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NEW CYCLOADDITION REACTIONS OF 1-PHENYL-4-VINYLPYRAZOLE

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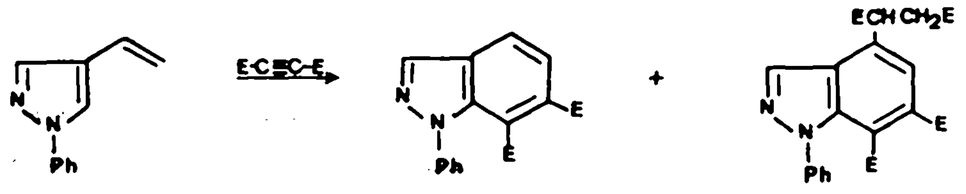
Abstract: 1-Phenyl-4-vinylpyrazole reacts with methyl propiolate and N-phenylmaleimide giving via the Diels-Alder 1:1 adducts, products (4) and (8), and also the 1:2 adducts (5), (6) and (9) resulting from an "ene" reaction of the initially formed cycloadducts. The obtention of the adducts (5) and (6) in equimolecular amounts is a good example of the non-regioselective character of the "ene" reaction. The reaction with tetracyanoethylene takes place through the olefinic substituent giving the $_{\pi}2 + _{\pi}2$ adduct (10).

There are several examples where a pyrazole fails to undergo cycloaddition reactions under conditions similar to those in which other heterocyclic compounds will react.[1]

Our studies on 1-phenyl-4-vinylpyrazole (1) confirmed this lack of reactivity towards diethyl azodicarboxylate (DEAZD)[2] and even with the strong dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[3]. Only in the case of the reaction with dimethyl acetylenedicarboxylate (DMAD) in a sealed vessel under pressure and at high temperature were the indazole derivatives (2) and (3) obtained.[4]



1 E : CO₂Me 2 3

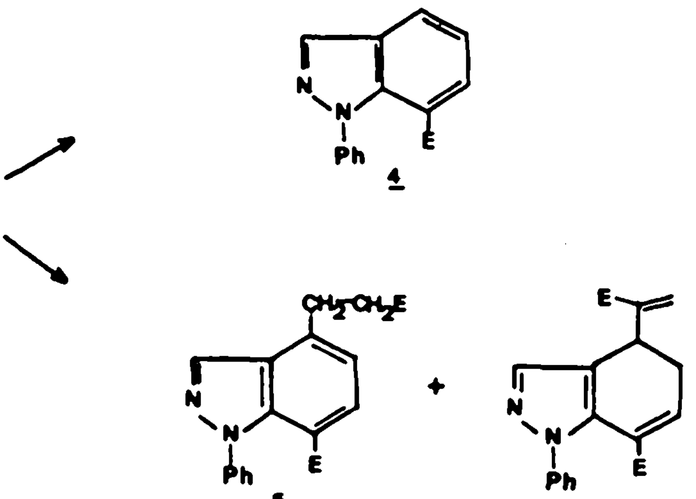
Now further work with other dienophiles reveals new examples of cycloaddition reactions, some of which involve participation of the pyrazole ring.

The reaction of the vinylpyrazole (1) with methyl propiolate (MP) was conducted at 150°C under pressure for five days. The crude mixture contained much polymer but, when it was purified by column chromatography, two major fractions were obtained which were further purified by h.p.l.c. In spite of this double purification process neither fraction comprised a single pure compound.

The ^{1}H nmr spectrum of the first fraction was consistent with the structure of the indazole (4), showing a singlet at δ3.24 (CO_2CH_3), with other signals located in the aromatic region. A singlet at δ8.28 can be assigned to H3 and the two doublets of doublets at δ7.96 (J 8 and 1 Hz) and 7.87 (J 7.5 and 1 Hz) must be H4 and H6, whilst the double doublet at δ7.25 (J 8 and 7.5 Hz) can be assigned to H5 on the basis of decoupling experiments. The coupling constants 8 Hz ($J_{4,5}$), 7.5 Hz ($J_{5,6}$) and 1 Hz ($J_{4,6}$) found for the indazole (4) are very close to the data reported for 1-methyl indazole.[5] The impurity (ca. 15%) in this fraction had two clear singlets at δ8.85 and 3.97 with relative intensities 1:3.

The second material eluted from the column was also rechromatographed by h.p.l.c. and elemental analysis showed a molecular formula $C_{19}H_{18}N_2O_4$. The ^{1}H nmr (200 MHz) suggested an equimolecular mixture of the isomers (5) and (6). These two 1:2 adducts are obtained from a Diels-Alder cycloaddition followed by a non-regioselective "ene" reaction. Little work has been reported on this reaction with propiolic ester and, although apparently the linear isomer predominates over the branched isomer in most cases,[6] a recent example is known where in the reaction of the 3-vinylthiophen with MP, this last isomer (7) was isolated exclusively.[7]

The adduct (5) is characterized by two triplets at δ3.36 (J 8 Hz) and 2.8 (J 8 Hz), two doublets at δ7.8 (J 8 Hz) and 7.1 (J 8 Hz) assigned to H6 and H5, and a singlet at 8.33 to H3. The ^{1}H nmr of compound (6) showed a double doublet at δ6.61 (J 5.6 and 4.4 Hz, H6), two singlets at δ6.28 and 5.5, a triplet at δ4.15 (J 6 Hz, H4) and a multiplet at δ2.66-2.76 (H5) with a very close similarity to the adduct (7).



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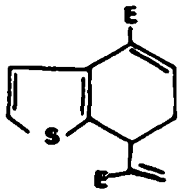

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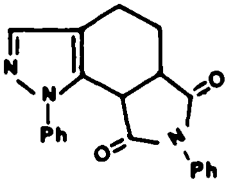
The reaction of (1) with N-phenylmaleimide was also carried out in a sealed vessel at 150°C. Two products were isolated from the reaction mixture and characterised spectroscopically. Elemental analysis of the first compound eluted from the column indicated the formula $C_{21}H_{17}N_3O_2$ and the ^1H and ^{13}C nmr spectral data were completely compatible with formation of the 1:1 adduct (8) produced by $_{\pi}4 + _{\pi}2$ cycloaddition and H-shift. The second compound was a 1:2 adduct (9) resulting from an "ene" reaction of the initally formed cycloadduct with a second molecule of N-phenylmaleimide.

Tetracyanoethylene (TCNE) reacted with (1) in a different way. The reaction took place in dichloromethane at room temperature and the $_{\pi}2 + _{\pi}2$ cycloadduct (10) was isolated in higher yield (80%) than the precedent cases.



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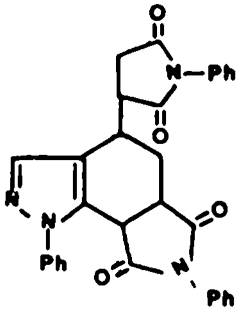

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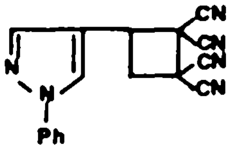

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The new results described in this work agree with those of our previous studies[2-4] on the reactivity of the 1-phenyl-4-vinylpyrazole with dienophiles and show that Diels-Alder adducts are obtained only at high temperatures under pressure when there are no competition reactions of the olefin substituent with the dienophile at lower temperatures.

EXPERIMENTAL

I.r. spectra were measured in $CHBr_3$, using a Perkin-Elmer 577 spectrometer. ^1H spectra were recorded in $CDCl_3$ (ca. 30%) at 200 MHz using a Bruker AC-200 and ^{13}C nmr at 20 MHz using a Bruker WP-80. Mps were determined in a Kofler hot stage. H.p.l.c. was performed on a Waters instrument using semipreparative silica carbowax column eluting with mixtures of ethyl acetate and hexane unless otherwise stated.

Reaction between 1-phenyl-4-vinylpyrazole and methyl propiolate.-1-Phenyl-4-vinylpyrazole (2 g, 0.0117 mol) and MP (1.95 g, 0.023 mol) in dichloromethane (20 ml) were heated at 150°C for 5 days in an enclosed steel bomb. The crude mixture was purified by column chromatography using hexane-diethyl ether (9:1). The first fraction eluted was further purified by h.p.l.c. (eluent hexane-ethyl acetate 4:1) to give an impure sample of methyl 1-phenylindazole-7-carboylate (4) (0.02 g, 0.65%). ν_{max} 1740 cm^{-1}; δ H 3.24 (s, 3 H), 7.25 (dd, J 8 and 7.5 Hz, H5), 7.6-7.4 (m, 5 H), 7.87 (dd, J 7.5 and 1 Hz, H6), 7.96 (dd, J 8 and 1 Hz, H4), 8.28 (s, 1 H, H3); δ C 51.5 (q), 116.4 (s), 120.9 (d), 124.1 (d), 125.3 (d), 126.6 (s), 127.4 (d), 129.0 (d), 129.7 (d), 134.5 (s) 135.9 (d), 142.0 (s).

The second fraction eluted (0.5 g, 13%) was also rechromatographed by h.p.l.c. (hexane-ethyl acetate 4:1) but the mixture of isomers (5) and (6) could not be resolved (0.2 g, 5.2%). (Found C 67.38, H 5.47, N 8.35, $C_{19}H_{18}N_2O_4$ requires C 67.44, H 5.36, N 8.28). ν_{max} 1735 cm^{-1}; δ H 2.66-2.76 (m, 2 H), 2.8 (t, J 8 Hz, 2 H), 3.1 (s, 3 H), 3.21 (s, 3 H), 3.36 (t, J 8 Hz, 2 H), 3.,67 (s, 3 H) 3.79 (s, 3 H), 4.15 (t, J 6 Hz, 1 H), 5.5 (s, 1 H), 6.28 (s, 1 H), 6.61 (dd, J 5.6 and 4.4 Hz, 1 H), 7.1 (d, J 8 Hz, 1 H), 7.25-7.48 (m, 11 H), 7.79 (d, J 8 Hz, 1 H) and 8.34 (s, 1 H). δ C 28.7 (t), 31.3 (t), 32.,6 (d), 34.8 (t), 51.,4 (q) 51.6 (q), 51.9 (q), 52.2 (q), and aromatic carbons 116.1, 120.4, 124.6, 126.2, 127.5, 127.7, 129.3, 130.4, 134.6, 137.6, 138.2.

Reaction between 1-phenyl-4-vinylpyrazole and N-phenylmaleimide.- A mixture of 1-phenyl-4-vinylpyrazole (2 g, 0.0116 mol), N-phenylmaleimide (2.04 g 0.0116 mol) in dichloromethane (10 ml) was heated in an enclosed steel bomb at 150°C for 14 h. The crude mixture was purified by column chromatography using hexane-ethyl acetate (2:1) and then with increasing proportions of ethyl acetate. The first fraction eluted (1.2 g 35%) was crystallized from cyclohexane-ethyl acetate giving the (1:1) adduct (8) m.p. 189°C. (Found C 73.9, H 5.0, N 12.26. $C_{21}H_{17}N_3O_2$ requires C 73.45, H 5.0, N 12.23). ν_{max} 1770 cm^{-1}. δH 1.93 (m, 1 H), 2.5 (m, 2 H), 2.7 (m, 1 H), 3.45 (m, 1 H, H6), 4.5 (d, J 8 Hz, H7). C 18.3 (t), 24.4 (t), 38.6 (d), 40.9 (d), and aromatic carbons 119.0, 124.9, 126.2, 127.7, 128.5, 128.9, 131.5, 137.8. 140.2, 172.9, and 176.9. The second fraction eluted (1 g 16.7%) was crystallized from methanol and it was identified as the 1:2 adduct (9) m.p. 170°C. (Found C 72.32, H 4.41, N 10.95, $C_{31}H_{24}N_4O_4$ requires C 72.1, H 4.68, N 10.85. ν_{max} 1705 cm^{-1}. δ H 1.84 (m, 1 H, H5), 2.64 (m, 2 H), 2.93 (m, 1 H), 3.34 (m, 1 H), 3.58 (m, 2 H, H6) 4.48 (d, J 8 Hz, H7), 7.48 (m, 11 H); δ C 28.6 (t), 30.5 (d), 30.96 (t), 38.1 (d), 39.7 (d), 43.6 (d), and aromatic carbons 117.9 125.0, 126.2, 128.3, 128.7, 129.0, 129.1, 131.5, 131.8, 132.7, 136.0, 140.0, 174.4, 176.3, and 176.8.

Reaction between 1-phenyl-4-vinylpyrazole and tetracyanoethylene.- TCNE (0.75 g, 0.0058 mol) in dichloromethane (10 ml) was added to 1-phenyl-4-vinylpyrazole (1 g, 0.0058 mol) in the same solvent (10 ml). The mixture was stirred for 15 min at R.T. The crude mixture was purified by column chromatography (carbontetrachloride-ethyl acetate 3:2). The only product isolated was crystallized from chloroform giving the adduct (10). (1.4 g, 80%). (Found C 68.37, H 3.67, N 28.32,m $C_{17}H_{10}N_6$ requires C 68.44, H 3.37, N 28.17). ν_{max} 3180 cm^{-1}. δ H 3.32, (dd, J 13 and 11.5 Hz, 1 H), 3.42 (dd, J 13 and 9.2 Hz, 1 H), 4.63 (dd, J 11.5 and 9.2 Hz, 1 H), 7.1-7.7 (m, 5 H), 7.8 (s, H5), 8.1 (s, H3). δ C 34.3 (s), 37.9 (t), 40.1 (d), 46.0 (s), 110.4 (s), 11.5 (s), 111.8 (s), 112.3 (s), 117.1 (s), 119.3 (d), 127.4 (d), 128.2 (d), 129.9 (d), 140.3 (s), 140.7 (d).

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