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REACTION OF HYDRAZINES AND HYDROXYLAMINE WITH TRIFLUOROMETHYL-β-DIKETONES: SYNTHESIS OF TRIFLUORO-METHYLPYRAZOLE AND ISOXAZOLE DERIVATIVES

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Abstract – The reaction of trifluoromethyl-β-diketones with hydrazines and hydroxylamine finds interesting application in the synthesis of trifluoromethylpyrazole and isoxazole derivatives. The review covers the literature of the reactions mentioned up to 2007. Mechanistic aspects leading to the formation of these heterocycles and their NMR spectral characteristics are also described.

1. INTRODUCTION

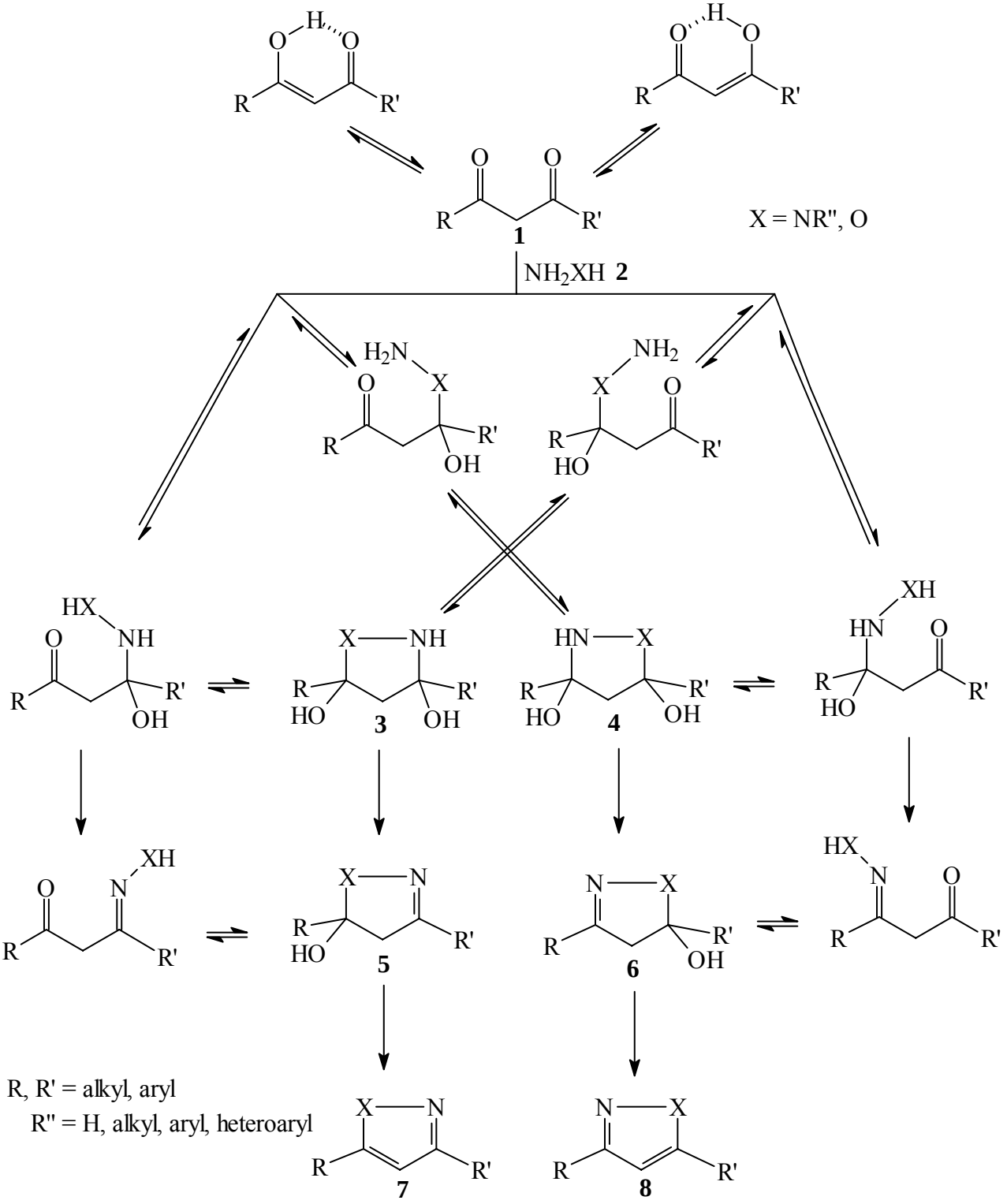
Trifluoromethylpyrazole and isoxazole derivatives[1-12] are important classes of compounds because of diverse biological properties associated with them. As a lot of work has been done in the past on the synthetic and mechanistic pathways of trifluoromethylpyrazole and isoxazole derivatives involving the reaction of trifluoromethyl-β-diketones with hydrazines and hydroxylamine, it is the aim of this review to update the status of this reaction. The reaction may proceed through a similar mechanism as has been established for the condensation of hydrazines or hydroxylamine with nonfluorinated-β-diketones.

Investigation of the mechanism of the reaction of β-diketones with hydrazines or hydroxylamine has been a subject matter of several studies. It was shown, that β-diketones exist in three tautomeric forms.[13, 14] Hydrazines or hydroxylamine (**2**), being binucleophilic in nature, may attack on any one of the electrophilic centers of β-diketone (**1**) to generate a number of intermediates which eventually lead to the formation of two regioisomeric products (**5** & **6**) after cyclization (Scheme 1).

2. REACTION OF TRIFLUOROMETHYL-β-DIKETONES WITH HYDRAZINES

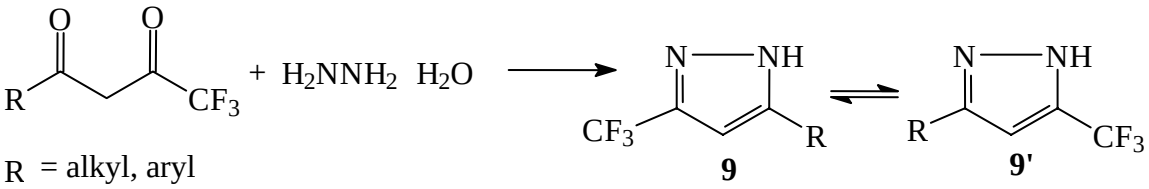
Reaction of trifluoromethyl-β-diketones with hydrazine was first reported by Wagner[15] in 1965. He

reported the synthesis of a number of biologically active 3 or 5-trifluoromethylpyrazoles (**9** or **9'**) by treating hydrazine hydrate with trifluoromethyl-β-diketones. Nishiwaki[16] has also repeated the similar reaction (R =Me) (Scheme 2).

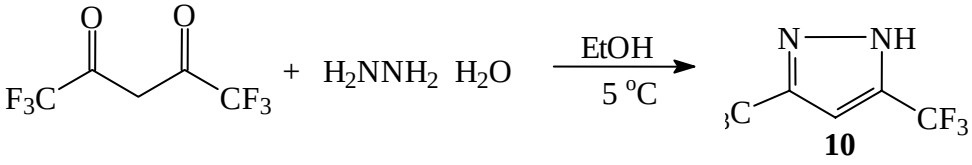


Scheme 1

Troflmenko[17] has reported that the slow addition of 1,1,1,5,5,5-hexafluoropentane-2,4-dione to hydrazine hydrate at 5 °C results in the formation of 3(5)-*bis*(trifluoromethyl)pyrazole (**10**) (Scheme 3).

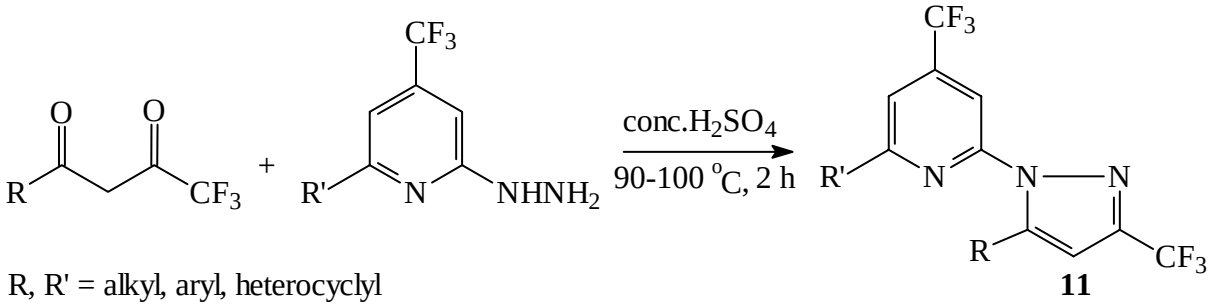


Scheme 2



Scheme 3

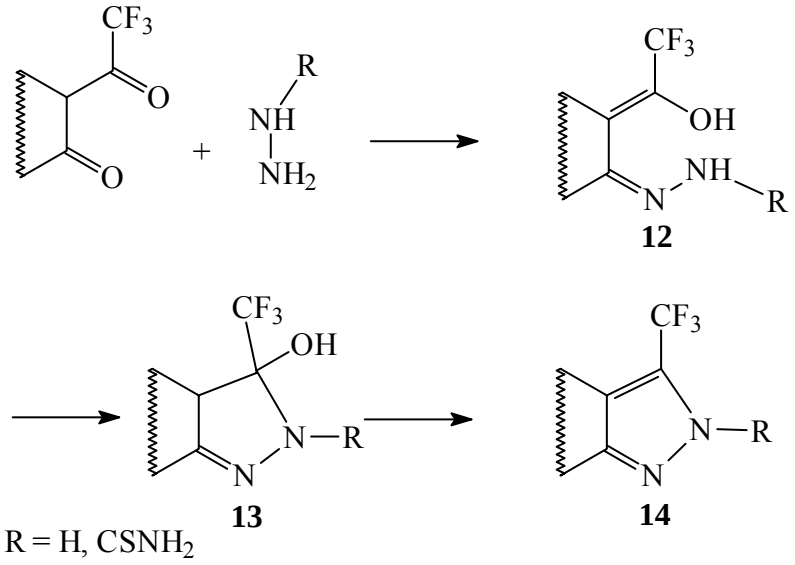
Portnoy[18] reported the synthesis of several 3-trifluoromethyl-1-(4-trifluoromethyl-2-pyridyl)pyrazoles (**11**) by the reaction of 2-hydrazino-4-trifluoromethylpyridines with trifluoromethyl-β-diketones. However, no evidence in support of the proposed structure was provided (Scheme 4).



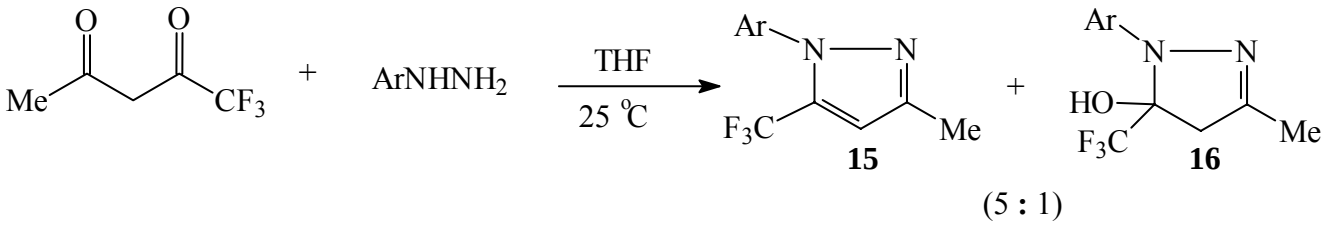
Scheme 4

Secor and Debardeleben[19] have reported that the reaction of several α-trifluoroacetylketones with hydrazine and thiosemicarbazide results in the formation of 5-trifluoromethylpyrazoles (**14**) in some cases or 5-hydroxypyrazolines (**13**) in other. Also, it has been observed that in the reaction of 2-trifluoroacetylcyclopentanone and thiosemicarbazide, a stable enol (**12**) was obtained which did not cyclize to **13** or **14** probably due to the hydrogen bonding (Scheme 5).

Lyga and Patera[20] have reported that reaction of arylhydrazines with 1,1,1-trifluoropentane-2,4-dione results in the formation of 1-aryl-3-methyl-5-trifluoromethylpyrazoles (**15**) as the major product along with minor amounts of the 5-hydroxy-5-trifluoromethylpyrazolines (**16**) (Scheme 6). They have also achieved the regioselective synthesis of (**19**, Ar = Ph) by treating trifluoromethyl-β-diketones first with pyrrolidine at 0 °C to yield Micheal addition product **17**, which on subsequent treatment with phenylhydrazine gives **18** exclusively. As expected, the compound **18** on treatment with acid gives the corresponding pyrazole **19** (Scheme 7).



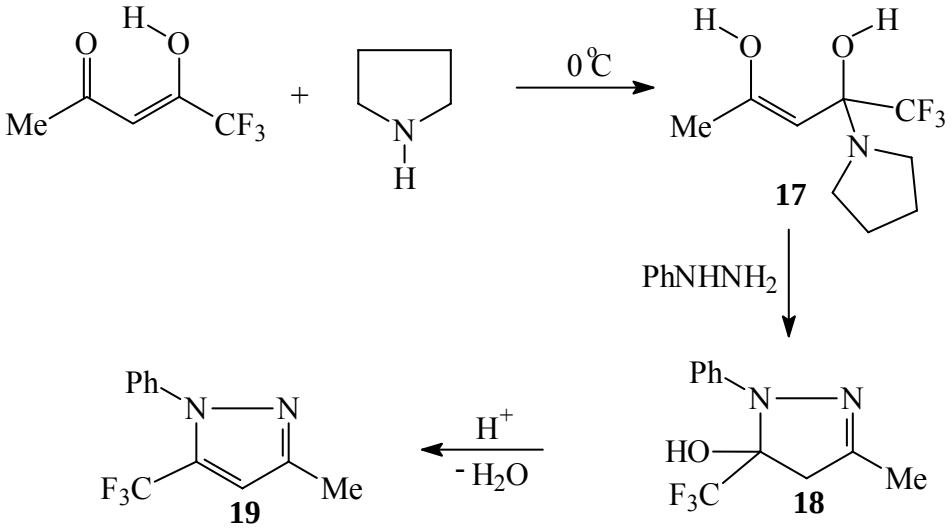
Scheme 5



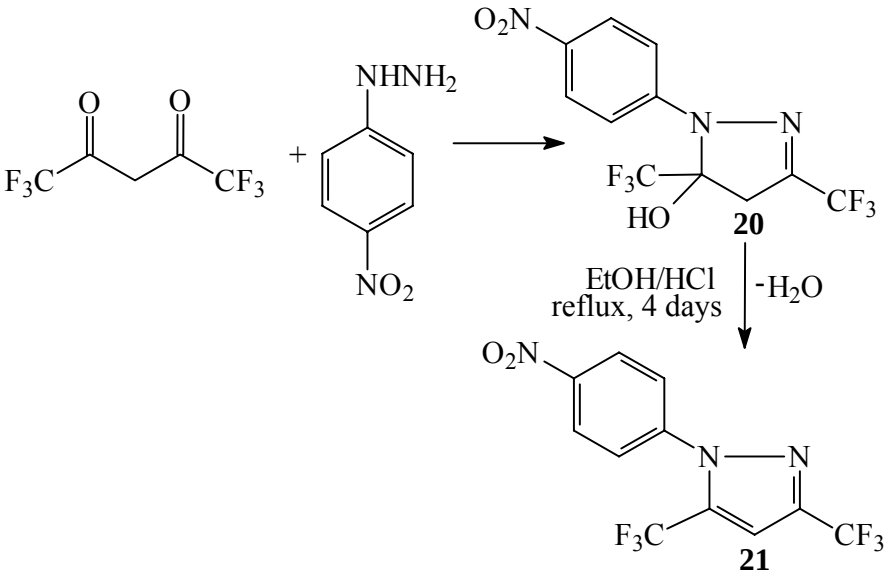
Scheme 6

It has been reported that dehydration of 3,5-*bis*(trifluoromethyl)-4,5-dihydro-5-hydroxy-1-(4'-nitrophenyl)pyrazole (**20**), obtained by the reaction of *p*-nitrophenylhydrazine with 1,1,1,5,5,5-hexafluoropentane-2,4-dione, could be achieved by treating it with a small quantity of acid in boiling ethanol. This method was found to be very effective and the pyrazole (**21**) was obtained in high yield (Scheme 8). Obviously, the presence of an acid favours the protonation of the hydroxyl group followed by facile dehydration.[21]

On the other hand, 3, 5-*bis*(trifluoromethyl)-4, 5-dihydro-5-hydroxy-1-(pentafluorophenyl)pyrazole (**22**), obtained by treating pentafluorophenylhydrazine with 1,1,1,5,5,5-hexafluoropentane-2,4-dione, did not undergo dehydration under these conditions. The compound was eventually dehydrated to the corresponding pyrazole (**24**) on treatment with acetic anhydride and acetic acid under reflux for 16 h. In the presence of Ac_2O the hydroxyl group was converted to an acetoxy group, which is indeed an efficient, leaving group[21] (Scheme 9).

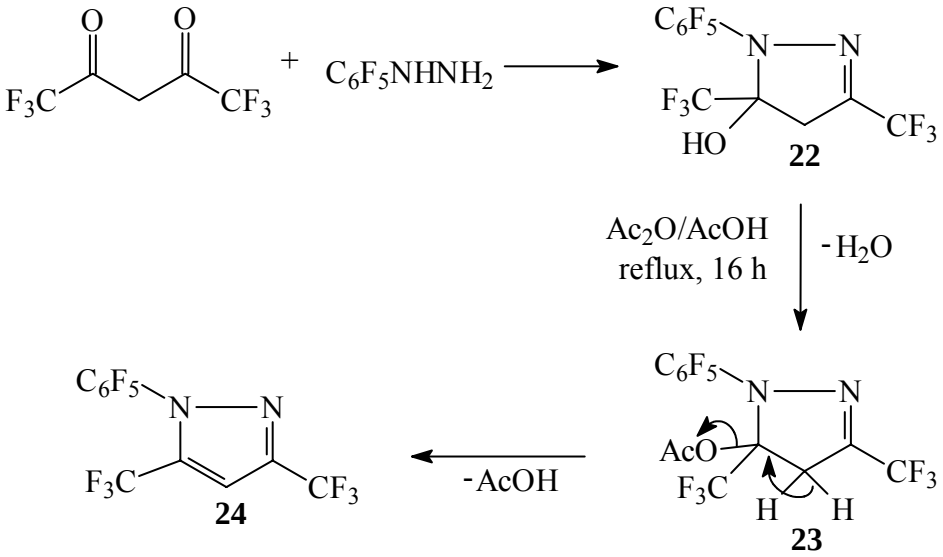


Scheme 7

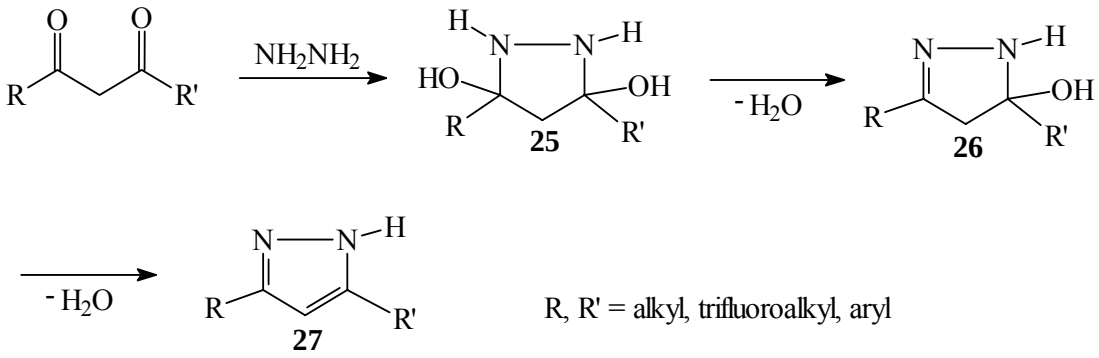


Scheme 8

In a careful study, Elguero and Yranzo[22] have established that the mechanism of formation of pyrazoles including trifluoromethylpyrazoles involves the intermediacy of 3,5-dihydroxypyrazolidines (**25**) and 5-hydroxypyrazolines (**26**). While the intermediate **26** has actually been isolated, **25** was found to be so unstable that it could be characterized only by NMR using special stop flow technique. Later on Elguero *et al.*[23] have isolated both the intermediates **25** and **26** successfully which were subsequently dehydrated to corresponding pyrazoles (**27**) (Scheme 10).



Scheme 9

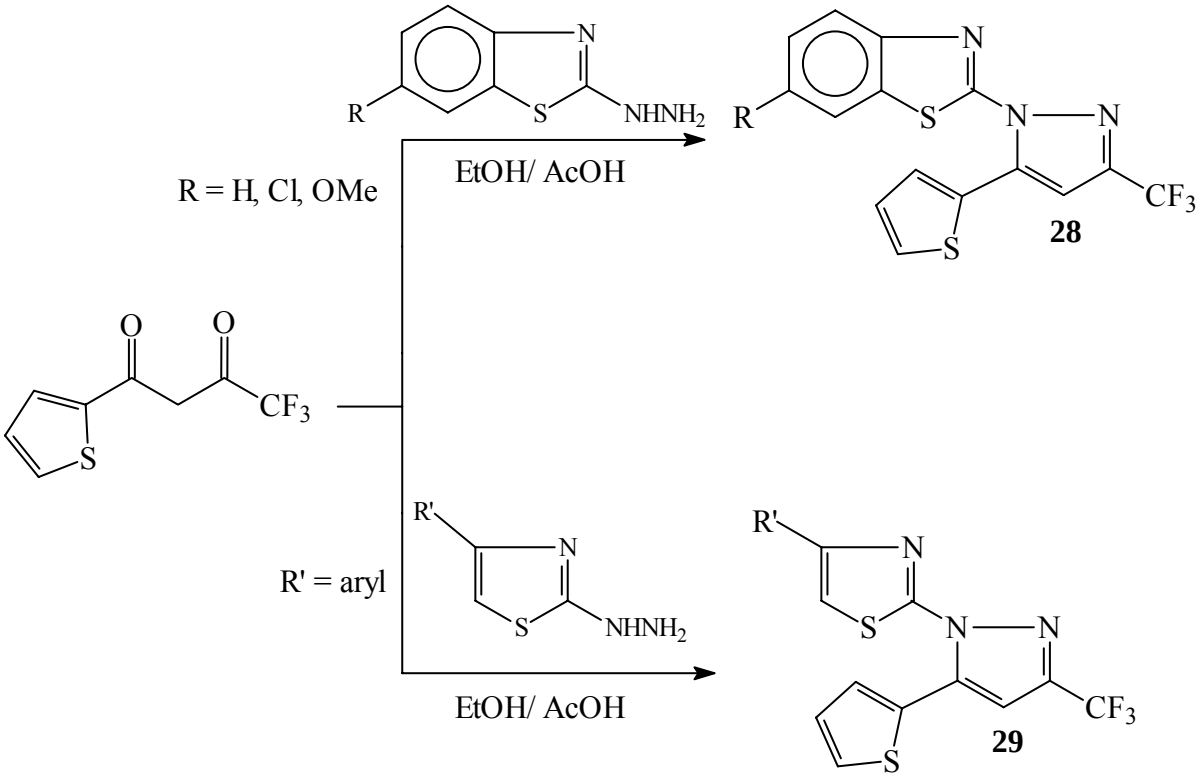


Scheme 10

Formation of 5-(2-thienyl)-3-trifluoromethylpyrazoles (**28**) and (**29**) has been reported from our laboratory.[24] These compounds were conveniently obtained by the condensation of 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione with 2-hydrazinobenzothiazoles and 2-hydrazinothiazoles, respectively (Scheme 11).

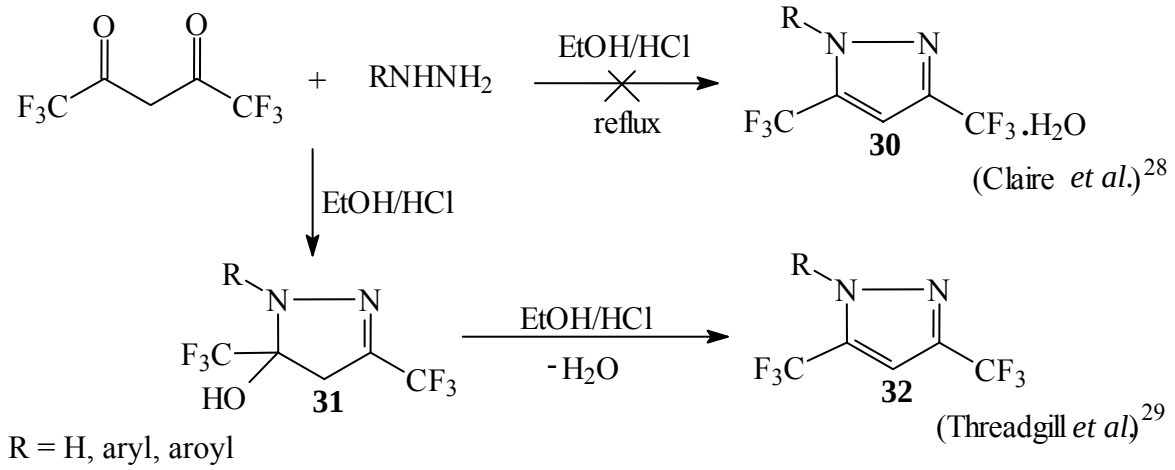
Several other heterocyclic hydrazines have similarly been treated with trifluoromethyl-1,3-diketones to yield corresponding 3-trifluoromethylpyrazoles.[3,25-27]

Joshi *et al.*[27] and Claire *et al.*[28] have reported that the reaction of 1,1,1,5,5,5-hexafluoropentane-2,4-dione with several hydrazines provides hydrated 3,5-*bis*(trifluoromethyl)pyrazoles (**30**). In the same report[28] synthesis of 1-aryl and aroyl-3,5-*bis*(trifluoromethyl)pyrazoles was claimed to have been achieved by the reaction of substituted hydrazines with 1,1,1,5,5,5-hexafluoropentane-2,4-dione in refluxing ethanol (Scheme 12). The structure of the products was subsequently reinvestigated by Threadgill *et al.*[29] The reaction was performed under identical conditions and the authors have assigned the structure as 5-hydroxy-5-trifluoromethylpyrazoline (**31**) primarily on the basis of ^{19}F spectral data of the products.[29] They observed that till date the pyrazole structure was assigned on the basis of ^{19}F NMR value of δ-80 ppm. It is actually a characteristic value for the CF_3 group located on a 5-hydroxypyrazoline ring at position-5. It thus became evident that previous authors[28] have indeed obtained 5-hydroxy-5-trifluoromethyl-1*H*-pyrazolines (**31**) instead of the erroneously reported pyrazole monohydrates (**30**). Corresponding pyrazoles (**32**) were subsequently obtained by the dehydration of **31** under strong acidic conditions (Scheme 12).



Scheme 11

In continuation of the work related to the reaction of hydrazines with trifluoromethyl-β-diketones, the synthesis of isomeric 3-trifluoromethyl-5-methyl-1-[4'-(aryl)thiazole-2'-yl]pyrazole (**33**) and 5-trifluoromethyl-3-methyl-1-[4'-(aryl)thiazole-2'-yl]pyrazole (**34**) was reported from our laboratory.[30]



Scheme 12

However, when 2-hydrazinobenzothiazole was treated with 1,1,1-trifluoropentane-2,4-dione, there was an exclusive formation of 5-trifluoromethylpyrazoles (**35**). In an attempt to isolate the intermediate of the reaction, 6-chloro-2-hydrazinobenzothiazole was treated with trifluoromethyl-β-diketones in absolute ethanol at rt. This reaction indeed provided the intermediate 5-hydroxy-5-trifluoromethylpyrazoline (**36**) rather than the hydrazone or pyrazole. The other regioisomer 3-trifluoromethylpyrazole could not be isolated even in traces. **36** underwent ready dehydration on refluxing in acetic acid-sulphuric acid or ethanol-HCl yielding the corresponding 5-trifluoromethylpyrazoles (**35**) (Scheme 13).

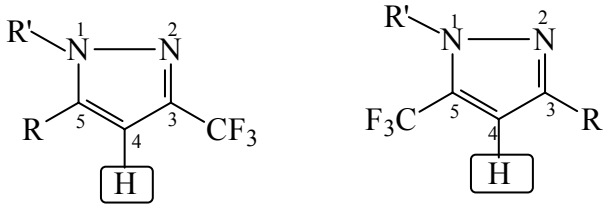
However, in order to make unambiguous assignments of the location of the trifluoromethyl group at positions-3 or 5, isomeric trifluoromethylpyrazoles (**35** & **38**) were synthesized by the condensation of 2-chlorobenzothiazole (**37**) and the sodium salt of NH-pyrazoles (**9**) (R = Me, phenyl, 2-thienyl) (Scheme 14).[31] The isomeric products, obtained in 1:4 ratio, (**35** & **38**) were separated by column chromatography and were characterized by NMR spectral analysis.

STEREOCHEMICAL ASSIGNMENT OF REGIOISOMERS FOR PYRAZOLES

NMR spectroscopy (^{1}H, ^{13}C and ^{19}F) has been extensively used for the assignment of trifluoromethyl substituent in the pyrazole derivatives.

^{1}H NMR SPECTROSCOPY

The structure of isomeric 1-subsituted-3(5) trifluoromethylpyrazoles can be easily predicted on the basis of 4-H proton of pyrazoles as a characteristic signal in ^{1}H NMR spectra.[30-32]



R, R' = alkyl, aryl, heteroaryl

Table 1. Signal due to 4-H of pyrazoles

CF_3-Position	R	δ (ppm)
3	alkyl	~ 6.4-6.5
5	alkyl	~ 6.6-6.7
3	aryl/heteroaryl	~ 6.8-6.9
5	aryl/heteroaryl	~ 7.1-7.3

As shown in **Table 1**, in case of 1-substituted-3-trifluoromethylpyrazoles, signal due to 4-H proton always appears upfield while in case of 5-trifluoromethylpyrazoles it appears downfield.

^{13}C NMR SPECTROSCOPY

This technique has been found to be superior to that of the ^{1}H NMR spectroscopy for the characterization of trifluoromethylpyrazole derivatives[30-32,] particularly where the reaction results in the formation of isomeric products. As ^{13}C NMR spectra of several differently substituted isomeric 1-aryl/heteroaryl-3(5)-trifluoromethylpyrazoles have been analyzed in this review, it is relevant to report the data available in the literature concerning these heterocycles. The detailed study of the effect of substituents on the ^{13}C NMR parameters of pyrazoles has been reported by Begtrup *et al*.[33, 34]

In case of 1-aryl/heteroaryl-3, 4, 5-unsubstitutedpyrazoles, the carbons C-3, C-4 and C-5 appear in the range δ ~142-144, δ ~108-110 and δ ~ 127-129 ppm, respectively in ^{13}C NMR spectra.[35-39]

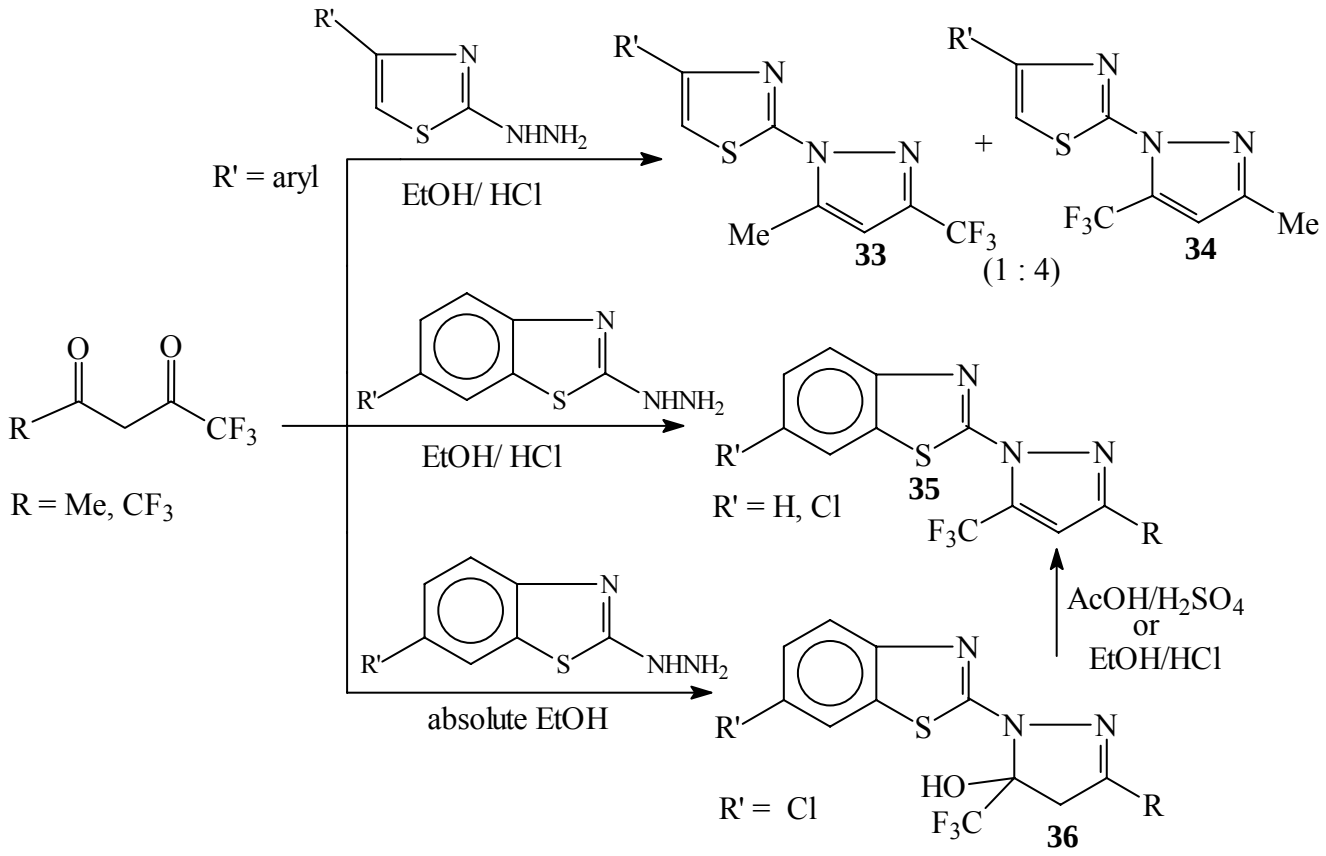
Table 2. Effect of Me and CF_3 group on C-3 and C-5 carbons of pyrazole

Carbons	C-3	C-5
H	~142-144	~ 127-129
Me	~152-154	~ 142-144
CF_3	~143-145 ppm (q, $^2J_{C-F}$ = ~ 40 Hz)	~133-135 (q, $^2J_{C-F}$ = ~ 42 Hz)

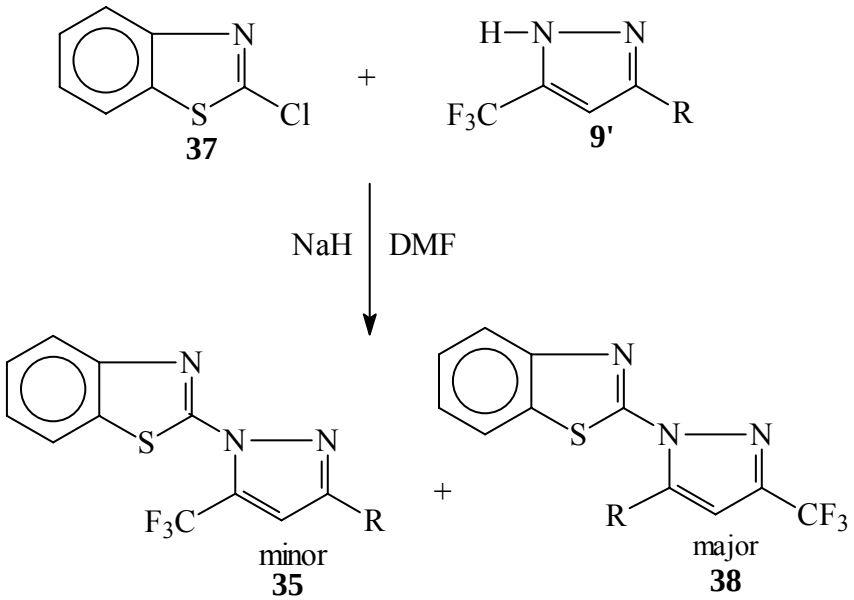
It has been reported that the carbons C-3 and C-5 of pyrazoles appears at δ ~143-145 ppm (q, $^2J_{C\text{-}F}$ = ~ 40 Hz) and δ ~133-135 (q, $^2J_{C\text{-}F}$ = ~ 42 Hz), respectively, in the presence of carbon bearing trifluoromethyl group at these positions.[30-32] It has been already reported from our laboratory that in case of 1-substituted-3, 5-dimethylpyrazoles, carbons C-3 and C-5 of the pyrazole ring appear at about δ152-154 and 142-144, respectively.[35,36] Unsubstituted carbon C-4 of pyrazole nucleus appears in the range of about δ 104-109 ppm if methyl or trifluoromethyl groups are located at position 3 and 5 of pyrazole ring. Therefore, it may be concluded that replacement of a methyl group at position-3 and 5 by trifluoromethyl group causes shielding of that carbon by about 7 and 9 ppm, respectively. The ^{13}C NMR spectral analysis thus provided valuable information of general applicability to assign the structure of 1-substituted-3(5)-trifluoromethylpyrazoles.

^{19}F NMR SPECTROSCOPY

The ^{19}F NMR spectroscopy is proved to be an elegant tool to distinguish the position of trifluoromethyl group at pyrazole nucleus. It has been reported from our laboratory that the signal due to fluorine of trifluoromethyl group appear in the range of δ -60-63 ppm for 3-trifluoromethylpyrazoles and δ -57-60 ppm for 5-trifluoromethylpyrazoles.[30-32,40-43]



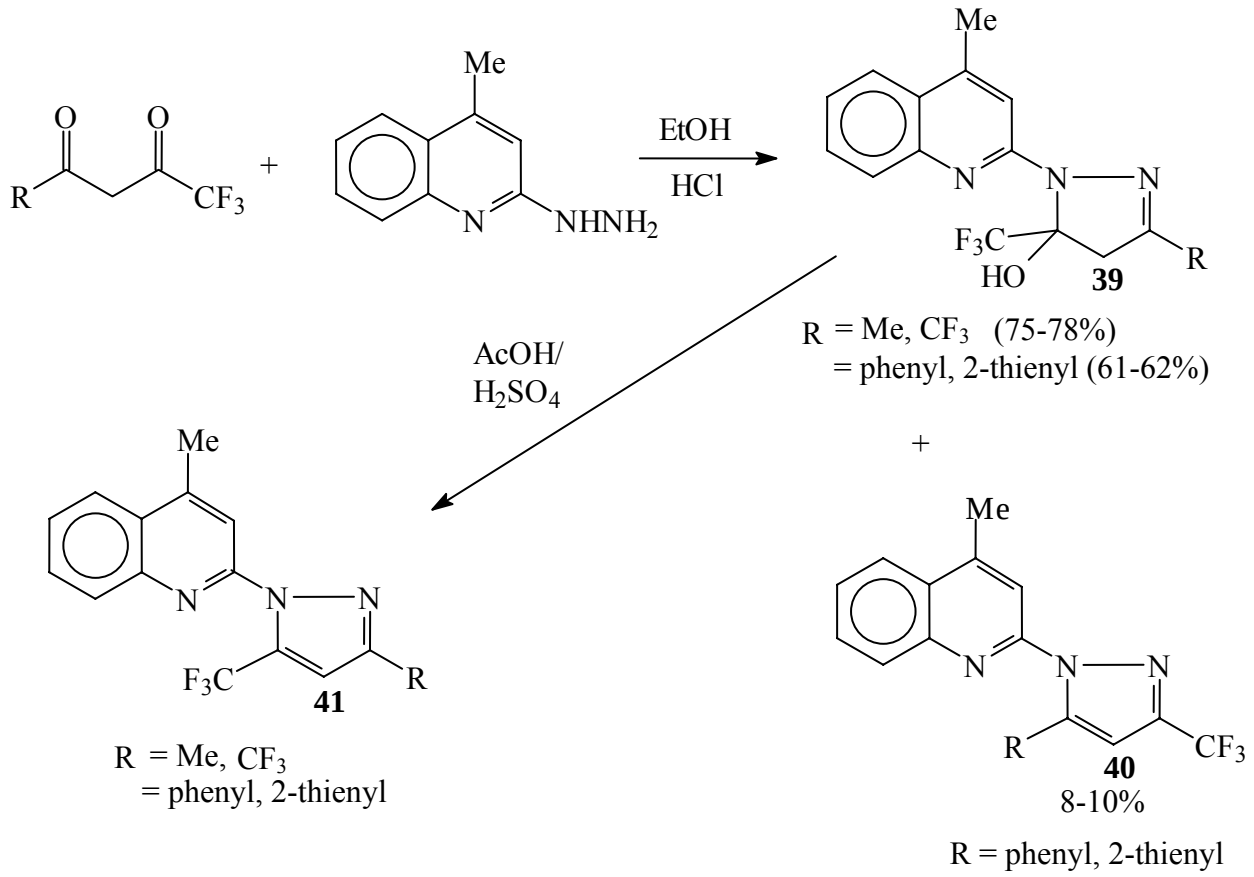
Scheme 13



R = methyl, phenyl, 2-thienyl

Scheme 14

In order to shed more light on the mechanistic course of these reactions, the reaction of 2- and 4-hydrazinoquinolines with trifluoromethyl-β-diketones was subsequently investigated.[32] The reaction of 2-hydrazino-4-methylquinoline with trifluoromethyl-β-diketones (R = Me, CF_3) provided 5-hydroxy-5-trifluoromethyl-1-(4-methylquinolin-2-yl)-4,5-dihydropyrazoles (**39**) as the only product. However, similar treatment of 2-hydrazino-4-methylquinoline with trifluoromethyl-β-diketones (R = phenyl, 2-thienyl) gave mixture of **39** and 3-trifluoromethyl-1-(4-methylquinolin-2-yl)-5-substituted pyrazoles (**40**). Dehydration of **39** was effected with sulphuric acid in acetic acid to give regioisomeric 3-substituted-1-(4-methylquinolin-2-yl)-5-trifluoromethylpyrazoles (**41**) (Scheme 15). The ratio of the yields of the two regioisomers depends on the ratio of the two enols at equilibrium. The elimination of water from **39** to **41** has been shown to be dependent on the electronic nature of substituent at position-5. Intermediacy of hydrazones in these reactions was established in the reaction of 7-chloro-4-hydrazinoquinoline with 1,1,1-trifluoropentane-2,4-dione. The reaction afforded for the first time the corresponding stable crystalline hydrazone **42**, whose structure was firmly established using IR and NMR spectral data. Cyclization followed by elimination of water could be effected by the treatment of **42** with sulphuric acid in acetic acid to yield to 3-methyl-5-trifluoromethyl-1-(quinolin-4-yl)pyrazole (**44**). There was no evidence for the formation of the other regioisomer (i.e. 5-methyl-3-trifluoromethylpyrazole) (Scheme 16). The intermediate 5-hydroxypyrazoline (**43**) could not be isolated in this case. It is not clear why the attachment of hydrazine at position-4 to the quinoline should have such an effect on the course of the reaction. It was indeed an unusual observation for such reactions.[32]

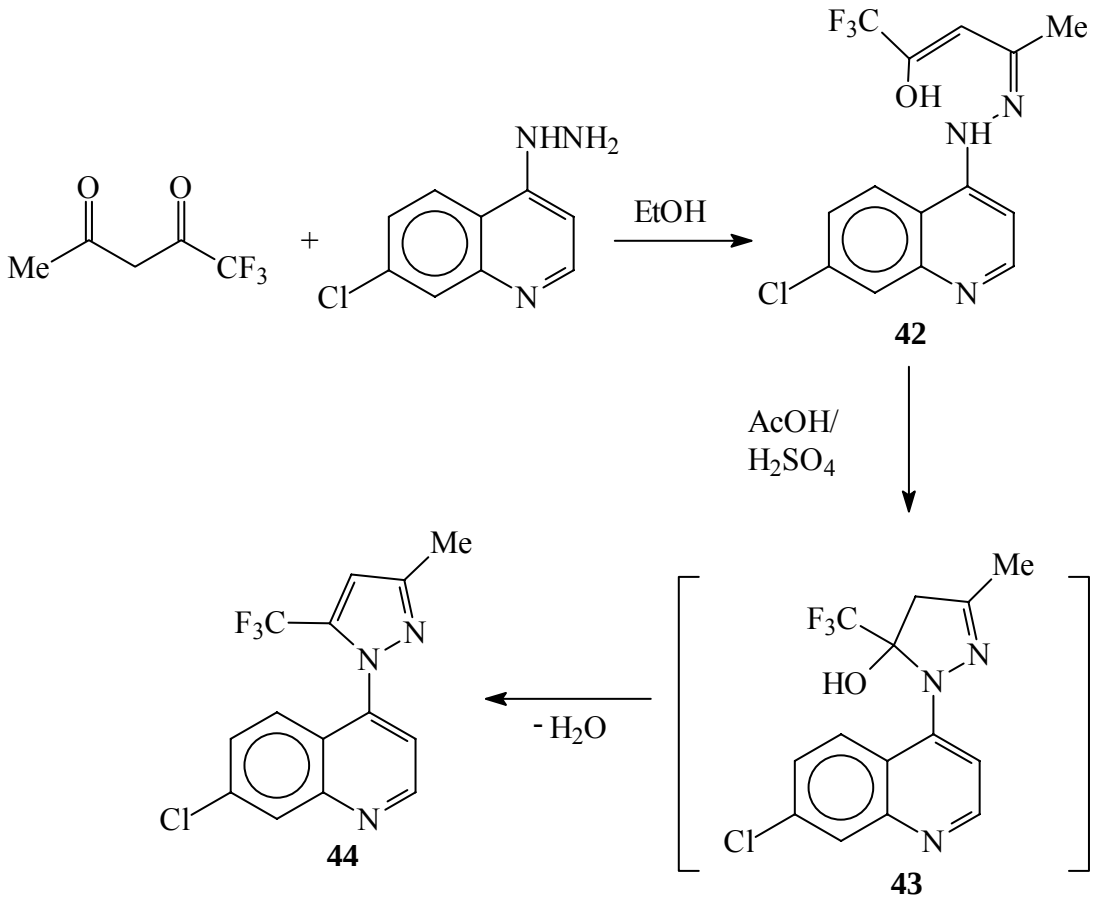


Scheme 15

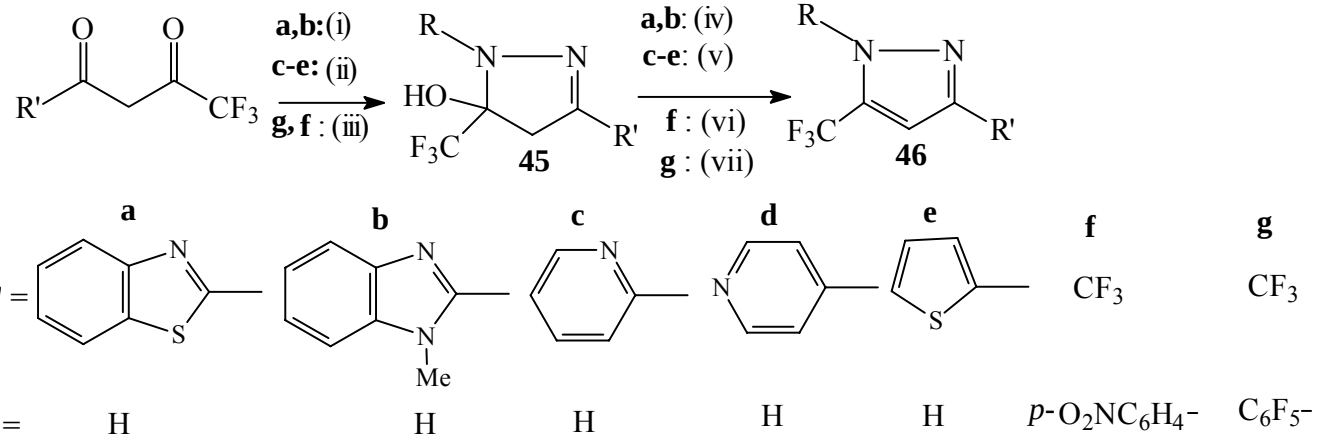
Reaction of various heteroaryltrifluoromethyl-β-diketones with different hydrazines under mild conditions was investigated in our laboratory.[40] Treatment of hydrazines with β-diketones under different conditions affords exclusively 5-hydroxy-5-trifluoromethylpyrazolines (**45**) which on subsequent treatment with acids undergo ready dehydration to give the corresponding pyrazoles (**46**) (Scheme 17).

It was also found that ^{19}F NMR spectroscopy is an elegant tool for assigning the structure of hydrazone, 5-trifluoromethyl-5-hydroxydihydropyrazole, and 3(5)-trifluoromethylpyrozole structures. The 5-hydroxypyrazoline such as **36**, **39** exhibited a signal at about -81 ppm for the 5-CF_3. The CF_3 group of the hydrazone **42** resonates at about -75 ppm. Finally, isomeric trifluoromethylpyrazoles can easily be distinguished by their ^{19}F NMR spectra. The 5-CF_3 of trifluoromethylpyrazoles resonates at about -58 ppm in contrast to the more upfield signal of the 3- CF_3 at -62 ppm.[40]

Reaction of 3-acetyl-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**47**) with various aryl and heteroarylhydrazines gives an exclusive product, which was formulated as 5-methyl-1-aryl/heteroaryl-4-trifluoroacetylpyrazoles (**48**). However, reaction of methylhydrazine with **47** under similar conditions, afforded a single crystalline compound, whose structure was established as 4-acetyl-1-methyl-3-trifluoromethylpyrazole (**49**) (Scheme 18).[41]

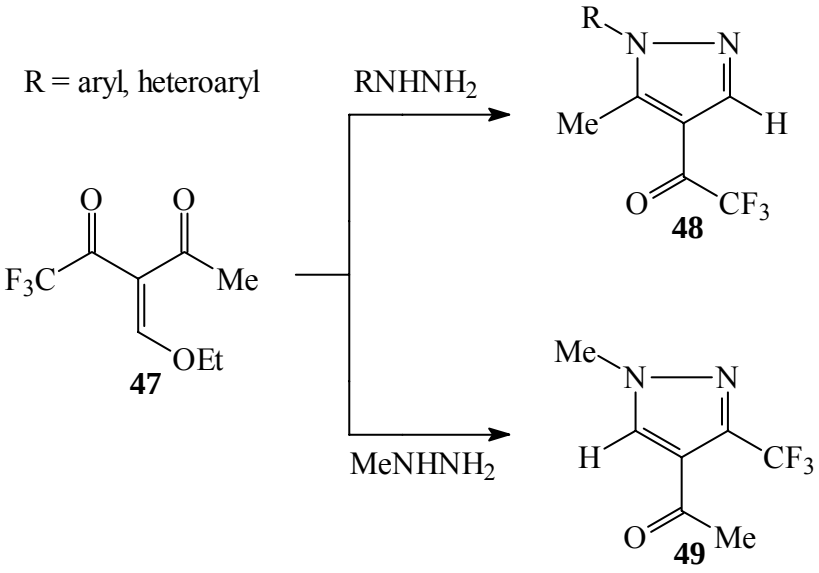


Scheme 16



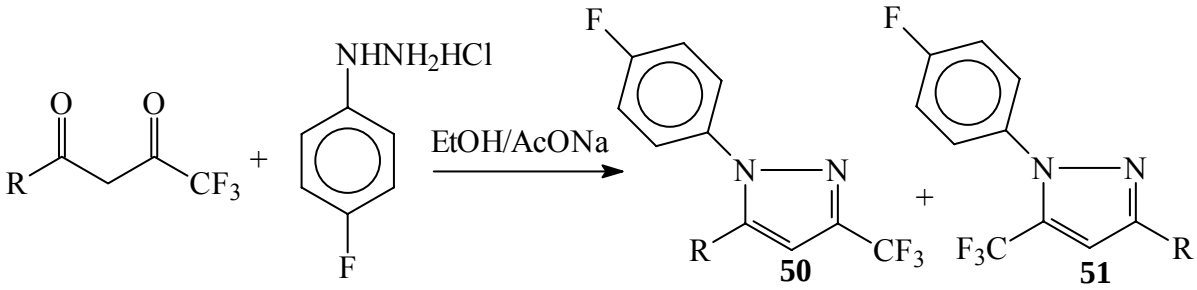
Reagents and conditions: (i) = N_2H_4, EtOH; (ii) = N_2H_4, Et_2O; (iii) = $RNHNH_2$, EtOH, Δ; (iv) = AcOH, EtOH, Δ; (v) = conc. H_2SO_4, EtOH, Δ; (vi) = aq. HCl, EtOH, Δ ; (vii) = Ac_2O, AcOH, Δ.

Scheme 17



Scheme 18

The reaction of *p*-fluorophenylhydrazine with several trifluoromethyl-β-diketones was investigated in our laboratory.[42] The reaction of *p*-fluorophenylhydrazine with trifluoromethyl-β-diketone (R = methyl) results in the formation of two isomeric products which were characterized as 5-methyl-3-trifluoromethyl-1-(*p*-fluorophenyl)pyrazole (**50**) and 3-methyl-5-trifluoromethyl-1- (*p*-fluoro-phenyl)pyrazole (**51**) with **50** as the major product in ratio of 4:1 (Scheme 19). *p*-Fluorophenylhydrazine was subsequently treated with several other unsymmetrical trifluoromethyl-β-diketones (R = phenyl, 2-thienyl, 2-pyridyl). However, in all the cases the reaction led to the exclusive formation of pyrazoles (**50**) having the CF_3 moiety located at position-3.

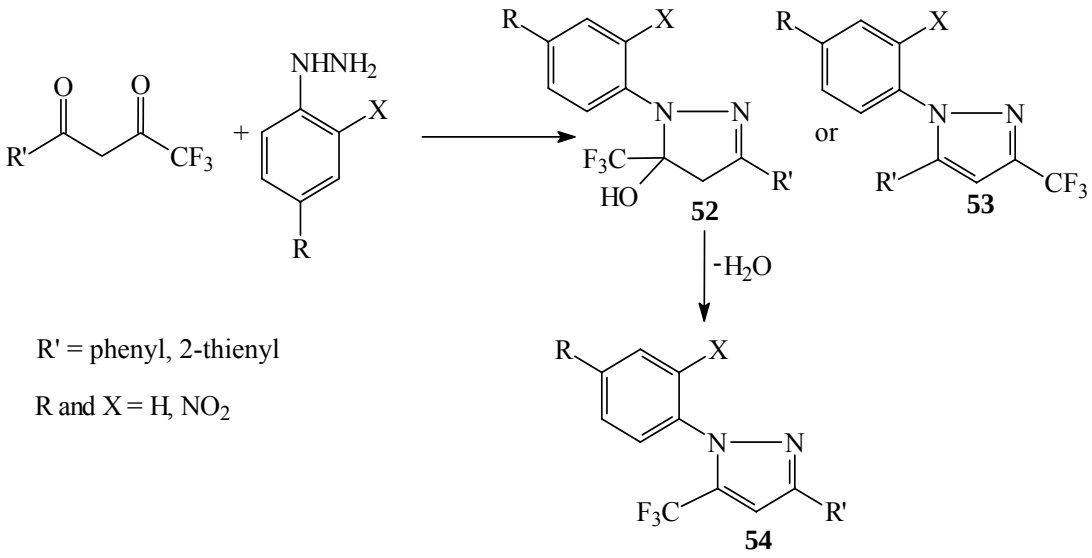


R = methyl, phenyl, 2-thienyl, 2-pyridyl

Scheme 19

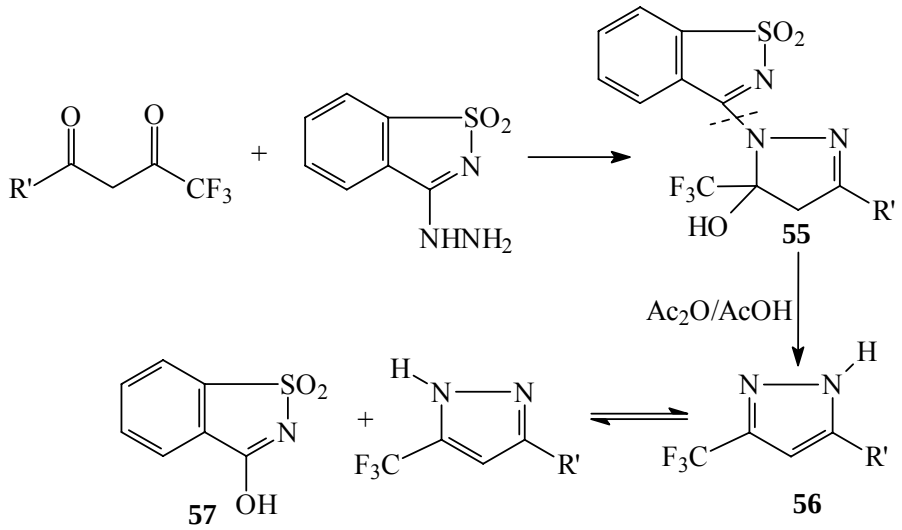
It was also reported from our laboratory[42] that with a given β-diketone such as benzoyltrifluoroacetone (R' = phenyl) and thienoyltrifluoroacetone (R' = 2-thienyl), there was formation of a pyrazole (**53**) having the CF_3 located at position-3 with phenylhydrazine and *p*-nitrophenylhydrazine. However, when

2,4-dinitrophenylhydrazine was used, 5-hydroxy-5-trifluoromethylpyrazolines (**52**) were obtained which underwent dehydration to the corresponding pyrazoles (**54**) (Scheme 20).



Scheme 20

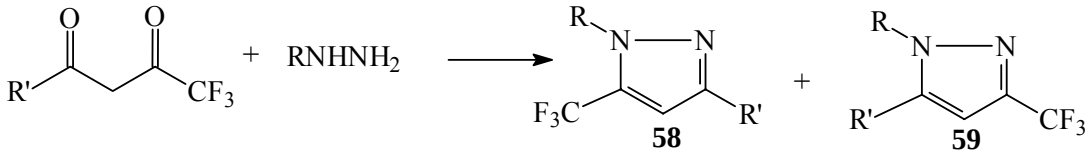
It was also observed[42] that the reaction of 3-hydrazino-1,2-benzoisothiazole-1,1-dioxide with diketone (R' = Me) in refluxing ethanol provided the intermediate 5-hydroxy-5-trifluoromethylpyrazoline (**55**) as revealed by the spectral data (Scheme 21). Attempts to dehydrate the pyrazoline **55** under different conditions resulted in the release of 3-hydroxy-1,2-benzoisothiazole-1,1-dioxide (**57**) due to the cleavage of the C-N bond and 3(5)-methyl-5(3)-trifluoromethyl-1-*H*-pyrazole (**56**) due to dehydration of pyrazoline ring (Scheme 21).



R' = methyl, phenyl, 2-thienyl, 2-pyridyl, trifluoromethyl

Scheme 21

During investigation of the reaction between aryl or heteroarylhydrazines and trifluoromethyl-β-diketones (CF_3COCH_2COR), an interesting observation came to light.[42] Spectral analysis of the products indicated that there was formation of either 3-trifluoromethyl or 5-trifluoromethylpyrazoles while using a particular trifluoromethyl-β-diketone such as benzoyltrifluoroacetone and thienoyltrifluoroacetone with a variety of monosubstituted hydrazines. It appeared that the orientation in these reactions depends, at least in some cases, on the substituent in the hydrazines. Such an observation is unprecedented in the literature, where focus has always been on the substituents in the β-diketone. It was, therefore, decided to investigate the mechanism of the reaction between monosubstituted hydrazines and unsymmetrical β-diketones leading to the formation of a mixture of pyrazole isomers **58**, **59** (Scheme 22) with an emphasis on the nature of substituent of hydrazines (R).

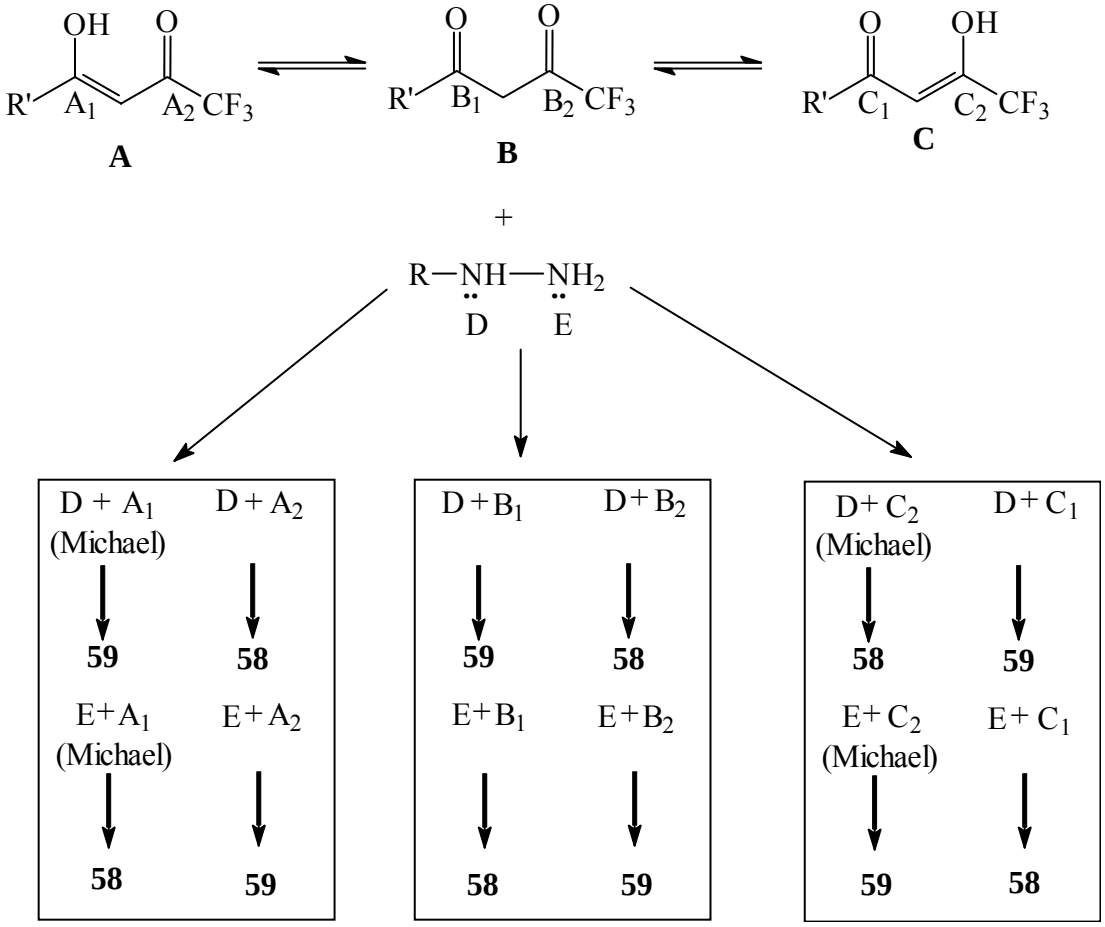


Scheme 22

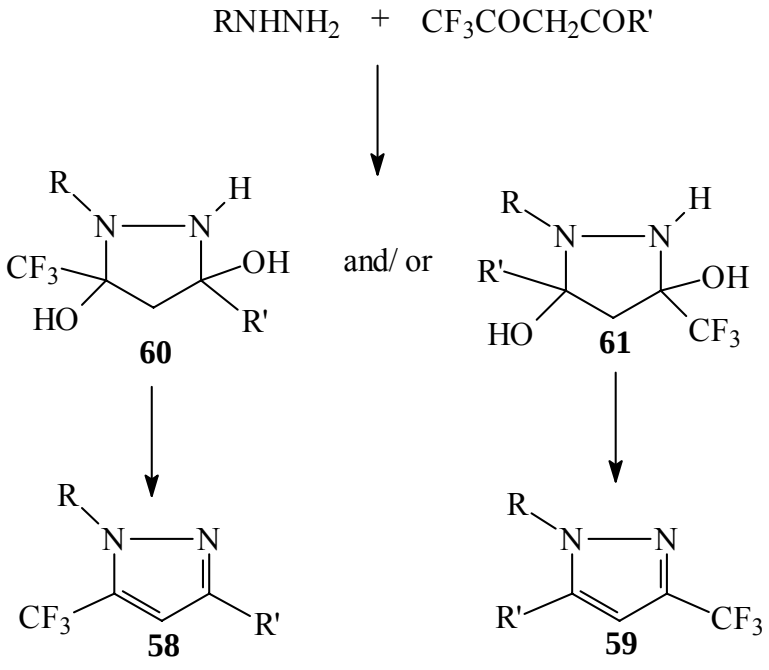
This apparently simple reaction conceals a complex mechanistic problem considering that hydrazines can react initially by the NH (D) or the NH_2 (E). **A** β-diketone has three tautomeric forms (**A**, **B** and **C**) with reactive centers, each isomer can be formed by six different routes (Scheme 23).

The mechanism of such reactions have been studied by several groups of workers,[22,44-47] however, all these publications dealt with the structure of β-diketones on the relative ratio of the isomeric pyrazoles for a given hydrazine. Semi-empirical calculations at PM3 level have been used to rationalize these results. It appears that the orientation in the reaction of hydrazines with β-diketones depends on the nature of substituent in the hydrazine as well. Although the differences in the orientation between alkyl- and arylhydrazines have been assigned to differences in reactivity of both nitrogen atoms (R, NH, D in alkyl and NH_2, E in arylhydrazines), this is certainly not the case of the reactions which have been investigated. All these reactions are initiated by the NH_2. The outcome that emerges seems to be that the difference in the rate of dehydration of the two 3,5-dihydroxypyrazolidines (**60**, **61**) in equilibrium controls the isomer formed (Scheme 24).[42]

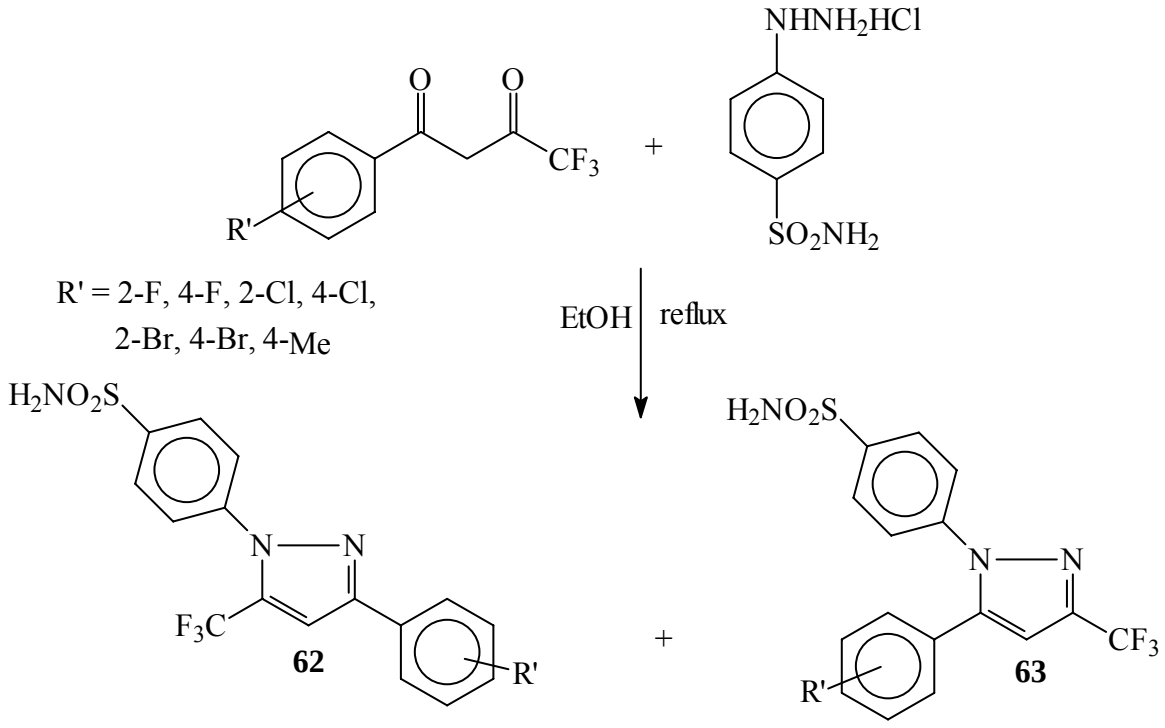
Penning *et al.*[48] have reported the synthesis of a series of selective inhibitors of cyclo-oxygenase-2 (COX-2) by treating 4-amiosulfonylphenylhydrazine hydrochloride with 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione in refluxing ethanol. The reaction provided a mixture of isomeric products (**62** & **63**) (Scheme 25).



Scheme 23

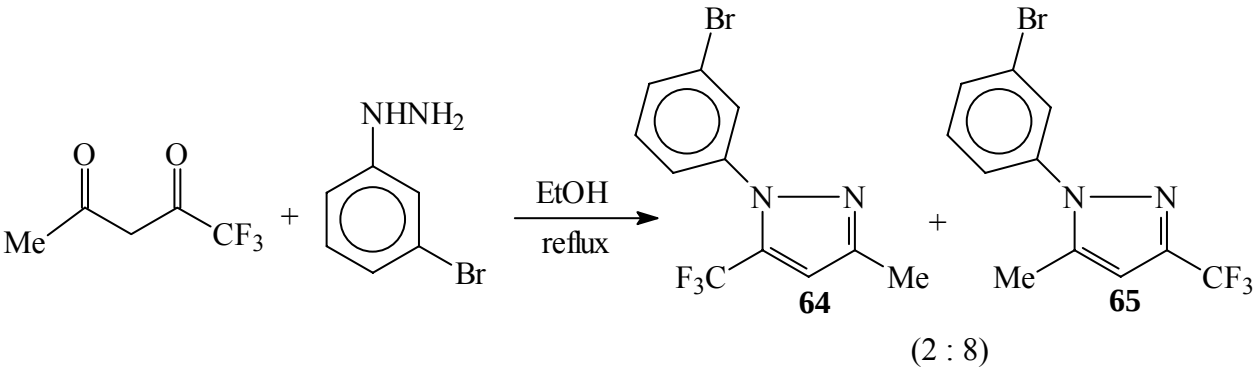


Scheme 24



Scheme 25

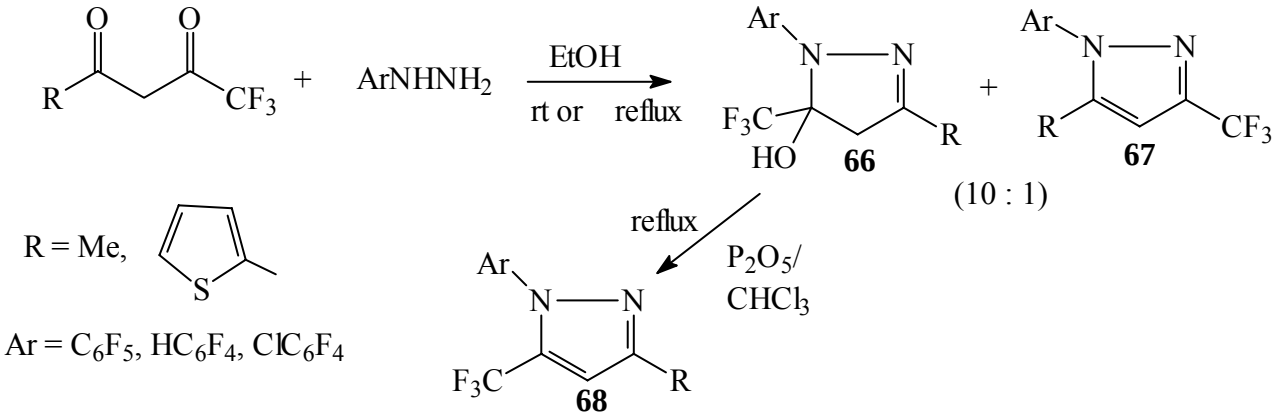
Synthesis of isomeric 3(5)-trifluoromethylpyrazoles (**64** & **65**) (Scheme 26) has been reported by Pinto *et al.*[6] **65** was found to be an intermediate of a highly potent, selective and orally inhibitor of blood coagulation factor Xa.



Scheme 26

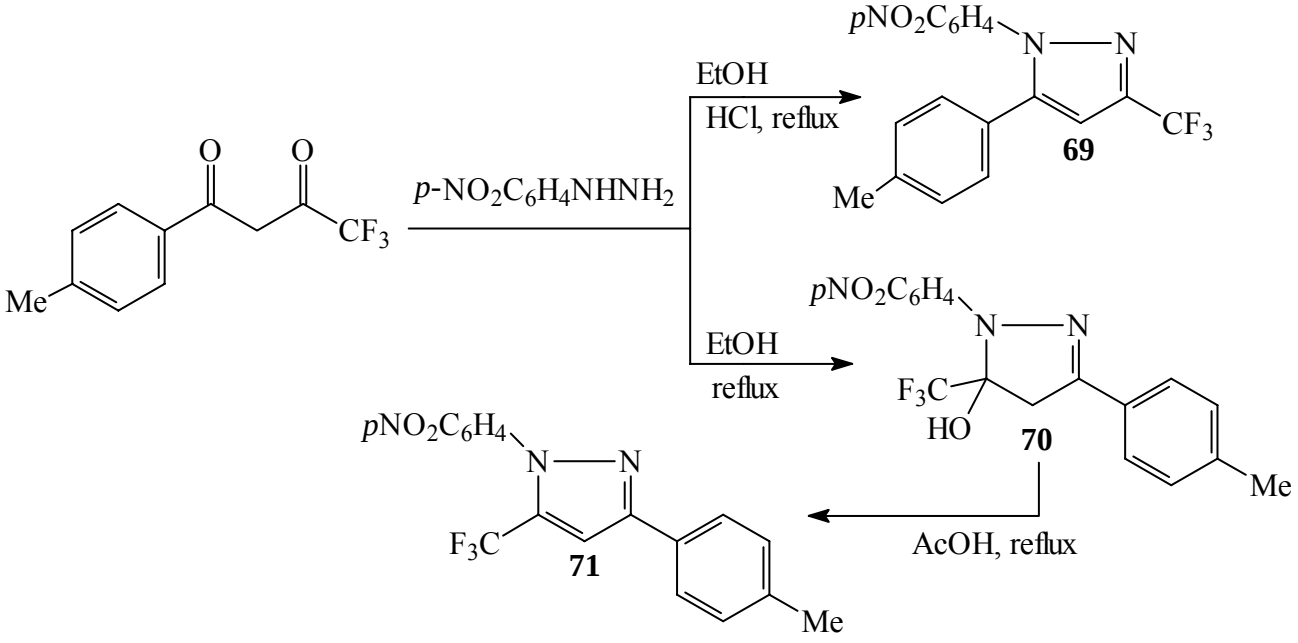
It has been reported that 1,1,1-trifluoropentane-2,4-dione and 1-(2-thienyl)-4,4,4-trifluorobutane-1,3-dione react readily with per(poly)fluorophenylhydrazines to give *N*-per(poly)fluorophenyl-3-methyl(or 2-thienyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazoles (**66**) and *N*-per(poly)fluorophenyl-5-methyl-(or 2-thienyl)-3-trifluoromethylpyrazoles (**67**), respectively.

Treatment of **66** with P_2O_5 yielded the dehydrated product *N*-per(poly)fluorophenyl-3-methyl(or 2-thienyl)-5-trifluoromethylpyrazoles (**68**) in good yield (Scheme 27).[49]



Scheme 27

Reaction of *p*-nitrophenylhydrazine with 4,4,4-trifluoro-1-(4-methylphenyl)-1,3-butanedione in refluxing ethanol containing hydrochloric acid has been reported to generate 3-trifluoromethylpyrazole (**69**) as the exclusive product.[10] However, when the reaction was performed in the absence of acid, 5-hydroxy-5-trifluoromethyl-pyrazoline (**70**) was obtained which underwent ready dehydration to 5-trifluoromethylpyrazole (**71**) on refluxing in acetic acid (Scheme 28).



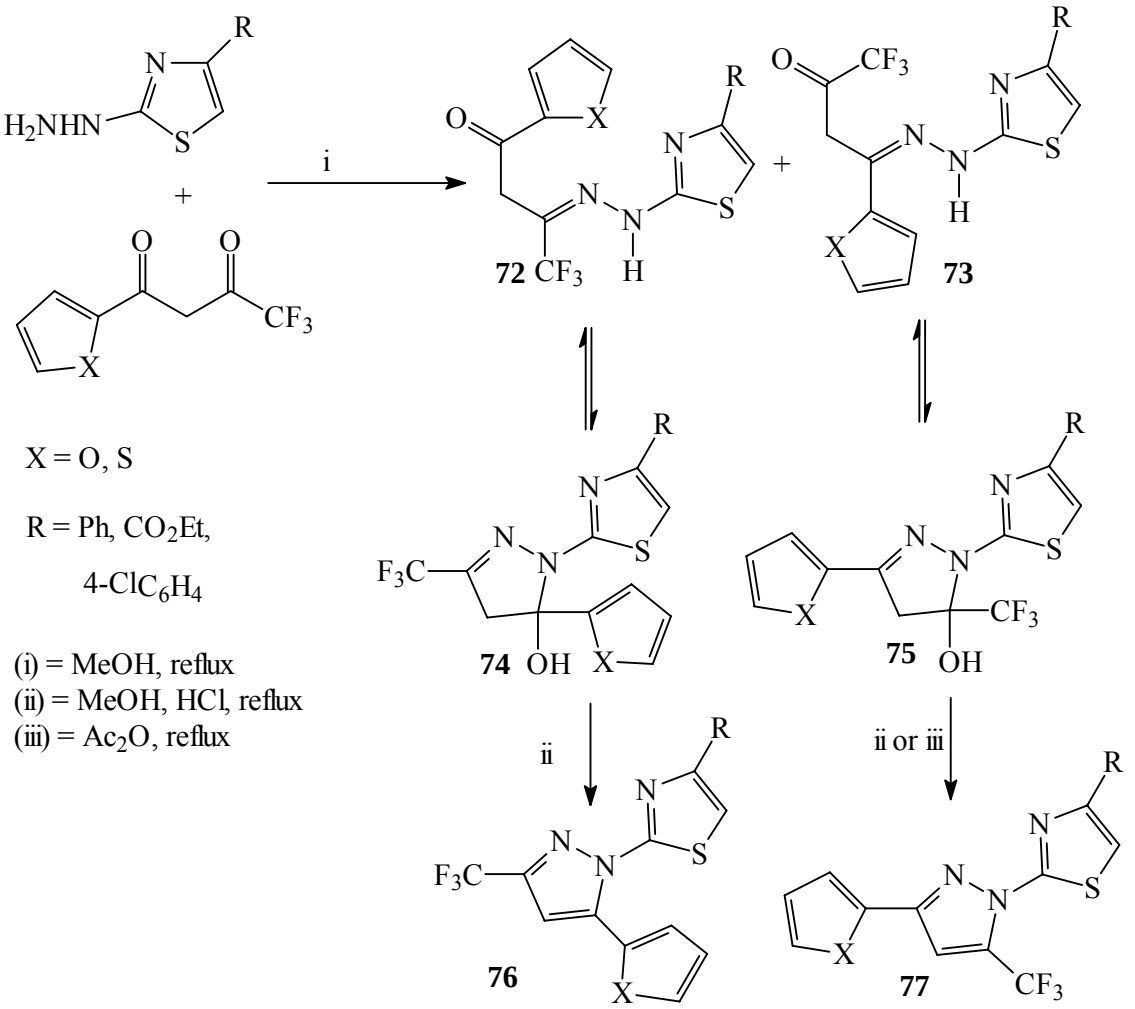
Scheme 28

Recently, Denisova *et al.*[50] have reported that the reaction of 2-hydrazinothiazoles with 4,4,4-trifluoro-1-heteroaryl-1,3-butanediones in methanol/HCl primarily leads to the formation of a mixture of pyrazoles (**76**) and pyrazolines (**75**) or pyrazoles (**76** & **77**) in strong acidic conditions. It was

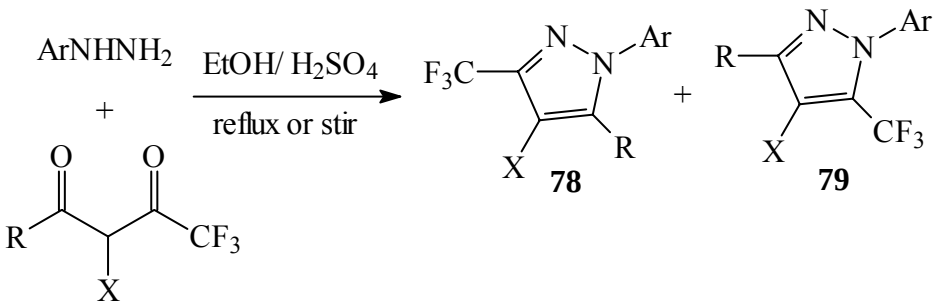
also reported that isomeric hydrazones (**72** & **73**) and pyrazolines (**74** & **75**) could be formed and isolated in these reactions in the absence of hydrochloric acid (Scheme 29).

Sloop *et al.*[51] have reported that the reaction of arylhydrazines with 2-fluorosubstituted-trifluoromethyl-β-diketones always results in the formation of a mixture of isomeric 4-fluoro-3(5)-trifluoromethylpyrazoles (**78** & **79**), while with trifluoromethyl-β-diketones, mixture of 3(5)-trifluoromethylpyrazoles or 3-trifluoromethylpyrazoles (**78**) is formed. The fluorine substituent at position-2 of the β-diketone effects the keto-enol tautomerism in favour of keto form due to which there was direct competition between two carbonyl groups, i. e. $COCF_3$ and COR of β-diketones leading to the formation of a mixture (Scheme 30).

The reaction of 3-cyanophenylhydrazine with 1-(2-furyl)-4,4,4-trifluorobutane-1,3-dione gives 1-(3-cyanophenyl)-3-trifluoromethyl-5-(2-furyl)pyrazole (**80**) in refluxing methanol containing a few drops of acetic acid (Scheme 31).[52]



Scheme 29

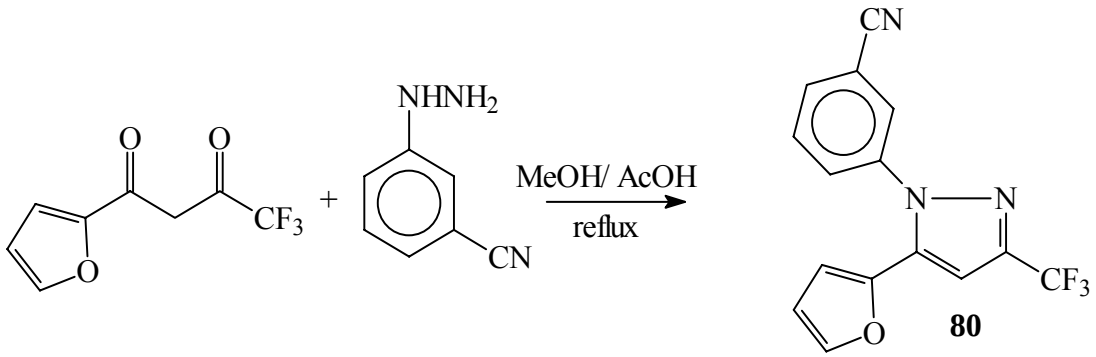


X = H, F

Ar = Ph, *p*MeOPh, *p*NO_2Ph

R = alkyl, aryl, heteroaryl

Scheme 30



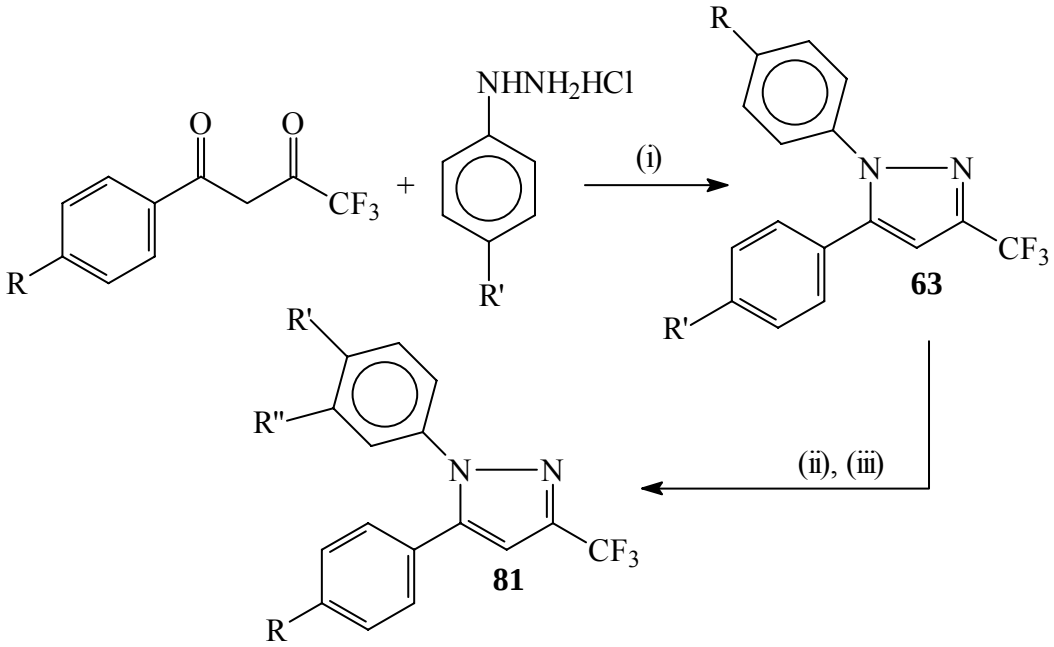
Scheme 31

Uddin *et al.*[53] have synthesized a series of novel 3-trifluoromethylpyrazole analogues (**81**) as selective COX-2 inhibitors by treating several arylsubstituted trifluoromethyl-β-diketones with phenyl or 4-sulphonamidophenylhydrazine hydrochlorides followed by further treatment of **63** with $ClSO_3H$ and NaN_3 **(**Scheme 32). Similar studies have been carried out by other workers.[9,10,54]

Reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones (**83**), obtained by the treatment of acetaldehyde/acetone dimethyl acetal (**82**) with trifluoroacetic anhydride, with hydrazine and methylhydrazine gave corresponding 5-trifluoromethylpyrazoles (**84**). However, treatment with phenylhydrazine provides 5-hydroxy-5-trifluoromethylpyrazolines (**85**) which on subsequent treatment with sulphuric acid afforded **84** (Scheme 33).[55]

Similarly, reaction of 4-methoxy-1,1,1-trifluoro-3-buten-2-ones (**83**) with thiosemicarbazide provided 1-aminothiocarbonyl-5-hydroxy-5-trifluoromethylpyrazolines (**86**) which on subsequent treatment with sulphuric acid afforded cleavage products 5-trifluoromethyl-1-*H*-pyrazoles (**9'**) (Scheme 34).[56]

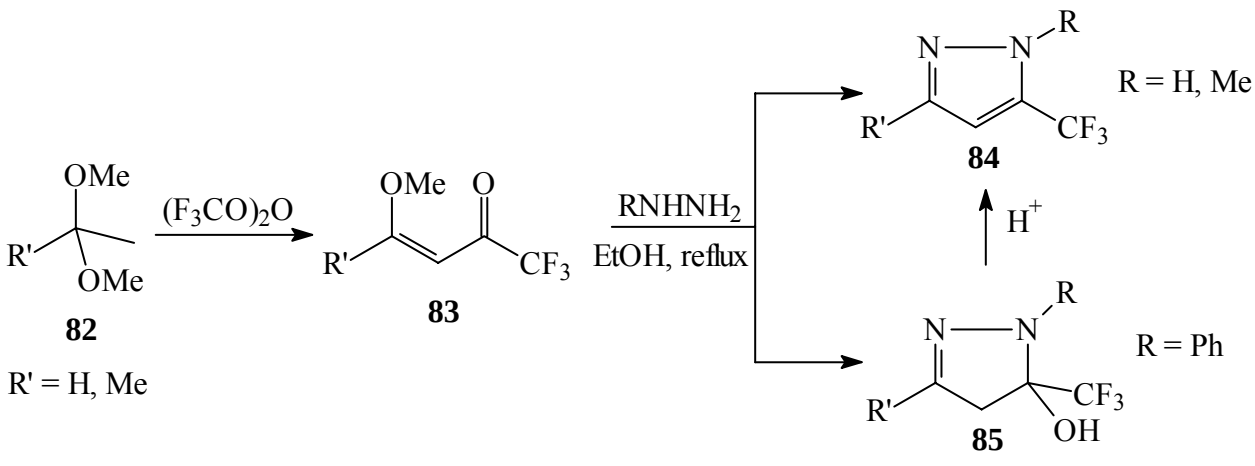
It has been reported that the reaction of 1,1,1-trifluoro-4-methoxy-4-(2-furyl)-buten-2-one (**87**, R = Me, X = O) and 1,1,1-trifluoro-4-methoxy-4-(2-thienyl)-buten-2-one (**87**, R = Me, X = S) with furoic hydrazide, 2-thiophenecarbo hydrazide and 3-pyridinecarbo hydrazide regioselectively provided 5-hydroxy-5-trifluoromethyl-1-heteroaroylpyrazolines (**88**, **89** & **90**), respectively, under mild conditions (Scheme 35).[57]



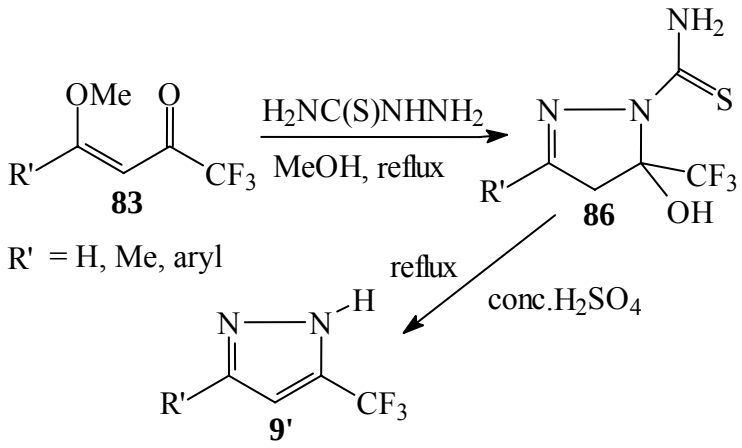
R = F, Cl, Br, Me, OMe; R' = H, SO_2NH_2 ; R'' = SO_2N_3

Reagents and conditions: (i) = EtOH, reflux, 24 h; (ii) = $ClSO_3H$, 25 °C; (iii) = NaN_3, acetone, H_2O, 0 °C, 3 h.

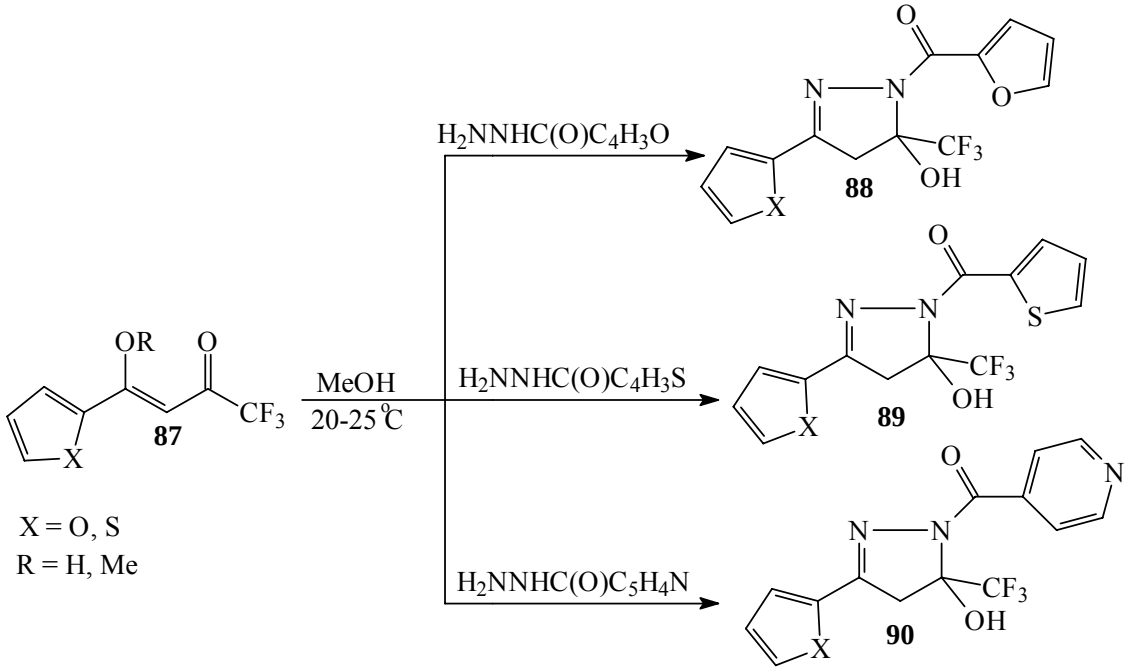
Scheme 32



Scheme 33

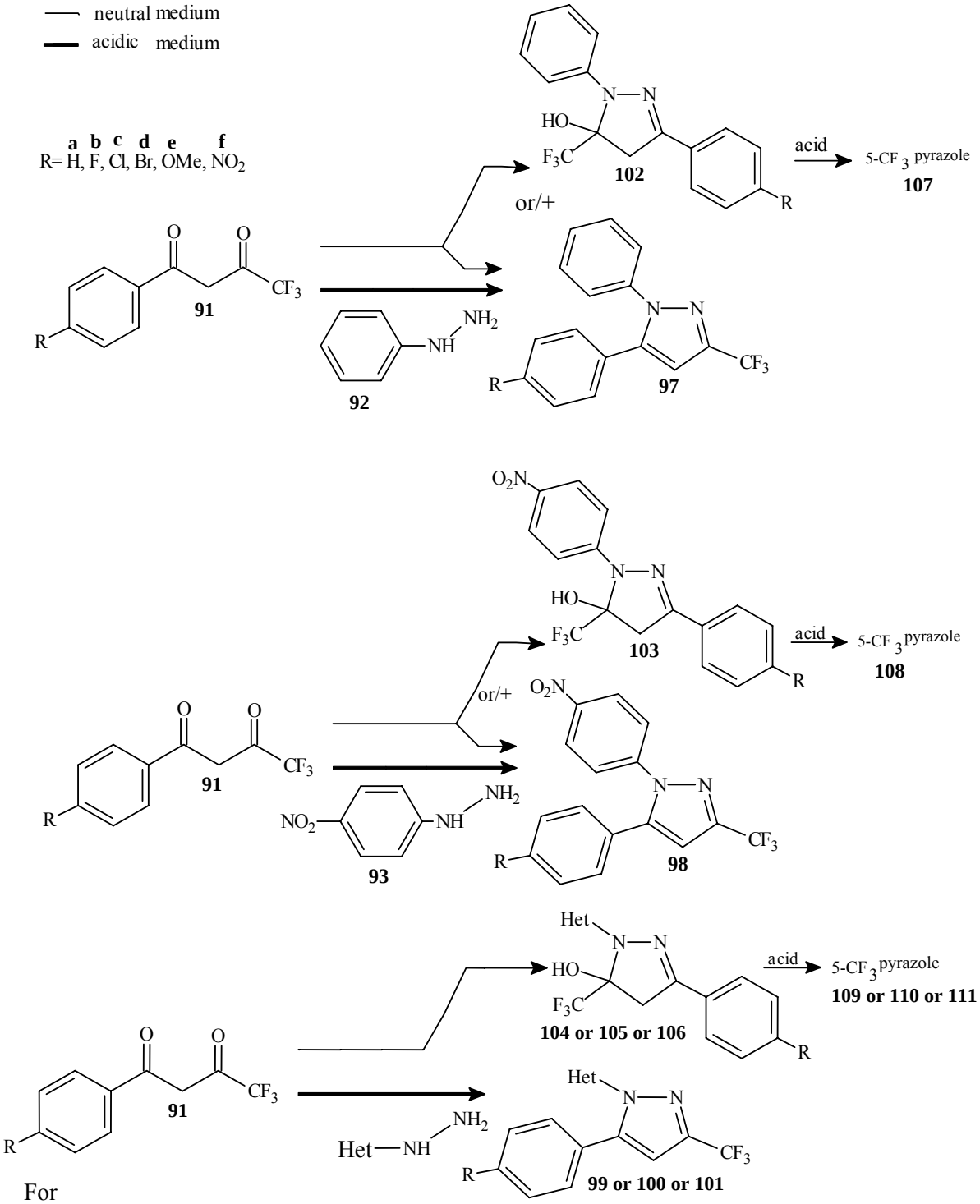


Scheme 34



Scheme 35

Recently, the reaction between a series of 1-aryl-4,4,4-trifluorobutane-1,3-diones **91**, which are differently substituted on the phenyl ring, with five hydrazines: phenylhydrazine **92**, *p*-nitrophenylhydrazine **93**, 6-methylbenzothiazol-2-ylhydrazine **94**, 6-fluorobenzothiazol-2-ylhydrazine **95** and 4-methylquinolin-2-ylhydrazine **96** were studied by us to understand the effect of substituents present on trifluoromethyl-β-diketones and hydrazines on the product composition.[58] The investigation was carried out under two experimental conditions i.e. in neutral and acidic media. It was found that either 3-trifluoromethylpyrazoles and /or 5-hydroxy-5-trifluoromethyl-Δ^2-pyrazolines are generated (Scheme 36).



For
99, 104, 109 ; R= Cl, NO_2 and Het = 6-methylbenzothiazol-2-yl (**94**)

100, 105, 110 ; R= Cl, Br and Het = 6-fluorobenzothiazol-2-yl (**95**)

101, 106, 111 ; R= Cl, Br and Het = 4-methylquinolin-2-yl (**96**)

[**Note:**- A mixture of **101, 106 & 111** is obtained in acidic medium when Het = **96**]

Scheme 36

The conclusions drawn from this investigation are as follow: (**Figure 1**)

i) Vertical or z-axis: on going from neutral to acidic conditions, the proportion of 3-trifluoromethylpyrazoles always increases (if these are not the 100% of the mixture).

ii) Horizontal or y-axis: the more the electron-withdrawing effect of the substituent on the hydrazine (from **92** to **96**), the percentage of 5-hydroxy-5-trifluoromethyl-Δ^2-pyrazolines also increases.

iii) Tilted or x-axis: in case of the presence of an electron-withdrawing substitutent on the phenyl ring of the β-diketones **91**, there is greater proportion of 5-hydroxy-5-trifluoromethyl-Δ^2-pyrazolines.

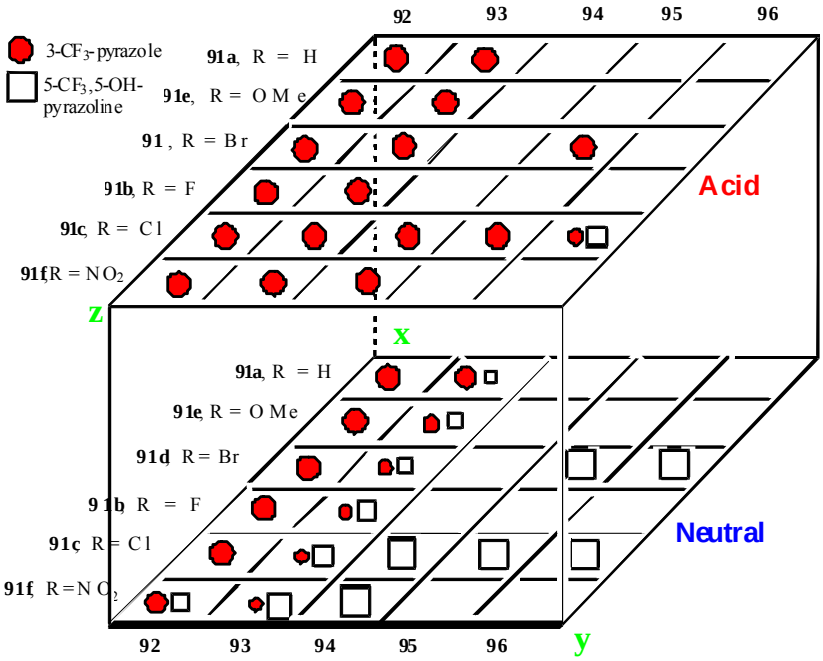
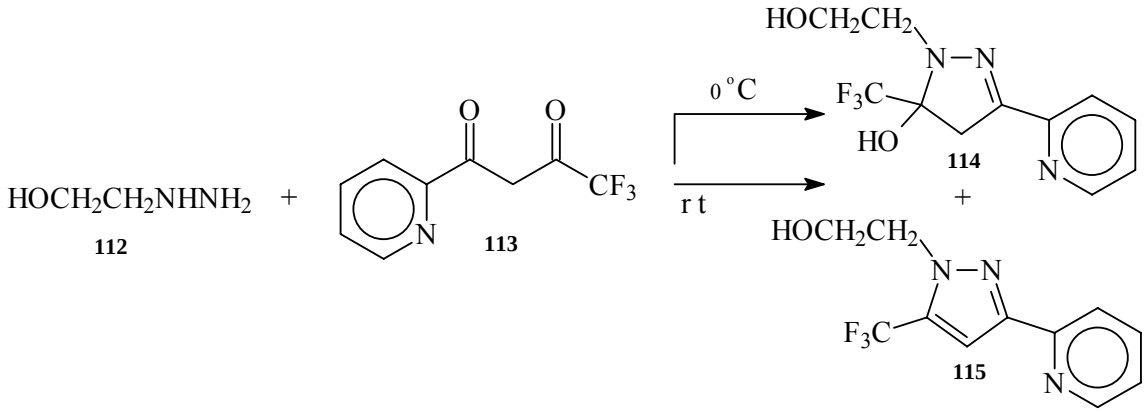


Figure 1. Proportions of the Products in Reaction Mixture Under Neutral and Acid Media: A Three-dimensional View

Recently it has been reported[59] that the reaction of the β-diketone 4,4,4-trifluoro-1-pyridin-2-yl-butane-1,3-dione (**113**) and the monosubstituted hydrazine, 2-hydroxyethylhydrazine (**112**) has been investigated (Scheme 37). Two products have been identified, 2-(2-hydroxyethyl)-3-pyridin-2-yl-5-trifluoromethyl-5-hydroxy-4,5-dihydropyrazole (**114**) and 2-(3-pyridin-2-yl-5-trifluoromethylpyrazol-1-yl)ethanol (**115**) in proportion 2:8, when the reaction was done at rt in ethanol for 15 h. The preparation of **114** as a pure product was performed in ethanol at 0 °C for 7 h. Compound **114** has been characterized by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and by other techniques as appropriate.



Scheme 37

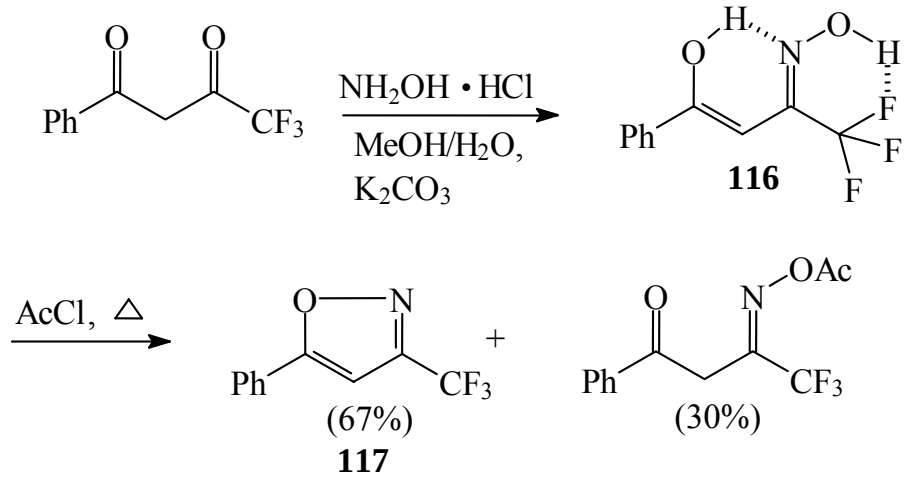
3. REACTION OF TRIFLUOROMETHYL-β-DIKETONES WITH HYDROXYLAMINE

Carr *et al.*[60] have reported that the reaction of 4,4,4-trifluoro-1-phenyl-1,3-butanedione with hydroxylamine hydrochloride in refluxing methanol-water in presence of K_2CO_3 gives monoxime (**116**) of *Z*-stereochemistry. The product is resistance to further reaction with hydroxylamine on the other carbonyl group due to the highly stabilized hydrogen bonded enol form. (*Z*)-stereochemistry to **116** was assigned on the basis of the absence of a carbonyl bond in the IR and the subsequent appearance of a methylene singlet at δ 3.7 ppm in the NMR when DMSO-d_6 was used as solvent. The ring closure of **116** to give 3-trifluoromethyl-5-phenylisoxazole (**117**) was affected by refluxing in acetyl chloride. Acetyl chloride forms an acetylated oxime that can undergo ring closure to the isoxazole along with the formation of another acetylated oxime as side product (Scheme 38). The other regioisomer, 5-trifluoromethyl-3-phenylisoxazole (**119**) was synthesized by 1,3-dipolar addition of benzonitrile oxide (**118**) [generated *in situ* by the reaction of triethylamine on benzhydoxyimioyl chloride, which in turn was obtained by the chlorination of benzaldehyde oxime] to 3,3,3-trifluoropropyne (Scheme 39).

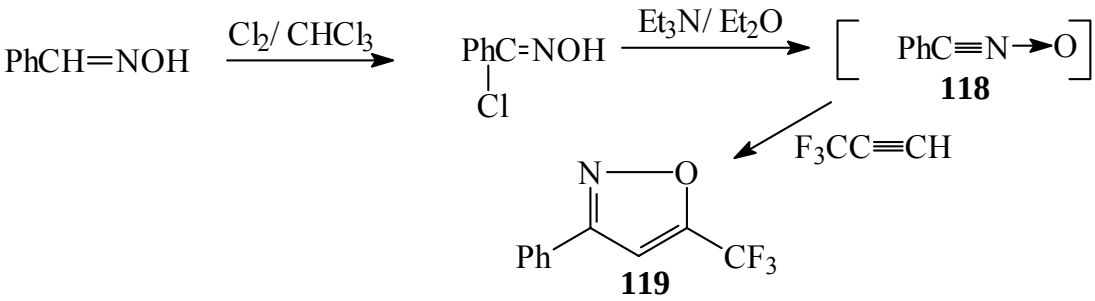
Martins *et al.*[61] have investigated the effect of halomethyl group on the regiochemistry of the reaction of 2-acetylcyclohexanones and β-methoxyvinyl trifluoromethyl ketone derivatives (**120**) with hydroxylamine under different conditions. The reaction affords 3,3*a*,4,5,6,7-hexahydro-3-trifluoromethyl-3-hydroxy[2,1]benzoisoxazoles (**121**) and the dehydrated products (Scheme 40).

It has been observed that when cyclization of 2-acetylcyclohexanone (R' = Me) with hydroxylamine hydrochloride was carried out in the same conditions, a mixture of [2,1]-benzoisoxazoles (**122**) and [1,2]-benzoisoxazoles (**123**) was obtained.

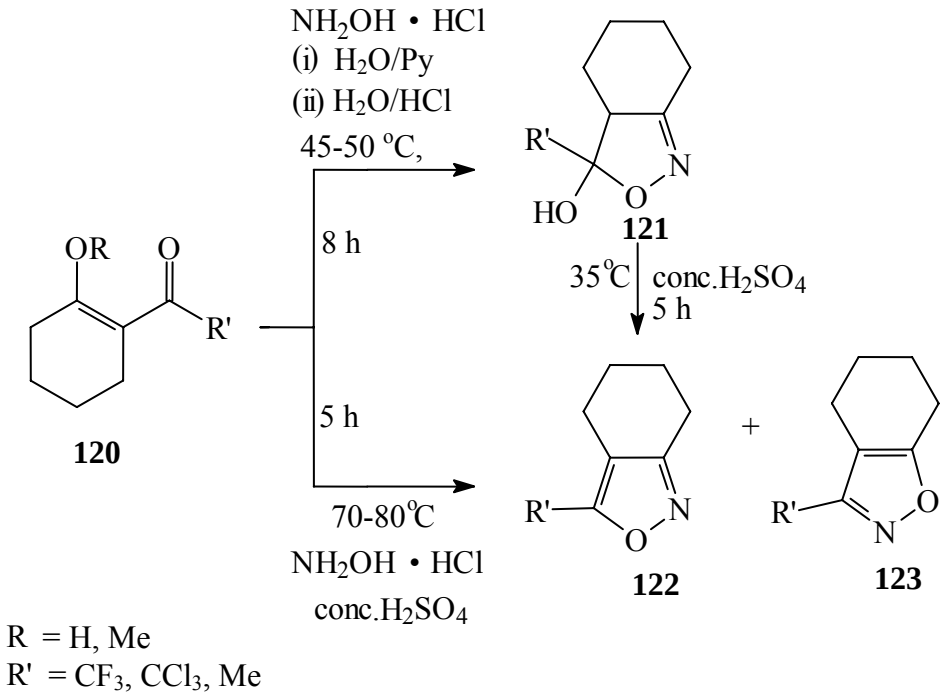
On the other hand, cyclocondensation of 2-acetylcyclopentanones and β-methoxyvinyl trifluoromethyl ketone derivatives (**124**) under acidic conditions gives the other isomer i.e. 4,5-trimethylene-5-hydroxy-4,5-dihydroisoxazoles (**125**). This showed the effect of ring size on the



Scheme 38



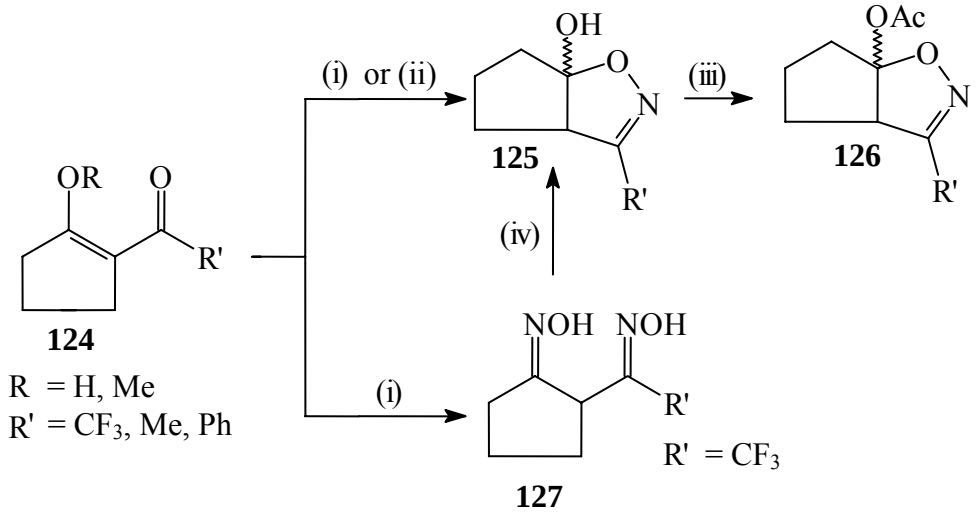
Scheme 39



Scheme 40

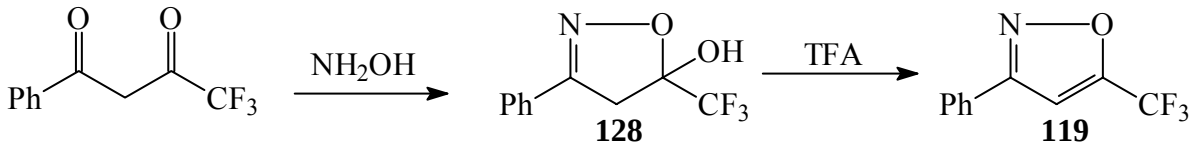
regioselectively of the reactions of **120** and **124** with hydroxylamine hydrochloride. These 5-hydroxyisoxazolines can be acetylated by the treatment of **126** with acetic anhydride. Double oxime (**127**) was obtained on treatment of **124** (R = CF_3) with hydroxylamine in pyridine, which undergoes cyclization on further treatment with HCl (0.1N) to give 5-hydroxy derivatives (**125**) (Scheme 41).[62]

Felix *et al.*[63] have reported that the reaction of 4,4,4-trifluoro-1-phenyl-1,3-butanedione with hydroxylamine generates 5-hydroxy-5-trifluoromethylisoxazoline (**128**) which on subsequent treatment with trifluoroacetic acid affords the 5-trifluoromethylisoxazole (**119**) (Scheme 42).



Reagents and conditions: (i) = NH_2OH HCl/H_2O, Py, 50 °C; (ii) = NH_2OH HCl/H_2O, HCl, 50 °C; (iii) = Ac_2O, CH_2Cl_2, 50 °C; (iv) = HCl 0.1 N, 50 °C.

Scheme 41

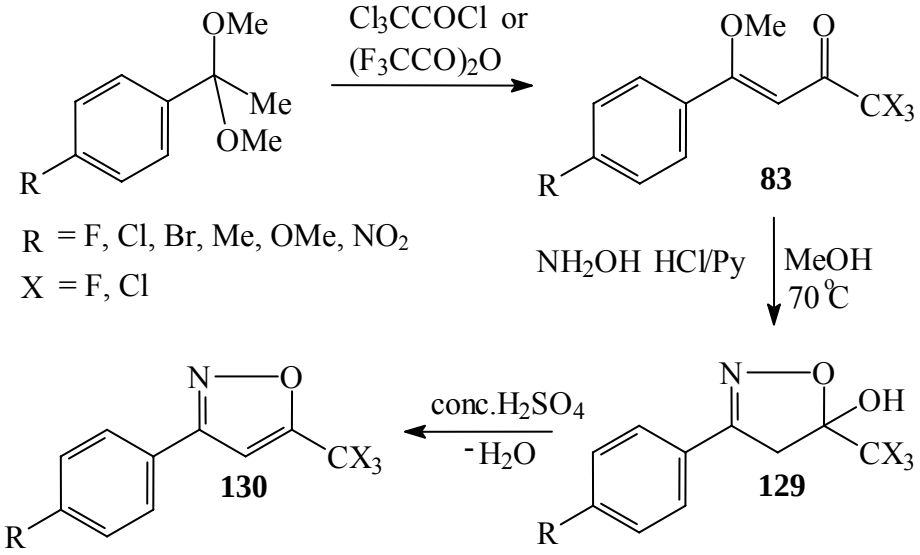


Scheme 42

It has also been reported[64] that β-aryl-β-methoxyvinyl ketones (**83**), obtained from the reaction of the corresponding acetophenone dimethyl acetals with trichloroacetyl chloride or trifluoroacetic anhydride, undergo cyclization with hydroxylamine hydrochloride in refluxing methanol-pyridine to give

3-aryl-5-hydroxy-5-trihalomethylisoxazolines (**129**). As expected isoxazolines (**129**) undergo easy dehydration on treatment with sulphuric acid (Scheme 43).

The reaction of 2-hydroxy-2-polyfluoromethylchroman-4-ones (**131**) with hydroxylamine yields 3-(2-hydroxyaryl)-5-polyfluoromethylisoxazoles (**135**) through the intermediacy of Δ^2-isoxazolines (**134**). Analogous reaction with 2-polyfluoromethylchromones (**132**) affords β-diketone monooximes (**133**), which in acidic medium undergo cyclodehydration to yield 5-(2-hydroxyaryl)-3-polyfluoro methylisoxazoles (**136**) (Scheme 44).[65]



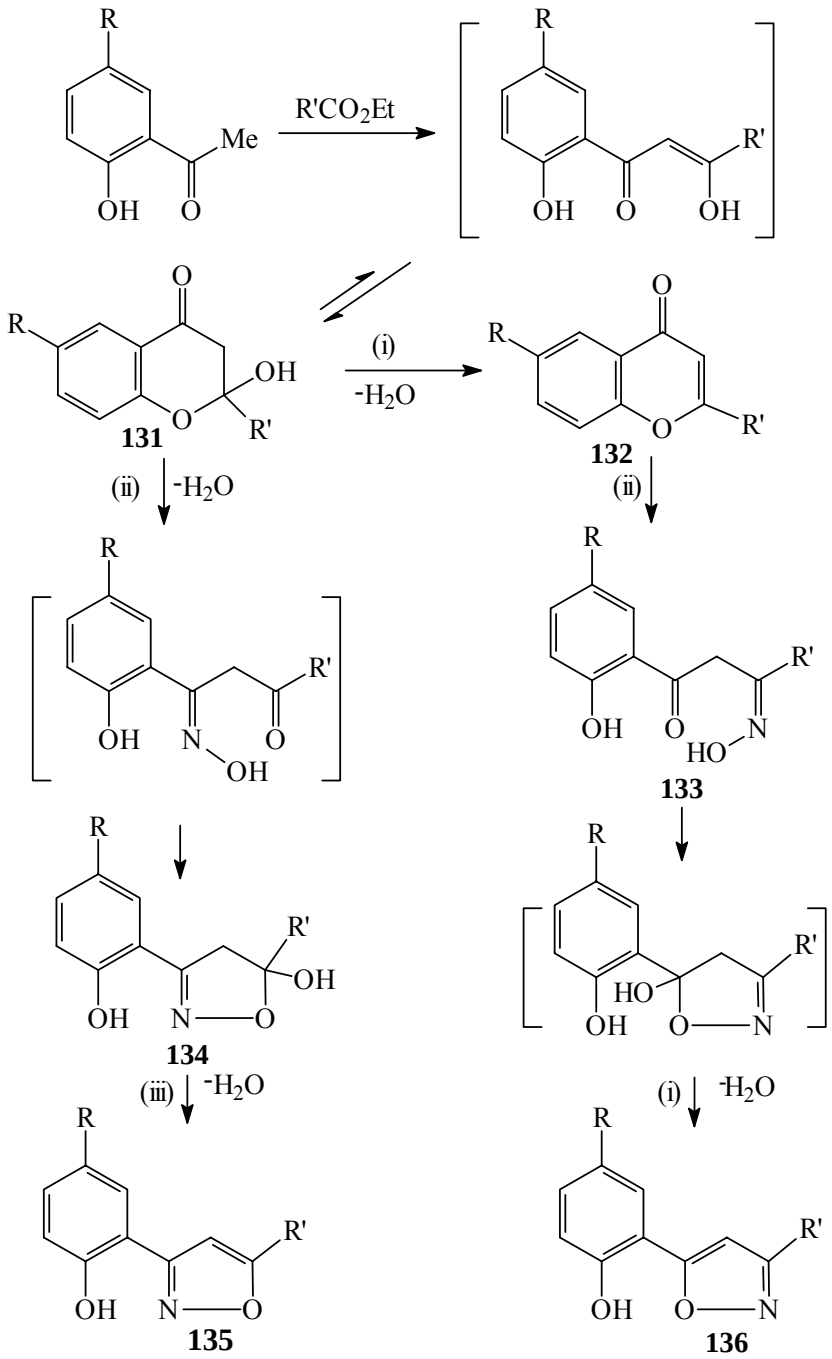
Scheme 43

Sloop *et al.*[51] have reported that the reaction of trifluoromethyl-β-diketones with hydroxylamine in presence of sulphuric acid gives a mixture of 3(5)-trifluoromethylisoxazoles (**137** & **138**) (R = Me) or a single product i.e. 3-trifluoromethylisoxazole (**137**) (R = Ph) depending upon the nature of β-diketones (Scheme 45).

It has recently been reported[14] that 1-phenyl-2-(*p*-fluorophenyldiazo)-4,4,4-trifluorobutane-1,3-dione on treatment with hydroxylamine hydrochloride in presence of sodium acetate affords corresponding 3-trifluoromethylisoxazoles (**139**) (Scheme 46).

In contrast to these finding, we have observed the formation of a single product while reinvestigating the reaction at different pH values with hydroxylamine hydrochloride (Scheme 47). [66, 67] A careful analysis of the NMR data (^{1}H, ^{13}C and ^{19}F) established the formation of 5-hydroxy-5-trifluoromethyl-Δ^2-isoxazolines (**140**) rather than the reported 3-trifluoromethylisoxazoles (**139**).[67] The formation of this product indicates that NH_2 of hydroxylamine attacks on COAr group instead of COCF3 group. The corresponding isoxazole **141** was obtained by the dehydration of **140**. Similar results were obtained when the reactions were carried out between 1-aryl-2-(*p*-fluorophenylazo)-4, 4, 4-trifluorobutane-1,3-diones (**142**) and

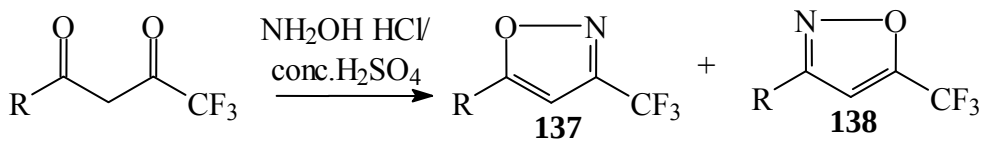
hydroxylamine, only **142** was obtained as an exclusive product, (Scheme 48) instead of the formation of the reported corresponding 3-trifluoromethylisoxazole. The compound **143** on treatment with acid gives the dehydrated product **144**.



R = H, Me; R' = CF_3, CF_2H

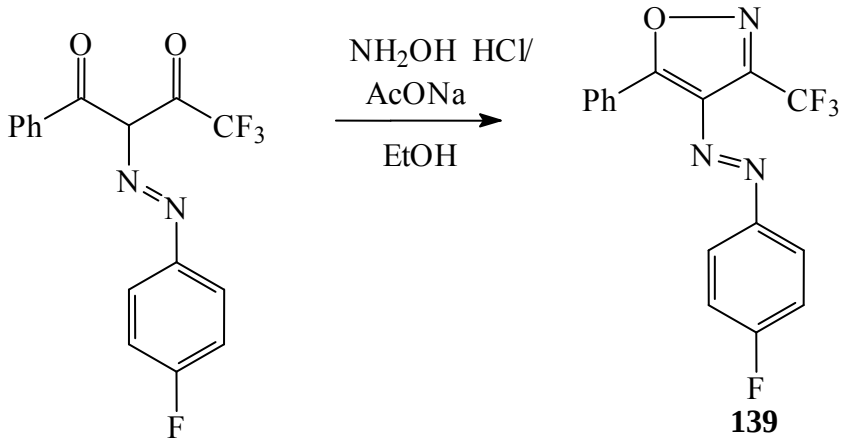
Reagents: (i) = AcOH, HCl; (ii) = NH_2OH HCl, AcONa, EtOH, H_2O; (iii) = $SOCl_2$, PhMe, pyridine

Scheme 44

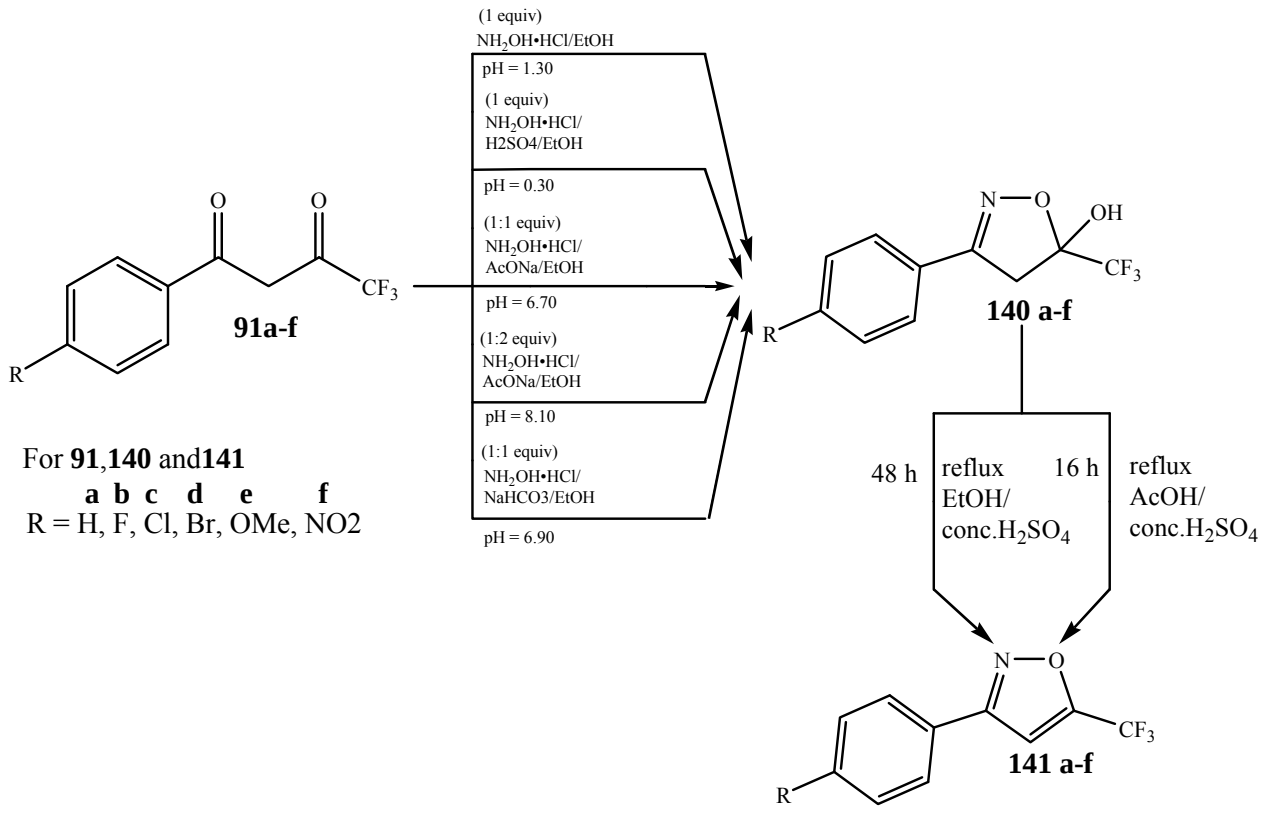


R = Me, CF_3, Ph

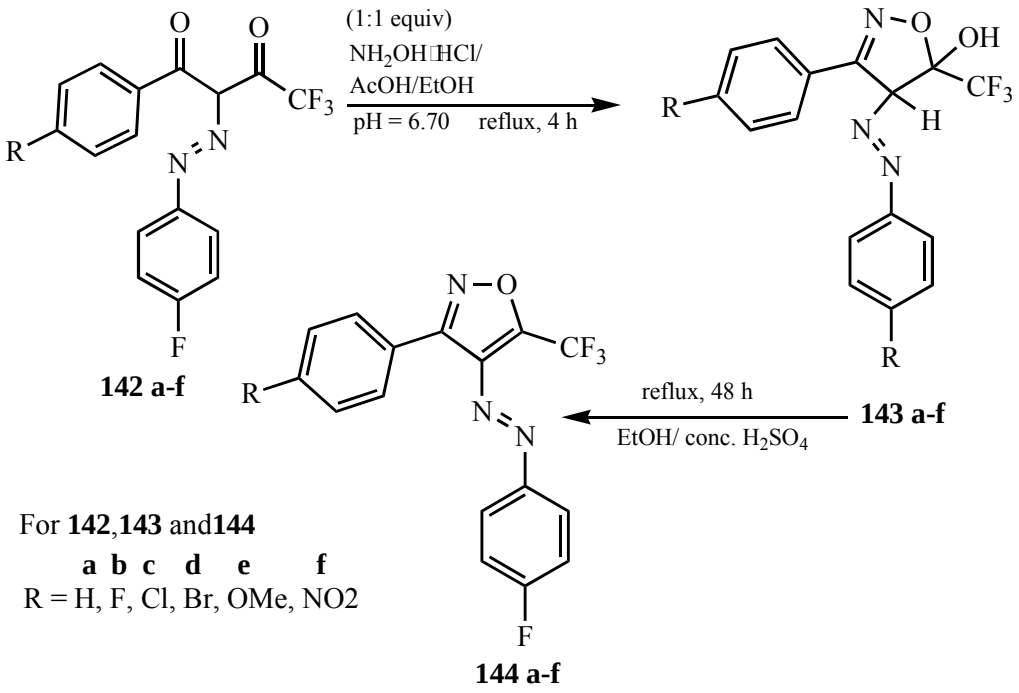
Scheme 45



Scheme 46



Scheme 47

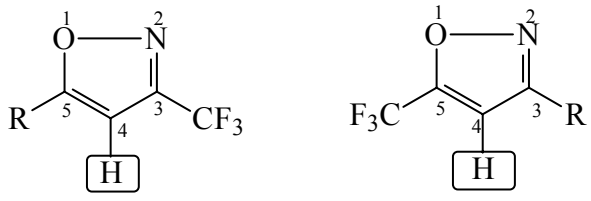


Scheme 48

STEROCHEMICAL ASSIGNMENT OF REGIOISOMERS FOR ISOXAZOLES

^{1}H NMR SPECTROSCOPY

In ^{1}H NMR spectra of isomeric 3(5)-trifluoromethylisoxazoles signal due to 4-H is a key signal for distinguishing the isomeric structures.



R = alkyl, aryl

Table 3. Signal due to 4-H of isoxazoles

CF_3-Position	R	δ (ppm)
3	alkyl	~ 6.4
5	alkyl	~ 6.6
3	aryl	~ 6.7
5	aryl	~ 7.00

As given in **Table 3**, the characteristic signal due to 4-H in ^{1}H NMR spectra of such compounds is expected to appear upfield for 3-trifluoromethylisoxazoles and downfield for 5-trifluoromethylisoxazoles.[68-70]

^{13}C NMR SPECTROSCOPY

Signals due to C-3 and C-5 carbons of isoxazoles bearing trifluoromethyl substituent are sufficient to distinguish the structure of isomeric 3(5)-trifluoromethylisoxazoles. The signals for isoxazole carbons 3, 4 and 5 in 5-trifluoromethylisoxazoles appear at δ ~162 (s), ~102 (s) and at ~159 (q) ppm, respectively[66-68] while in case of 3-trifluoromethylisoxazoles, the signals for C-3, C-4 and C-5 would appear at δ ~152 (q), ~104 (s) and at δ ~162 (s) ppm, respectively.[68,70]

^{19}F NMR SPECTROSCOPY

The ^{19}F NMR spectroscopy is proved to be an elegant tool to distinguish the position of trifluoromethyl group at pyrazole nucleus but ^{19}F NMR is not of much help for distinguishing a pair of isomeric 3(5)-trifluoromethylisoxazoles as the values are very close (δ -64-65 ppm for both the isomers).[69]

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