REACTIVITY OF BISOLEFINIC SYSTEMS WITH DIAZOMETHANE AND HYDRAZINE HYDRATE - PART III

V. Padmavathi*, M.Rajagopala Sarma, A. Padmaja and D. Bhaskar Reddy
Department of Chemistry, Sri Venkateswara University, Tirupati - 517 502, India

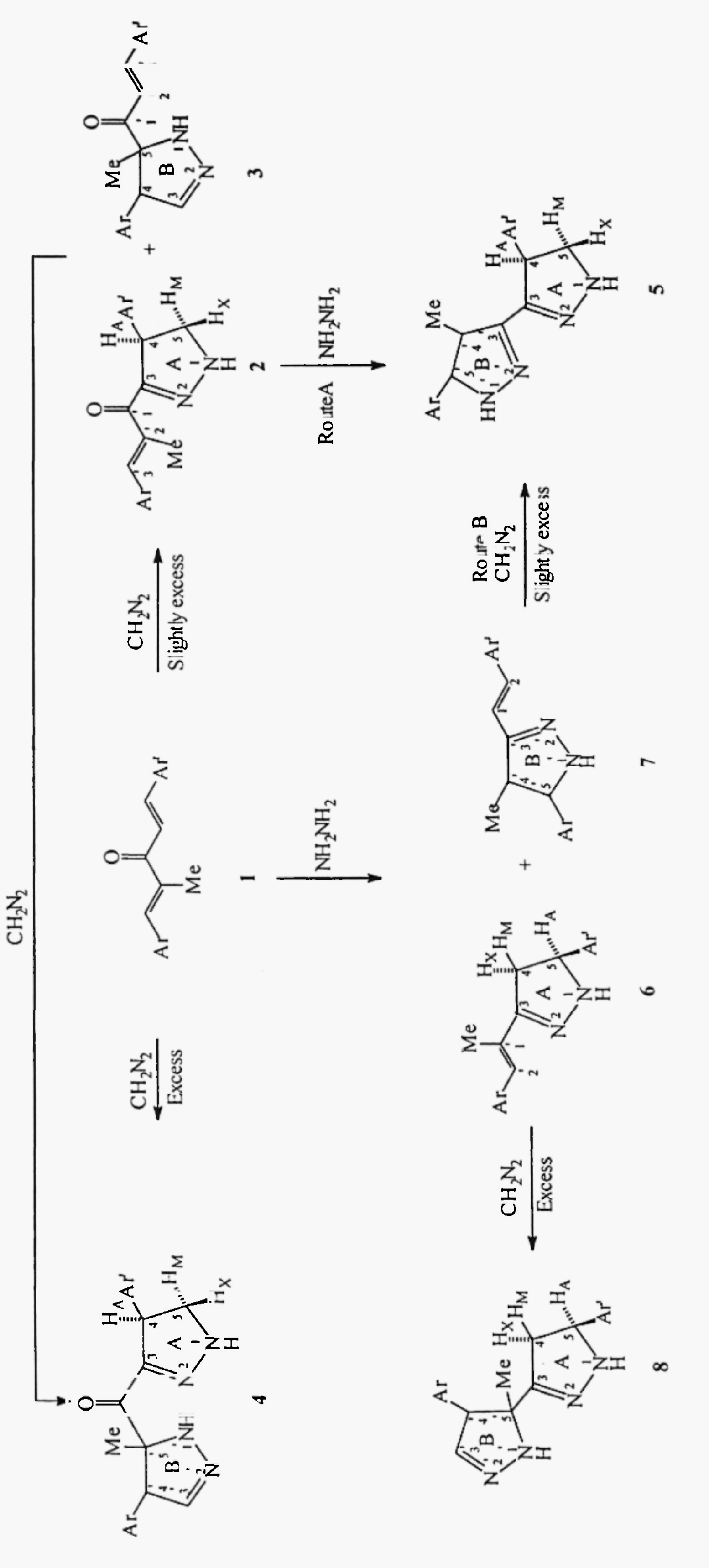
Abstract : Mono and bis pyrazolines were prepared by the cycloaddition and cyclocondensation reactions of diazomethane and hydrazine hydrate with bis olefinic systems.

Introduction :

The chemistry of heterocyclic compounds particularly nitrogen containing five membered heterocycles is one of the well attended branches of chemistry due to their broad spectrum of physiological action and diverse physicochemical properties.[1-5] Amongst them pyrazole and its derivatives have acquired importance due to their wide spectrum of biological properties.[6] Various methods were developed for their synthesis over the years, of which the cycloaddition of diazomethane and cyclocondensation of hydrazine hydrate with Micheal acceptors have gained importance. In our earlier communications, the reactivity of bifunctional olefins with diazomethane and hydrazine hydrate was reported.[7,8]

Results and Discussion :

The synthetic scheme involves the treatment of 1,5-diaryl-3-methyl-1,4-pentadien-3-one (1) with two-fold excess of diazomethane. After work-up the reaction mixture indicated the formation of two adducts in TLC and they were separated by column chromatography. They were identified as 4-aryl-3-(3′-aryl-2′-methyl-2-propenone)-2-pyrazoline (2) as major (60-73%) and 4-aryl-5-methyl-5-(3′-aryl-2′-propenone)-2-pyrazoline (3) as minor (12-25%) products by their ^1H NMR spectra (Scheme and Tables 1 & 2). The **2** showed AMX splitting pattern for methine and methylene protons of pyrazoline ring. The H_A displayed a double doublet at 4.47-4.51 (J_{AM} = 12.60-12.62, J_{AX} = 5.42-5.55 Hz), H_M at 3.64-3.68 (J_{MX} = 10.01-10.05 Hz) and H_X at 3.52-3.58. The J values



Ar = Ar' = Ph
Ar = Ph ; Ar' = 4-OMe.Ph
Ar = Ph ; Ar' = 4-Cl.Ph

SCHEME

indicate that H_A, H_M and H_A, H_X are *cis* and *trans* oriented while H_M, H_X are *geminal* (Table 2). However the spectra of **3** showed two doublets at 3.92-3.99 (C_4-H) and 4.12-4.15 (C_3-H) for pyrazoline ring B protons. On the other hand when **1** was heated with excess diazomethane, 4,4′-diaryl-5′-methyl-3,5′-bis (2-pyrazolinyl)-3,5′-ketone (**4**) was obtained. The methine and methylene protons (C_4-H and C_5-H) of the pyrazoline ring 'A' exhibited AMX splitting pattern and the resonance signals are observed almost in the same region as in **2** (Table 2). The two methine protons (C_3'-H and C_4'-H) of the pyrazoline ring 'B' showed two doublets as in **3**. The **2** and **3** when subjected to cycloaddition with diazomethane gave a compound which was found to be identical to **4** by its m.m.p and ^{1}H NMR. When the major product **2** was condensed with hydrazine hydrate a different type of bis pyrazoline, 4,5′-diaryl-4′-methyl bis(2-pyrazoline) (**5**) was obtained. The two methine protons of the pyrazoline ring 'B' of **5** displayed a multiplet in the region 2.28-2.42 (C_4'-H) and a doublet at 4.32-4.38 (C_5'-H).

On the other hand the reaction of **1** with hydrazine hydrate gave mixture of products, 5-aryl-3-(1′methylstyryl)-2-pyrazoline (**6**) and 5′-aryl-4′-methyl-3′-styryl-2-pyrazoline (**7**) in almost equal ratio. The **6** exhibited AMX splitting pattern for pyrazoline ring protons. However **7** showed a multiplet for (C_4'-H) and a doublet for (C_5'-H) of pyrazoline ring (Table 2). The reaction of **6** with diazomethane gave 5,4′-diaryl-5′-methyl-3,5′-bis(2-pyrazolines) (**8**), whereas **7** resulted **5**. The authenticity of **5** was confirmed by m.mp and ^{1}H NMR spectra. In the case of **8**, the pyrazoline ring protons of A exhibited signals as in **6** whereas ring B protons as in **4** (Table 2).

Thus the sequence of reactions exemplifies a method for the synthesis of different pyrazolines by cycloaddition and cyclocondensation reactions of diazomethane and hydrazine hydrate with 1,5-diaryl-3-methyl-1,4-pentadien-3-ones.

Experimental

Melting points were determined on Mel-Temp apparatus and are uncorrected. IR spectra were measured in KBr on Perkin-Elmer grating infrared spectrophotometer model-337 (ν_{max} in cm^{-1}). ^{1}H NMR spectra were recorded on Bruker Spectrospin instrument operating at 200 MHz in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. TLC was performed on silica gel (Merck) using hexane - ethyl acetate (3:2) as eluents. The elemental analyses were obtained from microanalytical laboratory, University of Pune, Pune, India.

The starting materials 1,5-diaryl-3-methyl-1,4-pentadien-3-ones (**1**) were prepared according to the literature procedure.[9]

Cycloaddition of diazomethane to 1.

A solution of **1** (0.01 mol) in dichloromethane (20 ml) was cooled at ice-salt bath temperature. To this, an ethereal solution of diazomethane (80 ml, 0.4 M) and a catalytic amount of triethylamine was added. The reaction mixture was kept at -20° to -15°C for 48 hrs. The solvent was removed under reduced pressure. The resultant product indicated a mixture in TLC which was separated by column chromatography (silica gel, BDH) using ethyl acetate - hexane (1:3) as eluents and identified as **2** and **3**.

However **1** with excess diazomethane (120 ml, 0.4 M) under the above conditions afforded a single product **4**. It was purified by recrystallization from ethanol. Similarly, **4** was also obtained when a solution of **2/3** (0.01 mol) was treated with ethereal solution of diazomethane (40 ml, 0.4 M) and triethylamine.

Cyclocondensation of 1 and 2 with hydrazine hydrate.

The compound **1/2** (0.01 mol) in ethanol (20 ml) and hydrazine hydrate (0.02 mol) was refluxed for 2-3 hrs and cooled. The gummy substance obtained in **1** was solidified on treatment with pet. ether. The crude compound indicated two spots in TLC which were separated by column chromatography and were identified as **6** and 7. However in the case of **2** a solid product was separated which was filtered, dried and recrystallized from ethanol to get pure **5**.

Cycloaddition of diazomethane to 6/7.

To a solution of **6/7** (0.01 mol) in dichloromethane kept in ice-salt bath, an ethereal solution of diazomethane (40 ml, 0.4 M) and a catalytic amount of triethylamine was added. The reaction mixture was kept at -20 to -15°C for 48 hrs. The solvent was removed under vacuo. The resultant product was purified by recrystallization from ethanol to obtain **8/5**.

Acknowledgement :

One of us (VP) thanks to the Department of Science and Technology, New Delhi for financial support.

Table 1 : Physical data of compounds 2-8

Compd. No.	Yield (%)		M.P. (°C)	Compd. No.	Yield (%)	M.P. (°C)
2a	65		148-149	6a	48	157-159
2b	73		154-155	6b	42	146-148
2c	60		132-133	6c	46	161-163
3a	19		126-127	7a	35	145-146
3b	12		112-113	7b	46	153-154
3c	25		143-144	7c	40	142-143
4a	87		178-180	8a	82	136-137
4b	88		187-189	8b	85	142-143
4c	85		171-173	8c	84	161-163
	Route A	Route B				
5a	82	85	149-150			
5b	86	87	137-139			
5c	81	80	154-156			

Satisfactory elemental analysis were obtained : C ± 0.24, H ± 0.15, N ± 0.18

Table 2 Spectroscopic data of compounds 2-8

Compd. No.	IR (KBr) cm^{-1}	^{1}H NMR ($CDCl_3$) δ, ppm
2a	1560 ; 1645 3370 : 1620	2.12 (s, 3H, CH_3), 3.58 (dd, 1H, H_X), 3.64 (dd, 1H, H_M; J_{MX} = 10.01) 4.47 (dd, 1H, H_A ; J_{AM} = 12.60 ; J_{AX} = 5.55), 6.48 (s, 1H, N$\underline{H}$), 7.02-7.85 (m, 11H, C_3'-H & Ar-H).
2b	1565 ; 1652 3378 ; 1610	—
2c	1648 : 1565 3375 : 1630	2.05 (s, 3H, $C\underline{H}_3$), 3.52 (dd, 1H, H_X), 3.68 (dd, 1H, H_M ; J_{MX} = 10.05), 4.51 (dd, 1H, H_A ; J_{AM} = 12.62; J_{AX} = 5.42), 6.46 (s, 1H, N$\underline{H}$), 6.98-7.89 (m, 10H, C_3'-H & Ar-H).
3a	1564 ; 1639 3365 ; 1610	1.81 (s, 3H, CH_3), 3.92 (d, 1H, C_4-H), 4.15 (d, 1H, C_3-H), 6.20 (d, 1H, C_2'-H), 6.48 (s, 1H, N$\underline{H}$), 6.92-7.64 (m, 11H, C_3'-H & Ar-H).
3b	1564 ; 1642 3365 ; 1610	1.83 (s, 3H, $C\underline{H}_3$), 3.72 (s, 3H, Ar-$OC\underline{H}_3$), 3.99 (d, 1H, C_4-H), 4.12 (d, 1H, C_3-H), 6.22 (d, 1H, C_2'-H), 6.48 (s, 1H, N$\underline{H}$), 6.90-7.58 (m, 10H, C_3'-H & Ar-H).
3c	1648 ; 1555 3360 : 1620	—
4a	1560 ; 1660 3370	1.83 (s, 3H, $C\underline{H}_3$),3.58 (dd 1H H_X), 3.64 (dd, 1H, H_M J_{MX} = 10.01),3.89 (d, 1H, C_4'-H), 4.09 (d, 1H, C_3'-H), 4.53 (dd, 1H, H_A) ; J_{AM} = 12.62 ; J_{AX} = 5.55), 6.46 (brs, 2H, N$\underline{H}$), 6.97-7.64 (m, 10H, Ar-$\underline{H}$).
4b	1565 ; 1652 3374	—
4c	1565 ; 1662 3365	1.85 (s, 3H, $C\underline{H}_3$), 3.61 (dd, 1H, H_X), 3.69 (dd, 1H, H_M ; J_{MX} = 9.98), 3.92 (m, 1H, C_4'-H), 4.15 (d, 1H, C_3'-H), 4.62 (dd, 1H, H_A ; J_{AM} = 12.62 ; J_{AX} = 5.58), 6.47 (brs, 2H, NH), 6.98-7.88 (m, 9H, Ar-$\underline{H}$).
5a	1560 ; 3370	1.32 (s, 3H, CH_3), 2.28-2.40 (m, 1H, C_4'-H), 3.57 (dd, 1H, H_X), 3.68 (dd, 1H, H_M ; J_{MX} = 10.02), 4.32 (d, 1H, C_5'-H), 4.75 (dd, 1H, H_A ; J_{AM} = 12.60 ; J_{AX} = 5.55), 6.48 (brs, 2H, N$\underline{H}$), 7.01-7.65 (m, 10H, Ar-H).
5b	1555 ; 3370	—

5c	1560 ; 3360	1.36 (s, 3H, CH_3), 2.28-2.42 (m, 1H, C_4'-H), 3.52 (dd, 1H, H_X), 3.69 (dd, 1H, H_M ; J_{MX} = 10.01), 4.38 (d, 1H, C_5'-H), 4.73 (dd, 1H, H_A ; J_{AM} = 12.61 ; J_{AX} = 5.55), 6.48 (brs, 2H, NH), 7.04-7.88 (m, 9H, Ar-$\underline{H}$).
6a	1560 ; 1620 3370	2.14 (s, 3H, $C\underline{H}_3$), 3.69 (dd, 1H, H_X), 4.03 (dd, 1H, H_M ; J_{MX} = 10.36), 4.47 (dd, 1H, H_A ; J_{AM} = 11.80 ; J_{AX} = 5.08), 6.51 (s, 1H, N$\underline{H}$), 7.01-7.94 (m, 11H, C_2'-H & Ar-$\underline{H}$).
6b	1570 ; 1625 3370	—
6c	1570 ; 1625 3370	2.15 (s, 3H, $C\underline{H}_3$), 3.84 (dd, 1H, H_X), 4.15 (dd, 1H, H_M ; J_{MX} = 10.40), 4.62 (dd, 1H, H_A ; J_{AM} = 11.94; J_{AX} = 5.05), 6.51 (s, 1H, N$\underline{H}$), 7.01-7.94 (m, 10H, C_2'-H & Ar-H).
7a	1560 ; 1620 3370	1.29 (s, 3H, $C\underline{H}_3$), 3.48-3.54 (m, 1H, C_4'-H), 4.35 (d, 1H, C_5'-H), 6.54 (s, 1H, NH), 6.23 (d, 1H, C_1-H), 7.04-7.80 (m, 11H, C_2-H & Ar-H).
7b	1560 ; 1630 3365	1.26 (s, 3H, $C\underline{H}_3$), 3.48-3.56 (m, 1H, C_4'-H), 3.82 (s, 3H, Ar-OCH_3), 4.39 (d, 1H, C_5'-H), 6.56 (s, 1H, NH), 6.29 (d, 1H, C_1-H), 6.98-7.86 (m, 10H, C_2-H&Ar-H).
7c	1558 ; 1628 3372	—
8a	1560 ; 3370	1.62 (s, 3H, $C\underline{H}_3$), 3.04 (dd, 1H, H_X), 3.46 (dd, 1H, H_M ; J_{MX} = 10.52), 3.99 (d, 1H, C_4'-H), 4.55 (d, 1H, C_3'-H), 4.88 (dd, 1H, H_A ; J_{AM} = 10.69 ; J_{AX} = 5.50), 6.52 (brs, 2H, NH), 6.92-7.51 (m, 10H, Ar-H).
8b	1565 ; 3375	1.64 (s, 3H, CH_3), 2.95 (dd, 1H, H_X), 3.33 (dd, 1H, H_M; J_{MX} = 10.52), 3.72 (s, 3H, Ar-OCH_3), 3.98 (d, 1H, C_4'-H), 4.57 (d, 1H, C_3'-H), 4.78 (dd, 1H, H_A ; J_{AM} = 10.64;J_{AX} = 5.51), 6.54 (brs, 2H, NH), 6.94-7.54 (m, 9H, Ar-H).
8c	1560 ; 3372	—

References

1. H.G. Garge and Chandrprakash. J. Pharm. Sci.. **14**, 649 (1971).

2. H.W. Robert. J. Heterocycl. Chem.. **13**. 545 (1976).

3. S.G. Roelofvan. C Arnold and K. Wellinga J. Agric. Food Chem., **27**, 406 (1979).

4. R. Krishna. B.R. Pandy, J.P. Bartwal and S.S. Parmar. Eur J. Med. Chem. Chim. Ther., **15**, 567 (1980).

5. E. Fischer and L. Knorr, Chem Ber., 16 (1983).

6. a J.P. Joseph, J.P. Dusza and S. Bernstein. US Pat. 4347251 (1982) ; Chem Abstr, 97 (1982) 246174 K.
   b. J.P. Dusza, J.P. Joseph and S. Bernstein, US Pat 4348527 (1982) ; Chem Abstr. 98 (1983) 16678 m.
   c. S. Nithyananda and N. Mukherjee, Polyhedron, III, 1135 (1984).

7. D. Bhaskar Reddy, M. Rajagopala Sarma, V. Padmavathi and A. Padmaja, Phosphorus, Sulfur and Silicon, **164**, 23 (2000).

8. D. Bhaskar Reddy. M. Rajagopala Sarma, N. Subba Reddy and A. Soma Sekhar Reddy, Indian J. Chem (in press).

9. K. Ramalingam, K.D. Berlin, R.A. Loghry, D.H. Helm and N. Satyamurthy J. Org. Chem., **44**, 447 (1979).

Received on April 2, 2001