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Review Article

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Advances in the chemistry of pyrazolopyrazoles

Rizk Elsyad KHIDRE,[1,2] **Hanan Ahmed MOHAMED,**[3,4] **Bakr Fathy ABDEL-WAHAB**[3,4,*]
[1]Chemical Industries Division, National Research Center, Dokki, 12622 Giza, Egypt
[2]Chemistry Department, Faculty of Science, Jazan University, Jazan, Saudi Arabia
[3]Applied Organic Chemistry Department, National Research Center, Dokki 12622 Giza, Egypt
[4]Preparatory Year, Shaqra University, Al Dawadmi, Saudi Arabia

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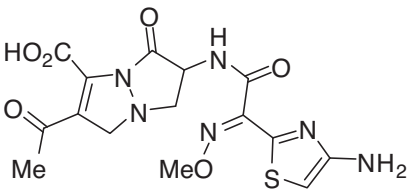
Abstract: Published data on the methods of preparation of pyrazolopyrazoles are summarized and described systematically. The title compounds are subdivided according to the position of fusion between the 2 pyrazole rings.

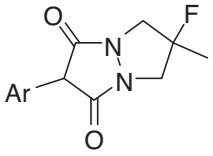
Key words: Pyrazoles, pyrazolo[1,2-*a*]pyrazoles, pyrazolo[3,4-*c*]pyrazoles, pyrazolo[4,3-*c*] pyrazoles

1. Introduction

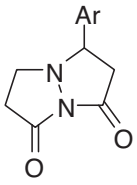
Recently, much attention has been paid to the synthesis of fused pyrazolopyrazole compounds since they have various applications. These include, for example, Lilly's bicyclic pyrazolidinone LY 186826, exhibiting antibiotic activity greater than that of several penicillins and cephalosporins,[1,2] and herbicides[3] and potent drugs for treatment of cognitive dysfunctions such as Alzheimer disease.[4]



LY 186826



Herbicides

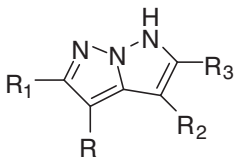


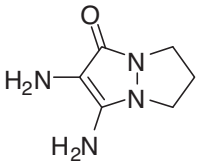
anti-Alzheimer

Additionally, pyrazolo[1,5-*b*]pyrazoles is used as hair dye[5,6] and 2,3-diamino-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-1-one or its salts are used as a hair dye with red nuances and/or intense copper tone.[7] The 3-oxo-3*H*-pyrazolo[1,2-*a*]pyrazol-4-ium-1-olates are nitrification inhibitors for use with fertilizers.[8]

In addition, pyrazolo[3,4-*c*]pyrazoles are useful for the treatment of esophageal and gastrointestinal mucosa injury[9] and brain injury,[10] and also as immunostimulatory,[11] antianginal,[12] and antitumor[13] agents. A review covering the literature data on the synthesis of compounds with 2 or more pyrazole rings linked to each other published before 1995 appeared in 1995.[14] In view of the above facts and in connection to our previous review articles about biologically active heterocyclic systems,[15–29] we decided to prepare this review to present to readers a survey of the literature of pyrazolopyrazoles. Some of the commercial applications of pyrazolopyrazole derivatives are also mentioned.

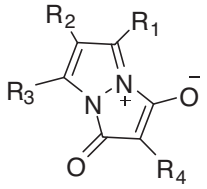
*Correspondence: bakrfatehy@yahoo.com





R = H or a coupling releasing group;
R_1, R_2, R_3 = H or a substituent

Hair dye



R_1, R_3 = H or a C_{1-4} alkyl;
R_2 = H, halo or C_{1-4}-alkyl;
R_1CCR_2 = 5- or 6-membered cycloalkyl;
R_4 = carboxyalkyl or (un)substituted Ph

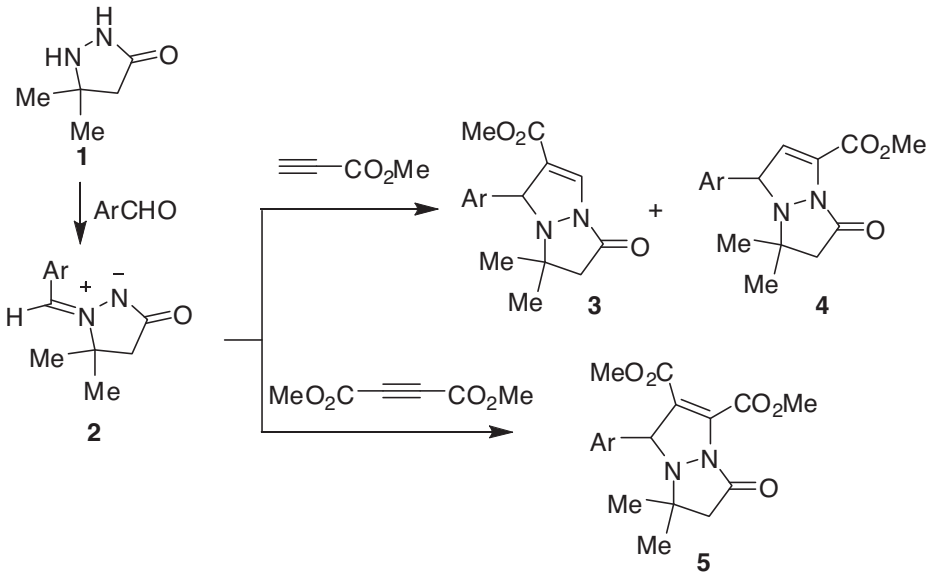
Nitrification inhibitors for use with fertilizers

2. Pyrazolo[1,2-*a*]pyrazoles

There are a number of practically important routes to the synthesis of pyrazolo[1,2-*a*]pyrazoles, e.g., (*i*) 1,3-dipolar cycloaddition of various acetylenes to azomethinimines, (*ii*) cycloaddition of azines to dipolarophiles, and (*iii*) reaction of pyrazoles with ketene, 1,3-dicarbonyl, or dinitrile compounds.

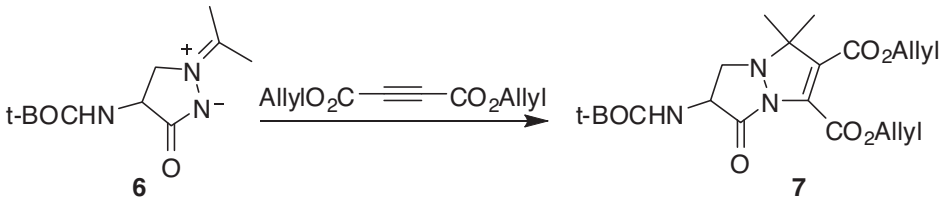
2.1. 1,3-Dipolar cycloaddition

Dimethylpyrazolidinone **1** was condensed with aromatic aldehydes to give [(*Z*)-arylmethylene]dimethylpyrazolidinone azomethine imines **2**. 1,3-Dipolar cycloaddition of **2** with methyl propiolate gave a mixture of the regioisomeric pyrazolo[1,2-*a*]pyrazoles **3** and **4**,[30] whereas 1,3-dipolar cycloaddition of the azomethine imines to dimethyl acetylenedicarboxylate (DMAD) afforded the corresponding pyrazolo[1,2-*a*]pyrazoles **5**.[31,32]

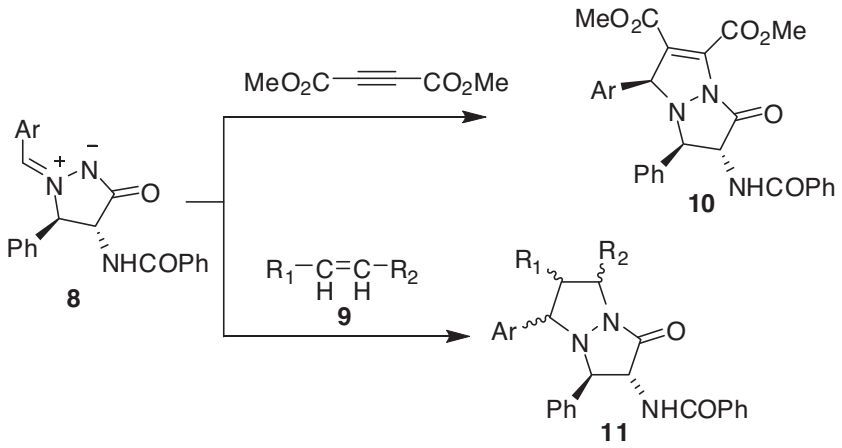


Ar = 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$,
2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 2,4,6-$Me_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$, 2,6-$(MeO)_2C_6H_3$

Cycloaddition of the ylide **6** with diallyl acetylenedicarboxylate gave the bicyclic pyrazolidinone **7**.[33]



rel-(2*R*,3*R*)-*N*-Benzoylamino-6,7-bis(methoxycarbonyl)-2,3-dihydro-1-oxo-1*H*,5*H*-pyrazolo [1,2-*a*] pyrazoles **10** were achieved by cycloaddition of DMAD to (1*Z*)-*rel*-(4*R*,5*R*)-1-aryl-methylidene-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azomethine imines **8**.[34,35] Additionally, 3-pyrazolidinone azomethine imines **8** underwent 1,3-dipolar cycloaddition with olefinic dipolarophiles **9** and afforded stereoisomeric tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **11**.[36]

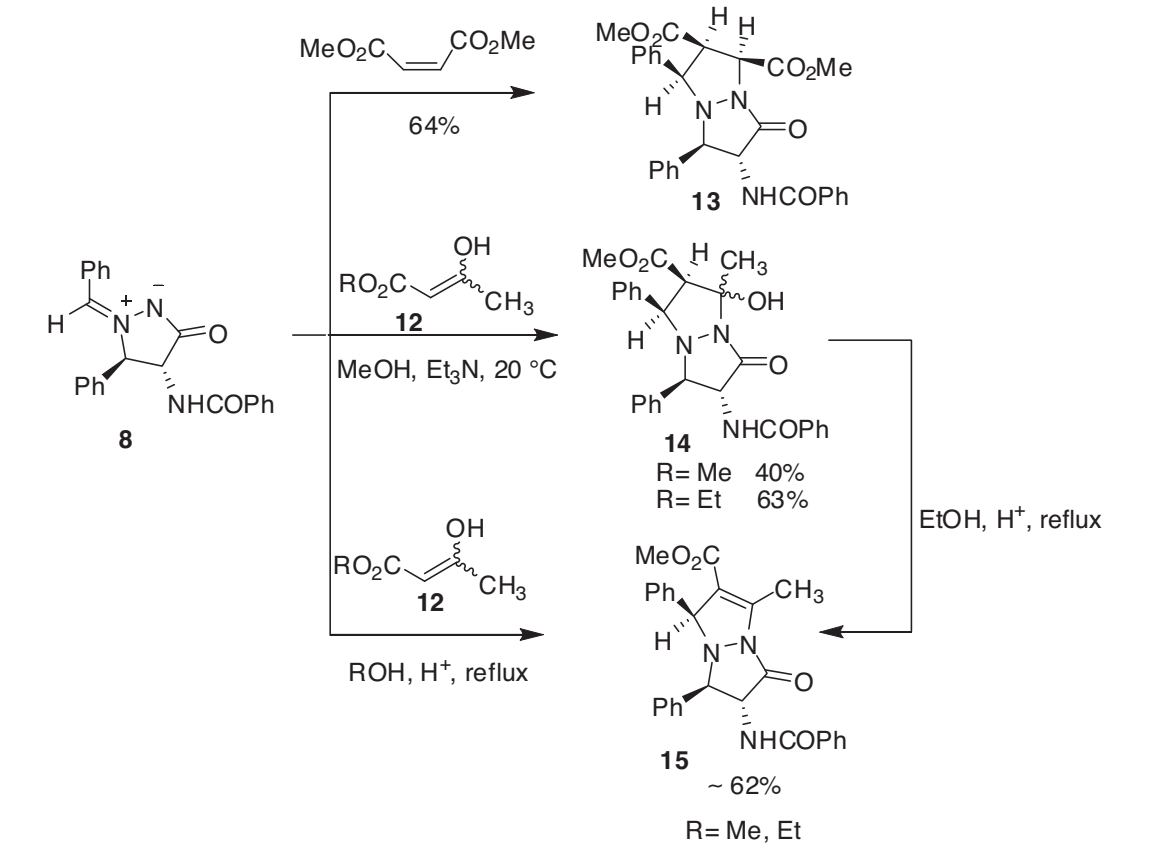


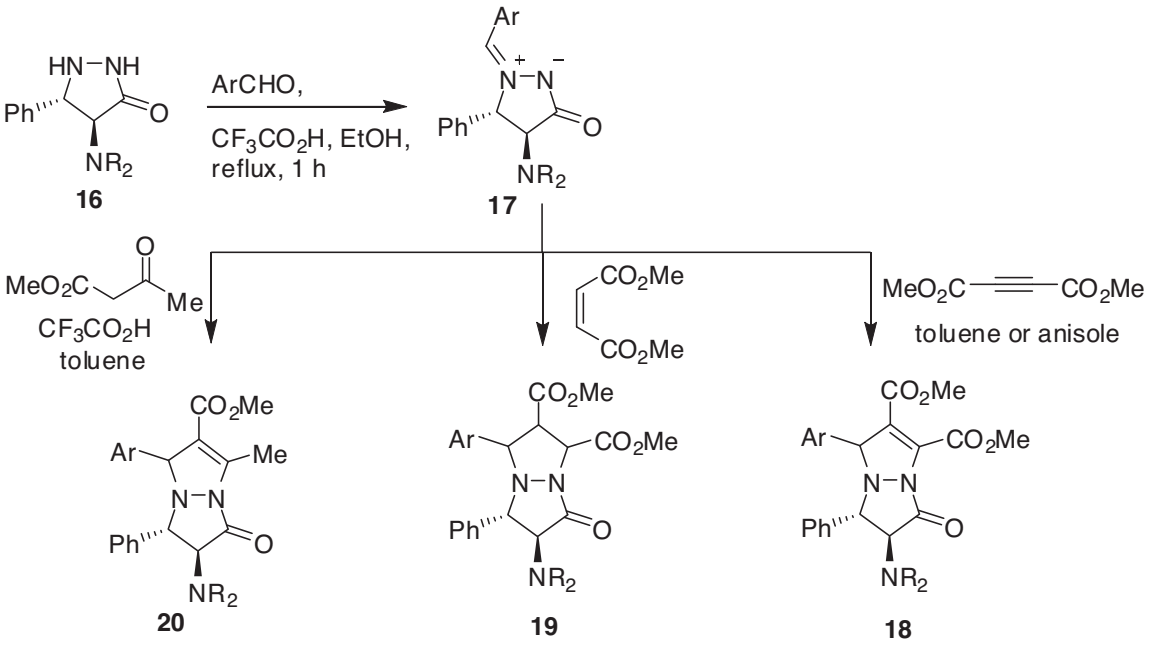
10: Ar = Ph, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$

11: Ar = Ph, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, mesityl, 2,6-$Cl_2C_6H_3$; R_1, R_2 = CO_2Me, H

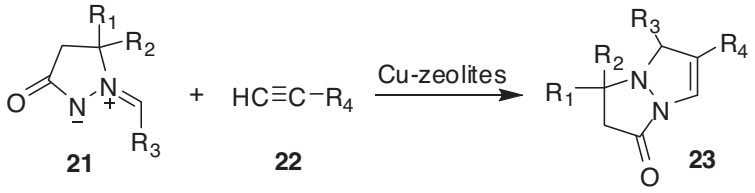
Svete et al., in 1997, reported the stereoselectivity reaction of (1*Z*)-*rel*-(4*R*,5*R*)-1-benzylidene-4-benzoylamino-5-phenyl-3-pyrazolidinon-1-azomethinimine (**8**, Ar = Ph) with different dipolarophiles such as dimethyl maleate and 3-hydroxybut-2-enoates **12** to afford pyrazolo[1,2-*a*]pyrazoles **13** and **14**, respectively. Compound **14** underwent dehydration by heating in acidic medium to afford **15**, and the latter compounds were prepared directly by heating of **8** with **12** in ethanol containing a catalytic amount of acid.[35]

Pyrazolidin-1-ium-2-ides **17** were synthesized, in good yield, by refluxing pyrazolidin-3-ones **16** with aromatic aldehydes for 1 h in absolute ethanol containing a catalytic amount of trifluoroacetic acid. 1,3-Dipolar cycloaddition of azomethines **17** with DMAD, dimethyl maleate, or methyl acetoacetate afforded pyrazolo[1,2-*a*]pyrazoles **18**–**20**, respectively.[37–39]



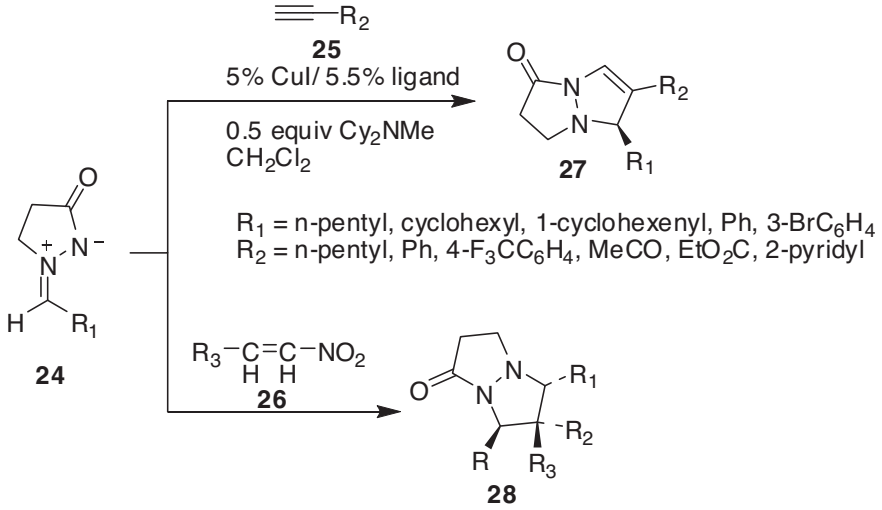


Copper(I)-exchanged zeolites were used as heterogeneous ligand-free catalysts for [3+2] cycloaddition of azomethine ylides **21** to terminal alkynes **22** to afford pyrazolopyrazolone derivatives **23**.[40]



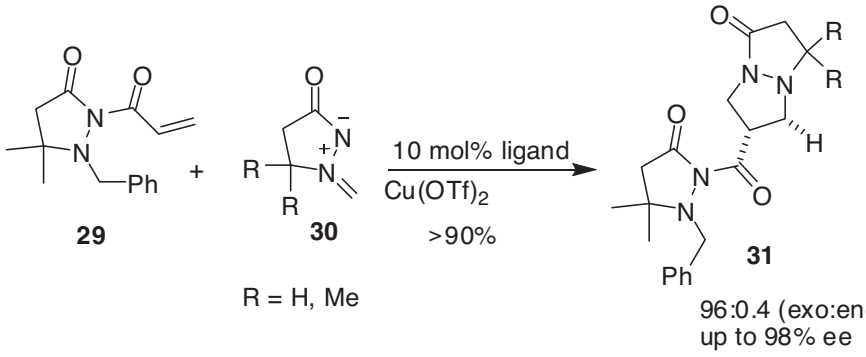
R_1, R_2 = H, Me; R_3 = n-C_5H_{11}, cyclohexyl, Ph, 4-ClC_6H_4, 4-$Et_2NC_6H_4$;
R_4 = $COCHMe_2$, CO_2Et, 4-$F_3CC_6H_4$

A copper-catalyzed regioselective 1,3-dipolar cycloaddition of azomethine imines **24** with terminal alkynes **25** in the presence of a chiral phosphaferrocene-oxazoline ligand gave dihydropyrazolo[1,2-*a*]pyrazolones **27** with very good enantiomeric excess (up to 95% ee).[41] 2-Nitro- and 2-amino-5-oxoperhydropyrazolo[1,2-*a*]pyrazoles **28** were prepared by the condensation of **24** with nitroalkenes **26**.[42,43]

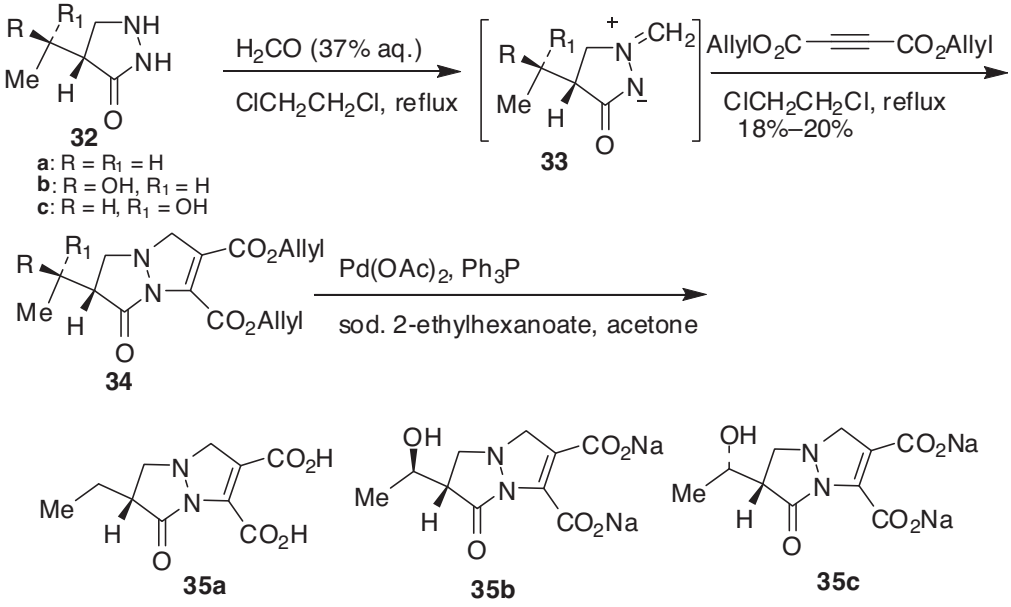


R_1 = Ph, 4-ClC_6H_4; R= H,NO_2; R_2 =H, NO_2, R_3 = H, NO_2

The enantioselective 1,3-dipolar cycloaddition of azomethine imines **30** to 2-acryloyl-3-pyrazolidinone **29** was catalyzed by $Cu(OTf)_2$/bis(oxazoline) to give cycloadducts **31** with high diastereoselectivities (up to >96:4 exo/endo) and enantioselectivities (up to 98% ee).[44]

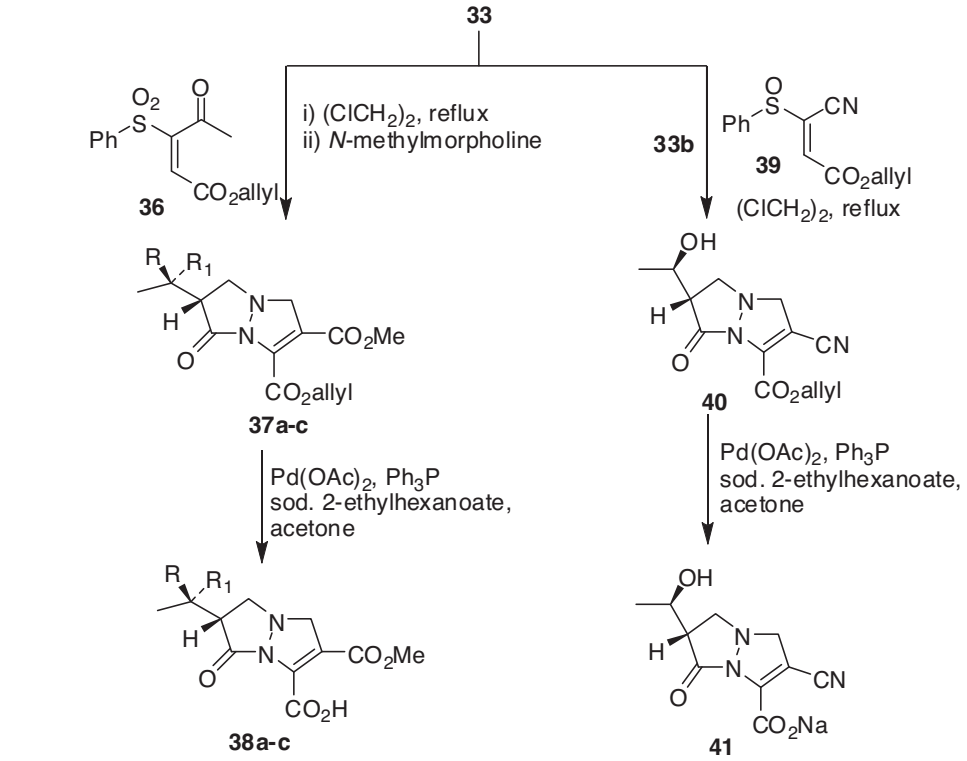


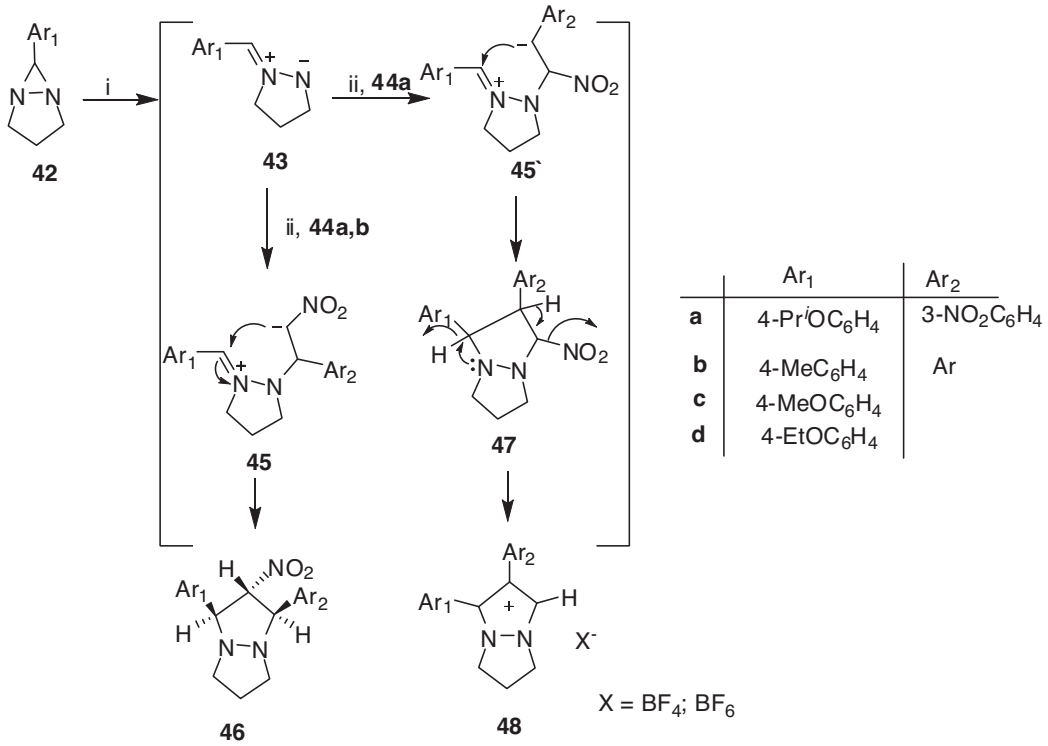
Jungheim in 1989 reported the conversion of pyrazolidinones **32a–c** to bicyclic compounds **35a–c** via 1,3-dipolar cycloaddition. Thus, ylides **33** were generated in situ by treating **32a–c** with aqueous formaldehyde followed by heating to reflux in 1,2-dichloroethane. Diallyl acetylenedicarboxylate readily underwent cycloaddition with **33** giving rise to **34**. Removal of the allyl esters via the method of McCombie[45] completed the preparation of C-3 carboxy-substituted bicyclic pyrazolidinones **35a–c**.[46]



Jungheim also reported in 1989 that the (*E*)-olefin geometry is required for high regioselectivity. Thus, ylides **33a–c** underwent 1,3-dipolar cycloaddition with vinyl sulfone **36** and subsequent base-catalyzed elimination of benzenesulfinic acid to give **37a–c**. Pd(0)-mediated allyl ester deprotection gave rise to acids **38a–c**. Nitrile **40** was prepared via cycloaddition of (*E*)-vinyl sulfoxide **39** followed by in situ thermal elimination of benzene sulfenic. Compound **40** was converted to sodium (*S*)-2-cyano-6-((*R*)-1-hydroxyethyl)-7-oxo-3,5,6,7-tetrahydropyrazolo[1,2-*a*]pyrazole-1-carboxylate **41** using diacetoxypalladium.[46]

In 2009, Syroeshkina et al. reported the synthesis of 1,3-diaryl-2-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **46** by the action of 1-nitro-2-(3-nitrophenyl)ethylene **44a** on 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **42** in ionic liquid with the $Et_2O.BF_3$ catalyst. The same reaction with unsubstituted β-nitrostyrene produced only 1,3-diaryl-2-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole derivatives **48**. Thus, there were reactions of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **42a-d** with dipolarophiles in ionic liquids. β-Nitrostyrenes **44a,b** were used as dipolarophiles and [bmim][BF_4] and [bmim][PF_6] as ionic liquids. $Et_2O \cdot BF_3$ in a catalytic amount was added to the reaction mixture to break the diaziridine ring in initial compounds **42a–d** to reactive azomethine iminic intermediates **43a–d**. It could be expected that the addition of β-nitrostyrenes **44a,b** to dipolar intermediates **45** should run via the Michael addition pathway through intermediates **45**, generating 1,3-diaryl-2-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **46a–d**, which are potential inhibitors of neuronal NO synthase.[47] The reaction was carried out at room temperature or with moderate heating. Compounds **48** were formed as a result of the interaction of β-nitrostyrene **44a** with dipolar intermediates **47b–d**, contrary to the Michael addition mechanism, generating second intermediates **45'**, which were then cyclized to bicycles **48**.[48]

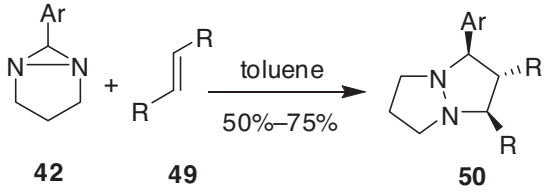




	Ar_1	Ar_2
a	4-Pr^{i}OC$_6$H$_4$	3-NO$_2$C$_6$H$_4$
b	4-MeC$_6$H$_4$	Ar
c	4-MeOC$_6$H$_4$	
d	4-EtOC$_6$H$_4$	

i, 0.5 mmol of 1, 0.4–0.6 g [bmim][BF_4] or [bmim][PF_6] and 2 drops of $Et_2O{\cdot}BF_3$
ii, 0.5 mmol of β-nitrostyrene **44**

Molchanov et al., in 2003, reported the reaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **42** with fumaric acid derivatives **49** in a stereoselective fashion to afford perhydropyrazolo[1,2-*a*]pyrazoles **50**.[49]

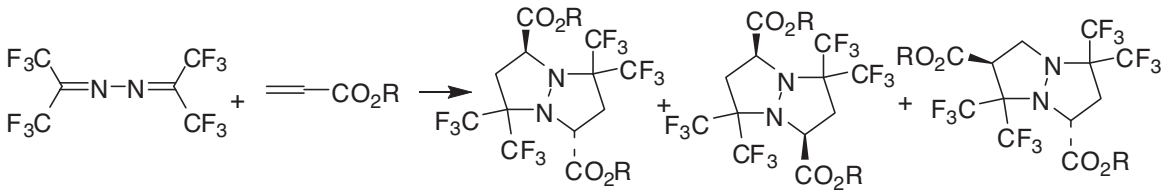


42 **49** **50**

Ar = Ph; R = CN, CO_2Ph
Ar = 4-$MeOC_6H_4$, 4-ClC_6H_4; R = CN

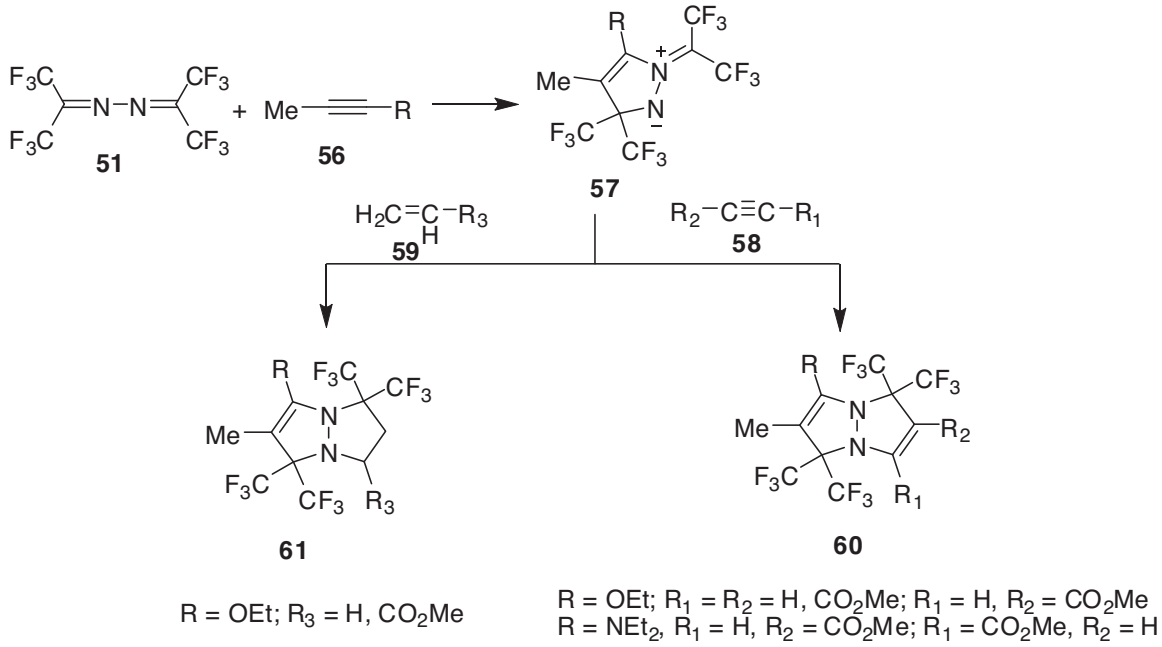
2.2. Cycloaddition of azines to dipolarophiles

Pyrazolopyrazoles **53**–**55** were obtained by a "crisscross" cycloaddition reaction of 1,2-bis(perfluoropropan-2-ylidene)hydrazine **51** with 2 equivalents of olefins **52**; the principal products were **53** obtained in yields of approximately 65%.[50]



51 **52** **53** **54** **55**

R = Me, Et, Bu

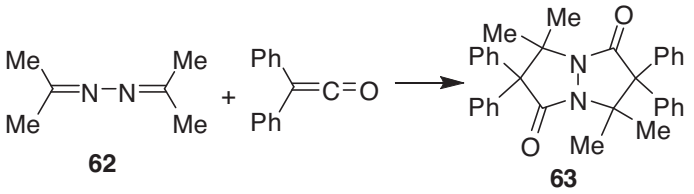


R = OEt; R_3 = H, CO_2Me

R = OEt; R_1 = R_2 = H, CO_2Me; R_1 = H, R_2 = CO_2Me
R = NEt_2, R_1 = H, R_2 = CO_2Me; R_1 = CO_2Me, R_2 = H

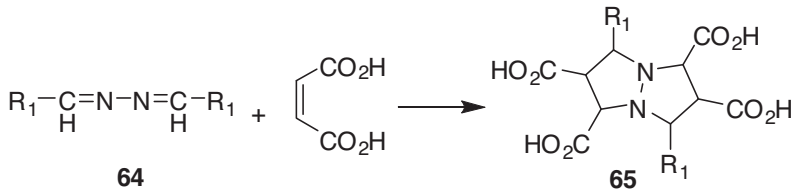
Similarly, the crisscross cycloaddition of **51** with 1-ethoxyprop-1-yne **56** gave 3-ethoxy-4-methyl-2-(perfluoropropan-2-ylidene)-5,5-bis(trifluoromethyl)-2,5-dihydropyrazol-2-ium-1-ide **57**, stable only in solution. Subsequently, the latter compound was reacted with alkynes **58** and alkenes **59** to give **60** and **61**, respectively, in good yields.[51–53]

1,2-Di(propan-2-ylidene)hydrazine **62** reacted with 2,2-diphenylethenone to give pyrazolopyrazole **63**.[54]



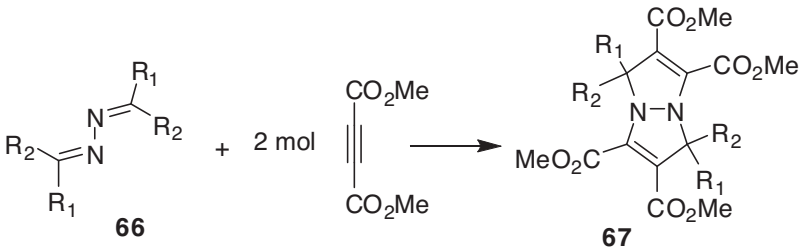
62 **63**

Cycloaddition of azines **64** with maleic acid gave tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2,3,6,7-tetracarboxylic acid **65**.[55]



64 **65**

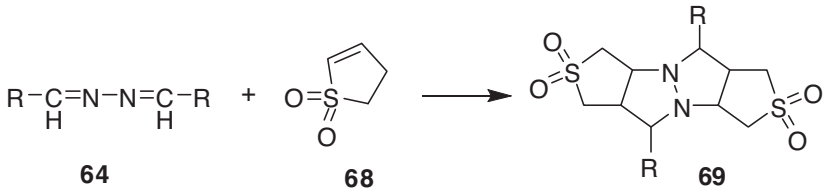
Aldazines or ketazines **66** were reacted with 2 equivalents of DMAD in [2+3] cycloaddition reactions to give pyrazolopyrazole **67**.[56]



66 **67**

R_1 = alkyl or aryl; R_2 = H, Me, alkyl

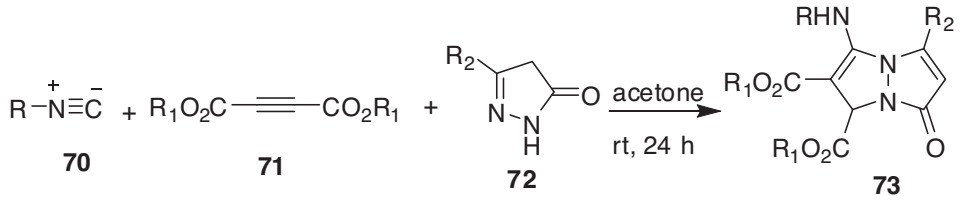
Pyrazolo[1,2-*a*]pyrazole derivatives **69** were synthesized via 2:1 equivalent cycloaddition of sulfolene **68** with aldazines **64**.[57]



64 **68** **69**

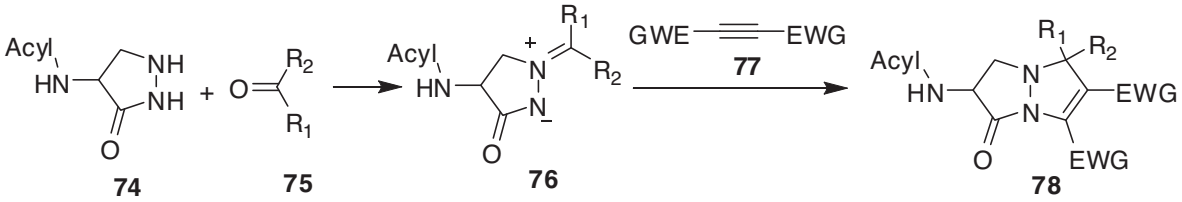
R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 2-furyl, 2-thienyl

Adib et al., in 2005, reported the synthesis of functionalized 7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazoles **73**. Thus, isocyanides **70** and dialkyl acetylenedicarboxylates **71** in the presence of 2,4-dihydro-3*H*-pyrazol-3-ones **72** undergo a smooth 1:1:1 addition reaction in acetone at ambient temperature to produce highly functionalized 7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole derivatives **73** in 69%–81% yields.[58]



R = cyclohexyl, Bu^{-t}, R_1 = Me, Et; R_2 = Me, Ph

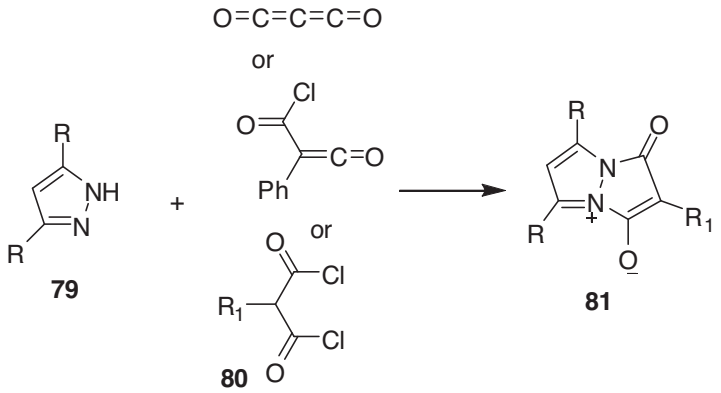
Bipyrazolidine antibiotics **78** were obtained from pyrazolidin-3-ones **74** by a 2-step reaction sequence involving formation of an azomethine-imine ylide **76**, which subsequently reacted in situ with acetylene derivative **77**.[59]



R_1, R_2 = alkyl

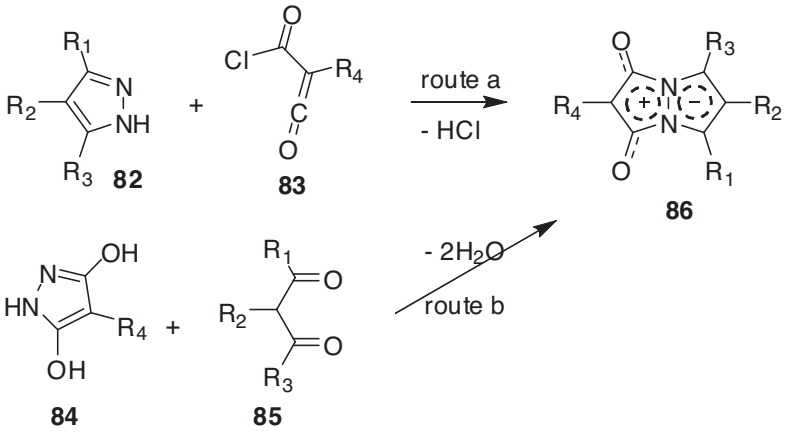
2.3. Reaction of pyrazoles with ketene, 1,3-dicarbonyl, or dinitrile compounds

Reactions of pyrazoles, with aryl(chlorocarbonyl)ketenes or alkylmalonyl dichlorides, were reported. Thus, pyrazoles **79** were treated with propa-1,2-diene-1,3-dione or 3-oxo-2-phenylacryloyl chloride to give cross-conjugated pyrazolium hydroxides **81**, respectively. Similarly, (**80**, R = Me) and 2-ethylmalonyl dichloride (**80**, R_1 = Et), 2-allylmalonyl dichloride (**80**, R_1 = allyl) gave **81**.[60,61]



R = H, Me, R_1 = H, Ph; R = Me, R_1 = Et, allyl

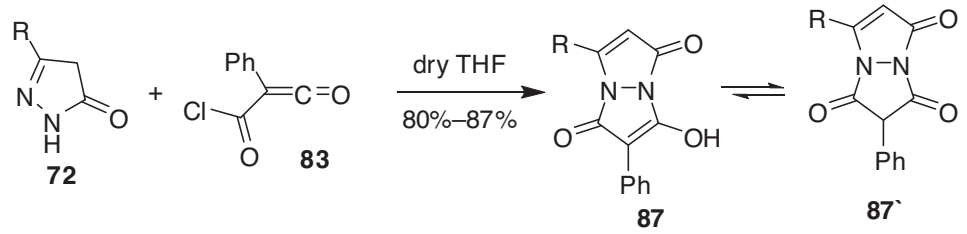
Substituted anhydro-1-hydroxy-3-oxopyrazolo[1,2-a]pyrazolium hydroxides **86** were prepared by treating 1,3-dicarbonyl compounds **83** or **85** with derivatives of pyrazoles **82** or **84**.[62]



82 **83** **84** **85** **86**

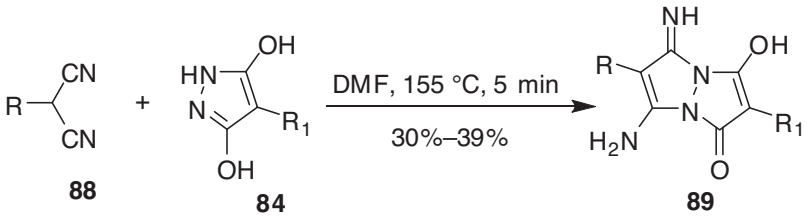
R_1= H, Me, Ph, R_2=H, benzyl, R_3 = H, Me, Ph, R_4 = aryl

The addition of (chlorocarbonyl)phenylketene **83** to pyrazol-3-one derivatives **72** led to 3-hydroxypyrazolo [1,2-a]pyrazolediones **87**.[63]



72 **83** **87** **87`**

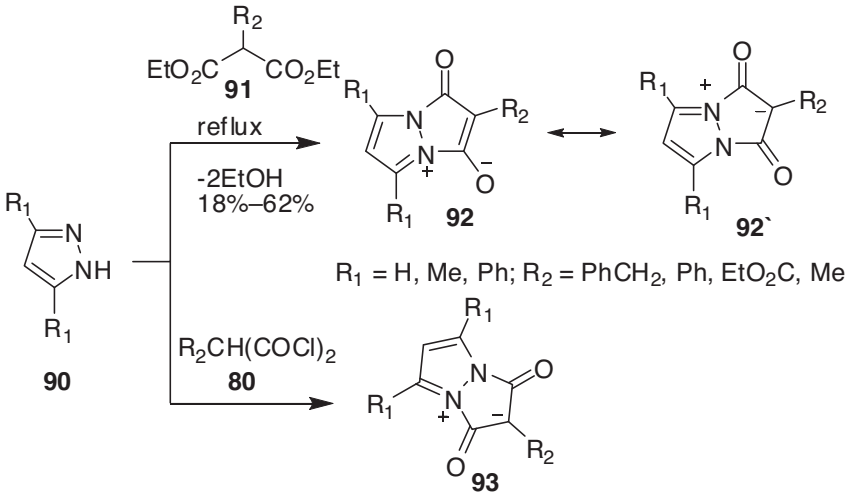
7-Amino-3-hydroxy-5-imino-2,6-diarylpyrazolo[1,2-a]pyrazol-1(5H)-ones **89** were prepared in yields of 30%–39% by cyclization of pyrazoles **84** with dinitriles **88**.[64]



88 **84** **89**

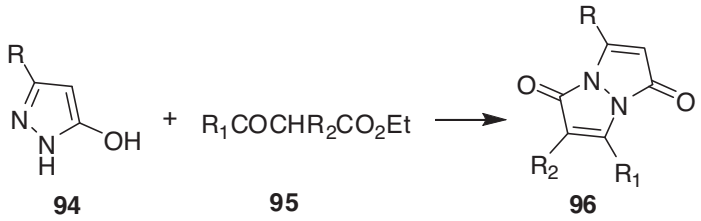
R = Ph, p-anisyl; R_1 = Ph, p-anisyl, p-ClC_6H_4

Thermal cyclocondensation of pyrazoles **90** with substituted diethyl malonates **91** yielded 1-oxo-1H-pyrazolo[1,2-a]pyrazol-4-ium-3-olates **92**.[65] Olates **93** were obtained by treating pyrazole **90** with diacyl dichloride **80**.[66]



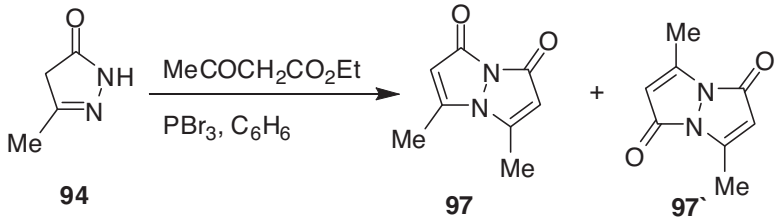
R = H, Me; R_1 = Et, Ph, 4-ClC_6H_4, $PhCH_2$

The reaction of 5-hydroxypyrazoles **94** with β-ketoesters **95** gave mainly pyrazolo[1,2-a]pyrazole-1,5 ($1H$,$5H$)-diones **96**.[67]



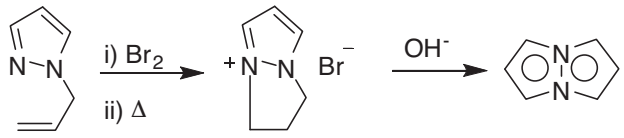
R = Me, Ph; R_1 = Me, CH_2Ph, Ph; R_2 = CO_2Et; R_1 = Me, R_2 = Ac

With the reaction of 3-methylpyrazolin-5-one (**94**, R = Me) with ethyl acetoacetate and phosphorus tribromide in benzene, both *syn*-**97** and *anti*-**97**‘ are formed.[68]

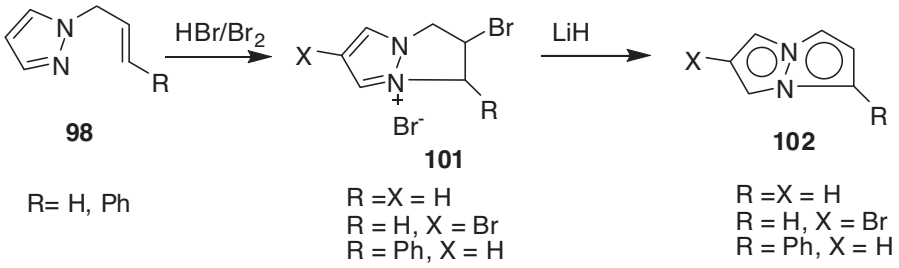


2.4. Cycloaddition of l-allylpyrazoles

1-Allylpyrazole **98** was brominated and the resulting product was thermally quaternized to yield **99**. Treatment of **99** with aqueous sodium hydroxide afforded **100**.[69]

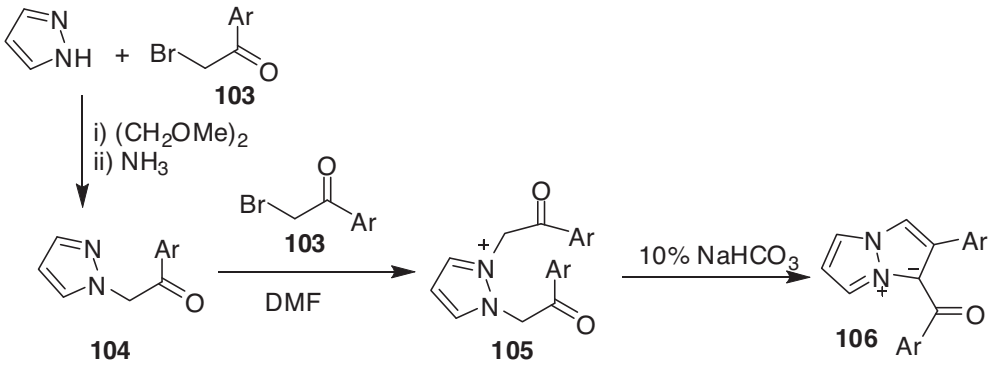


l-Allylpyrazole (**98**, R = H) was dissolved in 48% hydrobromic acid and treated with bromine. The dibromo compound that formed underwent cyclization in boiling acetone to give (**101**, R = X = H) in an 85% overall yield. When a similar bromination was carried out using chloroform as the solvent, the major product isolated after cyclization was the dibromobromide (**101**, R = H, X = Br). 1-Cinnamylpyrazole (**98**, R = Ph) was reacted with bromine in chloroform to yield the salt (**101**, R = Ph, X = H) directly. Conversion of the latter salt to the corresponding pyrazolo[l,2-*a*]pyrazoles (**102**, R = Ph, X = H) by dehydrobromination was possible with lithium hydride in deuteriodimethyl sulfoxide.[70]

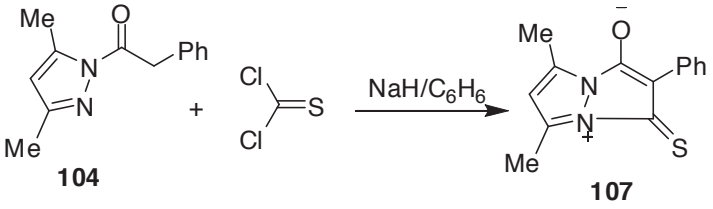


2.5. From pyrazoles

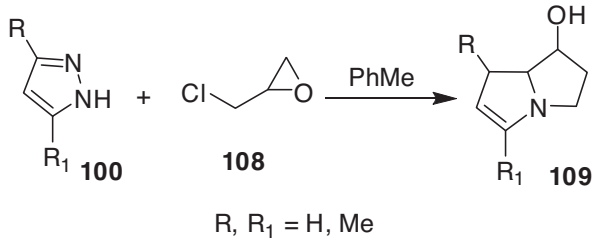
Pyrazole reacted with phenacyl bromides **103** in 1,2-dimethoxyethane to give a salt, which on treatment with aqueous ammonia gave 1-phenacylpyrazoles **104** in 48% yield. Alkylation of compound **104** by a second mole of phenacyl bromides **103** in dimethylformamide produced 1,2-diphenacylpyrazolium bromides **105** in 86% yield. Salts **105** were treated with 10% aqueous sodium bicarbonate and gave a 98% yield of 1-aroyl-2-aryl-1*H*-pyrazolo[1,2-*a*]pyrazol-8-ium-1-ide **106**.[71,72]



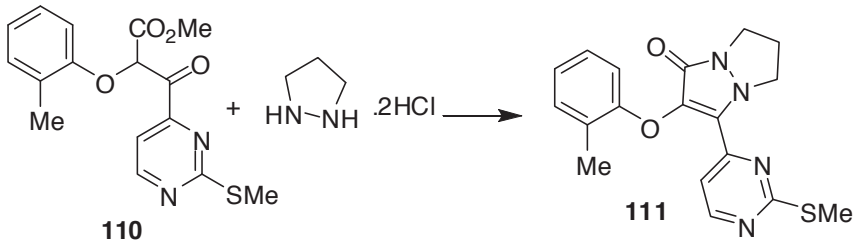
Treatment of 3,5-dimethyl-1-phenylacetylpyrazole (**104**, R = Ph) in benzene with NaH followed by thiophosgene at 0 °C gave 5,7-dimethyl-2-phenyl-1-thioxo-1*H*-pyrazolo[1,2-*a*]pyrazol-8-ium-3-olate **107**.[73]



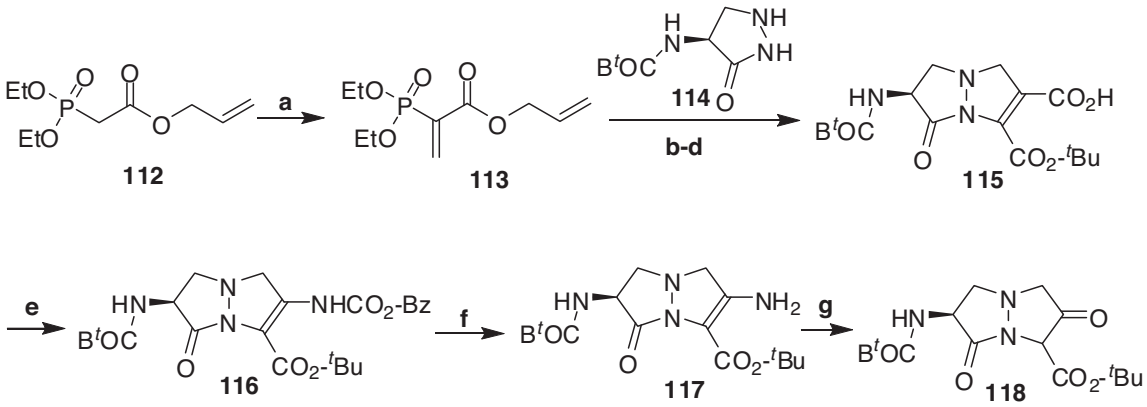
Treatment of pyrazole derivatives **100** with an equimolar amount of 2-(chloromethyl)oxirane **108** in toluene afforded pyrazolopyrazoles **109**.[74]



3-(2-(Methylthio)pyrimidin-4-yl)-2-(o-tolyloxy)-6,7-dihydropyrazolo[1,2-a]pyrazol-1(5H)-one **111** was prepared *via* heterocyclization of ketoester **110** with pyrazolidine dihydrochloride, used for the prevention of extracellular release of inflammatory cytokines.[75–77]

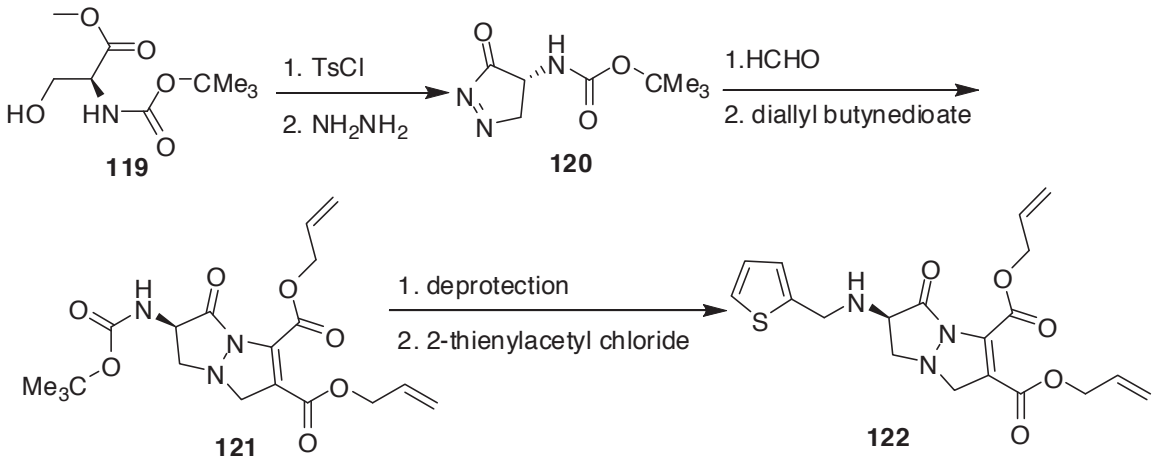


The synthesis of bicyclic pyrazolidinone **118** was described using a Curtius rearrangement. Vinyl phosphonate **113** was obtained by treatment of **112** with acetic anhydride and tetramethyl diamino methane as a formaldehyde equivalent. The crude vinyl phosphonate was used immediately in the Michael addition with **114**. The Michael addition was run in dichloromethane overnight followed by addition of t-butyl oxalyl chloride and 2 equivalents of Hunig's base in the same pot to provide **115** in 58% yield from **114** after chromatography. The allyl ester was deprotected using palladium catalysis to give **115**, which was purified by chromatography and subsequent trituration in ether/hexane to give 83% amorphous foam. Following Spry's one-pot procedure, **115** was converted to the acyl azide, rearranged to the isocyanate, and trapped as carbamate **116** with benzyl alcohol in 56% yield. Hydrogenation to enamine **117** was accomplished in 83% yield using 5% palladium on carbon in ethyl acetate at 40 psi on a Parr shaker. Acid-catalyzed hydrolysis of **117** was accomplished to give target compound **118** in 68% yield without substantial loss of the t-*Boc* and t-butyl ester protecting groups.[78]

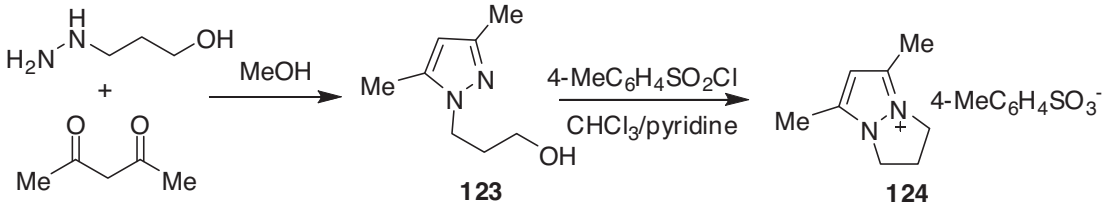


a) $(Ac)_2O$, $(Me)_2NCH_2N(Me)_2$; b) **114**, CH_2Cl_2; c) Hunig's base, $ClC(O)CO_2{}^{t}Bu$, CH_2Cl_2;
d) $Pd(OAc)_2/Ph_3P$, Et_3SiH, MeCN; e) 1) $(PhO)_2P(O)N_3$, Hunig's base, CH_2Cl_2/Benzene, 2) $PhCH_2OH$;
f) 5% Pd on C/$[H_2]$; g) THF/aqueous HCl, pH = 2.3

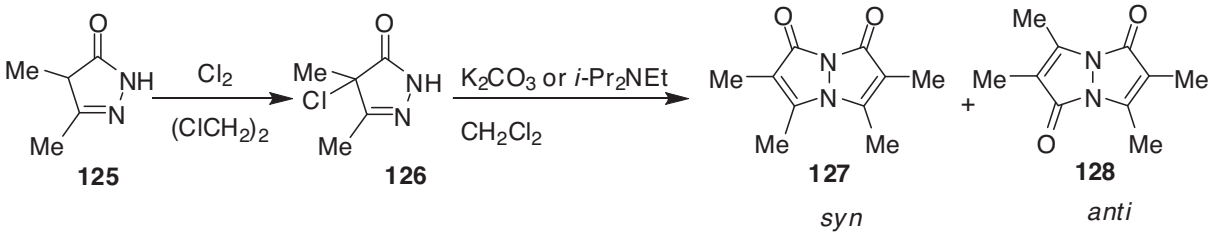
(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate **119** was tosylated and the product cyclocondensed with hydrazine to give 48% 4-(*R*,*S*)-(*tert*-butoxycarbonylamino)-3-oxo-1-pyrazoline **120**. Treatment of **120** with 37% aq. HCHO gave the 1-methylenepyrazolidinium ylide, which underwent cycloaddition with diallyl butynedioate to give 32.8% diallyl 7-(*R*,*S*)-(*tert*-butoxycarbonylamino)-8-oxo-1,5-diazabicyclo[3.3.0] oct-2-ene-2,3-dicarboxylate **121**. This was deprotected and the free amino group acylated with 2-thienylacetyl chloride to give 62% 7(*R*,*S*)-(*R*)-diallyl-7-oxo-6-(thiophen-2-ylmethylamino)-3,5,6,7-tetrahydropyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate **122**.[79−81]



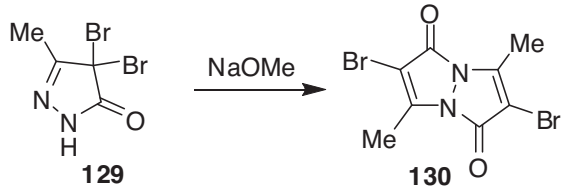
Cyclizing 3-hydrazinylpropan-1-ol in MeOH with acetylacetone gave 71% pyrazole **123**, which was tosylated at 0 °C with 4-tolylsulfonyl chloride in chloroform containing pyridine to give 5,7-dimethyl-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyrazol-4-ium toluenesulfonate **124**.[82]



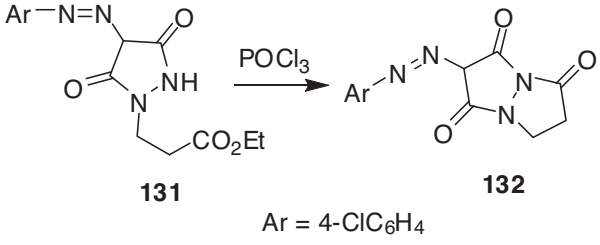
Chloropyrazolinone **126** was prepared by chlorination of pyrazolinone **125** by using chlorine in 1,2-dichloroethane, and was then hydrated with potassium carbonate in dichloromethane to afford both the fluorescent and no-fluorescent isomers 2,3,5,6-tetramethylpyrazolo[1,2-*a*]pyrazole-1,7-dione **127** and 2,3,6,7-tetramethylpyrazolo[1,2-*a*]pyrazole-1,5-dione **128**, respectively. The fluorescent isomer has the carbonyl groups in the proximal arrangement (*syn*, **127**) and the no-fluorescent isomer has carbonyl groups in the distal arrangement (*anti*, **128**).[83]



2,6-Dibromo-3,7-dimethyl-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-1,5-dione **130** was prepared by addition of 1 equivalent of sodium methoxide to pyrazolinone **129**. The molecular structure of **130** was determined by X-ray crystal structure.[84]

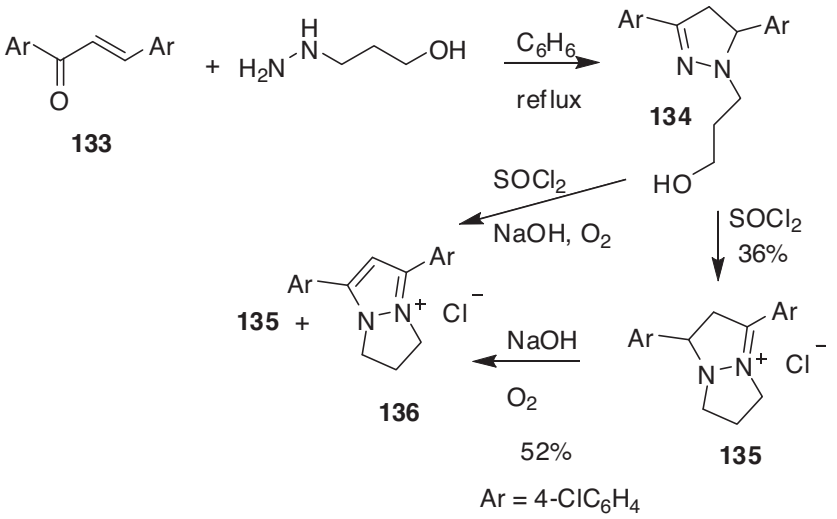


2-(p-Chlorophenylazo)tetrahydropyrazolo[1,2-*a*]pyrazole-1,3,7-trione **132** was prepared by the action of phosphorus oxychloride on **131**.[85]

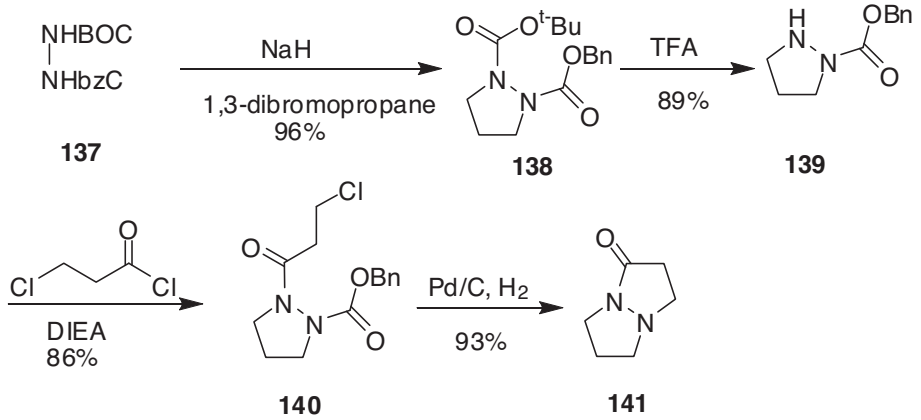


Chalcone **133** was treated with 3-hydrazinopropanol in refluxing benzene to give 3,5-bis(*p*-chlorophenyl)-2-pyrazoline **134**. Treatment of **134** with thionyl chloride in chloroform gave 5,7-bis-(*p*-chlorophenyl)-2,3,6,7-tetrahydro-1*H*-pyrazolo [1,2- *a*]pyrazol-4-ium chloride **135**. However, if the reaction of **134** with thionyl

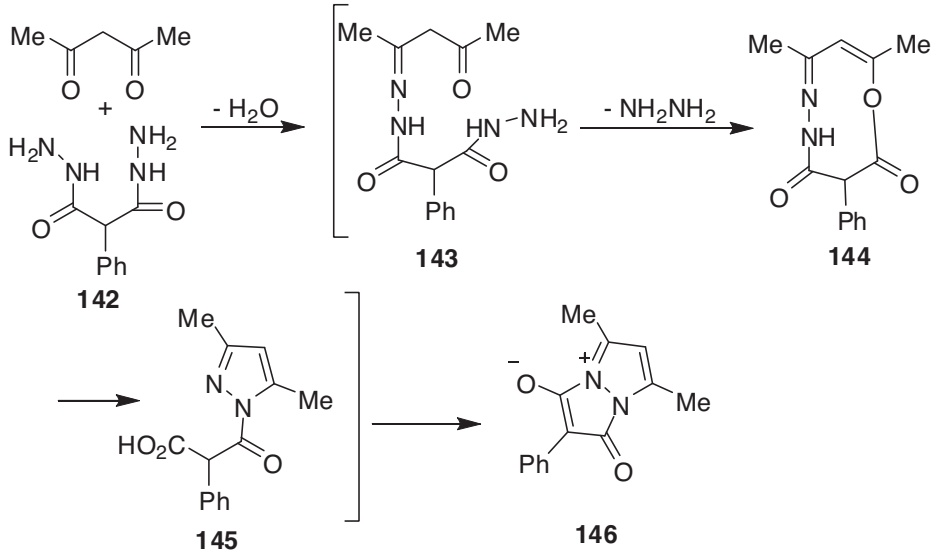
chloride was processed with aqueous sodium hydroxide, **135** and 5,7-bis-(*p*-chlorophenyl)-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyrazol-4-ium chloride **136** were obtained. Compound **136** could also be obtained by treating **135** with aqueous sodium hydroxide in the presence of air.[86]



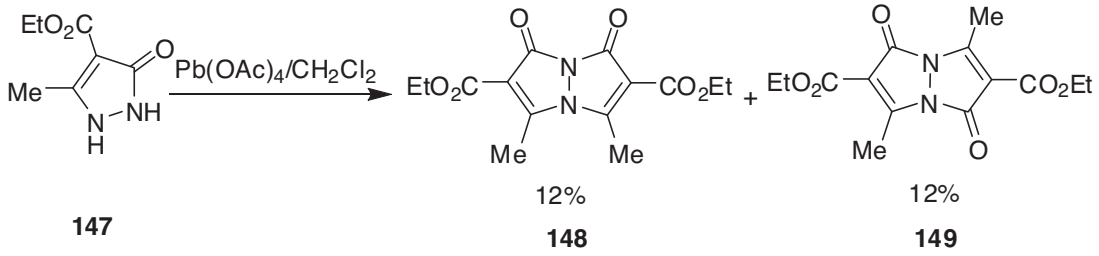
Generation of the carbamate dianion with sodium hydride and subsequent alkylation with dibromopropane provided pyrazolidine **138** in high yield (96%). At this stage, the BOC-protecting group was removed and monoprotected hydrazide **139** was acylated with commercially available 3-chloropropionyl chloride, giving key intermediate **140**. Catalytic hydrogenation to remove the Cbz-protecting group on **140** generated a transient intermediate that smoothly underwent an intermolecular exo-tet cyclization to tetrahydro-pyrazolopyrazolone **141**.[87]



Reaction of 2-phenylmalonic acid dihydrazide **142** with 2,4-pentandione in absolute ethanol at room temperature afforded pyrazolo[1,2-*a*]pyrazol-4-ium-3-olate **146**.[88]

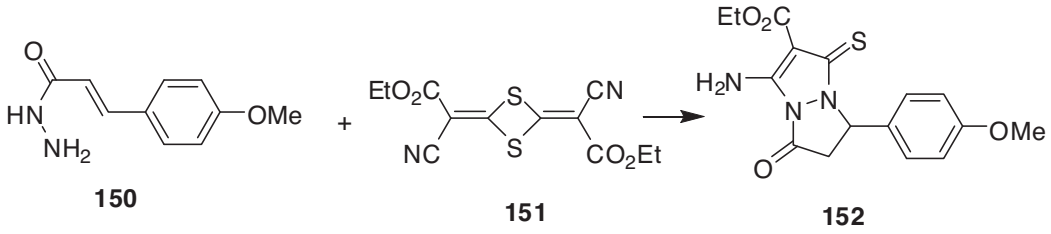


1,7-Dimethyl-3,5-di(oxo)-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2,6-dicarboxylic acid diethyl ester **148** (fluorescent substance) and 1,5-dimethyl-3,7-di(oxo)-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2,6-dicarboxylic acid diethyl ester **149** (phosphorescent substance) were prepared by action of palladium acetate on pyrazolinone **147**.[89]

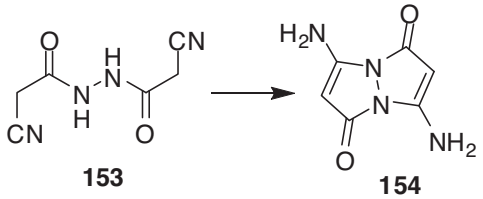


2.6. Miscellaneous methods

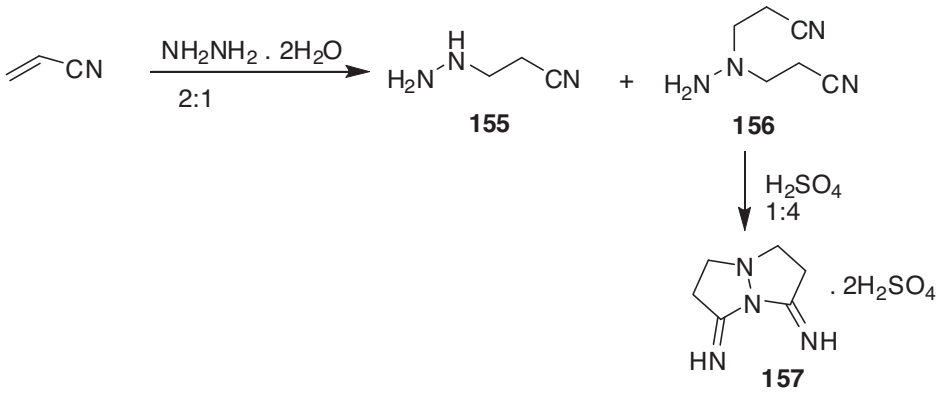
Pyrazolopyrazole **152** were prepared by treatment of 3-(4-methoxyphenyl)acrylohydrazide **150** with dithietane **151**.[90]



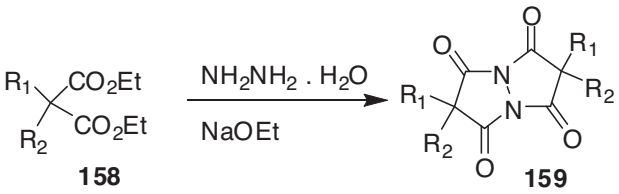
1,5-Diaminopyrazolo[1,2-*a*]pyrazole-3,7-dione **154**, useful as a coupling component for azo dyes, was prepared by cyclization of *N*,*N*'-bis(cyanoacetyl)hydrazine **153** in a solvent in the presence of an acid or base at 20 °C to the boiling point of the solvent.[91]



Acrylonitrile was treated with hydrazine hydrate in the ratio of 2:1 to give 3-hydrazinylpropanenitrile (8.8%) **155** and 3,3'-(hydrazine-1,1-diyl)dipropanenitrile **156** (82%). Treatment of **156** with sulfuric acid in the ratio of 1:4 gave 1,7-diiminoperhydropyrazolo[1,2-*a*]pyrazole-2H_2SO_4 **157** (65%).[92]

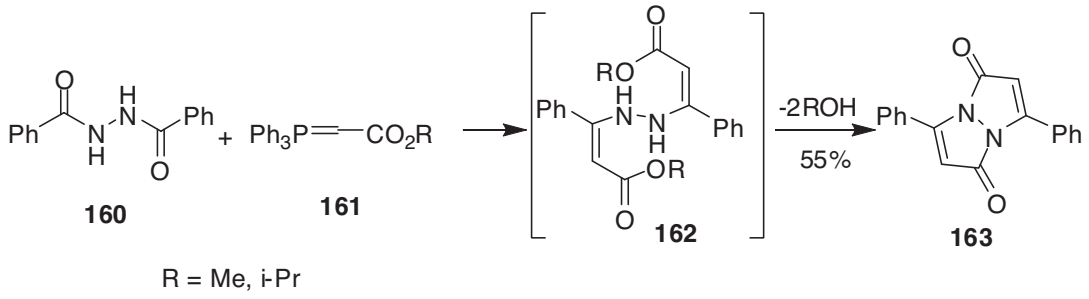


2,6-Dialkyl-l,3,5,7-tetraketopyrazo[1,2-*a*]pyrazoles **159** have been prepared by condensing esters of alkylmalonic acids **158** with hydrazine in the presence of sodium ethoxide.[93]



R_1 = R_2 = Et, Pr, Bu, isoamyl; R_1 = Et, R_2 = isoamyl, 4-hexyl, Ph

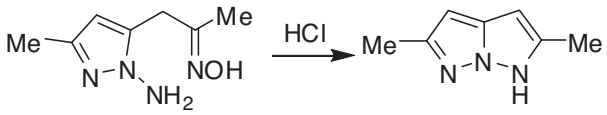
The reaction of dibenzoylhydrazide **160** with Wittig reagents **161** gave rise to 3,7-diphenylpyrazolo[1,2-*a*]pyrazole-1,5-diones **163**.[94]



R = Me, i-Pr

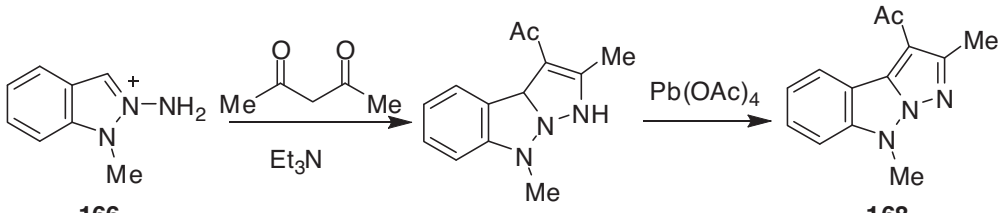
3. Pyrazolo[1,5-*b*]pyrazoles

Pyrazolo[1,5-*b*]pyrazole **165** was obtained by heating of 1-amino-3-methyl-5-(2-oxoiminopropyl)pyrazole **164** in acidic medium.[95]



164 **165**

Benzopyrazolopyrazole **168** was prepared in 30% yield from the reaction of 2-aminoindazolium salt **166** with acetyl acetone followed by treatment with lead acetate.[96]

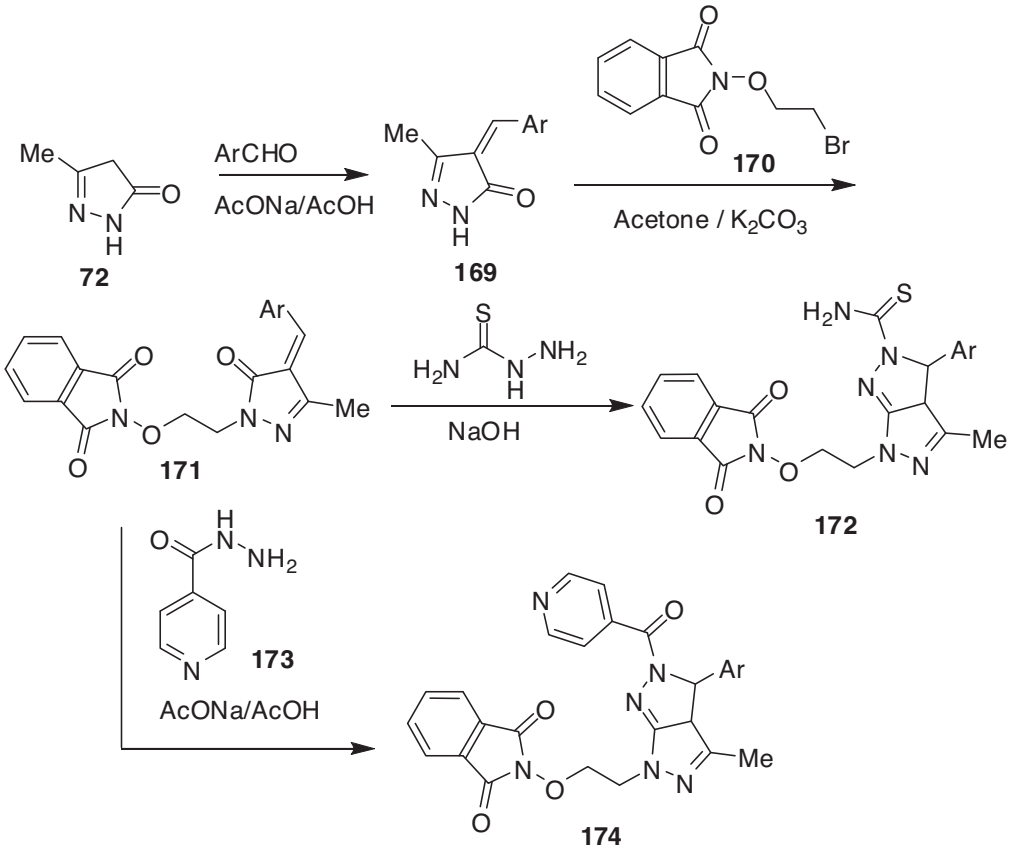


166 **167** **168**

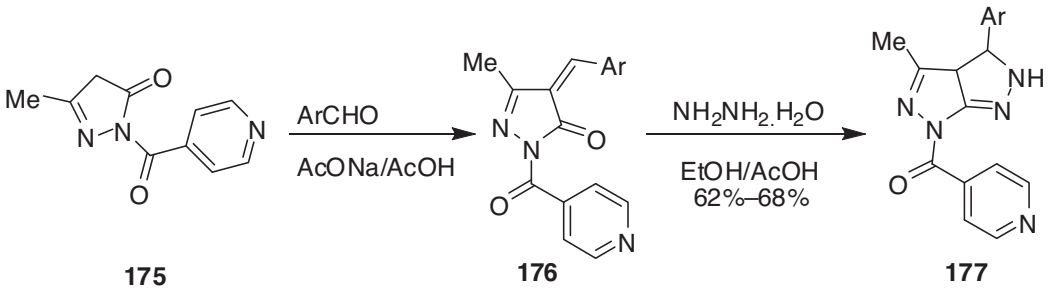
4. Pyrazolo[3,4-*c*]pyrazoles

4.1. Reaction of 4-arylidenepyrazol-5-ones with hydrazines and hydrazides

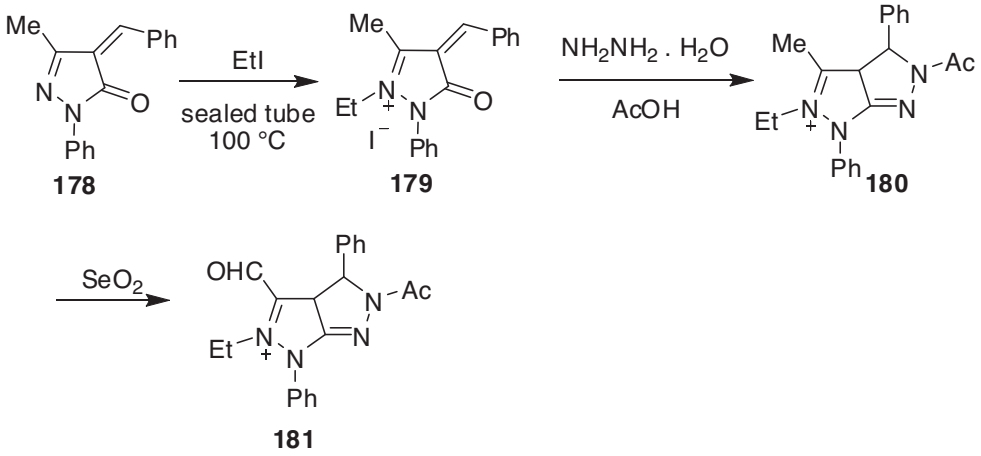
Compound **72** on condensation with substituted benzaldehydes in the presence of sodium acetate as a base furnished 5-methyl-4-substituted benzylidene-2,4-dihydro-3*H*-pyrazol-3-ones **169**. Treatment of **169** with phthalimidoxyethyl bromide **170** in acetone using K_2CO_3 as a base afforded 1-*N*-ethoxyphthalimido-3-methyl-4-(4-substituted benzylidene) pyrazol-5-one **171**. The 6-*N*-ethoxyphthalimido-4-methyl-3-(4-substituted phenyl)-2-thiocarbamoyl-3,3*a*-dihydro pyrazolo[3,4-*c*]pyrazoles **172**, in yields of 53%–65%, were obtained by the treatment of **171** with thiosemicarbazide in NaOH. Compounds **171** were converted to 6-*N*-ethoxyphthalimido-2-isonicotinoyl-4-methyl-3-(4-substitutedphenyl)-3,3*a*-dihydro pyrazolo[3,4-*c*]pyrazoles **174** in yields of 60%–67% by the cyclization with isonicotinohydrazide **173** in the presence of sodium acetate and acetic acid.[97]



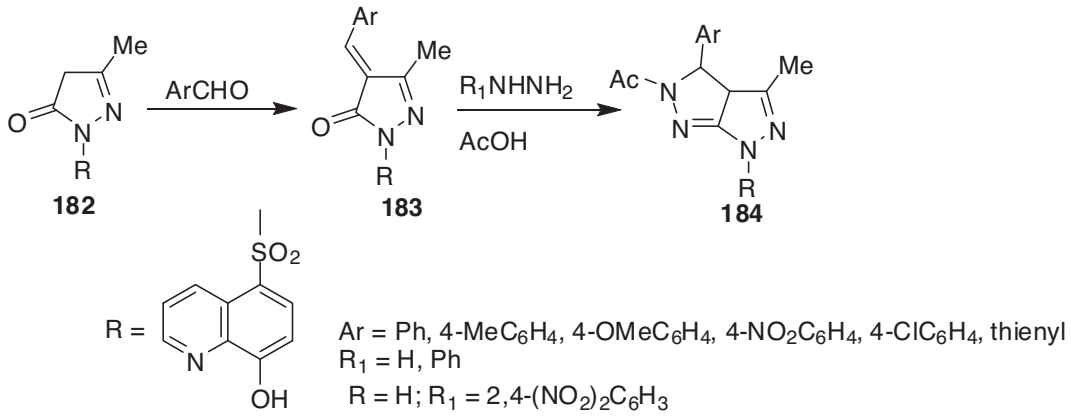
2-Isonicotinoyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **175**, upon condensation with various aldehydes, afforded the corresponding arylidene derivatives **176**. 1-Isonicotinoyl-3-methyl-4-(4-substituted phenyl)-3*a*,4-dihydropyrazolo[3,4-*c*]pyrazoles **177** were obtained via heterocyclization of arylidene derivatives **176** with hydrazine hydrate.[98]



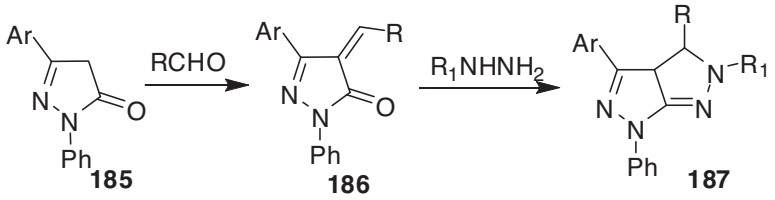
The reaction of ethyl iodide with 4-benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **178** gave quaternary salt **179**, which on reaction with hydrazine in acetic acid followed by oxidation with selenium oxide afforded tetrahydropyrazolo[3,4-*c*]pyrazol-2-ium derivative **181**.[99]



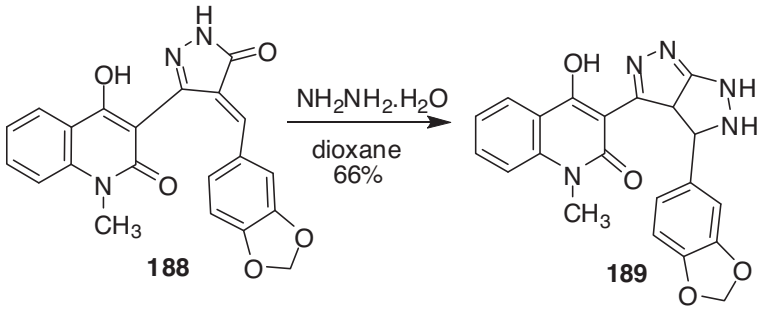
4-Arylidene-methyl-5-oxo-4,5-dihydropyrazoles **183** were prepared via the reaction of 3-methyl-5-oxo-4,5-dihydropyrazole **182** with aromatic aldehydes. Subsequently, compounds **183** were condensed with hydrazine to give 5-[(3'-ethyl-5'-acetyl-4'-substituted pyrazolo[3,4-*c*]pyrazoles **184**.[100−105]



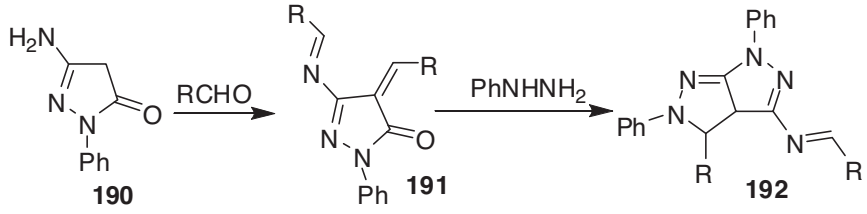
1,3-Diphenyl-2-pyrazolin-5-one **185** was condensed with *p*-methoxybenzaldehyde to give pyrazolinones **186**. Then condensed with hydrazine, it gave pyrazolopyrazole **187**.[103,106]



Cyclization of 3-[4-(benzo[1,3]dioxolylmethylene)-5-oxo-3-pyrazolyl]-4-hydroxy-1-methylquinolin-2(1*H*)-one **188** with hydrazine hydrate gave pyrazolopyrazole **189**.[107]

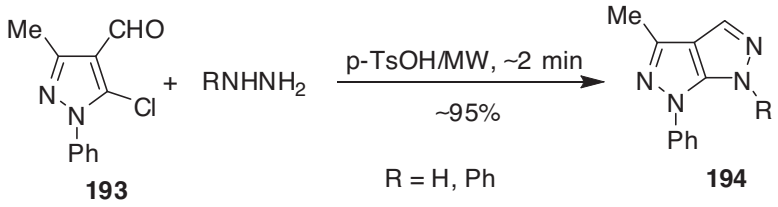


3-Amino-1-phenyl-2-pyrazolin-5-one **190** condensed with aromatic aldehyde in the presence of AcOH to give the corresponding dibenzylidene derivative **191**. The reactions of **191** with phenyl hydrazine gave pyrazolopyrazoles **192**.[108]

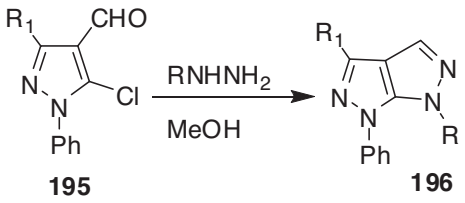


R = o-HOC$_6$H$_4$, p-MeOC$_6$H$_4$, p-Me$_2$NC$_6$H$_4$, p-HOC$_6$H$_4$, ferrocenyl

Reaction of 5-chloro-1*H*-pyrazole-4-carbaldehydes **193** with hydrazines under microwave irradiation in the presence of *p*-TsOH gave pyrazolo[3,4-*c*]pyrazoles **194**.[109]



Pyrazolo[3,4-*c*]pyrazoles **196** were prepared by reactions of 1,3-disubstituted-5-chloro-1*H*-pyrazole-4-carbaldehydes **195** with hydrazine hydrate or phenylhydrazine in methanol.[110−115]

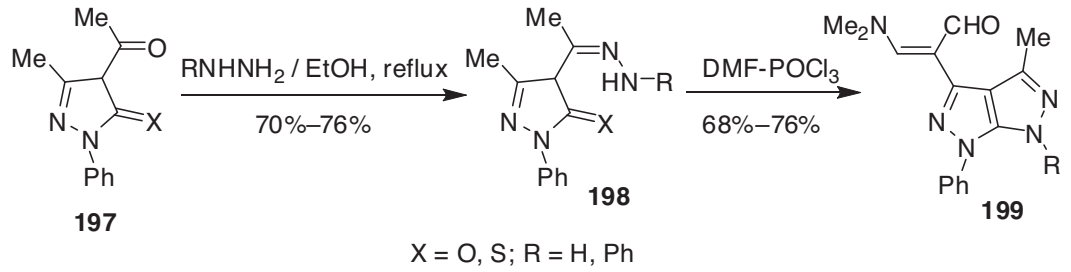


R = H, Ph, naphthyridine substituent; R$_1$ = Ph, Me, Pr

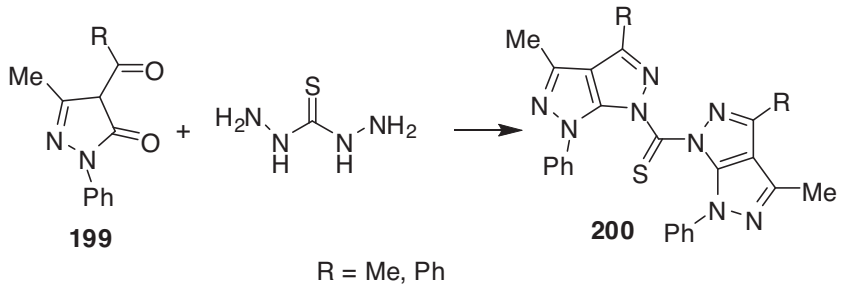
4.2. From 5-(oxo)thio-4-acylpyrazol

Hydrazonopyrazolone and thione derivatives **198** were prepared from 4-acetyl **197** by their condensation in boiling ethanol with hydrazine hydrate or phenyl hydrazine. Vilsmeier reaction on **198** at room temperature

(exothermic) simultaneously led to the deformylation of the 3-methyl group and ring closure to afford the corresponding fused pyrazolo[3,4-*c*]pyrazole aminoacroleins **199**.[116]

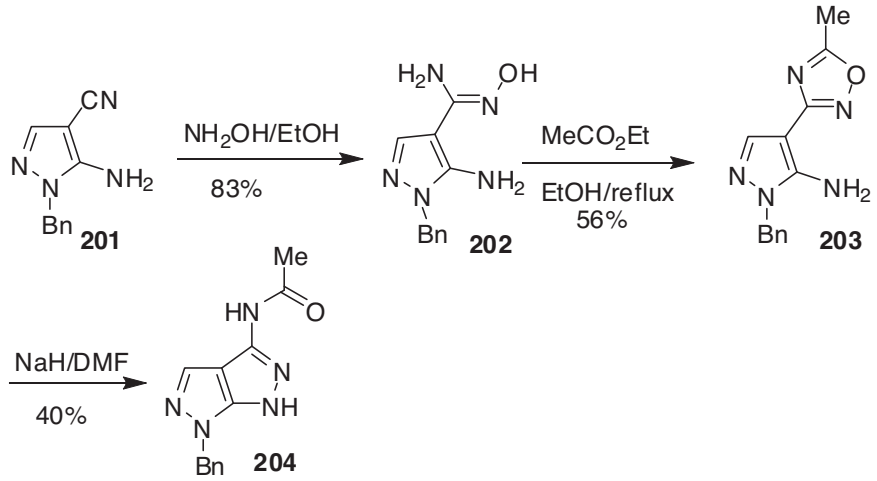


New bis[6-phenyl-4-methyl-3-substituted-pyrazolo[4,5-*d*]pyrazol-1-yl] thioketones **201** were obtained in good yield by the reaction of thiocarbohydrazide with 1-phenyl-3-methyl-4-acetyl/benzoyl-pyrazol-5-one **200**, followed by cyclization of the intermediate. These compounds exhibit excellent antimicrobial activity.[117]

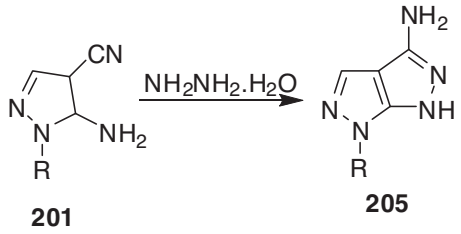


4.3. From 5-amino-4-cyanopyrazoles

The formation of pyrazolo[3,4-*c*]pyrazole **204** was accomplished by ring transformation of 1-benzyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-1*H*-pyrazol-5-amine **203** under thermal conditions.[118]

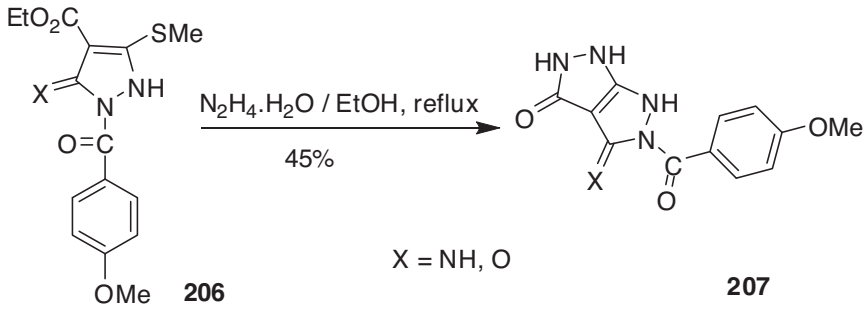


Pyrazolopyrazole **205** was prepared from aminocyanopyrazole **201** by reaction with hydrazine.[119,120]

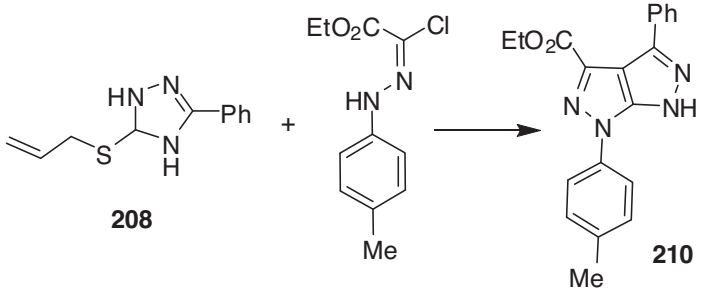


4.4. Miscellaneous methods

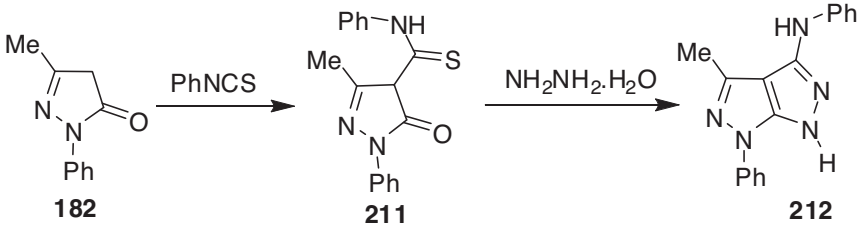
Pyrazolo[3,4-*c*]pyrazoles **207** in 45% yield were prepared by the cyclization of **206** with hydrazine in ethanol.[121,122]



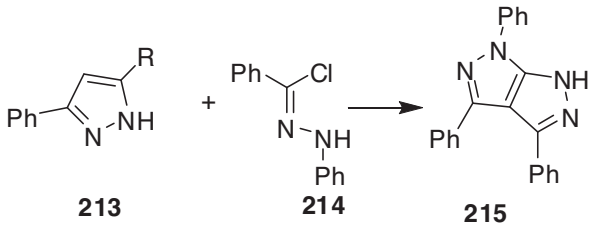
The cyclocondensation of 4,5-dihydro-3-phenyl-5-[(2-propenyl)thio]-1*H*-1,2,4-triazole **208** with ethyl 2-chloro-2-(2-p-tolylhydrazono)acetate **209** gave ethyl 4-phenyl-1-*p*-tolyl-1,6-dihydropyrazolo[3,4-*c*]pyrazole-3-carboxylate **210**.[123]



Compound **211** was prepared via reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one **182** with phenyl isothiocyanate. Compound **211** was converted to pyrazolopyrazole **212** through reaction with hydrazine.[124]



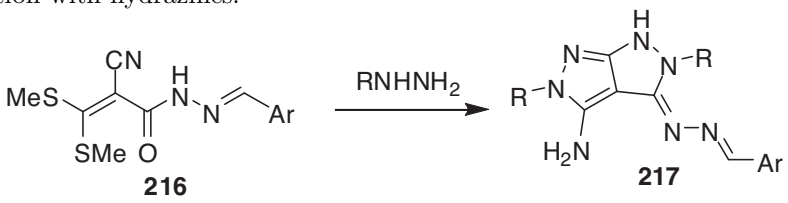
The behavior of several amino and hydroxy pyrazoles toward hydrazonyl halides is reported. Thus, pyrazoles **213** were reacted with hydrazonyl chloride **214** to give pyrazolopyrazole **215**.[125]



213 **214** **215**

R = H_2N, OH

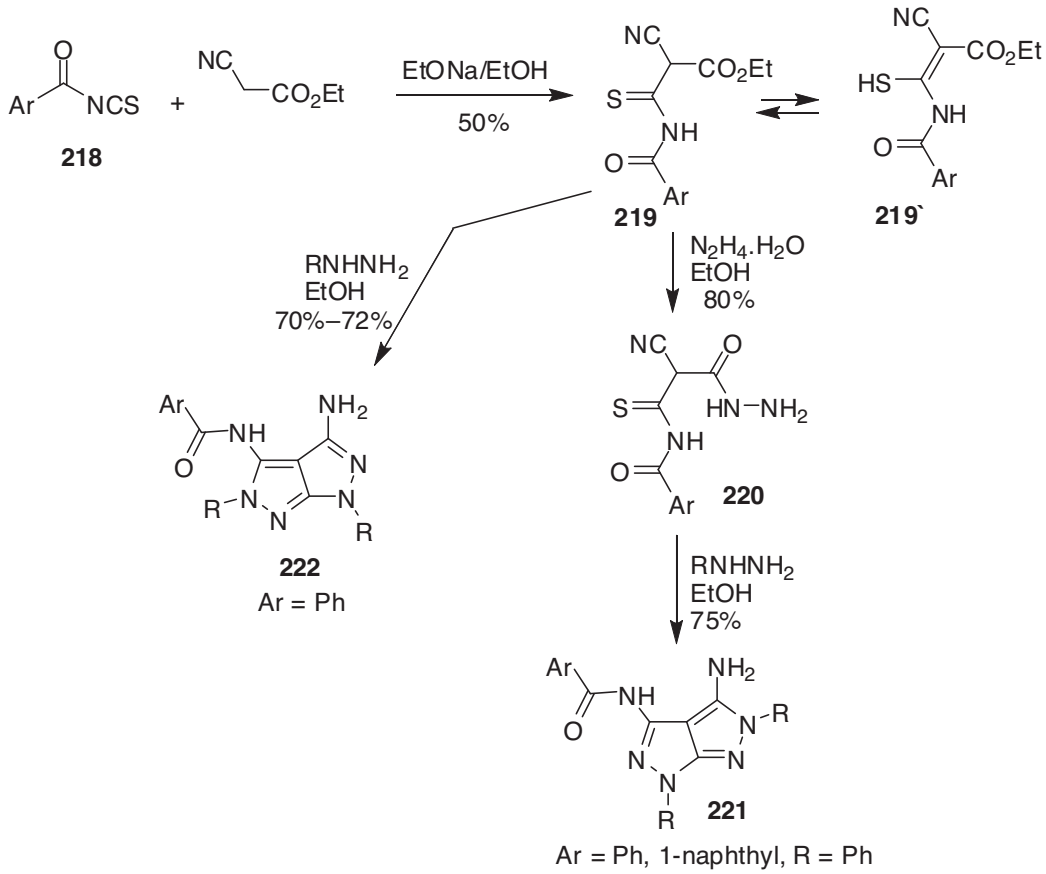
A convenient synthesis of pyrazolo[3,4-*c*]pyrazoles **217** using some novel α-cyanoketene dithioacetals **216** was reported by reaction with hydrazines.[126]



216 **217**

R = H, Ph; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

Aryl isothiocyanates **218** were reacted with the sodium salt of ethyl cyanoacetate to yield adducts **219**. Compounds **219** were reacted with hydrazine to give different products depending on the reaction conditions.



218 **219** **219`** **220** **221** **222**

Ar = Ph

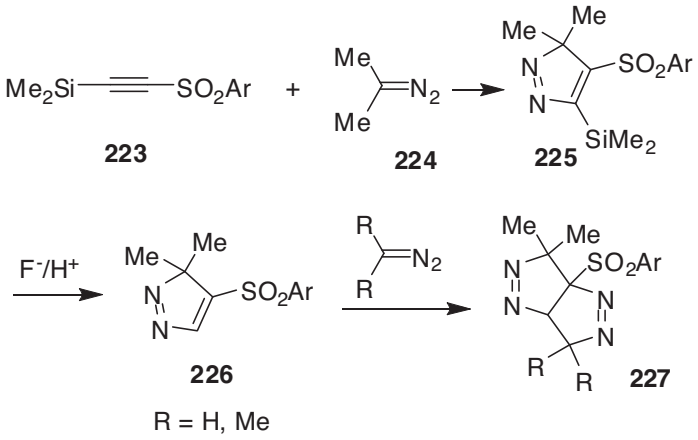
Ar = Ph, 1-naphthyl, R = Ph

Thus, they were reacted with hydrazine hydrate in the cold to give hydrazide derivative **220**. On the other hand, **219** or **220** reacted with excess phenylhydrazine in boiling ethanol to give pyrazolo[4,3-*c*]pyrazoles **221** or **222**, respectively.[127,128]

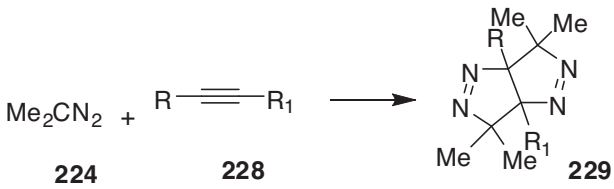
5. Pyrazolo[4,3-*c*]pyrazoles

5.1. Dipolar cycloaddition

1,3-Dipolar cycloaddition reaction of *p*-tolyl *P*-(trimethysilyl)-ethynylsulfone **223** with 2-diazopropane **224** in 16-crown-6 followed by potassium fluoride gave cycloadduct **225**. The desilylated 3*H*-pyrazoles **226** obtained were then allowed to react with either diazomethane or 2-diazopropane **224** to give **227**.[129]

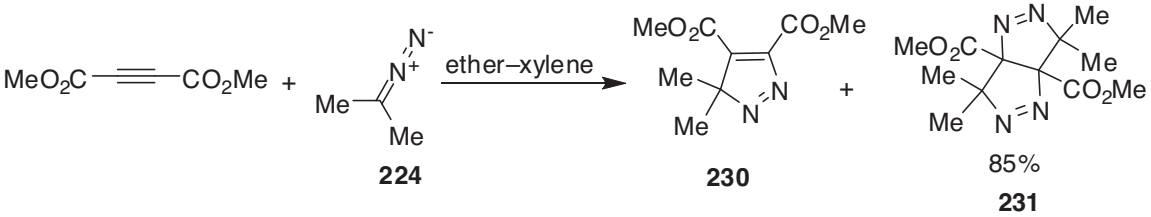


Pyrazolopyrazoles **229** were obtained in 60%–85% yield by a double 1,3-dipolar cycloaddition of 2-diazopropane **224** with alkynes **228**.[130]

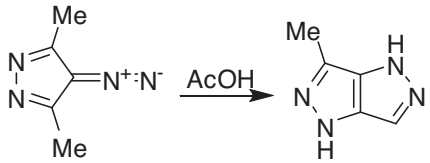


R = CO_2Me, R_1 = Ac, CN, Me; R = Ac, R_1 = CN

Dimethyl acetylenedicarboxylate is added dropwise at –20 °C to a solution of 2-diazopropane **224** in an ether–xylene mixture to give a mixture containing dimethyl 3,3-dimethyl-3*H*-pyrazole-4,5-dicarboxylate **230** and 85% dimethyl 3,3,6,6-tetramethyl-3,3a,6,6a-tetrahydropyrazolo[4,3-*c*]pyrazole-3a,6a-dicarboxylate **231**.[131]



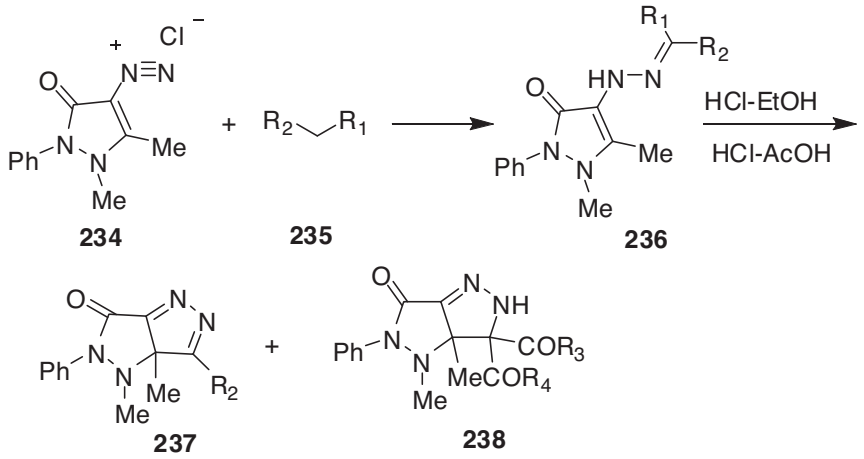
The intramolecular cyclization of 4-diazo-3,5-dimethylpyrazole **232** catalyzed by HOAc gave 1*H*,4*H*-3-methylpyrazolo[4,3-*c*]pyrazole **233**.[132]



232 **233**

5.2. From diazonium salts

Coupling reaction of pyrazolinediazonium chloride **234** with active methylene components **235** gave 55%–70% **236**, which on treatment with HCl-EtOH or HCl-AcOH gave 1,6a-dimethyl-2-phenyl-1,2-dihydropyrazolo[4,3-*c*]pyrazol-3(6a*H*)-one **237** and 1,1'-(3a,4-dimethyl-6-oxo-5-phenyl-2,3,3a,4,5,6-hexahydropyrazolo[4,3-*c*]pyrazole-3,3-diyl)dialkenone **238**.[133]



234 **235** **236**

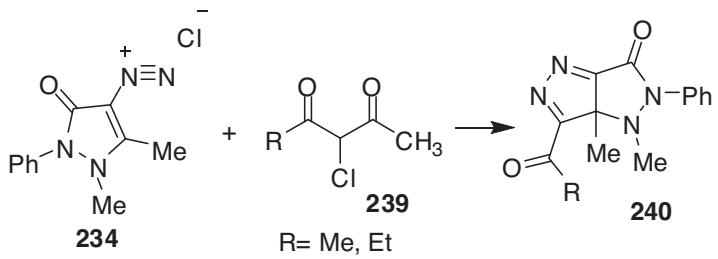
237 **238**

237: R_2 = CONHPh, $COC_6H_4NO_2$-3, $CONHC_6H_4Cl$-4

238: R_3 = Ph, R_4 = OEt; R_3 = Me, R_4 = NHPh

R_1 = cyano, R_2 = CONHPh, $COC_6H_4NO_2$-3;
R_1 = Ac, R_2 = $CONHC_6H_4Cl$-4, CONHPh, Ac, CO_2Et; R_1 = COPh, R_2 = CO_2Et

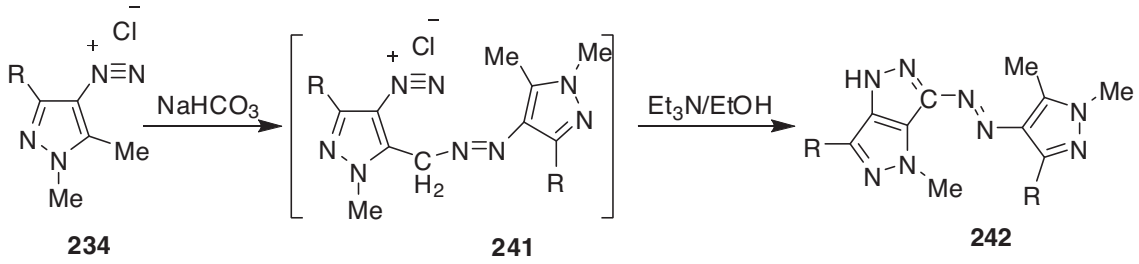
Reaction of diazotized **234** with α-chloro-β-diketones **239** in ethanol at room temperature for 2 h gave corresponding pyrazolopyrazolones **240** in 74% and 53% yield, respectively.[134]



234 **239** **240**

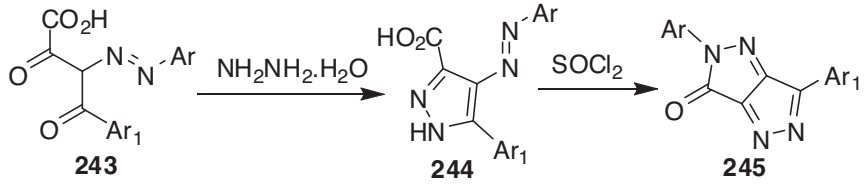
R= Me, Et

1,5-Dimethyl-3R-pyrazolyl-4-diazonium salts **234** were converted into corresponding 6-(1,5-dimethyl-3*R*-pyrazol-4-yl)azo-1-methyl-3*R*-*4H*-pyrazolo[4,3-*c*]pyrazoles **241** via intramolecular cyclization of intermediate **242**.[135]

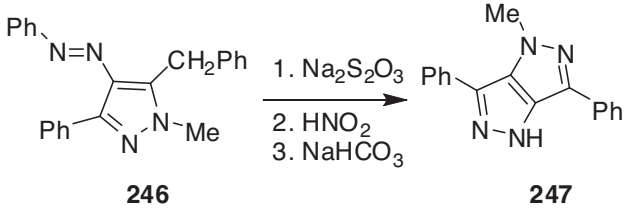


5.3. Miscellaneous methods

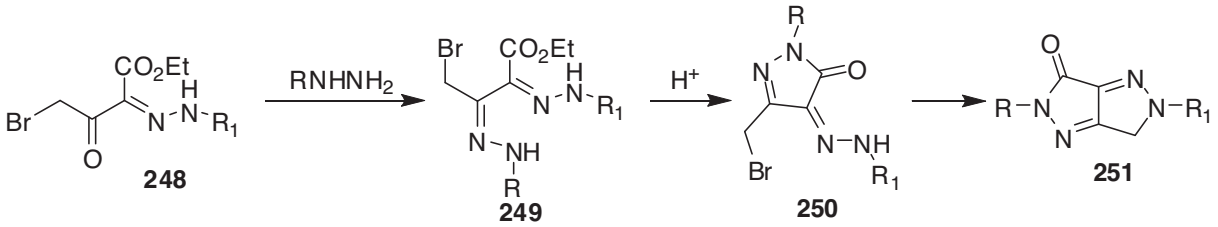
5-Aryl-4-(arylazo)-1*H*-pyrazole-3-carboxylic acids **244** were prepared by reaction of 4-aryl-3-(arylhydrazono)-2,4-dioxobutanoic acids **243** with hydrazine hydrate. Cyclization of **244** with thionyl chloride gave pyrazolopyrazolones **245**, which showed moderate activity against *Escherichia coli* and *Staphylococcus aureus*.[136]



Treatment of pyrazole **246** with disodium dithionite followed by diazotization with sodium nitrite and treatment with sodium bicarbonate gave 3,6-diphenyl-l-methyl-4*H*-pyrazolo[4,3-*c*]pyrazole **247**.[137]

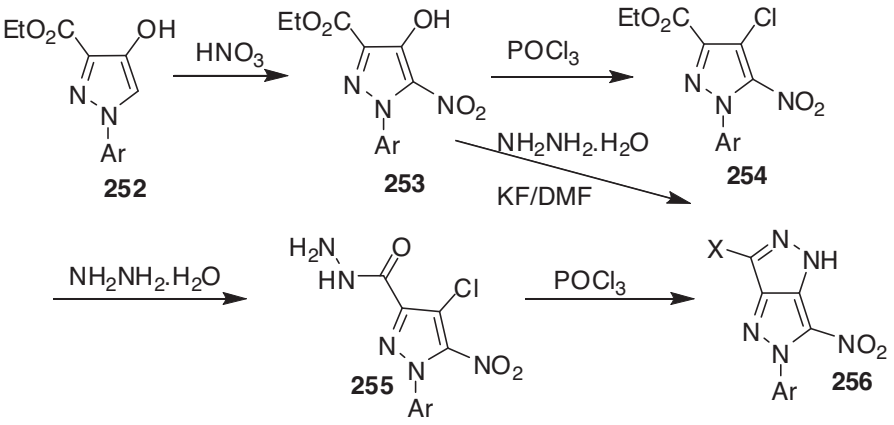


Arylhydrazonobromoacetoacetates **248** were reacted with arylhydrazines to give corresponding ethyl bromodioxobutanoate diarylhydrazones **249**, which on treatment with acid underwent cyclization to give corresponding hydropyrazolones **250**. Hydrazones **250** on treatment with a base underwent direct cyclization to give 2-substituted aryltetrahydropyrazolopyrazolones **251**.[138]



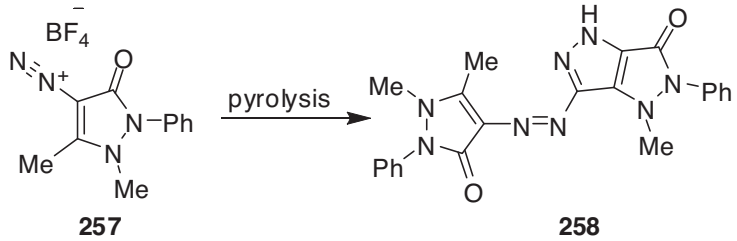
R = Ph or deriv., R_1 = 4-BrC_6H_4, 4-$O_2NC_6H_4$, 2,4,6-$Br_3C_6H_2$

Nitration of 1-aryl-3-carbethoxy-4-hydroxy-1*H*-pyrazoles **252** with concentrated nitric acid under different conditions gave corresponding 5-nitro derivatives **253**, which on treatment with phosphorus oxychloride afforded 1-aryl-3-carbethoxy-4-chloro-5-nitropyrazoles **254**. Treatment of **254** with hydrazine afforded acid hydrazide **255**, which on treatment with phosphorus oxychloride underwent chlorination–cyclization to form (**256**, R_1 = Cl). Alternatively, **253** on treatment with hydrazine in the presence of potassium fluoride in DMF afforded 5-aryl-1,5-dihydro-6-nitropyrazolo[4,3-*c*]pyrazol-3-ols (**256**, R_1 = OH), which on chlorination with $POCl_3$ furnished (**256**, R_1 = Cl).[139]

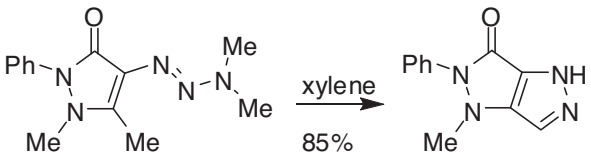


Ar = 4-$O_2NC_6H_4$, 2,4,6-$Br_3C_6H_2$; X = Cl; OH

The pyrolysis of antipyrine 4-diazonium fluoroborate **257** gave antipyrylazopyrazolopyrazolone **258**, which was formed by intermolecular and intramolecular coupling of the diazo compound at elevated temperature.[140]



1-Methyl-2-phenyl-1,2-dihydropyrazolo[4,3-c]pyrazol-3(4*H*)-one **260** was prepared by deamination and cyclization of either 1-(1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)-3,3-dimethyltriazen **259**.[141]



259 **260**

References

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