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Organic Chemistry

Arkivoc **2020**, part i, 20-60

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

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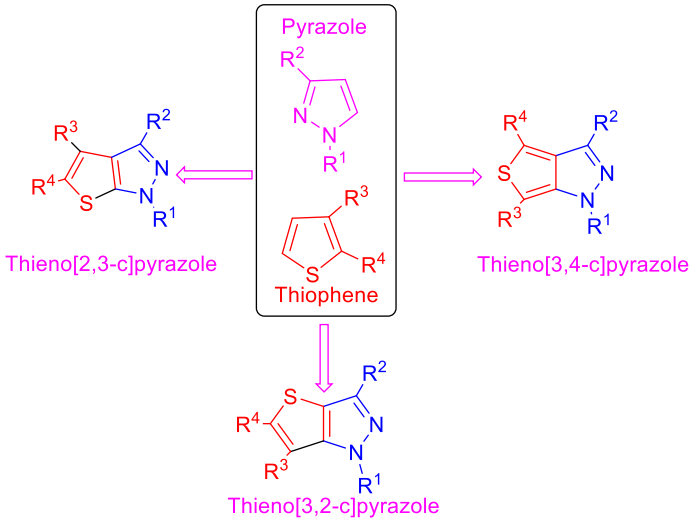
Received 11-05-2019 **Accepted** 01-22-2020 **Published on line** 03-14-2020

Abstract

Pyrazoles are five membered heterocycles constitute a higly 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.

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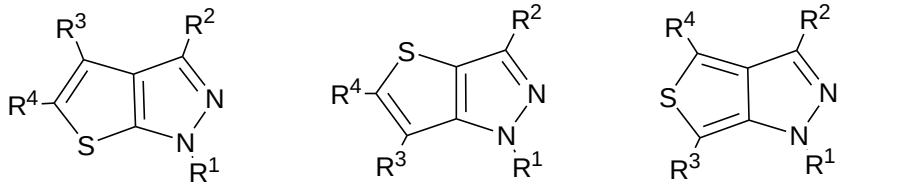
1. Introduction

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, [1] antiviral, [2] antimicrobial and anti-inflammatory activities.[3-5] They are used as antioxidants against the toxicity of 4-nonylphenol in *Clarias gariepinus* (African catfish).[6] Also, thieno[2,3-*c*]pyrazoles are an important class of potent kinase inhibitors,[7-10] potassium channel blockers,[11] inhibitors of interleukin-2-inducible tyrosine kinase[12-15] and selective inhibitors of PDE7A which is responsible for allergy, immunological and inflammatory diseases.[15-18] 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.[19] Also, thieno[3,2-*c*]pyrazoles were identified as a new class of bacterial cell wall biosynthesis inhibitors[20] and antimicrobial agents against different strains of fungi and bacteria[21,22] as well as anti-tubercular agents against *Mycobacterium tuberculosis H*$_{37}$*RV*.[23]

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).

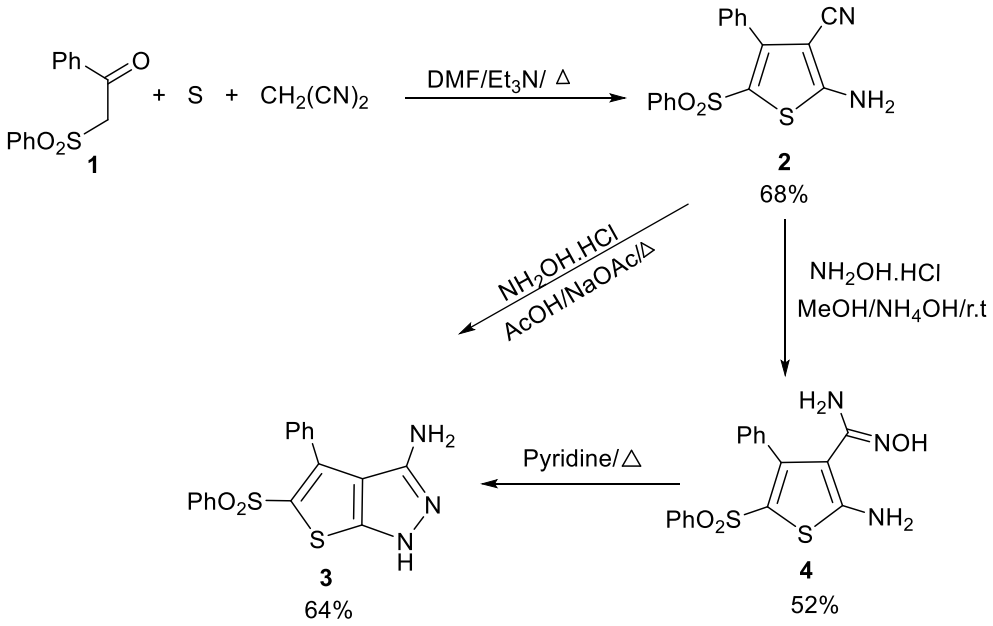


Thieno[2,3-c]pyrazole **A** **Thieno[3,2-c]pyrazole** **B** **Thieno[3,4-c]pyrazole** **C**

Figure 1. Structures of thieno[2,3-*c*]pyrazole, thieno[3,2-*c*]pyrazole and thieno[3,4-*c*]pyrazole.

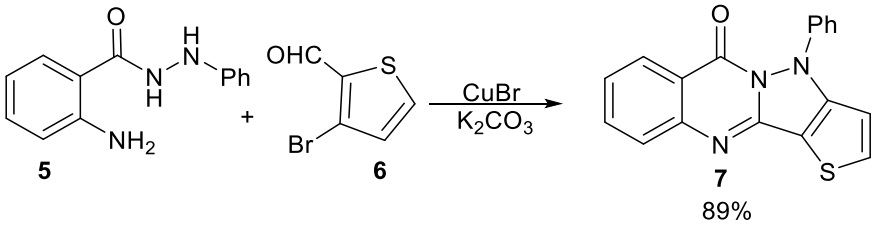
2. Synthesis of Thieno[2,3-*c*]pyrazole Compounds Starting from Thiophene

Sherif *et al*[24] reported that the Gewald-reaction of phenylsulfonylacetophenone **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.



Scheme 1

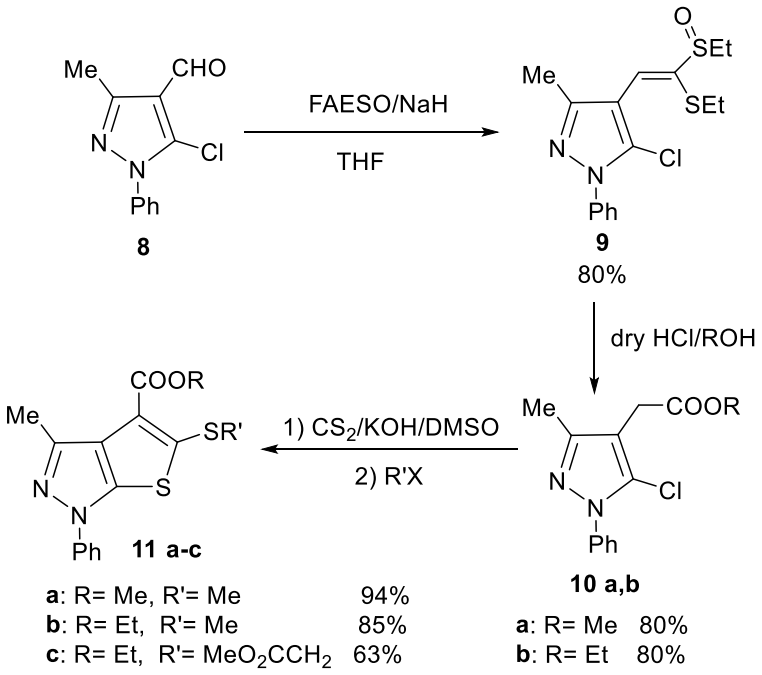
Reaction of 2-aminobenzhydrazide **5** and 3-bromothiophene-2-carbaldehyde (**6**) in presence of cuprous bromide and potassium carbonate afforded thieno[3',2':3,4]pyrazolo[5,1-*b*]quinazolin-6(4*H*)-one in good yield [25] Scheme 2.



Scheme 2

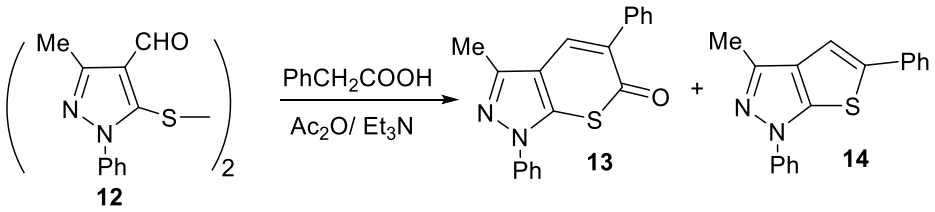
3. Synthesis of Thieno[2,3-*c*]pyrazoles Starting from Pyrazole

Zhongwen Wang *et al.*[26,27] synthesized thieno[2,3-*c*]pyrazoles **11a-c** starting from 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**8**).[28-40] Thus, reaction of **8** with formaldehyde diethyl dithioacetal S-oxide (FAESO) in THF in the presence of NaH afforded diethyldithioacetal **9**, which was converted into 5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl-acetic acid derivatives **10a,b** upon treatment with alcoholic HCl. Stirring of the carboxylic acid **10a,b** with CS_2 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.



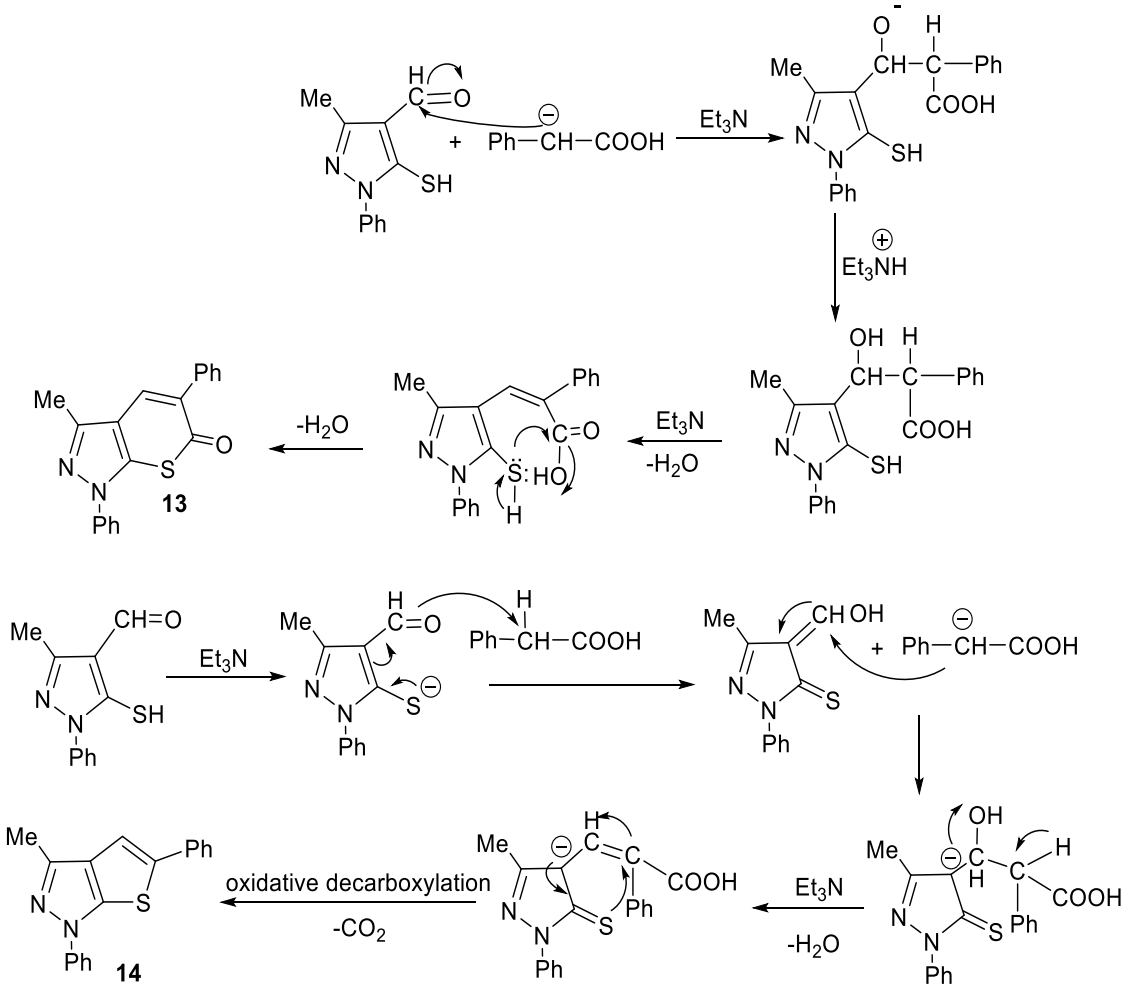
Scheme 3

Cyclocondensation of bis(3-methyl-1-phenyl-1*H*-pyrazole-4-form-5-yl)disulfane (**12**) with phenylacetic acid produced a mixture of thiopyranopyrazole **13** and thienopyrazole **14**[41] Scheme 4.



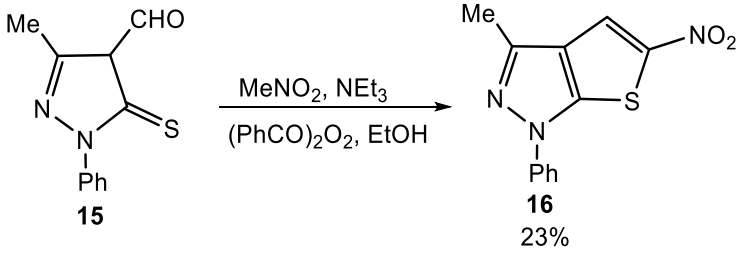
Scheme 4

The proposed mechanism for the formation of products **13**, **14** is described below in Scheme 5.



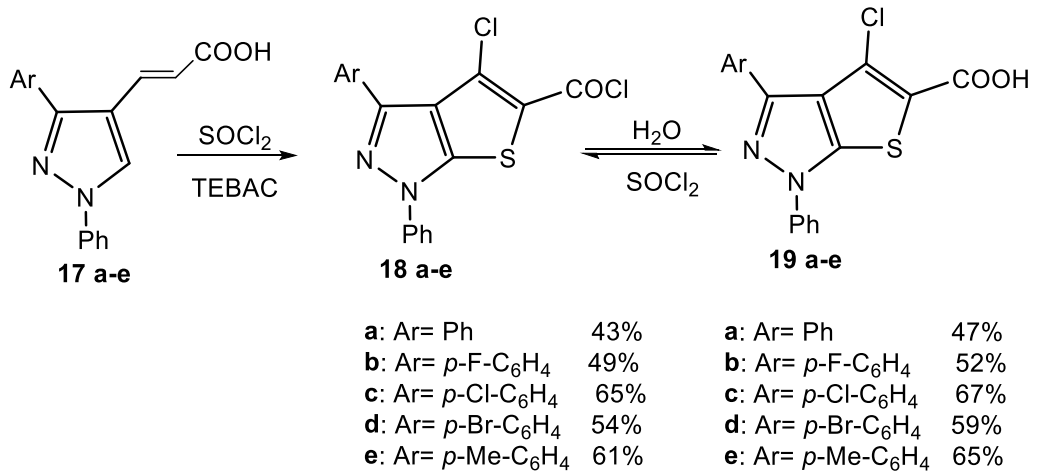
Scheme 5

4,5-Dihydro-3-methyl-1-phenyl-5-thioxo-1*H*-pyrazole-4-carboxaldehyde (**15**) was reacted with nitromethane in the presence of dibenzoyl peroxide, Et_3N in ethanol to produce 5-nitro-3-methyl-1-phenylthieno[2,3-c]pyrazole (**16**)[41] Scheme 6.



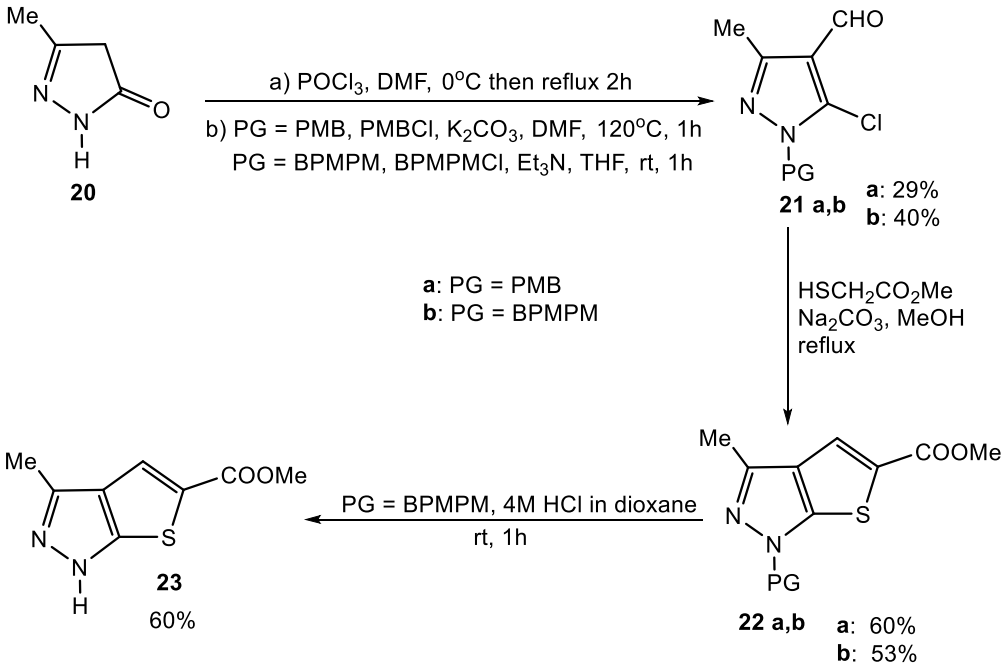
Scheme 6

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**[42] Scheme 7.



Scheme 7

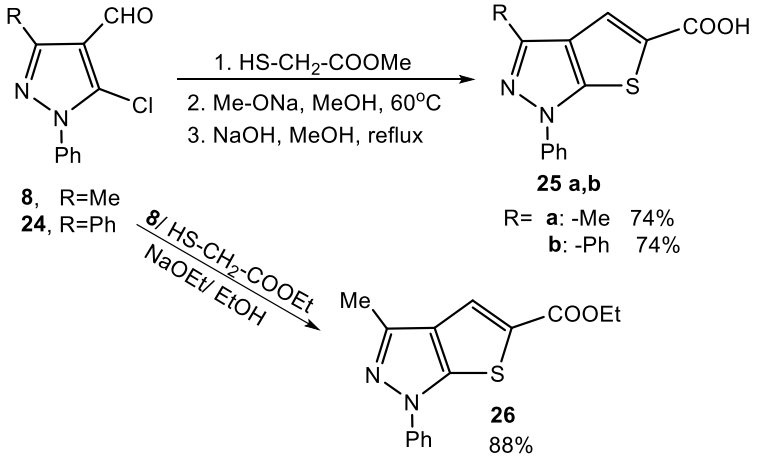
On the other hand, Akritopoulou-Zanze *et al* [1] reported that the protected 5-methyl-2,4-dihydro-pyrazol-3-one **20** with *p*-methoxybenzyl chloride was converted into 5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde using the Vilsmeier reagent, which in turn reacted with methyl thioglycolate in MeOH in the presence of Na_2CO_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

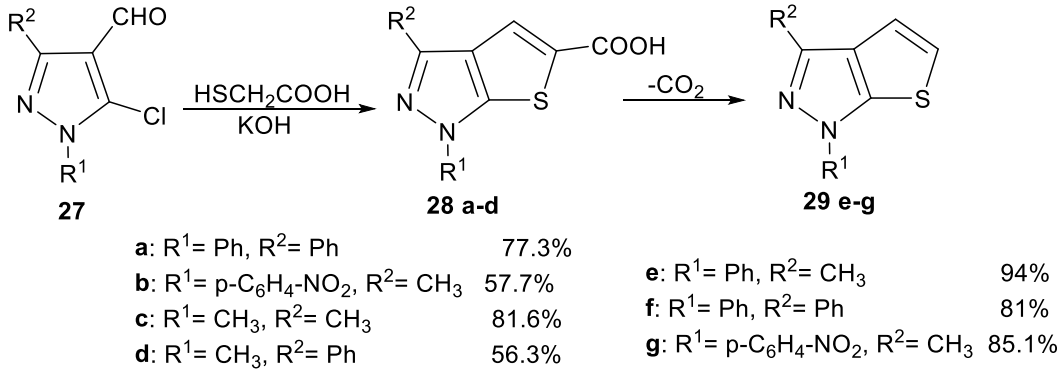
5-Chloro-3-methyl (or phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **24** was reacted with methyl thioglycolate in methanol in the presence of sodium methoxide to give methyl thienopyrazole carboxylate which was saponified with methanolic sodium hydroxide to produce the corresponding carboxylic acid **25a,b**[43] Scheme 9.

In a similar procedure, 3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid ethyl ester **26** was prepared from the reaction of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde with ethyl thioglycolate in EtOH in the presence of sodium ethoxide[44] (Scheme 9).



Scheme 9

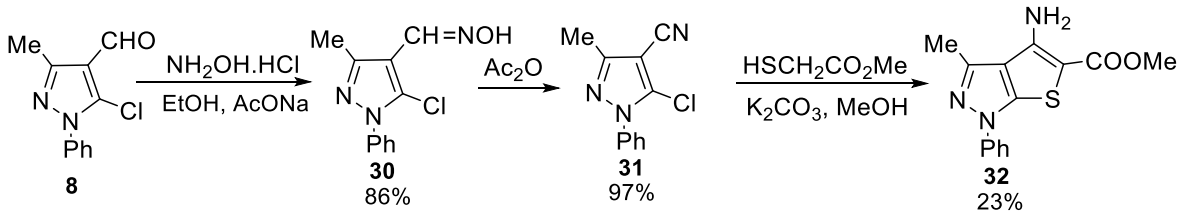
Chloropyrazole aldehydes **27a-d** reacted with thioglycolic acid in aqueous ethanolic alkali under displacement of the chloride atom by a thioglycolic acid residue followed by intramolecular condensation to form 3-substituted thieno[2,3-*c*]pyrazole-5-carboxylic acids **28a-d** which in turn underwent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



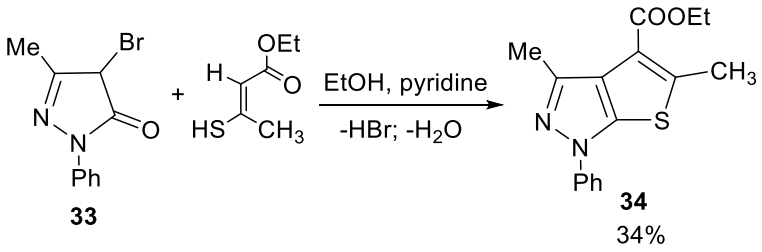
Scheme 10

Norbert Haider *et al*[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-1*H*-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**[47] (Scheme 12).



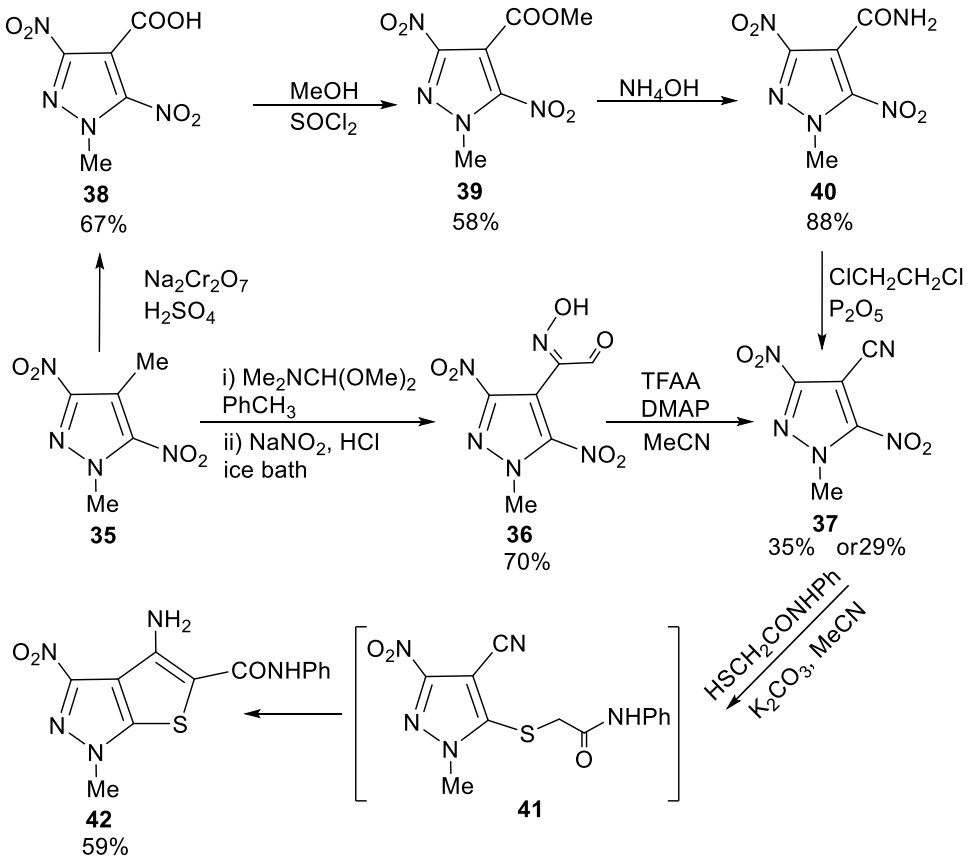
Scheme 11



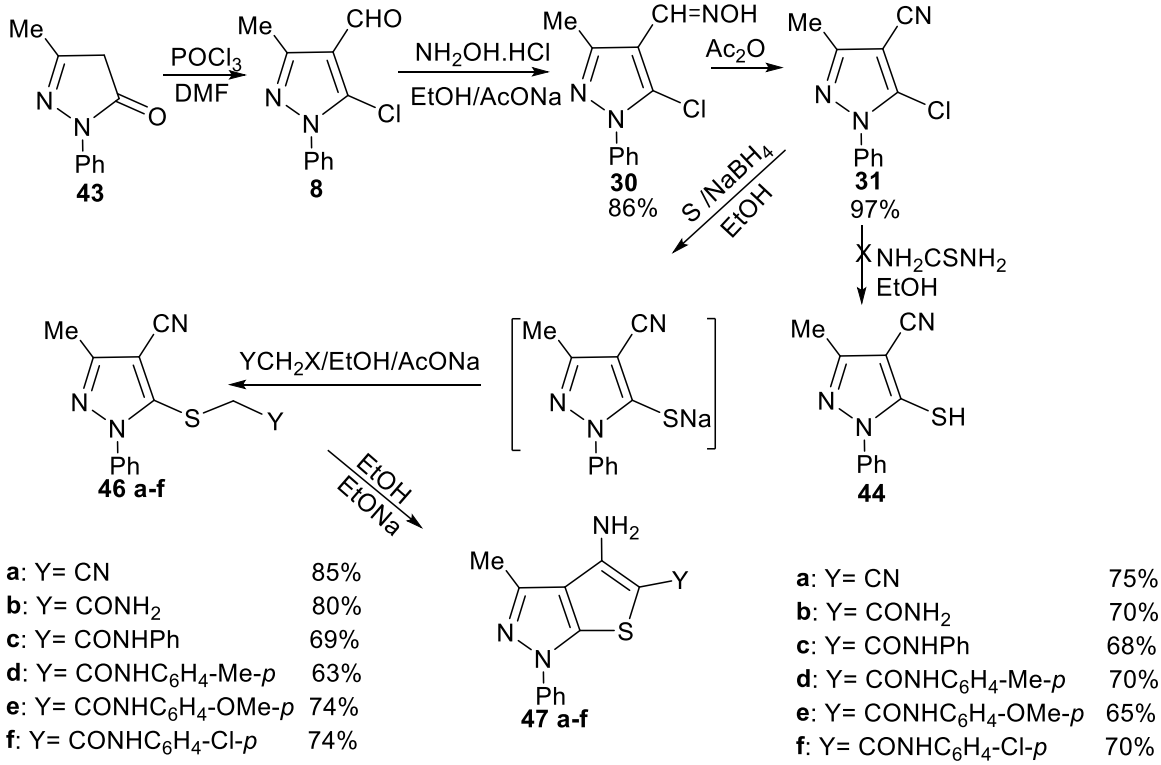
Scheme 12

Zaitsev *et al.*[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 trifluroacetic 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 **41** resulting from displacement of the 5-NO_2 group underwent *Thorpe-Ziegler*-cyclization in situ at the CN group to give bicyclic thienopyrazole compound **42** (Scheme 13).

Zaki *et al* [50] reported a new method for synthesizing 5-substituted 4-amino-3-methyl-1-phenyl-1*H*-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-1*H*-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-1*H*-pyrazole-4-carbaldehyde oxime (**30)**. The pyrazole aldehyde oxime **30** was dehydrated using acetic anhydride into the corresponding 5-chloro-3-methyl-1-phenyl-1*H*- 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.

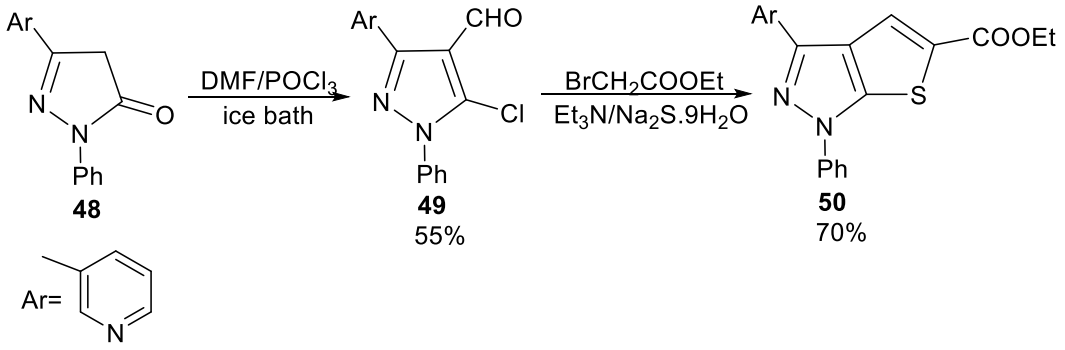


Scheme 13



Scheme 14

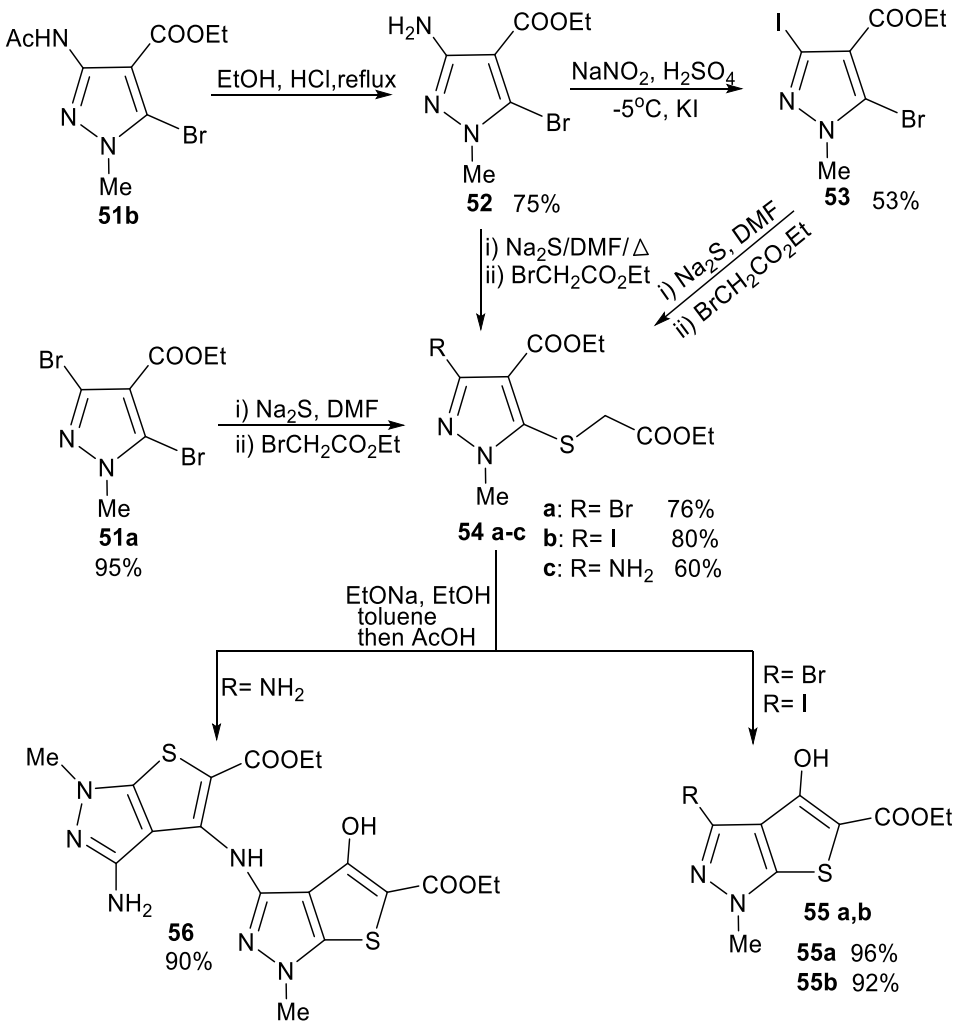
1-Phenyl-3-(pyridin-3-yl)-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid ethyl ester **(50)** was synthesized by the reaction of 5-chloro-1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazole-4-carbaldehyde **(49)** with ethyl bromoacetate and sodium sulfide. First, reaction of 2-phenyl-5-pyridin-3-yl-2,4-dihydro-pyrazol-3-one (**48)** with *Vilsmeier-Haack* reagent gave 5-chloro-1-phenyl-3-(pyridin-3-yl)-1*H*-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)-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid ethyl ester **(50)** in 70% yield[51] (Scheme 15).



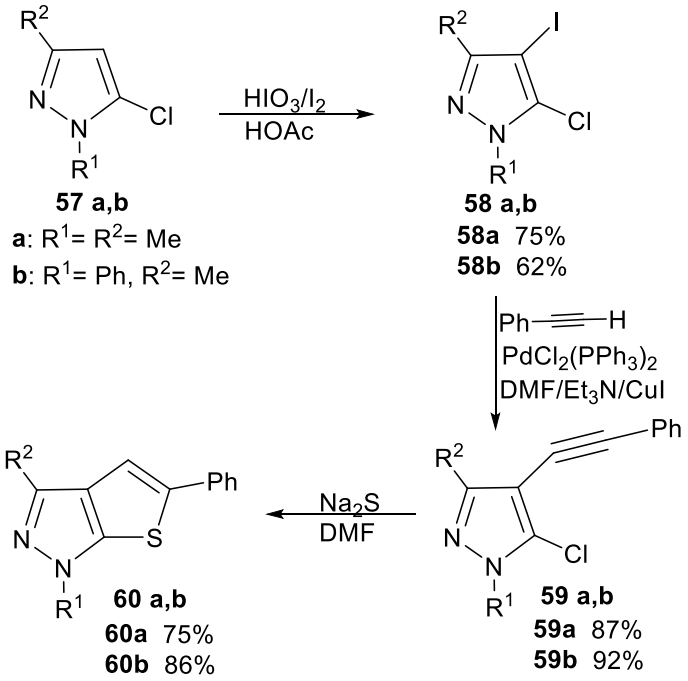
Scheme 15

A simple and practical six-step synthesis of new 1-methyl-1*H*-thieno[2,3-*c*]pyrazoles from 3-amino-1*H*-pyrazole-4-carboxylic acid ethyl ester were reported by Patrick Toto *et al*.[52]The alkylsulfonyl pyrazoles **54a-c** were prepared from **51a**, **52**, and **53** respectively, through the method reported by Morimoto *et al.*[53] 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 bromo acetate 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.*[54] 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-1*H*-pyrazoles **57a,b**, 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 **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.

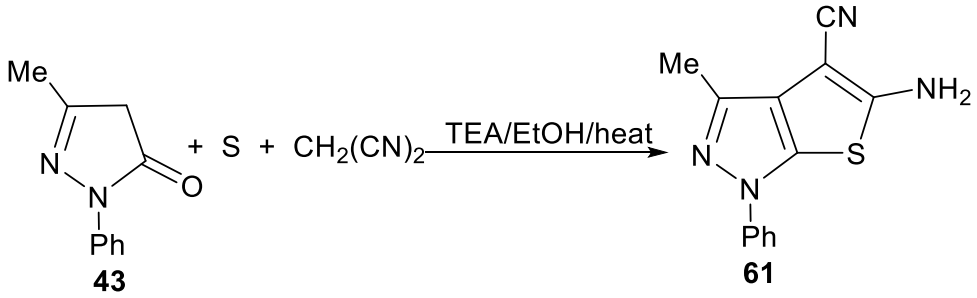


Scheme 16



Scheme 17

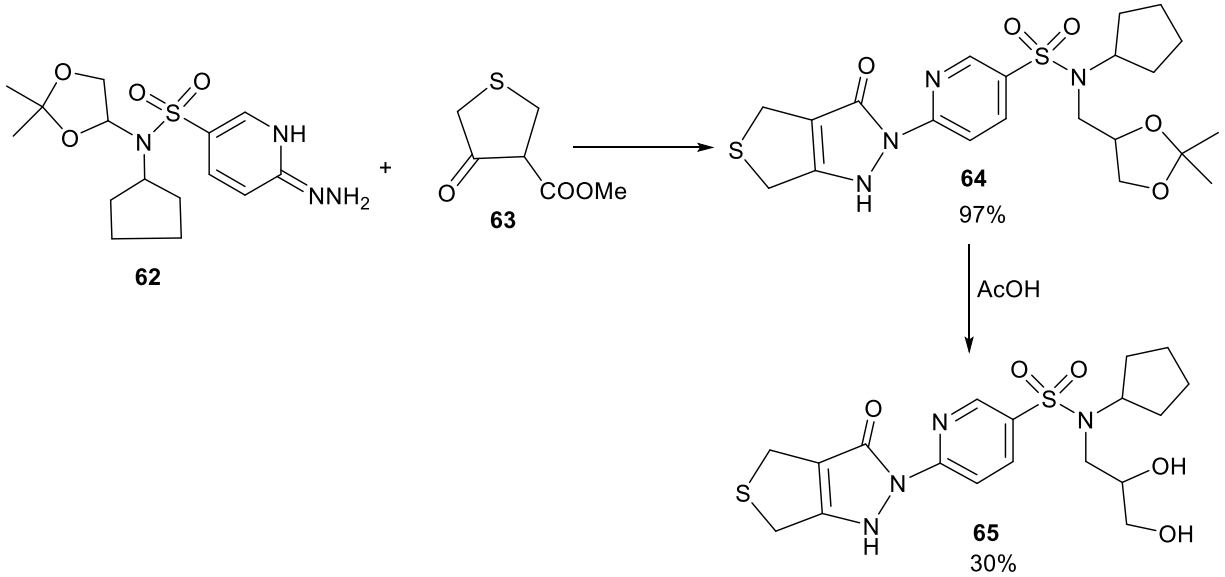
Magdy W. Sabaa *et al.*[55] and Samira T. Rabie *et al.*[56] have synthesized thieno[2,3-*c*]pyrazole using the *Gewald* reaction. The *N*-phenyl pyrazolone **43** undergoes the *Gewald* reaction and reacts with sulfur and malononitrile in equimolar ratios under reflux for 3 h in presence of triethyl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



Scheme 18

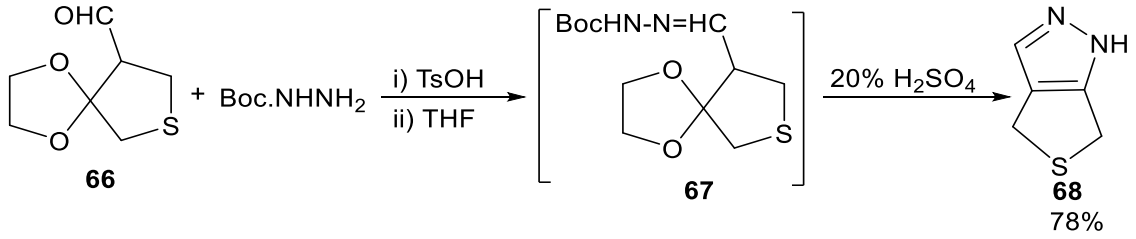
4. Synthesis of Thieno[3,4-*c*]pyrazoles Starting from Thiophene

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



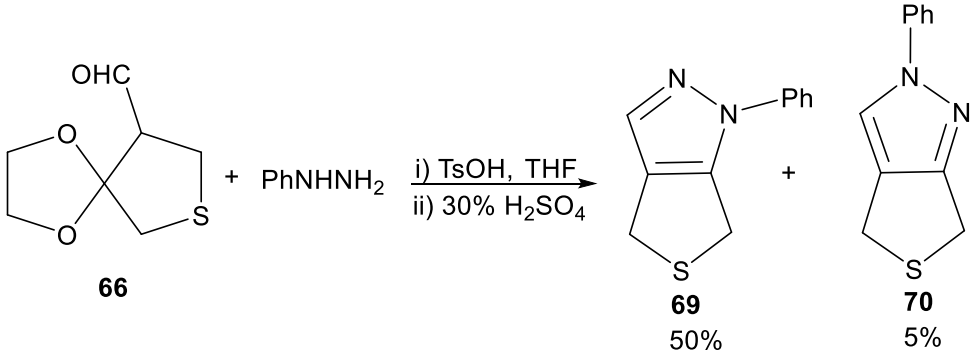
Scheme 19

Reaction of aldehyde **66** with protected hydrazine (tert-butyl carbazate t-BocNHNH$_2$) in THF in the presence of TsOH produced the corresponding hydrazone intermediate which upon treatment with 20% H_2SO_4 gave the thienopyrazole **68** in 78% yield[58-60] (Scheme 20).



Scheme 20

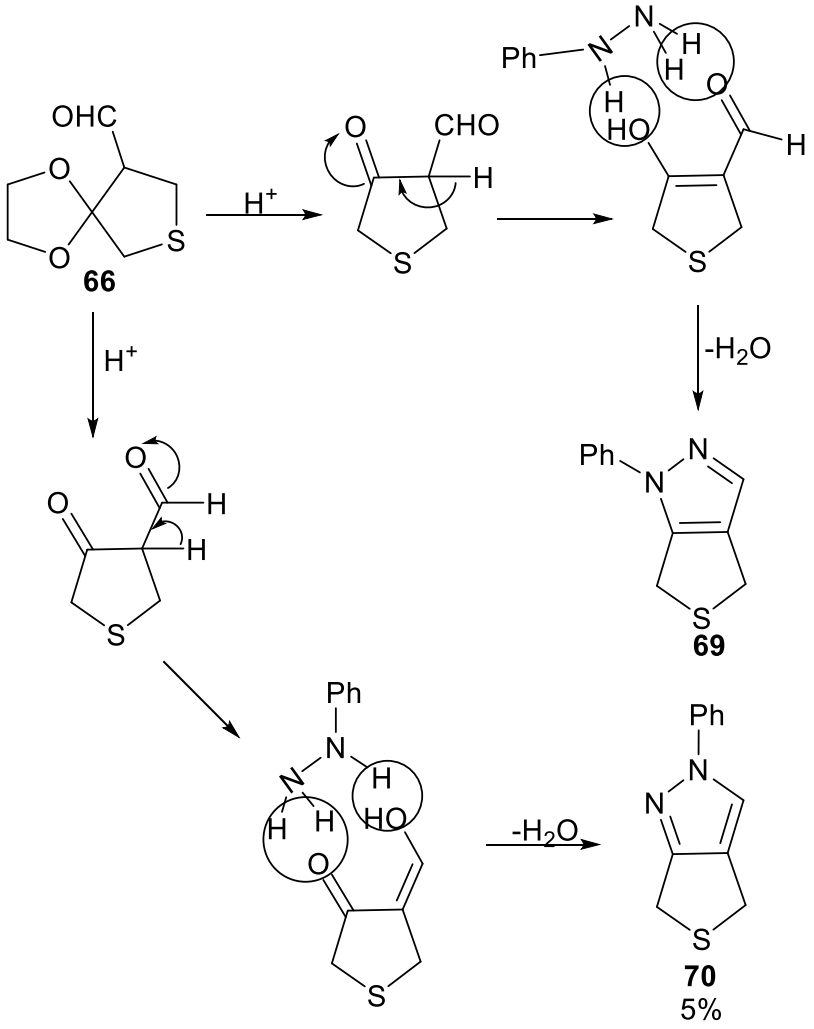
In similar manner, aldehyde **66** reacted with phenylhydrazine in the presence of TsOH in THF followed by treatment with 30% H_2SO_4 gave a mixture of two derivatives of thienopyrazole **69** and **70** in 50 and 5% yield respectively[58-60] (Scheme 21).



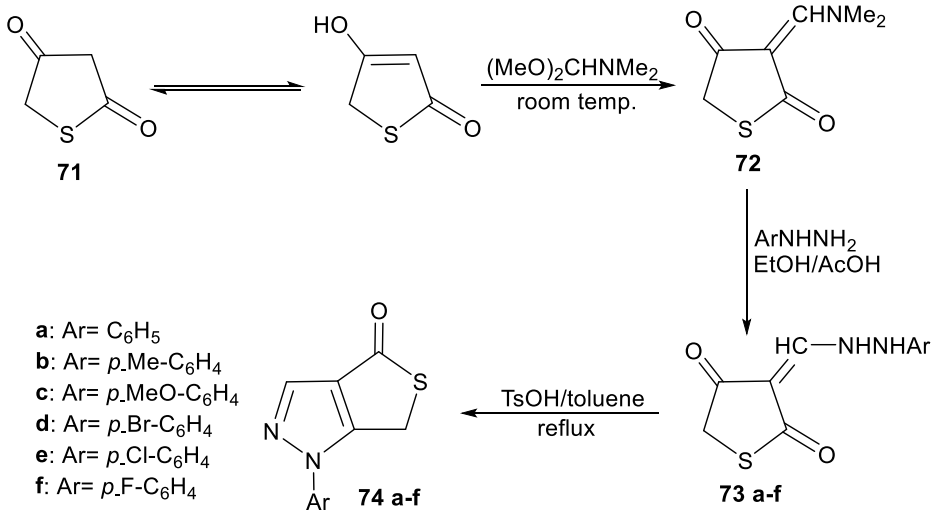
Scheme 21

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 H_2O of the enol form of keto group, or by condensation with ketone group followed by loss of H_2O from the enolised form of aldehyde as outlined below (Scheme 22).

Giulia Menozzi *et al*[19] reported synthesis of a series of 1-aryl-1,6-dihydro-4*H*-thieno[3,4-*c*]pyrazol-4-ones (**74 a-f)** by cyclization of 3-[(2-arylhydrazino)methylene]thiophene-2,4(3*H*,5*H*)-diones (**73 a-f)**. The thiophene-2,4-diones **73a-f** were prepared by the reaction of 3-dimethylaminomethylenethiophene-2,4-(3*H*,5*H*)-dione (**72)** with arylhydrazines (Scheme 23).



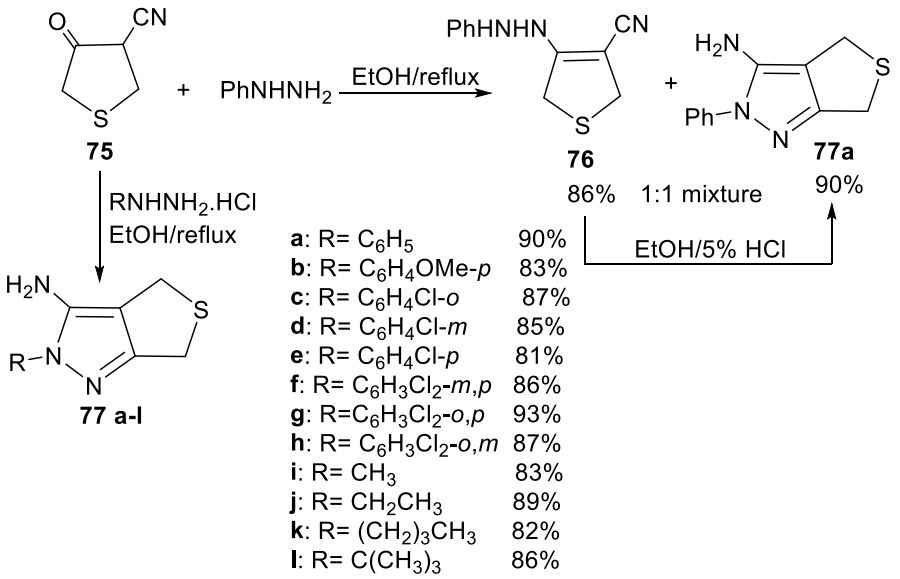
Scheme 22



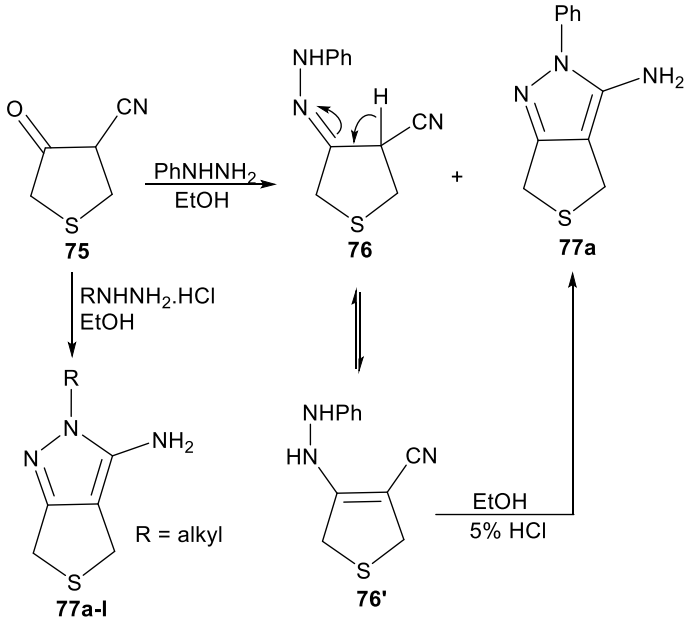
Scheme 23

Pier Giovanni Baraldi *et al.*[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



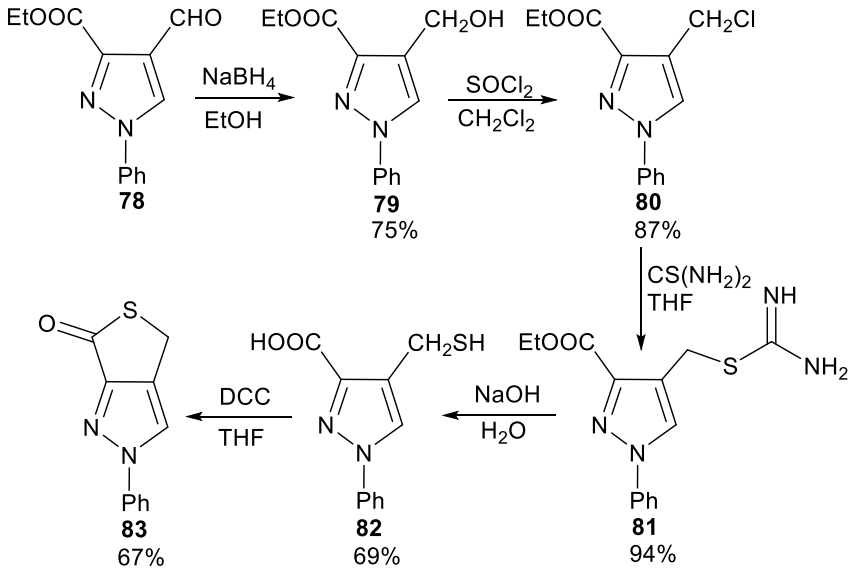
Scheme 25

Pier Giovanni Baraldi *et al*[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

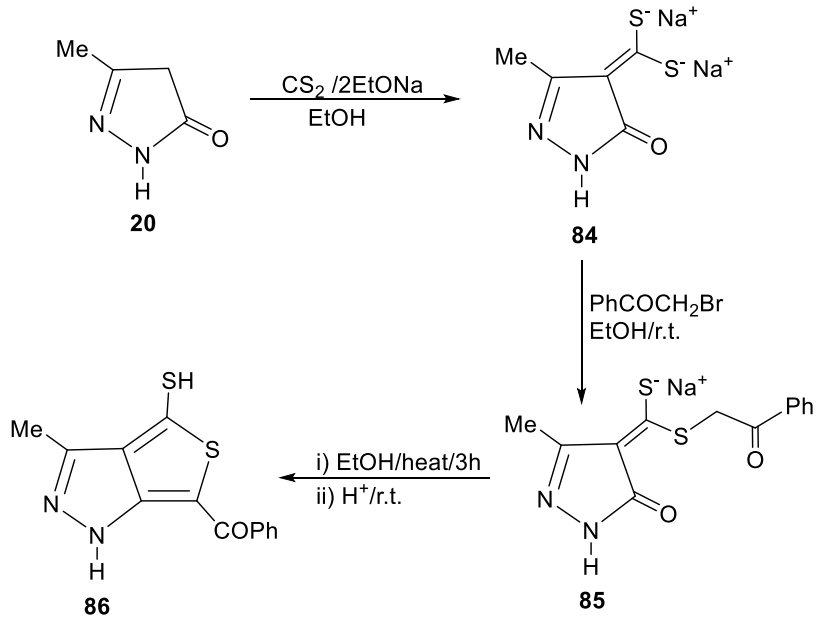
Bratenko *et al.*[63] reported the synthesis of 2,4-dihydro-6*H*-thieno[3,4-*c*]pyrazol-6-one **83** by means of an intramolecular cyclization of 4-sulfanylmethyl pyrazole-3-carboxylic acids **82** via treatment with DCC/THF. Ethyl *N*-phenyl-4-formylpyrazole-5-carboxylate **(78)** was reduced by sodium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



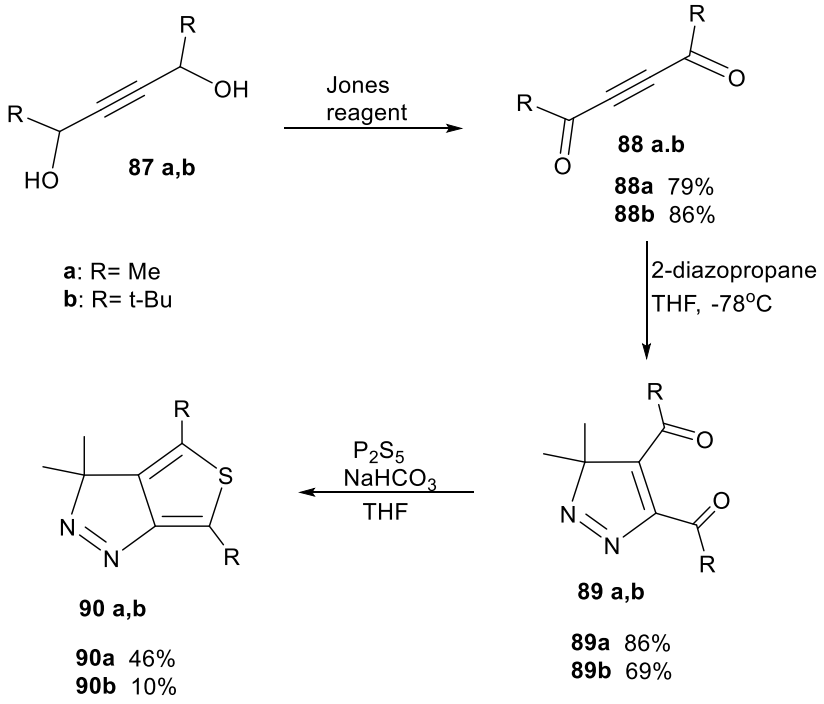
Scheme 26

Galal H. Elgemeie *et al.* [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 [65] synthesized 3*H*-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).

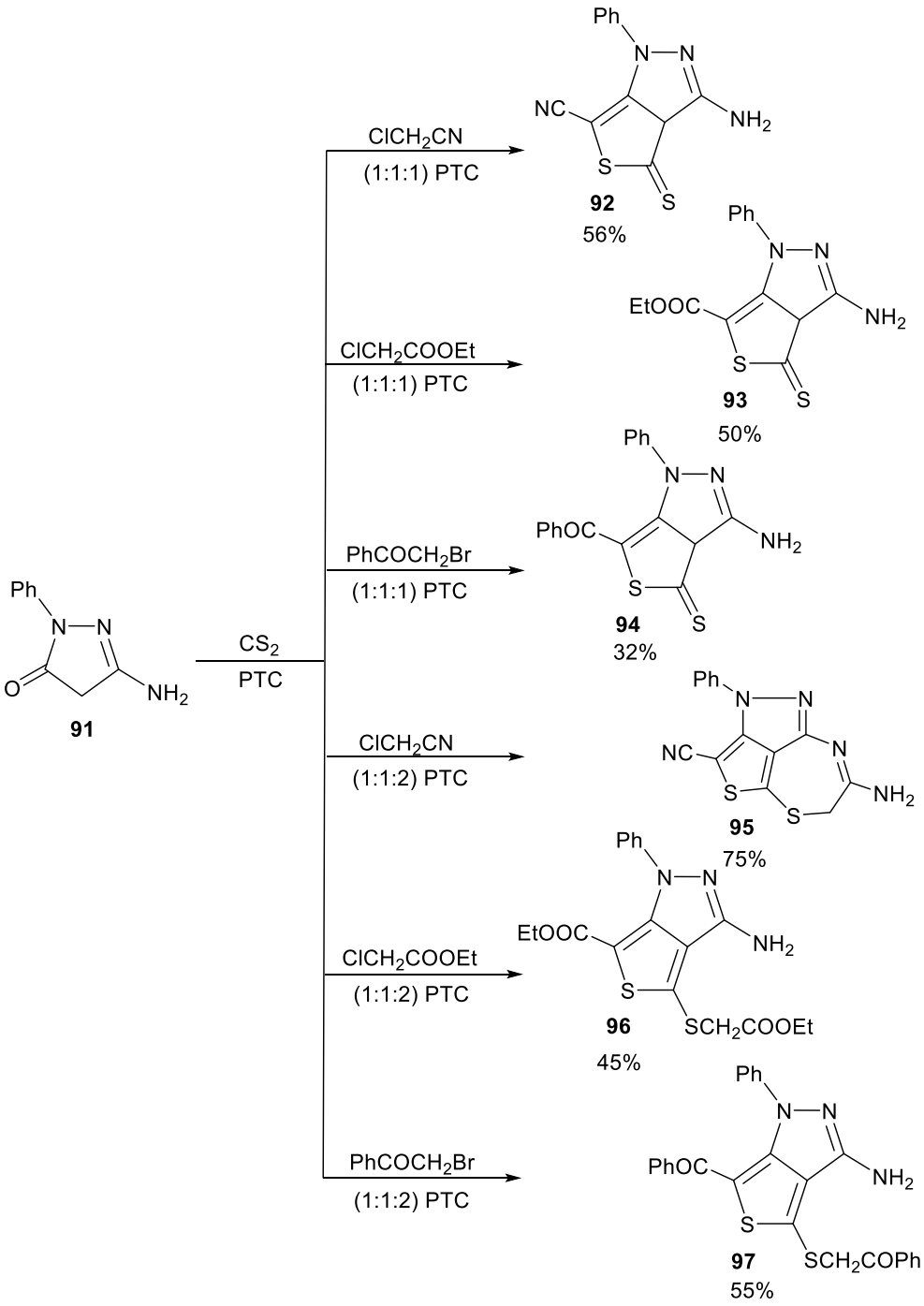


Scheme 27



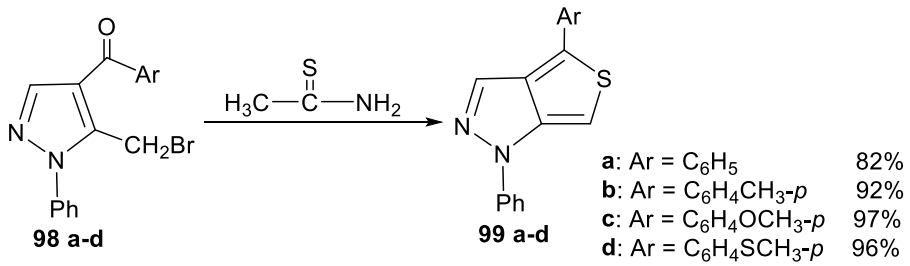
Scheme 28

A series of thieno[3,4-*c*]pyrazoles were prepared by El-Saraf *et al.* [66] 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).



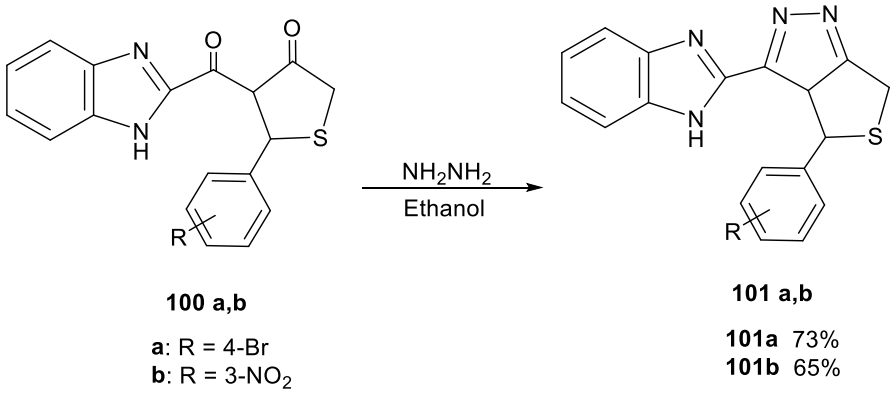
Scheme 29

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



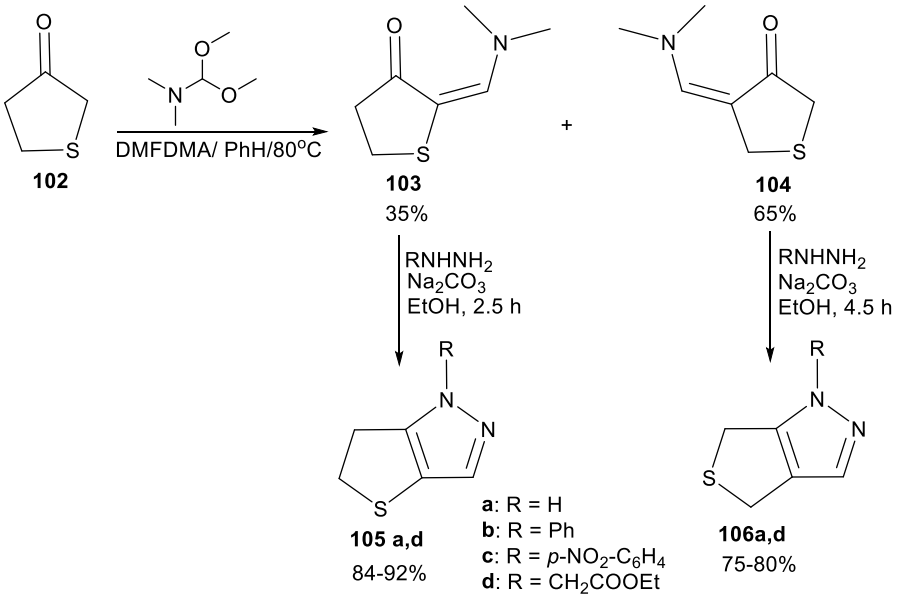
Scheme 30

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 ethanol[68] (Scheme 31).



Scheme 31

The reaction of thiolan-3-one **102** with DMF-DMA (1.2 equiv.) in $PhCH_3$at 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 Na_2CO_3 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).

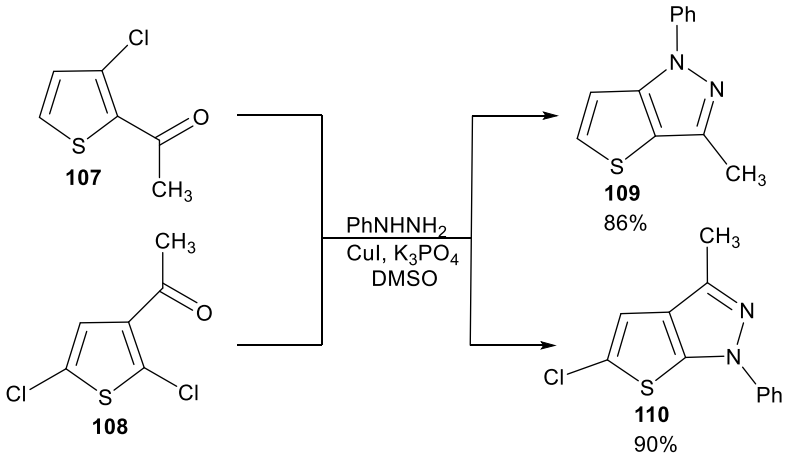


Scheme 32

6. Synthesis of Thieno[3,2-*c*]pyrazoles Starting from Thiophene

Gao, *et al*[70] have reported synthesis for two isomers of thieno[3,2-*c*]pyrazoles. 3-Methyl-1-phenyl-1*H*-thieno[3,2-*c*]pyrazole **109** and 5-chloro-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole **110** by the reaction of 1-(3-

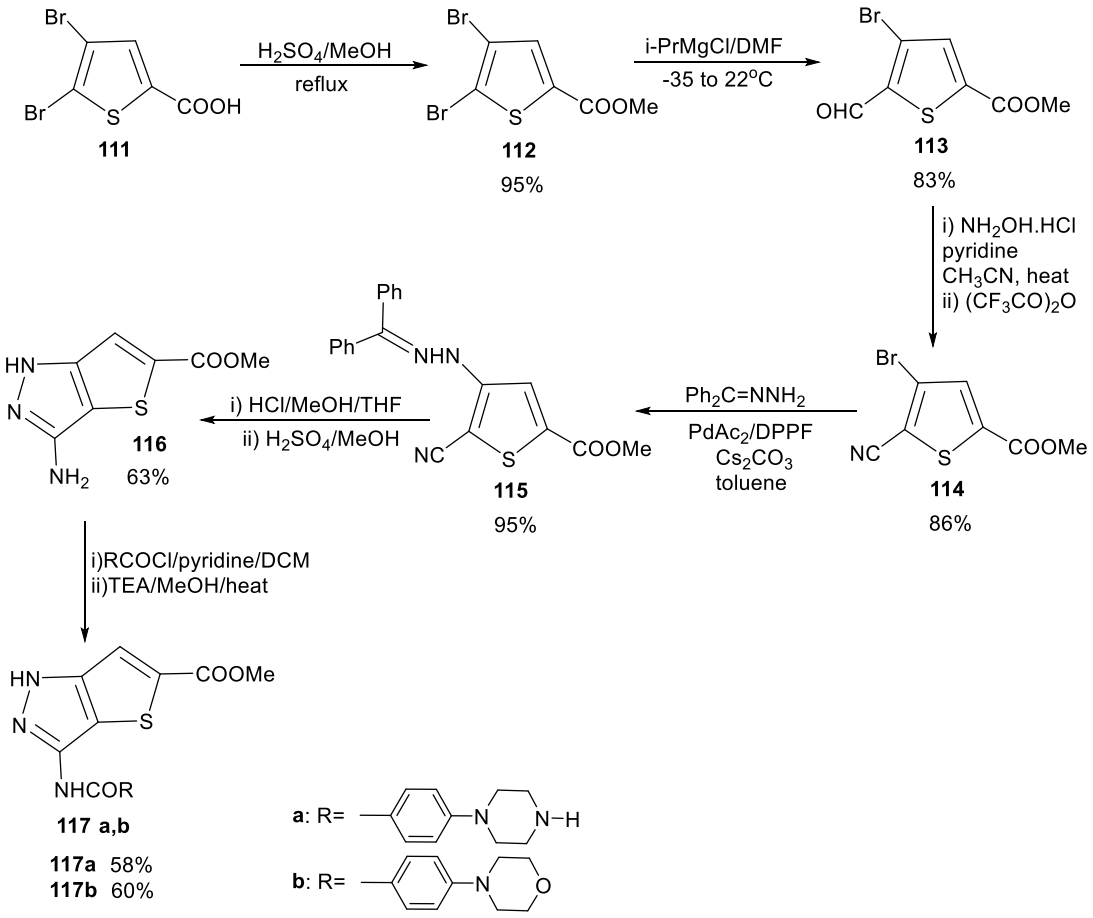
chloro-2-thienyl)-ethanone **107** or 1-(2,5-dichloro-3-thienyl)-ethanone **108** with phenylhydrazines followed by cyclization of the corresponding hydrazones using CuI and K_3PO_4 in DMSO (Scheme 33).



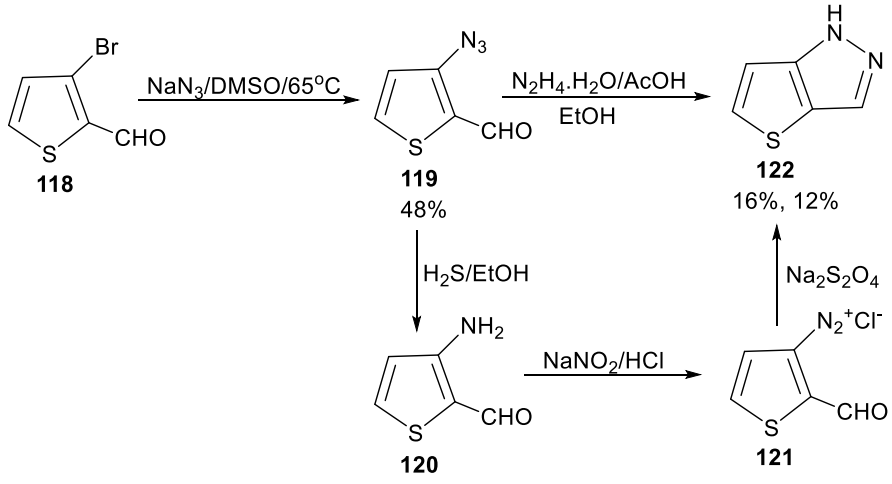
Scheme 33

Bindi *et al* [22] have reported a novel series of 3-amino-1*H*-thieno[3,2-*c*]pyrazole derivatives demonstrating high potency in inhibiting aurora kinases. The synthetic pathway to methyl 3-amino-1*H*-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-1*H*-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 1*H*-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).

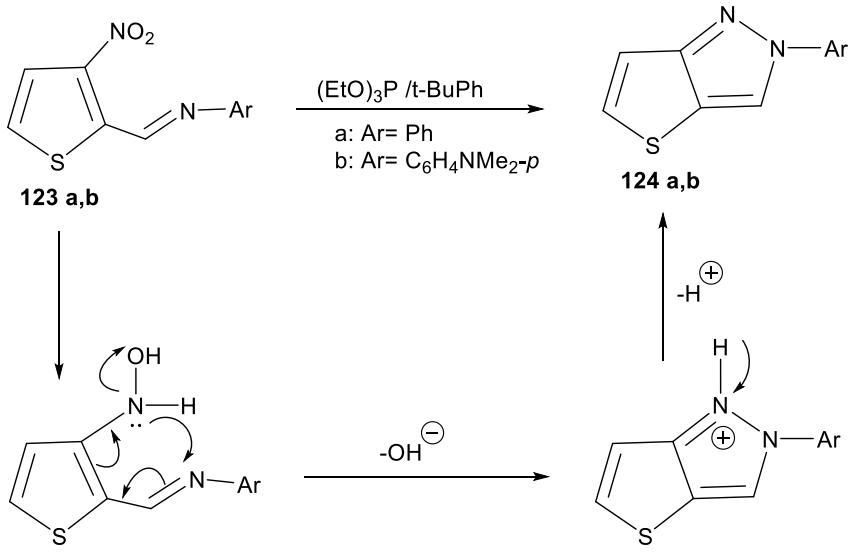


Scheme 34



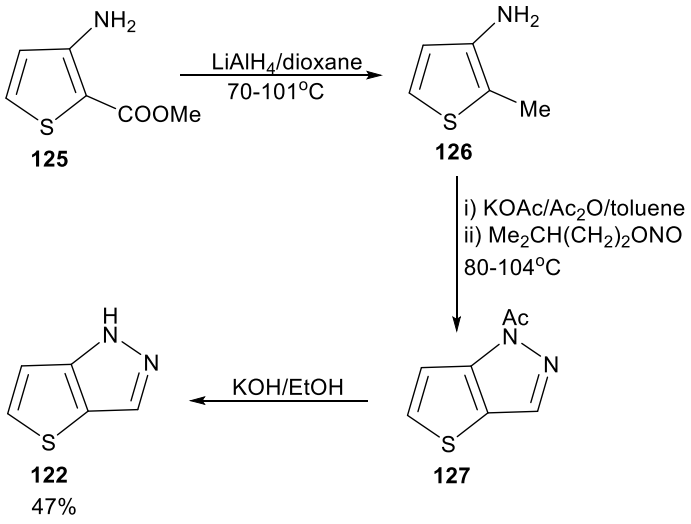
Scheme 35

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** [73] Scheme 36.



Scheme 36

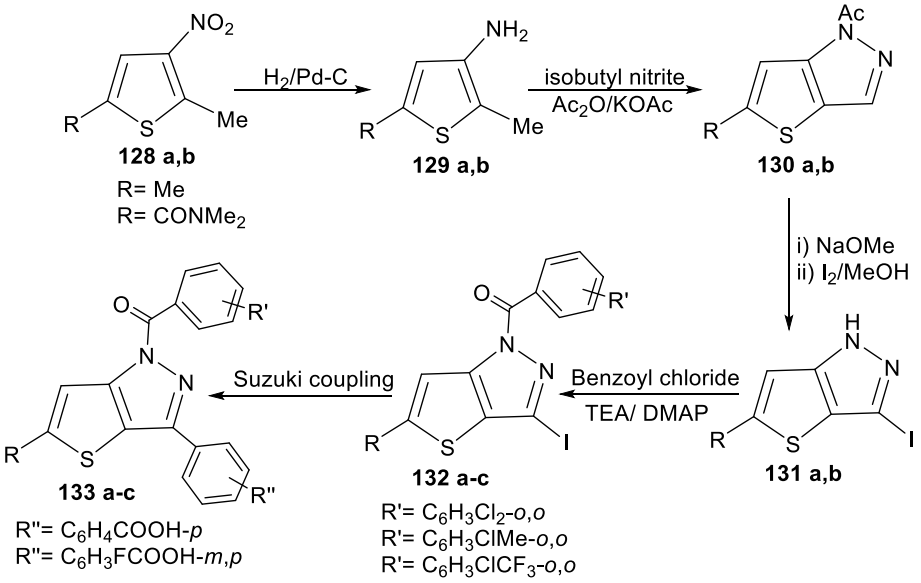
When a solution of ester **125** was added slowly to a suspension of lithium aluminum hydride in refluxing 1,4-dioxane,[74] subsequent work up gave crude (2-methyl-3-thienyl)amine **126** which was then used directly in the cyclization step as shown below. Cyclization of **126** was affected simply by 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 un-substituted 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

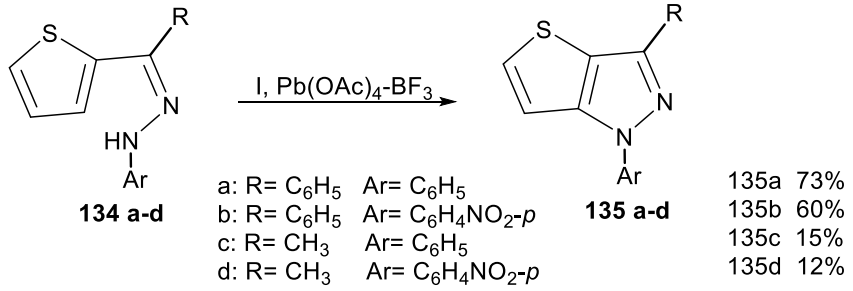
Another route for synthesizing the thieno[3,2-c]pyrazoles **130-133** according to a patent[75] is reported. Reduction of 2-methyl-3-nitrothiophenes **128a,b** with H_2/Pd-C led to the formation of the corresponding thienylamines **129a,b** which underwent nitrosation followed by cyclization reaction 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_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).



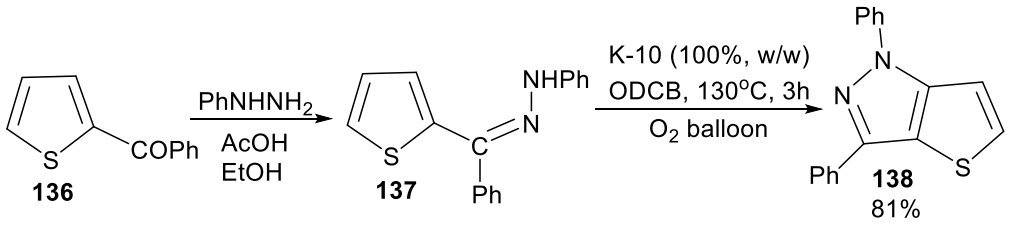
Scheme 38

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**[75] (Scheme 39).



Scheme 39

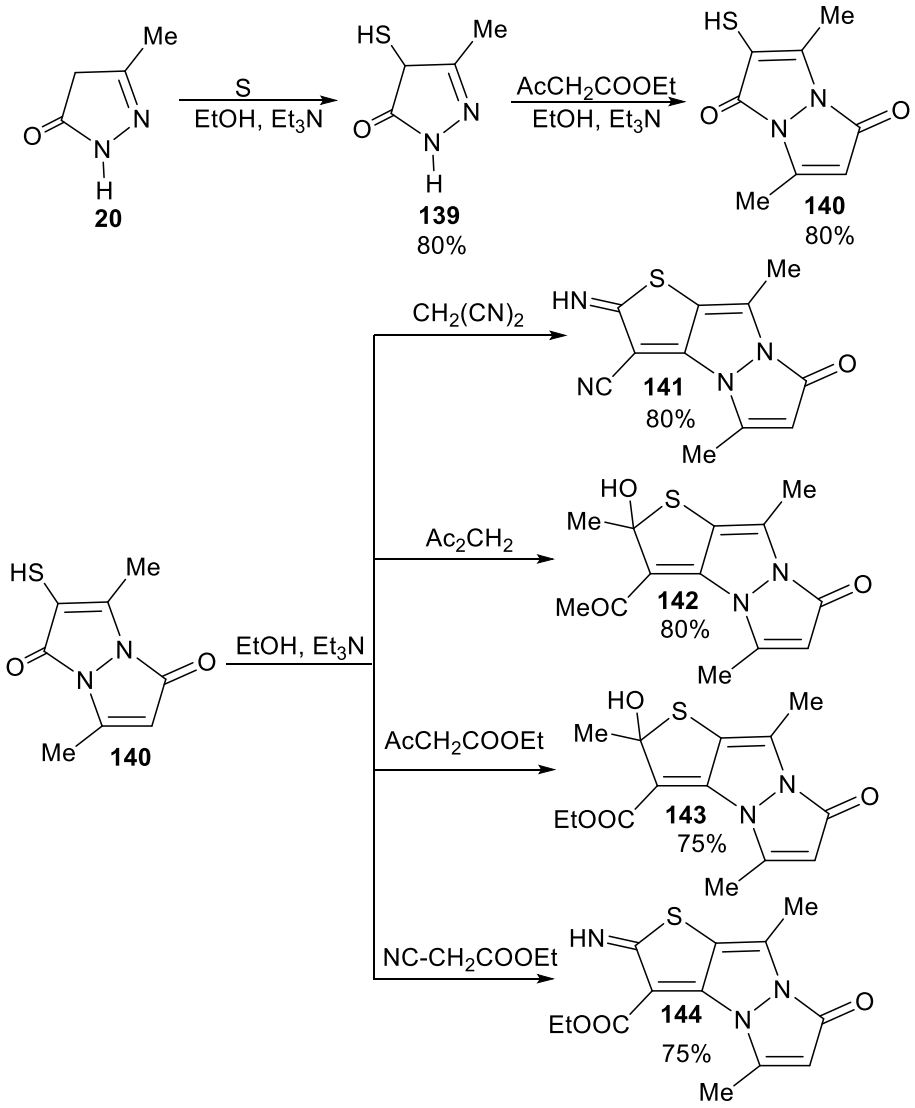
In a similar manner, reaction of phenylhydrazines in EtOH in the presence of AcOH at 80°C with thienyl phenyl ketone **136** gave the corresponding phenyl hydrazone **137** which in the presence of montmorillonite K-10 in 1,2-dichlorobenzene at 130°C under O_2 balloon atmosphere was cyclized into thieno[3,2-*c*]pyrazole **138** in 81% yield[76] (Scheme 40).



Scheme 40

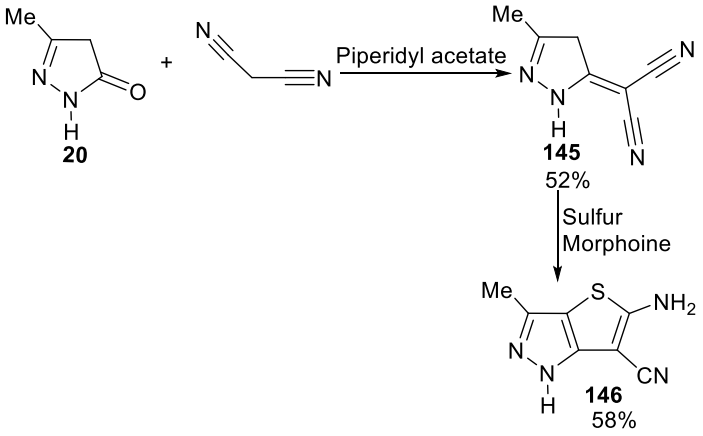
7. Synthesis of Thieno[3,2-*c*]pyrazoles Starting from Pyrazoles

3-Methyl-1*H*-pyrazol-5(4*H*)-one (**20)** was reacted with elemental sulfur in the presence of triethylamine in ethanol to give 4-mercapto-3-methyl-1*H*-pyrazol-5(4*H*)-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**[77] (Scheme 41).



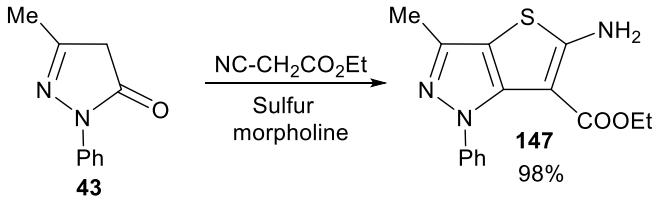
Scheme 41

Vaghasiya *et al* [23] have used the *Gewald* reaction to synthesize thieno[3,2-*c*]pyrazole. Synthesis of 5-amino-3-methyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile (**146)** was accomplished by refluxing (5-methyl-2,4-dihydro-3*H*-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-1*H*-pyrazol-5-one **(23)** with malonnoitrile in piperidyl acetate to afford the Knoevenagel intermediate (Scheme 42).



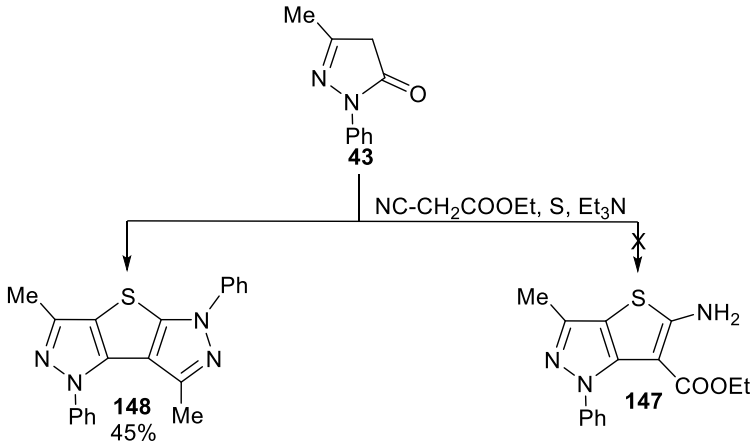
Scheme 42

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-1*H*-thieno[3,2-*c*]pyrazole-6-carboxylate (**147)**[21] (Scheme 43).



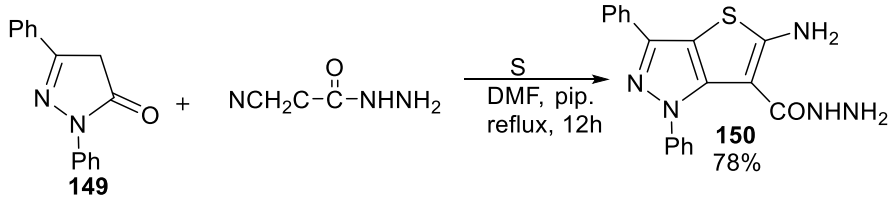
Scheme 43

Hamama *et al.* [78] reported that 3,7-dimethyl-1,5-diphenyl-1*H*,5*H*-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).



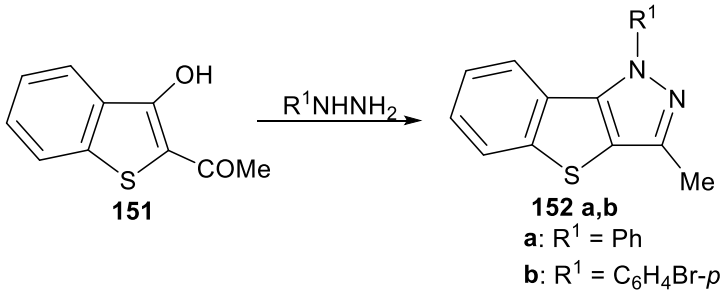
Scheme 44

Abdel Reheim *et al.* [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*H*-thieno[3,2-*c*]pyrazole-6-carbohydrazide (**150)** (Scheme 45).



Scheme 45

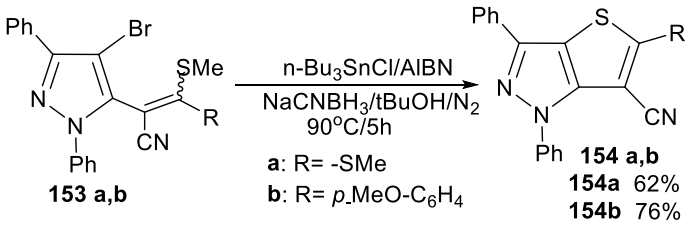
Benzothienopyrazoles were prepared from the reaction of 3-hydroxy-2-acetyl-1-thionaphthen **151** with phenylhydrazine or *p*-bromophenylhydrazine to give the thianaphthenopyrazoles **152a,b** [80] (Scheme 46).



Scheme 46

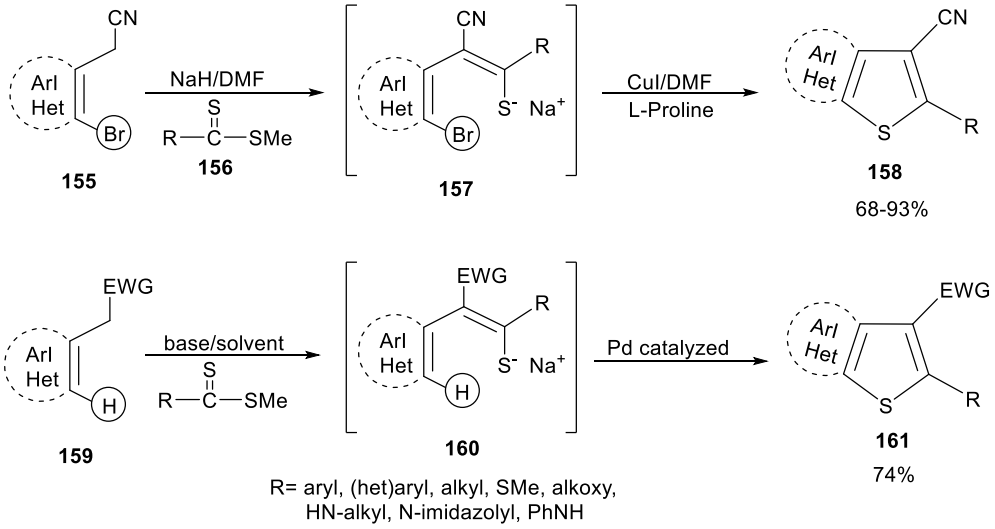
Ernest *et al.* [81] reported that the arylhydrazone in the previous reaction with substitution in ortho position failed to cyclized into pyrazole and they also reported the synthesis of pyrazole **152** from the 4-tolyl- and 4-methoxyphenyl hydrazones. Contrary, the ring formation is so rapid in case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

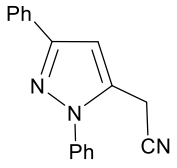
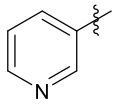
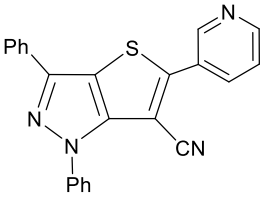
Singh *et al* [82] have reported a novel radical cyclization approach to thienopyrazole heterocycles. The scope and generality of this efficient radical-mediated thiophene annulation protocol was further evident by extending the methodology to the synthesis of tetra substituted thieno[3,2-*c*]pyrazoles. 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-*c*]pyrazole-6-carbonitrile **154a,b** (Scheme 47).



Scheme 47

Anand Acharya *et al* [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).

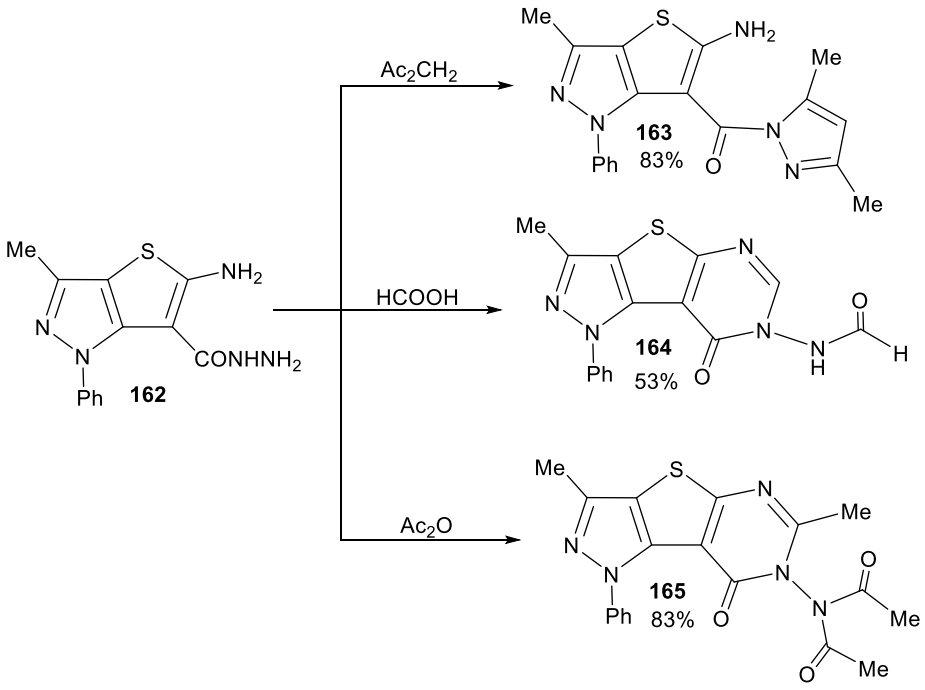


Heteroaryl	Aryl	Product
		

Scheme 48

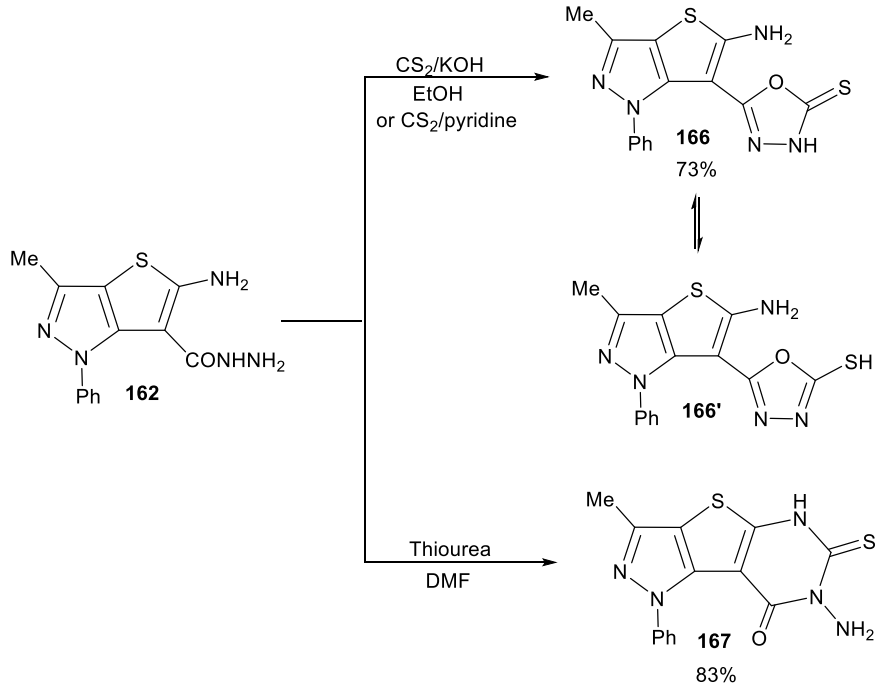
8. Miscellaneous Reactions of Thienopyrazoles

(5-Amino-3-methyl-1-phenyl-1*H*-thieno[3,2-*c*]-pyrazol-6-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl) methanone (**163**) was synthesized by the reaction of carbohydrazide derivative **162** with acetylacetone in ethanol[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-8*H*-pyrazolo[3′,4′:4,5]thieno[2,3-*d*]-pyrimidin-8-one (**165)** [21] (Scheme 49).



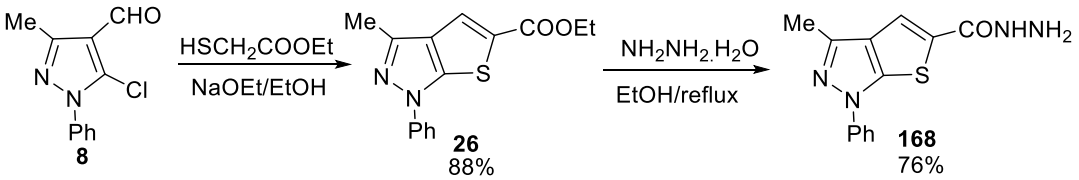
Scheme 49

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-1*H*-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-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-6-thione (**167)** was formed [21] (Scheme 50).



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-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylate **(26)** was reacted with hydrazine hydrate to afford the corresponding carbohydrazide **168** in 76% yield (Scheme 51).



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].

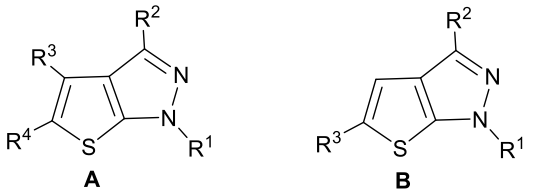
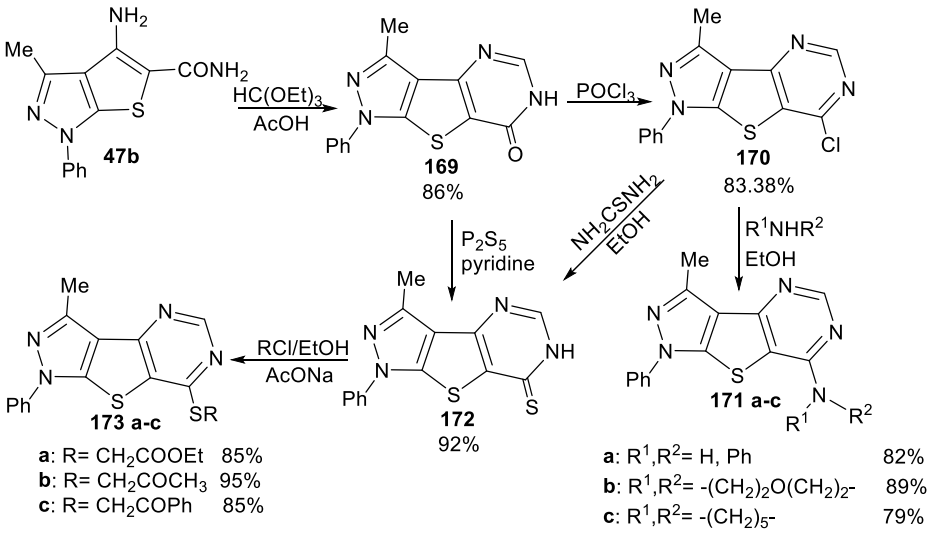
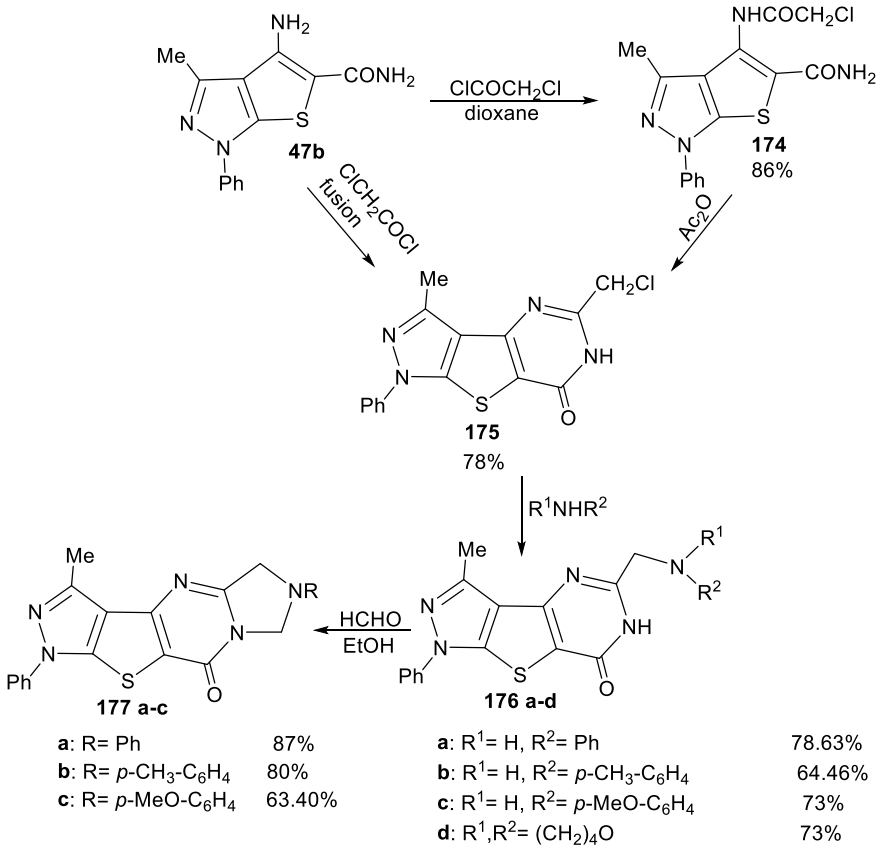


Figure 2. The substituent positions in thieno[2,3-c]pyrazole.

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(6*H*)-one **169** was obtained. The pyrazolothieno-pyrimidinone **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).



Scheme 52

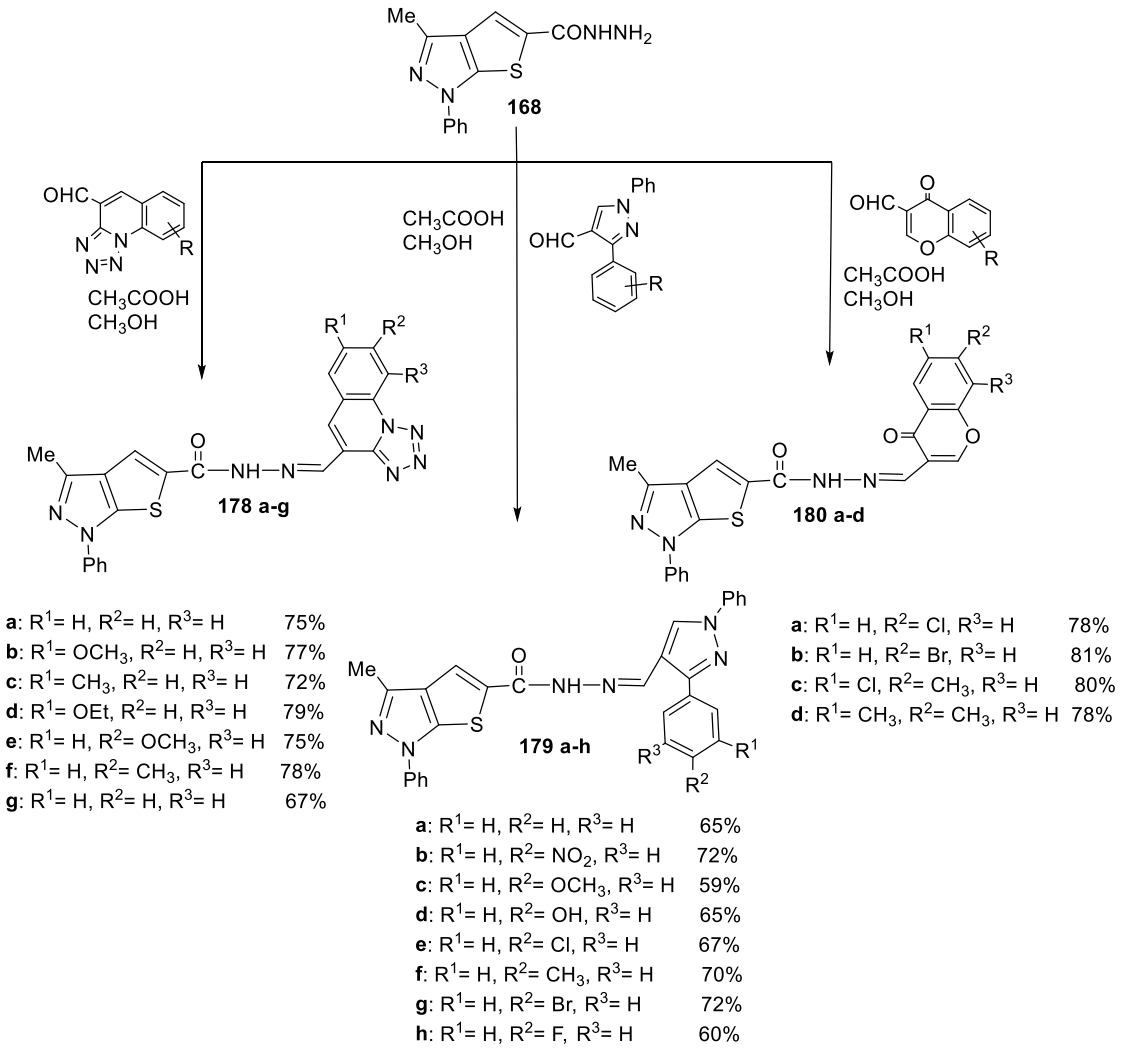


Scheme 53

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^{o}C followed by neutralization with dilute sodium carbonate solution afforded the chloromethylpyrazolothienopyrimidinone **175**. Compound **175** was obtained by an alternative

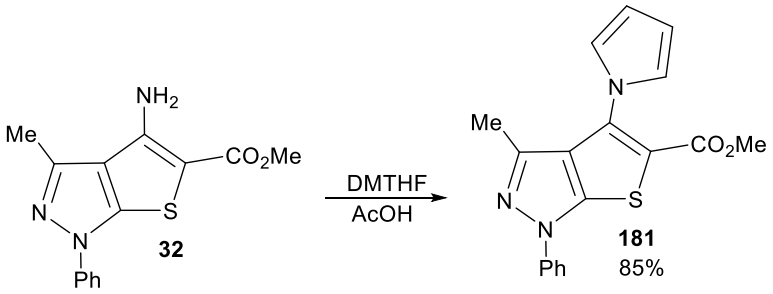
route, upon refluxing the chloroacetyl amino compound **174** in acetic anhydride. The produced compound **175** which was obtained by the two methods was in agreement with the postulated structure in all aspects. The chloromethyl pyrimidine derivative **175** underwent nucleophilic substitution reactions 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(6*H*)-ones **176a-d**. Compounds **176a-d**, upon treatment with formaldehyde under *Mannich* conditions, afforded the 3-methyl-1,6-diaryl-5,7-dihydroimidazo[1,5-*a*]pyrazolo[3',4':4,5]thieno[3,2-*d*] pyrimidin-9-ones **177a-c**[50] (Scheme 53).

The key material 3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbohydrazide (**168)** was prepared in a good yield according to the literature procedure[45]. Condensation of carbohydrazide **168** with the appropriate heterocyclic aldehydes namely substituted tetrazolo[1,5-*a*]quinoline-4-carbaldehyde, 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde and 4-oxo-4*H*-chromene-3carbaldehyde in methanol in the presence of acetic acid gave the corresponding stable solid *N*-acylhydrazones **178a–g**, **179a–h** and **180a–d**[92] (Scheme 54).



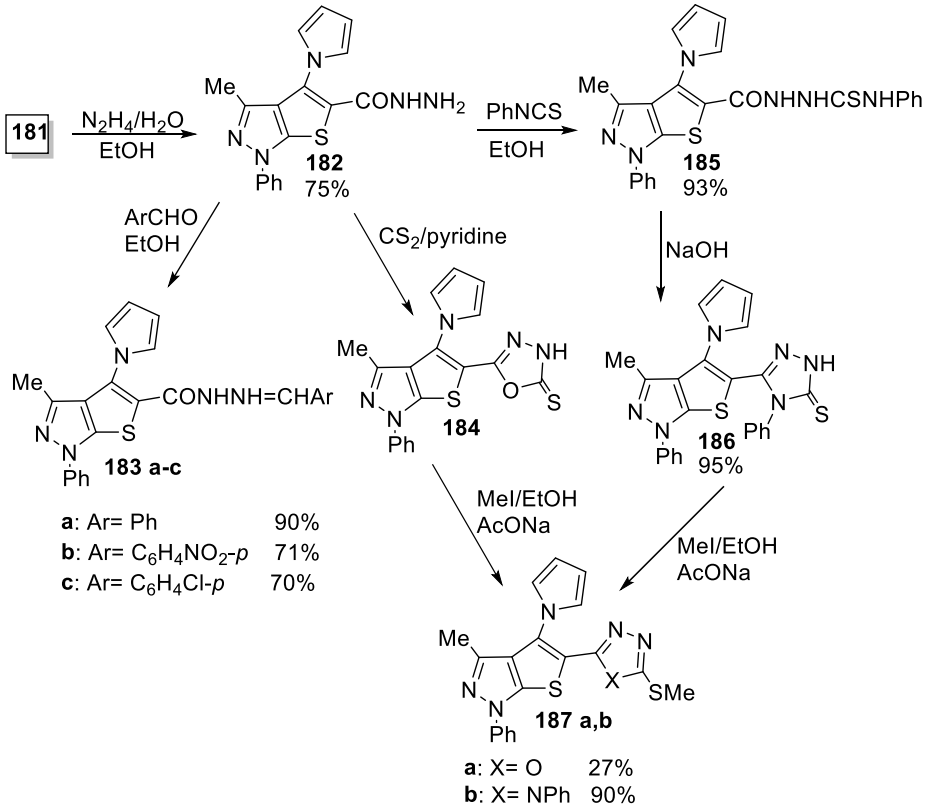
Scheme 54

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-dimethoxytetrahydrofuran (DMTHF) in refluxing acetic acid following the reported procedure to give **181**[46] (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).

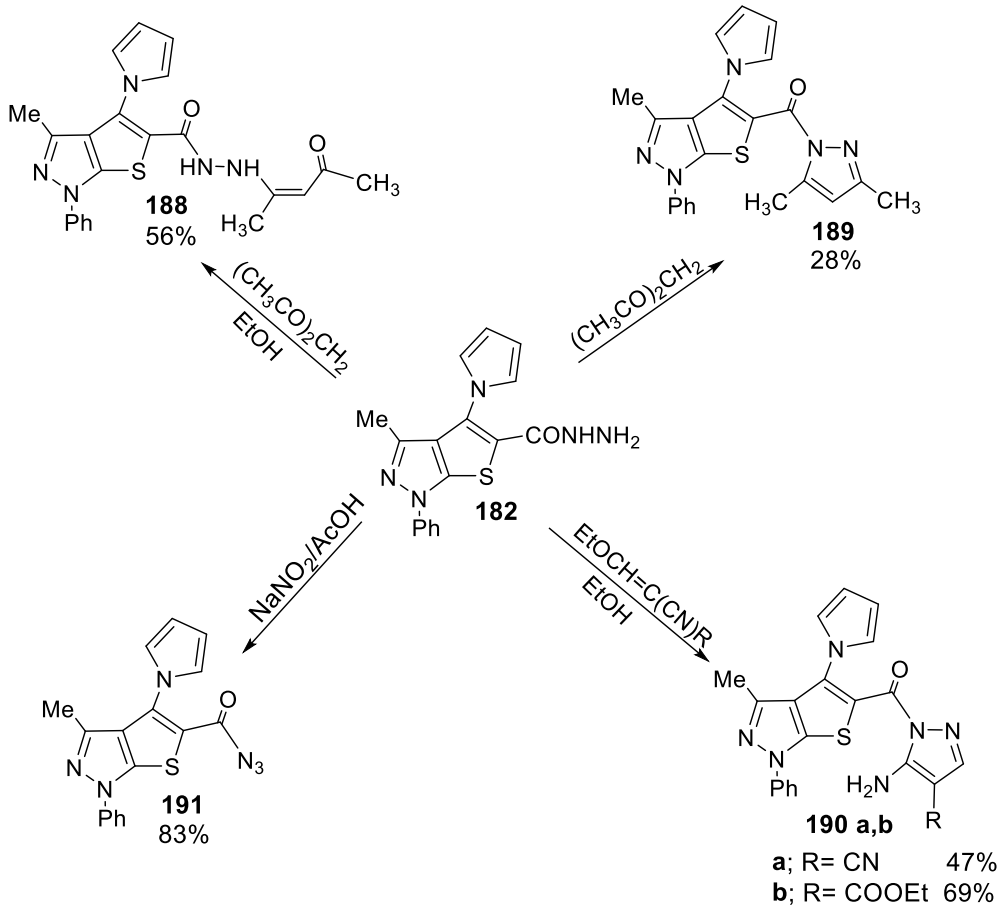


Scheme 56

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.

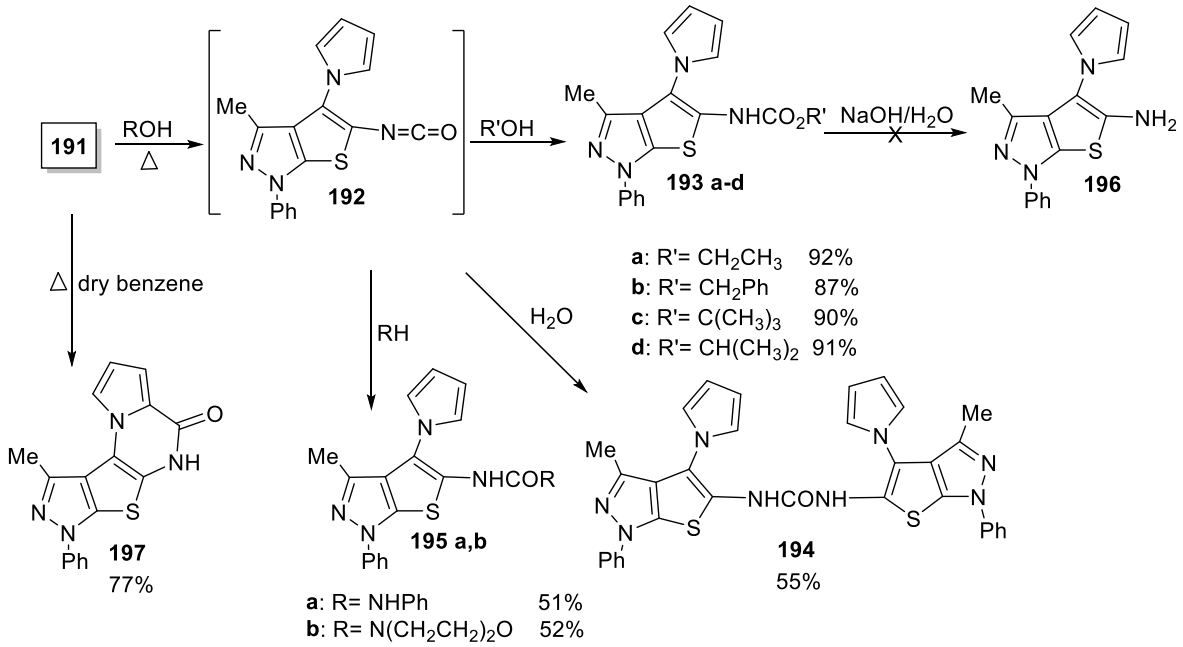
Treatment of **182** with nitrous acid resulted in the formation of 3-methyl-1-phenyl-4-(pyrrol-1-yl)-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl azide (**191)** in a good yield[46] (Scheme 57).



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-4*H*-pyrazolo[4',3':4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazin-4-one (**197)** (Scheme 58).



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 bi-functionalized 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.

10. Acknowledgements

The authors are very grateful to Prof. Dr./ Etaify A. Bakhite, Head of Chemistry Department, for all the facilities providing to us, and very grateful too to the staff members of Chemistry Department, Faculty of Science, Assiut University for their support during this work.

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