REINVESTIGATION OF NITROSATION OF METHYLPYRIDINES AND THEIR 1-OXIDES AND DEOXYGENATION OF 3-PYRIDINECARBALDEHYDE 1-OXIDE OXIME

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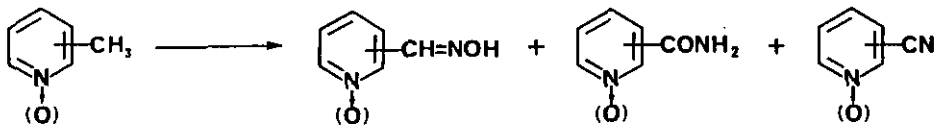
Abstract - Treatment of methylpyridines and their 1-oxides with t-butyl nitrite in the presence of potassium t-butoxide in liquid ammonia afforded the corresponding aldoximes in good yields except for the case of 3-methylpyridine. The reaction of 3-methylpyridine with t-butyl nitrite in the presence of lithium 2,2,6,6-tetramethylpiperidide and N,N,N',N'-tetramethylethylenediamine in tetrahydrofuran at -78°C led to 3-(3-methyl-4-pyridyl)methylpyridine. Deoxygenation of 3-pyridinecarbaldehyde 1-oxide oxime was effected in 78% yield by the action of t-butyldimethylsilyl chloride-imidzole-sodium iodide-zinc followed by desilylation with tetrabutylammonium fluoride to give 3-pyridinecarbaldehyde oxime.

In 1963, Kato and Goto reported that 2- and 4-methylpyridines and their 1-oxides readily reacted with amyl nitrite and an alkali amide in liquid ammonia (liq. NH_3) to give the corresponding aldoximes.[1] Since then, the reaction with an alkyl nitrite under similar conditions has been widely used for nitrosation of active methyl and methylene groups in pyridine,[2] benzopyridine[3] and pyrimidine[4] series. However, 3-methyl congeners resisted this nitrosation under the same conditions as described above. Recently we investigated the nitrosation of 1-methyl-, 1-ethylisoquinolines and their 2-oxides with alkyl nitrites under various conditions, and found that reactions with t-butyl nitrite (t-BuONO) in the presence of bases such as potassium t-butoxide (t-BuOK) or butyllithium (n-BuLi) were eventually effective for nitrosation of not only isoquinoline but also pyridine and quino-

line series.[5] These results prompted us to reinvestigate the nitrosation of methylpyridine derivatives. This paper deals with our observations obtained from such a study together with deoxygenation reactions of 3-pyridinecarbaldehyde 1-oxide oxime to 3-pyridinecarbaldehyde oxime. The configurations of oximes so far not determined were established.

We reexamined in some detail the nitrosation of 2-, 3- and 4-methylpyridines and their 1-oxides under various conditions, and found that treatment with t-BuONO and t-BuOK at -33℃ in liq. NH_3 (condition B) was most effective for the nitrosation. Table I shows the results obtained together with the original data[1] (condition A) by Kato and Goto for reference.

Table I. Reaction of Methylpyridines and Their 1-Oxides under the Various Types of Nitrosation Conditions



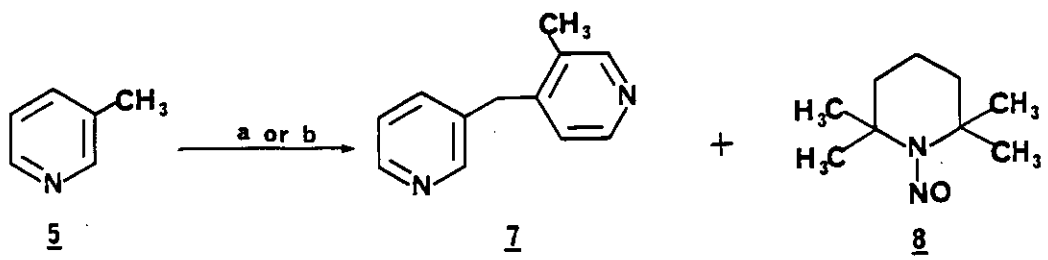
1: 2-CH_3, ≥N→O 4: 2-CH_3, ≥N
2: 3-CH_3, ≥N→O 5: 3-CH_3, ≥N
3: 4-CH_3, ≥N→O 6: 4-CH_3, ≥N

		Product(%)			Ratio of isomer	
Reactant	Conditions[a]	aldoxime	amide	nitrile	E : Z	Recovery(%)
1	A	57.2	16.0	--	1 : 0[6]	--
	B	66.0	14.0	--	0 : 1	--
2	A	--	--	--	--	70.0
	B	71.0	--	--	2 : 1	--
3	A	71.0	10.0	2.0	0 : 1[6]	--
	B	81.0	2.0	--	1 : 0	--
4	A	22.9	--	--	--	55.9
	B	75.0	--	--	2 : 1	4.0
	D	70.0	--	--	3 : 1	--
5	A	--	--	--	--	71.0
	B	9.0	--	--	1 : 0	68.0
	C	18.0	20.0	--	1 : 0	60.0
	E	5.2	28.0	--	1 : 0	--
6	A	65.9	5.0	--	--	8.0
	B	80.0	13.0	--	2 : 1	--

a) A: $C_5H_{11}ONO$, KNH_2, liq. NH_3, -33℃. B: t-BuONO, t-BuOK, liq. NH_3, -33℃.
C: t-BuONO, t-BuOK, liq. NH_3, room temperature. D: t-BuONO, LTMP-TMEDA, THF, -78℃.
E: t-BuONO, t-BuOK, 18-Crown-6, liq. NH_3, room temperature.

The configurations of oximes were unambiguously established using $\delta_{OH} - \delta_{CH-N}$ values in ^{1}H-nmr spectra as the criterion[5] for differentiation between E- and Z-forms. The use of tetrahydrofuran (THF) instead of liq. NH_3 was somewhat less effective as compared with condition B. It is remarkable that the reaction proceeded in high yield under condition B with 3-methylpyridine 1-oxide (2) which was quite inert to the reaction under condition A. It is also noteworthy that the configurations of oximes (E and Z) obtained from the above reactions of 2-methylpyridine 1-oxide (1) and 4-methylpyridine 1-oxide (3) under condition B, respectively, were found to be reverse to those under condition A reported previously.[6] The relationship between the oxime configuration and the reaction conditions has to be explored further in detail.

In contrast to the successful nitrosation of 2, the nitrosation of 3-methylpyridine (5) under condition B was very unsatisfactory and the (E)-oxime was formed only in a poor yield of 9% with 5 being recovered in 68% yield. The reaction at room temperature in liq. NH_3 (condition C) gave the oxime in a slightly better yield (18%) and the amide (20%), but the application of a crown-ether (condition E) was also fruitless. Further, we attempted the nitrosation with t-BuONO in the presence of lithium 2,2,6,6-tetramethylpiperidide (LTMP) and N,N,N',N'-tetramethylethylenediamine (TMEDA) in THF (condition D). The reaction followed a quite different course, and 3-(3-methyl-4-pyridyl)methylpyridine (7) and 1-nitroso-2,2,6,6-tetramethylpiperidine[7] (8) were obtained in 54 and 58% yields, respectively, in contrast to the reaction of 2-methylpyridine (4) in which the corresponding oximes were formed in 70% yield. Compound(7) was also produced by the reaction using lithium diisopropylamide (LDA) in place of LTMP(51%). Compound(7) was very stable toward refluxing with concentrated hydrochloric or hydrobromic acid. The 2D nmr analysis of 7 by means of COSY, C-H COSY, and long-range C-H COSY spectra strongly indicates that methyl group of 5 is bound to the carbon atom at the 4-position not 2- or 6-positions of another 5.



5 7 8

Scheme 1. Reagents and conditions: a. t-BuONO, LTMP-TMEDA, THF, -78°C; b. t-BuONO, LDA-TMEDA, THF, -78°C.

This assignment furthermore could be confirmed by NOE difference spectroscopy. A positive NOE was observed for CH_2 and H-2' protons upon irradiation of CH_3 group (δ 2.25) and for CH_3, H-2, H-4 and H-5' protons upon irradiation of CH_2 group (δ 3.96) (Figure 1). The structure of 7 could be decisively proven also by an unequivocal synthesis of 7 from 4-bromo-3-methylpyridine (9)[8] as shown in Scheme 2. Compound(9) was successively treated with n-BuLi, methyl nicotinate and boiling methanolic hydrochloric acid to furnish 3-methyl-4-nicotinoylpyridine (10), which was converted to 7 by the Wolff-Kishner reduction; reversely, 7 was smoothly oxidized to 10 with selenium dioxide in dioxane.

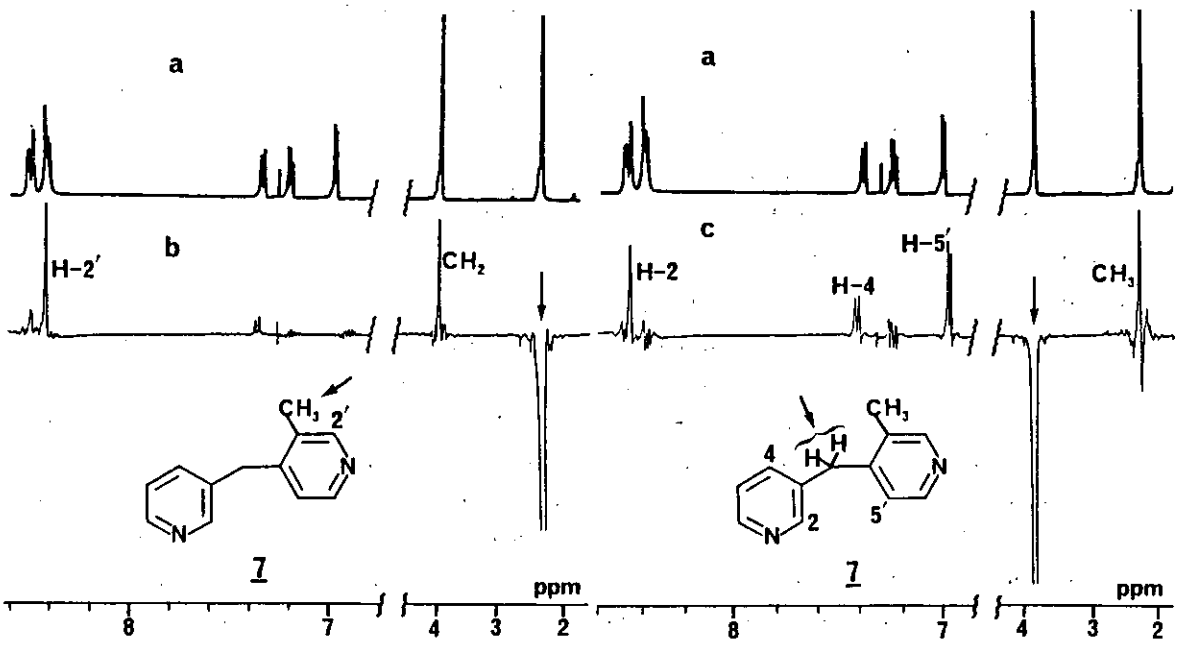
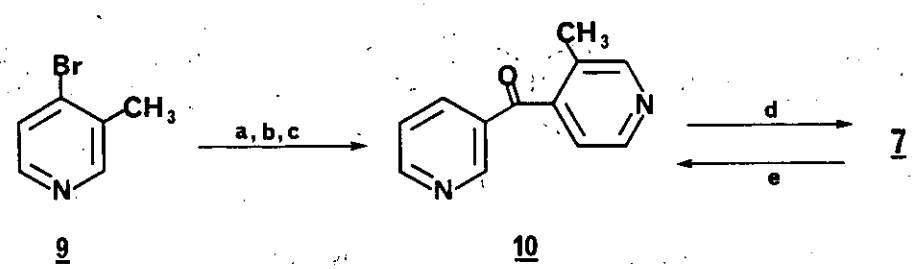
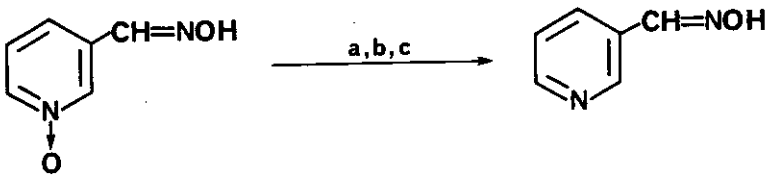


Figure 1. a) ^{1}H-nmr Spectrum of 7
b) NOE Difference Spectrum of 7 Resulting from Irradiation of CH_3
c) NOE Difference Spectrum of 7 Resulting from Irradiation of CH_2



Scheme 2. Reagents and conditions; a, n-BuLi, ether, -45°C; b, methyl nicotinate; c, HCl-MeOH; d, H_2NNH_2, KOH, diethylene glycol; e, SeO_2, dioxane.

Since 3-pyridinecarbaldehyde 1-oxide oximes (11) could be obtained in good yield from 2 but the preparation of 3-pyridinecarbaldehyde oxime (12) from 5 was quite unsatisfactory, the deoxygenation of 11 to 12 was explored as a route to 12. Treatment of 11 with phosphorous chloride in chloroform[9] or with aluminum triiodide in acetonitrile[10] (MeCN) resulted only in recovery of 11. Reduction of 11 in the presence of Raney nickel[11] or treatment of 11 with titanium tetrachloride-sodium iodide (NaI)-MeCN[12] gave 12 in 42 and 49% yields, respectively. Further it was disclosed that, whereas trimethylsilylation with trimethylsilyl chloride followed by treatment with NaI-zinc (Zn)-MeCN[13] gave also 12 in a rather low yield (19%), 12 was obtained in a high yield of 78% by one pot procedure involving trimethylsilylation with t-butyldimethylsilyl chloride (TBDMSCl) and imidazole, reduction with NaI-Zn-MeCN and desilylation with tetrabutylammonium fluoride.



11 12

Scheme 3. Reagents and conditions: a. TBDMSCl, imidazole, MeCN; b. Zn, NaI, 60°C; c. Bu_4NF.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometers or spectrometers: ir spectra, JASCO IR-810 ; ^{1}H-nmr spectra, JEOL GX-400 (400MHz) ; ^{13}C-nmr spectra, JEOL GX-400 (100MHz) ; COSY, C-H COSY, and long-range C-H COSY spectra, JEOL GX-400 ; ms, JEOL JMS-DX300. Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck). Medium-pressure liquid chromatography (MPLC) was performed on Yamazen 540 FMI-C pump using Kieselgel 60 (230-400 mesh, Merck).

General procedure for nitrosation of methylpyridines and their N-oxides with t-BuONO in the presence of t-BuOK at -33°C in liq. NH_3 (condition B)—In a 200 ml three necked flask equipped with a stirrer and a Dry Ice-acetone condenser was placed liq. NH_3 (100 ml), and t-BuOK (2.40 g, 21.4 mmol) was added to liq. NH_3. After stirring for 15 min, methylpyridine or its N-oxide (10.7 mmol) was added and the mixture was further stirred for 1 h. Then t-BuONO (3.31 g, 32.1 mmol) was added dropwise to the reaction mixture which was stirred

for 2.5 h, and liq. NH_3 was evaporated. The residue (or after neutralization with CH_3COOH) was chromatographed with the mixed solvent of $CHCl_3$ and MeOH to give oxime, amide or nitrile in the yields as shown in Table I.

Nitrosation of 3-methylpyridine (5) with t-BuONO in the presence of t-BuOK or t-BuOK-18-Crown-6 at room temperature in liq. NH_3 (conditions C and E)—Reactions were carried out as described in the previous paper[1] but using 5 (1.0 g, 10.7 mmol), t-BuOK (2.40 g, 21.4 mmol) or t-BuOK-18-Crown-6 (2.40 g, 21.4 mmol and 5.66 g, 21.4 mmol, respectively) instead of metal amide, and t-BuONO (3.31 g, 32.1 mmol) instead of amyl nitrite. Work-up of the products as described for reactions under condition B gave the results as shown in Table I.

General procedure for the reaction of 2-methylpyridine (4) or 5 with t-BuONO in the presence of LTMP (or LDA) and TMEDA at -78℃ in dry THF (condition D)—To a dry THF solution of LTMP (or LDA)-TMEDA prepared from 2,2,6,6-teramethylpiperidine (6.04 g, 43 mmol) (or diisopropylamine (4.34 g, 43 mmol)), 1.6 M n-BuLi in hexane (26.8 ml, 43 mmol) and TMEDA (5.0 g, 43 mmol), 4 or 5 (2.0 g, 21.5 mmol) in dry THF (10 ml) was added dropwise with stirring at -78℃ under nitrogen. After stirring for 1.5 h at -78℃, a solution of t-BuONO (6.64 g, 64.5 mmol) in dry THF (10 ml) was added dropwise to the mixture. The reaction mixture was further stirred at -78℃ for 2 h and was allowed to reach room temperature overnight with stirring. Ice water was added to the resulting mixture and after evaporation of solvent at as low temperature as possible, the residue was respectively post-treated in the manner as shown below.

Reaction of 4 using LTMP—After the residue was neutralized with CH_3COOH, the solvent was evaporated off and the resulting residue was chromatographed on MPLC with CH_2Cl_2 to afford the corresponding oxime in the yield as shown in Table I.

Reaction of 5 using LTMP—The residue was extracted with $CHCl_3$ and the residue from the $CHCl_3$ extract was chromatographed to give 1-nitroso-2,2,6,6-tetramethylpiperidine (8) (with CH_2Cl_2) and 3-(3-methyl-4-pyridyl)methylpyridine (7) (with the mixed solvent of CH_2Cl_2 : MeOH = 20 : 1). Compound (7) was distilled under reduced pressure to give pale yellow oil, bp 130-131℃ (0.033 mmHg), 2.14 g (54% yield). Picrate: yellow prisms, mp 214-215℃ (decomp.) (from H_2O). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found : C, 78.12; H, 6.75; N, 15.11. Ir (neat): 3400, 3028, 1594, 1479, 1425, 1027, 713 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): δ 2.25(3H, s, CH_3), 3.96(2H, s, CH_2), 6.96(1H, d, J=4.9 Hz, H-5'), 7.21-7.24(1H, m, H-5), 7.38-7.40(1H, m, H-4), 8.37-8.40(2H, m, H-2' and H-6'), 8.46-8.50(2H, m, H-2 and H-6). ^{13}C-Nmr ($CDCl_3$): δ 16.20(q, CH_3), 35.78(t, CH_2), 123.45(d, C-5), 124.05(d, C-5'), 131.79(s, C-3'), 133.73(s, C-3), 136.04(d, C-4), 146.41(s, C-4'), 147.73(d, C-6'), 147.96(d, C-6), 150.09(d, C-2),

150.89(d, C-2'). Ms m/z : 184(M^+, 100), 169(22), 105(33). Compound (8) was distilled under reduced pressure to give yellow oil, bp 97℃ (6 mmHg), 2.12 g (58% yield). The bp and ir spectrum coincided with those of an authentic sample.[7]

Reaction of 5 using LDA—The residue was treated as described for the reaction of 5 using LTMP to give 7 in 51% yield.

3-Methyl-4-nicotinoylpyridine (10)—To a solution of 4-lithio-3-methylpyridine prepared from 4-bromo-3-methylpyridine[8] (2.0 g, 11.6 mmol) and 1.6 M n-BuLi (11.2 ml, 17.4 mmol) in dry ether (50 ml) at -45℃ was added methyl nicotinate (4.78 g, 34.9 mmol) with stirring, and the mixture was stirred at -45℃ for 2 h. The solution was allowed to reach room temperature overnight with stirring. The mixture was treated with methanolic hydrochloric acid (methanol 50 ml, conc. HCl 10 ml, and water 50 ml); the ethereal solvent was removed in vacuo and the acidic aqueous solution was reflux for 6 h, cooled and then neutralized with Na_2CO_3, and extracted with $CHCl_3$. The residue from $CHCl_3$ extract was chromatographed with the mixed solvent of CH_2Cl_2 : MeOH = 20 : 1 to give 10, pale yellow viscous oil, bp 134-135℃ (0.03 mmHg), 0.3 g (26% yield). Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found : C, 72.87; H, 5.25; N, 14.03. Ir (neat) : 3036, 1668 (C=O), 1584, 1419, 1281, 935, 658. ^{1}H-Nmr ($CDCl_3$) : δ 2.31(3H, s, CH_3), 7.21(1H, d, J=4.9 Hz, Ar-H), 7.46-7.49(1H, m, Ar-H), 8.12-8.15(1H, m, Ar-H), 8.61(1H, d, J=4.9 Hz, Ar-H), 8.64(1H, s, Ar-H), 8.84-8.86(1H, m, Ar-H), 8.93(1H, d, J=2.0 Hz, Ar-H). ^{13}C-Nmr ($CDCl_3$) : δ 16.43(s, CH_3), 121.01(d,Ar), 123.59(d, Ar), 130.31(s, Ar), 131.48(s, Ar), 136.67(d,Ar), 144.16(s, Ar), 147.35(d, Ar), 151.24(d, Ar), 152.25(d, Ar), 154.09(d, Ar), 194.84(s, C=O). Ms m/z : 198(M^+, 100).

Wolff-Kishner Reduction of 10 to 7—A solution of 10 (1.0 g, 5.1 mmol), hydrazine monohydrate (1.39 g, 27.7 mmol), and KOH (1.67 g, 29.7 mmol) in diethylene glycol (25 ml) was stirred under nitrogen at 120-140℃ for 6 h. After cooling, the mixture was poured into ice water (70 ml) and extracted with ether. The residue from ether extract was distilled under reduced pressure to give 7, 0.55 g (59% yield).

Selenium dioxide oxidation of 7 to 10—A solution of 7 (2.0 g, 10.9 mmol) and selenium dioxide (1.3 g, 11.8 mmol) in dioxane (100 ml) was refluxed under nitrogen for 3 h. After filtration of the solution, the residue from the filtrate was chromatographed on MPLC with CH_2Cl_2 to afford 10, 1.64 g (76% yield).

Deoxygenation of 3-pyridinecarbaldehyde 1-oxide oxime (11) with TBDMSCl-NaI-Zn system to 3-pyridinecarbaldehyde oxime (12)—To a stirred solution of 11 (0.3 g, 2.17 mmol) and imidazole (0.38 g, 5.64 mmol) in MeCN (50 ml) was added TBDMSCl (1.31 g, 8.68 mmol) under nitrogen, and the mixture was stirred at room temperature for 3 h. Then Zn (0.43 g,

6.51 mmol) and NaI (1.30 g, 8.68 mmol) were added in turn to the solution, which became somewhat exothermic. After stirring at room temperature for 1 h, the resulting mixture was further stirred at 60℃ for 1 h, which was allowed to reach room temperature. The white precipitate was filtered off and washed enough with ether. The combined filtrate was poured into a 5% NaOH solution and the resulting white precipitate was filtered off, and washed enough with ether. The organic layer was separated, dried ($MgSO_4$), and after removal of the solvent, 1.0 M Bu_4NF in THF (6.5 ml, 6.51 mmol) was added to the residue and the reaction mixture was stirred under nitrogen at room temperature for 2 h. After evaporation of solvent, the residue was chromatographed with the mixed solvent of CH_2Cl_2 : CH_3COOEt = 10 : 1 to give 12, 0.21 g (78 % yield).

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