Bis-Enaminones as versatile precursors for terheterocycles: synthesis and reactions

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Abstract
This review summarizes the results of literature reports concerning synthesis and chemical reactions of bis(enaminones) reported by us and by other research groups from 1995 to mid 2011. It outlines their utility as versatile precursors for synthesis of various terheterocycles.

Keywords: Enaminones, heterocycles, nitrilimines, condensation, DMF-DMA

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1. Introduction

The term enaminones usually refers to the compounds that contain the conjugate system N-C=C-C=O. Sometimes they are referred to as β-aminovinyl ketones, β-aminoenones or α-enaminoketones. From the structural point of view, enaminones are usually classified according to the degree of substitution on the nitrogen atom into primary (1°), secondary (2°) and tertiary (3°) enaminones (Chart 1). Also, enaminones are usually classified according to their carbon skeleton into acyclic 1, endocyclic 2, exocyclic 3 and heterocyclic 4 enaminones (Chart 1). Furthermore, acyclic enaminones are further classified according to the degree of substitution at α- and β-carbons into α-substituted, β-substituted and α,β-disubstituted enaminones A-D, respectively (Chart 2).
A literature survey reveals that enaminones are very stable compounds and constitute a versatile class of useful precursors in organic synthesis, in pharmaceutical development and in heterocyclic synthesis. Although the chemistry of mono-enaminones 1-4 has been the subject of several reviews, the chemistry of bis-enaminones of type 5 has not been covered hitherto. The intention of this review is to focus mainly on publications dealing with the synthesis and reactions of various bis(enaminones) 5 that have been reported during the period from 1995 to mid 2011 is presented.
2. Synthesis

2.1. Condensation of diacetyl compounds with DMF-DMA

Heating a mixture of 2,6-diacetylpyridine 6 with two mole equivalents of dimethylformamide dimethylacetal in a microwave oven\textsuperscript{11} or by refluxing the mixture in xylene\textsuperscript{12-14} afforded 2,6-bis[(3-dimethylamino)acryloyl]pyridine 7.

\begin{align*}
\text{H}_3\text{C} & \quad \text{N} & \quad \text{O} & \quad \text{CH}_3 \\
\text{O} & \quad \text{C} & \quad \text{H}_3 & \quad \text{C} & \quad \text{H}_3
\end{align*}

\[
\begin{array}{c}
\text{DMF-DMA} \\
\text{Microwave oven}
\end{array}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{NMe}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{NMe}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{NMe}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{NMe}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}\]

Similarly, heating 2,5-diacetylpyrazine 8 with DMF-DMA in a microwave oven was reported to give (E,E)-2,5-bis[3-(N,N-dimethylamino)-acryloyl]pyrazine 9.\textsuperscript{15}

\begin{align*}
\text{H}_3\text{C} & \quad \text{N} & \quad \text{O} & \quad \text{CH}_3 \\
\text{O} & \quad \text{C} & \quad \text{H}_3 & \quad \text{C} & \quad \text{H}_3
\end{align*}

\[
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{NMe}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{NMe}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{NMe}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}\]

Also, the \textit{bis}(enaminone) 11 was obtained by refluxing a solution of 6,6'-diacetyl-2,2'-bipyridine 10 in dimethylformamide dimethylacetal in xylene under nitrogen.\textsuperscript{16}
Recently, the synthesis of the bis(enaminones) 15 was reported via reaction of the respective 3,4-diacetylpyrazole derivatives 14 with dimethylformamide-dimethylacetal (DMF-DMA) under reflux. The precursors 1-aryl-3,4-diacetyl-5-methylpyrazoles 14 were synthesized by reaction of 2,4-pentanedione 13 with each of N-aryl 2-oxopropanehydrazonoyl chlorides 12 in ethanol in the presence of sodium ethoxide.

Condensation of 1,3- and 1,4-diacylbenzenes 16a,b each with two mole equivalents of DMF-DMA in dry toluene was also reported to afford the bis(enaminones) 17. When this reaction was repeated in a pressure tube for a few minutes in a microwave oven at 360W, it gave also the respective bis(enaminones) 17.

Reaction of potassium salt 18, obtained upon treatment of 4-hydroxyacetophenone with ethanolic potassium hydroxide, with the appropriate dibromoalkanes in boiling DMF afforded
the corresponding \(\alpha,\omega\)-bis(4-acetylphenoxy)alkanes 19. Solventless heating of compounds 19a,b with DMF-DMA furnished the corresponding bis(enaminones) 20a,b in moderate yields.\(^{19}\)

In addition, a series of bis(enaminones) 23 was prepared as depicted below by initial reaction of 3-hydroxyacetophene 21 with the appropriate bis(halomethyl) linking unit followed by condensation of the resulting diacetyl derivative 22 with DMF-DMA.\(^{20}\)

2.2. Reaction of mono-enaminones with diamines
The reaction of the monoenaminines 24 each with 1,2-diaminoethane gave the respective bis(enaminones) 26 in 84% yield. Other monoenaminones 25 behaved identically with 1,4-diaminobutane to form the envisaged bis-enaminones 27 in good yields. The structures of the bis(enaminones) 26(27) were established with the help of spectral and analytical data and in all cases the enaminone moieties were found to exist exclusively in Z-form.\(^{21}\)
Similar reaction of 24a with o-phenylenediamine gave the bis-(enaminone) 28 in 94% yield, the structure of which was well established with spectral and analytical data.\textsuperscript{21}

Recently, a series of the bis(enaminones) namely bis-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-ones 30 were prepared by irradiation of a methanolic solution of a mixture of the respective diamine and enaminone 29 in a domestic microwave oven for specified period.\textsuperscript{22}

Similarly, when a mixture of the enaminone 31, 1,2-diaminoethane and formaldehyde in methanol was irradiated in a microwave oven, it afforded the respective bis(enaminones) 32a in 71% yield.\textsuperscript{23} The reaction was found to be general with other diamines to give the respective
product 32 in 51-68% overall yields. Use of 1,4-phenylenediamine in lieu of aliphatic diamines, the reaction yielded the corresponding bis(naminones 33).\(^{23}\)

\[
\begin{align*}
R & : a, H; b, Me & R' & = \text{PhCH}_2\text{CH}_2 \\
n & = 2, 3, 4
\end{align*}
\]

2.3. Reactions bis-acetive methylene compounds with DMF-DMA

The bis(enaminone) 35 was prepared by reaction of dimethyl acetonedicarboxylate 34 with DMF-DMA.\(^{24}\)

Treatment of 3,4-dimethylthieno[2,3-b]thiophene-2,5-dicarboxylate 36 with acetonitrile in the presence of sodium hydride in refluxing benzene afforded 3-[3,4-dimethyl-5-(3-nitropropanoyl)thieno[2,3-b]thiophen-2-yl]-3-oxopeopanoneitrile 37. Treatment of the latter with DMF-DMA in refluxing xylene yielded the bis(enaminone) 38.\(^{25}\)
Similarly, the *bis*(enaminones) 40 were readily obtained by reacting 39 with excess DMF-DMA.\textsuperscript{26}

\[ \text{R' = EtO} \quad \text{R : a, H; b, MeO} \]

*\(N,N'-(1,4\)-Phenylene\)-*\(bis\)(3-oxo-3-phenylpropanamide) 41, prepared from condensation of \(p\)-phenylenediamine with ethyl benzoylacetae, was reported to react with DMF-DMA in refluxing toluene to afford the *bis*-enaminone namely *\(N,N'-(1,4\)-phenylene\)-*\(bis\)\(\{2\)-benzoyl-3-dimethylamino-acrylamide\} 42.\textsuperscript{27}
2.4. Miscellaneous methods

Recently, a new series of ten *bis*-enaminones 44 was isolated in satisfactory yields of 47-91\%, by the reaction of enones 43 with 1,3-phenylenediamine at a molar ratio of 2:1, respectively. The reactions were reported to be carried out in ethanol, water, water/dichloromethane (1:1) or water/chloroform (1:1) at a temperature range of 25 to 80 °C. The best results were obtained when enones 43a-j were added to 1,3-phenylenediamine, in pure ethanol for 43a-d and 43f-j or in water/chloroform (1:1) solution for 43e.28

\[
\begin{align*}
\text{43} & \quad \text{44} \\
\text{R : a, H; b, Me; c-i, 4-XC}_6\text{H}_4; j, 2\text{-furyl} & \quad \text{R' = Me; Et} \\
\text{X : c, H; d, Me; e, MeO; f, F; g, Cl; h, Br; i, NO2}
\end{align*}
\]

Treatment of the *bis*-enaminones 20a,b each with piperidine in refluxing ethanol afforded the respective *bis*-enaminones 45a,b in 64-65\% yield. Similar treatment of 20a,b each with morpholine under similar conditions gave the *bis*-enaminones 45c,d in 60\% yields.19

\[
\begin{align*}
\text{VI: a, } X = (\text{CH}_2)_3; & \quad b, X = (\text{CH}_2)_4 \\
\text{45, } X/Y : a(c), (\text{CH}_2)_3 / \text{CH}_2; b(d), (\text{CH}_2)_4 / \text{O}
\end{align*}
\]

Buehrdel et al.29 reported that reaction of the *bis*-imidoyl chloride 46 with each of tetrahydro-1-naphthanone and methyl ketones in tetrahydrofuran in the presence of potassium t-butoxide at -70°C yielded the respective *bis*-enaminones 47 and 48.
Recently, the polyfunctional \textit{bis}(enaminones) 55 were successfully synthesized stereoselectively via reactions of a mixture of primary amines 49, aldehydes 50, propargylic acid 51, isocyanides 52, and piperazine 53 in one pot. The reaction was said to proceed via formation of an N-substituted-2-alkynamide 54 as an intermediate which contains an active triple bond suitable for further nucleophilic addition reaction.\textsuperscript{30}
3. Chemical Reactions

The chemical reactivity of enaminones is in general attributed to the fact that they combine the ambident nucleophilicity of enamines and the ambident electrophilicity of enones. For example, each enaminone can be attacked by a given nucleophile at the two sites namely the C-3 (the dialkylaminoethylene group) and C-1 (the carbonyl group) with reactivity order C-3 > C-1. Also, it can be attacked by an electrophile at C-2, oxygen and/or nitrogen sites with reactivity order C-2 > N > O.
3.1. Reactions with amines

3.1.1. Reaction with 1,2-diaminoethane. Condensation of the bis-enaminone 7 with ethylenediamine in refluxing etanol yielded 2,6-bis[1,2,3-trihydro[1,4]diazepin-5-yl]pyridine 56.\(^\text{14}\)

3.1.2. Reaction with morpholine and piperidine. Reaction of the bis-enaminones 20 each with morpholine and piperidine yielded the corresponding bis-enaminones 45.\(^\text{19}\)
Recently, it was reported that treatment of the bis-enaminone 35 with primary amine in n-propanol at 95° yielded the respective dimethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylate 57.\textsuperscript{24}

\begin{center}
\begin{tabular}{c}
\text{Me}_2\text{N} & \text{NMe}_2 \\
\text{MeOOCC} & \text{COOMe} \\
35 & \text{R} \\
\rightarrow & \text{R} \\
\text{MeOOCC} & \text{COOMe} \\
57 & \text{R} = \text{Pyrazinyl, pyridin-2-yl; 4-methylpyridin-2-yl; 5-methylpyridin-2-yl; 3-hydroxypyridin-2-yl; 5-chloropyridin-2-yl; 4-nitrophenyl; 4-fluorophenyl; 2-iodophenyl; 4-anisyl; 1,2-phenylene}
\end{tabular}
\end{center}

Similar reaction of 35 with 1,4-diaminobenzene under the same reaction conditions afforded the respective 1,4-bis(4-oxo-3,5-dimethoxycarbonyl -1,4-dihydropyridin-1-yl)benzene 58.\textsuperscript{24}

\begin{center}
\begin{tabular}{c}
\text{Me}_2\text{N} & \text{NMe}_2 \\
\text{MeOOCC} & \text{COOMe} \\
35 & \text{H}_2\text{N} \rightarrow \text{NH}_2 \\
\text{MeOOCC} & \text{COOMe} \\
58
\end{tabular}
\end{center}

3.2. Reactions with heterocyclic amines

3.2.1. Reaction with 5-aminopyrazoles. Reaction of a given enaminone with 5-amino-1\textit{H}-pyrazole can theoretically proceed through two possible routes to give 5-substituted pyrazolo[1,5-\textit{a}]pyrimidine \textbf{A} and/or 7-substituted pyrazolo[1,5-\textit{a}]pyrimidine \textbf{B} as shown below. However, literature reports indicate that such a reaction is site selective as it afforded in most cases 5-substituted pyrazolo[1,5-\textit{a}]pyrimidine derivatives \textbf{A}. 

\begin{center}
\begin{tabular}{c}
\text{Me}_2\text{N} & \text{NMe}_2 \\
\text{MeOOCC} & \text{COOMe} \\
\text{MeOOCC} & \text{COOMe} \\
\text{MeOOCC} & \text{COOMe} \\
\text{MeOOCC} & \text{COOMe} \\
\end{tabular}
\end{center}
Thus, the bis-enaminone 7 was reported to condense site-selectively with 5-aminopyrazoles to yield the corresponding 2,6-bis(2-substituted-pyrazolo[1,5-a]pyrimidin-7-yl)pyridine derivatives 59.14

3.2.2. Reactions with 2-amino-imidazole and 2-aminobenzimidazole. Reaction of a given 2-amino-1-unsubstituted imidazole with an enaminone can proceed through two possible routes to give 7-substitututed imidazo[1,2-a]pyrimidine A and / or 5-substitututed imidazo[1,2-a]pyrimidine B as depicted below. Literature reports revealed however that such a reaction is site selective yielding products of type B.
For example, the bis-enaminone 7 condensed with 2-aminobenzimidazole and yielded only the respective 2,6-bis(benzimidazol[1,2-a]pyrimidin-8-yl)pyridine derivative 60.14

3.2.3. Reactions with 3-amino-1H-1,2,4-triazole. Reaction of 3-amino-1H-1,2,4-triazole with a given enaminone can theoretically lead to one or more of the four possible condensation products A – D. This is because of the following: (1) 3-amino-1,2,4-triazole can exist in one of the two tautomeric forms namely 3-amino-4H-1,2,4-triazole and 3-amino-2H-1,2,4-triazole and (2) the reaction of each of such tautomers with an enaminone can proceed through two possible pathways involving initial attack by either exocyclic amino group or the cyclic –NH- group. The structures of the four possible expected products A – D are thus 5-R-1,2,4-triazolo[4,3-a]pyridine A, 7-R-1,2,4-triazolo[4,3-a]pyridine B (Chart 1), 5-R-1,2,4-triazolo[1,5-a]pyridine C and 7-R-1,2,4-triazolo[4,3-a]pyridine D as shown below.
Chart 1
However, various literature reports indicate that such a reaction is site- and regio-selective. For example, reaction of the bis-enaminone 7 with 5-amino-1,2,4-triazole yielded only one product namely the 2,6-bis(1,2,4-triazolo[4,3-a]pyrimidin-7-yl)pyridine 61.\(^{14}\)

Also, Shawali et al.\(^{35}\) reported that reaction of the bis-enaminones 15 with 3-amino-1,2,4-triazole is site selective although it can theoretically lead to either the 1,2,4-triazolo[1,5-
a]pyrimidine 62 and/or its [4,3-α] isomer 63. For example, reaction of 15a-c each with 3-amino-1,2,4-triazole in acetic acid under reflux yielded, in each case, only one isolable product which was identified as the respective 3,4-bis[1,2,4-triazolo-[1,5-α]pyrimidine-7-yl]pyrazole derivative 62 and not its 1,2,4-triazolo[4,3-α]pyrimidine isomers 63 on the basis of their 1H NMR spectral data.55

![Diagram of chemical reactions](image)

3.3. Reaction with amidines
3.3.1. Reaction with acid amidines. Reaction of 2,6-bis(N,N'-dimethylamino)-1-oxoprop-2-en-1-yl]pyridine 7 with five equivalents of each of acetamidine hydrochloride and sodium ethoxide in hot ethanol resulted in the formation of 2,6-bis[2-methylpyrimidin-6-yl]pyridine 64 in 90% yield.12

![Diagram of chemical reactions](image)

Similar reaction of 7 with five equivalents of formamidine acetate and five equivalents of sodium ethoxide in refluxing ethanol was reported to result in the formation of a mixture of 65 and 66 in 50% and 34%, respectively.12
The bis-enaminone 7 reacted also with 2-pipenecarboxamidine hydrochloride 67 led to dipineno[2',2'"]-2,6-bis(4',4"-pyrimidyl)pyridine 68 in 88% yield.\textsuperscript{13}

The condensation of 7 with the amidine 67 in 1:1 ratio gave 69 in 66% yield which is converted into 70 by condensation with pyridine-2-carboxamidine under standard conditions.\textsuperscript{13}
Very recently, it was reported that 1,4-\textit{bis}(2-phenyl-4-pyrimidyl)benzene 71 was synthesized by reaction of benzamidine hydrochloride with the \textit{bis}-enaminone 17b in an ionic liquid [BMIM][BF4] in the presence of sodium hydroxide.\textsuperscript{31}

\textbf{3.3.2. Reaction with guanidine.} The \textit{bis}-enaminone 7 was used to prepare the 2,6-\textit{bis}(2-aminopyrimidyl)pyridine 72 in quantitative yield either by heating it with guanidine nitrate in refluxing ethanol in the presence of sodium ethoxide\textsuperscript{12} or with guanidine hydrochloride and potassium carbonate in refluxing ethanol.\textsuperscript{14}
Similarly, 2,6-bis(2-aminopyrimidyl)pyridine 73 was produced quantitatively upon heating the bis-enaminone 7 with guanidine hydrochloride in refluxing ethanol in the presence of sodium ethoxide.32

Also, reaction of bis-enaminone 42 with guanidine hydrochloride in refluxing ethanol in the presence of triethylamine was reported to afford 74 which cyclized upon heating in ethanolic sodium ethoxide solution to give \( N,N'-(1,4\text{-phenylene})\)-bis-(2-imino-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) 75.27
Recently, it was reported that 1,4-\textit{bis}(2-aminopyrimidin-4-yl)benzene \textit{76} was obtained by reaction of guanidine hydrochloride with the \textit{bis}-enaminone \textit{17b} in an ionic liquid [BMIM][BF4] in the presence of sodium hydroxide.\textsuperscript{31}

3.4. Reaction with hydrazines
3.4.1. Reaction with hydrazine hydrate. When a mixture of the \textit{bis}-enaminone \textit{11} and hydrazine hydrate in ethanol was refluxed for 1 h, it gave 6,6'-\textit{bis}(pyrazol-3-yl)-2,2'-bipyridine \textit{77}.\textsuperscript{16}
Similar reaction of the bis-enaminone 7 and hydrazine hydrate in refluxing ethanol gave 2,6-bis(pyrazol-3-yl)pyridine 78.11,14

Reaction of bis-enaminone 42 with hydrazine hydrate in refluxing ethanol in the presence of piperidine afforded the substitution products 79. The latter product underwent cyclization when heated in ethanolic sodium ethoxide solution and gave N,N'-((1,4-phenylene)-bis(2-oxo-5-phenyl-1H-pyrazole-4-carboxamide) 80.27

Also, the bis-enaminone 17b reacted with hydrazine hydrate in ionic liquid ([BMIM][BF₄]) and gave 1,4-bis(pyrazol-5-yl)benzene 81.11,14
Stirring each of the *bis*-enaminones 45 with hydrazine hydrate in glacial acetic acid at room temperature was reported to yield the *bis*(pyrazolyl) derivatives 82.\(^{19}\)

Recently, Shawali et al.\(^ {17}\) reported that reaction of each of the *bis*-enaminones 15 with hydrazine hydrate in refluxing ethanol afforded the respective 3,3':4,3"-terpyrazoles 83.
3.4.2. Reaction with substituted hydrazines. Reaction of the bis-enaminone 7 and phenylhydrazine in refluxing ethanol for 2h gave 2,6-bis(1-phenylpyrazol-5-yl)pyridine 84.14

Reaction of the bis-enaminones 15 with phenylhydrazine in refluxing ethanol was reported to afford the respective 3,3′:4,3″-terpyrazoles 85.15
Similar reaction of\textit{bis}-enaminone 42 with phenylhydrazine in refluxing ethanol in the presence of piperidine afforded the substitution products 86. The latter product underwent cyclization when heated in ethanolic sodium ethoxide solution and gave $N,N'-(1,4$-phenylene)-\textit{bis}-(1,5-diphenyl-pyrazole-4-carboxamide) 87.\textsuperscript{27}

Cyclocondensation of\textit{bis}-enaminone 17\textit{b} with various substituted hydrazines in ionic liquids in the presence of an acid catalyst was reported to give the respective 1,4-\textit{bis}-[1-substituted-pyrazol-5-yl]benzenes 88 in good yields.\textsuperscript{31} The site selectivity in this reaction was found to depend on the structure of the hydrazine derivative used.
3.5. Reaction with hydroxylamine

Reaction of the bis-enaminone 7 and hydroxylamine hydrochloride in refluxing ethanol in the presence of anhydrous sodium acetate was reported to yield 2,6-bis(isoxazol-3-yl)pyridine 89 and not 2,6-bis(isoxazol-5-yl)pyridine 90.14

Similarly, when each of the bis-enaminones 15a-c was refluxed with hydroxylamine hydrochloride in ethanol in the presence of ammonium acetate, it yielded, in each case, a single product identified as the respective 3,4-bis(isoxazol-3-yl)pyrazole 92 rather than its bis(isoxazol-5-yl)pyrazole 94.35 The assigned structure 92 was confirmed by the alternate synthesis of 92b as a representative example of the series prepared. Thus, reaction of the bis-oxime 95b, prepared
from 1-p-tolyl-3,4-diacetyl-5-methylpyrazole 96 and two equivalents of hydroxylamine hydrochloride in refluxing ethanol in the presence of potassium hydroxide, with DMF-DMA in refluxing xylene gave a product that proved identical in all respects with 92b isolated from reaction of 15b with hydroxylamine hydrochloride.

Recently, reaction of the bis-enaminone 17b with hydroxylamine hydrochloride in an ionic liquid was reported to give 1,4-bis(5-isoxazolyl)benzene 97.31
3.6. Reaction with acetylenic ketones

Heating a mixture of each of the bis-enaminones 23A-C with aroyl acetylenes 98 in refluxing toluene for 12 h resulted in smooth trimerization to afford the respective 1,3,5-triaroylbenzene derivatives 99 in good yields.²⁰

\[
\begin{align*}
\text{Ar} &= \text{XC}_6\text{H}_4 \\
X &= \text{a, OMe; b, O2N} \\
R &= \text{A, 1,4-C}_6\text{H}_4; \text{B, 1,3-C}_6\text{H}_4; \text{4,4'-biphenyl}
\end{align*}
\]

3.7. Reaction with methyl ketones

2,5-Bis(2,2'-bipyridin-6-yl)pyrazine 100 was obtained when a mixture of the bis-enaminone 9 and two equivalents of acetylpyridine was stirred at room temperature in tetrahydro-furan in the presence of t-BuOK for 4 days, followed by treatment with ammonium acetate in acetic acid.¹⁵

\[
i = \text{t-BuOK / THF; AcOH/} \text{NH}_4\text{OAc}
\]
3.8. Reaction with active cyanomethylene compounds

3.8.1. Reaction with benzoylacetonitrile. When a mixture of the bis-enaminone 7 and benzoylacetonitrile was refluxed in acetic acid in the presence of ammonium acetate, it yielded 6,6''-diamino-5,5''-dibenzoyl-2,2':6',2''-terpyridine 101 in 60% yield.\(^\text{14}\)

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{NMe}_2 \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{N} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\text{N} & \quad \text{N} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\end{align*}
\]

However, in another report it was indicated that such a reaction of the bis-enaminone 7 with benzoylacetonitrile, when carried out in refluxing toluene, it yielded 5,5''-dibenzoyl-1,1''-dihydro-2,2':6',2''-terpyridine-6,6''-dione 102 in 40% yield.\(^\text{14}\)

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{NMe}_2 \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{N} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]
3.8.2. Reaction with ethyl cyanoacetate. 5,5''-Di(ethoxycarbonyl)-1,1''-dihydro-6,6''-dioxo-2,2':6',2''-terpyridine 103 was produced when the bis-enaminone 7 was refluxed with ethyl cyanoacetate in refluxing toluene in the presence of piperidine as a catalyst.\(^{14}\)

\[ \text{Me}_2\text{N} \rightleftharpoons \text{O} \rightleftharpoons \text{NMe}_2 \]

\[ \text{EtO} \rightleftharpoons \text{CH}_2\text{CN} \rightarrow \text{EtOOC} \]

3.8.3. Reaction with malononitrile. Reaction of the bis-enaminone 7 with malononitrile in refluxing ethanol in the presence of piperidine yielded 1H,1''H-6,6''-dioxo-5,5''-dicyano-2,2':6',2''-terpyridine 104.\(^{14}\) The latter product 104 was also obtained by refluxing the bis-enaminone 7 with cyanoacetamide in dry toluene.\(^{14}\)

\[ \text{Me}_2\text{N} \rightleftharpoons \text{O} \rightleftharpoons \text{NMe}_2 \]

\[ \text{CH}_2(\text{CN})_2 \rightleftharpoons \text{piperidine} \rightarrow \text{NCCH}_2\text{CONH}_2 \]
Shawali et al.\textsuperscript{35} also reported that reaction of malononitrile with each of the enaminones 15a-c in refluxing glacial acetic acid in the presence of ammonium acetate gave rise, in each case, a single product that proved to be the respective \textit{3,4-bis}(5-cyano-6-oxo-1\textit{H}-pyridin-2-yl)-1-aryl-5-methylpyrazole 105. The assigned structure 105 was further evidenced by alternate synthesis of 105a as an example of the series prepared. Thus, reaction of 15a with cyanoacetamide in refluxing dry toluene afforded that proved identical in all respects with that one obtained above from reaction of 15a with malononitrile.

\[
\begin{align*}
\text{15} & \rightarrow \text{105} \\
\text{15} + \text{NCCH}_2\text{CONH}_2 & \rightarrow \text{105} + \text{Me}_2\text{NH}
\end{align*}
\]

\[\text{Ar} = 4-\text{XC}_6\text{H}_4; \ X : \text{a, H; b, Me; c, MeO}\]

Similar reaction of the \textit{bis}-enaminone 42 with two fold excess of malononitrile in refluxing ethanol in the presence of few drops of piperidine was also reported to give \(N,N'-(1,4\text{-phenylene})\textit{bis}-(2\text{-cyano}4\text{-}(_{\text{dimethylamino}})\text{-phenylmethylene})\text{pent-2-enediamide 108.}^{27}\) The formation of the latter was considered to result \textit{via} initial substitution of the dimethylamino group to give the intermediate 106 followed by cyclization to give 107, which in turn reacted...
with dimethylamine to give 108 as end product. Refluxing the latter in ethanolic sodium ethoxide solution resulted in the formation of \( N,N'-(1,4\text{-diphenylene})\text{bis}(5\text{-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide}) \) 109 *via* elimination of dimethylamine.\(^{27}\)

**3.8.4. Reactions with cyanoacetamide and cyanothioacetamide.** The *bis*-enaminone 7 reacted with cyanoacetamide in refluxing toluene in the presence of piperidine as a catalyst and gave 1\(\text{H},1''\text{H}-6,6''-\text{dioxo-2,2':6,2''-terpyridine-5,5''-dicarbonitrile} \) 110 *via* substitution of the dimethylamino group followed by cyclization.\(^{14}\) The latter product was also obtained by reaction of 7 with malononitrile.\(^{14}\)
The bis-enaminone 42 was also reported to react with cyanoacetamide in refluxing ethanol in the presence of few drops of piperidine as a catalyst to give 111a via substitution of the dimethylamino group. Refluxing the latter in ethanolic sodium ethoxide solution furnished its cyclization and afforded the product 112a identical with that one obtained by reaction of 42 with malononitrile under the same reaction conditions.\textsuperscript{27} Use of cyanothioacetamide \textit{in lieu} of cyanoacetamide in this reaction gave the respective \(N,N'-(1,4\text{-phenylene})\text{-}\textit{bis}(5\text{-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide})\) 112b in 72% yield.\textsuperscript{27}

\begin{align*}
\text{PhCO} - \text{CONH} & \quad \text{Ar} \quad \text{n} \quad \text{Me}_2\text{N} \\
\text{NCCH}_2\text{C(X)-NH}_2 & \quad \text{EtONa} \quad \text{EtOH} \\
\text{Ph} & \quad \text{Ar} \\
\text{X} & \quad \text{CONH} \quad \text{Ph} \\
\text{CN} & \quad \text{Ar} \\
\text{X} \quad \text{CN} & \quad \text{CONH} \\
\text{X} & \quad \text{NH} \quad \text{X} \quad \text{NH} \\
\text{Ph} & \quad \text{Ar} \quad \text{n} \\
\text{n} = 2; \quad \text{X} : \text{a, O, b, S} \\
\text{Ar} = 1,4\text{-C}_6\text{H}_4
\end{align*}

3.8.5. \textbf{Reactions with 2,4-pentanedione}. The terpyridine derivative namely 5,5\textsuperscript{''}-diacetyl-6,6\textsuperscript{''}-dimethyl-2,2\textquoteleft:\textquoteleft 6,2\textsuperscript{''}-terpyridine 114 was reported to be formed by reaction of the \textit{bis}-enaminone 7 with acetylacetone in refluxing acetic acid in the presence of ammonium acetate \textit{via} the pathway depicted below.\textsuperscript{14}
3.8.6. Reactions with β-keto esters. When a mixture of ethyl acetoacetate and each of the bis-enaminone 15a-c was refluxed for 30 h in glacial acetic acid in the presence of ammonium acetate, it yielded, in each case, a single product. Both elemental analyses and spectral data indicate that the products isolated are the respective 3,4-bis[5-ethoxycarbonyl-6-methyl-pyrid-2-yl]-1-aryl-5-methylpyrazoles 119a-c.\(^{35}\) Ethyl benzoylacetoacetate reacted similarly with each of 15a-c under the same reaction conditions and afforded the respective 3,4-bis[5-ethoxycarbonyl-6-phenyl-pyrid-2-yl]-1-aryl-5-methylpyrazoles 120a-c.\(^{35}\)

The reaction pathway that was suggested to account for the formation of the products 119 and 120 involves initial addition of the active methylene moiety to the activated double bond of 15 to afford 115(116) as intermediates that undergo elimination of dimethylamine to afford 117(118) which in turn condenses with ammonium acetate to yield the respective 3,4-bis(pyridine-6-yl)pyrazoles 119(120) as end products.\(^{35}\)
The bis-enaminone 7 was also reported to react with ethyl acetoacetate in refluxing acetic acid in the presence of ammonium acetate to give 5,5''-diethoxycarbonyl-6,6''-dimethyl-2,2':6',2''-terpyridine 122. The formation of the latter product was considered to follow the sequence depicted in the following scheme. The reaction starts with addition of the keto ester to the double bond of the enaminone to yield the Michael adduct 121 which in turn cyclized in the presence of ammonium acetate to yield 122 as end product.
3.9. Reaction with N-benzoylglycine
When the bis-enaminones 45 was refluxed with N-benzoylglycine in acetic anhydride, it gave the respective 124.\(^{19}\)
3.10. Reactions with hydrazonoyl halides

Reaction of the bis-enaminone 7 with N-aryl-2-oxopropane hydrazonoyl chloride in refluxing dry benzene in the presence of triethylamine was reported to be regioselective as it gave only the respective 125 and not 126. The formation of 125 was considered to result via 1,3-dipolar cycloaddition of the nitrilimine, generated from hydrazonoyl chloride, with concurrent elimination of dimethylamine. The isolated product 125 condensed with hydrazine hydrate to give the corresponding 2,6-bis(4-methyl-1-aryl-pyrazolo[3,4-d]pyridazin-7-yl)pyridines 127.

In a similar manner, refluxing of the bis-enaminone 7 with ethyl N-arylhydrazonochloroacetates in benzene in the presence of triethylamine afforded the corresponding 2,6-bis(3-ethoxycarbonyl-1-arylpyrazole-4-carbonyl) pyridines 128, which reacted with hydrazine hydrate to give 2,6-bis-(4-oxo-1-arylpyrazolo[3,4-d]pyridazin-7-yl)pyridines 129.
The reactions of the bis-enaminones 15 with nitrilimines I, generated in situ by base-catalyzed dehydrochlorination of the respective hydrazonoyl chlorides 130A-C, were also reported by Shawali et al.17 Reaction of each of 15a-d with hydrazonoyl chlorides 130A-C in refluxing benzene in the presence of triethylamine yielded, in each case, a single product. The isolated products were identified, on the basis of their elemental analyses and spectral (IR, 1H NMR and Ms) data, as the respective 3,5-Bis-(1-phenyl-3-substituted-pyrazol-4-carbonyl)-5-methyl-1-aryl-pyrazoles 131-133.

Although the reaction of 131-133 with hydrazine hydrate can theoretically lead to two possible pyrazolopyridazines, Shawali et al reported that it is site selective. For example, when a mixture of 131a and hydrazine hydrate was refluxed, it yielded only one product as evidenced by TLC of the crude product. On the basis of the IR and other spectral data, the isolated product was identified as 134a.17 The site-selectivity of such a reaction was further confirmed by the finding that reactions of hydrazine hydrate with both 132a and 133a afforded, in both cases, one and the same product, whose spectra (IR, 1H NMR and Ms) and elemental analysis data proved it to have structure 135b.
$$\text{RCOC(Cl)=NNHAr}$$

\[\text{I} - \text{HCl} \quad \text{Et}_3\text{N} / \quad + \quad \text{RCO-C≡N-N-Ar}' \quad + \quad 15 \quad \text{II}\]

\[\text{Ar} / \text{Ar}' : \text{YPh} / \text{XPh}\]

\[\text{Y / X : a, H / H; b, 4-Me / H; c, 4-Cl / H; d, 4-MeO / H; e, H / 4-Me; f, H / 4-Cl}\]

R : 130A (131), Me; 130B (132), EtO; 130C (133), PhNH
3.11. Reactions with quinones
Refluxing the bis-enaminones 45 each with benzoquinone 138 in refluxing acetic acid was reported to afford the respective 1,3-bis-(benzofuran) derivatives 139a,b in 43-79% yields.19

\[
\begin{align*}
\text{45} & \quad \text{138} \\
R & \quad \text{X} \quad \text{2} \\
\text{R} : & \quad \text{A}, (\text{CH}_2)_3; \text{B}, (\text{CH}_2)_4 \\
\text{X} : & \quad \text{a}, \text{CH}_2; \text{b}, \text{O}
\end{align*}
\]

Similar reaction of the bis-enaminones 45 each with naphthoquinone in refluxing acetic acid afforded the respective 1,3-bis-(naphthofuran) derivatives 140.19

\[
\begin{align*}
\text{45} & \quad \text{140} \\
R & \quad \text{X} \quad \text{2} \\
\text{X} : & \quad \text{a}, \text{CH}_2; \text{b}, \text{O} \\
\text{R} : & \quad \text{A}, (\text{CH}_2)_3; \text{B}, (\text{CH}_2)_4
\end{align*}
\]

3.12. Reactions with urea and thiourea
Reaction of bis-enaminone 42 with each of urea 141a and thiourea 141b in refluxing ethanol in the presence of piperidine afforded the substitution products 142a and 142b, respectively. The latter products underwent cyclization when heated in ethanolic sodium ethoxide solution and
gave \( N,N'-(1,4\text{-phenylene})-\text{bis-(2-oxo-6-phenyl-1,2-dihydropyrimidine-5-carboxamide)} \) 143a and its thioxoisomer 143b, respectively.\(^{27}\)

![Diagrams](image-url)

**3.13. Reactions with nitrogen electrophiles**

**3.13.1. Reactions with aromatic diazonium salts.** Coupling of each of bis-enaminones 15a-c with diazotized aniline in ethanol in the presence of sodium acetate gave the corresponding coupling products 144a-c.\(^{33}\) Although the latter compounds can exist in the \( E- \) and/or \( Z- \)forms, their \(^1\)H NMR spectra revealed that they exist only in the form \( Z-3 \) (Figure 1) as such spectra reveal, in each case, two singlet signals in the regions \( \delta \) 10.35-10.37 and 12.79-12.88 due to the resonances of the -CHO and hydrazone NH protons, respectively.\(^{33}\)

Condensation of the product 144a with hydrazine hydrate yielded a single product that was identified, on the basis of its spectral and elemental analyses, as 145 rather than 146. The assigned structure 145 was confirmed by comparison of 145 with an authentic sample of 146, prepared by alternate unambiguous synthesis as depicted below.\(^{33}\) Thus, reaction of 3,6-dimethylpyrazolo[3,4-d]pyridazine 147 with dimethylformamide dimethylacetal yielded the bis-enamine 148. Coupling of the latter with benzenediazonium chloride afforded 146 which proved completely different from 145.\(^{33}\)
3.13.2. Reactions with heterocyclic diazonium salts. Coupling of 15a with diazotized 3-amino-1,2,4-triazole in ethanol in the presence of sodium acetate afforded a product that proved to be the respective 1-phenyl-5-methyl-3,4-bis[1,2,4-triazolo[3,4-c][1,2,4]triazin-6-yl]carbonyl]pyrazole 149a. Structure assignment of the latter was based on its spectral and elemental analysis data.33
The formation of 149 was suggested the initially formed azo coupling product A undergoes either in situ cyclization via elimination of dimethylamine to give 149 or hydrolysis to give the bis-aldehyde derivative B which in turn undergoes dehydrative cyclization to give 149. All attempts to isolate the intermediate B failed. This was considered to indicate that former route involving direct in situ cyclization of the intermediate A is the predominant route.\textsuperscript{33}

Condensation of the diketone 149 with hydrazine hydrate yielded 3,6-\emph{bis}([1,2,4]triazolo[3,4-\textit{c}][1,2,4]triazin-3-yl)-1-phenyl-7-methyl-pyrazolo-[3,4-\textit{d}]-pyridazine 150.\textsuperscript{33}

Heating of compound 150 in ethanol in the presence of sodium hydroxide, yielded the thermodynamically more stable [1,2,4]triazolo[5,1-\textit{c}][1,2,4]triazine derivative 151 via Dimroth type rearrangement through tandem ring opening and ring closure reactions.\textsuperscript{33}
3.14. Cyclization

Treatment of the acyclic bis-enaminones 44a–c with polyphosphoric acid, PPA (P₂O₅ + H₃PO₄) at 165 °C for 36 h resulted in their cyclization and the formation of the corresponding angular new series of bis-trifluoromethyl-substituted 1,7-phenanthrolines (152a–c) in 32–40% yields and 7-aminoquinolines (153b–c) in 38–40% yields.³⁴

Also, when an equimolar mixture of (Z,Z)-N,N′-bis(3-oxo-4,4,4-trifluorobut-1-en-1-yl)-1,3-phenylenediamine (44a) and p-toluidine was heated at 165 °C for 36 h in the presence of PPA, a
mixture of 2,8-bis(trifluoromethyl)-1,7-phenanthroline (154) (25%), 6-methyl-2-(trifluoromethyl)quinoline 155 (65%), and of p-toluidine (11%) was obtained.28

\[
\begin{align*}
\text{44} & \quad \text{H}_3\text{C} \quad \text{N} \quad \text{CF}_3 \\
\text{155} & \quad \text{H}_3\text{C} \quad + \quad \text{CF}_3 \\
\text{154} & \quad \text{i} \quad \text{= PPA / 165}^\circ \text{C / 36 h}
\end{align*}
\]

Treatment of the bis(enaminne) 35 with primary amines was reported to afford the N-substituted dimethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates 156 which upon treatment with arylhydrazine resulted in the formation of methyl 3-oxo-3,5-dihydro-2H-pyrazolo[4,3-c]pyridine-7-carboxylates 157.24

References


**Authors' Biographies**

![Prof. Ahmad Sami Shawali](image)

**Prof. Ahmad Sami Shawali** is presently Emeritus Professor of Physical Organic Chemistry, Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt. He graduated with B.Sc. from the University of Cairo 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, Massachusetts, USA. He was awarded the degree of Doctor of Science (D.Sc.) from the university of Cairo after recommendation from a British committee from the Royal Chemical Society in 1995. Prof. Shawali has been the recipient of the state award 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 appointed Vice-Dean for student affairs in 1989 and he was elected Dean of the Faculty of Science in 1991. He was visiting professor at the university of Texas at El Paso, Texas, USA from 1979 to 1980, University of Kuwait from 1973 to 1977 and King Abdulaziz University, Jeddah, Saudi Arabia from 1982 to 1988. He has published 236 scientific papers including 13 review articles, all in international journals. At present there are more than 1900 citations of his work from 1970 until 2010 (i.e about 50 citations / year or 8 citations / paper). He supervised till now 45 M.Sc. and 17 Ph.D. graduate theses. He was invited to present plenary lectures at 29 conferences. His research interests are in the fields of reaction mechanisms, applications of LFERs, chemistry of hydrazonoic acid derivatives, 1,3-dipolar cycloadditions and 1,5-electrocyclizations.