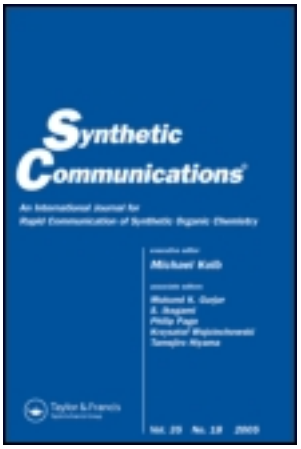

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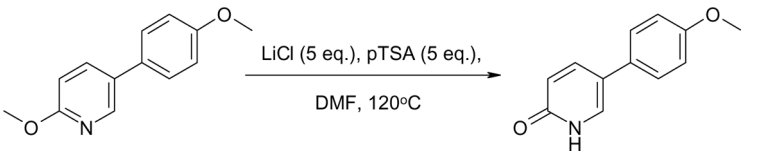
GRAPHICAL ABSTRACT



Abstract *A new and efficient method for the demethylation of 6-membered aza-heterocyclic methyl ethers is described using lithium chloride and* para-*toluenesulfonic acid. This process is chemoselective for aza-heterocyclic methyl ethers in the presence of aryl methyl ethers.*

Keywords Demethylation; lithium chloride; 2-methoxypyrdidine; *p*-toluenesulfonic acid; pyridine-2-one

INTRODUCTION

The methylation of the phenol hydroxy group is regarded as an effective protecting-group strategy in organic synthesis because of the stability of aryl methyl ethers to many reaction conditions.[1,2] However, the deprotection of the aryl methoxy group often involves rather harsh reaction conditions, which can cause side reactions when the molecule contains other sensitive functionalities. Under such circumstances, it is often necessary to standardize the demethylation reaction by trial and error and to investigate a number of different demethylating reagents and various reaction conditions.

We wished to convert a compound of general formula **A** that contained a 2-methoxypyridinyl group, a methoxy phenyl group, and other acid-sensitive functionalties to the 2-pyridone derivative **B** (Scheme 1). Unfortunately, several commonly known methods for the demethylation of aryl methyl ethers such as boron

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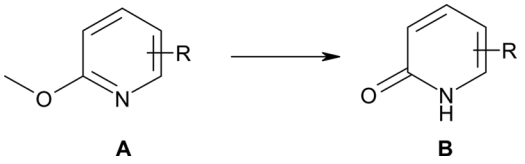


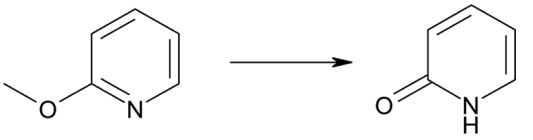
Scheme 1. Demethylation in vivo of 2-methoxypyridine **A** to form the 2-pyridone analog **B** (R = other acid-sensitive groups).

tribromide,[3] boron trichloride,[4] silyl iodides (e.g., trimethylsilyliodide or *tert*-butyldimethylsilyliodide),[5] protic acids (e.g., aqueous hydriodic or hydrobromic acids),[6] thiolates,[7] pyridine hydrochloride,[8] and aluminum trichloride[9] resulted in either poor conversions (10–20%) or decomposition because of the intolerance to the reaction conditions of other substituents present in the molecule.

We were pleasantly surprised, therefore, that heating compound **A** at 110 °C with 5 molar equivalents of sodium iodide in glacial acetic acid[10] or 5 molar equivalents of potassium iodide in neat phosphoric acid[11] produced a 40–50% yield of compound **B**, albeit with some decomposition products. We were equally intrigued by the fact that the in situ generation of hydrogen iodide from iodocyclohexane by thermal elimination[12] led to a reasonable conversion of compound **A** to **B** (60–70%). The conclusion drawn from these experiments is that hydrogen iodide is responsible for the dealkylation but its concentration is sufficiently low as not to induce too severe of a decomposition of other portions of molecule **A** or **B**. Therefore, we examined in more detail the conditions required for a high conversion of compound **A** to **B** by using 2-methoxypyridine **1** as a model substrate.

The reaction of compound **1** with 5 molar equivalents of potassium iodide in neat phosphoric acid at 110 °C, or with 5 molar equivalents of lithium iodide in neat glacial acetic acid at 110 °C, gave 2-pyridone **2** in quantitative yield (Table 1, entries 1 and 2). Application of the same reaction conditions to the demethylation of compound **A** led to some decomposition and suboptimal yields of compound **B**. In an attempt to attenuate the reactivity of the system, the reaction of compound **1** with lithium iodide in glacial acetic acid at lower reaction temperatures resulted only in incomplete reactions (Table 1, entries 3 and 4). It was evident, therefore, that relatively high temperatures were necessary to induce the dealkylation reaction but that such high temperatures and a highly acidic environment were proving detrimental to the stability of compound **A** or **B**. We chose to explore the use of high-boiling, polar, aprotic amides as solvents for the reaction but were disappointed when the reaction of compound **1** with 5 molar equivalents of both lithium iodide and glacial acetic acid in dimethylformamide (DMF) at 120 °C produced only a modest yield of product **2** (Table 1, entry 5). Acetic acid is a relatively weak acid, and we resolved to examine stronger acids. We were delighted that the reaction of compound **1** with 5 molar equivalents of phosphoric, sulfuric, methanesulfonic (MsOH), or *para*-toluenesulfonic (pTSA) acid and 5 molar equivalents of lithium iodide furnished compound **2** in excellent yields (Table 1, entries 6–9). Changing the solvent from dimethylformamide to dimethylacetamide (DMA) or *N*-methylpyrrolidone (NMP) produced lower yields of product (Table 1, entries 10 and 11).

Table 1. Demethylation of 2-methoxypyridine



1 **2**

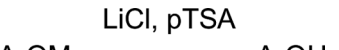
Entry	Salt (5 eq.)	Acid (5 eq.)	Solvent	Temp. (°C)	Yield by HPLC (%)[a]
1	KI	—	H_3PO_4	110	99
2	LiI	—	AcOH	110	100
3	LiI	—	AcOH	55	13
4	LiI	—	AcOH	80	36
5	LiI	AcOH	DMF	120	54
6	LiI	H_3PO_4	DMF	120	91
7	LiI	H_2SO_4	DMF	120	93
8	LiI	MsOH	DMF	120	96
9	LiI	pTSA	DMF	120	94
10	LiI	pTSA	NMP	120	75
11	LiI	pTSA	DMA	120	90
12	LiBr	pTSA	DMF	120	99
13	NaCl	pTSA	DMF	120	89
14	KCl	pTSA	DMF	120	86
15	CsCl	pTSA	DMF	120	95
16	CsF	pTSA	DMF	120	0
17	LiCl	pTSA	DMF	120	100

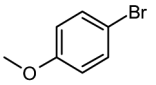
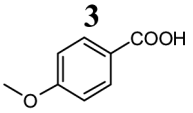
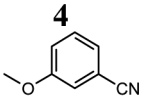
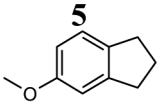
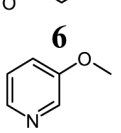
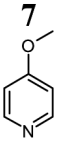
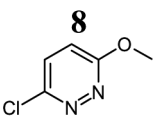
[a]The reactions were quenched after 30 min, and the extent of reaction was determined by HPLC.

Evaluation of the role of metal halides other than lithium iodide showed that most metal halides (e.g., lithium bromide, sodium chloride, potassium chloride, cesium chloride: Table 1, entries 12–15) gave good conversions of compound **1** to **2** in the presence of pTSA in dimethylformamide. The highly ionic cesium fluoride induced no reaction (Table 1, entry 16), whereas lithium chloride produced a quantitative yield of product **2** (Table 1, entry 17). By analogy with the metal iodide reactions,[10,11] the combination of lithium chloride and pTSA appears to generate hydrogen chloride, which is the agent responsible for demethylation. The effect of LiCl or pTSA alone on the demethylation reaction was evaluated by heating each reagent with 2-methoxypyridine in DMF at 110 °C. No reaction was observed in either case after 8 h.

The reaction of the phenyl ethers **3–6** with lithium chloride and pTSA gave only starting materials in dimethylformamide at 120 °C. Demethylated products could be produced, however, by employing a higher reaction temperature (180 °C), *N*-methylpyrrolidone as solvent, longer reaction time (8 h), and 10 molar equivalents of both lithium chloride and pTSA (Table 2, entries 1–4). The demethylation of the 3-methoxy- and 4-methoxypyridines **7** and **8** was more facile than that of the aryl methyl ethers **3–6** and occurred in the short reaction time of 1 h (Table 2, entries 5 and 6). The demethylation of 6-chloro-2-methoxypyridazine **9** was likewise rapid and could be achieved using dimethylformamide at 120 °C (Table 2, entry 7).

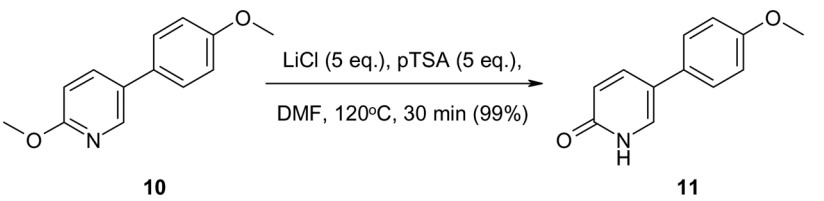
Table 2. Demethylation of aryl methyl ethers and other aza-containing heteroaromatic systems



Entry	Substrate	LiCl (molar equivalents)	pTSA (molar equivalents)	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)[a]
1		10	10	NMP	180	8	82
2	**3** 	10	10	NMP	180	8	95
3	**4** 	10	10	NMP	180	4	76
4	**5** 	10	10	NMP	180	4	86
5	**6** 	10	10	NMP	180	1	99
6	**7** 	10	10	NMP	180	1	85
7	**8**  **9**	5	5	DMF	120	0.5	92

[a]All products were purified by column chromatography and characterized by ^{1}H NMR and mass spectroscopy.

The data in Table 2 indicate clearly that six-membered aza-heterocyclic methyl ethers ought to be chemoselectively demethylated by lithium chloride and pTSA in the presence of aryl methyl ethers. This suggestion was confirmed by the result of the reaction of compound **10** with lithium chloride and pTSA in dimethylformamide at 120 °C wherein clean monodemethylation of the pyridinyl methyl ether group in the presence of a phenyl methyl ether gave compound **11** (Scheme 2). The same reaction conditions when applied to the compound **A** on a multigram scale (i.e., 30–50 mmol) pleasingly resulted in the formation of 2-pyridone compound **B** in 97% yield.



10 11

Scheme 2. Selective demethylation of pyridinyl methyl ether in the presence of a phenyl methyl ether.

General Demethylation Procedure

A solution of the methyl ether (1 mmol) in the desired solvent (2 ml) was treated with alkali halide (5 or 10 molar equivalents) and acid (5 or 10 molar equivalents), heated at the desired temperature for the set period of time, cooled to room temperature, quenched with water (10 ml), and extracted with ethyl acetate (2×10 ml). The combined extracts were washed with water (2×5 ml) and saturated aqueous brine (2×5 ml), dried (Na_2SO_4), and concentrated in vacuo to give the crude product.

Preparation of 5-(4-Methoxyphenyl)pyridin-2-one (11)

A solution of compound 10 (100 mg, 0.47 mmol) in DMF (2 ml) was treated with lithium chloride (97 mg, 2.33 mmol) and pTSA (441 mg, 2.33 mmol), heated at 120 °C for 30 min, cooled to room temperature, quenched with water (5 ml), and extracted with ethyl acetate (2×5 ml). The combined extracts were washed with water (2×5 ml) and saturated aqueous brine (2×5 ml), dried (Na_2SO_4), and concentrated in vacuo to give the desired product (93 mg, 99%).

CONCLUSION

In summary, the reaction of six-membered aza-heterocyclic methyl ethers such as pyridinyl methyl ethers or a pyridazinyl methyl ether in the presence of 5 molar equivalents of both lithium chloride and pTSA is a new method for smooth and efficient demethylation. This process is efficient and selective for aza-heterocyclic methyl ethers in the presence of aryl methyl ethers at 120 °C in dimethylformamide.

ACKNOWLEDGMENTS

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