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A New General Regiocontrolled Synthesis of Highly Substituted and Condensed Indoles via Heteroaromatic Annelation

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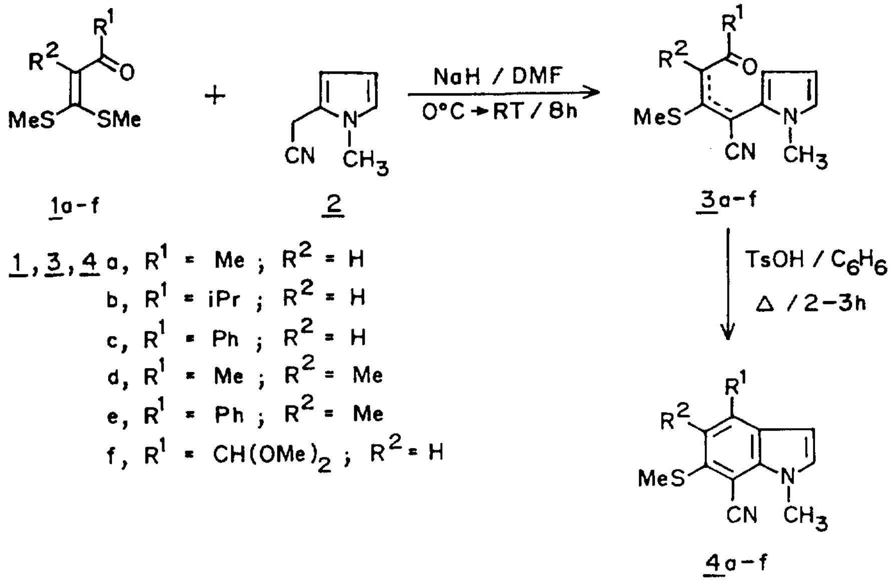
Abstract: A new general method for the synthesis of substituted and condensed indoles has been developed *via* heteroaromatic annelation involving base induced conjugate addition-elimination of 1-methylpyrrole-2-acetonitrile to various α-oxoketene acetals followed by cyclization of the resulting adducts in the presence of TsOH in refluxing benzene. © 1997 Elsevier Science Ltd.

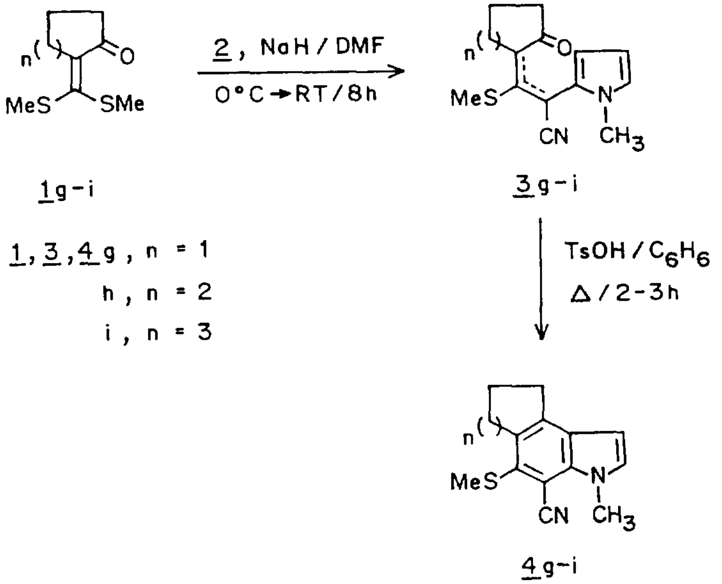
Synthesis of substituted indoles has attracted considerable attention due largely to their importance as building blocks for many therapeutically useful materials and wide ranging potential biological activity of both synthetic and naturally occuring derivatives.[1] Despite numerous age old elegant synthesis of these class of compounds, research in indole chemistry continues unabated with many groups devoting considerable efforts for developing new methods for synthesis and functionalization of indole ring system.[2-10] However, most of these syntheses rely upon functionalized benzene precursors in which a pyrrole ring is elaborated through various transformations.[6-9] On the other hand, only a few syntheses of these fused heteroaromatics starting from pyrrole derivatives are reported in the literature. Thus the reported methods include (a) Pd catalyzed cyclocarbonylation of 2-pyrrolylallyl acetates[11] (b) cycloaddition reaction of pyrrole-carbene chromium complex with alkynes[12] (c) Diels Alder cycloaddition of pyrrole-2,3-quinodimethane[13] or their stable cyclic analogs,[14] and 2- or 3-vinylpyrroles.[10,15] In a series of papers, Natsume and co-workers[16] have synthesized a number of different indoles and the related natural products *via* intramolecular electrophilic cyclization of 2 or 3 substituted pyrroles as key step followed by functionality manipulation and adjustment.[17] Recently Katritzky and co-workers have reported a new synthesis of indoles *via* [3+3] annelation of 2-(benzotriazol-1-ylmethyl)pyrroles with α,β-unsaturated aldehydes and ketones.[18] Despite these elegant approaches, development of new general methodologies for regiospecifically substituted indoles *via* benzoannelation of pyrrole derivatives is very much desirable. Over the past several years we have extensively investigated the chemistry of α-oxoketene dithioacetals[19] as versatile 3-carbon 1,3-dielectrophilic partners with 3-carbon binucleophiles in [3+3]cycloaromatization reactions to yield regiospecifically substituted benzenoids, naphthalenes and condensed aromatics.[20] These reactions are synthetically valuable because α-oxoketene dithioacetals are easily accessible from a wide variety of acyclic and cyclic active methylene ketones.[19] Extensive investigation of these cycloaromatization reactions has led to novel synthetic methods for fused ring heteroaromatics like benzisoxazoles,[21] quinazolones,[22] indazolones,[23] carbazoles[24] having substituents at specific positions. In continuation of these studies aimed at exploring further scope of these cycloaromatization reactions, we became interested to apply this strategy for indole synthesis. As a representative example, we herein report base induced conjugate addition-elimination of 1-methylpyrrole-2-acetonitrile to acyclic and cyclic oxoketene acetals and subsequent intramolecular electrophilic cyclization of the resulting adducts to afford regiospecifically substituted and condensed indoles in high yields.

In a typical experiment, 1-methylpyrrole-2-acetonitrile (**2**) was reacted with oxoketene dithioacetal **1a** in the presence of sodium hydride in DMF at ice cold temperature to afford the corresponding 1,4-addition-elimination adduct **3a** in nearly quantitative yield. Attempted purification of **3a** by column chromatography (silica gel) was not possible, since it was slowly transformed into cycloaromatized 7-cyano-1,4-dimethyl-6-(methylthio)indole (**4a**). This was further confirmed by TsOH induced cyclization of **3a** in refluxing benzene to furnish **4a** in 86% yield (Scheme 1). Similarly, the corresponding 4-isopropyl (**4b**), 4-phenyl (**4c**), 4,5-dimethyl (**4d**), 4-phenyl-5-methyl (**4e**)indoles were obtained in 72-88% overall yields by reacting the corresponding oxoketene dithioacetals **1b-e** with **2** under described reaction conditions (Scheme-1). The ketene dithioacetal **1f** derived from pyruvaldehyde dimethylacetal was also reacted with **2** to afford the corresponding adduct **3f** which yielded only an insoluble polymeric solid instead of indole **4f**, when treated with TsOH in refluxing benzene. However, **3f** underwent facile cyclization when passed through silica gel column to yield the expected indole **4f** in 68% yield.

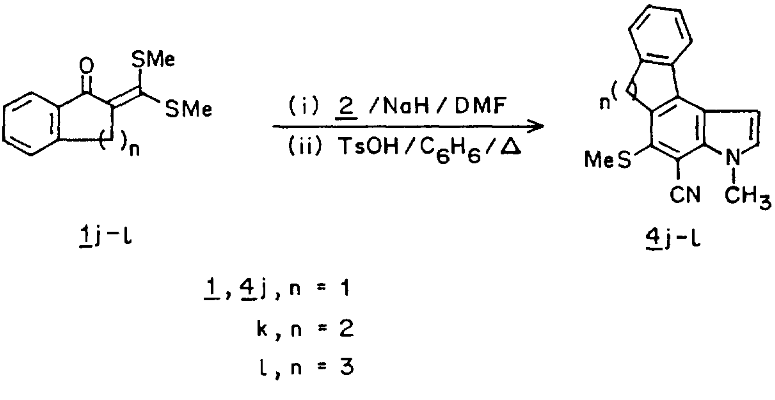


Scheme – 1

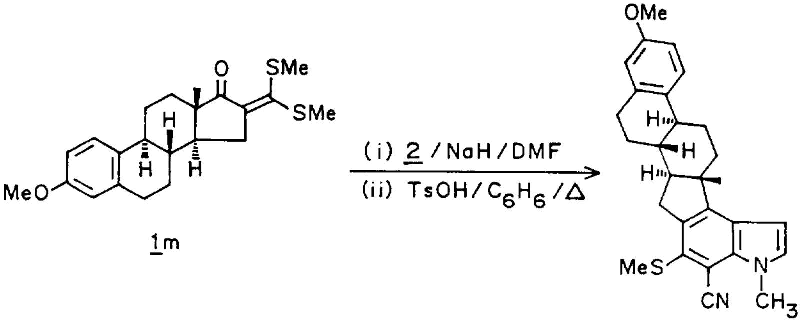
The strategy was successfully extended for the synthesis of 4,5-annelated indoles **4g-i** (Scheme-2). Thus treatment of cyclic ketenedithioacetals **1g-i** with **2** and subsequent cyclization of the resulting adducts (**3g-i**) under the described conditions gave the respective substituted cyclopentano[e]-, cyclohexano[e]- and cycloheptano[e]indoles **4g-i** in 68-78% overall yields (Scheme-2). Further extension of the reaction to cyclic ketenedithioacetals **1j-l** derived from indanone, α-tetralone and benzsuberone respectively gave the corresponding condensed indoles **4j-l** in 66-82% overall yields (Scheme-3). An interesting example of this series is the synthesis of optically active indole **4m** by reacting oxoketene dithioacetal **1m** derived from estrone methylether with **2** under similar reaction conditions (Scheme-4).



Scheme-2



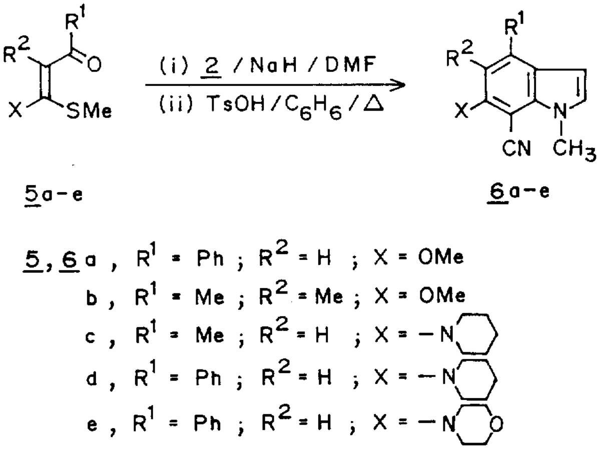
Scheme-3



Scheme -4

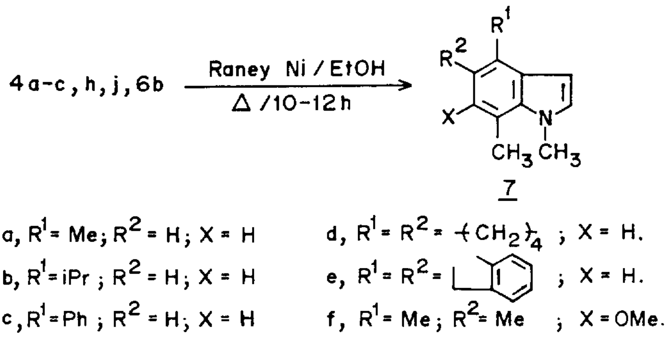
4m

In order to demonstrate the versatility of our benzoannelation methodology, as well as to develop this method for the synthesis of 6-oxygenated and 6-aminoindoles, the reactions of O,S-acetals and N,S-acetals with **2** were examined. Thus, oxoketene O,S-acetals **5a-b** derived from acetophenone and ethylmethyl ketone respectively were reacted with **2** under the described conditions to afford the corresponding 7-cyano-6-methoxy-1-methyl-4-phenylindole (**6a**) and 7-cyano-6-methoxy-1,4,5-trimethylindole (**6b**) in 80% and 86% yields respectively (Scheme-5). Apparently the methylthio group was found to be the sole leaving group in preference to OMe in these transformations, and the same trend was followed when the N,S-acetals **5c-e** were reacted with **2** yielding the corresponding 6-N-cycloaminoindoles **6c-e** in 65-73% overall yields (Scheme-5).



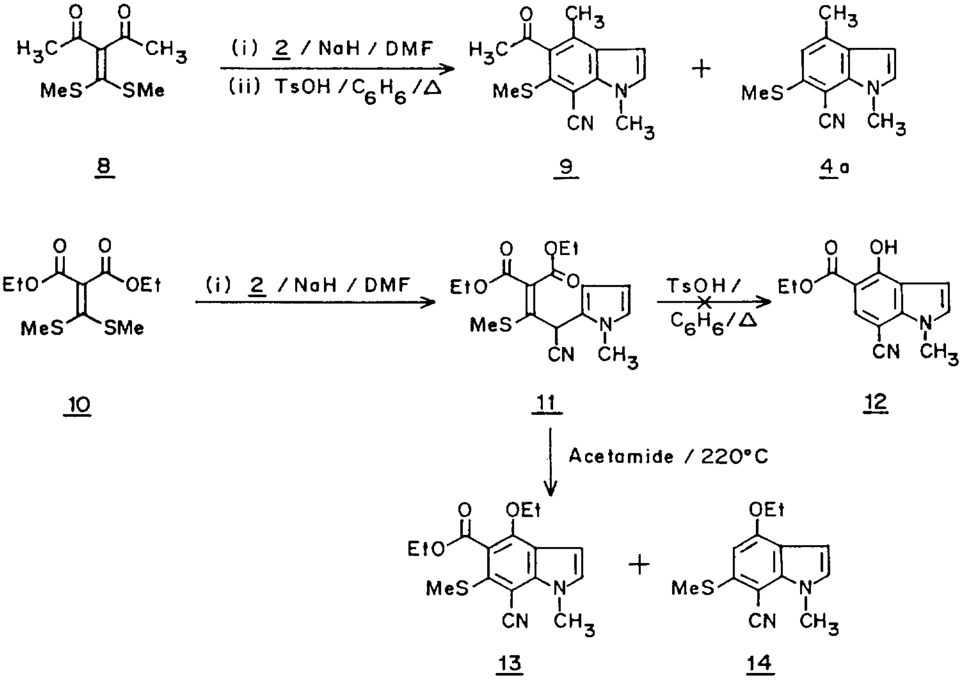
Scheme - 5

A few of the newly synthesized indoles (**4a-c**, **4h** and **4j**) were subjected to Raney nickel desulphurization in refluxing ethanol. However, the cyano group was also reduced along with dethiomethylation during these reactions to afford the corresponding 7-methylindoles **7a-e** in 85-94% yields (Scheme-6). Also, the reduction of indole **6b** with Raney nickel under identical conditions afforded 6-methoxy-1,4,5,7-tetramethylindole (**7f**) in 94% yield. When the reaction time was reduced (less than 10 hr) the reaction mixture showed several spots in TLC probably due to the products arising through different stages of nitrile group reduction. Therefore prolonged heating was necessary to get good yields of indoles **7a-f**.



Scheme-6

To further explore the scope of the reaction to obtain highly functionalized indole derivatives, doubly activated ketene dithioacetals **8** and **10** derived from acetylacetone and diethylmalonate respectively were subjected to cycloaromatization with **2** under similar reaction conditions (Scheme-7). Thus, **8** gave 4-methyl-5-acetylindole **9** along with 5-deacylated compound **4a** in 54% and 28% yields respectively. The mechanism of deacetylation is however not clear though it is likely to have been eliminated during base assisted adduct formation. Similarly the dithioacetal **10** reacted with **2** to give **11** which failed to give the corresponding 4-hydroxyindole **12** when treated with TsOH in refluxing benzene. However, when the adduct **11** was heated with acetamide at 220°C, cyclization occurred with the elimination of water to afford 5-carboethoxy-4-ethoxyindole **13** along with the decarboethoxylated product **14** in nearly equal amounts (Scheme-7).



Scheme - 7

In conclusion, the heteroaromatic annelation methodology described thus constitutes a new general route for the synthesis of indoles having control on the substituents at 4,5,6and 7 positions. The method is unequivocally good for the synthesis of 4- and 6-substituted indoles particularly the 6-oxygenated derivatives which are precursors of many natural alkaloids. Since the product indoles carry no substituents at 2- and 3-positions, they form an excellent pool of substituted indoles for transforming them to biologically important indole derivatives (tryptophans, tryptamines and indole-3-acetic acids etc.) and the corresponding ß-carbolines through tryptamines. The indoles can also be transformed into carbazoles by extending our heteroaromatic annelation methodology from the corresponding indole-3-acetonitriles.[24] Thus the versatility of this methodology should ensure that the route will enjoy wide applicability for the synthesis of biologically important and naturally occuring indole derivatives. Our efforts in this direction are currently under progress.

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 spectrophotometer. ^{1}H NMR (300 MHz), ^{13}C NMR (75.43 MHz) spectra were recorded on Bruker ACF-300 spectrometer. Chemical shifts are reported in δ (ppm) relative to Me_4Si and coupling constants (J) are given in Hertz. 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's) containing 13% calcium sulfate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying potassium permanganate (acidic) solution. Column chromatography was carried out using Acme's silica gel (60-120 mesh).

DMF was distilled from CaH_2 prior to use. 1-Methylpyrrole-2-acetonitrile was purchased from Aldrich and used as such.

The α-oxoketene S,S-acetals,[25] O,S-acetals[26] and N,S-acetals[27] were prepared according to the reported procedures. The data for the unknown α-oxoketene acetals are given below.

4,4-Bis(methylthio)-1,1-dimethoxy-3-butene-2-one (1f):
Viscous liquid; yield 92%;IR (CCl_4): 1642 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 2.50 (s, 3H), 3.38 (s, 3H), 3.39 (s, 3H), 4.44 (s, 1H), 6.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.56, 16.93, 53.96, 104.01, 107.83, 166.00, 187.48; Anal. Calcd. for $C_8H_{14}O_3S_2$ (222.328): C, 43.22; H, 6.35%. Found: C, 43.53; H, 6.47%.

4-Methoxy-4-methylthio-3-methyl-3-buten-2-one (5b):
Light yellow liquid; yield 32%; IR (CCl_4): 1620 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4): δ 2.00 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.98 (s, 3H). Anal. Calcd. for $C_7H_{12}O_2S$ (160.236): C, 52.47; H, 7.55%. Found: C, 52.82; H, 7.46%.

General Procedure for the Synthesis of Substituted and Condensed Indoles 4a-m, 6a-e and 9.

To a stirring suspension of NaH (10 mmol) in DMF (10 ml) at 0°C, a solution of 1-methyl-pyrrole-2-acetonitrile (5 mmol) in DMF (5 ml) was added dropwise. After 10 min, the appropriate α-

oxoketene acetal (5 mmol) in DMF (10 ml) was slowly added and the reaction mixture was allowed to warm to room temperature with stirring during 8-10 hr. It was poured into saturated NH_4Cl solution (200 ml) and extracted with chloroform (3x50 ml). The combined organic extracts were washed with water (3x100 ml), dried (Na_2SO_4) and evaporated to give the crude 1,4-adducts, which were used as such for further cyclization.

To a solution of crude 1,4-adduct (ca. 5 mmol) in dry benzene (40 ml), p-toluenesulphonic acid (10 mmol) was added and the reaction mixture was refluxed with stirring for 2-3h. The solvent was evaporated, the residue was dissolved in $CHCl_3$ (100 ml), poured into saturated $NaHCO_3$ solution (200 ml). The organic layer was separated, washed with water (2x100 ml), dried (Na_2SO_4) and evaporated to give crude indole which was purified by coloumn chromatography (silica gel) using hexane-ethylacetate (97:3) as eluent. The adduct **3f** was cyclized to the corresponding indole **4f** during column chromatography (silica gel).

7-Cyano-1,4-dimethyl-6-(methylthio)indole (4a):

Colourless crystals; mp 110-111°C (chloroform-ether); yield 86%; IR (KBr): 2200, 1583 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H), 2.58 (s, 3H), 4.10 (s, 3H), 6.47 (d, J=3.2 Hz, 1H), 6.93 (s, 1H), 6.99 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 17.94, 19.09, 34.94, 100.35, 116.97, 120.61, 128.28, 130.77, 135.41, 136.35, 137.80; MS: m/z 216 (M^+, 100%); Anal. Calcd. for $C_{12}H_{12}N_2S$ (216.307): C, 66.63; H, 5.59; N, 12.95%. Found: C, 66.92; H, 5.36; N, 13.16%.

7-Cyano-4-isopropyl-1-methyl-6-(methylthio)indole (4b):

Light yellow crystals; mp 64-65°C (chloroform-ether); yield 72%; IR (KBr): 2965, 2210, 1565 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 1.36 (d, J=7.2 Hz, 6H), 2.60 (s, 3H), 3.36 (septet, J=7.2 Hz, 1H), 4.12 (s, 3H), 6.58 (d, J=3.2 Hz, 1H), 7.03 (d, J=3.2 Hz, 1H), 7.08 (s, 1H); MS: m/z 244 (M^+, 100%); Anal. calcd. for $C_{14}H_{16}N_2S$ (244.36): C, 68.81; H, 6.60; N, 11.46%. Found: C, 69.04; H, 6.47; N, 11.63%.

7-Cyano-1-methyl-6-methylthio-4-phenylindole (4c):

Colourless crystals; mp 130-131°C (chloroform-ether); yield 85%; IR (KBr): 2197, 1567 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 4.06 (s, 3H), 6.55 (d, J=3.3 Hz, 1H), 6.98 (d, J=3.3 Hz, 1H), 7.12 (s, 1H), 7.38-7.48(m, 3H), 7.56-7.60(m, 2H); ^{13}C NMR (75 MHz): δ 17.72, 35.03, 93.30, 101.42, 116.56, 119.49, 126.53, 128.19, 128.63, 131.79, 136.20, 138.09, 139.13, 139.36; MS: m/z 278 (M^+, 100%); Anal. calcd. for $C_{17}H_{14}N_2S$ (278.378): C, 73.35; H, 5.07; N, 10.06%. Found: C, 73.78; H, 5.34; N, 10.44%.

7-Cyano-6-methylthio-1,4,5-trimethylindole (4d):

Colourless crystals; mp 107-108°C (chloroform-ether); yield 88%; IR (KBr): 2214, 1507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 4.06 (s, 3H), 6.45 (d, J=3.2 Hz, 1H), 7.01 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 17.13, 17.20, 20.11, 34.92, 98.26, 100.12, 117.98, 130.74, 130.93, 131.79, 133.91, 134.31, 134.80; MS: m/z 230 (M^+, 100%); Anal. calcd. for $C_{13}H_{14}N_2S$ (230.334): C, 67.79; H, 6.13; N, 12.16%. Found: C, 67.96; H, 6.20; N, 12.10%.

7-Cyano-1,5-dimethyl-6-methylthio-4-phenylindole (4e):

Colourless crystals; mp 123-124°C (chloroform-ether); yield 76%; IR (KBr): 2211, 1506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.47 (s, 3H), 4.13 (s, 3H), 6.09 (d, J=3.2 Hz, 1H), 7.00 (d, J=3.1 Hz, 1H), 7.26-7.29(m, 2H), 7.38-7.49(m, 3H); ^{13}C NMR (75 MHz): δ 18.59, 19.97, 34.96, 100.12, 101.59, 117.67, 127.51, 128.30, 129.15, 130.54, 130.76, 132.33, 134.35, 135.07, 139.09, 139.46; MS: m/z 292 (M^+, 100%); Anal. calcd. for $C_{18}H_{16}N_2S$ (292.404): C, 73.94; H, 5.52; N, 9.61%. Found: C, 74.22; H, 5.45; N, 9.78%.

7-Cyano-4-(dimethoxymethyl)-1-methyl-6-(methylthio)indole (4f):

Yellow crystals; mp 68-69°C (chloroform-ether); yield 68%; IR (KBr): 2208, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H), 3.35 (s, 6H), 4.11 (s, 3H), 5.68 (s, 1H), 6.68 (d, J=3.1 Hz, 1H), 7.04 (d, J=3.2 Hz, 1H), 7.32 (s, 1H); ^{13}C NMR (75 MHz): δ 17.70, 34.96, 52.79, 94.65, 101.07, 101.44, 116.63, 117.79, 126.16, 131.73, 135.06, 136.20, 137.76; MS: m/z 276 (M^+, 47.6%), 245 (100%); Anal. calcd. for $C_{14}H_{16}N_2O_2S$ (276.358): C, 60.85; H, 5.84; N, 10.14%. Found: C, 60.98; H, 5.96; N, 10.20%.

4-Cyano-3-methyl-5-(methylthio)cyclopenta[e]indole (4g):

Colourless crystals; mp 105-106°C (chloroform-ether); yield 74%; IR (KBr): 2924, 2213, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$: δ 2.20 (quintet, J=7.5 Hz, 2H), 2.48 (s, 3H), 3.15 (t, J=7.5 Hz, 4H), 4.13 (s, 3H), 6.37 (d, J=3.1 Hz, 1H), 7.03 (d, J=3.1 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.38, 24.47, 32.54, 33.01, 35.09, 99.84, 117.77, 126.88, 131.16, 132.11, 135.83, 139.17, 141.56; MS: m/z 242 (M^+, 100%); Anal. calcd. for $C_{14}H_{14}N_2S$ (242.345): C, 69.39; H, 5.82; N, 11.56%. Found: C, 69.54; H, 5.89; N, 11.68%.

4-Cyano-3-methyl-5-methylthio-6,7,8,9-tetrahydrobenzo[e]indole (4h):

Colourless crystals; mp 98-99°C (chloroform-ether); yield 68%; IR (KBr): 2923, 2214, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (m, 4H), 2.43 (s, 3H), 2.97-3.05 (m, 4H), 4.12 (s, 3H), 6.42 (d, J=3.2 Hz, 1H), 7.01 (d, J=3.1 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.76, 22.10, 23.46, 27.15, 28.11, 34.89, 98.86, 99.46, 117.63, 129.84, 131.51, 131.55, 133.52, 134.79, 135.36; MS: m/z 256 (M^+, 100%); Anal. calcd. for $C_{15}H_{16}N_2S$ (256.371): C, 70.28; H, 6.29; N, 10.93%. Found: C, 70.62; H, 6.40; N, 10.81%.

4-Cyano-3-methyl-5-(methylthio)cyclohepta[e]indole (4i):

Colourless crystals; mp 127-128°C (chloroform-ether); yield 78%; IR (KBr): 2907, 2216, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58-1.65 (m, 4H), 1.81-1.84 (m, 2H), 2.37 (s, 3H), 3.00-3.03 (m, 2H), 3.30-3.34 (m, 2H), 4.05 (s, 3H), 6.46 (d, J=3.3 Hz, 1H), 7.01 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.87, 27.01, 27.92, 31.43, 31.61, 32.17, 34.86, 98.11, 99.95, 117.91, 130.15, 131.87, 133.21, 134.32, 137.86, 141.71; MS: m/z 270 (M^+, 100%); Anal. calcd. for $C_{16}H_{18}N_2S$ (270.398): C, 71.07; H, 6.71; N, 10.36%. Found: C, 71.42; H, 6.58; N, 10.48%.

4-Cyano-3-methyl-5-(methylthio)indeno[1,2-e]indole (4j):

Light yellow crystals; mp 178-179°C (chloroform-ether); yield 82%; IR (KBr): 2208, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.76 (s, 2H), 4.02 (s, 3H), 6.69 (d, J=3.2 Hz, 1H), 7.01 (d, J=3.6 Hz, 1H), 7.28-7.39 (m, 2H), 7.46 (d, J=7.1 Hz, 1H), 7.74 (d, J=6.8 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.45, 35.14, 37.37, 97.03, 99.60, 117.75, 122.36, 123.65, 124.62, 126.83, 127.38, 130.71, 132.61, 136.35, 137.12, 138.39, 140.97, 144.47; MS: m/z 290 (M^+, 83%), 243 (100%); Anal. calcd. for $C_{18}H_{14}N_2S$ (290.389): C, 74.45; H, 4.86; N, 9.65%. Found: C, 74.68; H, 4.78; N, 9.54%.

4-Cyano-6,7-dihydro-3-methyl-5-(methylthio)naphtho[1,2-e]indole (4k):

Light brown crystals; mp 173-174°C (chloroform-ether); yield 66%; IR (KBr): 2209, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.79 (t, J=7 Hz, 2H), 3.23 (t, J=7 Hz, 2H), 4.16 (s, 3H), 6.92 (d, J=3.3 Hz, 1H), 7.13 (d, J=3.2 Hz, 1H), 7.30-7.38 (m, 3H), 7.97 (d, J=7 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.00, 26.86, 29.17, 35.31, 99.40, 101.65, 117.84, 126.52, 126.88, 127.40, 127.69, 128.26, 132.86, 132.95, 133.46, 133.61, 134.02, 135.82, 139.51; MS: m/z 304 (M^+, 88%), 256 (100%); Anal. calcd. for $C_{19}H_{16}N_2S$ (304.415): C, 74.97; H, 5.30; N, 9.20 %. Found: C, 75.34; H, 5.42; N, 9.06%.

4-Cyano-3-methyl-5-(methylthio)benzsubereno[e]indole (4l):

Colourless solid; mp 150-151°C (chloroform-ether); yield 72%; IR (KBr): 2921, 2213, 1509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.15-2.35 (m, 4H), 2.51 (s, 3H), 2.52-2.58 (m, 1H), 3.63-3.68 (m, 1H), 4.18

(s, 3H), 6.50 (d, J=3.2 Hz, 1H), 7.09 (d, J=3.2 Hz, 1H), 7.28-7.39(m, 3H), 7.54-7.58(m, 1H); ^{13}C NMR (75 MHz): δ 21.28, 28.23, 31.08, 33.55, 35.22, 100.04, 101.51, 117.94, 126.11, 128.37, 128.68, 128.92, 129.38, 132.89, 133.60, 134.14, 135.42, 138.20, 138.25, 140.22; MS: m/z 318 (M^+, 100%); Anal. calcd. for $C_{20}H_{18}N_2S$ (318.442): C, 75.44; H, 5.70; N, 8.80%. Found: C, 75.72; H, 5.63; N, 8.89%.

7-Cyano-3-methoxy-1-methyl-6-(methylthio)indolo[17,16-e]estra-1,3,5(6)-triene (4m):

Light brown crystals; mp 240-241°C (chloroform-ether); yield 74%; $[\alpha]^{23}_{D}$= +49° (c=0.48, dioxane); IR (KBr): 2920, 2211, 1603, 1494 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.10-3.60(m, 13H), 2.52 (s, 3H), 3.81 (s, 3H), 4.15 (s, 3H), 6.60 (d, J=3.2 Hz, 1H), 6.66-6.84 (m, 2H), 7.10 (d, J=3.2 Hz, 1H), 7.26 (d, J=8 Hz, 1H); MS: m/z 442 (M^+, 100%); Anal. calcd. for $C_{28}H_{30}N_2OS$ (442.624): C, 75.98; H, 6.83; N, 6.33%. Found: C, 76.42; H, 7.04; N, 6.18%.

7-Cyano-6-methoxy-1-methyl-4-phenylindole (6a):

Colourless crystals; mp 137-138°C (chloroform-ether); yield 80%; IR (KBr): 2206, 1591 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 4.03 (s, 3H), 4.12 (s, 3H), 6.58 (d, J=3.2 Hz, 1H), 6.84 (s, 1H), 7.00 (d, J=3.2 Hz, 1H), 7.44-7.76(m, 5H); MS: m/z 262 (M^+, 100%); Anal. calcd. for $C_{17}H_{14}N_2O$ (262.311): C, 77.84; H, 5.38; N, 10.68%. Found: C, 77.58; H, 5.44; N, 10.74%.

7-Cyano-6-methoxy-1,4,5-trimethylindole (6b):

Colourless crystals; mp 99-100°C (chloroform-ether); yield 86%; IR (KBr): 2219, 1593 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.48 (s, 3H), 3.96 (s, 3H), 4.08 (s, 3H), 6.50 (d, J=3.2 Hz, 1H), 7.00 (d, J=3.2 Hz, 1H); MS: m/z 214 (M^+, 81.2), 199 (100%); Anal. calcd. for $C_{13}H_{14}N_2O$ (214.267): C, 72.87; H, 6.59; N, 13.07%. Found: C, 73.18; H, 6.50; N, 13.15%.

7-Cyano-1,4-dimethyl-6-piperidinoindole (6c):

Brown viscous liquid; yield 65%; IR (CCl_4): 2936, 2210, 1592 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50-1.58(m, 2H), 1.72-1.80(m, 4H), 2.48 (s, 3H), 3.07-3.11 (m, 4H), 3.99 (s, 3H), 6.37 (d, J=3.2 Hz, 1H), 6.62 (s, 1H), 6.85 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.26, 24.20, 26.43, 34.65, 54.49, 86.15, 100.01, 112.04, 118.18, 124.93, 129.68, 135.49, 136.49, 155.68; MS: m/z 253 (M^+, 100%); Anal. calcd. for $C_{16}H_{19}N_3$ (253.347): C, 75.85; H, 7.56; N, 16.59%. Found: C, 76.32; H, 7.39; N, 16.73%.

7-Cyano-1-methyl-4-phenyl-6-piperidinoindole (6d):

Light yellow crystals; mp 130-131°C (chloroform-ether); yield 70%; IR (KBr): 2849, 2203, 1585 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.50-2.00(m, 6H), 3.12-3.32(m, 4H), 4.14 (s, 3H), 6.57 (d, J=3.2 Hz, 1H), 6.91 (s, 1H), 7.00 (d, J=3.2 Hz, 1H), 7.40-7.74 (m, 5H); MS: m/z 315 (M^+, 100%); Anal. calcd. for $C_{21}H_{21}N_3$ (315.418): C, 79.97; H, 6.71; N, 13.32%. Found: C, 80.48; H, 6.82; N, 13.17%.

7-Cyano-1-methyl-6-morpholino-4-phenylindole (6e):

Light yellow crystals; mp 169-170°C (chloroform-ether); yield 73%; IR (KBr): 2934, 2211, 1586 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 3.18-3.34(m, 4H), 3.88-4.04(m, 4H), 4.15 (s, 3H), 6.60 (d, J=3.2 Hz, 1H), 6.92 (s, 1H), 7.03 (d. J=3.2 Hz, 1H), 7.42-7.74(m, 5H); MS: m/z 317 (M^+, 100%); Anal. calcd. for $C_{20}H_{19}N_3O$ (317.39): C, 75.69; H, 6.03; N, 13.24%. Found: C, 75.92; H, 6.16; N, 13.35%.

5-Acetyl-7-cyano-1,4-dimethyl-6-(methylthio)indole (9):

Light brown crystals; mp 140-141°C (chloroform-ether); yield 54%; IR (KBr): 2214, 1693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 6H), 2.61 (s, 3H), 4.15 (s, 3H), 6.57 (d, J=3.2 Hz, 1H), 7.17 (d, J=3.3 Hz, 1H); ^{13}C NMR (75 MHz): δ 16.13, 21.58, 33.17, 35.14, 98.85, 101.05, 116.66, 129.12, 130.63, 131.08, 132.99, 134.98, 139.67, 204.96; MS: m/z 258 (M^+, 87.5%) 243 (100%); Anal. calcd. for $C_{14}H_{14}N_2OS$ (258.344): C, 65.09; H, 5.46; N, 10.84%. Found: C, 65.56; H, 5.28; N, 11.08%.

5-Carbethoxy-7-cyano-4-ethoxy-1-methyl-6-(methylthio)indole (13) and **7-Cyano-4-ethoxy-1-methyl-6-(methylthio)indole (14):**

The ketene dithioacetal **10** (10 mmol) was reacted with **2** (10 mmol) following the above mentioned procedure to afford the corresponding 1,4-adduct, (ca. 10 mmol) which was heated with acetamide (10 g) at 220-230°C for 3 hr, in a flask equipped with an air condenser. The warm solution was poured into water, extracted with chloroform, dried over anhydrous sodium sulfate, concentrated and chromatographed by passing through silica gel column using hexane-ethyl acetate (97:3) as eluent to afford indoles **14** and **13**.

13: Colourless crystals; mp 89-90°C (chloroform-ether); yield 36%; IR (KBr): 2984, 2209, 1729, 1579 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7 Hz, 6H), 2.53 (s, 3H), 4.11 (s, 3H), 4.43-4.47(m, 4H), 6.63 (d, J=3.2 Hz, 1H), 7.07 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 14.62, 15.68, 21.03, 35.29, 61.58, 69.39, 95.18, 100.63, 116.86, 121.15, 124.51, 132.25, 132.73, 138.02, 152.50, 166.77; MS: m/z 318 (M^+, 74.2%), 244 (100%); Anal. Calcd. for $C_{16}H_{18}N_2O_3S$ (318.395): C, 60.36; H,5.70; N, 8.80%. Found: C, 60.74; H, 5.82; N, 8.74%.

14: Light brown crystals; mp 101-102°C (chloroform-ether); yield 28%; IR (KBr): 2202, 1563 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (t, J=7 Hz, 3H), 2.59 (s, 3H), 4.06 (s, 3H), 4.22 (q, J=7 Hz, 2H), 6.54 (s, 1H), 6.55 (d, J=3.2 Hz, 1H), 6.88 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 14.69, 18.17, 34.93, 64.02, 88.28, 99.33, 102.20, 117.44, 118.96, 129.59, 136.84, 140.06, 166.82; MS: m/z 246 (M^+, 100%); Anal. calcd. for $C_{13}H_{14}N_2OS$ (246.333): C, 63.39; H, 5.75; N, 11.37%. Found: C, 63.68; H, 5.62; N, 11.48%.

General Procedure for Reaction of 4a-c, 4h, 4j and 6b with Raney Nickel.

To a solution of corresponding indole (2.5 mmol) in ethanol (30 ml), was added Raney nickel (W4, 4 times by weight) and the suspension was stirred at 60-70°C for 10-12 hr. (monitored by tlc). The reaction mixture was filtered through sintered funnel and the residue was washed with ethanol. The bulk of the ethanol was distilled off and chloroform was added. The solution was washed with water, dried over anhydrous sodium sulphate and concentrated to give crude products from which analytically pure compounds were obtained by passing through a small silica gel column using hexane as eluent.

1,4,7-Trimethylindole (7a):

Light brown solid; mp 64-65°C; yield 85%; IR (KBr): 2922, 1497 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.47 (s, 3H), 2.71 (s, 3H), 4.02 (s, 3H), 6.43 (d, J=3.2 Hz, 1H), 6.78 (br.s, 2H), 6.92 (d, J=3.2 Hz, 1H); MS: m/z 159 (M^+, 100%); Anal. calcd. for $C_{11}H_{13}N$ (159.231): C, 82.97; H, 8.23; N, 8.80%. Found: C, 83.34; H, 8.29; N, 8.73%.

1,7-Dimethyl-4-isopropylindole (7b):

Light brown solid; mp 52-53°C; yield 94%; IR (KBr): 2921, 1497 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.25 (d, J=7 Hz, 6H), 2.52 (s, 3H), 3.18 (septet, J=7 Hz, 1H), 3.77 (s, 3H), 6.32 (d, J=3 Hz, 1H), 6.65 (br.s, 3H); MS: m/z 187 (M^+, 100%); Anal. calcd. for $C_{13}H_{17}N$ (187.284): C, 83.37; H, 9.15; N, 7.48%. Found: C, 83.84; H, 9.02; N, 7.66%.

1,7-Dimethyl-4-phenylindole (7c):

Colourless crystals; mp 69-70°C (chloroform-hexane); yield 88%; IR (KBr): 1595, 1482 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.82 (s, 3H), 4.10 (s, 3H), 6.62 (d, J=3.2 Hz, 1H), 6.96-7.08 (m, 3H), 7.32-7.78 (m, 5H); MS: m/z 221 (M^+, 100%); Anal. calcd. for $C_{16}H_{15}N$ (221.302): C, 86.84; H, 6.83; N, 6.33%. Found: C, 86.57; H, 6.95; N, 6.24%.

3,4-Dimethyl-6,7,8,9-tetrahydrobenzo[e]indole (7d):
Colourless solid; mp 53-54°C; yield 85%; IR (KBr): 2930, 1493 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.76-1.96(m, 4H), 2.68 (s, 3H), 2.70-2.94(m, 4H), 4.00 (s, 3H), 6.36 (d, J=3.2 Hz, 1H), 6.64 (s, 1H), 6.90(d, J=3.2 Hz, 1H); MS: m/z 199 (M^+, 100%); Anal. calcd. for $C_{14}H_{17}N$ (199.295): C, 84.37; H, 8.60; N, 7.03%. Found: C, 84.73; H, 8.44; N, 7.14%.

3,4-Dimethylindano[1,2-e]indole (7e):
Colourless crystals; mp 140-141°C (chloroform-hexane); yield 92%; IR (KBr): 2922, 1599, 1514 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.83 (s, 3H), 3.90 (s, 2H), 4.12 (s, 3H), 6.92 (d, J=3.2 Hz, 1H), 7.05-7.64 (m, 5H), 8.00 (d, J=6.8 Hz, 1H); MS: m/z 233 (M^+, 100%); Anal. calcd. for $C_{17}H_{15}N$ (233.313): C, 87.52; H, 6.48; N, 6.00%. Found: C, 87.76; H, 6.57; N, 6.10%.

6-Methoxy-1,4,5,7-tetramethylindole (7f):
Colourless crystals; mp 103-104°C (chloroform-hexane); yield 94%; IR (KBr): 2934, 1518 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.32 (s, 3H), 2.55 (s, 3H), 3.60 (s, 3H), 3.88 (s, 3H), 6.16 (d, J=3 Hz, 1H), 6.60 (d, J=3 Hz, 1H); MS: m/z 203 (M^+, 100%); Anal. calcd. for $C_{13}H_{17}NO$ (203.283): C, 76.81; H, 8.43; N, 6.89%. Found: C, 77.28; H, 8.29; N, 6.72%.

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