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Synthesis and Reactions of 2-Bis(methylthio)methylene-1-methyl-3-oxoindole: A Facile Access to Benzo- and Heterocyclo-Fused Carbazoles and Indoles

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Abstract: The synthesis and reactions of 2-bis(methylthio)methylene-1-methyl-3-oxoindole **5** as a novel 3-carbon 1,3-bielectrophilic component are described. Thus cycloaromatization of **5** with allyl, methallyl and crotyl Grignard reagents affords substituted carbazoles **12a-c** in good yields. Cycloaromatization of **5** with various anions derived from aryl / heteroaryl acetonitriles and antipyrine gives novel benzo[*c*]- (**16**), naphtho[1,2-*c*]- (**19**), indolo[3,2-*a*]- (**21**), thieno[2,3-*c*]- (**23**), pyrrolo[2,3-*c*]- (**25**) and pyrazolo[4,3-*b*]- (**29**) carbazole ring systems in good yields. Similarly heterocyclo[*b*]-fused indoles like pyrido[3,4-*b*]- (**36**), pyrido[3,2-*b*]- (**39**) indoles and indolo[3,2-*b*]quinolizinium salt **42** were synthesized by cyclization of **5** with lithioacetonitrile, lithioaminocrotonitrile, and 2-picolyl lithium respectively *via* our heteroaromatic annelation protocol.

Development of new methods for the synthesis of functionalized carbazoles is currently attracting organic chemists due to the discovery of many carbazole alkaloids with varied biological activities.[1] Similarly benzo- and heterocyclo- fused carbazole[2-5] and indole[6-8] systems are of considerable contemporary interest and importance as many of these structural frameworks are present in natural products displaying remarkable pharmacological properties. Reported methods for carbazoles have been developed starting from 1,2,3,4-tetrahydrocarbazoles, biphenyls, diphenylamines and 2-(*o*-aminoarylcyclohexadiene) iron tricarbonyl *etc.*[1c,9] Recently a number of approaches involving [*b*]annelation of indoles have been successfully developed.[10] While many of these methods suffer due to poor yields and harsh reaction conditions, the methods developed in our laboratory, particularly based on our heteroaromatic annelation strategy have opened new avenues for the synthesis of highly functionalized carbazoles in excellent yields.[11] In continuation of our interest in carbazole chemistry[11] and also in α-oxoketene dithioacetals,[12] we became interested in developing indole intermediates such as 2-bis(methylthio)methylene-3-oxoindole **4** and its N-substituted derivatives **5-7** as 3-carbon 1,3-bielectrophilic components which can be reacted with various allyl, benzyl and heteroallyl anions to give either substituted carbazoles or their benzo- and heterocyclo-fused derivatives by employing our heteroaromatic annelation strategy.[13] Tominaga and coworkers have

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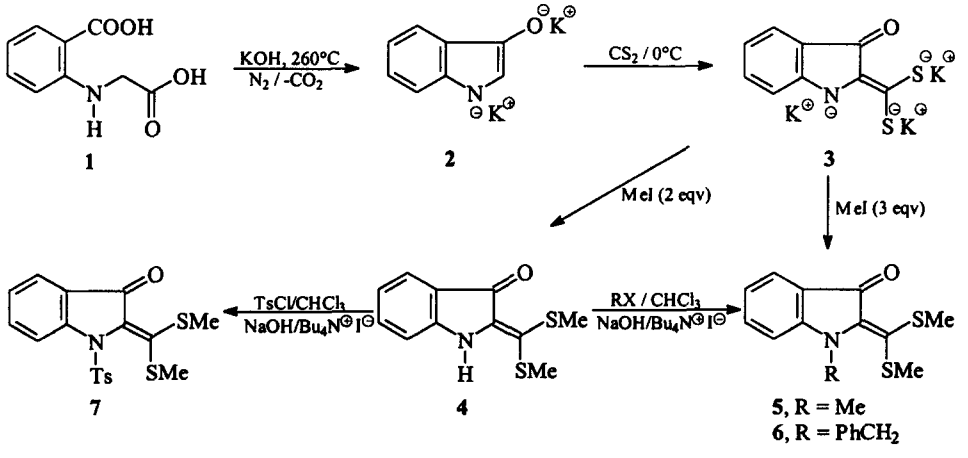
reported the reaction of 1-acetylindoxyl with carbon disulphide under various conditions to afford either mesoionic compound or 3-oxoindole-2-thioate after treatment with dimethyl sulphate.[14] However no attempts were made to isolate the corresponding 2-bis(methylthio)methylene-3-oxoindole or its N-substituted derivatives. In our approach, the envisaged compounds **4-7** were conceived through the reactions depicted in Scheme 1. It is well known that in the classical synthesis of indigo, the phenylglycine-*o*-carboxylic acid **1** is heated at high temperature in the presence of KOH to afford synthetic indigo.[15] We reasoned that if we were to carry out this reaction in inert atmosphere, the indoxyl enolate **2** could be prevented from undergoing oxidation so that we could trap this anion with CS_2 to afford the corresponding dithioate dianion **3** followed by alkylation with methyl iodide to yield either **4** or **5**. We have indeed been able to achieve the synthesis of **4** along with its N-substituted analogs **5-7** and explored their synthetic applications. We report in this paper the utility of these novel 3-carbon-1,3-bielectrophilic intermediates for efficient synthesis of substituted and heterocyclo- fused carbazoles and indoles.

Results and Discussion

The key intermediate 2-bis(methylthio)methylene-3-oxoindole **4** and the corresponding N-methyl derivative **5** were synthesized as follows; a mixture of phenylglycine-*o*-carboxylic acid **1** and KOH (5 eqv) dissolved in water was heated at 260°C under a nitrogen atmosphere. When the reaction mixture became a thick red slurry, heating was withdrawn and it was cooled to 0°C followed by addition of carbon disulphide / water and kept under stirring overnight. Methyl iodide (2 eqv) was then added to the cooled reaction mixture and it was further stirred for 6 h. After work-up, the desired compound **4** was obtained in 43% yield (Scheme 1). Treatment of the intermediate **3** with three equivalents of methyl iodide afforded the corresponding N-methyl derivative **5** in 45% overall yield. Alternatively, the corresponding N-methyl- (**5**),

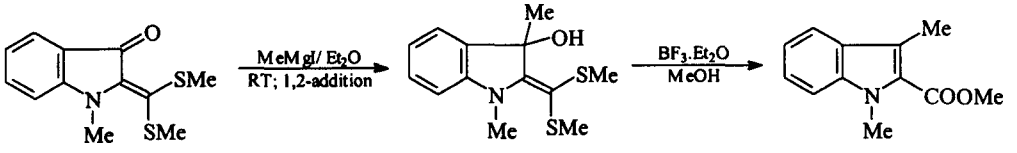


Scheme 1

N-benzyl- (**6**) and N-tosyl- (**7**) derivatives were obtained in good yields by treatment of **4** with methyl iodide, benzyl chloride and tosyl chloride respectively in the presence of a phase-transfer catalyst (Scheme 1). The N-methyl derivative **5** was selected as a model compound for studying all the reactions described in this paper.

Reaction of 5 with Allyl Grignard reagents: Synthesis of Substituted Carbazoles

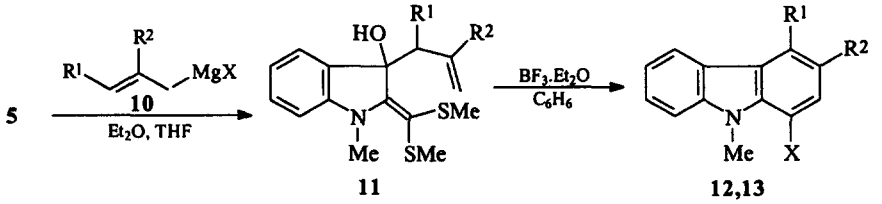
We first studied cycloaromatization of **5** with allyl, methallyl and crotyl Grignard reagents (Scheme 3). The ketene dithioacetal **5** is different from other oxoketene dithioacetals reported in the literature in that the nitrogen lone pair is in conjugation with the double bond. On the other hand, the carbonyl group at the 3-position is an electrophilic carbon centre which may facilitate charge controlled 1,2-addition of various allyl anions. As a model experiment, we first reacted **5** with methylmagnesium iodide to examine its reactivity towards Grignard reagents. Thus when **5** was treated with methylmagnesium iodide, the corresponding carbinol thioacetal **8** was indeed formed in quantitative yield which was subjected to methanolysis in the presence of boron trifluoride-etherate to afford the corresponding 2-carbomethoxy-1,3-dimethylindole **9** in 67% yield (Scheme 2). The dithioacetal **5** was next reacted with allylmagnesium bromide **10a** (Scheme 3).



5 **8** **9** (Yield 67%)

Scheme 2

he carbinol thioacetal **11a** thus obtained in excellent yield was treated with $BF_3.Et_2O$ in refluxing benzene to afford after work-up the corresponding carbazole **12a** in 63% yield (Scheme 3). Similarly the 3- and 4-methylcarbazoles **12b** and **12c** were obtained in good yields by reaction of **5** with methallyl and crotyl Grignard reagents following the same reaction sequence outlined for compound **12a**. Carbazole **12a** was subjected to Raney Nickel desulfurization to afford 9-methylcarbazole **13a** reported earlier in the literature. [16]



11 **12,13**

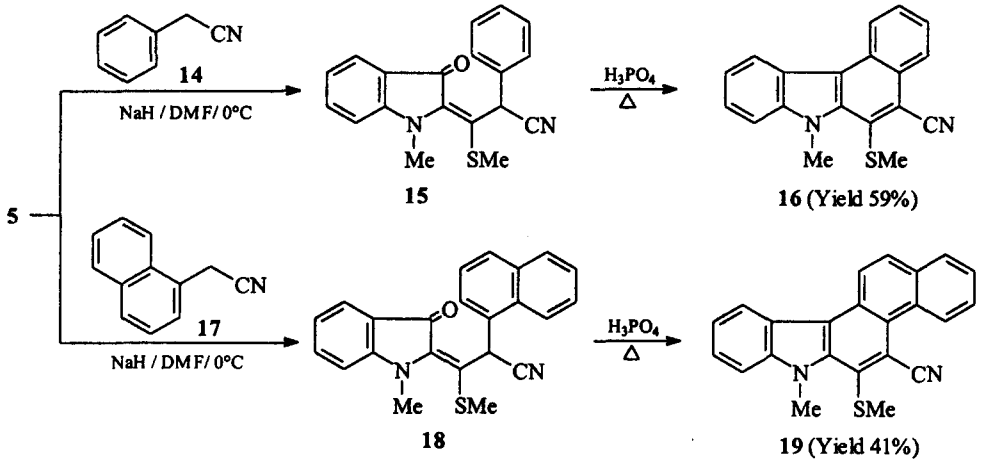
10, 11a, $R^1 = R^2 = H$
b, $R^1 = H$, $R^2 = Me$
c, $R^1 = Me$, $R^2 = H$

12a, $R^1 = R^2 = H$, X = SMe (Yield 63%)
b, $R^1 = H$, $R^2 = Me$, X = SMe (Yield 68%)
c, $R^1 = Me$, $R^2 = H$, X = SMe (Yield 65%)
13a, $R^1 = R^2 = X = H$ (Yield 94%)

Scheme 3

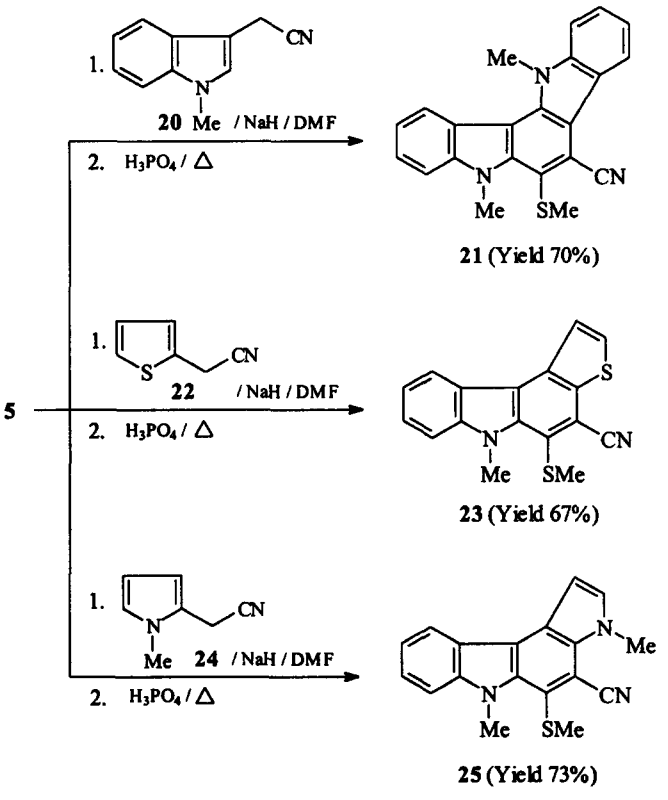
Synthesis of Benzo- and Heterocyclo- Fused Carbazoles

We next investigated cycloaromatization of **5** with stabilized anions derived from aryl, heteroaryl acetonitriles and 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (antipyrine) with a view to synthesize benzo- and heterocyclo- fused carbazoles (Schemes 4 - 6). Such structural frameworks are of considerable pharmacological interest as they have potential for development of compounds with antitumor activity.[17] Thus the reaction of the anion from phenylacetonitrile with **5** afforded addition-elimination product **15** in 80% yield. The intermediate **15** was cyclized in the presence of H_3PO_4 to afford benzo[*c*]carbazole **16** in 59% overall yield. Similarly, the corresponding naphtho[1,2-*c*]carbazole **19** was obtained in 68% yield by



Scheme 4

reacting **5** with 1-naphthylacetonitrile **17** under identical reaction conditions. Cyclocondensation of heteroaryl- acetonitriles like 1-methylindole-3-acetonitrile (**20**), thiophene-2-acetonitrile (**22**) and N-methylpyrrole-2-acetonitrile (**24**) with **5** under the above described conditions afforded novel heterocyclo-[*c*] fused carbazoles indolo[3,2-*a*]- (**21**), thieno[2,3-*c*]- (**23**) and pyrrolo[2,3-*c*]- (**25**) carbazoles in good yields (Scheme 5). The reaction thus provides a general approach for the construction of benzo-, naphtho- and heterocyclo[*c*]- fused carbazoles using readily available precursors. It is pertinent to note that although benzo[c]carbazole has been synthesized earlier,[17a] the corresponding naphtho[*c*]carbazole system, to our knowledge, was previously unknown in the literature. Similarly heterocyclo[*c*]- fused carbazoles have been little studied.[17c] Thus the synthesis of indolo[3,2-*a*]carbazole has been reported only by Mann and Wilcox[18] whereas **23** is the first example of a thieno[2,3-*c*]carbazole ring system. Some naturally occurring compounds incorporating the pyrrolo[2,3-*c*]carbazole skeleton[19] have been recently isolated from marine sponges and shown to be potent aldose reductase inhibitors thus showing promise in treatment of diabetes.

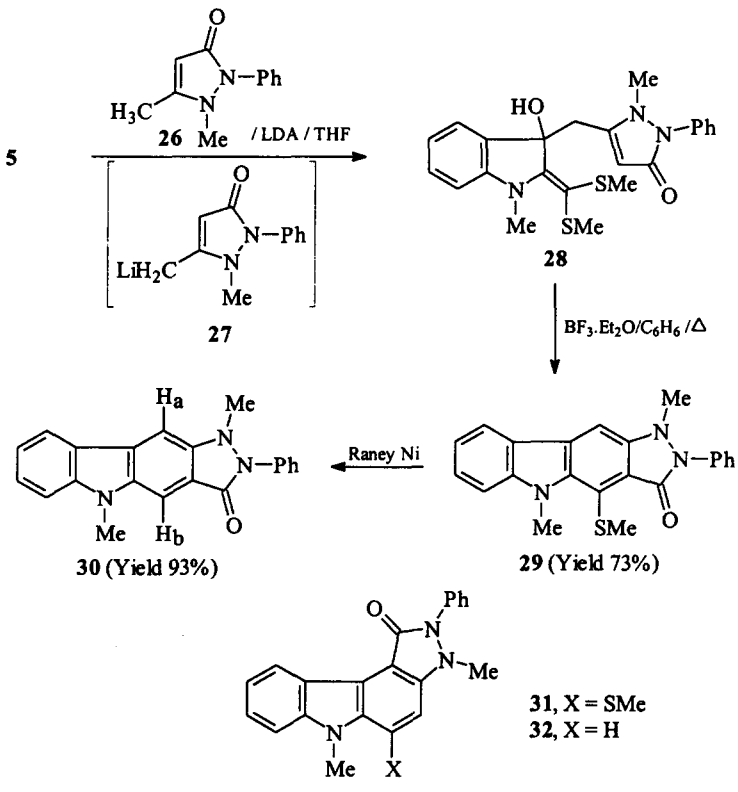


Scheme 5

The lithiomethylpyrazolone **27** (generated by deprotonation of antipyrine **26** under our earlier reported conditions[20]), when reacted with **5** followed exclusive 1,2-addition mode to yield the carbinol thioacetal **28**, which in the presence of boron trifluoride-etherate in refluxing benzene yielded the novel 1,2-dihydro-1,5-dimethyl-4-methylthio-3-oxo-2-phenyl-3*H*-pyrazolo[4,3-*b*]carbazole **29** as light yellow crystals in 65% yield (Scheme 6). The compound **29**, to our knowledge, is the first example of the pyrazolo[4,3-*b*]-carbazole ring system. The structure of **29** was confirmed with the help of spectral and analytical data while its regiochemistry was established by Raney nickel desulfurization to afford sulfur free **30** in 83% yield. The two singlets at δ 7.90 and 7.94 due to H_a and H_b protons in its ^1H NMR spectrum are indicative of the structure **30** whereas the other possible regioisomeric [*c*] annelated carbazole **32** formed by conjugate addition of **27** to **5** would have displayed signals due to these protons as doublets *via ortho*-coupling. It is pertinent to note that in our earlier studies involving reactions of lithioantipyrine with various oxoketene dithioacetals, we have observed the 1,4-addition pathway to afford angularly substituted indazolones.[20]

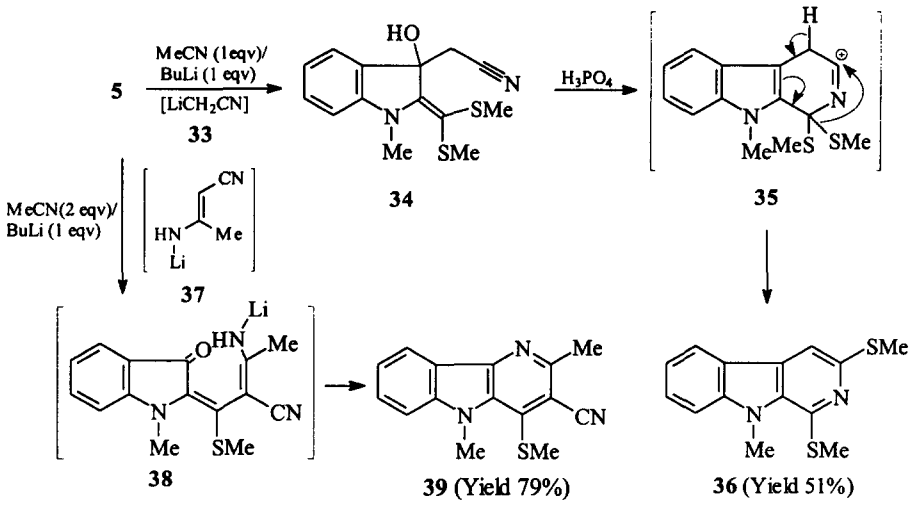
Synthesis of Heterocyclo[*b*]- Fused Indoles

The oxoketene dithioacetal **5** was next investigated for the synthesis of novel heterocyclo[*b*]- fused indoles by its reaction with 1,3-binucleophiles like azaallyl anions (Schemes 7-8) following our previously reported



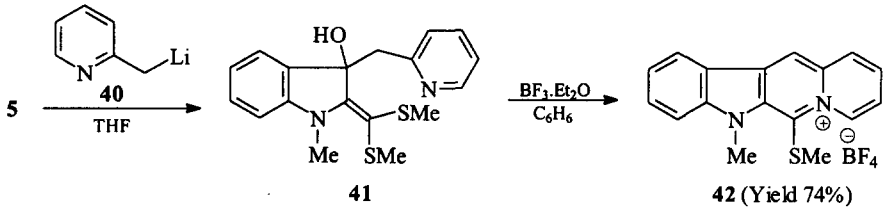
Scheme 6

heteroaromatic annelation protocol. Numerous heterocyclo[*b*]- fused indoles like pyrido[2,3-*b*, 3,4-*b*, 4,3-*b*]indoles[8,21-22], pyrrolo[2,3-*b*]indoles[23] are present in natural products exhibiting important biological activities which have made this class of compounds important synthetic targets for several research groups.[24] When **5** was reacted with lithioacetonitrile **33** (generated by treatment of acetonitrile with one equivalent of BuLi), the 1,2-adduct **34** was obtained in nearly quantitative yield. The adduct **34** on treatment with orthophosphoric acid underwent Ritter type cyclization with concomitant 1,3-MeS shift as reported earlier from this laboratory[25] to afford the corresponding 1,3-bis(methylthio)-9-methyl-9*H*-pyrido[3,4-*b*]indole **36** in 51% yield. In principle both methylthio groups in **36** could be replaced by alkyl groups or amino nucleophiles to develop more derivatives of **36** if needed. The regiochemistry of the reaction was altered when the corresponding lithioaminocrotononitrile **37** (generated *in situ* by treatment of one equivalent of butyllithium with two equivalents of acetonitrile) was reacted with **5**.[26] Thus **37** followed 1,4-addition-elimination mode with **5** to give intermediate adduct **38** which underwent *in situ* cyclization to yield δ-carboline derivative **39** in 69% yield. The structure and regiochemistry of **39** was established with the help of spectral and analytical data.



Scheme 7

The reaction of 2-picolyllithium with **5** gave the carbinol thioacetal **41** which on cyclization with boron trifluoride-etherate yielded the hitherto unknown indolo[3,2-*b*]quinolizinium ring system **42** in 86%



Scheme 8

yield as bright yellow needles (Scheme 8).[27] The compound **42** with a planar tetracyclic chromophore and cationic nitrogen shared between two aromatic ring is a potential DNA intercalator.[28,24e] It should be noted that there is very little precedent for such a structural type in the literature.[29]

In conclusion, 2-bis(methylthio)methylene-1-methyl-3-oxoindole **5** has been prepared and examined for its potential application for the synthesis of biologically important novel substituted, benzo- and heterocyclo- fused carbazoles and indole derivatives utilizing our heteroaromatic annelation methodology. A number of reactions of **5** with other carbon and heteronucleophiles can be envisaged which are under investigation and will be published later.

Experimental Section

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer-983 and Perkin Elmer-1320 spectrophotometers. NMR spectra were recorded on Bruker ACF-300, Bruker WP-80 and Varian EM-390 spectrometers. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane. Mass spectra were obtained on a Jeol D-300 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were conducted in oven-dried (120°C) glassware under a dry argon/nitrogen atmosphere. All reactions were monitored by TLC on glass plates coated with silica gel (Acme) containing 13% calcium sulfate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying with acidic potassium permanganate solution. Column chromatography was carried out using Acme silica gel (60-120 mesh). THF was distilled over sodium benzophenone ketyl prior to use. DMF was distilled over CaH_2 and stored over molecular seives. *n*-BuLi was purchased from Aldrich.

General Procedure for Synthesis of 2-Bis(methylthio)methylene-2,3-dihydro-3-oxoindole (4) and 2-Bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (5)

A mixture of phenylglycine-*o*-carboxylic acid (10 g, 0.051mol), potassium hydroxide (42 g, 0.75 mol) and water (10 mL) was heated with stirring at 220°C under nitrogen atmosphere until the complete evolution of carbon dioxide (1h). The appearance of an orange red colour indicated the complete formation of indoxyl enolate **2**. The reaction mixture was then cooled to 0°C and carbon disulfide (4 mL, 0.066 mol) was added followed by addition of 75 mL of water with stirring. The reaction mixture was allowed to stir at room temperature for another 6 h, cooled to 0°C followed by dropwise addition of MeI (6.5 mL, 0.105 mol for **4**; 10 mL, 0.16 mol for **5**). After further stirring for 6h at room temperature, the reaction mixture was poured into saturated ammonium chloride solution (300 mL), extracted with chloroform (2 x 100 mL), washed with water, dried (Na_2SO_4) and concentrated to give crude **4** or **5** which were purified by column chromatography over silica gel using hexane-ethyl acetate (19:1) as eluent.

4: Orange crystals (chloroform-hexane); mp 158-159°C; Yield 43%; IR (KBr): 3289, 1644, 1610, 1479, 1196 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.47 (s, 3H, SCH_3), 2.50 (s, 3H, SCH_3), 6.85-7.10 (m, 2H, ArH), 7.20 (brs, 1H, NH), 7.35-7.60 (m, 1H, ArH), 7.76 (d, 1H, J = 8 Hz, ArH); Anal Calcd. for $C_{11}H_{11}NOS_2$ (237.35): C, 55.67; H, 4.67; N, 5.90%. Found: C, 55.93; H, 4.76; N, 5.78%.

5: Orange viscous liquid; Yield 45%; IR (CCl_4): 1651, 1603, 1481, 1308 cm^{-1}; ^1H NMR (90 MHz, CCl_4): 2.36 (s, 3H, SCH_3), 2.50 (s, 3H, SCH_3), 3.47 (s, 3H, NCH_3), 6.85-7.15 (m, 2H, ArH), 7.36-7.65 (m, 1H, ArH), 7.76 (d, 1H, J = 8 Hz, ArH); MS: *m/z* (M^+, %): 251 (M^+, 100); Anal. Calcd. for $C_{12}H_{13}NOS_2$ (251.37): C, 57.34; H, 5.21; N, 5.57%. Found: C, 57.76; H, 5.14; N, 5.46%.

General Procedure for Phase Transfer Catalyzed N-Alkylation / Tosylation of 4

To a solution of **4** (7.1 g, 30 mmol) in CH_2Cl_2 (50 mL) tetrabutylammonium iodide (0.5 g, catalytic), the appropriate alkyl halide / tosyl chloride (35 mmol) and 50% NaOH solution in water (40 mL) were added.

General Procedure for the Reaction of Allyl, Methallyl and Crotyl Grignard reagents with 5: Synthesis of Carbazoles 12a-c

To an ice cooled solution of appropriate Grignard reagent (prepared from allyl bromide, methallyl chloride, crotyl chloride, 10 mmol and magnesium turnings, 0.5 g, 20.8 mmol) in dry ether (75 mL), a solution of **5** (1.26 g, 5 mmol) in dry THF (30 mL) was added dropwise and the reaction mixtute was further stirred at room temperature for 2 h. It was then poured into saturated aqueous NH_4Cl solution (200 mL), extracted with benzene (2 x 100 mL), the combined benzene extracts were washed with water, dried (Na_2SO_4) and evaporated to give crude carbinol **11** as viscous residue which was dissolved in benzene (50 mL) followed by addition of $BF_3.Et_2O$ (2 mL). The reaction mixture was then refluxed for 2 h (monitored by tlc), cooled, poured into saturated aqueous $NaHCO_3$ solution (100 ml), extracted with chloroform (2 x 100 mL), washed with water, dried (Na_2CO_3) and the solvent evaporated to give viscous residue which was purified by silica gel column chromatography using hexane-ethyl acetate (19:1) as eluent.

9-Methyl-1-(methylthio)carbazole (12a)

Pale yellow crystals (dichloromethane-hexane); mp 69-70°C; Yield 63%; IR (CCl_4): 2917, 1580, 1450 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.48 (s, 3H, SCH_3), 4.33 (s, 3H, NCH_3), 7.13-7.70 (m, 5H, ArH), 8.00-8.23 (m, 2H, ArH); MS (*m/z*, %): 227 (M^+, 100); Anal. Calcd. for $C_{14}H_{13}NS$ (227.33): C, 73.97; H, 5.76; N, 6.16%. Found: C, 74.24; H, 5.62; N, 6.07%.

3,9-Dimethyl-1-(methylthio)carbazole (12b)

Light yellow crystals (dichloromethane-hexane); mp 97-98°C; Yield 68%; IR (CCl_4): 2909, 1589, 1458, 1274 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.47 (s, 6H, CH_3, SCH_3), 4.30 (s, 3H, NCH_3), 7.15-7.47 (m, 4H, ArH), 7.73 (s, 1H, ArH), 7.97 (d, 1H, J = 8 Hz, ArH); MS (*m/z*, %): 241 (M^+, 100); Anal. Calcd. for $C_{15}H_{15}NS$ (241.36): C, 74.65; H. 6.26, N, 5.80. Found: C, 74.87; H, 6.12; N, 5.94%.

4,9-Dimethyl-1-(methylthio)carbazole (12c)

Light yellow crystals (dichloromethane-hexane); mp 92-94°C, Yield 65%; IR (CCl_4): 1543, 1249, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.43 (s, 3H, CH_3), 2.81 (s, 3H, SCH_3), 4.30 (s, 3H, NCH_3), 6.91 (d, 1H, J = 7.6 Hz, ArH), 7.20-7.25 (m, 1H, ArH), 7.35-7.48 (m, 3H, ArH), 8.14 (d, 1H, J = 7.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 20.61, 20.92, 32.06, 108.58, 115.91, 119.22, 121.13, 121.33, 122.45, 122.73, 123.16, 125.26, 131.13, 132.98, 141.82; Anal. Calcd. for $C_{15}H_{15}NS$ (241.36): C, 74.65; H, 6.26; N, 5.80%. Found: C, 74.89; H, 6.14; N, 5.95%.

9-Methylcarbazole (13a)

To a solution of **12a** (0.45 g, 2 mmol) in ethanol (25 mL), Raney nickel (W2, 5 times by weight) was added and the suspension was refluxed with stirring for 3 h (monitored by tlc). The reaction mixture was then cooled, filtered through a sintered funnel and the residue was washed with ethanol. The filtrate was evaporated under vacuum and the residue was dissolved in chloroform (50 mL), washed with water, dried (Na_2SO_4) and concentrated to give crude **13a** which was purified by passing through a small silica gel column using hexane as eluent: Colourless crystals (hexane); mp 87°C; lit.[16] mp 87-88°C; Yield 94%.

The reaction mixture was stirred at room temperature for 5-6 h (monitored by tlc), the dichloromethane layer was separated, washed with water (2 x 50 mL), dried (Na_2SO_4) and evaporated to give a viscous residue which was passed through a silica gel column using ethyl acetate-hexane (1:9) as eluent to give the corresponding 1-substituted products **5**, **6** or **7**. Compound **5** was obtained in 95% yield from **4**.

1-Benzyl-2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole (6)

Orange crystals (dichloromethane-hexane); mp 108-109°C; Yield 96%; IR (KBr): 1634, 1438, 1326, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.13 (s, 3H, SCH_3), 2.21 (s, 3H, SCH_3), 5.15 (s, 2H, CH_2), 6.86-6.96 (m, 3H, ArH), 7.05-7.09 (m, 4H, ArH), 7.36-7.43 (m, 1H, ArH), 7.66 (d, 1H, J = 7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 19.02, 21.51, 48.13, 111.90, 120.85, 123.80, 125.04, 127.49, 127.60, 128.07, 128.86, 134.23, 135.15, 137.42, 140.03, 153.98; Anal. Calcd. for $C_{18}H_{17}NOS_2$ (327.47): C, 66.02; H, 5.23; N, 4.28%. Found: C, 66.41; H, 5.29; N, 4.21%.

2-Bis(methylthio)methylene-2,3-dihydro-3-oxo-1-(*p*-toluenesulfonyl)indole (7)

Orange crystals (dichloromethane-hexane); mp 154-156°C; Yield 95%; IR (KBr): 1666, 1591, 1476, 1356, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.27 (s, 3H, CH_3), 2.63 (s, 3H, SCH_3), 2.73 (s, 3H, SCH_3), 7.02 (d, 2H, J = 8.3 Hz, ArH), 7.21-7.30 (m, 3H, ArH), 7.56-7.65 (m, 2H, ArH), 8.04 (d, 1H, J = 8.4 Hz, Ar H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.95, 21.38, 21.53, 120.23, 123.80, 126.31, 126.89, 127.84, 128.72, 129.15, 130.73, 133.88, 145.04, 147.20, 161.19, 178.44; Anal. Calcd. for $C_{18}H_{17}NO_3S_3$ (391.53): C, 55.22; H, 4.38; N, 3.58%. Found: C, 55.59; H, 4.30; N, 3.51%.

Methyl 1,3-dimethylindole-3-carboxylate (9)

To an ice cooled solution of methyl magnesium iodide (prepared from methyl iodide, 1.42 g , 10 mmol and magnesium turnings, 0.5 g, 20.8 mmol) in dry ether (75 mL), a solution of **5** (1.26 g, 5 mmol) in dry THF (30 mL) was added dropwise and the reaction mixtute was further stirred at room temperature for 2 h. It was then poured into saturated aqueous NH_4Cl solution (200 mL), extracted with benzene (2 x 100 mL) and the combined benzene extracts were washed with water, dried (Na_2SO_4) and evaporated to give carbinol thioacetal **8** as viscous residue. To a solution of **8** in absolute methanol (50 mL), $BF_3.Et_2O$ (2 mL) was added and the reaction mixture was refluxed for 3 h. It was then poured into saturated $NaHCO_3$ solution (100 mL), extracted with chloroform (2 x 100 mL), the organic layer washed with water, dried (Na_2SO_4) and evaporated to give viscous residue which on column chromatography over silica gel using hexane-ethyl acetate as eluent afforded pure **9**.

Colourless crystals (chloroform-hexane); mp 155-156°C; Yield 67%; IR(KBr): 1685, 1608, 1596, 1394 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.60 (s, 3H, CH_3), 3.96 (s, 3H, NCH_3), 4.03 (s, 3H, OCH_3), 7.15-7.55 (m, 3H, ArH), 7.78 (d, 1H, J = 9 Hz, ArH); Anal. Calcd. for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89%. Found: C, 71.16; H, 6.31; N, 6.97%.

General Procedure for Synthesis of Benzo[*c*]- (16), Naphtho[*c*]- (19) and Heterocyclo[*c*]- (21, 23, 25) fused Carbazoles.

To a stirred suspension of NaH (10 mmol) in DMF (10 mL) at 0°C, a solution of the appropriate aryl or heteroarylacetonitrile (5 mmol) in DMF (10 mL) was added dropwise. After 20 min, a solution of **5** (1.26 g, 5 mmol) in DMF (10 mL) was slowly added and the reaction mixture was brought to room temperature and further stirred for 7-10 h (monitored by tlc). It was then poured into saturated NH_4Cl solution (200 mL), extracted with chloroform (3 x 50 mL), the combined organic extracts were washed with water (3 x 100 mL), dried (Na_2SO_4) and evaporated to give the crude adducts which were dissolved in orthophosphoric acid (15 mL) The reaction mixture was then heated at 130°C with stirring for 3 h, cooled, poured into ice cold water (150 mL), extracted with chloroform (2 x 75 mL), washed with water (3 x 100 mL), dried (Na_2SO_4) and the solvent evaporated. The residue thus obtained was purified by passing through silica gel column chromatography using hexane-ethyl acetate (49:1) as eluent.

5-Cyano-7-methyl-6-(methylthio)benzo[*c*]carbazole (16)

Colourless crystals (chloroform-hexane), mp 173-174°C; Yield 59%; IR (KBr): 2885, 2220, 1600, 1505 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.99 (s, 3H, SCH_3), 4.20 (s, 3H, NCH_3), 7.18-7.24 (m, 1H, ArH), 7.40-7.50 (m, 6H, ArH), 7.89 (d, 1H, J = 8 Hz, ArH); MS (*m/z*, %): 302 (M^+, 100), 287 (M^+-15, 67.5); Anal. Calcd. for $C_{19}H_{14}N_2S$ (302.40): C, 75.47; H, 4.67; N, 9.26%. Found: C, 75.71; H, 4.51; N, 9.45%.

7-Cyano-9-methyl-8-(methylthio)naphtho[1,2-*c*]carbazole (19)

Colourless crystals (chloroform-hexane); mp 121-122°C; Yield 41%; IR (KBr): 2870, 2215, 1590, 1500, 1240 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): 1.82 (s, 3H, SCH_3), 4.27 (s, 3H, NCH_3), 7.40-7.70 (m, 7H, ArH), 7.85-8.10 (m, 3H, ArH); Anal. Calcd. for $C_{23}H_{16}N_2S$ (352.46): C, 78.38; H, 4.58; N, 7.95%. Found: C, 78.67; H, 4.72; N, 7.81%.

7-Cyano-5,12-dimethyl-6-(methylthio)indolo[3,2-*a*]carbazole (21)

Colorless crystals (chloroform-hexane); mp 180-181°C; Yield 70%; IR (KBr): 2220, 1715, 1560, 1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.55 (s, 3H, SCH_3), 4.40 (s, 3H, NCH_3), 4.55 (s, 3H, NCH_3), 7.32-7.68 (m, 6H, ArH), 8.54 (d, 1H, J = 8.1 Hz, ArH), 8.77 (d, 1H, J = 7.9 Hz, ArH); MS (*m/z*, %): 355 (M^+, 12.2), 149 (100); Anal. Calcd. for $C_{22}H_{17}N_3S$ (355.46): C, 74.34; H, 4.82; N, 11.82%. Found: C, 74.61; H, 4.74; N, 12.04%.

4-Cyano-6-methyl-5-(methylthio)thieno[2,3-*c*]carbazole (23)

Colourless crystals (chloroform-hexane); mp 160-161°C; Yield 67%; IR (KBr): 2215, 1600, 1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.60 (s, 3H, SCH_3), 4.51 (s, 3H, NCH_3), 7.37-7.45 (m, 1H, ArH), 7.56-7.68 (m, 2H, ArH), 7.83 (d, 1H, J = 5.7 Hz, ArH), 8.09 (d, 1H, J = 5.5 Hz, ArH), 8.35 (d, 1H, J = 8.0 Hz, ArH); MS (*m/z*, %): 308 (M^+, 56.2); Anal. Calcd. for $C_{17}H_{12}N_2S_2$ (308.43): C, 66.20; H, 3.92; N, 9.08%. Found: C, 66.47; H, 3.85; N, 9.27%.

4-Cyano-3,6-dimethyl-5-(methylthio)pyrrolo[2,3-*c*]carbazole (25)

Colourless crystals (chloroform-hexane); mp 148-149°C; Yield 73%; IR (KBr): 2220, 1598, 1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.51 (s, 3H, SCH_3), 4.22 (s, 3H, NCH_3), 4.40 (s, 3H, NCH_3), 7.00 (d, 1H, J = 2.6 Hz, 1H, ArH), 7.20-7.59 (m, 4H, ArH), 8.21 (d, 1H, J = 7.7 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 21.96, 32.50, 35.46, 99.42, 100.43, 109.30, 117.81, 118.06, 119.69, 121.79, 122.00, 124.05, 125.87, 126.59, 131.14, 132.75, 134.97, 142.92; Anal. Calcd. for $C_{18}H_{15}N_3S$ (305.40): C, 70.79; H, 4.95; N, 13.76%. Found: C, 70.48; H, 4.81; N, 13.93%.

1,2-Dihydro-1,5-dimethyl-4-methylthio-3-oxo-2-phenyl-3*H*-pyrazolo[4,3-*b*]carbazole (29)

To an ice cooled stirring solution of diisopropylamine (2 mL, 15 mmol) in dry tetrahydrofuran (20 mL) under dry and inert atmosphere, n-BuLi (7 mmol) was added. After 20 min, the resulting LDA solution was cooled to -78°C followed by addition of antipyrine (**26**) (0.94 g, 5 mmol) in dry THF (25 mL) and the reaction mixture was further stirred at the same temperature for 45 min. To the resulting red solution at -78°C, a solution of **5** (1.26 g, 5 mmol) in dry THF ((25 mL) was added dropwise and the reaction mixture was stirred at the same temperature for 30 min. It was then brought to room temperature followed by further stirring for for 3 h and then poured into saturated NH_4Cl solution (200 mL), extracted with chloroform (2 x 100 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated to give carbinol **28** as viscous residue which was dissolved in dry benzene (50 mL) followed by addition of $BF_3.Et_2O$ (2mL) and refluxed for 2 h (monitored by tlc). The reaction mixture was cooled, poured into saturated sodium bicarbonate solution (200 mL), the organic layer was separated and the aqueous layer was extracted with benzene (50 mL x 2). The combined organic extracts were washed with water, dried over sodium sulfate and concentrated to give crude **29** which was purified by silica gel column chromatography using hexane-ethyl acetate (8:2) as eluent.

Light yellow crystals (chloroform-hexane); mp 188-189°C; Yield 73%; IR (KBr): 2922, 1667, 1593, 1490, 1471 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.65 (s, 3H, SCH_3), 3.19 (s, 3H, NCH_3), 4.39 (s, 3H, NCH_3), 7.22-7.30 (m, 2H, ArH), 7.42 (d, 1H, J = 8.3 Hz, ArH), 7.46-7.59 (m, 3H, ArH), 7.70-7.74 (m, 2H, ArH), 7.87 (s, 1H, ArH), 8.09 (d, 1H, J = 7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 21.95, 33.47, 41.32, 103.28, 109.25, 116.24, 118.96, 119.38, 120.82, 121.46, 123.28, 125.76, 128.15, 128.99, 129.84, 135.78, 139.10, 144.59, 147.45, 161.73; Anal. Calcd. for $C_{22}H_{19}N_3OS$ (373.48): C, 70.75; H, 5.13; N, 11.25%. Found: C, 70.48; H, 5.27; N, 11.08%.

1,2-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-3*H*-pyrazolo[4,3-*b*]carbazole (30)

To a solution of **29** (0.75 g, 2 mmol) in ethanol (30 mL), Raney nickel (W2, 5 g) was added and the suspension was refluxed with stirring for 3 h (monitored by tlc). The reaction mixture was then cooled, filtered through sintered funnel and the residue was washed with ethanol. The filtrate was concentrated under vacuum, the residue was dissolved in chloroform (50 mL), washed with water, dried (Na_2SO_4) and concentrated to give crude **30** which was purified by silica gel column chromatography using hexane-ethyl acetate (19:1) as eluent.

Light yellow crystals (chloroform-hexane); mp 276-277°C; Yield 93%; IR (KBr): 1670, 1492, 1474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 3.22 (s, 3H, NCH_3), 3.89 (s, 3H, NCH_3), 7.23-7.32 (m, 2H, ArH), 7.40-7.60 (m, 4H, ArH), 7.71 (d, 2H, J = 7.6 Hz, ArH), 7.90 (s, 1H ArH), 7.94 (s, 1H, ArH), 8.16 (d, 1H, J = 7.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 29.43, 41.57, 102.64, 103.30, 108.78, 118.20, 118.94, 121.15, 121.74, 123.34, 125.91, 127.78, 128.58, 129.10, 135.70, 138.68, 143.18, 146.05, 162.87; Anal. Calcd. for $C_{21}H_{17}N_3O$ (327.39): C, 77.04; H, 5.23; N, 12.84%. Found: C, 76.81; H, 5.31; N, 12.62%.

1,3-Bis(methylthio)-9-methylpyrido[3,4-*b*]indole (36)

To a stirred solution of freshly distilled acetonitrile (0.6 mL, 11.5 mmol) in dry THF (25 mL), *n*-BuLi (12 mmol) was added under nitrogen atmosphere at -78°C and the reaction mixture was further stirred at the same temperature for 0.5 h. To the resulting suspension of lithioacetonitrile, a solution of **5** (2.51 g, 10 mmol) in dry THF (40 mL) was added and the reaction mixture was allowed to warm to room temperature during 2 h with continuous stirring. It was then poured into saturated NH_4Cl solution (200 mL), extracted with ether (2 x 75 mL), washed with water and concentrated to give crude carbinol acetal **34** which was then dissolved in orthophosphoric acid (15 mL) and heated at 130°C with stirring for 3 h. It was then cooled, diluted with water (150 mL) and extracted with chloroform (2 x 100 mL). The combined organic phase was washed with water, dried (Na_2SO_4) and concentrated to give viscous residue which was purified by passing through silica gel column using hexane-ethyl acetate (19:1) as eluent.

Light yellow crystals (chloroform-hexane); mp 108-109°C; Yield: 51%;; IR (KBr): 2923, 1616, 1529 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 2.73 (s, 3H, SCH_3), 2.80 (s, 3H, SCH_3), 4.23 (s, 3H, NCH_3), 7.20-7.80 (m, 4H, ArH), 8.10 (m, 1H, ArH); Anal. Calcd. for $C_{14}H_{14}N_2S_2$ (274 41): C, 61.28; H, 5.14; N, 10.21%. Found: C, 61.53; H, 5.03; N, 10.34%.

3-Cyano-2,5-dimethyl-4-(methylthio)pyrido[3,2-*b*]indole (39)

To a stirred solution of acetonitrile (0.8 mL, 15.3 mmol) in dry THF (25 mL), *n*-BuLi (7.5 mmol) was added under nitrogen atmosphere at -78°C and the reaction mixture was stirred for 0.5 h at the same temperature. To the resulting light reddish suspension of β-lithioaminocrotononitrile, a solution of **5** (1.26 g, 5 mmol) in dry THF (25 mL) was added dropwise and the reaction mixture was further stirred at room temperature for 12 h. It was then poured into saturated NH_4Cl solution, extracted with chloroform (2 x 100 mL), combined organic phase was washed with water, dried (Na_2SO_4) and concentrated to give crude 39 which was purified by column chromatography over silica gel using hexane-ethyl acetate (19:1) as eluent.

Light yellow crystals (chloroform-hexane); mp 227-228°C; Yield 79%; IR (KBr): 2213, 1616, 1436, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.62 (s, 3H, SCH_3), 2.89 (s, 3H, CH_3), 4.26 (s, 3H, NCH_3), 7.30-7.36 (m, 1H, ArH), 7.43 (d, 1H, J = 8.4 Hz, ArH), 7.60-7.66 (m, 1H, ArH), 8.32 (d, 1H, J = 7.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 20.59, 23.81, 32.06, 109.38, 111.21, 117.51, 120.78, 120.93, 121.80, 129.90, 130.48, 131.73, 143.91, 144.22, 153.51; MS (*m/z*, %): 267 (M^+, 100); Anal. Calcd. for $C_{15}H_{13}N_3S$ (267.35): C, 67.39; H, 4.90; N, 15.72%. Found: C, 67.62; H, 5.07; N, 15.49%.

6-Methyl-5-(methylthio)indolo[3,2-*b*]quinolizinium tetrafluoroborate (42)

To a stirred solution of 2-picoline (0.6 mL, 6 mmol) in dry THF (25 mL), *n*-BuLi (7 mmol) was added under nitrogen atmosphere at -20°C and the reaction mixture was stirred at the same temperature for 1h. A solution of **5** (1.26 g, 5 mmol) in dry THF (25 mL) was then added to the treaction mixture and stirring was continued for another 2.5 h at the same temperature. It was then poured into saturated NH_4Cl solution, extracted with chloroform (2 x 100 mL), washed with water, dried (Na_2SO_4) and concentrated. The residue obtained was dissolved in dry benzene (50 mL) followed by addition of $BF_3.Et_2O$ (2 mL) and refluxed for 3 h. It was then cooled and poured into saturated sodium bicarbonate solution to give bright yellow solid which was filtered and washed with water. The solid was dried and recrystallized from acetic acid.

Yellow needles (AcOH); mp 276-278°C (dec.); Yield 74%; IR (KBr): 1630, 1604, 1489, 1473, 1395, 1061 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6 /$CDCl_3$): 2.62 (s, 3H, SCH_3), 4.49 (s, 3H, NCH_3), 7.49 (t, J = 7 Hz, 1H, ArH), 7.70-7.90 (m, 2H, ArH), 8.10-8.22 (m, 2H, ArH), 8.47 (d, J = 7.8 Hz, 1H, ArH), 8.68 (d, J = 8.4 Hz, 1H, ArH), 9.43 (s, 1H, ArH), 10.27 (d, J = 7.1 Hz, 1H, ArH); MS (*m/z*, %): 279 (M^+-BF_4, 97%), 244 (100%); Anal. Calcd. for $C_{17}H_{15}N_2SBF_4$ (366.19): C, 55.76; H, 4.13; N, 7.65%. Found: C, 55.48; H, 4.28; N, 7.87%.

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