A FACILE METHOD FOR THE PREPARATION OF 4-NITROPYRIDINE AND -QUINOLINE DERIVATIVES: REDUCTION OF AROMATIC AMINE N-OXIDES WITH TRIMETHYLPHOSPHITE UNDER IRRADIATION[1]

Chikara Kaneko*, Atsushi Yamamoto, and Michiko Gomi
Faculty of Pharmaceutical Sciences, Kanazawa University,
Takara-machi, Kanazawa, 920, Japan

Abstract —Irradiation ($\geq$300 nm) of pyridine and quinoline 1-oxides having a nitro group at the 4-position in dichloromethane containing trimethylphosphite of relatively high concentration ($\geq 10^{-2}$mol/l) resulted in an almost quantitative formation of the deoxygenated products.

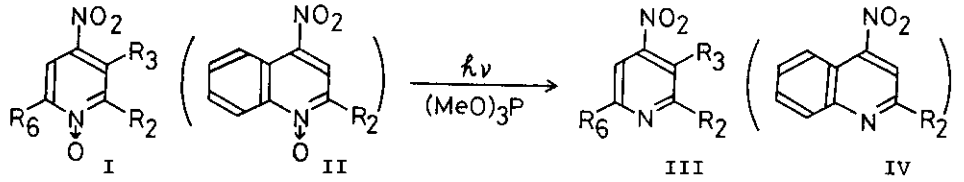
Recent years, synthetic manipulations of the pyridine and quinoline nuclei have been greatly facilitated through the use of the N-oxide function. Consequently, a number of methods have been developed for the deoxygenation of aromatic amine N-oxides. Among many deoxygenation methods so far reported,[2] the most fitted method for a preparative experiment is to treat N-oxides with phosphorous trihalides. However, this method gave undesirable by-products if applied to the deoxygenation of 4-nitropyridine and -quinoline 1-oxides.[3] Thus, for example, when 4-nitropyridine 1-oxide was treated with phosphorous trichloride, 4-chloropyridine was formed as a by-product. In general, the halogenated by-products exhibited quite similar properties with the desired deoxygenation products and, hence, a careful column chromatographic separation of the crude product was necessarily required. Recently, we reported that triphenylphosphine abstracted the oxygen atom efficiently from the N-oxides at room temperature only under irradiation ($\geq$300 nm) and demonstrated that the reaction proceeded by an oxygen transfer from a very-short lived oxaziridine species derived from the photo-excited N-oxide to the phosphine.[4,5,6] However, this method still needed chromatographic purification in order to remove the phosphine and phosphine oxide from the desired product.

In this paper, we report that the use of trimethylphosphite instead of triphenyl-

phosphine in the above reaction provides a simple and facile method for deoxygenation of aromatic amine N-oxides, because the phosphite can now be removed in vacuo readily (bp 111-112°) and the phosphate is soluble in water.

As a typical example, 950 mg (5×10^{-3}mol) of 4-nitroquinoline 1-oxide (IIa) in 500 ml of CH_2Cl_2 in the presence of 806 mg (6.5×10^{-3}mol) of trimethylphosphite was irradiated by a Toshiba 400P high-pressure mercury lamp using a Pyrex filter under nitrogen until the consumption of IIa was complete (ca. 15 min).[7] After irradiation, the whole was washed with water to remove the phosphate, dried over $MgSO_4$, and evaporated in vacuo to give the sufficiently pure 4-nitroquinoline (IVa)(85-90%). In most cases, one recrystallization is enough to obtain a pure sample in a good isolation yield (≳80%). When the deoxygenation products are sublimable such as 4-nitropyridine (Ia) and its methyl homologues, passing of the residue to a short column of silica gel is recommended to remove the phosphite, by which the phosphite is eluted only with hexane-CH_2Cl_2 (1:1 v/v) while the nitro compounds (III or IV) are eluted readily with hexane-CH_2Cl_2 (9:1 v/v).

Table. Deoxygenation of 4-Nitropyridine and -quinoline 1-oxides with Trimethylphosphite under Irradiation.[a]



I II III IV

N-oxide	R_2	R_3	R_6	deoxygenated base[b]	yield %	mp	NMR: in $CDCl_3$ (J in Hz) ring proton	methyl
Ia	H	H	H	IIIa[8]	93	47-48°	H-2: 8.83, d-d (4.6, 1.6) H-3: 7.97, d-d (4.6, 1.6)	—
Ib	CH_3	H	H	IIIb[9]	89	40-42°	H-3: 7.80, s H-5: 7.76, d (5.6) H-6: 8.70, d (5.6)	2.69, s
Ic	H	CH_3	H	IIIc[10]	88	oil picrate, 128-129°	H-2: 8.64, s H-5: 7.66, d (5.2) H-6: 8.60, d (5.2)	2.59, s
Id	CH_3	H	CH_3	IIId	85	38.5-39.5°	H-3: 7.57, s	2.67, s
IIa	H	H	H	IVa[11]	81	92-93°	H-2: 9.03, d (4.5) H-3: 7.77, d (4.5)	—
IIb	CH_3	H	H	IVb	91	78-80°	H-3: 7.70, s	2.81, s

a) The solution of N-oxide in CH_2Cl_2 (10^{-2}M) in the presence of 1.3 mol. equiv. (1.3×10^{-2}M) of the phosphite was irradiated.

b) All deoxygenated bases are purified by passing a short column of silica gel and recrystallized from hexane.

The deoxygenation method with trimethylphosphite under irradiation was applied successfully to 4-nitro-pyridine and -quinoline 1-oxides (I or II) and the results are summarized in the Table.

Since the phosphite and phosphate are both quite inactive reagents in a dark, this method is especially fitted for the deoxygenation of the N-oxide having a labile function.

The essential requisite of this novel deoxygenation reaction is the concentration of the phosphite to be more than 10^{-2}M as demonstrated in our recent works.[6,7,12] Hence, the deoxygenation of any oxide can be pre-examined by NMR spectroscopy, before the actual preparative experiment is carried out. All of the reactions shown in the Table have been examined by this technique in an NMR tube using 10^{-1}– 10^{-2}M $CDCl_3$ solution containing 1.5-2.0 mol equivalent of the phosphite and quantitative formations of the deoxygenated products were assured in all cases. Thus, by an external irradiation, the original spectrum of the N-oxide and the phosphite (δ 3.47, d, J=10.2 Hz) changed to that of the deoxygenated base, the phosphate (δ 3.73, d, J=10.6 Hz), and the recovered phosphite. Since, in this case, the reaction is run under an ordinary atmosphere and a slow photo-induced phosphite-phosphate conversion occurs, 1.5-2.0 mol equivalent of the phosphite should be used.

The wide applicability of this deoxygenation reaction as well as its detailed mechanism will be reported separately.

Acknowledgement. The authors thank the Ministry of Education, Science and Culture, Japan, for Grant-in-Aid for special project research: Chemical Research in Development and Utilization of Nitrogen-Organic Resources (No. 321708).

REFERENCES AND NOTES

1 This paper forms Part XXXI of "Studies on the N-Oxides of π-Deficient N-Heteroaromatics". Part XXX: S. Yamada and C. Kaneko, Tetrahedron, in press.

2 a) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967, pp. 184-206; b) A.R. Katrizky and J.M. Lagowski, "Chemistry of Heterocyclic N-Oxides", Academic Press, New York, 1971, pp 166-231.

3 a) E. Ochiai and I. Suzuki, Chem. Pharm. Bull.(Tokyo), 1954, 2, 247; b) M. Hamana, J. Pharm. Soc. Japan, 1955, 75, 127; c) R.A. Abramovitch and M. Saha,

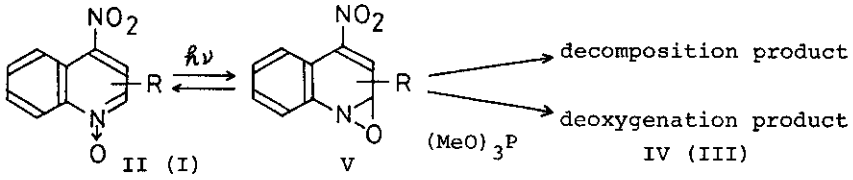
Can. J. Chem., 1966, 44, 1765.

4 C. Kaneko, M. Yamamori, A. Yamamoto, and R. Hayashi, Tetrahedron Lett., 1978, 2799.

5 K. Tokumura, M. Itoh, and C. Kaneko, J. Amer. Chem. Soc., submitted: Symposium of Photochemistry, Abstracts, pp. 64-65, Nov. 20, 1978, Kyoto, Japan.

6 C. Kaneko, A. Yamamoto, M. Yamamori, and R. Hayashi, Symposium of Photochemistry, Abstracts, pp. 66-67, Nov. 20, 1978, Kyoto, Japan: From the detailed studies on the concentration effect of the phosphite and its related trivalent phosphorous compounds upon the efficiency for the deoxygenation reaction, it was demonstrated that the deoxygenation reaction proceeded by an oxygen transfer (under diffusion-controlled) from the very short-lived oxaziridine species derived from the photo-excited N-oxides to these phosphorous compounds.

7 Irradiation of IIa (and the related nitro N-oxides) under identical conditions in the absence of the phosphite needed ca. 10 hr-irradiation for the complete consumption of IIa and any isolable product other than the deoxygenated product (IVa: $\lesssim$ 10%) was obtained. This fact suggests the existence of very facile reversion path from the oxaziridine (V) to IIa. Such reversion of the oxaziridine to the N-oxide has not been observed in the photolyses of quinoline 1-oxides having no nitro group.[4,6]



8 M. Hamana and H. Yoshimura, J. Pharm. Soc. Japan, 1952, 72, 1051.

9 E.V. Brown, J. Amer. Chem. Soc., 1954, 76, 3167.

10 W. Herz and L. Tsai, J. Amer. Chem. Soc., 1954, 76, 4184.

11 a) I. Nakayama, J. Pharm. Soc. Japan, 1951, 71, 1088; b) M. Hamana, J. Pharm. Soc. Japan, 1955, 75, 135.

12 The life-time of the oxaziridine species derived from 6-cyanophenanthridine 5-oxide was determined to be 380 ns (room temp. in ethanol) by flash photolysis.[5]

Received, 30th October, 1978