The oxidation of 4-alkyl and 4-aryl-1,4-dihydropyridines to pyridines with hydrogen peroxide in an ionic liquid

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An efficient oxidation of 4-alkyl and 4-aryl-1,4-dihydropyridines to the corresponding pyridines with hydrogen peroxide in ionic liquids at room temperature in excellent yields is described.

Keywords: 4-alkyl and 4-aryl-1,4-dihydropyridines, pyridines, hydrogen peroxide, ionic liquids

The Hantzsch 1,4-dihydropyridine (DHP) nucleus[1] is found in drugs including vasodilators,[2a] antihypertensives,[2b] and bronchodilator,[2c] as exemplified by therapeutic agents such as Nifedipine,[2d] Nitrendipine,[2e] Nimodipine.[2f]

In the human body, these 1,4-dihydropyridines drugs are oxidatively converted to the corresponding pyridine derivatives by the action of cytochrome P-450 or other related enzymes in the liver.[3a] Dihydropyridines are often produced in a synthetic sequence, and have to be oxidised to pyridines. This is the easiest method to obtain selectively substituted pyridine derivatives.

The oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives is well documented.[4] However, many of the reported oxidation procedures either require strong oxidants (HNO_3,[3a] CrO_3,[4k] $KMnO_4$[4b]), severe conditions (S[4p] and Pd/C dehydrogenations[4q]), excess of the oxidants (CAN,[4a] PCC[4l]), or a costly Pd/C catalyst,[4r] bismuth nitrate[4s] or cumbersome workup procedures.[4f,g] An additional drawback in almost all the reported procedures except the recently published paper,[4s] is the loss of isopropyl group from 4-isopropyldihydropyridine.

In view of the above limitations, we decided to develop a practical and efficient approach for this oxidative transformation. In continuation with our earlier work in developing efficient protocols for the oxidation of DHPs to pyridines using peroxides (TBHP)[5a] and molecular oxygen as oxidants,[5b] we explored the utility of H_2O_2 as an efficient oxidising agent. H_2O_2 is the obvious choice due to its ready availability, very high active oxygen content per mole, the by-product being water and its wide industrial acceptability.

In recent years, the use of room temperature ionic liquids (I.Ls.) as 'green' solvents in organic synthetic processes has gained importance due to their solvating ability, negligible vapour pressure, easy recyclability and reusability.[6] Many reactions have been reported recently using ionic liquid as reaction media[7a-f] and as rate enhancer.[8a-d] Recently a method of preparation of 1,4-dihydropyridines in Ionic liquids has also been reported.[9] Consequently we decided to develop a method for oxidative transformation using an ionic liquid.

We wish to report the oxidation of 1,4-dihydropyridines (**1a–i**) to pyridines (**2a–i**) with hydrogen peroxide in 1,3-di-*n*-butyl-imidazolium bromide ([bbim][Br]) or 1,3-di-*n*-butyl-imidazolium tetra fluoroborate ([bbim][BF_4]) in excellent yields (Scheme 1). The Ionic liquids ([bbim][Br] and [bbim][BF_4]) were prepared by the reported procedure.[9]

Initial oxidation reaction was performed on 2,6-dimethyl-1, 4-dihydro-4-(1-propyl)-3,5-pyridinedicarboxylic acid, diethyl ester (**1b**) with H_2O_2 (30%) in ionic liquid [bbim][BF_4] at room temperature for 4 h. The workup involved simple extraction with ether to furnish corresponding pyridine (**2b**) in high yield. The ionic liquid separated after the ether extraction was reused for oxidation of dihydropyridine with fresh H_2O_2 at room temperature and identical results were obtained, which proved the recyclability of ionic liquid.

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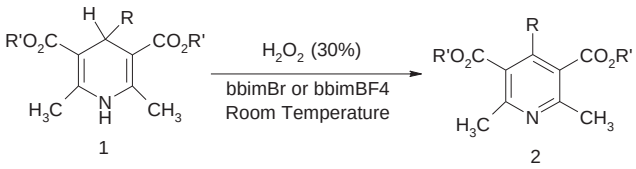

Scheme 1

Table 1 Oxidation of 2,4-Dihydropyridines (**1a–i)** with H_2O_2 in [bbim][Br] to pyridines (**2a–i**) at room temperature

Dihydro-pyridine	R	R'	Pyridine	Yield/% [bbim][BF_4]	Yield/% [bbim][Br]	m.p. (lit[ref])
1a	CH_3	CH_2CH_3	**2a**	69	71	Oil[4t]
1b	$CH_2CH_2CH_3$	CH_2CH_3	**2b**	83	82	Oil[4u]
1c	$CH(CH_3)_2$	CH_2CH_3	**2c**	76	73	Oil[4v]
1d	$(CH_2)_6CO_2Me$	CH_2CH_3	**2d**	65	71	Oil
1e	C_6H_5	CH_3	**2e**	82	86	136[4a]
1f	2-Cl-C_6H_4	CH_3	**2f**	79	73	70[4a]
1g	2-NO_2-C_6H_4	CH_3	**2g**	79	81	105[4a]
1h	4-NO_2-C_6H_4	CH_3	**2h**	69	89	148[5]
1i	4-OMe-C_6H_4	CH_3	**2i**	68	78	155[5]

In order to prove the generality of the above protocol, a variety of 1,4-DHPs **(1a–i)** were oxidised under the identical reaction conditions to pyridines (**2a–i,** Table 2). The purity of all the products was checked by HPLC and were characterised by the analysis of their ^{1}H NMR. The HPLC of the product was identical with authentic material prepared by reported procedure[5]. This showed the absence of pyridine N-oxide[5c] (**3**) as side product. A noteworthy feature is efficient aromatisation of DHPs to pyridines at room temperature. More importantly the 4-alkyl substituted DHPs (**1a–d**, Table 1) smoothly undergo oxidation to the corresponding 4-alkyl pyridines. This is in marked contrast to most of the earlier reported methods, which invariably furnish dealkylated pyridines.

Identical results were obtained when 1,3-di-*n*-butyl-imidazolium bromide ([bbim][Br]) was used as an ionic liquid.

In conclusion we have demonstrated an efficient oxidation of 1,4-dihydropyridines to pyridines at room temperature with H_2O_2 in ionic liquids. Our protocol is in accordance with the 'atom economy' and does not generate any byproducts since hydrogen peroxide is the only oxidant used and the Ionic liquid is recyclable.

Experimental

Preparation of ionic liquids: 1,3-Di-*n*-butyl-imidazolium bromide [bbim][Br] was prepared by heating 1-butylimidazole with 1-bromobutane at 70 °C for 2 h and distilling off excess 1-bromobutane under high vacuum to afford a thick brownish yellow liquid having density, 1.228 gcm^3. 1,3-Di-*n*-butyl-imidazolium tetra fluoroborate [bbim][BF_4] was obtained by the metathesis of [bbim][Br] with $NaBF_4$ in water to give a pale yellow free flowing liquid having density, 1.152 gcm ^{3}.

Preparation of diethyl 2,6-dimethyl-1,4-dihydro-4-(6-methoxy-carbonyl-hexyl)-3,5-pyridine dicarboxylate **(1d)**: A mixture of 8-oxo-octanoic acid methyl ester (0.500g, 2.906 mmol), ethyl acetoacetate (0.756g, 5.812 mmol), 30 % aqueous ammonia (15 ml) and 2-propanol (15 ml) was refluxed for 4 h. The reaction was monitored by TLC. After the completion of the reaction, 2-propanol was removed under reduced pressure and the residue was extracted with ethyl acetate (3 × 2.5 ml).The organic layer was separated and washed with brine (2 × 4 ml), and dried over anhydrous sodium sulfate. It was filtered and concentrated in vacuum to obtain **1d** (0.428 g, 37 %). Yellow solid; m.p. 111ºC; IR cm^{-1} : 3020, 2939, 1736, 1711, 1216, 755; ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.05–1.25 (bs, 16H), 1.51 (m, 2H), 2.21 (mixed s and t, 8H), 2.48 (s, 6H), 3.55 (s, 3H), 3.84 (m, 1H), 4.36 (q , *J* = 8 Hz, 4H), 6.22 (s, 1H). ^{13}C NMR: 14.0(C-10), 18.7 (C-7), 24.34, 24.61, 28.85, 29.14, 32.48 (C-18), 33.72, 36.47, 50.99 (C-4), 59.14 (C-9), 102.50 (C-3, C-5), 144.9 (C-2, C-6), 167.95 (C-8), 174.0 (C-17). Analysis calc for $C_{21}H_{33}NO_6$: C, 63.78; H, 8.41; N, 3.54 Found : C, 63. 95; H, 8.18; N 3.57%.

*Typical procedure for oxidation using aqueous H_2O_2 and [bbim][BF$_4$] (***2b,** *Table 1)*: A mixture of diethyl 2,6-dimethyl-1, 4-dihydro-4-(1-propyl)-3,5-pyridine dicarboxylate (**1b**, 0.295g, 1.0 mmol), H_2O_2 (30%, 2 ml) and [bbim][BF_4] (1.340g, 5.0 mmol) was stirred at room temperature for 4 h. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was extracted with diethyl ether (3 × 2.5 ml). The organic layer was separated and washed with brine (2 × 4 ml), dried over sodium sulfate. It was filtered and concentrated in vacuum to obtain diethyl-4-(1-propyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (**b,** 0.243 g, 83 %) as an oil. R_f : 0.32 (8:2 petroleum ether – ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.8–1.05 (m, 5H), 1.22 (t, *J*= 8 Hz, 2H), 1.44 (t, *J* = 8 Hz, 6H), 2.83 (s, 6H), 4.36 (q, *J* = 8 Hz, 4H).

*Typical procedure for oxidation using aqueous H_2O_2 and [bbim][Br] (***2b,** *Table 1)*: A mixture of diethyl 2,6-dimethyl-1, 4-dihydro-4-(1-propyl)-3,5-pyridinedicarboxylate ester (**1b**, 0.295g, 1.0 mmol), H_2O_2 (30%, 1 ml) and [bbim][Br] (1.305g, 5.0 mmol) was stirred at room temperature for 4 h. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was extracted with diethyl ether (3 × 2.5 ml). The organic layer was separated and washed with brine (2 × 4 ml), dried over anhydrous sodium sulfate. It was filtered and concentrated in vacuum to obtain diethyl-4-(1-propyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (**2b**, 0.240 g, 82 %) as an oil.

*Diethyl-4-(6-methoxycarbonyl-hexyl)-2, 6-dimethyl-3,5-pyridined-icaboxylate (***2d***)*: Diethyl 2,6-dimethyl-1,4-dihydro-4-(6-methoxy-carbonyl-hexyl)-3,5-pyridine dicarboxylate (**1d**) was oxidized in the similar manner to yield **2d**, R_f : 0.29 (8:2 petroleum ether – ethyl acetate); oil; IR cm^{-1} : 3151, 2964, 2876, 1728, 1566, 1466, 1382, 1239, 1166, 1060, 753; ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.24 (bs, 6H), 1.34 (t, *J* = 8 Hz, 6H), 1.52 (bs, 4H), 2.22 (t, *J* = 8, 2H), 2.48 (s, 6H), 3.58 (s, 3H), 4.36 (q , *J* = 8 Hz, 4H). Analysis calc to for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56 Found : C, 64. 57; H, 7.39; N, 3.61.

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