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4-Dimethylaminopyridine *N*-Oxide as an Efficient Oxidizing Agent for Alkyl Halides

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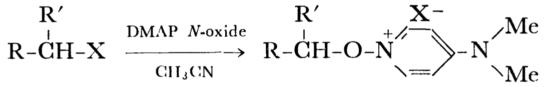
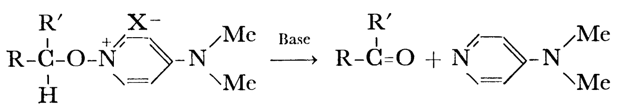
Synopsis. Various types of alkyl halides were converted into aldehydes or ketones in high yields with 4-dimethylaminopyridine *N*-oxide in the presence or absence of DBU.

Oxidation of alkyl halides with pyridine *N*-oxide[1] or trimethylamine *N*-oxide[2] has been known as a unique method to obtain carbonyl compounds. However, the former is only applicable to the relatively active substrates such as benzyl bromide[1a] because of the low nucleophilicity of pyridine *N*-oxide. While trimethylamine *N*-oxide can oxidize alkyl bromides and iodides, the yields are not satisfactory. In this paper is described the use of 4-dimethylaminopyridine *N*-oxide (DMAP *N*-oxide)[3] as an efficient oxidizing agent to afford aldehydes or ketones from primary or secondary alkyl halides, and α-keto esters from α-bromo esters, respectively.

The reaction was carried out in two steps, salt formation (1) and deprotonation (2).


(1)


(2)

X = Br or Cl

Acetonitrile was used as the solvent in which DMAP *N*-oxide was moderately soluble and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proved to be the best base for the deprotonation step (2). Alkyl halides were refluxed with the *N*-oxide in acetonitrile until the substrates were consumed, and then DBU was added. The reaction was followed by GLC by using appropriate internal standards. The results are summarized in Table 1.

Benzylic halides were easily oxidized to give the corresponding carbonyl compounds in quantitative yields. Primary alkyl halides (bromide and chloride) were converted into aldehydes. Secondary alkyl bromide also reacted to afford a ketone quantitatively. Cyclohexyl bromide, however, gave cyclohexanone in very low yield, and the formation of a large amount of cyclohexene was observed in the first step (1), though DMAP *N*-oxide is known to have a small pK_a value (3.88)[4] (entry 9).[5]

2-Formylpyridine was obtained in 82% yield by only heating 2-chloromethylpyridine hydrochloride[6] with three molar equivalents of the *N*-oxide in acetonitrile (entry 5).

Sliwa *et al.*[1b] reported the oxidation of α-bromo esters with pyridine *N*-oxide, but this method required the addition of silver nitrate to attain the effective formation of pyridinium salt. With 2.5 equivalents of DMAP *N*-oxide, however, α-bromo esters were rapidly oxidized to α-keto esters.

As is shown in Table 2, not only phenylglyoxylic acid ester but also aliphatic α-keto esters were produced in high yields.

Dimethyl sulfoxide is known to oxidize alkyl halides in a similar fashion.[7] However, it usually requires high reaction temperature (100—150 °C) and is only applicable to primary alkyl iodides, tosylates, or reactive substrates such as benzyl halides.[8] For the

Table 1. Oxidation of alkyl halides[a)]

	Substrate	Salt formation		Deprotonation		Product	Yield/%[b)]
		Temp	Time	Temp	Time		
1	$C_6H_5CH_2Br$	RT	1.5 h[c)]	Refl	20 min	C_6H_5CHO	>98[d)]
2	$C_6H_5CH_2Cl$	RT	2 h	Refl	20 min	C_6H_5CHO	>98
3	$C_6H_5CH(Br)CH_3$	Refl	8 min	Refl	5 h	$C_6H_5COCH_3$	>98
4	$C_6H_5CH(Br)C_6H_5$	Refl	10 min	Refl	3.3 h	$C_6H_5COC_6H_5$	>98
5	$C_5H_4NCH_2Cl\cdot HCl$[e)]			Refl	3 h[f)]	$C_5H_4N\cdot CHO$[g)]	82
6	$C_8H_{17}Br$	Refl	15 h	Refl	40 min	$C_7H_{15}CHO$	83
7	$C_8H_{17}Cl$	Refl	10 h	Refl	1 h	$C_7H_{15}CHO$	88
8	$C_3H_7CH(Br)CH_3$	Refl	40 min	Refl	16 h	$C_3H_7COCH_3$	>98
9	$C_6H_{11}Br$[h)]	Refl	6.5 h	Refl	2 h	$C_6H_{10}O$[i)]	13[j)]

a) Substrate (0.3 mmol), DMAP *N*-oxide (0.36 mmol), DBU (0.36 mmol), and CH_3CN (0.5 ml) were used except for entry 5. b) GLC yield. c) In a separate experiment, the salt, 1-benzyloxy-4-dimethylaminopyridinium bromide, was isolated. Mp 115 °C (sinter), 141 °C (decomp). Found: C, 54.50; H, 5.51; N, 9.16%. Calcd for $C_{14}H_{17}BrN_2O$: C, 54.38; H, 5.54; N, 9.06%. d) An 87% or 30% yield of benzaldehyde has been reported in the oxidation of benzyl bromide with pyridine *N*-oxide[1a] or with trimethylamine *N*-oxide,[2] respectively. e) 2-Chloromethylpyridine hydrochloride. f) Three molar equivalents of DMAP *N*-oxide was used *vs.* substrate without DBU. g) 2-Formylpyridine. h) Cyclohexyl bromide. i) Cyclohexanone. j) Cyclohexene (60—70%) was also produced.

Table 2. Oxidation of α-bromo esters[a)]

Substrate	Temp	Time/min	Product	Yield/%[b)]
$CH_3CH(Br)CO_2CH_3$	Refl	20	$CH_3COCO_2CH_3$	>90
$C_6H_{13}CH(Br)CO_2CH_3$	Refl	35	$C_6H_{13}COCO_2CH_3$	85[c)]
$C_6H_5CH(Br)CO_2C_2H_5$	Refl	26	$C_6H_5COCO_2C_2H_5$	92

a) Substrate (0.3 mmol), DMAP *N*-oxide (0.75 mmol), and CH_3CN (0.5 ml) were used. b) GLC yield. c) Isolated yield.

oxidation of α-bromo ester by dimethyl sulfoxide, one example is reported.[9)]

The high yields, mildness of the reaction conditions, and applicability to wide variety of alkyl halides are considered to make the present method synthetically useful one.

Experimental

All starting alkyl halides are commercially available except for 2-chloromethylpyridine hydrochloride[6)] and α-bromo esters which were obtained by esterification of the corresponding α-bromo acids. Products were identified with authentic samples by the comparison of their NMR and/or GLC data.

Two typical examples of oxidation are described below.

Oxidation of 2-Bromopentane. A mixture of 2-bromopentane (38 μl), DMAP *N*-oxide (41 mg), and absolute acetonitrile (0.5 ml) was refluxed for 40 min. Then, DBU (57.3 μl) was added and the reflux was continued. After 16 h quantitative formation of 2-pentanone was observed on GLC by the addition of toluene as an internal standard.

Oxidation of Methyl 2-Bromooctanoate. A mixture of the bromo ester (167 mg), DMAP *N*-oxide (201 mg), and acetonitrile (2 ml) was refluxed for 35 min. After cooling 1.1 equivalents of hydrochloric acid in acetonitrile (1 ml) was added. The resulting mixture was passed through a short silica gel column, concentrated, and chromatographed on preparative TLC (SiO_2, Merck) with benzene giving methyl 2-oxopentanoate[10)] (103 mg, 85%). NMR ($CDCl_3$) δ 0.89 (t, J=5.0 Hz, 3H), 1.0—2.0 (m, 8H), 2.84 (t, J=7.0 Hz, 2H), and 3.88 (s, 3H).

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