Catalytic Effect of Basic Alumina in the Dehydrogenation of 1,4-Dihydropyridines with Tetrabutylammonium Peroxydisulfate

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4-Alkyl- or 4-aryl-1,4-dihydropyridine derivatives were oxidized to the pyridine derivatives by tetrabutylammonium peroxydisulfate (n-$Bu_4N)_2S_2O_8$ (TBAPD) in combination with basic alumina in refluxing acetonitrile and also in the absence or presence of basic alumina under microwave irradiation. The presence of basic alumina plays an important role in the reaction mechanism. Whereas oxidation under thermal condition is assumed to occur through an ionic mechanism, ionic and also radical mechanisms are proposed for the reactions under microwave irradiation.

Key words: 1,4-Dihydropyridines, Heterocycles, Oxidation, Peroxydisulfates, Pyridines

Introduction

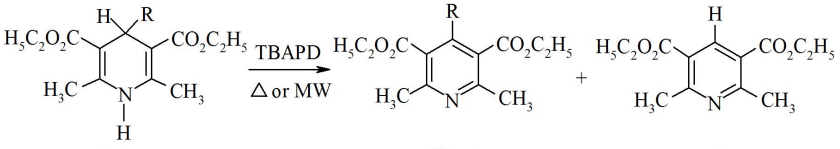
1,4-Dihydropyridines (1,4-DHPs) are well-known compounds of considerable interest as pharmaceuticals which have been described more than one century ago by Arthur Hantzsch [1]. These compounds are analogs of NADH coenzymes and an important class of drugs which are potent blockers of calcium channels with relevant applications in various cardiovascular diseases [2, 3]. It has been observed that in the human body 1,4-DHPs are generally oxidized to their corresponding pyridines [4 – 8]. Due to the biological importance of the oxidation step of 1,4-dihydropyridines, oxidation of these compounds has been the subject of a large number of studies and is still under investigation [9, 10].

In recent years, application of microwave irradiation for the optimization and acceleration of organic reactions has rapidly increased [11 – 13]. In organic synthesis especially it leads to shorter reaction times, higher yields, easier work-up, and environmental friendliness.

Recently, we have reported on the oxidation of various 1,4-dihydropyridines to pyridine derivatives using tetrabutylphosphonium dichromate (TBPDC) under conventional heating and microwave irradiation [14], and also on the electron transfer-induced oxidation of these compounds by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) at room temperature and under microwave irradiation [15]. Due to our general interest in the chemistry of 1,4-dihydropyridines, especially oxidation and photo-oxidation of these compounds [16], we were also interested to find an efficient and especially inexpensive oxidant for the conversion of these compounds to pyridine derivatives.

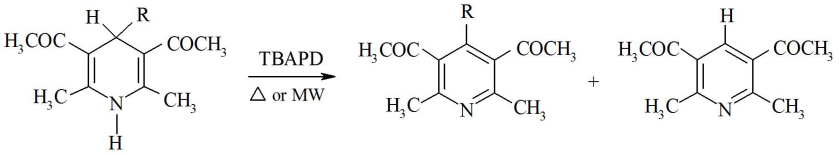
Tetrabutylammonium peroxydisulfate (TBAPD) is easily prepared by reaction of tetrabutylammonium hydrogensulfate and potassium peroxydisulfate in aqueous solution [17]. This reagent has been extensively used for a variety of transformations of functional groups in organic synthesis such as the one-pot synthesis of nitriles from primary alcohols [18] and aldehydes [19], as a selective approach to the oxidative deprotection of allyl ethers [20] and *O*-benzyl protective groups [21], epoxidation of α,β-unsaturated ketones [22], and iodination of aromatic compounds [23, 24]. In contrast to $K_2S_2O_8$, $Na_2S_2O_8$or $(NH_4)_2S_2O_8$, this reagent is easily soluble in various organic solvents such as acetonitrile, acetone, methanol, and dichloromethane.

The aim of the present work has been to investigate the oxidation of 1,4-dihydropyridines by using tetrabutylammonium peroxydisulfate (TBAPD) as oxidant in combination with a suitable catalyst to enhance its oxidizing ability. For this reason, TBAPD alone or in combination with various Lewis acids has been used for the oxidation of 1,4-dihydropyridine-3,5-diesters (Scheme 1) and 3,5-diacetyl-1,4-dihydropyridines (Scheme 2) under conventional heating or microwave irradiation.



1a–m **2b–m** **2a**

Scheme 1.



3a–j **4b–j** **4a**

Scheme 2.

Results and Discussion

At first we have carried out the thermal oxidation of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1e**) as a model substance in the presence of TBAPD alone or in combination with $AlCl_3$, acidic Al_2O_3, basic Al_2O_3, or montmorillonite in acetonitrile. The results presented in Table 1 show that basic Al_2O_3 is the most suitable catalyst for this purpose. Since the nature of the solvent has a great effect on the solubility of the oxidant, and since its boiling point can also affect the rate of oxidation under thermal condition, we studied also the oxidation of **1e** in the presence of TBAPD and basic alumina in a ratio of 1 : 1 : 0.5 in different solvents such as acetone, acetonitrile, chloroform, and dichloromethane under reflux conditions. It was found that acetonitrile is the best solvent for this purpose.

A comparison of the results obtained under reflux condition and under microwave irradiation (Tables 2 and 3) shows that i) the same product(s) are obtained in both reactions, ii) the reaction times are much shorter under microwave irradiation, and iii) oxidation of 1,4-DHPs also occurrs under microwave irradiation even in the absence of basic alumina, but at a slower rate.

The loss of the substituent in position 4 has earlier been observed in photochemical reactions of Hantzsch esters only in the cases of carboxyl groups [25], some heterocyclic groups [26, 27], and secondary alkyl and benzyl groups. Thermal oxidation of Hantzsch esters with expulsion of benzylic and secondary alkyl substituents in position 4 by various oxidants has been cited [28]. We have also reported earlier the expulsion of the 4-substituent on photochemical reaction of some keto-dihydropyridines [28].

Table 1. The effect of the catalyst on the rate of oxidation of **1e** by TBAPD in refluxing acetonitrile.

Catalyst	Time (h)	Conversion (%)
–	8	0
$AlCl_3$	5.5	100
Acidic Al_2O_3	3.5	100
Basic Al_2O_3	1	100
Montmorillonite	5	~40

It is interesting to compare the effect of the presence or absence of the catalyst under both reaction conditions. Since the thermal reaction without using of a catalyst does not work, we will propose a mechanism for the thermal reaction (Scheme 3).

According to the proposed mechanism, nucleophilic attack of basic alumina occurs at the sulfur atom of the oxidant (path 1), followed by a heterolytic cleavage of the peroxydisulfate anion (path 2). The deprotonation at the more acidic site of the 1,4-dihydropyridine by this reactive anion species and the following expulsion of 4-H (as H^-) or 4-R (as R^-) result in the formation of the pyridine derivative (path 3). The attack of hydride or alkyl ions of the aluminum complex releases the basic alumina, which goes back to the reaction cycle (path 4). This argument is supported by the formation of tributylamine, which is detected by the GC analysis of the reaction mixture. It is important to note that this amine was also formed by treatment of the oxidant with sodium hydride (as a hydride source) and basic alumina, as confirmed by the GC analyses. The anionic species formed in path 3 possibly are converted to water or alcohol and the sulfate anion (path 5). This explains the use of equimolar amounts of the oxidant. In the case of acidic alumina, Al-OH can attack the peroxydisulfate, which is not more nucleophilic compared with basic alumina (AlO^-); therefore, a slower reaction (longer re-

Table 2. Aromatization of 1,4-dihydropiridine-3,5-diesters **1a – m** using tetrabutylammonium peroxydisulfate and basic alumina in refluxing acetonitrile and under microwave irradiation.

		Thermal			Microwave irradiation		
1	R	Product	Yield (%)[a]	Time (min)[b]	Product[c]	Time (sec)[b] without cat.	Time (sec)[b] with cat.
a	H	**2a**	95	25	**2a**	60	30
b	CH_3	**2a/2b**	2.5/92	75	**2b**	135	80
c	$CH_3CH_2CH_2$	**2c**	93	90	**2c**	150	90
d	$Ph(CH)CH_3$	**2a**	88	100	**2a**	170	110
e	C_6H_5	**2e**	93	60	**2e**	120	60
f	2-ClC_6H_4	**2f**	90	150	**2f**	260	160
g	4- ClC_6H_4	**2g**	87	120	**2g**	220	100
h	4-$CH_3C_6H_4$	**2h**	93	100	**2h**	170	120
i	2,5-$(CH_3O)_2C_6H_3$	**2i**	86	45	**2i**	100	70
j	2-$NO_2C_6H_4$	**2j**	89	75	**2j**	150	90
k	3-$NO_2C_6H_4$	**2k**	86	150	**2k**	240	160
l	4-$NO_2C_6H_4$	**2l**	90	180	**2l**	270	165
m	2-Furyl	**2m**	76	65	**2m**	310	170

[a] Isolated yield; [b] the times are given for total disappearance of **1a – m**; [c] the products have not been isolated, and only their TLC was compared with that of authentic samples.

Table 3. Aromatization of 3,5-diacetyl-1,4-dihydropyridines **3a – j** using tetrabutylammonium peroxydisulfate and basic alumina in refluxing acetonitrile and under microwave irradiation.

		Thermal		Microwave irradiation		
3	R	Product[a]	Time (min)[b]	Product[a]	Time (sec)[b] without cat.	Time (sec) with cat.[b]
a	H	**4a**	5	**4a**	40	15
b	CH_3	**4b**	40	**4b**	130	80
c	C_6H_5	**4c**	35	**4c**	90	50
d	2-ClC_6H_4	**4d**	80	**4d**	210	140
e	4- ClC_6H_4	**4e**	70	**4e**	190	130
f	4-$CH_3C_6H_4$	**4f**	25	**4f**	80	50
g	2-$CH_3OC_6H_3$	**4g**	4	**4g**	115	80
h	3-$NO_2C_6H_4$	**4h**	60	**4h**	140	80
i	4-$NO_2C_6H_4$	**4i**	65	**4i**	180	110
j	2-Furyl	**4j**	120	**4j**	130	70

[a] The products have not been isolated, and only their TLC was compared with that of authentic samples; [b] the times are given for total disappearance of **3a – j**.

action time) is expected in the case of acidic alumina (Table 1).

It is interesting to compare the results obtained under microwave irradiation in the presence or in the absence of the catalyst. Since the presence of the catalyst increases the rate of oxidation, a heterolytic cleavage of the oxidant as mentioned for the thermal reaction (Scheme 3) and also a homolytic cleavage (Scheme 4) for the oxidation under microwave irradiation are proposed.

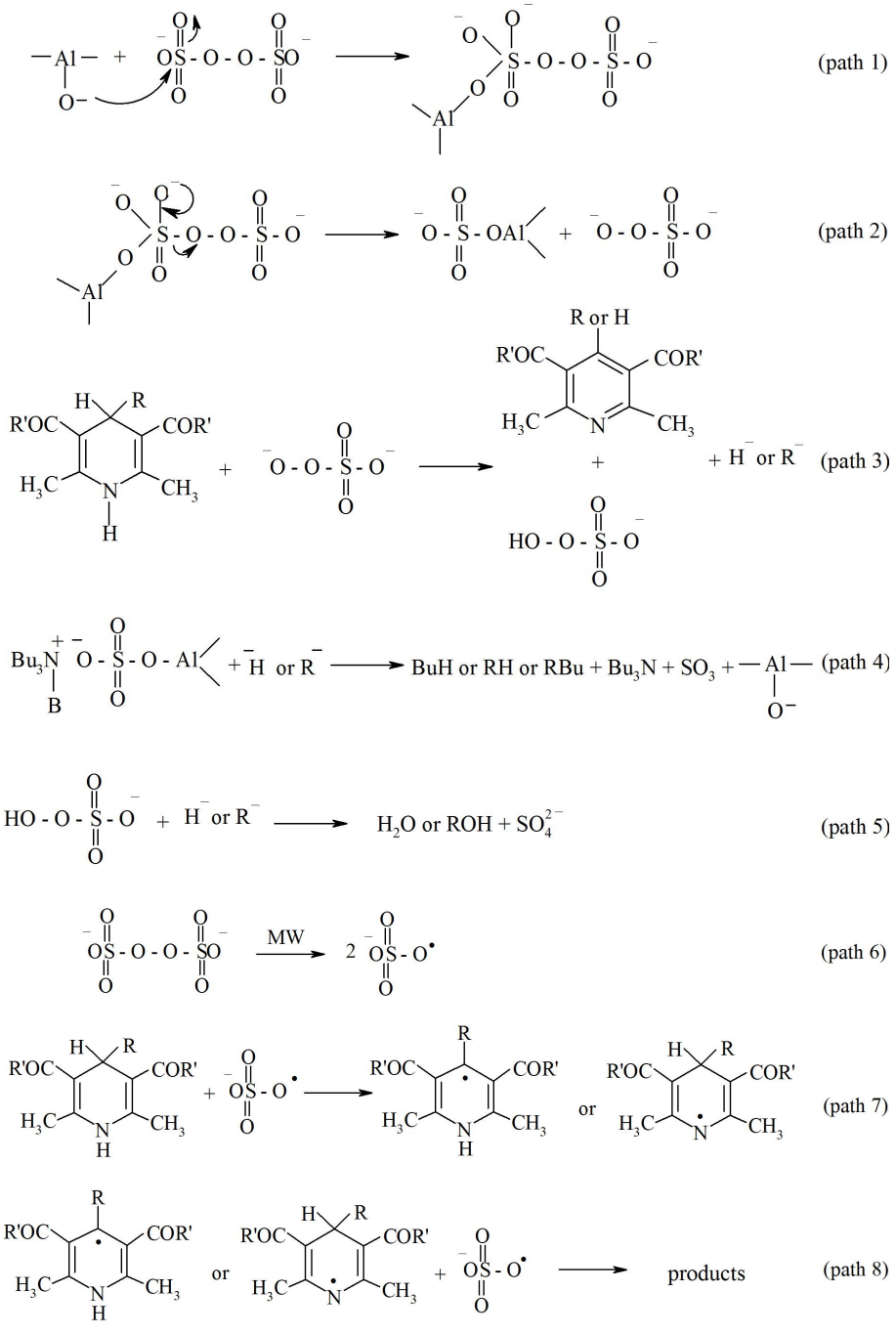
According to this mechanism, homolytic cleavage of the peroxy bond of the oxidant results in the formation of two sulfate radicals (path 6). This reactive species can abstract hydrogen either from 1- or 4-positions under formation of dihydropyridyl radicals (path 7). Elimination of a hydrogen or alkyl radical from dihydropyridyl radicals leads to the formation of pyridines (path 8).

Conclusion

In conclusion, we have found that tetrabutylammonium peroxysulfate in the presence of basic alumina in acetonitrile under thermal condition and/or microwave irradiation, and with or without this catalyst, is a suitable oxidant for the aromatization of 1,4-dihydropyridines. The nature of the 4-substituent plays an important role regarding the rate of oxidation.

Experimental Section

1,4-Dihydropyridines were synthesized according to the Hantzsch procedure [1]. Tetrabutylammonium peroxydisulfate (TBAPD) was prepared according to the known procedure [17]. Microwave irradiation was carried out using a commercial microwave oven (National) operating at 2450 MHz (900 W). All products were known, and their physical and spectroscopic data were compared with those of authentic samples. The spectroscopic data of the starting



Scheme 3.

Scheme 4.

materials and also the products have been reported earlier [27, 28 – 30]. Preparative layer chromatography (PLC) was carried out on 20 × 20 cm^2 plates, coated with a 1 mm layer of Merck silica gel PF_{254}, prepared by applying the silica as slurry and drying in air.

Thermal reactions

In an optimized reaction, a mixture of **1a** – **m** (0.3 mmol) or **3a** – **j** (0.3 mmol), TBAPD (0.3 mmol) and basic alumina (0.15 mmol) in acetonitrile (10 mL) was refluxed until total disappearance of 1,4-dihydropyridine (TLC). After com-

pletion of the reaction, the solvent was evaporated, and the product was isolated by PLC.

Microwave irradiation

A mixture of **1a – m** or **3a – j** (0.1 mmol), TBAPD (0.1 mmol) and basic alumina as catalyst (0.05 mmol) or without a catalyst in acetonitrile (0.5 mL) was irradiated with microwaves until all of the dihydropyridine was consumed.

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