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

Contents

1. Introduction

The term enaminones **1** usually refers to the compounds that contain the conjugate system N-C=C-C=O. Sometimes they are referred to as ß-aminovinyl ketones, ß-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^o), secondary (2^o) and tertiary (3^o) 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 ß-carbons into α-substituted, ß-substituted and α,ß-disubstituted enaminones **A-D**, respectively (Chart 2).

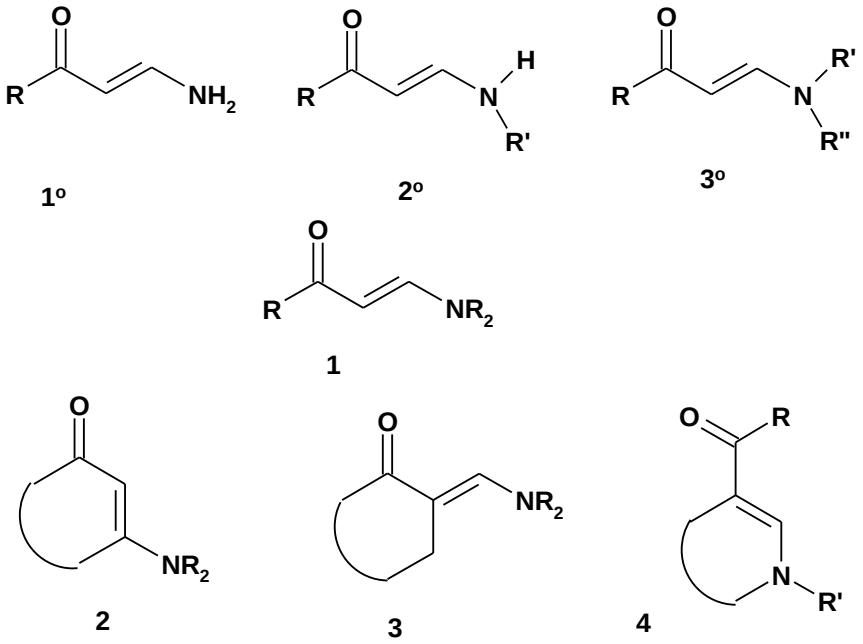


Chart 1

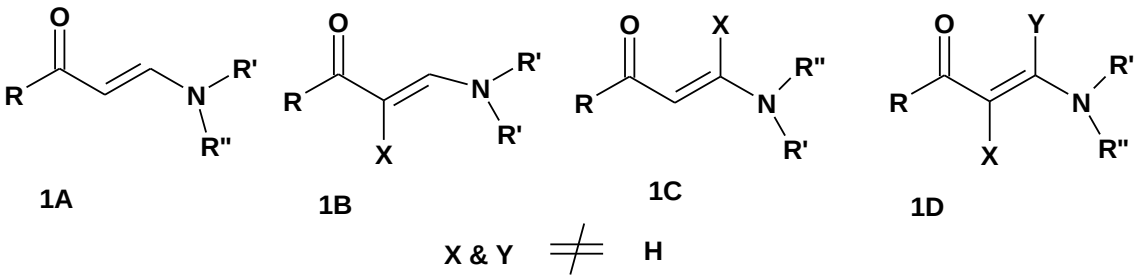
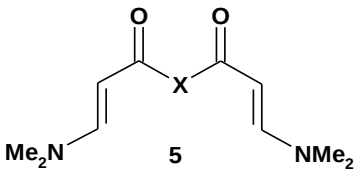


Chart 2

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.[1] Although the chemistry of mono-enaminones **1-4** has been the subject of several reviews,[2-10] 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.



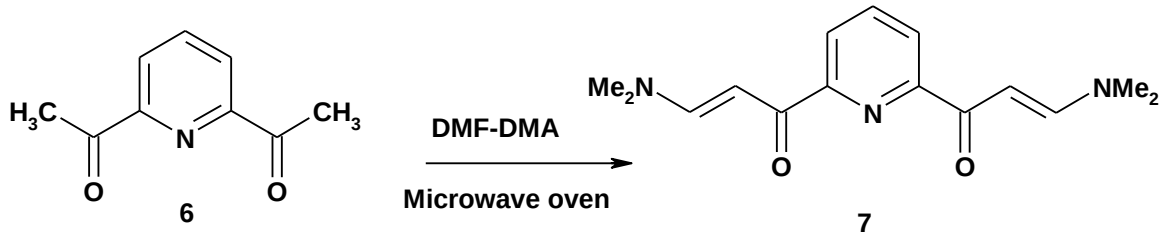
5

X = alkyl, aryl, Het

2. Synthesis

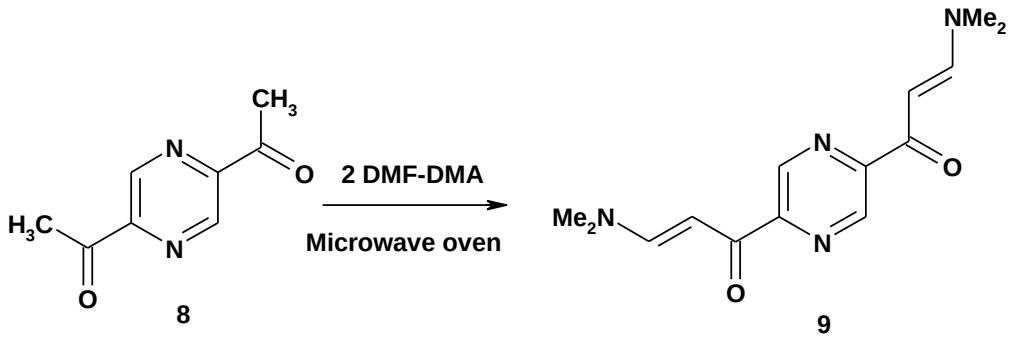
2.1. Condensation of diacetyl compounds with DMF-DMA

Heating a mixture of 2,6-diacetylpyridine **6** with two mole equivalents of dimethylformamide dimethylacetal in a microwave oven[11] or by refluxing the mixture in xylene1[12-14] afforded 2,6-*bis*[(3-dimethylamino)acryloyl]pyridine **7** .



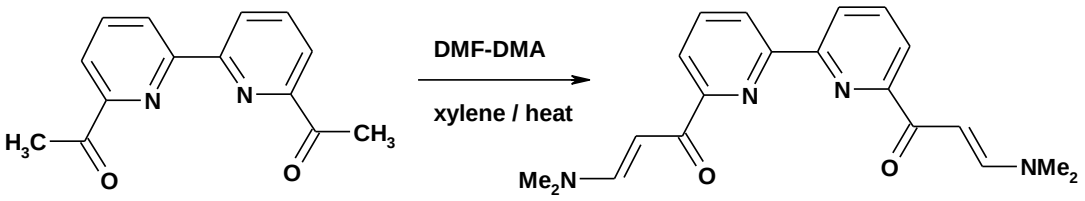
6 7

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**.[15]



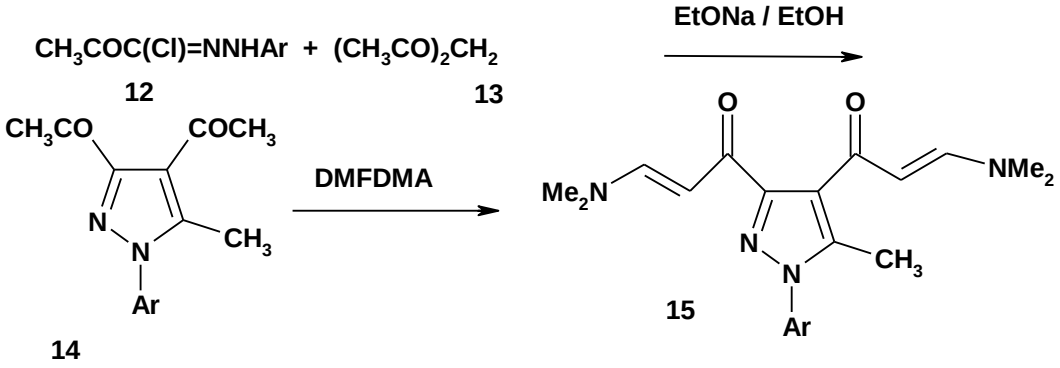
8 9

Also, the *bis*(enaminone) **11** was obtained by refluxing a solution of 6,6'-diacetyl-2,2'-bipyridine **10** in dimethylformamide dimethylacetal in xylene under nitrogen.[16]

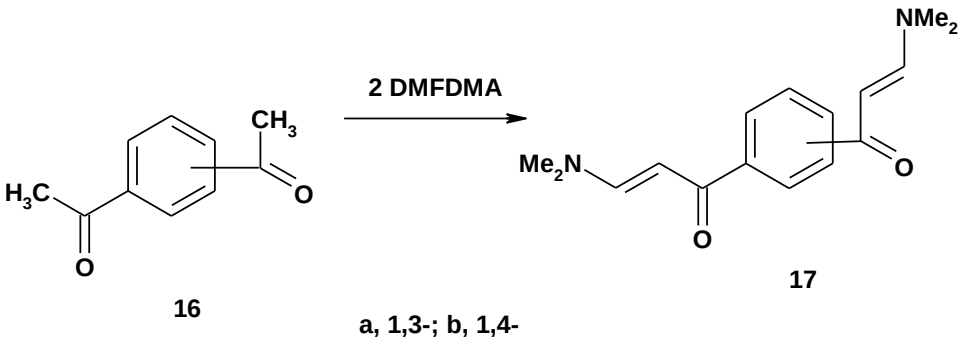


10 11

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.[17] 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.[17]

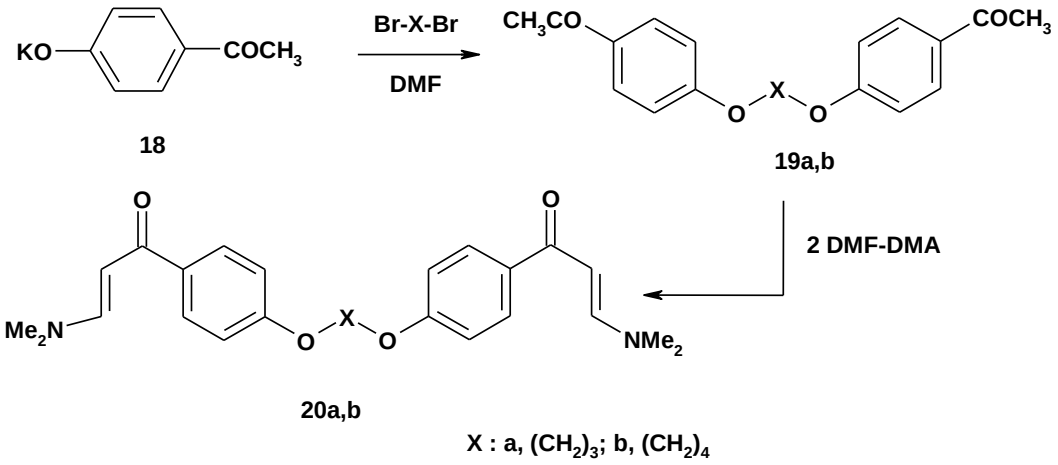


Condensation of 1,3- and 1,4-diacetylbenzenes **16a,b** each with two mole equivalents of DMF-DMA in dry toluene was also reported to afford the *bis*(enaminones) **17**.[11,18] When this reaction was repeated in a pressure tube for a few minutes in a microwave oven at 360W, it gave also the respective *bis*(enaminones) **17**.[11]

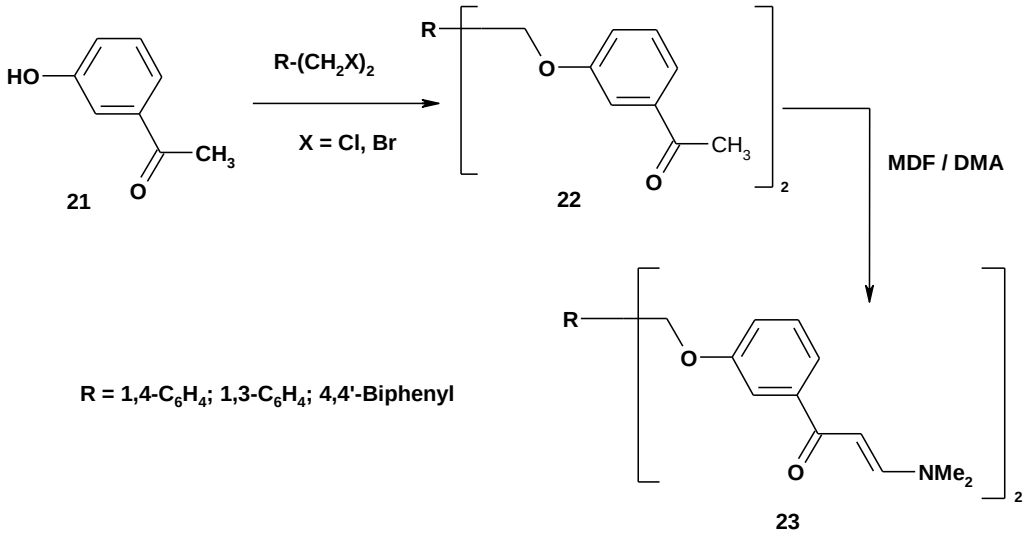


Reaction of potassium salt **18**, obtained upon treatment of 4-hydroxyacetophenone with ethanolic potassium hydroxide, with the appropriate dibromoalkanes in boiling DMF afforded

the corresponding α,ω-*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]

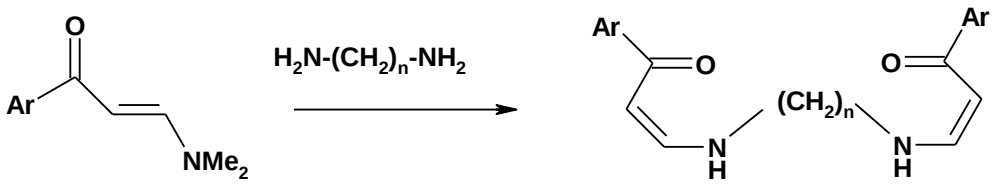


In addition, a series of *bis*(enaminones) **23** was prepared as depicted below by initial reaction of 3-hydroxyacetophene **21** with the appropriate *bis*(halomethyl) linking unit followed by condensation of the resulting diacetyl derivative **22** with DMF-DMA.[20]



2.2. Reaction of mono-enaminones with diamines

The reaction of the monoenamines **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]

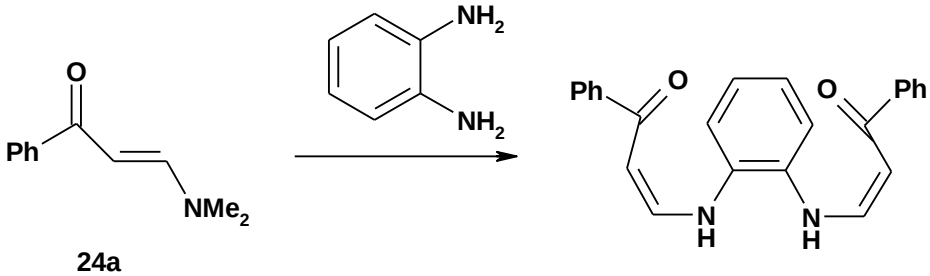


24(25) 26(27)

Ar: a, Ph; b, 4-MePh; c, 4-ClPh; d, 4-MeOPh

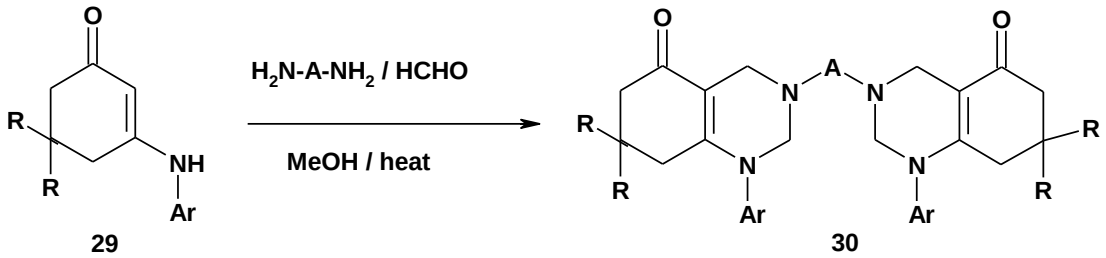
24(26), n = 2; 25(27), n = 4

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.[21]



24a 28

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.[22]



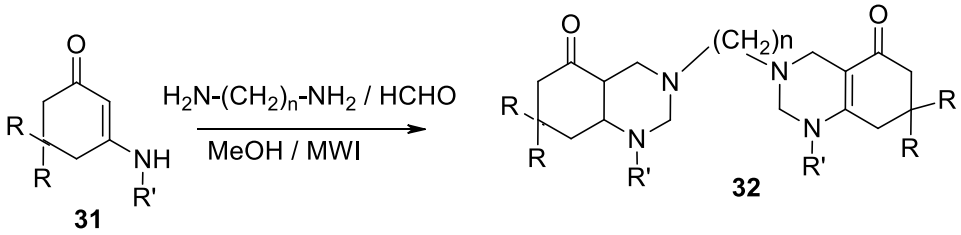
29 30

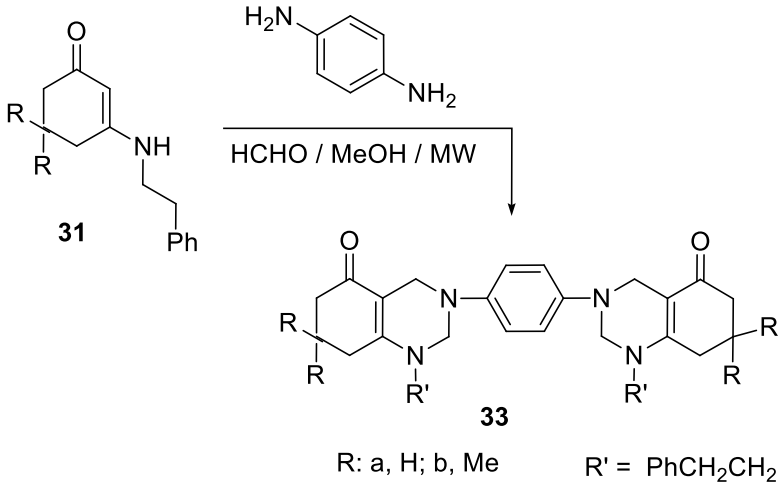
R = H, Me

A = -(CH2)n-; n = 2, 3,4; C6H4

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.[23] The reaction was found to be general with other diamines to give the respective

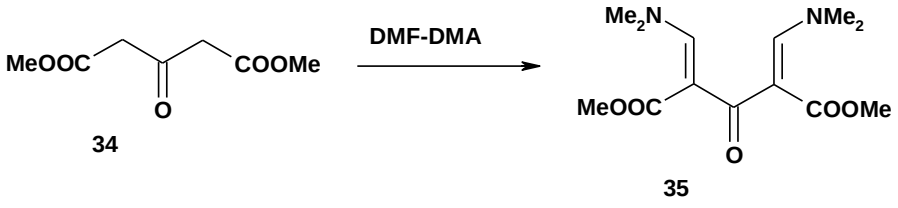
product **32** in 51-68% overall yields. Use of 1,4-phenylenediamine *in lieu* of aliphatic diamines, the reaction yielded the corresponding *bis*(naminones **33.**[23]



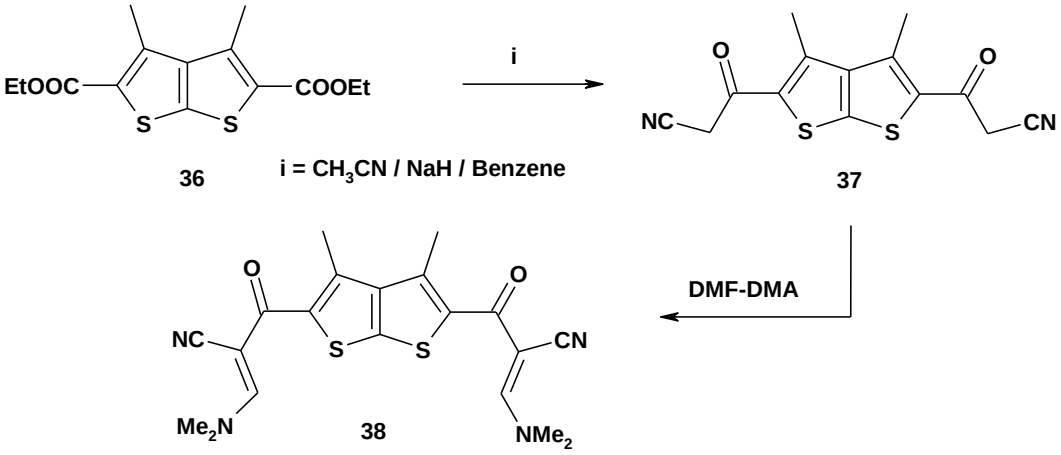


2.3. Reactions bis-acetive methylene compounds with DMF-DMA

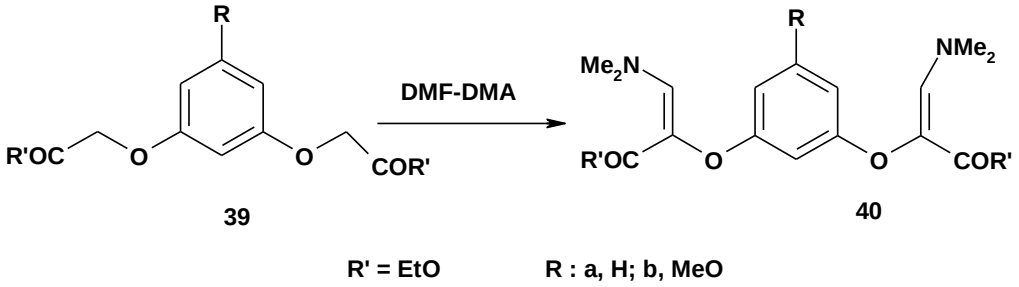
The *bis*(enaminone) **35** was prepared by reaction of dimethyl acetonedicarboxylate **34** with DMF-DMA.[24]



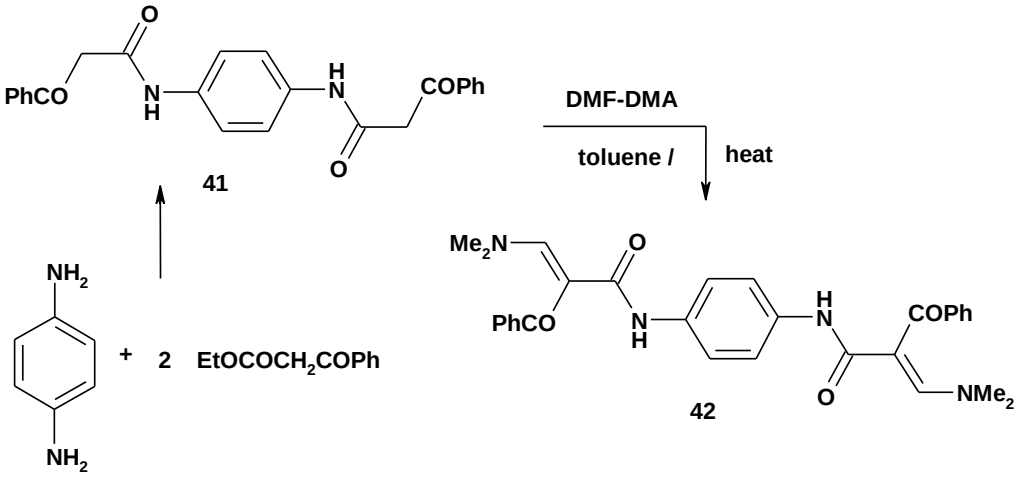
Treatment of 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate **36** with acetonitrile in the presence of sodium hydride in refluxing benzene afforded 3-[3,4-dimethyl-5-(3-nitrilopropanoyl)thieno[2,3-*b*]thiophen-2-yl]-3-oxopeopanonitrile **37**. Treatment of the latter with DMF-DMA in refluxing xylene yielded the *bis*(enaminone) **38**.[25]



Similarly, the *bis*(enaminones) **40** were readily obtained by reacting **39** with excess DMF-DMA.[26]

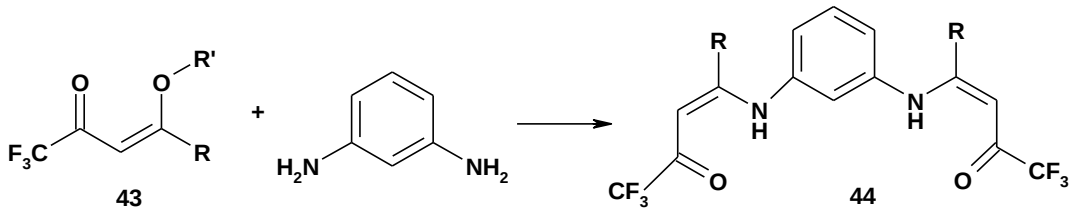


N,*N'*-(1,4-Phenylene)-*bis*(3-oxo-3-phenylpropanamide) **41**, prepared from condensation of *p*-phenylenediamine with ethyl benzoylacetate, was reported to react with DMF-DMA in refluxing toluene to afford the *bis*-enaminone namely *N*,*N'*-(1,4-pheneylene)-*bis*[2-benzoyl-3-dimethylamino-acrylamide] **42**.[27]



2.4. Miscellaneous methods

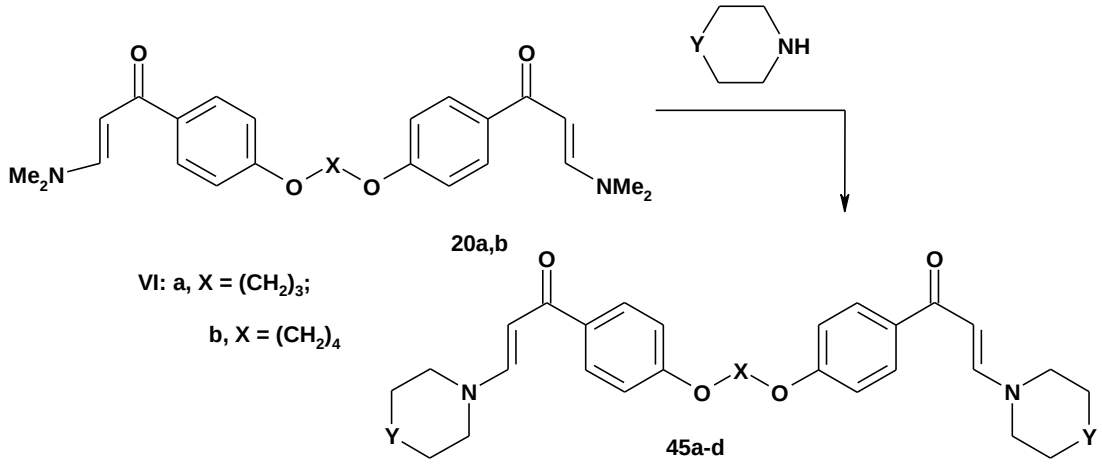
Recently, a new series of ten *bis*-enaminones **44** was isolated in satisfactory yields of 47-91%, by the reaction of enones **43** with 1,3-phenylenediamine at a molar ratio of 2:1, respectively. The reactions were reported to be carried out in ethanol, water, water/dichloromethane (1:1) or water/chloroform (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]



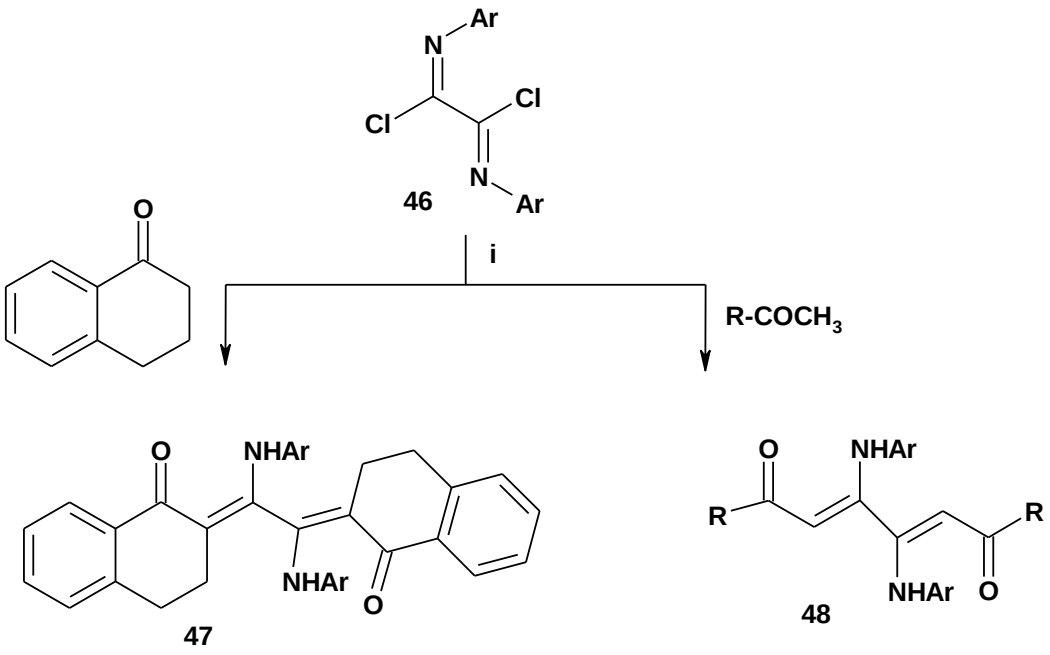
R : a, H; b, Me; c-i, 4-XC6H4 ; j, 2-furyl **R' = Me; Et**

X : c, H; d, Me; e, MeO; f, F; g, Cl; h, Br; i, NO2

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]

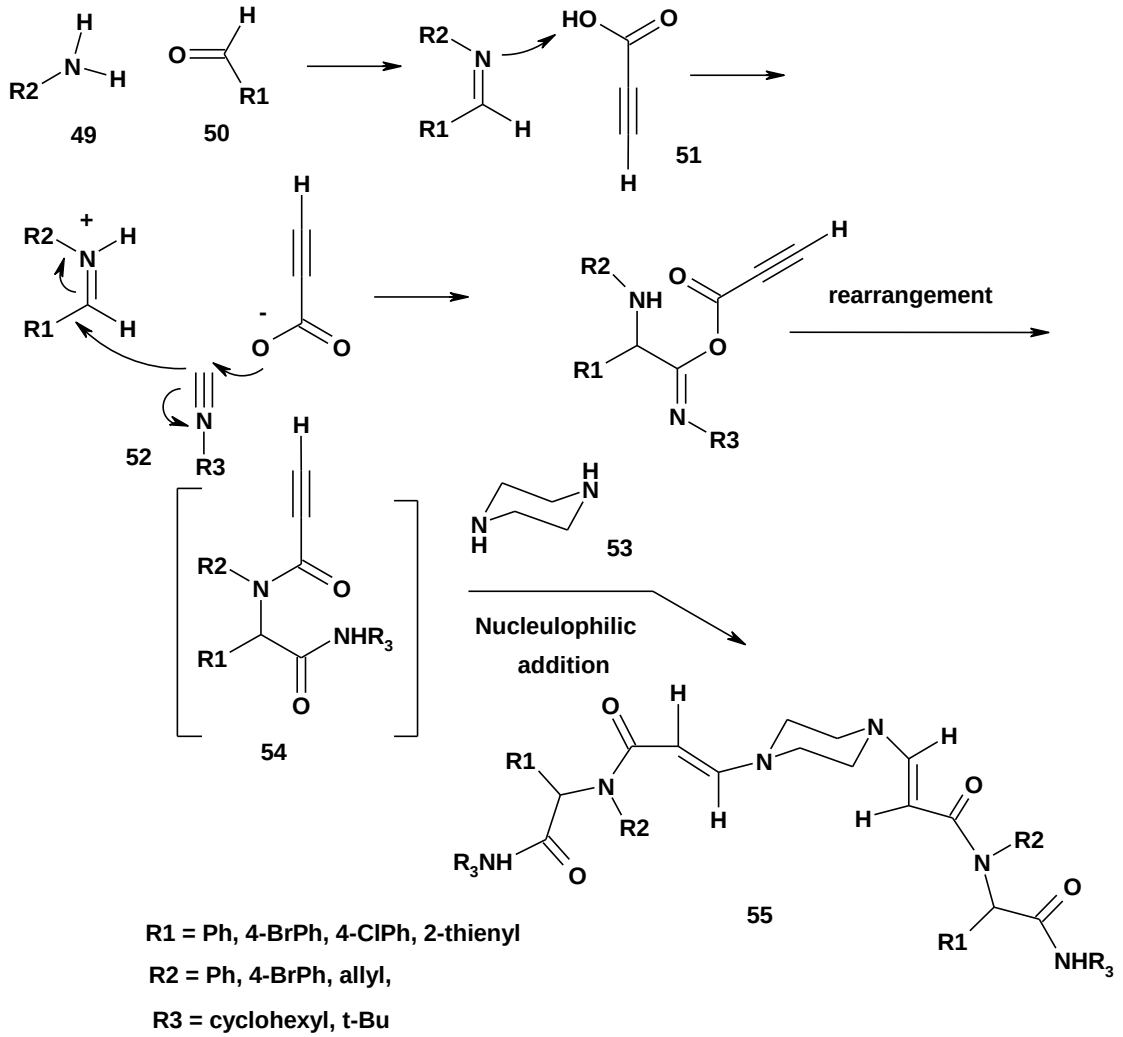


Buehrdel et al.[29] reported that reaction of the *bis*-imidoyl chloride **46** with each of tetrahydro-1-napthanone and methyl ketones in tetrahydrofuran in the presence of potassium t-butoxide at -70°C yielded the respective *bis*(enaminones) **47** and **48**.



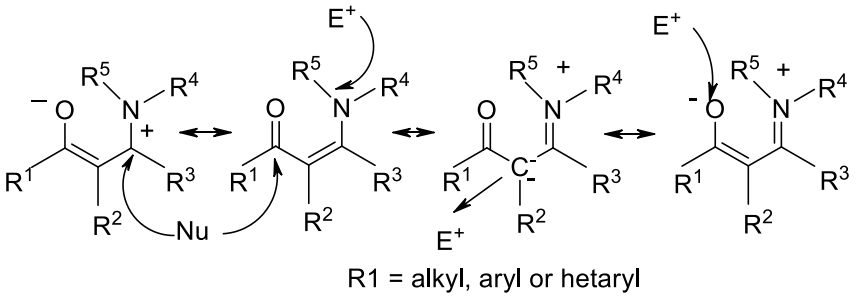
i = KOBu-t / THF / - 78°C

Recently, the polyfunctional *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.[30]



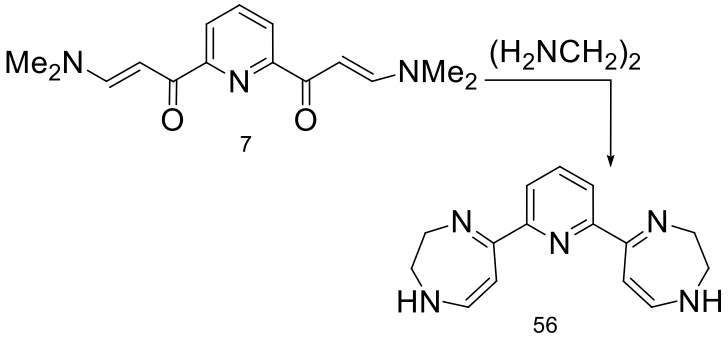
3. Chemical Reactions

The chemical reactivity of enaminones is in general attributed to the fact that they combine the ambident nucleophilicity of enamines and the amibident 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.

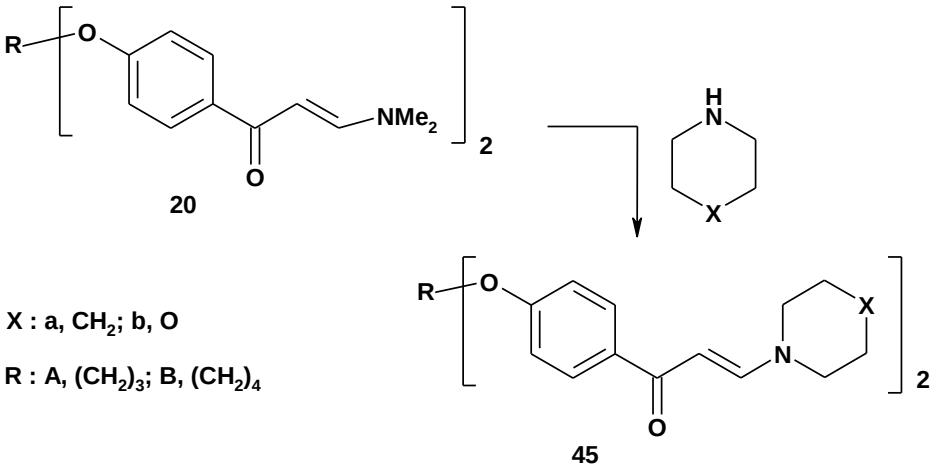


3.1. Reactions with amines

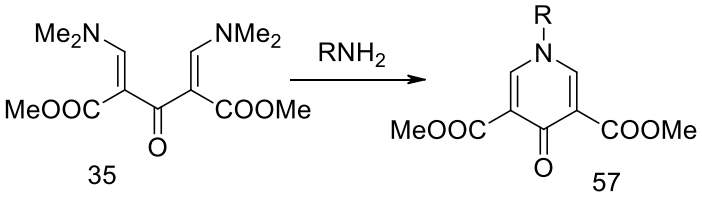
3.1.1. Reaction with 1,2-diaminoethane. Condensation of the *bis*-enaminone **7** with ethylenediamine in refluxing etanol yielded 2,6-*bis*[1,2,3-trihydro[1,4]diazepin-5-yl]pyridine **56**.[14]



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**.[19]

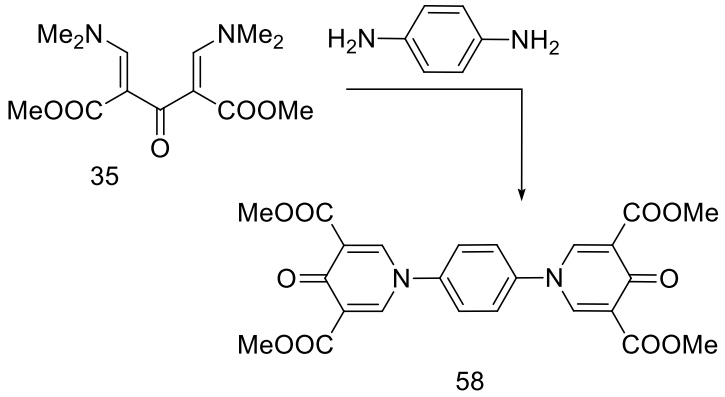


Recently, it was reported that treatment of the *bis*-enaminone **35** with primary amine in n-propanol at 95º yielded the respective dimethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylate **57**.[24]



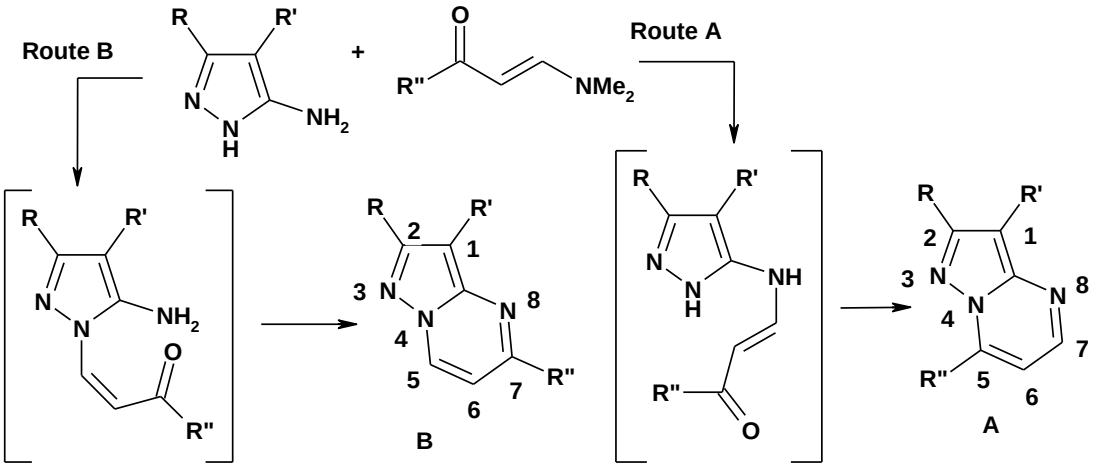
R = Pyrazinyl, pyridin-2-yl; 4-methylpyridin-2-yl; 5-methylpyridin-2-yl; 3-hydroxypyridin-2-yl; 5-chloropyridin-2-yl; 4-nitrophenyl; 4-fluorophenyl; 2-iodophenyl; 4-anisyl; 1,2-phenylene

Similar reaction of **35** with 1,4-diaminobenzene under the same reaction conditions afforded the respective 1,4-*bis*(4-oxo-3,5-dimethoxucarbonyl -1,4-dihydropyridin-1-yl)benzene **58**.[24]

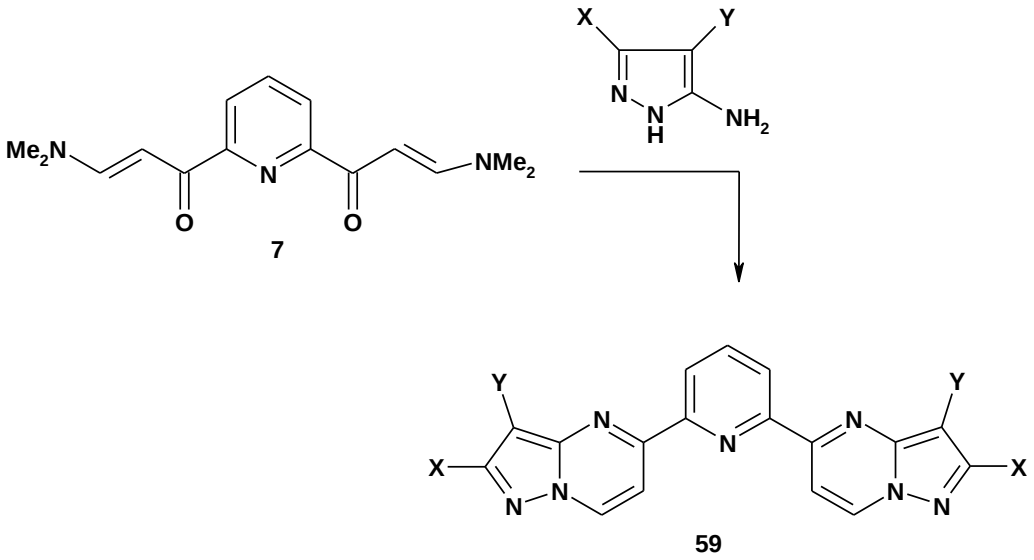


3.2. Reactions with heterocyclic amines

3.2.1. Reaction with 5-aminopyrazoles. Reaction of a given enaminone with 5-amino-1*H*-pyrazole can theoretically proceed through two possible routes to give 5-substitututed pyrazolo[1,5-*a*]pyrimidine **A** and/or 7-substitututed pyrazolo[1,5-*a*]pyrimidine **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-*a*]pyrimidine derivatives **A**.

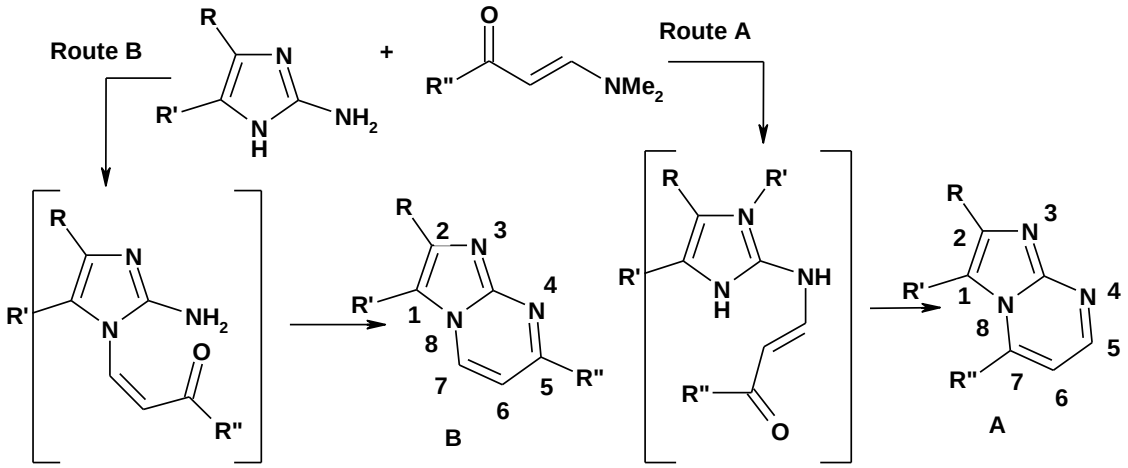


Thus, the *bis*-enaminone **7** was reported to condense site-selectively with 5-aminopyrazoles to yield the corresponding 2,6-*bis*(2-substituted-pyrazolo[1,5-*a*]pyrimidin-7-yl)pyridine derivatives **59**.[14]

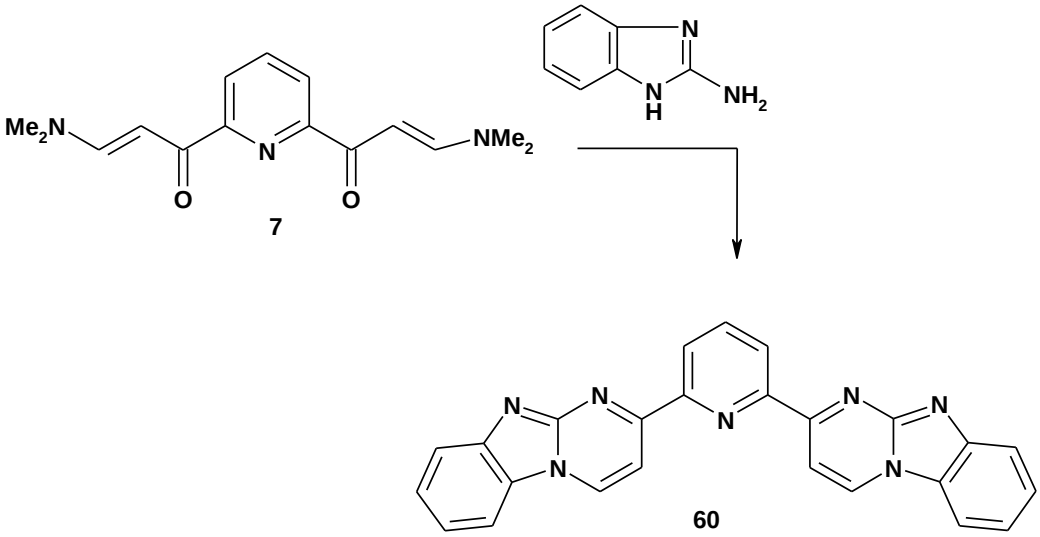


Y/X : a, H/Me; b, H/Ph; c, Ph/Me

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-1*H*-1,2,4-triazole. Reaction of 3-amino-1*H*-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-4*H*-1,2,4-triazole and 3-amino-2*H*-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.

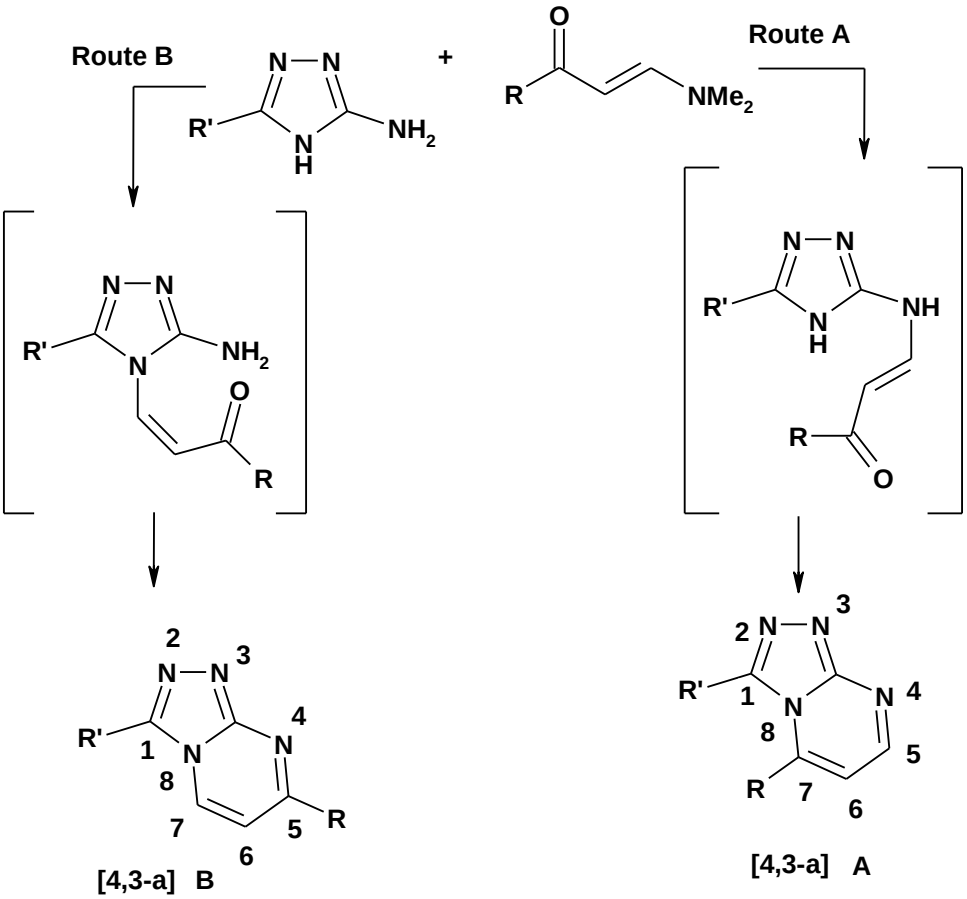


Chart 1

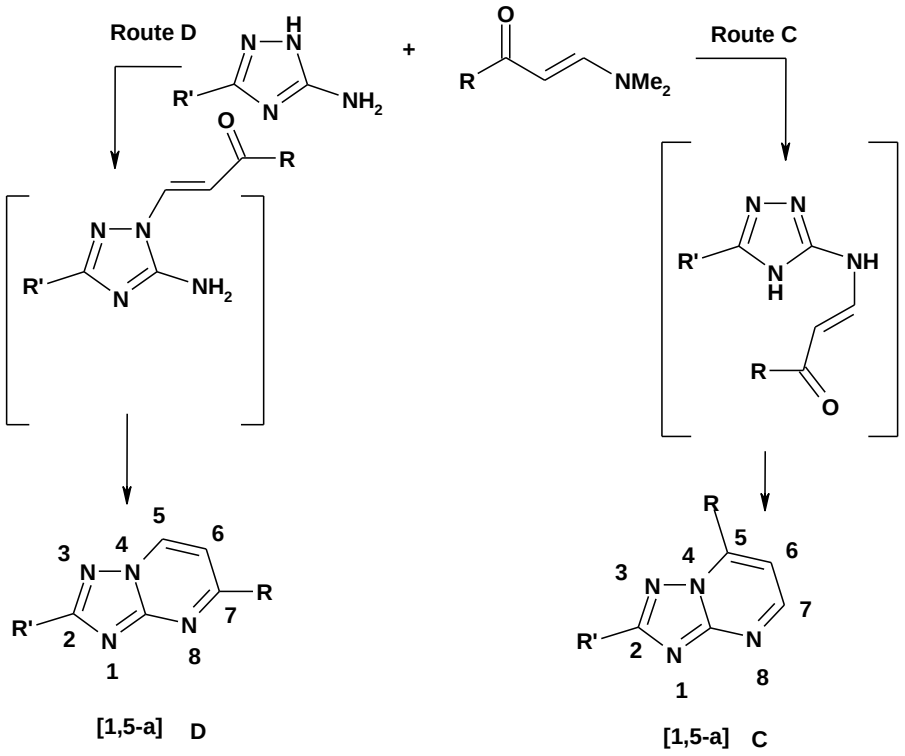
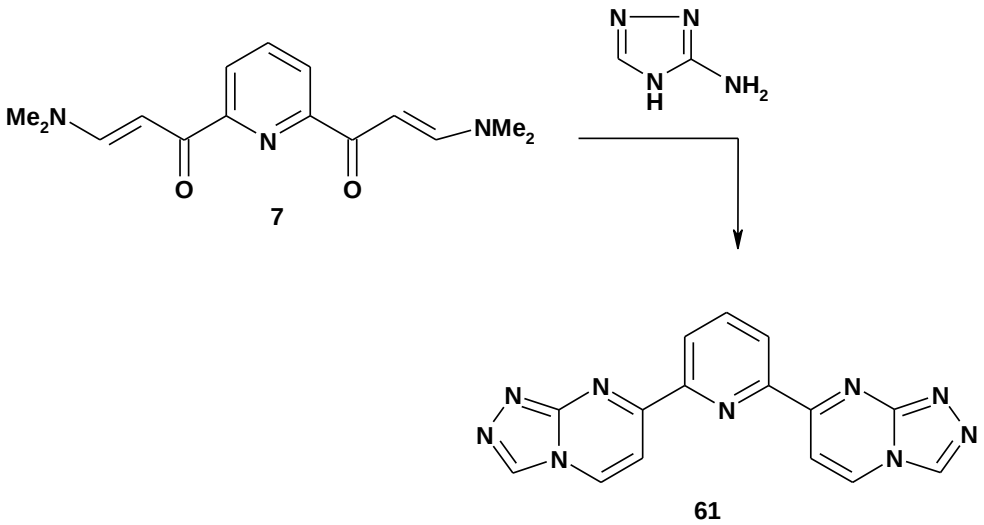


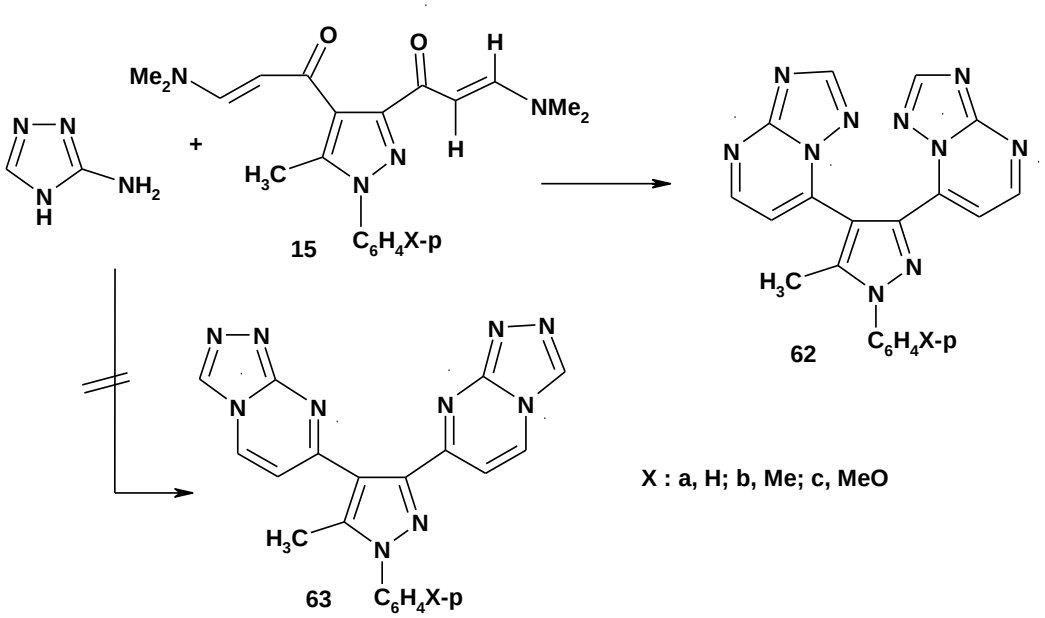
Chart 2

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-triazoloo[4,3-*a*]pyrimidin-7-yl)pyridine **61**.[14]



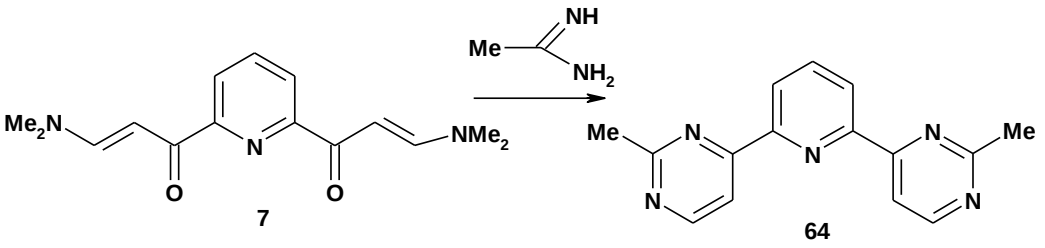
Also, Shawali et al.[35] reported that reaction of the *bis*-enaminones **15** with 3-amino-1,2,4-triazole is site selective although it can theoretically lead to either the 1,2,4-triazolo[1,5-

a]pyrimidine **62** and/or its [4,3-*a*] isomer **63**. For example, reaction of **15**a-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-*a*]pyrimidine-7-yl]pyrazole derivative **62** and not its 1,2,4-triazolo[4,3-*a*]pyrimidine isomers **63** on the basis of their ^{1}H NMR spectral data.[35]

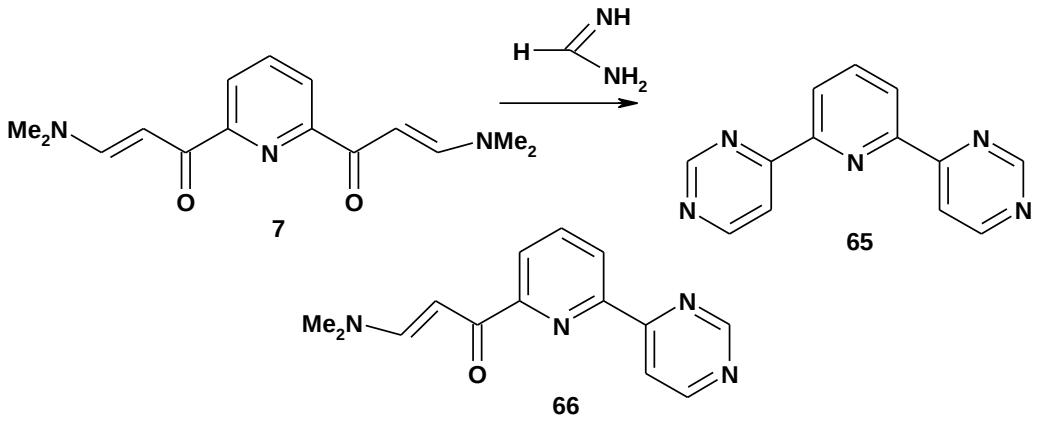


3.3. Reaction with amidines

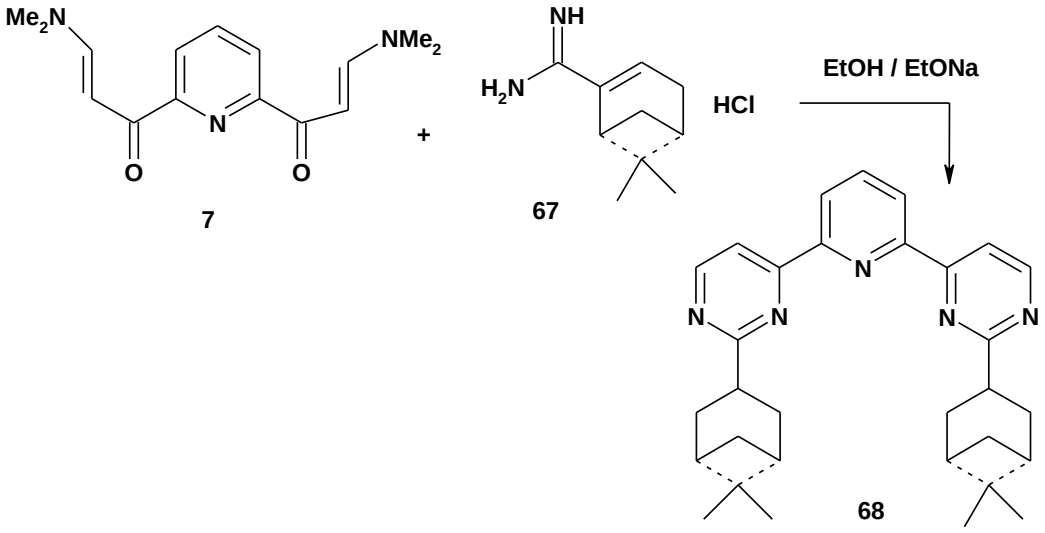
3.3.1. Reaction with acid amidines. Reaction of 2,6-*bis*(N,N'-dimethylamino)-1-oxoprop-2-en-1-yl]pyridine **7** with five equivalents of each of acetamidine hydrochloride and sodium ethoxide in hot ethanol resulted in the formation of 2,6-*bis*[2-methylpyrimidin-6-yl]pyridine **64** in 90% yield .[12]



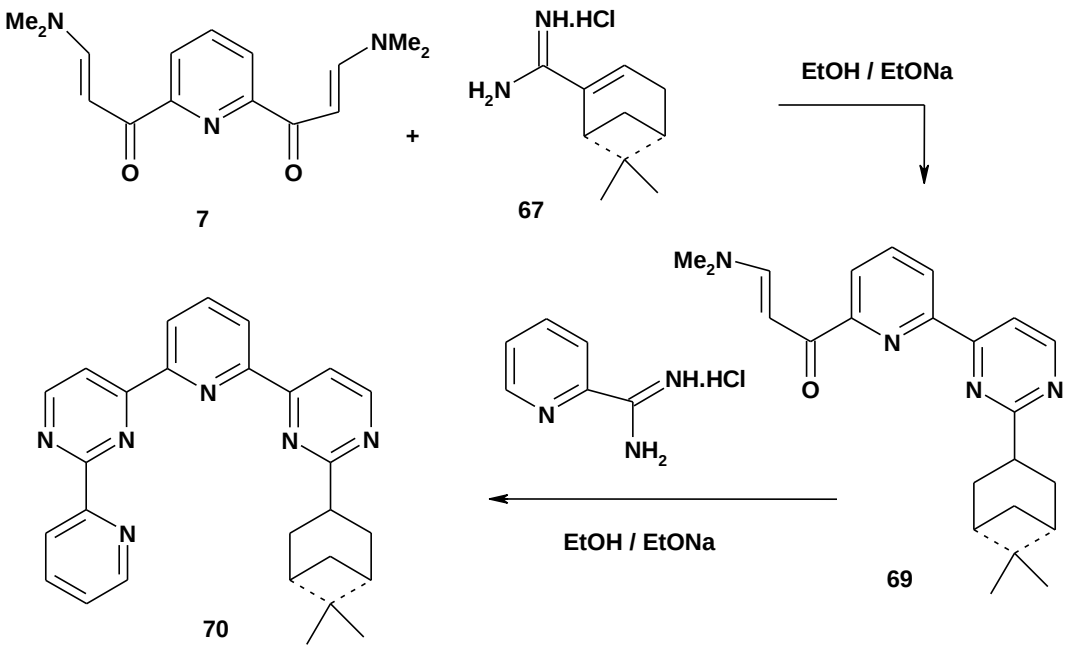
Similar reaction of **7** with five equivalents of formamidine acetate and five equivalents of sodium ethoxide in refluxing ethanol was reported to result in the formation of a mixture of **65** and **66** in 50% and 34%, respectively.[12]



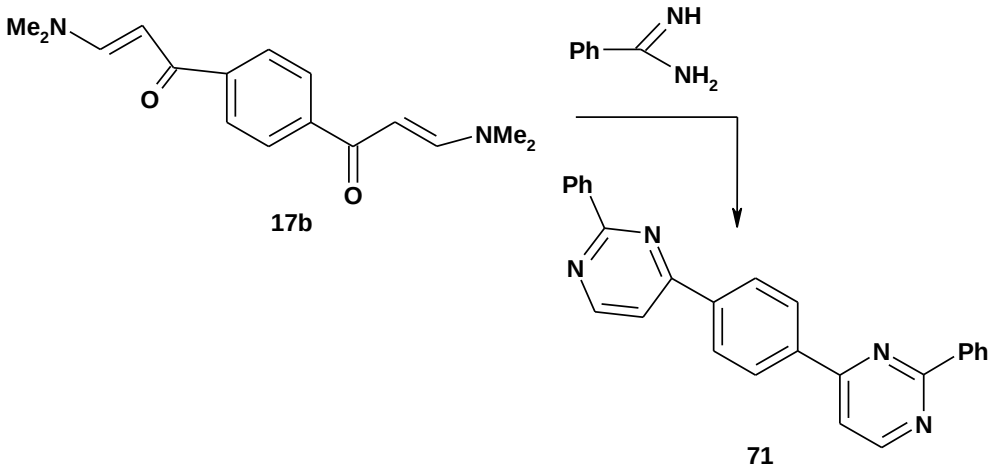
The *bis*-enaminone **7** reacted also with 2-pipenecarboxamidine hydrochloride **67** led to dipineno[2',2'']-2,6-*bis*(4',4''-pyrimidyl)pyridine **68** in 88% yield.[13]



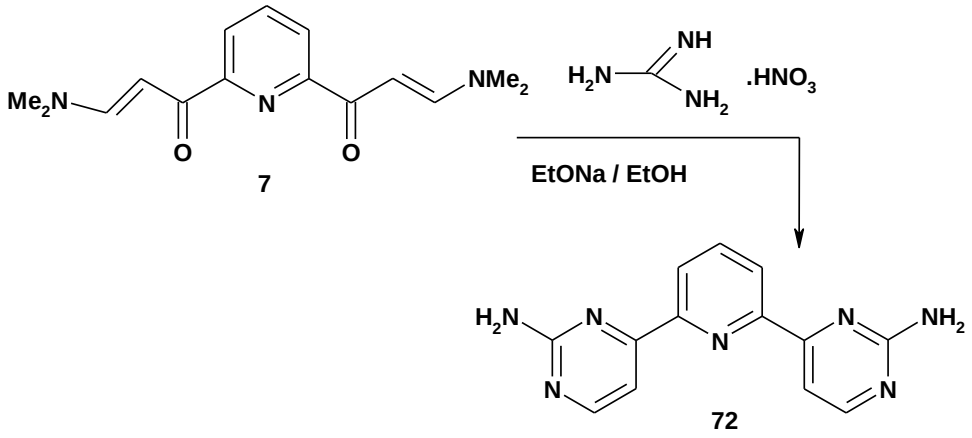
The condensation of **7** with the amidine **67** in 1:1 ratio gave **69** in 66% yield which is converted into **70** by condensation with pyridine-2-carboxamidine under standard conditions.[13]



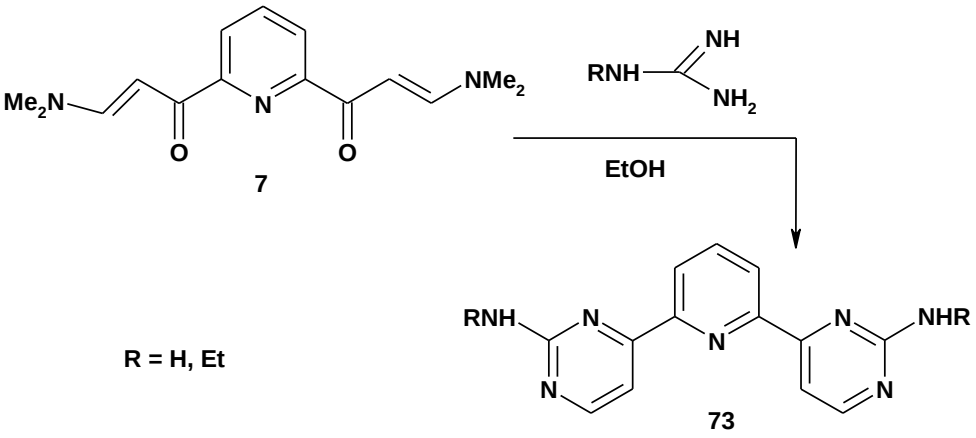
Very recently, it was reported that 1,4-*bis*(2-phenyl-4-pyrimidyl)benzene **71** was synthesized by reaction of benzamidine hydrochloride with the *bis*-enaminone **17b** in an ionic liquid [BMIM][BF4] in the presence of sodium hydroxide.[31]



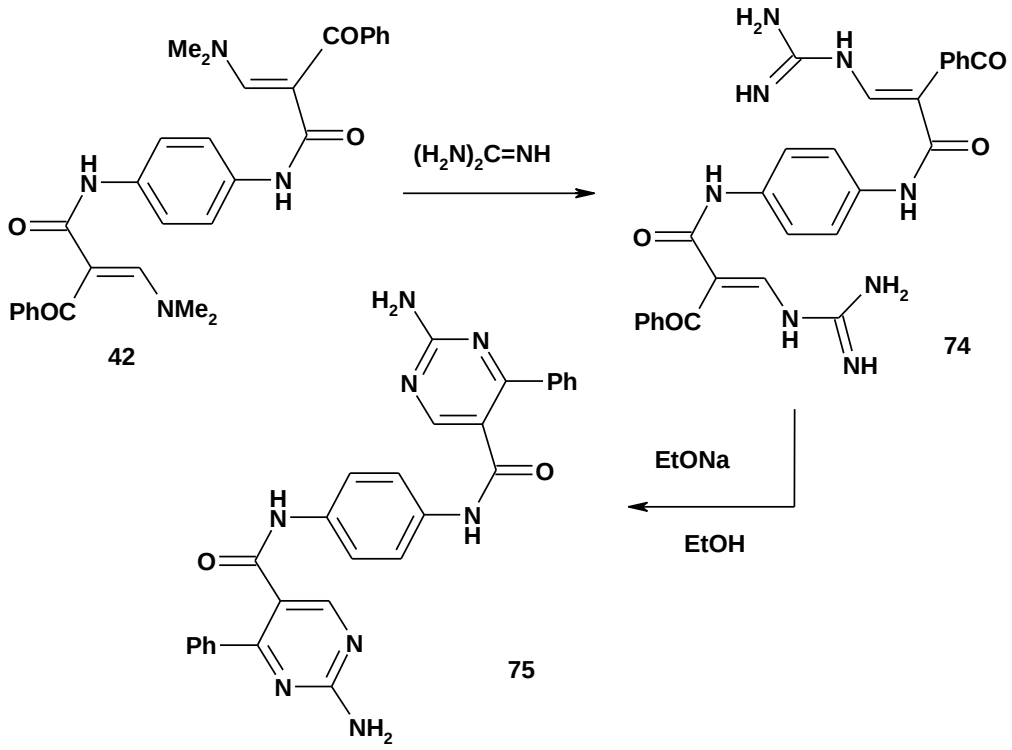
3.3.2. Reaction with guanidine. The *bis*-enaminone **7** was used to prepare the 2,6-*bis*(2-aminopyrimidyl)pyridine **72** in quantitative yield either by heating it with guanidine nitrate in refluxing ethanol in the presence of sodium ethoxide[12] or with guanidine hydrochloride and potassium carbonate in refluxing ethanol.[14]



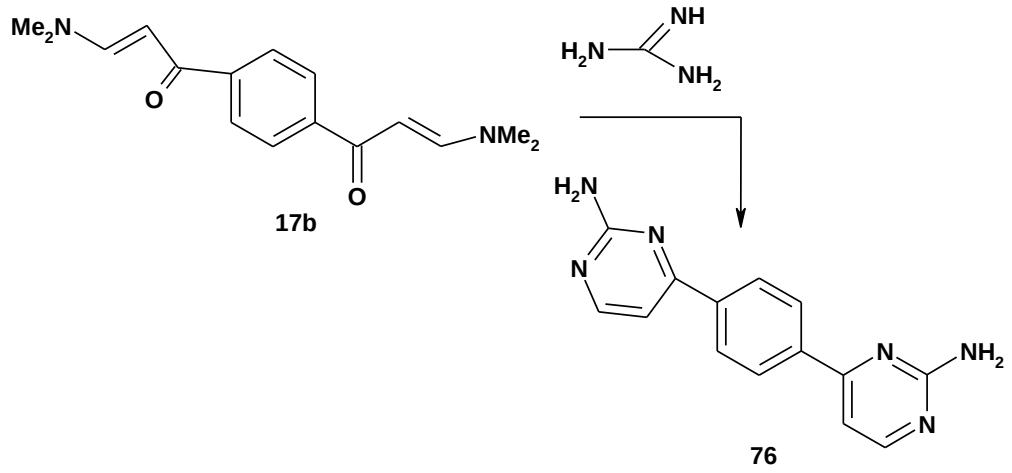
Similarly, 2,6-*bis*(2-aminopyrimidyl)pyridine **73** was produced quantitatively upon heating the *bis*-enaminone **7** with guanidine hydrochloride in refluxing ethanol in the presence of sodium ethoxide.[32]



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-phenylene)-*bis*-(2-imino-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) **75.**[27]

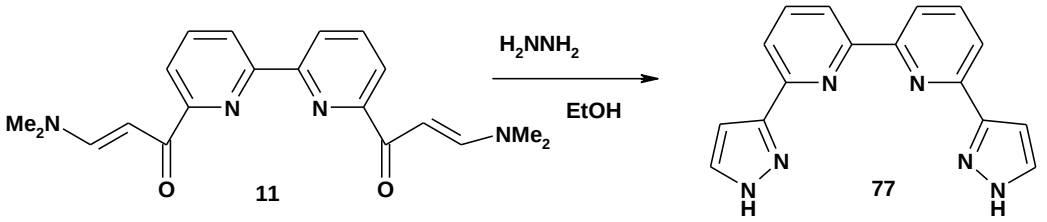


Recently, it was reported that 1,4-*bis*(2-aminopyrimidin-4-yl)benzene **76** was obtained by reaction of guanidine hydrochloride with the *bis*-enaminone **17b** in an ionic liquid [BMIM][BF4] in the presence of sodium hydroxide.[31]

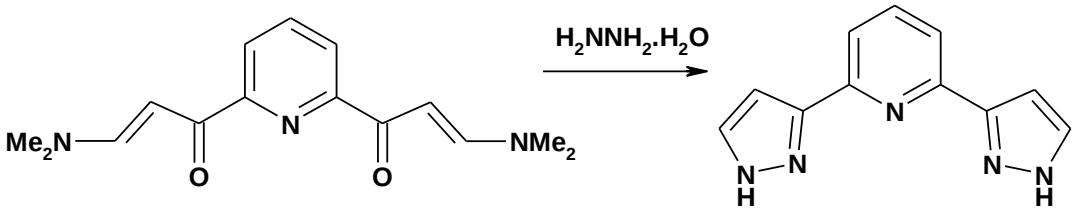


3.4. Reaction with hydrazines

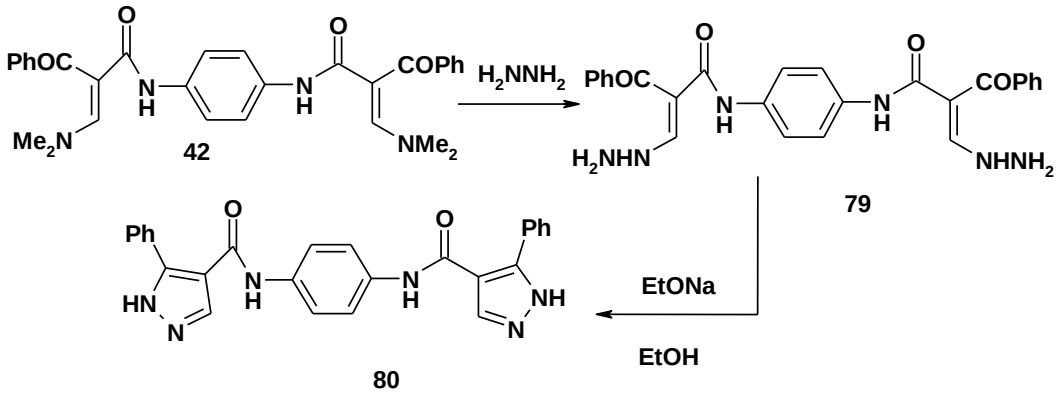
3.4.1. Reaction with hydrazine hydrate. When a mixture of the *bis*-enaminone **11** and hydrazine hydrate in ethanol was refluxed for 1 h, it gave 6,6'-*bis*(pyrazol-3-yl)-2,2'-bipyridine **77**.[16]



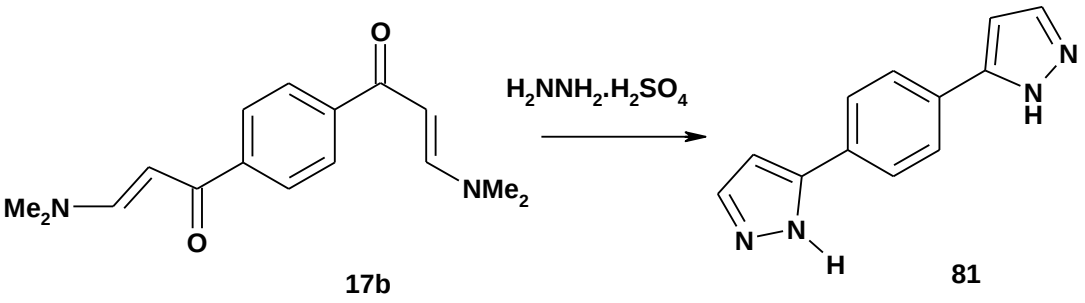
Similar reaction of the *bis*-enaminone **7** and hydrazine hydrate in refluxing ethanol gave 2,6-*bis*(pyrazol-3-yl)pyridine **78**.[11,14]



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]

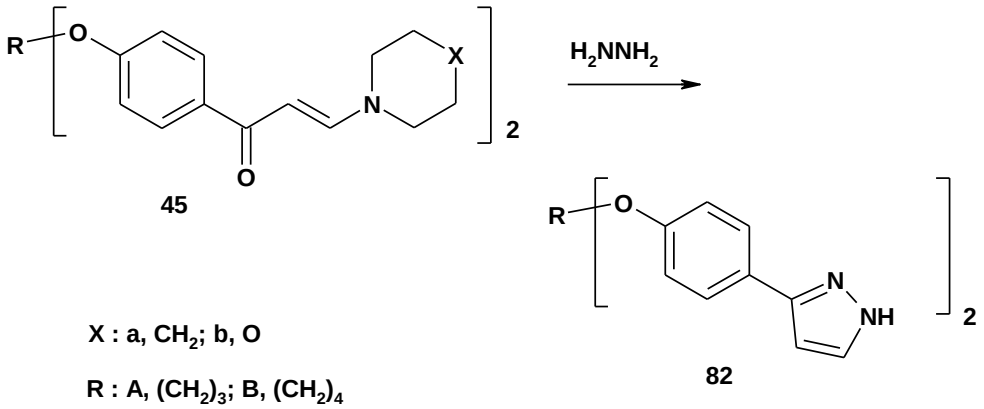


Also, the *bis*-enaminone **17b** reacted with hydrazine hydrate in ionic liquid ([BMIM][BF_4]) and gave 1,4-*bis*(pyrazol-5-yl)benzene **81**.[11,14]



17b **81**

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]



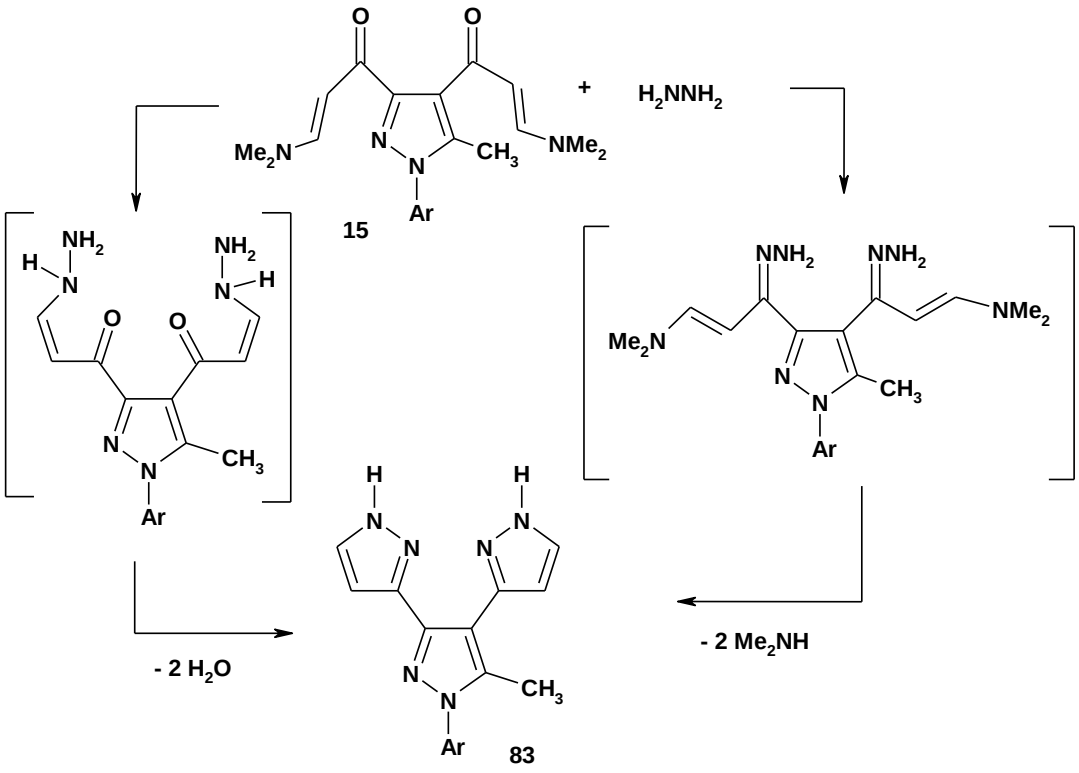
45

X : a, CH_2; b, O

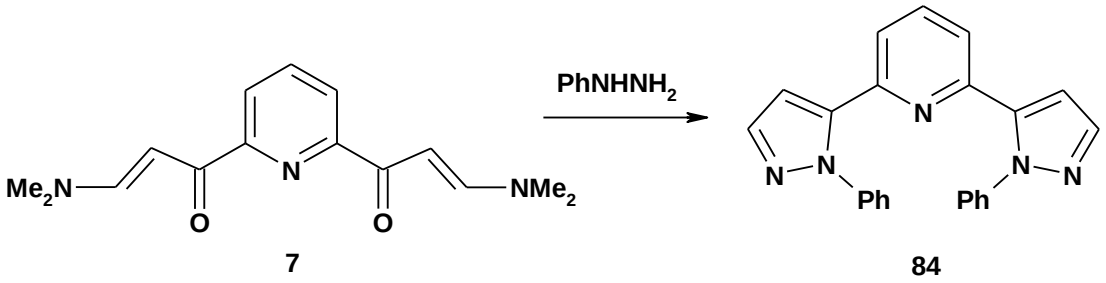
R : A, $(CH_2)_3$; B, $(CH_2)_4$

82

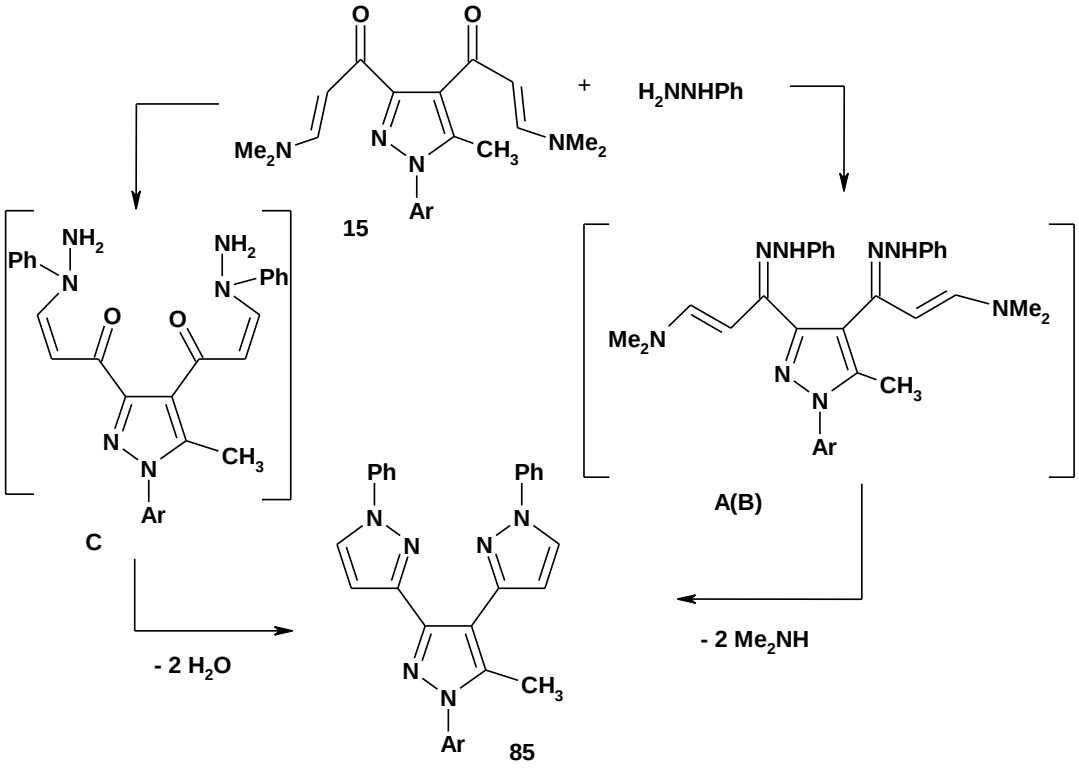
Recently, Shawali et al.[17] reported that reaction of each of the *bis*-enaminones **15** with hydrazine hydrate in refluxing ethanol afforded the respective 3,3':4,3"-terpyrazoles **83**.



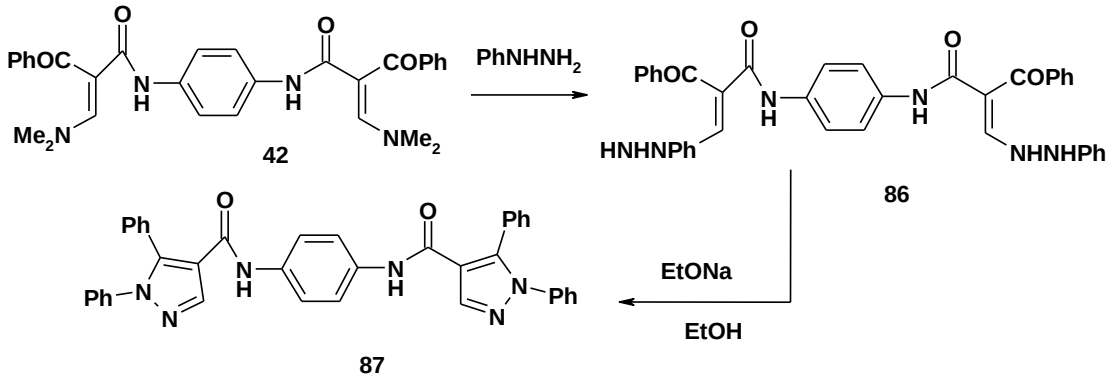
3.4.2. Reaction with substituted hydrazines. Reaction of the *bis*-enaminone **7** and phenylhydrazine in refluxing ethanol for 2h gave 2,6-*bis*(1-phenylpyrazol-5-yl)pyridine **84**.[14]



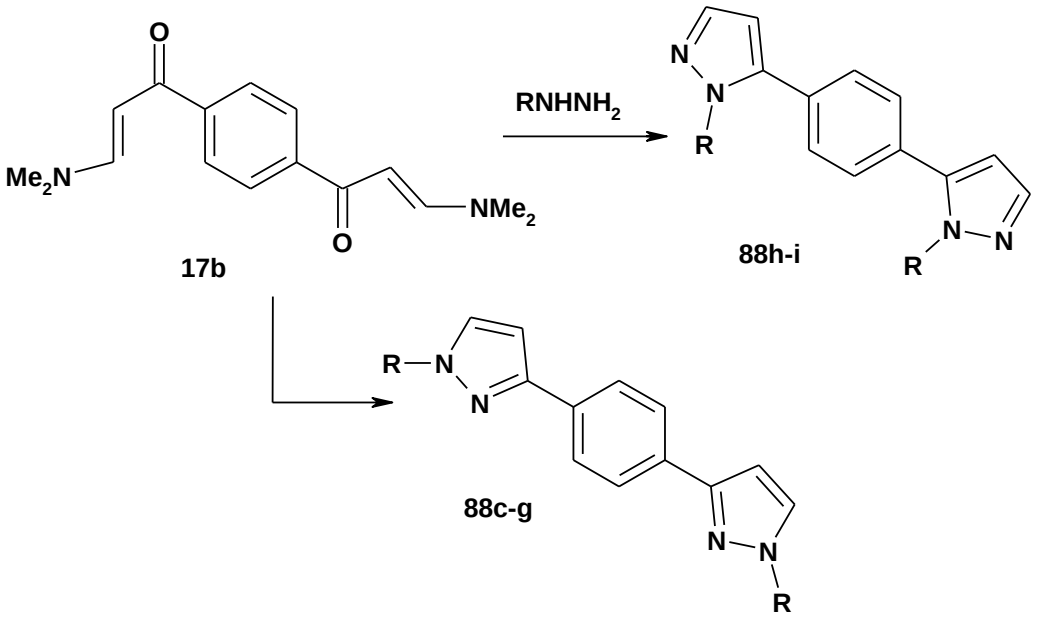
Reaction of the *bis*-enaminones **15** with phenylhydrazine in refluxing ethanol was reported to afford the respective 3,3':4,3''-terpyrazoles **85**.[35]



Similar reaction of *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)-*bis*-(1,5-diphenyl-pyrazole-4-carboxamide) **87**.[27]



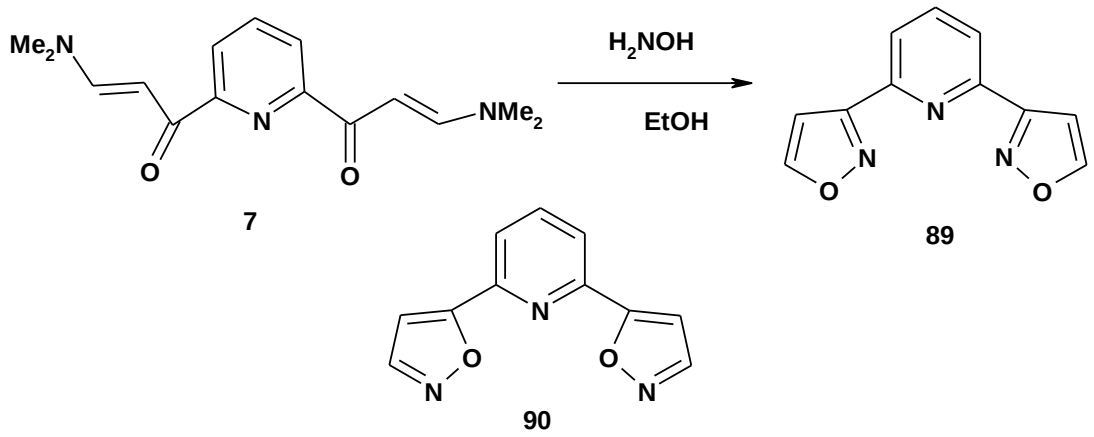
Cyclocondensation of *bis*-enaminone **17b** with various substituted hydrazines in ionic liquids in the presence of an acid catalyst was reported to give the respective 1,4-*bis*-[1-substituted-pyrazol-5-yl]benzenes **88** in good yields.[31] The site selectivity in this reaction was found to depend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



R: c, 4-$O_2NC_6H_4$; d, 2,4-$(O_2N)_2C_6H_3$; e, C_6F_5; f, MeOOC; g, H_2NCO; h, $HOCH_2CH_2$; i, t-Bu

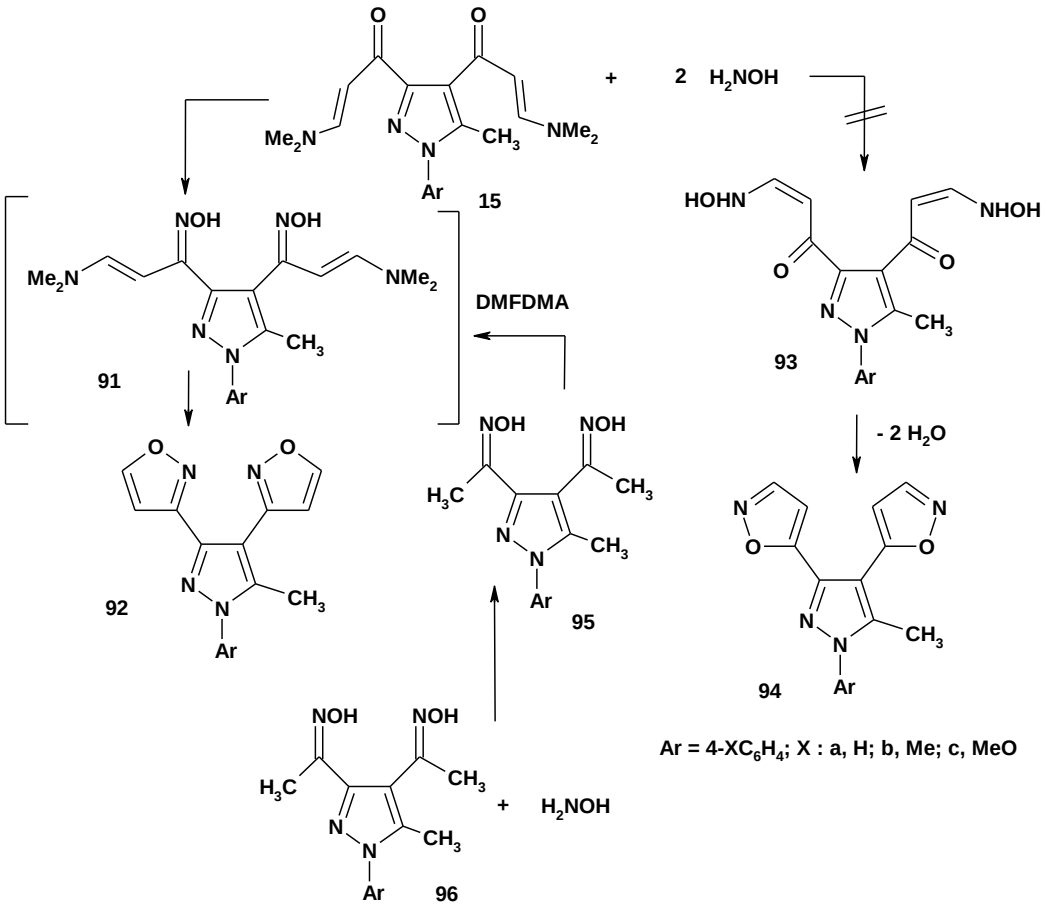
3.5. Reaction with hydroxylamine

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]

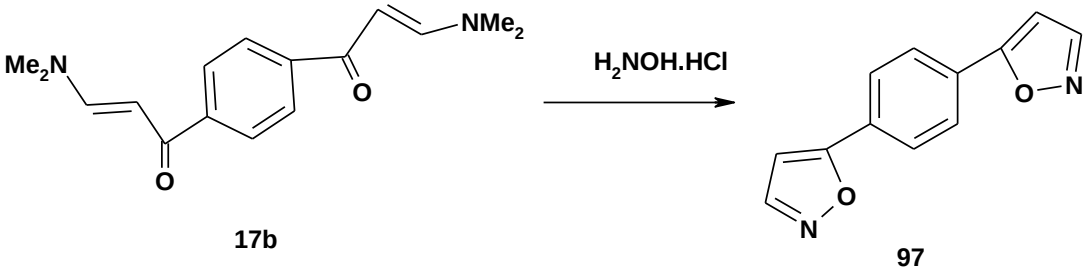


Similarly, when each of the *bis*-enaminones **15a-c** was refluxed with hydroxylamine hydrochloride in ethanol in the presence of ammonium acetate, it yielded, in each case, a single product identified as the respective 3,4-*bis*(isoxazol-3-yl)pyrazole **92** rather than its *bis*(isoxazol-5-yl)pyrazole **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.

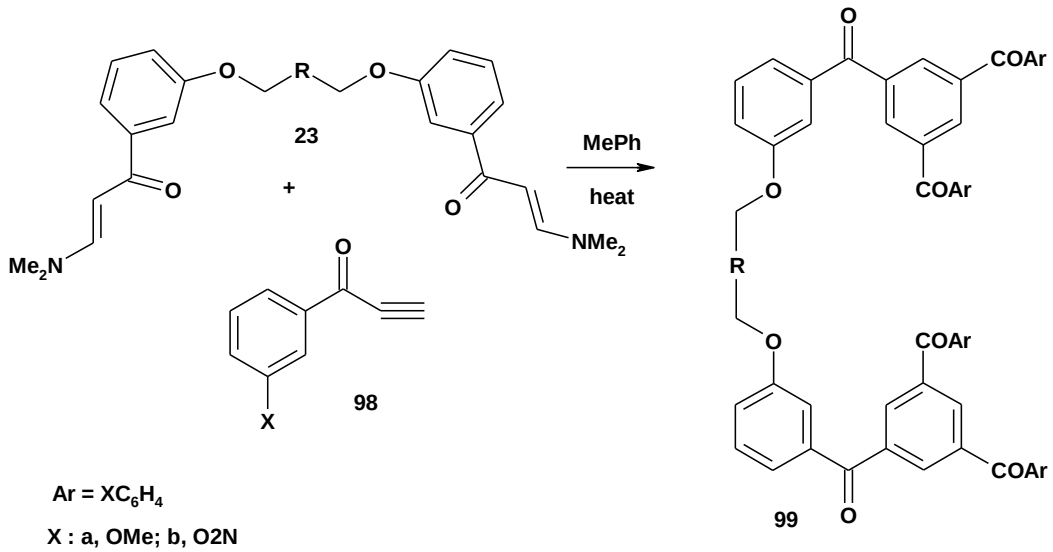


Recently, reaction of the *bis*-enaminone **17b** with hydroxylamine hydrochloride in an ionic liquid was reported to give 1,4-*bis*(5-isoxazolyl)benzene **97**.[31]



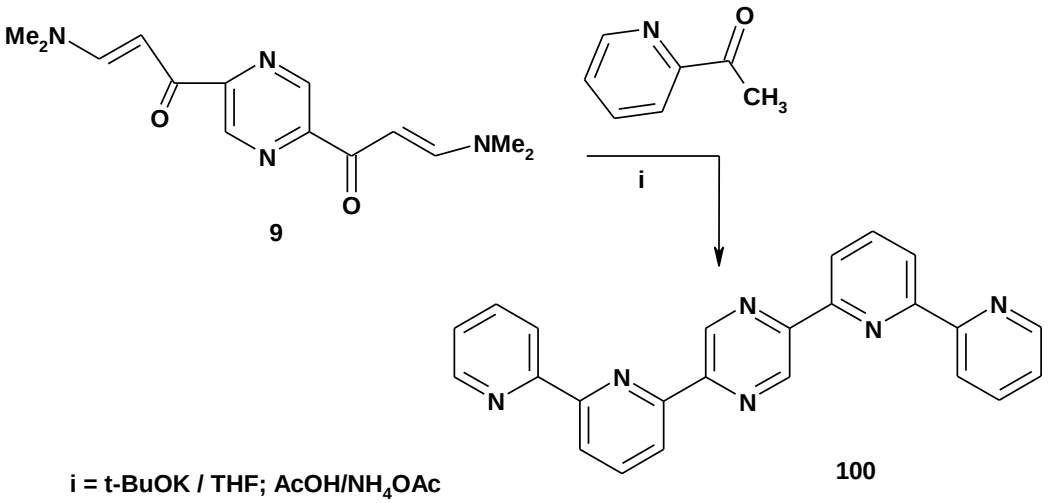
3.6. Reaction with acetylenic ketones

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]



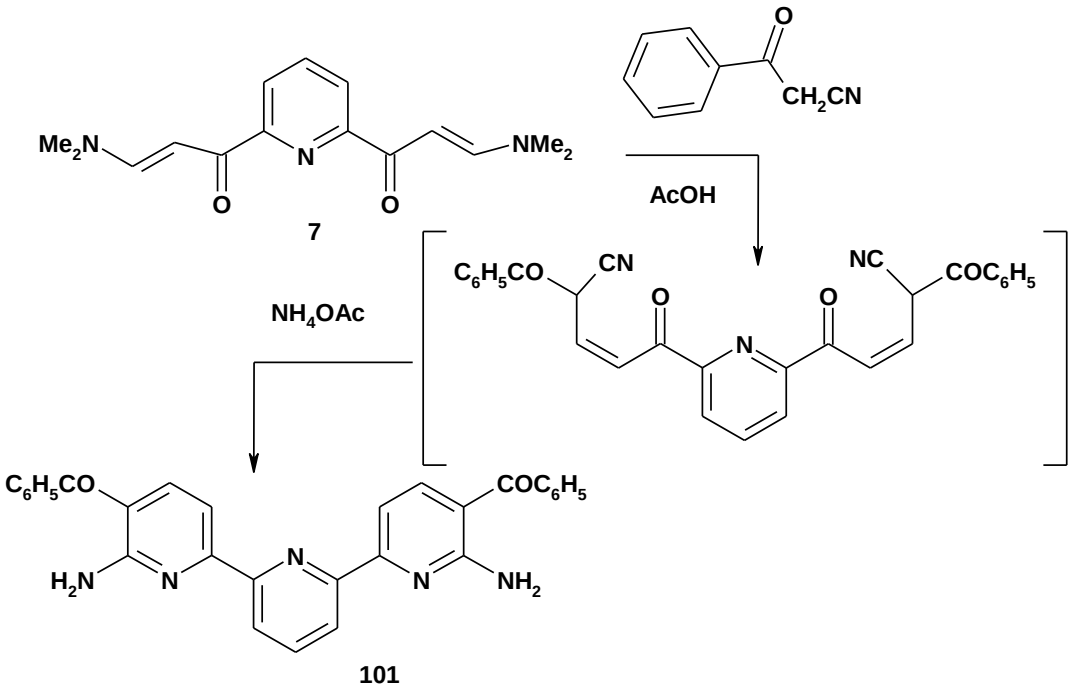
3.7. Reaction with methyl ketones

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]

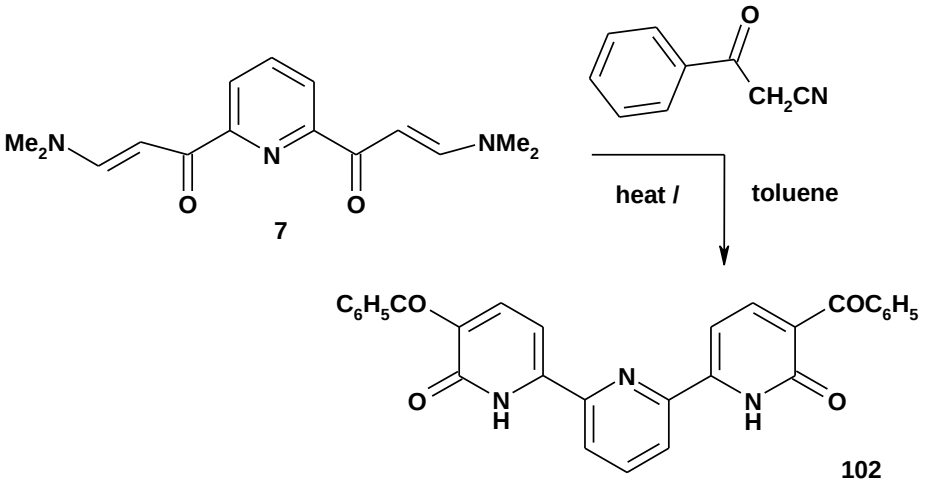


3.8. Reaction with active cyanomethylene compounds

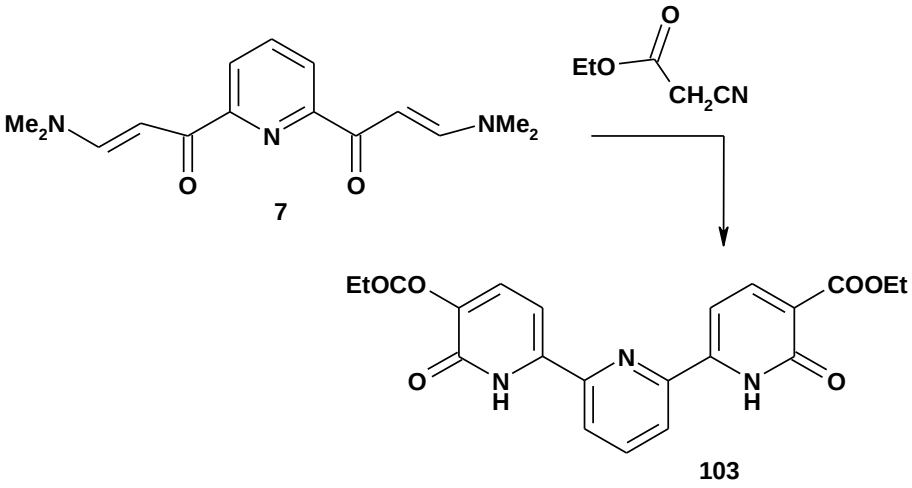
3.8.1. Reaction with benzoylacetonitrile. When a mixture of the *bis*-enaminone **7** and benzoylacetonitrile was refluxed in acetic acid in the presence of ammonium acetate, it yielded 6,6"-diamino-5,5"-dibenzoyl-2,2':6',2"-terpyridine **101** in 60% yield.[14]



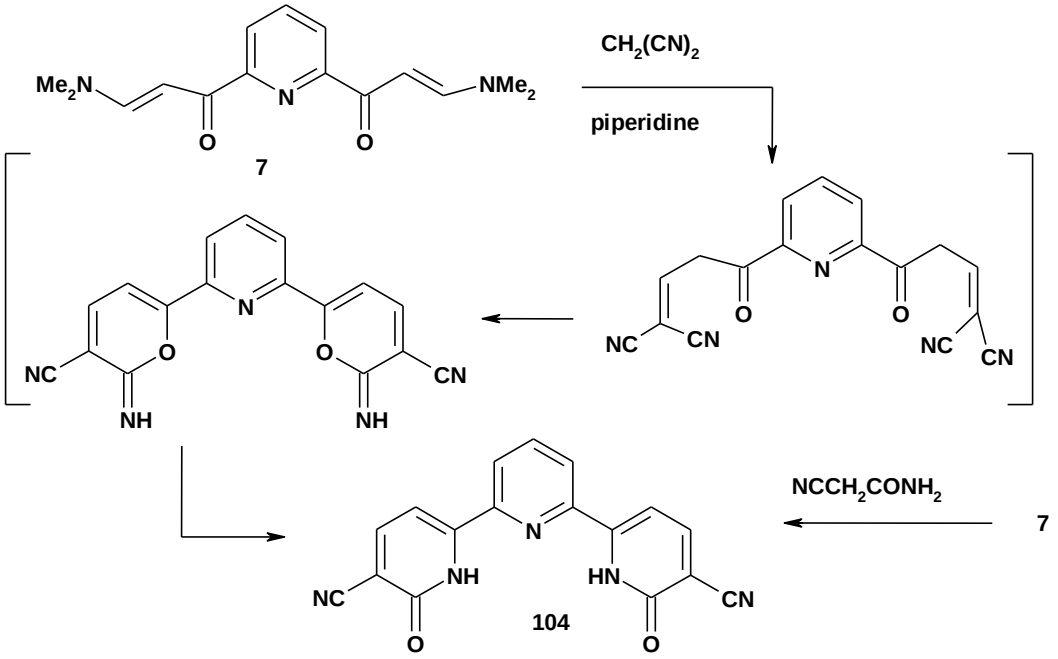
However, in another report it was indicated that such a reaction of the *bis*-enaminone **7** with benzoylacetonitrile, when carried out in refluxing toluene, it yielded 5,5"-dibenzoyl-1,1"-dihydro-2,2':6',2"-terpyridine-6,6"-dione **102** in 40% yield.[14]



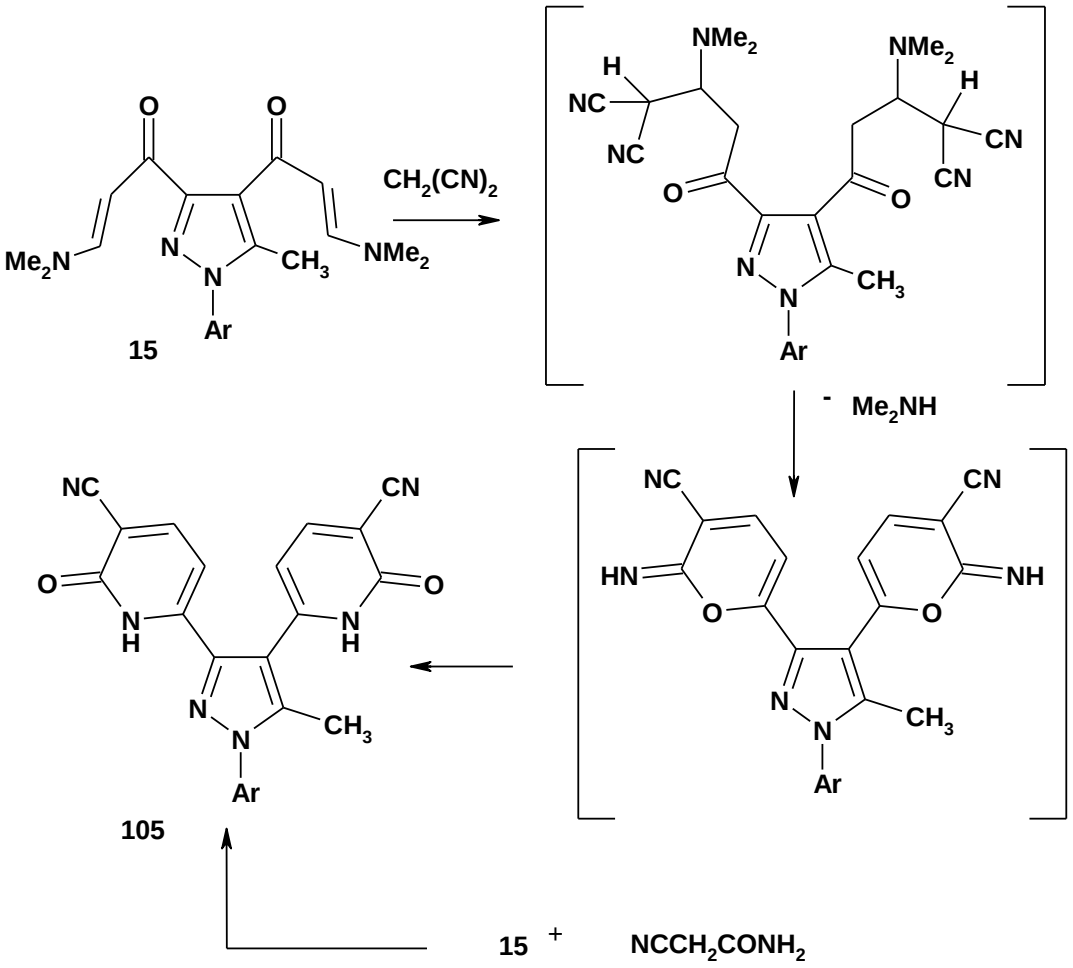
3.8.2. Reaction with ethyl cyanoacetate. 5,5''-Di(ethoxycarbonyl)-1,1''-dihydro-6,6''-dioxo-2,2':6',2''-terpyridine **103** was produced when the *bis*-enaminone **7** was refluxed with ethyl cyanoacetate in refluxing toluene in the presence of piperidine as a catalyst.[14]



3.8.3. Reaction with malononitrile. Reaction of the *bis*-enaminone **7** with malononitrile in refluxing ethanol in the presence of piperidine yielded 1*H*,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]



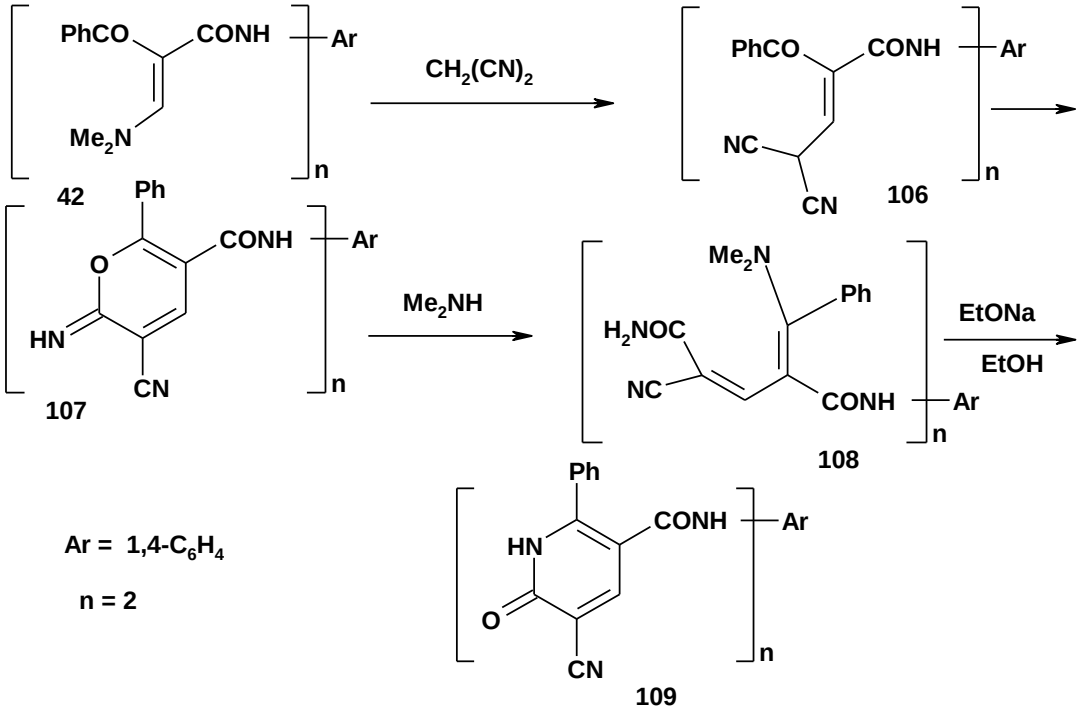
Shawali et al.[35] also reported that reaction of malononitrile with each of the enaminones **15**a-c in refluxing glacial acetic acid in the presence of ammonium acetate gave rise, in each case, a single product that proved to be the respective 3,4-*bis*(5-cyano-6-oxo-1*H*-pyridin-2-yl)-1-aryl-5-methylpyrazole **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.



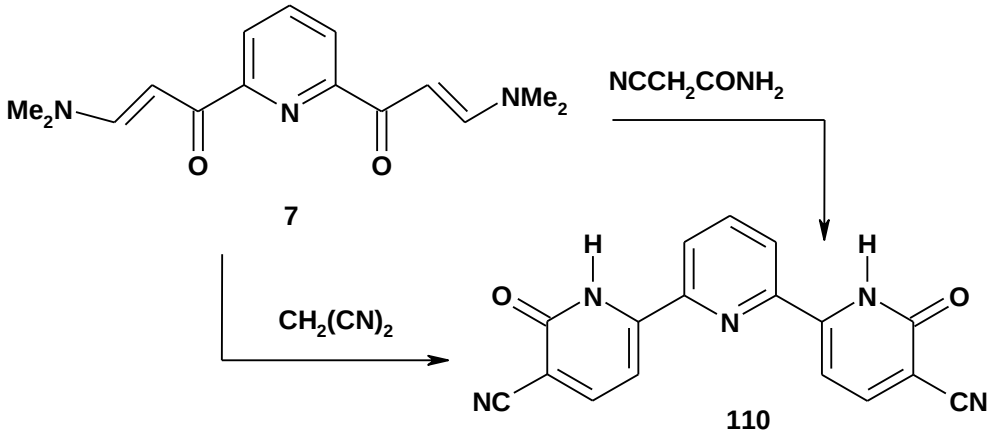
Ar = 4-XC$_6$H$_4$; X : a, H; b, Me; c, MeO

Similar reaction of the *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-phenylene)*bis*-(2-cyano-4-(dimethylamino)phenylmethylene)pent-2-enediamide **108**.[27] The formation of the latter was considered to result *via* initial substitution of the dimethylamino group to give the intermediate **106** followed by cyclization to give **107**, which in turn reacted

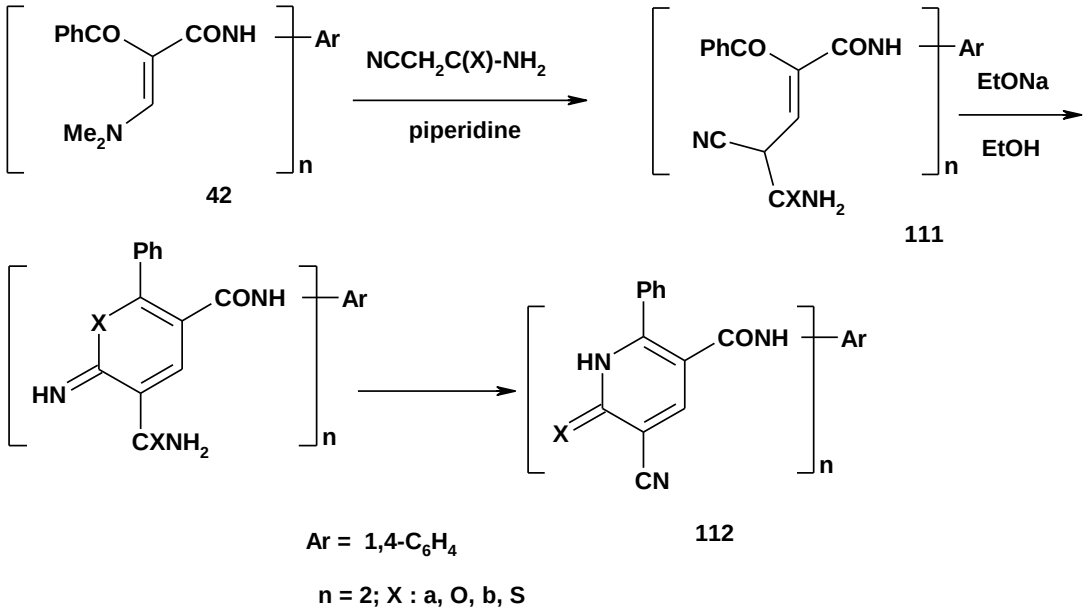
with dimethylamine to give **108** as end product. Refluxing the latter in ethanolic sodium ethoxide solution resulted in the formation of *N*,*N*'-(1,4-diphenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) **109** *via* elimination of dimethylamine.[27]



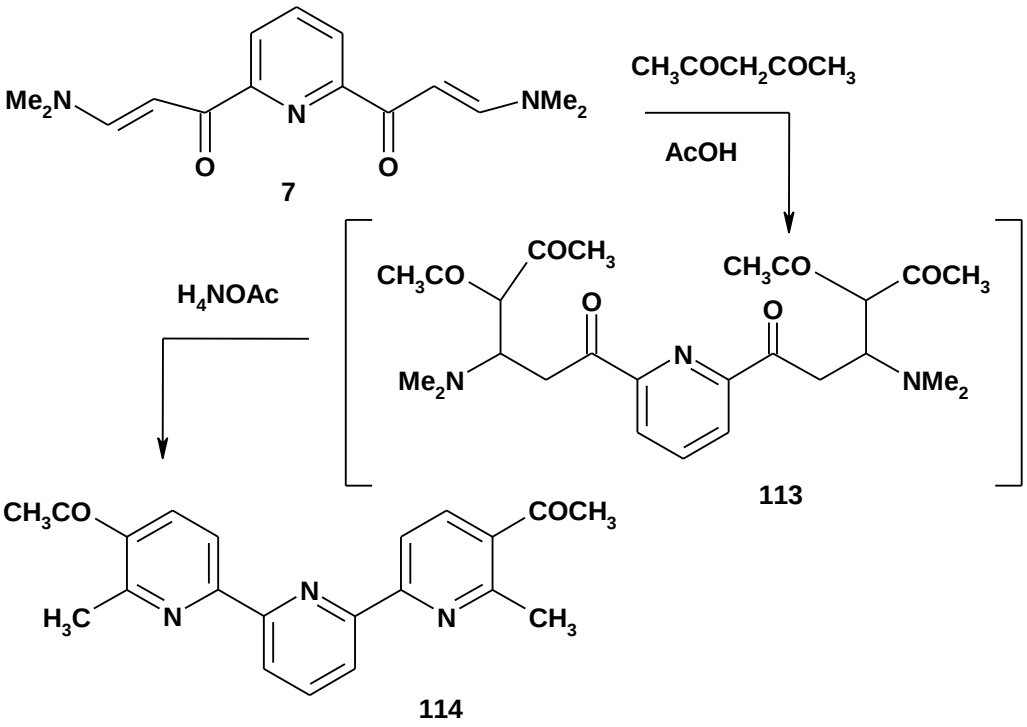
3.8.4. Reactions with cyanoacetamide and cyanothioacetamide. The *bis*-enaminone **7** reacted with cyanoacetamide in refluxing toluene in the presence of piperidine as a catalyst and gave 1*H*,1"H-6,6"-dioxo-2,2':6,2"-terpyridine-5.5"-dicarbonitrile **110** *via* substitution of the dimethylamino group followed by cyclization.[14] The latter product was also obtained by reaction of **7** with malononitrile.[14]



The *bis*-enaminone 4**2** 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.[27] Use of cyanothioacetamide *in lieu* of cyanoacetamide in this reaction gave the respective *N*,*N'*-(1,4-phenylene)-*bis*-(5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide) **112b** in 72% yield.[27]

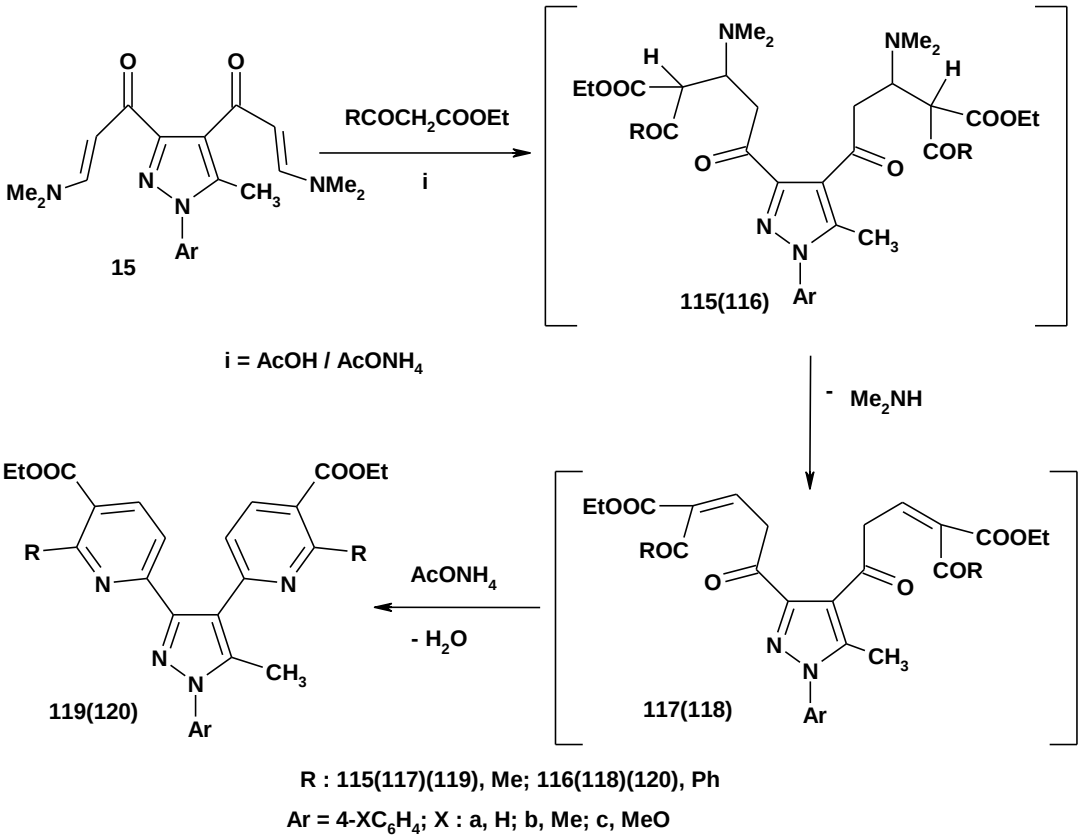


3.8.5. Reactions with 2,4-pentanedione. The terpyridine derivative namely 5,5"-diacetyl-6,6"-dimethyl-2,2':6',2"-terpyridine **114** was reported to be formed by reaction of the *bis*-enaminone **7** with acetylacetone in refluxing acetic acid in the presence of ammonium acetate *via* the pathway depicted below.[14]

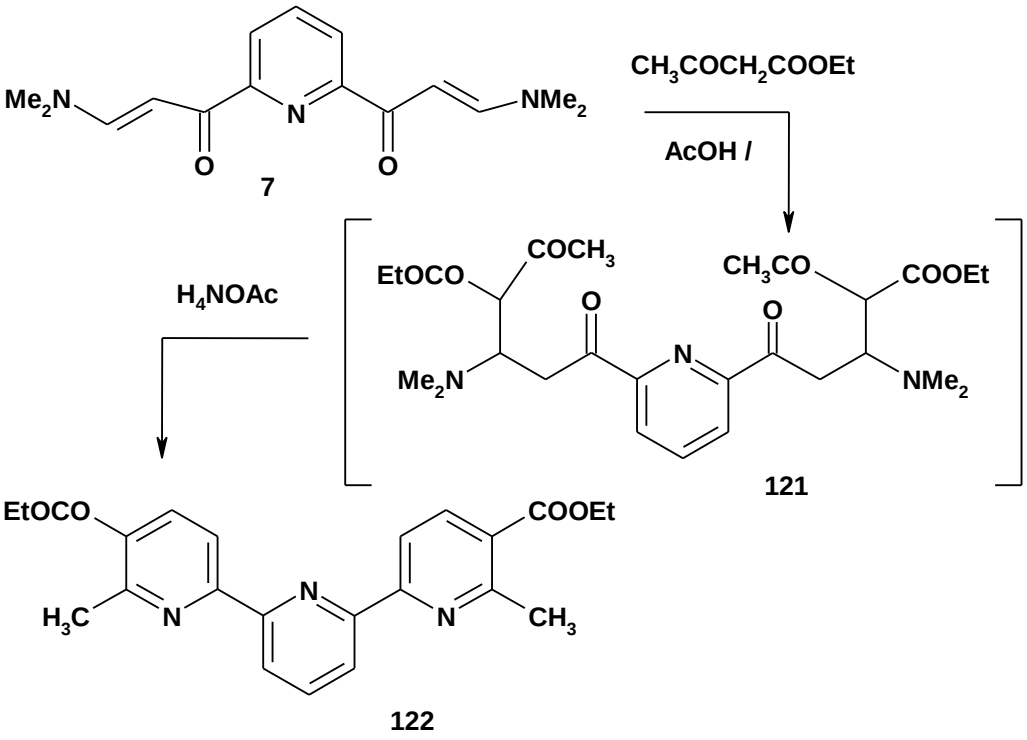


3.8.6. Reactions with β-keto esters. When a mixture of ethyl acetoacetate and each of the *bis*-enaminone **15a-c** was refluxed for 30 h in glacial acetic acid in the presence of ammonium acetate, it yielded, in each case, a single product. Both elemental analyses and spectral data indicate that the products isolated are the respective 3,4-bis[5-ethoxycarbonyl-6-methyl-pyrid-2-yl]-1-aryl-5-methylpyrazole **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]

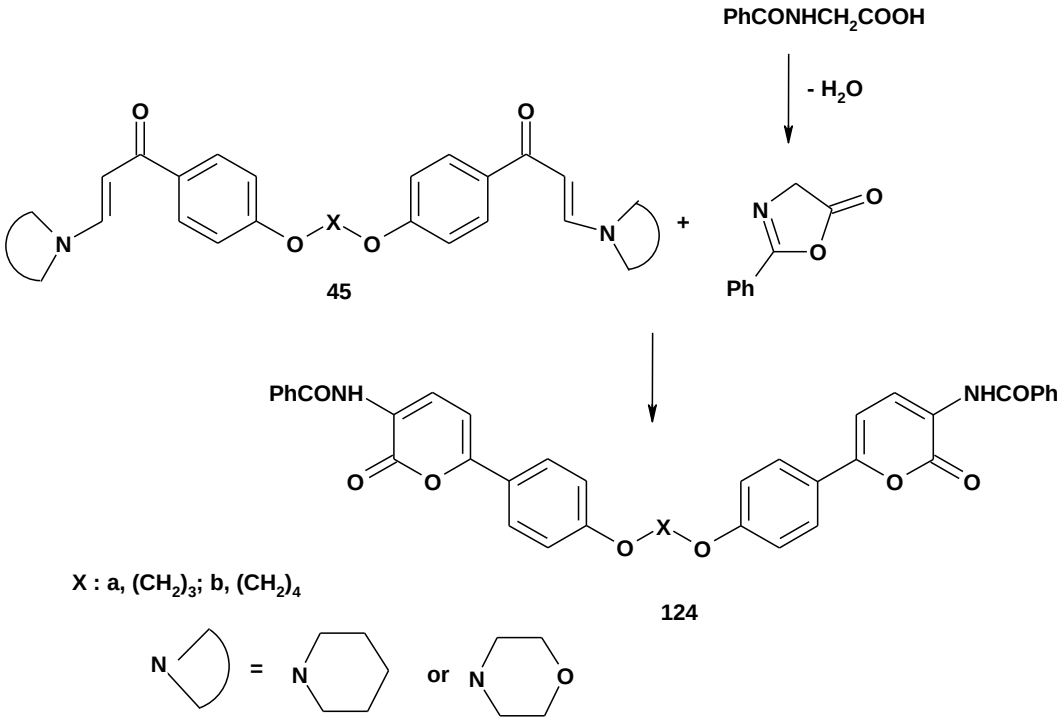


The *bis*-enaminone **7** was also reported to react with ethyl acetoacetate in refluxing acetic acid in the presence of ammonium acetate to give 5,5''-diethoxycarbonyl-6,6''-dimethyl-2,2':6',2''-terpyridine **122**.[14] The formation of the latter product was considered to follow the sequence depicted 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.[14]



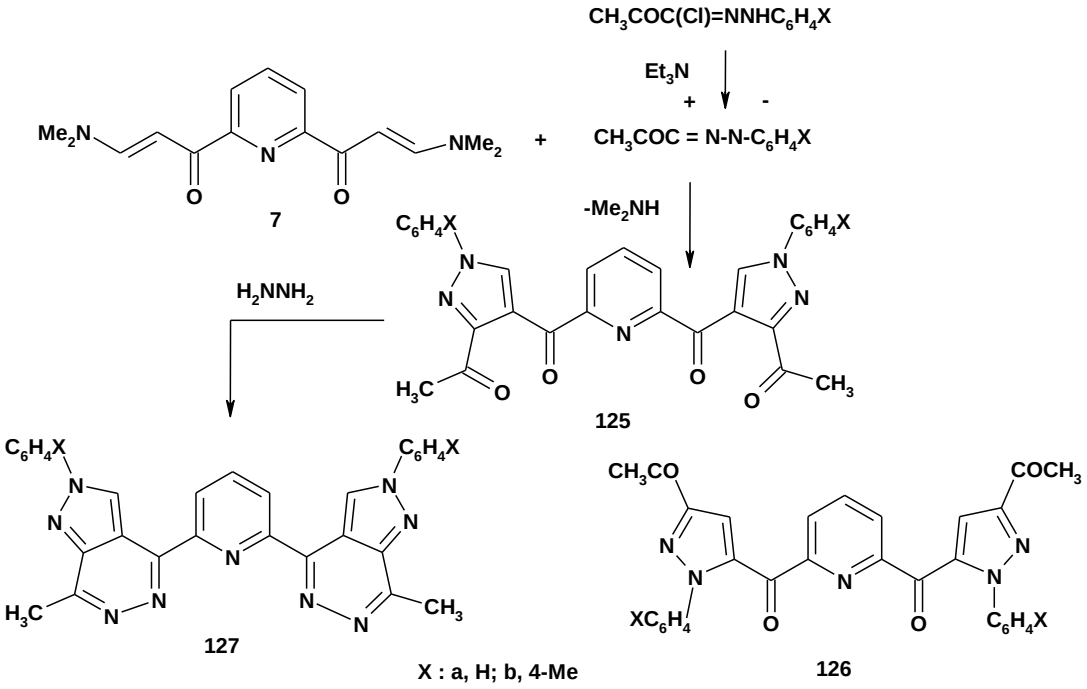
3.9. Reaction with N-benzoylglycine

When the *bis*-enaminones **45** was refluxed with *N*-benzoylglycine in acetic anhydride, it gave the respective **124**.[19]

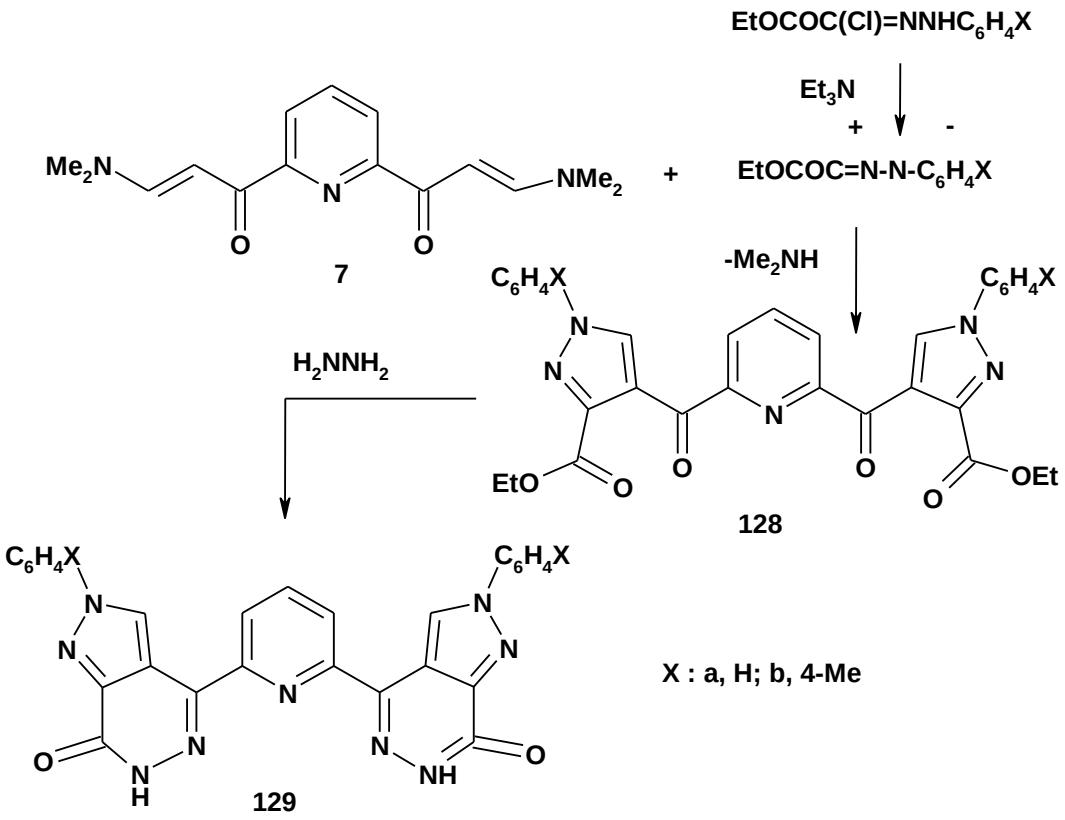


3.10. Reactions with hydrazonoyl halides

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**.[14] 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.[14] 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**.[14]

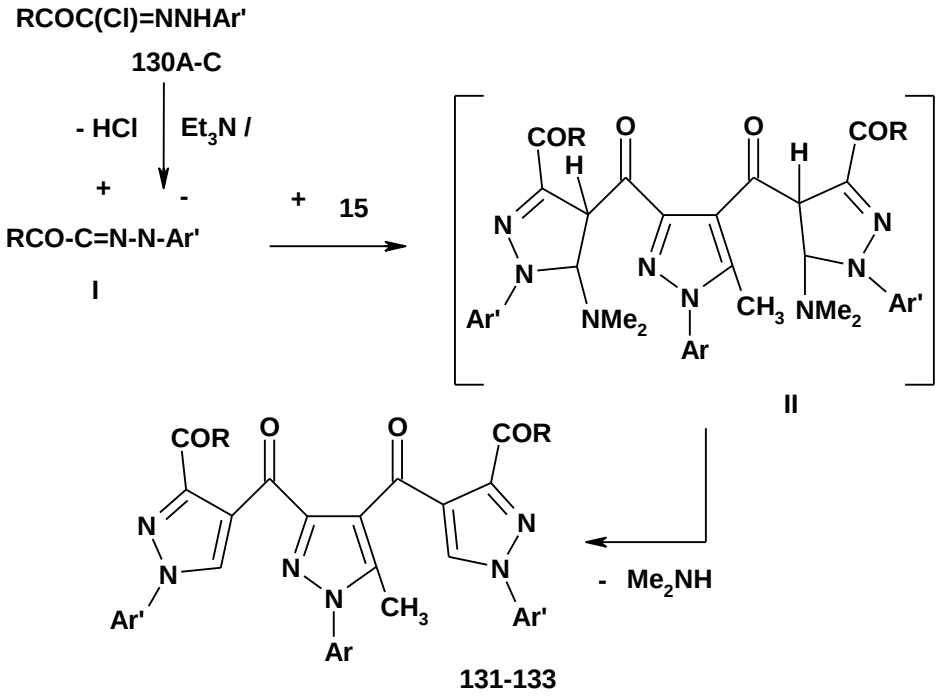


In a similar manner, refluxing of the *bis*-enaminone **7** with ethyl *N*-arylhydrazonochloroacetates in benzene in the presence of triethylamine afforded the corresponding 2,6-*bis*(3-ethoxycarbonyl-1-arylpyrazole-4-carbonyl) pyridines 1**2**8, which reacted with hydrazine hydrate to give 2,6-*bis*-(4-oxo-1-arylpyrazolo[3,4-*d*]pyridazin-7-yl)pyridines **129**.[14]



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, ^{1}H NMR and Ms) data, as the respective 3,5-*Bis*-(1-phenyl-3-substituted-pyrazol-4-carbonyl)-5-methyl-1-aryl-pyrazole**s 131-133**.

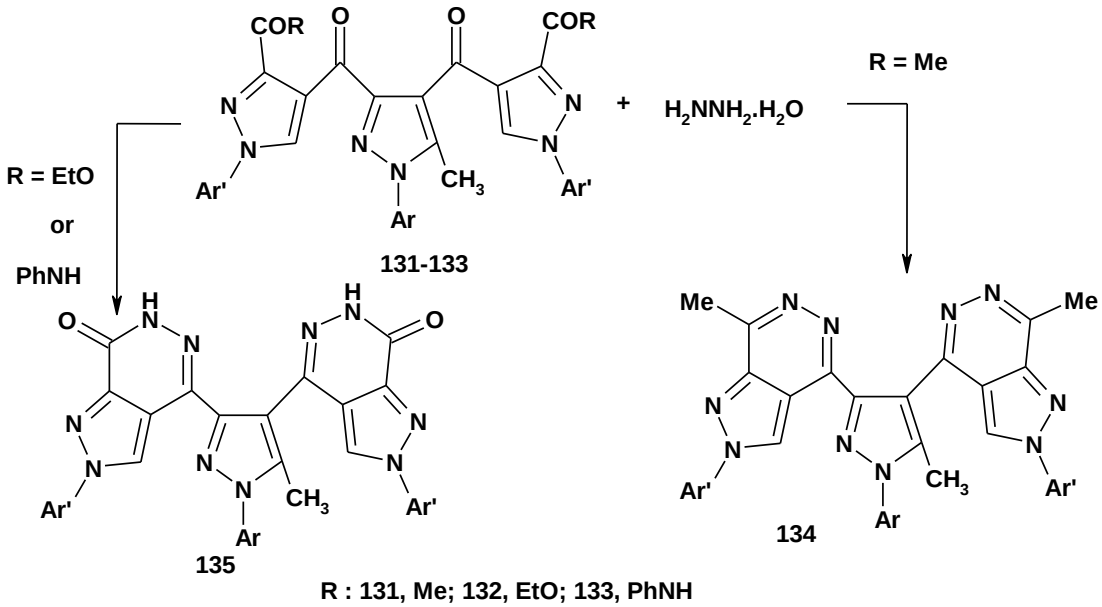
Although the reaction of **131-133** with hydrazine hydrate can theoretically lead to two possible pyrazolopyridazines, Shawali et al reported that it is site selective. For example, when a mixture of **131a** and hydrazine hydrate was refluxed, it yielded only one product as evidenced by TLC of the 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, ^{1}H NMR and Ms) and elemental analysis data proved it to have structure **135b**.



R : 130A (131), Me; 130B (132), EtO; 130C (133), PhNH

Ar / Ar' : YPh / XPh

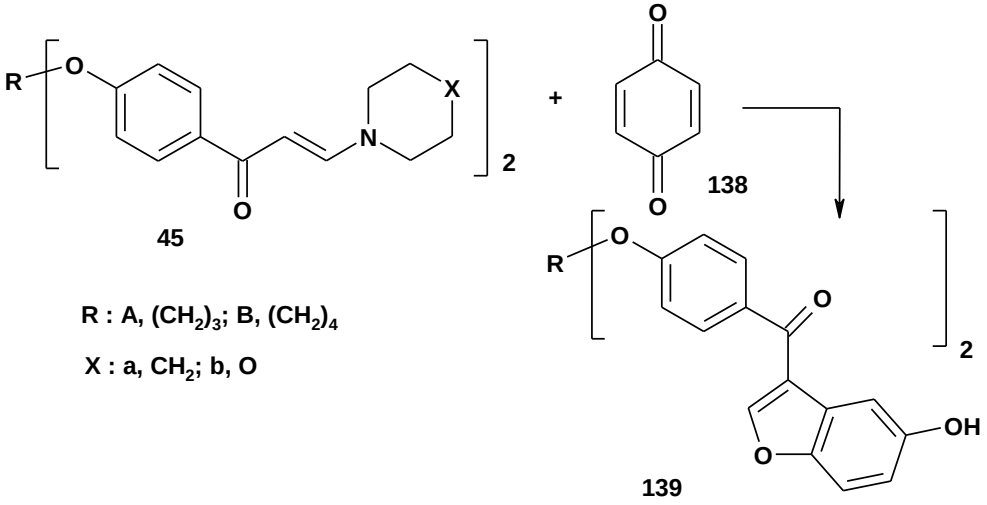
Y / X : a, H / H; b, 4-Me / H; c, 4-Cl / H; d, 4-MeO / H;
e, H / 4-Me; f, H / 4-Cl



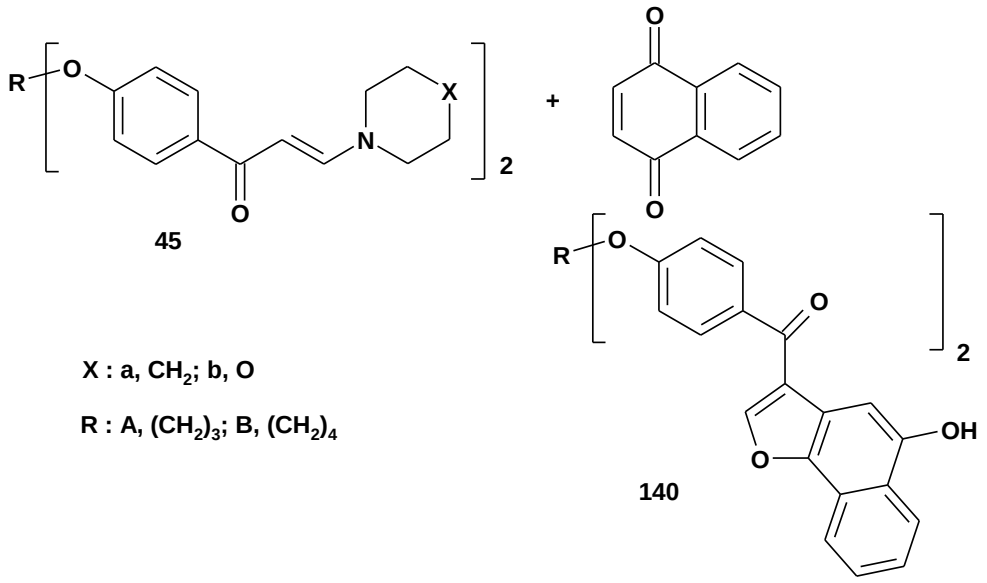
R : 131, Me; 132, EtO; 133, PhNH

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]



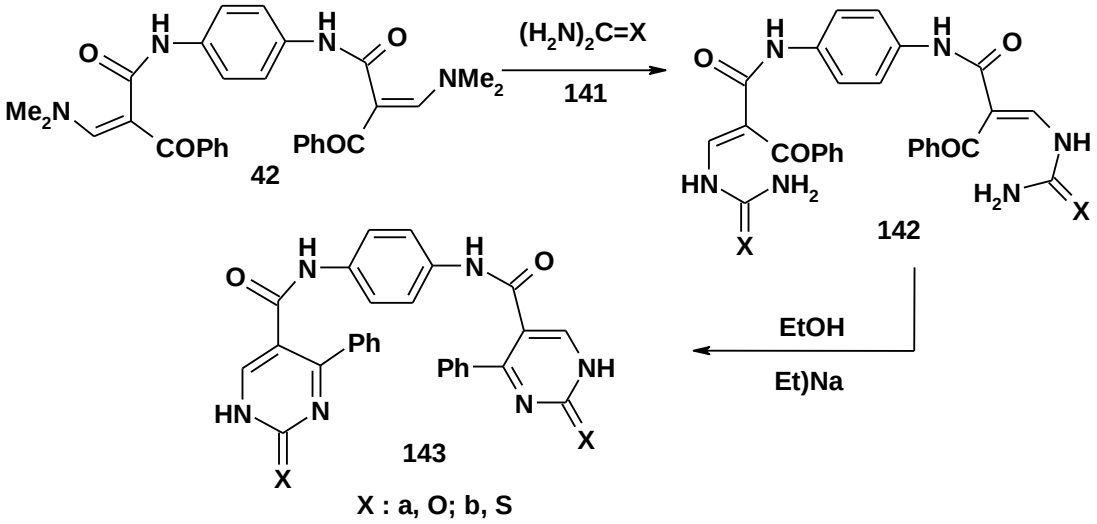
Similar reaction of the *bis*-enaminones **45** each with naphthoquinone in refluxing acetic acid afforded the respective 1,3-*bis*-(naphthofuran) derivatives **14**0.[19]



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-phenylene)-*bis*-(2-oxo-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) **143a** and its thioxo isomer **143b**, respectively.[27]



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 δ 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]

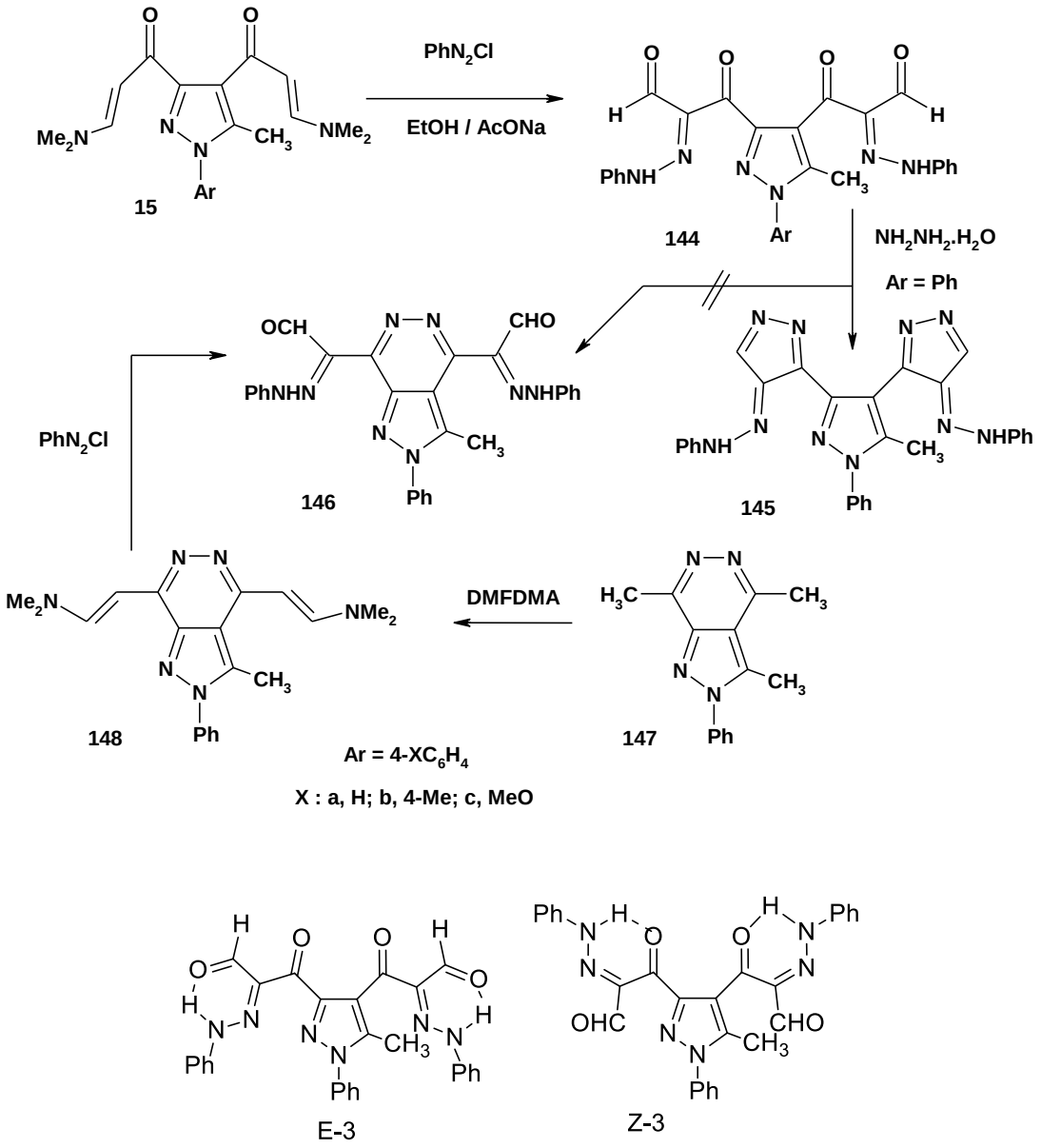
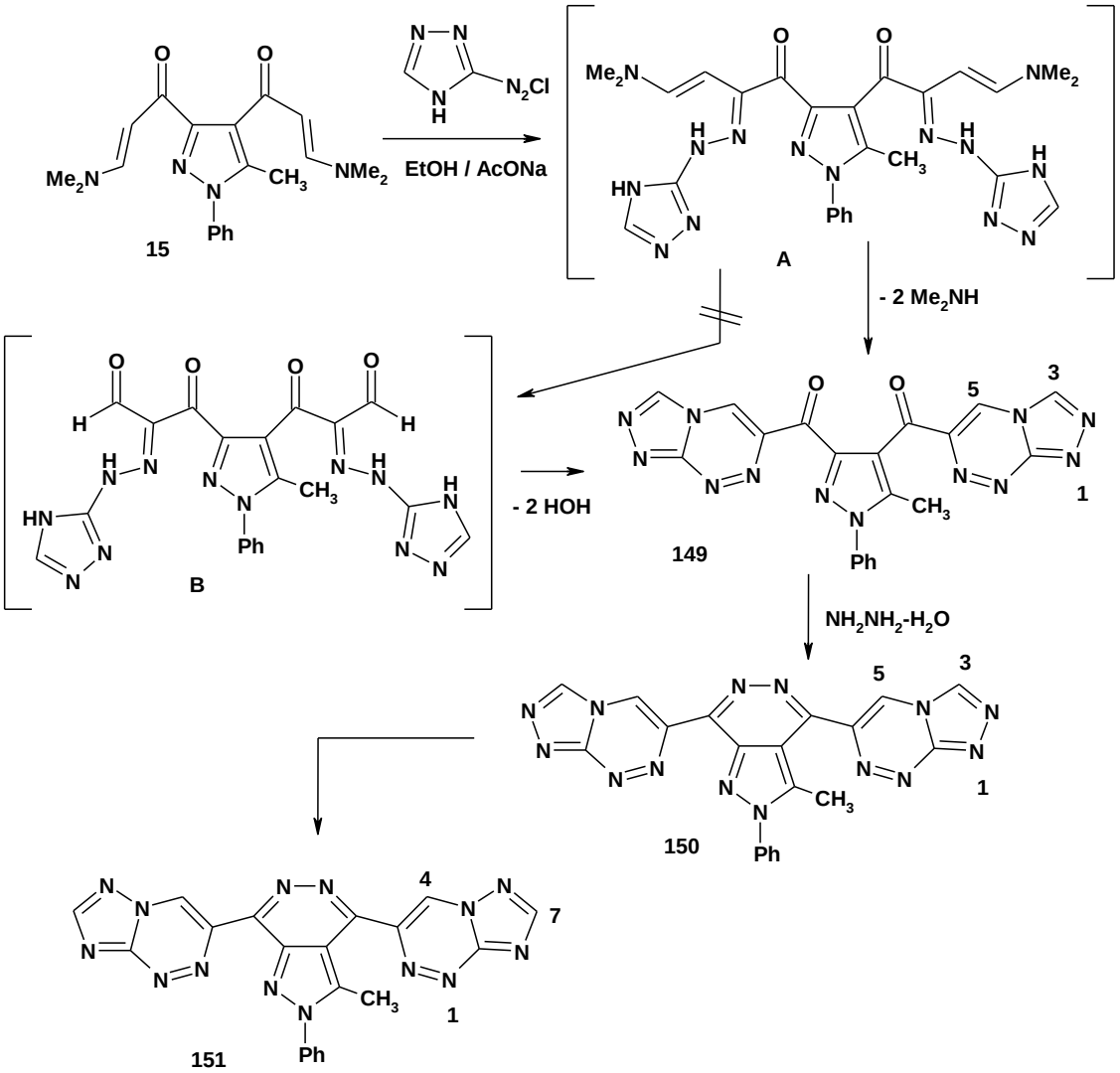


Figure 1

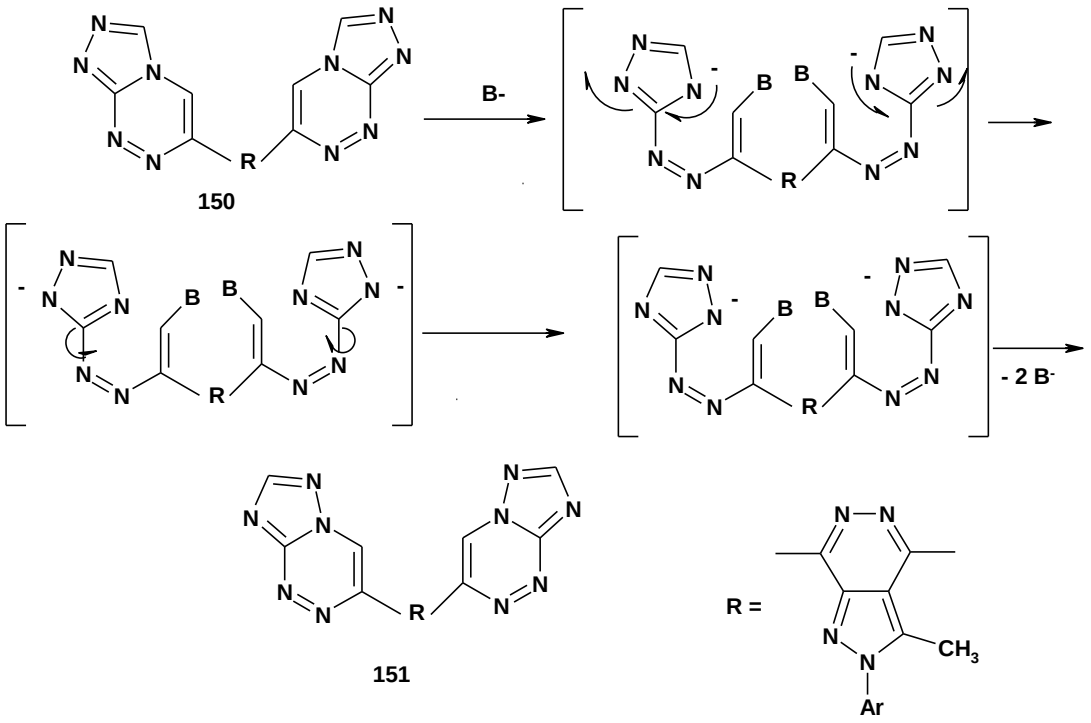
3.13.2. Reactions with heterocyclic diazonium salts. Coupling of **15a** with diazotized 3-amino-1,2,4-triazole in ethanol in the presence of sodium acetate afforded a product that proved to be the respective 1-phenyl-5-methyl-3,4-*bis*[1,2,4-triazolo[3,4-*c*][1,2,4]triazin-6-yl)carbonyl]pyrazole **149a**. 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.[33]

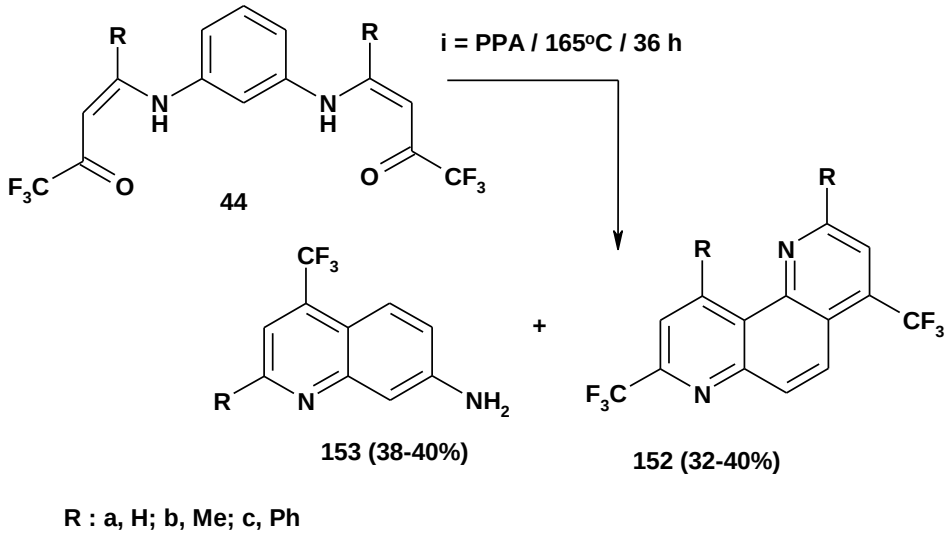
Condensation of the diketone **149** with hydrazine hydrate yielded 3,6-*bis*([1,2,4]triazolo[3,4-*c*][1,2,4]triazin-3-yl)-1-phenyl-7-methyl-pyrazolo-[3,4-*d*]-pyridazine **150**.[33]

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



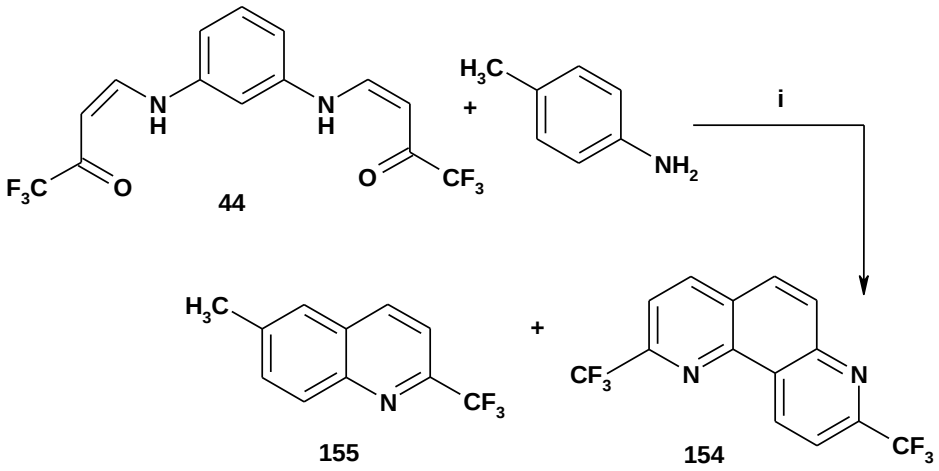
3.14. Cyclization

Treatment of the acyclic *bis*-enaminones **44a–c** with polyphosphoric acid, PPA (P_2O_5 + H_3PO_4) at 165 ºC 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]

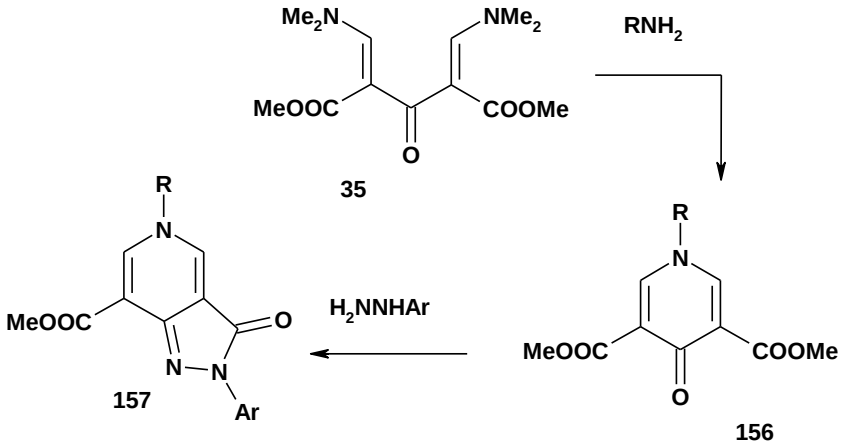


Also, when an equimolar mixture of (*Z*,*Z*)-*N*,*N'*-*bis*(3-oxo-4,4,4-trifluorobut-1en-1-yl)-1,3-phenylenediamine (**44a**) and *p*-toluidine was heated at 165 °C for 36 h in the presence of PPA, a

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]



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-2*H*-pyrazolo[4,3-c]pyridine-7-carboxylates **157**.[24]



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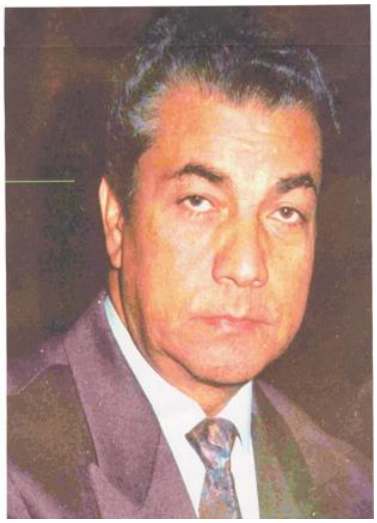
Authors' Biographies



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.

