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Mild and Efficient Method for Aromatization of Hantzsch Esters of 1,4-Dihydropyridines with HIO_3

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Aromatization of Hantzsch esters of 1,4-dihydropyridines was carried out efficiently by iodic acid, HIO_3, in refluxing CH_3CN. The corresponding pyridine compounds were obtained in quantitative yields within 7-55 min.

Key Words: Aromatization, Hantzsch, 1,4-Dihydropyridines, HIO_3.

INTRODUCTION

The aromatization of Hantzsch esters of 1,4-dihydropyridines (1,4-DHPs) to the corresponding pyridines has attracted a great deal of attentions due to relevance of this oxidative conversion to the biological NADH redox processes as well as the metabolic studies pertaining to 1,4-DHPs based cardiovascular drugs such as nifedipine, amoldipine and nitrendipine[1,2]. Furthermore, the aromatization of 1,4-DHPs provides an easy way to access pyridine derivatives. In this context, a number of methods and reagents including CrO_3[3], $KMnO_4$[4], HNO_3[5], MnO_2[6], SeO_2[7], $K_2S_2O_8$[8], $Mn(OAc)_3$[9], $H_2O_2/Co(OAc)_2$[10], ceric ammonium nitrate[11], pyridinium chlorochromate[12], *t*-butylhydroperoxide[13], I_2[14], $NaNO_2/C_2H_2O_4.2H_2O$, $NaNO_2/Mg(HSO_4)_2$, $NaNO_2$/wet SiO_2[15], [hydroxyl(tosyloxy)iodo]benzene[16] and $PhI(OAc)_2$[17] have been reported. However, most of these methods require an extended period of times for completion, utilize large excess of strong or toxic oxidants and produce modest yields of pyridine compounds. Ring nitration with metallic nitrates and the solvent-dependent oxidation of 2-methyl group occur in some cases. It is important to note that a complete dealkylation reaction of alkyl groups especially secondary alkyl groups at the 4-position of 1,4-DHPs is one major limitation which some of the mentioned protocols encountered with it. Therefore, the introduction and development of a convenient, mild and efficient method for the aromatization of 1,4-dihydropyridines to pyridine compounds is practically important and is still of interest.

EXPERIMENTAL

All Hantzsch esters of 1,4-dihydropyridines were prepared by standard methods[18]. HIO_3 and the solvents were purchased from commercially sources with the best quality and 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 ^{1}H NMR or IR spectra and comparison with the reported data in literature. Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. TLC over silica gel 60 F_{254} aluminum sheets was applied for the purity determination of the substrates, products and for reaction monitoring.

A typical procedure for aromatization of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (2) with HIO_3: In a round-bottom flask (10 mL) equipped with magnetic stirrer and condenser, to a solution of 1,4-DHP **2** (0.329 g, 1 mmol) in CH_3CN (4 mL), HIO_3 (0.176 g, 1 mmol) was added. The reaction mixture was stirred for 0.5 h under reflux condition. TLC monitored the progress of the reaction (CCl_4/Et_2O: 5/2). At the end of reaction, distilled water (5 mL) was added and the reaction mixture was continued to stirring for 5 min. The mixture was extracted with EtOAc (3 mL × 5 mL) and the extracts were then dried over anhydrous sodium sulfate. Evaporation of the solvent gives the pure pyridine compound **21** in 0.317 g (97 %, Table-1).

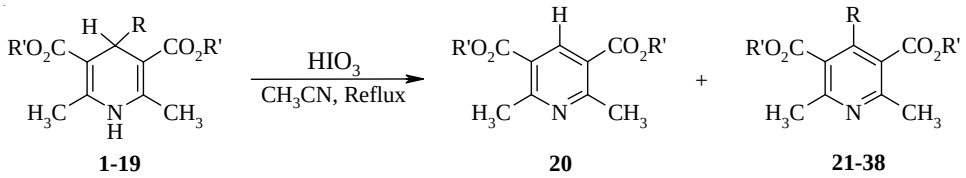
TABLE-1
AROMATIZATION OF 1,4-DHPs TO THEIR CORRESPONDING PYRIDINES WITH HIO_3[a]

Entry	R	R'	Product	Time (min)	Yield (%)[b]	m.p. (ºC)	Lit. m.p. (ºC)
1	H	Et	20	7	95	70-71	72[19a]
2	C_6H_5	Et	21	30	97	63-64	62-63[19a]
3	C_6H_5	Me	22	25	97	135-136	135-136[19a]
4	3-$NO_2C_6H_4$	Et	23	30	96	59-62	61-63[19a]
5	2-Furyl	Et	24	40	95	Oil	Oil[19a]
6	2-Furyl	Me	25	37	96	Oil	Oil[19a]
7	2-ClC_6H_4	Et	26	30	98	62-63	61-62[14]
8	4-ClC_6H_4	Et	27	20	98	65-66	65-66[7]
9	2,4-$Cl_2C_6H_3$	Et	28	15	97	78-79	78-80[17]
10	3-BrC_6H_4	Et	29	15	96	70-72	70-72[17]
11	4-$MeOC_6H_4$	Et	30	45	96	51-53	51-53[14]
12	4-MeC_6H_4	Et	31	15	98	71-72	72-73[14]
13	4-$(NMe_2)C_6H_4$	Et	32	45	94	–	–
14	C_6H_4CH=CH	Et	33	55	94	162-163	162-163[7]
15	4-MeO-3-OH-C_6H_3	Et	34	15	93	140-141	140-142[7]
16	4-OH-3-MeO-C_6H_3	Et	35	20	94	160-161	159-160[7]
17	CH_3	Et	36	40	95	Oil	Oil[7]
18[c]	$CH_3CH_2CH_2$	Et	37+20	50	60+40 (96)[d]	Oil	Oil[7]
19[c]	$(CH_3)_2CH$	Et	38+20	55	70+30 (96)[d]	Oil	Oil[14]

[a]All reaction were carried out with the molar ratio of 1,4-DHP/HIO_3 (1:1) in refluxing CH_3CN (4 mL); [b]Yields refer to isolated pure products; [c]Molar ratio of 1,4-DHP/HIO_3 (1:1.5); [d]Overall isolated yield.

RESULTS AND DISCUSSION

Literature review shows that iodic acid as a mild oxidizing agent has been found useful applications in organic synthesis[19]. As per our best of knowledge, as far as we know, the aromatization of 1,4-dihydropyridines with HIO_3 has not been reported yet. Our continuous efforts towards the development of this synthetic method[20] prompted us to report a new and practical protocol for the aromatization of substituted 4-aryl and 4-alkyl 1,4-dihydropyridines to the corresponding pyridines with HIO_3 in refluxing CH_3CN (**Scheme-I**).



1-19 **20** **21-38**

Scheme-I

Reaction conditions were optimized by performing the aromatization of 1,4-DHP **2** with HIO_3 under different conditions. The experiments showed that completion of the reaction requires one molar equivalent of HIO_3 in refluxing CH_3CN. Consequently, the pyridine compound **21** was obtained in 97 % yield. The utility of this synthetic method was further explored with the aromatization of a variety of 1,4-dihydropyridines bearing 4-substituted aryl, heteroaryl, styryl and alkyl groups by HIO_3 under the optimized experimental conditions. As shown in Table-1, during the aromatization reactions, the substituents of aryl, heteroaryl, styryl and methyl groups at the *para* position of 1,4-dihydropyridines (**2-17**) were remained intact and the corresponding pyridine compounds were obtained in quantitative yields within 15-55 min. However, propyl and isopropyl groups showed 30-40 % dealkylation reactions (entries 18, 19).

Conclusion

In this paper, a convenient and efficient method is developed for the aromatization of 4-substituted 1,4-dihydropyridines to their corresponding pyridines with HIO_3. The reactions were carried out in refluxing CH_3CN within 7-55 min. The low cost and easy availability of HIO_3, the perfect efficiency and shorter reaction times as well as the simple work-up procedure make this method a useful addition to the present methodologies.

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