Chapter 3

Study the functional group interconversion reaction (FGI) by conventional methodology of 5-substituted thieno[2,3-c]pyrazole derivatives

In this chapter we have reported the synthesis of ethyl-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate by condensation with cyclization of ethyl thioglycolate and 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde in presence of base. The ethyl-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate having C5 ester functionality were successfully utilized for the synthesis of novel 5-substituted thieno[2,3-c]pyrazole derivatives by functional interconversion reaction strategy (FGI).

3.1 Introduction:

Thieno-fused heterocycles such as thienopyridines [1,2], thienopyrimidines [3-5] and thienopyrroles [6,7] constitute a group of biologically active structures. Thienopyrazoles are diaza analogs of the corresponding thienopyrroles. Several heterocycles containing the pyrazole nucleus are known to possess biological activity [8-13]. Thieno[3,4-c]pyrazoles are biologically active compounds, currently employed in the field of medicinal chemistry owing to their remarkable anti-inflammatory [14-15], analgesic and antithrombotic activities, also for the treatment of cardiovascular or cerebrovascular diseases, and hyperglycemia [16]. Thieno[3,2-c] pyrazoles are used in the treatment of hypertension and glaucoma [17], selective MMP-13 exosite inhibitors utilizing a triple-helical FRET substrate [18], selective P2X3 receptor antagonist [19], antimicrobial [20], aurora inhibitors with favorable antitumor activity [21], submicromolar inhibitor of KDR [22], antioxidant and antitumor agents...
[23] PDE7 kinase inhibitors [24], inhibition of protein kinases, in particular interleukin-2 inducible tyrosine kinase (ITK) [25], kinase inhibitors [26]. Thieno[2,3-c]pyrazoles, represent a class of heterocyclic compounds which has received very little attention.

In literature the synthesis of fused thiophenes having biological activity [24, 27-29] are reported. We describe herein the synthesis of title heterocycles. On the other hand functional group interconversion, is the process of converting one functional group into another by substitution, addition, elimination, reduction, or oxidation etc reaction by the use of different reagent and reaction condition. These basic transformations gave platform in order to organic chemist perform multistep organic synthesis.

3.1.1 Literature updates of thienopyrazole
The chemistry of thienopyrazole has received considerable importance due to their wide range of applications. The work represented in current chapter is concerned with the synthesis and characterization of new class of thienopyrazoles.

1) M.K. Bratenko et al. and co-workers [30] reported the synthesis of 4-chlorothieno[2,3-c]pyrazole-5-carbonylchloride derivatives 2 obtained using 3-(3-pyrazolyl)-acrylic acid 1 and cyclization in presence of thionyl chloride and benzyltriethyl-ammoniumchloride (BTEAC) (Scheme 1).

![Scheme 1](image-url)
2) *G.H. Elgemeie et al.* and co-workers [31] reported the thienopyrazole thioglycoside 9 via one pot reaction of sodium thienopyrazolothiolate salt 7 with galactopyranosyl bromide 8. The sodium thienopyrazolothiolate salts 7 were prepared using pyrazoldithioic acids and their corresponding mono 5 and dithiolate 4 salts. Also, the (4-mercapto-3-methyl-1H-thieno[3,4-c]pyrazol-6-yl)(phenyl)methanone 6 was obtained from pyrazoldithioic mono acids 5 (Scheme 2).

![Scheme 2](image)

3) *Hussein El-kashef et al.* and co-workers [32] obtained methyl-4-amino-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate 12 from o-chloronitrile 10 by reaction with thioglycolate 11 in boiling methanol containing fused potassium carbamate afforded 12 in good yield (Scheme 3).
4) *M. Akssira et al.* and co-workers [33] reported the synthesis of alkyl sulfanyl pyrazoles 14 prepared from 13 following the method reported by *Morimto et al.* [34] and base added cyclization of pyrazole R = Br or I was accomplished by the use of sodium ethanolate in toluene gave compound 15 and 16. Moreover, cyclization of amine analog (R = NH₂), under same condition yielded 17 with self condensation of expected thienofused compound *(Scheme 4).*

**Scheme 4**

5) *Z. Wang et al.* and co-worker [35] reported the synthesis of pyrazoleacetate ester 19 obtained from pyrazolaldehyde 18 and FAESO (formaldehyde, dimethyl dithioacetal S-
oxide), by a new Tandem reaction, in which 4-pyrazolacetate ester reacted with carbon disulfide, iodomethane and thieno[2,3-c]pyrazole was synthesized 21 (Scheme 5).

![Scheme 5]

6) W. Holzer et al. and co-worker [36] reported the synthesis of 1,3-disubstituted-5-chloro-4-iodopyrazole 23, which was selectively coupled with phenylacetylene 24 under typical Sonogashira reaction condition to obtain the corresponding 5-chloro-4-(phenylethylene) pyrazole 25. Then it was smoothly cyclized with Na₂S in DMF to the corresponding thieno[2,3-c]pyrazole 26 (Scheme 6).

![Scheme 6]

7) O. Meth-Cohn et al. and co-worker [37] reported the synthesis of nitrothienopyrazole 28 from thione 27 in presence of benzoyl peroxide (Scheme 7).
8) *J. Liebscher et al.* and co-worker [38] reported the synthesis of thieno[3,4-c]pyrazol-3-ol 30 from thienofuranone 29 in presence of hydrazine hydrate. Hydrazine hydrate attacks on both electrophilic positions of 29 resulting the formation of enol structure 30 (Scheme 8).

As literature reports depicted various biological activities, where the C₅-functionality was altered. Hence, we decided to work on such moieties with different FGI reactions at C₅-position of thieno[2,3-c]pyrazole.

### 3.2 Present Work:

In this present work, we have reported the synthesis of ethyl-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate 33, having C₅ ester functionality which was successfully utilized for the synthesis of novel 5-substituted thieno[2,3-c]pyrazole derivatives. These compounds are depicted in the following retrosynthesis.

#### 3.2.1 Synthesis of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate, (33):
Synthesis of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate 33 can be achieved from 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 31 by cyclocondensation with thioglycolate 32 as depicted in the following retrosynthesis.

3.2.2 Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid, (34):

Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid 34 could be synthesized from ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate 33 by base hydrolysis. Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid 34 could be obtained from ester 33 by substitution reaction with hydrazine hydrate, also 3,5-dimethyl-1-phenyl-1H-thieno[2,3-c]pyrazole 46 and (3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-yl)methanol 47 could be synthesized from ester 33 by reduction.
3.2.3 Synthesis of azido(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanone (37) and 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonylchlorid, (36):

Compound 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonylchlorid 36 could be synthesized from 34 by substitution reaction. Synthesis of azido 37 could be achieved from 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbohydrazide 35 by diazotization and 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonylchlorid 36 by substitution reaction.

![Chemical structures](image)

3.2.4 Synthesis of 5-isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo (38) and thieno[2,3-c]pyrazol-5-yl(carbamate) 40/ (urea) 42/ (carbamothioate), (44):

Compound 5-isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo 38 could be synthesized from azido derivative 37 by rearrangement. Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate 40, 3-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)urea 42, and 3-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)carbamothioate 44 could be obtained by the reaction of 5-isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo 38 and alcohols, anilines and thiophenol respectively.
3.2.5 Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-amine, (45):

Compound amine 45 could be obtained from acid 34 by substitution followed by rearrangement, also 45 could be obtained from carbamate 40 and isocyanate 38 by hydrolysis.
3.2.6 Synthesis of 2-(3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)ethanamine, 52

Synthesis of 49 could be easily obtained from 47 by substitution reaction. The alcohol 47 on oxidation can yield aldehyde 48, which on reaction with nitromethane yield nitro styrene derivative 50. Synthesis of 51 could be obtained from nitro styrene 50 by reduction of olefin double bond by sodium borohydride, further reduction of nitro functionality yield 52.

3.2.7 Synthesis of (3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanamine, 55

The acid chloride derivative 36 on substitution reaction with ammonia can yield 53, further which on rearrangement can yield nitrile derivative 54. Synthesis of 57 could be obtained from 48 by condensation of hydroxyl amine hydrochloride and compound 55 could be obtained from 53, 54 and 57 by reduction reaction.
3.3 Results and Discussion:

3.3.1 Synthesis of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate, (33):

The reaction of aldehyde 31 with ethyl thioglycolate 32 in triethyl amine and DCM as solvent yield ester 33 in low yield (Method I). Hence we decided to use different reaction condition to improve yield of 33. We found that NaOEt in ethanol at room temperature (Method II) gave satisfactory yields (88%) of ester 33. The structure of 33 was established by spectral and analytical data, the compound 33 in its IR showed ester carbonyl functionality at 1708 cm$^{-1}$. The $^1$H NMR spectrum of 33 in DMSO-d$_6$ clearly
showed the triplet quartet pattern of ethoxy group at $\delta$ 1.30 & 4.32 with $J = 5.4$ Hz, respectively. Singlet at $\delta$ 8.01 corresponds to C$_4$-H of thiophene (Spectrum No. 1, Page No. 149). The $^{13}$C NMR of this compound in CDCl$_3$ show $\delta$ 13.04, 14.38, 61.42, 117.5, 122.7, 125.6, 129.6, 130.2, 130.5, 139.2, 143.9, 144.3, 162.9 (ester carbonyl) (Spectrum No. 2, Page No. 150). Mass spectrum $m/z = 286, 287$ (M+1) and the elemental analyses is in agreement with the proposed structure of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c] pyrazole-5-carboxylate 33 (Experiment No. 1, Page No. 177-178).
Spectrum No. 1: $^1$H NMR Spectrum of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate (33) in DMSO-d$_6$. 

IR: 3100, 1708, 1676 cm$^{-1}$
Mass: 286 (M+)
Mol. Wt.: 286.35
Spectrum No. 2: $^{13}$C NMR Spectrum of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate (33) in CDCl$_3$. 

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3.3.2 Synthesis of azido(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanone, (37):

Scheme 10
The ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate 33 was then converted ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid 34 by base hydrolysis in presence of NaOH. The IR of compound 34 showed carboxylic acid carbonyl functionality 1660 cm\(^{-1}\) and -OH stretching frequency at 3412 cm\(^{-1}\). \(^1\)H NMR spectrum of this compound in DMSO-d\(_6\) showed broad singlet at \(\delta\) 13.3 for to –OH (Spectrum No. 3, Page No. 153). The \(^{13}\)C NMR of this compound in DMSO-d\(_6\) showed peak at \(\delta\) 163.6 for acid carbonyl and all other carbon are there respective region (Spectrum No. 4, Page No. 154).

Mass spectrum and the elemental analyses is in agreement with the proposed structure of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid 34. The acid hydrazide 35 and acid chloride 36 were by obtained known functional group interconversion substitution reaction using hydrazine hydrate and thionyl chloride respectively. The structure of 35 and 36 were established by spectral and analytical data. The IR of compound 35 showed three broad peak 3305, 3267, 3190 cm\(^{-1}\) for NH\(_2\) and amide carbonyl stretching frequency at 1661 cm\(^{-1}\). \(^1\)H NMR spectrum of compound 35 in DMSO-d\(_6\) showed two broad singlet at \(\delta\) 4.52 and 9.89 corresponding to -NH\(_2\) and -CONH respectively (Spectrum No. 5, Page No. 155). The mass spectral analysis showed the molecular ion peak at \(m/z = 272\) and the elemental analysis was in agreement with the molecular formula C\(_{13}\)H\(_{12}\)N\(_4\)OS (Experiment No. 3, Page No 179-180). Also the compound 36 structure established by spectral and analytical data given in experimental section (Experiment No. 4, Page No 180).

The azido derivative 37 was obtained by two methods: Method 1 by diazotization of acid hydrazide 35 in acetic/NaNO\(_2\) with 90% yield. Method 2 the displacement of
chloride of acid chloride 36 with azide by sodium azide in DMF gave 37 with 75% yield. *Method 1* is superior that gave higher yield of compound 36 and avoid use of thionyl chloride which is unhealthy. Structure of 37 was established by spectral and analytical data showed in experimental section (*Experiment No. 5, Page. No 181-182*).
IR: 3412, 2924, 1660 cm\(^{-1}\)
Mass: 258 (M+)
Mol. Wt.: 258.30
Spectrum No. 4: $^{13}$C NMR Spectrum of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid (34) in DMSO-\textit{d$_6$.}

IR: 3305, 3267, 3190, 1661 cm$^{-1}$
Mass: 272 (M$^+$)
Mol. Wt.: 272.33
### 3.3.3 Synthesis of 5-isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo, (38) and 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate/urea/carbamothioate (40, 42, 44):

![Scheme 11](image)

- **Scheme 11**

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The azido methanone 37 undergoes rearrangement in benzene or toluene furnished intermediate 5-isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo 38, which cannot be isolated, was directly used for further reactions. The addition reaction of 5-isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo 38, with alcohol 39a-c, primary aromatic amines 41a-c and thiophenol 43 furnished 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate 40a-c, 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylurea 42a-c and 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl-carbamothioate 44, respectively. Out of this only carbamate reaction was slower as compared to other addition reaction. Structural assignment of compounds 40, 42 and 44 were performed by using IR, $^1$H NMR, $^{13}$C NMR, Mass and element analysis. The IR spectrum of compound 40b showed band at 3259 cm$^{-1}$ for amide -NH and 1693 cm$^{-1}$ for amide carbonyl. The $^1$H NMR of 40b in DMSO-d$_6$ showed one broad singlet for (-NHCO) at $\delta$ 10.73 (Spectrum No. 6, Page No. 158). The $^{13}$C NMR in DMSO-d$_6$ of this compound 40b showed $\delta$ 153.4 (amide carbonyl) (Spectrum No.7, Page No. 159). The mass spectral analysis showed the molecular ion peak at $m/z$ = 301 and the elemental analysis was in agreement with the molecular formula C$_{15}$H$_{15}$N$_3$O$_2$S (Experiment No. 6, Page No 182-183). The IR spectrum of compound 42b showed band at 3315 and 3259 cm$^{-1}$ for two amide -NH and 1642 cm$^{-1}$ for amide carbonyl. The $^1$H NMR of 42b in (DMSO-d$_6$) showed two broad singlet protons for (-NHCONH-) at $\delta$ 9.12 and 9.87 (Spectrum No. 8, Page No. 160). The $^{13}$C NMR in DMSO-d$_6$ of this compound 42b showed $\delta$ 12.8, 97.3, 116.5, 116.9, 117.9, 121.9, 124.8, 126.6, 129.8, 130.4, 133.2, 136.3, 137.4, 139.2, 140.8, 141.4, 151.8 (amide carbonyl) (Spectrum No. 9, Page No. 161). The mass spectral analysis showed the molecular ion peak at $m/z$ = 362 and the elemental analysis was in agreement with the
molecular formula C_{20}H_{18}N_{4}O_{5}. Similarly, the IR spectrum of compound 44 showed band at 3251 cm\(^{-1}\) for amide -NH and 1647 cm\(^{-1}\) for amide carbonyl. The \textsuperscript{1}H NMR of 44 in DMSO-d\(_6\) showed three singlet δ 2.44 (CH\(_3\)), 6.68 (C\(_4\)-H) and 10.73 (NH) respectively. The 10 protons showed multiplet at δ 7.22-7.78 for two phenyl rings (Spectrum No. 10, Page No. 162). The mass spectral analysis showed the molecular ion peak at \(m/z = 365\) and the elemental analysis was in agreement with the molecular formula C\(_{19}\)H\(_{15}\)N\(_3\)O\(_2\).
IR: 3359, 2985, 1693 cm\(^{-1}\)
Mass: 301 (M\(^+\))
Mol. Wt.: 301.36

Spectrum No. 6: \(^1\)H NMR Spectrum of Ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate (40b) in DMSO-d\(_6\).
Spectrum No. 7: $^{13}$C NMR Spectrum of Ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate (40b) in DMSO-$d_6$. 
IR: 3315, 3273, 1639 cm\(^{-1}\)
Mass: 362 (M+)
Mol. Wt.: 362.45

Spectrum No. 8: \(^1\)H NMR Spectrum of 1-(3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)-3-p-tolylurea (42b) in DMSO-d\(_6\).
Spectrum No. 9: $^{13}$C NMR Spectrum of 1-(3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)-3-p-tolylurea (42b) in DMSO-$d_6$. 
IR: 3251, 2920, 1647 cm⁻¹
Mass: 365 (M+)
Mol. Wt.: 365.47

Spectrum No. 10: ¹H NMR Spectrum of S-phenyl-N-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamothioate (44) in DMSO-d₆.
3.3.4 Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-amine, (45):

The ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid 34 was converted to 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-amine 45 by known Schmidt rearrangement (Method-I). The IR spectrum of compound 45 showed primary amine functionality at 3435, 3273 cm\(^{-1}\). \(^1\)H NMR spectrum in CDCl\(_3\) showed broad singlet for -NH\(_2\) at δ 8.46. Two singlet appeared at δ 2.59 and 6.94 were assigned to methyl protons and C\(_4\) aromatic proton respectively and all other protons were in their respective region.
The mass spectrum of 45 showed M+ 229 m/z and elemental analyses of 45 were in agreement with the molecular formula C_{12}H_{11}N_{3}S. On the basis of this spectral and analytical data structure 45 was assigned to this compound i.e. 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-amine 45. This compound 45 was also obtained by another two methods which is explained in experimental section. Out of three methods Method-II is good for obtained the target molecule (Experiment No. 9, Page. No 187-188).
Spectrum No. 11: $^1$H NMR Spectrum of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-amine (45) in CDCl$_3$.
3.2.5 Study of reduction, oxidation, halogenation and condensation reaction on thienopyrazole derivatives: Synthesis of compound, (46, 47, 48, 49, 50, 51 and 52):
Regioselective reaction of ester 33 in presence of LAH yielded alcohol 47, while over reductive yielded 3,5-dimethyl-1-phenyl-1H-thieno[2,3-c]pyrazole 46. The (3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanol 47 on halogenation using thionyl chloride gave 5-(chloromethyl)-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole 49. Also oxidation
on compound 47 by MnO₂ furnished 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbaldehyde 48 as useful intermediate for the synthesis of 3-methyl-5-(2-nitrovinyl)-1-phenyl-1H-thieno[2,3-c]pyrazole 50. Compound 50 was obtained by condensation reaction with nitromethane in base, which was further converted to 3-methyl-5-(2-nitroethyl)-1-phenyl-1H-thieno[2,3-c]pyrazole 51 by selective reduction of olefin bond with NaBH₄ at 5-10 °C (Scheme 13). Reduction of nitro group in compound 51 using iron powder in acetic acid yielded amine 2-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)ethanamine 52 in 45% yield. Structural assignment of compounds 46, 47, 48, 49, 50, 51 and 52 was done by IR, ¹H NMR, ¹³C NMR, Mass and element analysis. The IR spectrum of compound 47 showed stretching frequency at 3275 cm⁻¹ for OH while this OH stretching frequency was absent in compound 46. The ¹H NMR spectrum of compound 47 showed broad singlet at δ 5.74 assignable for OH (D₂O exchangeable), singlet at δ 4.66 for OCH₂ proton and all other protons appeared at their respective region (Spectrum No. 12, Page No. 167). The ¹³C NMR spectrum in DMSO-d₆ of compound 47 in DMSO-d₆ showed chemical shift at δ 60.5 for HOCH₂ and all other carbon signals appeared at expected chemical shift. The mass spectral analysis of compound 47 showed the molecular ion peak at m/z = 241 and the elemental analysis was in agreement with the molecular formula of compound 47 C₁₃H₁₂N₂OS (Experiment No. 10, Page No 188-189). Similarly, other compounds (46, 48, 49, 50, 51 and 52) were characterized by ¹H NMR and ¹³C NMR, Mass and elemental analysis are given in the experimental section (Page No. 189-195).
IR: 3275, 2889, 1597 cm$^{-1}$
Mass: 244 (M$^+$)
Mol. Wt.: 244.31

Spectrum No. 12: $^1$H NMR Spectrum of (3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanol (47) in DMSO-d$_6$. 
IR: 2924, 1739, 1670 cm$^{-1}$
Mass: 242 (M+)
Mol. Wt.: 242.30

Spectrum No. 14: $^{13}$C NMR Spectrum of (3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbaldehyde (48) in CDCl$_3$. 
3.2.6 Synthesis of (3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-yl) methanamine (55):

In order to carry functional group interconversion reactions, the compound 36 was reacted with 30% ammonia solution to gave 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxamide 53, which on further reaction with phosphorous oxychloride at room temperature gave unusual Beckman rearrangement yield to compound 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonitrile 54. On the other hand, 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbaldehyde 48 reacted with hydroxylamine hydrochloride 56 in basic condition yielded condensed product 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbaldehydeoxime 57 in 88% yield. Similarly carboxamide 53
and carbonitrile 54 reacted with LAH in THF at different reaction temperature yielded amine 55 in 42% and 65% yield respectively, also compound 55 was obtained by reaction of oxime 57 with Zn dust in NH₄OAc/ MeOH at reflux temperature.

Structural assignment of compounds 53, 54, 55 and 57 were performed by using IR, ¹H NMR, ¹³C NMR, Mass and element analysis. The IR spectrum of compound 53 showed stretching frequency at 3363, 3178 cm⁻¹ for amide -NH₂ and 1651 cm⁻¹ for amide carbonyl. The ¹H NMR spectrum of compound 53 in DMSO-d₆ showed broad singlet at δ 8.12 assignable for –CONH₂ (Spectrum No. 15, Page No. 172). In ¹³C NMR amide carbonyl showed at δ 163.6 and all other carbons are at their respective regions (Spectrum No. 16, Page No. 173). While IR of compound 54 showed nitrile frequency at 2206 cm⁻¹, in ¹³C NMR nitrile carbon appeared showed at δ 104.0. Further, elemental analyses of 53 and 54 were in agreement with the molecular formula C₁₃H₁₁N₃OS and C₁₃H₉N₃OS respectively. On the basis of this spectral and analytical data structure 53 and 54 were assigned to this compound i.e. 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxamide and 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonitrile.

Similarly, the IR spectrum of compound 55 showed two broad peak at 3433 cm⁻¹ and 3280 cm⁻¹ for -NH₂. The ¹H NMR spectrum of compound 55 in DMSO-d₆ showed broad singlet at δ 5.60 assignable for –NH₂. The mass spectral analysis of compound 55 showed the molecular ion peak at m/z = 243 and the elemental analysis was in agreement with the molecular formula of compound 55 C₁₃H₁₃N₃S. Similarly, compounds 55 were characterized by ¹H NMR and ¹³C NMR, Mass and elemental analysis, given in the experimental section (Experiment No. 17 Page. No 196-199).
IR: 3363, 3178, 1651 cm\(^{-1}\)
Mass: 257 (M+)
Mol. Wt.: 257.31

Spectrum No. 15: \(^1\)H NMR Spectrum of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxamide (53) in DMSO-d\(_6\).
Spectrum No. 16: $^{13}$C NMR Spectrum of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxamide (53) in DMSO-$d_6$ + CDCl$_3$. 
IR: 3178, 1627, 1597 cm$^{-1}$
Mass: 257 (M+)
Mol. Wt.: 257.31

Spectrum No. 18: $^1$H NMR Spectrum of N-hydroxy-1-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanimine (57) in DMSO-d$_6$. 
3.4 Conclusion:
Chemistry of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole derivatives at C₅ was explored by various functional group interconversion (FGI) reaction. 5-Chloro-4-carbaldehyde-pyrazole derivatives with ethyl thioglycolate yield C₅-carboxylate derivatives, which was conventionally converted to azide derivative using acid chloride or carbohydrazide derivative. Formation of azide by using carbohydrazide gave better yield and avoid toxic chemical like SOCl₂. The azido compound yield intermediate isocynate, which \textit{insitu} yield carbamate, urea and carbamothioate with alcohol, amine and thiophenol respectively. The C₅-amine derivative was easily obtained from acid, carbamate and isocynate in which carbamate in aqueous basic condition gave good yield of amine. Similarly the ethylamine derivative was obtained by FGI reaction on ester by reduction, oxidation and condensation with nitromethane and its further reduction. The acid chloride derivatives gave amide which gave nitrile derivatives using phosphorous oxychloride. The reduction of nitrile on reduction yield methylamine derivatives. The aldehyde by reaction with hydroxylamine and further reduction also yield the same methylamine derivative. These compounds are new addition to the library’s of heterocyclic compounds.
3.5 Experimental Part:

**Experiment No. 1: Synthesis of ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylate, (33):**

**Method I**

\[
\text{NEt}_3 / \text{DCM} \\
\text{heat 45 °C} \\
36 \text{ h}
\]

**Method II**

\[
\text{NaOEt / EtOH} \\
r.t. 12 \text{ h}
\]

![Chemical diagram](image)

**General procedure:**

**Method-I:** In the solution of ethyl thioglycolate 32 (16.2 g, 0.135 mol) and 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 31 (29.48 g, 1.34 mol) in dichloromethane (75 ml), triethylamine (4 ml) was added. The reaction mixture was refluxed in oil bath for 36 hours (TLC check, chloroform: methanol, 9:1). Excess of solvent was removed under reduced pressure and residue stirred in cold water (100 ml). The product was extracted with chloroform (3x100 ml). The solvent was removed completely and the obtained solid, was recrystallized from ethanol to furnish off-white prism solid.

**Method-II:** Ethyl thioglycolate 32 (16.2 g, 0.135 mol) was added to a cold, stirred solution of sodium (3.9 g) in dry ethanol (60 ml). A solution of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 31 (29.48 g, 1.34 mol) in ethanol (25 ml) was added drop wise during half an hour at 0-5 °C and the mixture was stirred overnight at room temperature, and further boil for 0.5 hour, cooled and poured in water. The solid product
obtained was filtered, dried and recrystallized from ethanol to get ester 33 as a off-white prisms.

Recrystallized from ethanol; off-white crystalline solid; Yield Method I: 18.59 g, (65%), Method II: 25.16g, (88%);

mp.: 118-120 °C; IR (KBr): $\nu$ 3100, 2741, 1708, 1676, 1533, 1381, 1285 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 1.30 (t, $J = 5.4$ Hz, 3H, CH$_3$), 2.48 (s, 3H, CH$_3$), 4.32 (q, $J = 5.4$ Hz, 2H, CH$_2$), 7.30-7.72 (m, 5H, ArH), 8.01 (s, 1H, ArH); $^{13}$C NMR (CDCl$_3$): $\delta$ 13.04, 14.38, 61.42, 117.5, 122.7, 125.6, 129.6, 130.2, 130.5, 139.2, 143.9, 144.3, 162.9; MS (70 eV) $m/z = 286, 287$ (M+1).

Analysis Calculated for C$_{15}$H$_{14}$N$_2$O$_2$S (286.35): Calcd: C, 62.92; H, 4.93; N, 9.78% Found: C, 62.84; H, 4.97; N, 9.71%

Experiment No. 2: Synthesis of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid, (34):

![Reaction Scheme](image)

Procedure:
A solution of 33 (2.86 g, 0.01 mol) in ethanol (10 ml) and ethanolic NaOH (0.4 g, 0.01 mol in 5 ml ethanol) was refluxed for 1 hour (TLC check, ethylacetate: hexane, 7:3). The solvent was removed under reduced pressure and the residue was stirred in ice-cold water (50 ml) for 15 minute. It was then neutralized with 0.1 N HCl (15 ml). The separated
solid was collected by filtration, washed with cold water and dried. The product was used without further purification.

**Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid, (34):**

Recrystallized from ethanol:DMF (9:1); colorless amorphous solid; Yield 2.32 g, (90%); mp.: 217-219 °C; IR (KBr): 3412, 2924, 2853, 1660, 1534, 1305, 1280 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 2.50 (s, 3H, CH\(_3\)), 7.31-7.72 (m, 5H, ArH), 7.90 (s, 1H, ArH), 13.3 (bs, 1H, OH); \(^1\)C NMR (DMSO-d\(_6\)): \(\delta\) 12.6, 117.0, 122.8, 125.6, 129.9, 130.5, 131.6, 138.5, 142.6, 144.2, 163.6; MS (70 eV) \(m/z = 258\).

Analysis Calculated for C\(_{13}\)H\(_{10}\)N\(_2\)O\(_2\)S (258.30): Calcd: C, 60.45; H, 3.90; N, 10.85%

Found: C, 60.36; H, 3.95; N, 10.80%

**Experiment No. 3: Synthesis of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-Carbohydrazide, (35):**

![Chemical structure of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-Carbohydrazide](image)

**Procedure:**

A mixture of compound 33 (2.86 g, 0.01 mol) and hydrazine hydrate (99%) (1 ml, 0.02 mol) in ethanol (25 ml) was heated under reflux for 2 hours (TLC check, ethylacetate :hexane, 6:4). The reaction mixture was then allowed to cool, the solid product was collected by filtration, dried and recrystallized.

Recrystallized from ethanol:DMF (9:1); colorless fluppy solid; Yield 2.12 g, (78%);
mp.: 120-121 °C; IR (KBr): $\tilde{\nu}$ 3305, 3267, 3190, 2916, 1661, 1597, 1327 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 2.48 (s, 3H, CH$_3$), 4.52 (bs, 2H, NH$_2$), 7.29-7.74 (m, 5H, ArH), 7.84 (s, 1H, ArH), 9.89 (bs, 1H, NH); $^{13}$C NMR (DMSO-d$_6$): $\delta$ 12.71, 116.7, 116.9, 125.60, 129.9, 130.9, 135.7, 138.6, 141.4, 143.2, 161.8; MS: (m/z) = 272.

Analysis Calculated for C$_{13}$H$_{12}$N$_4$OS (272.33): Calcd: C, 57.34; H, 4.44; N, 20.57% 
Found: C, 57.25; H, 4.39; N, 20.51%

**Experiment No. 4: Synthesis of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonyl chloride, (36):**

![Chemical Structure](image)

**Procedure:**

A solution of 34 (2.58 g, 0.01 mol) in excess of SOCl$_2$ (10 ml) was refluxed for 2 hours (TLC check, chloroform: methanol, 9:1). After completion of the reaction, the excess SOCl$_2$ was completely removed under reduce pressure. The solid separated was recrystallized from CCl$_4$.

Recrystallized from CCl$_4$; Brown amorphous solid; Yield 2.42 g, (88%);

mp.: 135-137 °C; IR (KBr): $\tilde{\nu}$ 2907, 2729, 1750, 1665, 1548, 1309 cm$^{-1}$; $^1$H NMR (CDC$_3$): $\delta$ 2.51 (s, 3H, CH$_3$), 7.22-7.69 (m, 5H, ArH), 7.90 (s, 1H, ArH): MS (70 eV) m/z = 276, 278 (M+2).

Analysis Calculated for C$_{13}$H$_9$ClN$_2$OS (276.74): Calcd: C, 56.42; H, 3.28; N, 10.12% 
Found: C, 56.37; H, 3.25; N, 10.10%
Experiment No. 5: Synthesis of azido(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanone, (37):

Method I
NaNO₂/ AcOH, 0 °C

Method II
NaN₃/DMF
rt 1 h

Procedure:

Method I: The solution of compound 35 (2.72 g, 0.01 mol) in acetic acid (25 ml), was cooled to 0-5 °C. To this a cold solution of sodium nitrite (0.69 g, 0.01 mol in 2 ml H₂O) was added drop wise with stirring. After complete addition, the reaction mixture was stirred at room temperature for 1 hour (TLC check, chloroform: methanol, 9:1). The solid product precipitated was filtered, washed abundantly with cold water and dried. The product was used without any further purification.

Method II: Sodium azide (NaN₃) (0.98 g, 0.015 mol) was added to a solution of acid chloride 36 in dry DMF (20 ml). The mixture was stirred for 2 hours at room temperature under N₂ (TLC check, chloroform:methanol, 9:1). After cooling the reaction mixture at room temperature, the solid separated was collected by filtration washed with water and dried.
Off white amorphous solid; Yield **Method-I** 2.54 g, (90%), **Method-II** 2.12 g, (75%); mp.: 123-125 °C; IR (KBr): $\tilde{\nu}$ 2910, 2150, 1670, 1616, 1587 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.50 (s, 3H, CH$_3$), 7.19-7.70 (m, 5H, ArH), 7.87 (s, 1H, ArH); MS (70 eV) $m/z$ = 283, 284 (M+1).

Analysis Calculated for C$_{13}$H$_9$N$_5$OS (283.31): Calcd: C, 55.11; H, 3.20; N, 24.72%; Found: C, 55.23; H, 3.25; N, 24.67%

**Experiment No. 6: Synthesis of 5-isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo (38) and 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate, (40):**

![Diagram](image_url)

**General procedure:**

5-Isocyanato-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazolo, (38) A solution of azido thieno[2,3-c]pyrazol 37 (10 mmol) in anhydrous toluene (50 ml) was refluxed for 2 hours (TLC check, chloroform: methanol, 9:1) after complete reaction further reaction with isocyante 38 were best conducted using these toluene solution.

3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate, (40) Appropriate alcohol 39a-c (10 ml) was added to the solution of isocyante (10 mmol) 38 in toluene (50 ml). The mixture was refluxed for 1 hour (TLC check, chloroform: methanol, 9:1). After completion of the reaction, the separated solid was isolated by filtration, wash with water, dried and recrystallized to yield carbamates 40a, 40b and 40c.
Methyl-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate, (40a).
Recrystallized from ethanol:DMF, (9:1); colorless amorphous solid; Yield 0.246 g, (86%); mp.: 132-134 °C; IR (KBr): \( \tilde{\nu} \) 3286, 2954, 1693, 1512, 1269 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): \( \delta \) 2.42 (s, 3H, CH\(_3\)), 3.72 (s, 3H, OCH\(_3\)), 6.58 (s, 1H, ArH), 7.24-7.67 (m, 5H, ArH), 10.79 (bs, 1H, NH); MS (70 eV) \( m/z = 287 \).
Analysis Calculated for C\(_{14}\)H\(_{13}\)N\(_3\)O\(_2\)S (287.34): Calcd: C, 58.52; H, 4.56; N, 14.62%
Found: C, 58.22; H, 4.51; N, 14.70%

Ethyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate, (40b).
Recrystallized from Ethanol:DMF, (9:1); white amorphous solid; Yield 0.282 g, (94%); mp.: 112-114 °C; IR (KBr): \( \tilde{\nu} \) 3259, 2985, 1693, 1537, 1261 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): \( \delta \) 1.24 (t, \( J = 5.4 \) Hz, 3H, CH\(_3\)), 2.48 (s, 3H, CH\(_3\)), 4.16 (q, \( J = 5.4 \) Hz 2H, OCH\(_2\)), 6.54 (s, 1H, ArH), 7.22-7.65 (m, 5H, ArH), 10.73 (bs, 1H, NH); \(^13\)C NMR (DMSO-d\(_6\)): \( \delta \) 12.6, 14.3, 61.1, 97.8, 116.5, 124.8, 126.8, 129.7, 135.5, 137.4, 139.0, 141.4, 153.4; MS (70 eV) \( m/z = 301 \).
Analytical Calculated for C\(_{15}\)H\(_{15}\)N\(_3\)O\(_2\)S (301.36): Calcd: C, 59.78; H, 5.02; N, 13.94%
Found: C, 59.48; H, 4.98; N, 13.99%

Isopropyl 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-ylcarbamate, (40c).
Recrystallized from Ethanol:DMF, (9:1); white amorphous solid; Yield 0.252 g, (80%); mp.: 220-222 °C; IR (KBr): \( \tilde{\nu} \) 3264, 2973, 1689, 1520, 1266 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): \( \delta \) 1.28 (d, \( J = 6.3 \) Hz, 6H, 2xCH\(_3\)), 2.41 (s, 3H, CH\(_3\)), 4.90 (septet, \( J = 6.3 \) Hz, 1H, CH), 6.57 (s, 1H, ArH), 7.23-7.71 (m, 5H, ArH), 10.74 (bs, 1H, NH); MS (70 eV) \( m/z = 315 \).
Experiment No. 7: Synthesis of 3-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)urea, (42):

General procedure
A appropriate primary amine 41a-c (10 mmol) was added to the solution of isocyante 38 (10 mmol) in toluene (50 ml) (As prepared in Experimental No. 6, Page No. 182). The mixture was refluxed for 0.5 hour (TLC check, chloroform: methanol, 9:1). After completion of the reaction the separated solid was collected by filtration, wash with water and dried. The solid was recrystallised Ethanol:DMF, 7:3 to afforded urea 42a-c.

1-(3-Chlorophenyl)-3-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)urea, (42a)
Recrystallized from Ethanol:DMF, (7:3); colorless amorphous solid; Yield 0.324 g, (85%);
mp.: 252-254 °C; IR (KBr) $\tilde{\nu}$ 3317, 3268, 2922, 1639, 1593, 1408, 1234 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 2.43 (s, 3H, CH$_3$), 6.59 (s, 1H, ArH), 7.10 (d, 2H, ArH), 7.23-7.69 (m, 7H, ArH), 8.78 (bs, 1H, NH), 9.69 (bs, 1H, NH); MS: (m/z) = 382, (M+2) 384.
Analysis Calculated for C19H15ClN4OS (382.87): Calcd: C, 59.60; H, 3.95; N, 14.63%
Found: C, 59.55; H, 3.90; N, 14.69%

1-(3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)-3-p-tolylurea, (42b).
Recrystallized from Ethanol:DMF, (7:3); colorless amorphous solid; Yield 0.325 g, (90%);
mp.: 231-233 °C; IR (KBr): ν 3315, 3273, 2918, 1642, 1597, 1508, 1249 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): δ 2.44 (s, 3H, CH\(_3\)), 2.49 (s, 3H, CH\(_3\)), 6.64 (s, 1H, ArH), 7.02-7.72 (m, 9H, ArH), 9.12 (bs, 1H, NH), 9.87 (bs, 1H, NH); \(^13\)C NMR (DMSO-d\(_6\)): δ 12.8, 97.3, 116.5, 116.9, 117.9, 121.9, 124.8, 126.6, 129.8, 130.4, 133.2, 136.3, 137.4, 139.2, 140.8, 141.4, 151.8; MS (70 eV) \(m/z\) = 362.

Analysis Calculated for C\(_{20}\)H\(_{18}\)N\(_4\)OS (362.45): Calcd: C, 66.28; H, 5.01; N, 15.46%
Found: C, 66.14; H, 5.02; N, 15.40%

1-(4-Methoxyphenyl)-3-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)urea, (42c).
Recrystallized from Ethanol:DMF, (7:3); gray amorphous solid; Yield 0.325 g, (86%);
mp.: 243-245 °C; IR (KBr): ν 3309, 3267, 2924, 1635, 1573, 1249 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): δ 2.49 (s, 3H, CH\(_3\)), 3.72 (s, 3H, OCH\(_3\)), 6.57 (s, 1H, ArH), 6.89 (d, \(J = 9\) Hz, 2H, ArH), 7.23-7.89 (m, 7H, ArH), 8.69 (bs, 1H, NH), 9.66 (bs, 1H, NH); MS (70 eV) \(m/z\) = 378.

Analysis Calculated for C\(_{20}\)H\(_{18}\)N\(_4\)O\(_2\)S (378.45): Calcd: C, 63.47; H, 4.79; N, 14.80%
Found: C, 63.53; H, 4.77; N, 14.84%
Experiment No. 8: Synthesis of S-phenyl-N-3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-y carbamo thioate, (44):

Procedure:

Thiophenol 43 (10 mmol) was added to a solution of isocyanate (10 mmol) 38 in toluene (50 ml). The mixture was refluxed for 1 hour (TLC check, chloroform: methanol, 9:1). After completion of the reaction the separated solid was collected by filtration, wash with water and dried. Carbamothioate 44 was recrystallized from ethanol:DMF, 8:2 Recrystallized from Ethanol:DMF, (8:2); pale yellow amorphous solid; Yield 0.292 g, (80%);

mp.: 257-259 °C; IR (KBr): \( \tilde{\nu} \) 3251, 2920, 1647, 1512, 1246 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): \( \delta \) 2.44 (s, 3H, CH\(_3\)), 6.68 (s, 1H, ArH), 7.22-7.78 (m, 10H, ArH), 11.90 (bs, 1H, NH);

MS (70 eV) \( m/z = 365 \).

Analysis Calculated for C\(_{19}\)H\(_{15}\)N\(_3\)OS\(_2\) (365.47): Calcd: C, 62.44; H, 4.14; N, 11.50%
Found: C, 62.34; H, 4.11; N, 11.53%
Experiment No. 9: Synthesis of 3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-amine, (45):

\[
\text{Procedure:}
\]

**Method I:** A solution of acid 34 (0.258 g, 0.01 mmol) in chloroform (20 ml) and Conc. H\(_2\)SO\(_4\) (4.8 ml), was heated in an oil bath at 40-45 °C, and (1.3g, 0.02 mmol) of sodium azide was added over a period of 1.5 hours. After complete addition of sodium azide, the reaction mixture was heated at 50 °C for 1.5 hours, and cooled in an ice bath. The cold solution of sodium hydroxide (10 g, 30 ml of water) was added slowly to reaction mixture until the pH of the mixture is approximately 12-13. The solid precipitated was
collected by filtration, dried, purified by column chromatography eluent hexan:ethylacetate (6:4).

**Method II:** A solution of carbamate 40b (10 mmol) in ethanol (20 ml) was refluxed by adding aqueous KOH (0.06 g, 0.01 mol) for 2 hours, (TLC check, ethylacetate: hexane 8:2). After completion of the reaction, cooled the reaction mixture and poured in ice cold water. The separated solid was collected by filtration.

**Method III:** Potassium hydroxide (1.12 g, 20 mmol) in H₂O (2 ml) was added under vigorous stirring to isocyanate 38 (10 mmol) in toluene (50 ml) at 0 °C. After 15 minute diethyl ether (50 ml) was added to promote the crystallization of potassium carbamate, which was filtered, washed with diethyl ether and poured into water (25 ml). By careful addition of 1N HCl (~40 ml), the pH was adjusted to 5 and the mixture was immediately extracted with DCM (3x 75 ml) when the emission of CO₂ subsided after drying. The solvent was evaporated and amine 45 thus obtained was recrystallized from suitable solvent Recrystallized from Ethanol:DMF, (9:1); off white amorphous solid;

Yield **Method-I:** 0.961 g, (42%); **Method-II:** 1.23 g, (54%); **Method-III:** 1.03 g, (45%);

mp.: 240-242 °C; IR (KBr): ν 3435, 3273, 2920, 2854, 2776, 1635, 1573, 1508, 1109 cm⁻¹; ¹H NMR (CDCl₃): δ 2.59 (s, 3H, CH₃), 6.94 (s, 1H, ArH), 7.39-7.60 (m, 5H, ArH), 8.46 (bs, 2H, NH₂); MS (70 eV) m/z = 229.

Analysis Calculated for C₁₂H₁₁N₃S (229.30):

Calcd: C, 62.86; H, 4.84; N, 18.33%

Found: C, 62.76; H, 4.87; N, 18.29%
Experiment No. 10: Synthesis of 3,5-Dimethyl-1-phenyl-1H-thieno[2,3-c]pyrazole, (46) and (3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanol, (47):

Procedure

3,5-Dimethyl-1-phenyl-1H-thieno[2,3-c]pyrazole (46).
A solution of 33 (0.286 g, 1 mmol) in tetrahydrofuran (THF) (5 ml) was slowly added into the dispersed lithium aluminium hydride (LAH) (0.114 g, 3 mmol) in tetrahydrofuran (5 ml) at 0-5 °C. After addition, the reaction mass was allowed to stand at RT and further stirred for 8 hours at 60 °C. After completion of reaction (TLC check, chloroform :methanol, 9:1), the reaction mass was quenched in saturated sodium sulphate solution (2-3 ml) at 0-5°C and extracted with ethyl acetate (15 x 3 ml). The combined organic layer was washed with water (5 x 3 ml), then dried over anhydrous sodium sulphate and
filtered. The solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered and dried under high vacuum.

Recrystallized from ethanol; off white amorphous solid; Yield 0.177 g, (78%); mp.: 153-155 °C; IR (KBr): $\tilde{\nu}$ 2962, 2924, 2854, 1593, 1500, 1261 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.32 (s, 3H, CH$_3$), 2.45 (s, 3H, CH$_3$), 6.87 (s, 1H, ArH), 7.19-7.64 (m, 5H, ArH); MS (70 eV) m/z = 228.

Analysis Calculated for C$_{13}$H$_{12}$N$_2$S (228.31): Calcd: C, 68.39; H, 5.30; N, 12.27%; Found: C, 68.47; H, 5.34; N, 12.22%

3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanol (47).

A solution of 33 (0.286 g, 1 mmol) in tetrahydrofuran (5 ml) was added slowly into the dispersed lithium aluminium hydride (0.076 g, 2 mmol) in tetrahydrofuran (5 ml) at 0-5 °C. After addition of LAH, the reaction mass was allowed to stand at RT and further stirred for 0.5 hour. After completion of reaction (TLC check, chloroform: methanol, 9:1), the reaction mass was quenched in saturated sodium sulphate solution (2-3 ml) at 0-5 °C and extracted with ethyl acetate (5 x 3 ml). The combined organic layer was washed with water (5 x 3 ml), then dried over anhydrous sodium sulphate, filtered and the solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered and dried under high vacuum.

Recrystallized from Ethanol; pale yellow crystalline solid; Yield 0.124 g, (51%); mp.: 98-100 °C; IR (KBr): $\tilde{\nu}$ 3275, 2889, 1597, 1504, 1408, 1226 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 2.45 (s, 3H, CH$_3$), 4.66 (s, 2H, CH$_2$), 5.74 (bs, 1H, OH), 7.04 (s, 1H, ArH), 7.26-7.71 (m, 5H, ArH); $^{13}$C NMR (DMSO-d$_6$): $\delta$ 12.8, 60.5, 112.9, 117.0, 124.9, 129.8, 139.2, 141.4, 141.5, 142.4; MS (70 eV) m/z = 244.
Analysis Calculated for C$_{13}$H$_{12}$N$_2$OS (244.31): Calcd: C, 63.91; H, 4.95; N, 11.47%
Found: C, 63.85; H, 4.97; N, 11.41%

**Experiment No. 11: Synthesis of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbaldehyde, (48):**

![Chemical Structures](image)

**Procedure:**
To the solution of 48 (0.244 g, 1 mmol) in acetonitrile (5 ml), manganese (IV) dioxide (0.150 g) was added. The reaction mixture was stirred at 25 °C for 12 hours. After completion of the reaction (TLC check, chloroform: methanol, 9:1), the reaction mass was filtered through celite and solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered and dried under vacum.

Recrystallized from aqueous ethanol; pale yellow crystalline solid; Yield 0.198 g, (82%); mp.: 121-123 °C; IR (KBr): 2924, 2796, 1739, 1670, 1512, 1219 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 2.53 (s, 3H, CH$_3$), 7.33-7.74 (m, 5H, ArH), 8.23 (s, 1H, ArH), 9.93 (s, 1H, H-C=O); $^{13}$C NMR (CDCl$_3$): $\delta$ 13.0, 117.3, 117.7, 126.0, 126.9, 129.4, 129.9, 131.0, 138.9, 141.3, 144.8, 145.3, 184.1; MS (70 eV) $m/z$ = 242.

Analysis Calculated for C$_{13}$H$_{10}$N$_2$OS (242.30): Calcd: C, 64.44; H, 4.16; N, 11.56%
Found: C, 64.37; H, 4.17; N, 11.59%

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Experiment No. 12: Synthesis of 5-(chloromethyl)-3-methyl-1-phenyl-1H-thieno [2,3-c]pyrazole, (49):

![Chemical Structure]

Procedure:
A mixture of thieno[2,3-c]pyrazol-5-yl)methanol 47 (0.244 g, 1 mmol) and excess of thionyl chloride (10 ml) stirred at refluxed temperature for 3 hours (TLC check, chloroform: methanol, 9:1) After completion of reaction, excess of thionyl chloride was removed under reduce pressure. The residue was poured in crushed ice (20 g), neutralized with saturated Na2CO3 (~20 ml), seprated solid was collected by filtration. Recrystalized from ethanol; yellow amorphous solid; Yield 0.199 g, (76%); mp.: 94-96 °C; IR (KBr): ν 2922, 1612, 1588, 1210 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.44 (s, 3H, CH\(_3\)), 4.49 (s, 2H, CH\(_2\)), 6.98 (s, 1H, ArH), 7.23-7.73 (m, 5H, ArH); MS (70 eV) \(m/z = 262, 264\) (M+2).

Analysis Calculated for C\(_{13}\)H\(_{11}\)ClN\(_2\)S(262.76): Calcd: C, 59.42; H, 4.22; N, 10.66%

Found: C, 59.49; H, 4.26; N, 10.70%
**Experiment No. 13: Synthesis of 3-Methyl-5-(2-nitrovinyl)-1-phenyl-1H-thieno[2,3-]pyrazole, (50):**

![Chemical Structure](image)

**Procedure:**

The reaction mixture of 48 (2.42 g, 0.01 mol) and nitromethane (7.3 g, 0.12 mol) was cooled to 0-5 °C. Aqueous NaOH (0.4 g, 0.01 mol) was added drop wise in reaction mixture with vigorous stirring for 30 minute. The reaction mixture was then poured in 1N HCl (~20-30 ml) ice cold water (50 ml). The yellow solid separated was collected by filtration, washed with cold water.

Recrystallized from aqueous methanol; yellow crystalline solid; Yield 1.93 g, (68%); mp.: 164-166 °C; IR (KBr): $\bar{\nu}$ 2958, 1608, 1508, 1323, 1261 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.49 (s, 3H, CH$_3$), 7.26-7.71 (m, 7H, ArH), 7.73 (d, $J$ = 8 Hz, 1H, =CH) 8.15 (d, $J$ = 8 Hz, 1H, =CH-NO$_2$); MS (70 eV) $m/z$ = 285.

Analysis Calculated for C$_{14}$H$_{11}$N$_3$O$_2$S (285.35): Calcd: C, 58.93; H, 3.89; N, 14.73%

Found: C, 58.83; H, 3.91; N, 14.68%
Experiment No. 14: 3-Methyl-5-(2-nitroethyl)-1-phenyl-1H-thieno[2,3-c]pyrazole, (51):

![Chemical Reaction](attachment:image.png)

**Procedure:**

To the stirred solution of compound 50 (0.285 g, 0.01 mol) in methanol (10 ml) at 0-10 °C, sodium borohydrde (NaBH₄) (0.037 g, 0.01 mol) was added portionwise with constant stirring for 1 hour (TLC check, chloroform: methanol, 9:1). After completion of the reaction, the mixture was poured into the icecold water (100 ml) and neutralized with aqueous acetic acid (~20 ml). The solid separated was collected by filtration and washed with cold water.

Recrystallized from Ethanol; Colorless amorphous solid; Yield 0.223 g, (78%);
mp.: 113-115 °C; IR (KBr): ν 2934, 1622, 1538, 1327, 1254 cm⁻¹; ¹H NMR (CDCl₃): δ 2.48 (s, 3H, CH₃), 4.65 (t, J = 7.8 Hz, 2H, CH₂), 5.64 (t, J = 7.8 Hz, 2H, CH₂), 7.02 (s, 1H, ArH), 7.27-7.72 (m, 5H, ArH); MS (70 eV) m/z = 287.

Analysis Calculated for C₁₄H₁₃N₃O₂S (287.34): Calcd: C, 58.52; H, 4.56; N, 14.62%

Found: C, 58.44; H, 4.59; N, 14.67%
Experiment No. 15: 2-(3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)ethanamine, (52):

Procedure:

A mixture of 51 (0.287 g, 0.01 mol), iron (powder) (0.275 g, 0.05 mol), acetic acid (20 ml) and THF (10 ml) was stirred at 60 °C under inert atmosphere for 3.0 hours. After cooling to 25 °C, the reaction mixture was filtered over celite and washed with THF (50 ml). The filtrate was basified with 10 N NaOH (10 ml). Solution was extracted in ethyl acetate (3x50ml), dried over anhydrous Na₂SO₄, filtered and concentrated to obtain crude product 52. Purification of crude product was done by column chromatography on silica using methanol:chloroform (1:9) as an eluent gave pure compound 52.

Pale yellow crystalline solid; Yield 0.115 g, (45%);

mp.: 163-165 °C; IR (KBr): $\overline{\nu}$ 3334, 3222, 2954, 1623, 1544, 1261 cm⁻¹; $^1$H NMR (CDCl₃): $\delta$ 2.45 (s, 3H, CH₃), 3.17 (t, $J = 6.9$ Hz, 2H, CH₂), 3.69 (t, $J = 6.9$ Hz, 2H, CH₂), 4.09 (bs, 2H, NH₂), 6.94 (s, 1H, ArH), 7.20-7.75 (m, 5H, ArH); MS (70 eV) m/z = 257.

Analysis Calculated for C₁₄H₁₅N₃S (257.35): Calcd: C, 65.34; H, 5.87; N, 16.33%
Experiment No. 16: Synthesis of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxamide, (53):

![Synthesis Reaction](image)

Procedure:
A mixture of compound 36 (0.276 g, 0.01 mol) and 30% ammonia solution (20 ml) was stirred at 0-5 °C for 3 hours (TLC check, chloroform: methanol, 9:1). After completion of the reaction, the reaction mixture was poured in ice cold water; the separated precipitate was collected by filtration, washed with cold water and dried.
Recrystalized from Ethanol:DMF 9:1; Colorless amorphous solid; Yield 0.226 g, (88%); mp.: 178-180 °C; IR (KBr): $\bar{v}$ 3363, 3178, 2924, 2854, 1651, 1600, 1504 cm$^{-1}$.
$^1$H NMR (CDCl$_3$): $\delta$ 2.46 (s, 3H, CH$_3$), 7.30-7.75 (m, 5H, ArH), 7.92 (s, 1H, ArH), 8.12 (bs, 2H, NH$_2$); $^{13}$C NMR (CDCl$_3$): $\delta$ 12.0, 116.1, 117.1, 124.3, 129.9, 136.0, 138.1, 141.6, 142.7, 163.6; MS (70 eV) m/z = 257.

Analysis Calculated for C$_{13}$H$_{11}$N$_3$OS (257.31): Calcd: C, 60.68; H, 4.31; N, 16.33%
Found: C, 60.57; H, 4.36; N, 16.30%
Experiment No. 17: Synthesis of 3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonitrile (54) and (3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanamine, (55):

Procedure:

3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazole-5-carbonitrile, (54)

The reaction mixture of 53 (0.257 g, 0.01 mol), in 25 ml POCl₃ was stirred at room temperature for 3 hours (TLC Check, chloroform: methanol, 9:1). After completion of the reaction; excess POCl₃ was removed under reduced pressure. The reaction mixture was poured on crush ice (50 g) and neutralized with solid Na₂CO₃ (~20-25 g). The separated solid was collected by filtration, washed with cold water and dried.
Recrystallized from ethanol:DMF, (9:1); pale yellow amorphous solid; Yield 0.167 g, (70%);
mp.: 93-95 °C; IR (KBr): $\nu$ 2924, 2206, 1597, 1535, 1508, 1280 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.44 (s, 3H, CH$_3$), 7.30-7.75 (m, 5H, ArH), 8.01 (s, 1H, ArH); $^{13}$C NMR (CDCl$_3$): $\delta$ 12.59, 104.0, 114.1, 116.9, 125.9, 129.0, 129.8, 137.9, 141.6, 142.9, 143.8.
MS (70 eV) $m/z$ = 239.
Analysis Calculated for C$_{13}$H$_9$N$_3$S (239.30): Calcd: C, 65.25; H, 3.79; N, 17.56%
Found: C, 65.31; H, 3.74; N, 17.59%

(3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanamine (55).

General Procedure:
**Method I**

To the solution of 53 (0.257 g, 1 mmol) in tetrahydrofuran (5 ml) dispersed lithium aluminium hydride (0.076 g, 2 mmol) in tetrahydrofuran (5 ml) was added slowly at 0-5 °C. After addition the reaction mass was stirred for 12 hours at 60 °C (TLC check, ethylacetate: hexane, 6:4). After completion of reaction, the reaction mass was quenched in saturated sodium sulphate solution (2-3 ml) and extracted with ethyl acetate (5 x 3 ml). The combined organic layer was washed with water (5 x 3 ml), then dried over anhydrous sodium sulphate and filtered. The solvent was evaporated under reduced pressure, the crude solid was washed with methanol, dried under high vaccum and recrystallized from ethanol.

**Method II**
A solution of 54 (0.239 g, 1 mmol) in tetrahydrofuran (5 ml) was added slowly in the dispersed lithium aluminium hydride (0.076 g, 2 mmol) in tetrahydrofuran (5 ml) at 0-5°C, after addition the reaction mass was stirred for 8 hours at 45°C (TLC check, ethylacetate: hexane, 6:4). The reaction mass was quenched in saturated sodium sulphate solution (2-3 ml) at 0-5°C and extracted with ethyl acetate (5 x 3 ml). The combined organic layer was washed with water (5 x 3 ml). Then dried over anhydrous sodium sulphate, filtered and the solvent was evaporated under reduced pressure, the crude solid was washed with methanol, filtered, dried under high vacuum and recrystallized with ethanol.

**Method I:** Yield 0.116 g, (48%); **Method II:** Yield 0.150 g, (62%); pale yellow crystalline solid;

mp.: 271-273°C; IR (KBr): \( \tilde{\nu} \) 3433, 3280, 3059, 2924, 1627, 1597, 1261 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)): \( \delta \) 2.50 (s, 3H, CH\(_3\)), 4.13 (s, 2H, CH\(_2\)), 5.60 (br, 2H, NH\(_2\)), 7.59-7.75 (m, 5H, ArH), 8.03 (s, 1H, ArH); MS (70 eV) \( m/z = 243 \).

Analysis Calculated for C\(_{13}\)H\(_{13}\)N\(_3\)S (243.33):

Calcd: C, 64.17; H, 5.39; N, 17.27%

Found: C, 64.12; H, 5.44; N, 17.29%

**Experiment No. 16:** Synthesis of N-hydroxy-1-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl) methanimine, (55) and (3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanamine, (57):
Procedue:

Synthesis of N-hydroxy-1-(3-methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanimine 57:

To a stirred solution of hydroxylamine hydrochloride 56 (0.125 g, 18 mmol) in ethanol (10 ml), potassium hydroxide (0.120 g, 20 mmol) was added. The resulting mixture was stirred at room temperature for 20 minute. Then solution of aldehyde 48 (0.363 g, 15 mmol) in ethanol (15 ml) was added dropwise. The mixture was then heated to reflux for 4 hours and then cooled to room temperature. The reaction mixture was poured in water (100 ml) and extracted with dichloromethane (4 × 40 ml). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to get oxime 44, which was used directly without further purification.

Colorless amorphous solid; Yield 0.226 g, (88%); mp.: 158-160 °C; IR (KBr): \( \nu \) 3178, 2781, 1627, 1597, 1512, 1215 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)): \( \delta \) 2.46 (s, 3H, CH\(_3\)), 7.28-7.74 (m, 5H, ArH), 7.89 (s, 1H, ArH), 8.35 (s, 1H, C=H), 11.29 (bs, 1H, OH); MS (70 eV) \( m/z \) = 257.

Analysis Calculated for C\(_{13}\)H\(_{11}\)N\(_3\)OS (257.31): Calcd: C, 60.68; H, 4.31; N, 16.33%

Found: C, 60.74; H, 4.38; N, 16.39%

Method III
(3-Methyl-1-phenyl-1H-thieno[2,3-c]pyrazol-5-yl)methanamine (55).

**Procedure:** To a solution of oxime 57 (5 mmole) in methanol (10 ml), ammonium formate (20 mmole) and zinc dust (10 mmol) was added. The mixture was stirred under reflux for 4-5 hours. (TLC check, ethylacetate/hexane, 8:2). After completion of the reaction, the reaction mixture was filtered through celite. The filtrate was evaporated under vaccum and the residue was stirred in chloroform, washed with water. The organic layer was dried over anhydrous sodium sulphate and the solvent was remove under reduced pressure. Solid was purified by column chromatography. **Method III :** Yield 0.157 g, (65%)

### 3.6 References:


[37] Brown, K. J.; Meth-Cohn, O. Tetrahedron, 1974, 46, 4069.