Research Note

AROMATIZATION OF 1,4-DIHYDROPYRIDINES WITH FREE RADICAL REAGENTS

M. M. M. Sadeghi*, H. R. Memarian and A. R. Momeni

Department of Chemistry, Faculty of Sciences, University of Esfahan, Esfahan, Islamic Republic of Iran

Abstract

Oxidation of different types of 1,4-dihydropyridines with diphenylpicrylhydrazyl (DPP) and benzoyl peroxide (Bz_2O_2) as free radical oxidizing agents to pyridine derivatives is reported and a mechanism for this oxidation is also proposed.

Introduction

A great deal of work has been done on the oxidation of 1,4-dihydropyridines to pyridine derivatives and a wide variety of reagents such as $KMnO_4$ [1], CrO_3 [2], HNO_3 [3], pyridinium chlorochromate (PCC) [4], ceric ammonium nitrate (CAN) [5], bismuth nitrate pentahydrate [6], manganese (III) acetate [7], tetrakis-pyridine cobalt (II) dichromate (TPCD) [8], 3-carboxypyridinium chlorochromate (CPCC) [9], nicotinium dichromate (NDC) [10], sodium nitrite/oxalic acid [11], sodium nitrite/sodium hydrogen sulfate [12], sodium nitrite/magnesium hydrogen sulfate [13], sodium nitrate in the presence of wet SiO_2 [14], barium manganate [15], and Potassium peroxodisulfate [16] have been reported for this purpose in the literature.

Very little work has been reported using reagents in the form of free radicals. Benzoyl peroxide, tert-butyl and acetyl peroxides [17,18] diphenylpicrylhydrazyl [18] and tert-butylhydroperoxide [19] have been used as free radical agents. However, no systematic work using 1,4-dihydropyridines with different substituents at 4-position has been reported.

Keywords: Oxidation, Free radical; 1,4-Dihydropyridine; Diphenylpicrylhydrazyl (DPP); Benzoyl peroxide (Bz_2O_2)

Results and Discussion

Herein, we report a systematic work in which we investigated the effects of different substituents at 4-position on the rate of oxidation and type of products, using diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing agents. The results are summarized in Table 1.

It was observed that dihydropyridine derivatives bearing secondary alkyl group (entry 3) and benzyl groups (entries 5 and 6) at 4-position were dealkylated during aromatization owing to the stability of the corresponding radicals, while in the cases of 2-furyl (entry 14) and 5-methyl-2-furyl (entry 15) substituents, different products were obtained.

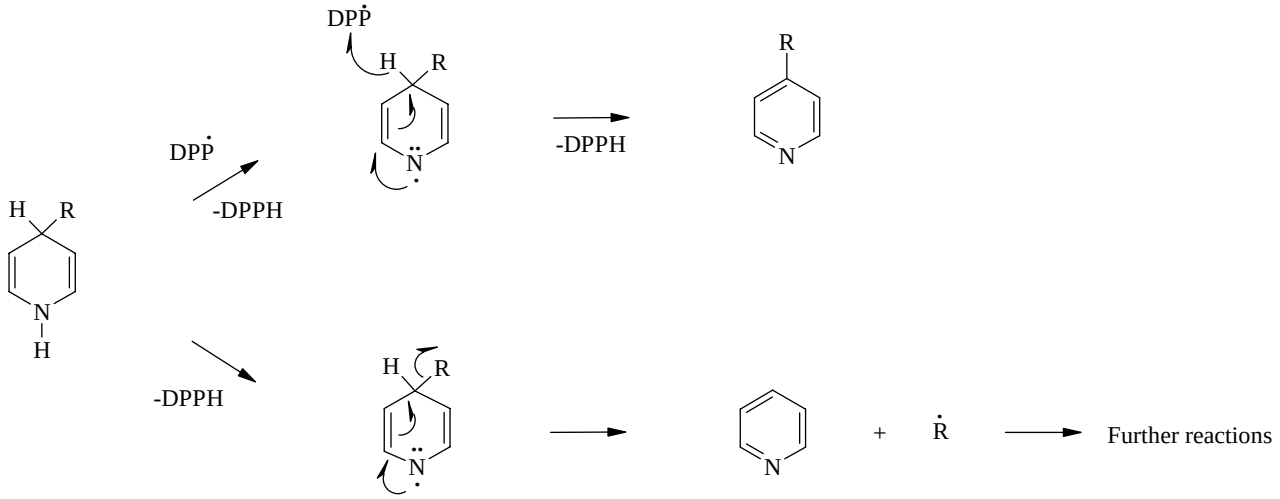
Electron-withdrawing groups such as 2-, 3-, and 4-nitrophenyl (entries 8-10) and also heteroaryls (entries

* *E-mail: m.sadeghi@sci.ui.ac.ir*

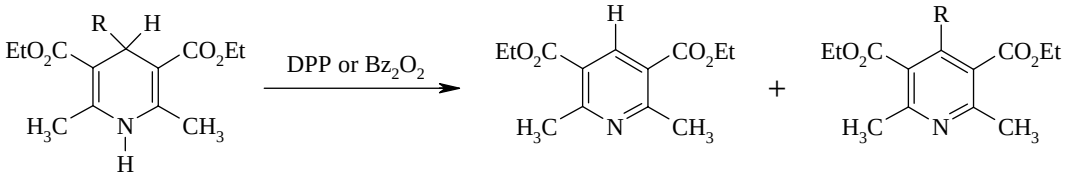
Table 1. Oxidation of 1,4-dihydropyridines with DPP and Bz_2O_2

Try	R	DPP[a]		Bz_2O_2[b]		Product
		Time(min)[c]	Yield(%)[d]	Time(min)[c]	Yield(%)[d]	
1	H	10	85	10	81	16
2	CH_3	60	75	60	71	17
3	$(CH_3)_2CH$	50	85	30	85	16
4	C_6H_5	60	80	80	80	18
5	$C_6H_5CH_2$	60	87	30	85	16
6	$C_6H_5CHCH_3$	40	83	90	90	16
7	2,5-$(CH_3O)_2C_6H_3$	15	85	90	85	19
8	2-NO_2-C_6H_4	240	90	120	75	20
9	3-NO_2-C_6H_4	240	76	120	81	21
10	4-NO_2-C_6H_4	180	83	90	80	22
11	2-Pyridyl	240	80	60	85	23
12	4-Pyridyl	480	77	240	76	24
13	2-Thienyl	240	82	240	88	25
14	2-Furyl	180	71+10	240	65+10	26+16
15	5-Methyl-2-furyl	210	51+20	150	68+15	27+16

[a]Reaction was performed in benzene. [b]Reaction was performed in acetonitrile. [c]The times are given after total disappearance of starting material (**1-15**). [d]Isolated yield. All of the products were characterized by comparison of their m.p., ^{1}H NMR and IR data with those of authentic samples.



1-15 **16** **17-27**



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11-15), decrease the rate of oxidation, while electron-releasing substituents such as alkyl groups (entries 2, 3, 5 and 6) increase it.

It is noteworthy that in the oxidation of 1,4-dihydropyridines with secondary alkyl or benzyl group at 4-position (entries 3, 5 and 6), only one equivalent of oxidizing agent was required but in other cases two equivalents were consumed.

Oxidation of dihydropyridines by diphenylpicryl-hydrazyl, as shown by a primary isotope effect (k_H / k_D = 1.8-2.7) in the reaction of N-deuterio derivatives of compounds 1, 3, 6 and 7, proceeds by a hydrogen abstraction mechanism. According to the above mentioned results, the following mechanism is proposed.

In conclusion, in this study we introduced a systematic work for the investigation of the mechanism of free radical oxidation of 1,4-dihydropyridines.

Experimental

A mixture of 1,4-dihydropyridine (1 mmol) and diphenylpicrylhydrazyl or benzoyl peroxide (2 mmol) in appropriate solvent (5 ml) was stirred magnetically under reflux condition. The progress of the reaction was followed by TLC. The resulting crude material was purified by PLC with an appropriate eluent.

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