

HYDRAZONES AS NEW 4-ELECTRONS THREE ATOMIC CENTERS IN  
CYCLOADDITION REACTIONS: A NOVEL APPROACH FOR THE  
SYNTHESIS OF PYRAZOLE DERIVATIVES

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Abstract- Aromatic aldehydes and acetophenone phenylhydrazones undergo cycloaddition reactions with maleimides to give the pyrrolo[3,4-d]pyrazole derivatives via a novel pericyclic reaction involving easily accessible  $4\pi$ -electrons neutral three atomic centers.

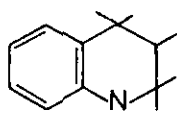
Schiff's bases have been shown to undergo mainly two types of cycloadditions. The first characteristic for Schiff's bases derived from aromatic amines and this leads to the formation of quinoline derivatives 1 by cycloadditions with vinyl ethers<sup>1,2</sup> and keten imines<sup>3</sup> where one conjugated  $\pi$ -bond from the benzene rings participates with N=C in a  $4\pi$ -diene system. The second interesting cycloaddition is termed "Dipolar Spiro-Addition"<sup>4,5</sup> for Schiff's bases specially derived from methylamine and aromatic aldehydes which react with maleimides in 1:2 molar ratio to give spiro derivatives 2. Azines, which might be considered as bis-Schiff's bases, undergo a completely different and a unique type of cycloaddition, viz; "Criss-Cross Addition" yielding bicyclic 2:1 (dienophile/azine) adducts 3, rather than the expected 1:1 adducts associated with butadienes<sup>5-13</sup>.

It seemed now of interest to investigate the possible cycloadditions of hydrazones which might be considered as N-amino derivatives of Schiff's bases, with ethylenic compounds. To the best of our knowledge, no previous report on such investigations was cited in literature. We have now found that the reaction of benzaldehyde and anisaldehyde phenylhydrazones (4a,b) with N-phenyl- and N-p-chlorophenylmaleimides (5a,b) at 160-180°C for 90 min leads mainly to the formation of pyrrolidino[3,4-d]-

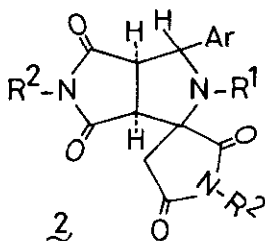
pyrazolidine-2,6-diones 6a-c and pyrrolidino[3,4-d]- $\Delta^2$ -pyrazoline-2,6-diones 7a-c. It has been found that when the reactants were mixed in a molar ratio compounds 6 and 7 were obtained in 20-25% and 40-50% yield respectively. However, increasing the ratio of maleimides leads to increasing the yield of compounds 7 and when two moles of the maleimide were used only compounds 7a,b were the sole reaction products. We also found that heating either of 6a,b with any of the maleimides 5a,b at 160-180°C for short time (30-60 min) leads to their conversion into the corresponding  $\Delta^2$ -pyrazoline derivatives 7a,b. Although we predicted to isolate N-arylsuccinimides, yet we could not detect any of these compounds among the reaction products, and most of the maleimides were recovered. Thus it seems that maleimides only catalyze hydrogen extrusion from 6 into their  $\Delta^2$ -pyrazolines 7. Although compounds 6a,b and 7a,b were readily separable from their reaction mixtures by fractional crystallization, no attempt could be able to separate compound 6c from 7c and always they were contaminated with each other as indicated in their  $^1\text{H}$  NMR, MS and IR spectra. Structures of 6a-c and 7a-c were inferred from the fact that: (i) all compounds gave correct molecular ions in mass spectra, (ii) whereas compounds 6a-c showed NH stretching vibration at  $3300\text{ cm}^{-1}$ , 7a-c did not, (iii)  $^1\text{H}$  NMR ( $\delta$  ppm) of 6a,b ( $\text{CDCl}_3$ ): 3.96, 4.05(t, 1H, J= 8Hz, Ha); 4.3-4.79(m, br, NH and Hb); 4.93(d, 1H, J= 8Hz, Hc) and 7-7.5, 6.6-7.6(m, ArH's).  $^1\text{H}$  NMR of 7a,b ( $\text{CDCl}_3$ ): 4.8(d, 1H, J= 12Hz, Ha); 5.1(d, 1H, J= 12Hz, Hb) and 6.9-7.5, 6.9-7.9(m, ArH's), (iv) compounds 7a,b were independently synthesised via the reaction of 5a,b respectively with diphenylnitrile imine (8) generated in situ by the action of triethylamine on diphenylhydrazoyl chloride in ether<sup>14</sup>.

In an attempt to convert the mixture of 6c and 7c completely into 7c, the mixture was heated either alone or with maleimides or in nitrobenzene for 8 hr (TLC monitored), and in each case the same product was isolated. This was assigned the pyrrolo[3,4-d]pyrazole structure 9b, which showed in its  $^1\text{H}$  NMR ( $\delta$  ppm) ( $\text{CDCl}_3$ ) only methoxy protons at 3.85(s, 3H) and ArH's at 6.88-8.22(m, 14H). Similarly, each of 6b and 7b when refluxed in nitrobenzene for 8 hr gave the same final pyrazole derivative 9a.

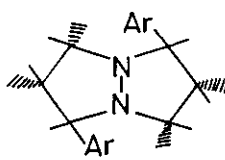
Under similar conditions (heating at 160-180°C for 90 min) acetophenone phenylhydrazone (4c) reacted with each of 5a,b to give the pyrrolidino[3,4-d]pyrazolidine-2,6-diones 10a,b respectively in 60-70% yield.



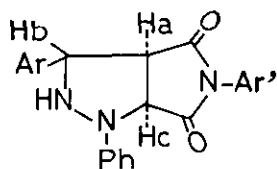
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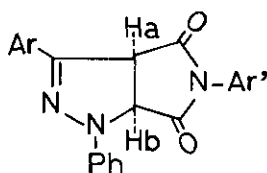
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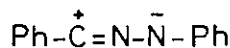
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6a-c

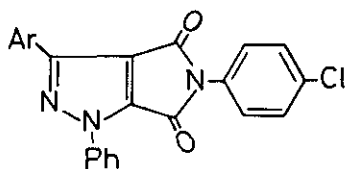


7a-c

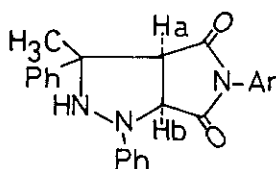


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a, Ar=Ar'=C<sub>6</sub>H<sub>5</sub>  
 b, Ar=C<sub>6</sub>H<sub>5</sub>; Ar'=C<sub>6</sub>H<sub>4</sub>Cl-p  
 c, Ar=C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-p; Ar'=C<sub>6</sub>H<sub>5</sub>



9a, Ar=C<sub>6</sub>H<sub>5</sub>  
 b, Ar=C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-p

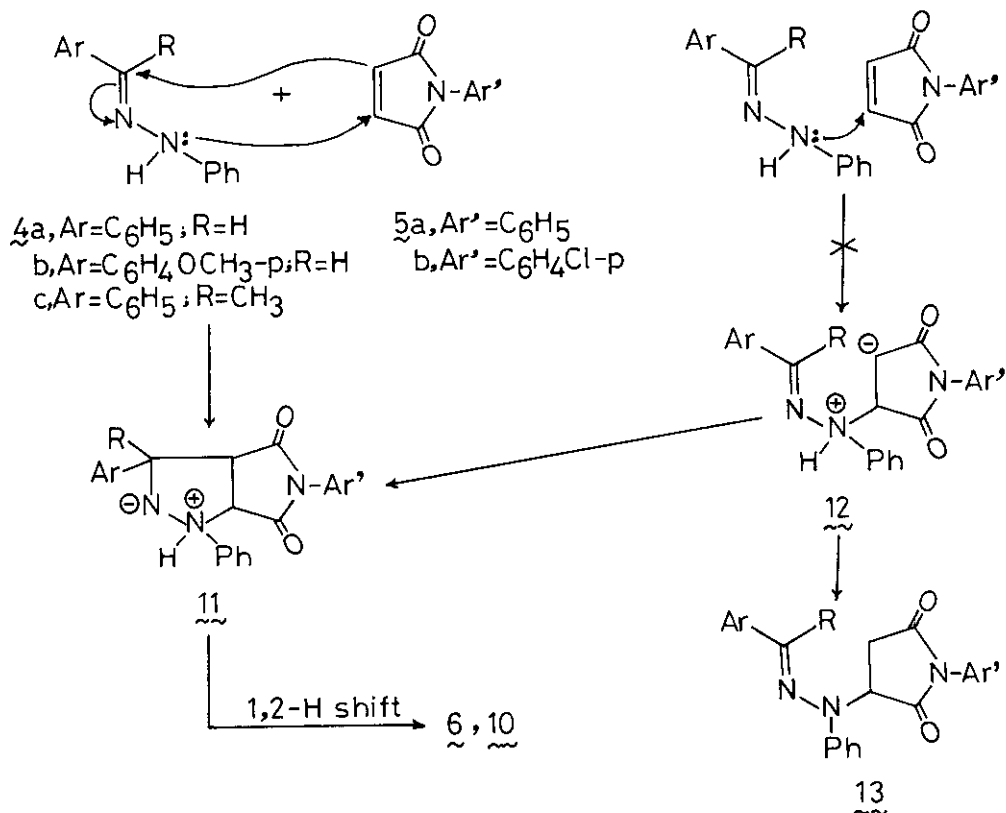


10a, Ar=C<sub>6</sub>H<sub>5</sub>  
 b, Ar=C<sub>6</sub>H<sub>4</sub>Cl-p

Compounds 10a,b gave the corresponding molecular ions in mass spectra and also NH stretching vibration at 3260 cm<sup>-1</sup> in their IR spectra (KBr). <sup>1</sup>H NMR (δ ppm) of 10a,b (CDCl<sub>3</sub>) 1.62, 1.6(s, 3H, CH<sub>3</sub>); 3.84, 3.85(d, 1H, J= 8Hz, Ha); 4.5(br, 1H, NH); 4.82(d, 1H, J= 8Hz, Hb) and 6.9-7.52, 6.85-7.63(m, ArH's).

Assignment of Ha, Hb and Hc and their coupling constants for 6, 7 and 10 is completely consistent with reported data for similar systems<sup>15,16</sup>.

The new cycloaddition reaction reported here for hydrazones, where the electrophilic C-N double bond is conjugated with the lone pair on nitrogen, represents the first example other than azines in that respect and the cycloaddition can be visualized as follows:



The diionic species 11 is certainly an intermediate in this reaction followed by 1,2-H shift to give 6 and 10 and as all pyrazolidines like 6 undergo facile dehydrogenation to give the more stable  $\Delta^2$ -pyrazolines 7<sup>17</sup> in cases where R=H. However, in case of R=CH<sub>3</sub> the resulting pyrazolidines 10 are stable enough to be the sole reaction products under our experimental conditions.

Our findings prove that the reaction constitutes a new type of concerted pericyclic reactions. This is further supported by the fact that no products like 13 were identified. The latter would arise from a stepwise reaction initiated by a Michael type addition via intermediate 12, which beside the plausible formation of 6 and 10 should if not predominantly give 13.

Further studies on the mechanistic, stereochemical and synthetic versatility of this reaction is now underway in our laboratory. All new products are under screening for any possible biological activity.

Comp. *	Yield %	M.p. °C	Mol. formula	Comp. *	Yield %	M.p. °C	Mol. formula
<u>6a</u>	25	230-2	$C_{23}H_{19}N_3O_2$	<u>7c</u>	--	215-20	$C_{24}H_{18}N_3O_2Cl$
<u>6b</u>	20	225-7	$C_{23}H_{18}N_3O_2Cl$	<u>9a</u>	95	236-8	$C_{23}H_{14}N_3O_2Cl$
<u>6c</u>	--	215-20	$C_{24}H_{20}N_3O_3Cl$	<u>9b</u>	92	268-70	$C_{24}H_{16}N_3O_3Cl$
<u>7a</u>	40	209-11	$C_{23}H_{17}N_3O_2$	<u>10a</u>	69	235-7	$C_{24}H_{21}N_3O_2$
<u>7b</u>	45	218-20	$C_{23}H_{16}N_3O_2Cl$	<u>10b</u>	61	244-6	$C_{24}H_{20}N_3O_2Cl$

\* Satisfactory analyses for the synthesised compounds were obtained; compounds 6a,b crystallized from acetone, 7a,b from ethanol, 9a,b and 10a,b from chloroform/acetone; compounds 6c,7c were obtained as inseparable mixture in 70% (from acetone).

#### ACKNOWLEDGEMENT

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