Electron Transfer Reactions of 1-Phenyl-4-vinylpyrazole Mediated by Cerium(IV) Ammonium Nitrate

M. Pitarch-Vinuesa[1], **M. A. Miranda**[2,*], **M. Medio-Simón**[1], and **J. Sepúlveda-Arques**[1,*]

[1] Departamento de Química Orgánica, Facultad de Farmacia, E-46100 Burjassot, Valencia, Spain
[2] Departamento de Química e Instituto de Tecnología Química UPV-CSIC, Universidad Politécnica de Valencia, E-46071 Valencia, Spain

Summary. The title compound is converted into the cyclic ethers **5** and the alcohol **6** upon treatment with ceric ammonium nitrate in acetone. Using methanol as a solvent the dimethoxy derivative **9** and the nitrate ester **10** are formed. No cross cycloaddition is observed in the presence of olefins such as ethyl vinyl ether, *DMAD*, or indene; however, with cyclopentadiene as co-reagent a mixture of the exo-endo Diels-Alder adducts **14** involving the vinylic system of **1** as 2π component is obtained. The results are rationalized through the intermediacy of the radical cation **1**[•+], generated by single electron transfer (SET) from the neutral precursor **1** to Ce(IV).

Elektrontransfer-Reaktionen von 1-Phenyl-4-vinylpyrazol mittels Cer(IV)-Ammonnitrat

Zusammenfassung. Die Titelverbindung wurde mittels Cer(IV)-Ammonnitrat in Aceton in die cyclischen Ether **5** und den Alkohol **6** umgewandelt. Mit Methanol als Lösungsmittel wurde das Dimethoxyderivat **9** und der Nitratester **10** gebildet. Bei Anwesenheit von Olefinen wie etwa Ethylvinylether, *DMAD* oder Inden wurden keine Cross-Cycloadditionen beobachtet. Hingegen wurde mit Cyclopentadien als Mitreagens eine Mischung von *exo-endo*-Diels-Alder-Produkten **14** erhalten, wobei das vinylische System von **1** als 2π-Komponente fungiert. Die Ergebnisse werden mittels eines intermediär auftretenden Radikalkation **1**[•+] als Produkt eines Einelektronentransfers (SET) des neutralen Vorläufers **1** zu Ce(IV) rationalisiert.

Introduction

Alkenylheterocycles can be involved in a variety of cycloaddition reactions, acting either as 4π components in [4 + 2] processes or as 2π components in [4 + 2], [2 + 2] or [2 + 2 + 2] processes. This role multiplicity is illustrated by the reaction of 1-phenyl-4-vinylpyrazole (**1**) with dimethyl acetylenedicarboxylate (*DMAD*) [1], methyl propiolate (*MP*) [2], N-phenylmaleimide (*NPMI*) [2], diethyl azodicarboxylate (*DEAZD*) [3] or tetracyanoethylene (*TCNE*) [2], which leads to

indazoles in the first three cases, oxadiazines or cyclobutane adducts, respectively. Moreover, using acetone as a solvent, 1 reacts with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), to afford a [2 + 2 + 2] cycloadduct whose formation involves trapping of a 1,4-dipolar intermediate by acetone [4].

In the last ten years it has been shown that Diels-Alder cycloadditions can take place under electron transfer conditions [5, 6]. These cycloadditions are specially favoured when the dienophile is in the radical cation form (version [4 + 1]) and proceed at room temperature with a high degree of regio and stereoselectivity; however, their synthetic interest is sometimes limited by the occurrence of competing reactions such as cyclobutane formation, trapping by nucleophiles and/or oxygen, dimerization etc.

The present work has been undertaken as an exploratory study on the possibilities of the electron transfer methodology in the field of alkenylheterocycles cycloadditions. In a first stage our attention has been focussed on 1-phenyl-4-vinylpyrazole (1) for two reasons: (a) it is a relatively unreactive substrate, so at room temperature the radical cation reaction should be expected to occur free from complications due to an overlapping "normal" cycloaddition, and (b) as stated above, 1 is very sensitive to the structure of the partners and the reaction conditions, therefore one can expect a differentiated reactivity pattern associated to electron transfer activation.

Results and Discussion

The reaction of 1-phenyl-4-vinylpyrazole (1) with the equivalent amount of ceric ammonium nitrate (CAN) in acetone, in the absence of any other diene or dienophile, was studied first. The main product (20%), was 2,5-bis-(1-phenyl-4-pyrazolyl)tetrahydrofuran (5), obtained as a cis-trans stereoisomeric mixture (4:3 ratio as determined by the relative intensity of the methine hydrogens in the ^{1}H-NMR). Traces of a minor product tentatively identified as 1,4-bis-(1-phenyl-4-pyrazolyl)-3-buten-1-ol (6) were also formed [7]. Some starting material (10%) remained unreacted and considerable amounts of polymers together with untractable mixtures of highly polar compounds were clearly observable at the starting point of the chromatographic plate.

Thus, Ce(IV)-mediated single electron transfer [8] oxidation of 1-phenyl-4-vinylpyrazole 1 must occur in the initial step, giving rise to the corresponding radical cation 1$^{·+}$. Electrophilic attack of the latter upon the β-position of a neutral molecule of 1, followed by nucleophilic trapping of the resulting dimeric radical of a second Ce(IV) equivalent and subsequent ring closure and/or deprotonation would account for the formation of the cyclic ether 5 or the alcohol 6, respectively (Scheme 1). The structure of 5 was initially assigned by means of the ^{1}H and ^{13}C-NMR spectra, where the aliphatic protons and carbons give rise to characteristic signals. This assignment was later confirmed by MS, on the basis of the molecular peak at m/z 356 and a fragmentation pattern compatible with the structure (Scheme 1).

It is worth mentioning that in the oxidation of styrene with peroxydisulfate anion in the presence of copper(II), which is thought to proceed via single electron transfer, two dimeric products were also formed [9]. Although these were not unambiguously
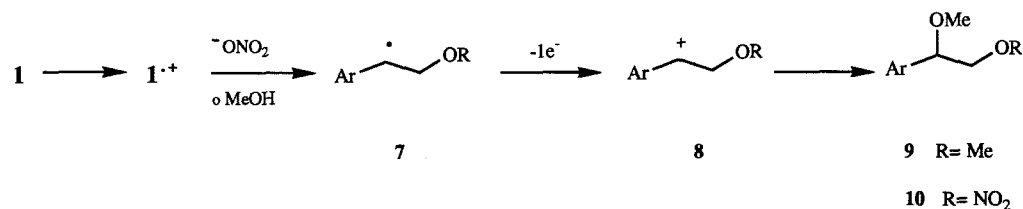
Ar = 1-phenyl-4-pyrazolyl
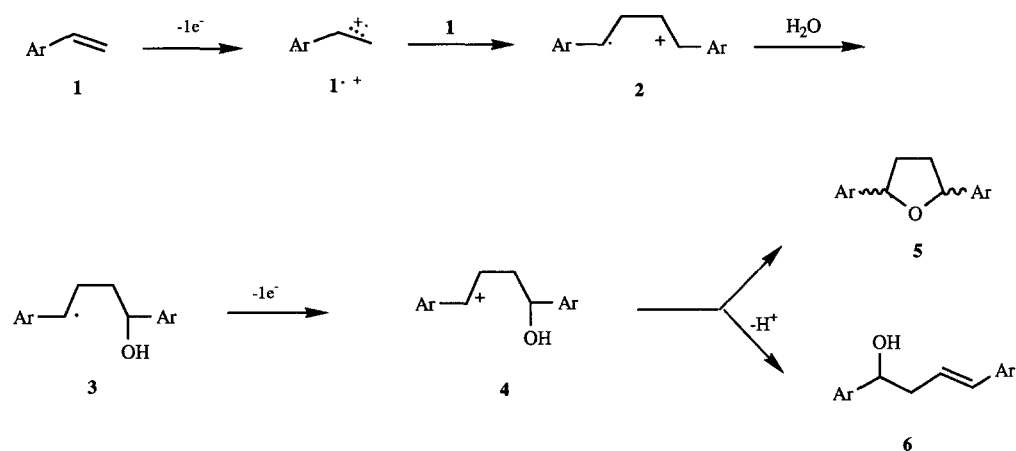
Scheme 1. Oxidation of 1 with *CAN* in acetone

identified, GC-MS analysis of the mixture led to assign to the major one the tentative structure of 2,4-diphenyltetrahydrofuran. In the same way, the minor product was assumed to be a dimeric hydrocarbon, presumably 1,3-diphenylbutadiene. As these proposals were based on the GC-MS data alone, we think that the above mentioned oxidation products of styrene might well be the phenyl analogues of 5 and 6, which seems reasonable in view of the similarity of the fragmentation patterns and also in terms of chemical analogy.

In another experiment, methanol was used as solvent for the oxidation of 1 with ceric ammonium nitrate. Under these conditions the major product (20%) was 4-(1,2-dimethoxyethyl)-1-phenylpyrazole (9), although small amounts (4%) of 2-methoxy-2-(1-phenyl-4-pyrazolyl) ethyl nitrate (10) were also obtained (Scheme 2). Again, some starting material (8%) was recovered unchanged and the formation of polymers and high polar compounds occurred to a substantial extent. These results can be rationalized by assuming that the initially formed radical cation $1^{\cdot+}$ is trapped by methanol or a nitrate anion giving rise to a benzylic radical 7, which is further oxidized by Ce(IV) to the corresponding cation 8. The final step would be nucleophilic trapping of this cation by the solvent. A related pathway might involve generation of the key intermediate $1^{\cdot+}$ via electron transfer from the vinylic system to a nitrate radical [10, 11]. However, this appears in principle unlikely due to the lack of photochemical activation, necessary to produce substantial amounts of the nitrate radical. On the other hand, no dinitrate adducts could be detected, which can be taken as an evidence for outer sphere oxidation involving the cation 8, instead of an oxidative ligand transfer between the radical 7 and ceric ammonium nitrate.

The next assay was directed to try the Ce(IV) mediated cycloaddition of 1 with olefins. Since under electron transfer conditions the [4 + 1] version must be favoured [5, 6], we decided to use ethyl vinyl ether (*EVE*), as an example of electron rich easily ionizable dienophile. In spite of these expectations, no cycloadducts could be isolated when a mixture of 1, *EVE* and *CAN* in acetone was allowed to react at room temperature for 2 h. Instead, a complex mixture resulted, from which the cyclic ether 5 (18%), phenylpyrazole (17%), and traces of the alcohol 6 [7] were isolated.

$$1 \longrightarrow 1^{\cdot+} \xrightarrow[\text{o MeOH}]{^-ONO_2} Ar\overset{\cdot}{\diagup}\diagdown OR \xrightarrow{-1e^-} Ar\overset{+}{\diagup}\diagdown OR \longrightarrow Ar\overset{OMe}{\diagup}\diagdown OR$$

$$\qquad\qquad\qquad\qquad\quad 7 \qquad\qquad\qquad\qquad 8 \qquad\qquad\quad 9 \quad R= Me$$

$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad 10 \quad R= NO_2$$
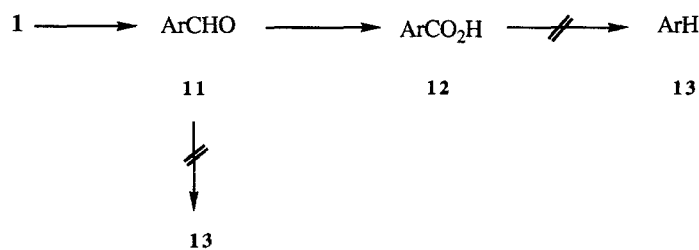
Scheme 2. Oxidation of **1** with *CAN* in methanol

Other olefins such as indene and *DMAD* were also employed as potential dienophiles but again no mixed cycloaddition product was detected. In both cases, the major product was the cyclic ether **5**.
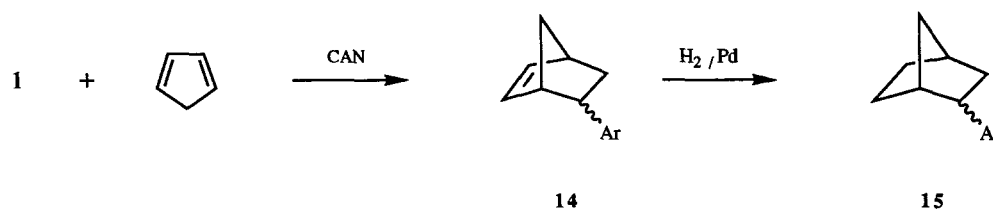
The formation of 1-phenylpyrazole (**13**) in the reaction of **1** with ethyl vinyl ether is difficult to rationalize. A possible explanation could be based on the oxidation to the aldehyde **11** and subsequently to the carboxylic acid **12**, followed by decarboxylation under the reaction conditions. However, this hypothesis was easily ruled out by means of a control experiment, in which neither **11** nor **12** were converted into **13** upon treatment with Ce(IV) in acetone (Scheme 3). Attempts to prove alternative routes were unsuccessful and therefore the mechanism remains to be determined in future experiments.

Finally, the reaction of 1-phenyl-4-vinylpyrazole with Ce(IV) in acetone was performed in the presence of an equimolecular amount of cyclopentadiene, to check the prospects of a Diels-Alder cycloaddition involving the vinylic system of **1** as dienophile. This assay led to a mixture of the *exo* and *endo* adducts **14** (yield: 20%) in a ratio of approximately 1:1 as determined by the relative intensity of the *endo* vs. *exo* methine protons. Column chromatography afforded **14** contaminated with "unreacted" starting material **1**. The composition of this eluted mixture was time dependent, as the percentage of **1** progressively increased to the detriment of that of the adducts **14**. This was taken as evidence for the thermal reversibility of the cycloaddition and led us to carry out a catalytic hydrogenation of the mixture, in order to confirm indirectly the structures of **14** and to achieve a more efficient separation from **1**. Operating in this way, a satisfactory chromatrographic resolution was achieved and the hydrogenation products were unambiguously characterized as 4-ethyl-1-phenylpyrazole [12] and 4-(bicyclo[2.2.1]-2-heptyl)-1-phenylpyrazole (**15**) as an *endo-exo* mixture (yield: 90% from **14**; *endo*-exo ratio 1:1) (Scheme 4).

That the cycloaddition of **1** and cyclopentadiene was catalyzed by electron transfer could be convincingly demonstrated by the lack of reactivity of both

$$1 \longrightarrow ArCHO \longrightarrow ArCO_2H \overset{}{\longrightarrow}\!\!\!\!\!/\!\!\!\!\!\longrightarrow ArH$$

$$\qquad\qquad\qquad 11 \qquad\qquad\qquad 12 \qquad\qquad\quad 13$$

$$\qquad\qquad\qquad \downarrow\!\!\!\!/$$

$$\qquad\qquad\qquad 13$$

Scheme 3

Scheme 4. Ce(IV) mediated cycloaddition of 1 with cyclopentadiene

reagents in acetone, in the absence of Ce(IV), even after prolonged heating at reflux temperature.

In summary, the radical cation of 1-phenyl-4-vinylpyrazole $1^{\cdot +}$ appears to be efficiently generated by single electron transfer (SET) from the vinylic system of the neutral precursor to Ce(IV). The fate of this intermediate strongly depends upon the reaction conditions, but the most general process appears to be nucleophilic trapping by the solvent, nitrate ions or a second molecule of 1. No electron transfer catalysed cycloaddition has been observed in which the vinylheterocycle is the 4π component but in the presence of dienes Diels-Alder adducts involving the vinyl system as 2π component are formed.

Experimental Part

^{1}H-NMR spectra were measured in $CDCl_3$ with 60 MHz Hitachi-Perkin Elmer R24B or 200 MHz Bruker AM-200 instruments. The latter was also used for 50 MHz ^{13}C-NMR spectra. Chemical shifts are reported in δ (ppm) values, using TMS as internal standard. Mass spectra were obtained with a Hewlett-Packard 5988 A spectrometer. The ratios m/z and the relative intensities (% in brackets) are reported. High resolution measurements were performed with Finnigan Massenspektometer MS8230. Isolation and purification were done by column chromatography (silica gel Merck 60, 0.063–0200 mm) or by preparative layer chromatography (silica gel 60 PF/254).

General Procedure for the Oxidations with Cerium(IV) Ammonium Nitrate

A solution of *CAN* (1.61 g, 2.94 mmol) in acetone or methanol (40 ml) was added dropwise and under magnetic stirring to a solution of 1-phenyl-4-vinylpyrazole (0.5 g, 2.94 mmol) in 25 ml of the same solvent. The mixture was allowed to react at room temperature during 2 h, whereby while solid Ce(III) salt separated from the pale yellow solution. After filtration of the latter and several extractions with the same solvent, the combined liquid phases were poured on water. The resulting solution was extracted with ethyl acetate and subsequently the organic layer was washed with water, dried over anhydrous Na_2CO_3 and evaporated to dryness. The residue was submitted to chromatographic purification using carbon tetrachloride-ethyl ether (4:1) as eluent. Eventually (see Results and Discussion) the reaction was carried out in the presence of equimolecular amounts of olefins (ethyl vinyl ether, indene, or *DMAD*) or dienes (cyclopentadiene) which were added to the initial solution of 1 in acetone before the addition of *CAN*.

Oxidation of 1 *with CAN in acetone.* Compounds isolated: starting material (50 mg, 10%); 5 (110 mg, 20%) as a *cis-trans* stereoisomeric mixture (isomer ratio 4:3); 6 (traces).

Oxidation of 1 with *CAN in methanol.* Compounds isolated: starting material (40 mg, 8%); 9 (60 mg, 8%); 10 (35 mg, 4%).

Oxidation of 1 *with CAN in acetone in the presence of ethyl vinyl ether.* Compounds isolated: 5 (100 mg, 18%); 6 (traces); 1-phenylpyrazole (70 mg, 17%).

CAN mediated cycloaddition of 1 *with cyclopentadiene.* Compounds isolated: starting material

(30 mg, 6%); **14** (105 mg, 20%) as an *endo-exo* mixture (siomer ratio 1:1). Adduct **14** was hydrogenated at atmospheric pressure, using Pd/C as catalyst and ethyl acetate as solvent, to give **15** (95 mg, 90% from **14**) as an *endo-exo* mixture (isomer ratio 1:1).

Spectral Data

2,5-Bis-(1-phenyl-4-pyrazolyl)tetrahydrofuran (**5**). ^{1}H-NMR: 7.95–7.20 (m, aromatic H), 5.25 and 5.05 (dd + dd, CH), 2.45 and 2.10 (m + m, CH_2). ^{13}C-NMR: 139.1 (d), 129.3 (d), 126.3 (d), 124.7 (d), 118.9 (d), 73.6 (d), 72.9 (d), 33.8 (t), 33.4 (t). MS: 356 (M^+, 8), 212 (16), 134 (100), 183 (36), 171 (39), 157 (39), 157 (19), 104 (13), 77 (71), 51 (20). $C_{22}H_{20}N_4O$, M^+ required 356.1637; found 356.1638.

4-(1,2-Dimethoxyethyl)-1-phenylpyrazole (**9**). ^{1}H-NMR: 7.9–7.1 (m, aromatic H), 4.5–3.2 (m, $CH-CH_2$), 3.4 and 3.3 (s + s, OCH_3). ^{13}C-NMR: 139.9 (d), 129.3 (d), 126.4 (d), 125.4 (d), 119.0 (d), 76.2 (d), 74.9 (t), 59.1 (q), 56.7 (q), MS: 232 (M^+, 8), 217 (2), 201 (7), 187 (100), 172 (50). $C_{13}H_{16}N_2O_2$, M^+ required 232.1212; found 232.1212.

2-Methoxy-2-(1-phenyl-4-pyrazolyl)ethyl nitrate (**10**). ^{1}H-NMR: 7.95–7.15 (m, aromatic H), 4.8–4.5 (m, $CH-CH_2$), 3.35 (s, OCH_3). ^{13}C-NMR: 139.7 (d), 129.5 (d), 126.9 (d), 125.6 (d), 119.2 (d), MS: 263 (M^+, 16), 216 (20), 202 (50), 187 (100), 172 (100), 158 (84). $C_{12}H_{13}N_3O_4$, M^+ required 263.0906; found 263.0912.

Exo-endo 4-(bicyclo[2,2,1]-2-heptyl)-1-phenylpyrazole (**15**). ^{1}H-NMR: 7.8–7.1 (m, aromatic H), 3.2–3.0 (m), 2.7–2.5 (m), 2.4–2.2 (m), 2.1–1.8 (m), 1.8–1.6 (m), 1.5–1.1 (m). ^{13}C-NMR: 141.0 (d), 140.4 (s), 140.1 (d), 130.6 (s), 129.4 (d), 126.6 (s), 125.9 (d), 124.7 (d), 123.8 (d), 118.7 (d), 43.8 (d), 42.1 (d), 39.9 (t), 39.4 (t), 37.9 (d), 37.2 (d), 36.6 (d), 36.4 (d), 36.2 (t), 36.0 (t), 30.3 (t), 29.8 (t), 29.0 (t), 23.1 (t), MS: $C_{16}H_{18}N_2$, M^+ required 238.1469; found 238.1460.

Acknowledgements

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[7] Spectral data for **6** Ir: broad band 3600–3300 cm^{-1}. ^{1}H-NMR: 7.8–7.0 (m, aromatic H), 6.6 (dd, $J = 9$ and 3 Hz, $CH_2-CH=CH$), 5.6 (ddd, $J = 9$, 6, and 3 Hz, $CH_2CH=CH$), 4.3 (dd, $J = 6$ and 2 Hz, CH-O), 2.8–2.6 (m + m, CH_2); MS: 338 (M-18, 92), 194 (17), 104 (16), 77 (100), 51 (72)

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