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Short Communication

Cycloaddition Reactions of 5-Deutero-1-phenyl-4-vinylpyrazole. Stereoselective *cis* "ene" Reaction and Simplification of NMR Spectra of Mixtures of Cycloadducts

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Summary. The reaction of methyl propiolate (*MP*) with 1-phenyl-4-vinylpyrazole deuterated in the five position has clarified the ^{1}H NMR spectrum of the mixture of the adducts 1 : 2 which are obtained as a result of a Diels-Alder cycloaddition followed by a non-regioselective "ene" reaction. The deuterated substrate allowed at the same time to establish the stereochemistry of the ene reaction as a concerted *cis* process.

Keywords. Cycloaddition; Ene-reaction; Vinylpyrazole; NMR; Deuteration.

Cycloadditionsreaktionen von 5-Deutero-1-phenyl-4-vinylpyrazol. Stereoselektive *cis*-„en"-Reaktion und Vereinfachung von NMR-Spektren von Mischungen der Cycloaddukte (Kurze Mitt.)

Zusammenfassung. Die Reaktion von Methylpropiolat (*MP*) mit an der 5-Stellung deuteriertem 1-Phenyl-4-vinylpyrazol wurde zur vereinfachten Interpretation der ^{1}H-NMR-Spektren einer 1 : 2 Mischung von Addukten aus der Diels-Alder-Cycloaddition mit nachfolgender nicht-regioselektiver „en-Reaktion" eingesetzt. Das deuterierte Substrat erlaubte zugleich auch die Bestimmung der Stereochemie der en-Reaktion als einen konzertierten *cis*-Prozeß.

Introduction

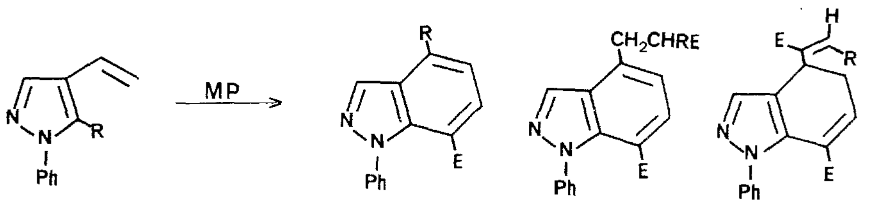
In the course of our studies on the reactivity of vinylheterocyclic compounds with dienophiles, we found in our previous work [1] that 1-phenyl-4-vinylpyrazole **1** reacted with methyl propiolate (*MP*) affording the indazole **2** along with an equimolecular mixture of the isomeric 1 : 2 adducts **3** and **4** that could not be resolved after column and HPLC chromatography.

The NMR study of the isomeric mixture **3** + **4** did not allow a clear assignment of some signals to the corresponding compounds. In order to overcome this problem and to get more information about the mechanism of the "ene" reaction we have studied the same reaction using as starting material the deuterated pyrazole **5**.

As the mechanism of the "ene" reaction has been postulated to occur through a six membered transition state [2], the deuterated substrate **5** can afford evidence of this *cis* addition.

Results and Discussion

The reaction of the pyrazole **5** with *MP* in CH_2Cl_2 was run in an enclosed steel vessel at 140°C for five days and the crude mixture was purified by column chromatography as in our precedent paper, however, the ratio of the compunds obtained was slightly different in this case. The yield of compounds **2** and **6** we expected in the first eluted fraction was even lower ($< 0.65\%$) than that obtained with the undeuterated substrate **1**; isolation and spectroscopic analysis was not possible. The mixture of the adducts **7** and **8** was obtained in the second fraction eluted with higher yield (13%) and was not resolved after a further purification by HPLC (Scheme 1).



1 R:H
5 R:D

2 R:H
6 R:D

3 R:H
7 R:D

4 R:H
8 R:D

E: CO_2CH_3

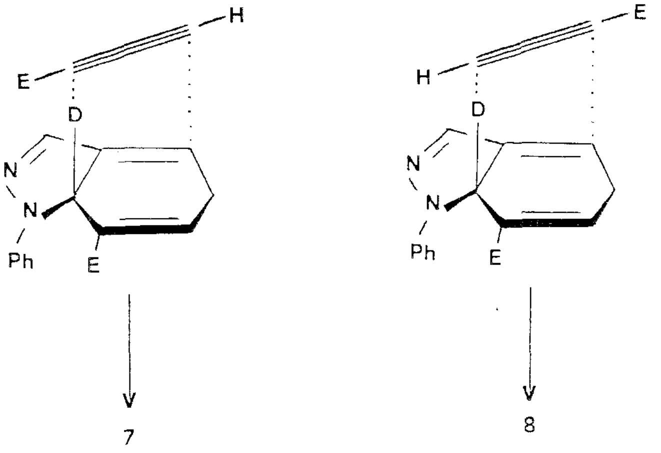
Scheme 1

The presence of deuterium in compound **7** allowed the unequivocal assignment of the signals of the aliphatic substituent at the C-4 of the indazole ring, now appearing as a doublet at δ 3.36 and a triplet at δ 2.80 (two triplets in the non-deuterated pyrazole).

We reported previously that the acrylic hydrogens in compound **4** have chemical shift values of 6.28 and 5.5. Only a singlet was observed in compound **8**. The disappearance of one signal is in agreement with the presence of a deuterium atom in this compound and the δ value shows that the only olefinic proton is *cis* to the methoxycarbonyl group because of the greater deshielding effect of this group on this hydrogen [3]. The mechanism of the "ene" reaction is thus confirmed as a *cis* concerted process via a 6-membered transition state (Scheme 2).

The relative position of the methoxy carbonyl group and the olefinic hydrogen in compound **8** was also confirmed by irradiation of the signal at δ 6.28 giving a positive NOE of the singlet at δ 3.10.

Further analysis of the ^1H NMR spectrum based on the relative areas of the carboxymethyl groups showed that in the present reaction the isomers **7** and **8** were in the ratio 1 : 1.5. This fact, along with the information deduced from the NOE experiment, allowed the assignment of the singlets at δ 3.10 and δ 3.75 (higher



Scheme 2

intensity) to ester groups of the side chain and C-7 in the adduct **8** and the singlets at δ 3.30 and δ 3.67 (with a lower intensity) to the adduct **7**.

The preparation of the pyrazole **5** is a clear example how deuteration can be useful in mechanistic studies and in the simplification of complex NMR spectra.

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ (ca. 3%) at 200 MHz using a Bruker Ac 200. M.p.s. were determined on a Kofler hot stage. H.p.l.c. was performed on a Waters instrument using a semipreparative silica carbowax column.

n-Butyl-lithium (11 ml, 1.6 *N*) was slowly added to 1-phenyl-4-vinylpyrazole (3 g, 0.0176 mol) in diethylether (30 ml), under an argon atmosphere. The solution was stirred for 2 h, at room temperature and then D_2O (1 ml) was added. The mixture was poured onto water and extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was distilled to afford *5-deutero-1-phenyl-4-vinylpyrazole* (2.5 g, 83%, 150°, 2 mm Hg). δ 755 (s, 1 H), 7.45–7.1 (m, 5 H), 6.35 (dd, J = 16 and 10 Hz, 1 H), 5.35 (dd, J = 16 and 2 Hz, 1 H), 4.90 (dd, J = 10 and 2 Hz, 1 H).

5-deutero-1-phenyl-4-vinylpyrazole (2.5 g, 0.0146 mol) and *MP* (2.45 g, 0.029 mol) in dichloromethane (15 ml) was heated in an enclosed steel vessel at 140°C for five days. The crude mixture was purified by column chromatography with hexane: ethyl acetate (4:1) affording the trimer of *MP* trimethyl trimesate [4] (0.8 g, 14%) and a mixture of the isomers **7** and **8** (0.7 g, 13%). δ Signals that could be atributed to the *isomer* **7**: 8.33 (s, 1 H), 7.79 (d, J = 8 Hz, 1 H), 7.4–7.2 (m, 11 H overlapped with the isomer **8**), 7.1 (d, J = 8 Hz, 1 H), 3.67 (s, 3 H), 3.36 (d, J = 8 Hz, 2 H), 3.30 (s, 3 H) 2.80 (t, J = 8 Hz, 1 H); signals for *isomer* **8**: 7.4–7.2 (m, 11 H overlapped with the isomer 7), 6.61 (dd, J = 5.6 and 4.4 Hz, 1 H), 6.28 (s, 1 H), 4.15 (t, J = 6 Hz, 1 H), 3.75 (s, 3 H), 3.10 (s, 3 H), 2.76–2.60 (m, 2 H).

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