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SHORT COMMUNICATIONS

Synthesis of 3-Substituted Pyrazoles by Oxidative Dehydrogenation of 4,5-Dihydro-3*H*-pyrazoles

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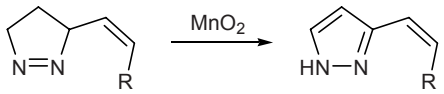
Nowadays considerable attention is given to the development of new methods for the preparation of pyrazole derivatives since the presence of pyrazole ring in organic molecules gives rise to versatile physiological activity of many compounds of both synthetic and natural origin [1]. 3-Alkenylpyrazoles and bipyrazoles attract specific interest [1–6]. For example, 3-(2-methylprop-1-en-1-yl)-1*H*-pyrazole was found to enhance soporific effect of Hexobarbital [1]. Pyrazole derivatives are also used as building blocks in the synthesis of practically important indazole derivatives [2], as well as of a new class of supramolecular complexes, organometallic cage-like structures and self-assembling metallomacrocycles with bipyrazole ligands, that are promising as catalysts, molecular mimics, molecular magnetic devices, sensors, etc. [3–6].

A convenient synthetic approach to 3-alkenylpyrazoles and 3,3′-bipyrazoles is based on 1,3-dipolar cycloaddition of diazo compounds to 1,3-dienes, followed by dehydrogenation of 4,5-dihydro-3*H*-pyrazoles thus obtained [7, 8]. However, we have found no published data on the synthesis of 3-substituted pyrazoles from dihydropyrazoles. The most probable reason is that 3-vinyldihydropyrazoles undergo decomposition above 120°C with liberation of nitrogen and formation of vinylcyclopropane and cyclopentene derivatives [9].

We have developed a simple and efficient procedure for the synthesis of 3-alkenyl-1*H*-pyrazoles and 3,3′-bipyrazoles via oxidative dehydrogenation of 3-vinyl-4,5-dihydro-3*H*-pyrazoles and 4,4′,5,5′-tetrahydro-3*H*,3′*H*-3,3′-bipyrazole with manganese dioxide. 3-Vinyl- and 3-[(*Z*)-prop-1-en-1-yl]-4,5-dihydro-3*H*-pyrazoles **Ia** and **Ib** reacted with 20 equiv of MnO_2 in benzene at room temperature to produce 3-vinyl- and 3-[(*Z*)-prop-1-en-1-yl]-1*H*-pyrazoles **IIa** and **IIb** in 36 and 49% yield, respectively (Scheme 1). No *cis–trans* isomerization of the propenyl substituent occurred under these conditions, as followed from the coupling constant $^3J_{1',2'}$ = 11.5 Hz in the ^{1}H NMR spectrum of compound **IIb**.

Scheme 1.

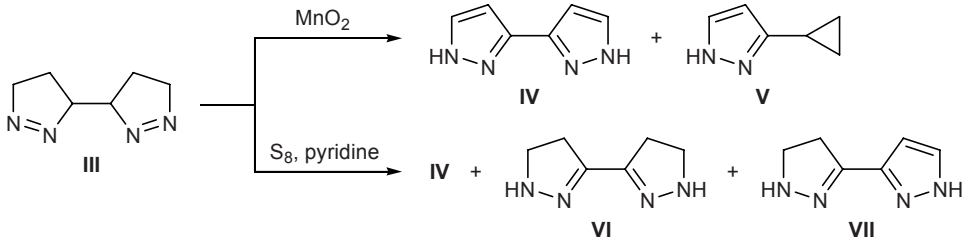


Ia, **Ib** **IIa**, **IIb**

R = H (**a**), Me (**b**).

Dehydrogenation of 4,4′,5,5′-tetrahydro-3*H*,3′*H*-3,3′-bipyrazole (**III**) having two dihydropyrazole rings was accompanied by elimination of nitrogen molecule from one dihydropyrazole ring, leading to the formation of a mixture of bipyrazole **IV** and 3-cyclopropyl-1*H*-pyrazole (**V**) in 27 and 18% yield, respectively. Compounds **IV** and **V** were isolated as individual substances by column chromatography. Unlike oxidative dehydrogenation by the action of manganese dioxide, the reaction of vinyldihydropyrazole **I** with 2 equiv of sulfur in pyridine at 110°C gave a complex mixture of products. Under analogous conditions, from bicyclic compound **III** we obtained a mixture of 1*H*,1′*H*-3,3′-bipyrazole (**IV**), 4,4′,5,5′-tetrahydro-1*H*,1′*H*-3,3′-bipyrazole (**VI**), and 4,5-dihydro-1*H*,1′*H*-3,3′-bipyrazole

Scheme 2.



(**VII**) at a ratio of 2.2 : 2.8 : 1 (overall yield 63%; Scheme 2).

The structure of compounds **IIa**, **IIb**, and **IV**–**VII** was determined on the basis of the ^{1}H and ^{13}C NMR and IR data. The ^{1}H NMR spectrum of pyrazole **IIa** in $CDCl_3$ contained signals from protons in the vinyl group and two doublets from protons in the pyrazole ring at δ 6.25 (4-H) and 7.40 ppm (5-H) with a coupling constant *J* of 1.8 Hz. Compounds **IIa**, **IIb**, and **V** displayed in the ^{13}C NMR spectra three downfield signals with equal intensities from one quaternary and two CH carbon atoms in the pyrazole ring [10].

Thus we have developed a convenient method for the synthesis of 3-alkenyl-1*H*-pyrazoles and 3,3′-bipyrazoles.

Initial dihydropyrazoles **Ia**, **Ib**, and **III** were synthesized as described in [9, 11].

3-Vinyl-1*H*-pyrazole (IIa). Compound **Ia**, 0.6 g (6.24 mmol), was dissolved in 100 ml of benzene, 12.0 g (138 mmol) of MnO_2 was added, and the mixture was stirred for 5 h at room temperature. The precipitate was filtered off, the solvent was removed from the filtrate under reduced pressure, and the residue was purified by chromatography on silica gel. Yield 0.21 g (36%), oily substance, R_f 0.55 (hexane–ethyl acetate, 2 : 1). Compound **IIa** was identified by comparing with an authentic sample [12].

3-[(*Z*)-Prop-1-en-1-yl)-1*H*-pyrazole (IIb). Compound **Ib**, 0.66 g (6 mmol), was dissolved in 100 ml of benzene, 9.94 g (0.114 mol) of MnO_2 was added, and the mixture was stirred for 5 h at room temperature. The precipitate was filtered off, the solvent was removed from the filtrate under reduced pressure, and the residue was purified by chromatography on silica gel. Yield 0.32 g (49%), oily substance, R_f 0.45 (hexane–ethyl acetate, 2 : 1). IR spectrum, ν, cm^{-1}: 3157, 2924–2958, 1400–1572, 1093, 781 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.98 d.d (3H, Me, *J* = 1.7, 7.1 Hz), 5.86 d.t (1H, 2′-H, *J* = 7.1, 11.5 Hz), 6.34 d (1H, 4-H, *J* = 2.1 Hz), 6.43 d.t (1H, 1′-H, *J* = 1.7, 11.5 Hz), 7.58 d (1H, 5-H, *J* = 2.1 Hz), 11.75 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.92 (Me), 104.76 (C^4), 119.52 ($C^{2'}$), 127.84 ($C^{1'}$), 134.83 (C^5), 143.80 (C^3). Mass spectrum: *m*/*z* 109 $[M + H]^+$. Found, %: C 66.66; H 7.42; N 25.92. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90. *M* 108.14.

Oxidative dehydrogenation of 4,4′,5,5′-tetrahydro-3*H*,3′*H*-3,3′-bipyrazole (III) with manganese dioxide. Compound **III**, 0.5 g (3.62 mmol), was dissolved in 100 ml of benzene, 12.0 g (138 mmol) of MnO_2 was added, and the mixture was stirred for 10 h at room temperature. The precipitate was filtered off, the solvent was removed from the filtrate under reduced pressure, and the residue was purified by chromatography on silica gel using petroleum ether–ethyl acetate (2 : 1) as eluent to isolate 0.131 g (27%) of bipyrazole **IV** {colorless crystals, mp 255–256°C; published data [11]: mp 258°C} and 0.07 g (18%) of cyclopropylpyrazole **V** (colorless crystals).

3-Cyclopropyl-1*H*-pyrazole (V). IR spectrum, ν, cm^{-1}: 3196, 2926–3003, 1450–1550, 1100, 1043, 763 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.74 m (2H, *trans*-2′-H, *trans*-3′-H), 0.96 m (2H, *cis*-2′-H, *cis*-3′-H), 1.95 m (1H, 1′-H), 5.96 br.s (1H, 4-H), 7.45 br.s (1H, 5-H), 10.06 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 7.78 ($C^{2'}$, $C^{3'}$), 13.86 ($C^{1'}$), 98.70 (C^4), 130.36 (C^5), 146.66 (C^3). Mass spectrum: *m*/*z* 109 $[M + H]^+$. Found, %: C 66.58; H 7.52; N 25.83. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90. *M* 108.14

Dehydrogenation of 4,4′,5,5′-tetrahydro-3*H*,3′*H*-3,3′-bipyrazole (III) with sulfur in pyridine. Elemental sulfur, 0.46 g (0.014 mol), was added to a solution of 1 g (7.24 mmol) of compound **III** in 5 ml of pyridine, and the mixture was stirred for 5 h at 110°C. The precipitate was filtered off, and the solvent was removed from the filtrate under reduced pressure to isolate 0.63 g (63%) of a mixture of compounds **IV**, **VI**, and **VII** at a ratio of 2.2 : 2.8 : 1.

4,4′,5,5′-Tetrahydro-1*H*,1′*H*-3,3′-bipyrazole (VI). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.71 t (4H, 4-H, 4′-H, *J* = 9.9 Hz), 3.27 t (4H, 5-H, 5′-H′, *J* =

9.9 Hz), 6.99 br.s (2H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 31.63 (C^4, $C^{4'}$), 47.69 (C^5, $C^{5'}$), 148.33 (C^3, $C^{3'}$). Mass spectrum: m/z 139 $[M + H]^+$.

4,5-Dihydro-1*H*,1′*H*-3,3′-bipyrazole (VII). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.86 t (2H, 4-H, J = 9.8 Hz), 3.27 t (2H, 5-H, J = 9.8 Hz), 6.46 br.s (1H, 4′-H), 6.99 br.s (1H, NH), 7.66 br.s (1H, 5′-H), 12.89 br.s (1H, NH). Mass spectrum: m/z 137 $[M + H]^+$.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C using tetramethylsilane as internal reference. The IR spectra were measured on UR-20 and Specord M-80 spectrometers from samples dispersed in mineral oil or neat substances. The mass spectra (electron impact, 70 eV) were obtained on a Thermo Finnigan MAT 95-XP high-resolution mass spectrometer (ion source temperature 250°C, direct inlet probe temperature programming from 50 to 270°C at a rate of 10 deg/min). The products were isolated by column chromatography on silica gel (Lancaster, 70–230 mesh).

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