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1-Aryl-5-methoxypyrrolones as synthons for fused heterocycles

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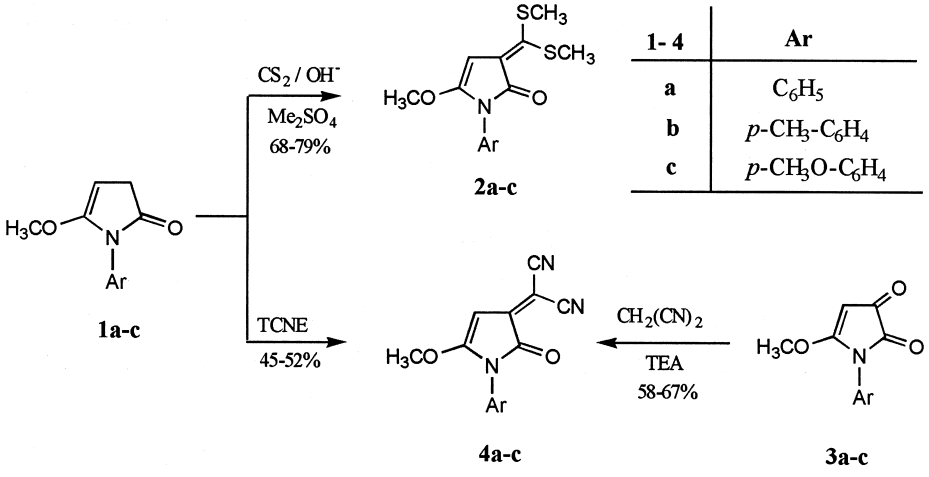
Abstract—3-Di(methylsulfonyl)methylene-pyrrol-2-one and 2-(1-aryl-5-methoxy-2-oxo-2,3-dihydro-1*H*-3-pyrrolylidene)malononitrile were obtained from 1-aryl-5-methoxypyrrolones. Aziridine and hydroxylamine reacted with pyrrol-2-one to afford 2,7-diazaspiro[4.4]-nona-3,6-diene and oxime derivatives, respectively. Pyrrolo[2,3-*c*]isoxazoles or pyrrolo[2,3-*c*]isothiazole were formed in high yield from oximes depending upon the reaction conditions employed for ring closure. Treatment of pyrrolylidene malononitrile with N^1,N^2-di(4-chlorophenyl)acetamidine in ethyl acetate furnished azepine derivatives in 70–75% yield.

1. Introduction

Pyrrolones have received considerable attention[1] as a result of the presence of the lactam ring in some antibiotics, in bile pigments[2] and in the natural alkaloid jatropham, which shows inhibitory activity towards P-388 Lymphocytic leukemia.[3] Pyrrole-2,3-diones have proved to be good synthons for different heterocycles.[4–8] Several attempts to modify the functional groups in pyrrole-2,3-diones have been made: transformation of carbonyl groups into the corresponding C=S moieties using Lawesson's reagent,[9] or to furnish nitrones, aldehydes[10] or C=C double bonds instead of C=O functionalities via the Wittig reaction.[11] Therefore, in order to extend our investigation on such 1-aryl-5-methoxypyrrolones[10] **1a–c** as potential precursors, the synthesis of 3-di(methylsulfanyl)methylene-pyrrol-2-one **2a–c** and 2-(1-aryl-5-methoxy-2-oxo-2,3-dihydro-1*H*-3-pyrrolylidene)malononitrile **4a–c** have been investigated. The reactivity of these compounds were examined towards aziridine, hydroxylamine and N^1,N^2-di(4-cholorophenyl)-acetamidine in order to obtain fused heterocyclic systems in a clean and direct synthesis.

2. Results and discussion

It is well known that active methylenes of heterocyclic compounds react with carbon disulfide in the presence of base.[12–14] Thus, treatment of 1-aryl-5-methoxypyrrol-2-ones[10] **1a–c** with carbon disulfide followed by treatment



Scheme 1.

Keywords: pyrrolones; malononitrile; aziridine; hydroxylamine; N^1,N^2-di(4-chlorophenyl)-acetamidine.

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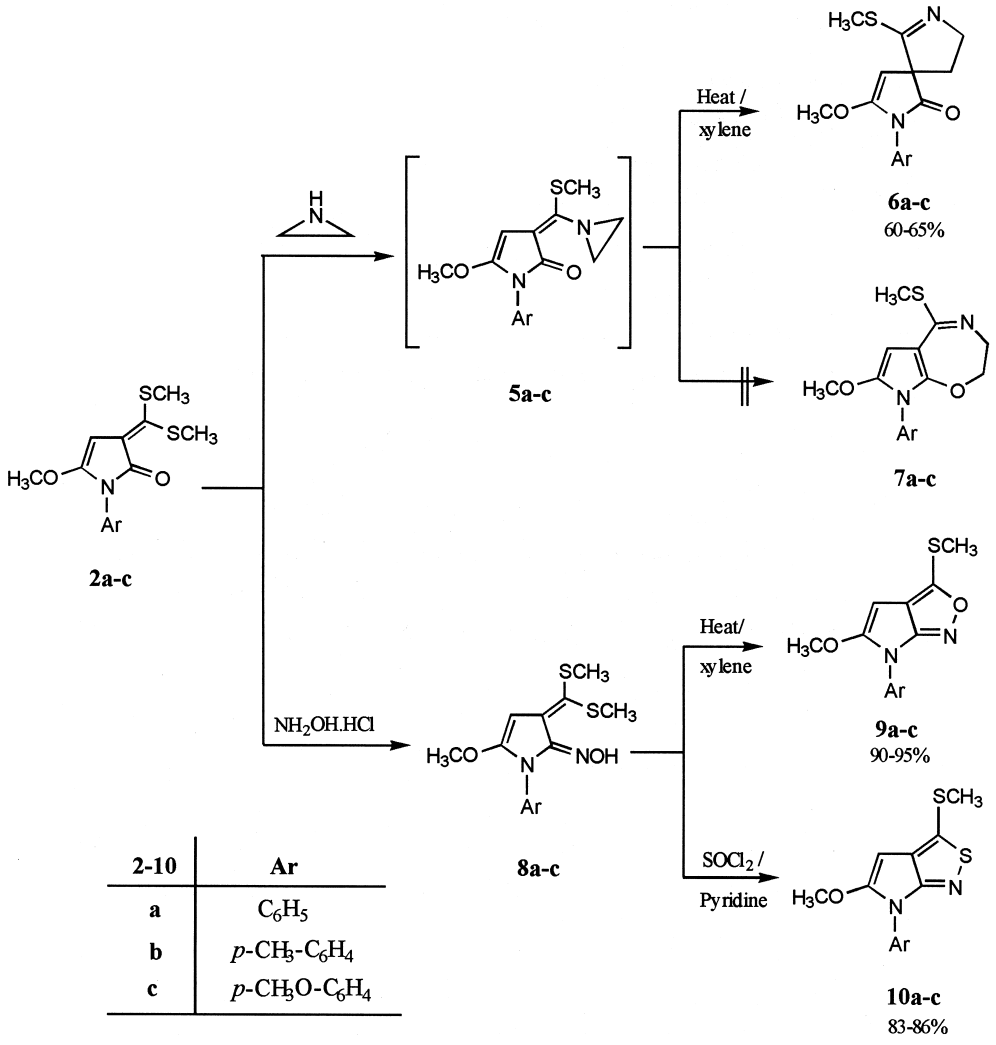
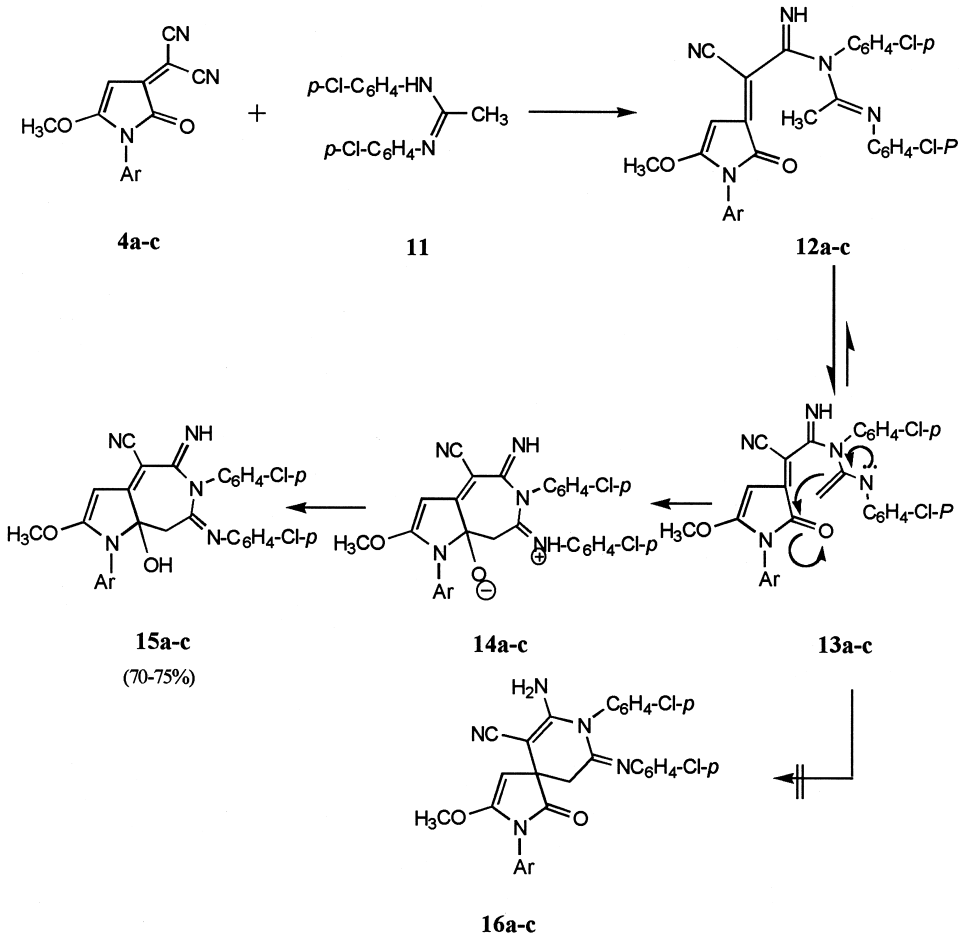


Scheme 2.

with dimethyl sulfate in the presence of sodium hydroxide and dimethyl sulfoxide gave 3-di(methylsulfonyl)methylenepyrrol-2-one **2a–c** as pale yellow needles in 68–79% yield. The structure of the product was confirmed beside elemental analysis by spectroscopic measurements that supported the suggested structure (Section 4). On the other hand, 2-(1-aryl-5-methoxy-2-oxo-2,3-dihydro-1*H*-3-pyrrolylidene)malononitriles **4a–c** were obtained in good yield 58–67% by refluxing equimolar amounts of pyrrole-2,3-diones[8] **3a–c** and malononitrile in acetonitrile with a catalytic amount of triethylamine. The structures of **4a–c** were confirmed by analytical and spectroscopic measurements and by synthesis of the same products from 1-aryl-5-methoxypyrrolones[10] **1a–c** with tetracyanoethylene as shown in Scheme 1. These results are in good agreement with a similar finding with 3-methyl-1-phenyl-2-pyrazoline-4,5-diones.[15,16]

The α-oxoketene dithioacetal functionality has proven to be a versatile three-carbon synthon[17] which is useful in the synthesis of heterocyclic compounds. Thus, thio-aziridine-methylene derivatives **5a–c** were easily obtained from **2a–c** on treatment with aziridine in diethyl ether at 0–5°C. Attempts to isolate **5a–c** in pure form were unsuccessful since they decomposed during purification, but their formation was established by heating in xylene for 2 h which gave either compounds **6** or **7** as pale yellow powders in 60–65% yield (Scheme 2). Structure **7** was excluded based on spectroscopic measurements which characterized the product as 2,7-diazaspiro[4.4]nona-3,6-dien-1-one **6a–c**. The IR spectra of **6a–c** showed characteristic absorption bands between 1685 and 1675 cm^{-1} for C=O, and between 1635 and 1630 cm^{-1} for C=N group. The ^1H NMR spectra showed a singlet between 2.43 and 2.47 ppm for SCH_3, and between 2.35–2.50 and 3.80–3.96 ppm for CH_2 and NCH_2, respectively. Final confirmation of structures **6a–c** were derived from their ^{13}C NMR spectra. The assignment of all ring carbons of **6a** brought a significant confirmation of the 2,7-diazaspiro-[4.4]nona-3,6-diene ring system: 171.85 (CO), 161.47 (C-6), 147.43 (C-3), 90.46 (C-4), 59.87 (spirocarbon C-5), 53.69 (OCH_3), 44.87 (NCH_2) and 34.95 (CH_2). The chemical shift value of the spiro carbon was found in the region usually known for such spiro ring system.[10,18]

On the other hand, treatment of **2a–c** with hydroxylamine in aqueous ethanol heated to reflux gave the corresponding oximes **8a–c** stereoselectively and in excellent yield. The



Scheme 3.

oxime, in general, is formed as a mixture of *syn*/*anti* geometrical isomers, the *syn* or *anti* geometry of oxime is readily determined from ^{13}C NMR spectroscopy since the α-carbons *syn* to the oxime hydroxyl group are shifted upfield relative to the *anti* α-carbons as a result of the γ-effect.[19] The allylic carbon C_γ or C_δ chemical shift remains fairly constant for a series of α-oxoketene dithioacetals and vinylogous thiol esters[20] and serves as a reference point in assignment of chemical shifts. The geometry of **8** is assumed to be *syn*. The geometrical assignment of **8a**–**c** in the absence of mixtures must be viewed as tentative. Structures **8a**–**c** were in agreement with elemental analysis and spectroscopic measurements. In a clean and direct pathway oximes, **8a**–**c** can be converted into either **9a**–**c** or **10a**–**c** by heating in xylene for 2 h or on treatment with thionyl chloride and pyridine as shown in Scheme 2. The results of analytical and spectroscopic measurements clearly revealed **9a**–**c** and **10a**–**c** as pyrrolo[2,3-*c*]isoxazoles and pyrrolo[2,3-*c*]isothiazoles, respectively. The IR spectrum of **9a** showed absorption bands at 3050 and 1640 cm^{-1} for aromatic-H and C=N, respectively, ^1H NMR spectrum showed single at 2.65 ppm for SCH_3, 3.95 for OCH_3, 4.78 for C4-H and 7.05–7.52 for aromatic-H; while ^{13}C NMR spectrum showed signals at 156.19 (C-5), 150.63 (C-6a), 136.16 (C-3), 117.76 (C-3a), 86.16 (C-4), 55.46 (OCH_3), 20.64 (SCH_3) and aromatic carbons at 139.80, 131.12, 122.10, 121.35 in support of the proposed structure. This procedure provided a convenient high yielding route to pyrrolo[2,3-*c*]isoxazole and pyrrolo[2,3-*c*]-isothiazole derivatives.

Finally, N^1,N^2-di(4-chlorophenyl)acetamidine **11** reacted with **4a**–**c** in ethyl acetate at reflux for 8 h to give novel pyrrolo[2,3-*d*]azepines **15a**–**c** in 70–75% yield (Scheme 3). The formation of **15a**–**c** is suggested to proceed via initial nucleophilic attack by N^2 of **11** on one nitrile carbon of **4a**–**c** gives rise to **12a**–**c** which must exist in equilibrium with tautomers **13a**–**c**. These tautomers, being ketene aminals, exhibit nucleophilic character at the terminal methylene carbon atom attacking either carbonyl carbon or C-3 of **4a**–**c** to furnish either pyrrolo[2,3-*d*]azepines **15** or spiro derivatives **16**. However, the shift difference observed in the methylene signals and the number of signals attributable to aryl-carbon atoms linked to hydrogen excluded a spiro structure for compound **16**.[18,21] The IR spectra of **15a**–**c** showed strong absorptions between 3310 and 3315 cm^{-1} for OH and between 3240 and 3235 cm^{-1} for NH with further bands in the range 2190–2195 cm^{-1} for CN and 1630–1640 cm^{-1} for C=N. ^1H NMR spectra AB patterns with δ_A in the range 3.55–3.62 and δ_B between 3.72 and 3.75 with (^2J) values between 16.24 and 16.85 Hz are assigned to the C-8 methylene group adjacent to the chiral carbon atom C-8a. The presence of this methylene group is also evident from the ^{13}C-DEPT-spectra exhibiting negative signals at δ 32.28 and 34.48. The broad-band ^1H-decoupled ^{13}C NMR spectra of **15a**,**b** showed signals at δ 92.30 and

93.85 for C-8a bearing the hydroxy group and one signal each at δ 116.40 and 118.40 for the cyano group.

3. Conclusion

In summary, we have proved that 1-aryl-5-methoxypyrrolones **1a–c** are good synthons for fused heterocyclic nitrogen compounds via converting them into 3-di(methylsulfonyl)methylene-pyrrol-2-ones **2a–c** and 2-(1-aryl-5-methoxy-2-oxo-2,3-dihydro-1*H*-3-pyrrolylidene)malononitriles **4a–c**. Aziridine and hydroxylamine reacted with **2a–c** to afford 2,7-diazaspiro[4.4]nona-3,6-dienes **6a–c** and oxime derivatives **8a–c**, respectively. On the other hand, pyrrolo[2,3-*c*]isoxazoles **9a–c** and pyrrolo[2,3-*c*]-isothiazoles **10a–c** were obtained from oximes **8a–c** depending upon the reaction conditions employed for ring closure. Azepine derivatives **15a–c** were established as the sole products from reaction of **4a–c** with N^1,N^2-di(4-chlorophenyl)acetamidine **11** in ethyl acetate.

4. Experimental

4.1. General

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were measured with a Perkin–Elmer Model 298 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-200 spectrometer with $CDCl_3$ as solvent and TMS as internal reference, chemical shifts are expressed as δ ppm. Analytical data were determined on C,H,N-Elemental Analyzer Carlo Erba 1106. Silica gel 60 (Merck, 230–400 mesh) was used for flash chromatography.

4.1.1. 1-Aryl-3-[di(methylsulfanyl)methylene]-5-methoxy-2,3-dihydro-1*H*-2-pyrrolone (2a–c). To a solution of **1a–c** (0.1 mol) in Me_2SO (100 mL), concentrated NaOH (10 g of NaOH in 30 mL of H_2O) was added under stirring and CS_2 (0.1 mol) was then added slowly dropwise under stirring over a period of 30 min while the temperature of the mixture was maintained at 5–10°C. The reaction mixture was stirred for 1 h and Me_2SO_4 (35 g) was added dropwise with cooling over a period of 20 min. The mixture was stirred for 2 h and poured into ice water. The precipitate was collected by filtration, washed with 5% NaOH and with H_2O, and recrystallized from benzene to give **2a–c** as pale yellow needles in 68–79% yield.

4.1.2. 3-[Di(methylsulfanyl)methylene]-5-methoxy-1-phenyl-2,3-dihydro-1*H*-2-pyrrolone (2a). 19.2 g, 68%; as pale yellow needles mp 127–128°C (Found: C, 57.03; H, 4.98; N, 4.63; S, 21.63. $C_{14}H_{15}NO_2S_2$ requires C, 57.31; H, 5.15; N, 4.77; S, 21.85%); R_f (benzene/acetone, 10:2) 0.37; ν_{max} (KBr) 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.26–7.69 (m, 5H, Ph), 5.24 (s, 1H, C4-H), 3.68 (s, 3H, OCH_3), 2.63 (s, 6H, $2SCH_3$). δ_C (100 MHz, $CDCl_3$, TMS) 160.06, 152.93, 138.77, 136.74, 131.37, 129.39, 126.55, 120.70, 94.72, 51.56, 16.95.

4.1.3. 3-[Di(methylsulfanyl)methylene]-5-methoxy-1-(4-methylphenyl)-2,3-dihydro-1*H*-2-pyrrolone (2b). 22.4 g, 73%; as pale yellow needles mp 142–143°C (Found: C, 58.42; H, 5.43; N, 4.42, S, 20.74. $C_{15}H_{17}NO_2S_2$ requires C, 58.60; H, 5.57; N, 4.56; S, 20.86%); R_f (benzene/acetone, 10:2) 0.42; ν_{max} (KBr) 1685 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.07–7.70 (m, 4H, Ar), 5.28 (s, 1H, C4-H), 3.70 (s, 3H, OCH_3), 2.67 (s, 6H, $2SCH_3$), 2.28 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$, TMS) 160.12, 154.02, 139.65, 137.82, 133.37, 133.15, 128.37, 123.22, 95.45, 52.78, 21.23, 17.35.

4.1.4. 3-[Di(methylsulfanyl)methylene]-5-methoxy-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-2-pyrrolone (2c). 25.5 g, 79%; as pale yellow needles mp 157–158°C (Found: C, 55.54; H, 5.11; N, 4.22; S, 19.71. $C_{15}H_{17}NO_3S_2$ requires C, 55.71; H, 5.30; N, 4.33; S, 19.83%); R_f (benzene/acetone, 10:2) 0.45; ν_{max} (KBr) 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 6.79–7.59 (m, 4H, Ar), 5.28 (s, 1H, C4-H), 3.72 (s, 3H, OCH_3), 3.65 (s, 3H, *p*-OCH_3), 2.60 (s, 6H, $2SCH_3$); δ_C (100 MHz, $CDCl_3$, TMS) 161.45, 154.73, 139.95, 131.85, 116.29, 129.69, 159.09, 120.70, 95.75, 58.30, 52.85, 17.55.

4.1.5. 2-(1-Aryl-5-methoxy-2-oxo-2,3-dihydro-1*H*-3-pyrrolylidene) malononitrile 4a–c. *Method A*. Dione **3a–c** (0.01 mol) was dissolved in dry acetonitrile (30 mL) and malononitile (0.01 mol) was added with two drops of TEA. The reaction mixture was heated at reflux on a water bath for 30 min, whereby a black precipitate was formed. This was filtered washed with cold ethanol and dried. Crystallization from ethanol/petroleum ether (1:1) furnished **4a–c** in 58–67% yield.

Method B. 1-Aryl-5-methoxypyrrolone **1a–c** (0.01 mol) was dissolved in ethyl acetate (30 mL) and teteracyanoethylene (0.01 mol) was added. The reaction mixture was refluxed for 2 h a black precipitate was formed. Treatment as in Method A gave **4a–c** in 45, 49 and 52% yield, respectively.

4.1.6. 2-(5-Methoxy-2-oxo-1-phenyl-2,3-dihydro-1*H*-3-pyrrolylidene) malononitrile 4a. 1.45 g, 58%; as deep red flakes mp 211–212°C (Found: C, 66.71; H, 3.58; N, 16.60. $C_{14}H_9N_3O_2$ requires C, 66.93; H, 3.61; N, 16.72%); R_f (benzene/chloroform, 10:3) 0.29; ν_{max} (KBr) 2200, 1680 and 1620 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.30–7.74 (m, 5H, Ph), 4.73 (s, 1H, C4-H), 3.79 (s, 3H, OCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 164.87, 162.78, 144.21, 136.91, 133.79, 131.56, 120.53, 115.57, 94.20, 83.91, 54.45.

4.1.7. 2-[5-Methoxy-1-(4-methylphenyl)-2-oxo-2,3-dihydro-1*H*-3-pyrrolylidene] malononitrile (4b). 1.64 g, 62%; as deep red flakes mp 227–228°C (Found: C, 67.74; H, 4.02; N, 15.63. $C_{15}H_{11}N_3O_2$ requires C, 67.92; H, 4.18; N, 15.84%); R_f (benzene/chloroform, 10:3) 0.33; ν_{max} (KBr) 2200, 1675 and 1620 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.12–7.73 (m, 4H, Ar), 4.65 (s, 1H, C4-H), 3.71 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$, TMS) 165.96, 163.58, 145.31, 137.45, 133.0, 132.94, 131.02, 114.32, 94.83, 84.35, 54.89, 22.12.

4.1.8. 2-[5-Methoxy-1-(4-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-3-pyrrolylidene] malononitrile (4c). 1.88 g, 67%; as deep red flakes mp 243–244°C (Found: C, 63.90; H, 3.93; N, 14.77. $C_{15}H_{11}N_3O_3$ requires C, 64.05; H, 3.94;

N, 14.94%); R_f (benzene/chloroform, 10:3) 0.36; ν_{max} (KBr) 2200, 1675 and 1620 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.23–7.84 (m, 4H, Ar), 4.79 (s, 1H, C4-H), 3.80 (s, 3H, OCH_3), 3.62 (s, 3H, *p*-OCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 166.07, 164.78, 158.92, 145.84, 134.26, 132.25, 116.47, 116.11, 95.20, 84.94, 57.30, 56.65.

4.1.9. 7-Aryl-8-methoxy-1-(methylsulfanyl)-2,7-diazaspiro[4.4]nona-1,8-dien-6-one (6a–c). A mixture of **2a–c** (1 mmol) and aziridine (5 mmol) in dry diethyl ether (100 mL) was stirred at 0–5°C for 2–4 h. Removal of the solvent under reduced pressure yielded **5a–c**. The isomerization of **5a–c** to **6a–c** was achieved by heating in xylene for 2 h yielded the spiro compounds **6a–c** in 60–65% yield which then recrystallized from ethanol.

4.1.10. 3-Methoxy-6-(methylsulfanyl)-2-phenyl-2,7-diazaspiro[4.4]nona-3,6-dien-1-one (6a). 0.187 g, 65%; as pale yellow powder mp 166–167°C (Found: C, 62.34; H, 5.52; N, 9.63; S, 10.89. $C_{15}H_{16}N_2O_2S$ requires C, 62.48; H, 5.59; N, 9.71; S, 11.12%); R_f (benzene/acetone, 10:2) 0.32; ν_{max} (KBr) 1685 and 1630 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.31–7.72 (m, 5H, Ph), 3.80–3.86 (m, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 4.29 (s, 1H, C4-H), 2.35–2.50 (m, 2H, CH_2), 2.45 (s, 3H, SCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 171.85, 161.47, 147.43, 134.68, 131.89, 127.58, 120.52, 90.46, 59.87, 53.69, 44.87, 34.95, 13.62.

4.1.11. 3-Methoxy-2-(4-methylphenyl)-6-(methylsulfanyl)-2,7-diazaspiro[4.4]nona-3,6-dien-1-one (6b). 0.181 g, 60%; as pale yellow powder mp 142–143°C (Found: C, 63.32; H, 5.87; N, 9.11; S, 10.32. $C_{16}H_{18}N_2O_2S$ requires C, 63.55; H, 6.00; N, 9.26; S, 10.60%); R_f (benzene/acetone, 10:2) 0.35; ν_{max} (KBr) 1675 and 1630 cm^{-1}. δ_H (200 MHz, $CDCl_3$, TMS) 7.23–7.58 (m, 4H, Ar), 3.84–3.90 (m, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 4.31 (s, 1H, C4-H), 2.37–2.48 (m, 2H, CH_2), 2.43 (s, 3H, SCH_3), 2.28 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$, TMS) 172.19, 162.42, 148.55, 135.72, 132.99, 131.86, 128.91, 91.88, 60.69, 55.73, 45.67, 35.59, 21.01, 13.58.

4.1.12. 3-Methoxy-2-(4-methoxyphenyl)-6-(methylsulfanyl)-2,7-diazaspiro[4.4]nona-3,6-dien-1-one (6c). 0.2 g, 63%; as pale yellow powder mp 186–187°C (Found: C, 60.12; H, 5.57; N, 8.71; S, 9.86. $C_{16}H_{18}N_2O_3S$ requires C, 60.36; H, 5.70; N, 8.80; S, 10.07%); R_f (benzene/acetone, 10:2) 0.41; ν_{max} (KBr) 1675 and 1635 cm^{-1}. δ_H (200 MHz, $CDCl_3$, TMS) 7.08–7.45 (m, 4H, Ar), 3.92–3.96 (m, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, *p*-OCH_3), 4.29 (s, 1H, C4-H), 2.40–2.47 (m, 2H, CH_2), 2.47 (s, 3H, SCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 173.25, 163.32, 159.75, 149.54, 131.54, 128.91, 116.45, 92.43, 59.47, 56.37, 57.30, 45.88, 36.31, 14.24.

4.1.13. 1-Aryl-3-[di(methylsulfanyl)methylene]-5-methoxy-2,3-dihydro-1*H*-2-pyrrolone oxime (8a–c). An aqueous ethanol hydroxylamine solution was generated from hydroxylamine hydrocloride (3.46 g, 5 mmol), KOH (2.8 g, 5 mmol) in water (10 mL), and 95% ethanol (50 mL). The clear solution was neutral to litmus paper. To this hydroxylamine solution was added 1 mmol of the appropriate ketene dithioacetal. The solution was heated to reflux and stirred for 24 h. The solution was cooled to room temperature, ethanol was removed in vacuo, and the concentrated reaction mixture was then poured into a separatory funnel containing ice cold water (100 mL) and methylene chloride (100 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo gave **8a–c** in 85–93% yields.

4.1.14. 3-[Di(methylsulfanyl)methylene]-5-methoxy-1-phenyl-2,3-dihydro-1*H*-2-pyrrolone oxime (8a). 0.261 g, 85%; as colorless needles mp 186–187°C (Found: C, 54.28; H, 5.02; N, 8.89; S, 20.61. $C_{14}H_{16}N_2O_2S_2$ requires C, 54.52; H, 5.23; N, 9.08; S, 20.79%); R_f (petroleum ether/ether, 1:1) 0.22; ν_{max} (KBr) 3500–3300 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 9.98 (s, 1H, OH), 7.18–7.57 (m, 5H, Ph), 5.76 (s, 1H, C4-H), 3.52 (s, 3H, OCH_3), 2.55 (s, 6H, $2SCH_3$). δ_C (100 MHz, $CDCl_3$, TMS) 156.52, 153.75, 147.91, 140.14, 137.85, 131.12, 123.84, 122.10, 87.96, 52.87, 17.64.

4.1.15. 3-[Di(methylsulfanyl)methylene]-5-methoxy-1-(4-methylphenyl)-2,3-dihydro-1*H*-2-pyrroloneoxime (8b). 0.289 g, 90%; as colorless needles mp 186–187°C (Found: C, 55.63; H, 5.42; N, 8.52; S, 19.67. $C_{15}H_{18}N_2O_2S_2$ requires C, 55.88; H, 5.63; N, 8.69; S, 19.89%); R_f (petroleum ether/ether, 1:1) 0.24; ν_{max} (KBr) 3500–3300 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 10.05 (s, 1H, OH), 7.22–7.78 (m, 4H, Ar), 5.64 (s, 1H, C4-H), 3.48 (s, 3H, OCH_3), 2.50 (s, 6H, $2SCH_3$), 2.28 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$, TMS) 157.60, 154.21, 148.12, 140.35, 138.90, 135.65, 130.58, 123.66, 88.15, 53.13, 21.01, 17.85.

4.1.16. 3-[Di(methylsulfanyl)methylene]-5-methoxy-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-2-pyrrolone oxime (8c). 0.314 g, 93%; as colorless needles mp 162–163°C (Found: C, 53.00; H, 5.09; N, 8.00; S, 18.74. $C_{15}H_{18}N_2O_3S_2$ requires C, 53.23; H, 5.36; N, 8.28; S, 18.95%); R_f (petroleum ether/ether 1:1) 0.26; ν_{max} (KBr) 3500–3300 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 9.95 (s, 1H, OH), 7.03–7.68 (m, 4H, Ar), 5.76 (s, 1H, C4-H), 3.69 (s, 3H, *p*-OCH_3), 2.55 (s, 6H, SCH_3), 2.52 (s, 3H, OCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 158.90, 158.49, 154.53, 149.21, 142.25, 133.31, 124.70, 116.03, 88.45, 57.30, 53.25, 17.85.

4.1.17. 6-Aryl-5-methoxy-3-(methylsulfanyl)-6*H*-pyrrolo-[2,3-*c*]isoxazole (9a–c). Heating of oxime **8a–c** (1 mmol) in dry xylene (30 mL) to reflux and stirred for 2–3 h. The progress of reaction was monitored by TLC and worked up when starting material had completely disappeared. Removal of the solvent in vacuo afforded crude isoxazoles **9a–c** as a pale yellow powder in 90–95% yields. The crude products were relatively clean. Analytical pure samples were obtained by flash chromatography using toluene/acetone (10:1).

4.1.18. 5-Methoxy-3-(methylsulfanyl)-6-phenyl-6*H*-pyrrolo[2,3-*c*]isoxazole (9a). 0.234 g, 90%; as colorless needles mp 198–199°C (Found: C, 59.69; H, 4.42; N, 10.46; S, 12.11. $C_{13}H_{12}N_2O_2S$ requires C, 59.98; H, 4.65; N, 10.76; S, 12.32%); R_f (petroleum ether/ether, 1:1) 0.27; ν_{max} (KBr) 3050, 1640 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.05–7.52 (m, 5H, Ph), 4.78 (s, 1H, C4-H), 3.95 (s, 3H, OCH_3), 2.65 (s, 3H, SCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 156.19, 150.63, 139.80, 136.16, 131.12, 122.10, 121.35, 117.76, 86.16, 55.46, 20.64.

4.1.19. 5-Methoxy-6-(4-methylphenyl)-3-(methylsulfanyl)-6*H*-pyrrolo[2,3-*c*]isoxazole (9b). 0.254 g,93%; as colorless needles mp 212–213°C (Found: C, 60.98; H, 4.97; N, 10.01; S, 11.49. $C_{14}H_{14}N_2O_2S$ requires C, 61.29; 5.14; N, 10.21; S, 11.69%); R_f (petroleum ether/ether, 1:1) 0.31; ν_{max} (KBr) 3050, 1635 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.35–7.75 (m, 4H, Ar), 4.86 (s, 1H, C4-H), 3.95 (s, 3H, OCH_3), 2.62 (s, 3H, SCH_3), 2.38 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$, TMS) 159.10, 152.45, 140.88, 138.32, 135.65, 130.58, 120.80, 119.45, 88.36, 56.15, 21.75, 21.01.

4.1.20. 5-Methoxy-6-(4-methoxyphenyl)-3-(methylsulfanyl)-6*H*-pyrrolo[2,3-*c*]isoxazole (9c). 0.275 g, 95%; as colorless needles mp 237–238°C (Found: C, 57.84; H, 4.63; N, 9.47; S, 10.85. $C_{14}H_{14}N_2O_3S$ requires C, 57.92; H, 4.86; N, 9.65; S, 11.04%); R_f (petroleum ether/ether, 1:1) 0.31; ν_{max} (KBr) 3050, 1635 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.12–7.51 (m, 4H, Ar), 4.86 (s, 1H, C4-H), 3.84 (s, 3H, OCH_3), 3.77 (s, 3H, *p*-OCH_3), 2.73 (s, 3H, SCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 160.49, 158.49, 151.53, 137.46, 133.31, 124.70, 117.76, 116.03, 88.45, 57.30, 53.25, 20.64.

4.1.21. 6-Aryl-5-methoxy-3-(methylsulfanyl)-6*H*-pyrrolo-[2,3-*c*]isothiazole (10a–c). Dry methylene chloride (25 mL) was cooled to 0–5°C. Thionyl chloride (1.25 mmol) was added dropwise and the solution was stirred for 10 min. Pyridine (1.25 mmol) was added to the thionyl chloride solution, which was stirred for an additional 15 min at 0°C. The oxime (1 mmol) in dry methylene chloride was added dropwise to the solution over a period of 10 min. The solution was stirred for 1 h at 0°C, warmed to room temperature, and then stirred for another 8–10 h. When TLC showed complete disappearance of oxime, the reaction mixture was diluted with 60 mL of diethyl ether and washed with 10% HCl (3×30 mL), saturated sodium bicarbonate (2×30 mL) and distilled water. The organic phase was dried over anhydrous $MgSO_4$. Filtration and removal of solvent in vacuo afforded crude isothiazoles **10a–c** in high yields (83–86%). Analytically pure samples were obtained by flash chromatography using benzene/acetone (10:2).

4.1.22. 5-Methoxy-3-(methylsulfanyl)-6-phenyl-6*H*-pyrrolo[2,3-*c*]isothiazole (10a). 0.229 g, 83%; as colorless needles mp 256–257°C (Found: C, 56.43; H, 4.38; N, 9.89; S, 22.95. $C_{13}H_{12}N_2OS_2$ requires C, 56.50; H, 4.38; N, 10.14; S, 23.20%); R_f (petroleum ether/ether, 1:1) 0.33; ν_{max} (KBr) 3045, 1635 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.15–7.58 (m, 5H, Ph); 5.11 (s, 1H, C4-H), 3.90 (s, 3H, OCH_3), 2.59 (s, 3H, SCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 148.44, 144.12, 138.90, 131.52, 129.07, 123.89, 122.10, 119.41, 86.88, 52.79, 19.52.

4.1.23. 5-Methoxy-6-(4-methylphenyl)-3-(methylsulfanyl)-6*H*-pyrrolo[2,3-*c*]isothiazole (10b). 0.249 g, 86%; as colorless needles mp 225–226°C (Found: C, 57.72; H, 4.80; N, 9.45; S, 21.87. $C_{14}H_{14}N_2OS_2$ requires C, 57.90; H, 4.86; N, 9.65; S, 22.08%); R_f (petroleum ether/ether, 1:1) 0.38; ν_{max} (KBr) 3050, 1640 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.21–7.82 (m, 4H, Ar), 5.19 (s, 1H, C4-H), 3.82 (s, 3H, OCH_3), 2.55 (s, 3H, SCH_3), 2.45 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$, TMS) 149.52, 146.32, 139.98, 135.65, 130.88, 129.87, 121.12, 123.71, 88.09, 53.43, 21.31, 20.23.

4.1.24. 5-Methoxy-6-(4-methoxyphenyl)-3-(methylsulfanyl)-6*H*-pyrrolo[2,3-*c*]isothiazole (10c). 0.260 g, 85%; as colorless needles mp 247–248°C (Found: C, 54.72; H, 4.58; N, 9.00; S, 20.77. $C_{14}H_{14}N_2O_2S_2$ requires C, 54.88; H, 4.61; N, 9.14; S, 20.93%); R_f (petroleum ether/ether, 1:1) 0.42; ν_{max} (KBr) 3050, 1645 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.12–7.65 (m, 4H, Ar), 5.23 (s, 1H, C4-H), 3.90 (s, 3H, OCH_3), 3.66 (s, 3H, *p*-OCH_3), 2.63 (s, 3H, SCH_3). δ_C (100 MHz, $CDCl_3$, TMS) 157.49, 146.81, 149.83, 136.23, 135.10, 123.12, 121.72, 116.44, 89.41, 58.89, 52.78, 20.63.

4.2. Reaction of N^1,N^2-di(4-chlorophenyl)acetamidine 11 with 4a–c to give 15a–c

To a stirred solution of the amidine **11** (1 mmol) in ethyl acetate (5 mL) a solution of **4a–c** (1 mmol) in ethyl acetate (20 mL) was added dropwise at room temperature. Heating the reaction mixture at reflux for 8 h, the reaction was monitored by TLC until all starting materials were consumed, ethyl acetate was removed in vacuo and the concentrated residue were subjected to flash chromatography using benzene/ethanol (10:3) to give **15a–c** in 70–75% yield.

4.2.1. 6-(4-Chlorophenyl)-7-[(4-chlorophenyl)imino]-8a-hydroxy-5-imino-2-methoxy-1-phenyl-1,5,6,7,8,8a-hexahydropyrrolo[2,3-*d*]azepin-4-yl-cyanide 15a. 0.386 g, 73%; as colorless powder mp 267–268°C (Found: C, 63.25; H, 3.87; Cl, 13.18; N, 13.00. $C_{28}H_{21}Cl_2N_5O_2$ requires C, 63.41; H, 3.99; Cl, 13.37; N, 13.20%); R_f (benzene/ethanol, 10:3) 0.35; ν_{max} (KBr) 3310–3240, 2190 and 1630 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.81 (broad s, 2H, NH and OH), 6.95–7.75 (m, 13H, Ph and 2Ar), 4. 65 (s, 1H, C4-H), 3.64 (s, 3H, OCH_3), 3.62(d, 1H, J=13.85 Hz, CH_AH_B), 3.72 (d, 1H, J=13.85 Hz, CH_AH_B); δ_C (100 MHz, $CDCl_3$, TMS) 163.34, 154.90, 149.62, 149.0, 137.63, 133.41, 127.55, 121.39, 116.40, 92.30, 85.77, 84.42, 55.67, 34.48.

4.2.2. 6-(4-Chlorophenyl)-7-[(4-chlorophenyl)imino]-8a-hydroxy-5-imino-2-methoxy-1-(4-methylphenyl)-1,5,6,7,8,8a-hexahydropyrrolo[2,3-*d*]azepin-4-yl-cyanide (15b). 0.408 g, 75%; as colorless powder mp 254–255°C (Found: C, 63.76; H, 4.21; Cl, 12.87; N, 12.64. $C_{29}H_{23}Cl_2N_5O_2$ requires C, 63.98; H, 4.26; Cl, 13.02; N, 12.86%); R_f (benzene/ethanol, 10:3) 0.38; ν_{max} (KBr) 3320–3235, 2190 and 1635 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.79 (broad s, 2H, NH and OH), 6.85–7.72 (m, 12H, 3Ar), 4.72 (s, 1H, C4-H), 3.70 (s, 3H, OCH_3), 3.59 (d, 1H, J= 13.85 Hz, CH_AH_B), 3.74 (d, 1H, J=13.85 Hz, CH_AH_B), 2.24 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$, TMS) 164.84, 155.62, 152.23, 150.15, 140.76, 131.68, 130.42, 126.08, 118.40, 93.85, 88.02, 86.81, 57.21, 32.28, 19.20.

4.2.3. 6-(4-Chlorophenyl)-7-[(4-chlorophenyl)imino]-8a-hydroxy-5-imino-2-methoxy-1-(4-methoxyphenyl)-1,5,6,7,8,8a-hexahydropyrrolo[2,3-*d*]azepin-4-yl-cyanide (15c). 0.392 g, 70%; as colorless powder mp 287–288°C (Found: C, 61.89; H, 4.00; Cl, 12.44; N, 12.33. $C_{29}H_{23}Cl_2N_5O_3$ requires C, 62.15; 4.14; Cl, 12.65; N, 12.50%); R_f (benzene/ethanol, 10:3) 0.41; ν_{max} (KBr) 3315–3235, 2195 and

1640 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.83 (broad s, 2H, NH and OH), 6.90–7.78 (m, 12H, 3Ar), 4.74 (s, 1H, C4-H), 3.74 (s, 3H, OCH_3), 3.55 (d, 1H, J=13.85 Hz, CH_AH_B), 3.70 (d, 1H, J=13.85 Hz, CH_AH_B), 3.63 (s, 3H, OCH_3).

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