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Short Communication

Effect of Metal Ions on the Bromination of 3,5-Dimethylpyridine-N-oxide in Acetic Acid

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Summary. The influence of metal ions on γ-bromination and N–O bond reduction of 3,5-dimethylpyridine-N-oxide (**2**) in acetic acid is described.

Keywords. Derivatives of 3,5-dimethylpyridine; Bromination; Reduction; Metal ions.

Effekt von Metallionen auf die Bromierung von 3,5-Dimethylpyridin-N-oxid in Essigsäure (Kurze Mitt.)

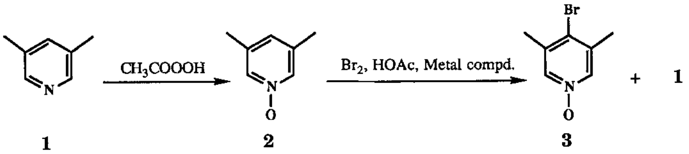
Zusammenfassung. Es wird der Einfluß von Metallionen auf die γ-Bromierung und die Reduktion der N–O-Bindung von 3,5-Dimethylpyridin-N-oxid in Essigsäure beschrieben.

To avoid difficult syntheses of various 4-bromopyridine-N-oxides [1–5] $Tl(OAc)_3$ was used as a bromination supporting compound under mild conditions and with good yields [6, 7]. Now I want to report results achieved in the bromination of 3,5-dimethylpyridine-N-oxide (**2**) in the presence of other metal salts.

The regioselective γ-bromination of **2** is compared with the competitive reduction of the N–O bond. The conditions of the reaction, which is fairly affected by the reaction temperature and the amount of a metal salt and bromine, were chosen so that the conversion was not too high for better evaluation of the experimental results (Table 1).

The mechanism of bromination, e.g. in the presence of $Hg(OAc)_2$ in acetic acid, is explained either by the formation of the brominating acetyl hypobromide [8, 9] or by a mechanism involving initial mercuration in the rate-determining step [10, 11]. For non-polar solvents as CCl_4 a radical mechanism was postulated [12]. On the contrary, the formation of the Tl–O bond in the complex of pyridine-N-oxide with $TlBr_3$ was proved by X-ray diffraction analysis [13].

The reaction (see formula scheme) was carried out as a one-pot synthesis. 3,5-Dimethylpyridine (**1**) was oxidized by peracetic acid [14] with 97.5% yield and a metal salt and acetic acid were added to the heated reaction mixture. The bromination with 1.1 equiv. of bromine was carried out for 10 h. The amount of the metal salt was chosen according to the oxidation state of the metal ion [1 equiv. of M^+, 0.5 equiv. of M^{2+}, 0.33 equiv. of M^{3+} and 0.25 equiv. of M^{4+} (M = metal)]. It



is probably not possible to compare the influence of cations with different oxidation states but the choice seems to be the most acceptable.

Results and Discussion

The bromination was carried out with the series of metal compounds and their effect on the course of the reaction is described in Table 1. Three principal products (**1**–**3**) were isolated from the reaction mixture by flash chromatography (4-bromo-3,5-dimethylpyridine as the product of the reduction of **3** was not isolated). By comparison of their yields by TLC it is possible to classify metal salts according to their abilities to support bromination and reduction. Most of the metal compounds used were acetates, however, some oxides, hydroxides, chlorides, bromides and nitrates were used as well. Acetates added gave the same results as the same acetates formed *in situ* from oxides. Bromides, chlorides and nitrates of one cation were less efficient bromination supporting agents than acetates (two examples in Table 1). No significant influence of crystal water of metal salts was found. The results might be compared to those of the reaction without a metal salt or with an addition of water. Both the high yield of **3** in the presence of $Co(OAc)_2$ and the low yields of **3** in the presence of $Cu(OAc)_2$ or $Fe(OH)_3$ (lower than in the reaction without a metal salt) deserve special attention.

From the results in Table 1 it is possible to consider Hg^{2+}, Hg^+, Pb^{2+}, Pb^{4+}, Bi^{3+}, Cd^{2+}, Co^{2+}, Zn^{2+} and Ag^+ acetates to be very good bromination supporting compounds. The use of a two- or three-fold molar excess of a metal salt enables to carry out the γ-bromination of the pyridine-N-oxide system with high yields [e.g. $Pb(OAc)_2$ used in two molar excess gave 67% of **3** – see Exp. Part].

Experimental Part

NMR spectra were obtained on a Bruker WP 80 SY and TLC results on a Camag TLC Scanner II (UV 254 nm; mobile phase: chloroform – methanol (30:1); HPTLC plates Merck Silica Gel 60, S_{254}, pre-coated).

General Procedure

3,5-Dimethylpyridine (16 ml, 0.14 mol) was stirred in a 250 ml round-bottom flask with a mechanical stirrer and 32% peracetic acid (31.1 ml, 0.15 mol) was dropped at such rate that the temperature reached 85 °C which was then maintained. Stirring was continued for 120 min.

Then, glacial acetic acid (100 ml) and metal salt (Table 1) were added at 70 °C. Bromine (7.7 ml, 0.15 mol) was immediately added dropwise to the reaction mixture during 20 minutes and the temperature and stirring were held for 10 h. Then the reaction mixture was cooled and neutralized by 10*M* NaOH to *pH* 8–9. After a multiple extraction of the mixture by $CHCl_3$ the chloroform solution was analyzed by TLC to the standards (mobile phase: $CHCl_3$:methanol = 10:1).

Table 1. Bromination of 3,5-dimethylpyridine-N-oxide (**2**)

Metal compd.	Equiv. of metal compd.	TLC yields of compounds (%)[d]		
		3	**2**[c]	**1**[b]
$NaOAc\cdot 3H_2O$	1	24.3	43.2	22.5
$Mg(OAc)_2\cdot 4H_2O$	0.5	26.1	38.7	24.3
$Ca(OAc)_2\cdot H_2O$	0.5	28.0	45.0	12.8
$Sr(OAc)_2\cdot 0.5H_2O$	0.5	27.2	43.4	14.5
$Ba(OAc)_2$	0.5	26.4	39.2	15.2
$La(OAc)_3\cdot 1.5H_2O$	0.33	22.4	40.8	16.8
$Cr(OAc)_3$	0.33	23.8	51.0	9.4
$Mn(OAc)_2\cdot 4H_2O$	0.5	22.5	38.7	29.7
$Fe(OH)_3$[a]	0.33	14.4	57.6	18.0
$Co(OAc)_2\cdot 4H_2O$	0.5	42.4	26.4	11.2
$Ni(OAc)_2\cdot 4H_2O$	0.5	23.4	40.5	27.0
$Cu(OAc)_2\cdot 2H_2O$	0.5	15.2	37.6	27.2
$Zn(OAc)_2\cdot H_2O$	0.5	33.6	35.2	11.2
$AgOAc$	1	33.6	20.8	25.6
$Cd(OAc)_2\cdot 2H_2O$	0.5	43.2	26.1	20.7
$HgOAc$	1	39.2	25.6	15.2
$Hg(OAc)_2$	0.5	45.6	16.8	17.6
$HgCl_2$	0.5	35.1	22.5	32.4
$Al(OAc)_2(OH)$	0.33	25.2	42.3	22.5
SnO	0.5	23.0	38.2	23.8
SnO_2	0.25	26.3	36.6	22.1
$Pb(OAc)_2$	0.5	41.6	28.0	10.4
PbO_2	0.25	42.0	12.8	20.3
$Pb(NO_3)_2$	0.5	28.9	37.4	18.7
Sb_2O_3	0.33	28.8	44.1	16.2
Bi_2O_3	0.33	39.2	32.8	8.8
H_2O (8 equiv.)		17.8	46.8	20.4
–		21.2	55.2	9.3

[a] Prepared from $FeCl_3$ and NaOH before the reaction.

[b] The sum of the non-reacted **1** (2.5%) from the first step and the product of the reduction of **2**.

[c] The non-reacted amount of **2** in the second step. The yield of **2** in the oxidation of **1** was 97.5% (TLC).

[d] The yields are calculated to 3,5-dimethylpyridine (**1**) and the rest of percentage belongs to unidentified products.

3,5-Dimethylpyridine-N-oxide (2)

The compound was prepared according to the first step in the general procedure. After 120 min of stirring the reaction mixture was evaporated *in vacuo* at 120 °C and neutralized by 1*M* NaOH. Then, the crude product was extracted with CH_2Cl_2 and the organic solution was dried with $MgSO_4$ and concentrated *in vacuo*. The yield of hygroscopic crystals after recrystallization from benzene was 77%. M.p. 102–104 °C. ^1H NMR ($CDCl_3$/*TMS*): $\delta = 2.21$ (6 H), 7.25 (1 H), 8.89 (2 H).

4-Bromo-3,5-dimethylpyridine-N-oxide (**3**)

The compound was prepared under the conditions of the general procedure with two equiv. of Pb(O*Ac*)$_2$. After neutralization by NaOH the crude product was filtered and recrystallized in a mixture of $CHCl_3$ and petroleum ether (5:1). The yield of **3** was 67% (98% purity by TLC). M.p. 197–199 °C. ^{1}H NMR ($CDCl_3$/*TMS*): $\delta = 2.36$ (dd. 6 H), 8.06 (qq. 2 H).

References

[1] Van Ammers M., Den Hertog H. J., Haase B. (1962) Tetrahedron **18**: 227
[2] Ochiai E., Okamoto T. (1947) Yakugaku Zasshi **67**: 86; (1951) Chem. Abstr. **45**: 9059
[3] Jerchel D., Fischer H., Thomas K. (1956) Chem. Ber. **12**: 2921
[4] Den Hertog H. J., Combé W. P. (1951) Rec. Trav. Chim. **70**: 581
[5] Ochiai E., Ito T., Okuda S. (1951) Yakugaku Zasshi **71**: 591; (1952) Chem. Abstr. **46**: 980
[6] Buchmann G. (1961) Z. Chem. **1**: 84
[7] Saito H., Hamana M. (1979) Heterocycles **12**: 475
[8] Bockemüller W., Hoffmann F. W. (1935) Liebigs Ann. Chem. **519**: 165
[9] Arnold R. T., Campos M. M., Lindsay K. L. (1953) J. Am. Chem. Soc. **75**: 1044
[10] Rao M. D. P., Ahmad M., Kanungo T. K. (1983) Indian Chem. Sect. **A22**: 699
[11] Ukay T., Yamamoto T., Hirano S. (1953) Yakugaku Zasshi **73**: 823; (1954) Chem. Abstr. **48**: 9946
[12] Ouertani M., Girard P., Kagan H. B. (1982) Bull. Soc. Chim. Fr. (**9–10**): 327
[13] Bermejo M. R., Castineiras A., Garcia-Vazquez J. A., Hiller W., Strähle J. (1991) J. Crystallogr. Spectrosc. Res. **21**: 93
[14] Mosher H. S., Turner L., Carlsmith A. (1963) Org. Synth. Coll. Vol. **4**: 828

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