Aromatization of Hantzsch Ester 1,4-Dihydropyridines with Iodine under Normal Conditions and Ultrasound Irradiation

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A variety of Hantzsch ester 1,4-dihydropyridines are efficiently oxidized to their corresponding pyridine compounds with iodine under normal conditions and ultrasound irradiation. The reactions were carried out in refluxing CH_3CN.

Keywords: Aromatization; Hantzsch 1,4-dihydropyridines; Iodine; Ultrasound.

INTRODUCTION

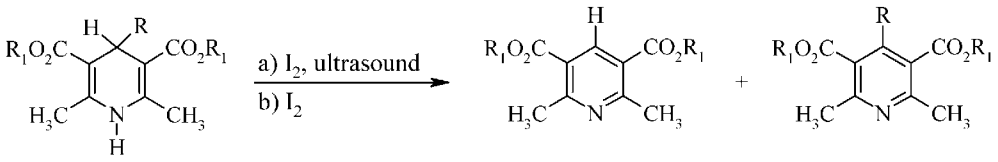
Hantzsch ester 1,4-dihydropyridines (1,4-DHPs) as important calcium channel blockers have been widely utilized for the treatment of hypertension and angina pectoris.[1] These compounds are oxidatively aromatized to their corresponding pyridine derivatives initially during the metabolism by the action of cytochrome P-450 in the liver.[2] Due to the relevance of this oxidative conversion to the biological NADH redox process, and that metabolic studies require reference standards, this transformation has attracted a great deal of attention.[1a,3] Furthermore, the aromatization of 1,4-DHPs provides an easy access to their pyridine compounds. Therefore, a wide variety of reagents have been developed for this oxidative conversion, e.g., $KMnO_4$,[4] CrO_3,[5] HNO_3, HNO_3/bentonite/microwave,[1b,6] MnO_2, MnO_2/bentonite,[7] DDQ,[7a] PCC,[8] CAN,[9] $Bi(NO_3)_3.5H_2O$,[10] $BaMnO_4$,[11] $K_2S_2O_8$,[12] $RuCl_3$,[13] clayfen,[14] diphenylpicrylhydrazyl and benzoylperoxide,[15] $PhI(O_2CCF_3)_2$ or sulfur,[16] microwave under solid phase condition,[17] silica supported $Cu(NO_3)_2$ or $Fe(NO_3)_3$,[14,18] nitric oxide,[19] *tert*-butylhydroperoxide,[20] $Mn(OAc)_3$,[21] tetra-kispyridine cobalt(II) dichromate,[22] 3-carboxypyridinium chlorochromate,[23] nicotinium dichromate,[24] and $NaNO_2$ in the presence of oxalic acid, sodium hydrogen sulfate, magnesium hydrogen sulfate or wet SiO_2.[25]

Some of reported methods suffer from limitations including low yield of products, the use of excess or strong oxidants, long reaction times, and the requirement for severe conditions. Therefore, the aromatization of Hantzsch ester 1,4-dihydropyridines still requires a need to develop a mild and high yielding protocol.

On the other hand, the acceleration of reactions with ultrasound as an interesting and modern synthetic strategy has been widely used in organic chemistry and numerous papers have demonstrated its importance.[26] Sonic conditions not only accelerate the chemical reactions but also reduces the number of steps which are required by using conventional reagents under normal conditions; in addition, the reactions can be initiated without any additives. In this context, ultrasound-assisted aromatization of 1,4-dihydropyridines by using clay supported cupric nitrate has also been reported.[27]

Herein, we report an efficient and improved method for the aromatization of 1,4-dihydropyridines to the corresponding pyridine compounds by using readily available and inexpensive iodine in the presence (a) and absence (b) of ultrasound irradiation in refluxing CH_3CN (Scheme I).

Scheme I



1-13 **14** **15-26**

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RESULTS AND DISCUSSION

Literature review shows that the aromatization of Hantzsch ester 1,4-dihydropyridines by using molecular iodine in the presence of an alkali or organic base in methanol has been reported recently.[28] Though the I_2-base system in MeOH is efficient for the aromatization of 1,4-DHPs, this method suffers from relatively long reaction times and basic conditions. Therefore, the biological importance of 1,4-dihydropyridines oxidation and our ongoing attention to the development of ultrasound-assisted organic reactions,[29] prompted us to reinvestigate the aromatization of 1,4-DHPs by molecular iodine in the presence and absence of ultrasound irradiation under an aprotic solvent system and neutral conditions.

At first, we investigated the optimum conditions for the oxidative-aromatization of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4-substituted 1,4-DHP) (**1**) as a model compound with iodine in aprotic solvents such as CH_2Cl_2, CH_3CN, THF, and C_6H_6 under normal conditions. We performed a set of experiments and found that using 2 molar equivalents of iodine and simply refluxing in CH_3CN are optimal for the complete aromatization of the 1,4-DHP (5 h, 96%). Then we applied these conditions for the aromatization of different 4-substituted alkyl and aryl 1,4-dihydropyridines. The reactions were performed with good to excellent yields of the corresponding pyridine compounds (60-97%). The results of these transformations are summarized in Table 1, which indicates the scope of our protocol to various 1,4-DHPs (**1**-**13**). Generally, the reactions were clean, efficient, and completed within 1-7 hrs. The method is mild and tolerates several substituted aryl groups on the 4-position of 1,4-DHPs. It was observed that oxidation of 1,4-dihydropyridine with a secondary alkyl group proceeded rapidly and gave dealkylated pyridine compound **14** in excellent yield. Substituted 2-furyl moiety on the 4-position of 1,4-DHPs (**5**, **6**) showed a complete aromatization; however, the corresponding pyridine compounds including 2-furyl group were obtained in 60-65% yields.

In the next attempt, we decided to investigate the influence of sonic conditions on the aromatization of 1,4-DHPs. We saw that the irradiation of compound **1** with ultrasound by using 2 molar equivalents of iodine in acetonitrile showed a little influence at room temperature. Whereas, when this reaction was irradiated with ultrasound in refluxing CH_3CN, the rate of reaction was increased dramatically and it was completed in 15 minutes. The irradiation was carried out with 30% power amplitude of sonicator (600 W) via a micro-tip probe.

To show the further utility of sonic conditions, we aromatized different 4-substituted alkyl, aryl, and heteroaryl 1,4-dihydropyridines with 2 molar equivalents of iodine in the presence of ultrasound in refluxing CH_3CN. The reactions were carried out in short reaction times, and the corresponding pyridine compounds were obtained in high to excellent yields (70-98%) (Table 1).

Investigation of the results showed that this system tolerated all substituted aryl groups on 1,4-dihydropyridines. Under sonic conditions, dihydropyridine **7** with isopropyl

Table 1. Oxidative aromatization of 1,4-dihydropyridines with iodine under normal conditions and ultrasound irradiation[a]

Compound	R	R_1	Normal Conditions			US Irradiation			Mp. (°C)	Lit. Mp. (°C)
			Product	Time (h)	Yield (%)[b]	Product	Time (min)	Yield (%)[b]		
1	C_6H_5	C_2H_5	**15**	5	96	**15**	15	98	63-64	62-63[7a]
2	C_6H_5	CH_3	**16**	6	94	**16**	20	96	135-136	135-136[31a]
3	3-$NO_2C_6H_4$	C_2H_5	**17**	7	95	**17**	30	95	59-62	61-63[7a]
4	2-$NO_2C_6H_4$	CH_3	**18**	4	91	**18**	40	94	103-104	104-105[31a]
5	2-Furyl	C_2H_5	**19+14**	5	60+40	**19+14**	10	70+30	40-42	Oil[21]
6	2-Furyl	CH_3	**20+14**	5.5	65+35	**20+14**	15	70+30	Oil	Oil[21]
7	$(CH_3)_2CH$	CH_3	**14**	1	96	**14**	5	98	69-70	69-70[7a]
8	4-(MeO)C_6H_4	C_2H_5	**21**	3	93	**21**	40	94	49-50	50[31b]
9	4-(MeO)C_6H_4	CH_3	**22**	4	93	**22**	45	94	114-115	115[31a]
10	4-MeC_6H_4	C_2H_5	**23**	4	95	**23**	30	97	71-72	72-73[21]
11	4-MeC_6H_4	CH_3	**24**	4	95	**24**	35	96	137-138	137-139[31a]
12	2-ClC_6H_4	CH_3	**25**	4	94	**25**	25	94	70-71	69-70[31a]
13	4-Hydroxy-3-methoxyphenyl	C_2H_5	**26**	1	97	**26**	20	98	-	-

[a] All reactions were performed with 2 molar equivalents of iodine in refluxing CH_3CN.
[b] Yields refer to isolated pure products.

group also showed a complete dealkylation reaction. In addition, the aromatization of 4-(2-furyl)-1,4-DHPs (**5**, **6**) under sonic conditions produced the corresponding pyridine compounds in 70% yield including 2-furyl moiety. Comparison of the results shows that though the behavior of the oxidation reaction is almost the same in both systems; however, performing the reactions under sonic conditions gives faster reaction rates and better efficiency than those under conventional conditions.

CONCLUSION

We have shown that iodine as an inexpensive and readily available reagent can efficiently oxidize varieties of 1,4-dihydropyridines to their corresponding pyridine compounds in the presence or absence of ultrasound irradiation in refluxing acetonitrile under neutral conditions. Sonic conditions not only accelerated dramatically the rate of reactions but also showed a better efficiency than normal conditions. The cheapness and availability of the oxidant and shorter reaction times are the advantages that could make this method an alternative or useful addition to the present methodologies.

EXPERIMENTAL

Ultrasound irradiations were performed by using a Cole Palmer high intensity ultrasonic processor (600 W, 20 KHz) via a micro-tip probe and 30% amplitude. All Hantzsch ester 1,4-dihydropyridines were synthesized by the reported procedures.[27,30] The products were characterized by a comparison with authentic samples (melting or boiling points) and their ^{1}H NMR or IR spectra. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel PolyGram SILG/UV 254 plates.

A Typical Procedure for Aromatization of Diethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1) with Iodine under Ultrasound Irradiation

In a two necked round-bottomed flask (10 mL) equipped with a magnetic stirrer and a condenser, to a solution of 1,4-DHP (**1**) (0.329 g, 1 mmol) in CH_3CN (5 mL), I_2 (0.507 g, 2 mmol) was added. The stirred reaction mixture was irradiated by ultrasound waves under reflux condition. Sonication was continued for 15 min and the progress of reaction was monitored by TLC (eluent; CCl_4/Et_2O: 5/3). At the end of reaction, a solution of sodium thiosulfate (2%, 5 mL) was added to the reaction mixture, and it was stirred for an additional 10 min. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent; CCl_4/Et_2O: 5/3) afforded the pure pyridine compound (**15**) (0.321 g, 98% yield, Table 1).

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