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Novel Reaction of Nitroxide with Hantzsch Dihydropyridines

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Abstract: 4-oxo-2, 2, 6, 6-tetramethylpiperidinyl-1-oxy radical (TEMPO), a nitroxide, oxidized 4-substituted Hantzsch 1,4-dihydropyridines (DHP) under UV irradiation in CH_3CN to give aromatic products in good yields. A possible mechanism for the oxidation was suggested.

Keywords: Nitroxide, Hantzsch dihydropyridines, photoinduced electron transfer.

Nitroxides have been found to be the intermediate in the *in vivo* metabolism of hydroxamic acid, a well-known biological molecule[1]. Structural modification of some antitumor drugs by introducing nitroxides can lower toxicity remarkably with retention or even increase of the antitumor activity[2]. Furthermore, the use of nitroxides as spin probes makes it possible to get information regarding the microenvironment of the reaction.

4-Substituted Hantzsch 1,4-dihydropyridines (DHP) are analogs of NADH coenzymes[3] and an important class of drugs which are potent blockers of calcium (Ca^{2+}) currents[4]. The oxidation of DHP has recently attracted more attention of chemists, essentially since the discovery that the metabolism of DHP involves an oxidation step which is catalyzed by cytochrome P-450 in the liver[5,6]. Generally, strong inorganic oxidants[7,8], such as nitric acid, ceric ammonium nitrate, must be used to accomplish the oxidation of the Hantzsch dihydropyridines. Recently, nitric oxide[9]and pyridinium chlorochromate[10] were used to improve the efficiency of the aromatization. However, yields are generally moderate or longer reaction times are required. So far as we know, the nitroxides have not been applied in this model reaction. The reactions of nitroxides with molecules of biological interest are of significance because of the application of nitroxides as spin labels in probing biology structures[11]. Herein, we wish to report our present work about the oxidation reactions of nitroxyl radicals with DHP derivatives.

DHP (0.1 mmol) and 4-oxo-2, 2, 6, 6-tetramethylpiperidinyl-1-oxy radical (TEMPO) (0.2 mmol) were dissolved in 5mL of CH_3CN and irradiated with a 250 W high pressure mercury lamp in a Pyrex bottle under argon atmosphere at ambient temperature (**Scheme 1**). After irradiation the solvent was removed under reduced pressure and the corresponding pyridine derivative obtained by column chromatography in good yields. One exception was 4-isopropyl-DHP (Ic) which gave 83% of the dealkylation product

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(IIa). The results are summarized in **Table 1**.

Scheme 1

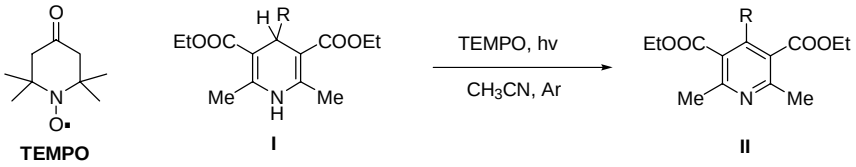


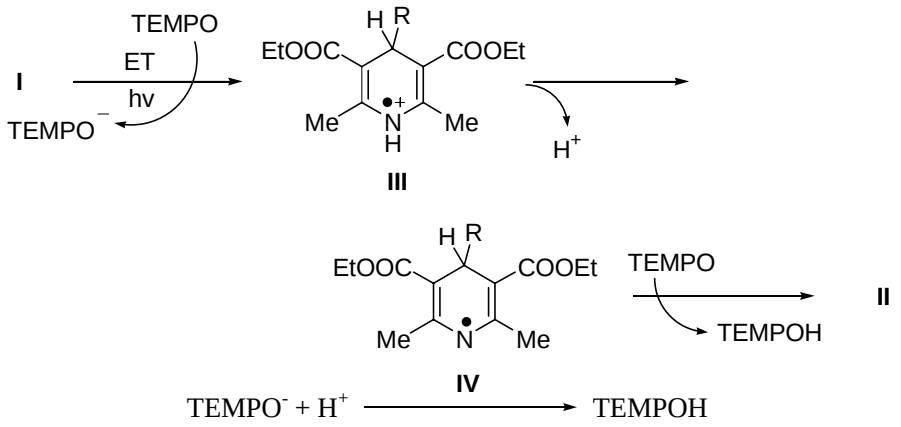
Table 1 Oxidation of DHP with TEMPO in CH_3CN under an Ar Atmosphere

substrate	R	time(h)	product	yield(%)
Ia	H	1	IIa	98
Ib	CH_3	2	IIb	89
Ic*	$(CH_3)_2CH$	2	IIa	83
Id[12]	Ph	3	IId[13]	90
Ie	F-Ph	3	IIe	92
If	CH=CHPh	3	IIf	80
Ig	*p*-methoxy-Ph	3	IIg	87
Ih	*m*-hydroxy-Ph	3	IIh	75
Ii	3′,4′-dihydroxy-Ph	3	IIi	67

*The dealkylation at the 4-position occurred[14,15,16]

To our knowledge, two mechanisms for the oxidation of NADH analogues, hydride transfer[17] or electron transfer[18], are possible. In this reaction we found that the nitroxide (TEMPO) was converted into hydroxylamide (TEMPOH) as evidenced by GC-MS. Therefore, a photoinduced electron transfer mechanism is proposed as outlined in **Scheme 2**.

Scheme 2



The reaction might commence with a one-electron transfer from dihydropyridine to TEMPO, yielding the radical cation III of DHP and the anion of TEMPO, $TEMPO^-$. It is reasonable that radical III loses a proton to give aminyl radical IV, which then reacts

with TEMPO to form pyridine II and TEMPOH.

In conclusion, we outlined herein an easy and efficient approach for the oxidation of this kind of compounds. Its advantages are that the reaction is performed under mild conditions, characterized by high speed, good yields and flexibility. The main point of this work, however, is mainly of its biochemical significance.

Acknowledgment

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References and Notes

1. H. Kehl, *Chemistry and Biology of Hydroxamic Acids*, Karger, Basel, **1982**.
2. N. M. Emanuel; *Pure & Appl. Chem*., **1980** *52*, 11.
3. R. J. Abeles, R. F. Hutton, F. H. Westheimer, *J. Am. Chem. Soc.*, **1957**, *79*, 712.
4. D. J. Triggle, D. A. Langs, R. A. Janis, *Med. Res. Rev.*, **1989**, *9*, 123.
5. R. H. Boecker, F. P. Guengerich, *J. Med. Chem.*, **1986**, *29*, 1596.
6. S. A. McCluskey, D. S. Riddick, J. E. Mackie, S. M. Kimmet, R. A. Whitney, G. S. Marks, *Can. J. Physiol. Pharmacol.*, **1992**, *70*, 1069.
7. R. H. Boecker, F. P. Guengerich, *J. Med. Chem.*, **1986**, *29*, 1596.
8. J. R. Pfister, *Synthesis*, **1990**, 689.
9. T. Itoh, K. Nagata, Y. Matsuya, M. Miyazaki, A. Ohsawa, *J. Org. Chem.*, **1997**, *62*, 3582.
10. J-J. V. Eynde, A. Mayence, A. Maquestiau, *Tetrahedron*, **1992**, *48*, 463.
11. J. Gaffney in *Spin-labelling*, ED. L. J. Berliner, Academic Press, New York, **1976**, p. 183.
12. Data for Compound **Id**: mp 157-159°C; ^{1}H NMR (200MHz, $CDCl_3$): δ 1.12 (t, 6H, J=7.1 Hz, 2×CH_3), 2.21 (s, 6H, 2×CH_3), 4.02 (q, 4H, J=7.1 Hz, 2×CH_2), 5.01 (s, 1H, CH), 7.01-7.33 (m, 5H, C_6H_5); EIMS (*m/z*): 329 (M^+, 15), 252 (100), 196 (40), 150 (10), 77 (5).
13. Data for Compound **IId**: mp 63-65°C; ^{1}H NMR (200MHz, $CDCl_3$): δ 1.21 (t, 6H, J=7.1 Hz, 2×CH_3), 2.52 (s, 6H, 2×CH_3), 4.37 (q, 4H, J=7.1 Hz, 2×CH_2), 7.11 (s, 5H, C_6H_5); EIMS (*m/z*): 327 (M^+, 54), 250 (100), 225 (40), 196 (22), 77 (16).
14. B. Love, K. M. Snader, *J. Org. Chem.*, **1965**, *30*, 1914.
15. R. G. R. Bacon and B. A. Osuntogun, *J. C. S. Chem. Commun.*, **1979**, 1159
16. L. M. Wu, W. Chen and Z. L. Liu, *Res. Chem. Intermed.*, **2001**, *27*, 219.
17. L. H. P. Meijer, U. K. Pandit, *Tetrahedron*, **1985**, *41*, 467.
18. S. Fukuzumi, *Adv. Electron-Transfer Chem.*, **1992**, *2*, 67.

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