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The orientation of the substituent groups in an 1,2,4-oxadiazole substituted pyrazole, formed by reaction of a phenylnitrile oxide with an unsymmetrically substituted hydrazine is determined. One-dimensional methods as the selective INEPT and  $^{13}\text{C}\{^1\text{H}\}$  nOe experiments are used. Both techniques provide also an unambiguous assignment of the  $^{13}\text{C}$  nmr spectrum.

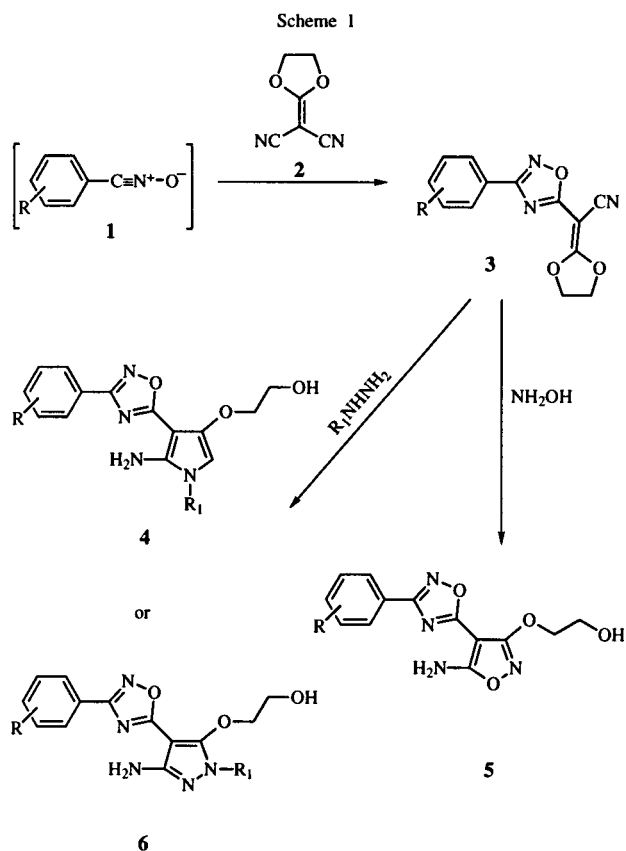
*J. Heterocyclic Chem.*, 35, 161 (1998).

In our recent research work [1,2] we have concentrated on the synthesis of a series of phenyloxadiazolypyrazole, phenyloxadiazolisisoxazole and phenyloxadiazolypyrimidine derivatives, which are based on the reactivity of phenylnitrile oxide undergoing an 1,3-cycloaddition with a double or a triple bond [3-5] and the sensitivity of the cyano group towards attack by nucleophilic reagents [6,7]. For the reactions of **3**  $\rightarrow$  **4** and **3**  $\rightarrow$  **5** (Scheme 1), the involvement of the cyano group in the ring formation was confirmed by ir spectroscopy. In order to determine the

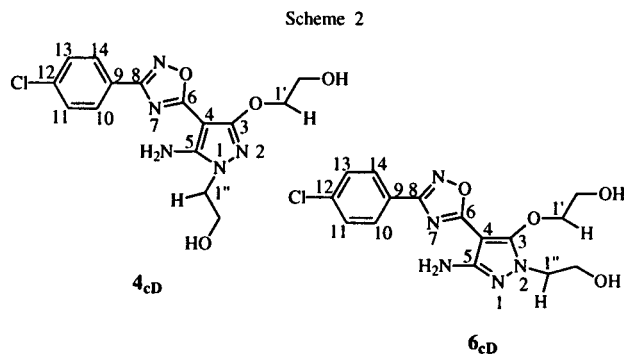
structure of the cyclization products, an X-ray diffraction analysis of the resulting compounds **5a** was performed and a reasonable reaction mechanism was suggested [2].

However, there is not yet any convincing evidence to verify the applicability of the mechanism to the reaction of **3**  $\rightarrow$  **4**, since the reactions of **3** with hydrazine hydrate or its derivatives  $\text{H}_2\text{NNHR}_1$  could theoretically also lead to substance **6**, a structural isomer of compound **4**. The attempt of an X-ray diffraction analysis was unsuccessful because of their unsuitable crystal forms.

In the present work, we used **4<sub>CD</sub>** (or **6<sub>CD</sub>**,  $\text{R} = 4\text{-Cl}$ ,  $\text{R}_1 = \text{CH}_2\text{CH}_2\text{OH}$ ) as a lead compound (Scheme 2) for structural determination. The selective INEPT-nmr experiment [8] was used to locate the position of the  $\text{CH}_2\text{CH}_2\text{OH}$  substituent group bound to one of the two nitrogen atoms in the pyrazole ring. This nmr technique is a modification of the refocused INEPT experiment in which "soft" proton pulses instead of the nonselective "hard" proton pulses are used to induce polarization transfer preferably in quaternary carbon atoms, which thus emphasize  $^2J_{\text{CH}}$  and  $^3J_{\text{CH}}$  long range couplings [9]. It can be considered as an alternative highly sensitive method to two-dimensional HMBC or selective inverse detection experiments [10].



$\text{R} = 4\text{-H}$  (a),  $4\text{-OCH}_3$  (b),  $4\text{-Cl}$  (c),  $3\text{-NO}_2$  (d),  $4\text{-NO}_2$  (e).  
 $\text{R}_1 = \text{H}$  (A),  $\text{CH}_3$  (B),  $\text{C}_6\text{H}_5$  (C),  $\text{C}_2\text{H}_4\text{OH}$  (D).



One of the two  $\text{CH}_2\text{CH}_2\text{OH}$ -groups at the pyrazole ring is attached to a nitrogen atom. Its location depends on the nucleophilic attack towards the cyano group of **3** by either

the primary or secondary nitrogen atom of the hydrazine derivative and two structures (regio isomers **4<sub>CD</sub>** and **6<sub>CD</sub>**) must be considered for the reaction product.

If structure **6<sub>CD</sub>** exists, the **OCH<sub>2</sub>'CH<sub>2</sub>OH**-protons should couple with the same quarternary carbon atom of the pyrazole ring (C-3; three bond C-H couplings) as the **NCH<sub>2</sub>"CH<sub>2</sub>OH**-protons do. In the case of structure **4<sub>CD</sub>**, each methylene group should couple with another carbon atom (C-3 and C-5, respectively).

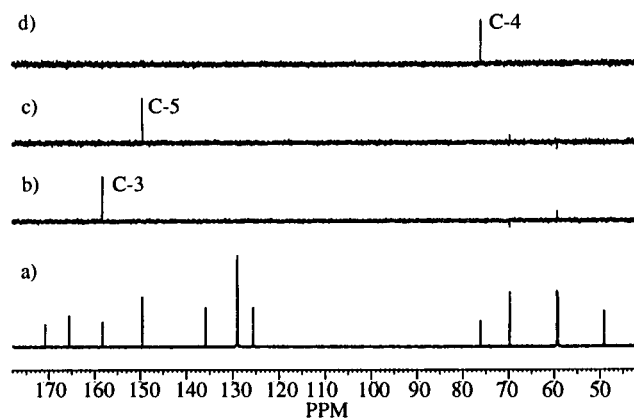


Figure 1. Spectra of **4<sub>CD</sub>**: (a) Regular <sup>13</sup>C spectrum; (b-d) selective INEPT spectra obtained by irradiation of **OCH<sub>2</sub>'CH<sub>2</sub>OH** ( $\delta = 4.12$ ), **NCH<sub>2</sub>"CH<sub>2</sub>OH** (3.92) and **NH<sub>2</sub>** (6.62) protons.

Figure 1 shows the normal broadband decoupled <sup>13</sup>C-nmr spectrum (Figure 1a) and the spectra obtained by selective irradiation of the **OCH<sub>2</sub>'CH<sub>2</sub>OH**- (Figure 1b) as well as the **NCH<sub>2</sub>"CH<sub>2</sub>OH**-protons (Figure 1c) [11]. As a result, two different signals are enhanced by polarization-transfer via <sup>3</sup>J<sub>CH</sub> coupling which must be assigned as C-3 and C-5 respectively. These observations are in full accordance only with the structure **4<sub>CD</sub>** and therefore exclude the regio isomer **6<sub>CD</sub>**. Furthermore, they could be also considered as a strong support to the reaction mechanism for this kind of reactions [1].

The identity of the selected protons is deduced from the larger downfield shift of the **OCH<sub>2</sub>'CH<sub>2</sub>OH**-protons with respect to the **NCH<sub>2</sub>"CH<sub>2</sub>OH**-protons. This assignment is supported by a selective heteronuclear nOe-experiment [11,13], in which the signal intensities of the neighbored ring carbon atoms C-5 and C-4 are increased by irradiation of the **NH<sub>2</sub>**-protons, whereas C-3 gives no effect because the distance is too large from the **NH<sub>2</sub>**-group (Figure 2). Thus the signal at 3.92 ppm in the proton nmr spectrum [2] must be assigned to the **NCH<sub>2</sub>"CH<sub>2</sub>OH**-group, because irradiation of these protons in a selective INEPT experiment induces a polarization-transfer in the carbon at 150 ppm.

The nOe experiment also allows for the complete assignment of the quarternary carbon atoms which are

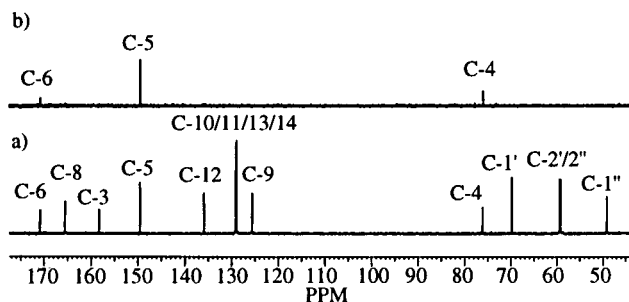


Figure 2. Spectra of **4<sub>CD</sub>**: (a) Regular <sup>13</sup>C spectrum; (b) selective <sup>13</sup>C{<sup>1</sup>H} nOe spectrum obtained by irradiation of **NH<sub>2</sub>** ( $\delta = 6.62$ ).

part of the two heterocyclic ring systems. The third signal in the <sup>13</sup>C{<sup>1</sup>H} nOe difference spectrum at 170.5 ppm arises from C-6 of the 1,2,4-oxadiazole ring; C-8 remains after the assignment of all other carbon atoms [14].

In contrast to the dipolar interaction however, no polarization transfer from the **NH<sub>2</sub>** protons to C-5 on the basis of scalar spin-spin coupling was observed in the INEPT experiment. As shown in Figure 1d, C-4 is the only carbon atom which is enhanced in the selective INEPT spectrum after irradiation of the **NH<sub>2</sub>** protons.

In summary, the application of the selective INEPT and heteronuclear nOe experiment proved to be a facile procedure for solving structural problems arising from regio isomerism and assignments of quarternary carbon atoms, which can be performed even on older instruments without capabilities for inverse detection.

#### Acknowledgment.

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[11] The  $^1\text{H}$ - and  $^{13}\text{C}$  nmr spectra were recorded on a Bruker AM 360 MHz spectrometer at 27° using 5 mm sample tubes and dimethyl- $\text{d}_6$  sulfoxide as the solvent; 128 scans were collected for each INEPT spectrum and 8704 scans resulting from 68 on- and 68 off-resonance spectra with 64 scans each were measured in the heteronuclear nOe experiment. Relaxation delays of 4.84 and 1.21 s were used in the INEPT and nOe experiments, respectively, and 4.84 s was the time for selective low-

power irradiation to build up the nOe in the  $^{13}\text{C}\{^1\text{H}\}$  nOe experiment. The standard Bruker software for the refocused INEPT experiment was accomplished by commands for switching the decoupler power, and additional delays of 5 and 10 ms were introduced to place the 90° and 180°  $^{13}\text{C}$  pulses in the middle of the proton pulses which were set to 10 and 20 ms for 90° and 180° flip angle, respectively. Omitting of these delays, *i.e.* the simultaneous beginning of the  $^1\text{H}$  and  $^{13}\text{C}$  pulses results in a loss of sensitivity. Both delays  $\Delta_1/2$  and  $\Delta_2/2$  were set to 25 ms. For calibration of the decoupler power the procedure proposed by A. Bax [12] was performed using a sample of dichloroacetic acid in perdeuterio-benzene (1:1, v/v).

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[14] The assignment of C-6 and C-8 given in literature [2] has to be reversed.