Electron Transfer-induced Aromatization of 1,4-Dihydropyridines

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A wide variety of 3,5-dicarboethoxy-1,4-dihydropyridines and 3,5-diacetyl-1,4-dihydropyridines are aromatized to the pyridine derivatives by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) at room temperature and under microwave irradiation. An electron transfer-induced mechanism is proposed for this reaction which is influenced by the nature of the solvent, the nature of the substituents located on 3-, 4- and 5-positions of the 1,4-dihydropyridine ring, and the presence of oxygen or argon atmosphere.

Key words: Aromatization, 1,4-Dihydropyridines, DDQ, Electron Transfer, Oxidation

Introduction

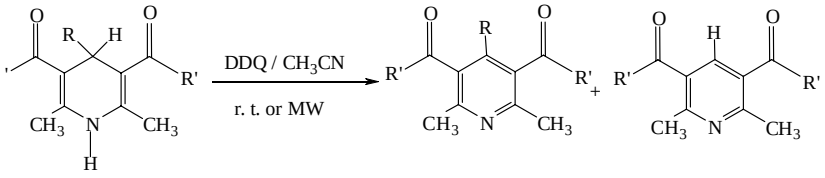
1,4-Dihydropyridines (DHPs) are interesting compounds, especially because of their pharmaceutical activities. They play also an important role in synthetic, therapeutic and bioorganic chemistry [1 – 4]. Formation of pyridine derivatives by the oxidation of 1,4-dihydropyridines has been of great interest for several years and is still under intensive investigation. Due to the oxidative metabolism of these compounds with pharmaceutical activity in the liver under formation of pyridine derivatives, the development of a convenient method for the conversion of 1,4-dihydropyridines to pyridine derivatives is critical for the identification of the metabolites.

In recent years, application of microwave irradiation in optimization and acceleration of organic reactions has rapidly increased. Many reactions that typically require high temperatures and long reaction times have been accelerated using microwave irradiation especially with high yield and clean reaction conditions [5 – 7].

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a versatile reagent for organic synthesis. Due to the ability of this reagent for oxidation reactions and also its relative stability under various reaction conditions, this reagent has been used for several organic transformations such as oxidation of benzhydrols [8], deprotection of benzyl ethers [9], ring opening of α-epoxyketones [10], anodic oxidation of naphthalenes [11], thiocyanation of aromatic and heteroaromatic compounds [12], and ion pair formation between the electrogenerated salts DDQ^{2-} 2 Na^{+} at platinum surfaces [13].

Various oxidative procedures, either thermal [14] or photochemical [15], have been used for aromatization of 1,4-dihydropyridines to pyridine derivatives to elucidate the effect of the nature of the substituents in the 3-, 4- and 5-positions of the DHP ring on the rate of reaction. Since 1,4-dihydropyridines behave as enamines and also as α,β-unsaturated carbonyl compounds, they are able to donate (accept) an electron to a suitable electron acceptor molecule (from an electron-donating molecule). Hence, various studies were devoted to electrochemical oxidation [16, 17] or reduction [18, 19] of these compounds. The results of the polarographic reduction of 1,4-dihydropyridine-3,5-dicarboxylic acid derivatives indicate that the nature of the additional substituent on the phenyl ring located in the 4-position of the DHP ring influences this reductive process. Whereas an electron acceptor substituent (*p*-ClC_6H_4) facilitates the electrochemical reduction, an electron donor substituent $\left(p\text{-}(CH_3)_2NC_6H_4\right)$ hinders the reduction [16].

DDQ as an electron acceptor species has been employed for the oxidation of 1,4-dihydropyridines at room temperature and under ultrasound irradiation [20]. In our recent study concerning the conformational analysis of some unsymmetrically substituted 1,4-dihydropyridines, we found that the DHP ring has a flat boat conformation, as expected, but the nature and position of the substituents in the DHP ring influ-



1a – **l** R' = OC_2H_5 **2a** – **l** **3**

4a – **l** R' = CH_3 **5a** – **l** **6**

Scheme 1.

Table 1. The effect of the solvent on the time of oxidation of **1f** by DDQ at room temperature and under microwave irradiation.

	r. t.		MW	
Solvent[a,b]	Time (min)	Conversion (%)	Time (sec)	Conversion (%)
CH_3CN	11	100	20	100
CH_3OH	150	95	30	95
CH_2Cl_2	40	85	40	85

[a] All starting materials were soluble in these solvents; [b] **1f** / DDQ = 1 : 1.

Table 2. The effect of the **1f** / DDQ molar ratio on the total oxidation of **1f** under microwave irradiation (conversion in %).

DHP / DDQ	1 : 1	1 : 1.1	1 : 1.2	1 : 1.3
CH_3OH[a]	95	100	100	100
CH_3CN[b]	100	100	100	100

[a] Irradiation time is 30 s; [b] irradiation time is 20 s.

ence the amount of deviation of C-4 and N atoms from planarity and the dihedral angles of the CO groups with respect to the C=C bond of the DHP ring [21]. All these factors influence the wavelength of the maximum absorption in the UV spectra and the wavenumber of the CO stretching band in the IR spectra of the corresponding 1,4-dihydropyridines, which confirms that the electronic behavior of 1,4-dihydropyridines is determined by the nature of the 4-substituent. In continuation of this work, we investigated the oxidation of various 1,4-dihydropyridines by DDQ as an electron acceptor species at room temperature and under microwave irradiation to elucidate the effect of the nature of the solvent and also of the nature of the substituents, located in the 3-, 4- and 5-positions of the DHP ring, on the rate of reaction.

Results and Discussion

Since the nature of the solvent and its boiling point have a great effect on the solubility of the starting materials and also on the rate of reactions, we first studied the oxidation of **1f** (for numbering see Scheme 1 and Table 3) in the presence of DDQ in three solvents, CH_3CN, CH_3OH and CH_2Cl_2, at room temperature and under microwave irradiation. The results are summarized in Table 1.

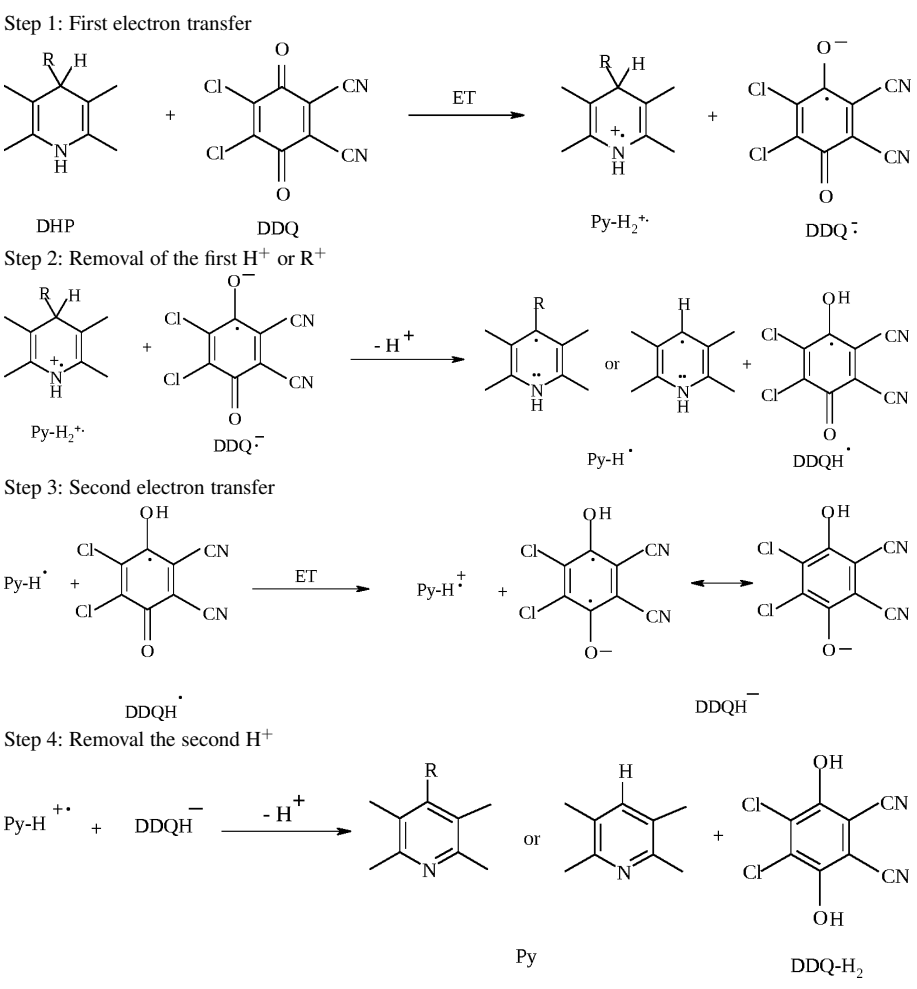
The results indicate that acetonitrile is the best solvent for this purpose, since it is able to produce pyridine derivatives in high yield and in shorter reaction time. For optimization of the amount of oxidant on the total oxidation of **1f**, mixtures of **1f** and DDQ with different molar ratios were irradiated with microwaves. The results are presented in Table 2.

Table 3. Oxidation times and competition rates obtained for the 1 : 1 mixtures of 1,4-dihydropyridine-3,5-diesters **1a** – **l** and DDQ in acetonitrile.

		r. t.		MW	
1	R	Time (min)	Product (%)	Time (sec)	Product (%)
a	Ph	25	**2a** (85)	100	**2a** (85)
b	2-$NO_2C_6H_4$	22	**2b** (90)	40	**2b** (100)
c	3-$NO_2C_6H_4$	12	**2c** (100)	40	**2c** (100)
d	4-$NO_2C_6H_4$	17	**2d** (95)	100	**2d** (95)
e	2-Thienyl	30	**2e** (90)	200	**2e** (90)
f	4-ClC_6H_4	11	**2f** (100)	20	**2f** (100)
g	2-$CH_3OC_6H_4$	17	**2g** (95)	40	**2g** (95)
h	3-$CH_3OC_6H_4$	19	**2h** (90)	40	**2h** (90)
i	4-$CH_3OC_6H_4$	30	**2i** (85)	20	**2i** (100)
j	CH_3	45	**2j** (85)	160	**2j** (85)
k	$Ph(CH_2)_2$	12	**2k** (90)	60	**2k** (90)
l	$Ph(CH_3)CH$	12	**2l** (5), **3** (95)	40	**2l** (5), **3** (95)

Table 4. Oxidation times and competition rates obtained for the 1 : 1 mixtures of 3,5-diacetyl-1,4-dihydropyridines **4a** – **l** and DDQ in acetonitrile.

		r. t.		MW	
4	R	Time (min)	Product (%)	Time (sec)	Product (%)
a	Ph	40	**5a** (100)	40	**5a** (100)
b	2-$NO_2C_6H_4$	21	**5b** (85)	280	**5b** (100)
c	3-$NO_2C_6H_4$	20	**5c** (90)	240	**5c** (90)
d	4-$NO_2C_6H_4$	20	**5d** (80)	100	**5d** (80)
e	2-Thienyl	51	**5e** (95)	250	**5e** (100)
f	4-ClC_6H_4	23	**5f** (90)	40	**5f** (90)
g	2-$CH_3OC_6H_4$	17	**5g** (95)	40	**5g** (95)
h	3-$CH_3OC_6H_4$	12	**5h** (70)	70	**5h** (70)
i	4-$_3OC_6H_4$	7	**5i** (100)	10	**5i** (100)
j	CH_3	15	**5j** (95)	120	**5j** (95)
k	$Ph(CH_2)_2$	22	**5k** (90)	350	**5k** (95)
l	$Ph(CH_3)CH$	12	**6** (95)	50	**6** (95)



Scheme 2.

Based on the results obtained in preliminary studies which are presented in Tables 1 and 2, the 1 : 1 mixtures of DDQ with 1,4-dihydropyridine-3,5-diesters **1a**–**l**, and 3,5-diacetyl-1,4-dihydropyridines **4a**–**l** in acetonitrile were subjected to the oxidation at room temperature and under microwave irradiation (Scheme 1). The results are presented in Tables 3 and 4.

The results presented in Tables 3 and 4 indicate that in most cases the DHP esters **1a**–**l** are oxidized faster than the corresponding diacetyl-DHP's **4a**–**l**. The loss of the substituent in position 4 has been observed earlier in photochemical reactions of Hantzsch esters, but only in cases with carboxy [22], some heterocyclic [23], and secondary alkyl and benzyl [23] groups. Thermal oxidation of Hantzsch esters with expulsion of benzylic and secondary alkyl groups in position 4 by various oxidants has also been reported [24, 25].

In contrast to the results reported on the oxidation of 1,4-dihydropyridines with a secondary alkyl or benzyl group in the 4-position, in which expulsion of these substituents using DDQ as oxidant at reflux condition had not been observed [20], we observed in our reaction dealkylation in the cases of **1l** and **4l** under formation of pyridine derivatives unsubstituted in the 4-position, namely **3** and **6**, respectively.

According to the obtained results, we propose the following mechanism for the electron transfer-induced oxidation by DDQ (Scheme 2):

In the first step, the electron transfer from DHP to DDQ leads to the formation of the dihydropyridyl radical cation ($Py\text{-}H_2^{\bullet+}$) and the radical anion $DDQ^{\bullet-}$. In the next step, removal of the first proton occurs, and a hydropyridyl radical ($Py\text{-}H^{\bullet}$) and $DDQH^{\bullet}$ are formed. The occurrence of the second electron transfer in the third step and removal of the second proton in the

Table 5. Comparison of the results of oxidation by DDQ under oxygen and argon atmosphere at room temperature.

	Ar		O_2	
Compound	Time (min)	Product (%)	Time (min)	Product (%)
1a	20	**2a** (95)	25	**2a** (85)
4a	10	**5a** (100)	40	**5a** (100)
1b	10	**2b** (95)	22	**2b** (90)
4b	5	**5b** (100)	21	**5b** (85)
4e	10	**5e** (100)	51	**5e** (95)
1g	10	**2g** (100)	17	**2g** (95)
1h	10	**2h** (90)	19	**2h** (90)

fourth step accomplish the reaction under formation of pyridine derivatives (Py) and $DDQH_2$.

The following points support the proposed mechanism:

1. The formation of the radical species in this reaction can be inhibited by the presence of oxygen. This can be deduced from the faster reaction observed under argon atmosphere (Table 5).

2. The observation of a faster reaction in a polar aprotic solvent, *i. e.* in acetonitrile, as compared to that in methanol. According to the results presented in Table 1, whereas total conversion of **1f** in acetonitrile solution at room temperature was observed after 11 min, the same reaction in methanol resulted in 95 % conversion after 150 min. A cyclic voltammetry study explains these phenomena.

A cyclic voltammetry study of DDQ in acetonitrile and methanol indicates that in acetonitrile DDQ can be reduced in two steps and produces $DDQ^{\bullet-}$ and DDQ^{2-} at +0.173 V and −0.663 V, respectively (Eqs. 1 and 2; Fig. 1).

$$DDQ + e^- \rightleftharpoons DDQ^{\bullet-} \quad E_1 = +0.173\,V \quad (1)$$

$$DDQ^{\bullet-} + e^- \rightleftharpoons DDQ^{2-} \quad E_2 = -0.0663\,V \quad (2)$$

In contrast to the reversible electrochemical oxidation of DDQ in CH_3CN (Fig. 1), irreversible behavior is observed in methanol solution. Due to the two-electron reduction of DDQ in methanol, DDQ is converted to $DDQH_2$ and cannot be re-oxidized to DDQ. This indicates the involvement of methanol as a protic solvent to donate two protons to the doubly reduced DDQ (DDQ^{2-}) to form $DDQH_2$ (Eq. 3).

$$DDQ + 2\,e^- + 2\,CH_3OH \rightleftharpoons DDQH_2 + 2\,CH_3O^- \quad E = -0.762\,V \quad (3)$$

We assume that in methanol solvated DDQ after reduction is converted to the protonated species

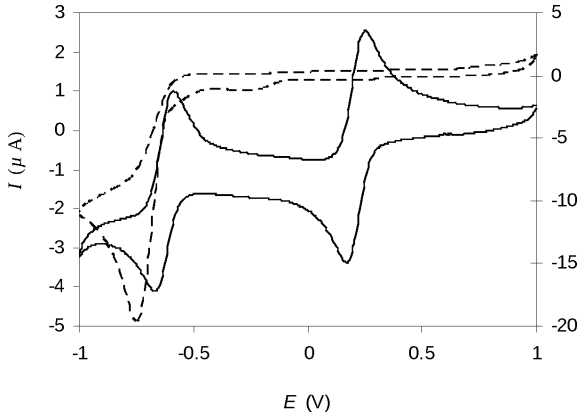
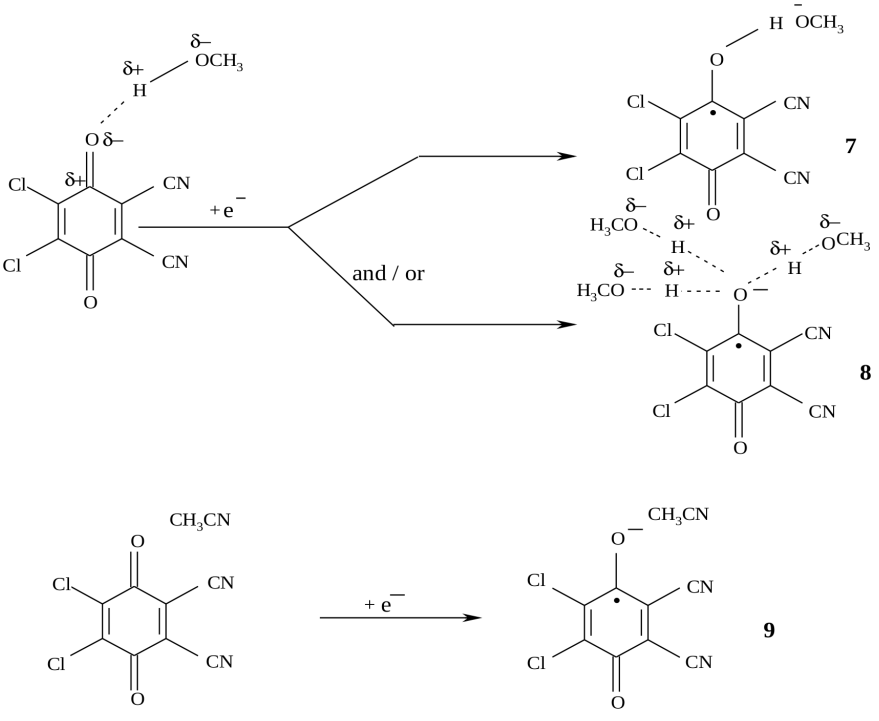


Fig. 1. Cyclic voltammogram of DDQ in acetonitrile (—; left scale) and methanol (---; right scale) solution containing tetrabutylammonium perchlorate (0.05 M) as the supporting electrolyte at a scan rate of 100 mV s^{-1} (Ag/AgCl electrode).

($DDQH^{\bullet}OCH_3^-$, **7**) or to the solvated species ($DDQ^{\bullet-}$ $HOCH_3$, **8**). Due to the failure of solvation of DDQ in acetonitrile solution as a polar aprotic solvent, the reduced species ($DDQ^{\bullet-}$, **9**) is not solvated or protonated. These arguments are supported by an increased rate of oxidation in acetonitrile compared with that in methanol solution, because according to step 2 in the proposed mechanism, the abstraction of the first proton is achieved by the presence of a proton-abstracting species, namely DDQ^-, which is freely present in acetonitrile solution (Scheme 3).

The important result of this work is the effect of the nature of the 4-substituent and the location of the additional substituent in the phenyl ring on the rate of oxidation. The results of the conformational analysis of some symmetrically and unsymmetrically substituted 1,4-dihydropyridines indicate that: i) the nature of the 4-substituent, ii) the location of the additional substituent in the phenyl ring located at C-4, and iii) the presence of the carboethoxy or the acetyl groups at C-3 and C-5 influence the amount of the deviation of C-4 and N-atoms from planarity and also the dihedral angles of the C-4 substituent and carbonyl groups on C-3 and C-5 with respect to the DHP ring atoms [21]. All these observations are due to the polar and steric effects of these substituents which influence the electron-donating ability of the N atom in the DHP ring towards DDQ, namely the rate of the first electron transfer as the key step in the reaction. It should be expected that the less-solvated and freely moving DDQ (DDQ in acetonitrile) is able to accept an electron from the DHP ring easier than the solvated



Scheme 3.

DDQ (DDQ in methanol). It might even be expected that the electron affinity of solvated DDQ in methanol should be greater than that of less-solvated DDQ in acetonitrile.

A comparison of the results of the oxidation at room temperature with and without microwave irradiation (Tables 1, 3 and 4) which both resulted in the same products indicates that, as expected, a comparatively very fast reaction was observed under microwave irradiation.

Experimental Section

All 1,4-dihydropyridines were synthesized according to reported procedures. DDQ, acetonitrile and methanol were purchased from Merck. The solvents were purified before use. The cyclic voltammetric experiments were performed on a Metrohm 797 VA computrace instrument. The electrochemical studies were conducted by using dried acetonitrile or methanol solution containing tetrabutylammonium perchlorate under argon. A three electrode system with an $Ag/AgNO_3$ electrode as the reference, a platinum foil as the counter electrode and a glassy carbon as the working electrode was used. Preparative layer chromatography (PLC) was carried out on a $20 \times 20\ cm^2$ plate coated with a 1 mm layer of Merck silica gel PF_{254} prepared by applying the silica as a slurry and drying in air.

Reactions at room temperature

In a small glass tube which was protected from light, a mixture of 8.8×10^{-3} mmol of **1a–l**, **4a–l** and 8.8×10^{-3} mmol of DDQ in 2 mL of dry acetonitrile was stirred at r. t. until maximum progression of the reaction.

Microwave irradiation

A solution of 8.8×10^{-3} mmol of **1a–l**, **4a–l** and 8.8×10^{-3} mmol DDQ in 2 mL of dry acetonitrile in a beaker was placed in a microwave oven (National, 900 W, 2450 MHz) and exposed to 10 s irradiation and 20 s relaxation to prevent splashing of solvent. The total irradiation times are given in Tables 3 and 4. The solvent was evaporated, and the products were isolated by PLC using petroleum ether / acetone as eluent.

For the preparative work mixtures of 0.2 mmol of each compound were reacted. After completion of the reaction, the products were isolated by PLC using petroleum ether / acetone as eluent and identified by comparison of their physical and spectral data with those of the authentic samples.

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