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, genearted in situ by base-catalyzed dehydrohalogenation of the respective hydrazonoyl 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, hydrazonoyl halides

Contents

1. Introduction  
2. Reactions with aminoazoles  
   2.1 Aminopyrazoles  
   2.2 Aminimidazoles  
   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 aminals
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).
2. Reactions with aminoazoles

2.1 Aminopyrazoles

Reactions of 3-aminopyrazole derivatives 4A\textsuperscript{18,19} and 4B\textsuperscript{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).\textsuperscript{18}
Similar reaction of 4-amino-2,3-dimethyl-1-phenyl-5(2H)-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).\textsuperscript{19, 21,22}

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\textsuperscript{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).\textsuperscript{22}
Different results were reported for the reaction of 3-phenyl-5-aminopyrazole (10A) with C-ethoxycarbonyl-N-aryl nitrimine. For example, in one report\textsuperscript{23} it was indicated that such a reaction yielded the pyrazolo[3,4-\textit{c}]pyrazole derivative 13. In another report\textsuperscript{24} it was found that such a reaction yielded a product that was assigned the structure of imidazo[1,2-\textit{b}]pyrazole derivative 14 and not the isomeric structure 15, because the isolated product was recovered unchanged after being subjected to an oxidation treatment.\textsuperscript{24} Compounds of type 15 are expected to be oxidized readily to give the respective arylazo derivatives 16 (Scheme 5).\textsuperscript{25-27}
Also, different results were reported for reactions of 3-phenyl-5-aminopyrazole 10A with C-acetyl-N-aryl-nitrilimines. Thus, in three reports, it was indicated that such a reaction afforded the respective imidazo[1,2-b]pyrazoles 17. In another report, 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. Heating 19 in ethanol in the presence of anhydrous sodium acetate afforded 21 in 52% yield (Scheme 7).

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).\(^{19, 22, 28}\)

\[
\text{RCO-C(Cl)=N-NHC}_6\text{H}_4\text{X} \quad \xrightarrow{\text{Et}_3\text{N} / \text{EtOH} / \triangle} \quad \text{Et}_3\text{N} / \text{EtOH} / \triangle \\

\]

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{NH}_2 \\
\text{Ph}
\end{array} 
+ \begin{array}{c}
\text{RCO-C}=\text{N-N-C}_6\text{H}_4\text{X}
\end{array} 
\rightarrow 
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{H} \\
\text{NNHC}_6\text{H}_4\text{X}
\end{array}
\]

\[
R / X : \text{Me / 4-NO}_2, \text{O(CH}_2\text{)_4N / H}
\]

\begin{align*}
\text{Scheme 8}
\end{align*}

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).\(^{18, 19}\)

\[
\begin{align*}
\text{XH}_4\text{C}_6\text{-C(Cl)=N-NHPh} & \quad \xrightarrow{\text{Et}_3\text{N} / \text{EtOH} / \triangle} \quad \text{Et}_3\text{N} / \text{EtOH} / \triangle \\
\text{MeCO-C(Cl) = N-NH-C}_6\text{H}_4\text{X} & \quad \xrightarrow{\text{Et}_3\text{N} / \text{EtOH} / \triangle} \quad \text{Et}_3\text{N} / \text{EtOH} / \triangle
\end{align*}
\]

\[
\begin{align*}
\text{Ph} \\
\text{Br} \\
\text{N} \\
\text{N} \\
\text{NH}_2 \\
\text{Ph}
\end{array} 
+ \begin{array}{c}
\text{MeCO-C}=\text{N-N-C}_6\text{H}_4\text{X}
\end{array} 
\rightarrow 
\begin{array}{c}
\text{Ph} \\
\text{Br} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{NNHC}_6\text{H}_4\text{X}
\end{array}
\]

\[
\begin{align*}
24, X : \text{H, 4-Me, 4-Cl} & \quad 23, X : \text{H, 4-Me, 4-Cl}
\end{align*}
\]

\begin{align*}
\text{Scheme 9}
\end{align*}
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\textsuperscript{18,19} and imidazo[1,5-b]pyrazole derivatives 26 in 90% yield, respectively (Scheme 10).\textsuperscript{18}

![Scheme 10](image)

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).\textsuperscript{18}

![Scheme 11](image)

Scheme 11
The reactions of C-aroyl-N-aryl nitrimines with 5-amino-3-phenyl-4-aryl azopyrazoles 10G were reported to give 3,7-bis(arylazo)-2,6-diphenyl-1H-imidazo[1,2-b]pyrazole derivatives 28 in 70-90% yields. 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 chromophore and the results of the correlations of their acid dissociation constants with the Hammett equation (Scheme 12).

![Scheme 12](image_url)

**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. Similar reaction of 29 with C-acetyl-N-arylnitrilimines yielded the 1,3- adducts 31 in 80-92% yields (Scheme 13).

\[
\begin{align*}
\text{Ph-C(Cl)=N-NHPh} & \quad \text{MeCO-C(Cl)= N-NH-Ar'} \\
\text{Et}_3\text{N} / \text{EtOH} / \triangle & \quad \text{Et}_3\text{N} / \text{EtOH} / \triangle \\
\text{Ph-C=N-N-Ph} + - & \quad \text{MeCO-C=N-N-Ar'} + - \\
\text{H}_2\text{N} & \quad \text{H}_2\text{N} \\
\text{N=N-C}_6\text{H}_4\text{X} & \quad \text{N=N-C}_6\text{H}_4\text{X} \\
\text{Ph} & \quad \text{Ar'} = \text{ZC}_6\text{H}_4 \\
\text{30, X : H, 4-Me, 4-MeO, 4-Cl} & \quad \text{31, X / Z : 4-Cl / 4-MeO, 4-Cl / 4-Cl,} \\
& \quad \text{H / 4-Me, H / H}
\end{align*}
\]

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. 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. 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-α]benzimidazole 37. Recently, it was reported, however, that reaction of C-acetyl-N-(p-chlorophenyl)nitrilimine with 2-aminobenzimidazole yielded the amidrazone adduct 38 (Scheme 14).
2.3 Aminoisoxazoles

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

Scheme 15
2.4 Aminothiazoles

C-AcyI-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).

\[
R-\text{CO-}C(Z) = N-NH-C_6H_4X
\]

\[
Z = \text{Cl or Br} 
\]

\[
\text{Et}_3N / \text{EtOH} / \triangle
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{NH}_2 \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{S} & \quad \text{S} & \quad \text{NH}_2
\end{align*}
\]

41A

\[
\begin{align*}
\text{Ph} & \quad \text{R} & \quad \text{N} & \quad \text{N} & \quad \text{C}_6\text{H}_4X \\
\text{N} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{NHC}_6\text{H}_4X \\
\text{S} & \quad \text{S} & \quad \text{N} & \quad \text{N} & \quad \text{NHC}_6\text{H}_4X
\end{align*}
\]

43

\[
\text{Et}_3N / \text{EtOH} / \triangle
\]

\[
\begin{align*}
\text{Ph} & \quad \text{R-CO-C=N-N-} & \quad \text{C}_6\text{H}_4X \\
\text{Ph} & \quad \text{R-CO-C=N-N-} & \quad \text{C}_6\text{H}_4X
\end{align*}
\]

42

\[
\begin{align*}
\text{Ph} & \quad \text{R} & \quad \text{X} : \text{Ph/H, Ph/4-Me, 4-MeC}_6\text{H}_4/\text{H, Ph/3-Me, 4-BrC}_6\text{H}_4/\text{H, Me/4-NO}_2
\end{align*}
\]

Scheme 16

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

\[
\begin{align*}
\text{EtOCO-C(Cl)} & = N-NH-\text{Ar} \\
\text{Et}_3N / \text{EtOH} / \triangle
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{NH}_2 \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{S} & \quad \text{S} & \quad \text{NH}_2
\end{align*}
\]

41A

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{N} & \quad \text{NNH} & \quad \text{Ar} \\
\text{Ph} & \quad \text{O} & \quad \text{N} & \quad \text{NNH} & \quad \text{Ar}
\end{align*}
\]

44

\[
\begin{align*}
\text{Ar} = 4-O_2NC_6H_4
\end{align*}
\]

Scheme 17
The amidrazones 46 were obtained in 88% yield from the reaction of 2-aminothiazole 41B with C-acetyl-N-phenylnitrilimine. Similar reactions of 2-aminobenzothiazole 45 with C,N-diphenylnitrilimine and C-acetyl-N-phenylnitrilimine afforded the respective amidrazones 47 (Scheme 18). 

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. In another report, 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).
Analogous reactions of 48 with each of $C_N$-diaryl nitrilimines$^{19, 22}$ and $C$-acetyl-$N$-aryl nitrilimines$^{19}$ 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).
Contradictory results were reported for the reaction of 48 with C-ethoxycarbonyl-N-aryl nitrilimines. In one report, it was indicated that such a reaction afforded 5-arylhydrazono-6-oxo-7H-imidazo[5,1-b][1,2,4]triazole 53. In another report, it was indicated that it yielded 3-ethoxycarbonyl-1-aryl-[1,2,4]triazolo[5,1-c][1,2,4]triazole 54 in 70% yield. Further work is needed to clarify this contradiction (Scheme 20).

Contradictory results were reported for the reaction of 48 with C-ethoxycarbonyl-N-aryl nitrilimines. In one report, it was indicated that such a reaction afforded 5-arylhydrazono-6-oxo-7H-imidazo[5,1-b][1,2,4]triazole 53. In another report, it was indicated that it yielded 3-ethoxycarbonyl-1-aryl-[1,2,4]triazolo[5,1-c][1,2,4]triazole 54 in 70% yield. Further work is needed to clarify this contradiction (Scheme 20).

Scheme 20
Reaction of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol 55 with C-aroyl-N-arylnitrilimines afforded 7-arylhydrazono[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines 56. 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).

\[
\text{RCO-C(Br) = N-NH-C}_6\text{H}_4\text{X} \quad \text{EtONa / EtOH /} \quad \Delta \quad \text{EtONa / EtOH /} \quad \text{RCO-C = N-N-C}_6\text{H}_4\text{X} \\
\text{55} \quad \text{56} \\
R = \text{2-Naphthyl} \\
X = \text{4-MeO, 4-Me, 3-Me, H, 4-Cl, 3-Cl, 3-NO}_2, 4-\text{NO}_2, 4-\text{Ac, 4-EtOCO}
\]

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). 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).
Scheme 23

Scheme 2
3. Reactions with aminooazines

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](attachment:Scheme_25.png)

However, the reaction of 63 with the nitrilimines, derived from N-(pyrazol-5-yl) 2-oxohydrazoneyl 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 report, 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).\(^{24}\)

\[
\begin{array}{c}
\text{RCO-C(Z) = N-NH-Ph} \\
\text{Z = Cl or Br} \\
\text{Et}_3\text{N / EtOH /} \triangle \\
\end{array}
\]

\[
\text{N=NPh}
\]

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).\(^{40}\)

\[
\begin{array}{c}
\text{Ph-C(Cl) = N-NH-SO}_2\text{Ph} \\
\text{THF / stirring / 2h} \\
\end{array}
\]

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(3H)-pyrimidinone 71B in refluxing ethanol in the presence of triethylamine afforded also 72 (Scheme 30).\textsuperscript{41, 42}

\[
\begin{align*}
\text{EtONa /} \\
\text{EtOH} \\
\text{3-5h} \\
\end{align*}
\]

\[
\begin{align*}
\text{R-C(Cl)}=\text{N} & - \text{NHC}_6\text{H}_4\text{X} \\
\text{EtONa /} \\
\text{EtOH} \\
\text{3-5h} \\
\end{align*}
\]

Similarly, 3-arylazo-1,4-dihydro-1,8-disubstituted-6\textit{H}-pyrimido[1,2-\textit{b}][1,2,4,5]-tetrazin-6-ones 73 were recently reported to be obtained in good yields by reaction of C-arylazo-\textit{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).\textsuperscript{43}
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(1H)-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(1H,9H)-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).\(^{45}\)
Similarly, 6-phenylamino-2-thiouracil and its 5-substituted derivative 79 reacted with C-ethoxycarbonyl-N-arylnitrilimines in chloroform and gave the respective 1,2,4-triazolo[4,3-a]pyrimidin-5(1H)-ones 80 in 65-72% yields. Heating each of the products 75 and 80 with acetyl chloride and chloroacetyl chloride was reported to result in C-acetylation rather than the N-acetylation and yielded the respective 6-acyl derivatives 81. Also, nitrosation and azo coupling of each of 75 and 80 yielded the respective 6-nitroso- and 6-arylazo derivatives 82 and 83 (Scheme 33).
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 $^{13}$C-NMR evidence.\textsuperscript{46} When compound 84 was refluxed with benzaldehyde in acetic acid, it yielded 86 in 80% yield (Scheme 34).

\begin{equation}
\text{Ph-C(Cl)=N-NPh} + \text{Dioxane, Et$_3$N} \xrightarrow{\text{reflux 10h}} \text{Ph-C=N-NPh}
\end{equation}
Reactions of various nitrilimines with 3-amino-4-oxo-2(3H)-quinazolinethione 87A in ethanol were reported to yield the respective 6H-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

\[
\begin{align*}
R-C(Cl) &= N-NH-C_6H_4X \\
+ \quad Et_3N / EtOH / \Delta &\quad \rightarrow \\
R-C &= N-N-C_6H_4X + \quad + \\
87A (R' = H) &\quad 87A(B) \quad 87B (R' = Me) \\
\downarrow \\
88 &\quad 89 \quad 90 \\
\end{align*}
\]

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).
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 36
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.\(^\text{18,19}\) 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).\(^\text{18}\)
Scheme 38

3.4 Amino-1, 2,4-triazines

Very recently Shawali et al.\textsuperscript{43, 50} reported that reaction of nitrilimines with either 4-amino-2,3-dihydro-6-substituted-3-thioxo-[1,2,4]triazin-5(4\textit{H})-ones 100\textit{A} or 4-amino-2,3-dihydro-3-methylthio-6-substituted-[1,2,4]triazin-5(4\textit{H})-ones 100\textit{B} gave the respective [1,2,4]triazino[4,3-\textit{b}][1,2,4,5]tetrazine derivatives 101 in 40-95\% yield (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 enaminonitriles, enaminones 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).
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-phenyl)amino]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
Other 1,3,4-trisubstituted-pyrazoles 112 were also prepared in 55-73% yields by reactions of enamines 111 with various nitrilimines (Scheme 41).\textsuperscript{52,53}

\[
\begin{align*}
R-C(Cl) &= N-NH-C_6H_4X \\
\text{EtOH, Et}_3\text{N} &+ \text{EtOOC-C=N-N-Ph} \\
&\text{R-C} = N-N-C_6H_4X - \text{YC}_6H_4-CH = CH-NR'_2 \rightarrow \text{R} = \text{MeCO, EtOCO} \\
X &= \text{H, 4-Me, 4-Cl, 3-Cl, 4-F, 3-F, 4-MeS, 4-MeSO, 2,4-Cl}_2 \\
Y &= \text{H, 4-MeO, 4-Cl, 4-Br, 4-F, 4-Me, 2,4-Cl}_2, 3,4-\text{Cl}_2, 4-\text{Ph, 4-O}_2\text{N, 4-NH}_2 \\
R'\text{_2N} &= \text{O(CH}_2\text{CH}_2)_2\text{N, Me}_2\text{N}
\end{align*}
\]

Scheme 41

The 1,3-dipolar cycloaddition of \textit{N}-aryl-\textit{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).\textsuperscript{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

- \( \text{R-CO-C(Cl) = NNHAr} \)
- \( \text{EtOCO-C(Cl) = NNHAr} \)
- \( \text{Ar = 4-MeOC}_6\text{H}_4 \)
- \( \text{Ar'} = Y\text{C}_6\text{H}_4, Y = \text{H}, 4-\text{NO}_2, 4-\text{Br}, 4-\text{Cl}, 4-\text{Me} \)

- \( \text{= copoly(styrene-1\%DVB)} \)
- \( \text{R} = \text{EtO, Me} \)
- \( \text{Ar} = X\text{C}_6\text{H}_4, X = 3-\text{MeO}, 4-l \)
The reaction of $\beta$-vinylamine 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

\[
\begin{align*}
\text{PhC(Cl)=NNHPh} & \quad \text{benzene, Et}_3\text{N} \\
\text{reflux, 2h} & \\
\text{119} & \quad \text{PhC=NNPh} \\
& \quad \text{PhC}=\text{NNPh} \\
& \quad \text{N(CH}_2\text{CH}_2\text{)}_2\text{O} \\
\text{120} & \quad \text{Ph} \\
\end{align*}
\]

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
The reactions of $C$-acyl-$N$-arylnitriilimines with the enamines 126 in benzene yielded the pyrazole derivatives 127 in 45-65% yields. 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).
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 respective pyrazole derivatives 134 in 90% yield (Scheme 48). \(^{59}\)
Scheme 48

C,N-Diphenylnitrilimine reacted with the enamines 135 and gave 1,3,4-triphenylpyrazole cycloadducts 136 (Scheme 49).60

Scheme 49

4.1.2 Enaminones
Reactions of several enaminones of type 137 with each of C-aryl-, C-acyl-, C-ethoxycarbonyl- and C-cyano-N-arylnitrilimines, generated in situ by base catalyzed dehydrohalogenation of the
respective hydrazonoyl halides, proved to be regioselective and afforded the corresponding 1-aryl-3,4-disubstituted-pyrazoles 138 in 2-90% yields (Scheme 50).\textsuperscript{61-66}

\[
\begin{align*}
R-C(Cl) & = N-NH-R' \\
\text{Benzene} \\
R-C & = N-N-R' \\
\text{stirring 24-48h} \\
+ & \quad \text{Me}_2NCH = CH-COR'' \\
\end{align*}
\]

\[
\begin{align*}
R = & \ XC_6H_4, \text{Ac, 2-thenoyl, EtOCO, 2-Benzothiazolyl, NC} \\
R' = & \ XC_6H_4, X = H, 4-Me, 4-O_2N, 4-Ac, 2,4-Me_2, 4-Cl \\
R'' = & \ XC_6H_4, 2-thienyl, 2-furyl, 2-pyrrolyl, 2-pyridyl, 2-benzothiazolyl, Et
\end{align*}
\]

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-\textit{d}]pyridazines 139 and 140 in 78-96% yields (Scheme 51).\textsuperscript{62-64, 66}

\[
\begin{align*}
R' & = \text{EtO} \\
R & = \text{Me}
\end{align*}
\]

\[
\begin{align*}
139, R' & = \text{Ph, 4-MeC}_6\text{H}_4; R'' = \text{Ph, 2-thienyl, 2-pyridyl, Et, 2-benzothiazolyl} \\
140, R' & = 4-O_2NC_6\text{H}_4; R'' = 2-pyridyl
\end{align*}
\]

Scheme 51
Also, the enaminone 141 reacted with C-acetyl-N-phenyl-nitrimine and afforded the pyrazole derivative 142 in 43% yield which upon treatment with hydrazine hydrate yielded 143 in 73% yield (Scheme 52).

\[
\text{MeCO-C(Cl)=N-NH-Ph} \rightarrow \text{MeCO-C=N-N-Ph} + \text{Et}_3\text{N / EtOH / } \triangle \rightarrow \text{143}
\]

\[
\begin{array}{c}
\text{141} \\
\text{142} \\
\text{143}
\end{array}
\]

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

\[
\begin{array}{c}
\text{R-C(Cl) =N-NH-R'} \\
\text{EtOH, Et}_3\text{N} \\
+ \\
\text{R-C =N-N-R' + XCH = CH-NMe}_2 \\
\rightarrow \\
\text{144} \\
\rightarrow \\
\text{145}
\end{array}
\]

\[
\begin{array}{c}
\text{X} = \text{EtOCO} / 4-\text{ClC}_6\text{H}_4, \text{EtOCO} / 4-\text{Me}, \text{MeCO} / 4-\text{ClC}_6\text{H}_4
\end{array}
\]

\[
\begin{array}{c}
\text{R / R'} = \text{EtOCO} / 4-\text{ClC}_6\text{H}_4, \text{EtOCO} / 4-\text{Me}, \text{MeCO} / 4-\text{ClC}_6\text{H}_4
\end{array}
\]

Scheme 53
Reaction of C-acetyl-N-phenylnitrilimine with ynaminonone 146 was reported to be site-selective. It yielded the pyrazole derivative 147 in 48% yield (Scheme 54).\(^6\)

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.\(^6\) This regiochemical result seems to need further confirmation (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).\(^7\)
Various 3,4-disubstituted-1-arylpurazoles 154 were prepared in 55-73% yields by reactions of enamines 153 with various nitrilimines (Scheme 57).

**Scheme 57**

4.1.4 Enaminonitriles

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

C,N-Diphenylnitrilimine reacted with the 1-substituted enaminoester 166 to afford the pyrazole derivative 167 in 26 % yield (Scheme 62).
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. 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 \textit{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. However, similar reaction of 172 with other
nitrilimines afforded the pyrazole derivatives 175 which upon treatment with hydrazine hydrate yielded 176 (Scheme 64).  

\[
\begin{align*}
\text{Ph-C(\text{Cl})=NNHPh} & \quad + \quad \text{Me}_2\text{N-CH=CH-COOEt} \\
\text{Ph-C=N-N-Ph} & \quad \rightarrow \quad \text{Ph-COOR} \\
\text{RCO-C(\text{Cl})=NNHAr} & \quad + \quad \text{Me}_2\text{N-CH=CH-COOEt} \\
\text{RCO-C=N-N-Ar} & \quad \rightarrow \quad \text{RCO-COEt} \\
\end{align*}
\]

\( R = \text{2-thienyl, Ph} \)

\( \text{Ar = 4-ClC}_6\text{H}_4 \)

Scheme 64

\( N-[\text{Bis(diisopropylamino)(methyl)phosphonio}-\text{C-[bis(diisopropylamino)-thioxophosphoranyl]}\text{nitrilimine 177} \) 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).  

\( \text{176} \text{ NH}_2\text{NH}_2 \)

\( \text{175} \)
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).
However, similar reaction of the same nitrilimine with the morpholinoenamine analog 183A afforded only the tetrazine derivative 165 in 48% yield.\textsuperscript{73} In this case, it seems that the enamine 183A functions only as a base catalyst (Scheme 67).

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme67}
\end{center}

\textbf{Scheme 67}

Cycloalkanone enamines 183A\textsubscript{(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 \textit{E}- and \textit{Z}-isomers of the amidrazone 185.\textsuperscript{78} In another report, this same reaction was reported to afford only 184 (Scheme 68).\textsuperscript{60}

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme68}
\end{center}

\textbf{Scheme 68}

\begin{itemize}
\item 183: A, \( n = 1 \), B, \( n = 2 \)
\item \( n = 1, X = H, 4\text{-Cl}, 3\text{-NO}_3 \), \( n = 2, X = H, 3\text{-NO}_3, 4\text{-Cl}, 4\text{-F}, 3\text{-F}_3\text{C}, 4\text{-Me} \)
\end{itemize}
The reactions of 2-arylidenecycloalkanone 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).\textsuperscript{79}

\[
\text{EtOCO-C(Cl)=N-NH-Ar} \\ \text{Benzene, reflux 10-12h} \\ \rightarrow \\
\bigg(\begin{array}{c}
\text{N} \\
\text{Ar'} \\
\end{array}\bigg)_{n} \\ \text{COOEt} \\
A, n = 1; B, n = 2
\]

\[
\text{EtOCO-C=NN-Ar} \\
\bigg(\begin{array}{c}
\text{N} \\
\text{Ar} \\
\end{array}\bigg)_{n} \\
\]

\[
\text{Ar} = XC_6H_4, \quad \text{Ar'} = X'C_6H_4
\]

\[
n = 1, X / X' = 4-F / H, 4-F / 4-NO_2, 3-F_3C / 2,4-Cl_2.
\]

\[
n = 2, X / X' = 4-F / H, 4-F / 4-Cl, 3-F_3C / 4-Cl.
\]

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).\textsuperscript{51}

\[
\text{EtOCOC(Cl)=NNHAr} \\ \rightarrow \\
\bigg(\begin{array}{c}
\text{N} \\
\text{Ar} \\
\end{array}\bigg)_{n} \\
\text{COOEt} \\
188, n = 1, 2
\]

\[
\text{R}_2N = O(CH_2CH_2)_2N
\]

\[
\text{Ar} = XC_6H_4; X = H, 4-Cl
\]

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

\[
\begin{align*}
R' & \quad \text{EtO / Me, EtO / H, Me / H, Me / Me} \\
192 & \quad \text{RCO-C}(\text{Cl})=\text{N-NH-Ph} \\
+ & \quad \text{Et}_3\text{N} \\
193 & \quad \text{ROC} \\
\end{align*}
\]

Scheme 71

Similarly, 1-phenyl-3-ethoxycarbonyl-8,9-dihyronaphtho[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

\[
\begin{align*}
\text{EtOOCC}(\text{Cl})=\text{N-NH-Ph} & \quad \text{Et}_3\text{N} \\
- & \quad \text{EtOOC} \\
194 & \quad \text{EtOOCC} \\
195 & \quad \text{Et}_3\text{N} \\
\text{OH}_2 & \quad \text{- CO}_2 \\
196 & \quad \text{EtOOCC} \\
\end{align*}
\]

Scheme 72
Reaction of phosphorinan-4-enamine (197) with C,N-diphenylnitrilimine yielded 198 in 21% yield (Scheme 73).\(^8^0\)

![Scheme 73](image)

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 \(^{13}\)C NMR spectra where the signal of C(3a) appears as doublet at \(\delta 58.8\) and that of C(8b) appears as singlet at \(\delta 98.3\) (Scheme 74).\(^8^1\)

![Scheme 74](image)
Reaction of 1,1-dimethyl-2-indenone enamines (202) with C,N-diarylnitrilimines was also reported to be regiospecific 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 1H-4,5-dihydropyrido[4,3-c]pyrazoles 206 and 1H-4,5-dihydropyrido[3,4-c]pyrazoles 208 in 52-70 and 57-75% yields, respectively (Scheme 76).82

206: \( R / R' = H / H, Me / H, H / Me \)
PhC(Cl)=NNHPh

\[ \text{Et}_3\text{N} \rightarrow \text{Benzene} \]

208: \( R / R' = H / H, \text{Me} / H, H / \text{Me} \)

**Scheme 76**

3-Pyrrolidinobenzo[\( b \)]furan (209) reacted with \( C,N \)-diaryl nitrilimines 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).\(^8^3\)

<table>
<thead>
<tr>
<th>( X )</th>
<th>211:212 Ratio / Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.5 / 48</td>
</tr>
<tr>
<td>4-O2N</td>
<td>0.7 / 81</td>
</tr>
</tbody>
</table>

**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. The latter 214 was assumed to result via prototropic shift from the initial cycloadduct 213 (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. 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).
Scheme 79

4.3 Exocyclic enamines

C,N-Diaryl nitrilimines 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. 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. 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).
The reaction of $C,N$-diphenyl-nitrilimine with the exocyclic enamine 226 led to a mixture of 227 and 228 in 36-38% and 23-39% yields, respectively. 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. When the products 227 were refluxed in trifluoroacetic acid, they underwent ring cleavage to give the respective 229 in 36-38% yields (Scheme 82).
In an earlier report, 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).  

Scheme 82

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).\(^{89}\)

\[
\begin{align*}
\text{MeCO-C(Cl)=N-NH-Ph} & \quad \text{THF, Et\textsubscript{3}N} \\
\text{MeCO-C=N-N-Ph} & \quad \text{RT 15 days} \\
+ & \quad \rightarrow \\
\text{MeCO-C=N-N-Ph} & \quad \triangle HCl \\
\text{232} & \quad \rightarrow \\
\text{233} & \quad \text{234} \\
\text{235} & \quad \text{236}
\end{align*}
\]

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 \textit{endo}-double bond followed by elimination of alcohol molecule from the initially formed cycloadducts (Scheme 85).\(^{90}\)
1-Methyl-2-methoxycarbonylpyrrole 239 reacted with C-acetyl-N-phenylnitrilimine afforded only the *bis*-cycloadduct 240 in 20% yield. 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).
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
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. 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).

Scheme 88
Reaction of the diazepine 260 with C-ethoxycarbonyl-N-aryl nitrilimines at room temperature yielded the bis-1,3-cycloadduct 261 and the adducts 262 in 10 and 65% yields, respectively (Scheme 89).92

\[
\begin{align*}
\text{EtOCO-C(Br)=N-N-Ar} & \quad \text{benzene, Et}_3\text{N} \\
& \quad \text{RT, 3 days}
\end{align*}
\]

\[\text{EtOCO-C=N-N-Ar} \quad + \quad \text{Ar} = \text{XC}_6\text{H}_4, \quad X = 4-\text{Me}, 4-\text{Cl} \]

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

\[
\begin{align*}
\text{R-C=N-N-Ph} & \quad + \quad \text{R} = \text{EtOOC, MeCO}
\end{align*}
\]

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).²⁶⁵

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} \quad \text{R} \quad \begin{array}{c}
\text{H} \\
\text{H}
\end{array} \quad + \quad \begin{array}{c}
\text{R} \quad \text{C} = \text{N} - \text{N} - \text{Ph}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \quad \text{R} \quad \begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\]

R / R’ : EtOCO / Me; EtOCO / Ph; MeCO / Me; MeCO / Ph

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).²⁶⁷

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} \quad \text{R} \quad \begin{array}{c}
\text{H} \\
\text{H}
\end{array} \quad + \quad \begin{array}{c}
\text{R} \quad \text{C} = \text{N} - \text{N} - \text{Ph}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \quad \text{R} \quad \begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\]

R / R’ : EtOCO / Me; MeCO / Ph; MeCO/ PhNHN=C(COMe)

Scheme 92

C,N-diaryl nitrilimines reacted with each of 1-methylindole²⁶⁶ and 1-ethylindole²⁶⁷ 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).²⁶⁸
Heating the latter cycloadducts 268 in acetic acid afforded 1,3-diaryl-4-(2-alkylaminophenyl)pyrazoles 270 in 90-95% yields. Also, the cycloadducts 268 were oxidized with lead tetraacetate in dichloromethane and gave the respective 8-alkylpyrazolo[3,4-b]indole derivatives 271 (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 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).
Scheme 95

Reaction of \( N \)-phenyl-\( C \)-acetyl\( \text{nitrilimine} \) with 1-methyl-2-ethoxycarbonylindole 276 was reported by Ruccia et al.\(^9^3\) 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.\(^9^7, 9^8\) 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).\(^9^8\)
Reactions of the indole derivative 283 with C-ethoxycarbonyl- and C-acetyl-N-phenylnitrilimines 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. Reactions of the indole derivative 286 with C-acetyl-N-phenylnitrilimines followed the same regiochemical pathway and yielded only the cycloadduct 287 (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

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 aminals

Reactions of C-acyl-N-arylnitrilimines with the ketene aminals 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).\(^ {57}\)
The reaction of C,N-diarylnitrilimines with the ketenaminals 298 in HCCl$_3$ at room temperature afforded the respective pyrazole derivative 299. However, similar reaction of N-(2,4-dinitrophenyl)-benzene-carbohydrazonoyl bromide with 298 under the same conditions furnished only the hydrazones 300 in 75-95% yield. Heating the latter 300 (n = 0, R = H) in xylene for 10 h gave the respective pyrazole derivative 301 in 45% yield. 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).
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.

References


Biographical Sketches

Ahmad Sami A. S. Shawali is presently Professor of Physical organic chemistry in the Chemistry Department, Faculty of Science, University of Cairo. He graduated with B.Sc. degree from the same university in 1958. He received his M.Sc. and Ph.D. degrees in 1962 and 1966, respectively, from Lowell Technological Institute, presently The University of Lowell, Lowell, Massachusetts, USA. He was awarded the degree of Doctor of Science (D.Sc.) from British Royal Chemical Society and the University of Cairo in 1995. Prof. Shawali has been the recipient of the state award for science and Egypt State Medal of Science and Arts in 1977. He holds several national and international certificates of merit for his distinguished services. He was visiting professor at the university of Texas, El Paso, Texas, USA from 1979 to 1980, University of Kuwait from 1973 to 1977 and King Abdulaziz University, Jeddah, Saudi Arabia.
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