A Metal-Free Catalytic Aerobic Aromatization of Hantzsch 1,4-Dihydropyridines by *N*-Hydroxyphthalimide

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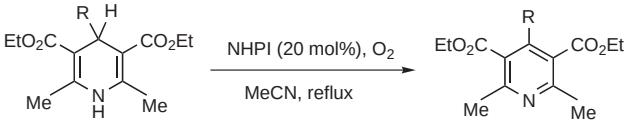
Abstract: 4-Alkyl- and 4-aryl-Hantzsch 1,4-dihydropyridines were oxidized to the corresponding pyridine derivatives in excellent yields by molecular oxygen using *N*-hydroxyphthalimide (NHPI) as the catalyst.

Key words: Hantzsch 1,4-dihydropiridines, aromatization, *N*-hydroxyphthalimide, molecular oxygen

Hantzsch 1,4-dihydropyridines (DHPs), a class of model compounds of NADH coenzyme,[1] have been extensively studied in view of the biological pertinence of these compounds to the NADH redox process,[2] and their therapeutic functions for treatment of a variety of deseases,[3] such as cardiovascular disorders,[3a] anticancer[3b] and anti-HIV.[3c] The oxidation of DHPs to the corresponding pyridine derivatives is the principal metabolic route in biological systems,[1,2] as well as a facile access to the corresponding pyridine derivatives from the easy available DHPs by Hantzsch reaction or its modifications.[4] Therefore, oxidative aromatization of DHPs has attracted continuing interests of organic and medicinal chemists and a plethora of protocols has been developed.[5–8] Early works mostly used strong oxidants, such as HNO_3,[5b] $KMnO_4$,[5c] or CAN.[5d] Recently, attention has been paid to more efficient and environmentally benign methods, such as electrochemical oxidation[6] and catalytic aerobic oxidation by using $RuCl_3$,[7a] Pd/C,[7b] activated carbon[7c] or $Fe(ClO_4)_3$[7d] as the catalyst. We have also reported a photochemically induced aromatization of DHPs.[8] Herein we wish to report a convenient metal-free catalytic aerobic oxidation of DHPs by using an organic catalyst *N*-hydroxyphthalimide (NHPI). Ishii has developed a series of NHPI-based catalytic systems for the functionalization of hydrocarbons under O_2, NO, or NO_2 atmosphere to give oxygen-containing compounds, such as alcohols, ketones, carboxylic acids and nitroalkanes.[9] It is of interest to observe that this Ishii catalysis can also be used for the aromatization of DHPs.

In a typical experiment a MeCN solution (3 mL) of Hantzsch 1,4-dihydropyridine (**1**, 1 mmol) and NHPI (0.2 mmol) was refluxed under stirring and oxygen atmosphere (1 atm). The reaction completed in a couple of hours as monitored by TLC, giving the corresponding pyridine derivative **2** in excellent yield (Scheme 1). The product **2** was easily separated by flash chromatography (silica gel, PE–EtOAc, 6:1 v/v) after removal of the solvent under reduced pressure. The results are summarized in Table 1.



1 **2**

Scheme 1

It is seen from Table 1 that excellent yields were obtained with most substrates except **1c** and **1j**. In the case of **1c**, in addition to the normal dehydrogenation product **2c**, 4-dealkylation product **2a** was also obtained in 26% yield (entry 3). Similar dealkylation has also been observed previously in the photochemically induced aromatization of DHPs,[8] as well as in the aromatization of DHPs by urea nitrate and peroxydisulfate-cobalt (II),[5i] and by nitric oxide.[5j] In the case of **1j** (entry 10), no appreciable reaction took place even after prolonged refluxing, demonstrating

Table 1 Catalytic Aerobic Aromatization of Hantzsch 1,4-Dihydropyridines (**1**) by NHPI[a]

Entry	Substrate	R	Product	Time (h)	Yield (%)[b]
1	**1a**	H	**2a**	0.5	99
2	**1b**	Me	**2b**	3	98
3	**1c**	*n*-Propyl	**2c**, **2a**	3	72, 26
4	**1d**	Ph	**2d**	4	99
5	**1e**	4-ClC_6H_4	**2e**	5	96
6	**1f**	4-MeC_6H_4	**2f**	3	96
7	**1g**	4-$MeOC_6H_4$	**2g**	1.5	98
8	**1h**	Ph-CH=CH	**2h**	4.5	95
9	**1i**	2-Furyl	**2i**	7	93
10	**1j**	4-$NO_2C_6H_4$	–	10	0

[a] For reaction conditions see text.
[b] Isolated yields. The products were identified by comparing their ^1H NMR and EI-MS spectral data and melting points with those reported in the literature.[5i]

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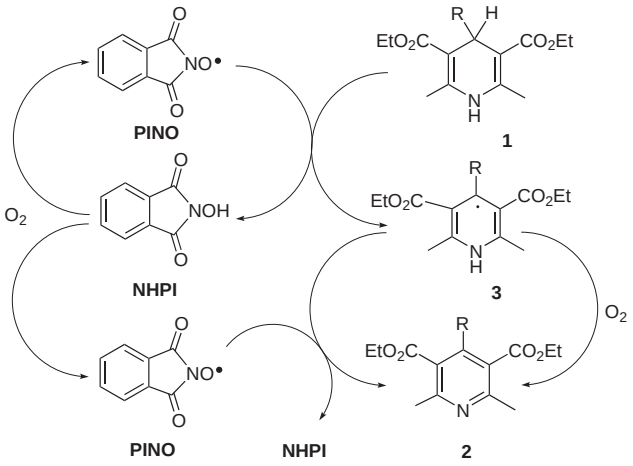
that the strong electron-withdrawing nitro substituent remarkably retarded the reaction. On the other hand, electron-donating methoxy substituent significantly facilitated the reaction (entry 7).

It was found that the turnover number (TON) of the catalyst depended on the concentrations of the catalyst and the substrate, as well as the reaction scale, because NHPI was found to partly decompose under the reaction condition, as having been reported previously.[10] At least 0.5 mmol (5 mol%) of NHPI must be used for the total conversion of **1d** on 10 mmol scale, corresponding to TON of 20. However, prolonged time (45 h) must be used to complete the reaction. Therefore, 20 mol% of NHPI was used for the best performance of the reaction.

The mechanism of the reduction of organic substrates by DHPs has been intensively investigated, which indicated that the reaction might proceed via either direct hydride transfer or electron transfer followed by proton transfer and second electron transfer, depending on the substrate and reaction conditions.[11] In the present case, however, no reaction occurred between excessive amount of NHPI and DHPs under argon atmosphere, demonstrating that NHPI could not directly oxidize DHPs. The reaction did not take place under oxygen atmosphere in the absence of NHPI, too. Therefore, this reaction is obviously an NHPI-catalyzed free radical oxidation (Scheme 2), similar to that proposed previously by Ishii.[9a] In the scheme the reaction is initiated by the reaction of NHPI with O_2 to generate phthalimide-*N*-oxyl radical (PINO) which has been detected by ESR.[9a,b] PINO abstracts hydrogen from DHP to produce alkyl radical **3**. Generally, alkyl radicals would react with oxygen to form alkyl peroxyl radical, which in turn, would produce oxygenated products.[9] In the present case, however, the strong driving force of aromatization makes the second hydrogen abstraction by PINO and/or O_2 very effective. Therefore, the pyridine derivative is formed exclusively rather than the oxygenated products.

In conclusion, this work provides a simple metal-free catalytic approach for the aromatization of Hantzsch 1,4-dihydropyridines with molecular oxygen as the terminal oxidant and NHPI as an organic catalyst. Extension of this method to other potential substrates is underway in this laboratory.



Scheme 2

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