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PECULIAR C-C BOND CLEAVAGES OF PYRAZOLYL PROPENONE EPOXIDES INDUCED BY GRIGNARD REAGENTS.

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Abstract- 1-Aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)prop-2-en-1-ones(2) yielded pyrazolylpropenone epoxides (3) on which peculiar C-C bond cleavages were induced by Grignard reagents giving the unexpected saturated secondary alcohols (4) bearing pyrazolyl nucleus.

Pharmacological studies of some pyrazolones and pyranopyrazoles show respiratory and cardio-vascular activities[1] in addition to their well known antianxiety, antipyritic, anti-inflammatory and anti-microbial properties[2,3].

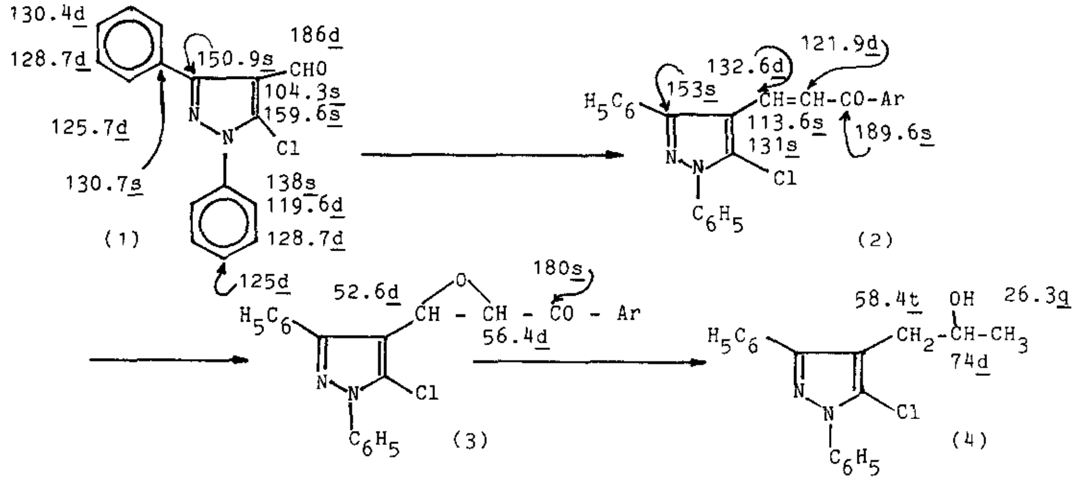
As an extension of our previous work[4], we report here a peculiar C-C bond cleavage of pyrazolylpropenone epoxides induced by Grignard reagent.

Formylation of 1,3-diphenyl-2-pyrazolin-5-one by Vilsmeier reagent[5,6] yielded 5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde(1) which was condensed with acetophenone or p-methylacetophenone in alcoholic KOH to give 1-aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)prop-2-en-1-ones(2) in 80-86% yield.

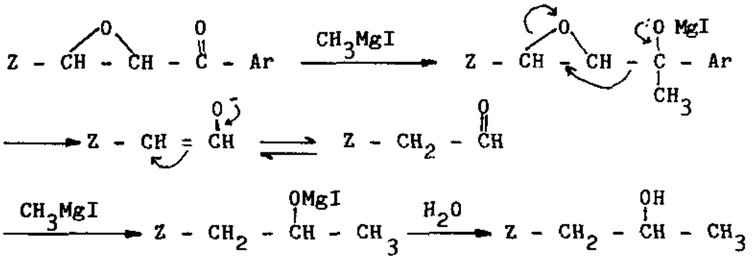
Epoxidation of the propenones(2) by H_2O_2/NaOH yielded 1-aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)-2,3-epoxypropan-1-ones (3a,b) in good yields. Treatment of the epoxide (3a,b) with methylmagnesium iodide in boiling ether gave 5-chloro-1,3-diphenyl-4-(2-hydroxypropyl)-1H-pyrazole (4). Both compounds 3a and 3b gave the same product 4. The structure of compound (4) was confirmed by elemental analysis, ir (cf table 1) (1595 cm^{-1} C=N, C=C; 3350 cm^{-1}, OH), ^{13}C-nmr(3 aliphatic carbons 58.4t, CH_2; 74.0d, -CHOH; 26.3q, $-CH_3$ plus a typical 5-chloropyrazolyl ring spectrum) and white ppt with $AgNO_3$ showing the presence of Cl. The ^1H-nmr showed the aromatic protons at 7.2-8 ppm and showed CH_3, CH and CH_2 at 1.2, 3.9 and 2.2 respectively as doublet, multiplet and doublet.

This C-C bond cleavage seems perfect with pyrazolyl propenone epoxides and methylmagnesium iodide. Other Grignard reagents proceeded differently e.g. phenylmagnesium iodide did not give the saturated secondary alcohol probably because of the bulky phenyl group. The epoxidation of 3-phenyl-2-propiophenone in methanol at 5-8°C was unsuccessful due to its insolubility. Moreover, other α,β-epoxy ketones under study gave cleavage products which will be reported seperately.

The ^{13}C data confirm the structure as shown below: [7-12]



The following mechanism is suggested (Z=5-chloropyrazolyl ring):



EXPERIMENTAL

Melting points reported are uncorrected. Physical data of the products (1-4) and their ir and ^1H-nmr spectral data were listed in Table 1. Ir spectra[11] were recorded in KBr on Pye Unicam SP 200 G spectrophotometer. The ^1H-nmr spectra[12] were determined on a Varian T-90 spectrometer. The ^{13}C-nmr spectra were recorded on Jeol FX 90 Q Fourier Transform instrument. In all nmr experiments the internal standard was TMS and the solvent was $CDCl_3$. All chemical shifts are in ppm downfield from TMS.

<u>5-Chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde(1)</u>- A solution of 1,3-diphenyl-5-pyrazolone (47.5 g, 0.2 mol) in DMF (100 ml) was cooled to 0°C in an ice-acetone bath, then phosphoryl chloride (55 ml, 0.6 mol) was added dropwise at such a rate as to maintain the temperature between 10-20°C. The reaction mixture was heated on steam-bath for 90 min after completion of addition. The mixture was then poured onto ice-water (2l) and the resulting mixture allowed to stand overnight at 25°C. The solid product thus obtained was filtered, washed with water, dried and crystallized from petr. ether (80-100°C) to give the aldehyde (1) as colourless crystals in 60% yield.

<u>1-Aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)prop-2-en-1-ones (2a,b)</u>:
A mixture of aldehyde (1) (2.8 g, 0.01 mol) and acetophenone (1.8 g, 0.015 mol) or p-methylacetophenone (2 g, 0.015 mol) in alcoholic KOH (2 g in 100 ml) was stirred at 0°C for 2h. The solid product separated during stirring was filtered off, washed with water, dried and crystallized from benzene-petr. ether (80-100°C)(1:1) mixture to give propenones (2) as colourless crystals in 80-86% yield.

Table 1: Physical data of compounds 1-4:

Compd.	Mp (°C)	Yield (%)	Mol. formula	Analysis% calcd/(found)			Ir spectral data in cm^{-1}
1*	110	60	$C_{16}H_{11}N_2O\ Cl$	68.00 (67.74	3.90 3.97	9.90 9.89)	1590(C=N,C=C) 1670(C=O).
2a**	150	80	$C_{24}H_{17}N_2O\ Cl$	74.90 (74.76	4.42 4.37	7.28 7.30)	1590(C=N,C=C) 1660(C=O).
2b**	142	86	$C_{25}H_{19}N_2O\ Cl$	75.28 (75.36	4.76 4.74	7.02 6.71)	1595(C=N,C=C) 1660(C=O).
3a$^+$	158	85	$C_{24}H_{17}N_2O_2Cl$	71.91 (71.73	4.25 4.33	6.99 6.92)	1075(C-O-C),1595 (C=N,C=C),1680(C=O)
3b$^+$	187	80	$C_{25}H_{19}N_2O_2Cl$	72.38 (72.57	4.58 4.51	6.76 6.50)	1085(C-O-C), 1600(C=N,C=C),1685(C=O)
4‡	130	33	$C_{18}H_{17}N_2O\ Cl$	69.12 (69.07	5.44 5.28	8.96 8.79)	1595(C=N,C=C),3350(OH).

* <u>1</u>, ^{1}H-nmr : 7.2-7.9 (<u>m</u>, 10H, Ar-<u>H</u>) and 10.0 ppm(<u>s</u>, 1H, C<u>H</u>O)

** 2a, ^{1}H-nmr : 7.2-8.2 ppm (<u>m</u>, 17H, Ar-<u>H</u> and olefinic C_6-<u>H</u> & C_7-<u>H</u>) while <u>2b</u> gives an additional signal at 2.4 ppm (<u>s</u>, 3H, Ar-C<u>H</u>$_3$).

\+ <u>3a</u> ^{1}H-nmr : 4.2 (<u>d</u>, 1H, C_3-<u>H</u>), 4.7 (<u>d</u>, 1H, C_2-<u>H</u>) and 7.2-8.0 ppm(<u>m</u>, 15H, Ar-<u>H</u>) while <u>3b</u> gives also signal at 2.9 ppm (<u>s</u>, 3H, Ar-C<u>H</u>$_3$).

‡ 4 ^{1}H-nmr : 1.2 ppm (<u>d</u>, 3H, C<u>H</u>$_3$), 2.2 (<u>d</u>, 2H, C<u>H</u>$_2$),3.9 (<u>m</u>, 1H, C<u>H</u>-OH) 4.5 (<u>s</u>, 1H, O<u>H</u>), 7.2-8.0 (<u>m</u>, 10H, Ar-H).

1-Aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)-2,3-epoxypropan-1-ones(3a,b): A solution of 2 (2g) in methanol (20 ml) was kept between 5-8°C and a mixture of hydrogen peroxide (4 ml, 18%) and NaOH (1.0 ml, 4N) was added dropwise during 2h. The solution was stirred for further 2h at 25°C. The mixture was neutrallized with H_2SO_4 (10%) and the solid product separated was filtered, washed with water, dried and crystallized from benzene to give epoxides (3) as colourless crystals.

5-Cloro-1,3-diphenyl-4-(2-hydroxypropyl)-1H-pyrazole (4): An ethereal solution of methylmagnesium iodide, (0.06 mol) was added to a solution of 3 (0.01 mol) in dry ether (50 ml) with stirring, then the ethereal solution was refluxed after complete addition for 2h and the solution was set aside overnight at 25°C, and then excess Grignard reagent decomposed with cold saturated solution of ammonium chloride. The product was extracted with ether and the ether layer was dried with $MgSO_4$. The solid separated after evaporation of ether was crystallized from benzene-petr. ether (80-100°C)(1:1) mixture to give compound 4.

REFERENCES:

1. R. Benigini, Minerva. Med., 1941, 1, 436.
2. G. Tacconi, G. Gatti, G. Desimoni, and V. Messori, J. Prakt. Chem., 1980, 322, 831.
3. Y. Sato, Y. Shimoji, K. Endo, H. Nishino, H. Koike, and S. Kumakura, Yakugaku Zasshi, 1978, 98, 335; Chem. Abstr., 1978, 89, 43223.
4. A. G. El-Shekeil, M. A. Hassan, A. S. Babaqi, and S. A. Shiba, Acta Chim. Sinica, 1985, 43, 1215.
5. S. B. Barnela, R. S. Pandit, and S. Seshadri, Indian J. Chem., 1976, 14, 665.
6. W. Dymek, B. Janik, and R. Zimon, Acta Polon Pharm., 1963, 20, 9.
7. S. N. Ege, A. D. Adams, E. J. Gess, K. S. Ragone, B. J. Kober, M. B. Lampert, P. Umrigar, D. C. Lankin, and G. W. Griffin, J. Chem. Soc. Perkin Trans. I, 1983, 325.
8. F. W. Wehrli and J. Wirthlin " Interpretation of Carbon-13-NMR Spectra ", Hyden and Son, London, 1976.
9. E. Kleinpeter and R. Borsdorf "^{13}C-NMR Spektroskopie in der Organischen Chemie ", Akademie-Verlag, Berlin, 1981.
10. J. T. Clerc, E. Pretsch, and S. Sternhell "^{13}C-Kernresonanz Spektroskopie ", Akadem Verlagsgesellschaft, Frankfurt, 1973.
11. L. J. Bellamy " The Infrared Spectra of Complex Molecules ", Methuen & Co. Ltd., London, 1968.
12. R. M. Silverstein and G. C. Bassler " Spectrophotometric Identification of Organic Compounds ", John Wiley and Sons Inc., New York, 1980.

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