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Note

Superoxide induced oxidative aromatization of Hantzsch 1,4-dihydropyridines

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Tetraethylammonium superoxide, obtained *in situ* by the phase transfer reaction of potassium superoxide and tetraethylammonium bromide, accomplishes an easy and efficient oxidative aromatization of Hantzsch 1,4-dihydropyridines to their corresponding pyridines under mild reaction conditions, at room temperature.

Keywords: Superoxide ion, phase transfer catalyst, Hantzsch 1,4-dihydropyridines

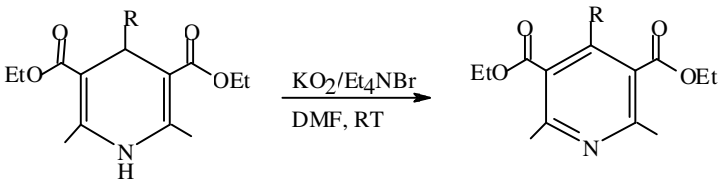
Hantzsch 1,4-dihydropyridines (Hantzsch 1,4-DHPs) have been extensively utilized as the analogs of NAD(P)H coenzyme to study the mechanism and synthetic potential of various redox processes[1,2]. Calcium entry blockers of Hantzsch 1,4-DHP type are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular disease[3]. In addition, DHP nucleus is common to numerous bioactive compounds which include vasolidator, antihypertensive, bronchodilator, antitumour and antidiabetic agents[4,5]. The oxidation of 1,4-dihydropyridine ring is the main metabolic route for these compounds[1-5]. Further, the oxidation of the Hantzsch 1,4-DHPs provides an easy access to pyridine derivatives, which show antihypoxic and antiischemic activities. Some of these derivatives also exhibit acaricidal, insecticidal, bactericidal and herbicidal activities[6].

In a typical Hantzsch procedure, an aldehyde, ammonia and a β-keto ester are condensed to give a dihyropyridine, which is subsequently oxidized to pyridine[7]. In fact, dihyropyridines have been aromatized to pyridines by various reagents such as HNO_3 (Ref. 5), DDQ (Ref. 8), $NaNO_2$ (Ref. 9), $(NH_4)_2Ce(NO_3)_6$ (Ref. 10), $Cu(NO_3)_2$ (Ref. 11), $Bi(NO_3).5H_2O$ (Ref. 12), $Mn(OAc)_3$ (Ref. 13), $Zr(NO_3)_4$ (Ref. 14), Pd/C or $KMnO_4$ (Ref. 15), $RuCl_3/O_2$ (Ref. 16), CrO_2 (Ref. 17), NO (Ref. 18), co-naphthenate/O_2 (Ref. 19), O_2/activated carbon[20], $Fe(ClO_4)_3$ (Ref. 21), 4-phenyl-1,3,4-triazole-3,5-dione[22] and $Mn(TPP)Cl/(Bu_4N)IO_4$ (Ref. 23). However, some method suffers from strong oxidative conditions, tedious workup and side-product formation.

Superoxide ($O_2^{-\cdot}$) is a reactive oxygen species in biological systems, as well as, a novel reagent for organic synthesis[24-28]. For reactivity purposes, superoxide ion is generated either by one electron potentiostatic reduction of molecular oxygen or by the solubilization of potassium superoxide (KO_2) through crown ethers[29]. But, since crown ethers are expensive reagents, their use for large scale preparation has yet limited applications. In place of KO_2/18-crown-6 combination, the use of tetraethylammonium superoxide (Et_4NO_2), obtained by the phase transfer reaction of KO_2 and tetraethylammonium bromide (Et_4NBr), is being explored as an useful and inexpensive alternative in organic chemistry[30].

In continuation to the interest in superoxide[31], herein is reported a milder and convenient method to effect 1,4-DHP to pyridine conversion. Tetraethylammonium superoxide, generated *in situ* by the phase transfer reaction of potassium superoxide and tetraethylammonium bromide, serves as an excellent oxidant for a variety of 4-substituted Hantzsch 1,4-DHP system as shown in the generalized **Scheme I**.

A number of Hantzsch 1,4-DHPs *viz*., diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate **1a**, diethyl 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicerboxylate **1b**, diethyl 1,4-dihydro-4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate **1c**, diethyl 1,4-dihydro-4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate **1d**, diethyl 1,4-dihydro-4-(4-methylphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate **1e**, diethyl 1,4-dihydro-4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate **1f**, diethyl 1,4-dihydro-4-(2-phenylethenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate **1g** were reacted with KO_2 in the presence of Et_4NBr in dry DMF at RT. As an outcome, under the mild reaction conditions of Et_4NO_2, the Hantzsch 1,4-DHPs **1a-g** are oxidized to their corresponding pyridine derivatives **2a-g** in good yield. The results are summarized in **Table I**.



1a-g **2a-g**

1a: R = H	**2a :** R = H
1b: R = Me	**2b :** R = Me
1c: R = Ph	**2c :** R = Ph
1d: R = *p*-$NO_2C_6H_4$	**2d :** R = *p*-$NO_2C_6H_4$
1e: R = *p*-$CH_3C_6H_4$	**2e:** R = *p*-$CH_3C_6H_4$
1f: R = *p*-ClC_6H_4	**2f:** R = *p*-ClC_6H_4
1g: R = C_6H_5-CH=CH	**2g:** R = C_6H_5-CH=CH

Scheme I

A 2-fold molar excess of KO_2 with respect to the substrate was employed for achieving the oxidation in dry DMF. When the reaction was completed as indicated by TLC, saturated aqueous sodium chloride solution was added to destroy the unreacted KO_2. The reaction mixture was then worked up to afford the products. The products were fully identified by their m.p. and spectral data which were in full agreement with the values described in literature.

Tetraethylammonium superoxide has been found to be a valuable new addition to the existing methods available for the oxidation of Hantzsch 1,4-DHP with added advantages of efficient and mild conditions at RT.

Experimental Section

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. NMR spectra were run on a Jeol AL300 FT-NMR and the chemical shifts are expressed as δ (ppm), using TMS as internal reference. Potassium superoxide and tetraethyl-ammonium bromide were procured from E. Merck, and were used as received. Dry DMF of Aldrich, was stored over molecular sieves (4Å) prior to use. Substrates used in the present investigation were prepared according to literature procedure[9].

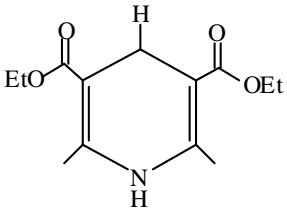
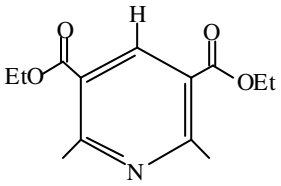
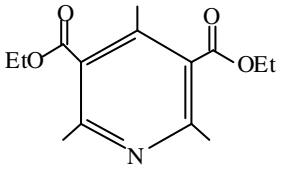
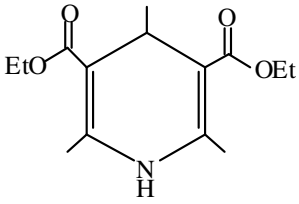
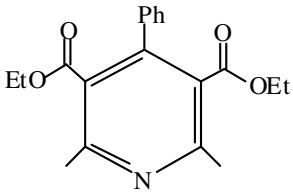
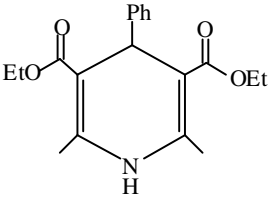
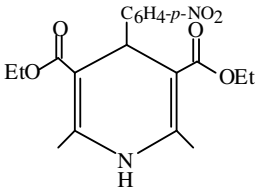
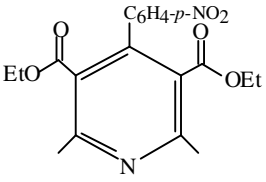
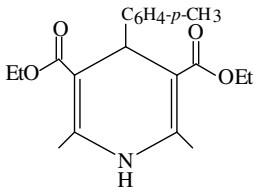
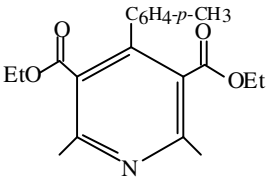
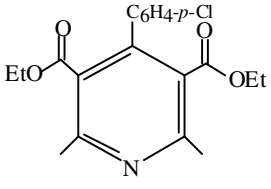
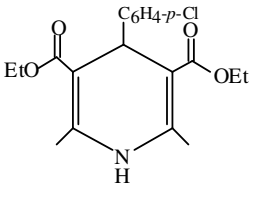
General procedure for the reaction of in-situ generated tetraethylammonium superoxide with Hantzsch 1,4-DHPs 1a-g. Potassium superoxide (0.43 g; 0.006 mole) and tetraethylammonium bromide (0.63 g; 0.003 mole) were weighted under nitrogen atmosphere using an atmosbag and were transferred into the three necked round bottom flask equipped with a magnetic stirrer, nitrogen inlet and a Liebig condenser protected by calcium chloride drying tube. Dry DMF (30 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of tetraethylammonium superoxide. Finally, the substrate Hantzsch 1,4-DHP (0.003 mole) was admitted to it and the stirring was continued at RT for 2-6 hr in the presence of nitrogen to avoid atmospheric moisture until the complete loss of starting material was indicated by TLC. After the reaction was over, the reaction mixture was treated with brine solution (20 mL) to decompose the unreacted potassium superoxide. Saturated sodium hydrogen carbonate solution (20 mL) was added to it and the solution was extracted with ether (3×20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to furnish a residue which was passed through silica gel column to afford the corresponding pyridine **2a-g**.

Diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate, 2a: m.p. 71-72°C (Lit[13] 71°C); IR (KBr): 2982, 2980, 2927, 2914, 1719, 1590, 1556, 1545, 1442, 1380, 1367, 1300, 1256, 1222, 1202, 1125, 1110, 1040, 1027, 772 cm^{-1}; ^1H NMR: δ 1.4 (t, 6H), 2.9 (s, 6H), 4.4 (q, 4H), 8.7 (s, 1H).

Diethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate, 2b: IR (KBr): 2980, 2935, 2906, 2870, 1725, 1570, 1445, 1410, 1372, 1282, 1243, 1220, 1171, 1108, 1045, 936, 860, 835, 776, 568 cm^{-1}; ^1H NMR: δ 1.4 (t, 6H), 2.3 (s, 3H), 2.5 (s, 6H), 4.4 (q, 4H).

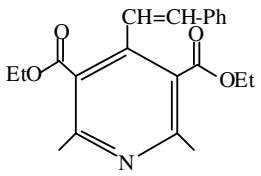
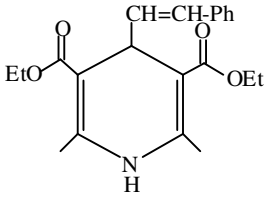
Diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate, 2c: m.p. 62°C (Lit[13] 63-64°C); IR (KBr): 3000, 2982, 2952, 2930, 1735, 1714, 1558, 1468, 1376, 1300, 1292, 1229, 1213, 1174, 1098, 1046, 862, 776, 758, 708 cm^{-1}; ^1H NMR: δ 0.9 (t, 6H), 2.6 (s, 6H), 4.0 (q, 4H), 7.1-7.3 (m, 5H).

Table I — Reaction of Et_4NO_2 with Hantzsch 1,4 DHPs

Entry	Substrate **1**	Product **2**	Yield (%)
1	 **1a**	 **2a**	74
2	 **2b**	 **1b**	76
3	 **2c**	 **1c**	68
4	 **1d**	 **2d**	60
5	 **1e**	 **2e**	70
6	 **2f**	 **1f**	69

—Contd

Table I — Reaction of Et_4NO_2 with Hantzsch 1,4 DHPs— *Contd*

Entry	Substrate **1**	Product **2**	Yield (%)
7	 **2g**	 **1g**	58

Diethyl 4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate, 2d: m.p. 115°C (Lit[13] 114-15°C); IR (KBr): 3112, 2980, 2925, 1723, 1604, 1554, 1520, 1352, 1317, 1225, 1218, 1119, 1109, 1042, 862, 842, 801, 742, 701, 664 cm^{-1}; ^1H NMR: δ 1.0 (t, 6H), 2.6 (s, 6H), 4.0 (q, 4H), 7.3-7.4 (m, 2H), 8.1-8.2 (m, 2H).

Diethyl 4-(4-methylphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate, 2e: m.p. 72°C (Lit[14] 72-73°C); IR (KBr): 3090, 1740, 1726, 1546, 1242, 1115, 1025 cm^{-1}; ^1H NMR: δ 1.2 (t, 6H), 2.4 (s, 6H), 2.6 (s, 6H), 4.1 (q, 4H) 7.2 (m, 4H).

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate, 2f: m.p. 66°C (Lit[14] 65-67°C); IR (KBr): 3162, 1739, 1724, 1548, 1230, 1106, 1022 cm^{-1}; ^1H NMR: δ 1.2 (t, 6H), 2.3 (s, 6H), 4.1 (q, 4H), 7.1-7.2 (m, 4H).

Diethyl 4-(2-phenylethenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate, 2g: m.p. 164°C (Lit Ref. 9, 162-65°C); ^1H NMR: δ 1.3 (t, 6H), 2.5 (s, 3H), 4.3 (q, 4H), 6.5-6.8 (m, 2H), 7.3-7.5 (m, 5H).

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