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Aromatic and heteroaromatic annelation studies on 3-[bis(methylthio)methylene]-1-methyloxindole: synthesis of carbazoles and an efficient route to pyrido[2,3-*b*]indoles

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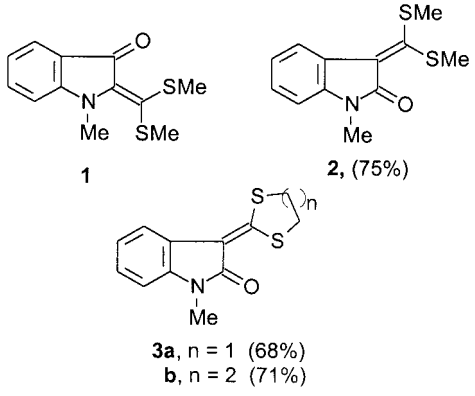
Abstract—The 3-[bis(methylthio)methylene]-1-methyloxindole (**2**) is shown to undergo cycloaromatization with allyl and methallyl magnesium chlorides to afford substituted carbazoles. A novel route to 2-substituted-3-cyano-4-methylthio/aminopyrido[2,3-*b*]indoles has been developed via heteroaromatic annelation of **2** with in situ generated 2-lithioamino-2-substituted acrylonitriles.

1. Introduction

The synthesis of substituted carbazoles[1,2] and heterocyclo-[*b*]-fused indoles such as pyrido[2,3-*b*, 4,3-*b*, 3,4-*b*]-indoles[3–8] has attracted considerable attention in recent years as this class of compounds constitute structural frameworks of several naturally occurring compounds displaying a wide range of biological activity. Many elegant approaches have been developed for the synthesis of benzo and heterocyclo-fused carbazoles,[9–11] indoles[3–8] and related natural products involving [*b*] annulation of indoles. Our own interest in the synthesis of these compounds relies upon application of our aromatic and heteroaromatic annelation methodology involving novel (or known) α-oxoketene dithioacetals as three carbon synthons for developing efficient synthetic methods for a wide variety of aromatic and heterocyclic compounds of biological importance. We have recently reported a novel and efficient route to functionalized/annulated carbazoles[12] and pyrido[2,3-*b*]indoles[3] based upon these strategies. Also in a recent publication, we have described the first synthesis of 2-[bis(methylthio)methylene]-3-oxoindole **1** and demonstrated its utility as a versatile building block for the construction of substituted benzo-, heterocyclo-fused carbazoles and indoles such as pyrido[3,4-*b*]-, pyrido[3,2-*b*]-indoles and indolo[3,2-*b*]quinolizinium ring system.[13] These studies and our continued interest in the development of new general methods for biologically important heterocycles[14] prompted us to examine reactivity and synthetic application of 3-[bis(methylthio)methylene]-2-oxoindole **2** and its cyclic derivatives **3a**–**b** for the preparation of substituted indoles, carbazoles and indolo[*b*]-fused heterocycles. In the present paper we report the results of these investigations.



2. Results and discussion

The ketene dithioacetal **2** derived from 1-methyloxindole is already known in the literature, first prepared by Kobayashi and co-workers[15a,b] by reaction of 1-methyloxindole with carbon disulfide in the presence of sodium hydride in THF followed by alkylation with dimethyl sulfate. They have further reacted **2** with several primary and secondary amines, diamines, hydrazine and amidines to afford respective *N*,*S*- and *N*,*N*-acetals as potential antibacterial and antiviral agents.[15] Similarly stabilized carbanions derived from diethyl malonate,[16a,b] ethyl cyanoacetate[16c–e] and phenylacetonitrile[16f] are shown to undergo conjugate displacement on **2** to give 1,4-adducts which are found to exhibit antifungal and anti-inflammatory activities. However no cyclocondensation reactions involving the amide group of **2**

Keywords: α-oxoketene dithioacetals; aromatic annelation; carbazoles; pyrido[2,3-*b*]-indoles.

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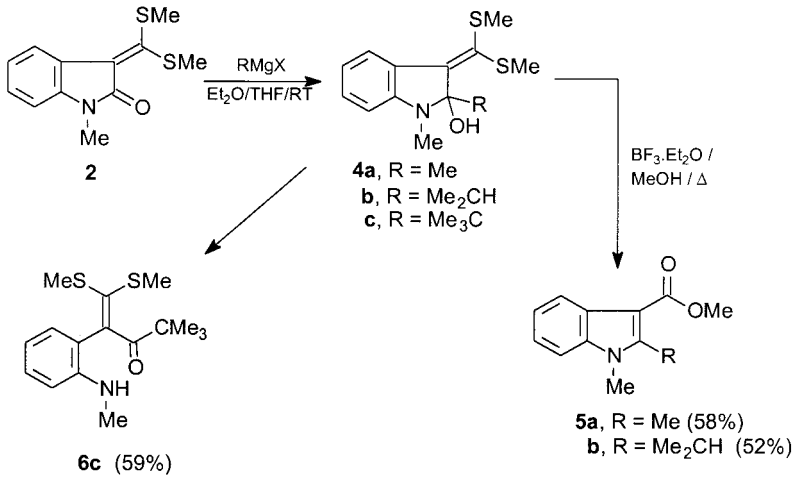
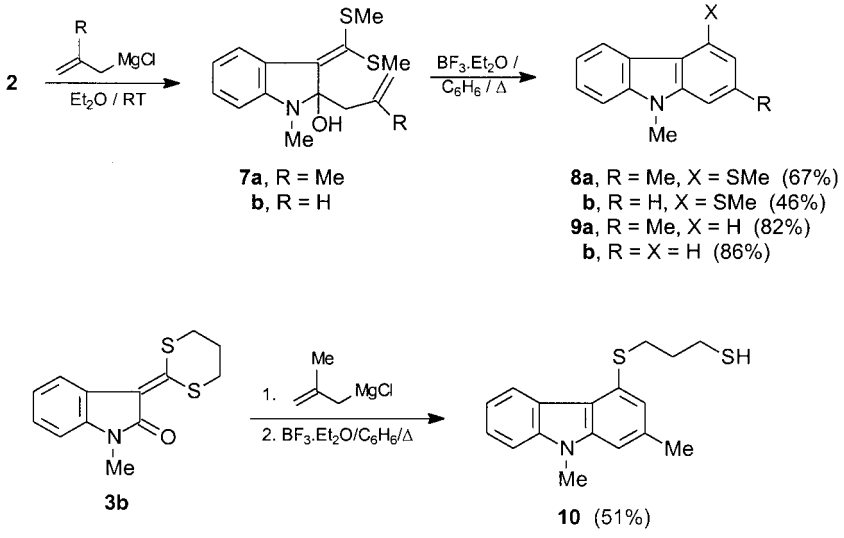


Scheme 1.

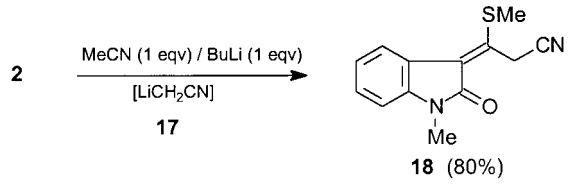
were reported by these authors with a sole exception of the formation of anti-inflammatory pyrano[2,3-*b*]indole derivatives when the 1,4-adducts from diethyl malonate and ethyl acetoacetate with **2** were subjected to thermal or acid induced cyclization.[16d] We thus became interested in exploring reactivity of **2** as potential three carbon 1,3-dielectrophilic synthon in our [3+3] aromatic and heteroaromatic annelation protocol leading to indolo[*b*]-fused carbocycles and heterocycles.

We first examined the addition and cycloaromatization of **2** and its cyclic analogs **3** with allyl and methallyl Grignard reagents (Scheme 2). The ketene dithioacetals **2** and **3** differ from other oxoketene dithioacetals, in that they possess a less electrophilic amide carbonyl group which may resist charge controlled 1,2-addition of allyl anions. We therefore reacted **2** first with alkyl magnesium halides with a view to examine its reactivity towards Grignard reagents. Thus, when **2** was reacted with methylmagnesium iodide (1.2 equiv.) it was transformed to the carbinol **4a** which on methanolysis in the presence of $BF_3{\cdot}Et_2O$ afforded methyl 1,2-dimethylindole-3-carboxylate (**5a**) in 58% yield. Similarly the addition of **2** with isopropyl magnesium chloride followed by methanolysis under identical conditions afforded the corresponding methyl 2-isopropyl-1-methylindole-3-carboxylate (**5b**) in moderate (52%) yield. Interestingly, the *t*-butyl Grignard reagent also underwent preferential 1,2-addition with **2** yielding *t*-butyl ketone **6c** as major product (59%) which is apparently formed by ring opening of initial carbinol **4c** (Scheme 1).

The ketene dithioacetal **2** was next reacted with methallyl magnesium chloride which gave the carbinol adduct **7a** in nearly quantitative yield as monitored by tlc (Scheme 2). The carbinol **7a** was found to be unstable and used as such for further transformation without characterization. Thus **7a** underwent smooth cycloaromatization in the presence of $BF_3{\cdot}Et_2O$ in benzene to give 2,9-dimethyl-4-(methylthio)-carbazole **8a** in 67% yield. Similarly the corresponding 9-methyl-4-(methylthio)carbazole **8b** was obtained in moderate yield (46%) under identical conditions from allyl magnesium chloride. Both the carbazoles **8a–b**



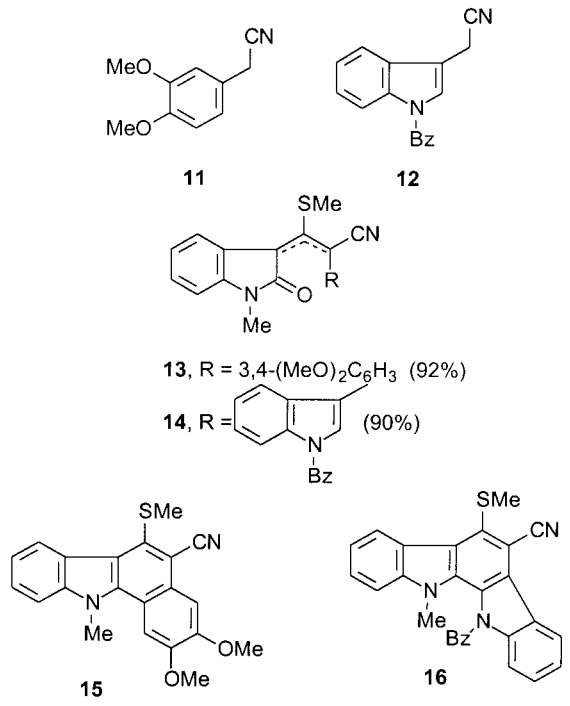
Scheme 2.



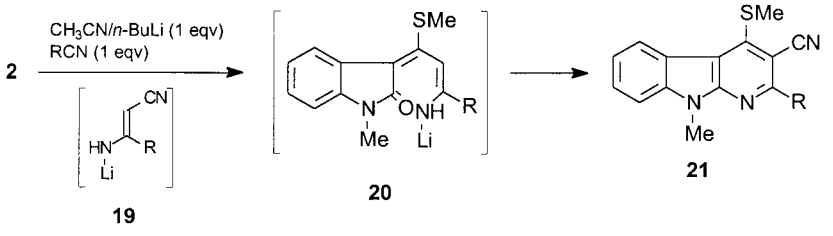
Scheme 3.

underwent smooth dethiomethylation in the presence of Raney Ni (W2) to give sulfur free compounds **9a–b** in excellent yields. Interestingly, cycloaromatization of cyclic ketenedithioacetal **3b** with methallylmagnesium chloride under the above described conditions yielded novel 2,9-dimethyl-4-(3-mercaptopropylthio)carbazole **10** which is apparently formed by opening of 1,3-dithiane ring during $BF_3{\cdot}Et_2O$ induced cyclization (Scheme 2). However addition of methallylmagnesium chloride to the corresponding dithiolan derivative **3a** gave only an intractable mixture of several products under identical conditions. Thus both intermediates **2** and **3** have been found to be useful precursors for the synthesis of functionalized indoles and carbazoles.

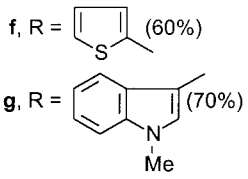
We next examined conjugate addition of stabilized carbanions derived from aryl and heteroaryl acetonitriles on **2** and subsequent cyclization of the resulting 1,4-adducts with a view to synthesize benzo[*a*]- and heterocyclo[*a*]-fused carbazoles. As model examples we examined conjugate addition-displacement of 3,4-dimethoxyphenylacetonitrile **11** and 1-benzylindole-3-acetonitrile **12** with **2** in the presence of sodium hydride which afforded the corresponding adducts **13** and **14** in high yields. We were particularly interested in cyclocondensation of the adduct **14** from indole-3-acetonitrile **12** to give the indolo[2,3-*a*]-carbazole derivative **16** possessing the basic framework present in naturally occurring indolocarbazole alkaloids staurosporine[17] and rebeccamycin.[18] However our all attempts to cyclize either **13** or **14** to the desired **15** or **16** in the presence of various condensation agents ($POCl_3$, H_3PO_4, TfOH, Tf_2O, $BF_3{\cdot}Et_2O$) or under thermal conditions did not meet with any success and only gave an intractable mixture of products.



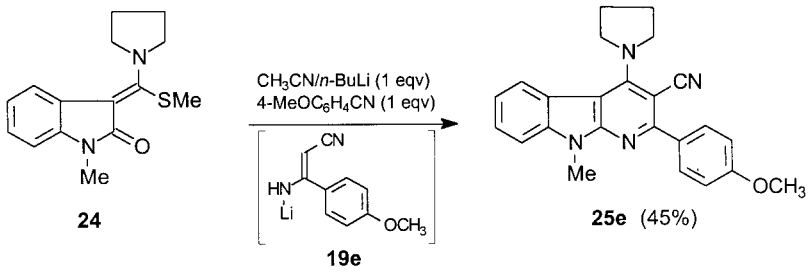
We next focussed our attention on heterocyclization of ketene dithioacetal **2** with lithioacetonitrile and substituted β-(lithioamino)acrylonitriles with a view to the construction of carboline frameworks following our earlier reported methods.[19] Interestingly, reaction of **2** with lithioacetonitrile (1 equiv.) gave exclusively the adduct **18** formed by 1,4-addition-displacement instead of 1,2-addition product as observed earlier (Scheme 3).[19] Attempted cyclization of **18** to a pyrido[2,3-*b*]indole derivative in the presence of H_3PO_4 or ammonium acetate did not yield any identifiable product. However when **2** was reacted with lithioaminocrotonitrile **19a** [generated in situ from acetonitrile (2 equiv.) and butyl lithium (1 equiv.)], work-up of the reaction mixture afforded only one product (71%) which was characterized as 3-cyano-2,9-dimethyl-4-(methylthio)pyrido-[2,3-*b*]indole (**21a**) on the basis of its spectral and analytical data (Scheme 4). The reaction was found to be general and other 2-alkyl/aryl/heteroaryl-3-cyano-4-(methylthio)pyrido-[2,3-*b*]indoles **21b–g** were obtained smoothly in 60–76%



19-21a, R = CH_3 (71%)
b, R = C_2H_5 (68%)
c, R = CH_2OCH_3 (75%)
d, R = C_6H_5 (66%)
e, R = 4-$MeOC_6H_4$ (76%)

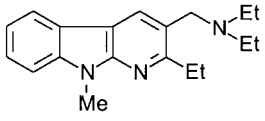


Scheme 4.

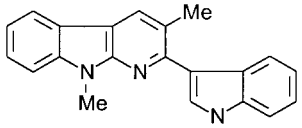


Scheme 5.

overall yields by reacting **2a** with various in situ generated 2-substituted lithioaminoacrylonitriles **19b–g** derived from the respective nitriles (Scheme 4). Compound **21b** was subjected to Raney nickel (W2) desulfurization to afford sulfur free **22b** (80%) in which the cyano group is transformed into the diethylaminomethyl functionality. Similarly, in another experiment, the pyridoindole **21g** was reacted with W4 Raney nickel under identical conditions to afford 4-dethiomethylated 3-methyl derivative **23g** with complete reduction of 3-cyano group. To further examine the scope of the methodology, the *N*,*S*-acetal **24** prepared from **2** and pyrrolidine, was reacted with lithioaminoacrylonitrile **19e** under similar conditions to afford the corresponding 3-cyano-2-(4-methoxyphenyl)-4-(*N*-pyrrolidino)-pyrido[2,3-*b*]indole **25e** in 45% yield (Scheme 5).



22b (76%)



23g (70%)

In summary, we have demonstrated that 3-[bis(methylthio)-methylene]-1-methyloxindole **2** is a useful precursor for functionalized indoles and carbazoles, whereas its reaction with 3-substituted-3-lithioaminoacrylonitriles provides a new and efficient route to a variety of 2-substituted-3-cyano-4-methylthio/aminopyrido[2,3-*b*]indoles. It should be noted that pyrido[2,3-*b*]indoles are important targets for synthetic organic chemists because of the presence of this framework in marine alkaloids Grassularine 1 and 2[20] and Mescengricin[21] displaying a broad spectrum of biological activity. Most of the synthetic approaches for these compounds described in the literature involve construction of pyridine ring from 2-amino-3-substituted indole derivatives[22] which are not easily accessible or *via* construction of pyrrole ring involving cross coupling between an appropriately substituted pyridine and substituted aniline precursor.[23] The present method along with our recently reported method[3] provides a facile access to a wide variety of pyrido[2,3-*b*]indoles from easily available starting materials. Our efforts to utilize **2** and **3** in further cyclocondensation processes are in progress.

3. Experimental

Melting points were obtained on Thomas Hoover and Mel-Temp capillary melting point apparatus. IR spectra were recorded on a Perkin–Elmer-983 and Perkin–Elmer-1320 spectrophotometers. NMR spectra were recorded on Bruker ACF-300 and Jeol LA-400 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 a 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 sieves. *n*-BuLi was purchased from Aldrich.

3-Bis(methylthio)methylene-2,3-dihydro-1-methyl-2-oxoindole (**2**) was prepared by a literature procedure.[15a,b] The corresponding cyclic ketene dithioacetals **3a–b** were prepared by a similar procedure and the analytical and spectral data of all these ketene dithioacetals are given below.

3.1. 3-Bis(methylthio)methylene-2,3-dihydro-1-methyl-2-oxoindole (2)

Yellow crystals (chloroform–hexane); mp 83–84°C; lit.[15a,b] mp 85–88°C; Yield 75%; IR (KBr): 2923, 1670, 1605, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.49 (s, 3H, SCH_3), 2.62 (s, 3H, SCH_3), 3.27 (s, 3H, NCH_3), 6.81 (d, 1H, J=7.8 Hz, ArH), 7.05 (td, 1H, J=7.8, 1.1 Hz, ArH), 7.23 (td, 1H, J=7.8, 1.2 Hz, ArH), 8.16 (dd, 1H, J=7.8, 1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 19.17, 19.37, 25.92, 107.55, 121.55, 122.67, 123.35, 123.41, 127.60, 141.55, 158.02, 165.06; Anal. Calcd for $C_{12}H_{13}NOS_2$ (251.37): C, 57.34; H, 5.21; N, 5.57%. Found: C, 57.53; H, 5.14; N, 5.68%.

3.2. 3-(Ethylenedithio)methylene-2,3-dihydro-1-methyl-2-oxoindole (3a)

Yellow crystals (chloroform–hexane); mp 112–113°C; Yield 68%; IR (KBr): 1627, 1571, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 3.30 (s, 3H, NCH_3), 3.48–3.57 (m, 4H, $-(CH_2)_2-$), 6.83 (d, 1H, J= 7.6 Hz, ArH), 7.07 (t, 1H, J=7.6 Hz, ArH), 7.20 (t, 1H, J=7.6 Hz, ArH), 7.62 (d, 1H, J=7.6 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 25.98, 37.70, 37.74, 107.47, 113.50, 121.48, 121.52, 122.82, 126.39, 140.55, 158.06, 165.91; MS: *m/z* (%): 249 (M^+,

100); Anal. Calcd for $C_{12}H_{11}NOS_2$ (249.37): C, 57.80; H, 4.45; N, 5.62%. Found: C, 57.78; H, 4.49; N, 5.71%.

3.3. 3-(Trimethylenedithio)methylene-2,3-dihydro-1-methyl-2-oxoindole (3b)

Yellow crystals (chloroform–hexane); mp 148–149°C; Yield 71%; IR (KBr): 1616, 1590, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.31 (tt, 2H, J= 7.0 Hz, $-CH_2-$), 3.08 (t, 2H, J=7.0 Hz, $-CH_2-$), 3.15 (t, 2H, J=7.0 Hz, $-CH_2-$), 3.27 (s, 3H, NCH_3), 6.82 (d, 1H, J= 7.8 Hz, ArH), 7.04 (t, 1H, J=7.7 Hz, ArH), 7.19–7.24 (m, 1H, ArH), 8.05 (d, 1H, J=7.6 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 23.54, 25.70, 28.53, 29.28, 107.33, 120.12, 121.34, 122.83, 122.89, 126.68, 140.81, 158.19, 165.53; Anal. Calcd for $C_{13}H_{13}NOS_2$ (263.38); C, 59.28; H, 4.97; N, 5.32%. Found: C, 59.53; H, 5.05; N, 5.25%.

3.4. General procedure for the reaction of alkyl Grignard reagents with 2

To an ice cooled solution of alkyl magnesium halide [prepared from the respective alkyl halides namely methyl iodide, *i*-propyl bromide, *t*-butylchloride (10 mmol) and magnesium turnings (0.5 g, 20.8 mmol)] in dry ether (75 mL), a solution of **2** (1.26 g, 5 mmol) in dry THF (30 mL) was added dropwise and the reaction mixture was further stirred at room temperature for 2 h. It was then poured into saturated aqueous NH_4Cl solution (200 mL), extracted with benzene (2×100 mL) and the combined benzene extracts were washed with water, dried (Na_2SO_4) and evaporated to give carbinol thioacetals **4** as viscous residue. To a solution of **4** in absolute methanol (50 mL), $BF_3{\cdot}Et_2O$ (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 (2×100 mL), the organic layer washed with water, dried (Na_2SO_4) and evaporated to give viscous residue which was purified by silica gel chromatography using hexane–ethyl acetate (19:1) as eluent.

3.4.1. Methyl 1,2-dimethylindole-3-carboxylate (5a). Colorless crystals (chloroform–hexane); mp 137–138°C; lit.[24] mp 141–142°C; Yield 58%.

3.4.2. Methyl 1-methyl-2-(*i*-propyl)indole-3-carboxylate (5b). Colorless crystals (chloroform–hexane); mp 92–93°C; Yield 52%; IR (KBr): 2966, 1690, 1528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.45 (d, 6H, J=7.3 Hz, $(CH_3)_2$), 3.79 (s, 3H, NCH_3), 3.92 (s, 3H, OCH_3), 4.42 (septet, 1H, J= 7.3 Hz, CH), 7.20–7.30 (m, 3H, ArH), 8.08–8.12 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 20.16, 25.10, 31.49, 50.68, 102.96, 109.05, 121.68, 121.81, 122.13, 126.64, 136.86, 153.57, 166.44; MS: *m/z* (%): 231 (M^+, 100); Anal. Calcd for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06%. Found: C, 72.97; H, 6.32; N, 6.11%.

3.4.3. 1,1-Bis(methylthio)-4,4-dimethyl-2-(2-*N*-methylaminophenyl)-1-penten-3-one (6c). Viscous yellow liquid; Yield 59%; IR (CCl_4): 2911, 7124, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.05 (s, 9H, *t*-butyl), 2.07 (s, 3H, SCH_3), 2.27 (s, 3H, SCH_3), 2.76 (s, 3H, NCH_3), 4.58 (brs, 1H, NH), 6.53 (d, J=7.6 Hz, 1H, ArH), 6.58–6.63 (m, 1H, ArH), 7.03 (dd, 1H, J=7.6, 1.7 Hz, ArH), 7.12–7.17 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 16.61, 18.01, 27.47, 30.43, 44.69, 110.16, 115.84, 120.81, 129.93, 130.62, 130.64, 135.36, 146.40, 147.11; MS: *m/z* (%): 309 (M^+, 27), 276 (100); Anal. Calcd for $C_{16}H_{23}NOS_2$ (309.50): C, 62.09; H, 7.49; N, 4.53%. Found: C, 62.35; H, 7.41; N, 4.57%.

3.5. General procedure for the reaction of allyl and methallyl Grignard reagents with 2 and 3: synthesis of carbazoles 8a–b and 10

To an ice cooled solution of appropriate Grignard reagent (prepared from allyl bromide or methallyl chloride, 10 mmol and magnesium tunings, 0.5 g, 20.8 mmol) in dry ether (75 mL), a solution of **2** or **3b** (5 mmol) in dry THF (30 mL) was added dropwise and the reaction mixture was further stirred at room temperature for 2 h. It was then poured into saturated aqueous NH_4Cl solution (200 mL), extracted with benzene (2×100 mL), the combined benzene extracts were washed with water, dried (Na_2SO_4) and evaporated to give crude carbinol as viscous residue which was dissolved in dry benzene (50 mL) followed by addition of $BF_3{\cdot}Et_2O$ (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 (2×100 mL), washed with water, dried (Na_2SO_4) and the solvent evaporated to give viscous residue which was purified by silica gel column chromatography using hexane–ethyl acetate (99:1) as eluent.

3.5.1. 2,9-Dimethyl-4-(methylthio)carbazole (8a). Colorless crystals (chloroform–hexane); mp 132–133°C; Yield 67%; IR (KBr): 2916, 1593, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.50 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 3.64 (s, 3H, NCH_3), 6.83 (s, 1H, ArH), 6.90 (s, 1H, ArH), 7.20–7.27 (m, 2H, ArH), 7.37–7.42 (m, 1H, ArH), 8.49 (d, 1H, J=7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 15.39, 22.19, 28.86, 105.69, 107.84, 117.09, 117.75, 118.87, 122.71, 123.10, 124.71, 133.32, 135.80, 140.70, 141.35; 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, 74.91; H, 6.33; N, 5.75%.

3.5.2. 9-Methyl-4-(methylthio)carbazole (8b). Colorless crystals (chloroform–hexane); mp 80–81°C; Yield 46%; IR (KBr): 2919, 1579, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.57 (s, 3H, SCH_3), 3.63 (s, 3H, NCH_3), 6.98 (d, 1H, J=7.5 Hz, ArH), 7.07 (d, 1H, J=8.0 Hz, ArH), 7.22–7.44 (m, 4H, ArH), 8.55 (dd, 1H, J=7.6, 1.2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 15.33, 28.88, 105.19, 107.93, 115.54, 118.94, 119.78, 122.62, 123.52, 125.20, 125.56, 133.85, 140.61, 140.83; 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, 73.66; H, 5.84; N, 6.25%.

3.5.3. 2,9-Dimethyl-4-(3-mercaptopropylthio)carbazole (10). Colorless crystals (Chloroform–hexane); mp 120–121°C; Yield 51%; IR (KBr): 2919, 1595, 1469 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):1.33 (t, J=8.0 Hz, 1H, SH), 1.93–2.05 (m, 2H, $-CH_2-$), 2.53 (s, 3H, CH_3), 2.63–2.69 (m, 2H, $-CH_2-$), 3.17 (t, J=8.0 Hz, 2H, $-CH_2-$), 3.74 (s, 3H, NCH_3), 7.01 (s, 2H, ArH), 7.20–7.26 (m, 1H, ArH), 7.33

(d, J=8.0 Hz, 1H, ArH), 7.40–7.45 (m, 1H, ArH), 8.60 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 22.12, 23.48, 28.98, 31.54, 32.97, 106.90, 107.97, 118.96, 119.36, 121.22, 122.67, 123.19, 125.04, 130.52, 135.72, 140.90, 141.65; MS: m/z (%): 301 (M^+, 93) 227 (100); Anal. Calcd for $C_{17}H_{19}NS_2$ (301.48): C, 67.73; H, 6.35; N, 4.65%. Found: C, 67.97; H, 6.43; N, 4.59%.

3.5.4. 2,9-Dimethylcarbazole (9a) and 9-methylcarbazole (9b). To a solution of **8a** or **8b** (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 **9a** or **9b** which was purified by passing through a small silica gel column using hexane as eluent.

3.5.5. 2,9-Dimethylcarbazole (9a). Colorless crystals (hexane); mp 82–83°C; lit.[25] mp 85–87°C; Yield 82%.

3.5.6. 9-Methylcarbazole (9b). Colorless crystals (hexane); mp 87°C; lit.[26] mp 87–88°C; Yield 86%.

3.6. General procedure for the reaction of 3,4-dimethoxyphenylacetonitrile and 1-benzylindole-3-acetonitrile with 2

To a stirred suspension of NaH (10 mmol) in DMF (10 mL) at 0°C, a solution of 3,4-(dimethoxyphenyl)acetonitrile or 1-benzylindole-3-acetonitrile (5 mmol) in DMF (10 mL) was added dropwise. After 20 min, a solution of **2** (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 tlc). It was then poured into saturated NH_4Cl solution (200 mL) and the solid obtained was filtered, dried and recrystallized.

3.6.1. 3-[2-Cyano-2-(3,4-dimethoxyphenyl)-1-methylthio]-ethylidine-2,3-dihydro-1-methyl-2-oxoindole (13). Yellow crystals (methanol); mp 135–136°C; Yield 92%; IR (KBr): 2930, 2240, 1684, 1608, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.42 (s, 3H, SCH_3), 3.28 (s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.96 (s, 1H, CHCN), 6.84–6.92 (m, 2H, ArH), 6.98–7.18 (m, 3H, ArH), 7.26–7.41 (m, 2H, ArH); MS: m/z (%): 380 (M^+, 92), 332 (100); Anal. Calcd for $C_{21}H_{20}N_2O_3S$ (380.47): C, 66.30; H, 5.30; N, 7.36%. Found: C, 66.56; H, 5.24; N, 7.47%.

3.6.2. 3-[2-(*N*-Benzylindol-3-yl)-2-cyano-1-methylthio]-ethylidine-2,3-dihydro-1-methyl-2-oxoindole (14). Light yellow crystals (methanol); mp 136–137°C; Yield 90%; IR (KBr): 2923, 2210, 1697, 1608 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.37 (s, 3H, SCH_3), 3.26 (s, 3H, NCH_3), 5.13 (s, 1H, CHCN), 5.32 (s, 2H, CH_2Ph), 6.85 (d, J=7.6 Hz, 1H, ArH), 7.00–7.35 (m, 11H, ArH), 7.91 (s, 1H, ArH), 8.00–8.02 (m, 1H, ArH); MS: m/z (%): 449 (M^+, 25), 91 (100); Anal. Calcd for $C_{28}H_{23}N_3OS$ (449.58): C, 74.81; H, 5.16; N, 9.35%. Found: C, 74.48; H, 5.31; N, 9.54%.

3.7. Reaction of lithioacetonitrile with 2

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 **2** (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 chloroform (2×100 mL), washed with water and concentrated to give viscous residue which was purified by passing through silica gel column using hexane–ethyl acetate (19:1) as eluent.

3.7.1. 3-[2-Cyano-1-(methylthio)ethylidene]-2,3-dihydro-1-methyl-2-oxoindole (18). Yellow crystals (chloroform–hexane); mp 155–156°C; yield 80%; IR (KBr): 1615, 1516, 1473 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.72 (s, 3H, SCH_3), 3.23 (s, 3H, NCH_3), 4.78 (s, 2H, CH_2), 6.80 (d, 1H, J=7.8 Hz, ArH), 7.05–7.09 (m, 1H, ArH), 7.26–7.31 (m, 1H, ArH), 7.97 (d, 1H, J=7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 14.06, 17.59, 25.85, 107.61, 116.12, 122.06, 122.67, 122.89, 125.16, 128.89, 141.85, 144.35, 165.53; Anal. Calcd for $C_{13}H_{12}N_2OS$ (244.32): C, 63.91; H, 4.95; N, 11.47%. Found: C, 64.13; H, 4.91; N, 11.56%.

3.7.2. Procedure for the generation of lithioaminocrotononitrile (19a) and its reaction with 2: synthesis of 3-Cyano-2,9-dimethyl-4-(methylthio)pyrido[2,3-*b*]-indole (21a). 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 **2** (1.26 g, 5 mmol) in dry THF (25 mL) was added dropwise and the reaction mixture was further stirred at refluxing temperature for 48 h. It was then cooled and poured into saturated NH_4Cl solution, extracted with chloroform (2×100 mL), combined organic phase was washed with water, dried (Na_2SO_4) and concentrated to give crude **21a** which was purified by column chromatography over silica gel using hexane–ethyl acetate (19:1) as eluent.

21a: Colorless crystals (ether–hexane); mp 162–163°C; Yield 71%; IR (KBr): 2200, 1540, 1458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.73 (s, 3H, CH_3), 2.81 (s, 3H, SCH_3), 3.86 (s, 3H, NCH_3), 7.31–7.39 (m, 2H, ArH), 7.51–7.56 (m, 1H, ArH), 8.50 (d, 1H, J=7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.17, 24.26, 27.72, 102.94, 109.14, 114.28, 118.03, 119.79, 121.20, 123.89, 127.34, 140.30, 145.24, 150.96, 159.58; 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, 67.67; H, 4.81; N, 15.56%.

3.8. General procedure for the generation of 2-substituted 2-lithioaminoacrylonitriles 13b–g and their reaction with 2: synthesis of 2-substituted-3-cyano-4-(methylthio)-pyrido[2,3-*b*]indoles 21b–g

To a stirred solution of acetonitrile (0.4 mL, 7.6 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 white suspension of lithioacetonitrile, a solution of alkyl/aryl or heteroarylnitrile (7.5 mmol) in dry THF (10 mL) was added dropwise and the reaction mixture was further stirred at the same temperature for 0.5 h to obtain a light reddish solution of 2-substituted 2-lithioaminoacrylonitrile. To this in situ generated 2-lithioaminoacrylonitrile **19**, a solution of **2** (1.26 g, 5 mmol) in dry THF (25 mL) was added dropwise and the reaction mixture was further stirred at refluxing temperature for 40–48 h (monitored by tlc). It was then cooled and poured into saturated NH_4Cl solution, extracted with chloroform (2×100 mL), combined organic phase was washed with water, dried (Na_2SO_4) and concentrated to give crude **21** which was purified by column chromatography over silica gel using hexane–ethyl acetate (19:1) as eluent.

3.8.1. 3-Cyano-2-ethyl-9-methyl-4-(methylthio)pyrido[2,3-*b*]indole (21b). Colorless crystals (ether–hexane); mp 151–152°C; Yield 68%; IR (KBr): 2924, 2213, 1560, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.45 (t, 3H, *J*=7.6 Hz, CH_2CH_3), 2.77 (s, 3H, SCH_3), 3.19 (q, 2H, *J*=7.6 Hz, CH_2CH_3), 3.95 (s, 3H, NCH_3), 7.35–7.39 (m, 1H, ArH), 7.45 (d, 1H, *J*=8.4 Hz, ArH), 7.55–7.60 (m, 1H, ArH), 8.61 (d, 1H, *J*=7.6 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 13.41, 18.36, 27.86, 30.83, 102.74, 109.28, 114.71, 118.04, 120.10, 121.28, 124.14, 127.47, 140.67, 145.58, 151.54, 164.74; MS: *m/z* (%): 281 (M^+, 100), 248 (54); Anal. Calcd for $C_{16}H_{15}N_3S$ (281.38): C, 68.30; H, 5.37; N, 14.93%. Found: C, 68.57; H, 5.28; N, 15.04%.

3.8.2. 3-Cyano-2-methoxymethyl-9-methyl-4-(methylthio)-pyrido[2,3-*b*]indole (21c). Colorless crystals (ether–hexane); mp 180–181°C; Yield 75%; IR (KBr): 2202, 1600, 1541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.79 (s, 3H, SCH_3), 3.59 (s, 3H, NCH_3), 3.97 (s, 3H, CH_2OCH_3), 4.85 (s, 2H, CH_2OCH_3), 7.37–7.42 (m, 1H, ArH), 7.48 (d, 1H, *J*= 8.3 Hz, ArH), 7.59–7.63 (m, 1H, ArH), 8.63 (d, 1H, *J*= 7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.36, 28.10, 59.38, 74.64, 103.30, 109.45, 115.90, 117.18, 119.84, 121.54, 124.45, 127.98, 140.90, 146.03, 151.09, 158.02; MS: *m/z* (%): 297 (M^+, 27), 267 (100); Anal. Calcd for $C_{16}H_{15}N_3OS$ (297.38): C, 64.62; H, 5.08; N, 14.13%. Found: C, 64.35; H, 5.17; N, 14.29%.

3.8.3. 3-Cyano-9-methyl-4-methylthio-2-phenylpyrido[2,3-*b*]indole (21d). Colorless crystals (ether–hexane); mp 171–172°C; Yield 66%; IR (KBr): 2210, 1546, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.83 (s, 3H, SCH_3), 4.00 (s, 3H, NCH_3), 7.40–7.44 (m, 1H, ArH), 7.49–7.57 (m, 4H, ArH), 7.60–7.65 (m, 1H, ArH), 7.98–8.01 (m, 2H, ArH), 8.71 (d, 1H, *J*=7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.57, 28.02, 102.52, 109.41, 115.65, 118.60, 120.01, 121.60, 124.52, 128.00, 128.42, 128.49, 129.54, 129.81, 138.33, 141.22, 146.76, 159.70; MS: *m/z* (%): 329 (M^+, 100); Anal. Calcd for $C_{20}H_{15}N_3S$ (329.43): C, 72.92; H, 4.59; N, 12.76%. Found C, 73.18; H, 4.65; N, 12.63%.

3.8.4. 3-Cyano-2-(4-methoxyphenyl)-9-methyl-4-(methylthio)pyrido[2,3-*b*]ndole (21e). Colorless crystals (ether–hexane); mp 209–210°C; Yield 76%; IR (KBr): 2200, 1596, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.82 (s, 3H, SCH_3), 3.90 (s, 3H, NCH_3), 4.00 (s, 3H, OCH_3), 7.05–7.08 (m, 2H, ArH), 7.39–7.43 (m, 1H, ArH), 7.49 (d, 1H, *J*=8 Hz, ArH), 7.59–7.64 (m, 1H, ArH), 7.98–8.02 (m, 2H, ArH), 8.70 (d, 1H, *J*=8 Hz, ArH); MS: *m/z* (%): 359 (M^+, 100); Anal. Calcd for $C_{21}H_{17}N_3OS$ (359.45): C,70.17; H, 4.77; N, 11.69%. Found: C, 70.41; H, 4.68; N, 11.61%.

3.8.5. 3-Cyano-9-methyl-4-methylthio-2-(2-thienyl)pyrido[2,3-*b*]indole (21f). Colorless crystals (ether–hexane); mp 228–229°C; Yield 60%; IR (KBr): 2202, 1550, 1490 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): 2.77 (s, 3H, SCH_3), 3.97 (s, 3H, NCH_3), 7.17–7.20 (m, 1H, ArH), 7.36–7.41 (m, 1H, ArH), 7.45 (d, 1H, *J*=8.3 Hz, ArH), 7.53 (dd, 1H, *J*=5.1, 1 Hz, ArH), 7.57–7.62 (m, 1H, ArH), 8.34 (dd, 1H, *J*=3.7, 1 Hz, ArH), 8.64 (d, 1H, *J*=8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.64, 27.97, 99.64, 109.38, 115.74, 118.71, 120,09, 121.66, 124.29, 128.03, 128.52, 129.03, 129.88, 141.33, 142.77, 146.76, 151.06, 151.61; MS: *m/z* (%): 335 (M^+, 100); Anal. Calcd for $C_{18}H_{13}N_3S_2$ (335.45): C, 65.45; H, 3.91; N, 12.53%. Found: C, 64.69; H, 4.02; N, 12.41%.

3.8.6. 3-Cyano-9-methyl-2-(*N*-methyl-3-indolyl)-4-(methylthio)pyrido[2,3-*b*]indole (21g). Colorless crystals (ether–hexane); mp 219–220°C; Yield 70%; IR (KBr): 2200, 1554, 1505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.76 (s, 3H, SCH_3), 3.88 (s, 3H, NCH_3), 4.01 (s, 3H, NCH_3), 7.28–7.45 (m, 5H, ArH), 7.54–7.58 (m, 1H, ArH), 8.28 (s, 1H, ArH), 8.60–8.67 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.63, 28.10, 33.44, 100.28, 109.17, 109.61, 109.65, 113.02, 113.86, 119.99, 120.40, 121.21, 121.30, 122.68, 122.77, 123.93, 127.28, 132.05, 137.33, 140.99, 146.47, 151.85, 154.97; MS: *m/z* (%): 382 (M^+, 100); Anal. Calcd for $C_{23}H_{18}N_4S$ (382.49): C, 72.23; H, 4.74; N, 14.65%. Found: C, 72.06; H, 4.78; N 14.77%.

3.9. General procedure for the reaction of 15b and 15g with Raney nickel

To a solution of **21b** or **21g** (2 mmol) in ethanol (25 mL), Raney nickel (W2 or W4, 5 times by weight) was added and the suspension was refluxed with stirring for 3–4 h (monitored by tlc). The reaction mixture was then cooled, filtered through 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 products which were purified by passing through a small silica gel column using hexane as eluent.

3.9.1. 3-(Diethylamino)methyl-2-ethyl-9-methylpyrido[2,3-*b*]indole (22b). Colorless crystals (hexane–chloroform); mp 109–110°C; Yield 76%; IR (KBr): 2968, 2788, 1597, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.06 (t, *J*= 7.1 Hz, 6H, $(CH_2CH_3)_2$), 1.38 (t, *J*=7.6 Hz, 3H, CH_2CH_3), 2.57 (q, 4H, *J*=7.1 Hz, $(CH_2CH_3)_2$), 3.05 (q, *J*=7.6 Hz, 2H, CH_2CH_3), 3.69 (s, 2H, CH_2), 3.94 (s, 3H, NCH_3), 7.21–7.25 (m, 1H, ArH), 7.39 (d, *J*=8 Hz, 1H, ArH), 7.44–7.48 (m, 1H, ArH), 8.03 (d, *J*=7.8 Hz, 1H, ArH), 8.25 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 11.73, 13.81, 27.55, 28.43, 46.70, 55.21, 108.79, 113.20, 119.33, 120.65, 123.57,

125.72, 125.78, 129.86, 140.27, 150.92, 159.61; MS: *m/z* (%): 295 (M^+, 41), 221 (100); Anal. Calcd for $C_{19}H_{25}N_3$ (295.43): C, 77.25; H, 8.53; N, 14.22%. Found: C, 77.51; H, 8.42; N, 14.31%.

3.9.2. 3,9-Dimethyl-2-(1-methyl-2-indolyl)pyrido[2,3-*b*]-indole (23g). Colorless crystals (ether–hexane); mp 151–152°C; Yield 70%; IR (KBr): 2924, 1599, 1477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.63 (s, 3H, CH_3), 3.89 (s, 3H, NCH_3), 4.01 (s, 3H, NCH_3), 7.21–7.52 (m, 7H, ArH), 8.03–8.06 (m, 1H, ArH), 8.21 (s, 1H, ArH), 8.29 (d, *J*=7.8 Hz, 1H, ArH); MS: *m/z* (%): 325 (M^+, 100); Anal. Calcd for $C_{22}H_{19}N_3$ (325.41): C, 81.20; H, 5.88; N, 12.91%. Found: C, 81.47; H, 5.81; N, 13.03%.

3.9.3. 2,3-Dihydro-1-methyl-3-[(*N*-pyrrolidino)(methylthio)methylene]-2-oxoindole (24). A solution of **2** (5 g, 0.02 mol) and pyrrolidine (1.8 mL, 0.021 mol) in ethanol (150 mL) was refluxed for 3.5 h (monitored by tlc) and then the solvent was removed under vacuum. The residue obtained was dissolved in chloroform washed with water, dried and evaporated to obtain the crude **24** which was purified by recrystallization from chloroform–ether. Yellow crystals (chloroform–ether); mp 137–138°C; Yield 90%; IR (KBr): 2920, 1631, 1604, 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.00–2.04 (m, 4H, CH_2CH_2), 2.40 (s, 3H, SCH_3), 3.34 (s, 3H, NCH_3), 3,83 (brs, 4H, CH_2–N–CH_2), 6.85–6.87 (m, 1H, ArH), 6.96–7.05 (m, 2H, ArH), 7.45 (d, *J*=7.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.86, 25.29, 25.82, 53.53, 93.48, 106.73, 118.05, 120.07, 121.34, 124.52, 137.50, 163.98, 165.26; Anal. Calcd for $C_{15}H_{18}N_2OS$ (274.39): C, 65.66; H, 6.61; N, 10.21%. Found: C, 65.92; H, 6.72; N, 10.03%.

3.9.4. 3-Cyano-2-(4-methoxyphenyl)-9-methyl-4-(*N*-pyrrolidino)pyrido[2,3-*b*]indole (25e). Procedure is same as that of **21e** except *N*,*S*-acetal **24** was used instead of **2**. Colorless crystals (chloroform–hexane); mp 229–230°C; Yield 45%; IR (KBr): 2823, 2219, 1568, 1444 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): 2.01 (brs, 4H, $-CH_2-CH_2-$), 3.28 (s, 3H, NCH_3), 3.66 (brs, 4H, $-CH_2-N-CH_2-$), 3.88 (s, 3H, OCH_3), 6.99 (d, *J*=8.4 Hz, 2H, ArH), 7.20–7.48 (m, 5H, ArH) 8.77 (d, *J*=7.8 Hz, 1H, ArH); MS: *m/z* (%): 382 (M^+, 100), 357 (49); Anal. Calcd for $C_{24}H_{22}N_4O$ (382.46): C, 75.37; H, 5.80; N, 14.65%. Found: C, 75.66; H, 5.87; N, 14.53%.

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