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Review

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Recent developments in the synthetic strategies, reactions and biological importance of thieno[2,3-*c*]pyrazoles

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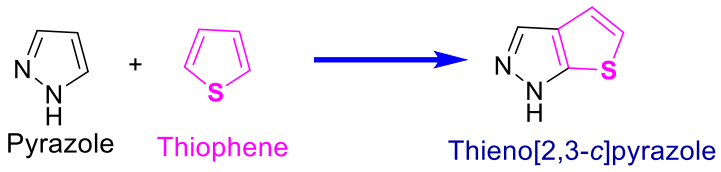
Abstract

Five-membered heterocycles like pyrazoles are an extremely important class of molecules in medicinal chemistry. Nowadays, scientists are paying great attention to pyrazoles and condensed thienopyrazoles because of their exceptional pharmacological and agrochemical properties. Anticancer, antioxidant, anti-inflammatory, antipyretic, analgesic, antimicrobial, antidepressant, antiviral, antihypertensive, anti-glaucoma, anti-tubercular, sodium channel blocker, anxiolytic, neuroprotective, and anti-diabetic properties are just a few of the many pharmacological effects that pyrazole derivatives exhibit.

This review sheds insight on current different synthetic methods used in the synthesis, divers reactions and pharmacological importance of thieno[2,3-*c*]pyrazoles.



Keywords: Thieno[2,3-*c*]pyrazole, synthetic methods , reactions and pharmacological activity

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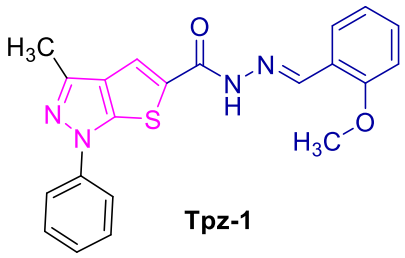
1. Introduction

Pyrazoles and thiophenes are common scaffolds in small-molecule drug design and are two well-researched pharmacophores with outstanding biological activity.[1-3] Pyrazole derivatives are approved for the treatment of different tumors, lymphomas, and leukemias.[3-5] Three carbon atoms and two nitrogen atoms connected to each other make up the five-membered heterocycles known as pyrazoles (Figure 1). Furthermore, several pyrazole derivatives have a significant demonstrated role in vitro apoptosis and antiproliferative action against a variety of cancer types.[6-8] On the other hand, thiophene, is a five-membered heterocycle that has one sulfur atom and four carbon atoms, thiophene derivatives, which are authorized for the treatment of a variety of cancers and other illnesses, are widely used in drug design.[9]

The pyrazole and thiophene represent interesting moieties combined to form thienopyrazoles which were adopted as antiproliferative, antiviral, antibacterial and anti-inflammatory therapeutics.[10,11] Also, pyrazole derivatives were found to possess potential antiviral activity,[12] It was reported that thieno[2,3-*c*] pyrazoles represent a class of heterocyclic compounds which has received very little attention compared to their other isomers, despite mounting evidence describing their significant inhibition of phosphodiesterase 7A (PDE7A,[13,14] purinergic receptor P2X3,[15] non-receptor tyrosine kinase ABL,[16] Aurora kinase (AURK), insulin-like growth factor type 1 receptor (IGF-1R), and cyclin-dependent kinase 2 (CDK2) .[17,18] Recently, Tpz-1 was identified (Figure 1), a novel small-molecule thieno[2,3-c]pyrazole derivative for novel anticancer drugs.[19] All findings above and in continuation to our recent publications[20-24] encouraged us to shed light on the different recent synthetic methods of thieno[3,2-*c*]pyrazole and its different reactions to encourage the scientists for further study in this class of heterocyclic chemistry.



Tpz-1

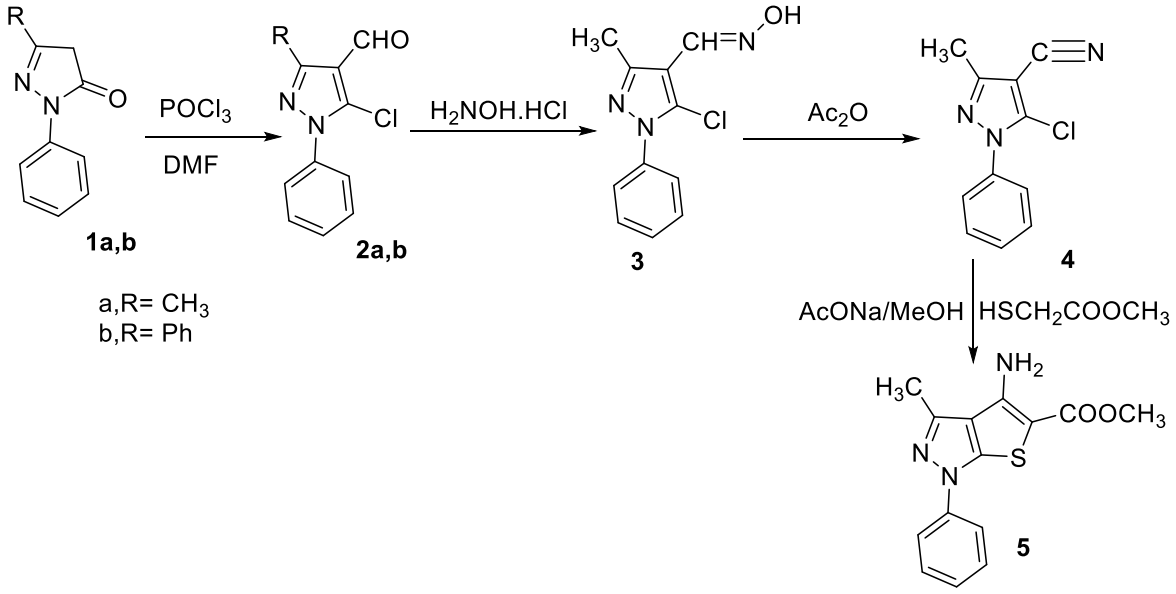
Figure 1. Thieno[2,3-*c*]pyrazole derivative (Tpz-1) with potent and selective cytotoxic effects on cancer cells.

2. Synthesis of Thieno[2,3-*c*]pyrazoles

It is noteworthy that the thieno[2,3-*c*]pyrazoles have received a very little attention. Two strategies of synthesis of these heterocycles were followed: a) using either suitably functionalized pyrazoles and then a thiophene ring is built up (Method 1), b) alternatively by using a suitably functionalized thiophene derivative as a starting material, then the pyrazole ring is constructed (Method 2). These two strategies are demonstrated in the following syntheses.

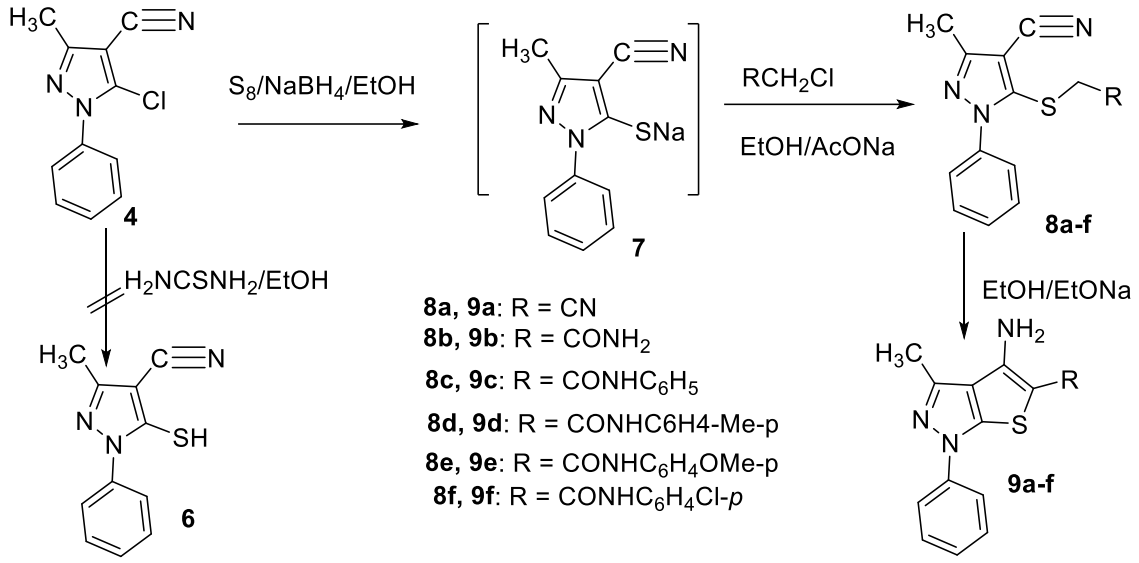
2.1. Starting from pyrazoles and then a thiophene ring is built up

Haider *et al*.[25] and El_Dean *et al*.[26] reported that the 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonitrile derivative (**4**) was prepared by dehydration of the oxime **3** which was prepared by the reaction of chloroaldehyde derivative **2** with hydroxyl amine. The chloroaldehyde derivative **2** was obtained by the reaction of pyrazolone **1** with phosphoryl chloride via a Vilsmeier reaction. Interaction of compound **4** with methyl thioglycolate in boiling methanol containing fused potassium carbonate afforded methyl 4-amino-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylate (**5**)(Scheme 1).[25]



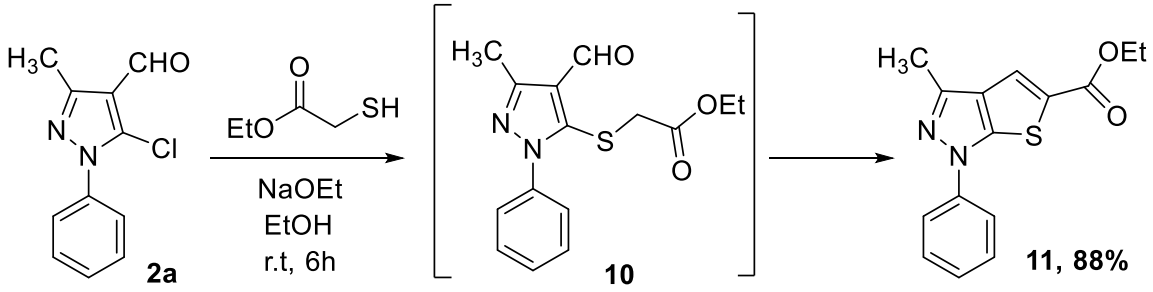
Scheme 1. Reaction of chlorocyano derivative **4** with methyl thioglycolate to afford thieno[2,3-*c*]pyrazole **5**.

An attempt[26,29,30] to synthesize thieno[2,3-*c*]pyrazole **9** through converting chloro pyrazole carbonitrile **4** into mercaptopyrazole **6** using thiourea in ethanol, followed by reaction with α-halogenated compounds, failed. The authors[26] thus tested another method to synthesize thienopyrazole **9**. To this end, the reaction of chloropyrazole **4** with sulfur in the presence of sodium borohydride as a reductant in ethanol afforded the intermediate sodium salt **7**, which used directly in the next reaction step without purification with α-halogenated carbonyl compounds to afford *S*-alkylated mercaptopyrazole carbonitrile **8a–f**. The latter compounds **8a–f** underwent Thorpe-Ziegler cyclization upon heating in ethanolic sodium ethoxide solution to afford thieno[2,3-*c*]pyrazoles **9a–f** (Scheme 2).



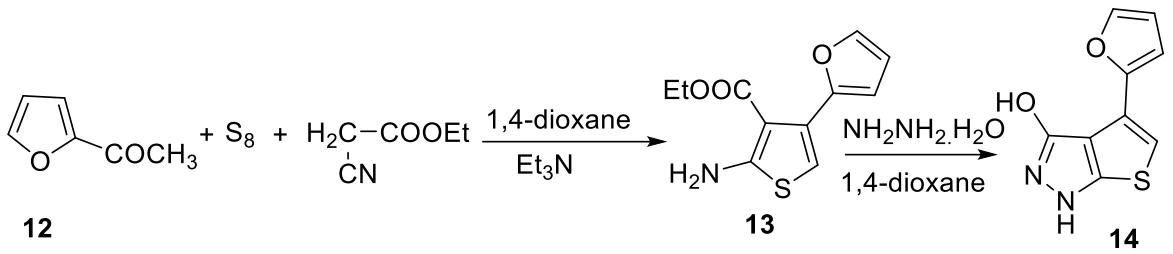
Scheme 2. Reaction of chlorocyano derivative **4** with sulfur followed by reaction with α-halogenated compounds.

In 2014, It was reported that[27] the reaction of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**2a)** with ethyl thioglycolate in the presence of sodium ethoxide and ethanol afforded the corresponding thioacetate intermediate **10** which not isolated but converted directly to the corresponding ethyl 3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylate (**11**) in 88% yield, which was also prepared by Gowda, G. B. *et al*.[31] in 2016 in 71% yield. (Scheme 3).



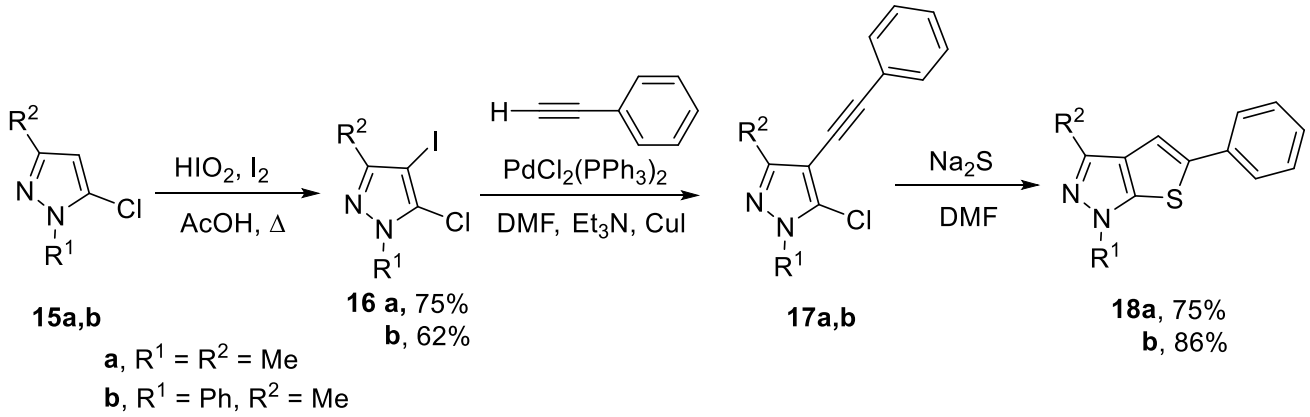
Scheme 3. Synthesis of ethyl carboxylate derivative of thieno[2,3-*c*]pyrazole **11**.

Mohammed *et al*[28] reported that, the reaction of 2-acetylfuran **12** with elemental sulfur and ethyl cyanoacetate gave the thiophene derivative **13**. Reaction of compound **13** with hydrazine hydrate gave the corresponding thieno[2,3-*c*]pyrazole derivative **14**. The latter product was obtained through the formation of the carbohydrazide derivative first followed by elimination of ammonia molecule (Scheme 4).



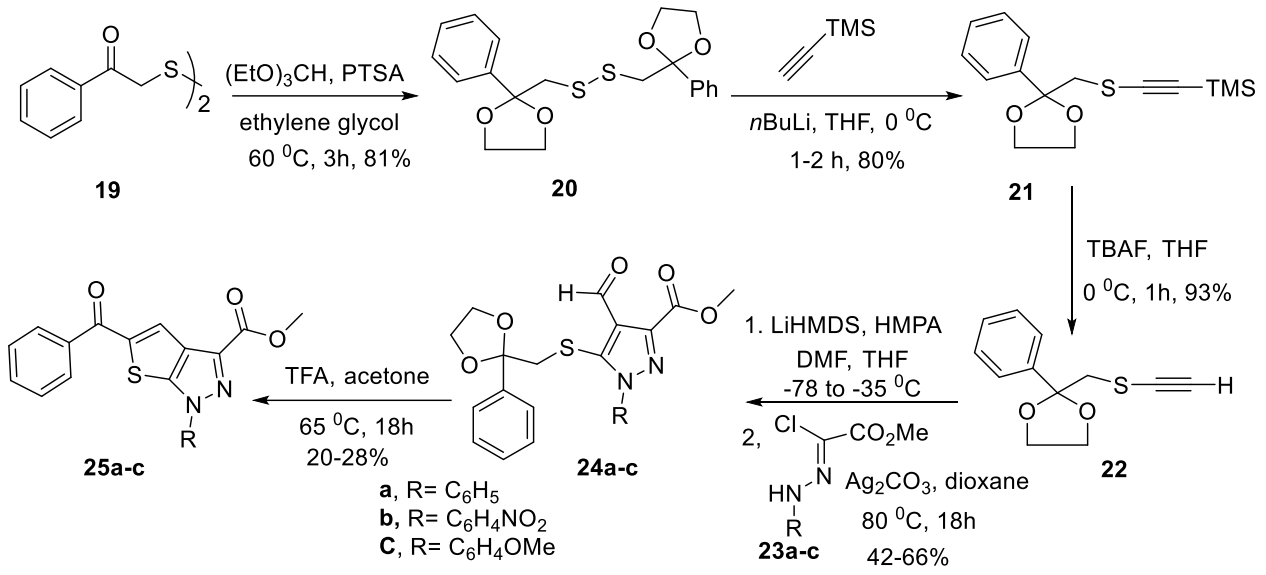
Scheme 4. Hydrazinolysis of thiophene aminoester **13** affording the thienopyrazole **14.**

In 2011, Gernot *et al* mentioned that,[32] starting from easily accessible 1,3-disubstituted-5-chloro-1*H*-pyrazoles **15**, a second halogen substituent was introduced at position 4 of the pyrazole nucleus by a standard halogenation protocol (I_2/IO_3^-) to obtain the corresponding 5-chloro-4-iodopyrazoles **16**. The latter derivatives were selectively linked to phenylacetylene through Sonogashira cross-coupling reaction, yielding only the 4-(phenylethynyl) pyrazoles **17** in good yields (87–92%). Treatment of compounds **17** with sodium sulfide in dimethyl formamide gave the targeted compounds **18** (Scheme **5**).



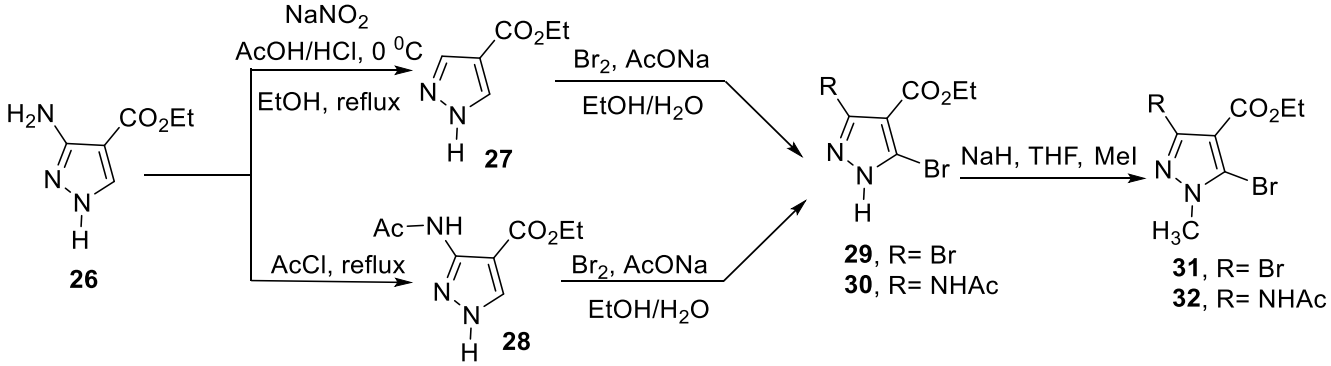
Scheme 5. New synthetic route for the synthesis of thieno[2,3-*c*]pyrazoles **18**.

In 2010, Chandanshive *et al*[33] have been used regiocontrolled synthesis of thieno[2,3-*c*]pyrazoles achieved by 1,3-dipolar cycloaddition of nitrile imines with sulfur-based acetylenes. The starting material was Bis(phenacyl)disulfide **19**, prepared easily and in high yield through a modified literature method[34] from phenacyl mercaptan.[35] After protection of **19** as dioxolane **20**[36] in 81% yield, acetylene **21** was obtained by reaction of **20** with lithium trimethylsilyl acetylene in THF at 0 °C in 80% yield. Compound **22** was obtained through desilylation of acetylene **21** with TBAF at 0 °C, which occurred in 93% yield (Scheme 5). The formyl group was introduced by reaction with LiHMDS in THF at –78 °C followed by addition of a mixture of DMF and HMPA. The disubstituted acetylene was not isolated but immediately treated with C-carboxymethyl-*N*-arylnitrile imines **23a–c** under the usual conditions. The corresponding cycloadducts were obtained with good overall yields, 66% for **24a**, 42% for **24b**, and 43% for **24c**. Deprotection of the dioxolanes of **24a–c** and condensation occurred in one step by reaction with trifluoroacetic acid in acetone to give the corresponding thieno[2,3-*c*]pyrazoles **25a–c** in 20–28% overall yield (Scheme 6).



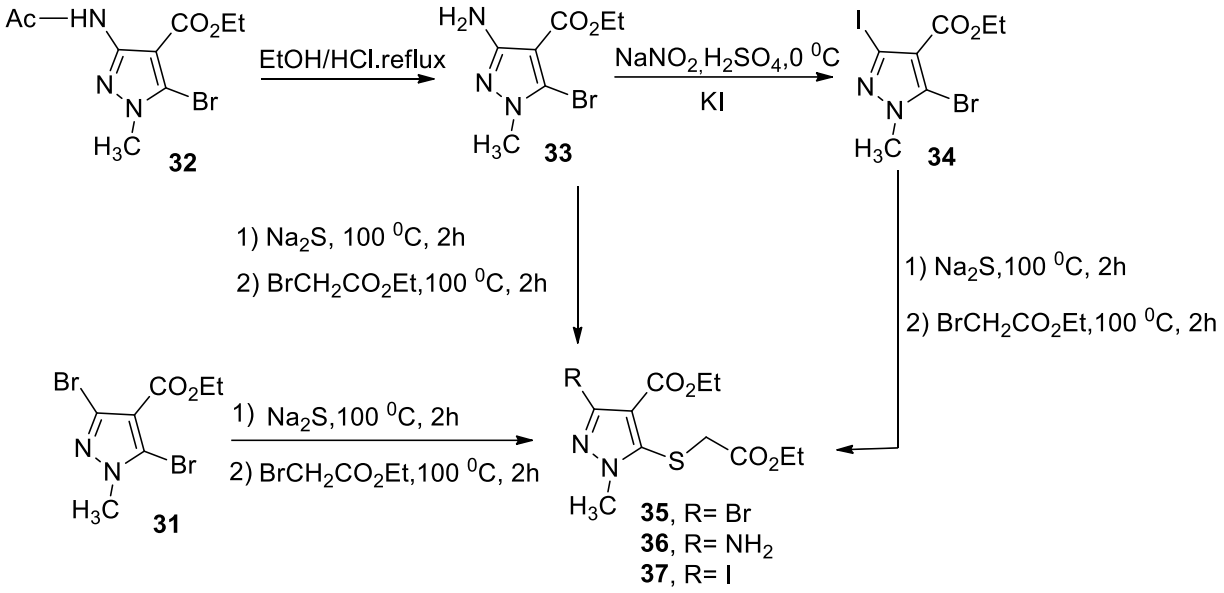
Scheme 6. General method for the synthesis of ring-fused thieno[2,3-*c*]pyrazoles **25a**–**c**.

It was reported that[37] condensation of hydrazine hydrate and ethyl 2-cyano-3-ethoxyacrylate[38] gave the corresponding 3-amino-1*H*-pyrazole-4-carboxylic acid ethyl ester **26**, which was transformed in the derivatives **27** and **28** by reductive diazotation and acylation, respectively. Electrophilic bromination of these derivatives afforded the corresponding bromine derivatives **29** and **30** Methylation of bromine derivatives **29** and **30** gave the corresponding *N*-methylated derivatives **31** and **32** in very good yields (Scheme 7).



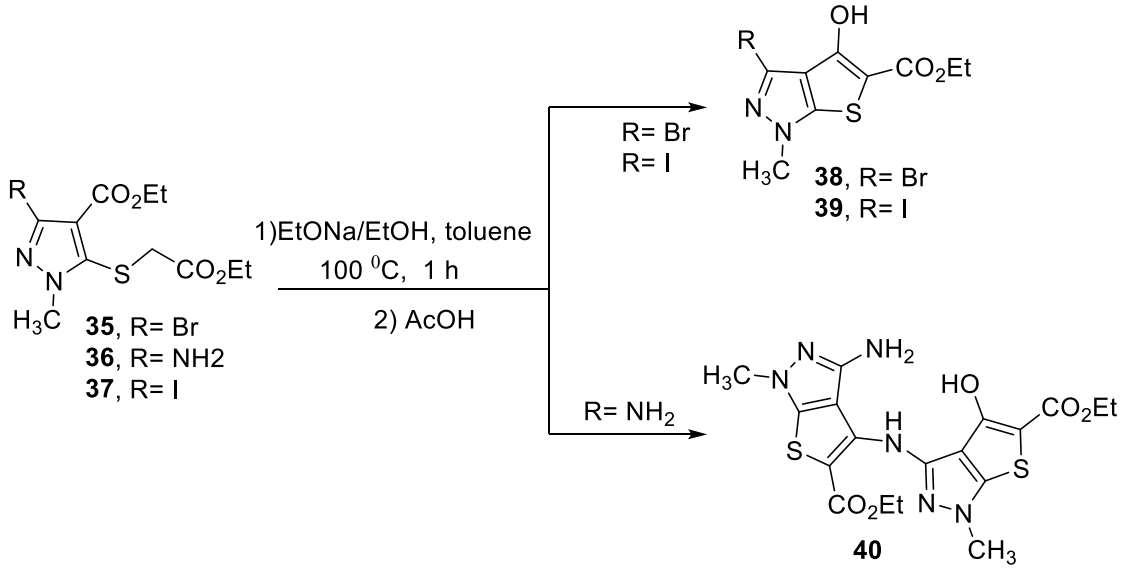
Scheme 7. Synthesis of N-methylated derivatives **31** and **32.**

Also,[37] the other brominated precursors **33** and **34** were easily prepared from **32** by simple selective N-deprotection and by the sequential deprotection diazotation substitution set of reactions shown in Scheme 7. The alkylsulfanylpyrazoles **35**, **36**, and **37** were prepared from **31**, **32** and **33** respectively, following the method reported by Morimoto *et al*.[39] for the synthesis of 3,5-dichloropyrazole-4-carboxylic acids. Sodium sulfide nucleophilic substitution and homologation of the resulting thiolate by reaction with ethyl bromoacetate installed the required *S*-containing chain for the next ring-closing step (Scheme 8).



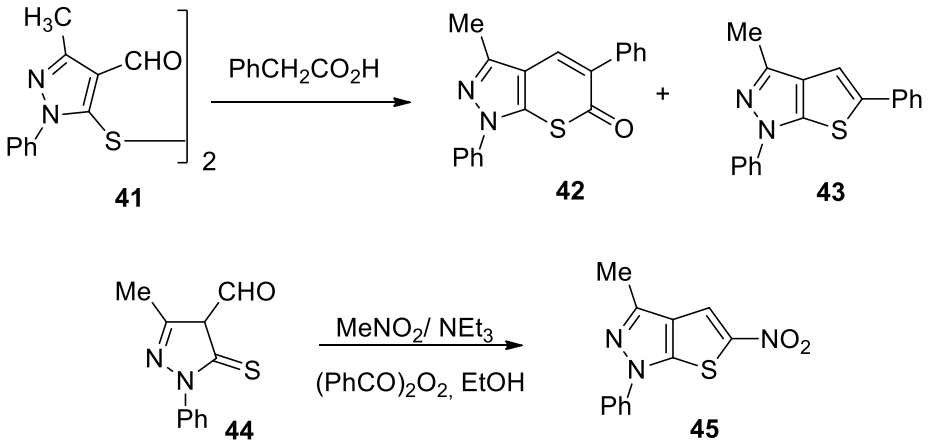
Scheme 8. Synthesis of alkylsulfanylpyrazoles **35**, **36**, and **37.**

Base-added cyclization[37] of pyrazoles **35** and **37** was accomplished by the use of sodium ethanolate in toluene, affording the expected thieno[2,3-*c*]pyrazoles **38** and **39**. Moreover, cyclization of the amine analog **11**, under the same conditions, yielded the imine derivative **40**, which probably comes resulted from the self-condensation of the expected thieno-fused compound (Scheme 9).



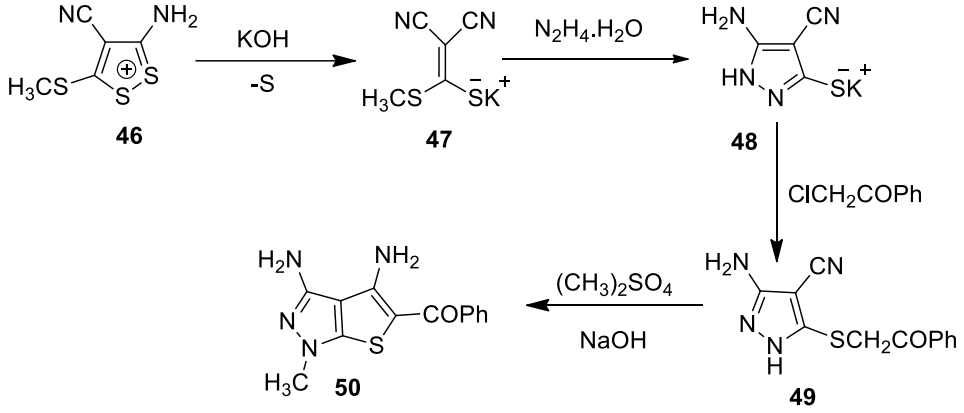
Scheme 9. Synthesis of thieno[2,3-*c*]pyrazoles **38**-**40**.

Brown and Meth-Cohn[40] reported that the reaction between the 5-mercapto-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**41**) and phenylacetic acid led to a mixture of thiopyrano[2,3-*c*]pyrazole **42** and thieno[2,3-*c*]pyrazole **43**. However, the 3-methyl-1-phenyl-5-thioxo-4,5-dihydro-1*H*-pyrazole-4-carbaldehyde (**44**) gave the nitro thieno[2,3-*c*]pyrazole **45** via its reaction with nitro methane in the presence of TEA followed by oxidation with benzoyl peroxide (Scheme 10).



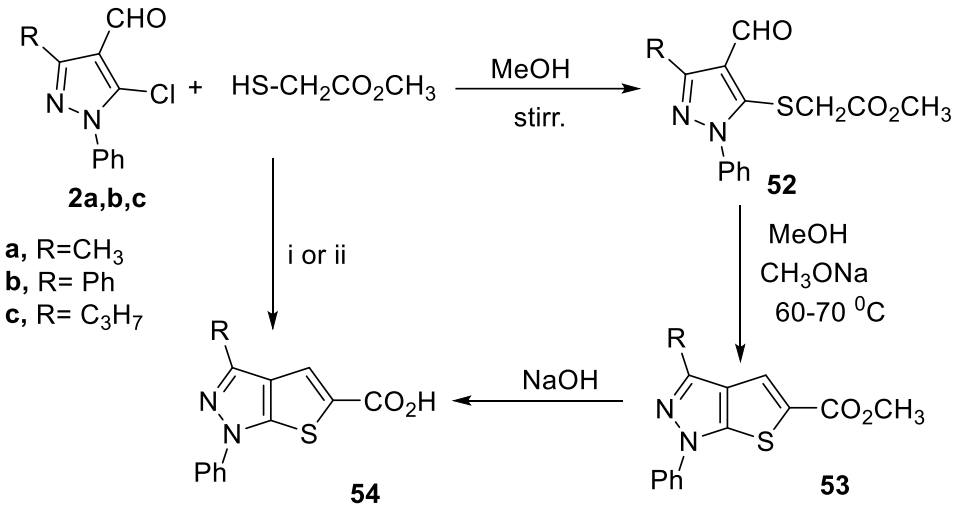
Scheme 10. Synthesis of 3-methyl-1,5-diphenyl-1*H*-thieno[2,3-*c*]pyrazole **43** and nitro analogue **45.**

Gewald *et al*.[41] reported that the reaction of potassium-(2,2-dicyano-1-methylthioethen-1-yl)thiolate (**47**), obtained from the dithiolium salt **46**, with hydrazine hydrate gave the salt **48**. *S*-Alkylation of **48** with α-chlorocarbonyl compounds yielded **49**. The latter compound was cyclized via Thorpe-Ziegler-cyclization to 3,4-diamino thieno[2,3-*c*]pyrazoles **50** (Scheme 11).



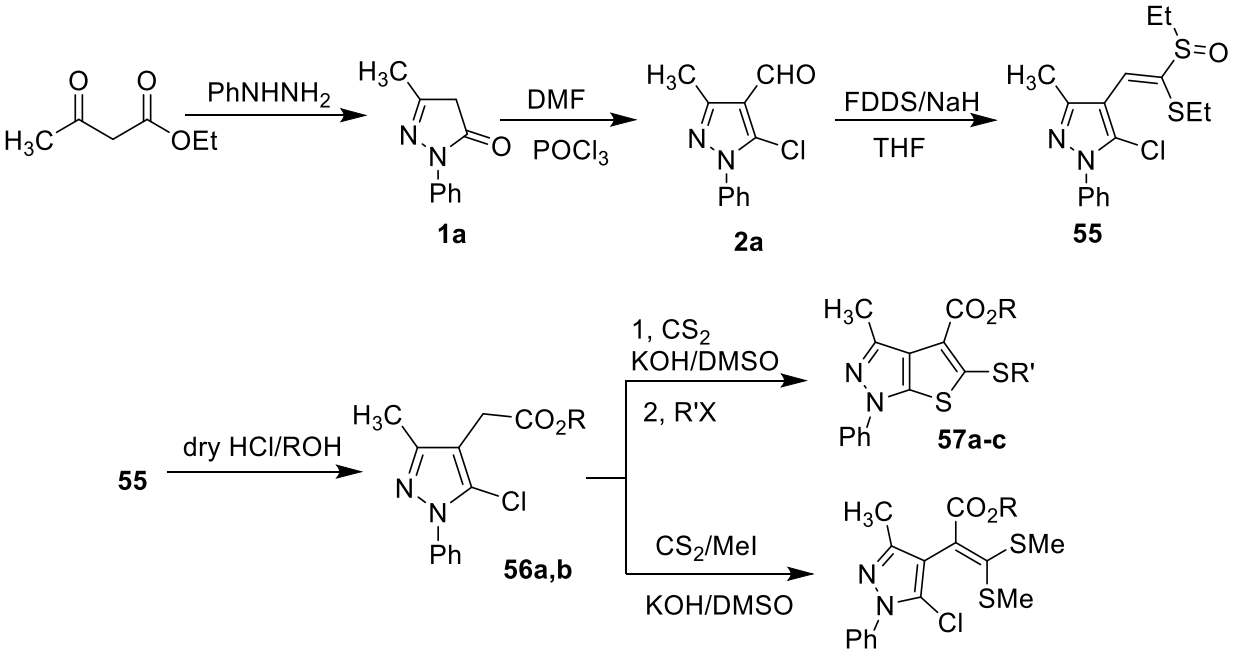
Scheme 11. Synthesis of 3,4-diamino thieno[2,3-*c*]pyrazoles **50.**

A third procedure[42] involved the reaction of chloropyrazole aldehydes **2** with methyl mercaptoacetate to give the 5-carboethoxymethylthio derivative **52**. The latter intermediate was then cyclized using sodium methoxide in refluxing methanol to give the thieno[2,3-*c*]pyrazole methyl ester **53** which gave the corresponding acid **54** upon hydrolysis. The latter compound **54** was also prepared when the reaction was carried out in aqueous ethanolic potassium hydroxide under reflux, the chlorine atom was replaced by a thioglycolic acid residue and intramolecular condensation took place.[43,66](Scheme 12).



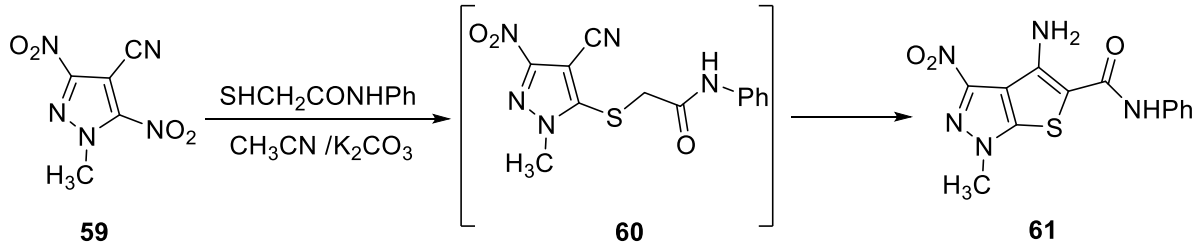
Scheme 12. Synthesis of 3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid **54.**

Wang[44] described another synthesis of thieno[2,3-*c*]pyrazoles using the same pyrazole chloro aldehyde as a starting material. Thus, the treatment of ethyl acetoacetate with phenylhydrazine gave the pyrazolone **1.** The pyrazolone **1**[45] could be converted to the chloropyrazole aldehyde **2** via Vilsmeier-Haack reaction.[46-49] The latter compound was converted into **55** using formaldehyde diethyl dithioacetal *S*-oxide (FDDS) which was then subjected to dry hydrochloride acid in alcohols to give the corresponding esters **56a,b**. The latter compounds were stirred with carbon disulfide, potassium hydroxide in dimethylsulphoxide, followed by addition of alkyl halide to give the ring-closed products **57a-c.** When iodomethane was mixed with compound **56**, under the same condition, the products were **58a,b**, instead of **58a,b** as shown in the following scheme 13.



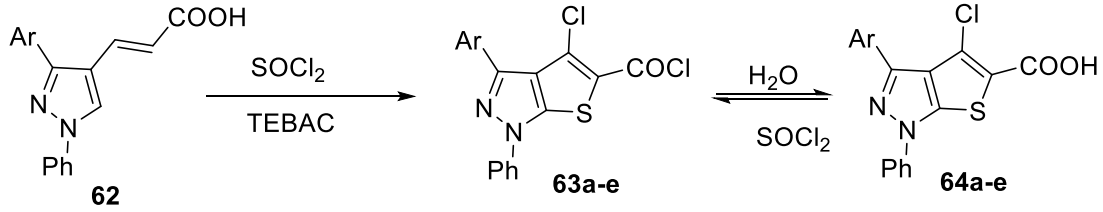
Scheme 13. Synthesis of thieno[2,3-*c*]pyrazoles **57a-c**.

Reaction of Nitrile **59** reacts with thioglycolic acid N-phenylamide in the presence of two equivalents of potassium carbonate in boiling acetonitrile to give substituted thieno[2,3-c]pyrazole **61** Evidently, nitrile **60** resulting from displacement of the 5-NO_2 group cyclizes in situ at the CN group to give bicyclic compound **61** (Scheme 14).[50]



Scheme 14. Use of nitropyrazole **59** in the synthesis of thieno[2,3-*c*]pyrazole **61.**

Heating of 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)acrylic acid **62** with an excess of thionyl chloride in the presence benzyl triethylammonium chloride (BTEAC) of instead of pyridine under reflux for 10 h at 160 °C gave 3-Aryl-4-chloro-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl chloride (**63**). Hydrolysis of the latter compound **63** gave the corresponding acid **64** (Scheme 15).[51]

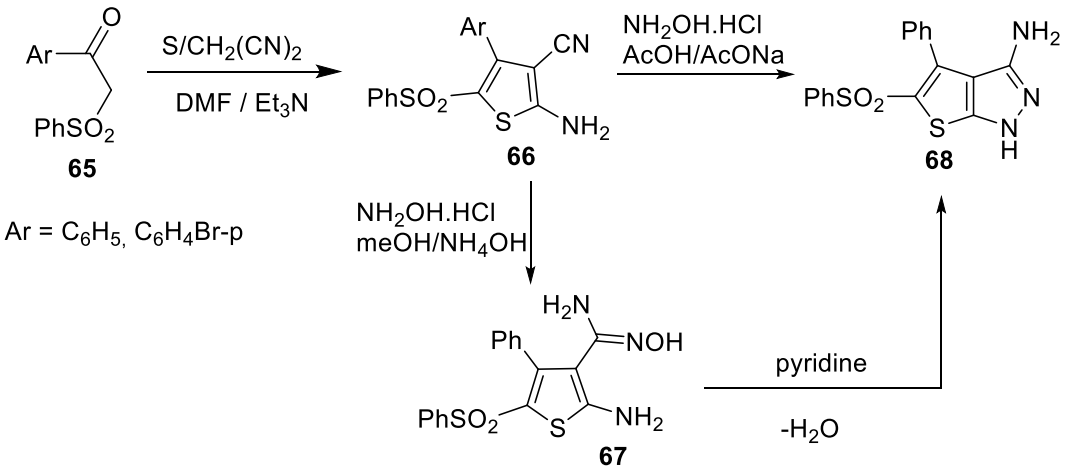


a, Ar = Ph, b) Ar = 4-F-C_6H_4,
C) Ar = 4-ClC_6H_4, d) Ar = 4-BrC_6H_4
e) 4-MeC_6H_4

Scheme 15. Synthesis of thieno[2,3-*c*]pyarzole derivatives **64a-e.**

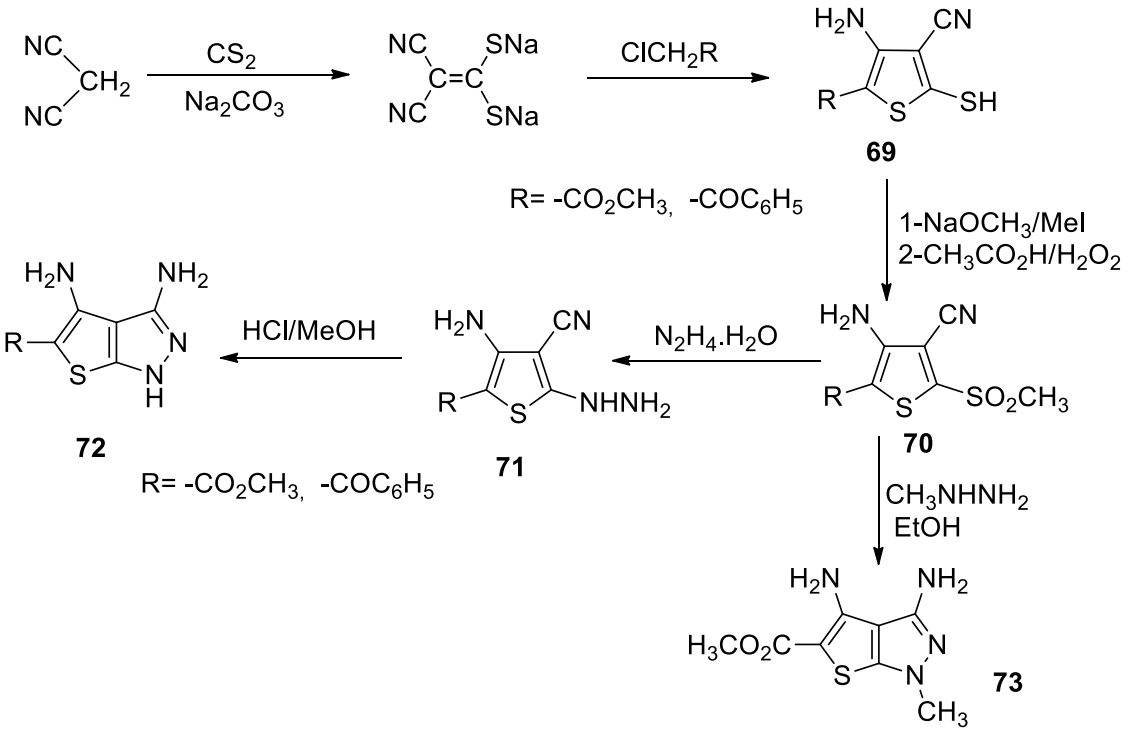
2.2. Syntheses involves the use of properly substituted thiophene as starting materials

Sherif *et al*.[52] has prepared the thiophene amino nitrile **66** using Gewald synthesis starting from phenylsulfonyl acetophenones **65**, sulfur and malononitrile in DMF in the presence of triethylamine.[52] The reaction of **66** with an equimolar amount of hydroxyl amine hydrochloride in methanol containing NH_4OH at room temperature provided 3-amidoximo-2-amino-4-phenyl-5-phenyl sulfonyl thiophene **67**. This compound was transformed in to 3-amino-4-phenyl-5-phenylsulfonyl-1*H*-thieno[2,3-*c*]pyrazole (**68**) via loss of water molecule upon prolonged heating in pyridine. Interestingly, the latter compound **68** was prepared directly by the reaction of compound **66** with hydroxylamine hydrochloride in glacial acetic acid in the presence of anhydrous sodium acetate (Scheme 16).



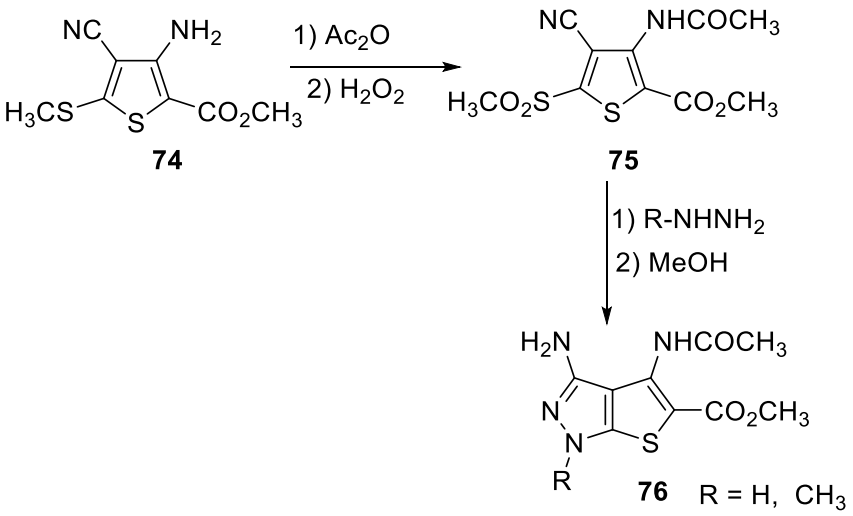
Scheme 16. Synthesis of 3-amino-4-phenyl-5-phenylsulfonyl-1*H*-thieno[2,3-*c*]pyrazole (**68**).

Briel.[53] was able to synthesize different derivatives of diamino thieno[2,3-*c*]pyrazole using a different strategy than that of Gewald[52] previously mentioned. Thus, 4-amino-2-mercapto-5-substituted thiophene-3-carbonitrile **63**[54] was interacted with methyl iodide in the presence of sodium methoxide followed by oxidation of the *S*-methylated product into the corresponding sulfone **64**. Treatment of this sulfone with hydrazine hydrate gave the corresponding hydrazine derivative **65** which was ring closed into the diamino thieno pyrazole **66** in methanolic hydrochloric acid solution Whereas, when methyl hydrazine was used instead of hydrazine hydrate, the 1-methyl derivative **67** was obtained (Scheme 17).



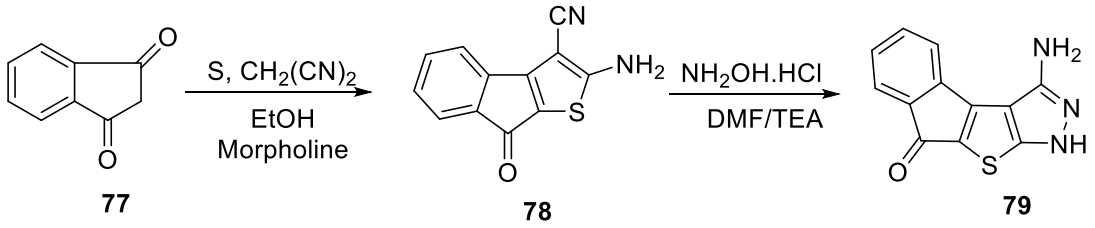
Scheme 17. Synthesi of different derivatives of diamino thieno[2,3-*c*]pyrazole **72** and **73**.

When the methyl 3-amino-4-cyano-5-methylthiothiophene-2-carboxylate (**74**) was allowed to react with acetic anhydride followed by oxidation with H_2O_2, the methyl 3-acetylamino-4-cyano-5-methylsulfonylthiophene-2-carboxylate (**75**) was formed. The latter compound was converted to the thieno[2,3-*c*]pyrazole derivative **75**[55] by reaction with hydrazine hydrate or methyl hydrazine as shown in scheme 18.



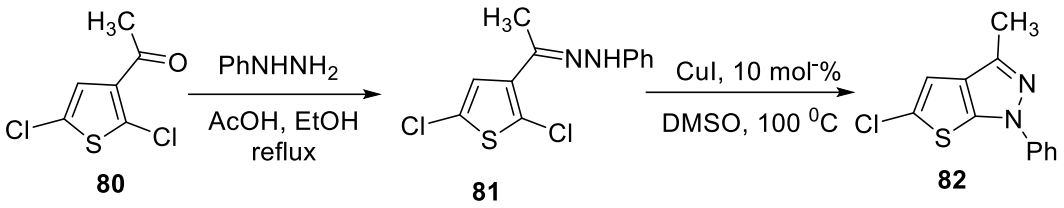
Scheme 18. Synthesis of thieno[2,3-*c*]pyrazole derivative **76.**

The Gewald reaction of 1,3-indanedione **77** with elemental sulfur and malononitrile in absolute ethanol containing a catalytic amount of morpholine furnished upon heating exclusively and in reasonable good yield a product that could be formulated as 2-amino-8-oxo-8*H*-indeno[2,1-*b*]thiophene-3-carbonitrile (**78**) On the other hand, β-enaminonitrile moiety in **78** proved to be highly reactive towards nitrogen nucleophiles. Thus, compound **78** reacted with hydroxylamine hydrochloride in refluxing glacial acetic acid containing anhydrous sodium acetate to afford 3-aminoindeno[1,2:4,5]thieno[2,3-*c*]pyrazol-8-(1*H*)-one (**79**) (Scheme 19).[56]



Scheme 19. Synthesis of thieno[2,3-*c*]pyrazole derivative **79.**

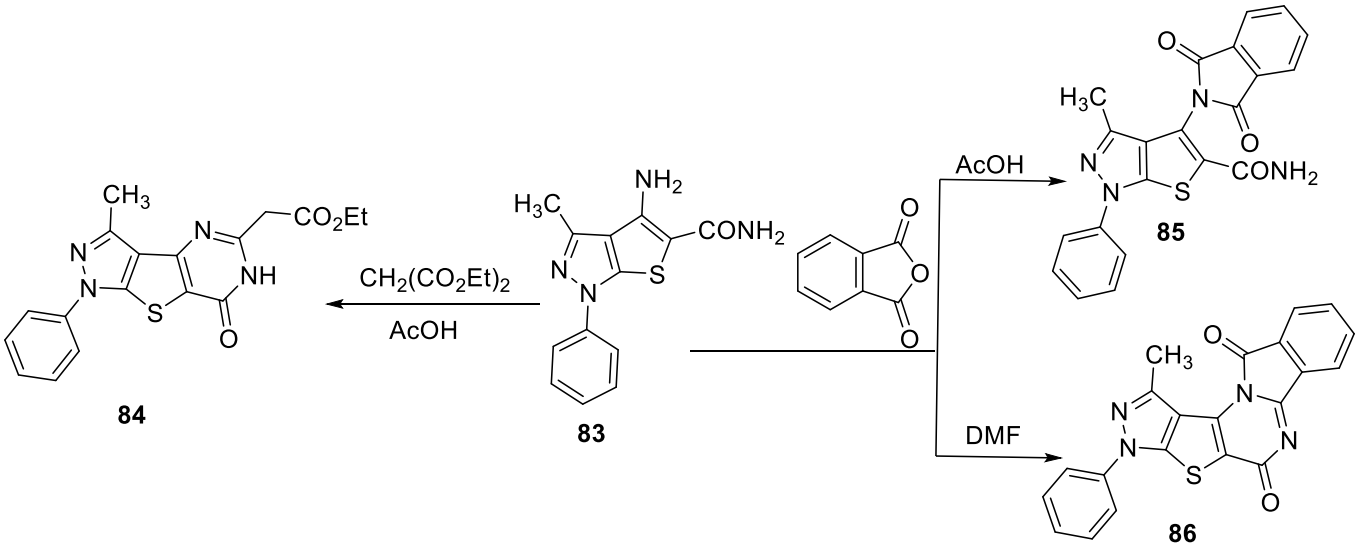
Mingshan, G. et *al*.[57] found that intermolecular condensation of 2,5 dichloro-3-acetylthiophene **80** with phenylhydrazine gave the corresponding **81** followed by a ligand-free copper-catalyzed intramolecular Ullmann-type coupling reaction afforded the corresponding 5-chloro-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*] pyrazole **82** (Scheme 20).



Scheme 20. Synthesis of 5-chloro-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole **82.**

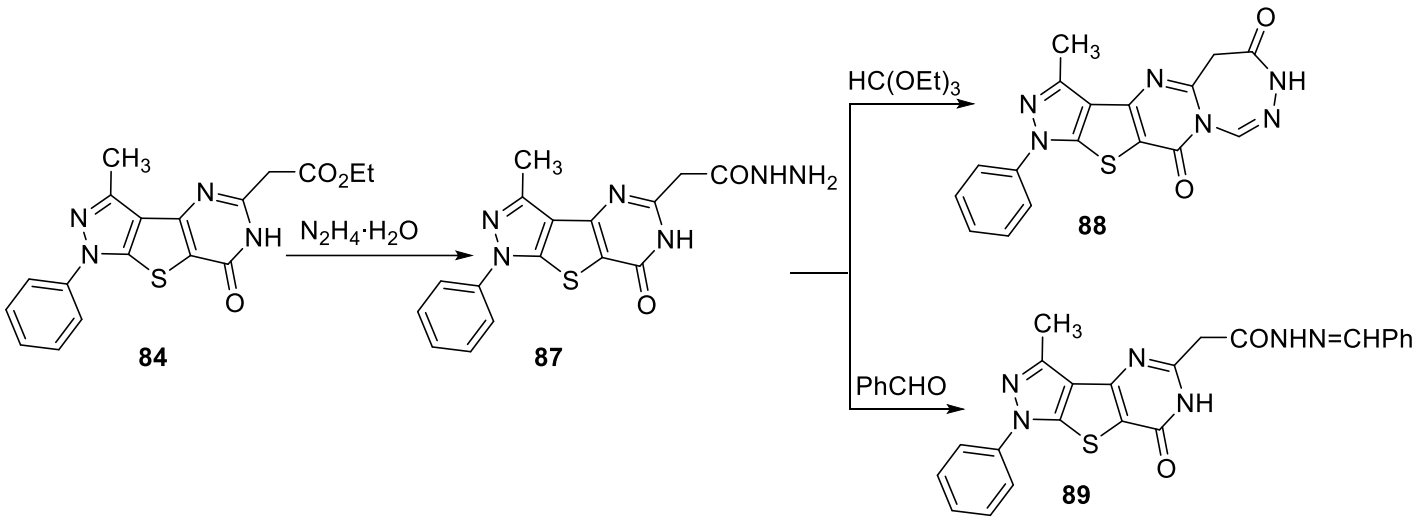
3. Reactions of thieno[2,3-*c*]pyrazoles

In 2020, Saber et *al*. reported[58] that the cyclocondensation of the aminocarboxamide **83** with diethyl malonate in boiling acetic acid afforded the ethyl pyrazolothienopyrimidinyl acetate **84**. The reaction might be performed by elimination of ethanol followed by tautomerism of the carboxamide intermediate then, elimination of water molecule to yield the target ethyl pyrimidinyl acetate **84**. Also, reaction of the amino carboxamide **83** with phthalic anhydride produced two different products depending on the solvent used in the reaction. When the reaction was carried out in acetic acid, the reaction gave the phthalimido derivative **85**. Whereas, by using DMF as solvent, the reaction occurred to produce the corresponding 1-methyl-3-phenyl-3*H*-pyrazolo[4'',3'':4',5']thieno[2',3':5,6]pyrimido[2,1-*a*]isoindole-5,11-dione (**86**) (Scheme 21).



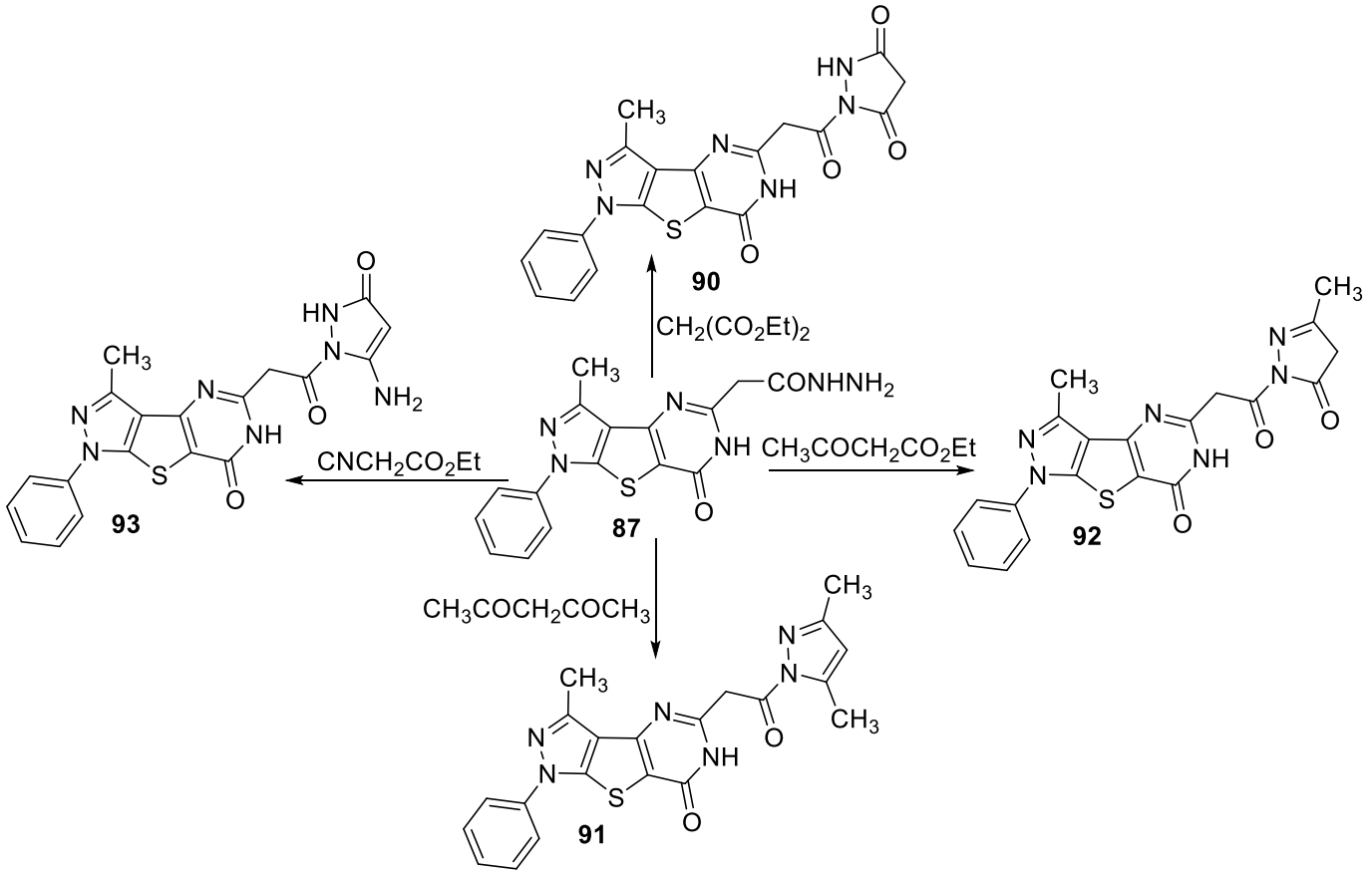
Scheme 21. Reaction of the amino carboxamide **83** with phthalic anhydride.

Furthermore,[58] hydrazinolysis of the ester group in the ethyl pyrimidinyl acetate compound **84** upon fusion with hydrazine hydrate (99%) under solvent-free conditions furnished the corresponding acetohydrazide derivative **87**. The latter compound **87** was used as a starting material for construction of other heterocyclic compounds. Thus, cyclization of acetohydrazide **87** with triethyl orthoformate in the presence of few drops acetic acid afforded the triazepinone **88**. Also, condensation of the carbohydrazide derivative **87** with benzaldehyde gave the carbohydrazone **89** (Scheme 22).



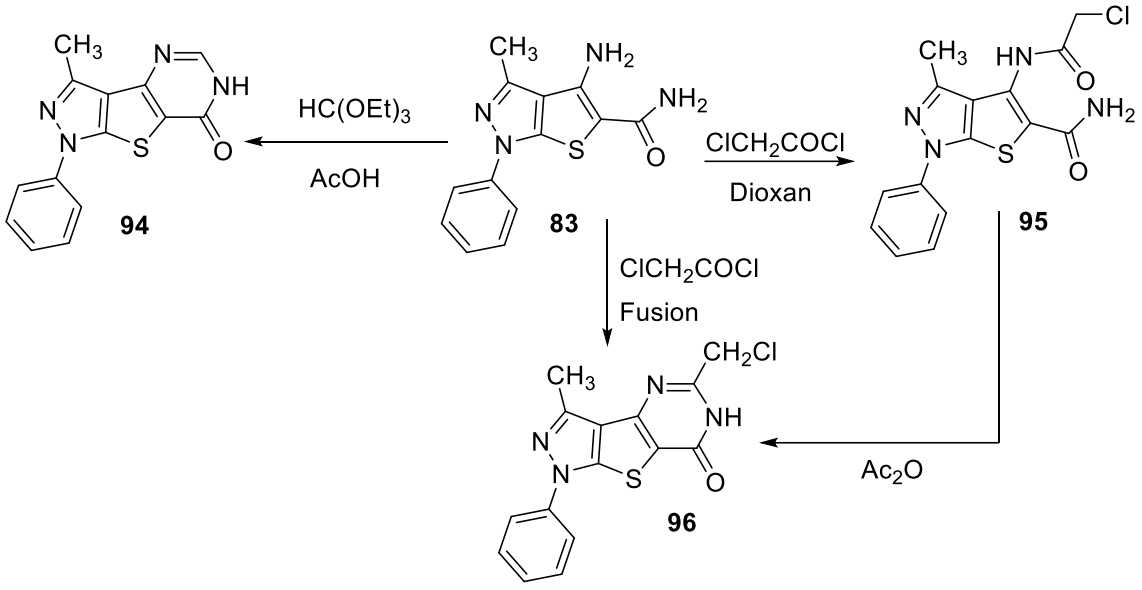
Scheme 22. Reaction of Synthesis of acetohydrazide **87** with triethyl orthoformate and/or benzaldehyde.

A series of new pyrazolyl derivatives **90-93** attached to the pyrazolothienopyrimidine moiety was formed by the reaction of acetohydrazide **75** with different 1,3-bifunctional compounds like diethyl malonate, acetyl acetone, ethyl acetoacetate, and ethyl cyanoacetate under solvent-free conditions.[58] The hydrazone intermediates formed were not isolated but followed by cyclization with elimination of water and/or ethanol affording compounds **90-93**, except in the reaction with ethyl cyanoacetate. In the latter case, the reaction performed by loss one of ethanol molecule followed by Thorpe-Ziegler addition cyclization of NH to the carbonitrile group followed by tautomerization to afford the aminopyrazole derivative **93** (Scheme 23).



Scheme 23. Formation of pyrazolyl derivatives **90-93** based on the pyrazolothienopyrimidine moiety.

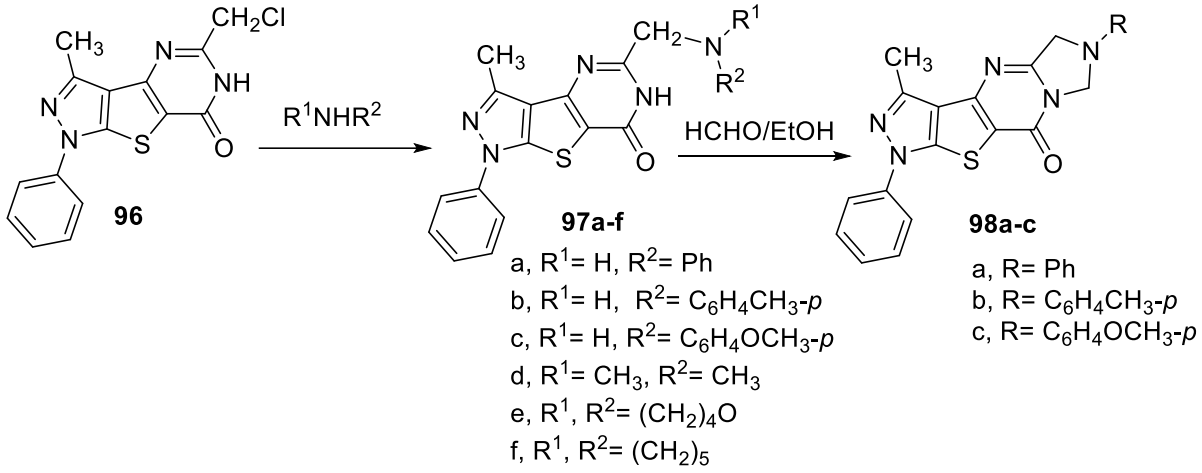
In 2015,[26] it was mentioned that when aminocarboxamide compound **83** was allowed to react with triethyl orthoformate in presence of catalytic amount of acetic acid, the pyrazolothienopyrimidinone **94** was obtained. On the other hand, the reaction of **83** with chloroacetyl chloride in dioxane followed by neutralization with sodium carbonate solution afforded chloroacetamide **95**. When the reaction was carried out under neat conditions,[59] the chloromethyl pyrazolothieno-pyrimidinone **96** was obtained instead. The latter compound was alternatively obtained by refluxing the chloroacetylamino compound **95** with acetic anhydride (Scheme 24).



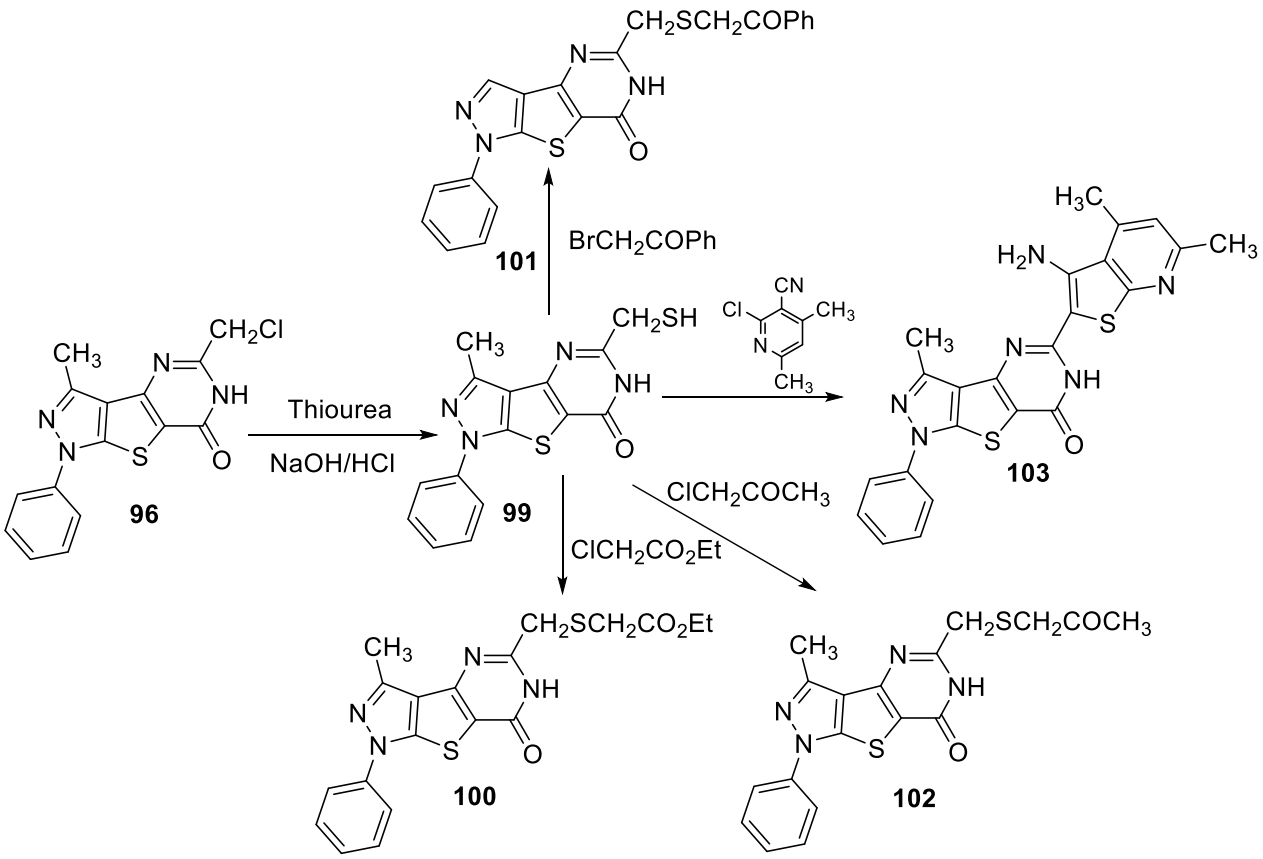
Scheme 24. Synthesis of 5-(chloromethyl)-3-methyl-1-phenyl-1*H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-7(6*H*)-one **96**.

The chloromethyl pyrimidine derivative **96** underwent nucleophilic substitution reactions with various primary and secondary amines in refluxing ethanol to afford 3-methyl-1-phenyl-5-(alkyl(aryl)amino methyl)pyrimido[4',5':4,5]thieno[2,3-c]pyrazol-7(6*H*)-one compounds (**97a-f**). Thus, compounds **97a-c**, upon treatment with formaldehyde under Mannich conditions, afforded the 3-methyl-1,6-diaryl-5,7-dihydroimidazo[5'',1'':2',3']pyrimido[5',6':2,3]thieno[5,4-c]pyrazol-9-one compounds (**98a-c**)[59] (Scheme 25).

In 2017,[59] it was found that treatment of compound **96** with thiourea followed by reaction with sodium hydroxide and acidification with HCl furnished the corresponding 5-(mercaptomethyl)-3-methyl-1-phenyl-1*H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-7(6*H*)-one (**99**)**.** Alkylation of mercaptomethylpyrazolothieno-pyrimidine **99** with α-halogenated compounds like, ethyl chloroacetate, phenacyl bromide and chloroacetone gave the corresponding *S*-alkylated products respectively **100-102**. While the reaction with 2-chloro-4,6-dimethylnicotinonitrile, afforded thienopyridinyl pyrazolothienopyrimidine **103** (Scheme 26).



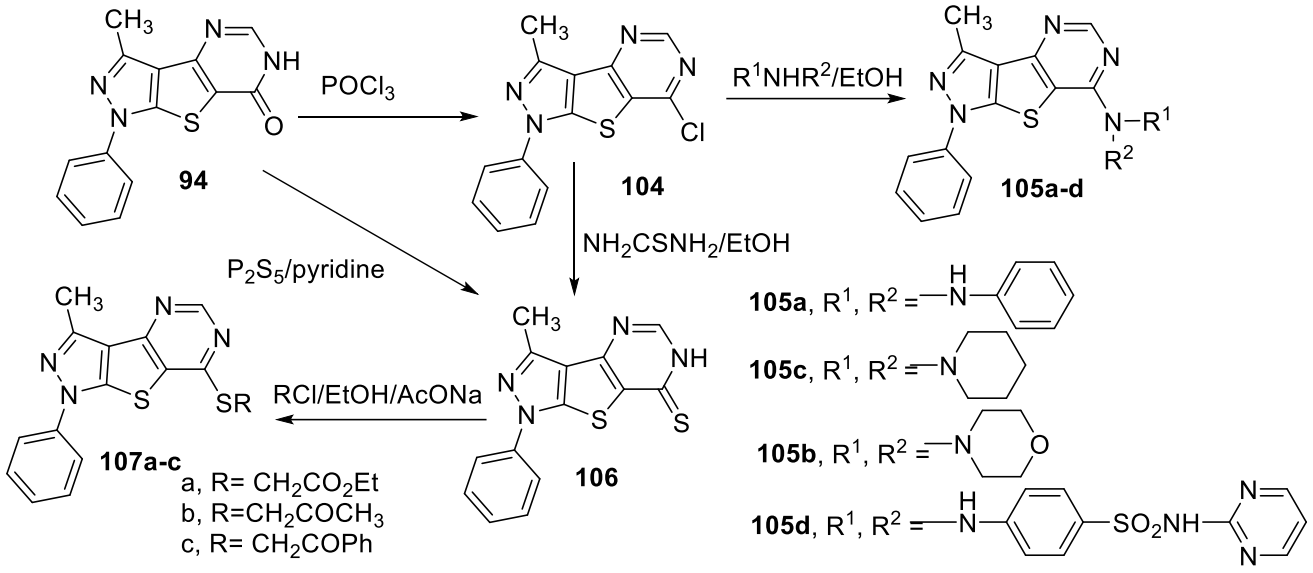
Scheme 25. Synthesis of 3-methyl-1,6-diaryl-5,7-dihydroimidazo[5'',1'':2',3']pyrimido[5',6':2,3]thieno[5,4-*c*] pyrazol-9-one compounds (**98a-c**)**.**



Scheme 26. Synthesis of *S*-alkylated mercaptomethylpyrazolothienopyrimidine derivatives **100-102**.

In 2015,[29] it was reported that interaction of pyrazolothienopyrimidinone **94** with phosphorus oxychloride gave the corresponding chloropyrimidine compound **104**. The chloro compound **104** underwent nucleophilic substitution reactions with aromatic and/or heterocyclic amines by reflux in ethanol to afford the corresponding 4-aryl (heterocyclic) aminomethyl compounds **105a-d**. Also, compound **104** was converted to

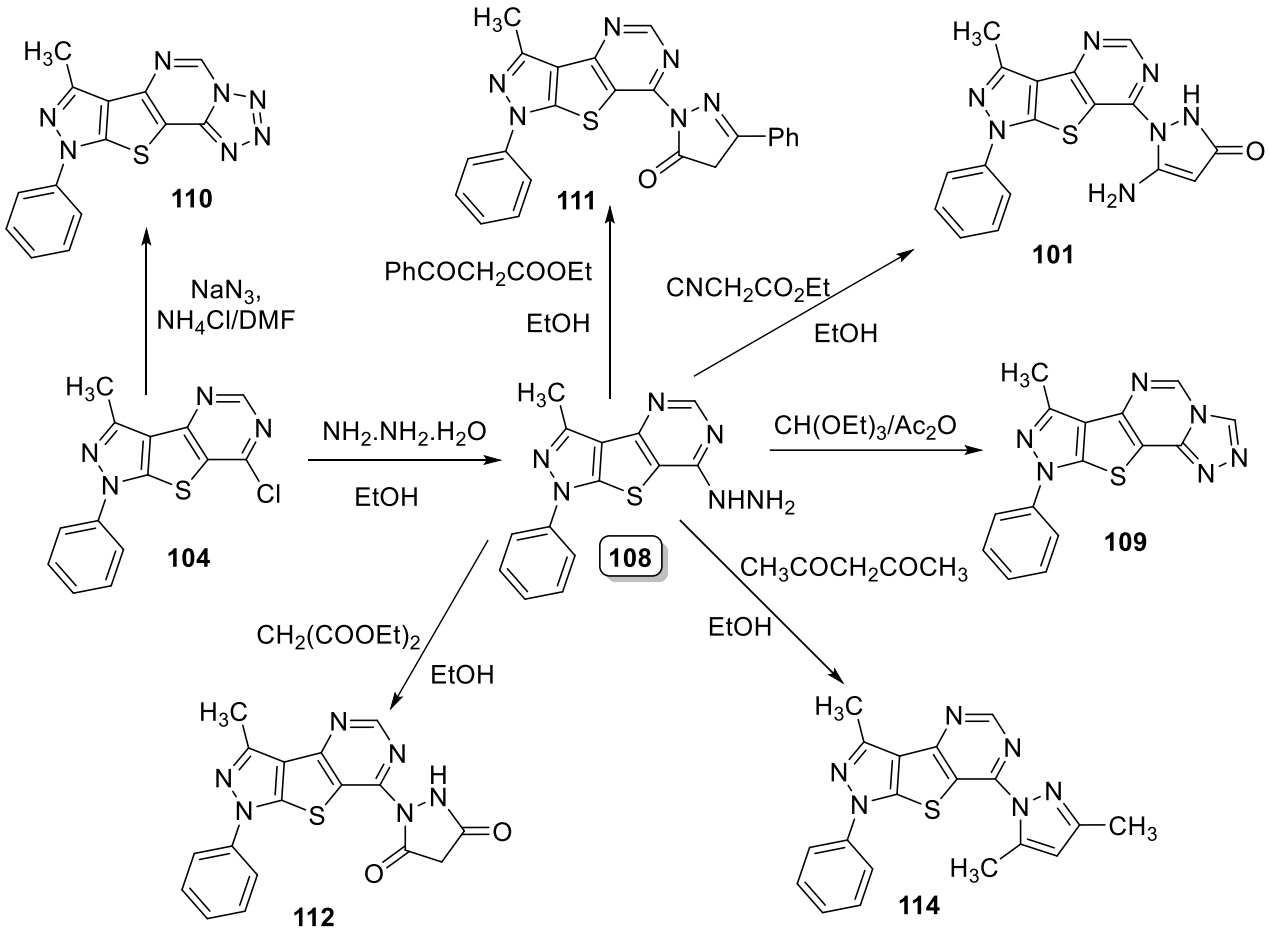
pyrazolothienopyrimidinethione **106** using phosphorus pentasulphide in refluxing pyridine. Compound **106** was obtained via an alternative route by the reaction of chloropyrimidine derivative **104** with thiourea. Alkylation of the thione **106** using different α-halocarbonyl compounds like ethyl chloroacetate, chloroacetone and/or phenacyl bromide in ethanol in the presence of sodium acetate afforded the *S*-alkylated mercaptopyrimidoselenolopyrazole derivatives **107a-c** (Scheme 27).



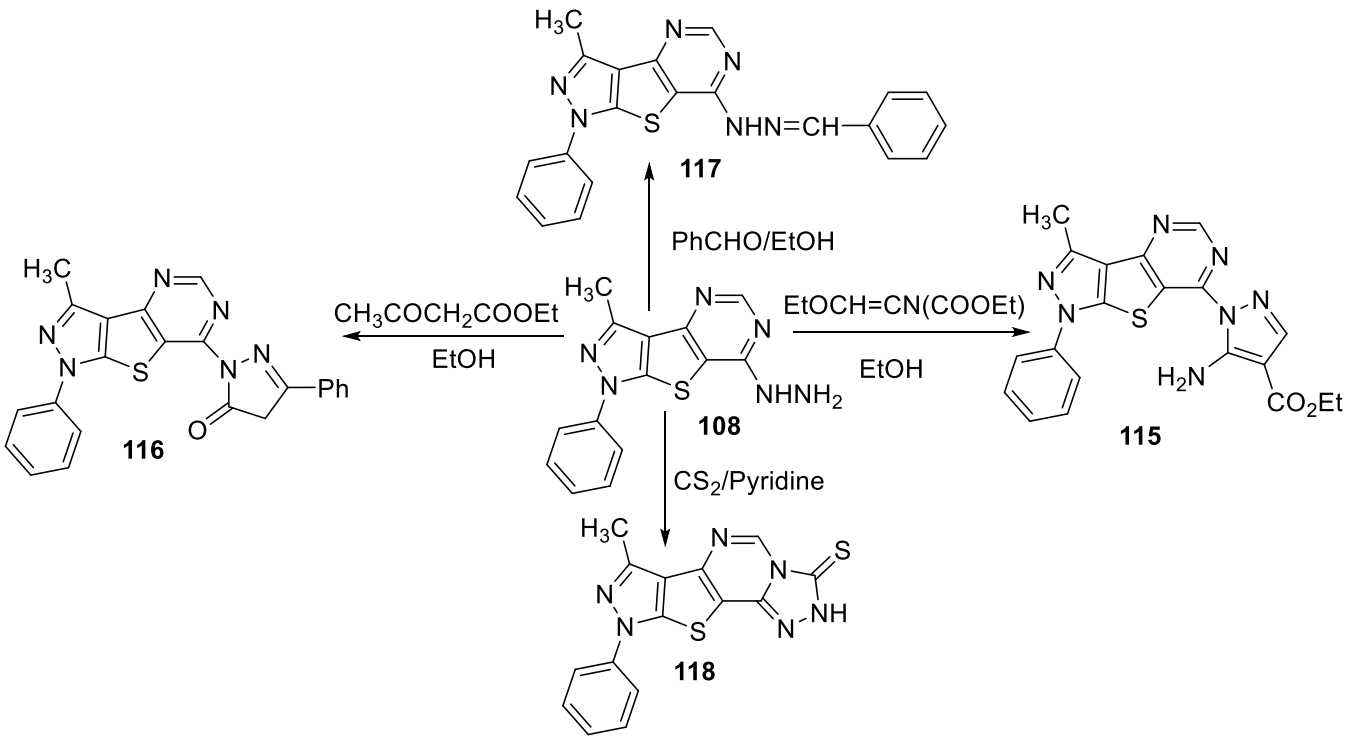
Scheme 27. Nucleophilic substitution reactions of the chloro derivative **92.**

Treatment of compound **104** with hydrazine hydrate in refluxing ethanol induced a nucleophilic substitution reaction to afford the corresponding hydrazinopyrimidine compound **108**. The latter was used as a starting material for synthesis of other new heterocyclic systems fused with the pyrazolothienopyrimidine moiety. Thus, when compound **108** was allowed to react with triethyl orthoformate in the presence of a catalytic amount of acetic acid, 7-methyl-9-phenyl-9*H*-pyrazolo[4',3':4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (**109**) was obtained. Reaction of the chloropyrimidine **104** with sodium azide in DMF produced the tetrazolo derivative **110**. Moreover, condensation of the hydrazinopyrazolothieno-pyrimidine derivative **108** with various activated bifunctional compounds such as ethyl benzoylacetate, diethyl malonate, acetylacetone, and ethyl cyanocetate by heating under solvent-free conditions yielded the non-isolated intermediates, which were subjected to heterocyclization in situ under the same reaction conditions to produce the pyrazolylpyrimidines **111-114** (Scheme 28).[60]

Also, compound **108** was reacted with ethyl(ethoxymethylene)cyanoacetate in boiling ethanol to give the pyrazolyl compound **115**. Condensation of the hydrazino compound **108** with ethyl acetoacetate afforded the pyrazolone derivative **116**. Furthermore, the reaction of the hydrazinopyrimidine compound **96** with benzaldehyde in refluxing ethanol produced the 7-(2-benzylidenehydrazino)-3-methyl-1-phenyl-1*H*-pyrazolo[4',3';4,5]thieno[3,2-*d*] pyrimidine Schiff's base (**117**). In the same manner, compound **96** was cyclized by the reaction with carbon disulfide in pyridine to afford 7-methyl-9-phenyl-2,9-dihydro-3*H*-pyrazolo[4',3';4,5]thieno[2,3-*e*][1,2-4]triazolo[4,3-*c*]pyrimidine-3-thione (**118**) (Scheme 29)[60].

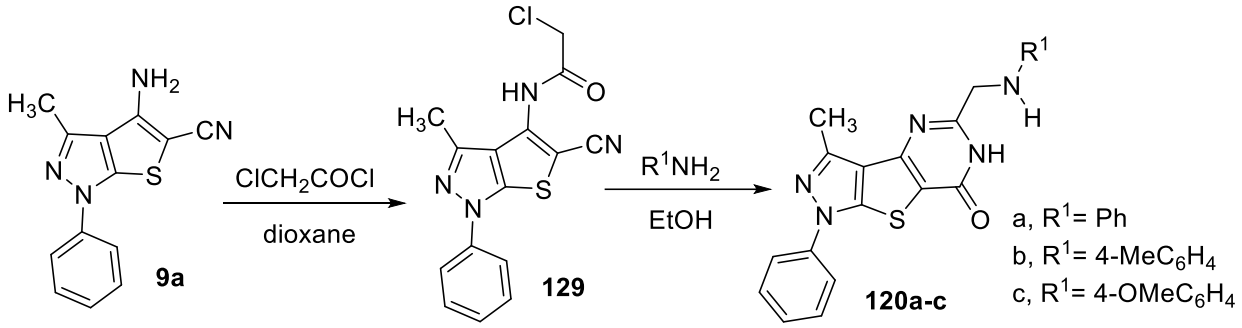


Scheme 28. Synthesis of pyrazolo[4′,3′:4,5]thieno[3,2-*d*]pyrimidine derivatives **108-114**.



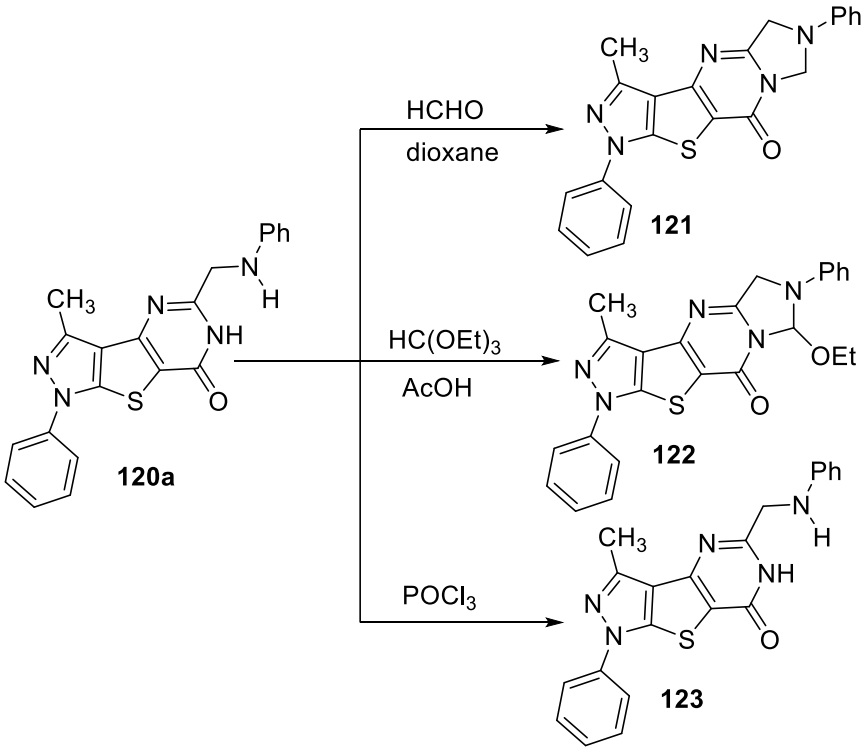
Scheme 29. Synthesis of pyrazolo[4′,3′:4,5]thieno[3,2-*d*]pyrimidine derivatives **115-118**.

In 2019, it was reported that the chloroacetylation reaction of 4-amino-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbonitrile (**9a**) afforded the chloroacetamido derivative **119**. Reaction of **119** with various primary aromatic amines furnished the unexpected pyrimidinones **120a-c** in good yields (Scheme 30)[61] This reaction apparently proceeds by nucleophilic substitution of the chloride ion with the primary amino group followed by Dimroth rearrangement in the presence of excess of the amine[62]



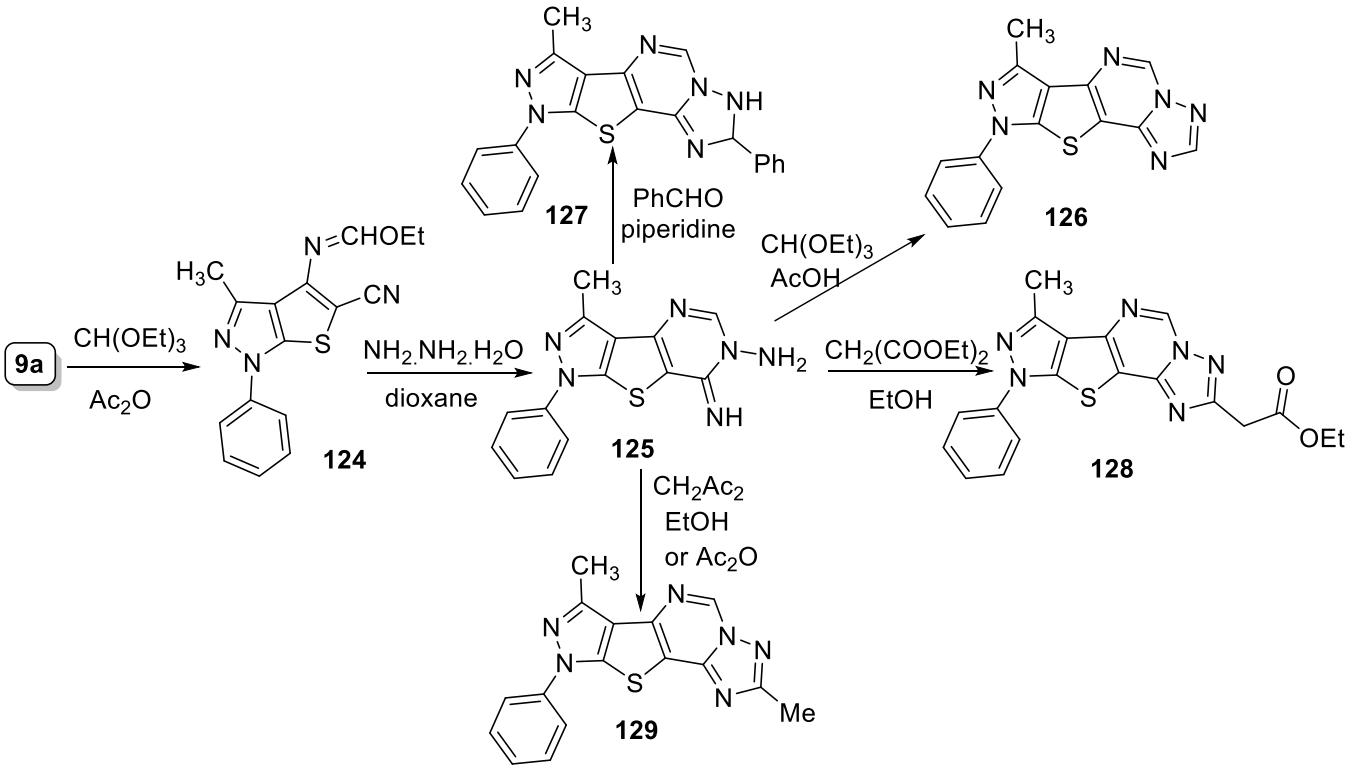
Scheme 30. Synthesis of pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidine derivatives **120a-c**.

Treatment of the 5-(phenylaminomethyl)pyrimidinone **120a** with formaldehyde in dioxane and the reaction with triethyl orthoformate afforded the respective tetracyclic pyrimidinones **121** and **122**. Moreover, chlorination of the pyrimidinone **120a** with phosphorus oxychloride furnished the chloropyrimidine **123** (Scheme 31).[61]



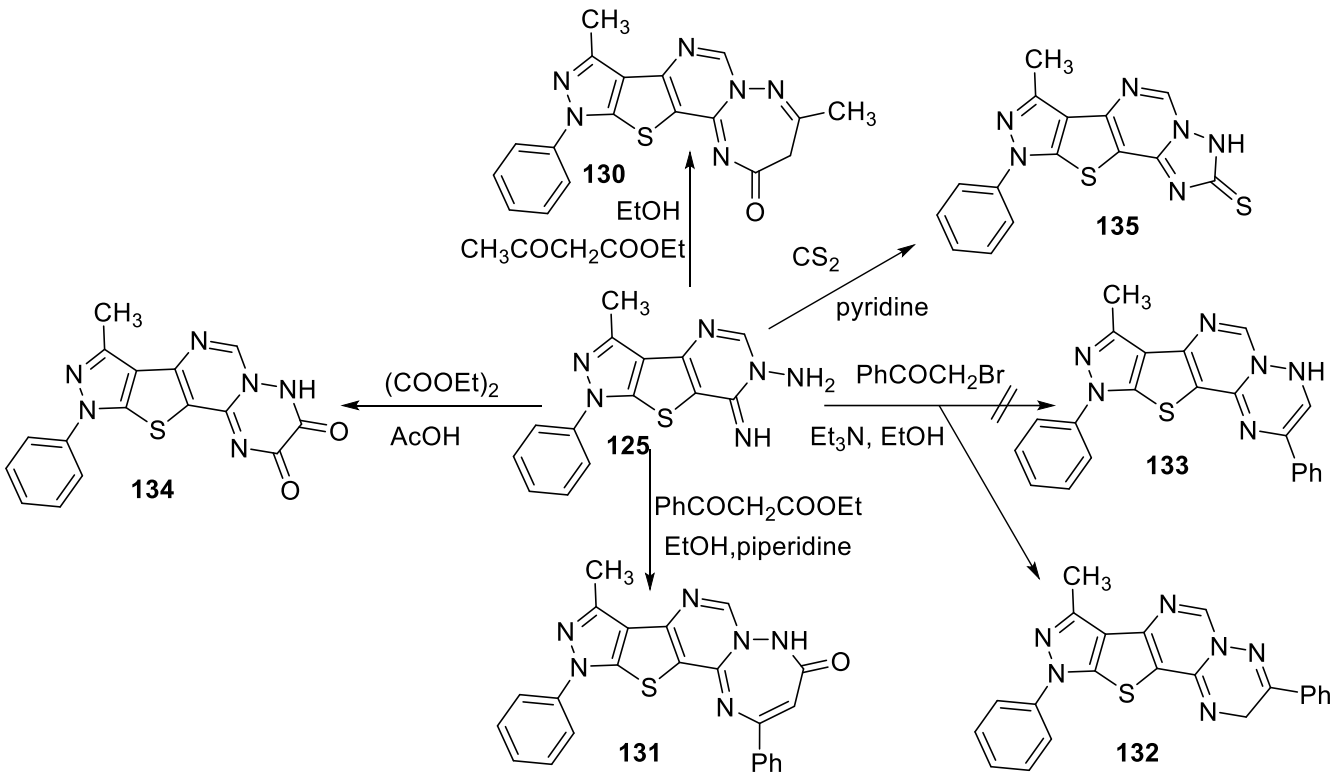
Scheme 31. Synthesis of tetracyclic pyrimidinones **121** and **122.**

Condensation of *o*-aminocarbonitrile **9a** with triethyl orthoformate in the presence of a catalytic amount of acetic anhydride produced compound **124.** Stirring of **124** with an equivalent amount of hydrazine hydrate yielded iminopyrimidine derivative **125**. Condensation of the amino-imino compound **125** with triethyl orthoformate produced the corresponding triazolopyrimidine **126** in an excellent yield, and dihydropyrazolopyrimidine **127** was obtained in low yield upon treatment of **126** with benzaldehyde. An additional series of novel tetracyclic pyrimidines **128-131** were synthesized by condensation of the amino-imino derivative **114** with different 1,3-dicarbonyl compounds. Thus, condensation of compound **125** with diethyl malonate afforded the ethyl triazolopyrimidinyl acetate **128**, while condensation with acetyl acetone produced triazolopyrimidine **129** instead of the expected diazepine product (Scheme 32).[61]



Scheme 32. Reaction of the amino-imino derivative **125** with different 1,3-dicarbonyl compounds.

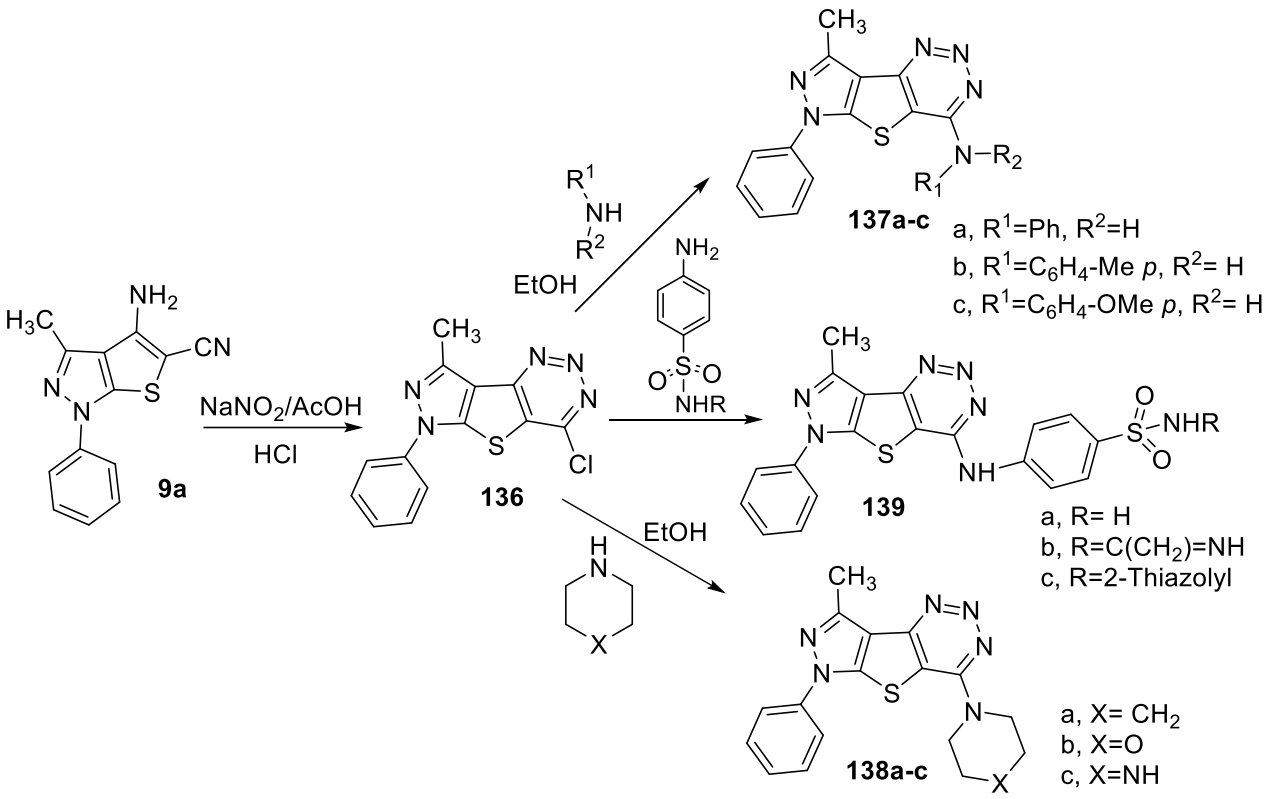
In a similar manner, condensation of **125** with ethyl acetoacetate and ethyl benzoylacetate afforded the corresponding triazepinones **130** and **131**. Surprisingly, the treatment of **125** with phenacyl bromide in refluxing ethanol in the presence of triethylamine yielded the 3,8-diphenyltriazine **132** rather than its 2,8-diphenyl isomer **133**. Formation of **132** can be explained by condensation between NH_2 of the amino-imino **125** and carbonyl group of phenacyl bromide. Fusion of compound **125** with diethyl oxalate in the presence of acetic acid produced the corresponding triazinedione **134** in good yield. Triazolethione **135** was obtained upon heating of **125** with carbon disulfide in pyridine at 100 °C (Scheme 33).[61]



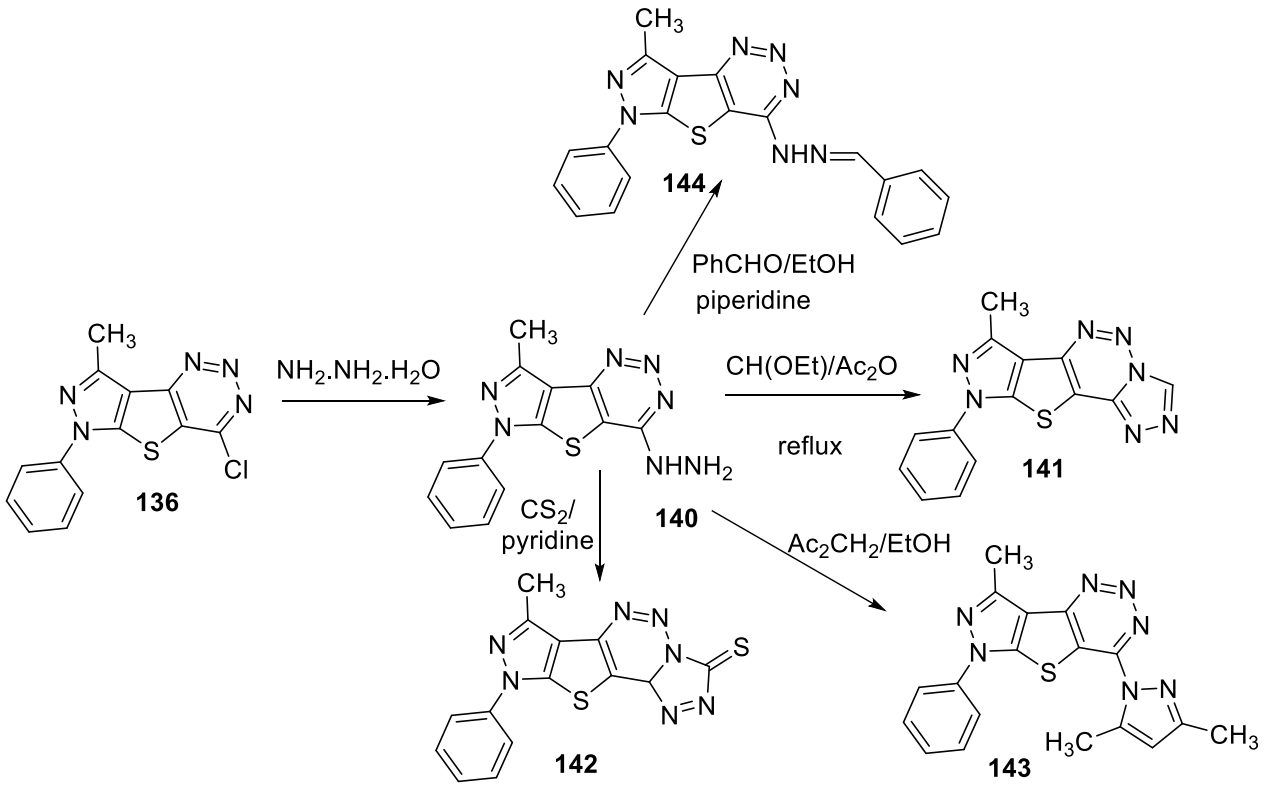
Scheme 33. Formation of triazepinones **130** and **131**.

Zaki *et al*.[63] reported that diazotization of the o-aminothienopyrazole carbonitrile **9a** with sodium nitrite solution (10%) in a mixture of acetic acid and concentrated HCl, at room temperature, afforded the corresponding chloropyrazolothienotriazine **136**. Furthermore, the chloride ion in compound **136** underwent nucleophilic substitution reactions with various primary and secondary amines upon heating in absence of solvent under neat conditions for a short time, followed by refluxing in ethanol to give the N-substituted aminopyrazolothienotriazine derivatives **137-139** (Scheme 34).

Consequently, hydrazinolysis of the chlorotriazine compound **136** with hydrazine hydrate upon heating under neat conditions for a short time, followed by addition of ethanol, furnished the hydrazinopyrazolothienotriazine **140**. The latter compound **140** was used as a versatile precursor for synthesis of other heterocyclic rings attached or fused to pyrazolothienotriazine ring system to afford compounds **141-144**. Thus, the reaction of hydrazino compound **140** with triethyl orthoformate, in presence of a catalytic amount of acetic acid, afforded the pyrazolothienotriazolotriazine **141**. Also, nucleophilic addition of NH_2 group of hydrazino compound **140** to carbon disulfide, followed by elimination of H_2S, yielded the corresponding triazolotriazinethione derivative **142**. On the other hand, condensation of **140** with acetyl acetone and benzaldehyde gave the corresponding dimethylpyrazolyl **143** and the benzylidenehydrazinotriazine (Schiff's base) **144**, respectively (Scheme 35).[63]

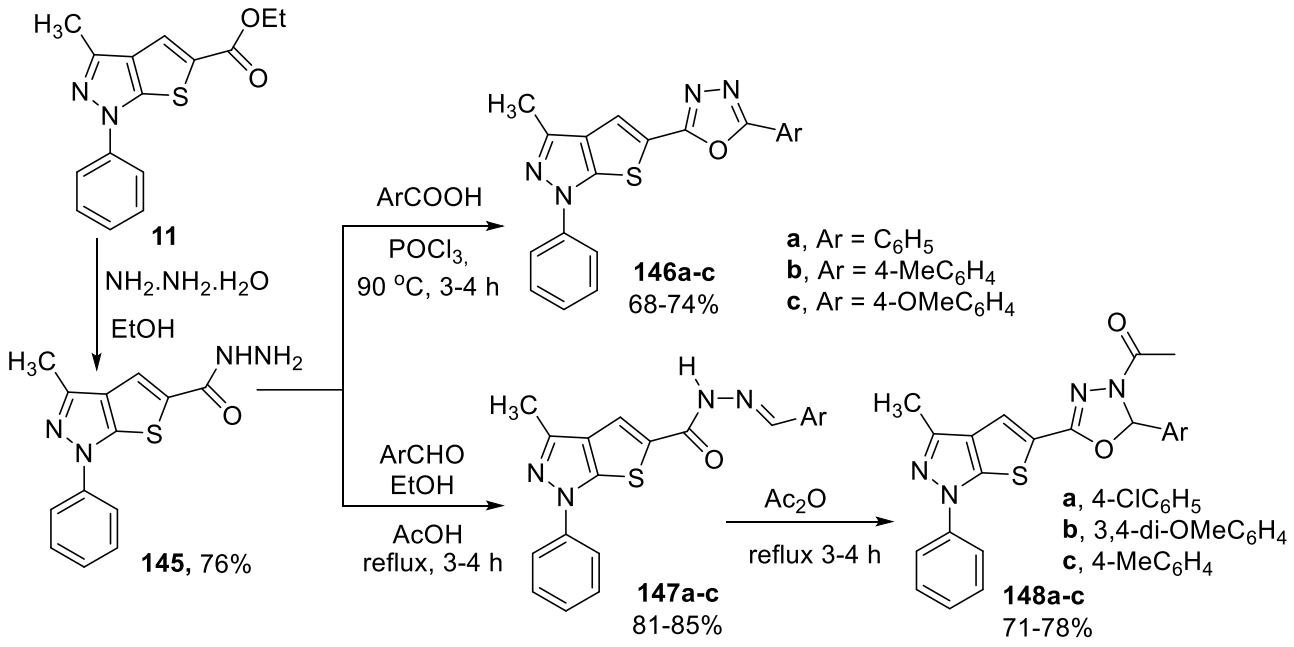


Scheme 34. Synthesis of N-substituted aminopyrazolothienotriazine derivatives **137-139.**



Scheme 35. Use the hydrazine derivative **140** for synthesis of other heterocyclic rings attached or fused to the pyrazolothienotriazine ring system (**141-144**).

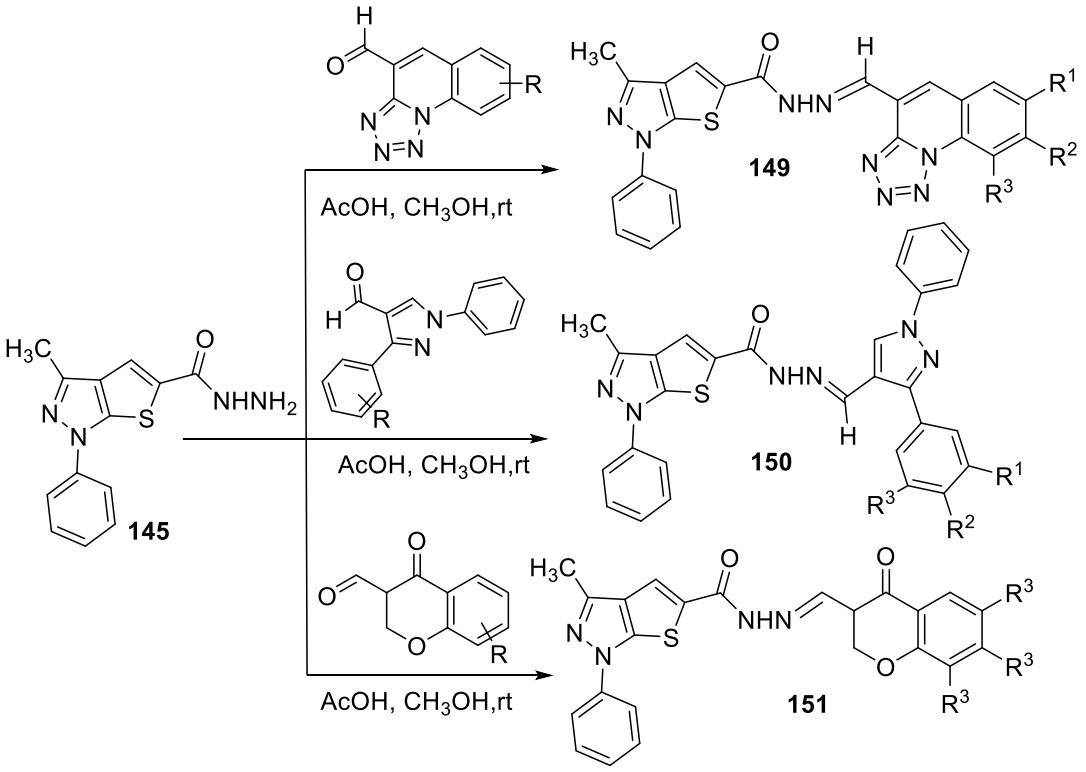
In 2014, Patil et *al*.[27] indicated that the interaction of ethyl-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*] pyrazole-5-carboxylate **11** with hydrazine hydrate afforded corresponding carbohydrazide **145** in 76% yield. Treatment of the carbohydrazide **145** with aryl carboxylic acid in phosphoryl chloride resulted in cyclization to give 2,5-disubstituted-1,3,4-oxadiazole **146a-c**.[64] Whereas, the reaction of **145** with various aldehydes in ethanol gave Schiff bases **147a-c**, which were cyclized in acetic anhydride at reflux to afford the 1,3,4-oxadiazole derivatives **148a-c** in71–78% yield (Scheme 36).



Scheme 36. Synthesis of 1,3,4-oxadiazole derivatives based thieno[2,3-*c*]pyrazole **146** and **137**.

Mahajan *et al*.[65,66] reported that the condensation of carbohydrazide **145** with the appropriate heterocyclic aldehydes in methanol gave the corresponding stable solid *N*-acylhydrazones (**149a–g**, **150a–h**), and (**151a–d**), respectively (Scheme 37).

The carbohydrazide **145** gave different products with carbon disulfide, potassium hydroxide in absolute ethanol at slightly different conditions. This reaction gave 5-(3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)-1,3,4-oxadiazole-2(3*H*)-thione **152**[64] at reflux, whereas at room temperature, the potassium salt of hydrazinecarbodithioate **152** was obtained. This salt was cyclized with excess of 99% hydrazine hydrate in water to give 4-amino-5-(3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)-4*H*-1,2,4-triazole-3-thiol **154** in 65% yield. The resulting triazole was converted to triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **155a–c** in one-step reaction by condensation with aromatic acids in $POCl_3$ at reflux (Scheme 38). [27]

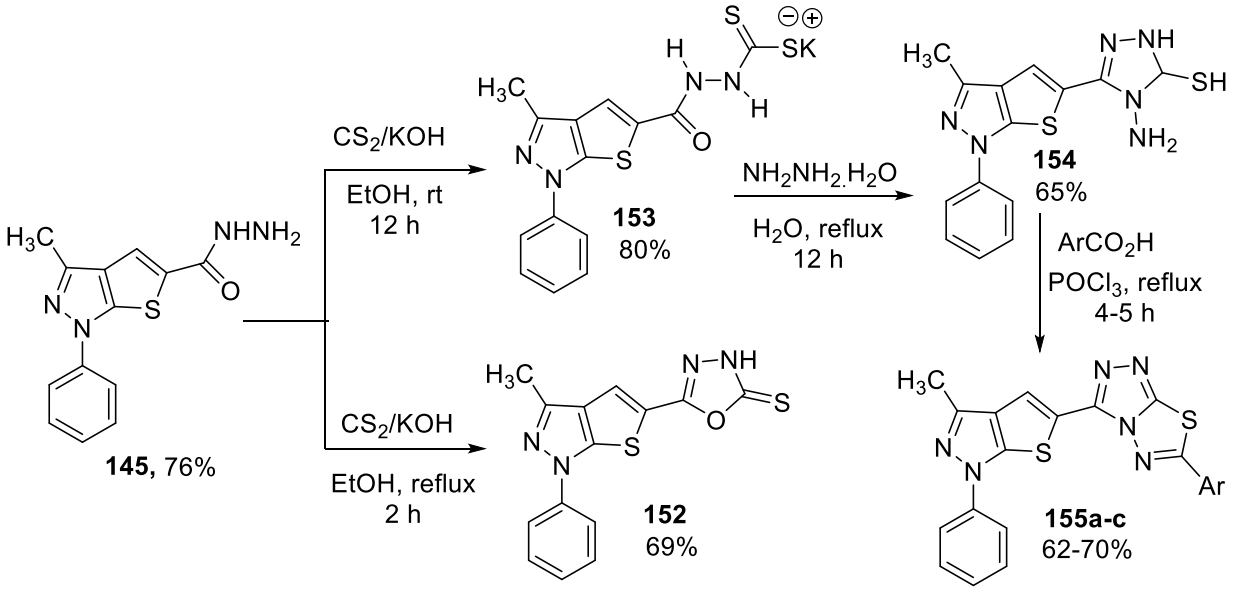


149 a, R^1= OCH_2CH_3, R^2= H, R^3= H
b, R^1= H, R^2= H, R^3= H
c, R^1= OCH_3, R^2= H, R^3= H
d, R^1= H, R^2= OCH_3, R^3= H
e, R^1= CH_3, R^2= H, R^3= H
f, R^1= H, R^2= CH_3, R^3= H
g, R^1= H, R^2= H, R^3= CH_3

150,a, R^1= OCH_2CH_3, R^2= H, R^3= H
b, R^1= H, R^2= NO_2, R^3= H
c, R^1= H, R^2= OCH_3, R^3= H
d, R^1= H, R^2= F, R^3= H
e, R^1= H, R^2= OH, R^3= H
f, R^1= H, R^2= Cl, R^3= H
g, R^1= H, R^2= CH_3, R^3= H
h, R^1= H, R^2= Br, R^3= H

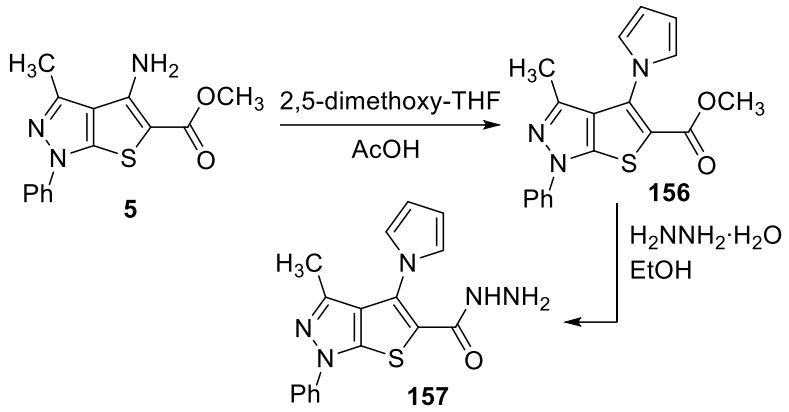
151, a,R^1= H, R^2= Cl, R^3= H
b,R^1= H, R^2= Br, R^3= H
c,R^1= Cl, R^2= CH_3, R^3= H
d,R^1= CH3, R^2= CH_3, R^3= H

Scheme 37. Synthesis of N-acylhydrazones **149-151**.



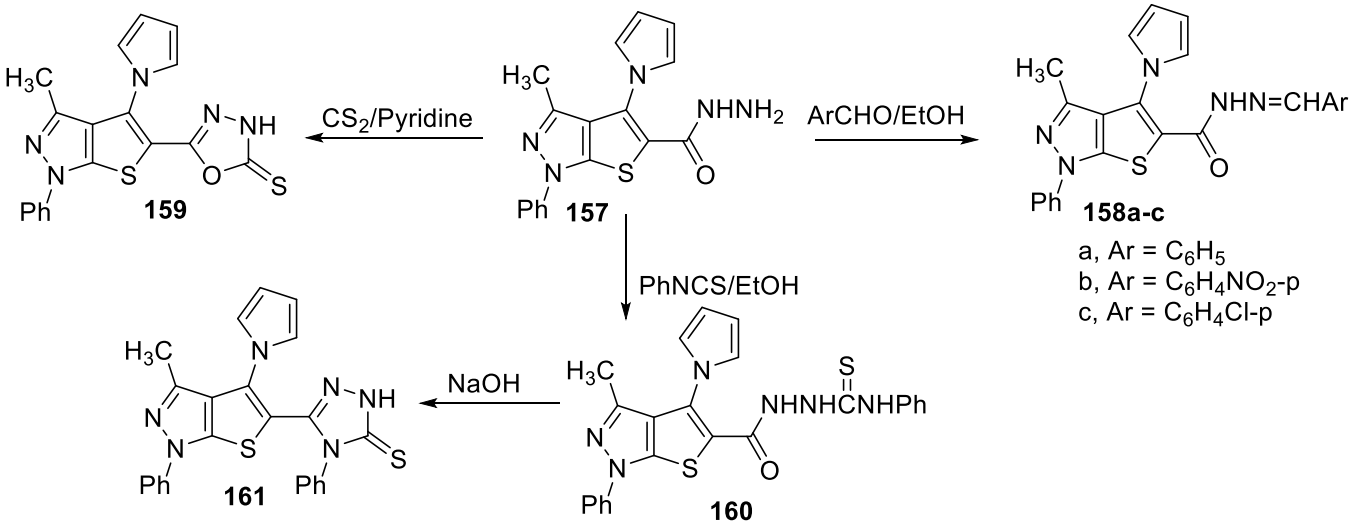
Scheme 38. One pot synthesis of triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **155a–c**.

In 2005, Haider et *al*.[25] mentioned that the amino function of **5** could be easily converted into a pyrrol-1-yl group following our previously reported procedure[33] to give the corresponding methyl 3-methyl-1-phenyl-4-(1*H*-pyrrol-1-yl)-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylate (**156**). Treatment the pyrrolyl ester **156** with hydrazine hydrate afforded the pyrrolyl hydrazide **157** (Scheme 39).



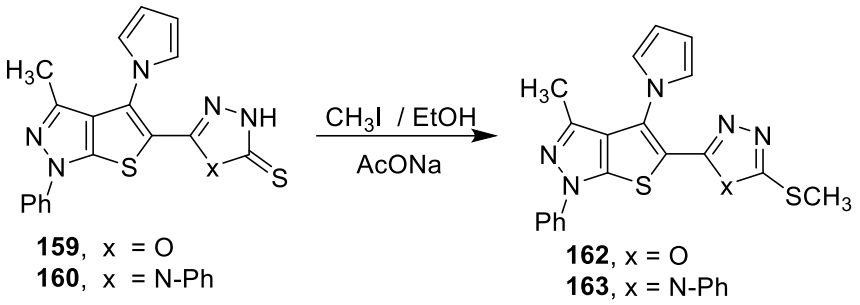
Scheme 39. Synthesis of (pyrrol-1-yl)-derivatives **145** and **146**.

The carbohydrazide **157**[25] proved to be a versatile compound that led to the synthesis of several thieno[2,3-*c*]pyrazole derivatives. Thus, condensation of **157** with some aromatic aldehydes yielded the expected hydrazones **158a-c**. The oxadiazolethione **159** was obtained by the reaction of **157** with carbon disulfide in the presence of pyridine. The triazolethione **161** however was obtained *via* the reaction of **157** with phenyl isothiocyanate, followed by heating the resulted thiosemicarbazide **160** in aqueous NaOH solution (Scheme 40).



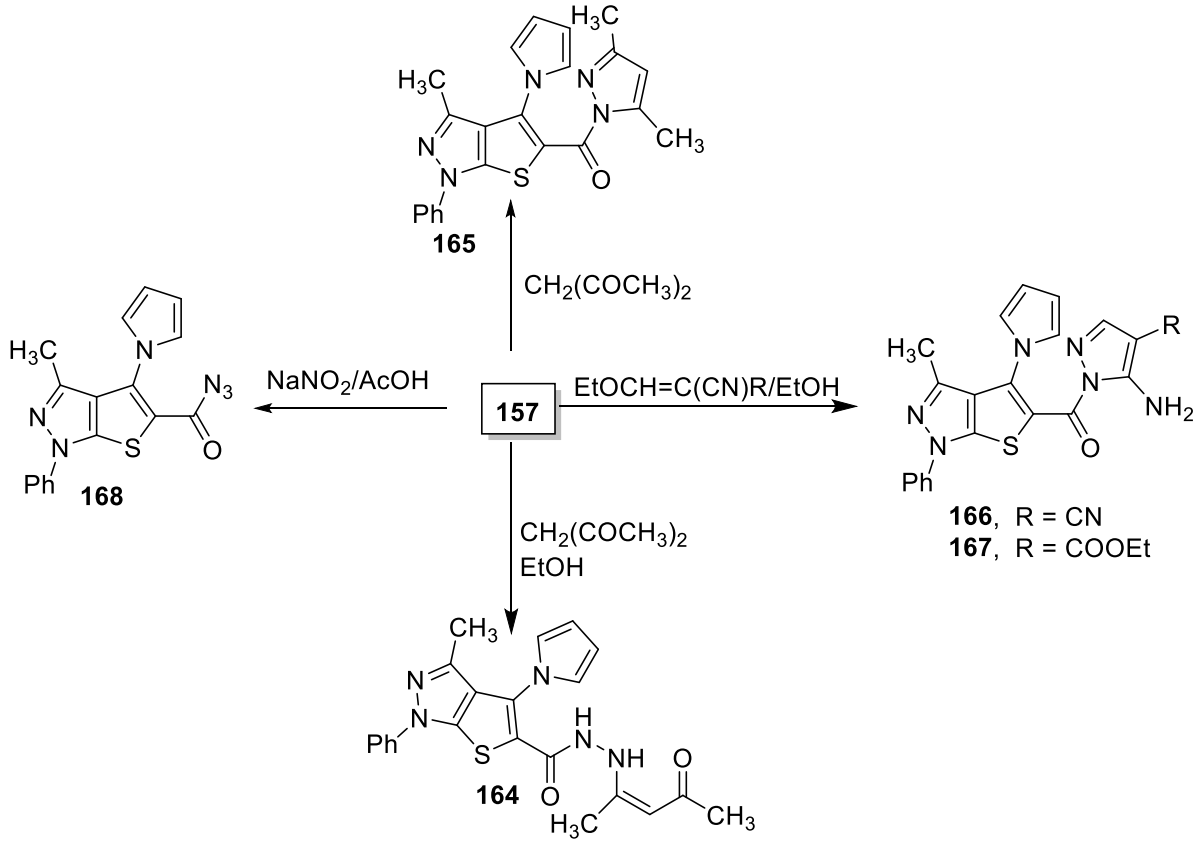
Scheme 40. Synthesis of several thieno[2,3-*c*]pyrazole derivatives **158-161**.

The mercapto group of both **159** and **161** could be easily alkylated by methyl iodide in the presence of sodium acetate to give the corresponding methylthio derivatives **162** and **163** respectively[25] (Scheme 41).



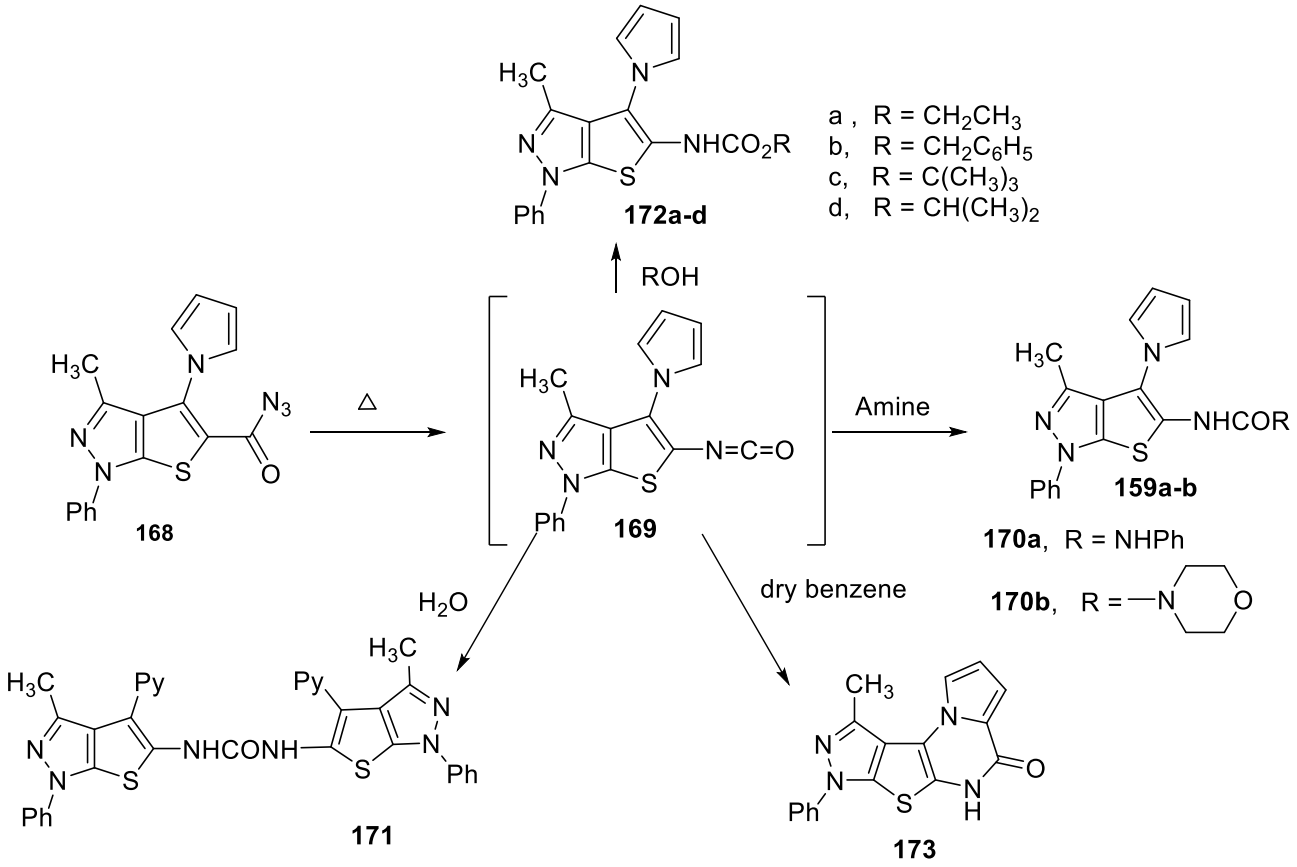
Scheme 41. Alkylation of thione derivatives **159** and **161** with methyl iodide.

The reaction of **157**[25] with an equimolar ratio of acetylacetone in refluxing ethanol led to a dehydration reaction with the loss of one molecule of water to yield the *N*[1](4-oxo-2-penten-2-yl)-3-methyl-1-phenyl-1*H*-4-(pyrrol-1-yl)-theino[2,3-*c*]pyrazole)-5-carbohydrazide (**164**). However, when the same reaction was conducted by using an excess of neat acetylacetone, two molecules of water were eliminated *via* a cyclodehydration reaction leading to the dimethylpyrazolyl derivative **154.** On the other hand, the reaction of the carbohydrazide **157** with ethoxymethylene malononitrile, and ethyl ethoxymethylenecyanoacetate gave the substituted pyrazol-1-yl-theino[2,3-*c*]pyrazoles **166** and **167** respectively. Treatment of a cold solution of **157** in glacial acetic acid with ice-cold solution of sodium nitrite resulted in the formation of 3-methyl-1*H*-phenyl-4-(pyrro-1-yl)-1*H*-thieno[2,3-*c*] pyrazole-5-carboazide (**157**) in a good yield (Scheme 42).[25]



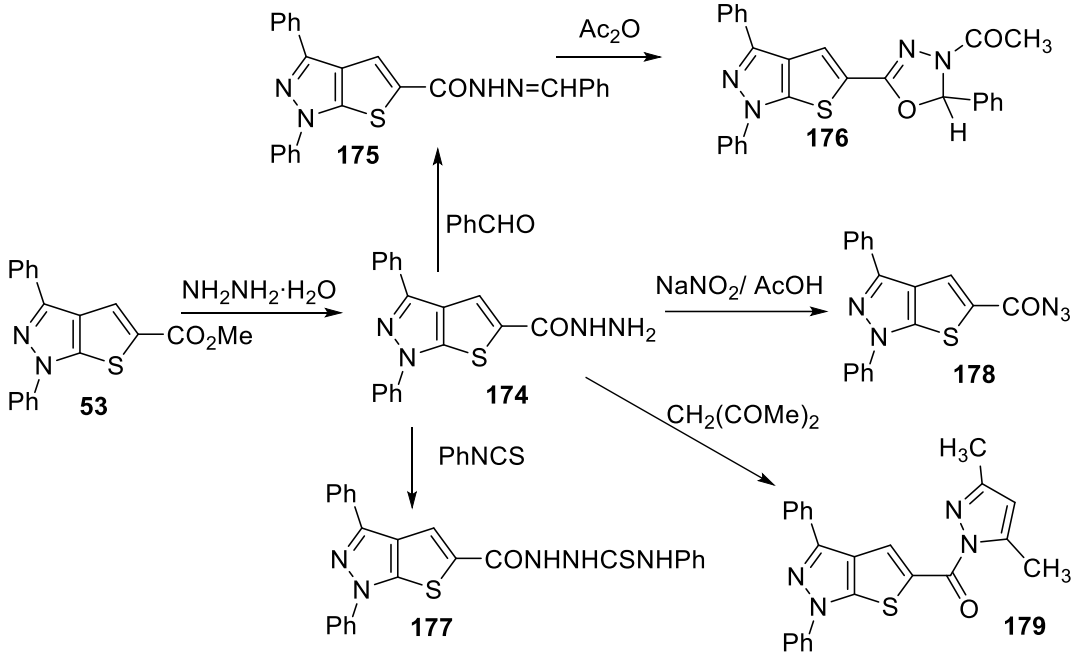
Scheme 42. Synthesis of pyrazolyl derivatives **164-168**.

In continuation to above work,[25] the synthetic utility of acid azide **168** as a useful key intermediate in the synthesis of thienopyrazole derivatives is shown in Scheme 5. Thus, when **168** was heated with different amines, Curtius rearrangement occurred to give the isocyanate intermediate **169** which reacted concomitantly with amines to afford the corresponding urea derivatives. Thus, the reaction of acid azide **168** with primary amines (aniline) gave the disubstituted urea **170a**, while its reaction with secondary amines (morpholine) gave the trisubstituted urea **159b**. The symmetrically disubstituted urea **171** was obtained when the acid azide **168** was heated in boiling water. It is worth mentioning that the reaction of acid azide **168** with alcohols proceeded also *via* Curtius rearrangement and afforded the corresponding carbamates **172a-d**. However, when the acid azide **168** was heated in an inert high boiling point solvent such as dry benzene and in absence of any reactive entity, Curtius rearrangement took place with subsequent intramolecular ring closure to give 3-methyl-1-phenyl-1*H*-pyrazolo[4`,3`:4,5]thieno[2,3-*e*]pyrrolo-[1,2-*a*]pyrazin-8(9*H*)-one (**173**) (Scheme 43).



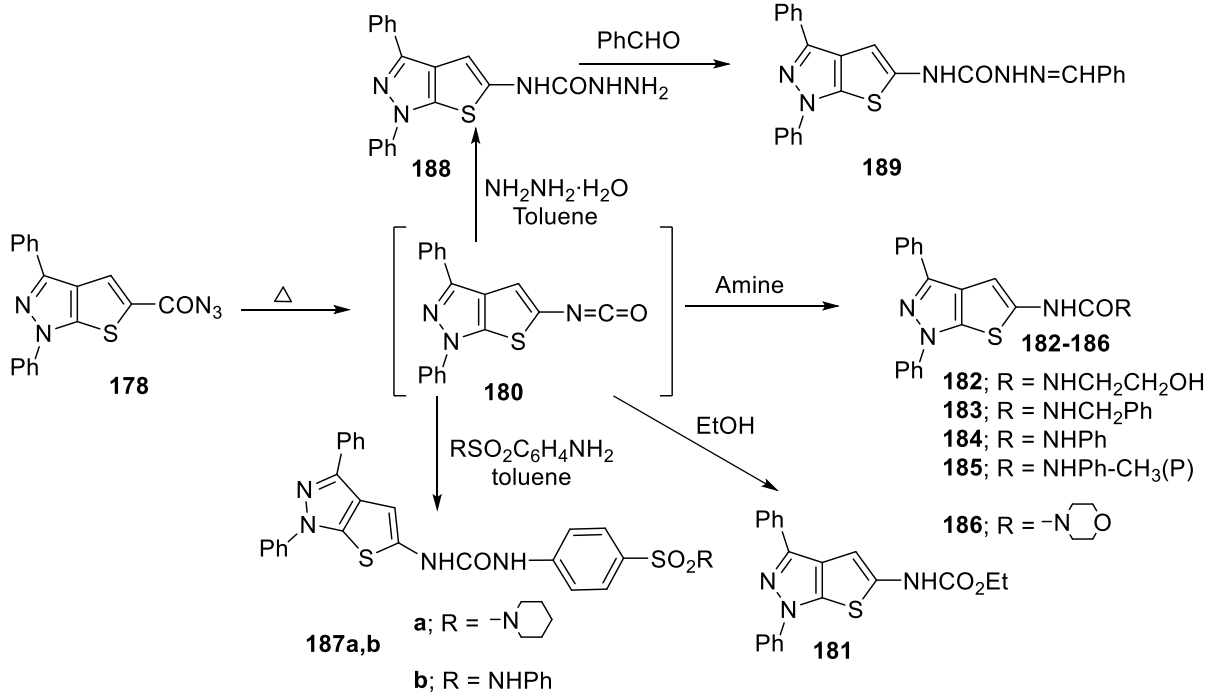
Scheme 43. Use of the azide derivative **169** as key intermediate in the synthesis of thienopyrazole derivatives **170-173**.

It was reported[67] that the treatment of the thieno[2,3-*c*]pyrazole **53** with hydrazine hydrate afforded the corresponding hydrazide **174** which was used as a key intermediate in the synthesis of the other thienopyrazoles **123-127**. Thus, the condensation of **174** with benzaldehyde yielded the hydrazone **175** which was cyclized into oxadiazoline derivative **165** by heating in boiling acetic anhydride. The carbohydrazide **174** was also reacted with phenyl isothiocyanate, acetylacetone and nitrous acid to give the thiosemicarbazide **177**, the dimethylpyrazole derivative **178** and the acid azide **179,** respectively (Scheme 44).



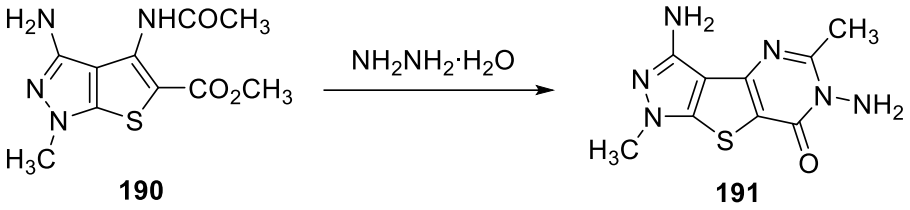
Scheme 44. Synthesis of the thienopyrazoles **174-179**.

Curtius rearrangement[67] occurred when the acid azide **178** was heated in boiling ethanol where the isocyanate intermediate **180** was formed. The latter intermediate reacted concomitantly with the ethanol, used as a solvent and reactant, to give the corresponding ethyl carbamate **181**. When the alcohol was replaced by amines or conducted in dry toluene in the presence of *N*[1]-substituted sulfanilamides, the corresponding urea derivatives **171-175** and **187a,b** were obtained. When the acid azide **178** was first heated in dry toluene to ensure the Curtius rearrangement of **178** into the isocyanate **180** followed by the addition of an excess of hydrazine hydrate, the expected semicarbazide **188** was obtained. The latter compound **188**, upon reaction with benzaldehyde, gave the benzylidene derivative **189** (Scheme 45).



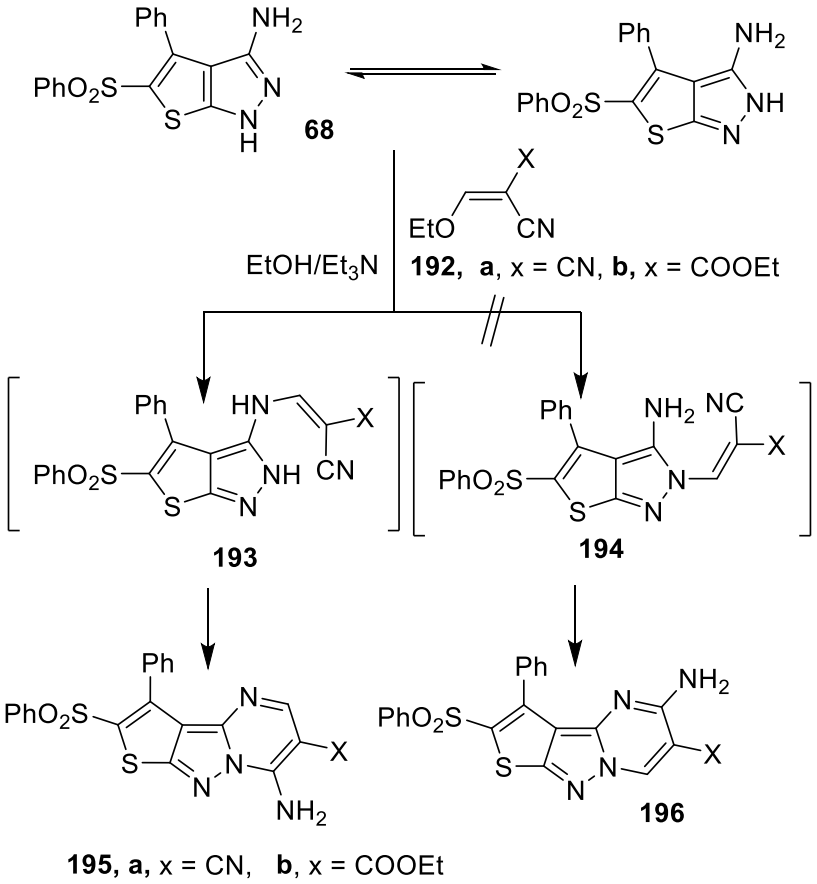
Scheme 45. Reactions of acid azide **178** with different amines and alcohols**.**

Furthermore, reaction of methyl 4-acetylamino-3-amino-1-methyl-1*H*-thieo[2,3-*c*]pyrazole-5-carboxylate (**190**) with hydrazine hydrate gave the pyrazolothienopyrimidine derivative [55]**191**[55] (Scheme 46).



Scheme 46. Synthesis of pyrazolothienopyrimidine derivative **191**.

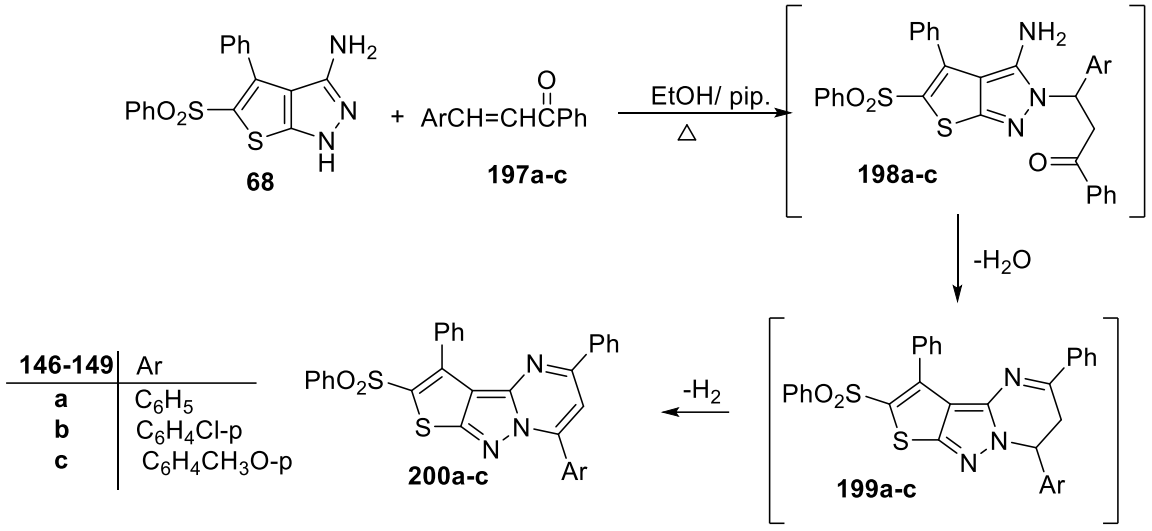
The thieno[2,3-*c*]pyrazole derivative **68** was reported[52] to react with ethoxymethylenemalanonitrile **192a** in refluxing EtOH/Et_3N solution yielding thienopyrazolopyrimidine derivative **195a** *v*ia EtOH elimination. Similarly, compound **68** was reacted with ethyl ethoxymethylenecyanoacetate **192b** to furnish the corresponding ethyl-7-amino-thieno[2',3':3,4]pyrazolo[1,5-a]pyrimidine-6-carboxylate derivative (**195b**) as shown in scheme 48.



Scheme 48. Synthesis of ethyl-7-amino-thieno[2',3':3,4]pyrazolo[1,5-a]pyrimidine-6-carboxylate derivative (**195b**).

The behavior of **68** towards α,β-unsaturated ketones has also been investigated[52] Thus, compound **68** reacted with chalcones **197a-c** in absolute ethanol containing a catalytic amount of piperidine, under reflux, to

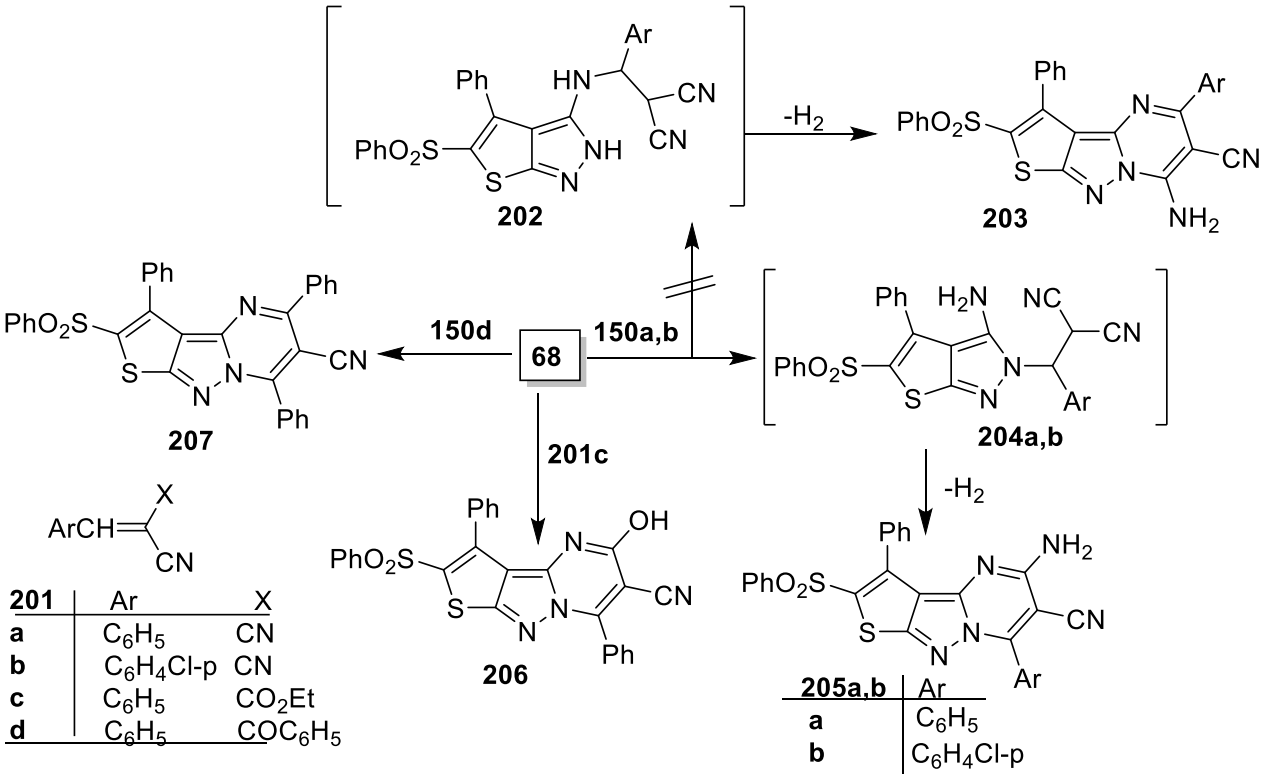
yield the corresponding thieno[2`,3`:3,4]pyrazolo[1,5-*a*]pyrimidine derivatives **200-c** in acceptable yields . Formation of **200** is assumed to proceed *via* a 1,4-Michael type addition on the most basic pyrazole ring nitrogen of compound **68**, intramolecular cyclodehydration, and spontaneous autoxidation under the reaction conditions[52] (Scheme 49).



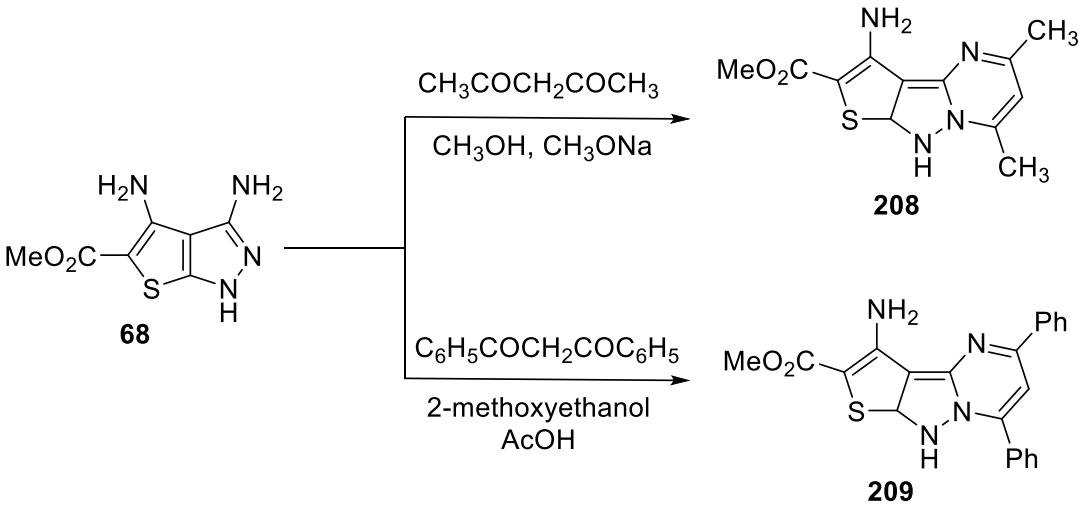
Scheme 49. Synthesis of thieno[2`,3`:3,4]pyrazolo[1,5-*a*]pyrimidine derivatives **200a-c.**

Compound **68** reacted with an equimolar amount of benzylidenemalononitrile (**201a**) in refluxing pyridine solution to give **205a** *v*ia acyclic intermediate **204a**, intramolecular cyclization (Michael type addition of the NH_2 protons to the C≡N function) and spontaneous autoxidation. Similarly, compound **68** reacted with **201b** to yield **205b**. Compound **68** reacted with an equimolar amount of ethyl benzylidenecyanoacetate (**201c**) under the same experimental conditions to yield the corresponding 5-hydroxy-7-phenylthieno [2`,3`:3,4]pyrazolo[1,5-*a*]pyrimidine derivative **206** *v*ia an initial Michael type addition of the pyrazole NH function to the α,β-unsaturated center, cyclization was done *v*ia ethanol elimination, and subsequent autoxidation. Likewise, compound **68** was reacted with benzylidene-ω-cyanoacetophenone (**201d**) to yield compound **207** (Scheme 50).[52]

The reaction of methyl-3,4-diamino-1*H*-thieno[2,3-*c*]pyrazole-5-carboxlate **68** with acetylacetone in absolute methanol in the presence of sodium methoxide gave methyl 3-amino-5,7-dimethyl-thieno[2`,3`:3,4]pyrazolo[1,5-*a*]pyrimidine-2 carboxylate (**208**).[53] Also, the reaction of compound **68** with dibenzoylmethane in 2-methoxyethanol and acetic acid gave methyl-3-amino-5,7-diphenylthieno[2`,3`:3,4] pyrazolo[1,5-*a*]pyrimidine-2-carboxylate (**209**) (Scheme 51).



Scheme 50. Intramolecular cyclization for synthesis of thienopyrazolopyrimidines **206-207.**

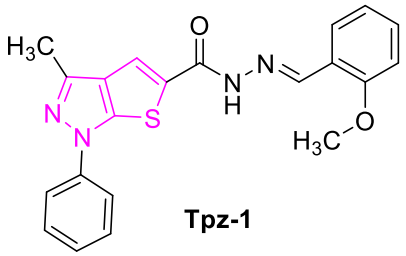


Scheme 51. Synthesis of thienopyrazolopyrimidine derivatives **208** and **209.**

4. Biological Importance of Thieno[2,3-*c*]pyrazoles

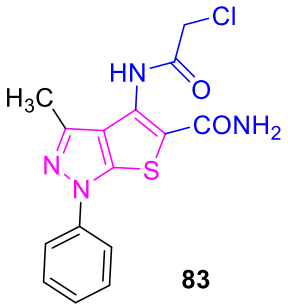
Thienopyrazole moiety has become known as a pharmacologically active scaffold that possesses kinase inhibitory and antitumoral properties in recent times. The thieno[2,3-*c*]pyrazoles are a class of active compounds currently employed in the field of medicinal chemistry.[68] Recently,[19] it was reported that the (*E*)-

N'-(2-methoxy-benzylidene)-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbohydrazide (Tpz-1) represents a novel anticancer agents which is possess potent and selective cytotoxic effects on cancer cells. It consistently induced cell death at low micromolar concentrations (0.19 ?M to 2.99 ?M) against a panel of 17 human cancer cell lines. Also, for their remarkable anti-inflammatory,[69] analgesic and antithrombotic activities, and for the treatment of cardiovascular or cerebrovascular diseases, hyperglycemia, hyperlipemia[70] and antihypertensive agents with a probable mechanism of potassium channel openers.[71] Precursors of thieno[2,3-*c*]pyrazoles were tested for their antibacterial activity *in vitro* against *Escherichia coli* and *Bacillus subtilis* and were found to be active against both the bacteria.[34]



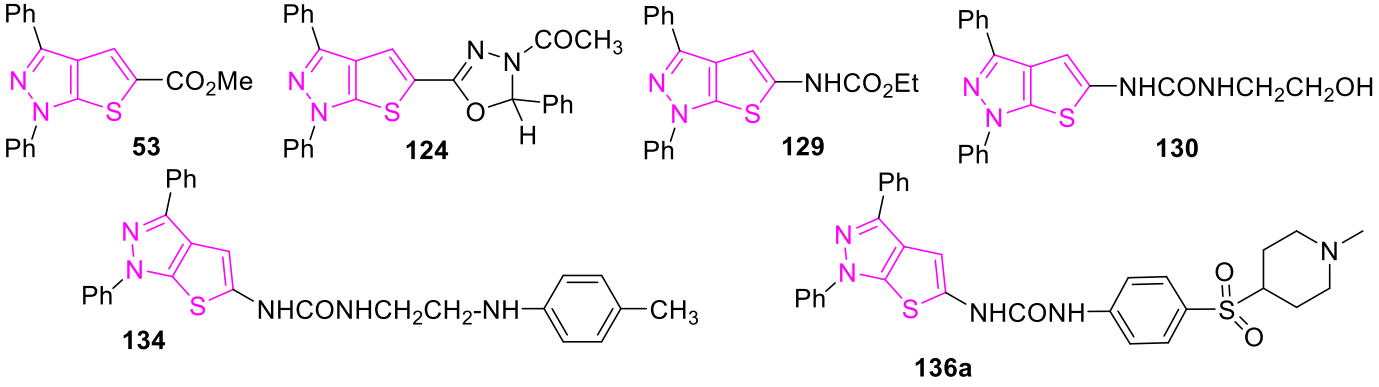
Tpz-1

In 2015, Sayed and co-workers[72] reported that the potent role of thieno[2,3-*c*]pyrazoles like compound **83**[59] indicates their potential as possible leads for the treatment of oxidative stress and repair the damage resulting from the toxicity of chemical pollutants such as (4-nonylphenol).

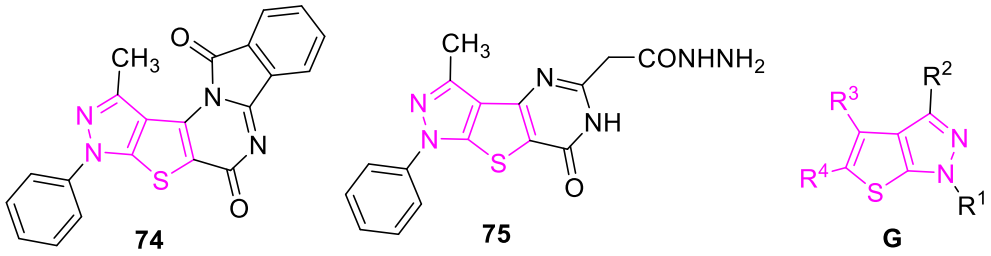


83

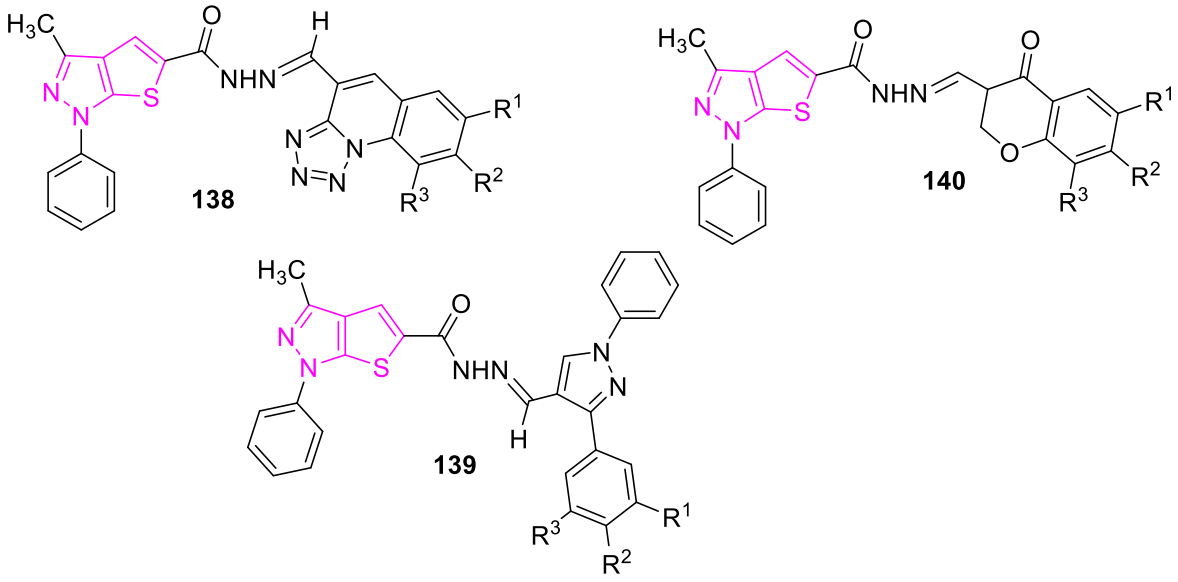
It was reported that some thieno[2,3-c]pyrazoles (**53, 124, 129, 130, 134 and 136a**)[67] were screened *in vitro* for their antibacterial activity against four different species of bacteria namely; *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus cereus* and *Staphylococcus aureus* and for their antifungal activity against five species of fungi, namely *Alternaria alternata*, *Aspergillus flavus*, *Fusarium solani*, *Penicllium citrinum* and *Trichoderma pesii*.[67] It was found that all compounds under investigation were inactive against both two species of gram-negative bacteria and the five species of fungi studied. However, concerning the gram-positive bacteria only three compounds **53, 124**, and **136a** showed growth inhibition activity against *Staphylococcus aureus*.



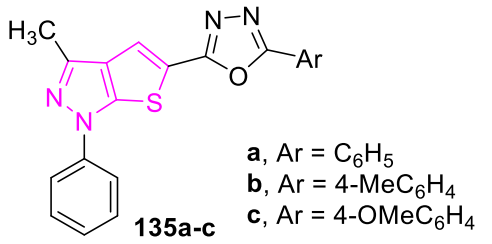
In 2020,[58] it was reported that compounds **74** and **75** have a significant antifungal activity compared to clotrimazole as a reference drug. Also, it was mentioned that, the thieno[2,3-c]pyrazole derivatives[33] with structure **G** are an important class of potent kinase inhibitors.[30]

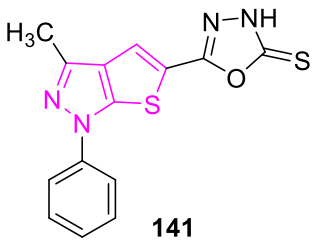


In 2015,[66] It was mentioned that *N*-acylheteroaryl hydrazone derivatives **138-140** were found to exhibit significant antioxidant activity and anti-inflammatory activity and showed good drug-like properties and can be developed as an oral drug candidate as well as good antimicrobial activity.[65]

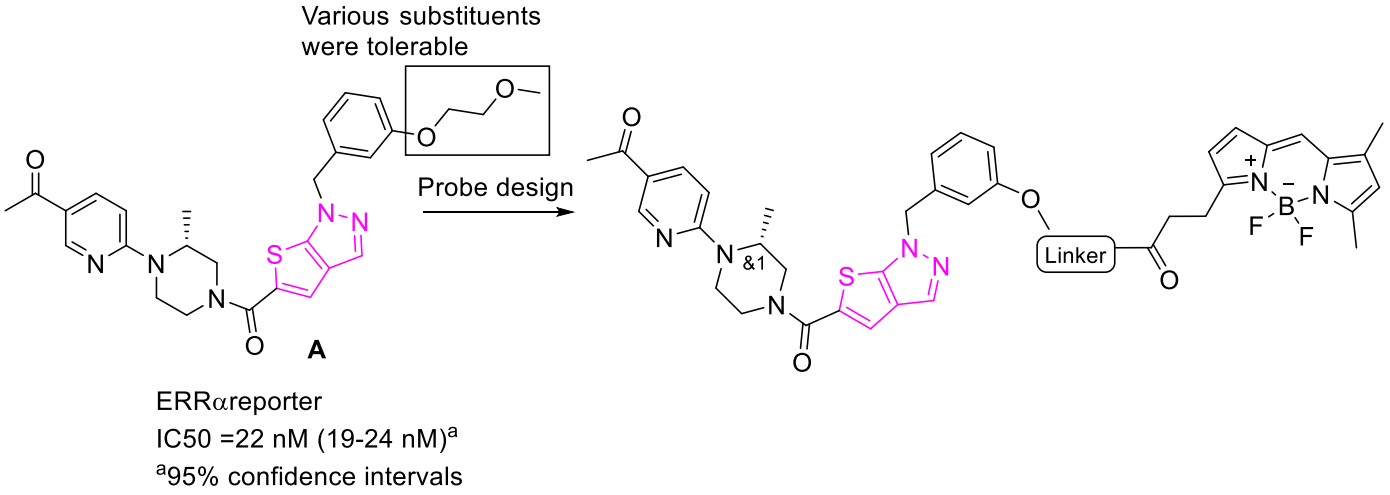


It was reported that,[64] the 5-(3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)-1,3,4-oxadiazole-2(3*H*)-thione **141** and 2-aryl-5-(3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)-1,3,4-oxadiazole **135a-c** showed remarkable antioxidant and anti-inflammatory activity.





In 2017, Katoh T. et *al*.[73] reported that a reporter gene assay was utilized to identify the thieno[2,3-*c*] pyrazole derivatives **A** as ligands for the estrogen receptor ERRα (IC_{50} = 22 nM). According to preliminary structure-activity relations, meta-substituents on the 1-benzyl group of thienopyrazole **A** were found to be acceptable, indicating that the meta-substituent was exposed to a solvent region, and the detrimental effect on ERRα inverse agonistic activity is reduced by the addition of linkers and the BODIPY scaffold on the benzene ring.



BODIPY FL-labeled fluorescent probe for the estrogen receptor (**ERRα**).

Conclusions

Thieno[2,3-*c*]pyrazole derivatives have been a fascinating compounds in the field of pharmaceutical chemistry it is utilized in a large number of medicinal aspects and have received very little attention. This follow-up could motivate the researchers to develop new approaches to obtain the nucleus of thieno[2,3-*c*]pyrazoles with significant biological activity.

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