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Catalytic Oxidation of Hantzsch 1,4-Dihydropyridines by $RuCl_3$ under Oxygen Atmosphere

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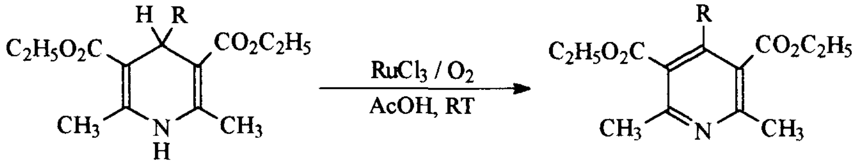
Abstract : The first catalytic oxidation of Hantzsch 1,4-dihydropyridines is described using a catalytic amount (5 mol %) of $RuCl_3$ in acetic acid under oxygen at room temperature. A tentative mechanism is proposed to account for the experimental observations.

Oxidation of Hantzsch 1,4-dihydropyridines (Hantzsch1,4 -DHP) and analogs to the corresponding pyridines is of interest because of its relevance to the biological NADH redox processes[1,2] as well as to the metabolic studies pertaining to 1,4-DHP based cardiovascular drugs such as Nifedipine and Niguldipine[3,4]. Besides, the oxidation of readily accessible Hantzsch 1,4-DHP provides one of the shortest routes to pyridine derivatives. However, the literature methods[5] using, e.g., HNO_3, CrO_3 , $KMnO_4$, PCC etc. to effect the oxidations of 1,4-DHP require stoichiometric or greater amounts of the oxidants, whereas 1,4-DHP oxidations using high potential organic oxidants are preparatively unattractive because of the contamination from the reduced by-products generated during the redox processes[1].

Currently, there is an ongoing interest in developing catalytic oxidation methods using metals in their high oxidation states (e.g., Co(III), Mn(III), Ce(IV) and Ru(III)) along with a suitable co-oxidant to reoxidize the reduced metal species[6,7]. In this context, it was deemed of interest to investigate the potential of Ru(III) / molecular oxygen system in order to develop a catalytic oxidation of 1,4-DHP . The Ru(III) / O_2 motif appeared appealing on three counts; a) Ru(III) is known catalytically to oxidize alcohols[8], sulfides[9] and amines[10], b) an electron transfer from Hantzsch 1,4-DHP to Ru(III) (reduction potential ~ -0.380 mv and -0.230 mv, respectively)[11,12] is expected to be favourable on account of positive potential difference between the two and c) the reduced Ru(II) is known to be reoxidized to Ru(III) by molecular oxygen so as to make the process catalytic[8-10].



1-9 10-17 (1)

As a test case, the oxidation of the Hantzsch 1,4-DHP (**1**, R = H) using a catalytic amount of $RuCl_3$ (5 mol %) was investigated in different solvents under aerobic condition (generalized eq 1). The oxidation proceeded very slowly in toluene, THF and methanol (ca.5-10% conversion), but a little faster in CH_3CN (ca.

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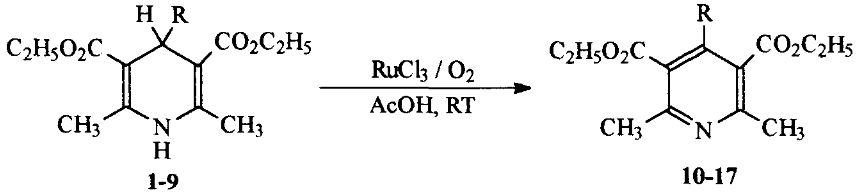

(1)

As a test case, the oxidation of the Hantzsch 1,4-DHP (**1**, R = H) using a catalytic amount of $RuCl_3$ (5 mol %) was investigated in different solvents under aerobic condition (generalized eq 1). The oxidation proceeded very slowly in toluene, THF and methanol (ca.5-10% conversion), but a little faster in CH_3CN (ca.

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30% conversion) after 30h at room temperature. Fortunately, in acetic acid, which was subsequently used as a solvent of choice, the oxidation of **1** occurred relatively efficiently (quantitative oxidation, 75% isolated yield) to the oxidized pyridine (**10**, R=H) during the same time.

Following the success of oxidation of **1** with $RuCl_3$ / O_2 system, we extended this method to several 4-alkyl and aryl substituted Hantzsch 1,4-DHP's (Table) using 5 mol % of the catalyst in acetic acid medium. The yields of the purified products are fair to good (35 -75%), the only exception being the 4-(2-phenylethenyl) substituted Hantzsch ester **9**, which proved to be a poor substrate giving only 20% conversion even after 100 h . Phenolic and olefinic substituted substrates (Table) were compatible under the present procedure. The 4-isopropyl Hantzsch analog **3** (R= $(CH_3)_2CH$-) was oxidized exceptionally rapidly (only 12h), relative to other Hantzsch esters, but it provided the dealkylated pyridine **10**. Such dealkylations have precedents in nitric acid[5a], $Bi(NO_3)_3.5H_2O$[5b] and PCC[5f] promoted oxidations of 4-isopropyl and 4-benzyl 1,4-DHP systems.

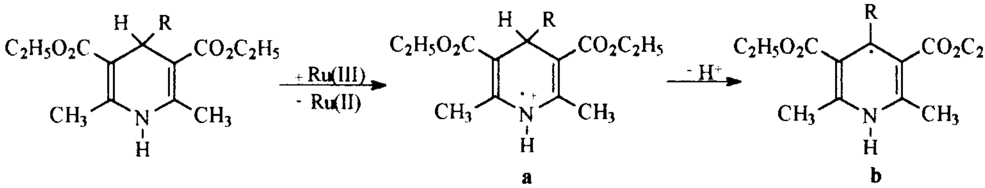
Table: Oxidation of Hantzsch 1,4-dihydropyridines by $RuCl_3$/ O_2 system[a] :

Hantzsch esters[b] 1-10	**Oxidized Products[b] 9-15**	**R[c]**	**Time (h)**	**Yield[d] (%)**	**mp (°C)**	**lit. mp (°C)**
1	**10**	H	30	75	70-71	72-72.5[16]
2	**11**	CH_3	60	45	liq[17]	-
3[e]	**10**	H	12	65	70-71	72-72.5[16]
4	**12**	C_6H_5	53	55	62-64	63-64[17]
5	**13**	4-$(NO_2)C_6H_4$	100	40	113-15	115[18]
6	**14**	4-$(OCH_3)C_6H_4$	80	48	50	50[19]
7	**15**	4-$(OH)C_6H_4$	40	40	171	171-73[19]
8	**16**	CH_3-CH=CH-	100	35	liq[20].	-
9	**17**	C_6H_5-CH=CH-	100	20	162-63	162-165[17]

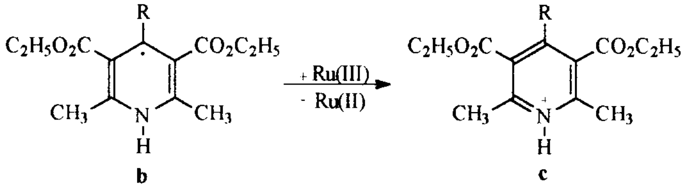
a) All reactions conducted at room temperature in AcOH using 5 mmol of Hantzsch 1,4-DHP and 5 mol % $RuCl_3$ under O_2 atm b) Hantzsch esters (**2-9**) and the corresponding oxidized products (**10-17**) are fully characterized by their mps and/or spectral data c) R is the same for Hantzsch esters and the corresponding oxidized pyridines except where otherwise noted d) Yields are for isolated products and are unoptimized e) R is $(CH_3)_2CH$- in the substrate.

A few observations pertaining to the mechanism of Ru (III)/ O_2 oxidation are i) with the exception of the plain Hantzsch ester **1**, all 4-substituted analogs did not suffer any detectable oxidation in the presence of oxygen alone without added $RuCl_3$ after an extended period of time. For the case of **1**, however, ca. 30% oxidation was noticed under aerobic condition in the absence of $RuCl_3$ after 30h reaction . With 5 mol% of the catalyst, a quantitative oxidation of **1** is observed during the same period. Thus, $RuCl_3$ is essential for the catalysis, ii) under control conditions, the uptake of O_2 was found to fall short of the required stoichiometric volume by 30-40% thereby suggesting that Hantzsch esters are at least partly being oxidized by a secondary oxidant generated during the oxidation, iii) $RuCl_3$ alone when used in stoichiometric amount (2 equivalents) effected complete oxidation of **1** in 20 h under N_2 atmosphere and iv) most of the oxidation reactions acquired a bluish colour at the end of the reaction suggesting the presence of 'ruthenium blue'which is characteristic of the presence of Ru (II) species[13].

Based on these observations, we propose a tentative mechanism as depicted below. In analogy to the mechanisms involving high valence metal ions[7,14], the oxidation of 1,4-DHP is presumed to be initiated by a single electron transfer to acceptor Ru(III) to produce a radical cation **a** and Ru(II). This is followed by a proton loss from radical cation **a** to generate radical **b** (eq 2). The latter is further oxidized by another molecule of Ru(III) to form the oxidized pyridine **c** (in the protonated form) and Ru (II) (eq 3). Ru(II) is oxidized by molecular oxygen to regenerate Ru (III) along with the formation of hydroperoxide radical via superoxide ion. Hydroperoxide radical can, in turn, oxidize another Ru (II) ion to produce H_2O_2 (eq 4 and 5). Both the hydroperoxide radical and H_2O_2 can oxidize 1,4-DHP , thereby accounting for less than the stoichiometric consumption of O_2 in the oxidation . Since commercial $RuCl_3$ is contaminated with $RuCl_4$ which can also be formed by air oxidation of Ru(III)[15], the role of Ru(IV) in 1,4-DHP oxidations at least in part can not be excluded from the mechanistic considerations.



(2)



(3)

$$Ru(II) + O_2 \xrightarrow{+H^+} Ru(III) + HO_2^{\bullet} \quad (\text{via } O_2^{\bullet-}) \qquad (4)$$

$$Ru(II) + HO_2^{\bullet} \xrightarrow{+H^+} Ru(III) + H_2O_2 \qquad (5)$$