Tetrahedron Vol. 46, No. 19, pp. 6771-6782, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

STUDIES ON CYCLOADDITION REACTIONS OF 1,3-DIPHENYL-2-AZAALLYL LITHIUM AND ETHYL(BENZYLIDENEAMINO)ACETATE ANION WITH α-OXOKETENE DITHIOACETALS

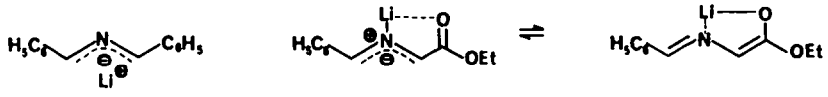
Maliakel P. Balu, Hiriyakkanavar Ila* and Hiriyakkanavar Junjappa*
Department of Chemistry, North-Eastern Hill University
Shillong 793 003, Meghalaya, India

(*Received in UK* 14 *June* 1990)

Abstract: *The α-oxoketene dithioacetals undergo anionic [1,3] cycloaddition with 1,3-diphenyl-2-azaallyllithium (1) to give either pyrroles or spiropyrrolines with two exceptions. Lithium bromide/triethylamine induced cycloaddition of ethyl (benzylideneamino)acetate (17) with acyclic α-oxoketene dithioacetals afforded either pyrrolidine, pyrrole or the corresponding 3-benzylideneamino-pyran-2-one derivatives depending on the reaction conditions and the structural variations in the α-oxoketene dithioacetals. Nitroketene dithioacetal also underwent anionic [1,3] cycloaddition with either 1 or 17 under described conditions to afford pyrrolidine or pyrrole derivatives. Probable mechanisms for the formation of various products are suggested.*

As a part of our programmed studies on aromatic[1] and heteroaromatic annelation through α-oxoketene dithioacetals, we had recently reported the reactions of 1-azaallyl anions such as 2-lithioacetonitrile[2a] and 2-picolyllithium[2b] with these intermediates, initially to afford the corresponding carbinol acetals which on Lewis acid assisted cyclization yielded the respective pyridine and quinolizinium fluoroborate derivatives in high yields. Apparently, the 1-azaallyl anions have exhibited their propensity of 1,2-addition mode to the α-oxoketene dithioacetals, known for their behaviour as reagents for directed aldol-condensation[3]. In contrast, the pioneering work of Kauffmann[4] has shown that 2-azaallyl anions like 1,3-diphenyl-2-azaallyllithium (1) undergo anionic [1,3]-cycloadditions with unsaturated compounds containing CC,CN,NN and CS double bonds as well as those containing CC and CN triple bonds, although their reactions with carbonyl compounds were shown to yield only the open-chain carbinol adducts. Similarly, conjugated carbonyl compounds were reported[4] to be unsuitable for anionic [1,3]-cycloaddition owing to the pronounced nucleophilic character of the anionic reagent 1. However, subsequently it has been demonstrated that the α-cyano-β-phenyl cinnamate[5a] and the phenylpropiolic acid amide[5b] undergo cycloaddition on CC double and triple bonds with 1 to afford pyrrolidine and pyrrole derivatives respectively. These studies clearly demonstrate that the 2-azaallyl anions behave more like lithio 1,3-dipolar species rather than mere nucleophilic reagents even towards carbonyl activated double bonds[6]. It has been demonstrated[4] that the heteroallyl anions best suited for anionic [1,3]-cycloadditions are the 2-azaallyl anions where a relatively electronegative nitrogen is located at the center of the heteroallyl systems. The negative charge in these systems is largely located at the terminal carbon atoms and during the cycloaddition reactions the charge migrates to the more electronegative

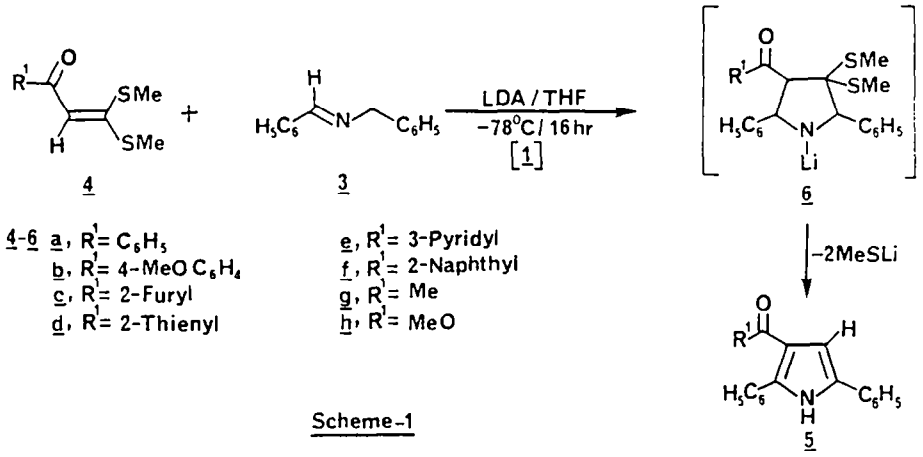
central nitrogen atom in the five membered cycloadducts thus making them efficient 1,3-dipolar systems[4]. We therefore became interested in the reaction of these anions with α-oxoketene dithioacetals, whether they would occur via [3+2] cycloaddition to β,β-bis(methylthio) double bond or by intial aldol type nucleophilic addition to the carbonyl group. The two azaallyl anions investigated have indeed behaved as 1,3-anionic dipolar systems with a few exceptions, undergoing [3+2] cycloadditions with mercapto double bond to yield the respective pyrrolidine or the corresponding pyrrole derivatives in good yields. We have investigated the reaction of 1,3-diphenyl-2-azaallyllithium (1) and ethyl (benzylidene amino)acetate anion 2 with α-oxoketene dithioacetals and our results are reported herein.



1 2A 2B

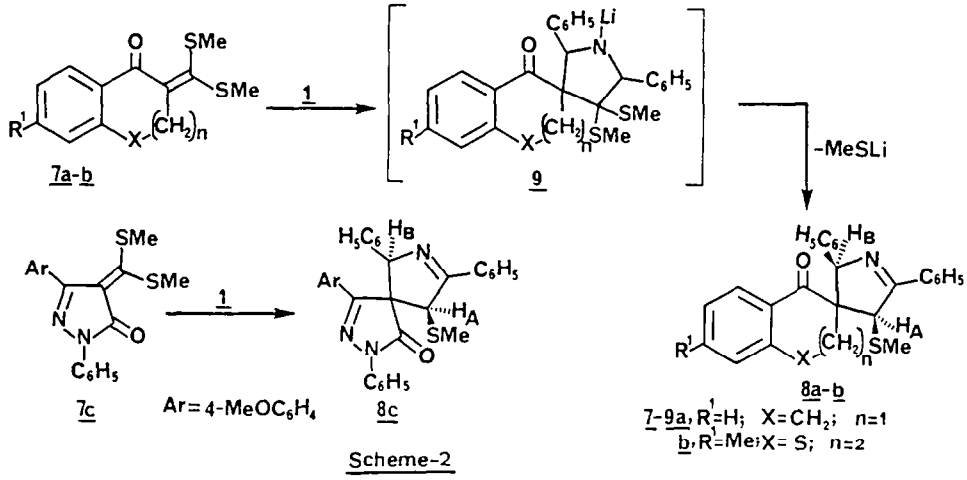
Cycoladdition Reactions of 1,3-Diphenyl-2-Azaallyllithium with α-Oxoketene Dithioacetals

Kauffmann and coworkers[4] have shown that the 2-azaallyl anion 1 generated by deprotonation of N-benzylidenebenzylamine 3 with lithium diisopropyl amide undergoes [1,3] anionic cycloaddition with conjugated and activated double bonds in a highly stereoselective and stereospecific manner to afford the corresponding pyrrolidine derivatives. The reaction of 1 with α-oxoketene dithioacetals under identical reaction conditions was therefore examined. In a typical experiment, when the dithioacetal 4a was reacted with 1 at -78°C, work-up of the reaction mixture yielded a product (79%) which was characterized as 3-benzoyl-2,5-diphenylpyrrole (5a) on the basis of spectral and analytical data (Scheme 1). Apparently the reaction involves an intial [3+2] cycloaddition of 4a and 1 to afford the corresponding pyrrolidine lithium 6a which on successive prototropic shift followed by methylthio group elimination affords 5a. The cycloaddition of other acyclic oxoketene dithioacetals 4b-g and the carbomethoxyacetal 4h also gave the corresponding 3-acyl (5b-g) and 3-carbomethoxy (5h) pyrroles in 71-78% overall yields (Scheme 1). Similarly when the cyclic oxoketene dithioacetal 7a derived from α-tetralone was treated with 1, the corresponding spiropyrroline 8a was formed (75%) by elimination of methylthiolithium from an unstable cycloadduct 9. The structure of 8a was confirmed with the help of spectral and analytical data. The observed long range coupling (2Hz) between H_A and H_B protons confirms the *cis* stereochemistry in accordance with the earlier observations[7]. The other cyclic oxoketene dithioacetals 7b and 7c derived from benzothiepinone and 5-pyrazolone also underwent [3+2] cycloaddition with 1 to yield the corresponding spiropyrrolines 8b and 8c in 68% and 71% yields respectively (Scheme 2).



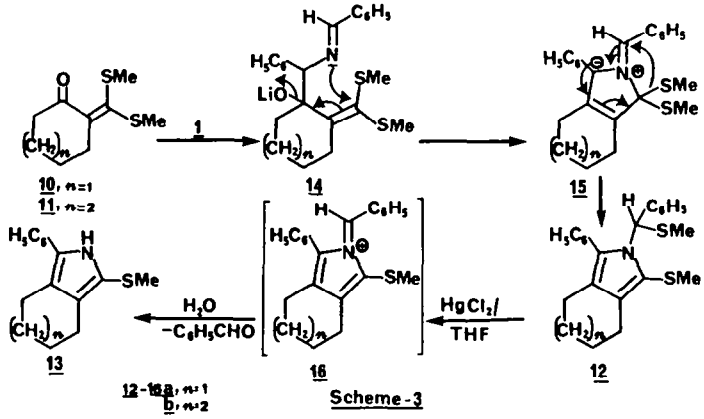
4-6 a, R^1= C_6H_5
b, R^1= 4-MeO C_6H_4
c, R^1= 2-Furyl
d, R^1= 2-Thienyl
e, R^1= 3-Pyridyl
f, R^1= 2-Naphthyl
g, R^1= Me
h, R^1= MeO

Scheme-1



Scheme-2

Interestingly the cyclic oxoketene dithioacetal 10 derived from cyclohexanone did not react in the expected manner to yield the corresponding spiropyrroline cycloadduct and the product thus obtained was characterized as the N-substituted isoindole derivative 12a (79%), on the basis of spectral and analytical data (Scheme 3). The structure of 12a was further confirmed by its mercuric chloride catalyzed hydrolytic cleavage to the isoindole 13a (Scheme 3). Similarly 11 from cycloheptanone reacted with 1 to give the corresponding 3,4 annelated pyrrole 12b (76%), which on treatment with mercuric chloride afforded the corresponding dealkylated derivative 13b in 68% yield (Scheme 3). The probable mechanism for the formation of 12a-b from 10 and 11 is described in Scheme 3. Apparently 1 reacted in the 1,2-fashion followed by nitrogen lone pair assisted intramolecular cyclization to give zwitterionic intermediate 15, which on 1,3-methylthio shift affords the corresponding stable pyrrole derivatives 12a-b (Scheme 3).



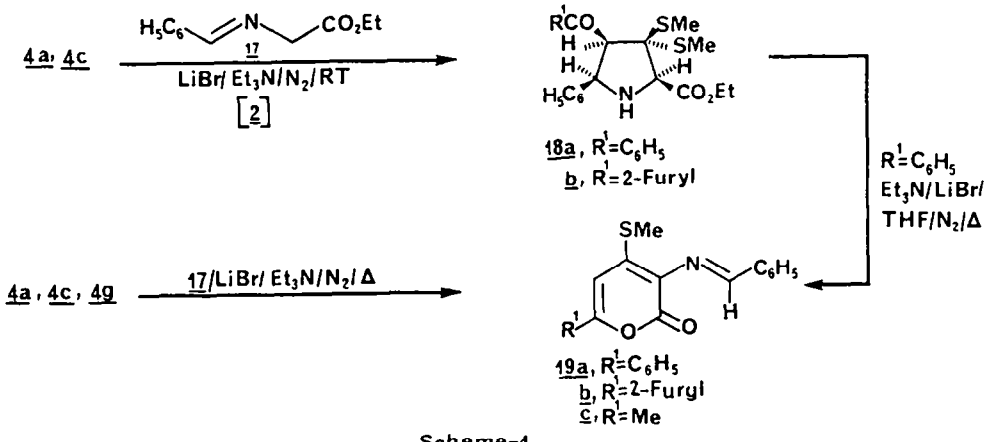
Scheme-3

Lithium Bromide/Triethylamine Induced Cycloaddition of Ethyl (Benzylideneamino) acetate to α-Oxoketene Dithioacetals

The deprotonation studies of N-alkylidene-2-amino esters have been investigated by several groups[8]. Generally the deprotonation is achieved by sodium or potassium alkoxides or Triton B either in protic (MeOH/EtOH) or aprotic solvents. The resulting azaallyl anions are trapped by electron deficient olefins to yield the corresponding Michael adducts in most of the cases. However Grigg and co-workers have reported in some cases, competetive formation of both Michael adducts and stereoselective cycloadducts and proposed a mechanism involving sequential Michael adduct mediated cyclization[9]. The same group was the first to demonstrate the facile thermal tautomerism in imines of α-amino esters to N-protonated azomethine ylides which were shown to undergo cycloaddition with a variety of dipolarophiles[10]. Attempts to generate the N-metalated azomethine ylides by deprotonation of ethyl (benzylideneamino) acetate 17 with strong bases such as LDA, n-BuLi, NaH and EtMgBr and to trap them by conjugated carbonyl compounds resulted in complex reaction mixture. However, subsequently it was shown[11] that a combination of metal salt (Ag,Li,Zn,Ti) and triethylamine in polar aprotic solvent affects rapid regio and stereospecific cycloaddition of imines of α-amino esters to a range of dipolarophiles. The nature of the reactive species in these Lewis acid catalyzed cycloadditions is not clear, though an equilibrium involving metallo 1,3-dipoles and N-protonated azomethine ylide has been suggested[11c,11e].

The addition mode of these anionic species from N-benzylideneaminoacetate with α-oxoketene dithioacetals was therefore examined under the above reaction conditions. When 4a was refluxed with 17 in toluene, the envisaged cycloaddition of N-protonated azomethine ylide was not observed and the starting materials were recovered unchanged. Similarly the formation of N-lithiated azomethine ylide could not be observed by

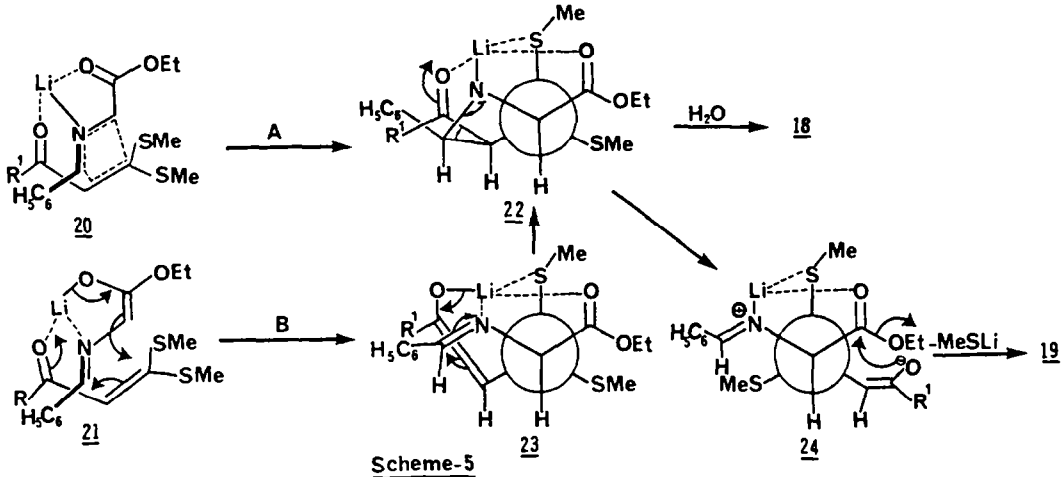
deprotonation of 17 by treatment with either LDA or n-BuLi in the presence of 4a and the reaction mixture resulted only in an intractable tar. However when 17 was treated with lithium bromide and triethylamine in the presence of 4a in THF at room temperature the reaction mixture after work-up gave the expected pyrrolidine cycloadduct 18a in high yield as a single stereo and regioisomer (Scheme 4). The structure of 18a was established by its analytical and spectral data. The stereochemistry at 2,4 and 5 carbon atoms was assigned on the basis of vicinal coupling constants measured from molecular models as well as through the known stereochemical mode of their cycloadditions[8c]. However in an another experiment, when 17 and 4a were refluxed in the presence of lithium bromide and triethylamine in THF under a N_2 atmosphere a different product was isolated which was characterized as 3-(benzylideneamino)pyran-2-one 19a (81%) (Scheme 4). The intermediacy of 18a in the formation 19a was established by treating 18a with $LiBr/Et_3N$ in refluxing THF (16 hr), when the full conversion of 18a to 19a was observed. Similarly the α-(2-furoyl)ketene dithioacetal 4c reacted with 17 under similar reaction conditions to afford 18b or 19b in 69% and 61% yields respectively. However the cycloadditions of α-acetylketene dithioacetal 4g with 2 under the described temperature conditions gave only the corresponding pyran-2-one (19c) and no trace of the corresponding 4-acetylpyrrolidine-2-carboxylate was observed (Scheme 4).



Scheme-4

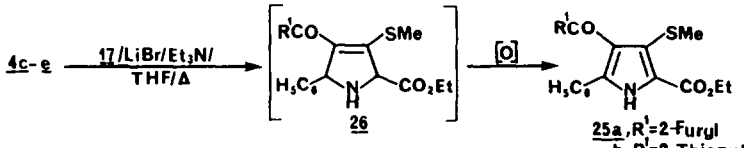
The possible mechanism for the formation of highly stereo and regioselective pyrrolidines 18 and the corresponding pyran-2-ones 19 is described in the Scheme 5 which is similar to that proposed by Tsuge and cowokers[8c]. The pyrrolidine 18 can be formed either through path A involving a concerted cycloaddition of the *syn* N-lithiated azomethine ylide 2A in *endo* fashion through a chelated intermediate 20. Alternatively the lithium enolate 2B may undergo tandem Michael imine addition as depicted in 21 and 23 (path B). The lithiated pyrrolidine 22 suffers rapid bond cleavage at higher temperature leading to N-lithiated betaine intermediate 24 that follows intramolecular enollactonization and loss of methylthio group to afford the thermodynamically more stable pyran-2-one.The formation of betaine 24 from 22 appears to proceed due to steric crowding in 22 as

well as by the anion stabilization offered by aryl and acyl group[12]. The exclusive formation of only the pyran-2-one 19c from α-acetylketene dithioacetal 4g both at room temperature and under refluxing conditions may be rationalized in terms of higher stability of the betaine intermediate 24 due to the increased anion stablizing ability of the acetyl group.



Scheme-5

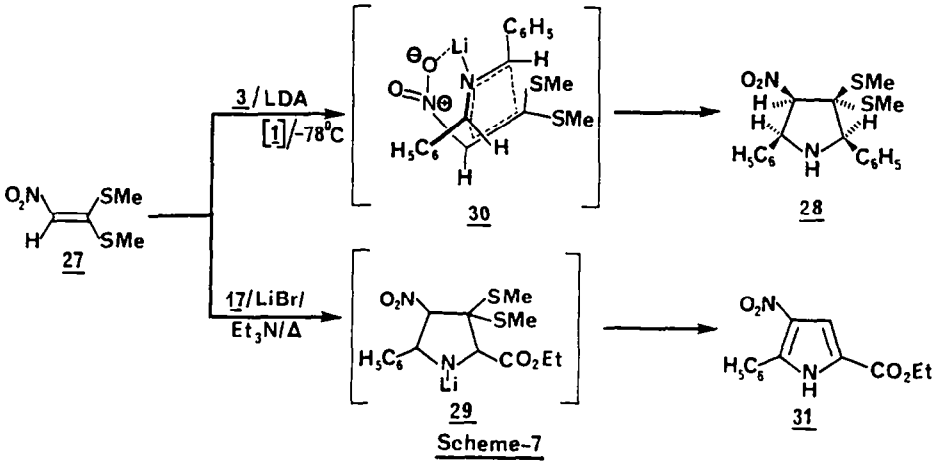
When the α-(2-thienoyl) (4d) and α-(3-pyridinoyl) (4e) ketene dithioacetals were reacted with 2 under identical reaction conditions, starting materials along with intractable tar were recovered. However, when the same reaction mixtures were refluxed for prolonged time (30 hr) in the absence of nitrogen, the products isolated were found to be pyrrole-2-carboxylates 25b (69%) and 25c (79%) respectively (Scheme 6). Similarly 4c and 2 under indentical prolonged reaction conditions, yielded the corresponding 3-(2-furoyl)pyrrole-2-carboxylate 25a in 73% yield. Obviously the intially formed lithiated pyrrolidines 22 undergo a facile elimination of methylthiolithium followed by dehydrogenation of the resulting pyrrolines 26 to afford the corresponding pyrroles 25a-c. The structures of these pyrroles were fully established by their analytical and spectral data.



Scheme-6

As an extension of these studies the cycloaddition of nitroketene S,S-acetal 27 with 2-azaallyl anion 1 and the enolate anion 2 was also examined. Thus 27 underwent cycloaddition with 3 in the presence of LDA at -78°C to afford the corresponding pyrrolidine 28 as single stereoisomer in 64% yield (Scheme 7). the corresponding 3-nitro-2,5-diphenyl pyrrole however could not be isolated even after prolonged heating of the reaction mixture. High stereoselectivity and the stability of the cycloadduct 28

indicates the participation of chelated *endo* intermediate 30 through *syn* conformation of azaallyl anion 1. The cylcoaddition of 27 with 17 at room temperature in the presence of $LiBr/Et_3N$ did not proceed in the expected manner and no clear-cut product could be isolated. However when the same reaction mixture was refluxed in the presence of a N_2 atmosphere, the corresponding 3-nitropyrrole-2-carboxylate 31 was isolated in 56% yield (Scheme 7). The formation of 31 could be explained through successive elimination of methylthio groups as described earlier.



Scheme-7

In conclusion, the 2-azaallyl anions behave as 1,3-anionic dipolar species towards α-oxoketene dithioacetals through cycloaddition to the mercapto double bond rather than nucleophilic addition to the carbonyl group with a few exceptions. The formation of fully aromatized pyrroles from open-chain oxoketene dithioacetals and 1 (or 2) clearly qualifies these intermediates as corresponding acylacetylene equivalents.

EXPERIMENTAL

Meling points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were run as KBr discs on a Perkin-Elmer 297 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in deuteriochloroform with tetramethylsilane as internal standard unless otherwise stated. Chemical shifts are expressed as δ(ppm) downfield from TMS. ^{13}C NMR spectra were recorded on a Brucker WM-400 spectrometer. Mass spectra were obtained using a Jeol JMS D-300 spectrometer. Elemental analysis were carried out on Heraeus CHN-O-RAPID instrument. All α-oxoketene dithioacetals were prepared according to the general procedure reported earlier[13]. Ethyl (benzylideneamino)acetate was prepared as reported[13].

General Procedure for the Generation and Reaction of 1,3-Diphenyl-2-Azaallyllithium with α-Oxoketene Dithioacetals:

To a stirred solution of lithium diisopropylamide [(11 mmol) freshly prepared from n-butyllithium (11 mmol) and diisopropylamine (1.10gm, 11

mmol) in dry THF (20 ml)], N-benzylidenebenzylamine (1.95gm, 10 mmol) in THF (5 ml) was added slowly at -78°C under nitrogen atmosphere. The lithiation was indicated by the appearance of reddish brown colour. The solution was stirred for 15 min at -78°C followed by addition of oxoketene dithioacetal (10 mmol) in THF (30 ml) and further stirring for 1 hr at -78°C. The temperature was raised to ambient (30 min) and stirring was further continued for 15 hr. The reaction mixture was poured into satd. NH_4Cl solution and the organic layer was separated, the aqueous layer extracted with ether (2x50 ml) and the combined organic layer was washed with water (100 ml), dried (Na_2SO_4) and evaporated to give viscous residue which were purified by column chromatography over silica gel using hexane-EtOAc as eluent (5:1) to give pyrroles 5a-h, spiropyrrolines 8a-c and fused pyrroles 12a,b which were further purified by crystallization from EtOAc/hexane.

Benzoyl-2,5-diphenylpyrrole (5a) colourless crystals; 79%; m.p. 168-169°C; IR ν_{max} 3200,1595,1572 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.75 (d, J=1.5Hz, 1H,H-4); 7.62-7.81 (m,13H,arom);7.59-7.83 (m,2H,arom); 11.93 (brs,1H,NH,exchangeable with D_2O); (Found: C, 85.71,H,5.21;N,4.62.Calc. for $C_{23}H_{17}NO$: C,85.42; H, 5.30; N, 4.36%); m/z 323 (M^+, 100%); 246 (72); 218 (7).

3-(4-Methoxybenzoyl)-2,5-diphenylpyrrole (5b) light yellow crystals; 82% m.p.183-184°C;IR ν_{max} 3150,1605,1594,1565 cm^{-1};^1H NMR ($CDCl_3$) δ3.78(s, 3H, OCH_3); 6.72-6.88(m,3H,arom and H-4);7.05-7.58(m,10H,arom);7.68-7.90 (m,2H,arom);9.10(brs,1H,NH,exchangeable with D_2O);(Found:C,81.78;H,5.63, N, 3.86 Calc.for $C_{24}H_{19}NO_2$:C,81.56;H,5.42;N,3.96%);m/z353 (M^+,100%);246 (24).

2,5-Diphenyl-3-(2-furoyl)pyrrole (5c) yellow crystals; 76%; m.p. 162-163°C; IR ν_{max} 3240, 1602, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.31 (dd, J=3 and 1.5 Hz, 1H, H-4' furyl); 6.79-7.56 (m, 13H, arom); 9.60 (brs, 1H, NH, exchangeable with D_2O); (Found: C, 80.68; H, 4.58; N, 4.23; Calc. for $C_{23}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47%); m/z 313 (M^+, 100%); 296(17).

2,5-Diphenyl-3-(2-thienoyl)pyrrole (5d) yellow crystals; 78%; m.p. 145-146°C; IR ν_{max} 3200,1600,1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74-7.58 (m, 14H, arom);9.51(brs,1H,NH,exchangeable with D_2O);(Found:C,76.69;H, 4.38; N, 4.18;Calc.for $C_{21}H_{15}NOS$:C,76.57;H,4.59;N,4.25%);m/z 329 (M^+, 100%).

2,5-Diphenyl-3-(3-pyridinoyl)pyrrole(5e) light yellow crystals;81%;m.p.266-267°C IR ν_{max}3150,1645,1600,1582 cm^{-1};^1H NMR($CDCl_3$)δ6.73(d,J=1.5Hz,1H,H-4); 6.94-7.99(m,12H,arom and pyridyl);8.38(d,J=6Hz,1H,H-6'pyridyl);8.70(s,1H,H-2'pyridyl);10.61(brs,1H,NH,exchangeable with D_2O); (Found C,81.23;H,4.82,N, 8.73.Calc.for $C_{22}H_{16}N_2O$:C,81.46;H,4.97;N,8.64%);m/z324(M^+,100%);247(22).

2,5-Diphenyl-3-(2-naphthoyl)pyrrole (5f) yellow crystals; 84%; m.p. 181°C, IR ν_{max} 3255,1601,1570 cm^{-1}; ^{1} NMR ($CDCl_3$) δ 6.81 (d,J=1.5Hz,1H, H-4); 7.02-7.98 (m,16H,arom); 8.31 (s,1H,H-1'naphthyl); 9.30 (brs,1H, NH, exchangeable with D_2O); (Found: C, 86.58; H, 5.24; N, 3.86. Calc. for $C_{27}H_{19}NO$: C, 86.84; H, 5.13; N, 3.75%); m/z 373 (M^+,100%); 344(5).

3-Acetyl-2,5-diphenylpyrrole (5g) colourless crystals; 74%; m.p. 169°C; IR ν_{max} 3240,1605,1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H, CH_3); 6.90 (d,

J=1.5Hz, 1H, H-4); 7.19-7.61 (m,10H,arom); 9.08 (brs,1H,NH,exchangeable with D_2O); (Found: C,82.54; H,5.82; N,5.23.Calc. for $C_{18}H_{15}NO$: C,82.73; H,5.79; N,5.36%); m/z 261 (M^+,70%);246(100);217(16).

Methyl-2,5-diphenylpyrrole-3-carboxylate (5h) colourless crystals; 71%; m.p.162°C; IR ν_{max} 3310,1670,1606,1591 cm^{-1},^1H NMR ($CDCl_3$) δ 3.70 (s,3H, OCH_3); 6.96(d,J=1.5Hz,1H,H-4); 7.15-7.72 (m,10H,arom); 8.69(brs, 1H, NH, exchangeable with D_2O);(Found:C,77.78;H,5.68;N,5.25. Calc.for $C_{18}H_{15}NO_2$: C,77.96; H, 5.45; N,5.05%); m/z 277 (M^+,100%), 246(58); 217(15).

Spiro[(3,4-dihydronaphthalene-1-oxo)-2(*1H*),3'-(2',5'-diphenyl-4'-methylthio-5'-pyrroline)] (8a) colourless crystals; 74%, m.p.163°C. IR ν_{max} 1670, 1605, 1595 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36-1.59 (m,2H,CH_2); 1.90 (s, 3H, SCH_3); 2.54-3.21 (m,2H,CH_2); 4.45(d,J=2Hz,1H,H_A); 6.22 (d, J=2Hz, 1H, H_B); 7.00-7.51 (m,11H,arom); 8.05-8.25(m,3H,arom);(Found:C,78.26,H,5.89;N,3.68. Calc.for $C_{26}H_{23}ONS$: C,78.55; H,5.83; N,3.52%); m/z 397 (M^+,25%); 350(100).

Spiro[(2,3-dihydro-8-methyl-5-oxo-[1]-benzothiepin)-4(*5H*),3'-(2',5'-diphenyl 4'-methylthio-5'-pyrroline)] (8b) colourless crystals; 68%; m.p. 173-174°C. IR ν_{max} 1659,1616,1600 cm^{-1}; ^1H NMR ($CDCl_3$): 1.82 (s,3H,CH_3); 2.34 (s, 3H, SCH_3); 2.48-2.95 (m,4H,$-CH_2-$); 5.05 (d, J=2Hz,1H,H_A) 5.90 (d, J=2Hz, 1H, H_B); 7.05-7.88 (m,12H,arom); 8.09 (d,J=9 Hz, H-6); (Found: C,72.94; H, 5.74; N, 3.28. Calc.for $C_{27}H_{25}ONS_2$ C,73.10; H,5.68; N, 3.16%); m/z 443 (M^+,14%); 397 (88).

Spiro[3-(4-methoxyphenyl)-1-phenyl-5-pyrazolone)-4,3'-(2',5'-diphenyl-4'-methylthio-5'-pyrroline)] (8c) yellow crystals; 71%; IR ν_{max} 1710, 1625, 1608, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s,3H,SCH_3);3.69 (s,3H, OCH_3); 5.00 (d, J=2Hz,1H,H_A); 6.02 (d,J=2Hz,H_B); 6.56-6.74 (m,2H,arom); 7.02-7.65 (m,13H,arom); 8.01-8.29 (m,4H,arom); (Found:C,74.38; H,5.16; N,8.32. Calc. for $C_{32}H_{27}O_2N_3S$: C, 74.25,H,5.26; N,8.12%).

1-(Methylthio)-2-N(α-methylthiobenzyl)-3-phenyl-4,5,6,7-tetrahydroisoindole (12a) colourless crystals; 77%; m.p. 155°C, IR ν_{max} 1605,1571,1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62-1.82 (m,4H,$-CH_2-$); 1.90 (s,3H,SCH_3); 2.15 (s, 3H, SCH_3); 2.50-2.74 (m,4H,$-CH_2-$); 6.38 (s,1H,H-3,ArCH); 7.21-7.50 (m,10H,arom). ^{13}C NMR ($CDCl_3$) δ 14.27,20.03 (SCH_3); 22.21,23.24,23.43,24.35 (CH_2); 64.10 (C_6H_5CH); 110.42(C-7a);112.52 (C-3a);126.64,127.64,127.77,128.21,128.49, 129.25 (CH,arom);130.93,132.09(C-,Ar);137.60,138.87 (C-1,C-3);(Found: C,72.53;H,6.82; N,3.43. Calc.for $C_{23}H_{25}NS_2$: C,72.78; H,6.64; N,3.69%); m/z 379 (M^+,96%); 332(40).

1-N(α-methylthiobenzyl)-2-(methylthio)-8-phenyl-5,6,7,8-tetrahydro-*4H*-cyclohepta[c]pyrrole (12b) colourless crystals; 76%; m.p. 157°C; IR ν_{max} 1600,1488,1463 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30-1.76 (m,6H,CH_2); 1.87 (s,3H, SCH_3); 2.07 (s,3H,SCH_3);2.28-2.90 (m,4H,CH_2); 6.38 (s, 1H, ArCH-); 7.13-7.55 (m,10H,arom); (Found: C,73.0;H,6.81; N,3.28. Calc. for $C_{24}H_{27}NS_2$: C, 73.23; H, 6.92; N,3.56%); m/z 393 (M^+,100%); 346(29); 256(17).

Mercuric Chloride Catalyzed Hydrolytic Cleavage of 12a and 12b: General Procedure: A suspension of N-substituted isoindole 12a or 12b(1 mmol) and $HgCl_2$ (0.27g, 1 mmol) in dry THF (10 ml) was stirred at room temperature

for 6 hr. The reaction mixture was filtered through a G-4 sintered funnel to remove traces of mercuric chloride and the filtrate diluted with chloroform (25 ml) washed with saturated sodium bicarbonate solution and evaporated to give the crude products 13a or 13b, which were purified by column chromatography over silica gel using hexane-EtOAc (20:1) as eluent.

1-(Methylthio)-3-phenyl-4,5,6,7-tetrahydroiosindole (13a) colourless crystals (EtOAc-hexane);73%;m.p.91-92°C;IR ν_{max} 3320,1600,1585,1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71-1.92 (m,4H,CH_2); 2.19 (s,3H,SCH_3); 2.48-2.72 (m,4H,CH_2); 7.21-7.54 (m,3H,arom); 7.61-7.82 (m,2H,arom); 8.01 (brs,1H,NH exchangeable with D_2O); (Found: C,74.12; H,7.28; N,5.54. Calc. for $C_{15}H_{17}NS$: C, 74.03, H,7.04; N,5.76%); m/z 243 (M^+,100%) 228(41).

2-(Methylthio)-8-phenyl-4,5,6,7-tetrahydro-*3H*-cyclohepta[c]pyrrole (13b) colourless crystals (EtOAc-hexane); 68%, m.p. 90-91°C; IR ν_{max} 3325, 1605, 1598 cm^{-1}, ^1H NMR (CCl_4) δ 1.45-1.82 (m,6H,CH_2); 1.99 (s, 3H, SCH_3); 2.38-2.79 (m,4H,CH_2); 7.01-7.35 (m,3H,arom); 7.42-7.64 (m,2H,arom); 7.74 (brs, 1H,NH exchangeble with D_2O); (Found: C,74.40; H,7.53; N,5.23. Calc. for $C_{16}H_{19}NS$: C,74.66; H,7.44; N,5.44%); m/z 257 (M^+,100%); 242(25).

Lithium Bromide/Triethylamine Induced Cycloaddition of Ethyl(benzylideneamino)acetate with α-Oxoketene Dithioacetals: General Procedure: To a solution of 17 (2.10g, 11 mmol) and the appropriate oxoketene dithioacetal (4a,4c,4g) (10 mmol) in dry THF (25 ml) was added lithium bromide (1.30g, 15 mmol) in THF (10 ml) and triethylamine (1.21g, 12 mmol) in THF (5 ml) with the help of a syringe. The mixture was stirred at room temperature for 14-16 hr under nitrogen (checked by TLC) and poured into concentrated aqueous ammonium chloride (50 ml), extracted with chloroform (50mlx3), dried over sodium sulphate and evaporated in vaccuo. The residue was chromatographed over silica gel by using hexane-EtOAc (5:1) as eluent to give the corresponding pyrrolidines, 18a,b and pyran-2-one 19c. When the same reaction mixture from 4a and 4c, after an initial 3 hr stirring at room temperature was refluxed for 16 hr at 70°C under an efficient atmosphere of nitrogen, work-up as described gave the pyran-2-one 19a and 19b. Pyrroles 25a,b,c were obtained when the same reaction mixture from 4c,d,e after an initial 3 hr stirring at room temperature was refluxed for 30 hr at 70°C in the absence of nitrogen.

Ethyl-4-benzoyl-3,3-bis(methylthio)-5-phenylpyrrolidine-2-carboxylate (18a) colourless crystals (EtOAc-hexane); 72%, m.p. 154°C; IR ν_{max} 3300,1750, 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t,J=7Hz, 3H, CH_3); 1.98 (s, 3H,SCH_3); 2.21 (s,3H,SCH_3); 2.59-2.71 (brs,1H,NH, exchangeable with D_2O) 4.31 (q,J=7Hz,2H,OCH_2); 4.68 (d,J=7Hz,1H,H-4);4.96 (brs,1H,H-2); 5.41 (brd, J=7Hz,1H,H-5); 6.98-7.69 (m,10H,arom); ^{13}C NMR ($CDCl_3$) 12.95 (CH_3); 13.81, 14.04 (SCH_3); 61.29 (OCH_2); 61.78, 63.78, 70.13 (CH,C-2,C-4,C-5); 70.69 (C-3); 126.93, 127.26, 127.63, 128.21, 132.61 (CH-phenyl) 139.60, 139.61 (quaternary Ar) 170.81 (C-OEt); 197.44 (C_6H_5C-); (Found: C, 63.39; H,6.01, N,3.22. Calc. for $C_{22}H_{25}NO_3S_2$: C,63.58; H,6.06; N,3.37%); m/z 368 (M^+-47, 100%); 225(59).

Ethyl-4-(2-furoyl)-3,3-bis(methylthio)-5-phenylpyrrolidine-2-carboxylate (18b) colourless crystals (EtOAc-hexane); 69%; m.p. 135-136°C; IR ν_{max} 3340,

1723, 1660, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (t, J=7Hz,3H,CH_3); 2.02 (s, 3H,SCH_3); 2.21 (s,3H,SCH_3); 3.05-3.20 (brs,1H,NH); 4.25 (q,J=7Hz,2H,OCH_2); 4.49 (d,J=7Hz,1H,H-4); 4.89 (brs,1H,H-3); 5.38 (d,J=6.5Hz,1H,H-5);6.48 (dd, J=3 and 1.5Hz, H-4' furyl);6.87-7.49 (m,7H,arom and furyl);(Found:C,59.12; H, 5.61; N,3.48. Calc. for $C_{20}H_{23}NO_4S_2$: C,59.23; H,5.72; N,3.45%); ,m/z 358 (M^+-47,14%); 312(4).

3-Benzylideneamino-4-(methylthio)-6-phenylpyran-2-one (19a) yellow crystals (EtOAc-hexane); 69%; m.p. 164-165°C; IR ν_{max} 1704,1688,1618,1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (s,3H,SCH_3); 6.68 (s,1H,H-5); 7.30-7.59 (m,6H,arom); 7.78-8.02 (m,4H,arom);9.49 (s,1H,CH=N-); (Found:C,71.18; H,4.79; N,4.46. Calc.for $C_{19}H_{15}NO_2S$: C,71.00; H,4.70; N,4.36%); m/z 321 (M^+,61%); 306(100).

3-Benzylideneamino-6-(2-furyl)-4-(methylthio)pyran-2-one (19b) yellow crystals (EtOAc-hexane); 61%; m.p. 119-120°C; IR ν_{max} 1705,1692,1625,1562 cm^{-1};^1H NMR ($CDCl_3$) δ 2.56 (s,3H,SCH_3); 6.58 (dd,J=3.0 and 1.5Hz, H-4'furyl); 6.73 (s,1H,H-5); 7.10 (d,J=3Hz,H-3'furyl); 7.31-7.53 (m,4H,arom); 7.81-8.04 (m,2H,arom); 8.52 (s,1H,$C_6H_5\underline{CH}$=N-); (Found: C,65.32; H,4.38; N,4.68. Calc. for $C_{17}H_{13}NO_3S$: C,65.58; H,4.21; N,4.68%); m/z 311 (M^+, 3%); 296(4); 214(22).

3-Benzylideneamino-6-methyl-4-(methylthio)pyran-2-one (19c) yellow crystals (EtOAc-hexane); 81%; m.p. 139-140°C; IR ν_{max} 1703,1690,1622,1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s,3H,CH_3); 2.43 (s,3H,SCH_3); 6.12 (s,1H,H-5); 7.31-7.56 (m,3H,arom); 7.74-8.08 (m,2H,arom); 9.53 (s,1H,$C_6H_5C\underline{H}$=N-); ^{13}C NMR ($CDCl_3$) 14.19 (CH_3); 19.78 (SCH_3); 101.22 (C-5); 122.95 (C-3);127.67,128.68,130.91 (CH,arom) 137.50 (quaternary Ar); 155.40 (C-4);156.16 (C-6);157.93 (C=O); 159.59 ($C\underline{H}$=N-); (Found: C,64.80; H,5.26; N,5.59.Calc.for $C_{14}H_{13}NO_2S$: C, 64.84; H,5.05; N,5.40%); m/z 259 (M^+ 60%); 244(100), 216(22).

Ethyl-4-(2-furoyl)-3-(methylthio)-5-phenylpyrrole-2-carboxylate (25a) colourless crystals (EtOAc-hexane); 73%; m.p.117-118°C; IR ν_{max} 3310,1680, 1668,1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t,J=7Hz,3H,CH_3); 2.35 (s,3H,SCH_3); 4.30 (q,J=7Hz,2H,OCH_2); 6.36 (dd,J=3 and 1.5Hz,1H,H-4'furyl); 6.91 (d, J=3Hz,1H,H-3'furyl); 714-7.52 (m,6H,arom and 5'furyl); 10.01 (brs,1H,NH exchangeable with D_2O); (Found: C,64.02;H,4.96; N,3.83. Calc.for $C_{19}H_{17}NO_4S$: C,64.21; H,4.82; N,3.94%); m/z 356 (M^++1,100%);309(17);280(18).

Ethyl 3-(methylthio)-5-phenyl-4-(2-thienoyl)pyrrole-2-carboxylate (25b) colourless crystals (EtOAc-hexane); 69%; m.p. 128-129°C; IR ν_{max} 3260,1680, 1620,1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t,J=7Hz,3H,CH_3); 2.45 (s, 3H, SCH_3); 4.31 (q,J=7Hz,2H,OCH_2); 7.05-7.49 (m,6H,arom and thienyl); 7.50-7.98 (m,2H,arom); 10.11 (brs,1H,NH, exchangeable with D_2O) (Found: C,61.48; H,4.58; N,3.71; Calc.for $C_{19}H_{17}NO_3S_2$: C,61.43;H,4.60;N,3.77%).

Ethyl 3-(methylthio)-5-phenyl-4-(3-pyridinoyl)pyrrole-2-carboxylate (25c) colourless cyrstals(EtOAc-hexane);79%; m.p.141-142°C;IR ν_{max} 3410,1718,1640 cm^{-1};^1H NMR($CDCl_3$)δ 1.32 (t,J=7Hz,3H,CH_3);2.31(s,3H,SCH_3);4.31(q,J=7Hz,2H, OCH_2);7.21-7.49 (m,6H,arom and H-5'pyridyl); 8.08 (dt,J=8 and 1.5Hz,1H,H-4' pyridyl);8.65(dd,J=6 and 1.5Hz,1H,H-6'pyridyl);8.98(d,J=1.5Hz,H-2'pyridyl); 10.61(brs,1H,NH,exchangeable with D_2O);(Found:C,65.32;H,4.91,N,7.72;Calc. for $C_{20}H_{18}N_2O_3S$:C,65.55;H,4.95;N,7.65%);m/z 366 (M^+,100%); 320(34).

3,3-Bis(methylthio)-2,5-diphenyl-4-nitropyrrolidine (28) colourless crystals (EtOAc-hexane); 64%; m.p. 118°C; IR ν_{max} 3342,1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s,3H,SCH_3); 2.08 (s,3H,SCH_3); 2.39 (brs,1H, exchangeable with D_2O); 4.80 (brs,1H,H-2); 4.69 (d,J=7Hz,1H,H-4); 4.92 (brd,J=7Hz, 1H, H-5); 7.12-7.75 (m,10H,arom); (Found: C,59.81; H,5.48; N,3.63. Calc. for $C_{18}H_{20}N_2O_2S_2$: C, 59.97; H,5.59; N,3.89%); m/z 360 (M^+,4%), 266(37).

Ethyl 3-nitro-2-phenylpyrrole-5-carboxylate (31) colourless crystals (EtOAc-hexane); 56%; m.p. 128-129°C; IR ν_{max} 3250,1700,1580,1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t,J=7Hz,3H,CH_3); 4.12 (q,J=7Hz,2H,OCH_2); 7.08-8.02 (m,6H,H-4 and arom); 10.35 (brs,1H,NH,exchangeable with D_2O); (Found: C, 59.68; H,4.59; N,10.73. Calc.for $C_{13}H_{12}N_2O_4$: C,59.99; H,4.65; N,10.84%).

Acknowledgement: M.P.B. thanks CSIR, New Delhi for S.R.F. Financial assistance under COSSIST programme by UGC, New Delhi is also acknowledged.

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