Synthesis and Antimicrobial Activity of Novel Spirocompounds with Pyrazolone and Pyrazolthione Moiety

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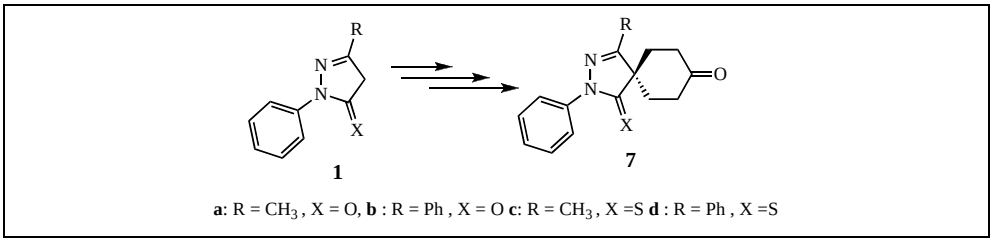

The paper focuses on the utility of 2-pyrazoline-5-ones and 2-pyrazoline-5-thiones as active Michael donors for the synthesis of novel spirocyclohexanone derivatives. The sulphur containing compounds when screened for antimicrobial activity showed promising inhibition of *S.Typhi, S Aures* and *E Coli* bacteria.

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INTRODUCTION

Michael addition is one of the oldest well-known reactions, which involves the formation of a carbon-carbon bond and has found extensive applications in organic synthesis. The reaction, usually carried out in basic conditions, deals with the addition of compounds containing active methylene group (donors) to activated π systems (acceptors). More recently, the use of organometallics [1] and ionic liquids [2] has gained considerable importance to carry out this reaction, since it leads to products with high enantioselectivity.

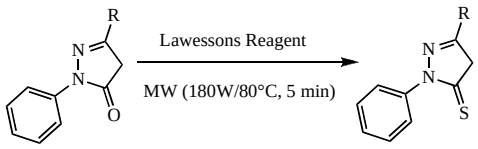
Spiro compounds are well known to possess varied pharmacological activities and hence their synthesis has always been a challenge and of attraction to organic chemists. Over the past decade we have reported some exciting synthetic strategies for the synthesis of this exclusive class of compounds [3].

Recently, we have been actively exploring the Michael addition reaction on heterocyclic and carbocyclic systems bearing active methine [4] and methylene [5] groups. We have successfully employed the Michael adducts as key intermediates for synthesis of some interesting spirocompounds. Thus, continuing our work along this line, we herein wish to report the efficacy of pyrazoline-5-thiones and pyrazoline-5-ones as Michael donors for synthesis of biologically active novel spirocyclohexanone derivatives.

RESULTS AND DISCUSSION

2-Pyrazoline-5-ones **1a,b** and 2-pyrazoline-5-thiones **1c,d** are active Michael donors because of the methylene group at position 4. Although, 2-pyrazoline-5-one **1a,b** can be easily synthesized [6], the synthesis of 2-pyrazoline-5-thiones **1c,d** from 2-pyrazoline-5-ones **1a,b** according to literature methods using P_2S_5 or Lawessons reagent resulted in poor yields [7]. The application of microwave irradiation was used as an alternative for this reaction. As anticipated, the microwave-assisted reaction of 2-pyrazoline-5-one **1a** with Lawessons reagent gave 2-pyrazoline-5-thione **1c** in 70% yield (Scheme 1). The reaction was clean without any major side products. Similarly 1,3-diphenyl-2- pyrazoline-5-thione **1d** [8] was obtained from 1,3-diphenyl – 2 - pyrazoline-5-one **1b** in 75% yield.

Scheme 1



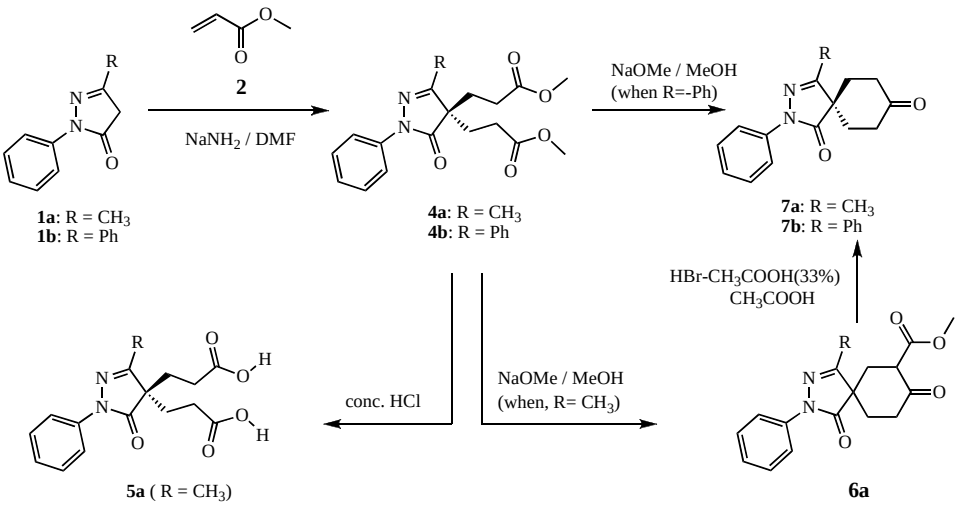
1a: R = CH_3 **1c**: R = CH_3
1b: R = Ph **1d**: R = Ph

The Michael addition of **1a,b** with acceptors like methyl acrylate **2** and acrylonitrile **3** proceeded smoothly leading to diadducts. Thus diadducts **4a,b** were obtained by interaction of 2-pyrazoline-5-ones **1a**,**b** respectively with two equivalents of methyl acrylate **2** and two equivalents of sodium amide in DMF at ambient temperature. If equimolar ratios of 2-pyrazoline-5-ones **1a,b** and Michael acceptor **2** were used the diadducts **4a,b** were isolated together with unreacted starting material. The existence of the carbonyl peak due to 2-pyrazoline-5-one in ^{13}C-NMR spectra of both the diadducts **4a,b** rules out the possibility of the O-alkylated diadducts and

suggests a regioselective Michael addition [8,9]. Compound **4a** on hydrolysis afforded the dicarboxylic acid **5a** [10].

Studies of the Michael addition on **1** was further extended to acrylonitrile **3**. In case of 1-phenyl-3-methyl-2-pyrazoline-5-one **1a** with two moles of

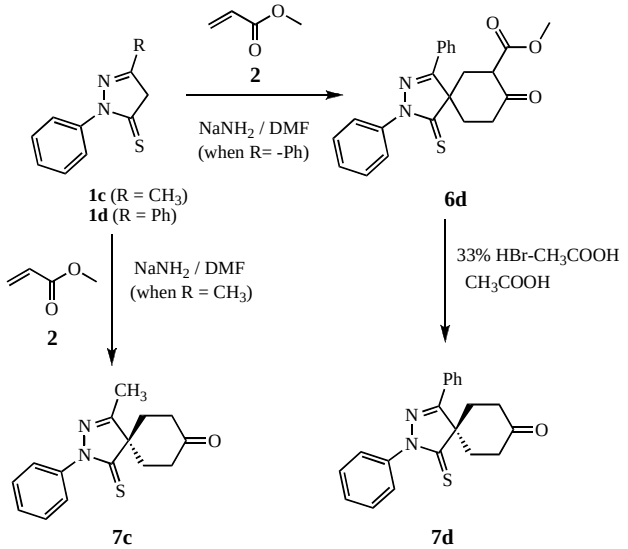
Scheme 2



Dieckmann condensation of **4a** in presence of alkoxide afforded the spirocyclohexyl-β-ketoester **6a**, which on hydrolysis and decarboxylation furnished the spirocyclohexanone derivative **7a**. Compound **4b** on Dieckmann condensation directly furnished **7b** (Scheme 2).

However, under identical conditions used for **1a,b**, the Michael addition of 2-pyrazoline-5-thiones **1c,d** and methyl acrylate **2** led directly to the formation of the spirocyclohexanone derivatives. Thus, **6d** obtained from **1d** was hydrolysed and decarboxylated to give **7d**. Interestingly, **1c** directly afforded **7c** after workup (Scheme 3). Diadducts were not isolated in these reactions.

Scheme 3



acrylonitrile under identical reaction conditions used for **1a-d** gave a mixture of mono adduct **8a** [11a] and spiroderivative **10a**.

These two compounds were separated on the basis of their solubility difference in benzene. The formation of **10a** could be envisaged as an *in situ* Thorpe-Ziegler cyclization of the diadduct **9a** [10]. However, **1b-d** under similar reaction conditions furnished only the Thorpe-Ziegler cyclized product, **10b-d** [12,Note]. The cyclohexanone derivatives **7a-d** was obtained by the hydrolysis and decarboxylation of the respective spiro compounds **10a-d**. Therefore, an alternative, unambiguous and independent method for the synthesis of compounds **7a-d** has been established (Scheme 4).

The spirocyclohexanone derivatives containing the sulfur atoms were screened for their antimicrobial activity. The results showed inhibition of *S. Typhi, S. Aureus* and *E. Coli* bacteria.

The details are outlined in Table 1. In case of *E. coli*, the data has been compared with standard drugs like silver sulphadiazine and gentamicin while the activity of 2-pyrazoline-5-thione derivatives seems to be very promising.

In conclusion, we have described a mild, efficient and convenient method for the synthesis of 1-phenyl-3-substituted-2-pyrazoline-5-thiones from the corresponding 2-pyrazoline-5-ones. We have been successful in utilizing the pyrazoline-5-ones and pyrazoline-5-thiones as Michael donors for the synthesis of novel and rather inaccessible spirocompounds with potential biological activity. Compounds **4, 6, 7, 10, 11** reported are new and have been characterized by spectral and analytical data.

Scheme 4

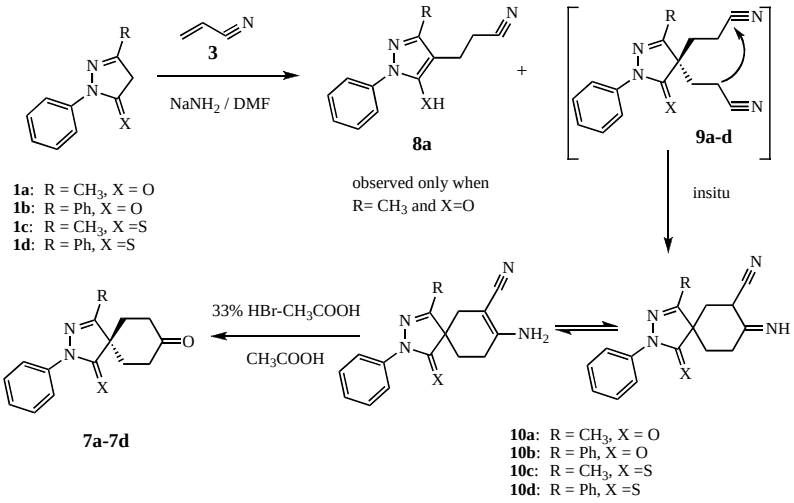


Table 1: Antibacterial activity studies by drug diffusion method [5d]

Compound	Concentration µg/ml	diameter of zone of inhibitory (mm)		
		E. coli	*S. typhosa*	*S. aureus*
7c	40	9	8	7
7c	60	10	9	9
7c	100	14	12	11
7d	40	10	9	7
7d	60	12	11	7
7d	100	13	13	10
Silver sulphadiazine		14		
Gentamicin		12		

EXPERIMENTAL

General Procedure for the Thiation of 2-pyrazoline-5-ones (**1a,b**) with Lawessons reagent.

The appropriate 2-pyrazoline-5-one **1a,b** (10 mmoles) and Lawesson's reagent (15 mmoles) were mixed together and subjected to microwave irradiation for 5 min. The sticky mass thus obtained was treated with hot 25% aqueous alkali (50 ml) and filtered. The filtrate was treated with cold 20% dilute HCl (35 ml) to regenerate the product. The sticky mass was triturated and crystallized from methanol to afford pure 2-pyrazoline-5-thiones **1c,d** in 70% and 75% yield respectively.

1-Phenyl-3-methyl-2-pyrazoline-5-thione (1c). This compound was obtained as colorless needles, m.p : 107° (lit [7], 109°C).

1,3-Diphenyl-4*H*-pyrazol-5-thione (1d). This compound was obtained as light yellow crystals, m.p: 82°C yield: 1.89 gm (75%). ^{1}HNMR ($CDCl_3$, 300MHz): δ 2.56 (s, 2H, CH_2), 7.35-8.07 (m, 10H, phenyl protons). ^{13}CNMR ($CDCl_3$, 300MHz): δ 29.85, 125.37, 125.63, 125.72, 128.28, 128.66, 128.72, 132.18, 134.50, 138.85, 151.81 ppm.; EI ms: m/z 252(100), 224(20),148(25), 102(20), 77(40). *Anal*. Calcd. for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.36; H, 4.76; N, 11.11.

General Procedure for the Reaction of 2-Pyrazoline-5-ones (1a,b) and 2-Pyrazoline-5-Thiones (1c,d) with Methyl Acrylate (2). To a stirred solution of sodium amide (20 mmoles) in dry DMF (25 mL) in nitrogen atmosphere, was added the appropriate 2-pyrazoline-5-one or 2-pyrazoline-5-thione, **1a-d** (10 mmoles) at 10–15°C. After the addition was complete methyl acrylate (1.72 g, 20 mmoles) was added dropwise over a period of 5 minutes. Stirring was continued for 7 hours and then the reaction mixture was poured into crushed ice (30 g) and acidified with 20% aqueous hydrochloric acid to pH 3. The resulting mixture was triturated with ice-water and extracted with ethyl acetate (2 x 25 ml). The combined organic layers were washed with water (3 x 40 ml), brine and dried (Na_2SO_4). Removal of solvent under vacuum afforded the crude product, which was crystallised using appropriate solvent to give **4a,b**, **6d** and **7c** in 92%, 82%, 53% and 42% respectively.

1–Phenyl–3–methyl-4,4–di[carbmethoxyethyl]-2-pyrazoline-5-one (4a). This compound was obtained as brown oil (purified by column chromatography, 5% ethyl acetate: 95% hexane) ir (CCl_4): 2976, 2864, 1739, 1712, 1597 cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ 2.06 - 2.28 (m, 11H, 4x-CH_2 and -CH_3), 3.63 (s, 6H, 2x-OCH_3), 7.19-7.89 (m, 5H, phenyl protons). ^{13}CNMR ($CDCl_3$, 500 MHz): δ 13.6, 28.6 & 29.3 (4x-CH_2), 51.7 (2x-OCH_3), 57.3, 118.8, 125.3, 128.8, 137.4, 161.7, 172.3, 174.0 & 175.3. *Anal*. Calcd. for $C_{18}H_{22}N_2O_5$ (346): C, 62.42; H 6.40; N, 8.09, Found: C, 62.39; H, 6.42; N, 8.04.

1,3-Diphenyl-4,4-di[carbmethoxyethyl]-2-pyrazoline-5-one (4b). This compound was obtained as light orange crystals (methanol), m.p 180°, ir ($CHCl_3$): 2975, 2858, 1740, 1711, 1597 cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ 2.05-2.49 (m, 8H, 4x-CH_2), 3.54 (s, 6H, 2x-OCH_3), 7.18-8.04 (m, 10H, phenyl protons).

^{13}CNMR ($CDCl_3$, 500 MHz): δ 23.2 (2x-CH_2), 29.0 (2x-CH_2-CO), 51.9 (2x-OCH_3), 59.6, 118.7, 125.0, 127.9, 128.3 128.6, 129.1, 131.1, 136.1, 156.7, 170.9, 171.3, 171.8.

Anal. Calcd. for $C_{23}H_{24}N_4O_5$ (408): C, 67.63; H, 5.92; N, 6.86. Found; C, 67.62; H, 5.89; N, 6.84.

9-Carbmethoxy-2,3-diaza–2,4-diphenyl-8-oxo-1-thio-spiro-[5.4]-dec-3-ene (6d). This compound was obtained was brown oil (purified by column chromatography, 5% ethyl acetate: 95% hexane), ir ($CHCl_3$) 3065, 2929, 1741, 1712 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.55 (m, 2H, -CH_2), 2.94 (m, 4H, 2x-CH_2), 3.61(s, 3H, O-CH_3), 3.75 (t, 1H, -CH) and 7.31- 7.87 (m, 10H, phenyl protons). ^{13}C NMR ($CDCl_3$, 300 MHz): 30.44, 33.96, 42.76, 51.86, 109.17, 110.67, 120.37, 125.64, 125.76, 128.22, 128.66, 128.77, 132.21, 134.54, 138.88, 151.84, 171.66, 210.98. EI ms: m/z: 392(90), 353(60), 315(25), 284(32), 193(55), 154(100), 137(41), 110(40), 77(15).

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$ (392): C, 60.74%; H, 5.10%; N, 8.85%, Found: C, 60.76%; H, 5.18%; N, 8.82%.

2,3-Diaza-4-methyl-8-oxo-2-phenyl-1-thio-spiro[5.4]dec-3-ene (7c). This compound was obtained as offwhite crystals (petroleum ether:chloroform (90:10) mixture), m.p 152°C, ir ($CHCl_3$): 2927, 1714, 1598 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.10 (m, 4H, 2 x -CH_2), 2.27 (m, 4H, 2 x CH_2-C=O), 2.31 (s, 3H, CH_3) and 7.24-7.47 (m, 5H, phenyl protons). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 13.19, 29.92, 32.57, 109.75, 125.60, 127.35, 128.48, 138.92, 149.01, 151.93, 210.04 ppm. EI ms: m/z: 272(8), 256(10), 240(12), 207(40), 180(100), 164(25), 135(13), 117(20), 108(9), 77(28). *Anal*. Calcd. for $C_{15}H_{16}N_2OS$ (272): C, 66.18; H, 5.88; N,10.32. Found: C, 66.15; H, 5.87; N,10.26.

9-Carbmethoxy-2,3-diaza-4-methyl-2-phenyl-1,8-dioxo-spiro[5.4]dec-3-ene (6a). To freshly prepared sodium methoxide solution [(125 mg, 5 mmoles) of sodium in dry methanol (30 ml)] was added **4a** (1.73 g, 5 mmoles) at room temperature and refluxed for 5 hrs. The reaction mixture was then cooled and poured onto crushed ice containing a few drops of conc. HCl. A brown solid separated which became a sticky mass at room temperature. This oily residue was purified by column–chromatography (10% ethyl acetate: 90% hexane) to yield 1.27 g (81%) of **6a** as a semi-solid. ^{1}HNMR ($CDCl_3$, 500 MHz): δ 2.04-2.33 (m, 9H, 3x-CH_2 & 1x-CH_3), 3.62 (s, 3H,-OCH_3), 4.60 (br,1H,-CH-CO tautomeric), 7.19-7.87 (m, 5H, phenyl protons). *Anal*. Calcd. for $C_{10}H_{14}N_2O_4$(314): C, 64.96; H, 5.77; N, 8.91. Found: C, 64.94; H, 5.74; N, 8.88.

2,3-Diaza-2,4-diphenyl-1,8-dioxospiro[5.4]dec-3-ene (7b) from 4b. Compound **4b** (2.04 g, 5 mmoles), was added to a solution of freshly prepared sodium methoxide solution, [(125 mg, 5 mmoles) of sodium in dry methanol (30 ml)] at room temperature and refluxed for 5 hrs. The reaction mixture was then cooled, poured onto crushed ice (30 g) and acidified with cold 10% dil HCl (pH 2). The product which separated was collected by filtration and crystallized from 50% ethanol as pale yellow crystals, yield, 1.20 g (76%), m.p 105°C, ir ($CHCl_3$): 3011, 1709, 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.09-2.85 & 3.85 (m, 8H, 4x-CH_2), 7.05 – 7.98 (m, 10H, phenyl protons). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 28.78, 31.17, 57.57, 118.75, 126.52, 128.14, 128.55, 129.33, 129.82, 130.76, 137.23, 158.28, 173.28, 212.58 ppm. *Anal*. Calcd. for $C_{20}H_{18}N_2O_2$ (318): C, 75.45; H, 5.70; N. 8.80. Found: C, 75.44; H 5.69; N, 8.78.

Synthesis of 2,3-Diaza-2,4-diphenyl-8-oxo-1-thio-spiro[5.4]-dec-3-ene (7d). 9-Carbmethoxy-2,3-diaza-2,4-diphenyl-8-oxo-1-thio-spiro[5.4]dec-3-ene **6d** (3.92 g, 0.01 mol) was taken in glacial acetic acid (25 ml) and 33% hydrobromic acid in acetic acid solution (10 ml) was added. The contents were refluxed for 5 hr and poured onto 25 g crushed ice. The solid which separated was collected by filtratioin, dried and crystallised 50% methanol as light brown solid, yield 2.33 g (70%), mp >250°. Under similar reaction conditions **7a** was synthesized from **6a**. ir ($CHCl_3$): 2966, 1709, 1593 cm^{-1}. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz): δ 2.29-2.86 (m, 8H, -CH_2), 7.31-8.09 (m, 10H, phenyl protons). ^{13}CNMR spectrum ($CDCl_3$, 300 MHz): 29.62, 34.75, 109.92, 123.73, 125.33, 125.62, 126.23, 127.29, 128.24, 132.18, 138.89, 140.10, 152.02, 207.70 ppm. Mass spectrum (m/z): 334(9%), 266(100%), 199(8%), 148(15%), 135(12%), 91(30%) and 77(80%). *Anal*. Calcd. for $C_{20}H_{18}N_2OS$ (334): C, 71.86; H, 5.39; N, 8.38. Found: C, 71.90; H 5.35; N, 8.32.

1-Phenyl-3-methyl-4,4-di(carboxyethyl)-2-pyrazoline-5-one (5a). Compound **4a** (1.73 g, 5 mmoles) was refluxed in conc. HCl (30 ml) for 5 hrs. The reaction mixture was cooled and solid that separated was collected by filtration, washed with water and dried, then dissolved in aq. saturated sodium bicarbonate (25 ml) and filtered. The filtrate on acidification with 10% dil HCl (10ml) furnished dicarboxylic acid **5a** as colorless solid in pure form, yield 1.10 g (70%), mp 130°C (lit [10], 142°C), ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.90-2.09 (m, 8H, 4x-CH_2), 2.11 (s, 3H, CH_3), 7.21-7.08 (m, 5H, phenyl protons), 12.25 (br, 2H, 2x-COOH; D_2O exchangeable). ^{13}CNMR ($CDCl_3$, 500 MHz): δ 13.48, 28.56 & 29.27 (4x-CH_2), 57.26, 118.64, 124.93, 128.55, 137.43, 161.82, 173.58, 174.05 ppm. *Anal*. Calcd. for $C_{16}H_{18}N_2O_5$ (318): C, 60.37; H,5.70; N,8.80. Found : C, 60.36; H, 5.68; N,8.74.

General Procedure for the Reaction of 2-Pyrazoline-5-ones 1a,b and 2-Pyrazoline-5-Thiones 1c,d with Acrylonitrile (3). To a stirred solution of sodium amide (20 mmoles) in dry DMF (25 mL) in nitrogen atmosphere, was added the appropriate 2-pyrazoline-5-one (or 2-pyrazoline-5-thione) **1a-d** (10mmoles) at 10–15°C. After the addition was complete acrylonitrile (1.06 g, 20 mmoles) was added dropwise over a period of 10 minutes. Stirring was continued for 7 hours and then the reaction mixture was poured into crushed ice (35 g) and acidified with 20% aqueous hydrochloric acid to pH 3. The resulting mixture was triturated with ice-water and extracted with ethyl acetate (2x25ml). The combined organic layers were washed with water (3x40ml), brine and dried (Na_2SO_4). Removal of solvent under vacuum afforded the crude product, which was crystallized using appropriate solvent to give **8a**, **10a-d** in 30%, 45%, 94%, 60%, 71% respectively.

4-Cyano-3-methyl-1-phenyl-2-pyrazoline-5-one (8a) (benzene insoluble). 1 g of the crude product from the reaction of **1a** and **3** was dissolved in benzene resulting in a partially soluble mixture. The insoluble residue was collected by filtration and crystallized from benzene to give **8a** (colorless shining needles). mp 162°C (lit [11a], 160°C) yield ; 0.4 g. ^{1}H NMR spectrum (CD_3COCD_3, 300 MHz): δ 2.28 (broad singlet, 2H, -CH_2CN), 2.68 (broad singlet, 2H, -CH_2), 2.87 (s, 3H, -CH_3), 7.17 (t, 1H, phenyl proton), 7.42 (t, 2H, phenyl protons), 7.82 (d, 2H, phenyl proton), 9.70 (broad, 1H,-OH) ppm. M^+ (CI) m/z: 227 (100%), 174 (20%), 117(18%). *Anal*. Calcd. for $C_{13}H_{13}N_3O$ (227): C, 68.71%; H, 5.77%; N, 18.49%. Found: C, 68.69%; H, 5.77%; N,18.42%.

2,3-Diaza-4-methyl-2-phenyl-9-cyano-8-imino-1-oxospiro-[5.4]-dec-3-ene 10a (benzene soluble). The benzene soluble product from the reaction of **1a** and **3** was crystallized from a mixture of benzene: pet ether (50:50) (light brown solid). mp 164°C ir ($CHCl_3$): 3325, 3026, 2245, 1708, 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$ 500MHz): δ 1.37 (br, 1H,-NH, D_2O exchangeable), 2.05

(s, 3H, CH_3), 2.22-3.27 (m, 10H, 3x-CH_2 & 1x-CHCN), 7.23-7.91 (m, 5H, phenyl protons). ^{13}CNMR spectrum ($CDCl_3$, 300 MHz): 12.29, 22.92, 23.54, 29.48, 32.06, 58.28, 117.23, 118.98, 126.44, 129.27, 136.52, 156.21, 158.26, 170.21. M^+ (m/z): 280(12%), 187(54%), 159(18%), 122(20%), 105(26%), 77(100%). *Anal*. Calcd. for $C_{16}H_{16}N_4O$ (280): C, 68.55%; H, 5.75%; N, 19.99%. Found: C, 68.52%; H, 5.73%; N, 19.94%.

2,3-Diaza-2,4-diphenyl-9-cyano-8-amino-1-oxo-spiro[5.4]-dec-3,8-diene (10b). This compound was obtained as light brown solid (50% benzene:pet ether) mp 90°, ir ($CHCl_3$)**:** 3325, 3021, 2251,1708, 1669 (weak, -NH_2 bending vibrations), 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.13-2.85 (m, 6H, 3x-CH_2), 5.30 (br, 2H, -NH_2, tautomeric), 7.07-7.71 (m, 10H, phenyl protons). ^{13}C NMR spectrum ($CDCl_3$, 300 MHz): 23.94, 26.38, 31.90, 59.05, 118.63, 119.57, 126.91, 127.12, 127.54, 127.93, 128.22, 128.61, 129.18, 132.37, 136.72, 156.52, 170.12. *Anal*. Calcd. for $C_{21}H_{18}N_4O$ (342): C, 73.67%; H, 5.30%; N, 16.36%. Found: C, 73.64%; H, 5.26%; N, 16.31%.

2,3-Diaza-4-methyl-2-phenyl-9-cyano-8-amino-1-thio-spiro-[5.4]-dec-3,8-diene (10c). This compound was obtained was grey solid (50% methanol). mp 195°C, ir (KBr): 3421, 2930, 2248 1596 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.65 (br, 1H N*H*, D_2O exchangeable), 2.16-2.43 (m, 10H, 3 x -CH_2, 1x-CH_3, -CHCN), 6.29 (broad, D_2O exchangeable, -NH_2 tautomeric) 7.20-7.50 (m, 5H, phenyl protons). ^{13}CNMR ($CDCl_3$, 500MHz): 12.37, 13.66, 28.67, 29.71, 107.51, 110.04, 114.80, 125.12, 127.97, 128.94, 133.81, 139.43, 149.41, 152.38 ppm. *Anal*. Calcd. for $C_{16}H_{16}N_4S$ (296): C, 64.84%; H, 5.44%; N, 18.90%. Found: C, 64.88%; H, 5.46%; N, 18.84%.

2,3-Diaza-2,4-diphenyl-9-cyano-8-amino-1-thio-spiro[5.4]-dec-3,8-diene (10d). This compound was obtained as grey solid (50% methanol). mp >250°, ir (KBr): 3439 (-NH), 3062, 2204, 1597 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300MHz) δ 1.75 (s, broad, C=NH, D_2O exchangeable), 2.05-2.81(m, 7H, 3x-CH_2, -CHCN), 7.01 - 7.82 (m, 10H, phenyl protons). DEPT NMR experiment of the compound showed methylene carbons at 22.60, 29.58, and 31.23 (3x-CH_2), methine carbons at 111.41 (*C*H-C≡N), 124.94, 125.70, 125.86, 127.84, 128.33, 128.75, 128.80, 128.95. ^{13}CNMR ($CDCl_3$ 300 MHz): 22.60, 29.58, 31.23, 104.90, 111.41, 118.83, 124.94, 125.70, 125.86, 127.84, 128.33, 128.75, 128.80, 128.95, 138.78 and 151.73 ppm. M^+ (m/z): 358(35%), 235(20%), 135(8%), 132(12%), 103(100%), 91(60%), 77(45%). *Anal*. Calcd. for $C_{21}H_{18}N_4S$ (358): C, 70.36; H, 5.06; N, 15.63. Found: C, 70.34; H, 5.07; N, 16.58.

General Procedure for the Hydrolysis and Decarboxylation of 10. Compounds **10a-d** (10 mmoles), glacial acetic acid (25 ml) and 33% hydrobromic acid in acetic acid (10 ml) were heated under reflux for 6 hr. The reaction mixture was cooled and poured onto crushed ice to obtain crude **7a-d**. Crystallization using appropriate solvent, as discussed earlier in this section, gave the pure compound in 71%, 83%, 42% & 65%. The structure was confirmed by mixed melting point, co-tlc and co-ir with the authentic sample obtained by the alternate route *via* methyl acrylate.

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[12] Note: When the reaction conditions were altered by replacing sodamide/DMF with TEA/C_2H_5OH the diadduct was isolated in one of the reactions. Thus for example, **1c** (0.01 mol), **3** (0.02 mol) and triethylamine (0.02 mol) in ethanol (20 ml) were refluxed for 12 hrs. The reaction mixture was poured onto 20 g crushed ice and acidified with 5 ml of 15% dil HCl. The oil, which separated, was extracted in ethyl acetate. The organic phase was washed well with water, brine and dried over sodium sulphate. Removal of organic solvent afforded a brown oil, which on column chromatography gave the diadduct **9c** in 45% yield. The IR spectrum displayed the characteristic peak at 2245 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H, -CH_3), 2.48 (t, 4H, 2 x –C*H*$_2$-CN, *J* = 7.5 Hz), 2.79 (t, 4H, 2 x –C*H*$_2$-CH_2, *J* = 7.5 Hz) and 7.40 - 7.57 (m,5H, phenyl protons). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.21, 17.58, 17.87, 29.20, 30.32, 108.96, 117.09, 124.71, 127.57, 128.53, 131.55, 149.25, 152.47 ppm.