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BIOMIMETIC AROMATIZATION OF HANTZSCH 1,4-DIHYDROPYRIDINES BY S-S BONDS UNDER MILD CONDITIONS

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Abstract – For the first time Hantzsch 1,4-dihydropyridines were oxidized to the corresponding pyridines by diphenyl disulfide in ionic liquid.

INTRODUCTION

Hantzsch 1,4-dihydropyridines (DHPs) and their derivatives are an important class of bioactive molecules in the field of drugs and pharmaceuticals, and have been extensively studied in view of the biological pertinence of these compounds to the NADH redox process.[1] Aromatization of DHPs has attracted considerable attention due to the fact that DHPs based antihypertensive drugs (Ca^{2+} chanel blockers) are oxidatively converted to pyridine derivatives by cytochrome p-450 in the liver.[2] In addition, the corresponding pyridine derivatives show antihypoxic and antiischemic activities.[3] The oxidation of DHPs is one of the ubiquitous problems in organic chemistry and numerous reagent and procedures have been recommended for this purpose, such as NO,[4] $KMnO_4$,[5] CAN,[6] I_2-MeOH,[7] SeO_2,[8] heteropolyacid/$NaNO_2$,[9] $Zr(NO_3)_4$,[10] $Bi(NO_3)_3$,[11] photochemical oxidation,[12] sodium nitrite or nitrate,[13] $Fe(ClO_4)_3$,[14] N-hydroxy phethalimide,[15] Mn(TPP)Cl,[16] Mn(III) salophen/$NaIO_4$,[17] $Tl(NO_3)_3.3H_2O$[18] and UHP/Maleic anhydride.[19] Some of reported methods suffer from limitations including low yield of products, the use of strong oxidants and tedius work-up procedures. Nicotinamide adenine dinucleotide (NADH) and its phosphate derivative (NADPH) have long been known to act as coenzymes in biological redox reactions. It was established that in the reduced form of the coenzyme the active part is 1,4-dihydropyridine.[21] Thus Hanzsch 1,4-dihydropyridine derivatives are widely used as models to mimic the function of NAD(P)H in biological reductions of various compounds.

Ionic liquids attracts great interest as environmentally frierndly reaction media and reaction promotion media for organic synthesis.[20] Thus, these solvents possesses interesting and useful advantages such as

negligible vapor pressure, nonflammability, high thermal stability at a wide range of temperature, and easy reusability.

In this paper, for the first time we report a very convenient, clean, and efficient approach for the oxidation of DHPs by diphenyl disulfide in ionic liquid (Scheme 1).

1 **2**

Scheme 1

RESULTS AND DISCUSSION

Treatment of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1c**) with diphenyl disulfide in 1-butyl-3-methylimidazolium bromide ([bmim]Br) at 80°C for 60 min afforded the corresponding pyridine (**2c**) in 90% yield (Table 1, entry 3).

Table 1. Oxidation of Hantzsch 1,4-dihydropyridine derivatives by Ph_2S_2.

Entry	Substrate (**1**)	R	Product (**2**)	Time (min)	Yield (%)[a,b]	mp (°C)	Lit. mp (°C)
1	a	H	a	20[60][c]	98[70][c]	69-70	70-71 [11]
2	b	Me	b	120	80	oil	oil [11]
3	c	C_6H_5	c	60[120][c]	90[20][c]	63-65	62-64 [11]
4	d	4-Me-C_6H_4	d	80	85	71-72	72-73 [23]
5	e	3-NO_2-C_6H_4	e	80	70	61-62	62-63 [7]
6	f	4-NO_2-C_6H_4	f	75	80	112-114	113-115 [11]
7	g	4-Br-C_6H_4	g	40	90	51-53	52-54 [22]
8	h	4-HO-C_6H_4	h	80	80	169-172	172-173 [24]
9	i	2-furyl	i	150	80	oil	oil [22]
10	j	2-thienyl	j	140	75	75-77	75[12c]
11	k	2-MeO-C_6H_4	k	70	85	59-61	59-60[18]
12	l	3-MeO-C_6H_4	l	75	85	103-105	110[25]

Table 1. (*Continued*)

Entry	Substrate (**1**)	R	Product (**2**)	Time (min)	Yield (%)[a,b]	mp (^{o}C)	Lit. mp (^{o}C)
13	m	4-MeO-C_6H_4	m	70	70	50-51	50[11]
14	n	*n*-pentyl	n	80	90	oil	oil[19]
15	o	CH=CH-C_6H_5	o	90	80	161-162	162-163[11]
16	P	CH_2CH_2-C_6H_5	p	80	85	oil	oil[19]

[a] Isolated yield.

[b] All products were identified by comparsion with authentic sample(mp, IR, NMR).

[c] The reaction was carried out in the absence of Ph_2S_2.

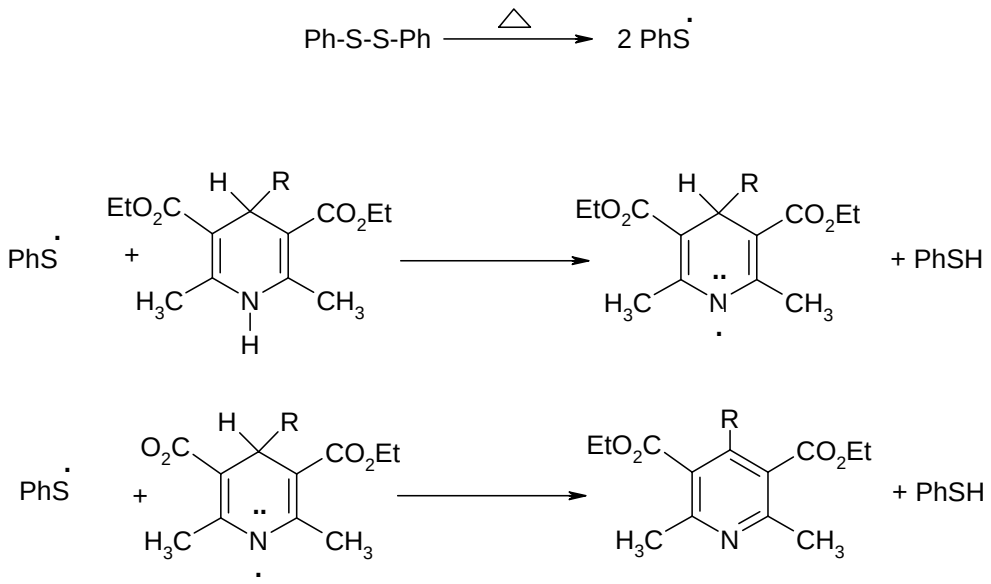
Table 2. Effect of solvent on the reaction yield of **1c** with diphenyl disulfide.

Entry	Solvent	Time(min)	Yield (%)
1	MeCN	120	60
2	*n*-hexane	120	25
3	H_2O	120	20
4	CH_2Cl_2	120	20
5	MeOH	120	35
6	Et_2O	120	30
7	xylene	120	70
8	[bmim]Br	60	90

The DHPs possessing a variety of substituents such as hydrogen, methyl, alkyl, aryl and heterocyclic substituent at the 4-position were oxidized to the corresponding pyridine derivatives in high yield (Table 1). It should be mentioned that among the DHPs we examined substrate **1a** exhibited high reactivity in particular. In this case, the reaction proceded even without diphenyl disulfide (Table 1, entry 1[c]).

To promote the aromatization of DHPs to pyridines the presence of diphenyl disulfide is necessary and with respect to the yields of the products, a 1:1 mol ratio of DHPs and Ph_2S_2 was optimal. That is, when the reaction was run in the absence of Ph_2S_2, slow conversion was observed (Table 1, entry 3[c]). The influence of the various solvent on the yield of the reaction was investigated using compound **1c** as the substrate (Table 2).

In this reaction we found that the diphenyl disulfide was converted to thiophenol via the proposed mechanism out lined in Scheme 2. The proposed mechanism is merely tentative and the study of the detailed reaction mechanism, including the role of ionic liquid is now in progress in our laboratory.



Scheme 2

CONCLUSIONS

The present work indicates that aromatization of NADPH models Hantzsch 1,4-DHPs proceeded by diphenyl disulfide. The most advantageous features of the synthetic procedure are (i) the reaction yields are high; (ii) the workup of the reaction mixtures is simple and (iii) metal oxides are not necessary.

Even so, the main purpose of this article is not only to provide a new synthetic method but also to show the action of S-S bond in oxidation of DHPs which has an active role in a wide range of human physiological process.

EXPERIMENTAL SECTION

The Hantzsch 1,4-dihydropyridine derivatives (**1a-1r**) were prepared from condensation of ethyl acetoacetate, ammonia, and the corresponding aldehydes according to a literature procedure and were characterized by comparsion of their physical and spectral data with those of the authentic sample. FTIR spectra were recorded on Nicolet Impact 400 spectrometer as KBr pellets for solid and net for liquid samples. NMR spectra were obtained on Bruker 500 MHz instrument in $CDCl_3$ using TMS as internal standard. Diphenyl disulfide was purchased from Merck.

GENERAL PROCEDURE FOR THE OXIDATION OF DHPs

A mixture of the DHPs (1 mmol) and diphenyl disulfide(1 mmol) were added to [bmim]Br and heated to 80°C for the time given in Table 1. Progress of the reaction was monitored by TLC or GC. After the reaction was completed, 10 mL water was added and filtered. Pyridine derivatives were purified by crystalization or silica gel column(eluent: CCl_4: Et_2O, 6:1).

SPECTROSCOPIC DATA:

Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (2a)

Colorless solid; mp 69-70°C(lit.,[11] 70-71°C); IR(KBr) 2981, 2932, 1719, 1591, 1441, 1369, 1295, 1222, 1120, 1043, 771, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 4.41 (q, 4H, *J*=7.3 Hz), 2.84 (s, 6H), 1.42 (t, 6H, *J*=7.3 Hz).

Diethyl 2,4,6-trimethylpyridine-3,5-dicarboxylate (2b)

Pale yellow colored oil [11]; IR(KBr) 2981, 2937, 1725, 1567, 1239, 1107, 1041, 857cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (q, 4H, *J*=7.2 Hz), 2.53 (s, 6H), 2.28 (s, 3H), 1.40 (t, 6H, *J*=7.2 Hz).

Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (2c)

Colorless solid; mp 63-65°C (lit.,[11] 62-64°C); IR(KBr) 2981, 2934, 1716, 1556, 1290, 1228, 1096, 1040, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (br s, 2H), 7.27 (br s, 3H), 4.01 (q, 4H, *J*=7.3 Hz), 2.62 (s, 6H), 0.90 (t, 6H, *J*=7.3 Hz).

Diethyl 2,6-dimethyl-4-(*p*-methylphenyl)pyridine-3,5-dicarboxylate (2d)

Pale yellow colored solid; mp 71-72°C (lit.,[11] 72-73°C); IR(KBr) 2985, 2922, 2849, 1735, 1615, 1204, 1125, 1052, 859 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J*=8.0 Hz), 7.23 (d, 2H, *J*=8.0 Hz), 4.06 (q, 4H, *J*=7.0 Hz), 2.91 (s, 6H), 2.40 (s, 3H), 0.95 (t, 6H, *J*=7.0 Hz).

Diethyl 2,6-dimethyl-4-(*m*-nitrophenyl)pyridine-3,5-dicarboxylate (2e)

Pale yellow colored solid; mp 61-62°C (lit.,[7] 62-63°C); IR(KBr) 3075, 2982, 2921, 2855, 1732, 1534, 1349, 1224, 1012, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (m, 1H), 8.18 (m, 1H), 7.58 (m, 2H), 4.12 (q, 4H, *J*=7.0 Hz), 2.92 (s, 6H), 1.02 (t, 6H, *J*=7.0 Hz).

Diethyl 2,6-dimethyl-4-(*p*-nitrophenyl)pyridine-3,5-dicarboxylate (2f)

Pale yellow colored solid; mp 112-114°C (lit.,[11] 113-115°C); IR(KBr) 3095, 2920, 2853, 1730, 1524, 1351, 1205, 866, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, 2H, *J*=8.5 Hz), 7.46 (d, 2H, *J*=8.5 Hz), 4.05 (q, 4H, *J*=7.5 Hz), 2.78 (s, 6H), 0.99 (t, 6H, *J*=7.5 Hz).

Diethyl 2,6-dimethyl-4-(*p*-bromophenyl)pyridine-3,5-dicarboxylate (2g)

Colorless solid; mp 51-53°C (lit.,[22] 52-54°C); IR(KBr) 2980, 2919, 2847, 1722, 1552, 1485, 1382, 1230, 1102, 1045, 861 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 2H, *J*=8.2 Hz), 7.11 (d, 2H, *J*=8.2 Hz), 4.04 (q, 4H, *J*=7.1 Hz), 2.62 (s, 6H), 0.98 (t, 6H, *J*=7.1 Hz).

Diethyl 2,6-dimethyl-4-(*p*-hydroxyphenyl)pyridine-3,5-dicarboxylate (2h)

Colorless solid; mp 169-172°C (lit.,[24] 172-173°C); IR(KBr) 3541, 2980, 2919, 2847, 1722, 1652, 1485, 1382, 1230, 1102, 1045, 861 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, 2H, *J*=8.5 Hz), 6.85 (d, 2H, *J*=8.5 Hz), 5.92 (br, 1H), 4.09 (q, 4H, *J*=7.2 Hz), 2.45 (s, 6H), 1.02 (t, 6H, *J*=7.2 Hz).

Diethyl 2,6-dimethyl-4-(2-furyl)pyridine-3,5-dicarboxylate (2i)

Yellow colored oil [22]; IR(KBr) 3115, 2921, 1719, 1659, 1600, 1395, 1151, 1098, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 1H), 6.51-6.62 (m, 2H), 4.13 (q, 4H, *J*=7.0 Hz), 2.63 (s, 6H), 1.31 (t, 6H, *J*=7.0 Hz).

Diethyl 2,6-dimethyl-4-(2-thienyl)pyridine-3,5-dicarboxylate (2j)

Brown colored solid; mp 75-77°C (lit.,[12c] 75°C); IR(KBr) 3102, 2925, 2852, 1733, 1634, 1197, 1131, 1019, 860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.70 (m, 1H), 7.21-7.31 (m, 1H), 7.16 (m, 1H), 4.49 (q, 4H, *J*=7.0 Hz), 3.27 (s, 6H), 1.45 (t, 6H, *J*=7.0 Hz).

Diethyl 2,6-dimethyl-4-(*o*-methoxyphenyl)pyridine-3,5-dicarboxylate (2k)

Pale yellow colored solid; mp 59-61°C (lit.,[18] 59-60°C); IR(KBr) 2922, 1728, 1602, 1198, 1052, 873, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 1H), 7.26 (m, 1H), 7.03 (m, 1H), 6.83 (m, 1H), 4.11 (q, 4H, *J*=7.5 Hz), 3.81 (s, 3H), 2.99 (s, 6H), 0.97 (t, 6H, *J*=7.5 Hz).

Diethyl 2,6-dimethyl-4-(*m*-methoxyphenyl)pyridine-3,5-dicarboxylate (2l)

Colorless solid; mp 103-105°C (lit.,[25] 110°C); IR(KBr) 2929, 2856, 1728, 1605, 1204, 1052, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, 1H, *J*=8.0 Hz), 7.26 (s, 1H), 6.98-7.11 (m, 1H), 6.91 (d, 1H, *J*=8.0 Hz), 4.11 (q, 4H, *J*=7.5 Hz), 3.73 (s, 3H), 2.99 (s, 6H), 0.97 (t, 6H, *J*=7.5 Hz).

Diethyl 2,6-dimethyl-4-(*p*-methoxyphenyl)pyridine-3,5-dicarboxylate (2m)

Colorless solid; mp 50-51°C (lit.,[11] 50°C); IR(KBr) 2985, 2922, 1735, 1609, 1304, 1198, 1058, 859 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, 2H, *J*=8.0 Hz), 6.95 (d, 2H, *J*=8.5 Hz), 4.10 (q, 4H, *J*=7.5 Hz), 3.85 (s, 3H), 2.91 (s, 6H), 1.00 (t, 6H, *J*=7.5 Hz).

Diethyl 2,6-dimethyl-4-*n*-pentylpyridine-3,5-dicarboxylate (2n)

Pale yellow colored oil [19]; IR(KBr) 2925, 2859, 1733, 1237, 1197, 1019, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.47 (q, 4H, *J*=7.0 Hz), 2.90 (s, 6H), 2.72-2.86 (m, 2H), 1.40-1.44 (m, 6H), 1.10 (t, 6H, *J*=7 Hz), 0.86 (t, 3H, *J*=7.5 Hz).

Diethyl 2,6-dimethyl-4-cinnamylpyridine-3,5-dicarboxylate (2o)

Pale yellow colored solid; mp 161-162°C (lit.,[11] 162-163 °C); IR(KBr) 2985, 2922, 2865, 1728, 1655, 1456, 1204, 1025, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22-7.44 (m, 4H), 6.91 (d, 1H, *J*=14.5 Hz), 6.46 (d, 1H, *J*=14.5 Hz), 4.05 (q, 4H, *J*=7.5 Hz), 3.04 (s, 6H), 1.26 (t, 6H, *J*=7.5 Hz).

Diethyl 2,6-dimethyl-4-(2-phenylethyl)pyridine-3,5-dicarboxylate (2p)

Pale yellow colored oil [19]; IR(KBr) 2982, 2925, 2852, 1733, 1634, 1383, 1197, 1025, 794, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.50 (q, 4H, *J*=7.0 Hz), 3.26 (s, 6H), 2.79-2.99 (m, 2H), 1.46-1.70 (m, 2H), 1.45 (t, 6H, *J*=7.0 Hz).

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