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Oxidative aromatization of Hantzsch 1,4-dihydropyridines by sodium chlorite

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ABSTRACT

Hantzsch 1,4-dihydropyridines were converted to the corresponding pyridines efficiently by sodium chlorite under mild conditions in excellent yields.

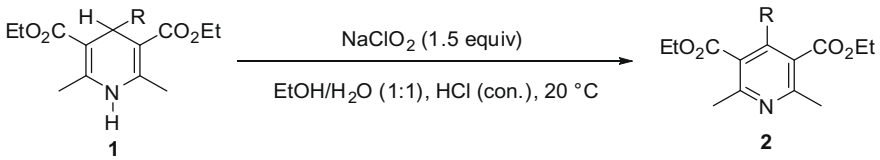
1. Introduction

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are important cardiovascular drugs due to their calcium antagonistic effect.[1] The oxidation of 1,4-DHPs into the corresponding pyridines is one of the main metabolic pathways of these drugs. This process is catalyzed by the cytochrome P450 (CYP) 3A4 isoform.[2] In addition, 1,4-DHPs were also used in modeling the coenzymes NADH in its biological redox processes.[3] In order to understand these biological systems, as well as to develop new methods for preparing polysubstituted pyridines, considerable attention has been paid to the oxidative aromatization of 1,4-DHPs. However, most reported methods involved strong oxidants, such as HNO_3,[4] $KMnO_4$,[5] CAN,[6] and PCC.[7] Alternative efforts have been made to electrochemical oxidation and catalytic aerobic oxidation using $RuCl_3$, Pd/C, or activated carbon as catalysts.[8–11] These processes still exist with at least one of the following drawbacks, such as long reaction time, only modest yields, harsh reaction conditions, expensive or toxic reagents, inconvenient preparation of reagents and tedious workup procedures. In particular, the undesirable dealkylation on 4-position or the formation of side products was detectable.[12] Therefore, development of efficient, mild, and environmentally friendly methods for aromatization of 1,4-DHPs are still desirable.

Sodium chlorite ($NaClO_2$) is a relatively inexpensive and green reagent which is widely used in disinfection of drinking water. To our knowledge, the use of sodium chlorite to oxidize 1,4-DHPs has never been reported before. Herein, we described an efficient, convenient, and economic method for the aromatization of 1,4-DHPs by sodium chlorite in the presence of hydrochloric acid as in Scheme 1.

2. Results and discussion

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** was chosen as the model compound to establish a general procedure for the reaction. A series of solvent systems were screened with 1.0 equiv of $NaClO_2$ at 20 °C (Table 1, entries 1–6). Presumably, the oxidation was conducted by chlorine dioxide (ClO_2) which can be readily generated from hydrochloric acid-activated $NaClO_2$,[13] the reaction was designed to run under acidic conditions. The reactions in THF, CH_2Cl_2, Et_2O, and EtOH all proceeded smoothly to give modest to excellent yields when concd HCl (12 M) was added. Nonetheless, the use of CH_3COOH without HCl dramatically decreased the yield (Table 1, entry 5), and the use of water could not afford any product even in the presence of HCl (Table 1, entry 6). Mixed solvents, EtOH/H_2O (1:1) gave an excellent yield (up to 92%) (Table 1, entry 7). In terms of oxidant loading, 1.5 equiv of $NaClO_2$ gave the best yield in much shorter time (Table 1, entry 8).



Scheme 1. Oxidative aromatization of 1,4-DHPs by sodium chlorite.

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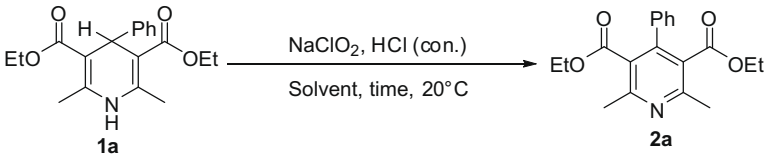
Table 1
Oxidative aromatization of **1a** under different conditions



Entry[a]	Solvent	Oxidant loading (equiv)	Time (min)	Yield[d] (%)
1	THF[b]	1.0	90	85
2	CH_2Cl_2[b]	1.0	90	93
3	Et_2O[b]	1.0	90	94
4	EtOH	1.0	90	75
5	CH_3COOH[c]	1.0	90	33
6	H_2O[b]	1.0	120	n.r.[e]
7	EtOH/H_2O (1:1)	1.0	90	92
8	EtOH/H_2O (1:1)	1.5	20	96
9	EtOH/H_2O (1:1)	2.0	15	95
10	EtOH/H_2O (1:1)[c]	2.0	360	n.r.[e]

[a] Reaction conditions: 1,4-DHP (1 mmol), $NaClO_2$ (designed amount), solvent (5 mL), concd HCl (12 M, 0.2 mL), 20 °C.
[b] 0.1 equiv of n-$Bu_4N^+Br^-$ was added.
[c] No concd HCl was added.
[d] Isolated yields.
[e] No reaction.

Table 2
Aromatization of 4-substituted 1,4-DHPs[a]

Substrate	R	Yield of **2**[b] (%)	Mp (°C)	Ref. mp (°C)
1a	Ph	96	60–61	62–63[15]
1b	H	99	71–72	69–70[15]
1c	Me	97	Oil	Liquid[12b]
1d	4-HO–C_6H_4	92	172–173	171[16]
1e	4-MeO–C_6H_4	89	49–50	51–53[16]
1f	4-O_2N–C_6H_4	94	115–116	114–115[16]
1g	2-O_2N–C_6H_4	95	77–78	74–76[17]
1h	4-F–C_6H_4	98	90–92	88–90[16]
1i	4-Cl–C_6H_4	95	64–65	64–66[18]
1j	3-MeO-4-HO–C_6H_4	97	159–160	159–160[19]
1k	3-HO-4-MeO–C_6H_4	99	140–141	140–142[16]
1l	3,4-Cl_2–C_6H_4	95	63–65	66–68[20]
1m	3,4,5-$(MeO)_3$–C_6H_4	91[21]	107–108	no ref.
1n	2-Furyl	95	oil	oil[16]

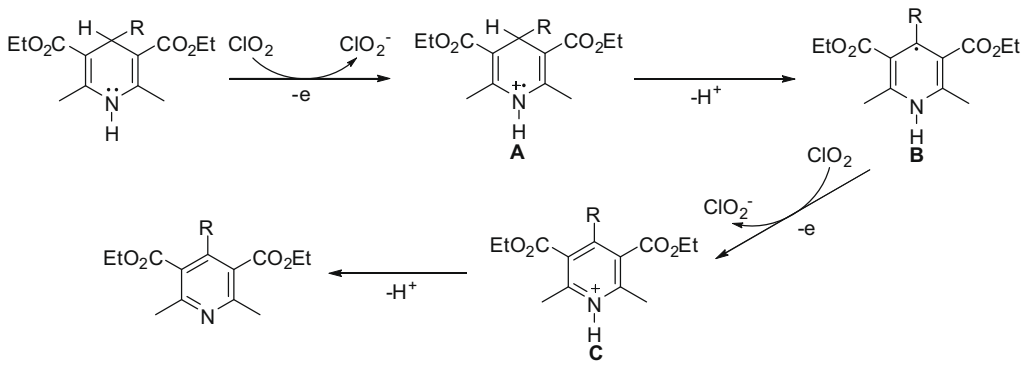
[a] Reaction conditions: 1,4-DHP (1 mmol), $NaClO_2$ (1.5 mmol), solvent (5 mL), concd HCl (12 M, 0.2 mL), 20 °C, 30 min.
[b] Isolated yields, and all compounds were characterized by spectroscopic techniques and the data were compared with those reported (except **1m**).

To investigate the scope of the reaction, a series of 1,4-DHPs **1** were prepared with a modified Hantzsch reaction procedure,[14] and each was converted to the corresponding pyridine derivative **2** by the general procedure (see below). The results are summarized in Table 2. Despite varying the substituents with electron-withdrawing or electron-donating groups, and bulky or small groups, the yields fell between 89% and 99%. The considerably close yields revealed that both electronic and steric nature of the substituents on 4-position had no significant influence on the reaction.

It was well known that the reaction between sodium chlorite and hydrochloric acid generated chlorine dioxide (ClO_2, Eq. 1) and the reaction was catalyzed by chlorine.[22] Furthermore, ClO_2 can oxidize organic species with the formation of a chlorite ion (ClO_2^-).[23] The fact that the reaction yielded undetectable product without the addition of hydrochloric acid (Table 1, entry 10) suggested that ClO_2 played a significant role in the aromatization process. Based on our experimental observations, an electron transfer mechanism promoted by ClO_2 is proposed as in Scheme 2.

$$5NaClO_2 + 4HCl \rightarrow 5NaCl + 4ClO_2 + 2H_2O \quad (1)$$

As demonstrated in Scheme 2, the oxidation of 1,4-DHPs was initiated by ClO_2-promoted single electron transfer to produce radical cation **A** and (ClO_2^-). This was followed by a proton loss from 4-position to afford radical **B**. Further oxidation of radical **B** by another molecule of ClO_2 resulted in the protonated pyridine **C**. The aromatization was accomplished by the loss of a proton from **C**.



Scheme 2. Proposed mechanism for the aromatization process.

In summary, we have developed an efficient, convenient, and environmentally benign protocol for the aromatization of various 1,4-DHPs in very good yields under mild conditions.

3. Experimental

3.1. General procedure for the aromatization of 1,4-DHPs

To a stirred solution of 1,4-DHP (1 mmol) and $NaClO_2$ (1.5 mmol) in EtOH/H_2O (1:1) (5 mL), HCl (concd) (12 M, 0.2 mL) was added dropwise. The mixture was allowed to stir at 20 °C for specified time (Table 1). The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was concentrated under reduced pressure. The residue was diluted with 10% $NaHCO_3$ (5 mL) and extracted with EtOAc. The organic layer was washed with iced water and brine, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude products were crystallized from EtOH or EtOH/H_2O or chromatographed on silica gel column to give pure products.

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21. Compound **1m**: *2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-3,5-pyridine dicarboxylate*; white solid; mp: 107–108 °C, HR-ESI-MS: calcd for $C_{22}H_{28}NO_7$, *m*/*z*: 418.1860 $[M+H]^+$, found 418.1854, Err 1.59 ppm; IR (KBr, cm^{-1}) ν_{max}: 2930, 1726, 1557, 1508, 1465, 1349, 1296, 1232, 1125, 1106, 1047, 1003, 851, 709; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.00 (t, 6H, *J* = 7.0 Hz, 6H), 2.60 (s, 6H), 3.82 (s, 6H), 3.85 (s, 3H), 4.08 (q, *J* = 7.0 Hz, 4H), 6.51 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.7, 22.79, 52.1, 60.9, 61.4, 105.6, 126.8, 131.9, 138.1, 145.7, 153.0, 155.3, 168.0.
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