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Synthesis and Structure of 1-(Buta-1,3-dien-2-yl)pyrazoles and Their Behavior in Diels–Alder Reactions

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Abstract—A convenient procedure has been developed for the synthesis of *cis*- and *trans*-isomeric 1-(buta-1,3-dien-1-yl)-1*H*-pyrazoles by reaction of the corresponding pyrazoles with β-methylacrolein diethyl acetal and subsequent 1,4-cleavage of the nucleophilic substitution products. The behavior of the title compounds in Diels–Alder reactions with maleic anhydride has been studied. According to the ^{1}H NMR data, 1-(buta-1,3-dien-1-yl)-1*H*-pyrazole is a mixture of *cis* and *trans* isomers. Butadienylpyrazoles having methyl groups in the pyrazole ring do not react with maleic anhydride.

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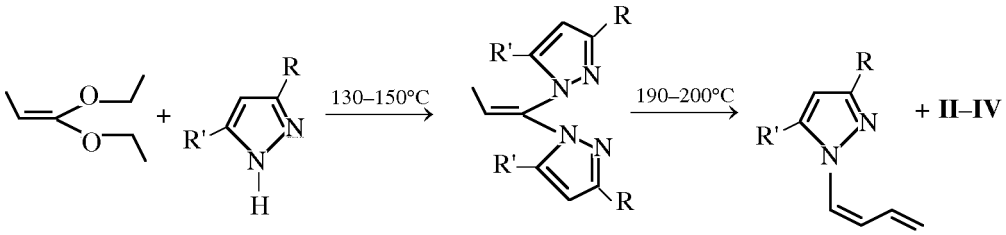
Pyrazoles **II** and **IV** are aromatic compounds which do not react with dienophiles according to Diels–Alder [1]. In reactions with vinyl-containing compounds, pyrazoles **II** and **IV** behave as nucleophiles to give the corresponding addition products at the nitrogen atom [2–13]. While searching for new convenient synthetic routes to 1-(buta-1,3-dien-1-yl)-1*H*-pyrazoles **VIII–X** [14] with a view to examine their behavior in Diels–Alder reactions, pyrazoles **II–IV** were brought into reaction with β-methylacrolein diethyl acetal (**I**) in the presence of a catalytic amount of *p*-toluenesulfonic acid [15]. The process occurred at 130–150°C as double nucleophilic replacement, and the products were compounds which were formed in 75–80% yield. By heating substitution products **V–VII** at higher temperature, 190–200°C (20 mm), we obtained 50–65% of target butadi-enylpyrazoles **VIII–X**.

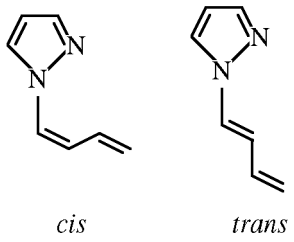


I **II–IV** **V–VII** **VIII–X**

II, V, VIII, R = R' = H; **III, VI, IX**, R = CH_3, R' = H (R = H, R' = CH_3); **IV, VII, X**, R = R' = CH_3.

According to the ^{1}H NMR and GLC data, compound **VIII** was isolated as a mixture of *cis* and *trans* isomers at a ratio of 1 : 1.

1-(Buta-1,3-dien-1-yl)-3(5)-methyl-1*H*-pyrazole (**IX**) displayed a complex pattern in the ^{1}H NMR spectrum. Individual 3- and 5-methyl isomers were isolated by fractional distillation. Their structure was determined on the basis of the ^{1}H NMR data, taking into account the chemical shifts of the ring protons and protons in the methyl group; the spectra were recorded

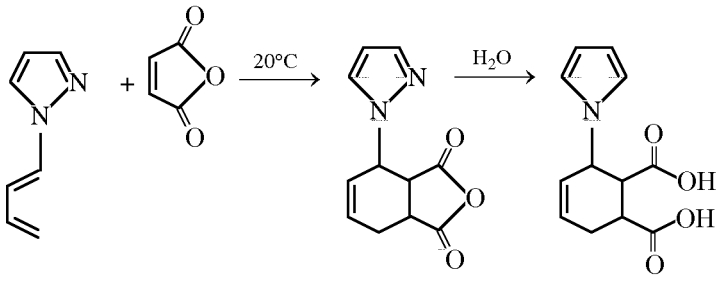


cis *trans*

in carbon tetrachloride and benzene [16]. In keeping with the ^{1}H NMR data, both isomers **IX**, 3-CH_3 and 5-CH_3, have *cis* configuration of the butadienyl fragment. 1-(Buta-1,3-dienyl)-3,5-dimethyl-1*H*-pyrazole (**X**) is also characterized by *cis* configuration of the exocyclic double C=C bond.

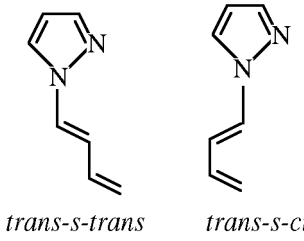
Thus introduction of electron-donor methyl groups into the pyrazole ring favors formation of the coresponding *cis*-butadienylpyrazoles (**IX**, **X**) in which the butadienyl group is likely to adopt transoid conformation; therefore, they are inactive in Diels–Alder reactions. In the ^{1}H NMR spectra of dienylpyrazoles **VIII**–**X**, signals from the vinylic protons in the N–CH=CH fragment appear as doublets at δ 5.60–7.17 ppm, while terminal CH_2= protons give rise to a doublet of multiplets or a triplet of doublets in the δ range from 5.10 to 5.30 ppm.

Among two stereoisomers of 1-(buta-1,3-dien-1-yl)-1*H*-pyrazole (**VIII**), only the *trans* (*s-cis*) isomer reacts with maleic anhydride according to Diels–Alder with formation of compound **XI**. The cycloaddition occur spontaneously at 20°C and is accompanied by exothermic effect.



VII **IX** **XII**

Treatment of the reaction mixture with water was accompanied by hydrolysis of **XI** to give dicarboxylic acid **XII** which was isolated. Monitoring of the Diels–Alder reaction course by GLC and NMR showed that only 30% of the *trans* isomer of **VIII** reacted with maleic anhydride, while the remaining amount failed to react even at 60°C. Therefore, we presumed that *trans*-butadienylpyrazole **VIII** exists as a mixture of two rotamers, *trans-s-trans* and *trans-s-cis*, the first of which being more stable.



trans-s-trans *trans-s-cis*

The structure of 3-(1*H*-pirazol-1-yl)cyclohex-4-ene-1,2-dicarboxylic acid (**XII**) was confirmed by the IR and ^{1}H and ^{13}C NMR spectra. The IR spectrum of **XII** contained absorption bands due to vibrations of the pyrazole ring (1540 cm^{-1}) and carboxy group (1730 cm^{-1}). Signals in the ^{1}H NMR spectra were assigned using double-resonance techniques and NOESY two-dimensional correlation experiment; ^{13}C signals were assigned on the basis of HMQC two-dimensional ^{1}H–^{13}C correlation spectrum.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR instrument from thin films. The ^{1}H and ^{13}C NMR spectra were measured on a Mercury 300 Vx spectrometer at 300.077 and 75.462 MHz, respectively. GLC analysis was performed on an LKhM-8MD chromatograph equipped with a 1-m column packed with Inerton AW-HMDS impregnated with 10% of

Carbowax-20M; carrier gas helium , flow rate 40 ml min^{-1}; detector temperature 220°C.

General procedure for the synthesis of compounds V–VII. A mixture of 0.2 mol of pyrazole **II–IV**, 0.12 mol of β-methylacrolein diethyl acetal (**I**), and 0.5 g of *p*-toluenesulfonic acid was heated at 130–150°C until ethanol no longer distilled off. The residue was neutralized with aqueous sodium hydroxide and extracted with chloroform, the extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure.

1,1′-[(*E*)-But-2-ene-1,1-diyl]bis(1*H*-pyrazole) (V). Yield 15.6 g (83%), bp 121–122°C (1 mm), n_D^{20} = 1.5300. IR spectrum, ν, cm^{-1}: 1510 (ring), 1640 (C=C). Found, %: C 63.52; H 6.78; N 29.99. $C_{10}H_{12}N_4$. Calculated, %: C 63.82; H 6.38; N 29.78.

1,1′-[(*E*)-But-2-ene-1,1-diyl]bis[3(5)-methyl-1*H*-pyrazole] (VI). Yield 17.3 g (80%), bp 130–135°C (1 mm), n_D^{20} = 1.5320. IR spectrum, ν, cm^{-1}: 1520 (ring), 1640 (C=C). Found, %: C 66.31; H 7.77; N 25.48. $C_{12}H_{16}N_4$. Calculated, %: C 66.67; H 7.40; N 25.92.

1,1′-[(*E*)-But-2-ene-1,1-diyl]bis(3,5-dimethyl-1*H*-pyrazole) (VII). Yield 18.3 g (75%), bp 152–154°C (1 mm), mp 110–111°C (from hexane). IR spectrum, ν, cm^{-1}: 1540 (ring), 1640 (C=C). Found, %: C 68.42; H 7.88; N 23.32. $C_{14}H_{20}N_4$. Calculated, %: C 68.85; H 8.19; N 22.95.

General procedure for the synthesis of compounds VIII–X. A mixture of 0.1 mol of bis-pyrazole **V–VII** and 0.5 g of *p*-toluenesulfonic acid was distilled at 190–200°C at a residual pressure of 20 mm. The distillate was neutralized with an aqueous solution of sodium carbonate and extracted with chloroform, the extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure.

1-(Buta-1,3-dien-1-yl)-1*H*-pyrazole (VIII). Yield 7.8 g (65%), bp 47°C (1 mm), n_D^{20} = 1.5768, d_4^{20} = 0.9975. IR spectrum, ν, cm^{-1}: 1510 (ring), 730, 970, 1640 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): *cis* isomer: 5.18 d.m (1H, $=CH_2$, ^3J = 10.2), 5.30 d. m (1H, $=CH_2$, ^3J = 17.1), 5.71 d.d (1H, NCH=C*H*, ^3J = 11.0, 9.6), 6.29 d.d (1H, 4-H, ^3J = 2.4, 1.7), 6.73 d (1H, NCH, ^3J = 9.6), 7.56 d (1H, 3-H, ^3J = 1.7), 7.57 d.d.d (1H, C*H*=CH_2, ^3J = 17.1, 11.0, 9.6), 7.71 d (1H, 5-H, ^3J = 2.4); *trans* isomer: 5.10 d.m (1H, $=CH_2$, ^3J = 10.0), 5.30 d.m (1H, $=CH_2$, ^3J = 17.0), 6.30 d.d (1H, 4-H, ^3J = 2.4, 1.7), 6.41 d.d.d (1H, CH=CH_2, ^3J = 17.0, 10.8, 10.0), 6.69 d.d (1H, C*H*=CHN, ^3J = 14.0, 10.8), 7.17 d (1H, NCH, ^3J = 14.0), 7.49 d (1H, 3-H, ^3J = 1.7), 7.78 d (1H, 5-H, ^3J = 2.5). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: *cis* isomer: 105.52 (C^4), 116.44 ($=CH_2$), 118.39 (=CH), 127.86 (=CH), 132.16 (C^5), 133.34 (=CH), 140.30 (C^3); *trans* isomer: 106.34 (C^4), 116.27 ($=CH_2$), 116.61 (=CH), 123.92 (=CH), 129.33 (=CH), 130.56 (C^5), 140.01 (C^3). Found, %: C 70.44; H 6.32; N 23.18. $C_7H_8N_2$. Calculated, %: C 70.00; NH 6.65; N 23.30.

1-(Buta-1,3-dien-1-yl)-3(5)-methyl-1*H*-pyrazole (IX). Yield 8.0 g (60%), bp 53–58°C (1 mm), n_D^{20} = 1.5732, d_4^{20} = 0.9963. Found, %: C 71.36; H 7.28; N 20.58. $C_8H_{10}N_2$. Calculated, %: C 71.64; H 7.46; N 20.89.

Isomer mixture **IX** (3-CH_3/5-CH_3) was separated by fractional distillation using a 30×4-cm column charged with a metal filling (column head temperature 65–70°C, still temperature 120°C, residual pressure 3 mm). The still was charged with 100 g of the isomer mixture (1:1), and distillation gave 30 g of 1-[(*Z*)-buta-1,3-dien-1-yl]-3-methyl-1*H*-pyrazole and 20 g of 1-[(*E*)-buta-1,3-dien-1-yl]-5-methyl-1*H*-pyrazole.

1-[(*Z*)-Buta-1,3-dien-1-yl]-3-methyl-1*H*-pyrazole. bp 52°C (1 mm), n_D^{20} = 1.5700. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.29 s (3H, CH_3), 5.14 d.m (1H, $=CH_2$, ^3J = 10.2), 5.25 d.d (1H, $=CH_2$, ^3J = 17.1, ^4J = 2.2), 5.60 d.d (1H, NCH=C*H*, ^3J = 11.0, 9.6), 6.06 d (1H, 4-H, ^3J = 2.4), 6.60 d (1H, NCH, ^3J = 9.6), 7.56 d (1H, 5-H, ^3J = 2.4), 7.60 d.d.d (1H, C*H*=CH_2, ^3J = 17.1, 11.0, 10.2).

1-[(*E*)-Buta-1,3-dien-1-yl]-5-methyl-1*H*-pyrazole. bp 58–59°C (1 mm), n_D^{20} = 1.5741. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.43 s (3H, 5-CH_3), 5.05 d.m (1H, $=CH_2$, *J* = 10.3), 5.15 d.m (1H, $=CH_2$, *J* = 17.2), 5.65 d.d (1H, NCH=C*H*, *J* = 11.0, 9.8), 4.00 d (1H, NCH, *J* = 9.8), 6,53 d (1H, 4-H, ^3J = 2.1), 7.35 d (1H, 3-H, ^3J = 2.1), 7.60 d.d.d (1H, C*H*=CH_2, *J* = 17.2, 11.0, 10.3).

1-(Buta-1,3-dien-1-yl)-3,5-dimethyl-1*H*-pyrazole (X). Yield 7.4 g (50%), bp 78°C (1 mm), n_D^{20} = 1.5680, d_4^{20} = 0.9741. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.21 s (3H, 3-CH_3), 2.27 s (3H, 5-CH_3), 5.11 d.m (1H, $=CH_2$, *J* = 10.0), 5.23 d.m (1H, $=CH_2$, *J* = 17.2), 5.63 d.d (1H, NCH=C*H*, *J* = 10.9, 9.5), 5.81 s (1H, 4-H), 6.44 d.m (1H, NCH, *J* = 9.5), 7.67 m (1H, C*H*=CH_2). Found, %: C 72.68; H 7.84; N 18.69. $C_9H_{12}N_2$. Calculated, %: C 72.90; H 8.10; N 18.91.

3-(1*H*-Pyrazol-1-yl)cyclohex-4-ene-1,2-dicarboxylic acid (XII). Maleic anhydride, 5 g, was added

in portions at 20–25°C to a mixture of 12.0 g of 1-(buta-1,3-dien-1-yl)-1*H*-pyrazole (**VIII**) and 50 ml of benzene at such a rate that the temperature did not exceed 30°C. When the reaction was complete, the mixture was washed with an aqueous solution of sodium hydroxide, the aqueous phase was separated and neutralized with hydrochloric acid, and the precipitate was filtered off. Yield 2.1 g (60%), mp 173°C (from water). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 2.32 d.m (1H, CH_2, ^2J = 18.2), 2.71 d.m (1H, CH_2, ^2J = 18.2), 2.98 d.d.d (1H, C*H*CH_2, ^3J = 11.2, 5.9, 3.7), 3.57 d.d (1H, C*H*CHN, ^3J = 6.4, 3.7), 5.35 m (1H, NCH), 5.80 d.m (1H, =C*H*CHN, ^3J = 10.3), 6.01 d.d (1H, =C*H*CH_2, ^3J = 10.3, 5.0, ^4J = 2.2), 6.15 d.d (1H, 4-H, ^3J = 2.3, 2.0), 7.35 d (1H, 3-H, ^3J = 2.0), 7.46 d (1H, 5-H, ^3J = 2.3), 11.88 br.s (2H, COOH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 24.24 (CH_2), 39.91 (H*C*CH_2), 44.74 (*C*HCHN), 58.97 (NCH), 104.45 (C^4), 123.35 (=*C*HCCHN), 127.61 (C^5), 129.58 (=*C*HCH_2), 137.94 (C^3), 170.97 (CO), 173.24 (CO). Found, %: C 55.73; H 5.38; N 11.56. $C_{11}H_{12}N_2O_4$. Calculated, %: C 55.93; H 5.12; N 11.86.

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