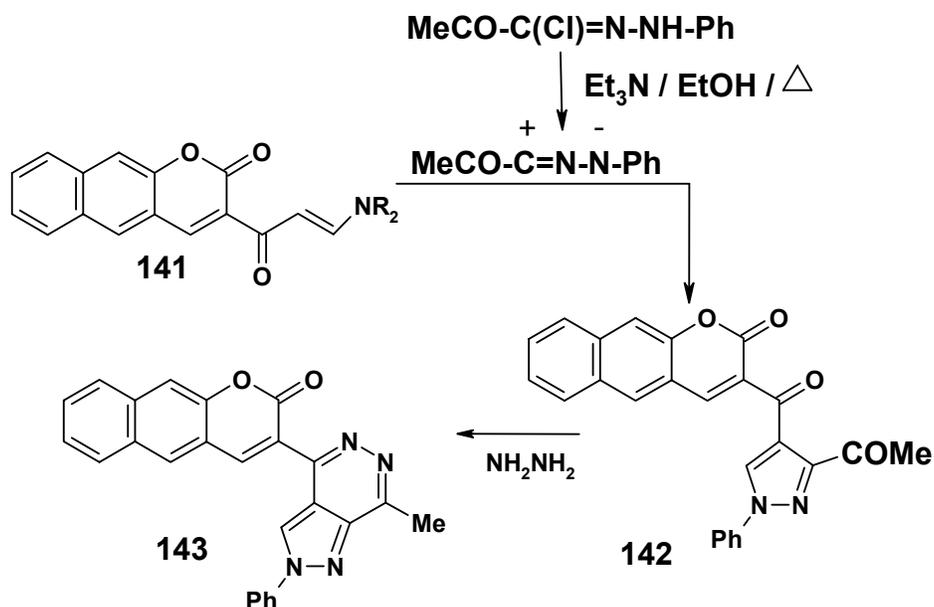


139, R' = Ph, 4-MeC₆H₄; R'' = Ph, 2-thienyl, 2-pyridyl, Et, 2-benzothiazolyl

140, R' = 4-O₂NC₆H₄, R'' = 2-pyridyl

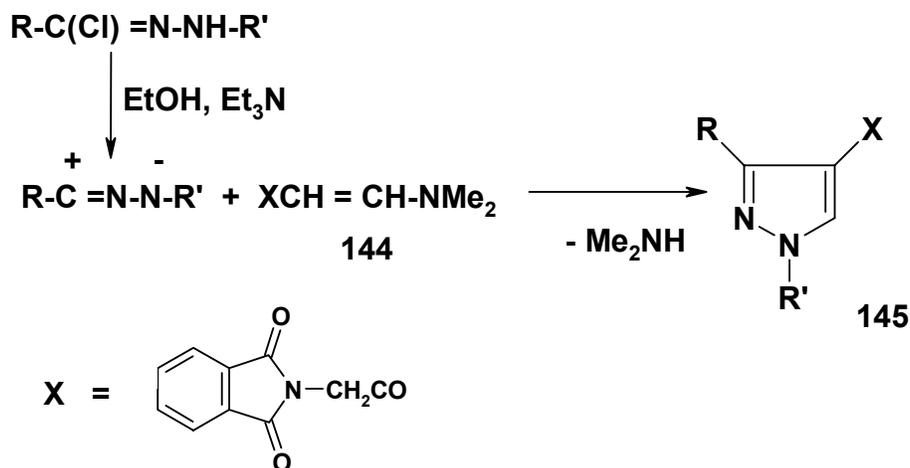
Scheme 51

Also, the enaminone **141** reacted with *C*-acetyl-*N*-phenylnitrilimine and afforded the pyrazole derivative **142** in 43% yield which upon treatment with hydrazine hydrate yielded **143** in 73% yield (Scheme 52).⁶⁷



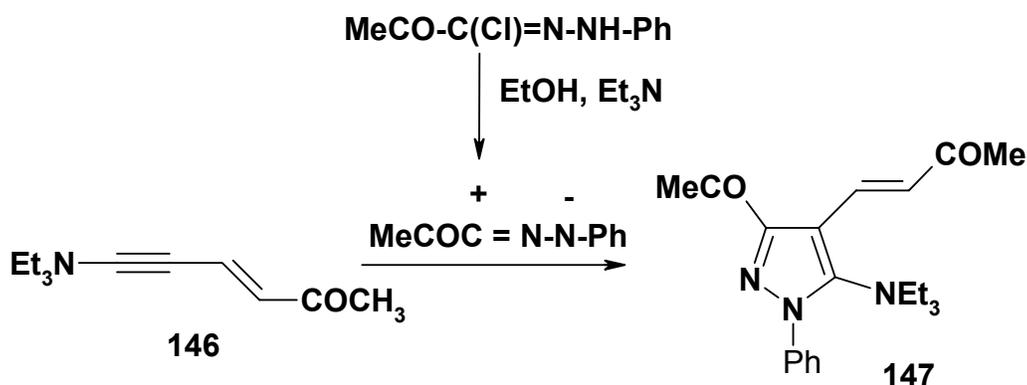
Scheme 52

Other 1,3,4-trisubstituted pyrazoles **145** were also prepared in 55-73% yields by reactions of enaminones **144** with various nitrilimines (Scheme 53).⁵²



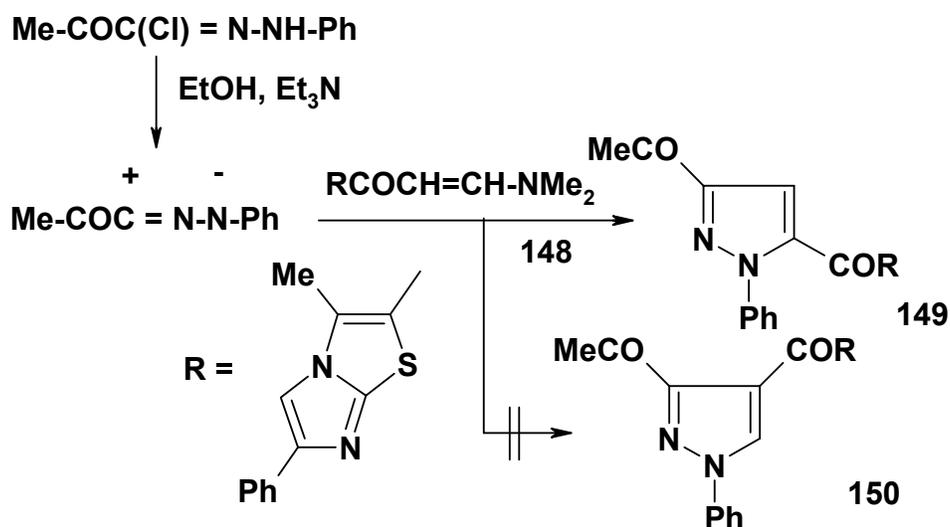
Scheme 53

Reaction of *C*-acetyl-*N*-phenylnitrilimine with ynaminone **146** was reported to be site-selective. It yielded the pyrazole derivative **147** in 48% yield (Scheme 54).⁶⁸



Scheme 54

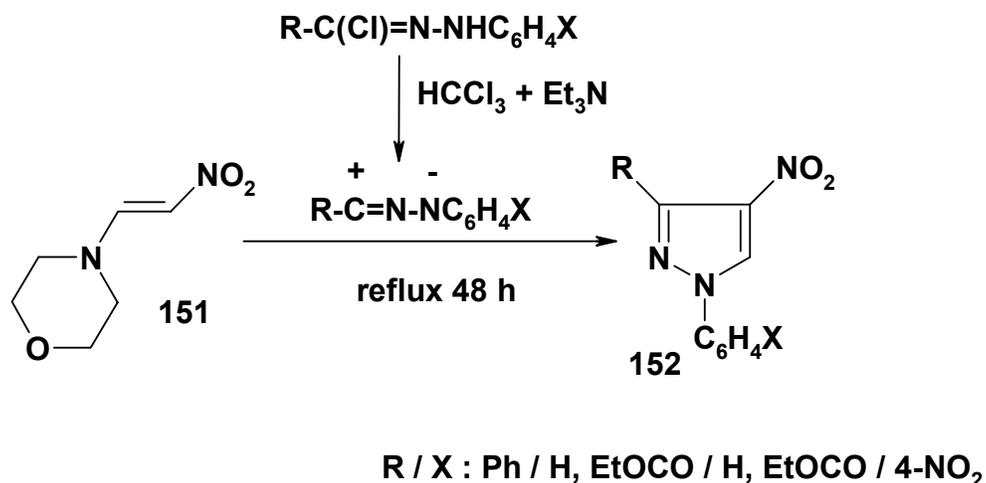
In contrast to the foregoing results, it was indicated in one report that reaction of *C*-acetyl-*N*-phenylnitrilimine with the enaminone **148** afforded the 3,5-diacylpyrazole derivative **149** in 58 % yield instead of the expected 3,4-diacyl- analog **150**.⁶⁹ This regiochemical result seems to need further confirmation (Scheme 55).



Scheme 55

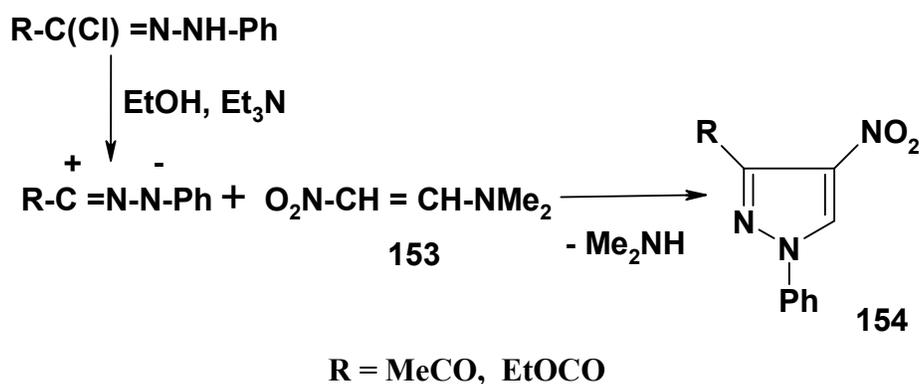
4.1.3 Nitroenamines

Also, *N*-aryl nitrilimines reacted with nitroenamine **151** and afforded the respective 1-aryl-3-nitro- 4-substituted pyrazoles **152** in 5-20% yields (Scheme 56).⁷⁰



Scheme 56

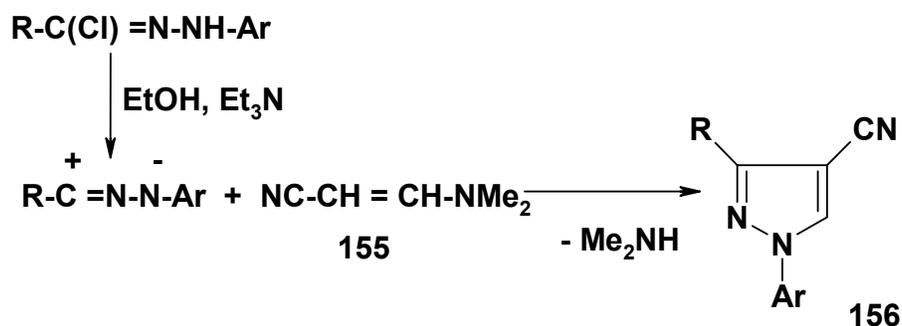
Also, various 3,4-disubstituted-1-arylpiperazines **154** were prepared in 55-73% yields by reactions of enaminones **153** with various nitrilimines (Scheme 57).⁵²



Scheme 57

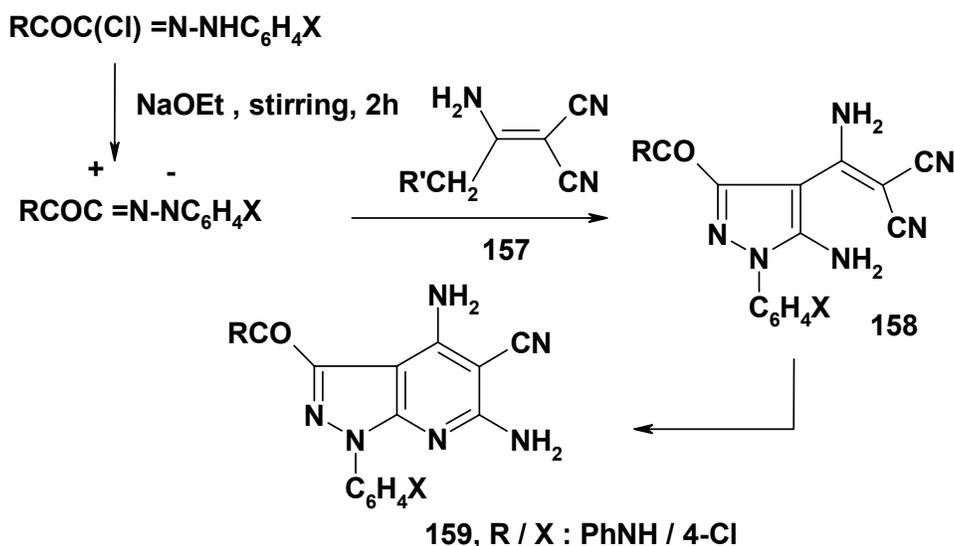
4.1.4 Enaminonitriles

Various 1-aryl-4-cyano-3-substituted-piperazines **156** were also prepared in 55-73% yields by reactions of enamines **155** with various nitrilimines (Scheme 58).⁷¹



Scheme 58

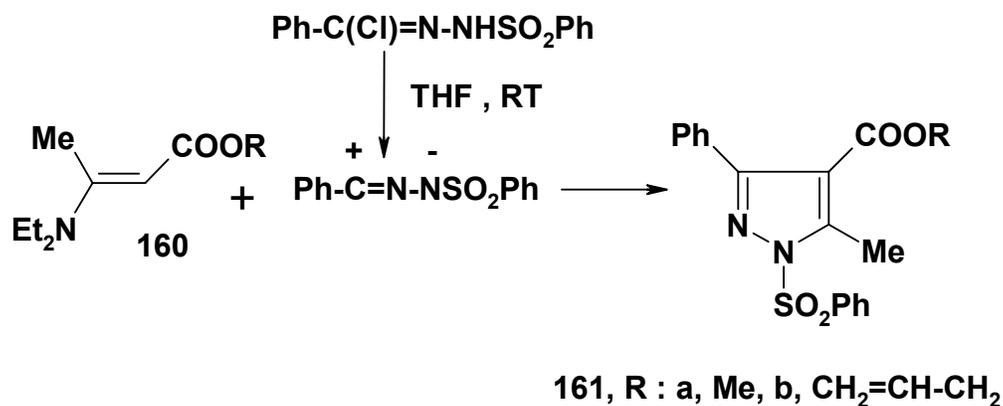
Also, the reactions of *N*-aryl *C*-ethoxycarbonyl- and *C*-phenylaminocarbonyl- nitrilimines were reported to react with 1-cyanomethylenaminonitriles **157** in ethanol to give the respective pyrazolo[3,4-*b*]pyridines **159** in 55% yield.⁷² In this case the reaction proceeds to give the pyrazole derivatives **158** that cyclize *in situ* to give **159** as end products (Scheme 59).



Scheme 59

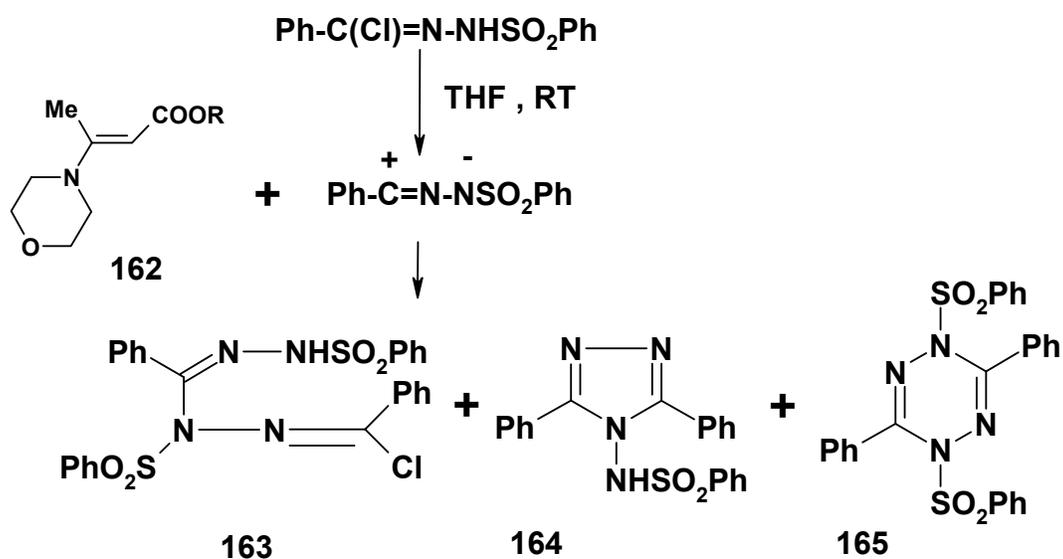
4.1.5 Enaminoesters

When a mixed solution of *C*-phenyl-*N*-benzenesulfonyl-nitrilimine and one equivalent of each of the enamino esters **160** in tetrahydrofuran was allowed to stand at room temperature, the respective pyrazole derivatives **161** were obtained in 87 - 89% yields. The same result was obtained when two equivalents of **160** were used (Scheme 60).⁷³



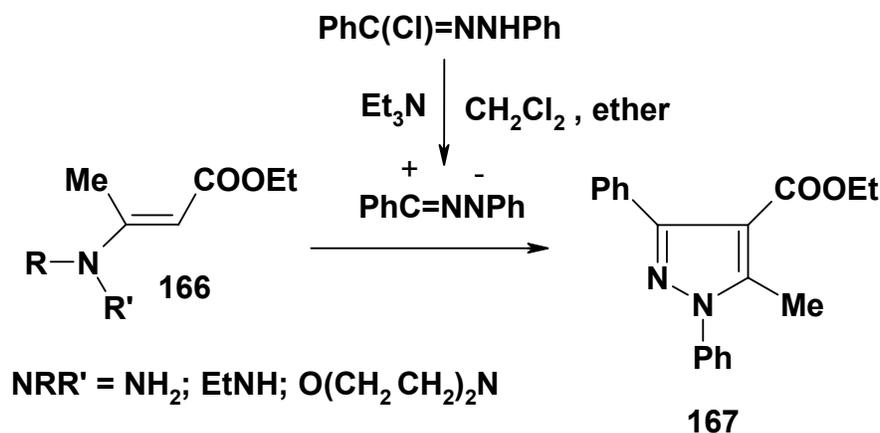
Scheme 60

However, similar reaction of *C*-phenyl-*N*-phenylsulphonylnitrilimine with enaminoester **162** yielded no pyrazole. It gave instead a mixture of **163** and **164** (13% yield) and/or **165** in 48% yield (Scheme 61).⁷³



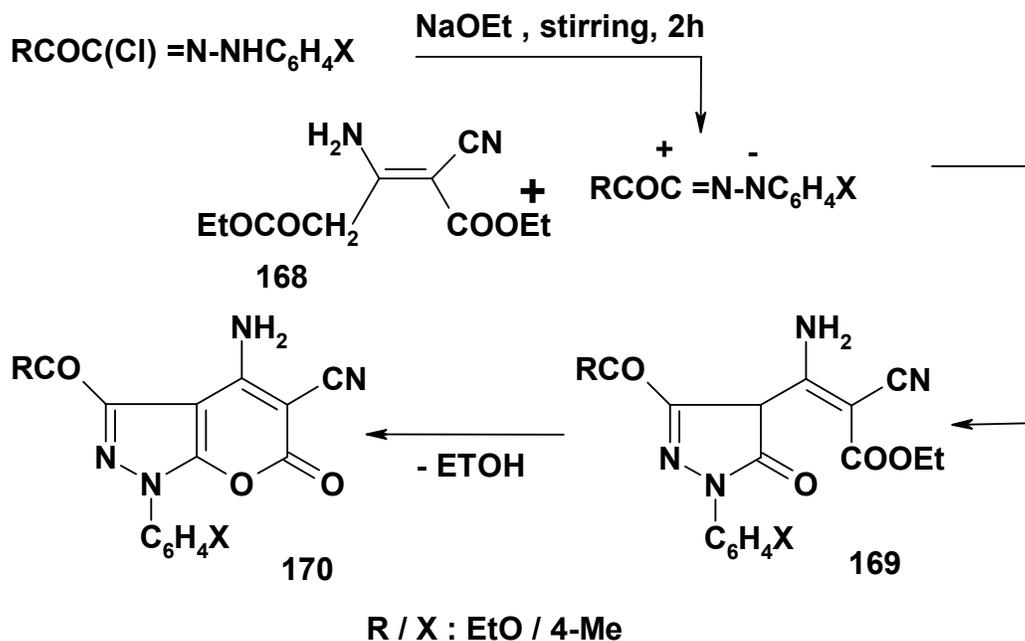
Scheme 61

C,N-Diphenylnitrilimine reacted with the 1-substituted enaminoester **166** to afford the pyrazole derivative **167** in 26 % yield (Scheme 62).⁷⁴



Scheme 62

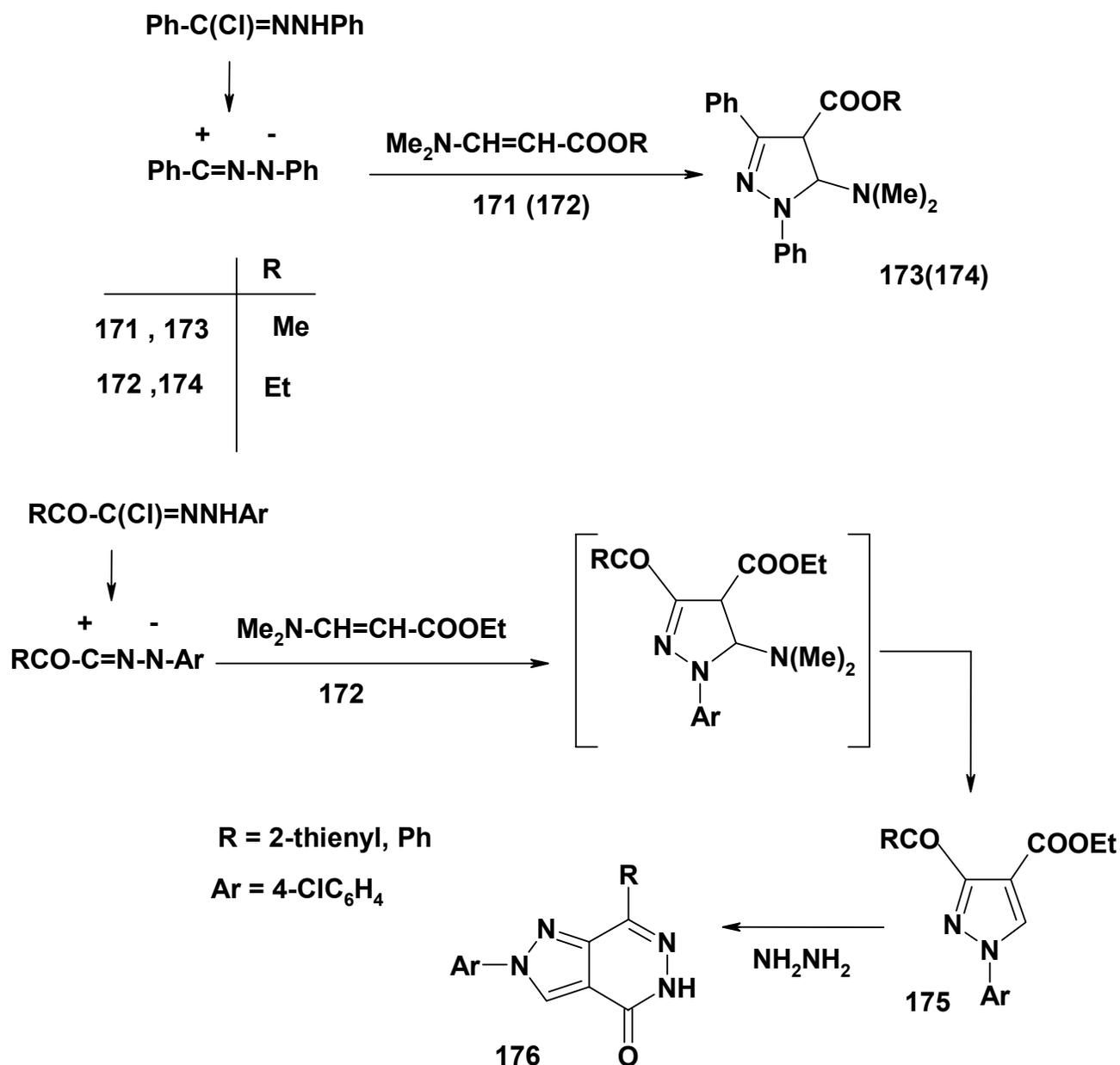
Reaction of *N*-aryl-*C*-ethoxycarbonyl-nitrilimine with 1-ethoxycarbonylmethyl-enaminonitriles **168** gave the respective pyrano[2,3-*c*]pyrazole **170** in 52% yield.⁷² In this case, it seems that the enamine **168** behaves as active methylene compound that reacts with nitrilimine to give the pyrazolone intermediate **169** which cyclizes *in situ* to yield **170** as end product (Scheme 63).



Scheme 63

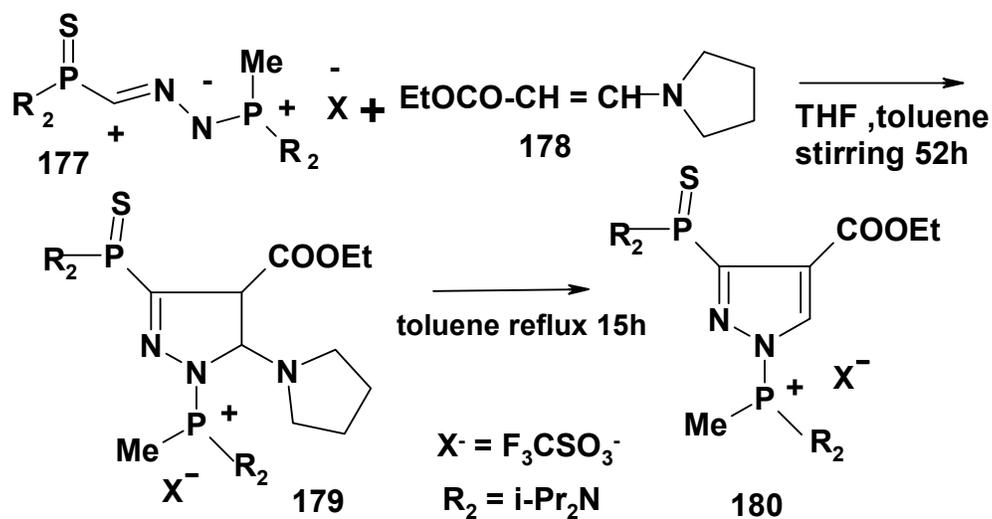
C,N-Diphenylnitrilimine reacted with the enamines **171** and **172** and gave the pyrazoline cycloadducts **173** and **174**, respectively.⁶⁰ However, similar reaction of **172** with other

nitrilimines afforded the pyrazole derivatives **175** which upon treatment with hydrazine hydrate yielded **176** (Scheme 64).^{75,76}



Scheme 64

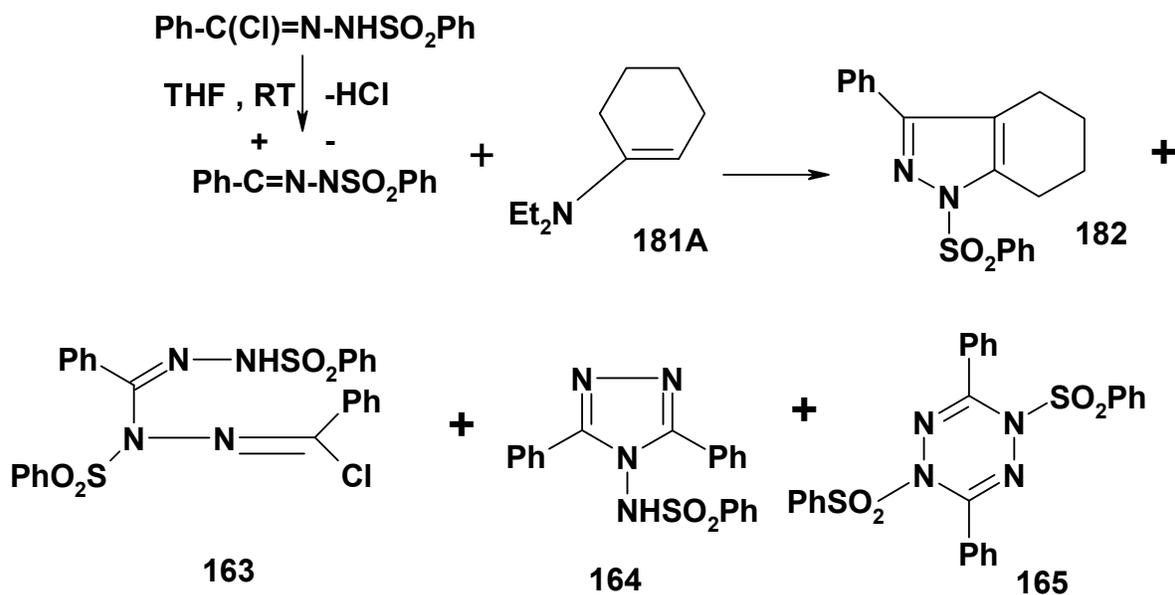
N-[Bis(diisopropylamino)(methyl)phosphonio]-*C*-[bis(diisopropylamino)-thioxophosphoranyl]nitrilimine **177** was reported to undergo cycloaddition to the enamino-ester **178** via LUMO(dipole) controlled reaction to give the cycloadduct **179** in 78 % yield which upon heating afforded the pyrazole derivatives **180** in 75 % yield (Scheme 65).⁷⁷



Scheme 65

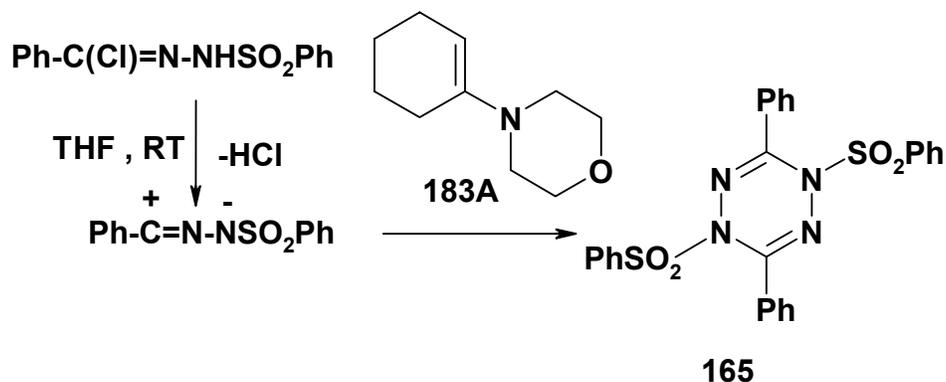
4.2 Endocyclic enamines

Reaction of *C*-phenyl-*N*-benzenesulfonylnitrilimine with 1-diethylaminocyclohexene **181A** was reported to give a mixture of four products namely **163-165** in 1.4, 42, 2.7 and 4 % yields, respectively (Scheme 66).⁷³



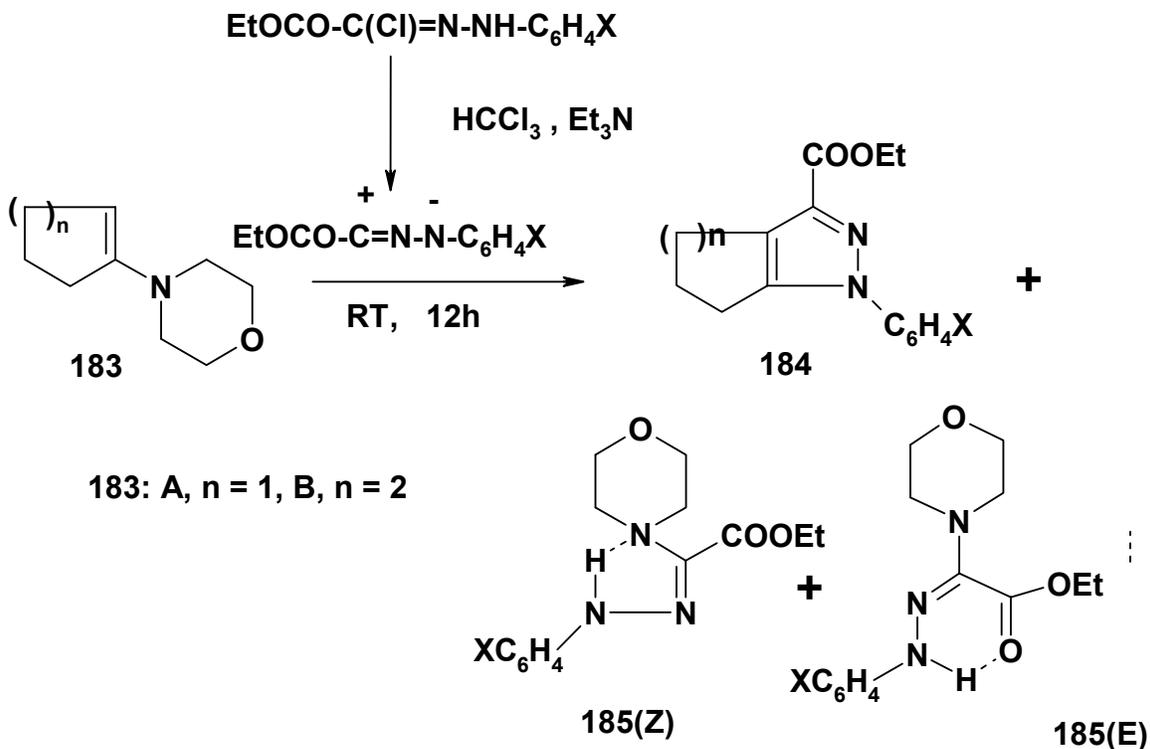
Scheme 66

However, similar reaction of the same nitrilimine with the morpholinoenamine analog **183A** afforded only the tetrazine derivative **165** in 48% yield.⁷³ In this case, it seems that the enamine **183A** functions only as a base catalyst (Scheme 67).



Scheme 67

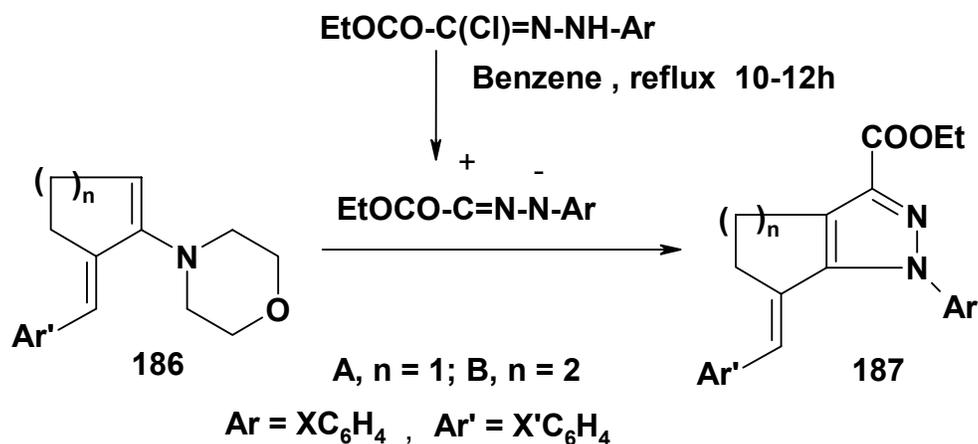
Cycloalkanone enamines **183A(B)** were also reported to react with *C*-ethoxycarbonyl-*N*-phenylnitrilimine to yield in each case the respective cycloalka[*c*]pyrazoles **184** in 32-67 % yields and a mixture of *E*- and *Z*-isomers of the amidrazone **185**.⁷⁸ In another report, this same reaction was reported to afford only **184** (Scheme 68).⁶⁰



$n = 1, X = \text{H}, 4\text{-Cl}, 3\text{-NO}_3, n = 2, X = \text{H}, 3\text{-NO}_3, 4\text{-Cl}, 4\text{-F}, 3\text{-F}_3\text{C}, 4\text{-Me}$

Scheme 68

The reactions of 2-arylidencycloalkanone enamines **186** with the same nitrilimines were reported to be site selective as they yielded the respective cycloalka[*c*]pyrazoles **187** in 20-37% yields (Scheme 69).⁷⁹

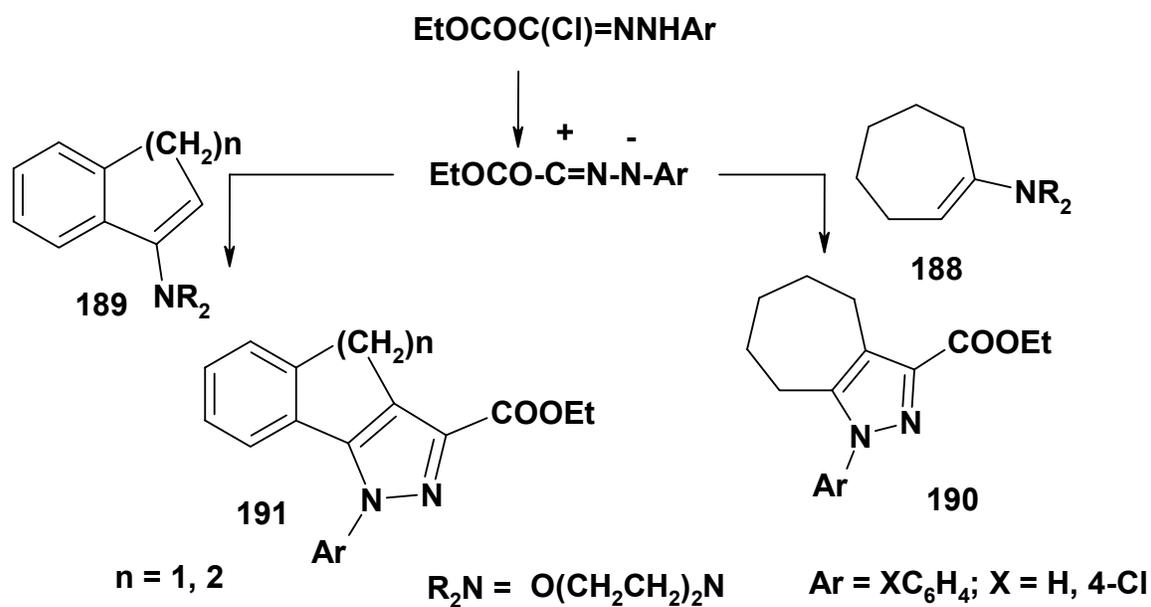


n = 1, X / X' = 4-F / H, 4-F / 4-NO₂, 3-F₃C / 2,4-Cl₂.

n = 2, X / X' = 4-F / H, 4-F / 4-Cl, 3-F₃C / 4-Cl.

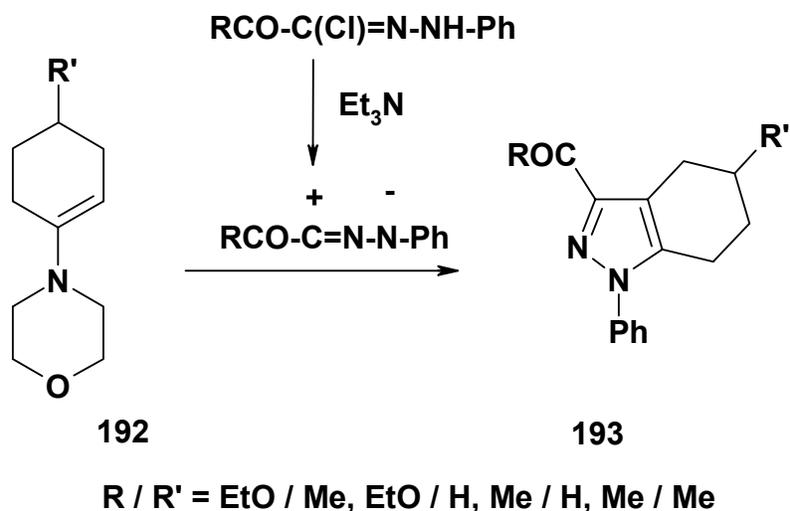
Scheme 69

Similarly, the cycloalkapyrazole derivatives **190** and **191** were prepared by reaction of the respective cycloalkenone enamines **188** and **189** each with aryl-*C*-ethoxycarbonyl-*N*-nitrilimines in chloroform (Scheme 70).⁵¹



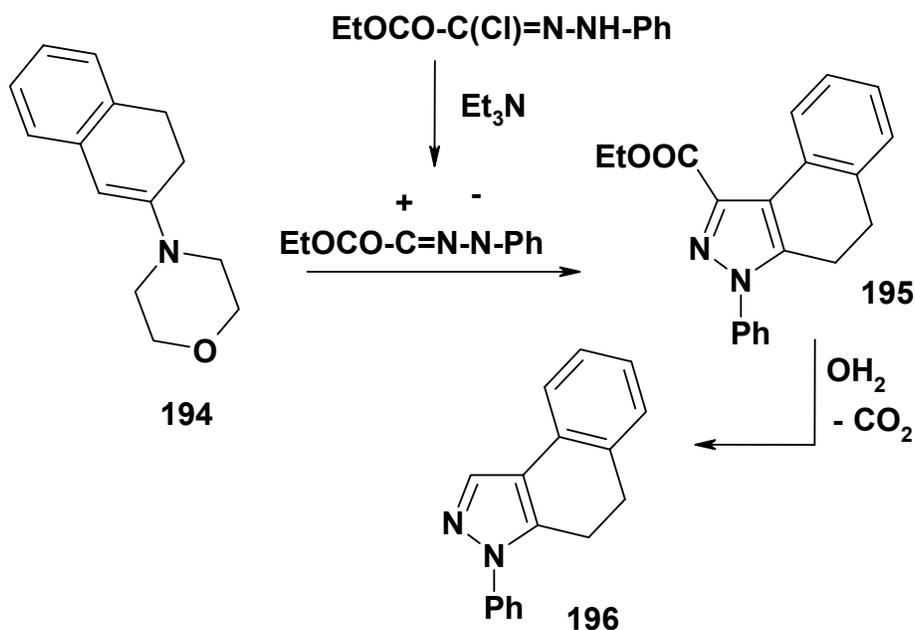
Scheme 70

Reaction of *N*-phenylnitrilimines with each of 1-morpholinocyclohexene and its 4-methyl derivative **192** yielded the respective 1-phenyl-3-acetyl-4,5,6,7-tetrahydroindazoles **193** (Scheme 71).⁵¹



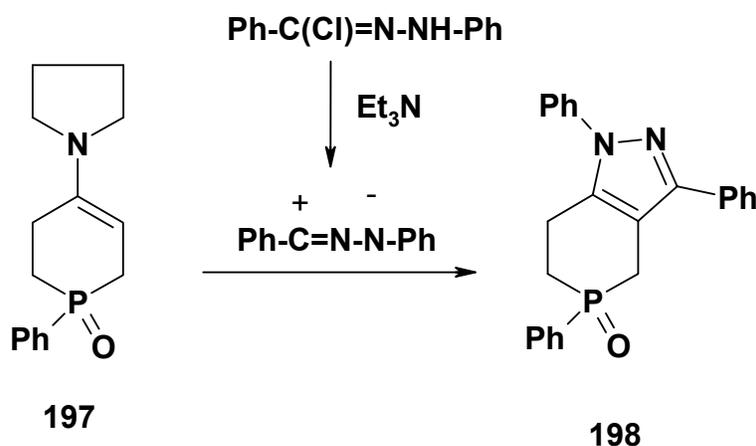
Scheme 71

Similarly, 1-phenyl-3-ethoxycarbonyl-8,9-dihydronaphtho[1,2-*c*]pyrazole **196** was obtained from reaction of **194** with nitrilimine. Hydrolysis of the **195** followed by decarboxylation of the resulting acid afforded **196** (Scheme 72).⁵¹



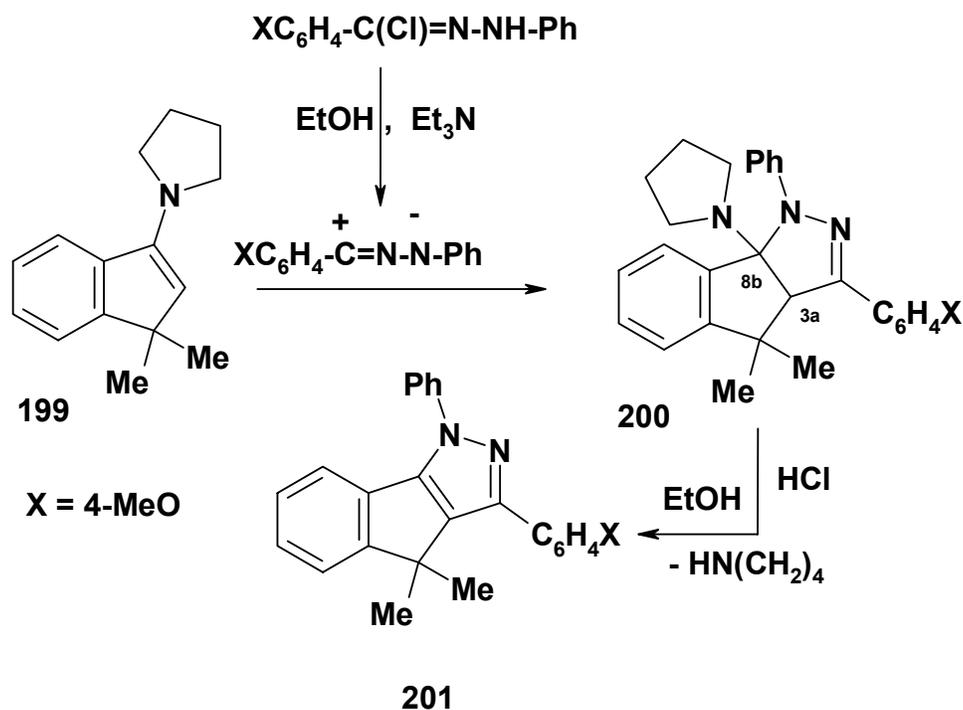
Scheme 72

Reaction of phosphorinanon-4-enamine (**197**) with *C,N*-diphenylnitrilimine yielded **198** in 21% yield (Scheme 73).⁸⁰



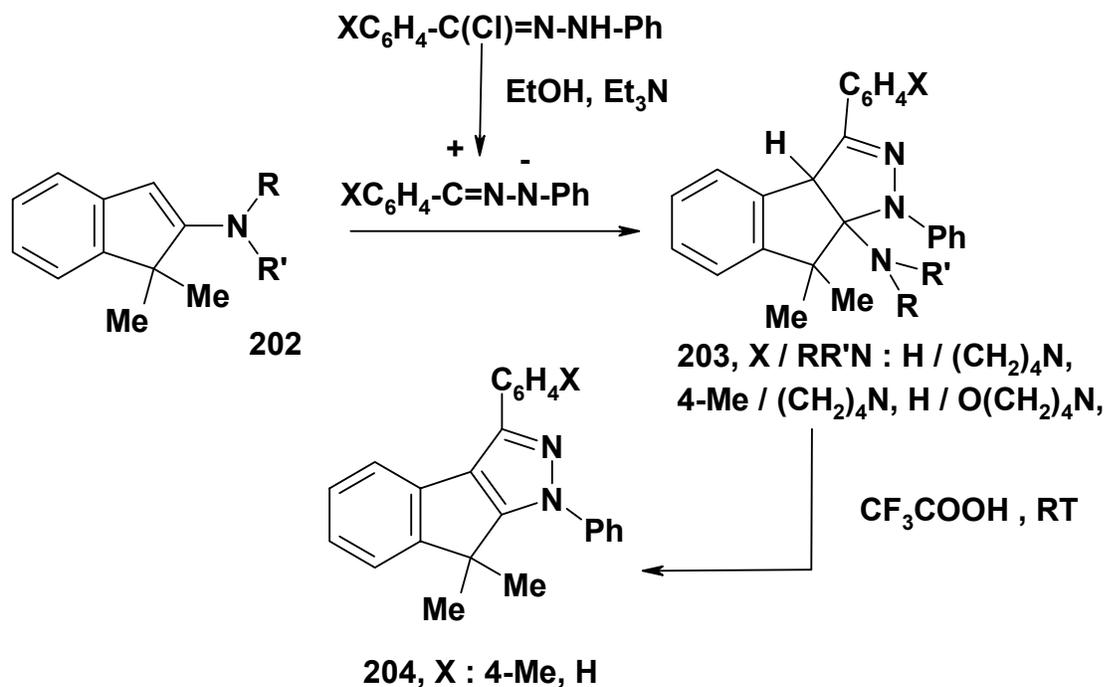
Scheme 73

The reaction of 3,3-dimethyl-1-indanone-enamine **199** with *C,N*-diarylnitrilimine gave the cycloadducts **200** in 50% yield which, by treatment with 2M aqueous hydrochloric acid in refluxing ethanol, led to the indeno[3,2-*c*]pyrazoles **201**. The regiochemistry of the cycloadduct was established by ¹³C NMR spectra where the signal of C(3a) appears as doublet at δ 58.8 and that of C(8b) appears as singlet at δ 98.3 (Scheme 74).⁸¹



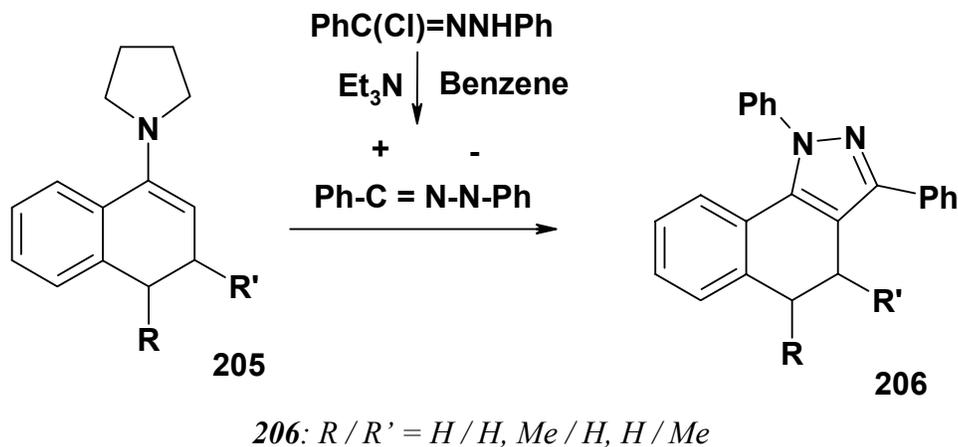
Scheme 74

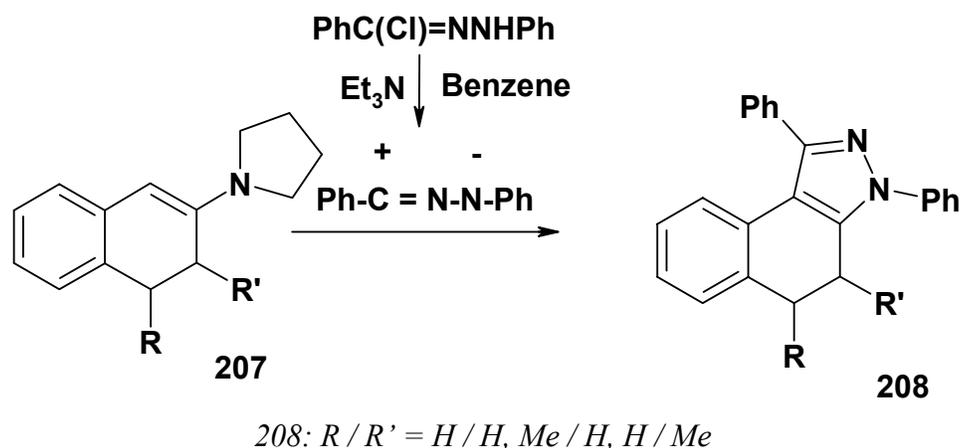
Reaction of 1,1-dimethyl-2-indenone enamines (**202**) with *C,N*-diarylnitrilimines was also reported to be regioselective yielding the respective cycloadduct **203** in 80-88% yields. Treatment of the latter with trifluoroacetic acid at room temperature afforded indeno[2,3-*c*]pyrazoles **204** (Scheme 75).⁸¹



Scheme 75

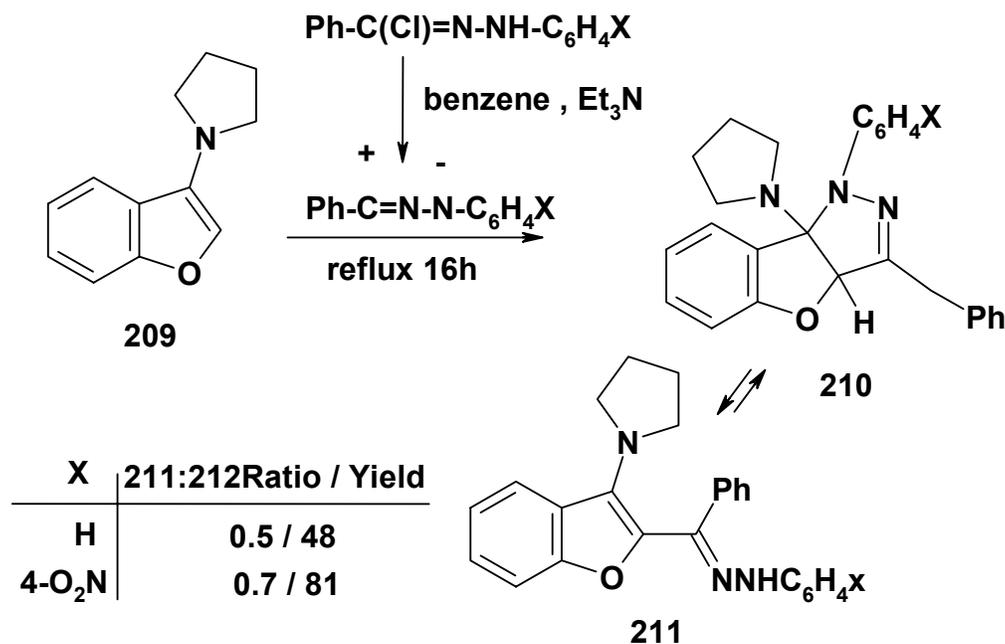
Reactions of *C,N*-diphenylnitrilimine with each of the isomeric enamines **205** and **207** are regioselective and afforded the isomeric 1*H*-4,5-dihydronaphtho[4,3-*c*]pyrazoles **206** and 1*H*-4,5-dihydronaphtho[3,4-*c*]pyrazoles **208** in 52-70 and 57-75% yields, respectively (Scheme 76).⁸²





Scheme 76

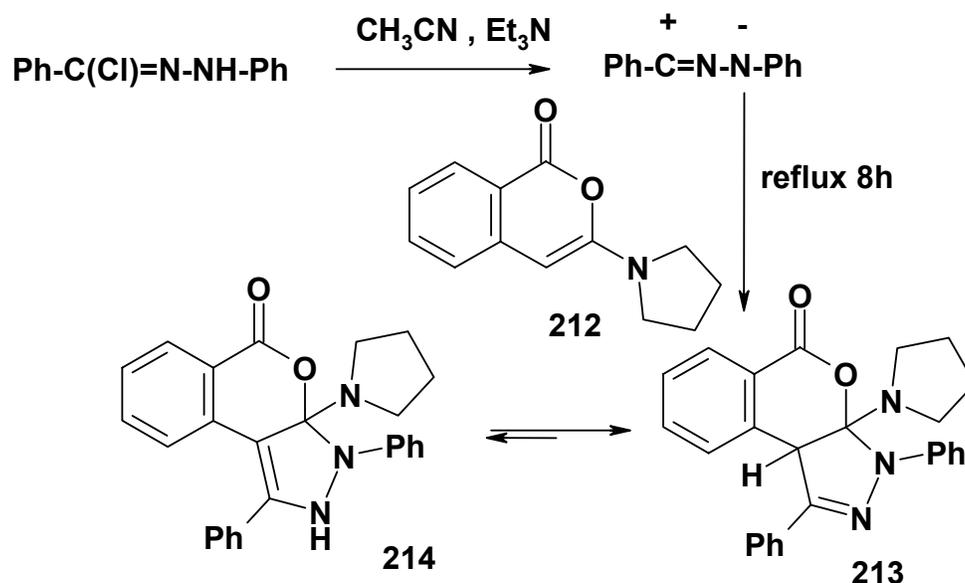
3-Pyrrolidinobenzo[*b*]furan (**209**) reacted with *C,N*-diarylnitrilimines in benzene and gave a mixture of the tautomeric adducts **210** and **211**. The latter product **211** was found to be the major product and it was assumed to result from ring cleavage of **210** (Scheme 77).⁸³



Scheme 77

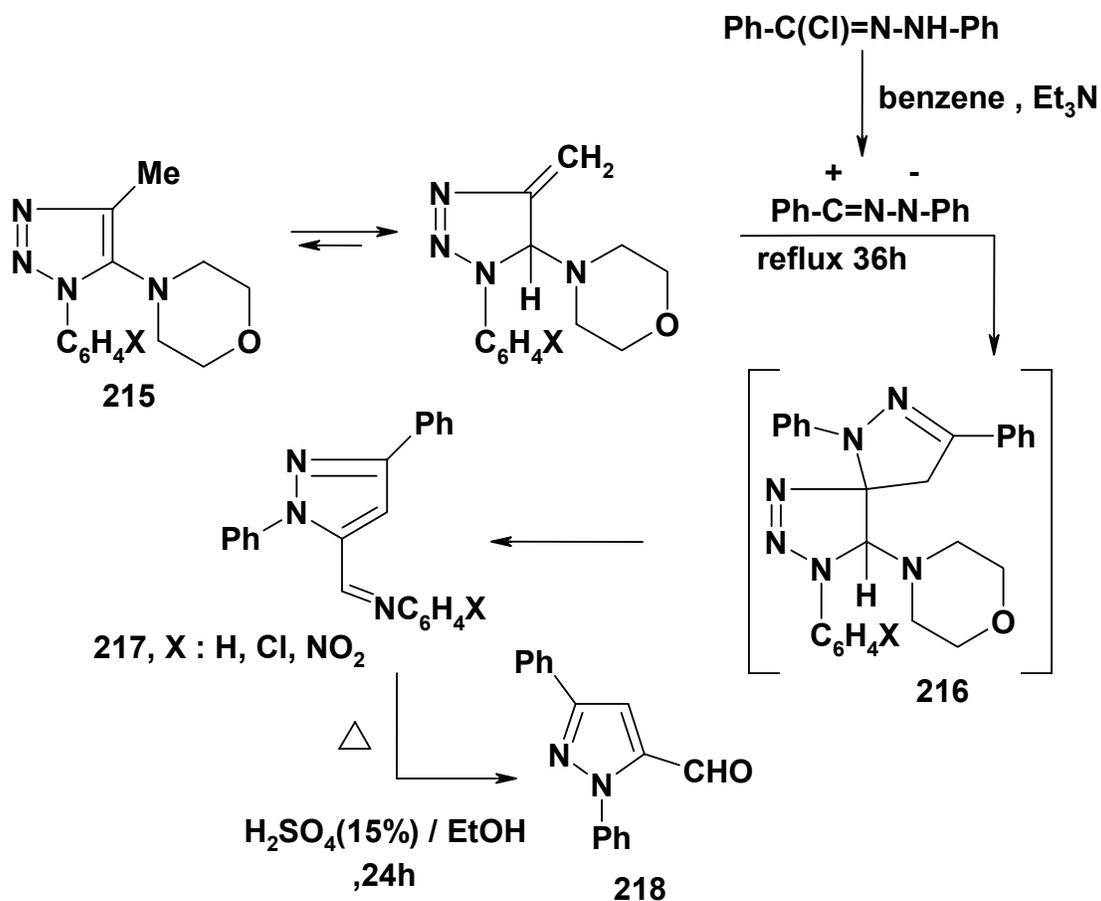
However, reaction of the enamine **212** with *C,N*-diphenylnitrilimine in benzene was reported to give 3,3a-dihydro-1,3-diphenyl-3a-pyrrolidino-pyrazolo[3,4-*c*][2]benzopyran-5(2*H*)-one

(**214**) in 44% yield.⁸⁴ The latter **214** was assumed to result *via* prototropic shift from the initial cycloadduct **213** (Scheme 78).



Scheme 78

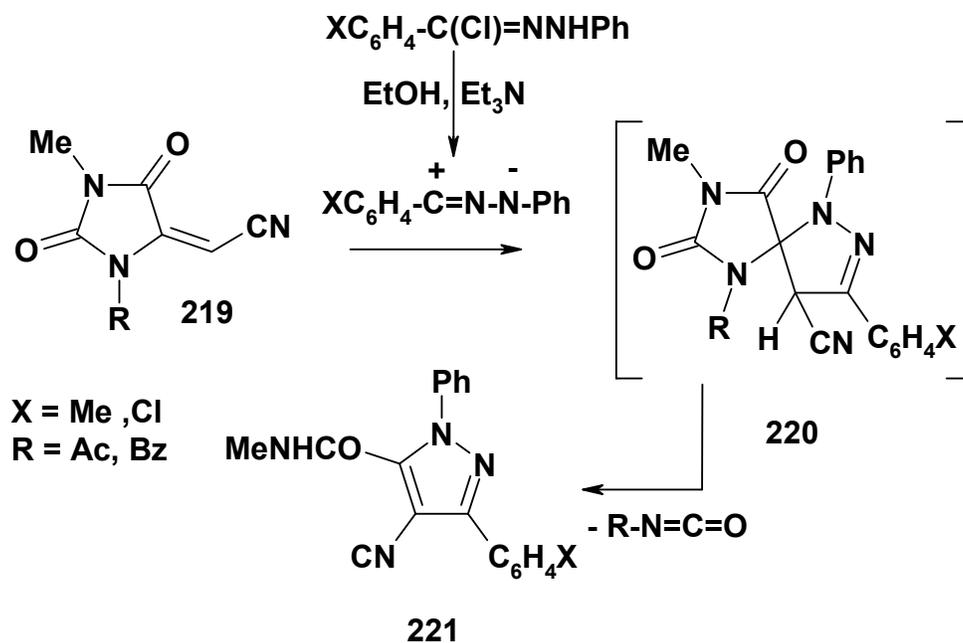
1-Aryl-4-Methyl-5-(1-morpholinyl)-1,2,3-triazole (**215**) reacted with *C,N*-diphenyl-nitrilimine in benzene to give 1,3-diphenyl-5-arylaminomethylene-pyrazoles (**217**) in 17-50% yields.⁸⁵ In this case it seems that nitrilimine cycloadded to the methylene tautomer of **215** to give the spirocycloadduct **216** which then underwent *in situ* ring cleavage to give **217** in 17-50% yields as end product. Acid hydrolysis of the latter **217** afforded the aldehyde **218** (Scheme 79).⁸⁵



Scheme 79

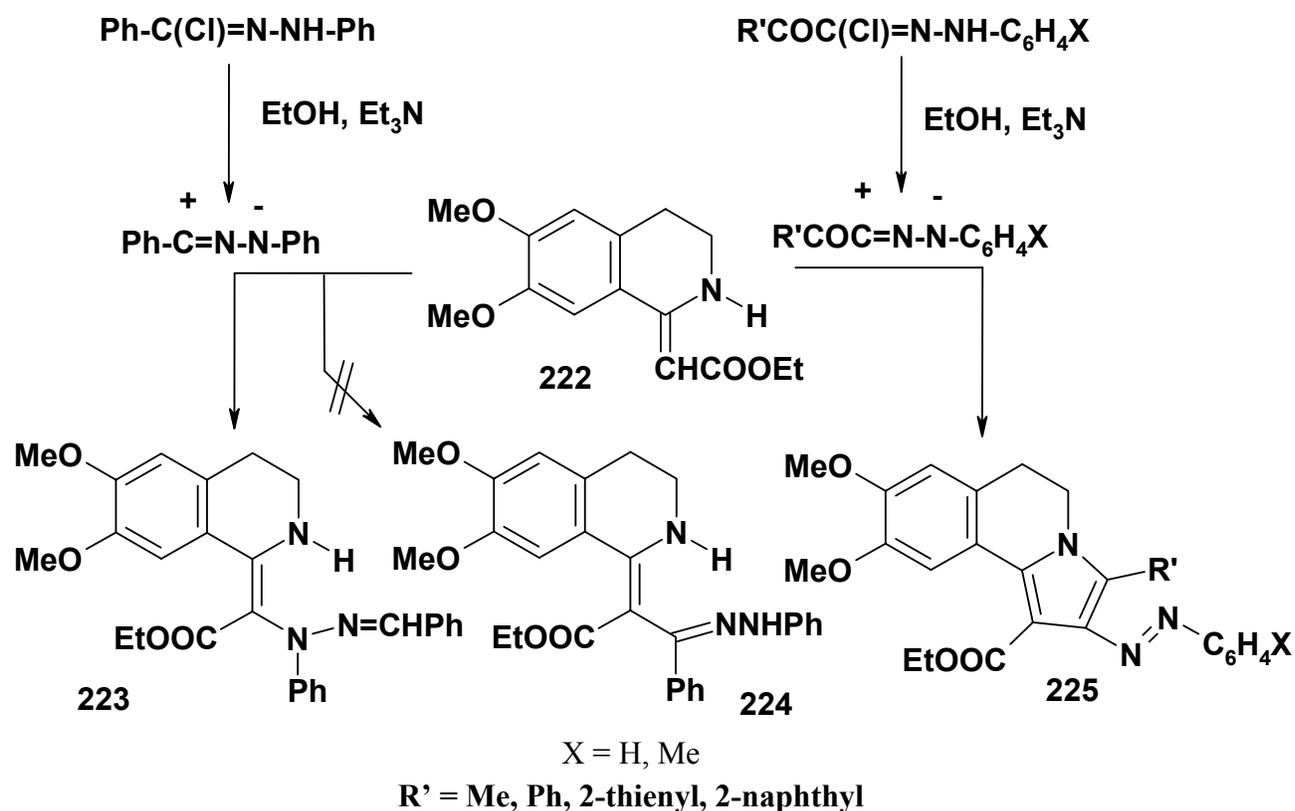
4.3 Exocyclic enamines

C,N-Diarylnitrilimines were reported to cycloadd to the exocyclic enamine **219** to give the respective cycloadducts **220** which underwent *in situ* ring cleavage and elimination of isocyanate molecule to yield the pyrazolecarboxamides **221** as end products (Scheme 80).⁸⁶



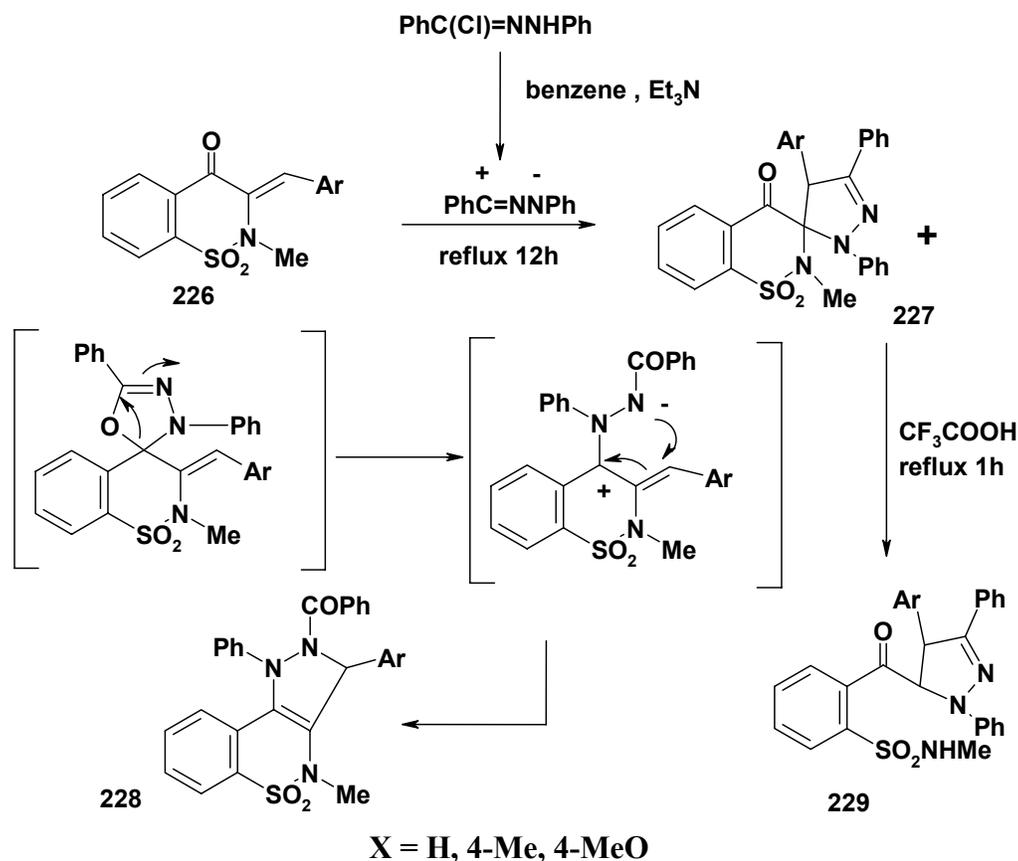
Scheme 80

The reaction of 1-ethoxycarbonylmethylene-3,4-dihydro-6,7-dimethoxy-isoquinoline (**222**) with *C,N*-diphenylnitrilimine in chloroform was reported to yield **223** in 80% yield instead of the expected 1,3-adduct **224**.⁸⁷ However, reaction of **222** with *C*-acyl-*N*-arylnitrilimines gave the respective 5,6-dihydropyrrolo[2,1-*a*]-5,6-dihydroisoquinolines (**225**) in 78-82% yields.⁸⁷ Further evidence is required to confirm the structure of the claimed product **225** and to explain why the regiochemistry of *C*-diphenylnitrilimine is different from that of *C*-acylnitrilimines in their reactions with **222** (Scheme 81).



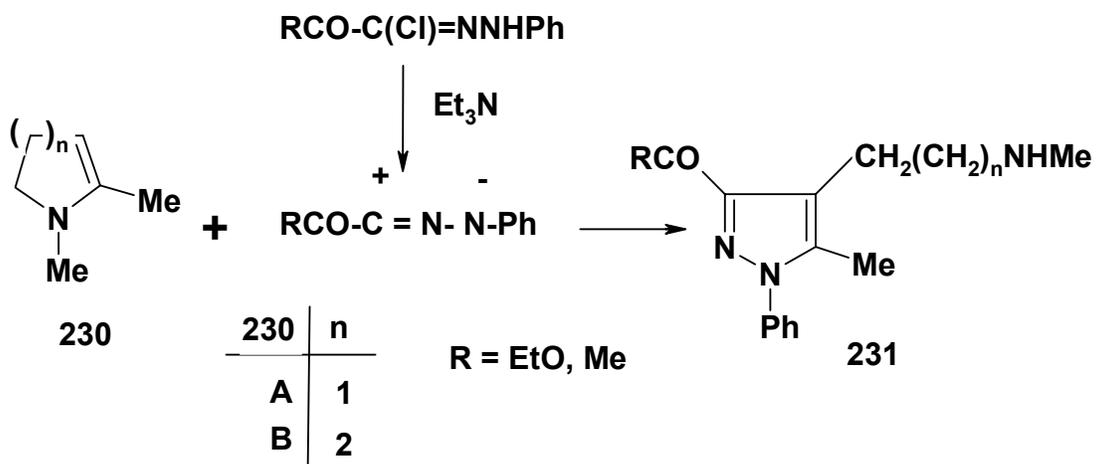
Scheme 81

The reaction of *C,N*-diphenylnitrilimine with the exocyclic enamine 226 led to a mixture of 227 and 228 in 36-38% and 23-39% yields, respectively.⁸⁸ The latter product 228 was assumed to be formed *via* cycloaddition to the carbonyl group followed by opening of the 1,3,4-oxadiazoline ring and recyclization.⁸⁵ When the products 227 were refluxed in trifluoroacetic acid, they underwent ring cleavage to give the respective 229 in 36-38% yields (Scheme 82).⁸⁸



Scheme 82

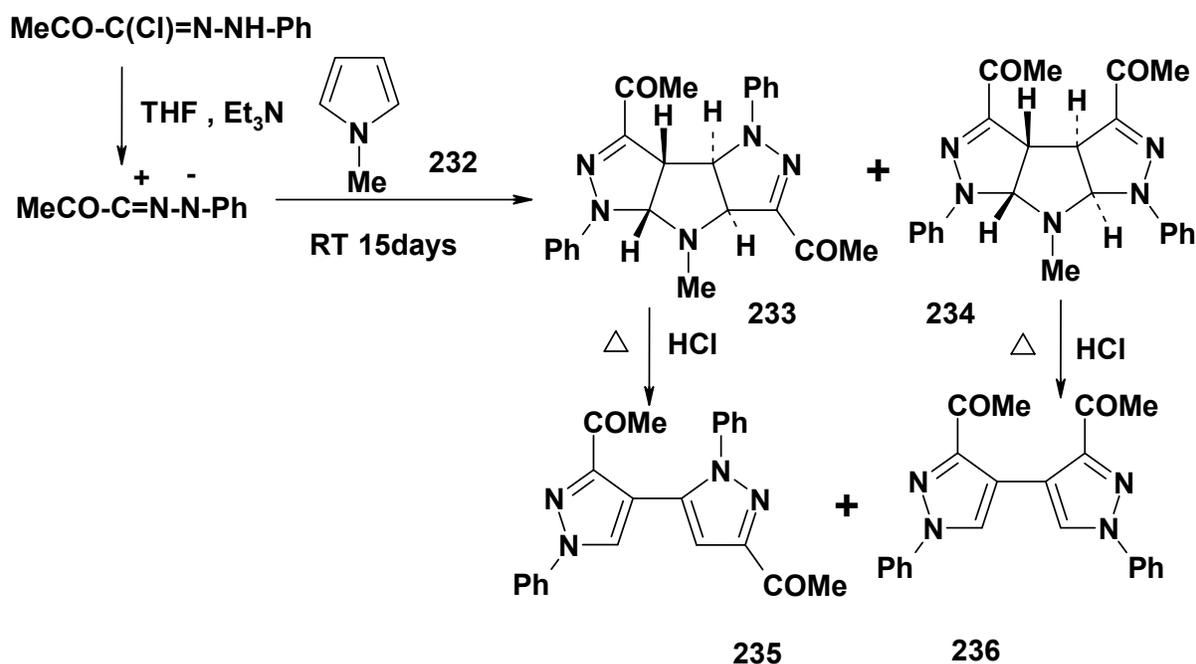
In an earlier report,⁵¹ it was reported however that reactions of *C*-acetyl- and *C*-ethoxycarbonyl-*N*-phenylnitrilimines each with 1,2-dimethyl-4,5-dihydropyrrole 230A and 1,2-dimethyl-1,4,5,6-tetrahydropyridine 230B in chloroform in the presence of triethylamine afforded the respective pyrazole derivatives 231 (Scheme 83).⁵¹



Scheme 83

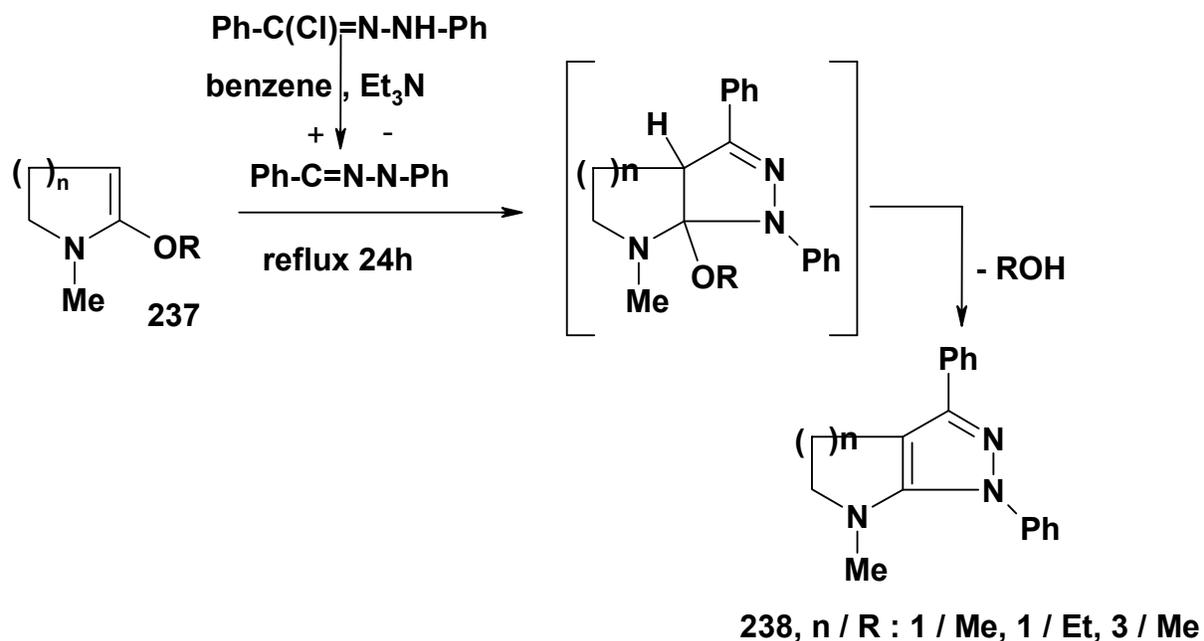
4.4 Heterocyclic enamines

Reaction of *N*-methylpyrrole **232** with *C*-acetyl-*N*-phenylnitrilimine gave a mixture of the two isomeric *bis*-cycloadducts **233** and **234** in 20% and 60% yields, respectively.⁸⁴ Refluxing each of the latter products in concentrated hydrochloric acid in ethanol furnished 4,4- and 3,4-*bis*-pyrazoles **235** and **236** each in 90% yield, respectively (Scheme 84).⁸⁹



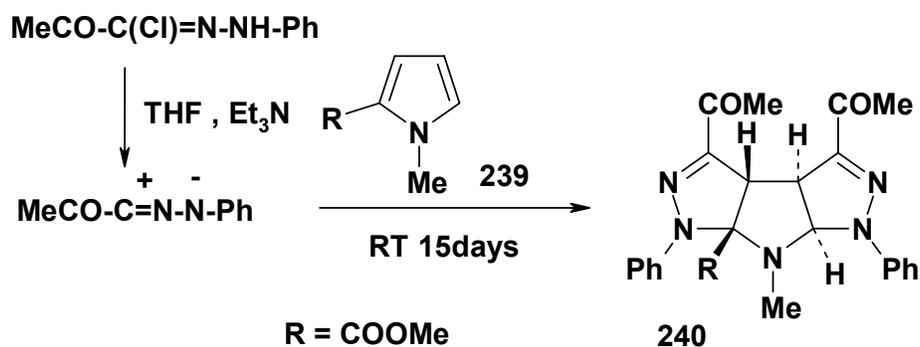
Scheme 84

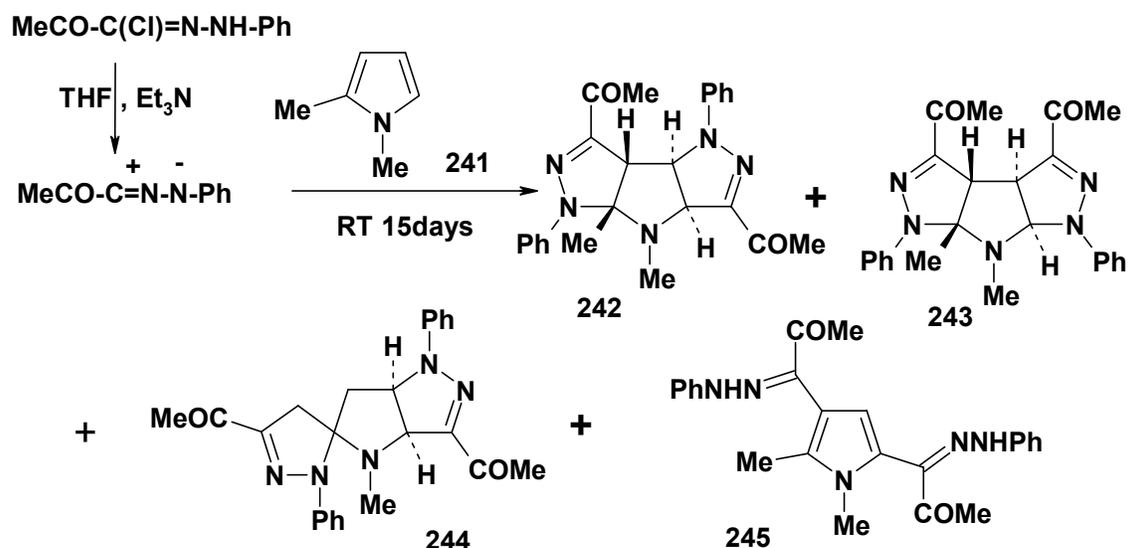
Similar reaction of *C,N*-diphenylnitrilimine with 1-methyl-2-alkoxy derivatives of cyclic enamines **237** afforded the respective fused pyrazoles **238** in 70-79% yields *via* cycloaddition to *endo*-double bond followed by elimination of alcohol molecule from the initially formed cycloadducts (Scheme 85).⁹⁰



Scheme 85

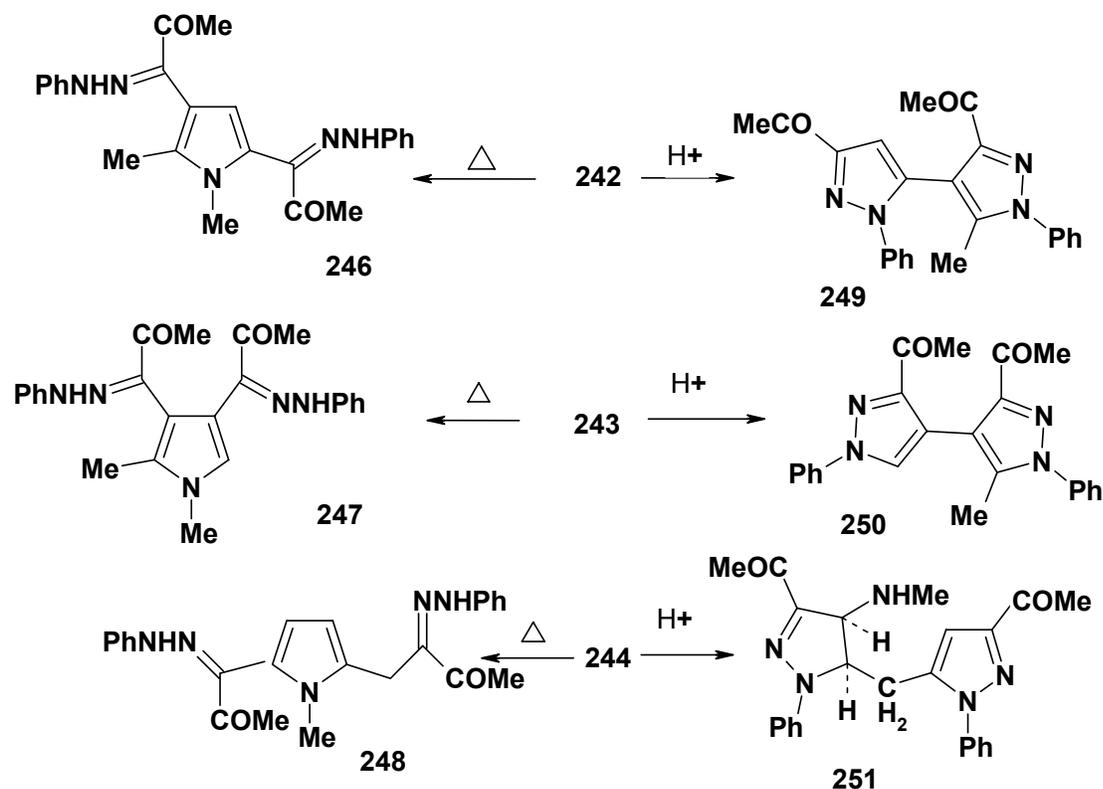
1-Methyl-2-methoxycarbonylpyrrole **239** reacted with *C*-acetyl-*N*-phenylnitrilimine afforded only the *bis*-cycloadduct **240** in 20% yield.⁹¹ On the other hand, reaction of the same nitrilimine with 1,2-dimethylpyrrole (**241**) yielded four different products namely the *bis*-cycloadducts **242** and **243**, the spirocycloadduct **244** and the acyclic *bis*-adduct **245** in 40, 30, 10 and 11% yields, respectively (Scheme 86).⁹¹





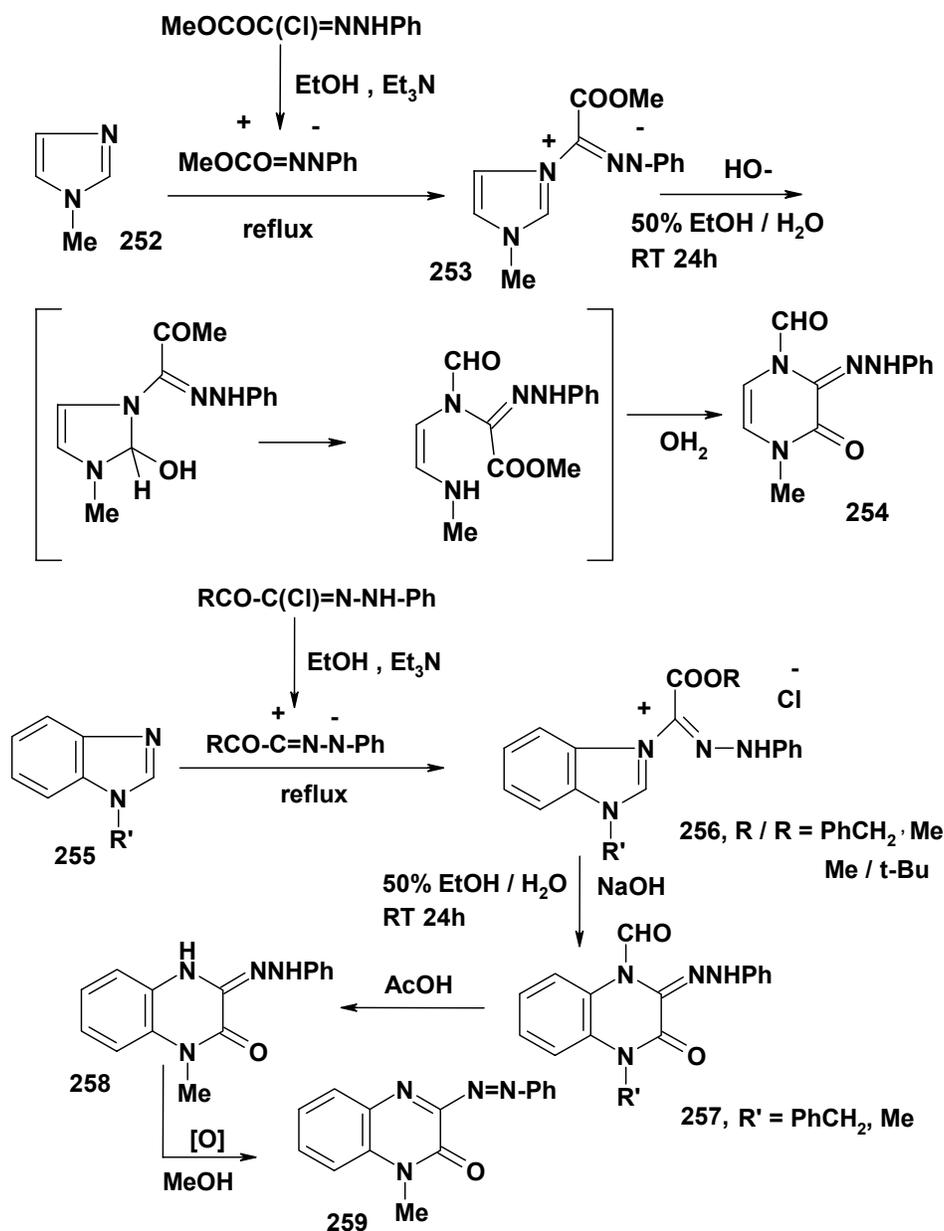
Scheme 86

Heating the products **242-244** at 170°C resulted in cleavage of the pyrazoline ring to give the *bis*-hydrazones **246 - 248**, respectively. However, refluxing the products **242-244** in ethanol in the presence of hydrochloric acid resulted in the cleavage of the pyrrolidine ring and the formation of the *bis*-pyrazoles **249-251**, respectively (Scheme 87).⁹¹



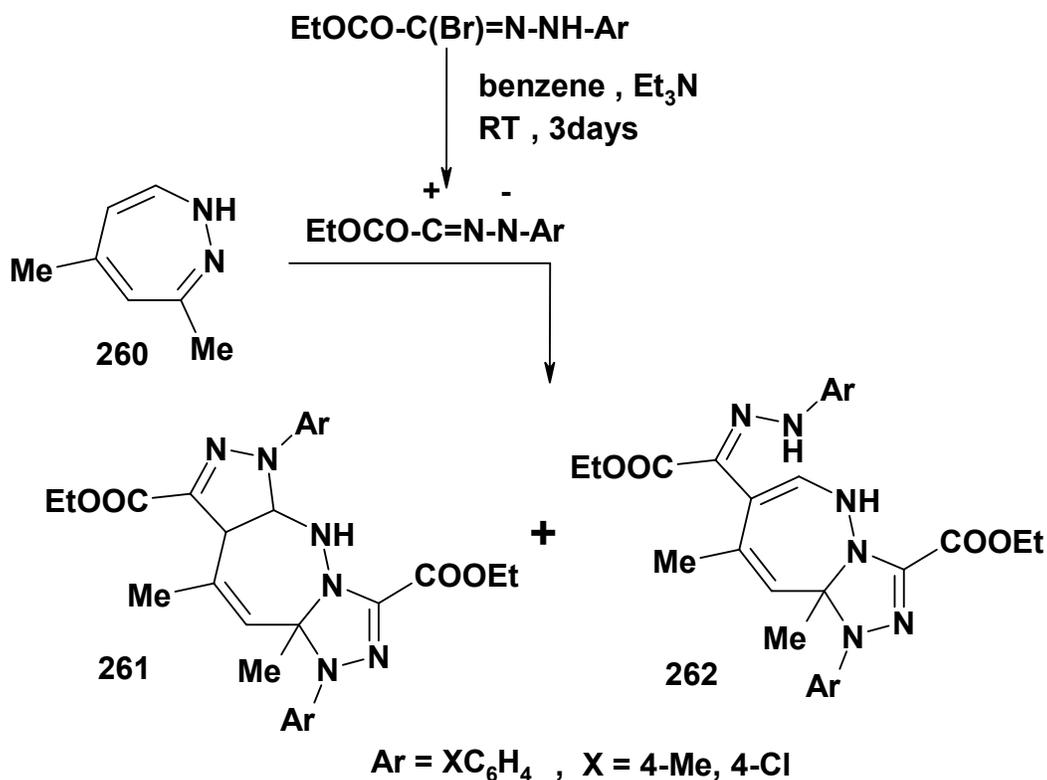
Scheme 87

1-Methylimidazole (**252**) reacted with nitrilimines in a different fashion. For example, its reaction with *C*-methyloxycarbonyl-*N*-phenylnitrilimine yielded the ring opened 1:1 adduct **253** in 75% yield. Treatment of the latter with sodium hydroxide afforded the pyrazin-2-one **254** in 55% yield.²⁷ Similar reaction of *N*-substituted benzimidazoles **255** with the same nitrilimine afforded an adduct **256** which gave, upon treatment with sodium hydroxide, the quinoxalin-2-one derivative **257** via ring expansion. Treatment of **257** with acetic acid gave **258** which underwent air oxidation to yield the azo derivative **259** as end product (Scheme 88).²⁷



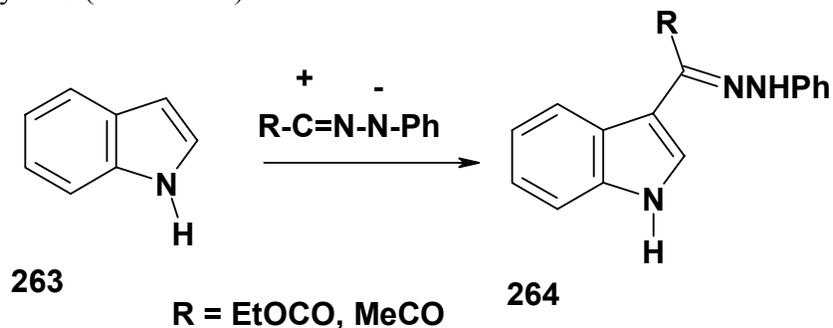
Scheme 88

Reaction of the diazepine **260** with *C*-ethoxycarbonyl-*N*-arylnitrilimines at room temperature yielded the *bis*-1,3-cycloadduct **261** and the adducts **262** in 10 and 65% yields, respectively (Scheme 89).⁹²



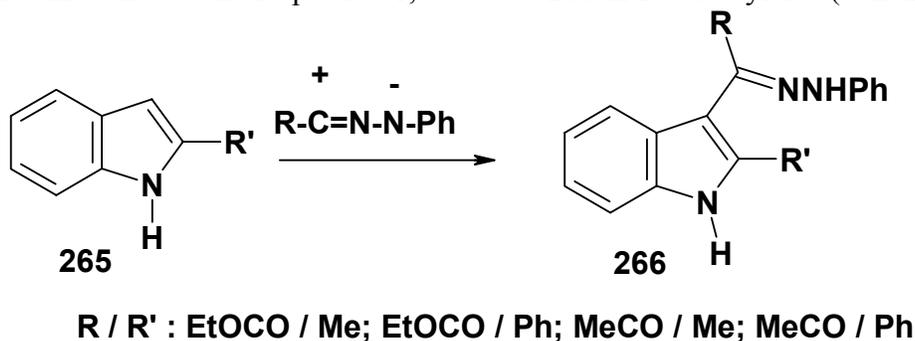
Scheme 89

Reactions of nitrilimines with indole derivatives **263** were reported to give products that depend on the type and site of the substituent(s) present. For example, unsubstituted indole reacted with *C*-acetyl- and *C*-ethoxycarbonyl- nitrilimines and gave the respective 1,3-adducts **264** in 24-30% yields (Scheme 90).⁹³



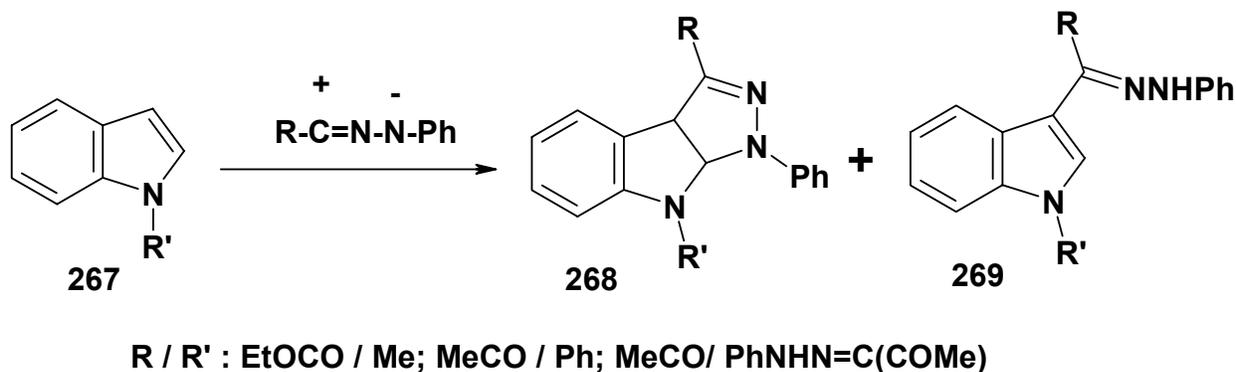
Scheme 90

Similar reactions of 2-methyl- and 2-phenylindoles **265** with the same nitrilimines were reported to give in each case the respective 1,3-adducts **266** in 14-45% yields (Scheme 91).⁹³



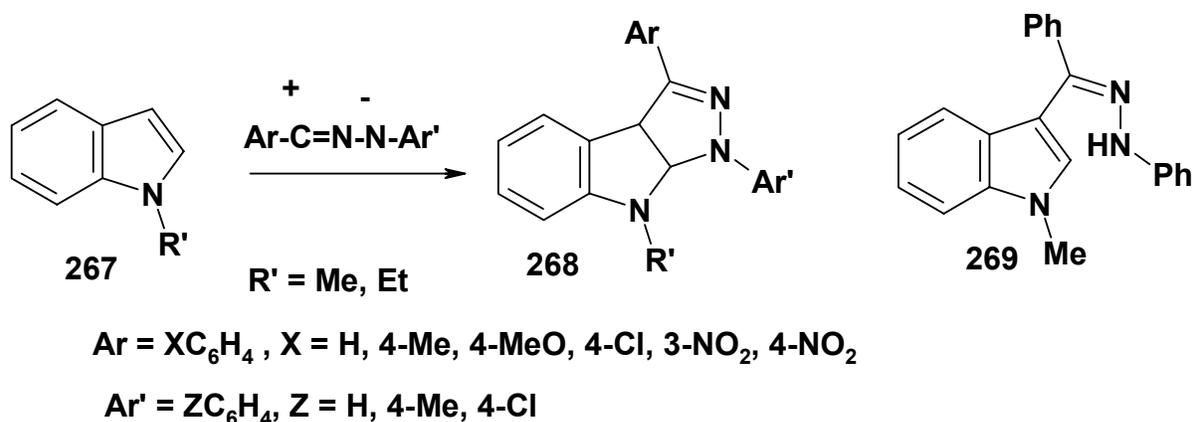
Scheme 91

On the other hand, Ruccia *et al.* reported that reactions of *N*-substituted indoles **267** with nitrilimines gave a mixture of the respective 1,3-cycloadduct **268** (in 35-36% yields) and 1,3-adduct **269** (8-13% yields) (Scheme 92).^{89, 93-95}



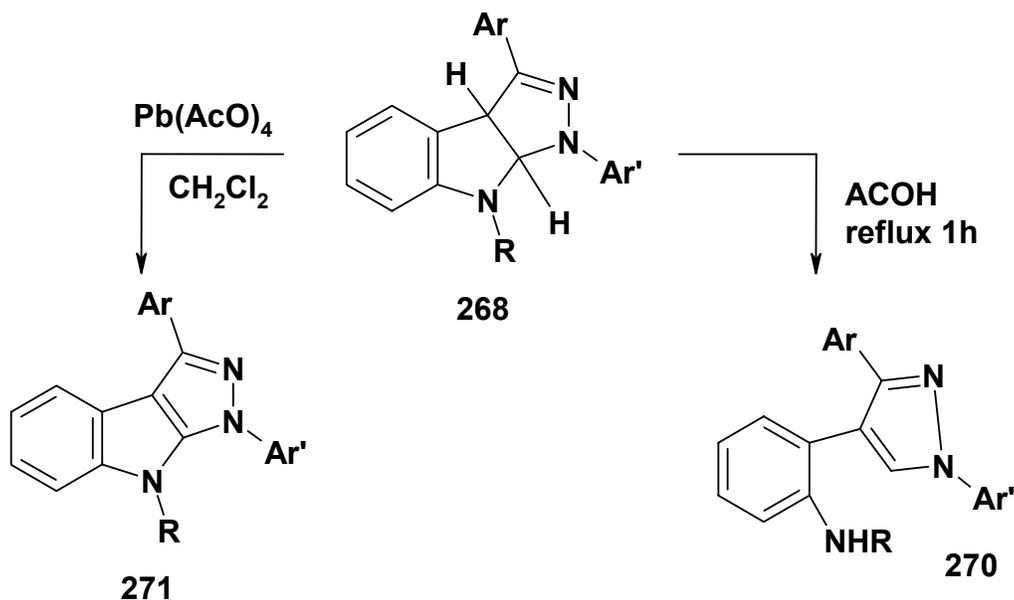
Scheme 92

C,N-diarylnitrilimines reacted with each of 1-methylindole⁹⁶ and 1-ethylindole⁹⁷ **267** and gave in each case only the respective 1,3-cycloadducts **268**. However, a mixture of the respective cycloadducts **268** and the 1,3-adducts **269** was produced in reaction of diphenylnitrilimine with 1-methylindole (Scheme 93).⁹⁶



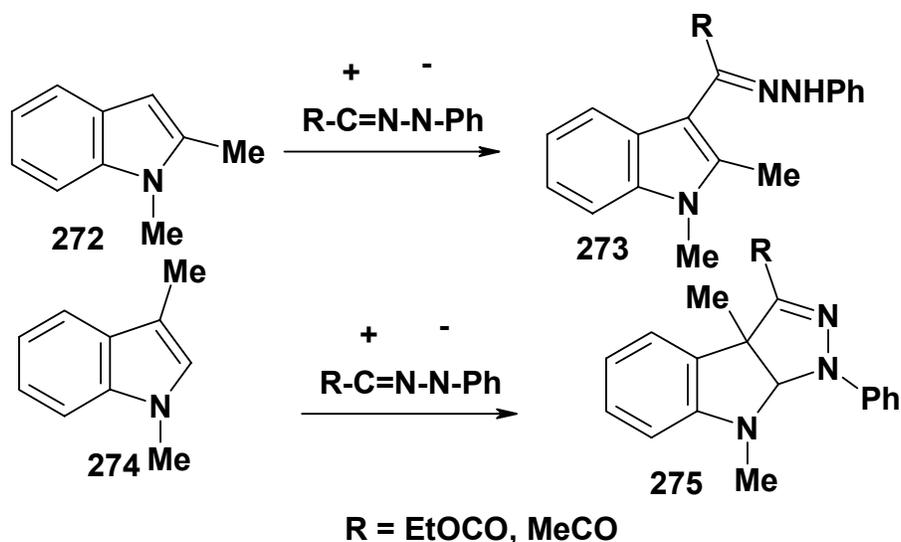
Scheme 93

Heating the latter cycloadducts **268** in acetic acid afforded 1,3-diaryl-4-(2-alkylaminophenyl)pyrazoles **270** in 90-95% yields.^{96, 97} Also, the cycloadducts **268** were oxidized with lead tetraacetate in dichloromethane and gave the respective 8-alkylpyrazolo[3,*b*]indole derivatives **271** (Scheme 94).⁹⁶



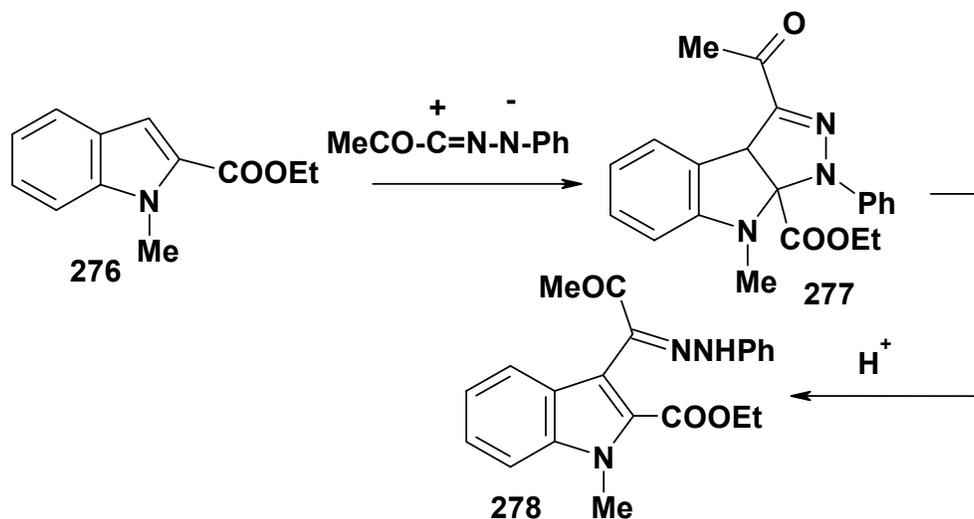
Scheme 94

Furthermore, while 1,2-dimethylindole **272** reacted with each of *C*-acetyl- and *C*-ethoxycarbonyl-*N*-phenylnitrilimine and gave the respective 1,3-adducts **273**⁹³ in 63-64% yield, reactions of 1,3-dimethylindole **274** with the same nitrilimines gave the 1,3-cycloadduct **275** in 4% yield (Scheme 95).⁹³



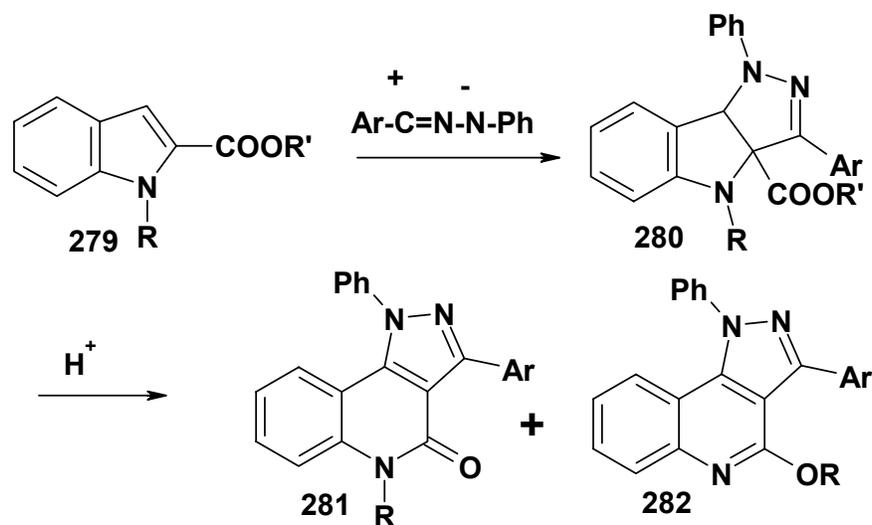
Scheme 95

Reaction of *N*-phenyl-*C*-acetylnitrilimine with 1-methyl-2-ethoxycarbonylindole **276** was reported by Ruccia *et al.*⁹³ to give the cycloadduct **277** which was converted into the hydrazone derivative **278** upon heating in acetic acid (Scheme 96).



Scheme 96

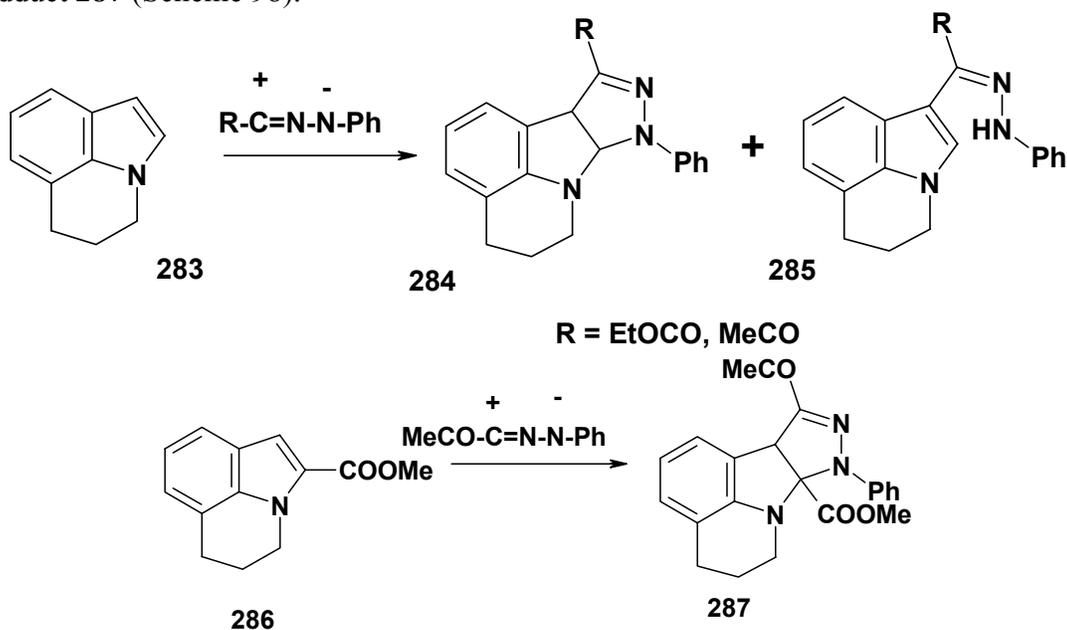
However, similar reactions of diarylnitrilimines with other 1-alkyl-2-alkoxycarbonylindoles **279** in benzene were reported to follow a different regiochemical pathway to give **280**.^{97, 98} Heating the latter products in acetic acid or in ethanol in the presence of hydrochloric acid afforded in each case a mixture of **281** and **282** (Scheme 97).⁹⁸



$R / R' = Et / Me; Me / Et; PhCH_2 / Et$
 $Ar = Ph, 4-MeC_6H_4$

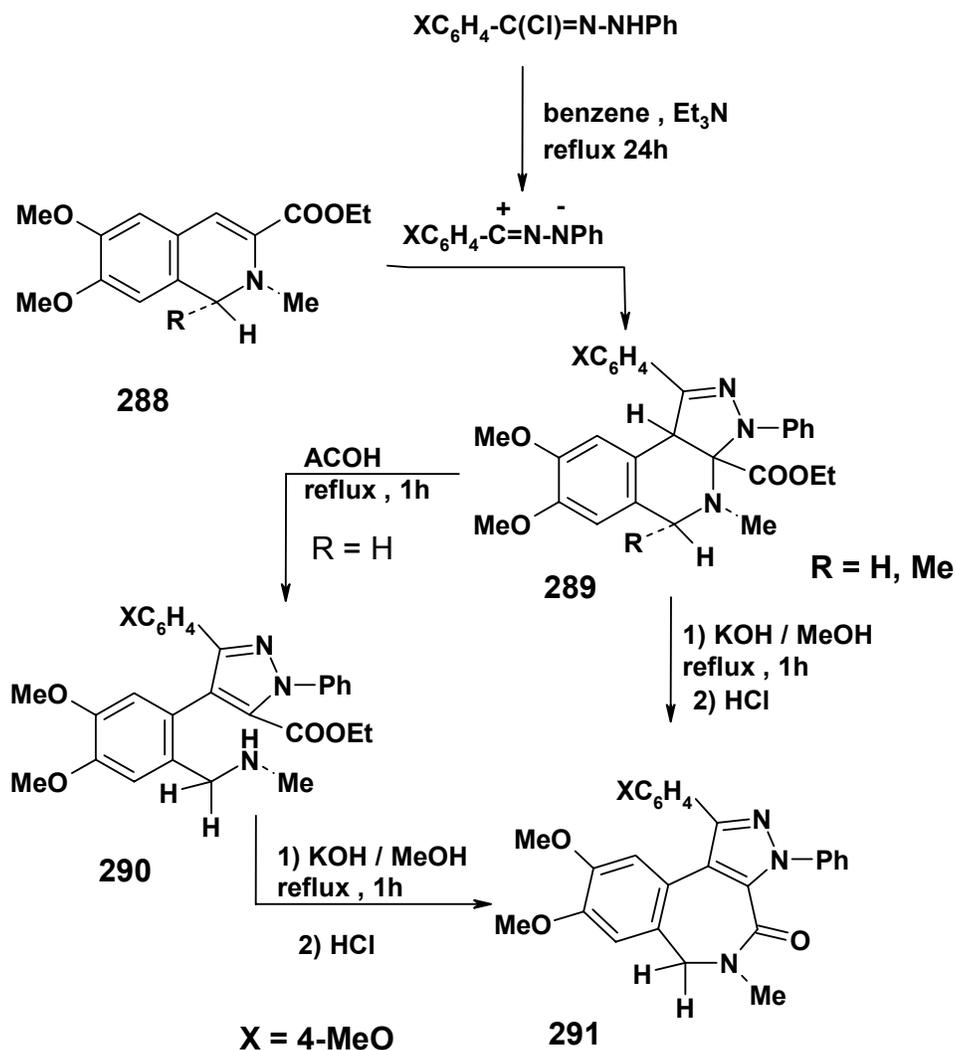
Scheme 97

Reactions of the indole derivative **283** with C -ethoxycarbonyl- and C -acetyl- N -phenylnitrimines yielded in each case a mixture of the respective cycloadduct **284** in 27-60% yields and the 1,3-adducts **285** in 7-8% yield.⁹³ Reactions of the indole derivative **286** with C -acetyl- N -phenylnitrimines followed the same regiochemical pathway and yielded only the cycloadduct **287** (Scheme 98).⁹³



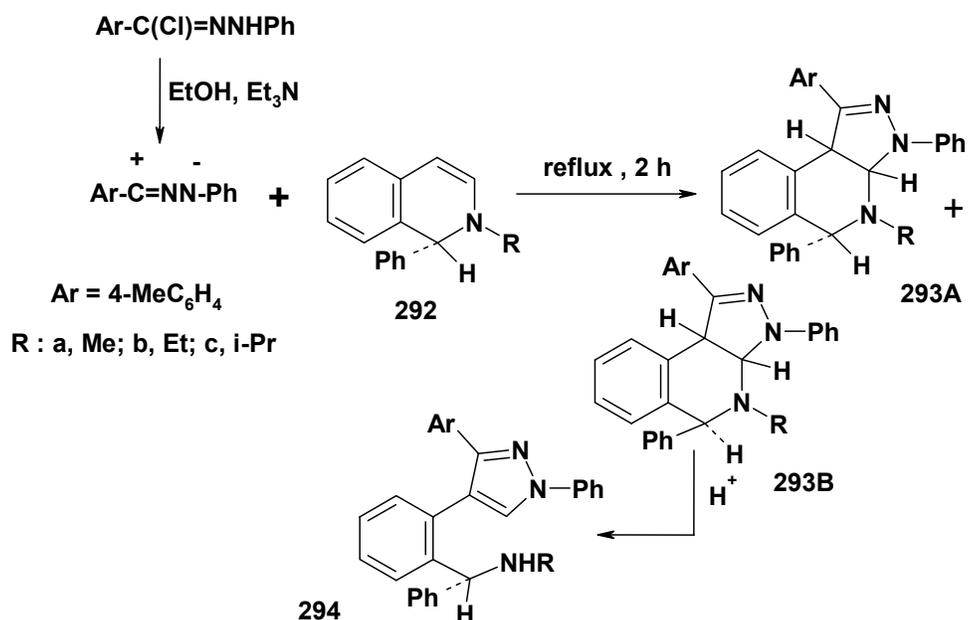
Scheme 98

Reaction of *C,N*-diarylnitrilimine with the heterocyclic enamine **288** proceeded regio- and stereoselectively to yield the cycloadducts **289** as the sole product. Heating this product in acetic acid for 1h afforded **290**. Saponification of either **289** or **290** with 2N methanolic KOH followed by acidification yielded, in both cases, the respective tricyclic derivative **291** in 58% yield (Scheme 99).⁹⁹



Scheme 99

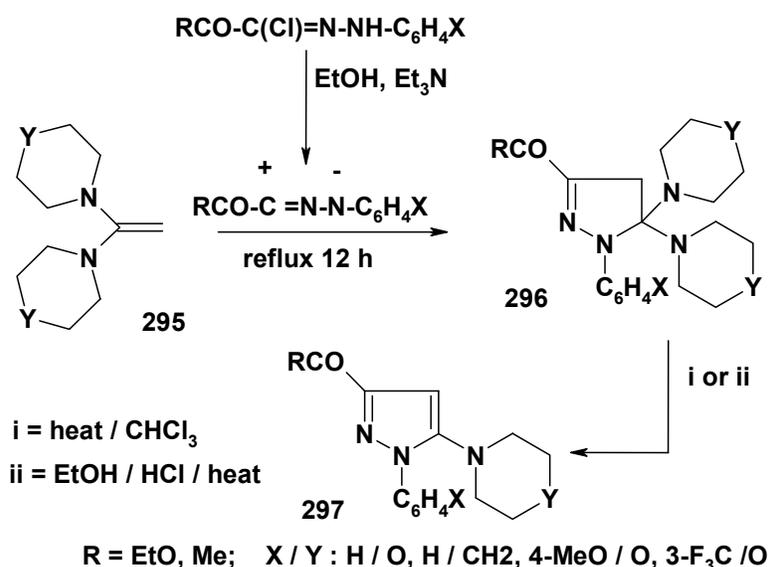
Also, reaction of *C,N*-diarylnitrilimines with 2-alkyl-1-phenyl-1,2-dihydroisoquinolines (**292**) was reported to give mainly the cycloadducts **293** as a mixture of stereoisomers which underwent ring cleavage upon acid treatment to yield the respective pyrazole derivatives **294** (Scheme 100).¹⁰⁰



Scheme 100

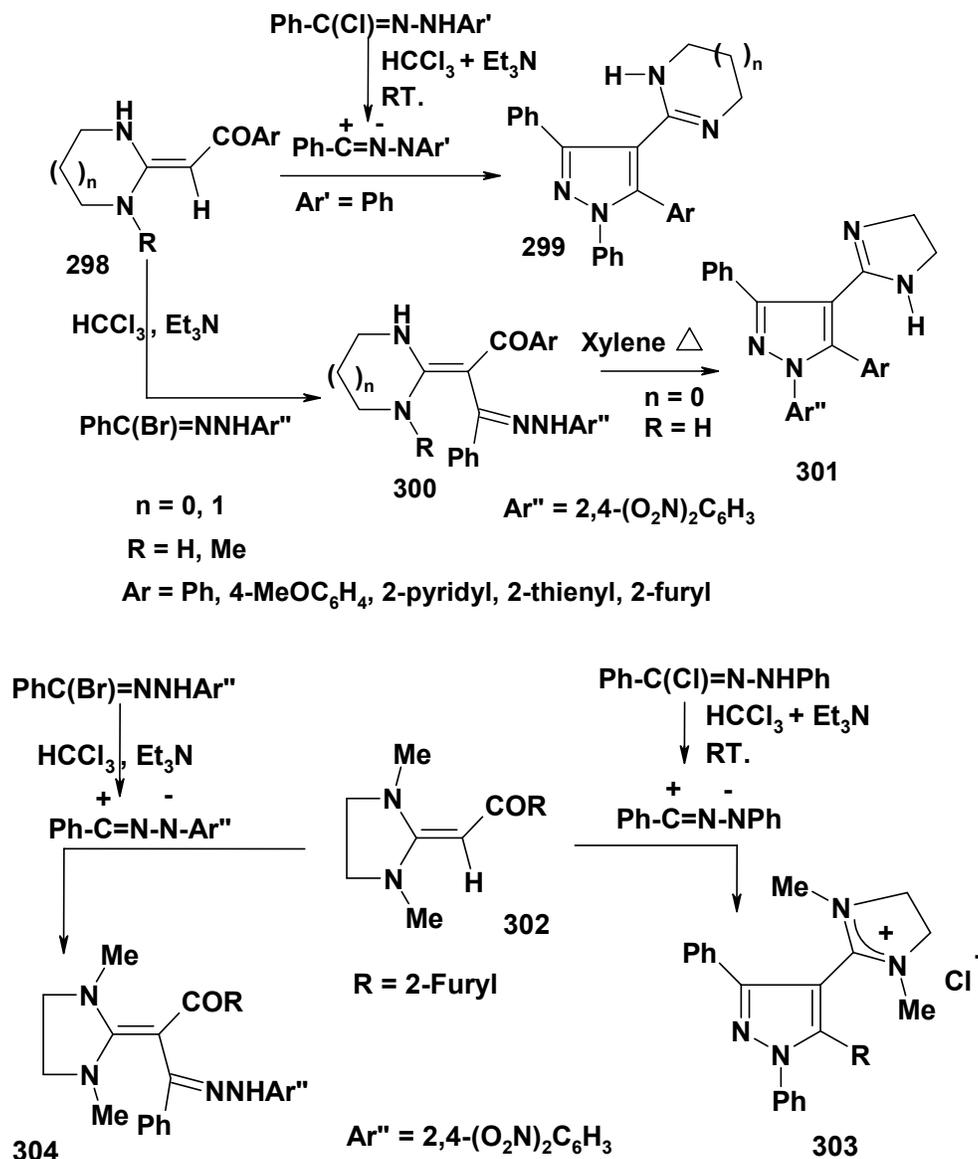
4.5 Ketene amins

Reactions of *C*-acyl-*N*-arylnitrilimines with the ketene amins **295** at room temperature in dry benzene in the presence of triethylamine were reported to give the pyrazole derivatives **296** in 80-85% yield.⁵⁷ The latter products underwent deamination upon heating in chloroform or in ethanol in the presence of HCl to give rise the respective aminopyrazoles **297** in 85-90% yields (Scheme 101).⁵⁷



Scheme 101

The reaction of C,N-diarylnitrilimines with the ketenaminals **298** in HCCl_3 at room temperature afforded the respective pyrazole derivative **299**.¹⁰¹ However, similar reaction of N-(2,4-dinitrophenyl)-benzenecarbohydrazonoyl bromide with **298** under the same conditions furnished only the hydrazones **300** in 75-95% yield. Heating the latter **300** ($n = 0$, $R = \text{H}$) in xylene for 10 h gave the respective pyrazole derivative **301** in 45% yield.¹⁰¹ Such results were considered to indicate that reaction of nitrilimines with **298** is stepwise reaction. It starts with the formation of 1,3-adduct followed by the cyclization. This was further confirmed by the finding that reaction of the ketene aminal **302** with C,N-diphenylnitrilimine and N-(2,4-dinitrophenyl)-C-phenylnitrilimine under similar conditions afforded **303** (55% yield) and **304** (80% yield), respectively (Scheme 102).¹⁰¹



Scheme 102

5. Conclusions

From the foregoing reports that have been covered in this review, it is obvious that the reactions of nitrilimines with both heterocyclic amines and enamines provide wide synthetic strategies for annulation and ring-transformation of various heterocycles. It is hoped that it will stimulate further research groups throughout the world to explore more the utility of such reactions in the synthesis of novel heterocycles and natural products.

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