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Chemoselective Demethylation of Methoxypyridine

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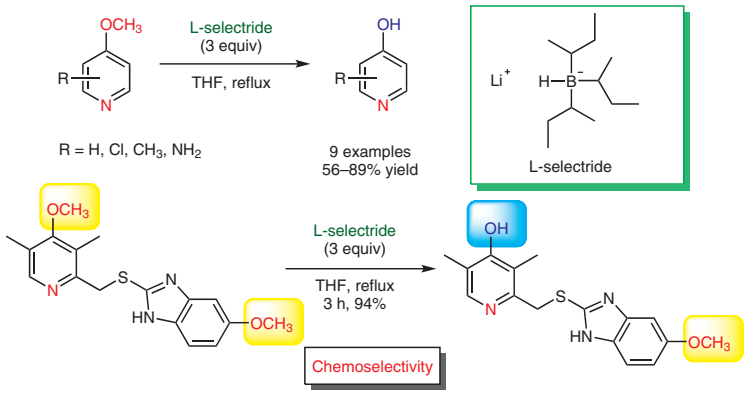

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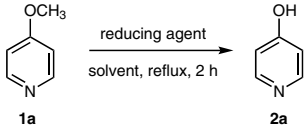
Abstract A chemoselective demethylation method for various methoxypyridine derivatives has been developed. Treatment of 4-methoxypyridine with L-selectride in THF for 2 h at reflux temperature afforded 4-hydroxypyridine in good yield; no reaction to anisole occurred. The utility of our method was demonstrated by the efficient synthesis of the metabolic substances of the antiulcer agent omeprazole. Chemoselective demethylation at the site of 3,5-dimethyl-4-methoxypyridine in the presence of 4-methoxybenzimidazole was achieved.

Key words L-selectride, pyridine, anisole, chemoselective, demethylation

Methyl ether is considered to be the most useful and effective protective group for phenols in synthetic chemistry because of its tolerance of a variety of reaction conditions.[1] For the demethylation of aromatic methyl ethers, a variety of cleavage methods have been developed, including strong acids[2] or bases,[3] nucleophilic reagents,[4] alkali metals,[5] and oxidizing[6] or reducing[7] reagents. These methods are often drastic, in many cases resulting in side reactions and lower reaction yields. In the course of our synthetic study of drug metabolites consisting of heterocyclic aromatic ethers, we found that L-selectride[8] is an efficient chemoselective agent to fit the purpose. Here, a new method for nucleophilic cleavage of the methyl group in methoxypyridine using L-selectride, which is unresponsive to methoxybenzene (anisole), is reported. The simple method was applied to the chemoselective synthesis of the metabolic substances of the antiulcer agent omeprazole.[9]

L-Selectride is known to be a highly stereoselective reducing agent.[10] In 1994, Majetich et al. found that L-selectride is useful for the nucleophilic deprotection of methyl phenyl ethers.[11] In their report, the reactions proceeded rapidly when the phenyl ring had more electron-withdrawing substituents. Inspired by this, we envisioned that L-selectride could lead to the efficient demethylation of the methoxy group in electron-poor heterocyclic aromatics. For the purpose of our synthesis of drug metabolites, a new chemoselective demethylation method for heterocyclic

Table 1 Optimization of Reaction Conditions

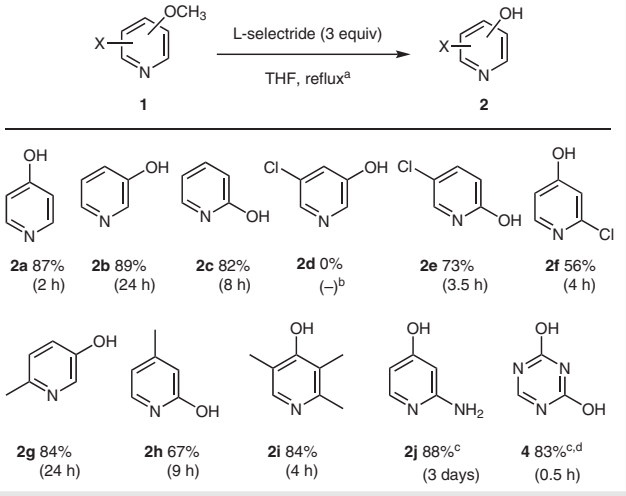


Entry	Reducing agent	Equiv	Solvent	Yield (%)
1	L-selectride	1	THF	32
2	L-selectride	2	THF	58
3	L-selectride	3	THF	87
4	L-selectride	3	toluene	86
5	L-selectride	3	1,4-dioxane	65
6	L-selectride	3	Et_2O	23
7	L-selectride	3	CH_2Cl_2	0
8	N-selectride	3	THF	7
9	K-selectride	3	THF	4
10	$LiBHEt_3$	3	THF	30
11	$LiBH_4$	3	THF	0

compounds seemed advantageous. Therefore, we started a survey of the reaction conditions of L-selectride to 4-methoxy pyridine **1a** (Table 1).

The use of 1 to 2 equivalents of L-selectride under reflux conditions in THF did not complete the reaction (Table 1, entries 1 and 2). However, using 3 equivalents of L-selectride provided satisfactory yield of 4-hydroxypyridine **2a** (entry 3). Screening revealed that THF was the best solvent (entries 3–7). Changing the counterion of L-selectride decreased the yields (entries 8 and 9). A similar bulky reagent, $LiBHEt_3$ (entry 10), and less bulky $LiBH_4$ (entry 11) were not suitable for this reaction. Examination of anisole **3** under the same conditions (THF, reflux, 2 h) showed that the reaction did not proceed at all, and intact **3** was recovered. It was clear that electron-poor heterocyclic pyridine was more reactive than benzene. Further examination revealed that some demethylation in **3** was observed after prolonged reflux conditions in THF (12 h). Thus, chemoselective demethylation of 4-methoxy pyridine **1a** in the presence of anisole **3** should be performed by refluxing in THF within 12 h.

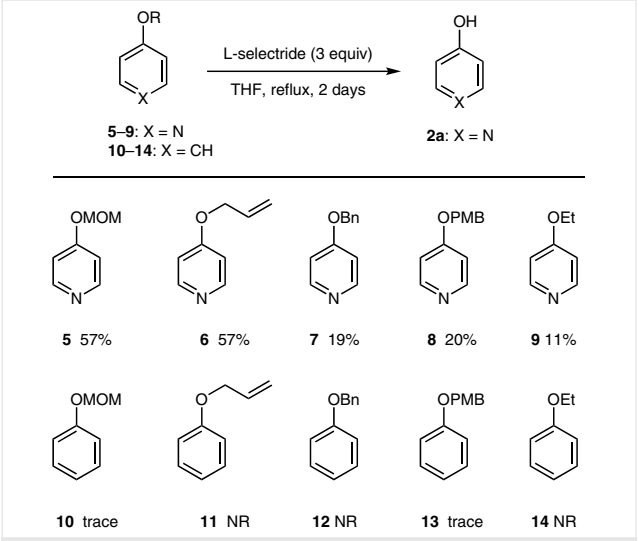
After determining the suitable reaction conditions, we then investigated the generality of our protocol. As shown in Scheme 1, a broad range of methoxypyridines **1a–j** was subjected to treatment with L-selectride in THF at reflux temperature. Intriguingly, the position of the -OCH_3 group had a profound influence on the reactivity for demethylation, and the reaction was completed in 2 h for **2a**, while 24 h was needed for **2b**. With the exception of **1d**, which provided strangely complex mixtures, other methoxypyridines, irrespective of their electronic nature (electron-rich/electron-poor), furnished the corresponding demethylated compounds **2e–i** in 56–84% yields.



Scheme 1 Demethylation of methoxyheterocycles.[12] [a] Reaction times are shown in parentheses. [b] See main text. [c] L-Selectride (6 equiv) was used. [d] 2,4-Dimethoxy-1,3,5-triazine was used as the substrate.

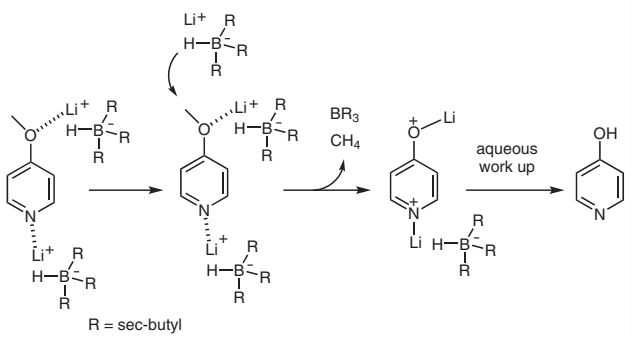
It is noteworthy that sterically hindered and electron-rich **1i** afforded **2i** in 84% yield. In contrast, the reaction of 2-amino-4-methoxypyridine **1j** was very slow, and thus additional agent (6 equiv) and a longer reaction time (3 days) were utilized to obtain **2j** in 88% yield. Examination of 2,4-dimethoxy 1,3,5-triazine under slightly modified conditions [L-selectride (6 equiv), THF, reflux, 0.5 were selectively providedh] showed that it underwent demethylation to provide **4** in 83% yield.

We questioned whether we could further apply our method to various 4-alkoxypyridines **5–9** (Scheme 2). Compared with the methoxypyridines, these compounds were poorly reactive and therefore a longer reaction time (2 days) was necessary. MOM-protected **5** and allyl-protected **6** were converted into **2a** in moderate yields. Disappointingly, other protected compounds (benzyl-protected **7**, *p*-methoxybenzyl-protected **8**, ethyl-protected **9**) furnished **2a** in only 11–20% yields. Examination of the corresponding 4-alkoxybenzenes **10–14** under the same reaction conditions confirmed that benzene derivatives were nonreactive. Although the yields were not satisfactory, it is worth noting that the reaction is rather chemoselective, and only the 4-alkoxy pyridines were transformed into 4-hydroxypyridine **2a**.



Scheme 2 Dealkylation of 4-alkoxy pyridines and 4-alkoxybenzenes

We have only limited information on the possible mechanism of this nucleophilic deprotection. Considering that 3 equivalents of L-selectride were necessary to complete the reaction (Table 1, entry 3), the N atom of pyridine forming a complex with L-selectride should activate the methoxy group remotely. Added to this, the formation of a lithium cation-activated complex at the reaction site, which was proposed by Majetich,[11] facilitates nucleophilic attack by hydride to generate methane (Scheme 3).

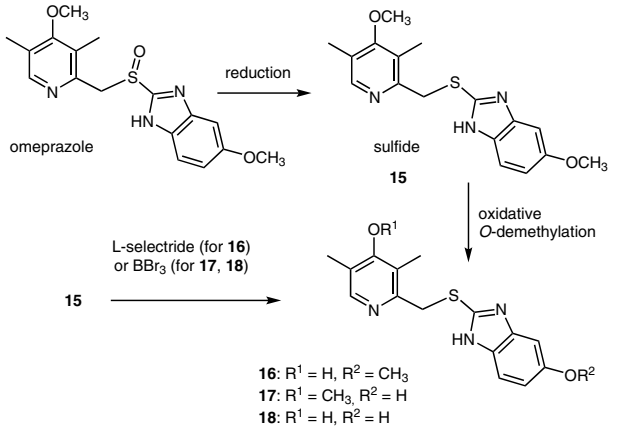


Scheme 3 Proposed reaction mechanism for demethylation of methoxypyridine

Omeprazole, 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1*H*-benzimidazole, is a potent, long-acting inhibitor of gastric acid secretion.[9] In the metabolic pathway, the sulfoxide group of omeprazole is reduced to give the corresponding sulfide **15**.[13] When the methoxy groups in the pyridine and benzimidazole rings are oxidatively *O*-demethylated, the phenolic metabolites **16**, **17**, and **18** are generated.[14] Thus, the practicality of our demethylation method was demonstrated by the synthesis of the metabolic substance **16**. The synthetic plan started from sulfide **15**, from which the metabolites **16**, **17**, and **18** were selectively provided[15] using diverse reaction conditions (Table 2). Central to this issue is the problem of chemoselective demethylation at the site of 3,5-dimethyl-4-methoxypyridine in the presence of 4-methoxybenzimidazole. Gratifyingly, treatment of **15** with 3 equivalents of L-selectride resulted in only the deprotection of the sterically bulky congested methoxypyridine, and thus the 4-hydroxy pyridine derivative **16** was obtained in 94% yield (entry 1). It is important to note that no reaction occurred at the 4-methoxybenzimidazole site. For the selective synthesis of metabolite **17**, the acidic reagent BBr_3 was suitable. The treatment of 2.5 equivalents of BBr_3 with **15** in CH_2Cl_2 at 0 °C for 12 h provided 4-hydroxybenzimidazole derivative **17** in 79% yield, and 9% of dihydroxy compound **18**, which were easily separated by silica-gel chromatography (CH_2Cl_2/MeOH, 9:1; entry 2). It was elucidated that partial chemoselectivity for 4-methoxybenzimidazole was achieved by using BBr_3 at a lower temperature. To obtain dihydroxy compound **18**, harsher conditions (5 equivalents of BBr_3 in CH_2Cl_2 at r.t. for 5 h) were employed, which provided **18** in 82% yield (entry 3).

In summary, we described the demethylation of methoxypyridine derivatives using L-selectride.[16] The reaction occurs at the methoxypyridine derivatives chemoselectively, without reaction to the corresponding methoxybenzene analogues. The usefulness of our method was demonstrated by the efficient synthesis of metabolite **16** of the antiulcer agent omeprazole, in which only the 3,5-dimethyl-4-methoxypyridine moiety reacted without affecting the 4-methoxybenzimidazole moiety. We anticipate that this method will be useful in preparing biologically active heterocyclic compounds. Related studies are under way in our laboratory.

Table 2 Selective Synthesis of Omeprazole Metabolites **16–18**



Entry	Agent	Reaction conditions	Yield (%)		
			16	**17**	**18**
1	L-selectride	3.0 equiv, THF reflux, 3 h	94	0	0
2	BBr_3	2.5 equiv, CH_2Cl_2, 0 °C, 12 h	0	79	9
3	BBr_3	5.0 equiv, CH_2Cl_2, rt, 4 h	0	0	82

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(12) **Demethylation of Methoxypyridines; General Procedure:** To a solution of **1** (1.00 mmol) in THF (7.0 mL) was added L-selectride (1 M in THF, 3.0 mL, 3.00 mmol, 3 equiv) under an argon atmosphere. After being refluxed and monitored by TLC, the reaction mixture was quenched with MeOH and evaporated in vacuo. The residue was purified by silica gel column chromatography to give the desired compound **2**.

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(15) **Synthetic procedure and characterization of compounds:**
2-{[(6-Methoxy-1*H*-benzimidazol-2-yl)thio]methyl}-3,5-dimethyl-4-pyridinol (16): To a solution of **15** (103.1 mg, 0.299 mmol) in THF (2.1 mL) was added L-selectride (1 M in THF, 0.90 mL, 0.897 mmol) under an argon atmosphere. After being refluxed for 3 h, the reaction mixture was quenched with MeOH and evaporated in vacuo. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:19) to give **16** (88.1 mg, 0.280 mmol, 94%) as colorless crystals; mp 140–143 °C. ^1H NMR (600 MHz, CD_3OD): δ = 7.56 (s, 1 H), 7.37 (br, *J* = 9.0 Hz, 1 H), 6.97 (br, 1 H), 6.83 (dd, *J* = 3.0, 9.0 Hz, 1 H), 4.38 (s, 2 H), 3.79 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD): δ = 180.6, 158.4, 158.4, 148.5, 144.8, 144.8, 136.1, 124.9, 124.9, 124.3, 124.3, 113.7, 56.4, 33.9, 14.4, 11.2; IR (ATR): 3057, 1487 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{18}N_3O_2S$: 316.1114; found: 316.1113.
2-{[(4-Methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio}-1*H*-benzimidazol-6-ol (17): To a solution of **15** (104 mg, 0.300 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C was added BBr_3 (1 M in CH_2Cl_2, 0.75 mL, 0.750 mmol) under an argon atmosphere. After being stirred at 0 °C for 12 h, the reaction mixture was quenched with MeOH and evaporated in vacuo. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:9) to give **17** (73.6 mg, 0.234 mmol, 78%) and **18** (9.0 mg, 0.028 mmol, 9%) as colorless crystals; mp 117–118 °C; ^1H NMR (600 MHz, CD_3OD): δ = 8.10 (s, 1 H), 7.29 (d, *J* = 9.0 Hz, 1 H), 6.85 (br, 1 H), 6.74 (dd, *J* = 1.8, 9.0 Hz, 1 H), 4.50 (s, 2 H), 3.74 (s, 3 H), 2.24 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD): δ = 166.3, 166.3, 155.6, 155.6, 155.0, 149.7, 149.7, 127.6, 127.6, 127.2, 127.2, 113.1, 60.6, 38.0, 13.4, 11.3; IR (ATR): 3208, 1434 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{18}N_3O_2S$: 316.1114; found: 316.1115.
2-{[(4-Hydroxy-3,5-dimethyl-2-pyridinyl)methyl]thio}-1*H*-benzimidazol-6-ol (18): To a solution of **15** (104 mg, 0.300 mmol) in CH_2Cl_2 (1.5 mL) at 23 °C was added BBr_3 (1 M in CH_2Cl_2, 1.50 mL, 1.50 mmol) under an argon atmosphere. After being stirred at 23 °C for 4 h, the reaction mixture was quenched with MeOH and evaporated in vacuo. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:9) to give **18** (73.8 mg, 0.245 mmol, 82%) as colorless crystals; mp 214–216 °C; ^1H NMR (600 MHz, CD_3OD): δ = 7.66 (s, 1 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 6.86 (dd, *J* = 2.4 Hz, 1 H), 6.76 (dd, *J* = 2.4, 9.0 Hz, 1 H), 4.42 (s, 2 H), 2.02 (s, 3 H), 1.98 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD): δ = 179.4, 155.3, 147.4, 145.0, 140.2, 136.3, 135.3, 124.6, 124.1, 116.6, 113.6, 99.6, 33.8, 14.0, 10.9; IR (ATR): 3345, 1483 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}N_3O_2S$: 302.0958; found 302.0959

(16) For general experimental methods, see the Supporting Information.