A concise review on synthesis, reactions and biological Importance of thienopyrazoles

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Abstract

Pyrazoles are five membered heterocycles constitute a highly significant class of compounds in organic synthesis. Nowadays, pyrazoles and condensed pyrazoles have attracted substantial attention of the scientists owing to their excellent pharmacological and agrochemical properties. Pyrazole derivatives exhibit a wide range of pharmacological effects such as: anticancer, antioxidant, anti-inflammatory, antipyretic, analgesic, antimicrobial, antidepressant, antiviral, antihypertensive, anti-glaucoma, anti-tubercular, sodium channel blocker, anxiolytic, neuroprotective and anti-diabetic activities. This review casts light on recent methodologies for the synthesis and reactions of thienopyrazole moiety. This follow-up may encourage scientists to create new routes towards the thienopyrazole nucleus with important biological activity.

Keywords: Thieno[2,3-c]pyrazoles, thieno[3,4-c]pyrazoles, thieno[3,2-c]pyrazoles, synthesis, reactions.
1. Introduction

Thienopyrazoles occupy a unique position in medicinal chemistry as a result of their broad spectrum of biological activities. Thieno[2,3-c]pyrazoles are considered as important scaffolds in medicinal chemistry which exhibit antitumor, antiviral, antimicrobial and anti-inflammatory activities. They are used as antioxidants against the toxicity of 4-nonylphenol in Clarias gariepinus (African catfish). Also, thieno[2,3-c]pyrazoles are an important class of potent kinase inhibitors, potassium channel blockers, inhibitors of interleukin-2-inducible tyrosine kinase and selective inhibitors of PDE7A which is responsible for allergy, immunological and inflammatory diseases. Moreover, thieno[3,4-c]pyrazoles show remarkable analgesic, anti-inflammatory and antipyretic activities in mice or rats, as well as a anti platelet-aggregation activity in vitro. Also, thieno[3,2-c]pyrazoles were identified as a new class of bacterial cell wall biosynthesis inhibitors and antimicrobial agents against different strains of fungi and bacteria as well as anti-tubercular agents against Mycobacterium tuberculosis H37RV.

Thienopyrazoles are organic compounds in which a pyrazole and a thiophene ring are fused to form a single unit. Depending on the position of the sulfur atom in the thiophene ring with respect to diazo group in pyrazole ring, there are three different regioisomers Figure (1).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Structures of thieno[2,3-c]pyrazole, thieno[3,2-c]pyrazole and thieno[3,4-c]pyrazole.
2. Synthesis of Thieno[2,3-c]pyrazole Compounds Starting from Thiophene

Sherif et al\textsuperscript{24} reported that the Gewald-reaction of phenylsulfonylacacetophenone 1 with a mixture of elemental sulfur and malononitrile in DMF and triethylamine led to the formation of the corresponding 2-amino-4-phenyl-5-phenylsulfonyl-thiophene-3-carbonitrile 2 in 68\% yield. Compound 2 could be annulated to the corresponding thieno[2,3-c]pyrazole derivative 3 upon reaction with hydroxylamine hydrochloride followed by heating in pyridine. The reaction might proceed by nucleophilic addition of hydroxylamine to the nitrile group to afford the corresponding oxime 4 which underwent ring closure by loss of a water molecule upon heating in pyridine to give aminothieno[2,3-c]pyrazole 3. The latter compound could be obtained directly by the reaction of amino-cyano compound 2 with hydroxylamine in acetic acid and sodium acetate Scheme 1.

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle] (a) at (0,0) {\textbf{Scheme 1}};
\node[draw,rectangle,minimum width=5cm] (b) at (2,0) {\textbf{Scheme 2}};
\end{tikzpicture}
\end{center}


\begin{center}
\begin{tikzpicture}
\node[draw,rectangle] (a) at (0,0) {\textbf{Scheme 2}};
\node[draw,rectangle,minimum width=5cm] (b) at (2,0) {\textbf{Scheme 2}};
\end{tikzpicture}
\end{center}
3. Synthesis of Thieno[2,3-c]pyrazoles Starting from Pyrazole

Zhongwen Wang et al. synthesized thieno[2,3-c]pyrazoles starting from 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (8). Thus, reaction of 8 with formaldehyde diethyl dithioacetal S-oxide (FAESO) in THF in the presence of NaH afforded diethyl dithioacetal 9, which was converted into 5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl-acetic acid derivatives 10a,b upon treatment with alcoholic HCl. Stirring of the carboxylic acid 10a,b with CS₂ and KOH in DMSO overnight at room temperature followed by addition of alkyl halide yielded the ring-closed thieno[2,3-c]pyrazoles 11a-c Scheme 3.

![Chemical structure of 8, 9, 10a, b, 11a, c, and 12]

**Scheme 3**

Cyclocondensation of bis(3-methyl-1-phenyl-1H-pyrazole-4-form-5-yl)disulfane (12) with phenylacetic acid produced a mixture of thiopyranopyrazole 13 and thienopyrazole 14 Scheme 4.

![Chemical structures of 12, 13, and 14]

**Scheme 4**

The proposed mechanism for the formation of products 13, 14 is described below in Scheme 5.
4,5-Dihydro-3-methyl-1-phenyl-5-thioxo-1H-pyrazole-4-carboxaldehyde (15) was reacted with nitromethane in the presence of dibenzoyl peroxide, Et₃N in ethanol to produce 5-nitro-3-methyl-1-phenylthieno[2,3-c]pyrazole (16) Scheme 6.

Reaction of 3-(4-pyrazolyl)acrylic acids (17a-e) with excess thionyl chloride in the presence of benzyl triethyl ammonium chloride afforded 4-chlorothieno[2,3-c]pyrazole-5-carbonyl chlorides 18a-e, which were converted into the corresponding acids 19a-e Scheme 7.
Scheme 7

On the other hand, Akritopoulou-Zanze et al. reported that the protected 5-methyl-2,4-dihydro-pyrazol-3-one 20 with p-methoxybenzyl chloride was converted into 5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde using the Vilsmeier reagent, which in turn reacted with methyl thioglycolate in MeOH in the presence of Na$_2$CO$_3$ and gave 22a,b. Removing of the protecting group (e.g. p-methoxybenzyl (PMB) or bis(p-methoxyphenyl) methyl (BPMPM)) from 22 afforded the corresponding methylthieno[2,3-c]pyrazole-5-carboxylate 23 (Scheme 8).

Scheme 8

5-Chloro-3-methyl (or phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde 24 was reacted with methyl thioglycolate in methanol in the presence of sodium methoxide to give methyl thienopyrazole carboxylate which was saponified with methanolic sodium hydroxide to produce the corresponding carboxylic acid 25a,b.

Scheme 9.
In a similar procedure, 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid ethyl ester 26 was prepared from the reaction of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde with ethyl thioglycolate in EtOH in the presence of sodium ethoxide\(^\text{64}\) (Scheme 9).

\[
\text{Scheme 9}
\]

Chloropyrazole aldehydes 27a-d reacted with thioglycolic acid in aqueous ethanolic alkali under displacement of the chloride atom by a thioglycolic acid residue followed by intramolecular condensation to form 3-substituted thieno[2,3-c]pyrazole-5-carboxylic acids 28a-d which in turn underwent decarboxylation to produce the corresponding thieno[2,3-c]pyrazoles 29e-g\(^\text{45}\) (Scheme 10).

\[
\text{Scheme 10}
\]

Norbert Haider et al\(^\text{46}\) reported that condensation of chloropyrazole carbaldehyde 8 with hydroxylamine in ethanol at ambient temperature led to the formation of the corresponding oxime 30. The latter compound was subjected to dehydration in boiling acetic anhydride to give the chloro-carbonitrile 31. Interaction of compound 31 with methyl thioglycolate in boiling methanol containing fused potassium carbonate afforded methyl 4-amino-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate (32) (Scheme 11).

4-Bromo-3-methyl-1-phenyl-2-pyrazolin-5-one (33) was reacted with ethyl 3-mercaptocrotonate in equimolar ratio in ethanol to afford thieno[2,3-b]pyrazole 34\(^\text{47}\) (Scheme 12).
Zaitsev et al.\textsuperscript{48,49} found a new method for preparing of thieno[2,3-c]pyrazole derivatives starting from dinitropyrazole derivative 35. The carbonitrile 37 was synthesized from dinitropyrazole 35 by two methods. According to the first method, reaction of 35 with dimethyl formamide dimethyl acetal (DMF-DMA) followed by nitrosation with sodium nitrite solution in HCl afforded the isonitroso-aldehyde 36. Treatment of 36 with trifluoroacetic anhydride and 4-dimethylaminopyridine (DMAP) resulted in the corresponding pyrazole carbonitrile 37 according to the reported procedure. In the second method, oxidation of the methyl group of 4-methyl-3,5-dinitropyrazole 35 afforded the corresponding carboxylic acid 38, which was esterified to give ester 39. By treatment with aqueous ammonia, ester 37 was converted into carboxamide 40, which was treated with phosphorus pentoxide to give the carbonitrile 37. Carbonitrile 37 was reacted with thioglycolic acid anilide in the presence of two equivalents of potassium carbonate in boiling acetonitrile to give the substituted thieno[2,3-c]pyrazole 42. Evidently, carbonitrile resulting from displacement of the 5-NO\textsubscript{2} group underwent Thorpe-Ziegler-cyclization in situ at the CN group to give bicyclic thienopyrazole compound 42 (Scheme 13).

Zaki et al.\textsuperscript{50} reported a new method for synthesizing 5-substituted 4-amino-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazoles (47a-f). When 3-methyl-1-phenyl-1,4-dihydropyrazole-5-one (43) was subjected to react with Vilsmeier’s reagent, the 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (8) was obtained in a quantitative yield. Condensation of aldehyde 8 with hydroxylamine hydrochloride in ethanol in the presence of sodium acetate yielded the corresponding 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde oxime (30). The pyrazole aldehyde oxime 30 was dehydrated using acetic anhydride into the corresponding 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbonitrile (31). All attempts to synthesize thieno[2,3-c]pyrazole through the converting of chloro-pyrazolecarbonitrile 31 into the mercaptopyrazole carbonitrile 44 using thiourea in ethanol, the traditional method for other substrates, followed by reaction with α-halogenated compounds, failed to give the same starting material 33. The previous results forced them to search for another method to synthesize thienopyrazoles 47a-f. The desired result was achieved by the reaction of elemental sulfur with chloropyrazole in the presence of sodium borohydride through reduction of sulfur in ethanol to afford non-isolated intermediate sulfonyl sodium salt 45, which was used in-situ for the next reaction with α-halogenated compound to afford S-alkylated mercaptopyrazole carbonitrile 46a–f. The latter compounds 46a–f underwent Thorpe-Ziegler cyclization upon heating in ethanolic sodium ethoxide solution to give the target 4-amino-5-substituted thieno[2,3 c]pyrazoles 47a-f Scheme 14.
Scheme 13

Scheme 14
1-Phenyl-3-(pyridin-3-yl)-1H-thieno[2,3-c]pyrazole-5-carboxylic acid ethyl ester (50) was synthesized by the reaction of 5-chloro-1-phenyl-3-(pyridin-3-yl)-1H-pyrazole-4-carbaldehyde (49) with ethyl bromoacetate and sodium sulfide. First, reaction of 2-phenyl-5-pyridin-3-yl-2,4-dihydro-pyrazol-3-one (48) with Vilsmeier-Haack reagent gave 5-chloro-1-phenyl-3-(pyridin-3-yl)-1H-pyrazole-4-carbaldehyde (49) in 55% yield. Treatment of 49 with ethyl bromoacetate and sodium sulfide in ethanol produced 1-phenyl-3-(pyridin-3-yl)-1H-thieno[2,3-c]pyrazole-5-carboxylic acid ethyl ester (50) in 70% yield (Scheme 15).

![Scheme 15](image)

A simple and practical six-step synthesis of new 1-methyl-1H-thieno[2,3-c]pyrazoles from 3-amino-1H-pyrazole-4-carboxylic acid ethyl ester were reported by Patrick Toto et al. The alkylsulfonyl pyrazoles 54a-c were prepared from 51a, 52, and 53 respectively, through the method reported by Morimoto et al. for the synthesis of 3,5-dichloropyrazole-4-carboxylic acids. The 3-substituted ethyl pyrazole-5-sulfonylacetate derivatives 54a-c were synthesized by the reaction of 3-substituted ethyl 4-bromo-N-methyl- (bromo, amino and iodo) pyrazole-4-carboxylate 51a, 52 and 53 respectively with ethyl bromoacetate and sodium sulfide in DMF. Base-catalyzed cyclization of the S-alkylated pyrazoles 54a and 54b was accomplished by the use of sodium ethoxide in toluene, to afford the expected ethyl 4-hydroxythieno[2,3-c]pyrazole-5-carboxylate derivatives 55a and 55b. Moreover, cyclization of the amine analog 54c under the same conditions yielded the imine derivative 56, which probably came from the self-condensation of the expected amino thieno fused compound 54c Scheme 16.

Gernot A. Eller et al. have synthesized thieno[2,3-c]pyrazole from pyrazole derivatives using Sonogashira coupling method, starting from easily accessible and commercially available 1,3-disubstituted-5-chloro-1H-pyrazoles 57a,b, a second halogen substituent was introduced at position 4 of the pyrazole nucleus by a standard halogenation protocol (I₂ – IO₃⁻) to obtain the corresponding 5-chloro-4-iodopyrazoles 58a,b. The latter compounds were selectively linked to phenylacetylene in a Sonogashira cross-coupling reaction, yielding only the 4-(phenylethynyl)pyrazoles 59a,b in good yields (87–92%). In the final reaction step, compounds 59a,b were reacted with sodium sulfide in dimethyl formamide to produce the target fused heterocyclic ring system of compounds 60a,b Scheme 17.
Scheme 16

Scheme 17
Magdy W. Sabaa et al.\textsuperscript{55} and Samira T. Rabie et al.\textsuperscript{56} have synthesized thieno[2,3-c]pyrazole using the Gewald reaction. The N-phenyl pyrazolone \textbf{43} undergoes the Gewald reaction and reacts with sulfur and malononitrile in equimolar ratios under reflux for 3 h in presence of triethyl amine (TEA) and absolute ethanol as a solvent to give the aminocyano derivative of thienopyrazole \textbf{61} (Scheme 18).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme18.png}
\captionof{scheme}{Scheme 18}
\end{scheme}

### 4. Synthesis of Thieno[3,4-c]pyrazoles Starting from Thiophene

\textit{N-}Cyclopentyl-\textit{N}-(2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydrazono-1,6-dihydropyridine-3-sulfonamide \textbf{(62)} was reacted with methyl 4-oxotetrahydrothiophene-3-carboxylate \textbf{(63)} to give \textit{N-}cyclopentyl-\textit{N}-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-6-(3-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazol-2(3H)-yl)pyridine-3-sulfonamide \textbf{(64)} in 97\% yield, which, upon treatment with acetic acid, gives \textit{N-}cyclopentyl-\textit{N}-(2,3-dihydroxypropyl]-6-(3-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazol-2(3H)-yl)pyridine-3-sulfonamide \textbf{(65)} in 30\% yield\textsuperscript{57} (Scheme 19).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme19.png}
\captionof{scheme}{Scheme 19}
\end{scheme}

Reaction of aldehyde \textbf{66} with protected hydrazine (tert-butyl carbazate t-BocNHNH\textsubscript{2}) in THF in the presence of TsOH produced the corresponding hydrazone intermediate which upon treatment with 20\% H\textsubscript{2}SO\textsubscript{4} gave the thienopyrazole \textbf{68} in 78\% yield\textsuperscript{58-60} (Scheme 20).
Scheme 20

In similar manner, aldehyde 66 reacted with phenylhydrazine in the presence of TsOH in THF followed by treatment with 30% H₂SO₄ gave a mixture of two derivatives of thienopyrazole 69 and 70 in 50 and 5% yield respectively (Scheme 21).

Scheme 21

The reaction might proceed by hydrolysis of the 1,4-dioxolane ring to ketone group followed by condensation of phenyl hydrazine with an aldehyde group and loss of H₂O of the enol form of keto group, or by condensation with ketone group followed by loss of H₂O from the enolised form of aldehyde as outlined below (Scheme 22).

Giulia Menozzi et al.²⁹ reported synthesis of a series of 1-aryl-1,6-dihydro-4H-thieno[3,4-c]pyrazol-4-ones (74 a-f) by cyclization of 3-[(2-arylhydrazino)methylene]thiophene-2,4(3H,5H)-diones (73 a-f). The thiophene-2,4-diones 73a-f were prepared by the reaction of 3-dimethylaminomethylene thiophene-2,4-(3H,5H)-dione (72) with arylhydrazines (Scheme 23).
Pier Giovanni Baraldi et al.\textsuperscript{61, 62} reported the synthesis of 2-alkyl- or 2-aryl-3-aminothieno[3,4-c]pyrazoles (77a-l) from the reaction of alkyl or aryl hydrazine hydrochlorides with 4-cyano-3-oxotetrahydro-thiophene.
(75) in refluxing ethanol. Alternatively, condensation of 75 with phenylhydrazine in refluxing ethanol afforded a mixture of hydrazine thiophene 76 and amino-N-phenylthienopyrazole 77a in equivalent yields. Furthermore, compound 76 was converted to thienopyrazole 77a in excellent yield upon treatment with 5% HCl in ethanol Scheme 24.

Scheme 24

Pier Giovanni Baraldi et al.\textsuperscript{61} utilized this method for the regioselective synthesis of 2-alkyl- or 2-aryl-3-aminothieno[3,4-c]pyrazoles 77. Several alkyl- or arylhydrazine hydrochlorides on condensation with 4-cyano-3-oxotetrahydrothiophene (75) in refluxing ethanol gave the thienopyrazoles in excellent yields. The regioselectivity of this process has been confirmed by the treatment of 75 with phenylhydrazine, which
generated a mixture of hydrazone intermediate 76 and 2-phenyl-3-amino thieno[3,4-c]pyrazole (77a). Hydrazones 76 on treatment with 5% HCl in ethanol underwent tautomerization followed by cyclization to afford the thieno[3,4-c]pyrazole derivative 77a through formation of intermediate 76’. (Scheme 25).

5. Synthesis of Thieno[3,4-c]pyrazoles Starting from Pyrazole

Bratenko et al.\textsuperscript{63} reported the synthesis of 2,4-dihydro-6H-thieno[3,4-c]pyrazol-6-one 83 by means of an intramolecular cyclization of 4-sulfanyl-methyl pyrazole-3-carboxylic acids 82 via treatment with DCC/THF. Ethyl N-phenyl-4-formylpyrazole-5-carboxylate (78) was reduced by sodium borohydride to the corresponding alcohol 79. Treatment of 79 with thionyl chloride followed by reaction with thiourea afforded the corresponding compound 81 (Scheme 26).

![Scheme 26](image)

Galal H. Elgemeie et al.\textsuperscript{64} reported synthesis of thieno[3,4-c]pyrazole ring system by a new method. It has been found that pyrazolin-5-one 20 reacts with carbon disulfide in the presence of sodium ethoxide to afford the sodium dithiolate 84. The latter compound 84 was readily monoalkylated to give the stable sodium salt of monoalkylthio derivative 85. Thus, one equivalent of phenacyl bromide gave the corresponding sodium salt of monoalkylated product 85. Compound 85 was cyclized to afford the thienopyrazole-4-thiol 86 upon refluxing with sodium ethoxide followed by acidification (Scheme 27).

Alan D. Payne\textsuperscript{65} synthesized 3H-thieno[3,4-c]pyrazoles substituted with methyl and tert-butyl substituents 90a,b from 3-hexyne-2,5-diol 96a,b. Compounds 87a,b were oxidized by the Jones reagent to afford dione 88a,b. The crude diones 88a,b were not purified but used directly in the 1,3-dipolar addition reaction with 2-diazopropane to give the known adducts 89a,b. The reaction of 89a,b in anhydrous tetrahydrofuran at room temperature under argon with phosphorus pentasulfide and sodium hydrogen carbonate gave the thienopyrazoles 90a,b in variable yields, 10-46% (Scheme 28).
A series of thieno[3,4-c]pyrazoles were prepared by El-Saraf et al. via reaction of the 3-aminopyrazolin-5-one 91 with CS$_2$ and different molar ratios of a variety of halo compounds having an active methylene under phase transfer condition (PTC) which afforded compounds 92-97 (Scheme 29).
Scheme 29

The reaction of aryl 5-bromomethyl-1H-1-phenylpyrazole-4-yl ketone 98a-d with thioacetamide in ethanol gave 4-aryl-1-phenyl-1H-thieno[3,4-c]pyrazoles 99a-d in high yields\(^{67}\) (Scheme 30).

Scheme 30
6-(Benzimidazol-2-yl)-5-(substituted phenyl)-3,5-dihydro-5a-H-thieno[3,4-c]pyrazoles 101a,b were prepared by reaction of benzimidazolyl ketones 100a,b with hydrazine hydrate in ethanol68 (Scheme 31).

Scheme 31

The reaction of thiolan-3-one 102 with DMF-DMA (1.2 equiv.) in PhCH3at 110°C over 4 h was found to afford a mixtures of isomeric dimethylaminovinyl ketones 103 and 104 in a ratio of 35:65 and overall yield 98%.69 The latter two compounds 103, 104 upon treatment with hydrazine derivatives in the presence of Na2CO3 and EtOH gave 3,4-dihydrothieno[3,2-c]pyrazoles 105a-d and 3,5-dihydrothieno [3,4-c]pyrazoles 106a-d, respectively (Scheme 32).

Scheme 32


Gao, et al70 have reported synthesis for two isomers of thieno[3,2-c]pyrazoles. 3-Methyl-1-phenyl-1H-thieno[3,2-c]pyrazole 109 and 5-chloro-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole 110 by the reaction of 1-(3-
chloro-2-thienyl)-ethanone 107 or 1-(2,5-dichloro-3-thienyl)-ethanone 108 with phenylhydrazines followed by cyclization of the corresponding hydrazones using CuI and K$_3$PO$_4$ in DMSO (Scheme 33).

Scheme 33

Bindi et al.$^{22}$ have reported a novel series of 3-amino-1H-thieno[3,2-c]pyrazole derivatives demonstrating high potency in inhibiting aurora kinases. The synthetic pathway to methyl 3-amino-1H-thieno[3,2-c]pyrazole-5-carboxylate 116 is outlined below. Thus 4,5-dibromo-thiophene-2-carboxylic acid methyl ester (112) was obtained from commercially available 4,5-dibromo-thiophene-2-carboxylic acid (111) by treatment with methanol and sulfuric acid at reflux temperature. The formylation was performed exploiting an efficient halogen–Mg exchange with i-PrMgCl and subsequent reaction with DMF to obtain 4-bromo-5-formyl-thiophene-2-carboxylic acid methyl ester (113). Next, compound 113 was converted to the corresponding oxime by treatment with hydroxylamine hydrochloride and dehydrated with trifluoroacetic anhydride to give the 5-cyano-derivative 114. The reaction of benzophenone hydrazone with compound 114 in toluene at 100°C using palladium acetate (3 mol %) and 1,10-bis (diphenylphosphino)-ferrocene (DPPF) (6 mol %) as a catalytic system gave 4-(N-benzylidenehydrazino)-5-cyano-thiophene-2-carboxylic acid methyl ester (115). Treatment of 115 with hydrochloric acid efficiently gave the condensed amino pyrazole nucleus with loss of benzophenone. Thus, the desired scaffold 3-amino-1H-thieno[3,2-c]pyrazole-5-carboxylic acid methyl ester (116) was produced along with its corresponding acid (30%), which was reconverted to its methyl ester by treatment of the crude residue with methanol and sulfuric acid at reflux. The subsequent class expansion was carried out by synthesizing different amides at positions 3 and 5. Reaction of compound 116 with an excess of acyl halide in DCM led to the 1,3-bisacyl-derivatives, which were easily converted to the 3-acylamino derivatives 117a,b by treatment with TEA/MeOH (Scheme 34).

Airey et al.$^{71}$ have reported a practical synthesis of multi gram quantities of 1H-thieno[3,2-c]pyrazole in which the Jacobson reaction serves as the key step. Two methods of synthesis of 122 have been reported by Gronowitz and co-workers.$^{72}$ The first synthesis started from 3-bromothiophene-2-carbaldehyde 118, which was subjected to aromatic nucleophilic substitution with sodium azide to give the azide 119 in 48% yield. Treatment of azide 119 with hydrazine hydrate in boiling ethanol containing a small amount of acetic acid gave the desired thieno[3,2-c]pyrazole 122. In the second method, also starting from azide 119, the azide group was reduced to amine 120, which was then diazotized. Reduction of the resulting diazonium salt 121 gave the unsubstituted thieno[3,2-c]pyrazole 122. Thus, 122 was available in a 7.7% overall yield by a two-step sequence or in a 5.7–12% yield through a four-step sequence (Scheme 35).
A possible route to 122, which they discarded, involved reduction of the nitro thienyl imine 123 by triethylphosphite to give the 2-arylthieno[3,2-c]pyrazole 124. Scheme 36.
Scheme 36

When a solution of ester 125 was added slowly to a suspension of lithium aluminum hydride in refluxing 1,4-dioxane,\textsuperscript{74} subsequent work up gave crude (2-methyl-3-thienyl)amine 126 which was then used directly in the cyclization step as shown below. Cyclization of 126 was affected simply by acetylation of the amine group in toluene in the presence of potassium acetate, followed by treatment of the resulting mixture with isoamyl nitrite and heating for several hours. The overall yield of this three-steps sequence to unsubstituted thieno[3,2-c]pyrazole 122 was 47%. Condensation of the methyl group of compound 126 with the nitroso group followed by ring closure upon elimination of ROH gave 127 Scheme 37.

Scheme 37

Another route for synthesizing the thieno[3,2-c]pyrazoles 130-133 according to a patent\textsuperscript{75} is reported. Reduction of 2-methyl-3-nitrothiophenes 128a,b with H\textsubscript{2}/Pd-C led to the formation of the corresponding thienylamines 129a,b which underwent nitrosation followed by cyclization reaction upon treatment with isobutyl nitrite in acetic anhydride to give the N-acetyl thienopyrazoles 130a,b. Replacement of H3 in pyrazole by iodide was carried out by the reaction with I\textsubscript{2} in sodium methoxide solution followed by decarboxylation to
afford 131a,b. Reaction of 131a,b with benzoyl chloride yielded the $N$-substituted benzoyl derivatives 132a-c. The latter compounds underwent Suzuki coupling reactions to give the corresponding $N$-benzoyl-3-phenylthieno[3,2-c]pyrazoles 133a-c (Scheme 38).

**Scheme 38**

Reaction of 2-benzoyl thiophene phenyl hydrazones 134a-d with lead tetraacetate in the presence of boron trifluoride-etherate in methylene chloride and benzene at room temperature by shaking for one minute afford 1,3-disubstituted thieno[3,2-c]pyrazoles 135a-d\(^7\) (Scheme 39).

**Scheme 39**

In a similar manner, reaction of phenylhydrazines in EtOH in the presence of AcOH at 80°C with thienyl phenyl ketone 136 gave the corresponding phenyl hydrazone 137 which in the presence of montmorillonite K-10 in 1,2-dichlorobenzene at 130°C under O\(_2\) balloon atmosphere was cyclized into thieno[3,2-c]pyrazole 138 in 81% yield\(^7\) (Scheme 40).
7. Synthesis of Thieno[3,2-c]pyrazoles Starting from Pyrazoles

3-Methyl-1H-pyrazol-5(4H)-one (20) was reacted with elemental sulfur in the presence of triethylamine in ethanol to give 4-mercapto-3-methyl-1H-pyrazol-5(4H)-one (139). Compound 139 was reacted with ethyl acetoacetate in the presence of triethylamine in ethanol to give mercapto pyrazolopyrazoledione 140, which in turn was reacted with compounds containing activated methylene in the presence of triethylamine to give thienopyrazolopyrazoles 141-144 (Scheme 41).
Vaghasiya et al.\textsuperscript{23} have used the \textit{Gewald} reaction to synthesize thieno[3,2-c]pyrazole. Synthesis of 5-amino-3-methyl-1H-thieno[3,2-c]pyrazole-6-carbonitrile (146) was accomplished by refluxing (5-methyl-2,4-dihydro-3H-pyrazole-3-ylidene)malononitrile (145) and sulfur in the presence of morpholine for 6 h. Compound 145 was prepared by the reaction of 3-methyl-1H-pyrazol-5-one (23) with malononitrile in piperidyl acetate to afford the Knoevenagel intermediate (Scheme 42).

\textbf{Scheme 42}

Also, ethyl cyanoacetate was used in the above reaction instead of malononitrile to react with pyrazolone 43 to afford ethyl 5-amino-3-methyl-1-phenyl-1H-thieno[3,2-c]pyrazole-6-carboxylate (147)\textsuperscript{21} (Scheme 43).

\textbf{Scheme 43}

Hamama \textit{et al.}\textsuperscript{78} reported that 3,7-dimethyl-1,5-diphenyl-1H,5H-pyrazolo[3′,4′:4,5]thieno [2,3-c]pyrazole (148) was obtained when pyrazolone 43 was subjected to react with ethyl cyanoacetate in the presence of elemental sulfur and triethylamine (Scheme 44).

\textbf{Scheme 44}
Abdel Reheim et al.\textsuperscript{79} reported that the reaction of diphenylpyrazolone 149 with cyanoacetic hydrazide and elemental sulfur in DMF containing a catalytic amount of piperidine yielded 5-amino-1,3-diphenyl-1\textit{H}-thieno[3,2-\textit{c}]pyrazole-6-carbohydrazide (150) (Scheme 45).

![Scheme 45](image)

Benzothienopyrazoles were prepared from the reaction of 3-hydroxy-2-acetyl-1-thionaphthen 151 with phenylhydrazine or \textit{p}-bromophenylhydrazine to give the thianaphthenopyrazoles 152a,b\textsuperscript{80} (Scheme 46).

![Scheme 46](image)

Ernest\textit{ et al.}\textsuperscript{81} reported that the arylhydrazone in the previous reaction with substitution in ortho position failed to cyclized into pyrazole and they also reported the synthesis of pyrazole 152 from the 4-tolyl- and 4-methoxyphenyl hydrazones. Contrary, the ring formation is so rapid in case of the using 4-tolylhydrazone that the hydrazone is not isolate and the pyrazole is formed directly.

Singh\textit{ et al.}\textsuperscript{82} have reported a novel radical cyclization approach to thienopyrazole heterocycles. The scope and generality of this efficient radical-mediated thiophene annulation protocol was further evident by extending the methodology to the synthesis of tetra substituted thieno[3,2-\textit{c}]pyrazoles. Thus when acrylonitrile precursors 153a,b were subjected to radical cyclization under identical conditions, this led to the formation of 5-substituted thieno[3,2-\textit{c}]pyrazole-6-carbonitrile 154a,b (Scheme 47).

![Scheme 47](image)
Anand Acharya et al\textsuperscript{83,84} have developed a method for synthesis of thieno[3,2-c]pyrazole and other fused systems through palladium-catalyzed oxidative C-H functionalization-intramolecular aryl thiolation. The reaction might proceed through nucleophilic addition of active methylene group of 155, 159 to the C=S-bond of compound 156 followed by elimination of MeSH to give the non-isolated compounds 157, 160 which underwent cyclization to afford 158, 161 respectively (Scheme 48).

\begin{itemize}
  \item \textbf{Scheme 48}
\end{itemize}

8. Miscellaneous Reactions of Thienopyrazoles

(5-Amino-3-methyl-1-phenyl-1H-thieno[3,2-c]-pyrazol-6-yl)(3,5-dimethyl-1H-pyrazol-1-yl) methanone (163) was synthesized by the reaction of carbohydrazide derivative 162 with acetylacetone in ethanol.\textsuperscript{85,86} Also, heating the aminocarbohydrazide 162 with formic acid caused cyclization and led to the formation of the corresponding N-formylaminopyrazolo[3′,4′:4,5]thieno [2,3-d]pyrimidine 164 with a new ring system. Cyclocondensation of 162 with acetic anhydride produced 7-(diacetylamino)-3,6-dimethyl-1-phenyl-1,7-dihydro-8H-pyrazolo[3′,4′:4,5]thieno[2,3-d]-pyrimidin-8-one (165)\textsuperscript{21} (Scheme 49).
Moreover, treatment of the carbohydrazide derivative 162 with CS$_2$/KOH in ethanol or CS$_2$/pyridine led to the formation of (5-amino-3-methyl-1-phenyl-1H-thieno[3,2-c]pyrazol-6-yl)-1,3,4-oxadiazo-le-2-thiol (166). In the reaction of hydrazide 162 with thiourea in dimethyl formamide, 7-amino-3-methyl-1-phenyl-8-oxo-1,5,6,7-tetrahydro-8H-pyrazolo[3′,4′:4,5]thieno[2,3-d]pyrimidin-6-thione (167) was formed \( ^{21} \) (Scheme 50).
Previously, in literature, thieno[2,3-c]pyrazoles \(^{43,87-88}\) were reported to react with different substituted groups. In a recent communication, Bakhite et al. \(^{87}\) prepared ethylcarboxylate derivative of thieno[2,3-c]pyrazole \(^{26}\) by using 5-chloropyrazole-4-carbaldehyde \(^8\) and ethyl thioglycolate in the presence of sodium ethoxide and ethanol in 88% yield. This active precursor ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate \((26)\) was reacted with hydrazine hydrate to afford the corresponding carbohydrazide \(^{168}\) in 76% yield (Scheme 51).

\[
\text{Scheme 51}
\]

A literature survey on thienopyrazoles revealed that most of papers focus on synthesis of the thienopyrazole substituted at position 5 similar to structure B. Few reports deal with o-bifunctionalized thienopyrazole similar to structure A \(^{89-91}\). Kamal El-Dean et al. have continued their previous work in the synthesis of heterocyclic compounds containing the pyrazole moiety. They have reported a novel facile method of synthesis of thieno[2,3-c]pyrazoles substituted at positions 4 and 5 similar to structure A \(^4\).

\[
\text{Figure 2. The substituent positions in thieno[2,3-c]pyrazole.}
\]

When the amino thienopyrazole carboxamide compound \(47b\) was subjected to reaction with triethyl orthoformate in the presence of catalytic amount of acetic acid, 3-methyl-1-phenyl pyrazolo[3',4':5,4]thieno[3,2-d]pyrimidin-7(6H)-one \(^{169}\) was obtained. The pyrazolothienopyrimidinone \(^{169}\) was converted to the corresponding chloropyrimidine compound \(^{170}\) by the reaction with phosphorus oxychloride. The chloride atom in the chloropyrimidine compound \(^{170}\) underwent nucleophilic substitution reactions with various aromatic and/or heterocyclic amines upon reflux in ethanol to afford the corresponding 4-aryl (heterocyclyl) aminomethyl compounds \(^{171a-c}\). Also, compound \(^{169}\) was converted to the pyrazolothienopyrimidinethione \(^{172}\) using phosphorus pentasulfide in refluxing pyridine. The latter compound was obtained via an alternative route by the reaction of the chloropyrimidine derivative \(^{170}\) with thiourea. The products obtained from the two routes were identical in all aspects. Alkylation of thione \(^{172}\) by using different α-halocarbonyl compounds, namely: ethyl chloroacetate, chloroacetone and phenacyl bromide in ethanol in the presence of sodium acetate afforded the S-alkylated mercaptopyrazolothienopyrimidine derivatives \(^{173a-c}\) \(^4,50\) (Scheme 52).
The reaction of amino thienopyrazole carboxamide 47b with chloroacetyl chloride in dioxane followed by neutralization with diluted sodium carbonate solution afforded the chloroacetyl amino derivative 174. On the other hand, reaction of the amino carboxamide compound 47b with chloroacetyl chloride by heating in a water bath under neat conditions at 60-70°C followed by neutralization with dilute sodium carbonate solution afforded the chloromethylpyrazolothienopyrimidinone 175. Compound 175 was obtained by an alternative
route, upon refluxing the chloroacetyl amino compound 174 in acetic anhydride. The produced compound 175 which was obtained by the two methods was in agreement with the postulated structure in all aspects. The chloromethyl pyrimidine derivative 175 underwent nucleophilic substitution reactions with various primary and secondary amines in refluxing ethanol to afford 3-methyl-1-phenyl-5-(alkyl or aryl) aminomethyl) pyrimido[4',5':4,5]thieno[2,3-c]pyrazol-7(6H)-ones 176a-d. Compounds 176a-d, upon treatment with formaldehyde under Mannich conditions, afforded the 3-methyl-1,6-diaryl-5,7-dihydropyrimidazo[1,5-a]pyrazolo[3',4':4,5]thieno[3,2-d] pyrimidin-9-ones 177a-c\(^5\) (Scheme 53).

The key material 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbohydrazide (168) was prepared in a good yield according to the literature procedure\(^4\). Condensation of carbohydrazide 168 with the appropriate heterocyclic aldehydes namely substituted tetrazolo[1,5-a]quinoline-4-carbaldehyde, 1,3-diphenyl-1H-pyrazole-4-carbaldehyde and 4-oxo-4H-chromene-3-carbaldehyde in methanol in the presence of acetic acid gave the corresponding stable solid \(N\)-acylhydrazones 178a–g, 179a–h and 180a–d\(^9\) (Scheme 54).

Scheme 54

The amino function of 32 could be easily converted into a pyrrol-1-yl group in a Paal-Knorr-reaction on treatment with 2,5-dimethoxycyclohexanone (DMTHF) in refluxing acetic acid following the reported procedure to give 181\(^4\) (Scheme 55).
Scheme 55

The pyrrolyl ester 181 reacted with hydrazine hydrate to afford the corresponding hydrazide 182. Condensation of 182 with some aromatic aldehydes yielded the expected hydrazones 183a–c. The carbohydrazide 182 proved to be a versatile precursor for the synthesis of several thieno[2,3-c]pyrazole derivatives. Thus, the oxadiazole thione 184 was obtained directly by the reaction of 182 with carbon disulfide in the presence of pyridine. However, the 1,2,4-triazole thione 186, was obtained in two steps via the reaction of 182 with phenyl isothiocyanate, followed by heating the resulting aroyl thiosemicarbazide 185 in aqueous NaOH. The thioamide groups of both 184 and 186 were readily methylated by methyl iodide in the presence of sodium acetate to give the corresponding methylthio derivatives 187a and 187b respectively.46 (Scheme 56).

Scheme 56

The interaction of 182 with an equimolar amount of acetylacetone in refluxing ethanol led to a condensation reaction with the loss of one molecule of water, yielding the (4-oxo-2-penten-2-yl) carbohydrazide 188. However, using an excess of acetylacetone under neat conditions, two molecules of water
were eliminated in a cyclodehydration reaction led to the formation of dimethyl-pyrazolyl derivative 189. The reaction of the carbohydrazide 182 with ethoxymethylene malononitrile, and ethoxymethylene ethyl cyanoacetate gave the substituted pyrazol-1-yl-carbonyl thieno-[2,3-c]pyrazoles 190a,b respectively. Treatment of 182 with nitrous acid resulted in the formation of 3-methyl-1-phenyl-4-(pyrrol-1-yl)-1H-thieno[2,3-c]pyrazole-5-carbonyl azide (191) in a good yield46 (Scheme 57).

Scheme 57

The synthetic utility of the acid azide 191 as a key intermediate in the synthesis of new thienopyrazole derivatives is shown below.46 Thus, when 191 was heated with various alcohols, Curtius rearrangement occurred to give the isocyanate intermediate 192 which reacted with the alcohols to afford the corresponding carbamates 193 a–d. The symmetrical disubstituted urea 194 was obtained when the acid azide 191 was heated in boiling water. The urea derivatives 195 a,b were obtained when the acid azide 191 was heated with aniline and morpholine, again via Curtius rearrangement. Attempts to hydrolyse the carbamates 193 to the amino-thienopyrazoles 196 by boiling with aqueous ethanolic sodium hydroxide were unsuccessful; the starting carbamates were recovered unchanged.

When the acid azide 191 was heated in an inert solvent such as dry benzene and in the absence of any other reactants, the Curtius rearrangement was followed by intramolecular ring closure to give 5,7-dihydro-9-methyl-7-phenyl-4H-pyrazolo[4',3':4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazin-4-one (197) (Scheme 58).
9. Conclusions

This review described the several efficient synthetic approaches and reactions of thienopyrazoles and their related compounds. The synthetic strategies of these heterocyclic compounds designated in this review comprise the construction of the pyrazolopyrazine moiety starting with from thiophene, pyrazole, and bifunctionalized systems of them where indicated. We hope this review is useful and appealing to researchers in the field of heterocyclic synthesis. Also, it can help them to prepare novel thienopyrazole heterocycles with promising biological activities.

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