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Regiospecific Generation and Application of 3-Lithiomethyl-2-methyl-1-phenylpyrazolin-5-one as 1,3-Binucleophile in Aromatic Annelation: A Novel Approach for Synthesis of 1,2-Disubstituted Indazolones and their Condensed Analogs

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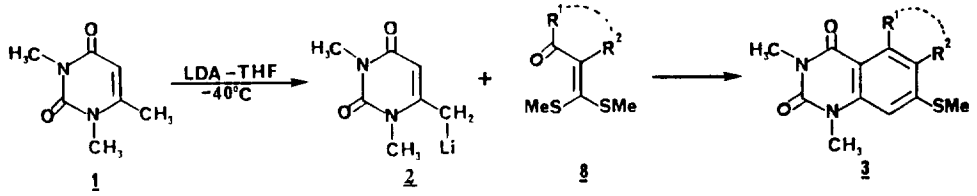
Abstract : The enolate anion **5A** generated by deprotonation of 2,3-dimethyl- 1-phenylpyrazolin-5-one is shown to undergo highly regioselective γ-1,4-addition to α-oxoketene dithioacetals followed by cycloaromatization in the presence of boron trifluoride etherate to afford wide range of novel substituted and condensed indazolones in good yields.

The classical synthetic approaches for five and six membered benzoheterocycles usually involve elaboration of a heterocyclic ring on to an appropriately substituted benzene ring. However, synthetic organic chemists have always been fascinated by developing unconventional non-classical synthetic strategies. Such kind of approaches not only result in development of new synthetic methodologies for target molecules but sometimes afford products with unusual substitution pattern/skeleton which is otherwise difficult to achieve by classical approaches. In this respect, a novel strategy for the synthesis of benzoheterocycles would be to build functionalized benzene rings on to preconstructed heterocycles. There are only scattered approaches in the literature in these lines involving elaboration of heterocyclic side chain into a benzene ring.[1] The only transformation of potential general scope which falls under this category is generation of heterocyclic analogs of o-quinodimethane and their Diels-Alder trapping with dienophiles to give six membered annelated (or benzoannelated) heterocycles.[2] During the course of our cycloaromatization studies involving condensation of α-oxoketene dithioacetals (as 1,3-bielectrophiles) with 3-carbon 1,3-binucleophilic species,[3] we have successfully demonstrated the viability of this approach for construction of the benzisoxazole ring. The overall transformation involves regiospecific 1,2-addition of 5-lithiomethyl-3-methylisoxazole to both acyclic and cyclic α-oxoketene dithioacetals and subsequent cycloaromatization of the resulting carbinols in the presence of boron trifluoride etherate.[4] This strategy not only afforded the regiospecifically substituted benzisoxazoles,

but also yielded hitherto unreported condensed and heterocondensed analogs. However, successful realization of this approach as a general synthetic method for benzoheterocycles require prior generation of lithiomethylheterocycles via regiospecific deprotonation of methyl substituted heterocycles which is often not a facile process and is complicated by simultaneous ring deprotonation of the heterocycles.[5] For the past few years, our efforts were directed towards generation of such species and study of their cyclocondensation with α-oxoketene dithioacetals. We have recently reported regiospecific deprotonation of ß-pyrrolidinocrotonate and 1,3,6-trimethyluracil and subsequent cycloaromatization of the resulting enolates with α-oxoketene dithioacetals to afford aminosubstituted benzene and substituted quinazoline derivatives respectively as an example of both acyclic and cyclic enaminone derived carbanions[6] (Scheme 1). These enolates are classical examples of nucleophiles capable of displaying



1 2 8 3

R¹ = aryl, alkyl; R²=H

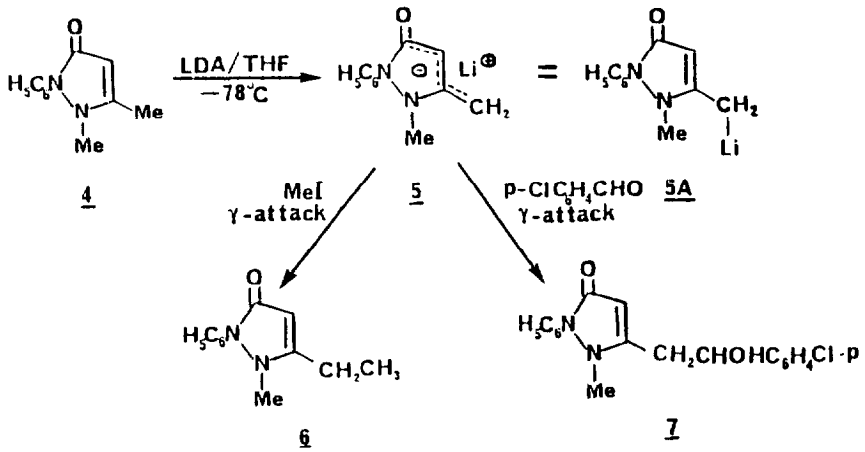
R¹ = R² = -(CH₂)₄-

Scheme1

ambident reactivity either at the α or γ site or at oxygen.[7] Thus regiocontrolled cyclization of these ambident nucleophiles with α-oxoketene dithioacetals as ambident 1,3-bielectrophiles to give regiospecifically substituted aromatic compounds was of interest to us. We have, therefore, developed this approach for the synthesis of substituted and condensed indazolones by generation of 3-lithiomethyl-2-methyl-1- phenylpyrazolin-5-one from Antipyrine using its regioselective γ-1,4-addition to α-oxoketene dithioacetals followed by cycloaromatization. We report results of these studies in this paper.

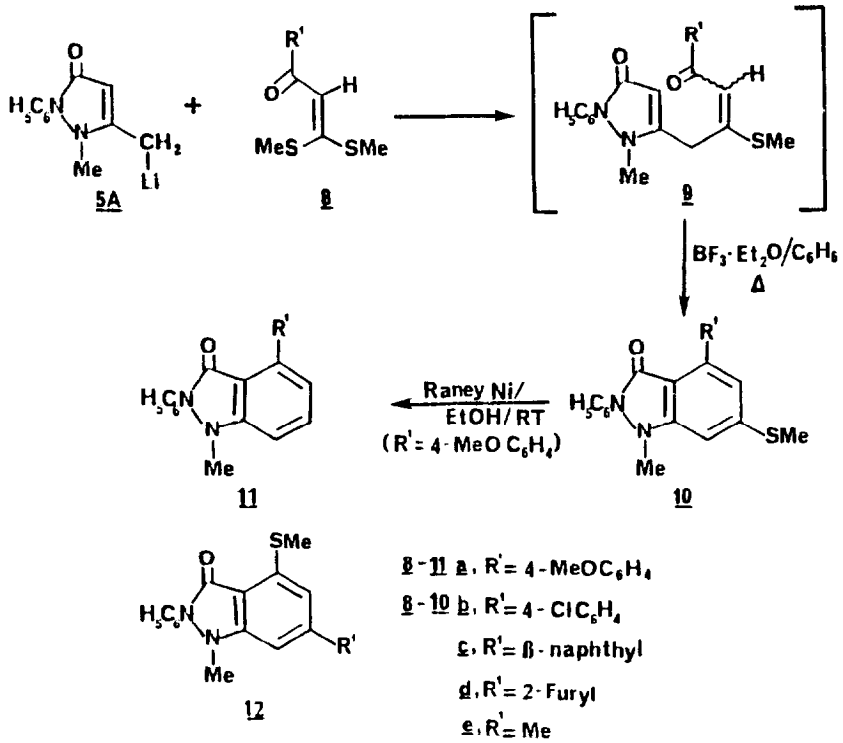
RESULTS AND DISCUSSION

We began our investigation by first studying the specificity of lithiation of 1-phenyl-2,3-dimethylpyrazolin-5-one (Antipyrine) **4** (Scheme 2). Treatment of a solution of **4** in THF with LDA at -78°C, followed by quenching of the enolate **5** with methyl iodide and work-up produced exclusively the γ-methylated derivative **6** in almost quantitative yield. The product **6** was found to be identical with that reported in the literature.[8] Similarly when the enolate **5** was quenched with 4-chlorobenzaldehyde, a good yield of the corresponding γ-secondary alcohol **7** was obtained. Thus the enolate **5** displays exclusive γ-selectivity in its reaction with electrophiles analogous to the anion **2** derived from 1,3,6-trimethyluracil (Scheme 1).



Scheme 2

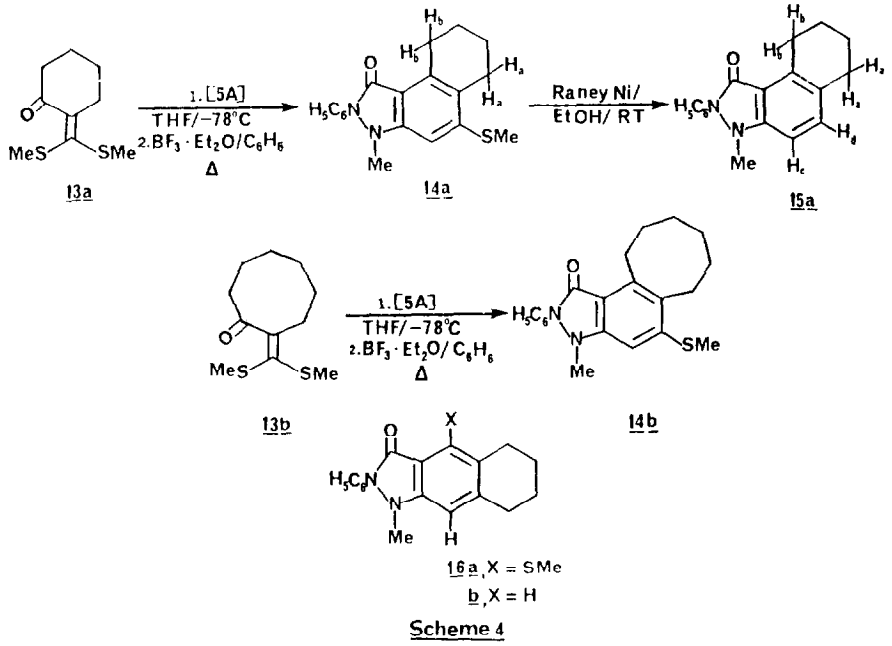
The reaction of 5A with various α-oxoketene dithioacetals was next investigated. Thus when 5A was reacted with the dithioacetal 8a, quantitative conversion to a new product was observed within 6hr. The ^{1}H NMR spectrum of the crude product characterized it as 1,4-adduct 9a. However, attempted



Scheme 3

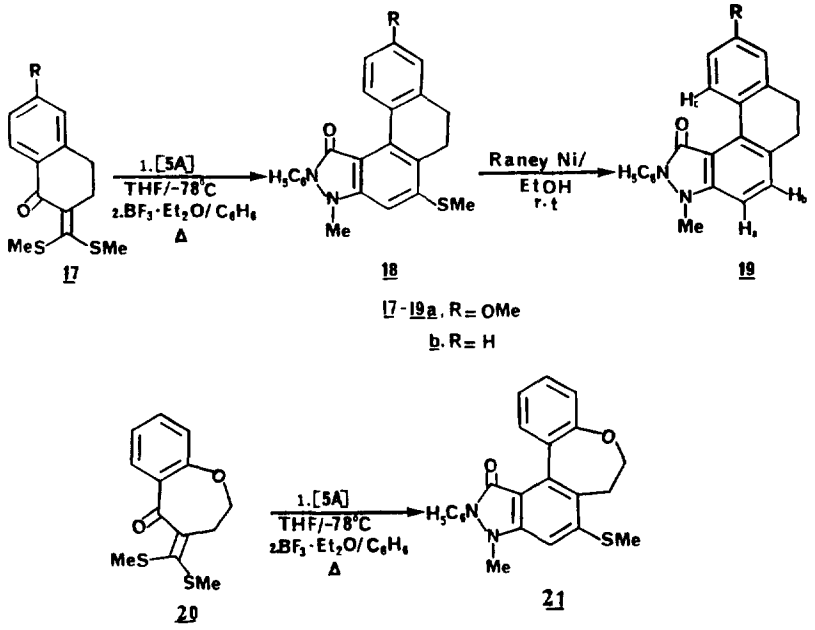
purification of the adduct by column chromatography (silica gel) was not possible since it was slowly transformed into the cycloaromatized product **10a**. This was further confirmed by $BF_3.Et_2O$ induced cyclization of **9a** in refluxing benzene to give **10a** in 87% yield (Scheme 3). The structure and regiochemistry of **10a** was confirmed with the help of spectral and analytical data and by its Raney Nickel dethiomethylation to afford **11a** in 98% yield. The other acyclic ketene dithioacetals **8b-e** were similarly reacted with **5A** under the identical conditions and the crude adducts were as such subjected to cyclization with $BF_3.Et_2O$ without any purification to afford the corresponding 1,2,4-trisubstituted-6-methylthioindazol-3-one **10b-e** in 64-88% overall yields (scheme 3). In none of these reactions was formation of regioisomeric products **12** (through γ-1,2-addition of **5A** to **8**) observed thus demonstrating highly regiospecific γ-1,4-mode of reactivity of **5A** towards α-oxoketene dithioacetals.

The cyclic ketene dithioacetals **13a** also displayed γ-1,4-reactivity pattern with **5A** to afford the corresponding angularly annelated indazolone **14a** in 62% yield (Scheme 4). The regiochemistry of 14a was established on the basis of its ^1H NMR spectrum and that of desulphurized product **15a**. The signal due to one set of benzylic methylene protons (Hb) appeared at lower field (δ H_b 3.33) than others (δH_a 2.76) in the ^1H NMR spectrum of **14a** due to deshielding effect of the carbonyl group. The two aromatic protons (H_c and H_d) in the ^1H NMR spectrum of desulphurized product **15a** displayed *o*-coupling (J=9Hz) and appeared as doublets at δ7.07 and δ7.37 respectively, thus ruling out regioisomeric linear structure **16a** (scheme 4). Similarly the novel cyclooctanoindazolone **14b** could also be synthesized from the respective **13b** in 69% yield under the described conditions.



Scheme 4

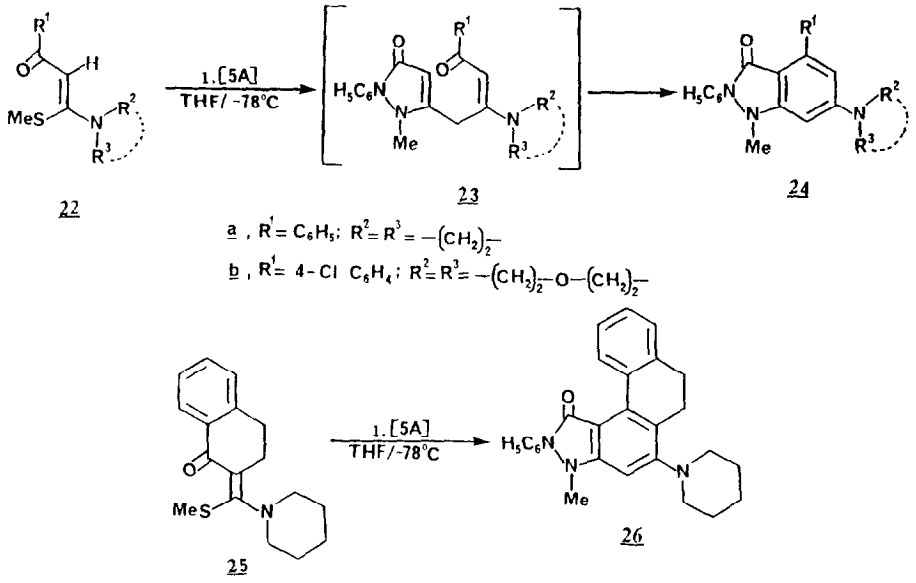
The cyclization of **5A** with dithioacetals **17a-b** from tetralone was of interest since the analogous open-chain adduct from **17a** and 6-lithiomethyl-1,3-dimethyluracil **2** failed to cycloaromatize under different conditions to give tetracyclic angularly benzoannelated product probably due to steric repulsion (*peri* interaction) in the transition state of cyclization.[6] However **5A** reacted smoothly with **17a-b** and the crude adducts underwent facile cyclization in the presence of $BF_3.Et_2O$ to afford novel angularly annelated tetracyclic condensed indazolones **18a-b** in 92% and 88% yields respectively. Apparently, the



Scheme 5

peri interaction is significantly absent in these systems. Both **18a-b** were transformed into sulfur free products **19a-b** by Raney Nickel desulphurization in nearly quantitative yields. The high resolution ^1H NMR spectrum of **19a** displayed *o*-coupled protons (H_a and H_b, J=9 Hz) at δ7.19 and δ 7.58 respectively thus supporting the angular arrangement of six membered ring in **18a-b** and **19a-b** (Scheme 5). The low field position of the signal due to *peri* proton in **18a-b** (δ8.4 and δ8.87) also supported the angular structure. Finally, as a representative example of elaboration of benzoheterocyclic ring over indazolone, **5A** was reacted with dithioacetal **20** to afford novel benzoxepinoindazolone **21** in 91% yield (Scheme 5).

In order to demonstrate further versatility and scope of our benzoannelation methodology, the reaction of **5A** with N,S-acetals **22a-b** and **25** was examined with a view to synthesize tertiary alkylamino substituted indazolones (Scheme 6). Thus **5A** reacted smoothly with **22a-b** to afford directly the 6-aminoindazolones **24a-b** in high yields through spontaneous base catalyzed cyclization of intermediate adducts **23** under the experimental conditions. Similarly the tetracyclic indazolone **26** with regiospecifically substituted piperidino group could be synthesized by reaction of cyclic N,S-acetal **25** with **5A** under the identical conditions.



Scheme 6

In summary, we have successfully developed a new approach for construction of the indazolone[9] framework by annelation of a benzene ring on to a pyrazolone ring. The methodology employs hitherto unreported 5-lithiomethyl-1-methyl-2-phenylpyrazolone as 3-carbon 1,3-binucleophilic species which reacts with both acyclic and cyclic oxoketene dithioacetals in a highly regioselective manner (γ-1,4) to provide ready access to wide range of substituted and annelated (condensed) indazolones. To our knowledge condensed indazolones are not known in the literature and have been synthesized for the first time by this methodology.

EXPERIMENTAL SECTION

M.ps were obtained on a "Thomas Hoover" melting point (capillary method) apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H NMR (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High resolution ^{1}H NMR (250 MHz, 300 MHz) spectra were recorded on Bruker ACF-300 spectrometers. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to tetramethylsilane as internal lock (for ^{1}H NMR). Mass spectra (MS) were measured on a Jeol JMS-D 300 Mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All anhydrous, low temperature reactions were carried out in oven dried (120°C) glassware under a stream of dry argon/nitrogen. Transfer of anhydrous solvents or mixtures was accomplished with oven dried (120°C) syringes using standard syringe-septum technique. Analytical thin layer chromatography (tlc) was performed on glass plates (18x6 and 18x4 cm) coated with Acme's silica gel containing 13% calcium sulfate as binder and various combinations of ethyl acetate-hexane and ethyl acetate-benzene were used as eluents. Chromatograms were developed either with iodine vapour or potassium

permanganate (acidic) spray. Acme's silica gel (60-120 mesh) was used for column chromatography, solvents for column chromatography were used after simple distillation of commercial materials.

n-Butyllithium[10] and Raney Ni (W4)[11] were prepared according to the reported procedures. Solvents were purified and dried by standard methods. All the α-oxoketene S,S-acetals **8a-e, 13a-b, 17a-b, 20**[12] and N,S-acetals **22a-b, 25**[13] required for the present investigations were prepared according to the literature procedures.

General procedure for the generation and reaction of 3-lithiomethyl 2-methyl-1-phenylpyrazolone 5A with electrophiles (iodomethane and 4-chlorobenzaldehyde): Synthesis of 3-ethyl-2-methyl-1-phenylpyrazolone 6 and 1,2-Dihydro-5-[2-(4-chlorophenyl)-hydroxyethyl]-1-methyl-2-phenyl-3H-pyrazol-3-one 7.

To a solution of diisopropylamine 2 ml (14 mmol) in sodium dried tetrahydrofuran (THF) 10 ml under dry and inert atmosphere was added 10 mmol of n-BuLi in ether with stirring for 20 min and temperature control at 0°C with an ice bath. To the resulting solution of lithium diisopropylamide (LDA) at -78°C was added a solution of 0.9g (5 mmol) of antipyrine in 25 ml dry THF, the reaction mixture was stirred at the same termperature for 30-40 min. To the resulting enolate solution at -78°C was added 4 mmol of electrophile in 15 ml dry THF dropwise and stirred for 30-45 min.(-78°C) and then allowed to warm to room temperature (monitored by tlc). The mixture was quenched with aqueous saturated ammonium chloride solution (100 ml) and extracted with chloroform (3x25 ml). The combined extracts were washed with water (3x25 ml), dried (sodium sulphate) and then evaporated to give the crude product, which was purified by column chromatography over silica gel using ethyl acetate-hexane (3:7) as eluent.

1,2-Dihydro-5-ethyl-1-methyl-2-phenyl-3H-pyrazol-3-one 6:
Light brown viscous liquid; yield 0.83g (82%); R_f 0.5 EtOAc/benzene (9:4). IR (KBr): νmax = 3417, 2963, 1642 (CO), 1298, 757 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.25 (t, 3H, J = 7Hz, CH_3); 2.49 (q, 2H, J=7Hz, CH_2); 2.99 (s, 3H, CH_3); 5.33 (s, 1H, vinylic); 7.25-7.60 (m, 5H, ArH). Anal: Calc. for $C_{12}H_{14}N_2O$ (202.246): C 71.26; H 6.98; N 13.85. Found C 71.50; H 6.95; N 13.90%.

1,2-Dihydro-5-[2-(4-chlorophenyl)-hydroxyethyl]-1-methyl-2-phenyl-3H-pyrazol-3-one 7:
Colourless crystals; yield 1.46g (86%); mp 160-163°C (chloroform-hexane); R_f 0.29 EtOAc/benzene (6:4). IR (KBr): νmax = 3095, 1622 (CO), 1478, 1064, 762 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 2.75 (d, 2H, J = 9Hz, CH_2); 2.90 (s, 3H, NCH_3); 3.35 (brs, 1H, OH exchangeable with D_2O); 4.88 (t, 1H, J = 9Hz, benzylic); 5.00 (s, 1H, vinylic); 7.24-7.58(m, 9H, ArH). Anal. Calc. for $C_{18}H_{17}ClO_2N_2$ (328.993): C 65.75; H 5.21; N 8.52. Found C 66.70; H 5.22; N 8.54%.

General procedure for the generation and reaction of 3-lithiomethyl-2-methyl-1-phenyl pyrazolone 5A with α-oxoketene dithioacetals 8a-e, 13a-b, 17a-b and 20; Synthesis of 1,2,4-trisubstituted-6-methylthio/1,2-disubstituted 4,5-annelated-6-methylthio 3H-indazol-3-one 10a-e, 14a-b, 18a-b and 21.

Under dry and inert atmosphere to an ice cold (0°C) solution of 2 ml (14 mmol) of diisopropyl amine in 10 ml of dry tetrahydrofuran (THF) was added 10 mmol of n-butyl lithium in ether. To the

resulting solution of lithium diisopropylamide (10 mmol) at -78°C was added a solution of 0.9g (5 mmol) of antipyrine in 25 ml dry THF. The reaction mixture was stirred at the same temperature for 30-40 min. To the resulting enolate solution at -78°C was added 4 mmol of α-oxoketene dithioacetal in 25 ml dry THF dropwise and the reaction mixture was kept for 30-40 min, allowed to warm to room temperature, stirred for 6-8 hr. (monitored by tlc), and quenched with aqueous saturated ammonium chloride solution (100 ml), extracted with chloroform (3x25 ml). The organic layer was washed with water, dried over anhydrous sodium sulfate, removal of organic layer gave a crude γ-1,4-adduct in quantitative yields.

To a solution of crude γ-1,4-adduct (ca. 5 mmol) in dry benzene (30 ml), boron trifluoride-etherate (7.5 mmol) was added and the reaction mixture was stirred under reflux for 30-45 min. After the reaction was complete (monitored by tlc), it was brought to room temperature and poured into aqueous saturated sodium bicarbonate solution (100 ml), extracted with chloroform (3x25 ml), the combined organic extracts were washed with water (2x50 ml), dried over anhydrous sodium sulfate and concentrated to give the crude cycloaromatized product which was chromatographed by passing through silica gel column using ethyl acetate-hexane (2:8) as eluent.

1,2-Dihydro-4-(4-methoxyphenyl)-1-methyl-6-methylthio-2-phenyl-3H-indazol-3-one 10a:
Brown coloured crystals; yield 1.64g (87%); mp 145-146°C (chloroform-hexane); R_f 0.44 EtOAc/benzene (1:9). IR(KBr): νmax = 1672(CO), 1588, 1242, 1023 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 2.50 (s, 3H, SCH_3); 3.10 (s, 3H, NCH_3); 3.79 (s, 3H, OCH_3); 6.88-7.08 (m, 4H, ArH); 7.40-7.67 (m, 7H, ArH). MS: m/z (%) = 376 (M^+, 100), 361 (M^+-15,53.9). Anal: Calc. for $C_{22}H_{20}N_2O_2S$ (376.304): C 70.21; H 5.36; N 7.45. Found C 70.22; H 5.38; N 7.50%.

1,2-Dihydro-4-(4-chlorophenyl)-1-methyl-6-methylthio-2-phenyl-3H-indazol-3-one 10b:
Colourless crystals; yield 1.67g (88%); mp 165-168°C (chloroform-hexane): R_f 0.88 EtOAc/benzene (5:5). IR (KBr): νmax = 1673 (CO), 1584, 1314, 1087 cm-1. 1H NMR (90 MHz, $CDCl_3$): δ = 2.51, (s, 3H, SCH_3); 3.10 (s, 3H, NCH_3); 6.94 (d, 2H, J = 3Hz, ArH); 7.26-7.63 (m, 9H, ArH). MS: m/z (%) = 380 (M^+, 100), 365 (M^+-15, 52.3). Anal: Calc. for $C_{21}H_{17}ClN_2OS$ (380.877): C 66.22; H 4.50; N 7.36. Found C 66.38; H 4.75; N 7.52%.

1,2-dihydro-1-methyl-6-methylthio-4-[2-naphthyl]-2-phenyl-3H-indazol-3-one 10c:
Colourless crystals; yield 1.48g (74.5%); mp 178-179°C (chloroform-hexane); R_f 0.74 EtOAc/benzene (2:8). IR (KBr): νmax = 1673 (CO), 1587, 1088, 817 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 2.56 (s, 3H, SCH_3); 3.11 (s, 3H, NCH_3); 7.01 (brs, 1H, ArH); 7.11 (brs, 1H, ArH); 7.37-7.65 (m, 5H, ArH); 7.74-7.98 (m, 4H, ArH); 8.02 (m, 2H, ArH); 8.46 (brs, 1H, ArH). MS: m/z (%) = 396 (M^+,29), 381 (M^+-15,20.1). Anal. Calc. for $C_{25}H_{20}N_2OS$ (396.488): C 75.73; H 5.08; N 7.07. Found C 75.75; H 5.06; N 7.09%.

1,2-Dihydro-4-(2'-furyl)-1-methyl-6-methylthio-2-phenyl-3H-indazol-3-one 10d:
Viscous liquid; yield 1.08g (64%); R_f 0.87 EtOAc/benzene (2:8). IR (KBr): νmax = 2992, 1666 (CO), 1574, 1311, 1094 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 2.57 (s, 3H, SCH_3); 3.13 (s, 3H, NCH_3); 6.63-6.67 (m, 2H, ArH); 6.93 (brs, 1H, 5'-Furyl); 7.35 (brs, 1H, 4'-Furyl); 7.55-7.71 (m, 5H, ArH); 8.39 (brs, 1H, 3'-Furyl). Anal: Calc. for $C_{19}H_{16}N_2O_2S$ (336.396): C 67.83; H 4.79; N 8.33. Found C 67.84; H 4.80; N 8.35%.

1,2-Dihydro-1,4-dimethyl-6-methylthio-2-phenyl-3H-indazol-3-one 10e:
Colourless crystals; yield 0.97g (68%); mp 90-92°C (chloroform-hexane); R_f 0.71 EtOAc/benzene (2:8). IR (KBr): νmax = 1654 (CO), 1584, 1305 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3); 2.66 (s, 3H, SCH_3); 3.09 (s, 3H, NCH_3); 6.81 (brs, 2H, ArH); 7.20-7.68 (m, 5H, ArH). MS: m/z(%) = 284 (M^+, 100), 269 (M^+-16,57.1). Anal: Calc. for $C_{16}H_{16}N_2OS$ (284.366): C 67.57; H 5.67; N 9.58. Found C 67.59; H 5.66; N 9.86%.

2,3,6,7,8,9-Hexahydro-3-methyl-5-methylthio-2-phenyl-1H-benz[e]indazol-1-one 14a:
Colourless crystals; yield 1g (62%); mp 158-160°C (chloroform-hexane): R_f 0.65 EtOAc/benzene (1:9). IR (KBr): νmax = 2904, 1665 (CO), 1303, 1127 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.75-2.03 (m, 4H, CH_2); 2.53 (s, 3H, SCH_3); 2.76 (brs, 2H, CH_2); 3.08 (s, 3h, NCH_3); 3.33 (brs, 2H, CH_2); 6.85 (s, 1H, ArH); 7.32-7.81 (m, 5H, ArH). MS: m/z(%) = 324 (M^+,100), 309 (M^+-15,44.9). Anal. Calc. for $C_{19}H_{20}N_2OS$ (324.434): C 70.38; H 6.21; N 8.64. Found C 70.34; H 6.23; N 8.66%.

2,3,6,7,8,9,10,11-Octahydro-3-methyl-5-methylthio-2-phenyl-1H-cycloocta[e]indazol-1-one 14b:
Colourless crystals; yield 1.22g (69%); mp 132-135°C (chloroform-hexane): R_f 0.2 EtOAc/benzene (1:9). IR (KBr): νmax = 2896, 1663 (CO), 1586, 1441, 1301, 1121 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.27-1.54 (m, 4H, CH_2); 1.57-2.04 (m, 4H, CH_2); 2.51 (s, 3H, SCH_3); 3.02 (t, 2H, CH_2); 3.12 (s, 3H, NCH_3); 3.45 (t, 2H, CH_2); 6.92 (s, 1H, ArH); 7.34-7.83 (m, 5H, ArH). MS: m/z (%) = 352 (M^+,100), 337 (M^+-15,73). Anal. Calc. for $C_{21}H_{24}N_2OS$ (352.48): C 71.55; H 6.86; N 7.95. Found C 71.57; H 6.85; N 7.98%.

2,3,6,7-Tetrahydro-9-methoxy-3-methyl-5-methylthio-2-phenyl-1H-naphth[1,2-e]-indazol-1-one 18a:
Colourless crystals; yield 1.85g (92%); mp 155-156°C (chloroform-hexane): R_f 0.63 EtOAc/benzene (1:9). IR(KBr): νmax = 1648 (CO), 1587, 1249, 1158 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 2.60 (s, 3H, SCH_3); 2.85 (s, 4H, CH2); 3.20 (s, 3H, NCH_3); 3.89 (s, 3H, OCH_3); 6.89 (brs, 1H, ArH); 6.99 (brs, 1H, ArH); 7.35 (s, 1H, ArH); 7.44-7.80 (m, 5H, ArH); 8.48 (d, 1H, J = 9Hz, ArH). MS: m/z(%) = 402 (M^+, 100), 387 (M^+-15,40.2). Anal. Calc. for $C_{24}H_{22}N_2O_2S$ (402.504): C 71.61; H 5.51; N 6.96. Found C 71.63; H 5.53; N 6.94%.

2,3,6,7-Tetrahydro-3-methyl-5-methylthio-2-phenyl-1H-naphth[1,2-e]indazol-1-one 18b:
Colourless crystas; yield 1.64g (88%); mp 180-182°C (chloroform-hexane); R_f 0.23 (benzene). IR(KBr): νmax = 3154, 1651 (CO), 1296 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3H, SCH_3); 2.78 (s, 4H, CH_2); 3.10 (s, 3H, NCH_3); 6.87 (s, 1H, ArH); 7.20-7.43 (m, 4H, ArH); 7.55-7.57 (m, 2H, ArH); 7.53-7.62 (m, 2H, ArH); 8.87 (d, 1H, J = 9Hz, ArH). MS: m/z(%) = 372 (M^+, 100) 357 (M^+-15, 42.5). Anal. Calc. for $C_{23}H_{20}N_2OS$ (372.474): C 74.16; H 5.41; N 7.52. Found C 74.17; H 5.43; N 7.55%.

2,3,6,7-Tetrahydro-3-methyl-5-methylthio-2-phenyl-1H-[1]-benzoxepino[5,4-e]indazol-1-one 21:
Light yellow crystals; yield 1.77g (91%); mp 175-176°C (chloroform-hexane): R_f 0.79 EtOAc/benzene (4:6). IR (KBr): νmax = 1672(CO), 1585, 1025 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 2.58 (s, 3H, SCH_3); 3.14 (s, 3H, NCH_3); 3.08-3.17 (m, 2H, CH_2); 4.41-4.66 (m, 2H, OCH_2); 7.10 (s, 1H, ArH); 7.22-7.91 (m, 9H, ArH). MS: m/z(%) = 388 (M^+,100), 373 (M^+-15.34). Anal. Calc. for $C_{23}H_{20}N_2O_2S$ (388.474): C

71.11; H 5.19; N 7.21. Found C 71.13; H 5.20; N 7.19%.

General procedure for dethiomethylation of 10a, 14a, 18a-b.

To a solution of 1,2,4-trisubstituted-6-methylthio/1,2-disubstituted-3,4-annelated-6-methylthio-3H-indazole-3-one (2.5 mmol) in ethanol (25 ml) was added Raney Nickel (W4, 3 times by weight) and the mixture was stirred at ambient temperature for 6-8 hr. (monitored by tlc). The reaction mixture was filtered through G-3 cintered funnel and the residue was washed with ethanol (3x10 ml). The bulk of the ethanol was distilled off and chloroform (20 ml) was added. The solution was washed with water (2x25 ml) dried over sodium sulfate and evaporated. Analytically pure compounds **11a, 15a, 19a-b** were obtained by passing through a short length silica gel column using hexane as eluent.

1,2-dihydro-4-(4-methoxyphenyl)-1-methyl-2-phenyl-3H-indazol-3-one 11a:
Colourless crystals; yield 0.80g (98%) mp 152-153°C (chloroform-hexane); R_f 0.5 EtOAc/benzene (1:9). IR(KBr): γmax = 1591 (CO), 1302, 1245, 825 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 3.21 (s, 3H, NCH_3); 3.92 (s, 3H, OCH_3); 7.04 (brs, 1H, ArH); 7.14 (brs, 1H, ArH); 7.26-7.81 (m, 9H, ArH); 8.05 (brs, 1H, ArH). MS: m/z(%) = 330 (M^+,100), 315(M^+-15,66.7). Anal: Calc. for $C_{21}H_{18}N_2O_2$ (330.37): C 76.34; H 5.50; N 8.48. Found C 76.31; H 5.51; N 8.49%.

2,3,6,7,8,9-Hexahydro-3-methyl-2-phenyl-1H-benz[e]indazol-1-one 15a:
Colourless crystals; yield 0.69g (99%); mp 185-186°C (chloroform/hexane): R_f 0.68 EtOAc/benzene (1:9). IR(KBr): γmax = 2915, 1654(CO), 1306 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.70-2.00(m, 4H, CH_2); 2.81 (brs, 2H, CH_2); 3.09 (s, 3H, NCH_3); 3.36 (brs, 2H, CH_2); 7.07 (d, 1H, J = 9Hz, ArH); 7.38 (d, 1H, J = 9Hz, ArH); 7.50-7.80(m, 5H, ArH). MS: m/z(%) = 278 (M^+,100), 263 (M^+-15,15). Anal: Calc. for $C_{18}H_{18}N_2O$ (278.34): C 77.67; H 6.52; N 10.07. Found C 77.68; H 6.55; N 10.06%.

2,3,6,7-Tetrahydro-9-methoxy-3-methyl-2-phenyl-1H-naphth[1,2-e]indazol-1-one 19a:
Colourless crystals; yield 0.87 (98%); mp 161-163°C (chloroform-hexane): R_f 0.68 EtOAc/benzene (1:9). IR(KBr): γmax = 2925, 1656 (CO), 1592, 1479 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 2.81 (s, 4H, CH_2); 3.13 (s, 3H, NCH_3); 3.85 (s, 3H, OCH_3); 6.89 (brs, 1H, ArH); 7.04 (d, 1H, J = 3Hz, ArH); 7.19 (d, 1H, J = 9Hz, ArH); 7.58 (d, 1H, J = 9Hz, ArH); 7.67-7.85 (m, 5H, ArH); 8.64 (d, 1H, J = 9Hz, ArH). MS: m/z(%) = 356 (M^+,100), 341 (M^+-15,54.1). Anal. Calc. for $C_{23}H_{20}N_2O_2$ (356.49): C 77.49; H 5.66; N 7.86. Found C 77.50; H 5.68; N 7.88%.

2,3,6,7-Tetrahydro3-methyl-2-phenyl-1H-naphth[1,2-e]indazol-1-one 19b:
Colourless crystals; yield 0.79g (97%); mp 196-197°C (chloroform-hexane); R_f 0.28 (benzene). IR (KBr): γmax = 1655 (CO), 1476, 1327, 1134 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): δ = 2.84 (s, 4H, CH_2); 3.15 (s, 3H, NCH_3); 7.24-7.84(m, 10H, ArH); 8.64 (d, 1H, J = 7.5Hz, ArH). MS: m/z (%) = 326 (M^+, 100), 311 (M^+-15,67.5). Anal. Calc. for $C_{22}H_{18}N_2O$ (326.38): C 80.95; H 5.56; N 8.59. Found C 80.96; H 5.58; N 8.60%.

General procedure for the generation and reaction of 3-lithiomethyl-2-methyl-1-phenylpyrazoline 5A with α-oxoketene N,S-acetals (23a-b, 25): Synthesis of 1,2,4-trisubstituted-6-dialkylamino 3H-indazolone 3 one 24a-b and 2,3,6,7-tetrahydro-3-methyl-5-piperidyl-2-phenyl-1H-naphth[1,2-e]indazol-1-one 26.

To an ice cold (0°C) solution of 3 ml (21 mmol) of diisopropylamine in 10 ml of dry tetrahydrofuran (THF) under dry argon was added 15 mmol of n-BuLi in ether. To the resulting solution of lithium diisopropylamide (15 mmol) under dry argon at -78°C was added 0.9g (5 mmol) of antipyrine in 25 ml of dry THF, and the solution was stirred for 30-40 min. To the resulting enolate solution at 78°C was added 4 mmol of α-oxoketene S,N-acetal in 25 ml dry THF dropwise and the mixture was kept for 30-45 min, allowed to warm at room temperture, stirred for 6-8hr. (monitored by tlc) and quenched with aqueous saturated ammonium chloride solution (100 ml) and extracted with chloroform. The combined organic phase was washed with water (3x25 ml) and dried over anhydrous sodium sulfate. Removal of organic phase gave crude product which was purified by column chromatography over silica gel. Elution with ethyl acetate-hexane (3:7) yielded the product which were further recrystallised from chloroform-hexane.

1,2-Dihydro-1-methyl-2,4-diphenyl-6-(1-pyrrolidyl)-3H-indazol-3-one 24a:
Light brown crystals; yield 1.81g (98%); mp 158-159°C (chloroform-hexane): R_f 0.45 EtOAc/benzene (2:8). IR (KBr): νmax = 1599 (CO), 1273, 1127 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.89-2.19(m, 4H, CH_2); 3.08 (s, 3H, NCH_3); 3.29-3.54(m, 4H, NCH_2); 6.18 (brs, 1H, ArH); 6.44 (brs, 1H, ArH); 7.33-7.80 (m, 10H, ArH). MS: m/z (%) = 369 (M^+, 71.2), 354 (M^+-15,100). Anal. Calc. for $C_{20}H_{23}N_3O$ (369.44): C 78.02; H 6.27; N 11.37. Found C 78.04; H 6.29; N 11.38%.

1,2-Dihydro-4-(4-chlorophenyl)-1-methyl-6-(1-morpholinyl)-2-phenyl-3H-indazol-3-one 24b:
Viscous liquid; yield 1.58g (78%); R_f 0.55 EtOAc/benzene (1:9). IR (KBr) νmax = 1590(CO), 1495, 1207 cm^{-1}. ^1H NMR (90 MHz, CCl_4): δ = 3.01-3.22 (m, 4H, NCH_2); 3.66-3.92 (m, 4H, OCH_2); 6.31 (d, 1H, J = 3Hz, ArH); 6.67 (d, 1H, J = 3Hz, ArH); 7.25-7.58(m, 7H, ArH); 7.66-8.03(m, 2H, ArH). Anal: Calc. for $C_{24}H_{22}N_3OCl$ (403.89): C 71.37; H 5.49; N 10.40. Found C 71.38; H 5.50; N 10.42%.

2,3,6,7-Tetrahydro-3-methyl-5-piperidyl-2-phenyl-1H-naphth[1,2-e]indazol-1-one 26:
Colourless crystals; yield 1.71g (83.5%); mp 169-171°C (chloroform-hexane): R_f 0.8 EtOAc/benzene (1:9). IR (KBr): νmax = 1591 (CO), 1204, 1109 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.75-1.82 (m, 6H, CH_2); 2.68-2.85 (m, 4H, NCH_2); 2.95 (brs, 4H, CH_2); 3.15 (s, 3H, NCH_3); 6.78 (s, 1H, ArH); 7.20-7.33 (m, 4H, ArH); 7.43-7.51 (m, 2H, ArH); 7.60 (d, 2H, J = 9Hz, ArH); 8.30 (d, 1H, J = 9Hz, ArH). MS: m/z(%) = 409 (M^+,100), 394 (M^+-15,27.5). Anal. Calc. for $C_{27}H_{27}N_3O$ (409.51): C 79.18; H 6.65; N 10.26. Found C 79.20; H 6.66; N 10.25%.

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