NaI Readily Mediated Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines with Hydrogen Peroxide at Room Temperature: A Green Procedure

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The oxidative conversion of 1,4-dihydropyridines to give the corresponding pyridine derivatives in excellent yields was easily effected using the catalytic amount of NaI in combination with H_2O_2 (30%) as a green external oxidant. The process is highly green wherein the solid products are easily filtered out after the addition of ice-water to the reaction mixture. This non-transition metal catalyst is cost-effective, affords simple work-up and easy separation of the product.

INTRODUCTION

1,4-Dihydropyridin (1,4-DHPs) derivatives containing the 1,4-dihydropyridine structure include calcium antagonists [1], antitubercular agents [2], antitumours [3], bronchodilatings [4], antidiabetics [5], antivirals [6], antianginals [7] and neuropeptide Y Y1 receptor antagonists [8]. The oxidative aromatization of 1,4-DHPs to the corresponding pyridine derivatives entails the principal metabolic route in particular in biologically significant NADH redox processes [9], as well as a facile access to the corresponding pyridine derivatives which show anti-hypoxic and anti-ischemic activities [10] from the easily available 1,4-DHPs [11].

Consequently, this aromatization reaction continues to attract the attention of many organic and medicinal chemists for the discovery of a plethora of protocols applicable to a wide range of 1,4-DHPs [12]. Although a variety of reagents are capable of effecting these oxidations, the transformation is not always easy to effectand may even be problematic if the substrate has functional groups sensitive to the oxidizing agent

and the reaction conditions. Most of the reported reagents produce by-products which are difficult to separate from the products. Therefore, the development of an efficient, cost-effective and green method for the aromatization of 1,4-DHPs under milder conditions is still desirable. The hydrogen peroxide was selected as the oxidant over other available oxidizing agents and sodium iodide was chosen as the catalyst since they were cheap, operationally safe, environmentally friendly, and easy to handle and work-up.

EXPERIMENTAL

All the chemicals were purchased from Merck Company. 4-Substituted Hantzsch 1,4-dihydropyridines were prepared using the appropriate aldehyde, ammonium carbonate and ethyl acetoacetate as reported earlier [19]. All products were known compounds and their physical and spectroscopic data were compared with those of authentic samples. Melting points were measured in capillary tubes using Buchi 545 instrument and are uncorrected. IR spectra were recorded as KBr pellets on Brucker Spectrum FT-IR. NMR spectra were obtained using an 11.7 T vertical bore spectrometer (^{1}H 500

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MHz; [13]C 125 MHz; [19]F 470 MHz). [1]H and ^{13}C chemical shifts are referenced to TMS as an internal standard, ^{19}F to a dilute solution of trifluoroacetic acid (TFA) in capillary column as an external reference.

The procedure for the oxidative aromatization of Hantzsch 1,4-dihydropyridines, and physical and spectral data for some selected synthesized pyridine derivatives are given below. The identities of the products were confirmed by mp, IR, ^{1}H, ^{13}C and ^{19}F NMR spectral data.

Diethyl-2,6-dimethyl-4-(2-fluorophenyl)-pyridine-3,5-dicarboxylate (Table 2, entry 2). To a mixture of Hantzsch 1,4-dihydropyridine (1 mmol), H_2O_2 30% (2.2 mmol, 0.25 ml) and acetic acid (3 ml), NaI (0.05 mmol, 0.008 g) was added and stirred at room temperature for the appropriate reaction time indicated in Table 2. After ascertaining the completion of the reaction by TLC, the product was precipitated by addition of ice-water to reaction mixture. The pure corresponding pyridines were collected with a simple filtration and consequently washing with cold water. The crud product was recrystallized in ethanol to give the pure product as a pale yellow solid. Yield 85%; m.p.: 45-47 °C; FT-IR: υ_{max} (KBr): 2982, 1722, 1557 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.00 (t, J = 7.1 Hz, 6H), 2.65 (s, 6H), 4.04 (q, J = 7.1 Hz, 4H), 7.11 (t, J = 8.6 Hz, 1H$_{arom}$), 7.14-7.21 (m, 2H$_{arom}$), 7.36-7.40 (m, 1H$_{arom}$) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.0, 23.6, 61.7, 115.6 ($^2J_{C-F}$ = 21.2 Hz), 124.1 ($^3J_{C-F}$ = 3.6 Hz), 124.8 ($^2J_{C-F}$ = 16.7 Hz), 127.5, 130.8 ($^3J_{C-F}$ = 7.9 Hz), 131.0 ($^4J_{C-F}$ = 2.6 Hz), 141.4, 156.6, 159.7 ($^1J_{C-F}$ = 246.4 Hz), 167.6 ppm; ^{19}F NMR (470 MHz, CDCl$_3$) δ -114.2 ppm.

Diethyl-2,6-dimethyl-4-(3-fluorophenyl)-pyridine-3,5-dicarboxylate (Table 2, entry 3). Oxidative aromatization of diethyl-2,6-dimethyl-4-(3-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1 mmol, 0.35 g) with H_2O_2 30% (2.2 mmol, 025 ml), acetic acid (3 ml) and NaI (0.05 mmol, 0.008 g), then work up as described above gave diethyl 2,6-dimethyl-4-(3-fluorophenyl)-pyridine-3,5-dicarboxylate as a pale yellow solid. Yield 80%, m.p.: 58-60 °C; FT-IR: υ_{max} (KBr): 2995, 1719, 1560 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.00 (t, J = 7.2 Hz, 6H), 2.62 (s, 6H), 4.06 (q, J = 7.2 Hz, 4H), 7.00-7.10 (m, 3H$_{arom}$), 7.35-7.36 (m, 1H$_{arom}$) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.2, 23.8, 62.0, 115.8 ($^2J_{C-F}$ = 18.4 Hz), 124.4, 125.1, 127.9, 130.1 ($^3J_{C-F}$ = 7.5 Hz), 131.2 ($^4J_{C-F}$ = 3.2 Hz), 141.5, 156.7, 159.9 ($^1J_{C-F}$ = 247 Hz), 168.3 ppm; ^{19}F NMR (470 MHz, CDCl$_3$) δ -113.1 ppm.

Diethyl-2,6-dimethyl-4-(4-fluorophenyl)-pyridine-3,5-dicarboxylate (Table 2, entry 4). Oxidative aromatization of diethyl-2,6-dimethyl-4-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1 mmol, 0.35 g) with H_2O_2 30% (2.2 mmol, 025 ml), acetic acid (3 ml) and NaI (0.05 mmol, 0.008 g), then work up as described above gave diethyl 2,6-dimethyl-4-(4-fluorophenyl)-pyridine-3,5-dicarboxylate as a white solid. Yield 85%, m.p.: 88-89 °C; FT-IR: υ_{max} (KBr): 2988, 1714, 1558 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.00 (t, J = 7.1 Hz, 6H), 2.62 (s, 6H), 4.06 (q, J = 7.1 Hz, 4H), 7.09 (t, J = 8.6 Hz, 2H$_{arom}$), 7.26-7.28 (m, 2H$_{arom}$) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.1, 23.3, 61.8, 115.6 ($^2J_{C-F}$ = 21.1 Hz), 127.4, 130.5 ($^3J_{C-F}$ = 8.1 Hz), 132.8 ($^4J_{C-F}$ = 3.4 Hz), 145.3, 155.9, 163.2 ($^1J_{C-F}$ = 247 Hz), 168.1 ppm; ^{19}F NMR (470 MHz, CDCl$_3$) δ -113.3 ppm.

Diethyl-2,6-dimethyl-4-(3-pyridyl)-pyridine-3,5-dicarboxylate (Table 2, entry 7). Oxidative aromatization of diethyl-2,6-dimethyl-4-(3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (1 mmol, 0.33 g) with H_2O_2 30% (2.2 mmol, 025 ml), acetic acid (3 ml) and NaI (0.05 mmol, 0.008 g), then work up as described above gave diethyl 2,6-dimethyl-4-(3-pyridyl)-pyridine-3,5-dicarboxylate as pale yellow solid. Yield 95%, m.p.: 78-81 °C; FT-IR: υ_{max} (KBr): 2985, 1717, 1558 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.00 (t, J = 7.1 Hz, 6H), 2.65 (s, 6H), 4.07 (q, J = 7.1 Hz, 4H), 7.34-7.37 (m, 1H$_{arom}$), 7.63-7.65 (m, 1H$_{arom}$), 8.54 (d, J = 1.8 Hz, 1H$_{arom}$), 8.66 (dd, J$_1$ = 4.9 Hz, J$_2$ = 1.6 Hz, 1H$_{arom}$) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.1, 23.5, 62.0, 123.2, 127.3, 133.0, 136.3, 143.0, 149.0, 150.0, 156.4, 167.7 ppm.

RESULTS AND DISCUSSION

Hydrogen peroxide has been used for the oxidation of a variety of substrates [13] and is generally considered to be a green oxidant because it is relatively non-toxic and breaks down in the environment to non-toxic by-products. Literature survey shows that only a limited number of catalytic methods employing H_2O_2 and its supports for the oxidation of 1,4-DHPs have been developed such as $Co(OAc)_2/H_2O_2$ [14a], maleic anhydride/urea-H_2O_2 [14b] and I_2/urea-H_2O_2 [14c].

As part of our recent studies directed towards the development of a practical, safe and environmentally friendly

procedure for some important transformations [15,16], we wish to report an efficient, convenient and green procedure for the oxidative aromatization of 1,4-DHPs by H_2O_2 30% in the presence of catalytic amount of sodium iodide (NaI).

Based on our initial optimization studies and adopting a more efficient way to minimize the time, the amount of the catalyst and oxidant, diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate was chosen as the model substrate. A mixture of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1 mmol) and aqueous hydrogen peroxide (30%) in acetic acid was stirred in the presence of some catalysts at room temperature (Table 1). We observed a drastic rate enhancement when we used NaI as the co-oxidant catalyst (Table 1, entry 6) to produce the desired pyridine in 98% isolated yield after a short reaction time (~5 min). Then, the amount of NaI and hydrogen peroxide was optimized and 2.2 mmol of H_2O_2 (0.25 ml) and 5 mol% of NaI were chosen as the optimized reaction conditions (Table 1, entries 6-10).

The reactions in the absence of catalysts did not yield any product after a prolonged reaction time (Table 1, entry 1). In order to show the merit of the presented protocol in comparison with the other catalysts used for similar reactions, we have presented the results in Table 1 (entries 11-13). As can be seen, our method is simpler, more efficient, and uses no toxic solvents in the reaction media and/or work-up. According to the obtained results, the catalytic role of NaI in the oxidation of DHPs can be explained as follows (Fig. 1).

I⁻, as a soft nucleophile, attacked soft oxy-electrophile group in HO-OH to in-situ production of I-OH. A softer N-group in DHPs molecule attacked I-OH that was thermodynamically an unstable and reactive molecule. HI was eliminated from N-iodo intermediate to produce pyridine derivatives. The pure solid product was simply filtered out after addition of ice-water to the reaction mixture.

The general applicability of this method was further evaluated for structurally diverse DHPs under optimized reaction conditions (Table 2). The results presented in Table 2 indicate the generality of the method and the high efficacy of this new oxidation system. The reaction was completed

Table 1. Optimization of Reaction Conditions[a]
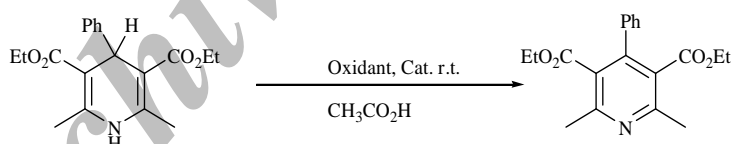
Entry	Oxidant	Cat (Mol-%)	Time (h)	Yield (%)
1	H_2O_2 30% (4 ml, 35 mmol)	-	24	0
2	H_2O_2 30% (4 ml, 35 mmol)	$CeCl_3.7H_2O$ (5)	24	60
3	H_2O_2 30% (4 ml, 35 mmol)	I_2 (5)	10	98
4	H_2O_2 30% (4 ml, 35 mmol)	KBr (5)	24	0
5	H_2O_2 30% (4 ml, 35 mmol)	NBS (5)	10	75
6	H_2O_2 30% (4 ml, 35 mmol)	NaI (5)	0.08	98
7	H_2O_2 30% (4 ml, 35 mmol)	NaI (2.5)	0.5	95
8	H_2O_2 30% (4 ml, 35 mmol)	NaI (1)	1	96
9	H_2O_2 30% (0.5 ml, 4.4 mmol)	NaI (5)	0.25	95
10	H_2O_2 30% (0.25 ml, 2.2 mmol)	NaI (5)	0.5	98
11	H_2O_2 30% (0.25 ml, 2 mmol)	$Co(OAc)_2$ (100)	0.5	97 [14a]
12	Urea-H_2O_2	Maleic anhydride	-	84 [14b]
13	Urea-H_2O_2	I_2 (20)	12	89 [14c]

[a]Reaction conditions: 1,4-DHPs (1 mmol), acetic acid (3 ml), room temperature.

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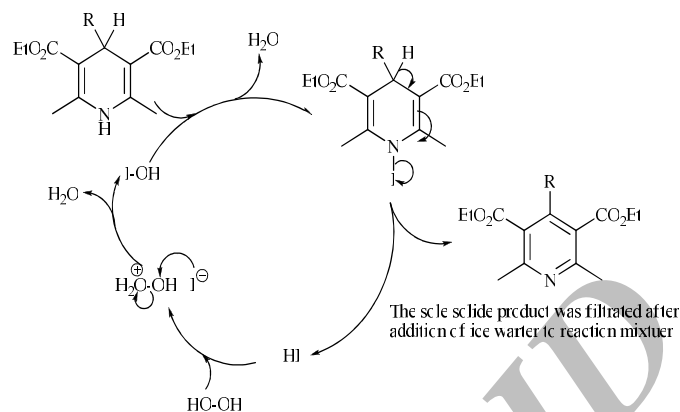
Fig. 1. Catalytic cycle of 1,4-DHPs oxidation mediated by I-OH.

Table 2. Oxidation of 1,4-DHPs with H_2O_2 in the Presence of Catalytic Amount of NaI at Room Temperature[a]
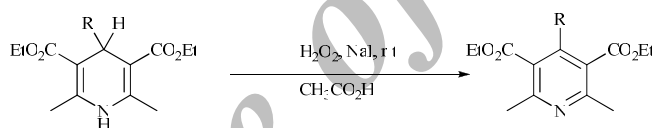
Entry	R	Time (min)	Yield (%)[b]	m.p. (°C) (Found)[Lit.]
1	C_6H_5	30	98	63-65 (62-64)[11m]
2	2-F-C_6H_4	25	85	45-47
3	3-F-C_6H_4	25	80	58-60
4	4-F-C_6H_4	25	85	88-89 (88-90)[11r]
5	4-CF_3-C_6H_4	20	88	56-57
6	2-Pyridyl	30	94	90-92
7	3-Pyridyl	30	95	78-81
8	4-Pyridyl	20	97	100-102
9	3-O_2N-C_6H_4	30	96	60-62 (61-62)[11m]
10	4-O_2N-C_6H_4	15	96	112-114 (115)[11m]
11	3-HO-C_6H_4	3 h	87	151-153
12	4-MeO-C_6H_4	20	95	56-58 (57-59)[11m]
13	2-Cl-C_6H_4	30	90	61-63 (61-62)[11s]
14	4-Cl-C_6H_4	30	92	66-68 (65-67)[11s]
15	2-Furyl	25	90	37-39 (38-41)[11r]
16	4-CH_3-C_6H_4	30	98	71-73 (72-73)[11m]

[a]Reaction conditions: 1,4-DHPs (1 mmol), acetic acid (3 ml), H_2O_2 (2.2 mmol), Na I (0.05 mmol), room temperature. [b]Yields refer to isolated pure products which are characterized by comparison of their mp, IR, ^1H, ^{13}C and ^{19}F NMR spectra with those of authentic samples.

between 20-30 min in excellent yields, except for the compound containing a hydroxyl group in substituent on the aromatic ring, which was oxidized within 3 h in good yields (Table 2, entry 11).

CONCLUSIONS

Sodium iodide acted as an efficient catalyst for the aromatization of 1,4-DHPs employing the hydrogen peroxide adduct as an environmentally benign oxidant. The reaction proceeded smoothly at room temperature in acetic acid. The products of high purity were isolated after a simple work-up procedure in good to high yields.

ACKNOWLEDGMENTS

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