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

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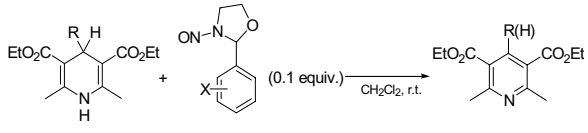
Abstract

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.

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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

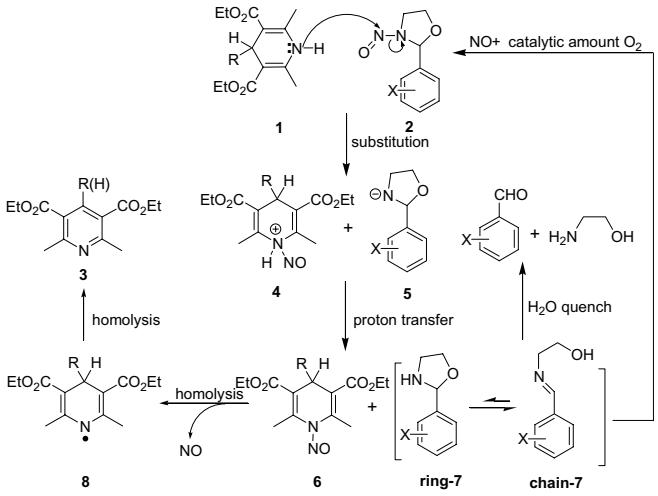
[a] Determined by GC.
[b] Isolated yield.

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) ν_{max} 2986, 2978, 2930, 2912, 1718, 1591, 1555, 1548, 1444, 1380, 1368, 1297 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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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