Advances in the chemistry of pyrazolopyrazoles

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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](image_url)

![Herbicides](image_url)

![anti-Alzheimer](image_url)

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.

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2. Pyrazolo[1,2-α]pyrazoles

There are a number of practically important routes to the synthesis of pyrazolo[1,2-α]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-α]pyrazoles 3 and 4,\(^{30}\) whereas 1,3-dipolar cycloaddition of the azomethine imines to dimethyl acetylenedicarboxylate (DMAD) afforded the corresponding pyrazolo[1,2-α]pyrazoles 5.\(^{31,32}\)

Cycloaddition of the ylide 6 with diallyl acetylenedicarboxylate gave the bicyclic pyrazolidinone 7.\(^{33}\)
**rel-(2R,3R)-N-Benzoylamino-6,7-bis(methoxycarbonyl)-2,3-dihydro-1-oxo-1H,5H-pyrazolo[1,2-a]pyrazoles 10** were achieved by cycloaddition of DMAD to (1Z)-rel-(4R,5R)-1-aryl-methylene-4-benzoylamino-5-phenyl-3-pyrazolidinone-1-azonmethine imines 8.\(^{34,35}\) Additionally, 3-pyrazolidinone azomethine imines 8 underwent 1,3-dipolar cycloaddition with olefinic dipolarophiles 9 and afforded stereoisomeric tetrahydro-1H,5H-pyrazolo[1,2-a]pyrazoles 11.\(^{36}\)

Svete et al., in 1997, reported the stereoselectivity reaction of (1Z)-rel-(4R,5R)-1-benzylidene-4-benzoylamino-5-phenyl-3-pyrazolidinon-1-azonmethinimine (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.
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).\textsuperscript{41} 2-Nitro- and 2-amino-5-oxoperhydropyrazolo[1,2-a]pyrazoles 28 were prepared by the condensation of 24 with nitroalkenes 26.\textsuperscript{42,43}

The enantioselective 1,3-dipolar cycloaddition of azomethine imines 30 to 2-acryloyl-3-pyrazolidinone 29 was catalyzed by Cu(OTf)\textsubscript{2}/bis(oxazoline) to give cycloadducts 31 with high diastereoselectivities (up to >96:4 exo/endo) and enantioselectivities (up to 98% ee).\textsuperscript{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 completed the preparation of C-3 carboxy-substituted bicyclic pyrazolidinones $35a$–$c$.

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 sulfinic. 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.

In 2009, Syroeshkina et al. reported the synthesis of 1,3-diaryl-2-nitrotetrahydro-1H,5H-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$_2$O.BF$_3$ catalyst. The same reaction with unsubstituted β-nitrostyrene produced only 1,3-diaryl-2-nitrotetrahydro-1H,5H-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$_2$O·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-1H,5H-pyrazolo[1,2-a]pyrazoles $46a$–$d$, which are potential inhibitors of neuronal NO synthase.

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 $48$. $48$. 

\[
\begin{array}{c}
\text{R} \quad \text{R} \quad \text{R} \quad \text{R} \\
\text{H} \quad \text{H} \quad \text{H} \quad \text{H}
\end{array}
\]
i) (ClCH₂)₂, reflux
ii) N-methylmorpholine

Pd(OAc)₂, Ph₃P
sod. 2-ethylhexanoate, acetone

N,N

CO₂allyl

CO₂Me

37a-c

R R₁

N

CO₂Me

38a-c

36

CO₂allyl

33

CO₂allyl

39

CO₂Me

40

CO₂allyl

33b

CO₂Me

41

Pd(OAc)₂, Ph₃P
sod. 2-ethylhexanoate, acetone

Ar₁

42

Ar₁

43

Ar₁

44a

Ar₁

44a

Ar₁

44b

Ar₁

45

Ar₂

45'

Ar₁

46

Ar₂

47

Ar₂

48

Ar₁

49

Ar₂

50

X = BF₄; BF₆

Ar₁

Ar₂

a 3-NO₂C₆H₄

b 4-MeC₆H₄

c 4-MeOC₆H₄

d 4-EtOC₆H₄

i, 0.5 mmol of 1, 0.4–0.6 g [bmim][BF₄]
or [bmim][PF₆] and 2 drops of Et₂O·BF₃

ii, 0.5 mmol of p-nitrostyrene 44

X = BF₄; BF₆
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.

\[
\begin{align*}
\text{Ar} = \text{Ph} &;& R = \text{CN, CO}_2\text{Ph} \\
\text{Ar} = 4\text{-MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4 &;& R = \text{CN}
\end{align*}
\]

2.2. Cycloaddition of azines to dipolarophiles

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

\[
\begin{align*}
\text{R} = \text{Me, Et, Bu}
\end{align*}
\]
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

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{N} \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{N} \quad \text{Me} \\
\text{Ph} & \quad \text{C}=\text{O} \\
\text{Ph} & \\
\end{align*}
\]

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

\[
\begin{align*}
\text{R}_1-\text{C}=\text{N} & \quad \text{N} \quad \text{C}=\text{N} \quad \text{R}_1 \\
\text{H} & \quad \text{H} & \quad \text{R}_1 & \quad \text{R}_1 \quad \text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{HO}_2\text{C} & \quad \text{HO}_2\text{C} & \quad \text{HO}_2\text{C} & \quad \text{HO}_2\text{C} \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} & \quad \text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{R}_1 & = \text{alkyl or aryl} \quad \text{R}_2 & = \text{H, Me, alkyl} \\
\text{2 mol CO}_2\text{Me} & \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{R} & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4, 2-\text{furyl}, 2-\text{thienyl} \\
\end{align*}
\]
Adib et al., in 2005, reported the synthesis of functionalized 7-oxo-1\textit{H},7\textit{H}-pyrazolo[1,2-\textit{a}]pyrazoles 73. Thus, isocyanides 70 and dialkyl acetylenedicarboxylates 71 in the presence of 2,4-dihydro-3\textit{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\textit{H},7\textit{H}-pyrazolo[1,2-\textit{a}]pyrazole derivatives 73 in 69\%–81\% yields.\(^{58}\)

\[
\begin{array}{c}
\text{R} = \text{cyclohexyl, Bu}, R_1 = \text{Me, Et; } R_2 = \text{Me, Ph}
\end{array}
\]

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.\(^{59}\)

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, \(R = \text{Me}\)) and 2-ethylmalonyl dichloride (80, \(R_1 = \text{Et}\)), 2-allylmalonyl dichloride (80, \(R_1 = \text{allyl}\)) gave 81.\(^{60,61}\)
Substituted anhydro-1-hydroxy-3-oxopyrazolo[1,2-α]pyrazolium hydroxides were prepared by treating 1,3-dicarbonyl compounds or with derivatives of pyrazoles or.

\[
\begin{align*}
\text{Route a:} & \quad \text{Cl}\text{-}\text{CO}\text{-R}_4 + \text{R}_2\text{-}N\text{=}\text{O}\text{=}\text{NH} \quad \xrightarrow{-\text{HCl}} \quad \text{R}_4\text{-}\text{N}\text{=}\text{O}\text{=}\text{N}\text{=}\text{O}\text{=}\text{R}_1 \\
\text{Route b:} & \quad \text{R}_4\text{-}\text{OH} + \text{R}_2\text{-}\text{CO}\text{-}\text{CO}\text{-}\text{R}_3 \quad \xrightarrow{-2\text{H}_2\text{O}} \quad \text{R}_4\text{-}\text{N}\text{=}\text{O}\text{=}\text{N}\text{=}\text{O}\text{=}\text{R}_1
\end{align*}
\]

\(R_1 = \text{H, Me, Ph}, \; R_2 = \text{H, benzyl}, \; R_3 = \text{H, Me, Ph}, \; R_4 = \text{aryl}\)

The addition of (chlorocarbonyl)phenylketene to pyrazol-3-one derivatives led to 3-hydroxypyrazolo[1,2-α]pyrazolediones.

\[
\begin{align*}
\text{7-Amino-3-hydroxy-5-imino-2,6-diarylpyrazolo[1,2-α]pyrazol-1(5H)ones} & \quad \text{were prepared in yields of 30%–39\% by cyclization of pyrazoles with dinitriles.}
\end{align*}
\]

Thermal cyclocondensation of pyrazoles with substituted diethyl malonates yielded 1-oxo-1\(H\)-pyrazolo[1,2-α]pyrazol-4-ium-3-olates. Olates were obtained by treating pyrazole with diacyl dichloride.
The reaction of 5-hydroxypyrazoles 94 with β-ketoesters 95 gave mainly pyrazolo[1,2-a]pyrazole-1,5-(1H,5H)-diones 96.67

With the reaction of 3-methylpyrazolin-5-one (94, \( R = \text{Me} \)) with ethyl acetoacetate and phosphorus tribromide in benzene, both \textit{syn}-97 and \textit{anti}-97' are formed.68

2.4. Cycloaddition of 1-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[1,2-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-aryloxy-2-aryl-1 H-pyrazolo[1,2-a]pyrazol-8-iun-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-iun-3-olate 107.73
Treatment of pyrazole derivatives 100 with an equimolar amount of 2-(chloromethyl)oxirane 108 in toluene afforded pyrazolopyrazoles 109.\textsuperscript{74}

3-(2-(Methylthio)pyrimidin-4-yl)-2-(o-tolyloxy)-6,7-dihydropyrazolo[1,2-a]pyrazol-1(5\textsubscript{H})-one 111 was prepared via heterocyclization of ketoester 110 with pyrazolidine dihydrochloride, used for the prevention of extracellular release of inflammatory cytokines.\textsuperscript{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.\textsuperscript{78}
(S)-Methyl 2-(tert-butoxycarbonylamino)-3-hydroxypropanoate 119 was tosylated and the product cyclodecondensed 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-methylene-pyrrozolidinium 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-1H-pyrazolo[1,2-a]pyrazol-4-ium tolenesulfonate 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).

2,6-Dibromo-3,7-dimethyl-1H,5H-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.

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

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-1H-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-1H-pyrazolo[1,2-a]pyrazol-4-iium chloride 136 were obtained. Compound 136 could also be obtained by treating 135 with aqueous sodium hydroxide in the presence of air.\(^8\)

![Chemical reaction diagram]

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.\(^8\)

![Chemical reaction diagram]

Reaction of 2-phenylmalonic acid dihydrazide 142 with 2,4-pentandione in absolute ethanol at room temperature afforded pyrazolo[1,2-a]pyrazol-4-iium-3-olate 146.\(^8\)
1,7-Dimethyl-3,5-di(oxo)-1\(^{1}H,5^{1}H\)-pyrazolo[1,2-\(a\)]pyrazole-2,6-dicarboxylic acid diethyl ester \(148\) (fluorescent substance) and 1,5-dimethyl-3,7-di(oxo)-1\(^{1}H,5^{1}H\)-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 \(20^\circ\) 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\(\text{SO}_4\) 157 (65%).

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

The reaction of dibenzoylhydrazide 160 with Wittig reagents 161 gave rise to 3,7-diphenylpyrazolo[1,2-\(a\)]pyrazole-1,5-diones 163.
3. Pyrazolo[1,5-b]pyrazoles

Pyrazolo[1,5-b]pyrazole 165 was obtained by heating of 1-amino-3-methyl-5-(2-oximinopropyl)pyrazole 164 in acidic medium.\(^9\)

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{N} \quad \text{NH}_2 \\
& \quad \text{Me} \quad \text{NOH} \\
\end{align*}
\]

HCl

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{N} \quad \text{Me} \\
& \quad \text{Me} \\
\end{align*}
\]

Benzopyrazolopyrazole 168 was prepared in 30% yield from the reaction of 2-aminoundazolium salt 166 with acetyl acetone followed by treatment with lead acetate.\(^9\)

\[
\begin{align*}
\text{N} \quad \text{N} \quad \text{NH}_2 & \quad \text{Me} \\
\text{O} \quad \text{Me} & \quad \text{O} \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Et}_3\text{N} & \quad \text{N} \quad \text{Me} \\
\text{Ac} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{N} \quad \text{N} \quad \text{Me} \\
\end{align*}
\]

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-3H-pyrazol-3-ones 169. Treatment of 169 with phthalimidoxethyl bromide 170 in acetone using K\(_2\)CO\(_3\) 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.\(^9\)
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].

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.

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

![Chemical structure](image)

**Reaction of 5-chloro-1H-pyrazole-4-carbaldehydes 193 with hydrazines under microwave irradiation in the presence of p-TsOH gave pyrazolo[3,4-c]pyrazoles 194.109**

![Chemical structure](image)

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

![Chemical structure](image)

### 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].

\[
\text{RNHNH}_2 / \text{EtOH, reflux} \rightarrow \begin{array}{c} \text{Me} \vphantom{\text{Me}} \\ \text{Ph} \vphantom{\text{Ph}} \end{array} \xrightarrow{\text{Me}_2N-\text{CHO}} \begin{array}{c} \text{Me}_2N \vphantom{\text{Me}_2N} \\ \text{Ph} \vphantom{\text{Ph}} \end{array}
\]

\( X = O, S; R = H, \text{Ph} \)

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.

\[
\begin{array}{c} \text{Me} \vphantom{\text{Me}} \\ \text{N} \vphantom{\text{N}} \\ \text{O} \vphantom{\text{O}} \\ \text{Me} \vphantom{\text{Me}} \\ \text{R} \vphantom{\text{R}} \end{array} + \begin{array}{c} \text{H}_2\text{N} \vphantom{\text{H}_2\text{N}} \\ \text{N} \vphantom{\text{N}} \\ \text{S} \vphantom{\text{S}} \\ \text{NH}_2 \vphantom{\text{NH}_2} \end{array} \rightarrow \begin{array}{c} \text{Me} \vphantom{\text{Me}} \\ \text{N} \vphantom{\text{N}} \\ \text{N} \vphantom{\text{N}} \\ \text{S} \vphantom{\text{S}} \\ \text{N} \vphantom{\text{N}} \end{array}
\]

\( R = \text{Me}, \text{Ph} \)

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)-1H-pyrazol-5-amine [203] under thermal conditions.

\[
\begin{array}{c} \text{CN} \vphantom{\text{CN}} \\ \text{NH}_2 \vphantom{\text{NH}_2} \\ \text{Bn} \vphantom{\text{Bn}} \end{array} \xrightarrow{\text{NH}_2\text{OH/EtOH}} \begin{array}{c} \text{N} \vphantom{\text{N}} \\ \text{N} \vphantom{\text{N}} \\ \text{Bn} \vphantom{\text{Bn}} \end{array} \xrightarrow{\text{MeCO}_2\text{Et}} \begin{array}{c} \text{Me} \vphantom{\text{Me}} \\ \text{N} \vphantom{\text{N}} \\ \text{NH}_2 \vphantom{\text{NH}_2} \\ \text{Bn} \vphantom{\text{Bn}} \end{array}
\]

Pyrazolopyrazole [205] was prepared from aminocyanopyrazole [201] by reaction with hydrazine.
4.4. Miscellaneous methods

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

The cyclocondensation of 4,5-dihydro-3-phenyl-5-[(2-propenyl)thio]-1\textsubscript{H}-1,2,4-triazole 208 with ethyl 2-chloro-2-(2-p-tolylhydrazono)acetate 209 gave ethyl 4-phenyl-1-\textit{p}-tolyl-1,6-dihydropyrazolo[3,4-c]pyrazole-3-carboxylate 210.\textsuperscript{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.\textsuperscript{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.\textsuperscript{125}
A convenient synthesis of pyrazolo[3,4-c]pyrazoles 217 using some novel α-cyanoketene dithioacetals 216 was reported by reaction with hydrazines.\textsuperscript{126} 

\[
\begin{align*}
\text{MeS} & \text{CN} \text{(NH)} \text{Ar} + \text{RNHNH}_2 \\
216 & \text{RNHNH}_2 \\
217
\end{align*}
\]

\[ R = \text{H, Ph; Ar = Ph, 4-MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4 \]

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.
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.\(^\text{127,128}\)

5. Pyrazolo[4,3-c]pyrazoles

5.1. Dipolar cycloaddition

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

Pyrazolopyrazoles 229 were obtained in 60%–85% yield by a double 1,3-dipolar cycloaddition of 2-diazopropane 224 with alkynes 228.\(^\text{130}\)

Dimethyl acetylenedicarboxylate is added dropwise at \(-20\,^\circ\text{C}\) 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,6a-tetrahydropyrazolo[4,3-c]pyrazole-3a,6a-dicarboxylate 231.\(^\text{131}\)
The intramolecular cyclization of 4-diazo-3,5-dimethylpyrazole 232 catalyzed by HOAc gave 1,4H,4H-3-methylpyrazolo[4,3-c]pyrazole 233. 132

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(6aH)-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

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

\[
\begin{align*}
\text{R} = \text{H, } & \text{C} = \text{C} - \text{Ph}
\end{align*}
\]

\[\begin{array}{c}
\text{N} & \text{N} & \text{Me} \\
\text{N} & \text{R} & \text{N} & \text{Cl} \\
\text{NaHCO}_3 \\
\end{array}\]

\[\begin{array}{c}
\text{N} & \text{N} & \text{Me} \\
\text{N} & \text{R} & \text{N} & \text{Cl} \\
\text{NaHCO}_3 \\
\end{array}\]

\[\begin{array}{c}
\text{N} & \text{N} & \text{Me} \\
\text{N} & \text{R} & \text{N} & \text{Cl} \\
\text{NaHCO}_3 \\
\end{array}\]

5.3. Miscellaneous methods

5-Aryl-4-(arylazo)-1H-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*.\(^\text{136}\)

\[
\begin{align*}
\text{Ar} = \text{Ph, 4-MeOC}_6\text{H}_4; \text{Ar}_1 = 4-\text{ClC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4
\end{align*}
\]

Treatment of pyrazole 246 with disodium dithionite followed by diazotization with sodium nitrite and treatment with sodium bicarbonate gave 3,6-diphenyl-1-methyl-1H-pyrazolo[4,3-c]pyrazole 247.\(^\text{137}\)

Arylhydrazonobromoacetoacetates 248 were reacted with arylhydrazines to give corresponding ethyl bromodioxobutanoate diarylhydrazones 249, which on treatment with acid underwent cyclization to give corresponding hydroxyrazolones 250. Hydrazones 250 on treatment with a base underwent direct cyclization to give 2-substituted aryltetrahydropyrazolopyrazolones 251.\(^\text{138}\)
Nitration of 1-aryl-3-carbethoxy-4-hydroxy-1H-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, R₁ = Cl). Alternatively, 253 on treatment with phosphorus oxychloride in the presence of potassium fluoride in DMF afforded 5-aryl-1,5-dihydro-6-nitropyrazolo[4,3-c]pyrazol-3-ols (256, R₁ = OH), which on chlorination with POCl₃ furnished (256, R₁ = Cl).¹³⁹

The pyrolysis of antipyrine 4-diazonium fluoroborate 257 gave antipyrazopyrazolopyrazolone 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(4H)-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
References


48. Syroeshkina, Y. S.; Kachala, V. V.; Ovchinnikov, I. V.; Kuznetsov, V. V.; Nelyubina, Y. V.; Lyssenko, K. A.; Makhova, N. N. *Mendeleev Commun.* 2009, 19, 276–278.


