Tetrahedron Vol 46, No 7, pp 2561-2572, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

CYCLOAROMATIZATION OF α-OXOKETENE DITHIOACETALS WITH LITHIOACETONITRILE AND LITHIOPROPIONITRILE: A FACILE ROUTE TO SUBSTITUTED AND ANNELATED PYRIDINES

Arun K. Gupta, Hiriyakkanavar Ila* and Hiriyakkanavar Junjappa*

Department of Chemistry, North-Eastern Hill University,
Shillong 793 003, Meghalaya, India

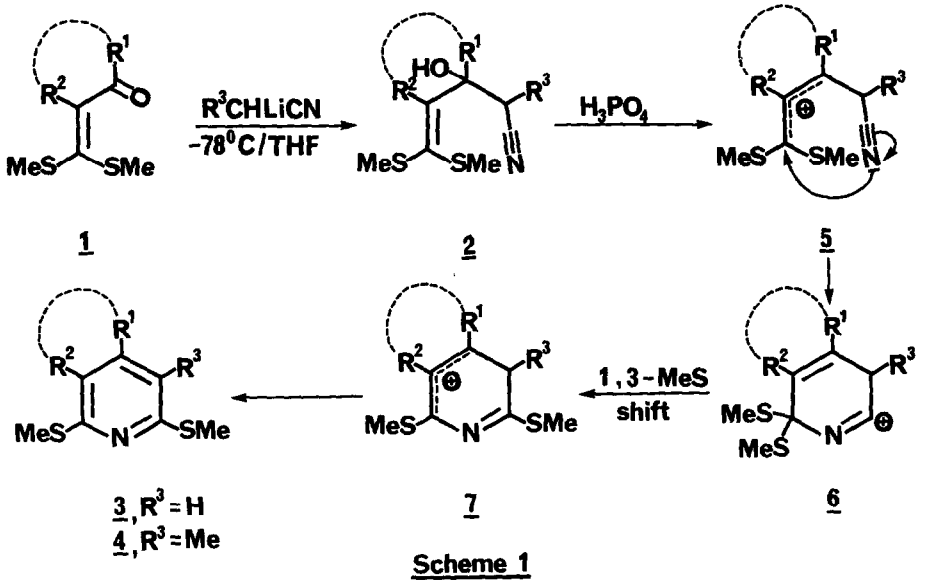
(*Received in UK 22 November* 1989)

Abstract: The enolacetals 2 obtained by 1,2-addition of lithioacetonitrile or lithiopropionitrile to α-oxoketene dithioacetals 1 undergo intramolecular Ritter reaction accompanied with 1,3-MeS shift in the presence of phosphoric acid to afford a variety of substituted and annelated 2,6-bis(methylthio)pyridines 3 and 4 respectively in good yields. Cyclization of 2 in the presence of bromine and acetic acid yielded the corresponding 2-bromo-6-methylthio-4,5-substituted and annelated pyridines 9 in good yields. The bis(methylthio) groups in 3 could either be removed with Raney Nickel or replaced by methyl group in the presence of triphenylphosphine-Nickel chloride complex to afford the corresponding desulphurized (8) or methylated (15) pyridines in good yields. Attempted cyclization of enolacetals 2a, 2p and 2s in the presence of borontrifluoride etherate and methanol yielded only the dienes 14a-b and β-cyanomethyl-α,β-unsaturated ester 14c respectively.

In a series of communications, we have recently reported the reactions of allyl[1], benzyl[2] Grignard reagents, 2-picolyllithium[3] and 3-methyl-5-lithiomethylisoxazole[4] with α-oxoketene dithioacetals to yield the corresponding aromatics as a part of our broad synthetic programme for the construction of aromatic and heteroaromatic ring from open-chain precursors. The propargylmagnesium halide[5] was shown to undergo exclusive 1,2-addition with 1 to give initially the corresponding carbinolacetals which underwent smooth cycloaromatization with participation of nucleophilic solvent through its triple bond to yield the corresponding functionalized aromatic compounds. We further considered of interest that the lithioacetonitrile should similarly add to 1 to give the corresponding enolacetals 2 (R^3=H) in which nitrogen atom is so positioned that it can participate in the new C-N bond formation involving Ritter type ring closure to yield the corresponding substituted and annelated pyridines. The acid assisted ring closure should permit the participation of nucleophiles either intra- or intermolecularly so that the product pyridine carries the appropriate substituents. The reaction was indeed found to proceed through envisaged course involving intramolecular 1,3-MeS shift through cyclic cations 6 to afford 2,6-bis (methylthio)-4-(or 3,4-) substituted and annelated pyridines 3 in good yields (Scheme 1). Some of these results have been reported earlier in a preliminary communication[6]. We herein describe the detailed study of this novel pyridine synthesis including its scope and limitations.

Earlier studies have shown that the 3-hydroxyglutaronitriles[7] (or glutacononitriles),ζ-ketonitriles[8], the corresponding enolethers[9] and malononitrile dimer undergo intramolecular Ritter reaction[10] in the presence of bromine or hydrobromic acid to afford the corresponding

2-bromopyridines. However, general methodology for the synthesis of these intermediates is not satisfactory and consequently the pyridine synthesis based on these compounds is not further explored. We therefore considered that the enolacetals 2 obtained by regioselective 1,2-addition of lithioacetonitrile[11] to α-oxoketene dithioacetals 1 should prove useful substrates for the synthesis of substituted and annelated pyridines. The easy accessibility of 1 from wide variety of active methylene ketones makes them attractive intermediates for the efficient general synthesis of pyridine derivatives. In a typical experiment, when 2a was heated with phosphoric acid, after work-up, the product isolated was characterized as 2,6-bis(methylthio)-4-phenylpyridine(3a)(82%) (Table 1), which is apparently formed through intramolecular 1,3-MeS shift in the intermediate carbonium ion 6 (Scheme 1). Similarly, 4- and 3,4-substituted 2,6-bis(methylthio) pyridines 3b-j were prepared from the corresponding dithioacetals 1b-j in 52-79% overall yields (Table 1, entries 2-10). The reaction was equally facile with α-cinnamoylketene dithioacetals 1k-n, which underwent exclusive 1,2-addition with lithioacetonitrile in highly regioselective manner and the resulting carbinolacetals thus formed yielded the corresponding 2,6-bis(methylthio)-4-styrylpyridines 3k-n (entries 11-14) in good yields under the identical conditions (Table 1). The enolacetal 2o(R^1=C_6H_5; R^2=Me; R^3=H) derived from dithioacetal of propiophenone, however failed to yield the corresponding 2,6-bis(methylthio)-3-methyl-4-phenylpyridine (4a) under identical conditions. The α-methyl substituent appears to sterically inhibit the new C-N bond formation in the carbenium ion 5. The pyridine 4a could however be prepared by alternatively reacting the lithiopropionitrile[12] with 1a under described conditions (Table 1, entry 15). The corresponding 2,6-bis(methylthio)-3-methyl-4-(2-furyl)pyridine (4b) was similarly obtained in 54% yield by reaction of 1b with lithiopropionitrile under identical conditions.



Scheme 1

Table 1: Synthesis of 2,6-Bis(methylthio)-3,4-Substituted Pyridines 3 and 4

Entry	Starting material	$R^3CHLiCN$	Product[a] 3,4	R^1	R^2	R^3	%Yield[b] 3,4
1	1a	$LiCH_2CN$	3a	C_6H_5	H	H	82
2	1b	$LiCH_2CN$	3b	2-Furyl	H	H	71
3	1c	$LiCH_2CN$	3c	2-Thienyl	H	H	75
4	1d	$LiCH_2CN$	3d	3-Pyridyl	H	H	77
5	1e	$LiCH_2CN$	3e	2-Naphthyl	H	H	79
6	1f	$LiCH_2CN$	3f	Me	H	H	78
7	1g	$LiCH_2CN$	3g	Et	H	H	61
8	1h	$LiCH_2CN$	3h	Me	Me	H	68
9	1i	$LiCH_2CN$	3i	Et	Me	H	58
10	1j	$LiCH_2CN$	3j	Me	n-Bu	H	52
11	1k	$LiCH_2CN$	3k	$C_6H_5CH=CH-$	H	H	65
12	1l	$LiCH_2CN$	3l	$4\text{-}ClC_6H_4CH=CH-$	H	H	58
13	1m	$LiCH_2CN$	3m	$2\text{-}ClC_6H_4CH=CH-$	H	H	61
14	1n	$LiCH_2CN$	3n	$4\text{-}NO_2C_6H_4CH=CH-$	H	H	51
15	1a	MeCHLiCN	4a	C_6H_5	H	Me	67
16	1b	MeCHLiCN	4b	2-Furyl	H	Me	54

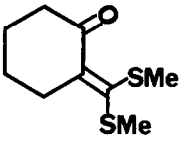
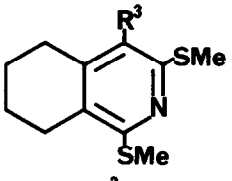
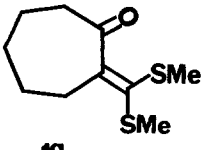
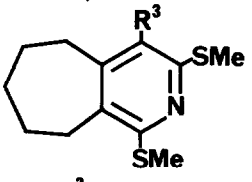
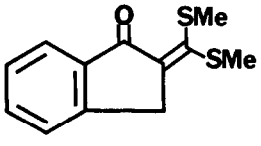
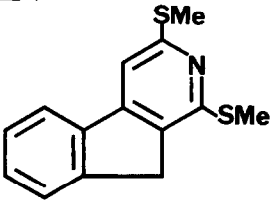
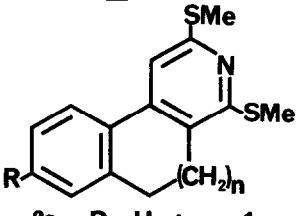
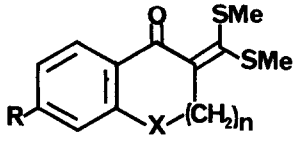
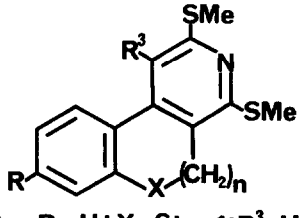
[a] Products obtained by phosphoric acid cyclization of the corresponding carbinolacetals 2;

[b] Yields of pure isolated products.

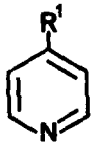
The reaction was successfully extended to cyclic ketene dithioacetals 1p-u to afford the corresponding tetrahydroisoquinoline 3p,4c and the other condensed pyridine derivatives 3q-u and 4d in 58-83% overall yields (Table 2, entries 1-8). Also the corresponding heteroannelated pyridines 3v-w and 4e were prepared under similar reaction conditions from the respective dithioacetals 1v and 1w in high yields (Table 2, entries 9-11). Some of the 2,6-bis(methylthio)pyridine (3a,3e,3f,3p and 3s) were desulphurized by treatment with Raney Nickel to yield the corresponding sulphurfree 4-substituted pyridines 8a-c, tetrahydroisoquinoline 8d and dihydrobenz[f]isoquinoline 8e respectively in good yields.

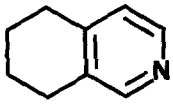
The plausible mechanism for the formation of 3 or 4 from 1 is described in Scheme 1. The formation of carbenium ion 5 through loss of OH group from 2 under acidic conditions facilitates the intramolecular Ritter type reaction at the end of chain to give cyclic cation 6 which on 1,3-methylthio shift and proton loss leads to product pyridines 3 or 4. The inter mediate cation 6 was trapped by bromide ion when the enolacetal 2a was subjected to cyclization in the presence of bromine in acetic acid to afford the corresponding 2-bromo-6-methylthio-4-phenylpyridine (9a) in 83% yield. The other substituted and fused bromopyridines 9b-d were similarly obtained from the corresponding carbinolacetals (2d, 2p and 2s) in 64-78%

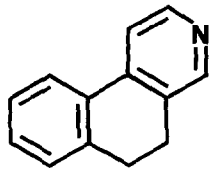
Table 2 Synthesis of 2,6-Bis(methylthio)-3,4-annelated Pyridines 3 and 4

Entry	Starting materials 1	RCHLiCN	Products 3, 4	%Yield 3, 4
				
1	1p	$LiCH_2CN$	3p, R^3= H	76
2	1p	MeCHLiCN	4c, R^3= Me	71
				
3	1q	$LiCH_2CN$	3q, R^3= H	70
4	1q	MeCHLiCN	4d, R^3= Me	73
				
5	1r	$LiCH_2CN$	3r	58
				
6	1s, R=H ; n=1	$LiCH_2CN$	3s, R=H ; n=1	83
7	1t, R=MeO; n=1	$LiCH_2CN$	3t, R=MeO; n=1	77
8	1u, R=H ; n=2	$LiCH_2CN$	3u, R=H ; n=2	68
				
9	1v, R=H ; X=S; n=1	$LiCH_2CN$	3v, R=H; X=S; n=1; R^3=H	76
10	1w, R=Me; X=S; n=2	$LiCH_2CN$	3w, R=Me; X=S; n=2; R^3=H	79
11	1w, R=Me; X=S; n=2	MeCHLiCN	4e, R=R^3=Me; X=S; n=2	75

overall yields (Scheme 2). The 1,3-MeS shift in the cation 6 was however found to be intramolecular since the corresponding asymmetrical dithioacetal 10 yielded only the 2-(ethylthio)-6-(methylthio)-4-phenylpyridine (12) (63%)(Scheme 3) under similar conditions and the products like 3a or the corresponding 2,6-bis(ethylthio)-4-phenylpyridine (13) expected from intermolecular migration of alkylthio group could not be detected in the reaction mixture.



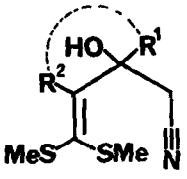


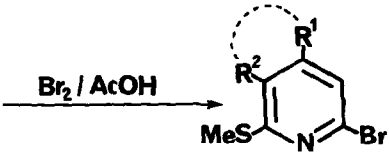


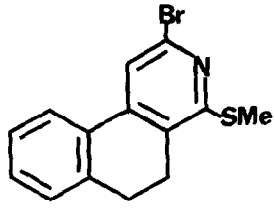
8a , R^1 = Ph
8b , R^1 = 2-naphthyl
8c , R^1 = Me

8d

8e





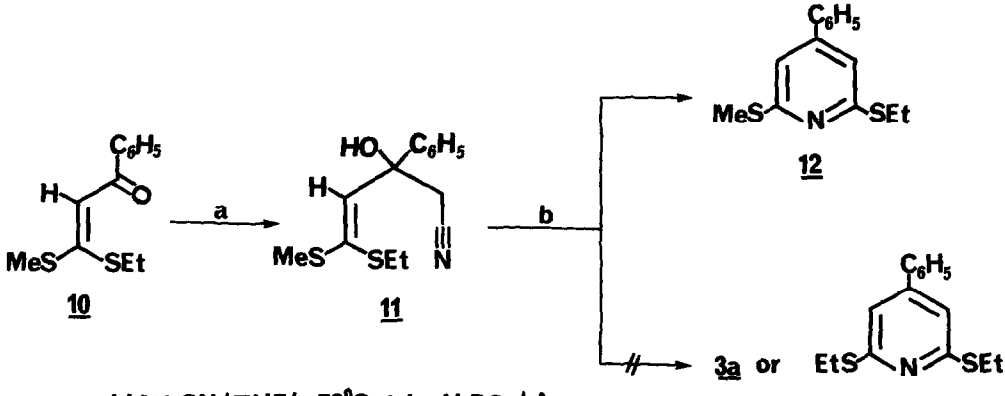


2a , 9a , R^1 = C_6H_5 ; R^2 = H
2d , 9b , R^1 = 3-pyridyl ; R^2 = H
2k , 9c , R^1 = R^2 = $-(CH_2)_4-$

9

9d

SCHEME 2



a , $LiCH_2CN$ / THF / -78°C ; b , H_3PO_4 / Δ

10

11

12

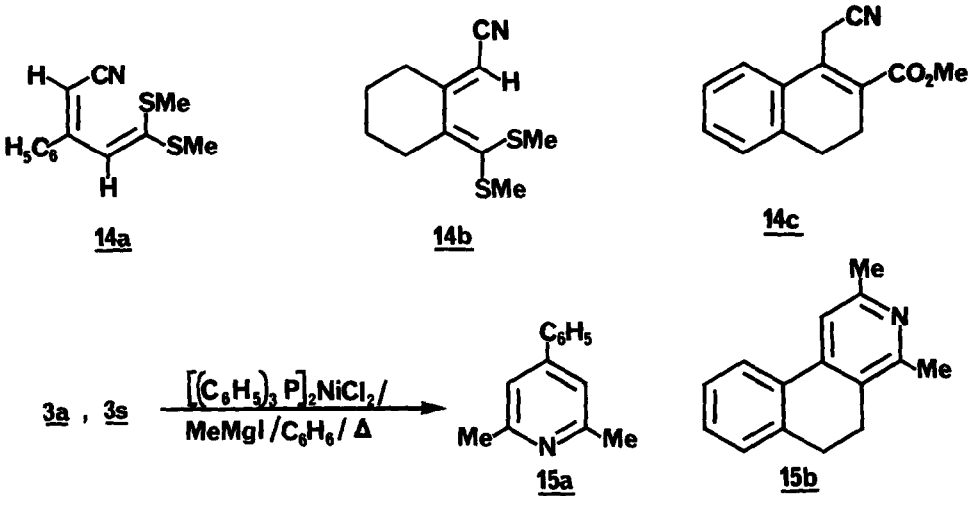
3a or

13

SCHEME 3

Attempts to trap the cation 6 with methanol by treatment of 2a with borontrifluoride etherate in refluxing methanol yielded only the diene 14a in 68% yield. The exocyclic diene 14b was similarly obtained from the carbinol 2p under identical conditions. The carbinolacetal 2s from ketene dithioacetal of α-tetralone, however, underwent methanolysis under these conditions to afford the corresponding β-cyanomethyl-α,β-unsaturated-O-methylester 14c in 69% yield.

The presence of two methylthio groups at 2,6-positions of the pyridine ring could be of considerable synthetic importance since these groups can be replaced by carbon nucleophiles. Thus when 3a was treated with methylmagnesium iodide in the presence of triphenylphosphine-Nickel chloride complex[13], the corresponding 2,6-dimethyl-4-phenylpyridine (15a) was obtained in 85% yield. Similarly the 2,4-dimethyl-5,6-dihydrobenz[f]isoquinoline (15b) was obtained from 3s in 79% yield under similar reaction conditions (Scheme 4).



Scheme 4

Thus in conclusion, with the availability of a wide structural variants of oxoketene dithioacetals from various active methylene ketones, their reaction with lithioacetonitrile and lithiopropionitrile provides a facile route to a variety of substituted and annelated pyridines with 2,6-bis(methylthio) groups which can either be removed completely to give sulphur free compounds or can be replaced by carbon nucleophiles. The intermediate carbonium ion 6 formed by intramolecular Ritter type reaction can be trapped intermolecularly by various nucleophiles. Further studies in this direction are in progress.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 297 spectrophotometer and ^{1}H NMR spectra were recorded at 90 MHz on a Varian EM 390 instrument with TMS as an internal standard. Mass spectra were determined on a Jeol JMS D-300 spectrometer and elemental

analyses were carried out by Heraeus CHN-O-RAPID instrument. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl immediately before use.

All oxoketene dithiocetals employed were reported earlier and prepared accordingly[14]. n-Butyllithium and W-4 Raney Nickel were prepared according to the reported procedures[15,16].

General Procedure for the Reaction of α-Oxoketene Dithioacetals with Lithioacetonitrile:

To a stirred solution of freshly distilled acetonitrile (0.5g, 12.5 mmol) in anhydrous THF (25 mL), n-BuLi(12.5 mmol) was added through syringe via a rubber septum under an efficient atmosphere of nitrogen at -78°C and the reaction mixture was further stirred for 0.5 hr at the same temperature. The resulting white suspension of lithioacetonitrile was treated (5 min.) with a solution of appropriate oxoketene dithioacetal 1 (10 mmol) in THF (50 mL) and the reaction mixture was allowed to warm to room temperature during 1 h with continuous stirring. It was then poured into saturated NH_4Cl solution, extracted with ether(2x50 mL), washed with water (150 mL), dried (Na_2SO_4) and concentrated in vacuo to give carbinolacetals 2 in nearly quantitative yield. In all the reactions, the crude carbinols 2 were used as such for subsequent transformations, while the crude 2a(2.5g) was purified by passing through silica gel column using hexane as eluent; colourless crystalline solid(hexane)(88%);mp 60-61°C; IR(KBr) 3415,2260,1567 cm^{-1}; ^1H NMR(CCl_4) δ 2.15(s,3H,SMe),2.31(s,3H,SMe),2.78(s, 2H,CH_2), 4.73(s,1H,OH,exchangeable with D_2O),6.30(s,1H,C=CH),7.18-7.53(m,5H,ArH).Anal.Calcd for $C_{13}H_{15}NOS_2$: C,58.83; H,5.70; N,5.28. Found: C,58.68; H,5.42; N,5.14.

General Procedure for the Reaction of α-Oxoketene Dithioacetals with α-Lithiopropionitrile:

To a stirred solution of diethylamine (1.01g, 12.5 mmol) and hexamethylphosphorus triamide (HMPT,2.03g,12.5 mmol) in 25 mL of THF at -15°C under N_2 atmosphere, n-butyllithium(12.5 mmol) was added rapidly followed by further stirring for 15 min. As soon as the blood red colour appeared, the reaction mixture was cooled to -78°C and a solution of propionitrile (0.65g,12.5 mmol) in THF (20 mL) was added through syringe via a rubber septum and it was further stirred for 10 min. A solution of appropriate oxoketene dithioacetal 1 (10 mmol) in THF(25 mL) was added and the reaction mixture was left at -78°C for 1 h. It was then quenched by pouring into saturated NH_4Cl solution (100 mL), extracted with ether(4x100 mL), the organic phase washed with water (150 mL),dried (Na_2SO_4) and evaporated to give crude carbinols which were used as such for subsequent transformations.

General Procedure for Cyclization of Carbinols 2 in the presence of Phosphoric Acid; Synthesis of Substituted and Annelated Bis(methylthio)pyridines 3 and 4: The crude carbinolacetals 2 obtained in above reactions were treated with orthophosphoric acid (25 mL,88%) at 130°C (3 hr), the reaction mixture after cooling was diluted with water (150 mL) and extracted with $CHCl_3$(4x100 mL). The combined organic phase was washed with water (100 mL), dried (Na_2SO_4) and evaporated to give crude 3 and 4 as viscous residues which were purified by column chromatography over silica-gel using EtOAc/hexane (1:20) as eluent.

2,6-Bis(methylthio)-4-phenylpyridine (3a): light yellow crystals (hexane); mp 86-87°C; IR (KBr) 1580,1525,1356 cm^{-1}; ^1H NMR(CCl_4) δ 2.56(s,6H,SMe),7.02(s,2H,H-3 and H-5),7.25-7.62(m, 5H,ArH);MS m/z 247(M^+,100%),213(24),201(12). Anal.Calcd for $C_{13}H_{13}NS_2$:C,63.12;H,5.30;N,5.66. Found: C,63.33; H,5.05; N,5.82.

2,6-Bis(methylthio)-4-(2-furyl)pyridine (3b): colourless crystals (hexane); mp 70°C; IR (KBr) 1601,1564,1530,1485 cm^{-1}; ^1H NMR(CCl_4) δ 2.54(s,6H,SMe), 6.44(brs,1H,H-4 furyl),6.74 (brd,1H,J=3.0Hz,H-3 furyl),7.04(s,2H,H-3 and H-5),7.46(brs,1H,H-5 furyl); MS m/z 237(M^+, 100%), 203(16), 191(12), 162(15). Anal. Calcd for $C_{11}H_{11}NOS_2$: C,55.67; H,4.67; N,5.70.Found: C,55.86; H,4.82; N,5.88.

2,6-Bis(methylthio)-4-(2-thienyl)pyridine (3c): light yellow crystals(hexane); mp 96-97°C; IR(KBr) 1580, 1532, 1517, 1373 cm^{-1}; ^1H NMR(CCl_4) δ 2.54(s,6H,SMe), 6.91(s,2H,H-3 and H-5), 7.00-7.42(m,3H,thienyl H); MS m/z 253(M^+,100%), 219(11), 207(15). Anal. Calcd for $C_{11}H_{11}NS_3$: C,52.14; H,4.38; N,5.53. Found: C,52.42; H,4.52; N,5.74.

2,6-Bis(methylthio)-4-(3-pyridyl) pyridine (3d): colourless crystals (EtOAc-hexane); mp 101-102°C; IR(KBr) 1578, 1514, 1364 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.60(s,6H,SMe), 7.04(s,2H,H-3 and H-5), 7.25-7.51(m,1H,pyridyl H), 7.76-7.93(m,1H,pyridyl H), 8.51-8.90(m,2H,pyridyl H); MS m/z 248(M^+,100%), 216(17), 201(12), 168(12). Anal. Calcd for $C_{12}H_{12}N_2S_2$: C,58.03; H,4.87; N,11.28. Found: C,58.27; H,4.65; N,10.99.

2,6-Bis(methylthio)-4-(2-naphthyl)pyridine (3e): colourless crystals ($CHCl_3$); mp 118-119°C; IR(KBr) 1570, 1520, 1498, 1430, 1368, 1330 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.61(brs,6H,SMe), 7.12(brs, 2H,H-3 and H-5), 7.22-8.02(m,7H,ArH); MS m/z 297(M^+,100%), 281(19), 263(17), 203(22). Anal. Calcd for $C_{17}H_{15}NS_2$: C,68.65; H,5.08; N,4.71. Found: C,68.42; H,4.88; N,4.98.

2,6-Bis(methylthio)-4-methylpyridine (3f): colourless crystals (hexane); mp 51-52°C; IR(KBr) 1569, 1503, 1404, 1364 cm^{-1}; ^1H NMR(CCl_4) δ 2.19(s,3H,Me), 2.54(s,6H,SMe), 6.61(s,2H,H-3 and H-5); MS m/z 185(M^+,100%), 151(24), 139(17), 105(20). Anal. Calcd for $C_8H_{11}NS_2$: C,51.85; H,5.98; N,7.56. Found: C,51.62; H,5.76; N,7.74.

2,6-Bis(methylthio)-4-ethylpyridine (3g): viscous oil; IR(neat) 1574, 1528, 1370, 1255 cm^{-1}; ^1H NMR(CCl_4) δ 1.16(t,3H,J=7.5 Hz,Me), 2.46(q,2H,J=7.5 Hz,CH_2), 2.50(s,6H,SMe), 6.60(s,2H, H-3) and H-5); MS m/z 199(M^+,100%), 165(26), 153(16). Anal. Calcd for $C_9H_{13}NS_2$: C,54.23; H,6.57; N,7.02. Found: C,54.39; H,6.32; N,6.81.

2,6-Bis(methylthio)-3,4-dimethylpyridine (3h): pale yellow crystals (hexane); mp 35-36°C; IR(KBr) 1568, 1548, 1433, 1414, 1368 cm^{-1}; ^1H NMR(CCl_4) δ 2.04(s,3H,Me), 2.11(s,3H,Me), 2.47 (s,6H,SMe), 6.56(s,1H,H-5); MS m/z 199(M^+,100%), 184(15), 166(90), 153(10), 138(19), 120(14). Anal. Calcd for $C_9H_{13}NS_2$: C,54.23; H,6.57; N,7.02. Found: C,54.08; H,6.38; N,7.22.

2,6-Bis(methylthio)-4-ethyl-3-methylpyridine (3i): light yellow viscous oil; IR(neat) 1568, 1530, 1410, 1370 cm^{-1}; ^1H NMR(CCl_4) δ 1.13(t,3H,J=7.5 Hz,Me), 2.10(s,3H,Me), 2.51(q,2H,J=7.5 Hz,CH_2), 2.54(s,6H,SMe), 6.63(s,1H,H-5); MS m/z 213(M^+,94%), 198(14), 180(100). Anal.Calcd for $C_{10}H_{15}NS_2$: C,56.29; H,7.09; N,6.57. Found: C,56.49; H,7.27; N,6.39.

2,6-Bis(methylthio)-3-(n-butyl)-4-methylpyridine (3j): light yellow crystals (pentane); mp 52-53°C; IR(neat) 1565, 1538, 1464,1434, 1410, 1375, 1340 cm^{-1}; ^1H NMR(CCl_4) δ 0.91(brt,3H, Me), 1.06-1.79(m,4H,CH_2), 2.14(s,3H,4-Me), 2.53(s,6H,SMe), 2.40-2.83(m,merged with SMe,2H, CH_2), 6.60(s,1H,H-5); MS m/z 241(M^+,36%). Anal. Calcd for $C_{12}H_{19}NS_2$: C,59.70; H,7.93;N,5.80. Found:C,59.51; H,7.67; N,5.52.

2,6-Bis(methylthio)-4-styrylpyridine (3k): colourless crystals (hexane); mp 106-107°C; IR (KBr) 1574, 1522, 1450, 1410, 1372 cm^{-1}; ^1H NMR($CDCl_3$) δ2.56(s,6H,SMe), 7.10(s,2H,H-3 and H-5), 7.20(d,J=17 Hz,1H,olefinic), 7.20-7.70(m,6H,ArH and olefinic); MS m/z 273(M^+,100%), 239(11). Anal. Calcd for $C_{15}H_{15}NS_2$: C,65.89; H,5.53; N,5.12. Found: C,65.67; H,5.74;N,4.91.

2,6-Bis(methylthio)-4-(4-chlorostyryl)pyridine (3l): yellow prisms (hexane); mp 154-155°C; IR(KBr) 1570, 1521, 1490, 1400, 1370 cm^{-1}; ^1H NMR($CDCl_3$) δ2.54(s,6H,SMe), 6.68(d,1H,J=18 Hz, olefinic), 6.81(s,2H,H-3 and H-5), 7.06(d,1H,J=18 Hz,olefinic), 7.11-7.42(m,4H,ArH); MS m/z 309(49%),307(M^+,100),273(10). Anal.Calcd for $C_{15}H_{14}ClNS_2$:C,58.52;H,4.58;N,4.55. Found: C,58.38; H,4.45; N,4.39.

2,6-Bis(methylthio)-4-(2-chlorostyryl)pyridine (3m): yellow prisms (hexane); mp 144-145°C; IR(KBr) 1572, 1524, 1464, 1436, 1368 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.60(s,6H,SMe),6.80(d,1H,J=18 Hz, olefinic), 6.94(s,2H,H-3 and H-5),7.12-7.70(m,4H,ArH), 7.60(d,1H,J=18 Hz,olefinic); MS m/z 309(42%),307(M^+,100). Anal. Calcd for $C_{15}H_{14}ClNS_2$: C,58.52;H,4.58;N,4.55. Found: C,58.29; H,4.35; N,4.72.

2,6-Bis(methylthio)-4-(4-nitrostyryl)pyridine (3n): yellow prisms ($CHCl_3$); mp 200-201°C;

IR(KBr) 1592,1571, 1521, 1505, 1432, 1409, 1372 cm^{-1}; ^1H NMR($CDCl_3$)δ 2.57(s,6H,SMe), 6.89 (d,1H,J=16 Hz,olefinic), 6.91(s,2H,H-3 and H-5), 7.20(d,1H,J=16 Hz,olefinic), 7.59(d,2H, A_2B_2,J=9 Hz,ArH), 8.20(d,2H,A_2B_2,J=9 Hz,ArH); MS m/z 318(M^+,100%). Anal. Calcd for $C_{15}H_{14}N_2O_2S_2$: C,56.58; H,4.43; N,8.80. Found: C,56.82; H,4.69; N,8.56.

2,6-Bis(methylthio)-3-methyl-4-phenylpyridine (4a): colourless crystals (hexane); mp 43-44°C; IR(KBr) 1542, 1459, 1372 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.04(s,3H,Me), 2.55(s,3H,SMe), 2.59(s, 3H,SMe),6.70(s,1H,H-5), 7.08-7.48(m,5H,ArH); MS m/z 261(M^+,100%), 228(44), 151(32). Anal. Calcd for $C_{14}H_{15}NS_2$: C,64.33; H,5.78; N,5.36. Found: C,64.21; H,5.64; N,5.24.

2,6-Bis(methylthio)-4-(2-furyl)-3-methylpyridine (4b): yellow crystals (hexane); mp 47-48°C; IR(KBr) 1588, 1554, 1530, 1490, 1410, 1324 cm^{-1}; ^1H NMR(CCl_4) δ 2.34(s,3H,Me), 2.56(s,6H, SMe), 6.51(m,1H,H-4 furyl), 6.65(brd,J=3 Hz,1H,H-3 furyl), 7.14(s,1H,H-5), 7.50(brs,1H,H-5 furyl); MS m/z 251(M^+,100%), 236(12), 218(85). Anal. Calcd for $C_{12}H_{13}NOS_2$: C,57.34;H,5.21; N,5.57. Found: C,57.08; H,5.07; N,5.41.

1,3-Bis(methylthio)-5,6,7,8-tetrahydroisoquinoline (3p): light yellow oil; IR(neat) 1570, 1542, 1440, 1415, 1330 cm^{-1}; ^1H NMR(CCl_4) δ 1.58-1.87(m,4H,CH_2), 2.44(s,3H,SMe), 2.46(s,3H, SMe), 2.32-2.72(m,merged with SMe signals,4H,CH_2), 6.51(s,1H,H-4); MS m/z 225(M^+,65%),210 (34), 192(100). Anal.Calcd for $C_{11}H_{11}NS_2$: C,58.62;H,6.71; N,6.22.Found: C,58.42;H,6.48;N,6.04.

1,3-Bis(methylthio)-6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridine (3q): colourless crystals (hexane); mp 77-78°C; IR(KBr) 1560, 1530, 1430, 1410, 1340, 1302 cm^{-1}; ^1H NMR(CCl_4) δ 1.40-1.84(m,6H,CH_2), 2.50(s,6H,SMe), 2.44-2.82(m,merged with SMe signal,4H,CH_2), 6.55(s,1H,H-4); MS m/z 239(M^+,79%), 206(100),178(17). Anal. Calcd for $C_{12}H_{17}NS_2$: C,60.20; H,7.16; N,5.85. Found: C,59.98; H,7.02; N,5.99.

2,4-Bis(methylthio)-indane-5H-[2,1-c]pyridine (3r): colourless crystals (hexane); mp 125-126°C; IR(KBr) 1582, 1534, 1460, 1430, 1405, 1348 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.64(s,3H,SMe),2.66 (s,3H,SMe),3.68(s,2H,CH_2), 7.20-7.90(m,5H,ArH); MS m/z 259(M^+,87%), 244(22), 226(100),196 (100),196(35).Anal.Calcd for $C_{14}H_{13}NS_2$:C,64.83; H,5.05; N,5.40.Found:C,64.59;H,5.22;N,5.27.

2,4-Bis(methylthio)-5,6-dihydrobenz[f]isoquinoline (3s): yellow needles (hexane); mp 108-109°C; IR(KBr) 1560, 1524, 1430, 1407, 1360, 1345, 1310 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.56(s,6H,SMe), 2.66-2.88(m,4H,CH_2), 7.09-7.24(m,4H,ArH), 7.50-7.72(m,1H,ArH); MS m/z 273(M^+,100%), 258(23), 240(76), 228(27). Anal. Calcd for $C_{15}H_{15}NS_2$: C,65.89; H,5.53; N,5.12.Found: C,65.61; H,5.75;N,5.32.

2,4-Bis(methylthio)-5,6-dihydro-8-methoxybenz[f]isoquinoline (3t): yellow needles (hexane); mp 115-116°C; IR(KBr) 1612, 1566, 1524, 1430, 1410, 1356 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.60(s,6H,SMe), 2.69-2.86(m,4H,CH_2), 3.80(s,3H,OMe), 6.69(brs,1H,H-7), 6.74(dd,1H,J=9,1.5 Hz,H-9), 7.11(s, 1H,H-1), 7.61(d,1H,J=9 Hz,H-10); MS m/z 303(M^+,100%), 270(70), 223(29). Anal. Calcd for $C_{16}H_{17}NOS_2$: C,66.33; H,5.65; N,4.62. Found: C,66.55; H,5.41; N,4.48.

2,4-Bis(methylthio)-6,7-dihydro-5H-benzocyclohepta[2,1-c]pyridine (3u): colourless crystals (hexane); mp 87-88°C; IR(KBr) 1566, 1520, 1485, 1449, 1435, 1411 , 1349, 1328 cm^{-1}; ^1H NMRδ ($CDCl_3$) 1.98-2.31(m,2H,CH_2), 2.32-2.70(m,4H,CH_2), 2.60(s,6H,SMe), 6.83-6.92(m,1H,ArH), 7.13-7.41(m,4H,ArH); MS m/z 287(M^+,100%), 272(56), 254(83). Anal. Calcd for $C_{16}H_{17}NS_2$: C,66.85; H,5.96; N,4.87. Found: C,66.74; H,6.12; N,4.98.

2,4-Bis(methylthio)-5H-benzothiapyrano[3,4-c][1]pyridine (3v): light yellow needles (hexane); mp 118-119°C; IR(KBr) 1564, 1522, 1470, 1404, 1335 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.59(s,3H,SMe),2.61 (s,3H,SMe), 3.73(s,2H,CH_2), 7.12-7.50(m,4H,ArH), 7.65-7.83(m,1H,ArH); MS m/z 291(M^+,66%), 276(100),258(36),243(16),228(30). Anal.Calcd for $C_{14}H_{13}NS_3$:C,57.69;H,4.49; N,4.81. Found: C,57.46; H,4.68; N,5.04.

2,4-Bis(methylthio)-5,6-dihydro-9-methylbenzothiepino[4,5-c][1]pyridine(3w): yellow needles (hexane/$CHCl_3$); mp 148-149°C; IR(KBr) 1593,1484,1390,1325 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.37(s,3H, Me),2.59(s,3H,SMe), 2.61(s,3H,SMe), 2.62-3.09(m,2H,CH_2), 3.15-3.50(m,2H,CH_2), 6.78(s,1H,ArH), 7.10-7.49(m,3H,ArH); MS m/z 319(M^+,100%), 304(84), 286(89), 272(14), 256(12), 252(13). Anal. Calcd for $C_{16}H_{17}NS_3$: C,60.14; H,5.36; N,4.38. Found: C,59.98; H,5.14; N, 4.18.

1,3-Bis(methylthio)-4-methyl-5,6,7,8-tetrahydroisoquinoline (4c): colourless crystals(hexane); mp 72-73°C; IR(KBr) 1544, 1445, 1432, 1365, 1302 cm^{-1}; ^1H NMR(CCl_4) δ 1.66-1.88(m,4H, CH_2), 2.08(s,3H,Me), 2.56(s,6H,SMe), 2.40-2.66(m,merged with SMe signal, 4H,CH_2); MS m/z 239(M^+,60%),224(31),206(100). Anal.Calcd for $C_{12}H_{17}NS_2$: C,60.20; H,7.16; N,5.85. Found:

C,59.98; H,7.06; N,6.02.

1,3-Bis(methylthio)-4-methyl-6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridine (4d): colourless crystals (hexane); mp 77-78°C; IR(KBr) 1542, 1435, 1357, 1345 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.34-1.88(m,6H,CH_2), 2.10(s,3H,Me), 2.49(s,3H,SMe), 2.51(s,3H,SMe), 2.69-2.84(m,4H,CH_2); MS m/z 253(M^+,92%), 238(52). Anal. Calcd for $C_{13}H_{19}NS_2$: C,61.61; H,7.56; N,5.53. Found: C,61.89; H,7.39; N,5.31.

2,4-Bis(methylthio)-1,9-dimethyl-5,6-dihydrobenzothiepino[4,5-c][1]pyridine (4e):colourless crystals (hexane); mp 145-146°C; IR(KBr) 1599, 1540, 1528, 1445, 1380, 1348 cm^{-1}; ^1H NMRδ ($CDCl_3$) 2.10(s,3H,Me), 2.38(s,3H,Me), 2.64(s,6H,SMe), 2.83-3.21(m,2H,CH_2), 3.22-3.56(m,2H, CH_2), 7.04-7.28(m,2H,ArH), 7.36-7.50(brs,1H,ArH); MS m/z 333(M^+,100%), 318(40). Anal. Calcd for $C_{17}H_{19}NS_3$: C,61.22; H,5.74; N,4.20. Found: C,61.02; H,5.89; N,4.41.

2-(Ethylthio)-6-(methylthio)-4-phenylpyridine (12): light yellow oil; 63%; IR (neat) 1574, 1518, 1490, 1360 cm^{-1}; ^1H NMR(CCl_4) δ 1.40(t,3H,J=7.5 Hz,Me), 2.57(s,3H,SMe), 3.12(q, 2H,J=7.5 Hz,CH_2), 7.00(s,2H,H-3 and H-5), 7.30-7.64(m,5H,ArH); MS m/z 261(M^+,78%), 246(44), 228(42). Anal.Calcd for $C_{14}H_{15}NS_2$: C,64.33; H,5.78; N,5.36. Found: C,64.18; H,5.54; N,5.12.

General Procedure for Desulphurization of Bis(methylthio)pyridine 3:

A suspension of appropriate pyridines 3 (4 mmol), Raney Ni(W-4) (ca.10 times by weight) in ethanol (30 mL) was stirred at RT for 3h (monitored by TLC). The reaction mixture was filtered and the residue washed with hot ethanol (3x20 mL). The combined filtrate was concentrated under vacuum to give crude dethiomethylated pyridines 8a-e which were purified by passing through silica gel column using hexane as eluent.

4-Phenylpyridine (8a): pale yellow solid ($CHCl_3$); 65%; mp 77°C (lit.[17] mp 77-78°C); IR(KBr) 1590, 1544, 1482, 1411 cm^{-1}; ^1H NMR($CDCl_3$)δ 7.18-7.80(m,7H,ArH); 8.50-8.80(m,2H,ArH).Anal. Calcd for $C_{11}H_9N$: C,85.13; H,5.85; N,9.03. Found: C,85.39; H,5.98; N,8.87.

4-(2-Naphthyl)pyridine (8b): colourless crystals (hexane); mp 130-131°C; 66%; IR(KBr) 1595, 1548, 1402 cm^{-1}; ^1H NMR($CDCl_3$) δ 7.39-8.16(m,9H,ArH), 8.60-8.88(m,2H,ArH). Anal.Calcd for $C_{15}H_{11}N$: C,87.77; H,5.40; N,6.82. Found: C,87.54; H,5.21; N,6.69.

4-Methylpyridine (8c): colourless oil; bp 142-143°C (lit.[18] bp 143.1°C); 65%; (superimposable IR and NMR spectra).

5,6,7,8-Tetrahydroisoquinoline (8d): viscous oil; 68%; (lit.[19] superimposable IR and NMR).

5,6-Dihydrobenz[f]isoquinoline (8e): Colourless oil; 58%; IR(neat) 1600, 1580, 1485, 1464 cm^{-1}; ^1H NMR(CCl_4) δ 2.50-2.86(m,4H,CH_2), 6.84-7.25(m,5H,ArH), 7.50-8.26(m,2H,ArH). Anal. Calcd for $C_{13}H_{11}N$: C,86.15; H,6.12; N,7.73. Found: C,85.92; H,6.33; N,7.92.

General Procedure for Substituted and Annelated Bromopyridines 9a-d:

To a cold solution of carbinolacetals 2 (10 mmol), in acetic acid (25 mL), bromine (2.4g, 15 mmol) was added dropwise and reaction mixture was allowed to stir for 2h. It was neutralized with a saturated solution of sodium bicarbonate extracted with chloroform (3x100 mL), washed with water (100 mL), dried (Na_2SO_4) and evaporated to give crude bromopyridines 9, which were purified by column chromatography over silica gel using hexane as eluent.

2-Bromo-6-(methylthio)-4-phenylpyridine (9a): colourless crystals (hexane); 83%; mp 134-135°C; IR(KBr) 1550, 1496, 1440, 1420, 1380 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.52(s,3H,SMe), 7.04(s,2H, H-3 and H-5), 7.36-7.48(m,5H,ArH); MS m/z 281(15%), 280(100), 279(M^+,21), 278(M^+-1,98).Anal. Calcd for $C_{12}H_{10}BrNS$: C,51.44; H,3.60; N,5.00. Found: C,51.19; H,3.34; N,4.88.

2-Bromo-6-(methylthio)-4-(3-pyridyl)pyridine (9b): colourless crystals ($CHCl_3$); 69%; mp 130-131°C; IR(KBr) 1602, 1586, 1479, 1433, 1385, 1355 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.60(s,3H,SMe), 7.12(s,1H,pyridyl H), 7.26(s,1H,pyridyl H), 7.31-7.52(m,1H,pyridyl H), 7.66-7.83(m,1H, pyridyl H), 8.56-8.86(m,2H,H-2,H-6 pyridyl); MS m/z 281(9%), 279(M^+-1,9). Anal. Calcd for

$C_{11}H_9BrN_2S$: C,46.98; H,3.23; N,9.97. Found: C,46.71; H,3.42; N,10.12.

3-Bromo-1-(methylthio)-5,6,7,8-tetrahydroisoquinoline (9c): colourless crystals (hexane); 64%; mp 49-50°C; IR(KBr) 1566, 1542, 1450, 1430, 1406, 1365 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.66-2.04 (m,4H,CH_2), 2.54-2,3H,SMe), 2.20-2.80(m,merged with SMe signal, 4H,CH_2), 6.86(s,1H,H-4); MS m/z 259(58%), 257(M^+,57). Anal. Calcd for $C_{10}H_{12}BrNS$: C,46.52; H,4.69; N,5.43. Found: C,46.35; H,4.41; N,5.18.

2-Bromo-5,6-dihydro-4-(methylthio)-benz[f]isoquinoline (9d): colourless crystals (hexane); 78%; mp 104-105°C; IR(KBr) 1606, 1582, 1553, 1530, 1428, 1402, 1363,1309 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.54(s,3H,SMe), 2.68-2.88(m,4H,CH_2), 7.11-7.74(m,5H,ArH); MS m/z 307(100%), 305 (M^+,99), 274(53), 272(58). Anal. Calcd for $C_{14}H_{12}BrNS$: C,54.91; H,3.95; N,4.57. Found: C, 54.78; H,3.72; N,4.79.

Dehydration (or Methanolysis) of Carbinolacetals 2 in the Presence of Borontrifluoride etherate/methanol; General Procedure:

A solution of carbinolacetals 2 (10 mmol), $BF_3.Et_2O$ (5 mL) in dry methanol (50 mL) was refluxed for 12h. The reaction mixture was cooled and poured into a saturated solution of sodium bicarbonate, extracted with $CHCl_3$ (2x100 mL), washed with water (2x100 mL) and dried (Na_2SO_4) and evaporated to give either crude dienes 14a-b or the ene ester 14c which were purified by column chromatography over silica gel using hexane as eluent.

1,1-Bis(methylthio)-4-cyano-3-phenyl-1,3-butadiene (14a): light yellow oil; 68%; IR(neat) 2208, 1640, 1560, 1490, 1447, 1434 cm^{-1}; ^1H NMR(CCl_4) δ 2.35(s,3H,SMe), 2.38(s,3H,SMe), 5.63(s,1H,H-2), 6.14(s,1H,H-4), 7.42(s,5H,ArH). Anal. Calcd for $C_{13}H_{13}NS_2$: C,63.12; H, 5.30; N,5.66. Found: C,63.36; H,5.09; N,5.81.

1-Bis(methylthio)methylene-2-cyanomethylenecyclohexane (14b): colourless oil; 71%; IR(neat) 2210, 1610, 1548, 1480 cm^{-1}; ^1H NMR(CCl_4) δ 1.60-1.94(m,4H,CH_2), 2.27(s,3H,SMe), 2.32(s,3H, SMe), 2.47-2.85(m,4H,CH_2), 5.19(s,1H,olefinic). Anal. Calcd for $C_{11}H_{15}NS_2$: C,58.62;H,6.71; N,6.22. Found: C,58.89; H,6.55; N,6.43.

Methyl 1-cyanomethyl-3,4-dihydronaphthalene -2-carboxylate (14c): yellow crystals (hexane-$CHCl_3$); 69%; mp 76-77°C; IR(KBr) 2240, 1710, 1620, 1580, 1464, 1448, 1438 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.50-2.85(m,4H,CH_2), 3.79(s,3H,OMe), 4.05(s,2H,CH_2CN), 7.08-7.58(m,4H,ArH). Anal. Calcd for $C_{14}H_{13}NO_2$: C,73.99; H,5.76; N,6.16. Found: C,74.24; H,5.98; N,5.95.

General Procedure for Nickel-Induced Grignard Reaction on 3;Synthesis of 15a-b:

To a suspension of methylmagnesium iodide [30 mmol, prepared from 0.72g (0.03g atom) of magnesium turnings and 4.26g (30 mmol) of methyl iodide] in dry ether (25 mL), a solution of bis(triphenylphosphino)nickel dichloride[$(C_6H_5)_3P]_2NiCl_2$ [13] ,[2g (3 mmol)]in dry benzene (15 mL) was added dropwise under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 15 min. A solution of appropriate bis(methylthio)pyridine (3a or 3s) (10 mmol) in dry benzene (25 mL) was added and the mixture was heated at 80°C for 12h. It was then cooled, poured into 100 mL of saturated NH_4Cl solution, extracted with ether (2x100 mL) dried (Na_2SO_4) and evaporated to give 15a-b as viscous residues,which were purified by column chromatography over silica gel using EtOAc-hexane (1:20) as eluent.

2,6-Dimethyl-4-phenylpyridine (15a): colourless crystals ($CHCl_3$); 85%; mp 49-50°C; IR(KBr) 1606, 1553, 1494, 1453, 1399, 1356, 1323 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.56(s,6H,Me), 7.15(s,2H,H-3 and H-5), 7.32-7.72(m,5H,ArH); MS m/z 183(M^+,100%). Anal. Calcd for $C_{13}H_{13}N$: C,85.20; H,7.15; N,7.64. Found: C,85.45; H,6.91; N,7.92.

5,6-Dihydro-2,4-dimethylbenz[f]isoquinoline (15b): colourless crystals ($CHCl_3$); 79%; mp 109-110°C; IR(KBr) 1590, 1549, 1445, 1385 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.53(s,6H,Me), 2.68-2.92(m, 4H,CH_2), 7.24-7.52(m,4H,ArH), 7.70-7.96(m,1H,ArH); MS m/z 209(M^+,100%), 194(53). Anal.

Calcd for $C_{15}H_{15}N$: C,86.08; H,7.22; N,6.69. Found:C,85.83; H,7.03; N,6.52.

Acknowledgements - A.K.G. thanks C.S.I.R., New Delhi for Senior Research Fellowship. Financial Assistance by U.G.C., New Delhi, under COSSIST programme is also acknowledged.

REFERENCES

1. Singh, G.; Ila, H.; Junjappa, H. Tetrahedron Lett. 1984, 25, 5095-5098.
2. Balu, M.P.; Singh, G.; Ila, H.; Junjappa, H. Tetrahedron Lett. 1986, 27, 117-120.
3. Balu, M.P.; Ila, H.; Junjappa, H.; Tetrahedron Lett. 1987, 28, 3023-3026.
4. Balu, M.P.; Pooranchand, D.; Ila, H.; Junjappa, H. Tetrahedron Lett. 1988, 29,501-504.
5. Gupta, A.K.; Ila, H.; Junjappa, H. Tetrahedron Lett. 1987, 28, 1459-1462.
6. Gupta, A.K.; Ila, H.; Junjappa, H. Tetrahedron Lett. 1988, 29, 6633-6636.
7. Johnson, F.; Panella, J.P.; Carlson, A.A.; Hunneman, D.H. J. Org. Chem. 1962, 27, 2473-2478.
8. Allen, C.F.H. J. Am. Chem. Soc. 1927, 49, 1112-1115.
9. Bryson, T.A.; Wisowaty, J.C.; Dunlap R.B.; Fisher, R.R.; Ellis, P.D. J. Org. Chem. 1974, 39, 3436-3438.
10. For a review,see: Johnson, F.; Madronero, R. Advances in Heterocyclic Chemistry, 1966, 6, 95-146.
11. Kaiser, E.M.;Hauser, C.R. J. Org. Chem. 1968, 33, 3402-3404.
12. Debal, A.; Cuvigny, T.; Larcheveque, M. Synthesis, 1976, 391-393.
13. Wenkert, E.; Hanna, Jr., J.M.; Leftin, M.H.; Michelotti, E.L.; Potts, K.T.; Usifer,D. J. Org. Chem. 1985, 50, 1125-1126.
14. (a) Chauhan, S.M.S.; Junjappa, H. Tetrahedron 1976, 32, 1779-1787; (b) Thuillier,A.; Vialle, J. Bull. Soc.Chim.Fr. 1962, 2186-2186.
15. Gilman, H.; Beel, J.A.; Brannen, C.G.; Bullock, M.W.; Dunn, G.E.; Miller, L.S. J. Am. Chem. Soc. 1949, 71, 1499-1500.
16. Paulic, A.A.; Adkins, H. J. Am. Chem. Soc. 1946, 68, 1471.
17. Haworth, J.W.; Heilbron, I.M.; Hey, D.H. J. Chem. Soc. 1940, 349-355.
18. Bailey, C.F.; McElvain, S.M. J. Am. Chem. Soc. 1930, 52, 1633-1640.
19. Ginos, J.Z. J. Org. Chem. 1975, 40, 1191-1195.