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Cycloadditions with 1-Phenyl-5-vinylpyrazole

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1-Phenyl-5-vinylpyrazole reacts with dimethylacetylenedicarboxylate (DMAD), *N*-phenylmaleimide (NPMI), tetracyanoethylene (TCNE), 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), and diethyl azodicarboxylate (DEAZD) to afford 1:1 adducts through Diels–Alder cycloadditions. Ene reaction products were not detected in these reactions. Treatment of the dihydroindazole from the reaction with DMAD, gave the corresponding indazole. In the reactions with methyl propiolate (MP) a 1:2 adduct was obtained from a double Diels–Alder reaction followed by extrusion of ethylene.

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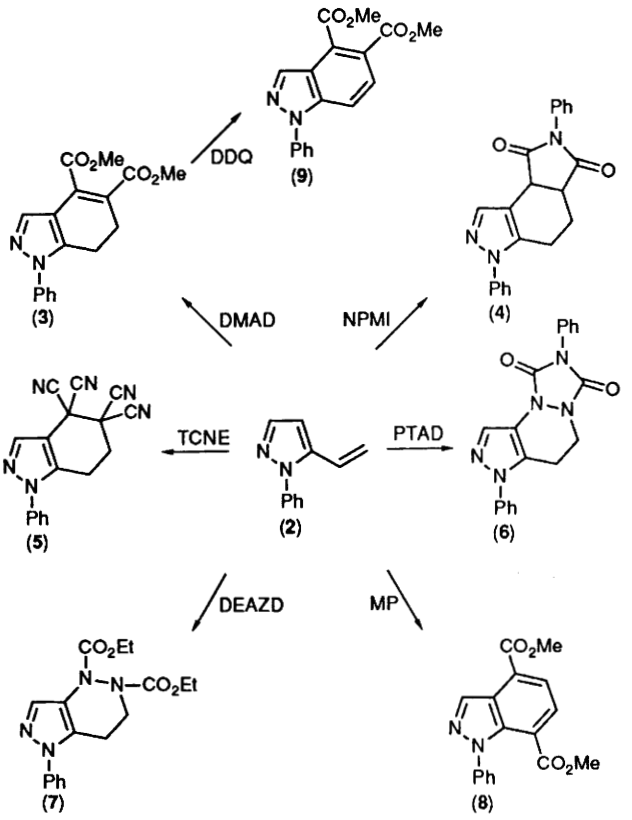
Previous work [1,2] on the reactivity of 1-phenyl-4--vinylpyrazole (**1**), has shown that this substrate reacts with dimethyl acetylenedicarboxylate (DMAD), methyl propiolate (MP), and *N*-phenylmaleimide (NPMI) under conditions of pressure and high temperature as a diene system to afford 1:1 adducts as a result of a Diels–Alder reaction and 1:2 adducts by a further ene reaction. With other dienophiles such as tetracyanoethylene (TCNE), diethyl azodicarboxylate (DEAZD), and 4-phenyl-1,2,4-triazole-3,5-dione (PTAD), the reactions occur at lower temperatures and involve only the olefinic substituent.

Since there are no other examples of cycloadditions with participation of the pyrazole ring in the literature we have considered important the preparation of 1-phenyl-5-vinylpyrazole (**2**) and the study of its reactivity towards different electron deficient dienophiles. Differences in electron densities and steric hindrance [4,5] for the 4 and 5 positions of 1-phenylpyrazole made it difficult to predict possible similarities in reactivity between 1-phenyl-5-vinylpyrazole (**2**) and the 1-phenyl-4-vinyl isomer (**1**). The present study has shown some important differences. In contrast with the reactivity of 1-phenyl-4-vinylpyrazole (**1**), the isomer (**2**) afforded Diels–Alder cycloadducts with all the reagents we used, the reactivity in such cycloadditions being lower, and reaction times much longer than those required for the vinylpyrazole (**1**). In the reaction with DMAD, NPMI, TCNE, PTAD, and DEAZD, the dihydroindazole (**3**), tetrahydroindazoles (**4**) and (**5**), and the pyridazines (**6**) and (**7**), respectively, were obtained.

In the reaction of the vinylpyrazole (**2**) with MP we obtained the indazole (**8**) as a result of a double Diels–Alder cycloaddition with extrusion of ethylene as has been reported for vinylpyrroles [6] and vinylthiophenes.[7] In the NMR spectra of compounds (**3**)–(**7**) the 3-H signal overlapped with the hydrogens of the phenyl substituent, whilst in the indazole (**8**) it appeared as a singlet at lower field (δ 8.5).

When the dihydroindazole (**3**) was aromatized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the indazole (**9**), a singlet at δ 8.35 for the 3-H was observed as a result of it being separated from the phenyl multiplet. Electrophilic attack of the dienophile on the olefinic substituent, without participation of the pyrazole ring, gave products in the reactions of TCNE, PTAD, and DEAZD with the pyrazole (**1**) at room temperature; 5-vinylpyrazole (**2**) failed to react in this manner. A further fact worthy of note in this study is the absence of 'ene' reaction products that were customary in reactions with other vinylazoles.[1,2,8]

In summary, the results of our study have shown a general reactivity as a diene for the vinylpyrazole (**2**). Diels–Alder cycloadducts that were obtained just in a few cases starting from 1-phenyl-4-vinylpyrazole (**1**), are the only reaction products we found when 1-phenyl-5-vinylpyrazole (**2**) reacted with dienophiles. The yields obtained although low in a few cases, are generally good, specially if we consider that the Diels–Alder reactions involve the very unreactive pyrazole ring.



NPMI = *N*-phenylmaleimide, MP = methyl propiolate, DMAD = dimethyl acetylenedicarboxylate, TCNE = tetracyanoethylene, DEAZD = diethyl azodicarboxylate, PTAD = 4-phenyl-1,2,4-triazole-3,5-dione.

Experimental

M.p.s were determined on a Kofler heated stage and are uncorrected. Column chromatography was performed on Merck silica gel. ^{1}H and ^{13}C NMR were determined using a Bruker WP-80 or a Bruker AM 400 WB. IR spectra were determined with a Perkin-Elmer 843 spectrometer.

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1-*Phenylpyrazole 5-carbaldehyde*.—Butyl-lithium in hexane (1.6M; 62.5 ml) was slowly added under argon to 1-phenylpyrazole (14.4 g, 0.1 mol) in dry THF (50 ml). The suspension was mechanically stirred for 2 h at room temperature. After a period of 2 h dimethylformamide (7.3 g, 0.1 mol) was added and the mixture stirred for an additional 1 h. The reaction mixture was poured into hydrochloric acid (1M; 100 ml) and the organic layer removed. The aqueous solution was basified (1M NaOH) to pH 8 and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated. The viscous oil (15 g) was distilled using a Vigreux column to yield 1-phenylpyrazole (**4g**) and 1-phenylpyrazole-5-carbaldehyde (8.6 g, 50%); δ_H(80 MHz; $CDCl_3$; Me_4Si) 9.65 (1 H, s), 7.55 (1 H, d, *J* 2 Hz), 7.30 (5 H, s), and 6.90 (1 H, d, *J* 2 Hz); δ_C 179.4 (d), 140.0 (d), 138.7 (s), 128.9 (d), 128.6 (d), 125.3 (d), 120.6 (s), and 112.1 (d); ν_{max} 1 680 cm^{-1}.

1-*Phenyl-5-vinylpyrazole*.—A solution of 1-phenylpyrazole-5-carbaldehyde (3.4 g, 20 mmol) in THF (40 ml) was added under argon to a stirred solution of methylenetriphenylphosphorane, obtained from methyltriphenylphosphonium bromide (8.0 g, 22 mmol) and sodium hydride (0.75 g) in THF (65 ml). The reaction mixture was heated under reflux for 3 h and then cooled and kept at 20 °C for 12 h. The liquid phase was decanted from the solid and the residue was washed with hexane (4 × 25 ml). Evaporation of the combined organic phases and distillation of the residual oil at 180 °C/2 mmHg gave the title compound (2.1 g, 63%); δ_H(80 MHz; $CDCl_3$; Me_4Si) 7.50 (1 H, d, *J* 2 Hz) 7.40–7.00 (5 H, m), 6.55 (1 H, dd, *J* 15 and 10 Hz), 6.45 (1 H, d, *J* 2 Hz), 5.60 (1 H, dd, *J* 15 and 1 Hz), and 5.15 (1 H, dd, *J* 10 and 1 Hz); δ_C 140.9 (s), 139.9 (d), 139.6 (s), 128.9 (d), 127.6 (d), 125.2 (d), 124.6 (d), 116.9 (d), and 104.3 (t); ν_{max} 3 000 cm^{-1}.

Reactions of 1-Phenyl-5-vinylpyrazole.—*Procedure a*. 1-Phenyl-5-vinylpyrazole (1.5 g, 9 mmol) and the appropriate dienophile were dissolved in dichloromethane (15 ml) and the solution was heated at 140 °C in a sealed vessel for various periods of time. The crude of reaction product was purified by column chromatography.

Procedure b. 1-Phenyl-5-vinylpyrazole (1.5 g, 9 mmol) and the appropriate dienophile were dissolved in acetone (50 ml) and the solution was heated to reflux. The precipitated product was filtered off.

Reaction with DMAD. Using procedure *a* (72 h), *dimethyl 6,7-dihydro-1-phenyl-1H-indazole-4,5-dicarboxylate* (**3**) (53%); m.p. 116 °C (from CCl_4); δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.65 (1 H, s), 7.45–7.30 (5 H, m), 3.95 (3 H, s), 3.80 (3 H, s), 2.98 (2 H, t, *J* 7.5 Hz), and 2.78 (2 H, t, *J* 7.5 Hz); δ_C 166.7 (s), 139.2 (s), 138.7 (s), 137.5 (s), 137.3 (d), 129.1 (d), 127.9 (s), 127.6 (d), 123.1 (d), 115.8 (s), 52.2 (q), 51.9 (q), 24.7 (t), and 20.4 (t); ν_{max} 1 715 cm^{-1} (Found: C, 65.3; H, 5.1; N, 8.9. $C_{17}H_{14}N_2O_4$ requires C, 65.3; H, 5.1; N, 8.9%).

Reaction with NPMI. Using procedure *a* (96 h), *3,7-diphenyl-4,5-dihydropyrrolo*[3,4-e]*indazole-6,8(7H,8aH)-dione* (**4**) (45%); m.p. 151 °C (from CCl_4); δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.60 (1 H, s), 7.30–6.60 (10 H, m), 4.12 (1 H, d, *J* 8.3 Hz), 3.37 (1 H, dt, *J* 8.3 and 5.4 Hz), 2.73 (2 H, m), 2.37 (1 H, dq, *J* 13.8 and 5.4 Hz), and 2.03–1.95 (1 H, m); δ_C($CDCl_3$) 177.1 (s), 175.6 (s), 138.8 (d), 137.8 (s), 129.9 (s), 128.9 (s), 128.7 (d), 128.2 (d), 128.1 (d), 127.1 (d), 126.0 (d), 123.0 (d), 111.3 (s), 39.7 (d), 38.2 (d), 22.3 (t), and 20.1 (t); ν_{max} 1 710 cm^{-1} (Found: C, 73.5; H, 4.9; N, 12.1. $C_{21}H_{17}N_3O_2$ requires C, 73.4; H, 4.9; N, 12.2%).

Reaction with TCNE. Using procedure *a* (12 h), *1-phenyl-4,5,6,7-tetrahydroindazole-4,4,5,5-tetracarbonitrile* (**5**) (41%); m.p. 197–198 °C (from acetone); δ_H(400 MHz; [$^2H_6$]acetone; Me_4Si) 7.90 (1 H, s), 7.40–7.00 (5 H, m), 3.20 (2 H, t, *J* 6 Hz), and 2.80 (2 H, t, *J* 6 Hz); δ_C 139.5 (s), 138.7 (d), 137.8 (s), 130.1 (d), 129.5 (d), 124.7 (d), 124.2 (s), 111.8 (s), 111.7 (s), 41.9 (s), 40.5 (s), 20.1 (t); ν_{max} 2 400 cm^{-1} (Found: C, 68.45; H, 2.95; N, 28.35. $C_{17}H_{10}N_6$ requires C, 68.45; H, 3.35; N, 28.19%).

Reaction with PTAD. Using procedure *b* (1 h), *3,8-diphenyl-4,5-dihydro-3H-pyrazolo*[4,3-c][1,2,4]*triazolo*[1,2-a]*pyridazine-7,9-dione* (**6**) (69%); m.p. 195 °C (from $CHCl_3$); δ_H(400 MHz, [$^2H_6$]acetone) 8.00 (1 H, s), 7.50 (10 H, s), 4.00 (2 H, t, *J* 6 Hz), and 3.25 (2 H, t, *J* 6 Hz); δ_C([$^2H_6$]acetone) 153.3 (s), 150.2 (s), 139.2 (s), 131.4 (s), 129.5 (d), 129.2 (d), 128.2 (d), 127.9 (d), 127.8 (d), 125.5 (d), 123.9 (s), 122.6 (d), 118.7 (s), 39.7 (t), and 22.8 (t); ν_{max} 1 770 and 1 720 cm^{-1} (Found: C, 66.1; H, 4.4; N, 20.3. $C_{19}H_{15}N_5O_2$ requires C, 66.08; H, 4.36; N, 20.29%).

Reaction with DEAZD. Using procedure *a* (72 h), *diethyl 1-phenyl-4,5,6,7-tetrahydropyrazolo*[4,3-c]*pyridazine-4,5-dicarboxylate* (**7**) (8%); m.p. 102 °C (from ether); δ_H(400 MHz; $CDCl_3$; Me_4Si) 8.00 (1 H, s), 7.50–7.25 (10 H, m), 4.60–4.55 (5 H, m), 3.20–3.10 (2 H, m), 2.75–1.70 (1 H, m), 1.35 (3 H, t, *J* 7 Hz), and 1.20 (3 H, t, *J* 7 Hz); δ_C($CDCl_3$) 153.12 (s), 152.8 (s), 139.4 (s), 131.4 (d), 129.1 (d), 127.0 (d), 125.4 (s), 122.3 (d + s), 62.8 (t), 41.9 (t), 22.1 (t), 14.3 (q), and 14.2 (q); ν_{max} 1 710 cm^{-1} (Found: C, 59.2; H, 5.45; N, 16.45. $C_{17}H_{20}N_4O_4$ requires C, 59.30; H, 5.81; N, 16.28%).

Reaction with MP. Using procedure *a* (168 h), *dimethyl 1-phenylindazole-4,7-dicarboxylate* (**8**) (7%); δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.50 (1 H, s), 7.75 (1 H, d, *J* 8 Hz), 7.55 (1 H, d, *J* 8 Hz), 7.20 (5 H, s), 3.90 (3 H, s), and 3.10 (3 H, s); δ_C 166.5 (s), 166.3 (s), 135.8 (d), 129.9 (s), 128.5 (d), 127.7 (d), 127.1 (d), 126.4 (s), 124.5 (s), 123.8 (d), 123.2 (d), 122.7 (s), 120.6 (s), 51.6 (q), and 51.1 (q).

Aromatization of Dihydroindazole (**3**).—DDQ (1.25 g, 5.5 mmol) in dry benzene (10 ml) was added to the dihydroindazole (**3**) (0.91 g, 5.5 mmol) in dry benzene (5 ml) and the solution refluxed for 30 min. The dihydroquinone was removed from the cooled solution and the filtrate evaporated to give *dimethyl 1-phenylindazole-4,5-dicarboxylate* (**9**) (0.8 g, 86%); m.p. 128 °C (from ether); δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.35 (1 H, s), 7.8–7.4 (7 H, m), 4.00 (3 H, s), and 3.92 (3 H, s); δ_C($CDCl_3$) 167.2 (s), 167.1 (s), 139.2 (s), 135.6 (d), 130.3 (s), 129.5 (d), 128.6 (s), 127.4 (d), 126.6 (s), 124.0 (s), 123.0 (d, d), 112.2 (d), 52.6 (q), and 52.4 (q).

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