

Novel Reaction of Nitrosonium(NO^+) with Hantzsch Dihydropyridines

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Abstract: The oxidation on 1,4-substituted Hantzsch 1,4-dihydropyridines with nitrosonium tetrafluoroborate (NO^+BF_4^-) in acetonitrile gave Hantzsch pyridines in good yields. In some cases the dealkylation occurred. The evidences to draw the mechanism were presented.

Keywords: Nitrosonium, hantzsch dihydropyridines.

Our interest in the reaction of Hantzsch 1,4-dihydropyridine with nitrosonium tetrafluoroborate (NO^+BF_4^-) was raised from two aspects. The first was biological activities and cytotoxic roles of nitric oxide and nitrosonium (NO^+)^{1,2}. NO^+ is a redox partner of NO, but its nature is in stark contrast to $\text{NO}^{2,3}$. The second was that Hantzsch 1,4-dihydropyridines are analogues of NADH coenzymes. The oxidation of Hantzsch 1,4-dihydropyridines is an old reaction. It has been attracted more attention of chemists in recent years, essentially since the discovery that their metabolism (used as drugs) involves an oxidation step which is catalyzed by cytochrome P-450 in the liver⁴. The previous studies^{5, 6a} on the oxidation of 4-substituted Hantzsch 1,4-dihydropyridines exhibited that the reaction gave either non-dealkylation or dealkylation products. The class of products was strongly dependent on the sort of oxidants applied as well as the media. Different mechanisms were postulated accordingly.

In the present work, we report the oxidation of a number of 4-substituted Hantzsch dihydropyridines⁶ with NO^+BF_4^- in acetonitrile at room temperature under the protection of Argon. The solid NO^+BF_4^- (0.05 mmole, sublimated) was placed on the bottom of a tube and Argon was introduced for a duration of about 20 minutes. Under Argon atmosphere the anhydrous and anaerobic acetonitrile solution (2.5 ml) of Hantzsch dihydropyridine (0.05 mmole) was added into the tube through a syringe. The liberated gas was identified to be NO by GC. The liberation of gas was immediately on the addition of Hantzsch dihydropyridine. When the bubble of gas was ceased, it showed the reaction was completed. It took about one hour. Then, the solvent was evaporated and the residue was treated either by washing with water (3x2.5 ml) to remove the inorganic compounds and crystallized from a mixed solvent of acetone and petroleum ether or by column chromatography, giving the product **II**, Hantzsch pyridine (**Scheme 1**), in good yields (**Table 1**). The byproducts can not be separated in the form of oligomer. Under

the indicated conditions, for most part, the corresponding 4-substituted Hantzsch pyridines were obtained. The dealkylation at the 4-position occurred mainly on **Id** and **Ie**. This result is much similar to Loev's and Bacon's results^{5a, k}, but in sharp contrast to Itoh^{5e, f}. In addition to **Ia**, the products derived from the fragment group were identified by GC to be the disproportionation products of alkyl radicals, for instance, in the case of **Id**, propane and propene (*ca.* 1:1). **Ic** and **II** gave only a small amount (less than 10 %) of dealkylation products.

Scheme 1

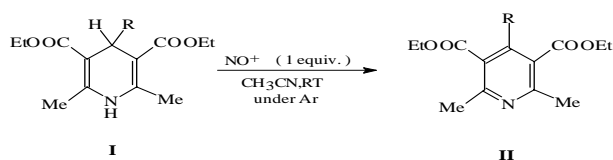


Table 1: Oxidation of Hantzsch dihydropyridines **I** with NO^+BF_4^- in acetonitrile under argon atmosphere

entry	substrate	R	product ^c	Yield/%
1	Ia	H	IIa	91
2	Ib	CH_3	IIb	79
3	Ic	CH_2CH_3	IIc^b	80 ^b
4	Id	$\text{CH}(\text{CH}_3)_2$	IIa	85
5	Ie	$\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	IIa	90
6	If^f	$\text{CH}=\text{CH}-\text{CH}_3$	IIg^g	90
7	Ig	$\text{CH}=\text{CH}-\text{C}_6\text{H}_5$	IIg	90
8	Ih	C_6H_5	IIh	92
9	II	<i>p</i> - $\text{N}(\text{CH}_3)_2-\text{C}_6\text{H}_4$	III^b	85 ^b
10	Im	<i>p</i> -methoxyl- C_6H_4	IIIm	95
11	In	3',4'-methylenedioxy- C_6H_3	IIIn	93
12	Ip^g	3',4'-dihydroxyl- C_6H_3	IIp	96
13	Iq	3'-hydroxyl- C_6H_4	IIq	92
14	Ir	<i>p</i> -Cl- C_6H_4	IIr	95
15	Is	2'-furyl	IIs	95

a For the known compounds of **I**, the corresponding products **II** were characterized by comparing their physical and spectroscopic data with the reported data^{5a, d}.

b The minor product was **IIa**. The yields were less than 10%.

Our finding that NO was released during the reaction was an important evidence to support that the first step of the oxidation of Hantzsch dihydropyridines by NO^+ is one-electron transfer (ET) from dihydropyridine to NO^+ . As a result, Hantzsch dihydropyridines should be reasonably oxidized to the ammoniumyl radical cation, postulated by J. Ludvik⁵ⁱ. The stoichiometry study showed there was an equal mole relationship between dihydropyridine, NO^+ and pyridine. The 1:1:1 stoichiometry implied that the sequent reaction involved NO generated in the first step.

The reaction with **Ib**, **Ic**, **Id** and **Ie** (**Table 1**) exhibited that the yield of the dealkylation product would go up with increasing bulk of the 4-alkyls. Associated with other experiments^{5a, d-f}, it can be also seen that the Hantzsch dihydropyridines containing a conjugated unsaturated or aromatic substitutes tend to resist the dealkylation. It might

be attributed to that a strong conjugation stabilizes the reaction intermediates. The intermediates seem not to decompose easily. The formation of disproportionation products forming from the fragment groups when the major products are the dealkylation products might suggest the fragmented groups are alkyl radicals. In comparison with the results of Itoh, particularly on the point of dealkylation occurrence, the oxidation of Hantzsch dihydropyridines performed in this work might follow a different pathway from Itoh's postulation^{5e, f}.

As compared with Itoh's works, where the reaction was carried out in a gas-liquid system and under a large excess amount of NO, and with the aromatization of the same series of heterocycles with MnO₂/DDQ^{5d} or pyridinium chlorochromate supported on an inorganic solid^{5j}, where it requires too much oxidant or longer reaction times, the present work seems to be an easy and efficient approach for the oxidation of this kind of compounds. Its great advantages are that the reaction is performed under mild conditions, characterized by high speed, good yields and flexibility.

The preliminary mechanism study implied that the oxidation of Hantzsch dihydropyridines by nitrosonium was *via* an initial ET step, mediated by radicals. The details of the reaction mechanism are now under investigation.

Acknowledgment

We thank the National Natural Science Foundation of China (Research Grant 29672016) and the Natural Science Foundation of Gansu Province for financial support.

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- 7 Data for compound **If**: m.p. 133-134 °C; ¹H NMR (200 MHz, CDCl₃): δ 1.33 (t, J=7.1 Hz, 6 H, CH₃), 1.82 (d, J=5.7 Hz, 3 H, CH₃), 2.31 (s, 6 H, CH₃-2), 4.16 (q, J=7.1 Hz, 4 H, CH₂), 4.41 (d, J=6.0 Hz, 1 H, H-4), 5.83 (s, 1 H, NH), 5.61 (dq, J=16.0, 5.7 Hz, 1 H, CH=CHCH₃), 5.74 (dd, J=16.0, 6.0 Hz, 1 H, CH=CHCH₃); EI-MS (m/z): 293 (M⁺), 264 (M-29), 252 (M-41); anal. calc. for C₁₆H₂₃NO₄: C, 65.53; H, 7.70; N, 4.78, found: C, 65.60; H, 7.70; N, 4.75.
- 8 Data for compound **III**: colorless oil; ¹H NMR (200 MHz, CDCl₃): δ 1.35 (t, J=7.1 Hz, 6 H, CH₃), 1.83 (d, J=6.5 Hz, 3H, CH₃), 2.52 (s, 6 H, CH₃-2), 4.35 (q, J=7.1 Hz, 4 H, CH₂), 6.00 (dq, J=16.0, 6.5 Hz, 1 H, CH=CHCH₃), 6.42 (d, J=16.0 Hz, 1 H, CH=CHCH₃); EI-MS (m/z): 291 (M⁺), 276 (M-15), 246 (M-45); anal. calc. for C₁₆H₂₁NO₄: C, 65.98; H, 7.17; N, 4.81, found: C, 66.05; H, 7.10; N, 4.79.
- 9 Data for compound **Ip**: m.p. 186-188 °C; ¹H NMR (200 MHz, d₆-DSMO): δ 1.13 (t, J=7.1 Hz, 6 H, CH₃), 2.22 (s, 6 H, CH₃-2), 3.98 (q, J=7.1 Hz, 4 H, CH₂), 4.69 (s, 1 H, H-4), 6.35-6.40 (m, 1 H, H-2'), 6.49-6.55 (m, 2 H, H-5', 6'); EI-MS (m/z): 361 (M⁺), 332 (M-29), 252 (M-109); anal. calc. for C₁₉H₂₃NO₄: C, 63.16; H, 6.37; N, 3.88, found: C, 63.26; H, 6.30; N, 3.86.

Received 7 July 1999