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# *N*-Nitroso-2-aryl-1,3-oxazolidines catalyzed aromatization of Hantzsch 1,4-dihydropyridines

Li-jun Peng [a], Jian-tao Wang [a], Zhou Lu [a], Zhong-quan Liu [b], Long-min Wu [a,*]

[a] *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China*
[b] *Institute of Organic Chemistry, Gannan Normal University, Ganzhou 341000, PR China*

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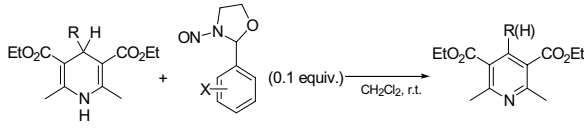
**Abstract**

A catalytic amount of *N*-nitroso-2-aryl-1,3-oxazolidines leading to the aromatization of Hantzsch 1,4-dihydropyridines (DHPs) was successfully achieved. A catalytic mechanism for the reaction is proposed.


Two lines of thought motivated the present study (a) Hantzsch 1,4-dihydropyridines (DHPs) are model compounds of NADH[1] and an important class of drug, which act as potent blockers of calcium ($Ca^{2+}$) currents.[2] The metabolism of DHPs involves an oxidation step catalyzed by cytochrome P-450 in the liver;[3] and (b) *N*-nitrosamines contained in the human diet are naturally occurring carcinogens. They undergo a cytochrome P-450-mediated α-oxidation that converts them into active carcinogens.[4] Hence, an investigation of the reaction of DHPs with *N*-nitrosamines will be of interest in this particular biochemical context.

Oxidation of DHPs has been carried out using various oxidants.[5] Reactions of DHPs with nitric oxide (NO),[6] nitrosonium ($NO^+$),[7] *S*-nitrosoglutathione,[8] and nitroxide[9] are especially relevant to the present study because *N*-nitrosamines are potential $NO^{\cdot}/NO^+$ donors through homolytic and heterolytic cleavage of the N–NO bond.[10] Based on these previous results, we examined the oxidation of DHPs with *N*-nitrosamines.

We carried out the oxidation of DHPs (**1**) with *N*-nitroso-2-aryl-1,3-oxazolidines (**2**). Oxazolidine **2** is a weak oxidant easily obtained from the reaction of (*E*)-2-(benzylidene-amino)ethanol with NO.[11] Its reduction potential is estimated to be −1.2 V versus $Fc^+/Fc$.[12] In a typical experiment, treatment of 1 mmol of **1a** with 0.1 mmol of *N*-nitroso-2-phenyl-1,3-oxazolidine **2a** in 20 mL of anhydrous $CH_2Cl_2$ at room temperature gave corresponding pyridine **3a** in 96% yield[13] in 6 h (Scheme 1). The reaction occurred efficiently. Side products were small amounts of benzaldehyde and 2-aminoethanol, which were produced from the decomposition of **2a**. Pyridine **3a** was characterized by $^1H$ NMR and mass spectroscopy. The reaction conditions were well optimized using **1a** as a substrate in several organic solvents and with various amounts of **2a**, respectively (Tables 1 and 2). They suggest that the oxidation of **1a** very favorably proceeds in $CH_2Cl_2$ and with 0.1 equiv of **2a**. Extension to other DHPs with different R-substituents also gave encouraging results (Table 3). Dealkylation inclusively occurred only when R is isopropyl group (entries 7 and 8).[5e,6,7,14]




Scheme 1.

* Corresponding author. Tel.: +86 931 891 2500; fax: +86 931 891 5557.
*E-mail addresses:* penglj04@lzu.cn, nlaoc@lzu.edu.cn (L. Wu).

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Table 1
Solvent effects on the aromatization of **1a** with **2a**

| Entry | Solvent | Amount of **2a** (mol %) | Conver.[a] (%) | Time (h) | Yield of **3a**[b] (%) |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 10 | 88 | 12 | 78 |
| 2 | $CH_2Cl_2$ | 10 | 100 | 6 | 96 |
| 3 | Toluene | 10 | 100 | 6 | 90 |
| 4 | EtOH | 10 | 78 | 12 | 70 |
| 5 | MeOH | 10 | 85 | 12 | 76 |
| 6 | THF | 10 | 100 | 12 | 88 |
| 7 | $H_2O$ | 10 | 50 | 12 | 20 |

[a] Determined by GC.
[b] Isolated yield.

Table 2
Optimization of the amount of **2a**

| Entry | Amount of **2a** (mol %) | Conver.[a] (%) | Time (h) | Yield of **3a**[b] (%) |
|---|---|---|---|---|
| 1 | 1 | 88 | 12 | 78 |
| 2 | 5 | 90 | 12 | 85 |
| 3 | 10 | 100 | 6 | 96 |
| 4 | 10 | 100 | 12 | 96 |
| 5 | 15 | 100 | 12 | 95 |
| 6 | 20 | 100 | 12 | 96 |

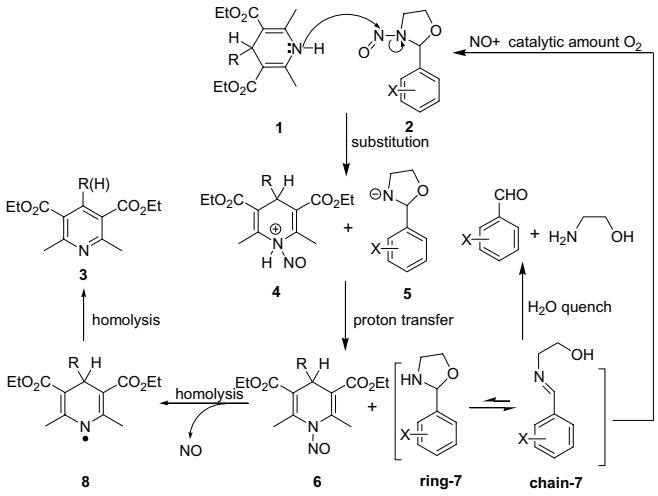
[a] Determined by GC.
[b] Isolated yield.

Table 3
Oxidation of DHPs with *N*-nitroso-2-aryl-1,3-oxazolidines

| Entry | Substrate | | Oxazolidine[a] | Product | | Yield of **3**[b] (%) |
|---|---|---|---|---|---|---|
| | | R | | | R | |
| 1 | **1a** | H | **2a** | **3a** | H | 96 |
| 2 | **1a** | H | **2b** | **3a** | H | 90 |
| 3 | **1b** | Me | **2a** | **3b** | Me | 90 |
| 4 | **1b** | Me | **2b** | **3b** | Me | 77 |
| 5 | **1c** | Et | **2a** | **3c** | Et | 88 |
| 6 | **1c** | Et | **2b** | **3c** | Et | 84 |
| 7 | **1d** | $(CH_3)_2CH$ | **2a** | **3d**[c] | H | 92 |
| 8 | **1d** | $(CH_3)_2CH$ | **2b** | **3d** | H | 89 |
| 9 | **1e** | Ph | **2a** | **3e** | Ph | 90 |
| 10 | **1e** | Ph | **2b** | **3e** | Ph | 88 |
| 11 | **1f** | *p*-$CH_3O$–Ph | **2a** | **3f** | *p*-$CH_3O$–Ph | 95 |
| 12 | **1f** | *p*-$CH_3O$–Ph | **2b** | **3f** | *p*-$CH_3O$–Ph | 95 |
| 13 | **1g** | *p*-Cl–Ph | **2a** | **3g** | *p*-Cl–Ph | 96 |
| 14 | **1g** | *p*-Cl–Ph | **2b** | **3g** | *p*-Cl–Ph | 95 |
| 15 | **1h** | *p*-$O_2N$–Ph | **2a** | **3h** | *p*-$O_2N$–Ph | 94 |
| 16 | **1h** | *p*-$O_2N$–Ph | **2b** | **3h** | *p*-$O_2N$–Ph | 93 |

[a] **2a**: X = H; **2b**: X = *p*-Cl.
[b] Isolated yield.
[c] **3d** is identical to **3a**.

A catalytic mechanism in the aromatization of **1** with **2** is depicted in Scheme 2. Although the oxidation of **1** with **2** is unfavorable in thermodynamics, yet, *N*-nitroso compounds are well-known nitrosotransfer agents,[7b] which have been widely used to nitrosate many compounds containing NH group to form the corresponding *N*-nitroso compounds via a nucleophilic substitution. A nucleophilic attack of




Scheme 2.

the nitrogen atom of **1** at the nitrogen atom of the *N*-nitroso of **2** most likely undergoes a transnitrosation[7b,15] to give a nitronium ion **4** and an oxazolidine anion **5**.[7b] Followed by a proton transfer, *N*-nitrosodihydropyridine **6** and oxazolidine ring-**7** with its acyclic tautomer chain-**7** are formed.[11] Oxazolidine ring-**7** and chain-**7** react with NO released from **6** in the presence of catalytic $O_2$ to regenerate **2**. The homolysis of **6** gives an aminyl radical **8** and NO.[7b,c,15] Followed by a homolysis, radical **8** then converts to pyridine **3**. Aldehyde and 2-aminoethanol are produced from the decomposition of ring-**7** and chain-**7**.

In conclusion, this work demonstrates a *N*-nitroso-2-aryl-1,3-oxazolidine catalyzed pathway for the aromatization of DHPs to pyridines. It will be of interest to both biochemistry and organic chemistry.

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12. The redox potentials of **2a** and DHP were measured at ambient temperature using cyclic voltammetry performed on an electrochemical analyzer (model CHI 760B), which was connected to a PC with Origin 6.0 software. Au flag was used as the working electrode, Pt flag as the auxiliary electrode, and $HgCl_2$/Hg as the reference electrode. $(C_2H_5)_4NBr$ was applied to a background electrolyte. The reduction potential of **2a** is $-1.2$ V versus $Fc^+$/Fc and the oxidation potential of DHP is 0.5 V versus $Fc^+$/Fc.
13. *Typical procedure*: A solution of 1 mmol **1a** and 0.1 mmol **2a** in 20 mL of anhydrous $CH_2Cl_2$ was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water. Extracted with 20 mL of $CH_2Cl_2$ and dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the products were isolated by flash chromatography on silica gel, purified by recrystallization from chloroform–hexane. Data for diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (**3a**): white solid; mp 70–71 °C; IR (KBr) $\nu_{max}$ 2986, 2978, 2930, 2912, 1718, 1591, 1555, 1548, 1444, 1380, 1368, 1297 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.41 (6H, t, $J = 7.2$ Hz), 2.84 (6H, s), 4.40 (4H, q, $J = 7.2$ Hz), 8.67 (1H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 14.2, 25.0, 61.4, 123.0, 140.9, 162.2, 165.9; MS *m*/*z* (relative intensity): 251 ($M^+$, 39.8), 206, 195, 178, 150, 106.
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