New Aspect of Methanesulfonyl Chloride: Unusual Deoxygenations of Pyridine *N*-Oxides with Methanesulfonyl Chloride and Triethylamine

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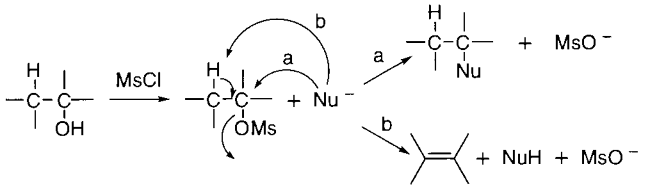
Treatment of several pyridine *N*-oxides with an excess of methanesulfonyl chloride and triethylamine brought about a deoxygenation reaction to give efficiently the corresponding reduction products without chlorination of the pyridine nucleus.

Methanesulfonyl chloride (MsCl) is one of the standard reagents most frequently used in organic synthesis. The major usage is the conversion of hydroxyl group into a leaving group, which is usually accompanied with substitution (path a) or elimination (path b) reaction, to be removed as a mesylate anion.[1] In addition, there is another minor role of protection for the hydroxyl (including phenol) and amino groups as well.[2] Anyway, the utilization of methanesulfonyl chloride is thought to be restricted to the above two subjects to the best of our knowledge.



In the course of our synthetic studies[3] on the macrocyclic marine alkaloids haliclamines,[4] we encountered a very interesting phenomenon concerning the reaction using methanesulfonyl chloride, which could never be explained by the usual mechanism for removal as the mesylate anion. When the pyridyl alcohol such as **1**[3] was treated with methanesulfonyl chloride and triethylamine (Et_3N) and subsequent *m*-chloroperbenzoic acid (*m*-CPBA), pyridine *N*-oxido mesylate **2**[5] was predictably obtained in 75% yield (Scheme 1). On the other hand, an exchange of the reaction sequence unexpectedly resulted in a deoxygenation of the pyridine *N*-oxide together with a normal mesylation of the hydroxyl group. At that time, an excess of methanesulfonyl chloride and triethylamine have been used in the mesylation and deoxygenation of *N*-oxido alcohol **3**. Generally, deoxygenations of pyridine *N*-oxides with such chlorine-containing dehydrating reagents as PCl_5, $POCl_3$, SO_2Cl_2, and $SOCl_2$ *etc.* suffer a chlorination of the pyridine nucleus.[6] It is thought that such a behavior of methanesulfonyl chloride has ever been unprecedented in the

Scheme 1.

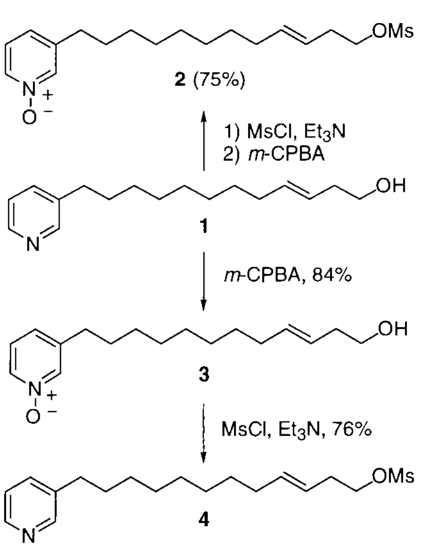
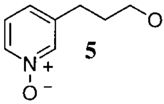
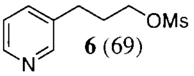
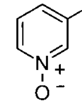
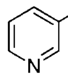
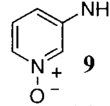
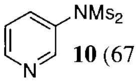
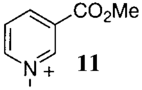
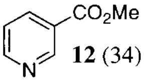
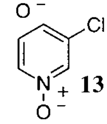
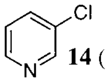
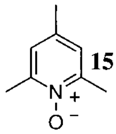
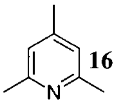
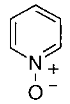
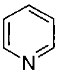
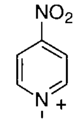


Table 1. Deoxygenations of Pyridine *N*-Oxide Derivatives with Methanesulfonyl Chloride and Triethylamine System[a]

entry	substrate	product (% yield)[b]
1	**3**	**4** (76)
2	 **5**	 **6** (69)
3	 **7**	 **8** (84)
4[c]	 **9**	 **10** (67)
5[d]	 **11**	 **12** (34)
6[d]	 **13**	 **14** (10)
7	 **15**	 **16** (95)
8	 **17**	 **18** (30)
9[d]	 **19**	**19** (72)

[a] Substrates were treated with MsCl (9 equiv) and Et_3N (12 equiv) in CH_2Cl_2 at 0 °C ~ rt for 1-5 h under N_2 atmosphere followed by standard workup, unless otherwise noted therein. [b] Isolated yield. [c] This reaction was carried out with MsCl (20 equiv) and Et_3N (30 equiv) in CH_2Cl_2–CH_3CN (1:1). [d] These reactions were performed for 18 h.

literature. In this paper we report the unusual deoxygenations[7] of various pyridine *N*-oxides[8] with the methanesulfonyl chloride and triethylamine system as a novel aspect of methanesulfonyl chloride.

A variety of pyridine *N*-oxides[9] were subjected to the deoxygenation (Table 1). *N*-Oxido alcohol **5** with a shorter side chain than **3** similarly underwent the deoxygenation accompanied with mesylation of the hydroxyl group (entry 2). It has been found that even the 3-picoline *N*-oxide (**7**) possessing no hydroxyl group affords the deoxygenated 3-picoline (**8**) in the same manner (entry 3), which means that the presence of hydroxyl group in the substrate is not necessarily requisite for the deoxygenation. The *N*-oxide **9** involving the electron-donating amino group provided the deoxygenated product **10** in 67% yield, while both the *N*-oxides **11** and **13** containing the electron-withdrawing methoxycarbonyl and chloro groups, respectively, gave somewhat lower yields (entries 4–6). These facts imply that an electron density on the pyridine ring may be implicated in the reactivity of the deoxygenation with methanesulfonyl chloride and triethylamine. The *N*-oxide **15** with a different substitution pattern and pyridine *N*-oxide (**17**) itself were also deoxygenated to the γ-collidine (**16**) and pyridine (**18**) in high and modest yields, respectively (entries 7 and 8), although the strong electron-withdrawing 4-nitro *N*-oxide **19** resulted in recovery of the starting material (entry 9).

In summary we have demonstrated that methanesulfonyl chloride and triethylamine, inexpensive and popular reagents, can bring about the deoxygenation reaction of various pyridine *N*-oxides under mild conditions. This discovery extends the utility of the methanesulfonyl chloride in addition to the conventional use as leaving and protective groups in organic synthesis. The scope and limitations of this deoxygenation and the reaction mechanism[10] are under investigation in our laboratory.

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References and Notes

1 R. T. Morrison and R. N. Boyd, "Organic Chemistry, 6th ed," Prentice-Hall, Inc., Englewood Cliffs, NJ (1992), Chap. 6, p. 233.

2 T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis, 2nd ed," John Wiley & Sons, Inc., New York (1991).

3 Y. Morimoto and C. Yokoe, *Tetrahedron Lett.*, **38**, 8981 (1997).

4 N. Fusetani, K. Yasumuro, S. Matsunaga, and H. Hirota, *Tetrahedron Lett.*, **30**, 6891 (1989).

5 All new compounds in this paper were satisfactorily characterized by ^{1}H and ^{13}C NMR, IR, MS, and HRMS spectra. The spectroscopic data of some compounds **2–4** and **10** are indicated as follows: **2**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11–8.04 (1H, m), 8.09 (1H, s), 7.20 (1H, t, *J* = 7.3 Hz), 7.12 (1H, d, *J* = 7.7 Hz), 5.57 (1H, dt, *J* = 15.3, 6.7 Hz), 5.36 (1H, dt, *J* = 15.2, 6.8 Hz), 4.21 (2H, t, *J* = 6.8 Hz), 3.01 (3H, s), 2.58 (2H, t, *J* = 7.7 Hz), 2.44 (2H, q, *J* = 6.8 Hz), 2.00 (2H, q, *J* = 6.7 Hz), 1.61 (2H, quintet, *J* = 7.3 Hz), 1.40–1.22 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 138.9, 136.7, 134.8, 126.7, 125.4, 123.4, 69.5, 37.4, 32.6, 32.4, 32.3, 30.2, 29.2, 29.15, 29.09, 28.9, 28.8; IR (neat) 1350, 1170 cm^{-1}; CI-MS *m/z* 356 [$(M + H)^+$]; CI-HRMS calcd for $C_{18}H_{30}O_4NS$ [$(M + H)^+$] 356.1896, found 356.1905. **3**, mp 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (2H, br s), 7.23 (1H, t, *J* = 7.3 Hz), 7.17 (1H, d, *J* = 7.8 Hz), 5.54 (1H, dt, *J* = 15.5, 6.9 Hz), 5.38 (1H, dt, *J* = 15.5, 6.8 Hz), 3.62 (2H, t, *J* = 6.3 Hz), 2.59 (2H, t, *J* = 7.6 Hz), 2.26 (2H, q, *J* = 6.2 Hz), 2.00 (2H, q, *J* = 6.6 Hz), 1.67–1.53 (2H, m), 1.40–1.17 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 139.1, 136.8, 134.0, 127.4, 125.9, 125.5, 62.0, 36.0, 32.7, 32.5, 30.2, 29.3, 29.2, 28.9, 28.8; IR ($CHCl_3$) 3340, 1602 cm^{-1}; EI-MS *m/z* 277 (M^+); EI-HRMS calcd for $C_{17}H_{27}O_2N$ (M^+) 277.2042, found 277.2031. **4**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (2H, br s), 7.53 (1H, d, *J* = 7.7 Hz), 7.24 (1H, dd, *J* = 7.6, 4.9 Hz), 5.57 (1H, dt, *J* = 15.2, 6.7 Hz), 5.36 (1H, dt, *J* = 15.2, 6.8 Hz), 4.21 (2H, t, *J* = 6.8 Hz), 3.00 (3H, s), 2.62 (2H, t, *J* = 7.7 Hz), 2.44 (2H, q, *J* = 6.5 Hz), 2.00 (2H, q, *J* = 6.6 Hz), 1.62 (2H, quintet, *J* = 7.3 Hz), 1.42–1.18 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 146.7, 138.3, 136.3, 134.9, 123.4, 69.6, 37.5, 33.0, 32.5, 32.4, 31.0, 29.31, 29.29, 29.2, 29.1, 29.0; IR (neat) 1578, 1355 cm^{-1}; EI-MS *m/z* 339 (M^+); EI-HRMS calcd for $C_{18}H_{29}O_3NS$ (M^+) 339.1868, found 339.1887. **10**, mp 190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (1H, dd, *J* = 4.8, 1.3 Hz), 8.63 (1H, d, *J* = 2.4 Hz), 7.70 (1H, ddd, *J* = 8.2, 2.6, 1.6 Hz), 7.44 (1H, dd, *J* = 8.2, 4.8 Hz), 3.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 151.1, 137.9, 130.7, 124.3, 42.8; IR (nujol) 1343, 1150 cm^{-1}; EI-MS *m/z* 250 (M^+); EI-HRMS calcd for $C_7H_{10}O_4N_2S_2$ (M^+) 250.0082, found 250.0102.

6 a) R. A. Abramovitch and J. G. Saha, *Adv. Heterocycl. Chem.*, **6**, 229 (1966). b) M. R. Grimmett, *Adv. Heterocycl. Chem.*, **58**, 271 (1993). For example of the deoxygenation with chlorine-containing reagent without chlorination of the pyridine nucleus, see: c) A. Katritzky and C. W. Rees, "Comprehensive Heterocyclic Chemistry," Pergamon Press, Oxford (1984), Vol. 2, p. 261.

7 For the relevant deoxygenations of pyridine *N*-oxide derivatives employing sulfur-containing reagents, see: a) F. A. Daniher and B. E. Hackley, Jr., *J. Org. Chem.*, **31**, 4267 (1966). b) B. F. Bonini, G. Maccagnani, G. Mazzanti, and P. Pedrini, *Tetrahedron Lett.*, **1979**, 1799. c) G. A. Olah, M. Arvanaghi, and Y. D. Vankar, *Synthesis*, **1980**, 660. d) D. J. R. Massy and A. McKillop, *Synthesis*, **1996**, 1477.

8 For reviews on the chemistry of pyridine *N*-oxides, see: a) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953). b) E. N. Shaw, Pyridine and Derivatives Part Two in "The Chemistry of Heterocyclic Compounds," ed by E. Klingsberg, Interscience Publishers, Inc., New York (1961), Chap. IV, p. 97.

9 The pyridine *N*-oxides **5**, **9**, **11**, **13**, and **15** except for the commercially available **7**, **17**, and **19** were prepared from the corresponding pyridine precursors via *m*-CPBA oxidation.

10 For the purpose of obtaining the mechanistic information, we have tried performing the deoxygenation of **7** with $BnSO_2Cl$ in place of MsCl. Although the deoxygenation itself proceeded even with $BnSO_2Cl$, such a compound concerning the leaving moiety as manifested the reaction mechanism could not be caught.