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STRUCTURAL REVISION IN PYRAZOLE CHEMISTRY

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Abstract – Reaction of several heteroarylhydrazines with β-diketones has been incorrectly reported to generate triazepines or diazepines. It has now been firmly established that these reactions lead to the formation of pyrazoles. Further, many workers have reported the formation of pyrazoles in the reaction of heteroarylhydrazines with trifluoromethyl 1,3-diketones, whereas the actual products were found to be 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles. It was also established that with a trifluoromethyl β-diketone and hydrazines, the location of the CF_3 group at position 3 or 5 of pyrazoles depends on the nature of the hydrazine. Erroneous reports concerning the structure of the products obtained by the reaction of dehydroacetic acid with hydrazines have also been revised.

INTRODUCTION

The growing interest in the pyrazole chemistry lies in designing new synthetic approaches, theoretical calculations and applications of newer spectroscopic techniques. The utility of many pyrazole derivatives in pharmaceuticals, agrochemicals, dyestuff etc. has undoubtedly created considerable attention in developing many different synthetic procedures. The recent developments in the synthetic routes and the chemistry of pyrazoles have been thoroughly reviewed.[1,2] The condensation of β-dicarbonyl compounds with hydrazines continues to be the most widely used method for constructing the pyrazole ring.

A large number of alkyl- and arylhydrazines have been treated with a variety of β-dicarbonyl compounds generating pyrazoles as the exclusive products. In some cases, the intermediate hydrazones, dihydropyrazoles were also isolated which were subsequently dehydrated to the corresponding pyrazoles.

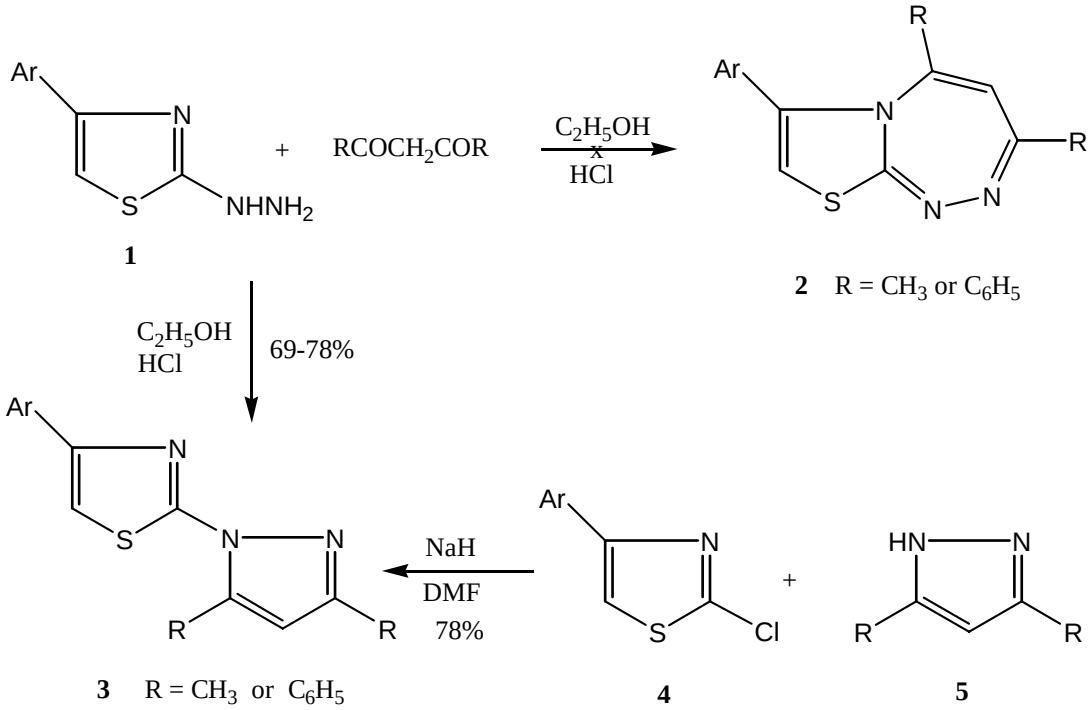
However, when heteroarylhydrazines were treated with β-dicarbonyl compounds (β-diketones, trifluoromethyl β-diketones, β-keto esters, dehydroacetic acid), many workers have assigned a seven - membered structure - triazepine or diazepine - instead of the expected isomeric pyrazole structure. We have reinvestigated such reactions and found that the reports are in error and the products are indeed pyrazoles. In view of these contradictory reports regarding the structure of the products formation, we present herein the present status of such reactions, which will help in eliminating the prevalent confusion in the literature.

RESULTS AND DISCUSSION

REACTION OF HYDRAZINES WITH 1,3-DICARBONYL COMPOUNDS

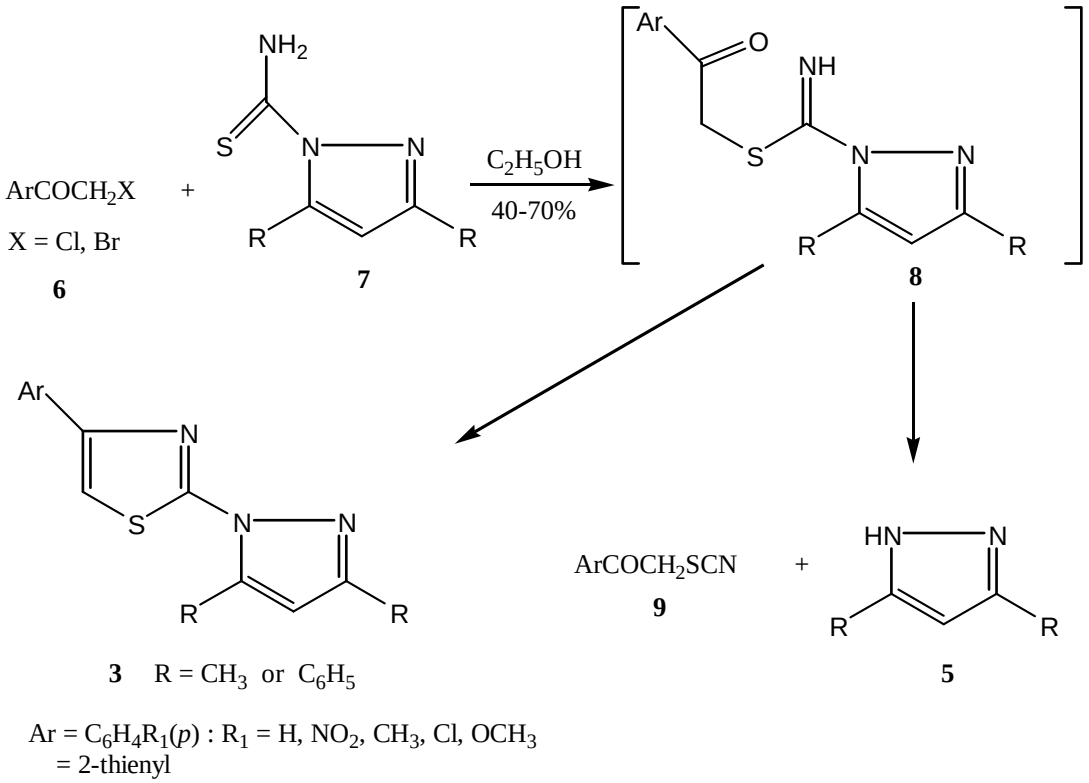
1 REACTION OF HETEROARYLHYDRAZINES WITH β-DIKETONES

1.1 The condensation of 2-hydrazino-4-arylthiazoles (**1**) with pentane-2,4-dione and benzoylacetone had been reported to afford 3-arylthiazolo[2,3-*c*][1,2,4]triazepines (seven - membered ring, triazepines)(**2**).[3,4] We repeated this reaction under similar conditions and also using different experimental conditions. In all these cases, the product obtained was shown to have pyrazole structure (**3**).[5,6] The assignment of **3** was based on unambiguous synthesis involving direct condensation of 2-chloro-4-arylthiazole (**4**) with the sodium salt of NH-pyrazole (**5**) (**Scheme 1**), melting point, mixed melting point, IR and NMR spectral analysis of the final products.



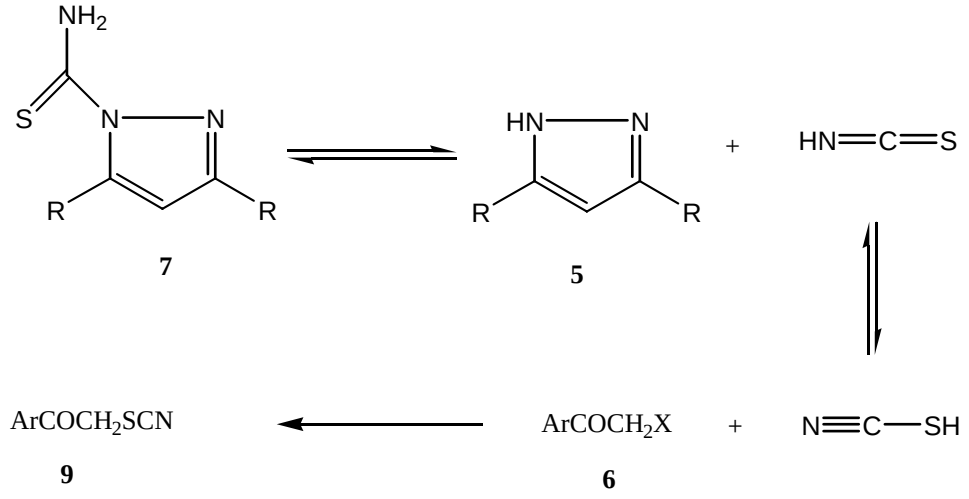
Scheme 1

It is interesting to mention that the reaction of α-halo ketones (**6**) with the pyrazole-1-thiocarboxamide (**7**) (Hantzsch synthesis) also resulted in the formation **3** besides **5** and α-thiocynato ketone (**9**). The formation of **9** was a hitherto unexpected observation (**Scheme 2**).[7] The formation of these products (**3**, **5** and **9**) may be explained through the intermediacy of **8**.



Scheme 2

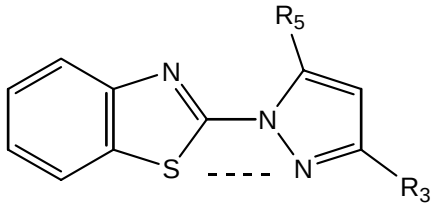
The other mechanism proposed might involve the self-decomposition of **7** (may be assisted by the HX) to produce **5** and HSCN, which further reacts with **6** to produce **9** (**Scheme 3**).



Scheme 3

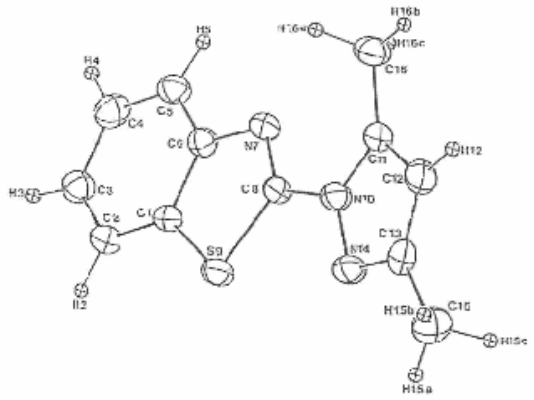
It is important to state that we had already reported the formation of 2-pyrazolylbenzothiazoles when 2-hydrazinobenzothiazole was treated with several β-diketones.[8] Subsequently, we carried out the

synthesis of selective 2-pyrazolylbenzothiazoles (**10**) and performed rigorous NMR (^{1}H and ^{13}C) spectral analysis in order to make unambiguous assignment of the 3- and 5-substituents of the pyrazole moiety.[9] It was established that the methyl group located at position-5 of the pyrazole was somehow deshielded in comparison to the methyl group at position-3. In addition to the methyl groups, H (or $–CH_2$ in a cyclic system), also experienced similar type of deshielding.[10] This observation could be explained on the basis of the repulsion between unshared pair of electrons of two sp^2 hybridized nitrogen atoms, and consequently the molecule adopting somewhat planar geometry where the substituent at position-5 (H, CH_2, CH_3) of the pyrazole moiety may form a very weak bond with the nitrogen of the heterocyclic ring. It may also be considered that the intramolecular nonbonded S…N interactions may influence the planar conformation of **10**.[11,12] Such geometry for the molecules was confirmed by X-Ray crystallography.[13] This study has provided a ready handle to distinguish between isomeric pairs of pyrazoles and eliminating the possibility of formation of triazepines or diazepines.



a, R_3= R_5= CH_3
b, R_3= CH_3, R_5= H
c, R_3= H, R_5= CH_3
d, R_3= R_5= H

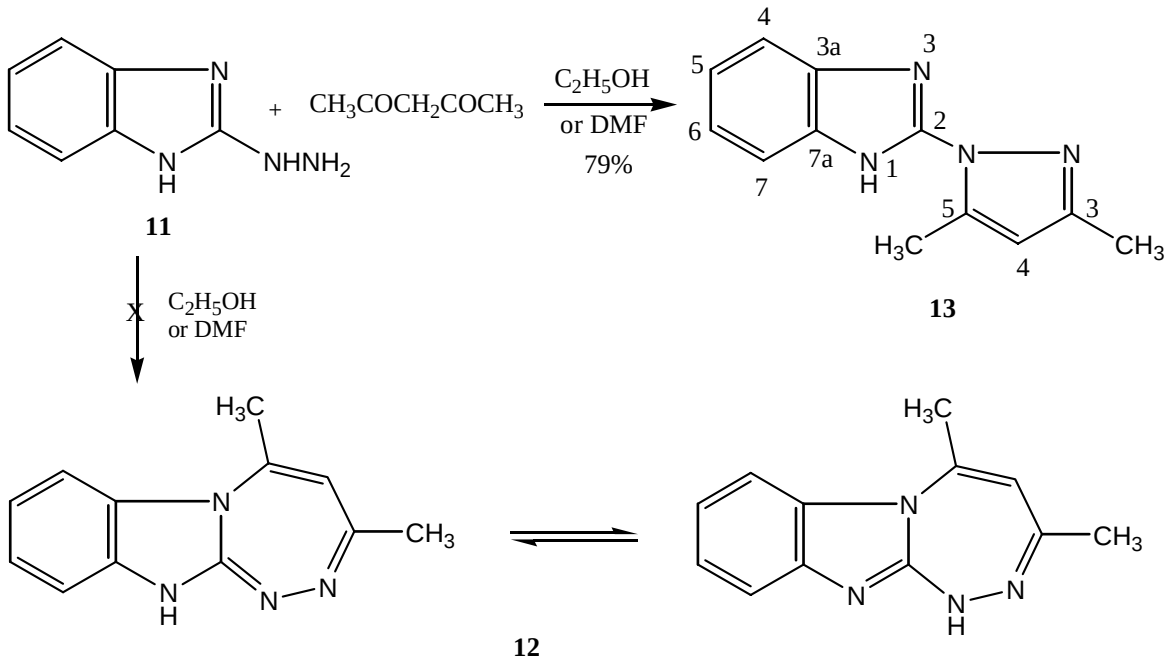
10



ORTEP diagram of 2-(3,5-dimethylpyrazolyl)benzothiazole

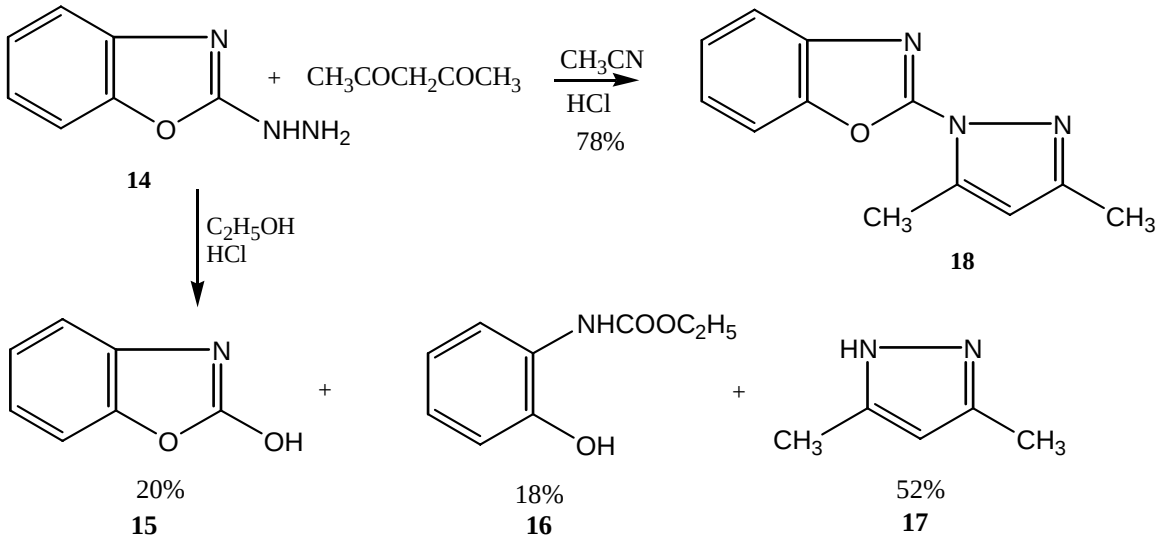
1.2 The prevailing confusion in the literature could be reflected by a simple reaction involving 2-hydrazinobenzimidazole (**11**) and pentane-2,4-dione. In 1985, Glatt *et al.*[14] reported a triazepine structure (**12**) for the product. Joshi *et al.*[15] and Badr *et al.*[16] repeated the work in 1988 and both the groups reported the formation of an isomeric pyrazole structure (**13**) for the reaction product. Interestingly, the NMR spectral data (^{1}H and ^{13}C) provided by these workers for **13** were inconsistent with a pyrazole structure. Badr *et al.*[16] reported that the proton located at C-4 of the pyrazole moiety was merged in the region of the aromatic protons in contrast to its normal position around δ 6.0 ppm.[9] Further, Joshi *et al.*[15] have assigned

the value of 128 ppm for C-4 of the pyrazole moiety, whereas this carbon resonates at about 109 ppm in similarly constituted molecules. We obtained a product which showed all the characteristic signals for a pyrazole structure (**13**) and further established that the mp and NMR (^{1}H and ^{13}C) spectral data reported by earlier workers were in error (**Scheme 4**).[17] Glatt *et al.*[14] reported mp 127-129°C. Joshi *et al.*[15] reported mp >300°C; ^{1}H NMR: δ 2.0 (s, CH_3), 2.4 (s, CH_3), 6.2 (s, 1H), 6.5-7.5 (m, 4H), 9.4 (s, 1H); ^{13}C NMR: δ 12, 110, 117, 119, 120, 128, 131, 140, 145, 149, 154. Badr *et al.*[16] reported mp 175°C; ^{1}H NMR: δ 2.15 (s, CH_3), 2.35 (s, CH_3), 7.15-7.77 (m, 5H). We repeated the synthetic procedure under different conditions as mentioned in articles of the above authors and in each case the product showed the following data clearly indicating the pyrazole structure having mp 135°C; ^{1}H NMR: δ 2.22 (s, 3H, C_3-CH_3), 2.81 (s, 3H, C_5-CH_3), 6.04 (s, 1H), 7.1-7.3 (m, 3H), 7.68 (m, 1H), 11.78 (brs, 1H); ^{13}C NMR: δ 13.42 (C_3-CH_3), 13.72 (C_5-CH_3), 109.36 (C_4, pyrazole), 110.40 (C_7), 119.04 (C_4), 122.20 (C_5), 122.60 (C_6), 132.16 (C_{7a}), 142.44 (C_5, pyrazole), 142.85 (C_{3a}), 146.68 (C_2), 151.39 (C_3, pyrazole).[17]



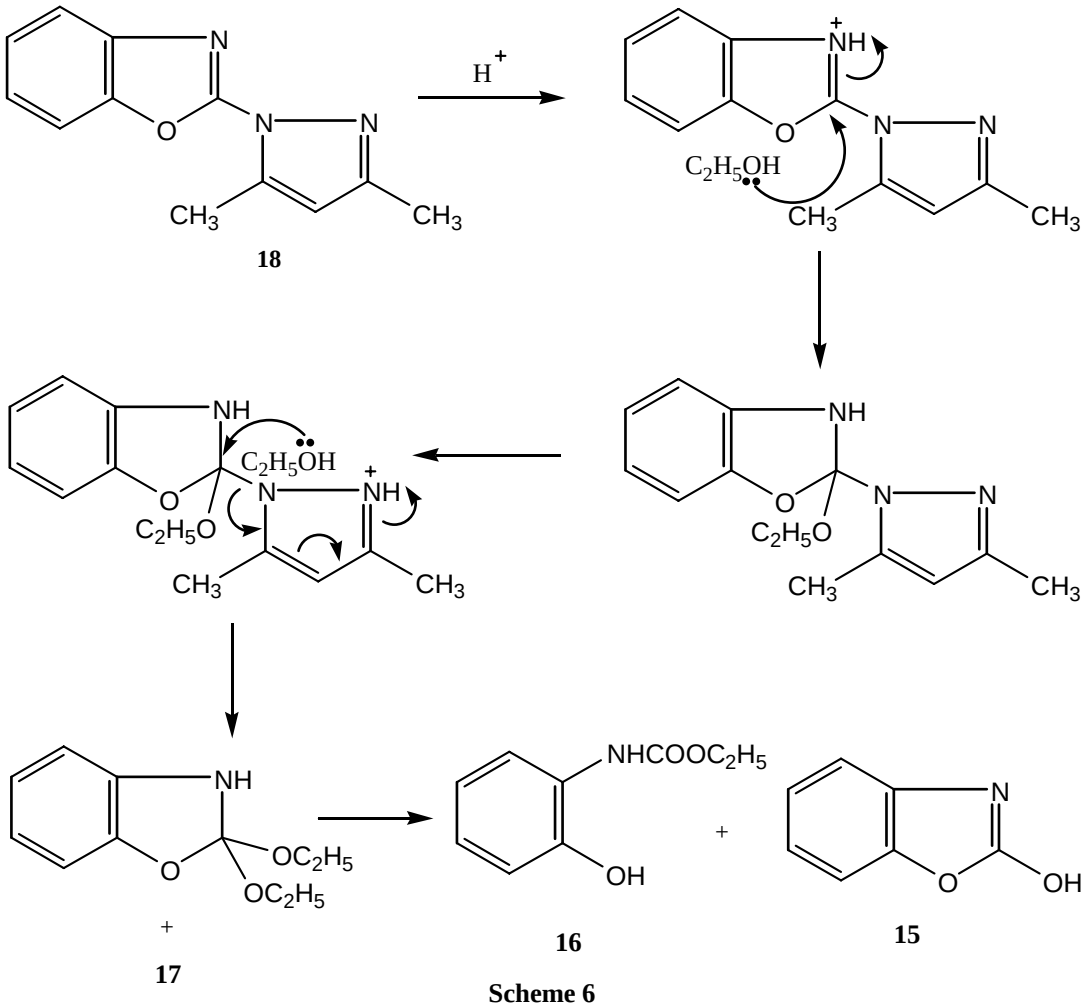
Scheme 4

In order to examine the effect of the nature of the heteroatom, 2-hydrazinobenzoxazole (**14**) was treated with several β-diketones. Surprisingly, the reaction generated a number of unexpected products on refluxing **14** with pentane-2,4-dione in ethanol-hydrochloric acid. The unexpected three products were identified as 2-hydroxybenzoxazole (**15**), N-(2-hydroxyphenyl)ethylcarbamate (**16**) and 3,5-dimethyl-1*H*-pyrazole (**17**) (**Scheme 5**).[18] However, when the reaction of **14** with pentane-2,4-dione was carried out in acetonitrile-hydrochloric acid, there was exclusive formation of 2-(3,5-dimethylpyrazolyl)benzoxazole (**18**). The conformational behaviour of compounds **3**, **13** and **18** were also found to be in consonance with the planarity of 2-(3,5-dimethylpyrazolyl)benzothiazole (**10a**).



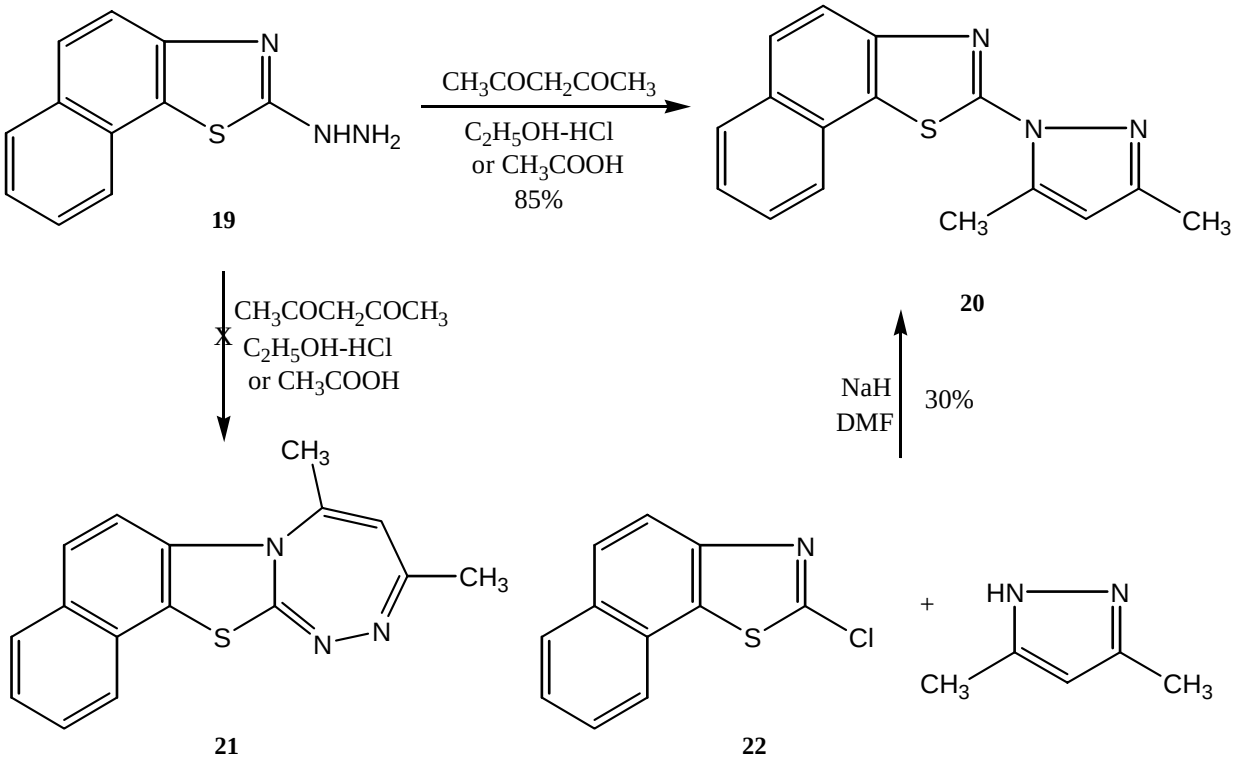
Scheme 5

The formation of these products may be rationalized by assuming the initial formation of **18**, followed by the hydrolytic fission of C-N pivot bond and subsequent ring cleavage. Support for this sequence is provided by the reaction of **18** under similar experimental condition, which resulted in the formation of **15-17** (**Scheme 6**).



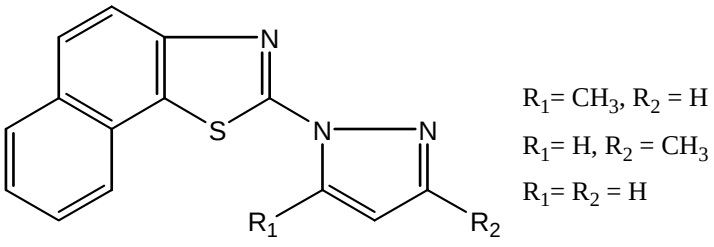
Scheme 6

1.3 We tried the condensation of 2-hydrazinonaphtho[2,1-*d*]thiazole (**19**) with pentane-2,4-dioneand found the formation of 2-(pyrazol-1-yl)naphtho[2,1-*d*]thiazoles (**20**)[19] instead of the erroneously reported naphtho[2',1':4,5]thiazolo[2,3-*c*][1,2,4]triazepines (**21**).[20] The structure assignment of **20** was based on NMR and MS spectral analysis. An unambiguous synthesis of **20** was achieved by the treatment of 2-chloronaphtho[2,1-*d*]thiazole (**22**) with the sodium salt of **17**, where **20** was identical in all respects with the reaction product obtained from **19** and pentane-2,4-dione (**Scheme 7**).



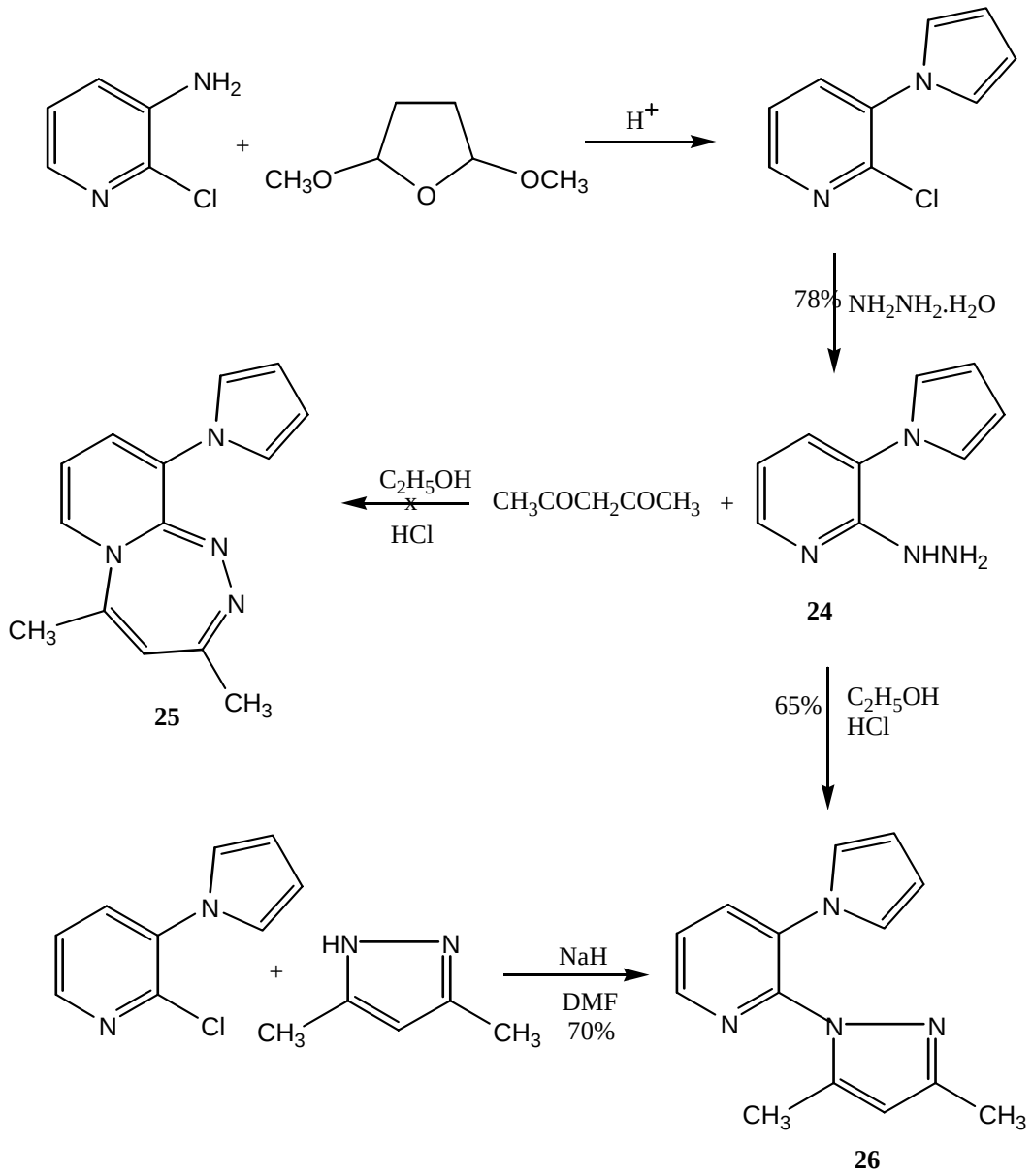
Scheme 7

To generalise the formation of pyrazole derivatives in this reaction, **19** was treated with acetylacetaldehyde dimethyl acetal and malonaldehyde bis(dimethyl acetal) to get compounds (**23**).



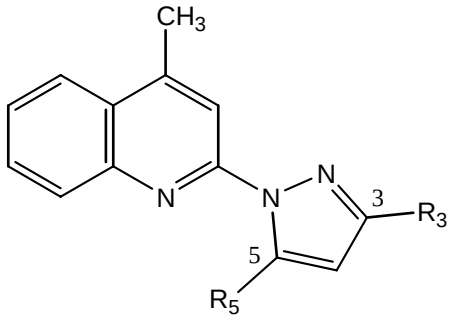
23

1.4 Lancelot *et al.*[21] have reported the synthesis of 2-hydrazino-3-(1*H*-pyrrole)pyridine (**24**), from 3-amino-2-chloro-3-(1*H*-pyrrole)pyridine and hydrazine hydrate, and its subsequent cyclisation with pentane-2,4-dione and formulated a triazepine structure (**25**). Peet and Sunder[22] have reinvestigated this work and a pyrazole structure (**26**) was established on the basis of spectral data as well as an unambiguous synthesis as shown in **Scheme 8**.



Scheme 8

1.5 Surana *et al.*[23] have reported the formation of diazepines in the reaction involving 2-hydrazino-quinolines and β-diketones. This report was shown to be incorrect independently by us[24] as well as Ahluwalia *et al.*[25] To study the conformational behaviour, 2-(pyrazol-1-yl)-4-methylquinolines (**27**) having different substituents at positions 3 and 5, were regioselectively synthesized either using the direct condensation of 2-chloro-4-methylquinoline and sodium salt of 3(5)-substituted pyrazoles or by treatment of 2-hydrazino-4-methylquinoline with appropriate β-keto aldehydes.[26] The preferred conformation of **27** was determined by calculating the heat of formation and torsion angles ϕ within AM1 approximations (**Table 1**).[27] The torsion angle corresponds to the conformations of minimum energy. For 5-unsubstituted derivatives (**27a-27d**) the conformation is almost planar and the lone pairs are in an *anti* position. The introduction of substituents ($CH_3 \rightarrow C_2H_5 \rightarrow i\text{-}C_3H_7 \rightarrow t\text{-}C_4H_9$) at position 5 increases progressively the ϕ value and for the 5-*tert*-butyl substituted derivative (**27i**), the conformation becomes nearly perpendicular.[26]

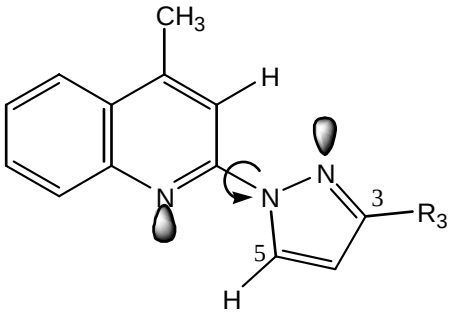


27

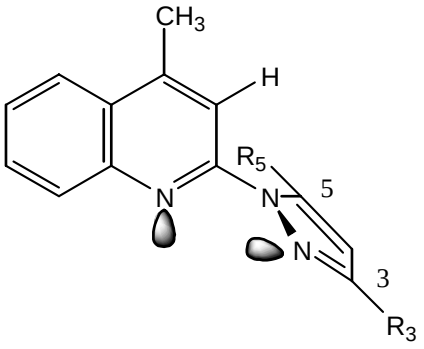
a, $R_3 = R_5 = H$
b, $R_3 = CH_3$, $R_5 = H$
c, $R_3 = C_2H_5$, $R_5 = H$
d, $R_3 = i\text{-}C_3H_7$, $R_5 = H$
e, $R_3 = t\text{-}C_4H_9$, $R_5 = H$
f, $R_3 = H$, $R_5 = CH_3$
g, $R_3 = H$, $R_5 = C_2H_5$
h, $R_3 = H$, $R_5 = i\text{-}C_3H_7$
i, $R_3 = H$, $R_5 = t\text{-}C_4H_9$

Table 1: Result of AM1 calculations

Compound No.	Substituent	ϕ (°)	ΔHf° (kcal mol^{-1})
27a	H	0.4	131.6
27b	3-CH_3	0.5	124.0
27c	3-C_2H_5	0.6	117.9
27d	3-*i*-C_3H_7	0.5	114.2
27e	3-*t*-C_4H_9	0.4	111.7
27f	5-CH_3	24.2	124.9
27g	5-C_2H_5	37.0	120.2
27h	5-*i*-C_3H_7	42.2	116.4
27i	5-*t*-C_4H_9	97.1	117.4

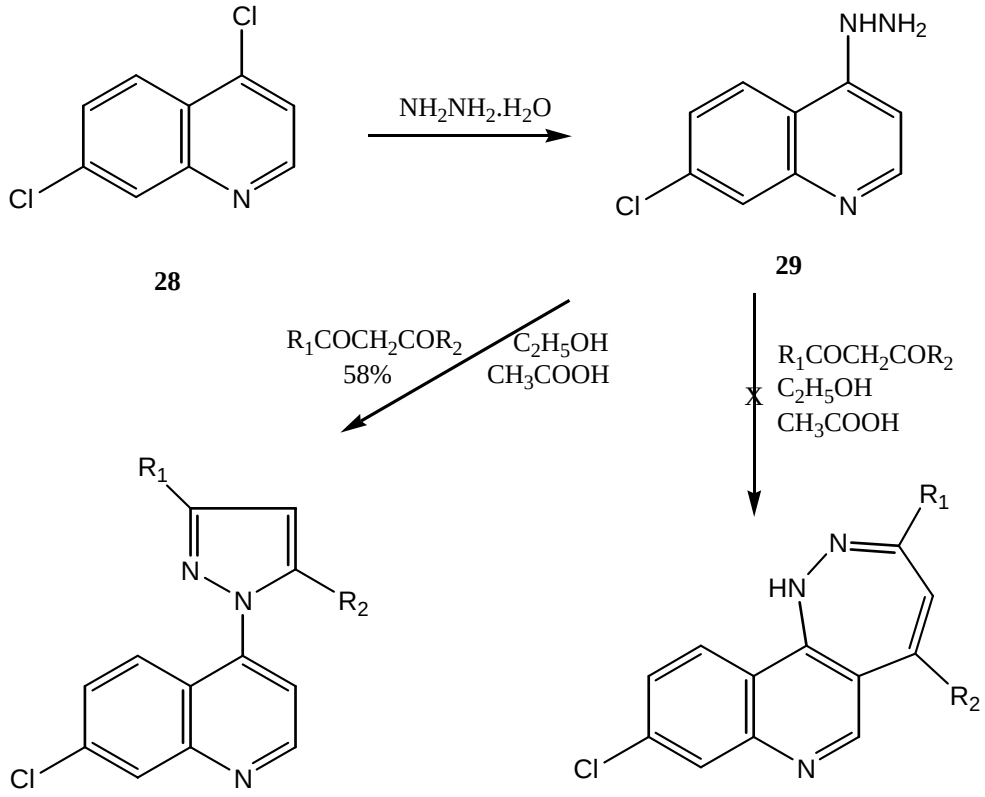


27a-e



27i

Similarly, reaction of the 7-chloro-4-hydrazinoquinolines (**29**), obtained from 4,7-dichloroquinoline (**28**) and hydrazine hydrate, with β-diketones has erroneously been reported to yield a diazepine derivative (**30**).[28] The reaction of **29** with various β-diketones was also repeated and the diazepine structure was revised to the isomeric pyrazole structure (**31**) by us[29] on the basis of ^1H, ^{13}C NMR and MS spectral analysis (**Scheme 9**).

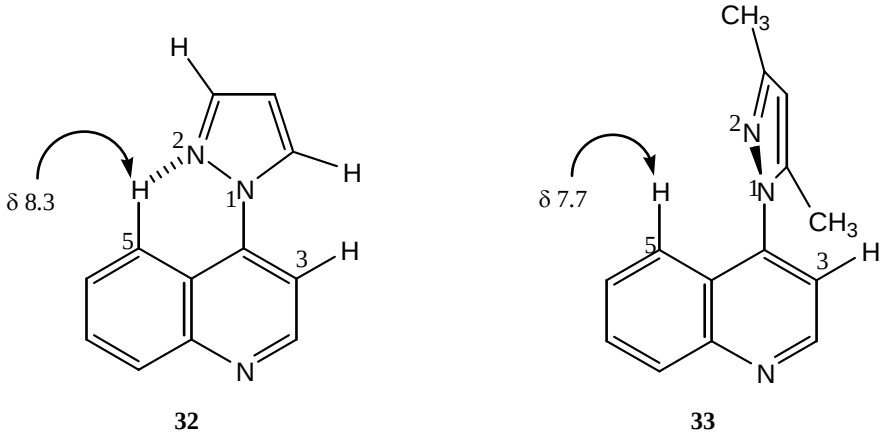


31 $R_1 = R_2 = H$
$R_1 = H,\ R_2 = CH_3$
$R_1 = CH_3,\ R_2 = H$
$R_1 = R_2 = CH_3$
$R_1 = R_2 = C_6H_5$

30 $R_1 = R_2 = CH_3$
$R_1 = R_2 = C_6H_5$

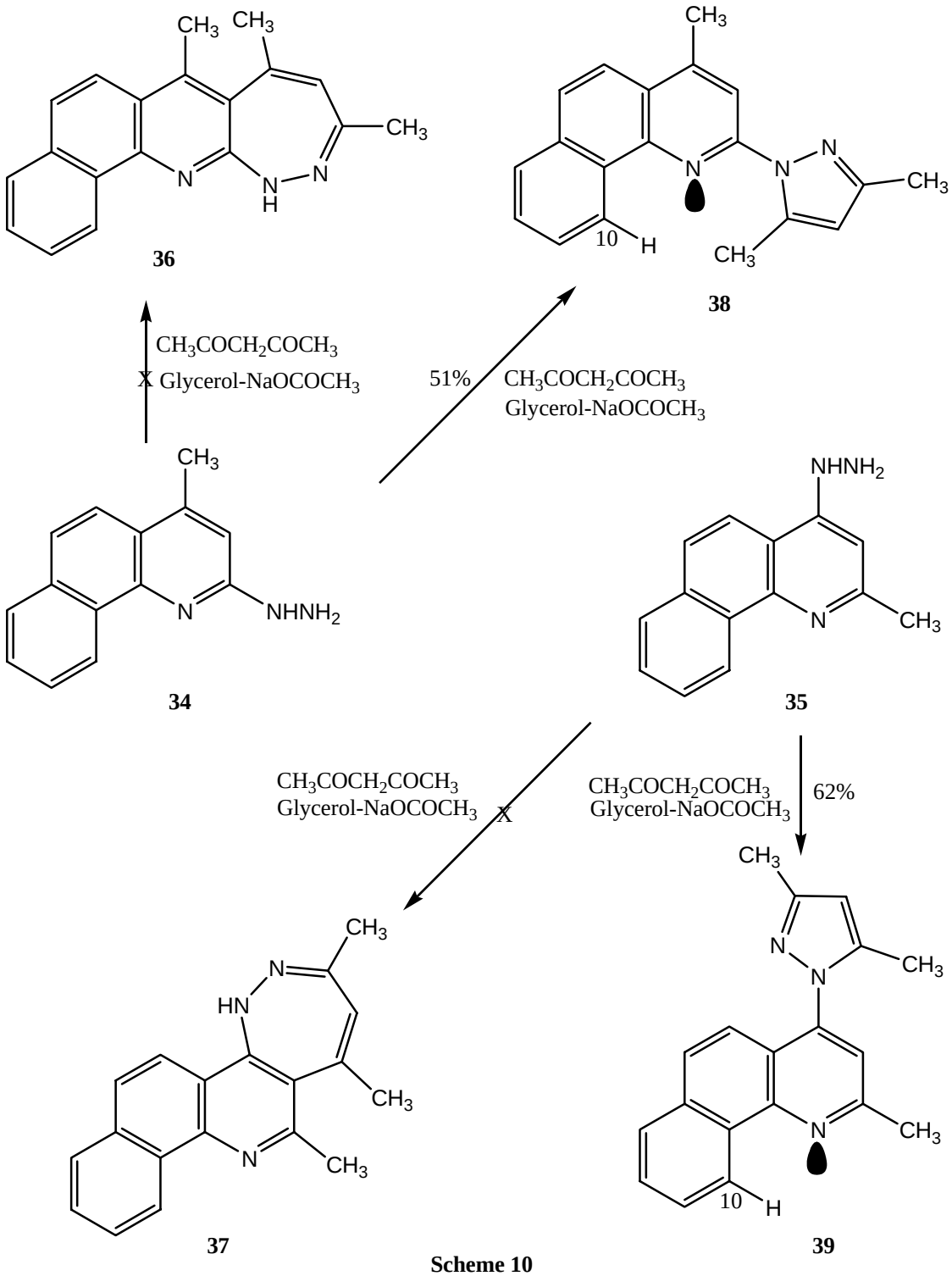
Scheme 9

In the 4-pyrazolylquinolines (**32**, **33**), the quinoline-5 proton is very sensitive in NMR to the presence or absence of a methyl group at the pyrazole 5-position. In **32**, Qu-H_5 resonates at about δ 8.3 ppm, whereas in **33**, this signal shifts to about δ 7.7 ppm. This can be assigned to a conformation where N-2 atom is near Qu-H_5 in **32**. The 5-methyl group due to steric hindrance with Qu-H_3, produces a rotation of both rings around the C-N bond, resulting in an almost perpendicular conformation in **33** thus shifting the signal to δ 7.7 ppm from δ 8.3 ppm.[29]



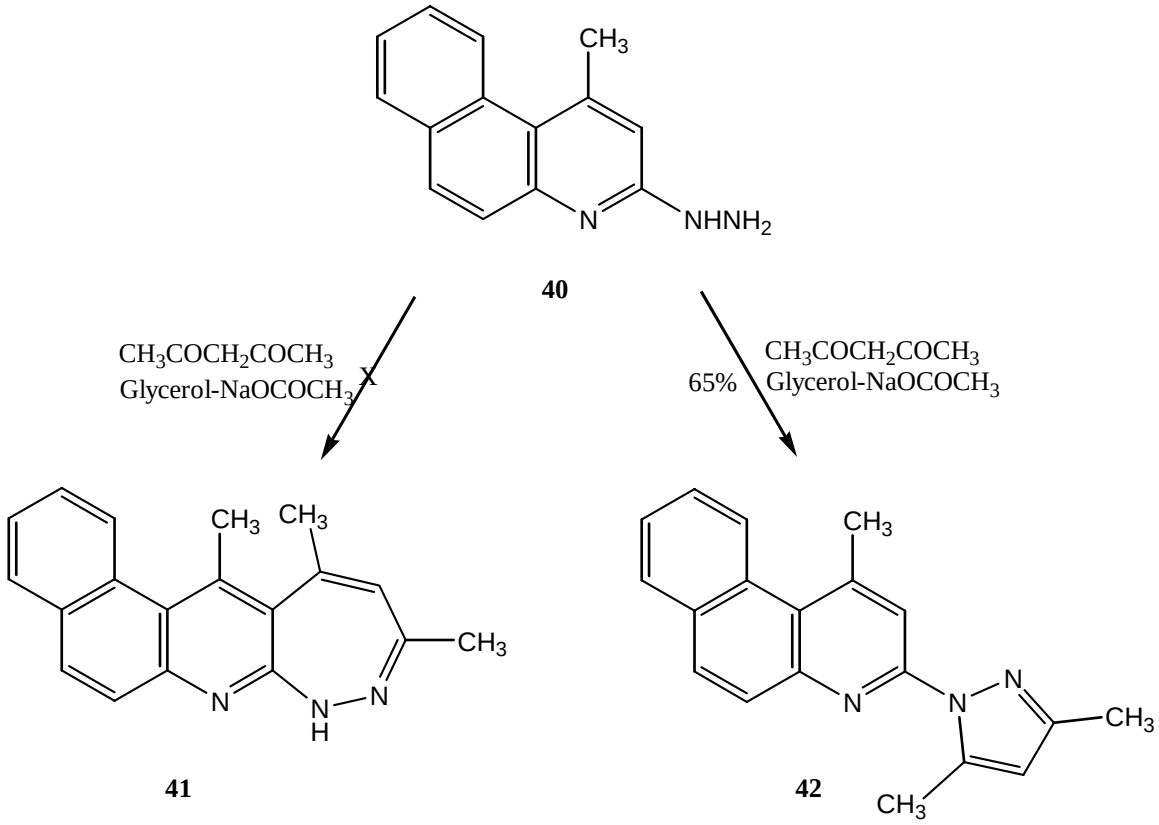
32 **33**

It was also reported by Tyagi and Joshi[30] that the condensation of 2-hydrazino-4-methyl- (**34**) and 4-hydrazino-2-methylbenzo[*h*]quinoloine (**35**) with β-diketones generates diazepines (**36**) and (**37**) respectively. However, in our hands, the products were found to be the isomeric pyrazoles (**38**) and **39**) (**Scheme 10**).[31] It is interesting that the signals in the ^{1}H NMR spectra which were incorrectly ascribed to the NH proton of the 'diazepines' (**36)** and (**37**), were actually due to the C_{10}-H (appeared at δ 9.32 ppm) of the benzo[*h*]quinolines in **38** and **39**.



Scheme 10

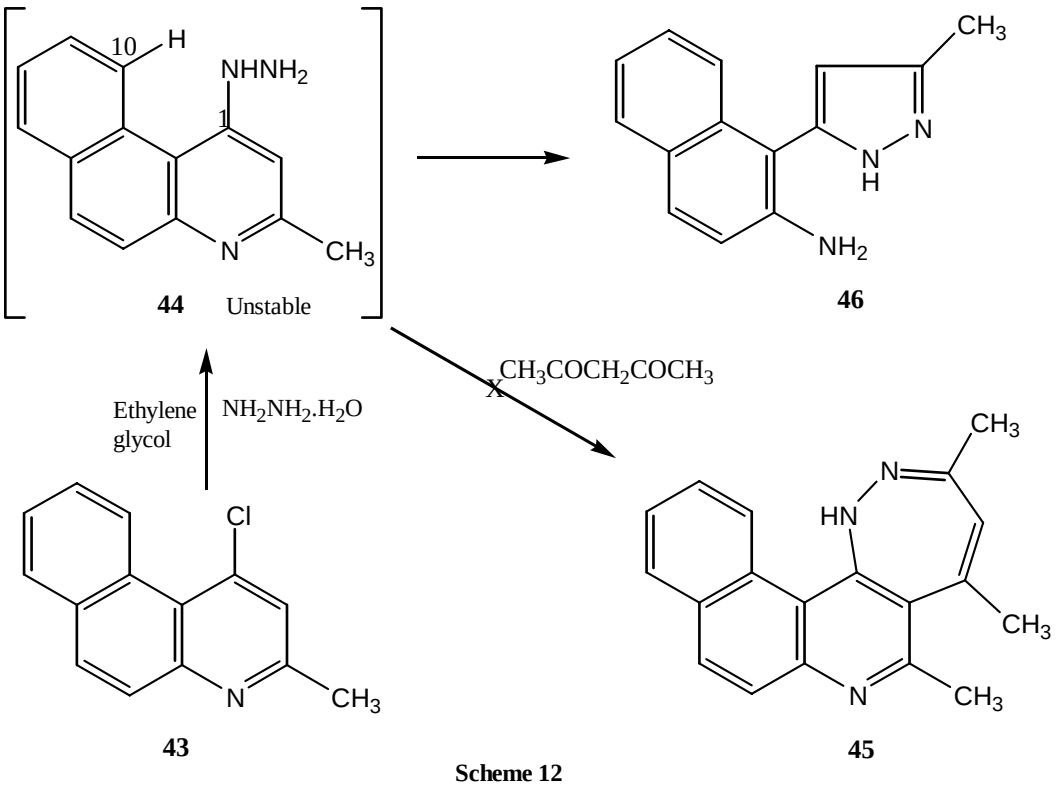
Tyagi and Joshi[30] further reported the formation of diazepine (**41**) by treating 1-methyl-3-hydrazinobenzo[*f*]quinoline (**40**) with pentane-2,4-dione. The work was repeated in our laboratory and it was found that the product is indeed 1-methyl-3-(3,5-dimethyl-1-pyrazolyl)-benzo[*f*]quinoline (**42**) (**Scheme 11**).[31] The structure assignment was based on IR and NMR spectral data of **42**.



Scheme 11

The reported formation of a diazepine derivative (**45**)[30] from 1-hydrazino-3-methylbenzo[*f*]quinoline (**44**) and pentane-2,4-dione did not merit reinvestigation as the structure of **44** itself was shown to be in error by Rees *et al.*[32] The hydrazine (**44**) claimed to have been synthesized by refluxing 1-chloro-3-methylbenzo[*f*]quinoline (**43**) with hydrazine hydrate in glycerol was actually highly unstable for isolation. The reaction, however, generated 5-(2-amino-1-naphthyl)-3-methylpyrazole (**46**) instead of **44** (**Scheme 12**)[32]. The unexpected behaviour of **43** on treatment with hydrazine hydrate may be traced to the greater steric interaction across the 1- and 10-positions in **44**. Therefore, the claim for the formation of **45** was highly arbitrary and ambiguous and the reaction was not considered for revision at all because **44** was not isolable.

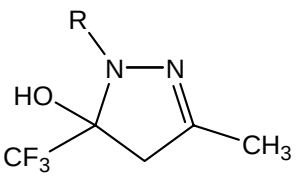
By employing a variety of simple techniques, we had established that the reaction between heteroarylhydrazines and β-diketones invariably leads to the formation of pyrazoles and the reports pertaining to the formation of seven-membered structures are in error.



Scheme 12

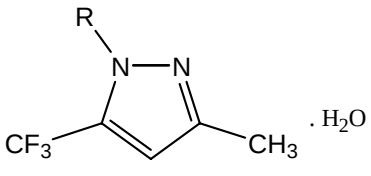
2 REACTION OF ARYL- AND HETEROARYLHYDRAZINES WITH TRIFLUOROMETHYL β-DIKETONES

2.1 During the course of investigation of the structure of pyrazoles, we came across with several literature reports[33-35] claiming to have obtained fluorinated pyrazoles in the reaction of aryl- and heteroarylhydrazines with trifluoromethyl β-diketones. Close scrutiny of the data provided in these reports revealed that the pyrazole structure was assigned on the basis of ^{19}F NMR value of δ –80 ppm. We found that this is a characteristic value for a CF_3 group located on a dihydropyrazole ring at position 5. It thus became evident that these authors have indeed obtained 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles (**47**) instead of the erroneously reported pyrazoles monohydrate (**48**). The structures of the products were reinvestigated by us[36] and Threadgill *et al*.[37] and a dihydropyrazole structure was assigned mainly on the basis of ^{19}F NMR spectral data. It was also observed that presence of a CF_3 group at position 5 of the dihydropyrazole apparently required stronger acid for the dehydration to pyrazole.



dihydropyrazole

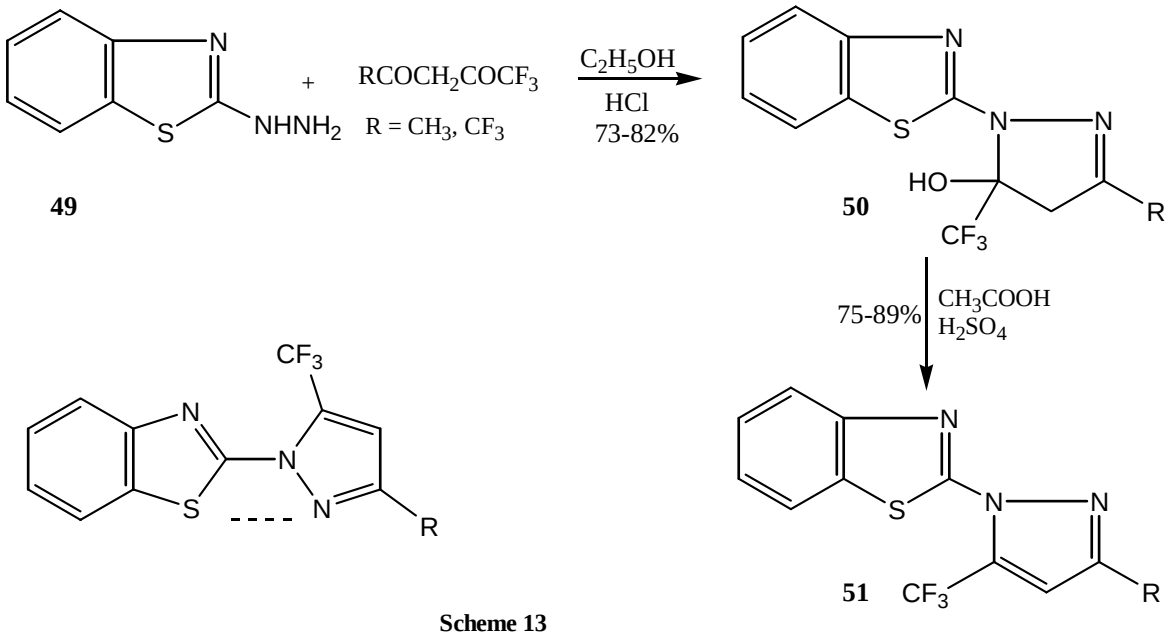
47



pyrazole monohydrate

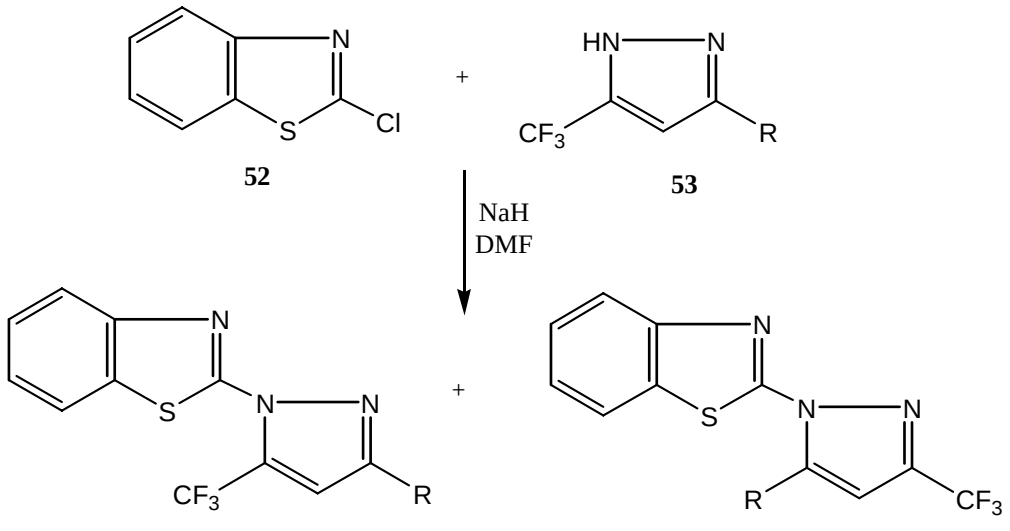
48

2.2 When 2-hydrazinobenzothiazole (**49**) was treated with 1,1,1-trifluoro-2,4-pentanedione and 1,1,1,5,5,5-hexafluoropentane-2,4-dione, there was an exclusive formation of isolable intermediate 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles (**50**) rather than pyrazole monohydrate. The other regioisomer was not formed even in traces. The dihydropyrazoles (**50**) underwent ready dehydration on refluxing in acetic acid-sulphuric acid yielding the corresponding pyrazole (**51**) (**Scheme 13**).[36]



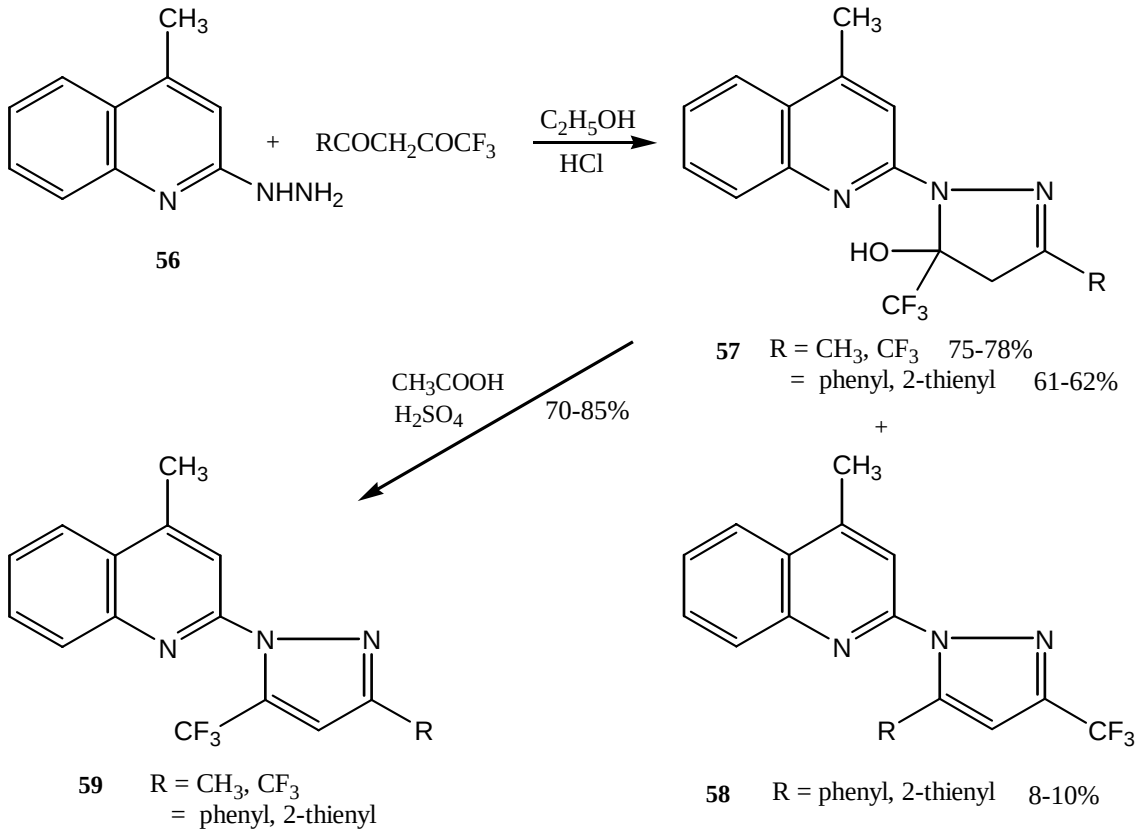
Scheme 13

However, in order to make unambiguous assignments of the presence of trifluoromethyl group in **51**, using NMR spectroscopy, the isomeric fluorinated pyrazoles (**54**, **55**) were synthesized by the condensation between 2-chlorobenzothiazole (**52**) and sodium salt of NH-pyrazole (**53**) (R = CH_3, C_6H_5, 2-thienyl) (**Scheme 14**).[36] The isomeric product obtained in 1:4 (**54**, **55**) ratio were separated by column chromatography and were characterized by NMR spectral analysis.



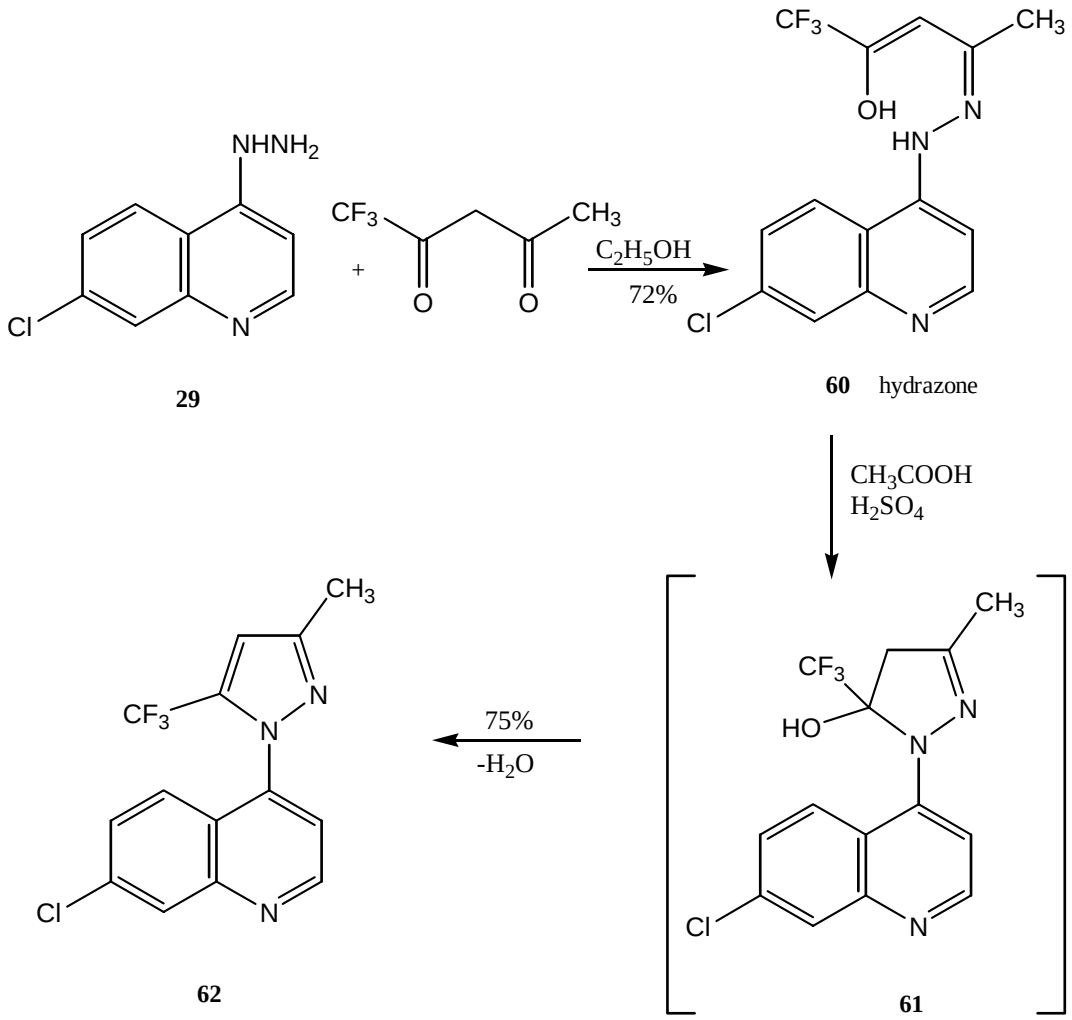
Scheme 14

2.3 The reaction of 2-hydrazino-4-methylquinoline (**56**) with trifluoromethyl β-diketones (R = CH_3, CF_3) was investigated and the sole products were identified as 5-hydroxy-5-trifluoromethyl-1-(4-methylquinolin-2-yl)-4,5-dihydropyrazoles (**57**). However, similar treatment of **56** with trifluoromethyl β-diketones (R = phenyl, 2-thienyl) gave a mixture of **57** and 3-trifluoromethyl-1-(4-methylquinolin-2-yl)pyrazoles (**58**). Dehydration of the **58** was effected with sulphuric acid in acetic acid to give the regioisomeric 3-substitued-1-(4-methylquinolin-2-yl)-5-trifluoromethylpyrazoles (**59**) (**Scheme 15**). The ratio of yields of the two regioisomers depends on the ratio of the two enols at equilibrium. The elimination of water from **57** to form **59** has been shown to be dependent on the electronic nature of the 5-substituent.[38]



Scheme 15

In contrast, the reaction of 7-chloro-4-hydrazinoquinoline (**29**) with 1,1,1-trifluoropentane-2,4-dione afforded for the first time the corresponding stable crystalline hydrazone (**60**), whose structure was firmly established using IR and NMR spectral data.[38] Elimination of water molecule could be effected only by treatment with sulphuric acid in acetic acid to yield 3-methyl-5-trifluoromethyl-1-(quinolin-4-yl)pyrazole (**62**). There was no evidence of formation of other regioisomer. We were unable to isolate the corresponding hydroxydihydropyrazole (**61**) although 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 (**Scheme 16**). It was indeed an unusual observation for such reactions.[38]

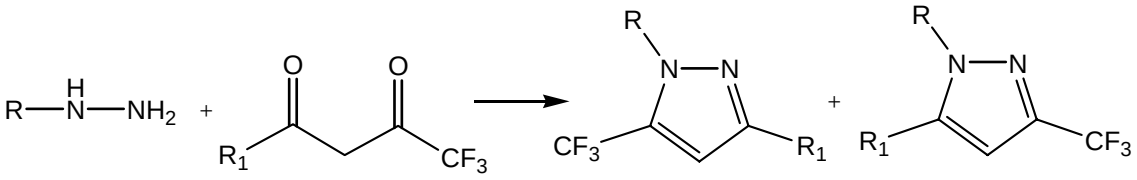


Scheme 16

2.4 It was also found that ^{19}F NMR spectrum is an elegant method for assigning the structure of hydrazone, trifluoromethylhydroxydihydropyrazole, and pyrazole structures. The hydroxydihydropyrazoles such as **50**, **57** exhibited a signal at about δ -81 ppm for the 5-C**F**$_3$, in contrast to δ -67 ppm for the 3-C**F**$_3$. The C**F**$_3$ group of the hydrazones (**60**) resonates at about δ -75 ppm. Finally, isomeric trifluoromethylpyrazoles can easily be distinguished by their ^{19}F NMR spectra.[39] The 5-C**F**$_3$ of trifluoromethylpyrazoles resonates at about δ –58 ppm, in contrast to the more upfield resonance of the 3-C**F**$_3$ at δ -62 ppm.

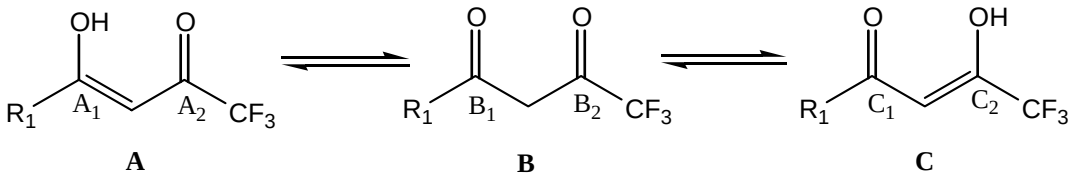
During the course of investigation of the reaction between aryl- or heteroarylhydrazines with trifluoromethyl β-diketones (CF_3COCH_2COR), an interesting observation came to light. ^{13}C and ^{19}F NMR spectral analysis of the products indicated that there was formation of either 3-trifluoromethyl- or 5-trifluoromethylpyrazoles while using a particular trifluoromethyl β-diketone such as benzoyltrifluoroacetone and thenoyltrifluoroacetone with a variety of monosubstituted hydrazines. It appeared that the orientation in the reaction 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-diketones. We, therefore, decided to investigate the mechanism of this reaction

between monosubstituted hydrazines and unsymmetrical β-diketones leading to the formation of a mixture of pyrazole isomers (**63**, **64**) with an emphasis on the nature of substituent at hydrazine (R).

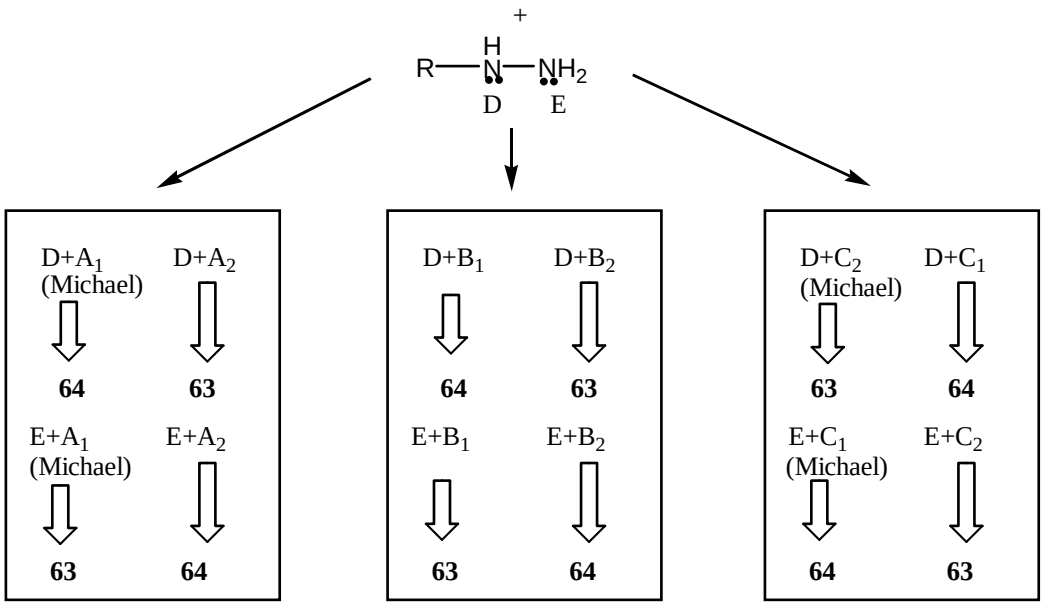


63 **64**

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

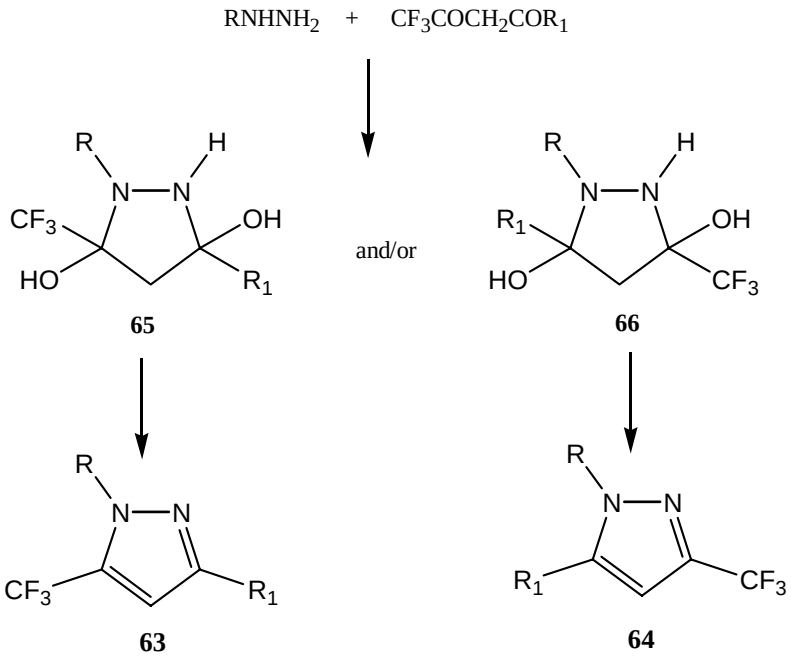


A **B** **C**



The mechanism of such reactions have been studied by several groups of workers,[40-44] however, all these publications dealt with the structure of β-diketones on the relative ratio of isomeric pyrazoles for a given hydrazine. Semi-empirical calculations at the 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. Although the differences in 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 we had investigated. All these reactions

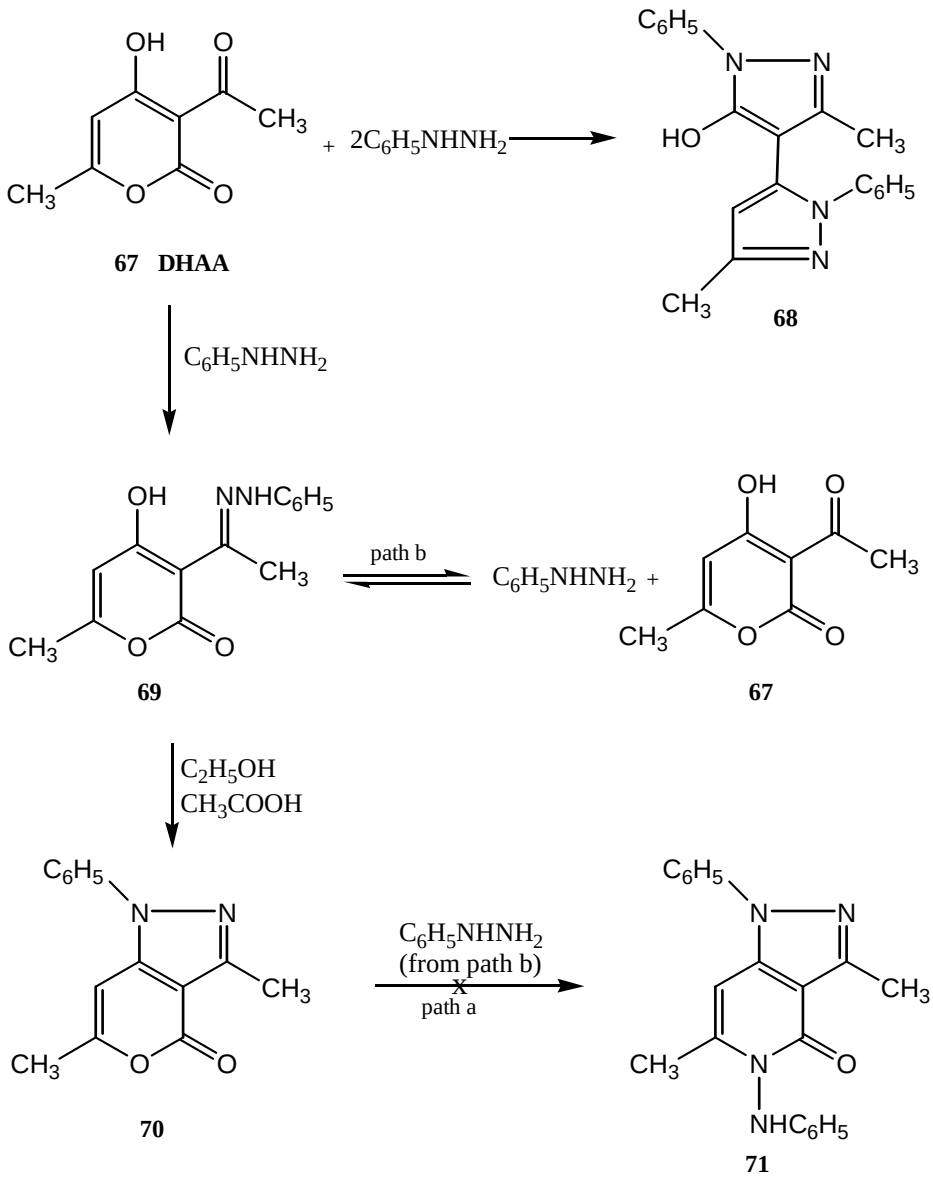
start reacting by the NH_2. The outcome that emerges seems to be that the difference in the rates of dehydration of the two 3,5-dihydroxypyrazolidines (**65**, **66**) in equilibrium controls the isomer formed.[45]



Our data indicate that with a given β-diketone such as benzoyltrifluoroacetone, there is formation of a pyrazole having CF_3 located at position 3 with phenylhydrazine and *p*-nitrophenylhydrazine. However, when hydrazines such as 2,4-dinitrophenylhydrazine and 2-quinolylhydrazine are used, the reaction product was invariably a pyrazole derivative having the CF_3 located at position 5.

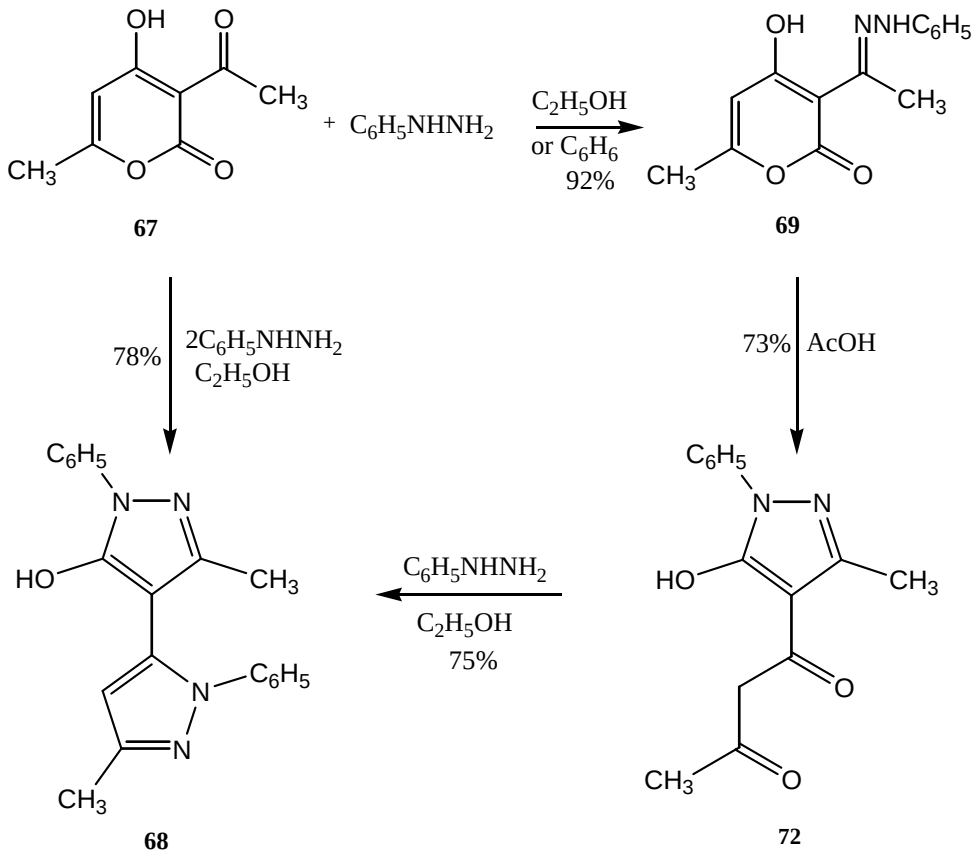
3 REACTION OF ARYL AND HETEROARYL HYDRAZINES WITH DEHYDROACETIC ACID

3.1 Dehydroacetic acid (**67**, DHAA), which has several reactive sites, is very susceptible to attack by the nucleophilic reagents at the carbonyl of the acetyl group, the carbon atom terminating the conjugated carbon chain at position 6, the lactone carbonyl and the carbonyl of the position 4. Long back, Stolle[46] and subsequently Benary[47] reported that the reaction of **67** with two molecules of phenylhydrazine afforded 1,1'-diphenyl-3,3'-dimethyl-(4,5'-bipyrazol)-5-ol (**68**). However, this facile synthesis was unnoticed till 1974, when this work was repeated and an isomeric structure 5-anilino-3,6-dimethyl-4-oxo-1-phenylpyrazolo[4,3-*c*]pyridine (**71**) was erroneously assigned.[48] These worker used equimolar quantities of **67** and phenylhydrazine and claimed to have obtained **71** through the intermediacy of hydrazone (**69**) and pyranopyrazole (**70**) without mentioning the isolation of **67** during the work up of the reaction mixture (**Scheme 17**).[48] As the structure (**71**) was not firmly established, the reaction was reinvestigated independently by us[49] and Gelin *et al.*[50] and it was found that the proposed structure (**71**) was indeed in error.



Scheme 17

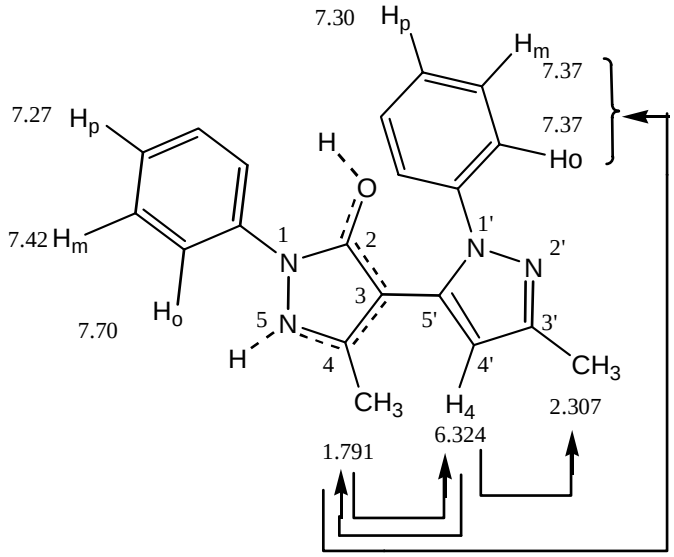
The reaction of **67** with phenylhydrazine was repeated and the product was identified as bipyrazole (**68**) identical with the one prepared by Stolle.[46] However, when **69** was refluxed in acetic acid, it underwent a rearrangement involving a nitrogen nucleophilic attack at the lactone carbonyl with the ring opening to yield (5-hydroxy-3-methyl-1-phenylpyrazol-4-yl)-1,3-butanedione (**72**). This procedure did not provide **71** as claimed in the literature.[48] The keto-enol tautomeric study of β-tricarbonyl system and structure confirmation of **72** was established by NMR spectroscopy.[51] The fragmentation behaviour of **72** was studied by MS spectral analysis and major processes were substantiated with the help of accurate mass measurement of the fragment ions.[52] The reaction of **72** with phenylhydrazine resulted in smooth cyclization to the corresponding bipyrazoles (**69**) (**Scheme 18**). To generalise the reaction sequence (**67** → **69** → **72** → **68**), **67** as well as **72** were treated with various alkyl-, aryl- and heteroarylhydrazine and in each case the final product bipyrazoles so obtained were characterized using IR, NMR and MS spectral data.[53]



Scheme 18

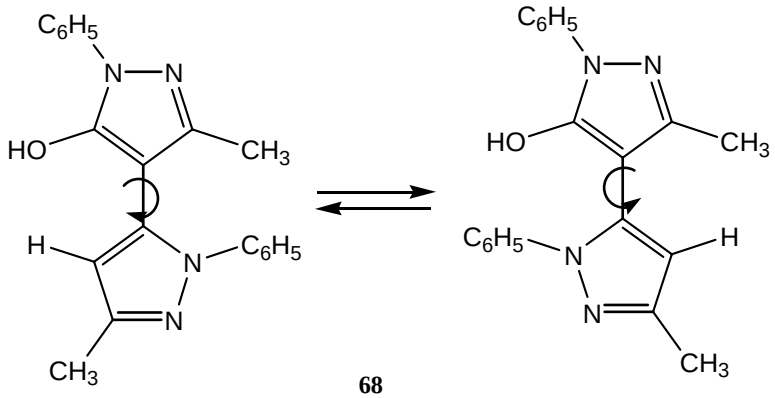
Although the reaction led to the formation of only one compound and not to a mixture of isomers, its structure assignment appeared to be a complex problem because this compound may present isomerism, tautomerism (O*H*/N*H*) and rotational isomerism (atropisomerism). The structure was eventually established by a combined use of X-Ray crystallography, NMR (^{1}H and ^{13}C) spectroscopy and the solid state NMR (CPMAS technique) spectrum of **68** and related bipyrazoles.[54] The structure corresponds more to the N*H*-tautomer of the pyrazolinone moiety rather than the O*H* tautomer. NMR spectrum of **68** allowed us to estimate the tautomeric equilibrium constant in solution and in the solid state.

Both the rotational barrier and the tautomeric barrier in **68** are very low, thus, only average NMR signals are expected. It is noteworthy that in the ^{1}H NMR spectrum of **68,** the 3-methyl signal (δ 1.791 ppm) was clearly shielded with regard to simple pyrazolinones (δ 2.307 ppm). This shielding was assigned to the proximity of the 1'-phenyl ring. This proximity was confirmed by the NOE experiments, which indicated that 1'-phenyl ring protons (*ortho* and *meta* at δ 7.37 ppm) are having more percentage enhancement in the signal in comparison to $C_{4'}$-H (δ 6.324 ppm) with the methyl protons (δ 1.791 ppm) of pyrazolinone moiety. The fact that the signal at δ 1.791 ppm shows both NOE's with phenyl protons and $H_{4'}$ further indicated that **68** exists as rotational isomers (atropisomers) as described above. The proximity of the 3-methyl group and the $H_{4'}$ proton is also clearly seen. ^{13}C NMR spectroscopy was not found useful for rotational isomer study, but allowed us to estimate tautomeric equilibrium constant in solution.



68

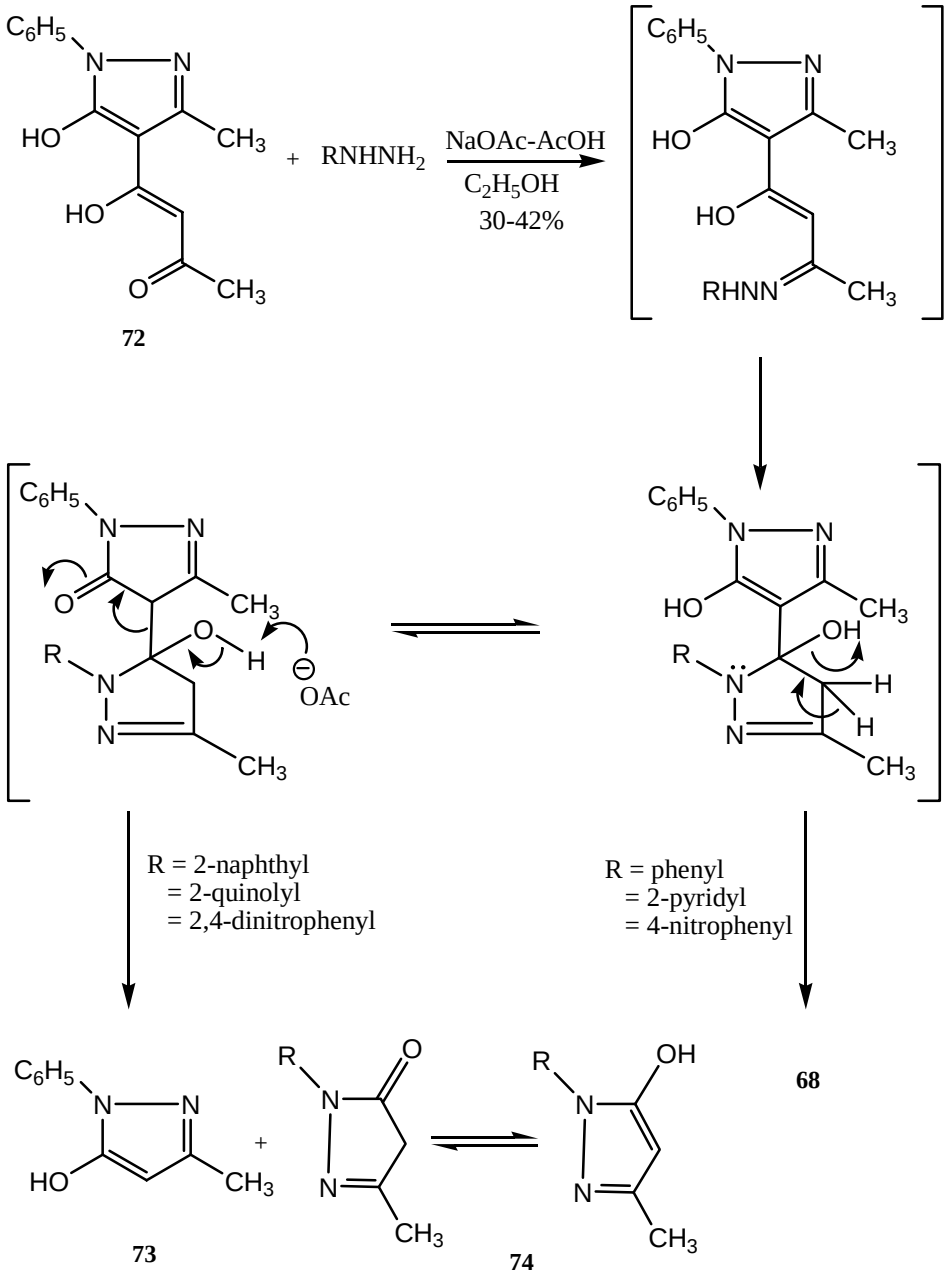
It was also found that if 1'-phenyl ring is replaced by hydrogen, alkyl, aryl or heteroaryl moiety, the 3-methyl signal jumps to about δ 2.4 ppm which provided another proof that the δ 1.791 ppm signal is shielded by the phenyl group.



68

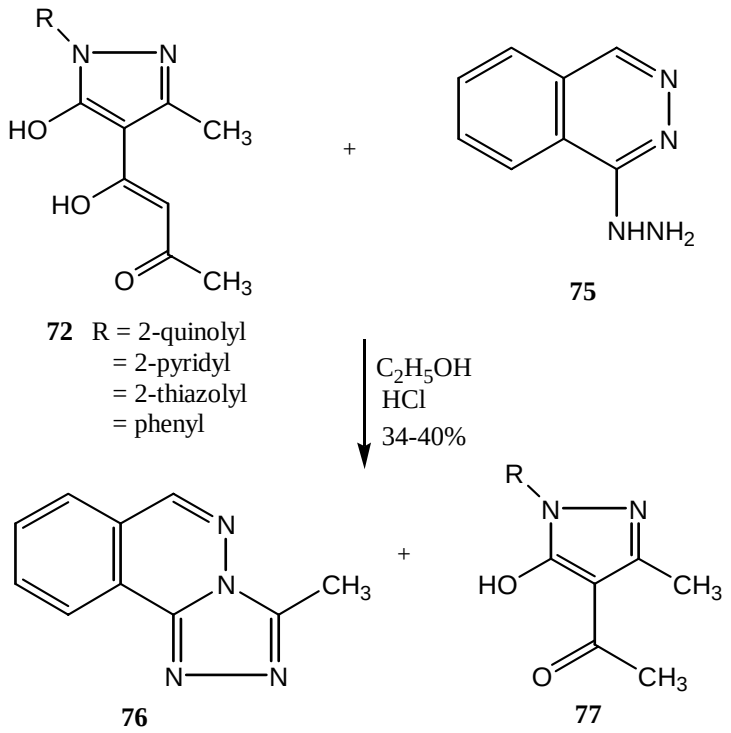
While treating **72** with a variety of hydrazines and employing different reaction conditions, an interesting observation concerning the mechanism of formation of **68** came to light. Whereas all the hydrazines provided the expected bipyrazole on treatment of **72** in the presence of strong acid, unexpected formation of pyrazol-5-ols (**73**, **74**) was observed with some hydrazines on performing the reaction in ethanol-acetic acid/sodium acetate. Formation of **73**, **74** clearly indicated the cleavage of C-C bond in the intermediate. In order to establish the mechanism of formation of pyrazol-5-ols (**73**, **74**), **72** was treated with various aryl- and heteroaryl hydrazines having electron withdrawing group and/or increasing the bulk of hydrazines. It was finally established that it is not the presence of electron withdrawing group, rather it is the bulk of the hydrazine that is responsible for the cleavage of C-C bond. The C-C bond cleavage generating **73**, **74** was observed in the case of 2-hydrazinoquinoline, 2-hydrazinonaphthalene and 2,4-dinitrophenylhydrazine while performing the reaction of **72** in ethanol-acetic acid/sodium acetate and in the case of phenylhydrazine, 4-nitrophenylhydrazine and 2-hydrazinopyridine there was formation of only

bipyrazoles.[55] However, in the reaction of **72** with all the above hydrazines in ethanol-hydrochloric acid, there was exclusive formation of bipyrazole. The probable mechanism for these processes has been postulated as shown in **Scheme 19**.



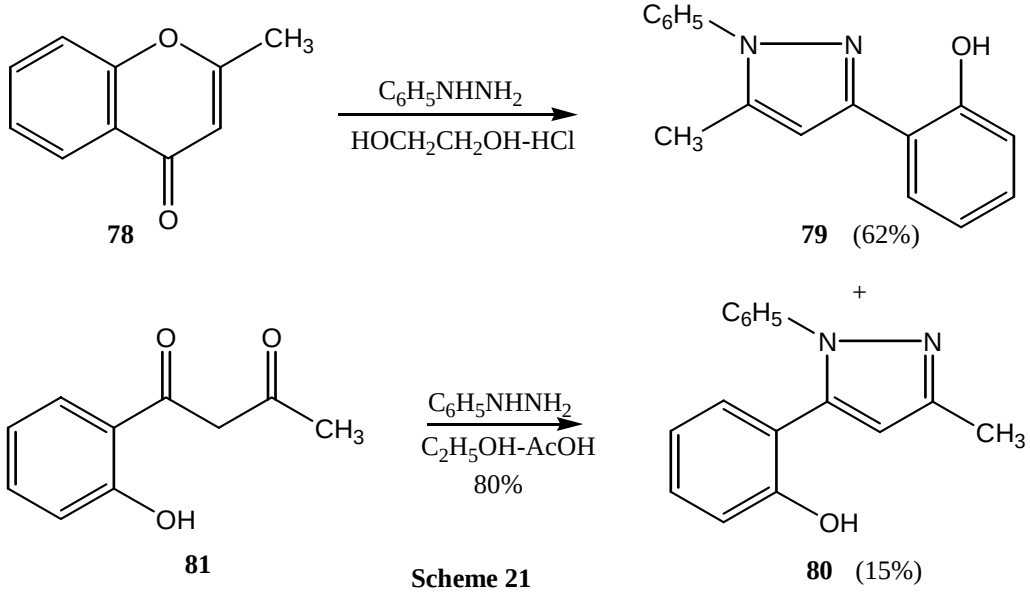
Scheme 19

However, when the reaction of 1-(4-pyrazolyl)-1,3-butanediones (**72**) was carried out with 1-hydrazinophthalazine (**75**), there was formation of two products in equal amounts identified as 3-methyl-*s*-triazolo[3,4-*a*]phthalazine (**76**) and 4-acetylpyrazol-5-ols (**77**)(**Scheme 20**).[56] The reaction was found to be of general nature when other 1-(4-pyrazolyl)-1,3-butanediones (**72**) (where phenyl group is replaced with 2-quinolyl, 2-pyridyl and 2-thiazolyl) were treated with **75**. The compounds of the type (**77**) are good metal extracting agent.



Scheme 20

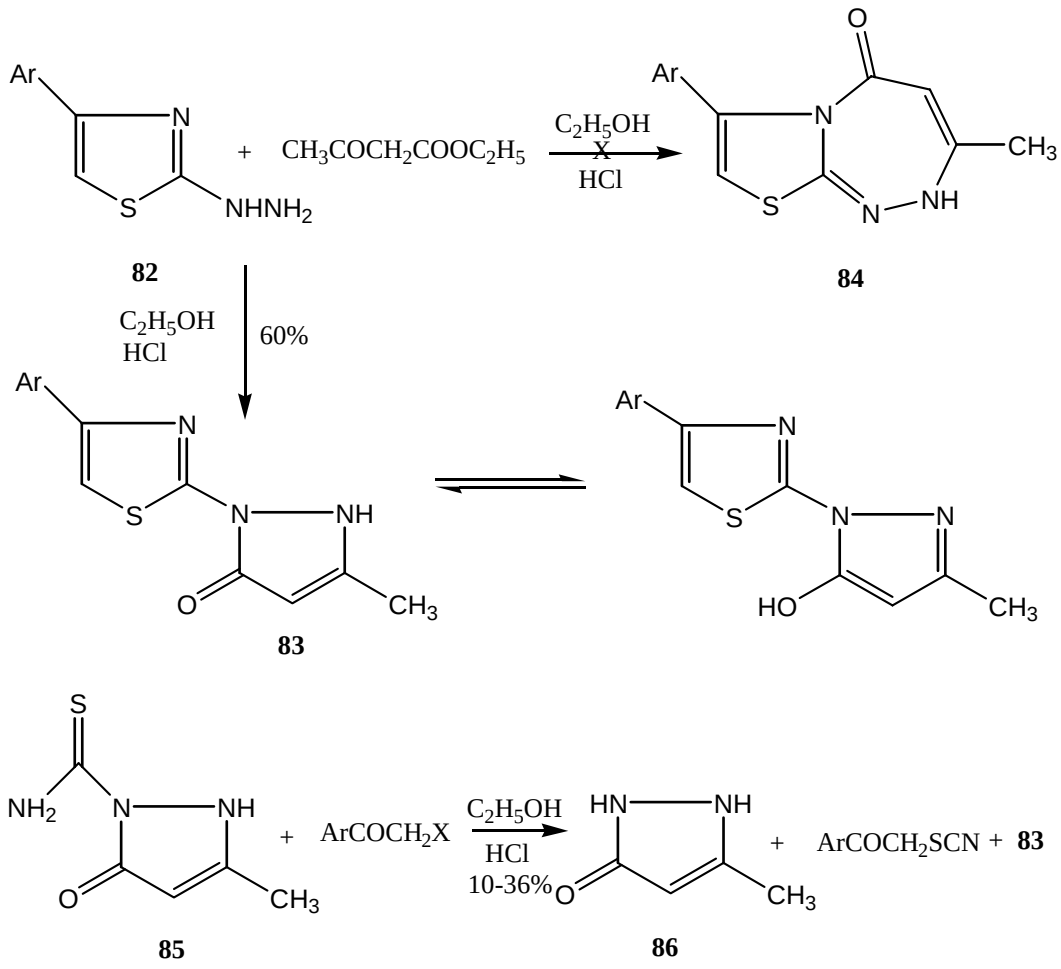
3.2 The reaction of 2-methylchromone (**78**) with phenylhydrazine was investigated by Alberti[57] and assigned the pyrazole structure for the product having methyl group located at position-5 (**79**). However, in a recent report,[58] the above reaction was repeated and the pyrazole structure was assigned having the methyl group at position 3 (**80**). In view of these contradictory reports, we reinvestigated this reaction under the same experimental conditions and found that there is formation of two isomeric pyrazoles (**79** and **80**) in 4:1 ratio, which were separated and characterized on the basis of a careful interpretation of NMR spectral data. In order to provide additional evidence in favor of **80**, it was synthesized by an alternate procedure involving the reaction of 1-(*o*-hydroxyphenyl)-1,3-butanedione (**81**) and phenylhydrazine (**Scheme 21**).[59]



Scheme 21

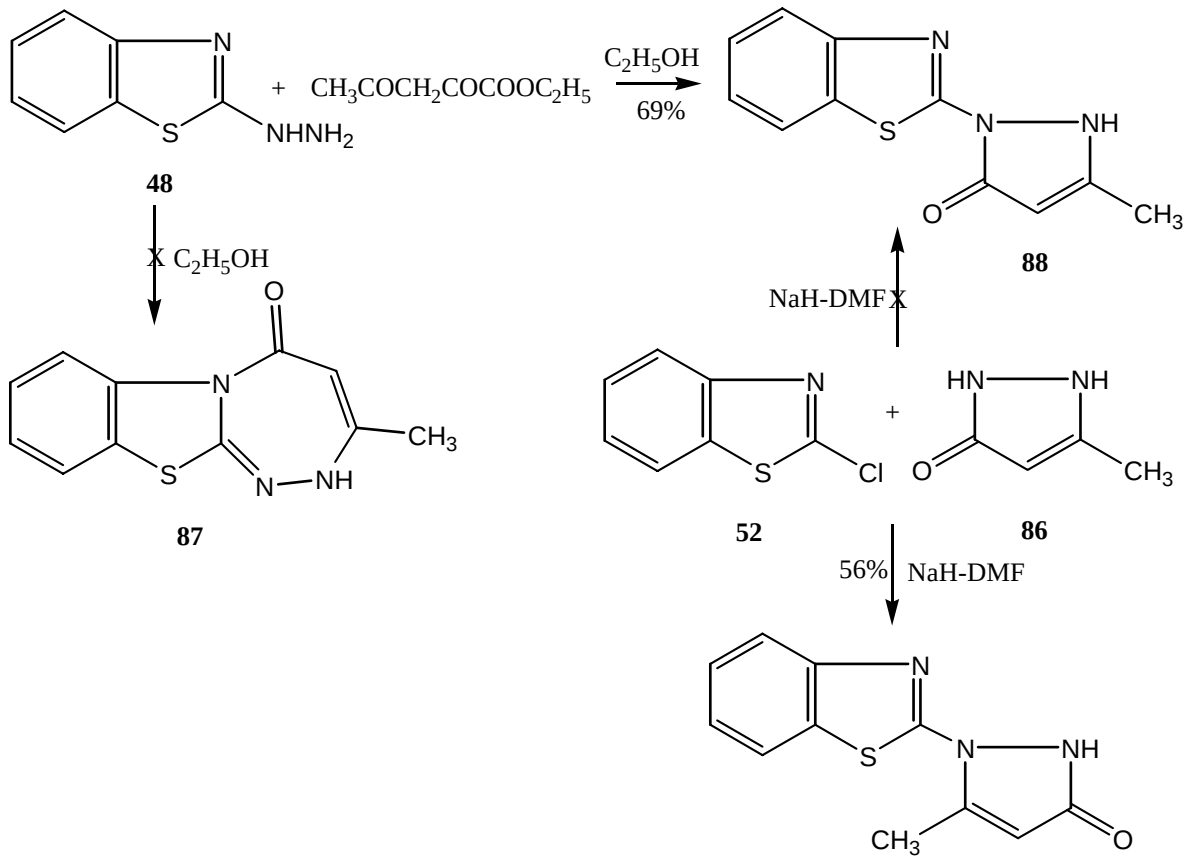
4 REACTION OF HETEROARYL HYDRAZINES WITH β-KETO ESTERS

4.1 The reaction of 4-aryl-2-hydrazinothiazoles (**82**) with ethyl acetoacetate afforded 2-(4-aryl-2-thiazolyl)-1,2-dihydro-3*H*-5-methylpyrazol-3-one (**83**)[60] rather than 3-arylthiazolo-[2,3-*c*][1,2,4]triazepin-5-one (**84**) as erroneously reported earlier.[61] Synthesis of **83** was also achieved through condensation of **85** (having preconstructed pyrazolone ring) and α-haloketones along with formation of 1,2-dihydro-5-methyl-3*H*- pyrazol-3-one (**86**) and α-thiocynato ketone (**Scheme 22**).



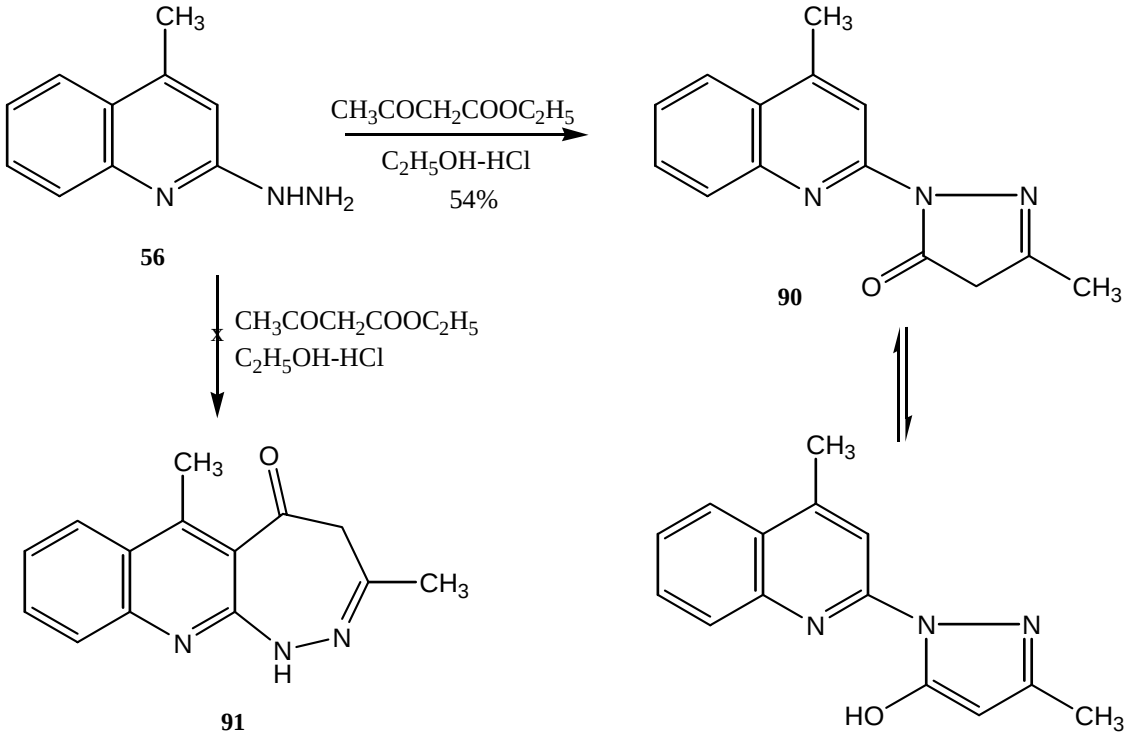
Scheme 22

4.2 Reaction of **49** with ethyl acetoacetate has been reported to yield a fused triazepinobenzothiazolone, namely 3-methyl[1,2,4]triazepino[3,4-*b*]benzothiazol-5(4*H*)-one (**87**).[60,62] This work was repeated by Peet *et al.*[63] and the product was characterized to be 2-(2-benzothiazolyl)-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one (**88**) on the basis of X-Ray crystallography. Treatment of 1,2-dihydro-5-methyl-3*H*-pyrazol-3-one (**86)** with **52** yielded a single product identified as 2-(2-benzothiazolyl)-1,2-dihydro-3-methyl-5*H*-pyrazol-5-one (**89**), which was isomeric with, but different from the product obtained by the reaction of **49** and ethyl acetoacetate (**Scheme 23**).



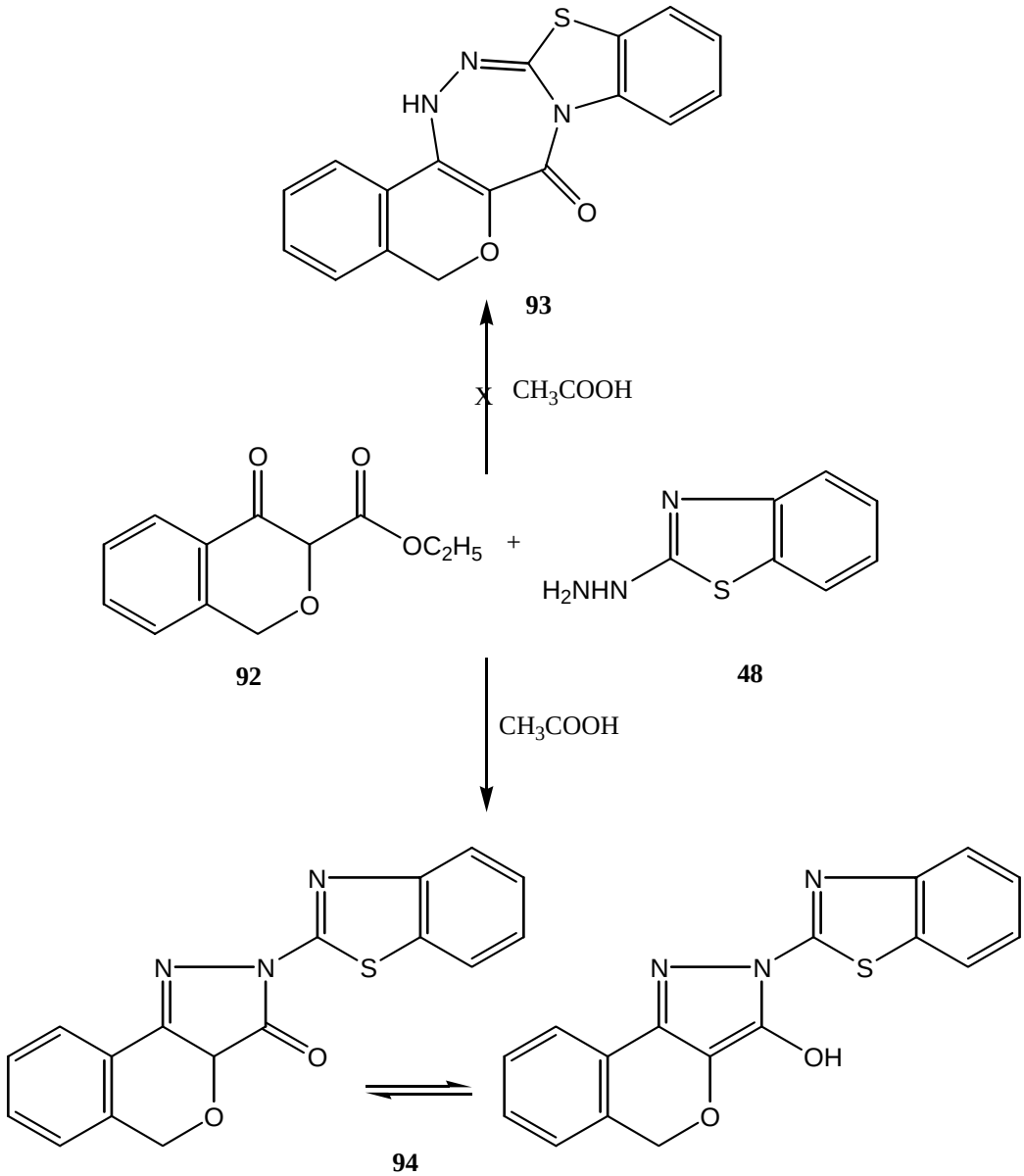
Scheme 23

4.3 Similarly, we found that 2-hydrazino-4-methylquinoline (**56**) on reaction with ethyl acetoacetate afforded 2-(2-quinolyl)-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one (**90**)[64] instead of the erroneously reported diazepinone (**91**).[62]



Scheme 24

4.4 There is still a report[65] to our knowledge that merits reinvestigation, i.e., reaction of 2-hydrazinobenzothiazole (**49**) with an isochroman derivative (**92**). In fact, the product has been claimed to be an isochromanotriazepinone derivative (**93**). However, on the basis of our experience, we expect the product should have a pyrazolone structure (**94**) (**Scheme 25**). The reaction remains to be investigated.



Scheme 25

CONCLUSIONS

1. The reaction of alkyl-, aryl- and heteroarylhydrazines with β-diketones always leads to the formation of pyrazoles instead of the erroneously reported seven-membered triazepine or diazepine structures.

2. Heteroarylpyrazoles assume planar structure around the C-N pivot bond, which can be disturbed by putting substituents at appropriate places.

3. In the reactions involving trifluoromethyl 1,3-diketones, the nature of hydrazine appears to play an important role in influencing the mechanistic pathway.

4. Dehydration of the intermediate dihydropyrazoles to pyrazoles becomes somewhat difficult in the presence of a CF_3 or (two CF_3) in the molecule.

5. The reaction of dehydroacetic acid with hydrazines results in the formation of bipyrazoles instead of the erroneously reported pyridinopyrazole.

6. The reaction of heteroarylhydrazines with β-diketo esters also leads to the formation of pyrazolones instead of the erroneously reported seven-membered triazepinnone or diazepinone structures.

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