Short communication

Mild and Convenient Method for Aromatization of Hantzsch Esters of 1,4-Dihydropyridines with Ag_2O

Behzad Zeynizadeh,* Karim Akbari Dilmaghani and Mansoor Mirzaei

** Corresponding author: Department of Chemistry, Faculty of Sciences, Urmia University, Urmia 57159-165, Iran*
E-mail: bzeynizadeh@gmail.com

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Abstract

Hantzsch esters of 1,4-dihydropyridines were readily aromatized to their corresponding pyridine compounds by Ag_2O in quantitative yields. The reactions were carried out in refluxing CH_3CN within 0.9–4.5 h.

Keywords: Aromatization, hantzsch esters of 1,4-dihydropyridines, Ag_2O.

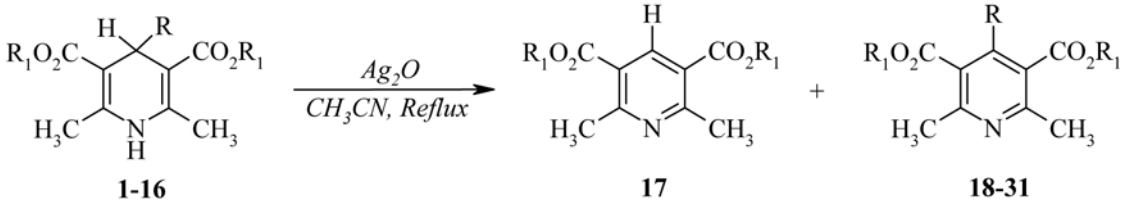
1. Introduction

Hantzsch esters of 1,4-dihydropyridine based drugs such as Nifedipine, Amoldipine and Nitrendipine are the calcium channel blockers and have been widely used in the treatment of various cardiovascular diseases.[1] In human body and during the first pass metabolism in the liver, it has been observed that 1,4-dihydropyridines undergo an oxidation reaction to produce pyridine compounds.[2] Because of the relevance of this oxidative conversion to biologically significant NADH redox processes and to the metabolic studies,[3] this transformation has attracted a great deal of attentions for the discovery of mild and general protocols applicable to a wide range of 1,4-dihydropyridines. In this context, a number of methods and reagents have been reported.[4–20] However; some of these methods have some disadvantages such as long reaction times, low yields of products, the requirement for severe conditions and the use of strong or toxic oxidants. Therefore, the introduction and development of a convenient, mild and efficient method for the oxidation of 1,4-dihydropyridines to pyridine compounds is practically important and is still demanded.

2. Results and Discussion

The literature review shows that silver (I) oxide, Ag_2O, has been found useful applications in organic synthesis as a mild oxidizing agent.[21] However, as far as we know, the aromatization of 1,4-dihydropyridines with Ag_2O has not been reported yet. Our continuous efforts toward the development of this synthetic protocol[22] prompted us to report a new and practical method for the aromatization of substituted 4-aryl and 4-alkyl 1,4-dihydropyridines to the corresponding pyridines with Ag_2O under mild conditions (Scheme 1).

The optimization experiments on the aromatization of 1,4-dihydropyridine (**2**) showed that CH_3CN was the solvent of choice for the excellent yield of product. The reaction in various other solvents such as CH_2Cl_2, C_6H_6, MeOH and THF was slow and had low efficiency (Table



1-16 **17** **18-31**

Schema 1

Table 1: Aromatization of 1,4-dihydropyridine (2) with Ag_2O in different solvents[a]

Entry	Solvent	Time (h)	Conversion (%)
1	CH_2Cl_2	3	20
2	C_6H_6	3.5	50
3	MeOH	4	30
4	CH_3CN	1.7	100
5	THF	4	80

[a] All reactions were carried out with the molar ratio of 1,4-dihydropyridine/Ag_2O (1:2) under reflux condition.

1). In addition, the results showed that the completion of reactions required two molar equivalents of Ag_2O and the Ag mirror was generated on the walls of the reaction flask during the progress of the reactions. Table 2 shows the general applicability and versatility of this oxidative conversion by subjecting of various 4-substituted 1,4-dihydropyridines towards Ag_2O. The aromatization reactions were performed in refluxing CH_3CN within 0.9–4.5 h and the corresponding pyridine compounds were obtained in quantitative yields. During the aromatization reactions, the substituents of aryl, heteroaryl and propyl groups at the *para* position of 1,4-dihydropyridines were remained intact, however, styryl and methyl groups showed 50–70% dealkylation reactions. In the case of isopropyl group, a complete dealkylation reaction was observed (Table 2, entry 16).

The exact mechanism of this synthetic method is not known. However, due to the formation of Ag mirror in the reaction mixture, we suggest the following mechanistic pathways in the production of pyridine compounds (Scheme 2).

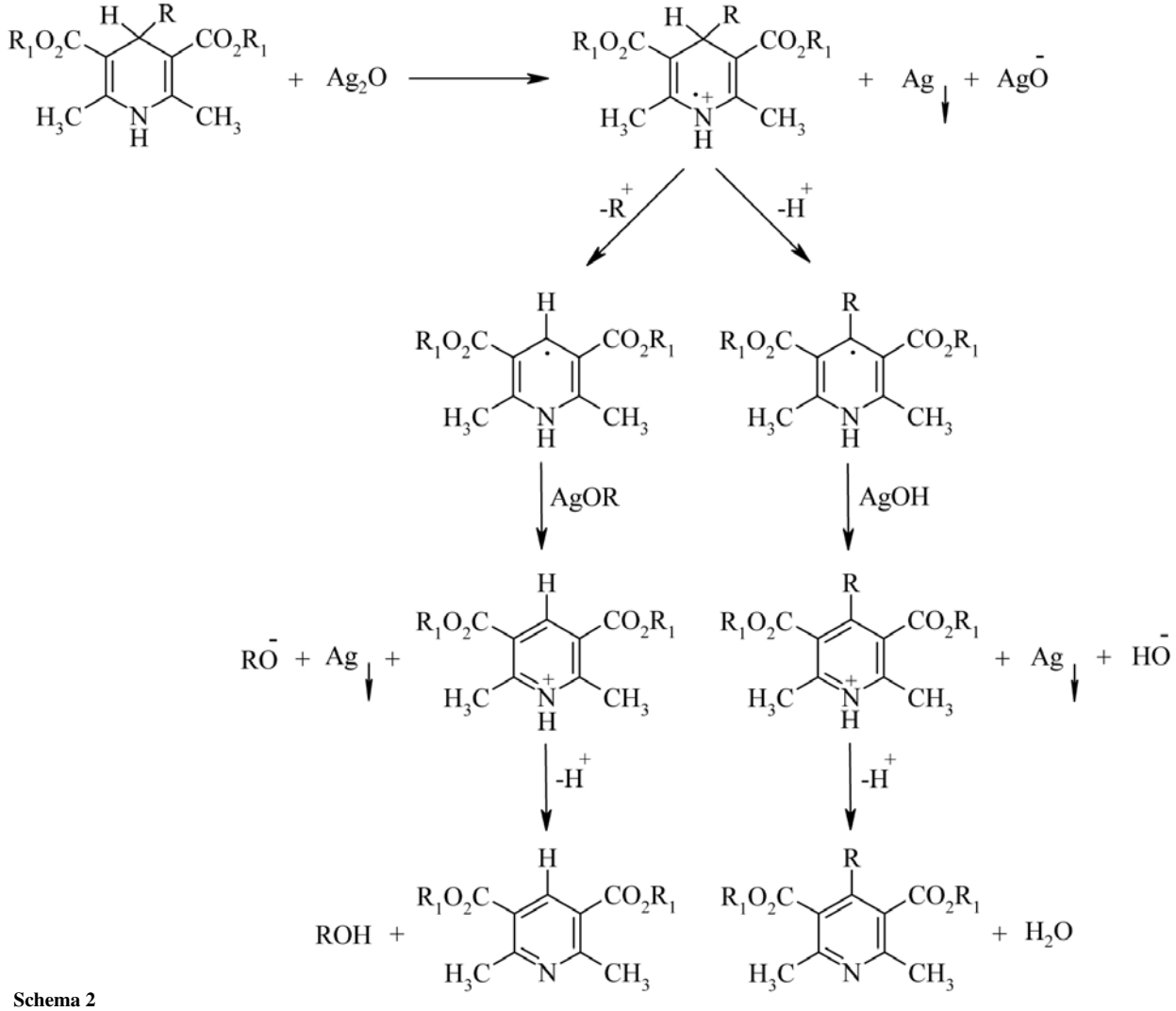
3. Conclusions

In conclusion, we have described a convenient and efficient procedure for the aromatization of 4-substituted 1,4-dihydropyridines to their corresponding pyridines with Ag_2O. The reactions were carried out in refluxing CH_3CN within 0.9–4.5 h. The availability of Ag_2O, excellent yields and simple work-up procedure make this protocol a useful addition to the present methodologies.

Table 2: Aromatization of 1,4-dihydropyridines to their corresponding pyridines with Ag_2O[a]

1,4-DHP[b]	R	R_1	Product	Time (h)	Yield (%)[c]	M.p. (°C)	Lit. M.p. (°C)
1	H	Et	17	0.9	98	70-71	72 [22a]
2	C_6H_5	Et	18	1.7	96	63-64	62-63 [22a]
3	C_6H_5	Me	19	1.8	97	135-136	135-136 [22a]
4	3-$NO_2C_6H_4$	Et	20	2.8	96	59-62	61-63 [22a]
5	2-Furyl	Et	21	3	95	40-42	Oil [22a]
6	2-ClC_6H_4	Et	22	4.5	98	70-71	69-70 [13]
7	4-ClC_6H_4	Et	23	1.7	98	67-68	68 [18]
8	2,4-$Cl_2C_6H_3$	Et	24	1	95	78-79	78-80 [18]
9	3-BrC_6H_4	Et	25	3	96	70-72	70-72 [18]
10	4-(MeO)C_6H_4	Et	26	2.6	95	49-50	50 [22a]
11	4-MeC_6H_4	Et	27	2.8	97	71-72	72-73 [22b]
12	4-$N(Me)_2C_6H_4$	Et	28	2	95	-	-
13	$CH_3CH_2CH_2$	Et	29	2	97	Oil	Oil [19]
14	C_6H_4CH=CH	Et	30+17	2.2	50+50 (96)[d]	162-163	162-163 [20]
15	CH_3	Et	31+17	1.2	30+70 (95)[d]	Oil	Oil [17]
16	$(CH_3)_2CH$	Et	17	1.7	98	70-71	72 [22a]

[a] All reactions were carried out with the molar ratio of 1,4-dihydropyridine/Ag_2O (1:2) in refluxing CH_3CN (4 mL).
[b] 1,4-DHP means 1,4-dihydropyridine. [c] Yields refer to isolated pure products. [d] Overall isolated yield.



Schema 2

4. Experimental

Hantzsch esters of 1,4-dihydropyridines were prepared by reported methods.[23] Ag_2O and the solvents were purchased from commercial sources with the best quality and they were used without further purification. IR and ^1H NMR spectra were recorded on Thermo Nicolet Nexus 670 FT-IR and 300 MHz Bruker Avance spectrometers, respectively. The products were characterized by their ^1H NMR or IR spectra and compared with authentic samples (melting or boiling points). Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F_{254} aluminum sheet.

A typical procedure for the aromatization of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (2) with Ag_2O

In a round-bottomed flask (10 mL) equipped with magnetic stirrer and condenser, to a solution of 1,4-dihydropyridine (**2**) (0.329 g, 1 mmol) in CH_3CN (4 mL), Ag_2O (0.463 g, 2 mmol) was added. The reaction mixture was then stirred under reflux condition for 1.7 h. The progress of the reaction was monitored by TLC (eluent; CCl_4/Et_2O: 5/2). At the end of the reaction, distilled water (5 mL) was added to the reaction mixture and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (CCl_4/Et_2O: 5/2) gave the pure pyridine compound **18** (0.314 g, 96%, Table 1).

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Povzetek

V prispevku je predstavljena hitra in kvantitativna aromatizacija Hantzsch-evih estrov 1,4-dihidropiridinov do ustreznih piridinov z uporabo Ag_2O. Reakcije potečejo v 0.9–4.5 ure v CH_3CN pod pogoji refluksa.