Chem. Pharm. Bull. 24(8)1839—1841(1976)

UDC 547.821'546.21.04 : 546.762.131.04

Deoxygenation of Heterocyclic N-Oxides by Chromium(II) Chloride

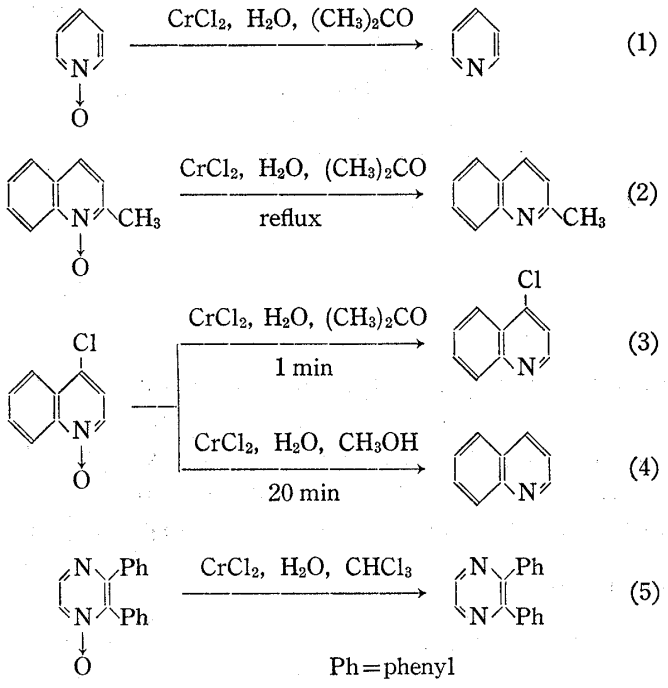
Yasuo Akita, Keiko Misu, Tokuhiro Watanabe, and Akihiro Ohta

Tokyo College of Pharmacy[1]

(Received November 27, 1975)

N-Oxides of pyridine, quinoline, and pyrazine derivatives were reduced with chromium(II) chloride in acetone, methanol, or chloroform at room temperature to give the deoxygenation products in excellent yields. Quinaldine and 2-ethoxyquinoline 1-oxides, possessing an electron donating group at 2-position of the quinoline ring, were not reduced at room temperature, but, under reflux, the reaction gave the deoxygenation products in good yields. In the case of the reaction of 4-chloroquinoline 1-oxide with chromium(II) chloride for 20 min occurred dechlorination and deoxygenation, but for 1 min only deoxygenation. The reaction of 4-nitropyridine 1-oxide and 3-, 4-, and 5-nitroquinoline 1-oxides was not successful.

Various methods have been used to deoxygenate heterocyclic amine oxides and this chemistry has been reviewed.[2-3] Recently, deoxygenation of amine oxides by aqueous titanium trichloride[4] and sulfoxides[5] has been reported. In the present paper reduction of heterocyclic N-oxides by chromium(II) chloride is described. Although chromium(II) chloride is useful in various reductions, this substance has never been used for the deoxygenation of aromatic amine oxides.



Formulae 1—5 exemplify the reduction of amine oxides with chromium(II) chloride. Chromium(II) chloride solution was prepared before use as described by Rosenkranz, *et al.*[6] and acetone, methanol, or chloroform were used as a solvent. Some data for deoxygenation are summarized in Table I and II. Assignment of products was made by direct comparison of their physical data with those of the known compounds and the yields given in the tables are on the purified products.

The typical experimental procedure for quinoline 1-oxide is cited below, the other pyridine and quinoline 1-oxides were treated under the same condition, and the results are shown in Table I. Quinoline 1-oxide dissolved in acetone was added to the chromium(II) chloride solution and the mixture was stirred under nitrogen at room temperature for 20 min. Extraction of the reaction mixture with chloroform after

1) Location: *1432-1, Horinouchi, Hachioji-Shi, Tokyo,*

2) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, pp. 184—209.
3) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, 1971, pp. 166—231.
4) J.M. McCall and R.E. TenBrink, *Synthesis*, **1975**, 335.
5) M.E.C. Biffin, G. Bocksteiner, J. Miller, and D.B. Paul, *Aust. J. Chem.*, **27**, 789 (1974).
6) G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950).

basification with potassium carbonate gave quinoline in 90% yield. Under the same condition, N-oxides of pyridine, picoline, 4-chloropyridine, lepidine, and 2-hydroxy-, 4-hydroxy-, 3-bromo-, and 2-cyano-quinolines gave the deoxygenated products in excellent yields. Deoxygenation of N-oxides of 4-nitropyridine and 3-, 4-and 5-nitro-quinolines was not successful. Namely, under a milder condition the starting material was recovered and only resinous products were obtained by heating.

The starting material was recovered by the reaction of quinaldine 1-oxide with chromium-(II) chloride at room temperature, but, under reflux, the conversion proceeded successfully to give quinaldine in 73% yield. Deoxygenation of 2-ethoxyquinoline 1-oxide at room temperature similarly gave the starting material in 76% yield and a small amount (9%) of 2-ethoxyquinoline, but, under reflux, the reduction gave 2-ethoxyquinoline in an excellent yield. In view of these facts the electron-donating groups at 2-position of the quinoline ring probably interfere with the deoxygenation of N-oxides.

It is also interesting that the reaction of 4-chloroquinoline 1-oxide with chromium(II) chloride for 20 min resulted in dechlorination and that for 1 min gave 4-chloroquinoline. This result is probably due to the high reactivity of 4-position of quinoline ring to nucleophilic reactions.

Table I. Deoxygenation of Pyridine and Quinoline 1-Oxides

Substance	Yield(%)	Substance	Yield(%)
Pyridine 1-oxide	67	2-Chloroquinoline 1-oxide	61
α-Picoline 1-oxide	79	4-Chloroquinoline 1-oxide	67[b] (63)[c]
4-Chloropyridine 1-oxide	41	2-Ethoxyquinoline 1-oxide	9 (76)[d]
4-Nitropyridine 1-oxide	—		91[e]
Quinoline 1-oxide	90	3-Bromoquinoline 1-oxide	96
Quinaldine 1-oxide	—(73)[a]	2-Cyanoquinoline 1-oxide	69
Lepidine 1-oxide	91	3-Nitroquinoline 1-oxide	—
2-Hydroxyquinoline 1-oxide	55	4-Nitroquinoline 1-oxide	—
4-Hydroxyquinoline 1-oxide	95	5-Nitroquinoline 1-oxide	—

a) under reflux for 2 hr
b) Reaction time is 1 min.
c) quinoline obtained, for 20 min
d) 2-Ethoxyquinoline 1-oxide was recovered.
e) under reflux for 30 min

Deoxygenation of N-oxides of pyrazines also takes place readily. Data for some pyrazine N-oxides are summarized in Table II. Under the same reaction condition for quinoline 1-oxide, 2-phenylpyrazine 4-oxide and 2-chloro-5-phenylpyrazine 1-oxide gave the deoxygenated products in 75% and 86.5% yield, respectively. Owing to less solubility in acetone, 2-chloro-5-phenylpyrazine 4-oxide and 2,3-diphenylpyrazine 1-oxide were suspended in

Table II. Deoxygenation of Pyrazine mono N-oxides

Substance	Deoxygenation product	
	Yield[a] (%)	Yield[b] (%)
2-Phenylpyrazine 4-oxide[c]	75	
2-Chloro-5-phenylpyrazine 1-oxide[c]	86.5	
2-Chloro-5-phenylpyrazine 4-oxide[c]	58	69
2,3-Diphenylpyrazine 1-oxide	39	86
2,5-Diphenylpyrazine 1-oxide		78

a) reaction solvent: MeOH, acetone
b) reaction solvent: $CHCl_3$
c) Akihiro Ohta, *et al.*, Abstracts of Papers, 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April, 1975, II p. 73.

acetone, but were reduced to give their deoxygenated products in 58% and 39% yield. The reaction condition was therefore a little modified, and chloroform was used as a solvent for their reactions. The N-oxides were dissolved in chloroform, its mixture with aqueous chromium(II) chloride solution was stirred at room temperature for 15 min, while bubbling nitrogen gas, to give deoxygenated compounds in 69% and 86% yield, respectively. 2,5-Diphenylpyrazine 1-oxide was also reduced to give 2,5-diphenylpyrazine under the same condition.

Chromim (II) chloride is useful for reduction of α-haloketones to parent ketones, for deoxygenation of epoxides to olefins, and dehalogenation of imide chlorides to imines. These various reductions and dehalogenations by chromium(II) chloride have been reviewed.[7] Our results seem to indicate that chromium(II) chloride is a preparatively useful reagent for deoxygenation of aromatic amine oxides.

Experimental

Chromium(II) Chloride Solution——The aqueous $CrCl_2$ solution was prepared just before use as described by Rosenkranz, *et al.*,[6] and dark blue solution was kept under nitrogen.

Deoxygenation of Quinoline 1-Oxide——To a solution of quinoline 1-oxide (725 mg, 5 mmol) in acetone (10 ml), the aqueous $CrCl_2$ (40 ml) was added at once and the mixture was stirred under nitrogen at room temperature. The color changed to brown immediately. After 20 min, the reaction mixture was basified with K_2CO_3 and extracted repeatedly with $CHCl_3$. The combined organic phase was dried over Na_2SO_4, concentrated, and the residue was distilled. Yield, 578 mg (90%). The spectral properties and thin-layer chromatography of the distillate were identical to those of quinoline.

Deoxygenation of Quinaldine 1-Oxide——To a solution of quinaldine 1-oxide (318 mg, 2 mmol) in acetone (5 ml), $CrCl_2$ solution (20 ml) was added and the mixture was stirred in a nitrogen stream under reflux for 2 hr. The reaction mixture was basified with K_2CO_3, extracted with CH_2Cl_2, and worked up similarly as for quinoline to give 214 mg (73%) of quinaldine.

4-Chloroquinoline from 4-Chloroquinoline 1-Oxide——A mixture of 4-chloroquinoline 1-oxide (179 mg, 1 mmol) in acetone (2 ml) and $CrCl_2$ solution (3 ml) was stirred for 1 min under nitrogen at room temperature. The $CHCl_3$ extraction in the usual manner gave the amine, which was purified by column chromatography over silica gel to give 110 mg (67%) of 4-chloroquinoline.

Quinoline from 4-Chloroquinoline 1-Oxide——To 4-chloroquinoline 1-oxide (700 mg, 5 mmol) in MeOH (10 ml), the $CrCl_2$ solution (100 ml) was added and the mixture was stirred for 20 min under nitrogen at room temperature. The reaction mixture was worked up similarly to give 518 mg (63%) of quinoline.

Deoxygenation of 2,3-Diphenylpyrazine 1-Oxide——A solution of 2,3-diphenylpyrazine 1-oxide (125 mg, 0.5 mmol) dissolved in $CHCl_3$ (10 ml), added with $CrCl_2$ (10 ml), was stirred under nitrogen at room temperature. After 15 min, the organic layer was separated and the aqueous layer was extracted repeatedly with $CHCl_3$. The combined organic phase was dried over Na_2SO_4, and concentrated to dryness. The residual amine was purified by column chromatography over silica gel and recrystallized from MeOH to 90 mg (86%) of 2,3-diphenylpyrazine (mp 119°).

7) *a*) J.R. Hanson and E. Premuzic, *Angew. Chem. Int. Ed.*, **7**, 247 (1968); *b*) M. Fieser and L.F. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York (1967).