DEMETHYLATION OF METHOXYPYRIDINES WITH SODIUM TRIMETHYLSILANETHIOLATE

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Abstract — Demethylation of methoxypyridines was accomplished in 55–87% yield by use of ~1.5–2.5 equivalents of $NaSSiMe_3$ in 1,3-dimethyl-2-imidazolidinone at 120–180 °C. This method was found applicable to a methoxyquinoline and methoxypyridines containing a second substituent, such as Cl, OMe, and COOMe.

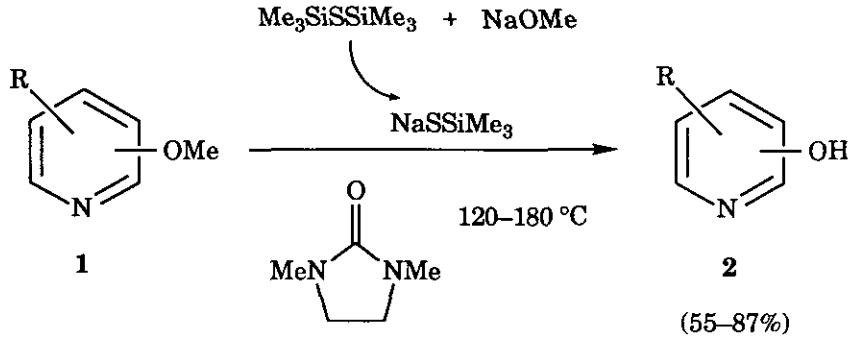
Protection of a hydroxyl group attached to a pyridine nucleus by methylation is a commonly used tool during the synthesis of heterocyclic compounds.[1–7] The methyl group in the resultant methoxypyridines often has to be removed later. Limited methods have been reported for the demethylation of methoxypyridines,[1–5,7,8] wherein none involves systematic studies.

Reagents for demethylation of methoxypyridines can be classified into the following categories: mineral acids,[9–11] alkylthiolates,[2,12] acylating agents,[8] and silicon compounds.[1,13,14] Recently, sodium trimethylsilanethiolate ($NaSSiMe_3$) has been used for the bis-*O*-demethylation of aryl methyl ethers.[15] To understand more about the utility of the silicon-containing reagents, we performed a systematic study on the demethylation of methoxypyridines using $NaSSiMe_3$.

A general method for removal of the methyl group from methoxypyridines was developed, as shown in Scheme I, and the results are listed in the Table. A methoxypyridine (e.g., **1a–h**) was treated with $NaSSiMe_3$ (~1.5–2.5 equivalents) in anhydrous 1,3-dimethyl-2-

imidazolidinone (DMEU) at 120–180 °C to give the corresponding hydroxypyridine (e.g., **2a–h**) in 55–87% yield. We found that DMEU was a better solvent than others, such as DMF and THF. The products were purified by column chromatography and recrystallized (for solids) from a mixture of CH_2Cl_2 and MeOH.

Scheme I



This newly developed method was applicable to a pyridine having a methoxy group attached at the 2-, 3-, and 4-positions (i.e., **1a** → **2a** (73%), **1b** → **2b** (61%), and **1c** → **2c** (60%)).[16] A disubstituted molecule 2-methoxy-6-methylpyridine (**1d**) was converted to 2-hydroxy-6-methylpyridine[16] (**2d**) in 70% yield. Furthermore, we found that the standard conditions can be used to demethylate a methoxyquinoline (**1e**). The corresponding 2-hydroxyquinoline[16] (**2e**) was produced in 87% yield.

Under the standard conditions, 6-chloro-2-methoxypyridine (**1f**) gave a 70% yield of 6-chloro-2-hydroxypyridine[16] (**2f**) as the major product, along with <5% yield of 2-hydroxy-6-methylthiopyridine as the by-product. The thiolated by-product came from demethylation of **1f** with $NaSSiMe_3$, followed by reaction of the resultant **2f** with $MeSSiMe_3$ generated in situ. The results indicate the feasibility for selective *O*-demethylation of a methoxypyridine that is attached a Cl substituent. On the other hand, use of ~2.5 equivalents of $NaSSiMe_3$ to react with methyl 6-methoxynicotinate (**1g**) gave 6-hydroxynicotinic acid[16] (**2g**) as the exclusive product (55% yield), which came from the demethylations of both the –OMe and the –COOMe moieties in **1g**. In a control

Table. Demethylation of Methoxypyridines with $NaSSiMe_3$, Generated from $Me_3SSiSMe_3$ and NaOMe, in DMEU to Afford the Corresponding Hydroxypyridines.

Starting Material 1	Molar Ratio 1:$Me_3SiSSiMe_3$:NaOMe	Reaction Time h	Temp °C	Product 2	Yield (%)	mp (°C) or bp (°C/torr) Found	Literature[16]
2-methoxypyridine (**1a**)	1: 1.8:1.5	18	180	2-hydroxypyridine (**2a**)	73	mp 103–105	105–107
3-methoxypyridine (**1b**)	1:1.8:1.5	24	180	3-hydroxypyridine (**2b**)	61	mp 125–127	126–129
4-methoxypyridine (**1c**)	1:1.8:1.5	24	180	4-hydroxypyridine (**2c**)	60	bp 140–143 /760	230–235/12
2-methoxy-6-methylpyridine (**1d**)	1:1.8:1.5	15	180	2-hydroxy-6-methyl-pyridine (**2d**)	70	mp 158–160	158–160
2-methoxyquinoline (**1e**)	1:1.8:1.5	4	140	2-hydroxyquinoline (**2e**)	87	mp 196–198	198–199
6-chloro-2-methoxypyridine (**1f**)	1:1.8:1.5	24	120	6-chloro-2-hydroxypyridine (**2f**)	70	mp 127–129	128–130
methyl 6-methoxynicotinate (**1g**)	1:2.8:2.5	24	180	6-hydroxynicotinic acid (**2g**)	55	mp >330	>330
2,4-dimethoxypyridine (**1h**)	1:2.8:2.5	24	180	2,4-dihydroxypyridine (**2h**)	75	mp 243–246	245

[a]The products contained 2-hydroxy-6-methylthiopyridine in <5% yield.

experiment, we treated nicotinate(**1g**) with 1.5 equivalents of $NaSSiMe_3$ at 110 °C for 18 h. The mono-demethylated product, methyl 6-hydroxynicotinate, was obtained in 40% yield. Thus we conclude that the removal of a methyl group from the methyl ether unit with $NaSSiMe_3$ is faster than that from a methyl ester group.

The feasibility of bis-*O*-demethylation of dimethoxypyridines with $NaSSiMe_3$ (~2.5 equivalents) was proven in the conversion of 2,3-dimethoxypyridine (**1h**) to 2,3-dihydroxypyridine (**2h**, 75% yield).[16] This method allowed facile removal of two methyl groups in one flask without the necessity of isolation of any intermediate.

EEXPERIMENTAL

All compounds were of reagent grade and purified before use. Merck silica gel (60 H) was used for column chromatography. The following instruments were used for recording the spectral data: Perkin–Elmer 882 Infrared Spectrophotometer; Bruker AC 200 and MSL 200 ^{1}H-nmr Spectrometers; and VG 7-250 GC–Mass Spectrometer. Elemental analyses were performed on a Perkin–Elmer 2400 Elemental Analyzer. 2-Methoxypyridine and 2-chloro-6-methoxypyridine were purchased from Aldrich Chemical Co. Hexamethyldisilthiane was from Fluka Chemical Co. and was stored in serum capped bottles under nitrogen over molecular sieves 4A. 3-Methoxypyridine and 4-methoxypyridine were prepared from 3-chloropyridine and 4-chloropyridine, respectively, with sodium methoxide in DMF.[17] 2-Methoxy-6-methylpyridine, 2,3-dimethoxypyridine, 2-methoxyquinoline were synthesized from commercially available 2-hydroxy-6-methylpyridine, 2,3-dihydroxypyridine, and 2-hydroxyquinoline, separately, by the method involving silver carbonate.[18] Methyl 6-methoxynicotinate was prepared from 6-hydroxynicotinic acid by use of diazomethane.[19]

2-Hydroxypyridine (2a): The standard procedure was described as follows.

To a two-necked flask equipped with a stirring bar and a rubber septum were added hexamethyldisilathiane (321 mg, 1.8 mmol), sodium methoxide (81 mg, 1.5 mmol), and anhydrous 1,3-dimethyl-2-imidazolidinone (3.0 ml). After 1 h of stirring at room temperature under an atmosphere of nitrogen, the mixture was added 2-methoxypyridine

(**1a**, 0.11 g, 1.0 mmol) and the solution was heated at 180 °C for 18 h. The reaction mixture was diluted with water and saturated with NH_4Cl at room temperature, and the resultant solution was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were washed with water (3 × 25 ml), dried over anhydrous Na_2SO_4, and condensed under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of CH_2Cl_2 and MeOH (20:1) as eluant to give pure **2a** (0.070 g) in 73% yield. The demethylation conditions and results for various methoxypyridines are summarized in the Table.

2-Hydroxy-6-methylthiopyridine: mp 183–185 °C (ethyl acetate); ir ($CHCl_3$) 1643, 1583, 1450 cm^{-1}; ^{1}H-nmr ($CDCl_3$/TMS): δ 2.54 (3H, s), 6.24 (1H, d, J = 7.2 Hz), 6.40 (1H, d, J = 8.4 Hz), 7.30 (1H, dd, J = 7.2, 8.4 Hz); ms (70 eV) m/z (%) 141 (M^+, 100), 95 (32), 67 (18). Hrms Calcd for C_6H_7NOS: 141.0248, Found: 141.0253.

Methyl 6-Hydroxynicotinate: mp 162–164 °C (CH_2Cl_2); ir ($CHCl_3$) 1720, 1680, 1659, 1409 cm^{-1}; ^{1}H-nmr ($CDCl_3$/TMS): δ 3.85 (3H, s), 6.51 (1H, d, J = 9.4 Hz), 7.97 (1H, dd, J = 2.4, 9.4 Hz), 8.18 (1H, d, J = 2.4 Hz). Anal. Calcd for $C_7H_7NO_3$: C, 54.90, H, 4.61, N, 9.15. Found: C, 54.61, H, 4.48, N, 9.05.

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