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Cycloaddition Reactions of 1-*tert*-Butyl-4-vinylpyrazole

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Summary. 1-*tert*-Butyl-4-vinylpyrazole **1a** reacts with dimethyl acetylenedicarboxylate (*DMAD*), methyl propiolate (*MP*) and N-phenylmaleimide (*NPMI*) affording the indazole derivatives **2**, **3**, and **5** as a result of a Diels-Alder ([4 + 2]) cycloaddition. With diethylazodicarboxylate (*DEAZD*), tetracyanoethylene (*TCNE*) and 4-phenyl-1,2,4-triazole-3,5-dione (*PTAD*) the reaction takes place exclusively through the olefinic substituent and the adducts **6**, **7**, and **9** were isolated. The alkenylpyrazoles **1b–d** reacted with *DMAD* and N-phenylmaleimide to give polymers.

Keywords. Cycloadditions; Diels-Alder; Vinylpyrazoles.

Cycloadditionen von 1-*tert*-Butyl-4-vinylpyrazol

Zusammenfassung. 1-*tert*-Butyl-4-vinylpyrazol **1a** reagiert mit Acetylendicarbonsäure-dimethylester (*DMAD*), Propiolsäuremethylester (*MP*) und N-Phenylmaleimid (*NPMI*) zu den entsprechenden Indazolderivaten **2**, **3** bzw. **5**, als Ergebnis einer Diels-Alder-([4 + 2])-Cycloaddition. Bei der Reaktion mit Azodicarbonsäure-diethylester (*DEAZD*), Tetracyanethylen (*TCNE*) und 4-Phenyl-1,2,4-triazol-3,5-dion (*PTAD*) wird exklusiv die Olefingruppe von **1a** angegriffen, wobei die Addukte **6**, **7** bzw. **8** isoliert werden. Die Alkenylpyrazole **1b–d** reagieren mit *DMAD* und N-Phenylmaleimid unter Bildung von Polymeren.

Introduction

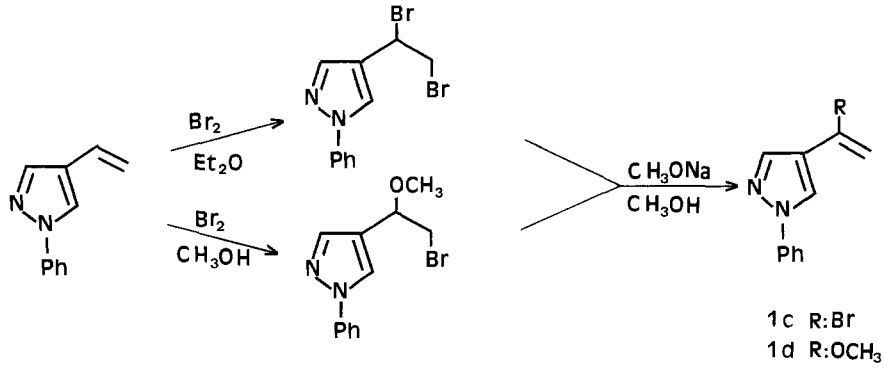
In earlier publications [1, 2] we reported that although the pyrazole ring is reluctant to participate in cycloaddition reactions, the 1-phenyl-4-vinylpyrazole can afford Diels-Alder [4 + 2]-cycloadducts under pressure and high temperature conditions.

In order to see if the presence of substituents either on the pyrazole ring or the vinyl group modifies favourably the yield of cycloadducts obtained from these reactions, we have prepared the alkenylpyrazoles **1a–d** and studied their reactivity towards dienophiles.

Results and Discussion

In the reaction of 1-*tert*-butyl-4-vinylpyrazole **1a** with *DMAD* we isolated the 1 : 2 adduct **2**, containing a small impurity which was impossible to remove even after a double chromatographic purification (column chromatography and HPLC). Similar difficulties in the resolution of mixtures were found in our previous paper for analogous compounds [2]. In contrast with the results obtained in the case of

1-phenyl-4-vinylpyrazole, the dihydroindazole **2** was stable and did not afford the corresponding aromatized indazole by means of two prototropic shifts. The configuration of maleate for the C-4 substituent was assigned by comparison with spectral data of similar compounds reported in literature [3, 4]. In case of compound **2**, the proton of the maleate residue appears at δ 5.50 as a doublet (J = 1 Hz) because of the allylic coupling with H-4. Another difference to be pointed out is the closer similarity of the chemical shifts of H-5 and H-5'.



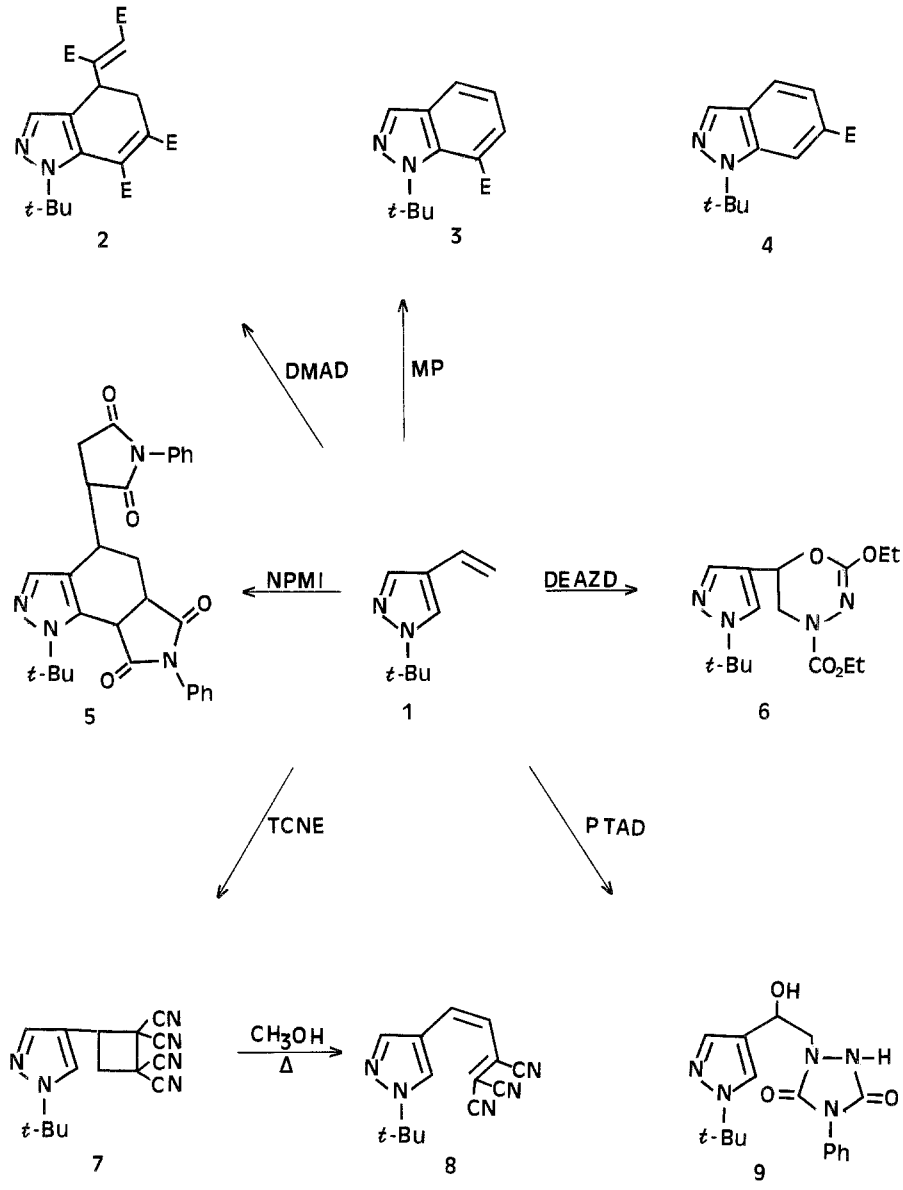
In the reaction with *MP*, no traces of 1 : 2 adducts could be detected. The 1 : 1 adduct **3** isolated from this reaction was also difficult to get in pure form (TLC and further HPLC). In the ^{1}H-NMR [along with the signals at δ 3.86, CO_2CH_3, and 1.61, $C(CH_3)_3$, from the adduct **3**] a smaller set of signals (in the ratio 2 : 1) at δ 3.76, CO_2CH_3, and 1.54, $C(CH_3)_3$, was tentatively assigned to the isomer **4**. The H-3 from adduct **3** appears as a singlet at δ 8.39 whereas the corresponding signal for this hydrogen in the adduct **4** is overlapped with the aromatic multiplet at higher field. The shift at lower field for the H-3 of indazoles has been reported in literature when there are electron withdrawing substituents on the N or the positions 5 or 7 of these compounds [1, 2, 5].

From the reactions with *NPMI*, *DEAZD* and *TCNE* the adducts **5**, **6** and **7** could be isolated from the crude reaction mixtures. The cyclobutane **7** gave the butadiene **8** when it was refluxed in methanol.

In a previous paper [6] we reported that 1-phenyl-4-vinylpyrazole reacted as an electron rich olefin with *PTAD* and the 1,4-dipole generated in this reaction could be captured with acetone and water. Now, with 1-*tert*-butyl-4-vinylpyrazole the trapping experiments succeed just with water, and the alcohol **9** was isolated with 82% yield. Spectral data were practically coincident with the adducts **10** and **11** obtained from reactions of 1-phenyl-4-vinylpyrazole with *DEAZD* and *PTAD*

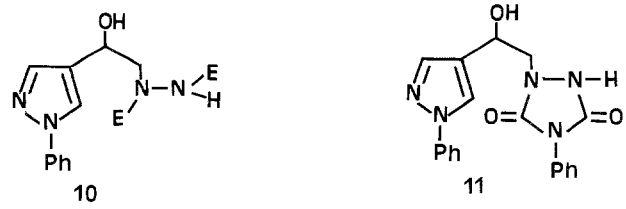
Table 1. Selected ^{13}C-NMR shifts of **9–11**

	C_3	C_5	CH	CH_2
9	135.9	127.4	62.1	52.1
10	138.9	129.3	63.9	58.2
11	138.8	128.1	62.3	52.2



[7, 8]. The structures of the latter compounds were unequivocally established by X-ray chrystallography. In Table 1 we show the remarkable parallelism of corresponding ^{13}C-NMR shifts.

The alkenylpyrazole **1b** was prepared by Wittig reaction from 4-acetyl-1-phenylpyrazole. The alkenylpyrazoles **1c** and **1d** were prepared from 1-phenyl-4-vi-



nylpyrazole by addition of bromine in ether or methanol and further treatment with base.

The stability of the alkenylpyrazoles **1b–d** was much lower than that of 1-phenyl and 1-*tert*-butyl-4-vinylpyrazoles and its reactivity against *DMAD* and *NPMI* was studied. The alkenylpyrazoles **1b** and **1c** gave polymeric mixtures in reactions carried out at 100°C and 70°C respectively. In the case of the enol ether **1d**, the tautomer 4-acetyl-1-phenylpyrazole was obtained (ca. 45%) at 150°C, along with polymeric material. This last transformation could be detected even at 40°C.

Conclusions

As a result of the present work it was shown that the capacity of vinylpyrazoles to participate in cycloaddition reactions is not restrained only to one kind of substituent on the nitrogen ring. Nevertheless the scope is limited and it fails with small changes by substitution on the vinyl group. Attempts of synthesis of indazoles through cycloaddition reactions under catalytic activation are in progress.

Experimental

IR spectra were measured in $CHBR_3$, using a Perkin-Elmer 577 spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ (ca. 3%) at 200 MHz using a Bruker Ac-200 and ^{13}C NMR at 20 MHz using a Bruker WP-80. M.p.s were determined in a Kofler hot stage. PCL was performed on a Waters instrument using a semipreparative silica carbowax column eluting with mixtures of ethyl acetate and hexane unless otherwise stated.

1-tert-Butyl-4-formylpyrazole and 1-tert-Butyl-4-vinylpyrazole

These compounds were obtained by similar procedures as reported in [7, 9].

1-tert-butyl-4-formylpyrazole was obtained with (49%) yield. IR (ν_{max}): 2793, 1676 cm^{-1}. NMR (δ H): 1.5 (s, 9H), 7.8 (s, 1H), 8.1 (s, 1H), 9.7 (s, 1H). δC 28.9 (q) 59.1 (s), 123.3 (d), 129.6 (s), 139.2 (d), 183.3 (d).

1-tert-butyl-4-vinylpyrazole was obtained with (58%) yield. NMR (δ H): 1.50 (s, 9H), 4.85 (dd, J = 10 and 2 Hz, 1H), 5.25 (dd, J = 18 and 2 Hz, 1H), 6.40 (dd, J = 18 and 10 Hz, 1H), 7.30 (s, 1H), 7.33 (s, 1H). NMR (δC): 29.5 (q), 58.0 (s), 111.1 (t), 120.1 (s), 123.2 (d), 127.1 (d), 136.2 (d).

4-Isopropenyl-1-phenylpyrazole

The compound was obtained by Wittig reaction from 4-acetyl-1-phenylpyrazole with 51% yield. NMR (δ H): 2.05 (s, 3H), 4.35 (s, 1H), 5.21 (s, 1H), 7.50–7.15 (m, 5H), 7.69 (s, 1H), 7.70 (s, 1H).

1-Bromo-1-(1-phenyl-4-pyrazolyl) ethene (**1c**)

A solution of bromine in ether (ca. 20%) was added to 1-phenyl-4-vinylpyrazole (3 g, 0.017 mol) in dry ether (15 ml) at 0°C under nitrogen until the yellow color was persistent. The reaction was practically quantitative and 4-(1,2-dibromoethyl)-1-phenylpyrazole (5.73 g, 98%) was used in the next step without purification. NMR (δ H): 3.85 (m, 2H), 5.20 (dd, J = 8 and 6 Hz, 1H), 7.10–7.60 (m, 5H), 7.70 (s, 1H), 7.97 (s, 1H).

The dibromo substituted pyrazole (5 g, 0.015 mol) in methanol (30 ml) was refluxed with sodium methoxide (1.7 g of sodium in 30 ml of methanol) for 1 h. The crude mixture was purified by column

chromatography using hexane : ethyl acetate (9 : 1) affording **1 c** (2.1 g, 56%). NMR (δ H): 5.50 (d, J = 3 Hz, 1 Hz), 6.00 (d, J = 3 Hz, 1 H), 7.60–7.20 (m, 5 H), 7.70 (s, 1 H), 8.00 (s, 1 H).

4-(2-Bromo-1-methoxyethyl)-1-phenylpyrazole (**1 d**)

A methanolic solution of bromide was added to 1-phenyl-4-vinylpyrazole (3 g, 0.017 mol) in methanol (15 ml) at 0°C under nitrogen until the yellow color was persistent. The 2-bromo-1-methoxy-1-(1-phenyl-4-pyrazolyl)ethane (4.53 g, 95%) was used in next step without further purification. NMR (δ H): 3.50 (s, 3 H), 3.70 (d, J = 6 Hz, 2 H), 4.70 (t, J = 6 Hz, 1 H), 7.90–7.50 (m, 5 H), 8.10 (s, 1 H), 8.20 (s, 1 H).

The bromomethoxy substituted pyrazole (3.6 g, 0.0128 mol) was heated with sodium methoxide (1.4 g of sodium in methanol 20 ml) at reflux temperature for 1.5 h. The crude mixture was purified by column chromatography using hexane ethyl acetate affording **1 d** (0.66 g, 25%) and 4-acetyl-1-phenylpyrazole (1.40 g, 45%).

Reactions of 1-tert-Butyl-4-vinylpyrazole

a. With dimethyl acetylenedicarboxylate. 1-*tert*-Butyl-4-vinylpyrazole (1 g, 0.006 mol) and *DMAD* (1.893 g, 0.013 mol) in dichloromethane (10 ml) were heated in an enclosed steel bomb at 120°C for 11 h. The crude mixture was purified by column chromatography using hexane : ethyl acetate (3 : 1). The product isolated was further purified by HPLC (eluent hexane-ethyl acetate 3 : 1) to give the dihydroindazole **2** as an impure sample (0.2 g, 6%). IR (ν_{max}): 1 740 cm^{-1}. NMR (δ H): 1.50 (s, 9 H), 2.56 (dd, J = 16 and 6.8 Hz, 1 H), 2.80 (dd, J = 16 and 6.2 Hz, 1 H), 3.90–3.50 (m, 13 H), 5.57 (d, J = 1.08 Hz, 1 H), 7.20 (s, H_3). NMR (δ C): 30.3 (q), 30.6 (t), 35.2 (d), 51.7 (q), 52.3 (2 × q), 52.5 (q), 61.9 (s), 121.2 (s), 121.7 (d), 128.9 (s), 130.6 (s), 133.7 (d), 134.0 (s), 148.7 (s), 165.1 (s), 166.7 (s), 167.2 (s), 168.2 (s).

b. With methyl propiolate. 1-*tert*-Butyl-4-vinylpyrazole (2 g, 0.013 mol) and *MP* (2.2 g, 0.026 mol) in dichloromethane (15 ml) were heated at 120°C for five days in an enclosed steel bomb. The crude mixture was purified by column chromatography using hexane: ethyl acetate (10 : 1). The product isolated was further purified by HPLC using the same eluent to give the indazoles **3** and **4** (0.47 g, 15%). NMR (δ H): 1.54 (s, 9 H), 1.61 (s, 9 H), 3.76 (s, 3 H), 3.86 (s, 3 H), 7.24–8.03 (m, 7 H), 8.39 (s, 1 H). NMR (δ C): 29.5 (q), 29.7 (q), 51.5 (q), 52.1 (q), 63.1 (s) and aromatic signals 110.9, 118.2, 127.2, 128.6, 129.2, 129.7, 133.4, 133.8, 136.4, 146.3, 160.7, 167.1.

c. With N-phenylmaleimide. A mixture of 1-*tert*-butyl-4-vinylpyrazole (1 g, 0.006 mol) and *NPMI* (2.07 g, 0.012 mol) in dichloromethane (10 ml) was heated in an enclosed steel bomb at 120°C for 11 h. The crude was purified by column chromatography using chloroform. The product isolated was crystallized from ethanol giving the 1 : 2 adduct **5** (0.150 g, 4%) m.p. 243°C. Anal. found: C 70.28, H 5.39, N 11.30: $C_{29}J_{28}N_4O_4$ requires C 70.17, H 5.64, N 11.29. IR (ν_{max}): 1 720 cm^{-1}. NMR (δ H): 1.45 (m, 2 H), 1.64 (s, 9 H), 2.64 (m, 2 H), 2.91 (m, 1 H), 3.32 (m, 1 H), 3.56 (m, 1 H), 4.90 (d, J = 8 Hz, H_7), 7.20–7.60 (m, 11 H). NMR (δ C): 29.2 (t), 29.7 (d), 30.6 (q), 39.4 (d), 40.5 (d), 63.2 (s), 116.9 (s), 126.3 (d), 126.4 (d), 128.7 (d), 128.9 (d), 129.2 (d × 2), 131.2 (s), 131.5 (s), 131.8 (s), 133.2 (d), 173.2 (s), 174.7 (s), 176.8 (s), 177.0 (s).

d. With diethyl azodicarboxylate. A mixture of 1-*tert*-butyl-4-vinylpyrazole (1 g, 0.006 mol) and *DEAZD* (2.29 g, 0.0132 mol) in dry acetonitrile (20 ml) was refluxed for 2 h. After evaporation of the solvent the residue was purified by column chromatography using hexane-ethyl acetate (3 : 1). The product isolated was further purified by HPLC to give an impure sample of the oxadiazine **6** (0.9 g, 54%). NMR (δ H): 1.6 (s, 9 H), 1.1–1.4 (m, 6 H), 4.1–4.7 (m, 6 H), 5.30 (dd, J = 8 and 3.5 Hz, 1 H), 7.30 (s, H_3), 7.40 (s, H_5). NMR (δ C): 13.6 (q), 13.7 (q), 28.9 (q), 58.1 (s), 62.8 (t), 64.7 (t), 69.7 (d), 115.8 (s), 124.1 (d), 136.1 (d), 153.1 (s), 159.6 (s).

e. With tetracyanoethylene. 1-*tert*-Butyl-4-vinylpyrazole (1 g, 0.006 mol) in dichloromethane (10 ml) was added to *TCNE* (0.84 g, 0.006 mol) in the same solvent (10 ml). The mixture was stirred for

30 min at room temperature. The product precipitated was crystallized from chloroform giving the cyclobutane **7** (1.54 g, 83%) m.p. 145°C. Anal. found C 64.73, H 5.22, N 30.48; $C_{15}H_{14}N_6$ requires C 64.75, H 5.03, N 30.21. IR (ν_{max}): 3 180 and 2 250 cm^{-1}. NMR (δ H): 1.60 (s, 9 H), 3.20 (dd, J = 13 and 11.5 Hz, 1 H), 3.35 (dd, J = 13 and 9.2 Hz, 1 H), 4.50 (dd, J = 11.5 and 9.2 Hz, 1 H), 7.55 (s, H_3), 7.63 (s, H_5). NMR (δ C): 29.5 (q), 33.2 (d), 38.3 (t), 40.6 (s), 45.6 (s), 59.5 (s), 108.1 (s), 109.9 (s), 110.1 (s), 110.7 (s), 112.0 (s), 125.7 (d), 137.6 (d).

When a solution of cyclobutane **7** in methanol (20 ml) was refluxed for 4 h the butadiene **8** was obtained (0.690 g, 95%) m.p. 160°C. Anal. found: C 67.14, H 4.82, N 28.31; $C_{13}H_{13}N_3$ requires C 66.93, H 5.17, N 27.88. IR (ν_{max}): 2 230, 1 600 cm^{-1}. NMR (δ H): 1.60 (s, 9 H), 6.87 (d, J = 18 Hz, 1 H), 7.57 (d, J = 18 Hz, 1 H), 7.77 (s, H_3), 7.82 (s, H_5). NMR (δ C): 29.3 (q), 60.1 (s), 110.8 (s), 111.6 (s), 111.7 (s), 117.4 (s), 118.1 (d), 129.2 (d), 140.2 (s), 140.3 (d), 142.9 (d).

f. With 4-phenyl-1,2,4-triazoline-3,5-dione. 1-*tert*-Butyl-4-vinylpyrazole (1 g, 0.006 mol) and *PTAD* (1.17 g, 0.006 mol) in acetone (not dried) were stirred for 15 min. The precipitate was crystallized from ethanol to give the alcohol **9** (1.7 g, 82%), m.p. 160°C. IR (ν_{max}): 3 200, 1 750, 1 700 cm^{-1}. NMR (δ H): 1.44 (s, 9 H), 3.60 (dd, J = 14.21 and 4.8 Hz, 1 H), 3.70 (dd, J = 14.21 and 8.63 Hz, 1 H), 4.50 (broad band, 1 H), 4.95 (dd, J = 8.63 and 4.8 Hz, 1 H), 7.2–7.5 (m, 7 H). NMR (δ C): 29.3 (q), 52.1 (t), 57.6 (s), 62.1 (d), 121.6 (s), 122.1 (d), 125.7 (d), 127.4 (d), 128.5 (d), 131.89 (s), 135.97 (d), 151.84 (s), 152.16 (s).

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References

[1] Jones R. A., Sepúlveda J., Medio M., Abarca B., Dawes H. M., Hursthouse M. B. (1985) J. Chem. Res. (M): 1128
[2] Medio M., Sepúlveda J. (1986) Tetrahedron **42**: 6683
[3] Abarca B., Ballesteros R., Enriquez E., Jones G. (1985) Tetrahedron **41**: 2435
[4] Davidson W. J., Elix J. A. (1968) Tetrahedron Lett.: 4589
[5] Elguero J. (1984) In: Potts K. T. (ed.) Comprehensive Heterocyclic Chemistry, Vol. 5. Pergamon Press, Oxford
[6] Sepúlveda J., Medio M. (1985) Tetrahedron Lett. **26**: 6357
[7] Jones R. A., Abarca B., Sepúlveda J., Quilez J., King T. J. (1984) J. Chem. Soc. Perkin Trans. I: 1423
[8] Medio M., Sepúlveda J. (1987) J. Chem. Res. (S): 384
[9] Finar I. L., Lord G. H. (1957) J. Chem. Soc.: 3314

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