

Demethylating Reaction of Methyl Ethers

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Abstract: The investigation of demethylating reaction of methyl ethers have been reviewed on chemical method,microwave-assisted method and biological technology respectively. The development prospects on this work have been discussed briefly.

Key words: methyl ethers ; demethylating reaction ; chemical method ; microwave-assisted method; biological technology

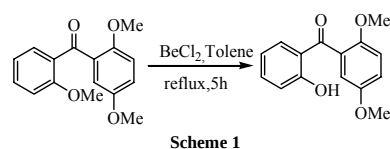
Introduction

Ethers are among the most useful protection groups in synthetic organic chemistry. Methylation of hydroxyl moiety is regarded as one of the most effective methodologies, due to its very high stability under numerous reaction conditions. But methyl ethers are difficult to dealkylate under mild reaction conditions. Some reagents developed for demethylation of aromatic methyl ethers include Lewis acids, mixed mineral acids, oxidants, reductants as well as silica and aluminum compounds. In recent years, new methods for demethylation have developed. Besides chemical method, there are also micro-assisted method and biological technology. The investigation of demethylating reaction of methyl ethers has been reviewed on chemical method, microwave-assisted method and biological technology respectively as follows.

1. Chemical methods

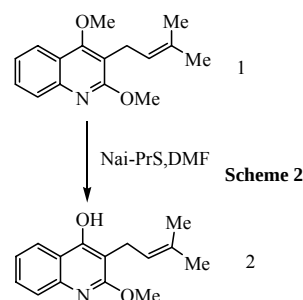
1.1 BeCl₂

BeCl₂ is a highly selective reagent for dealkylation of aryl-methyl ethers. Hashem Sharghi^[1] et al. used BeCl₂ in demethylation reaction, toluene as solvent, and refluxed for 5 hours in the yield of 95%. (Scheme 1).



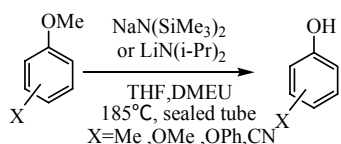
1.2 i-PrSNa

Boron tribromide is well known for aromatic methyl ethers' demethylation. As a Lewis acid it can avoid the addition to the double bond in the reactants. A non-acidic approach was investigated using thiolate ion, which is known to cleave aryl methyl ethers in the solvents such as DMF. Treatment of compound 1 with sodium isopropyl thiolate in DMF at reflux, gave compound 2 in the yield of 38% after chromatography. (Scheme 2)^[2].



1.3 NaN(SiMe₃)₂ and LiN(i-Pr)₂

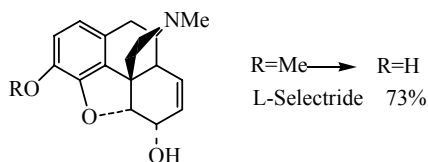
Alkali organomides NaN(SiMe₃)₂ and LiN(i-Pr)₂, often used as organic bases, have been developed as efficient deprotecting agents in demethylation of aryl-methyl ethers (Scheme 3)^[3].



Scheme 3

1.4 L-Selectride

L-Selectride is a good reagent for O-demethylation^[4].

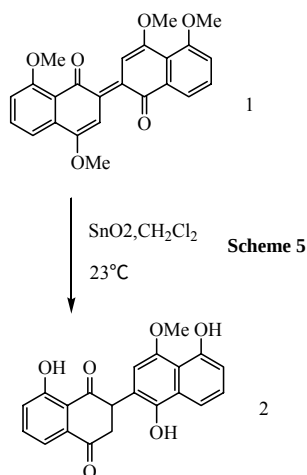


Scheme 4

O-demethylation of codeine to morphine was problematic until the use of BBr_3 (91%). The strongly basic reagent was expected to deprotonate the hydroxyl group and vigorous evolution of hydrogen was indeed observed. L-Selectride, occurred smoothly at reflux to give a 73% yield of the corresponding compound (Scheme 4).

1.5 SnO_2

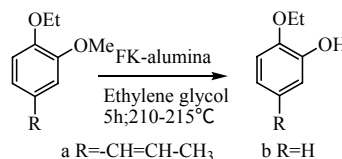
SnO_2 in CH_2Cl_2 was used in selective demethylation of compound 1 to efficiently give compound 2 under mild conditions in high yield (95%) (Scheme 5). As a semiconductor, SnO_2 is particularly useful from an environmental viewpoint, because it is almost nontoxic, stable, and inexpensive^[5].



Scheme 5

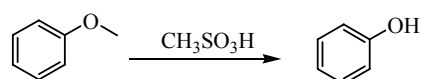
2. Microwave-assisted methods

Potassium fluoride coated on alumina, previous widely described as a strong base, was shown by Singh et al. to be also an effective reagent for the selective O-demethylation of aromatic methyl ethers^[6]. Abdelouahad Oussaïd et al. performed the reaction in mild heterogeneous solvent-free conditions and in a higher yield^[7] (Scheme 6).



Scheme 6

Microwave-assisted deprotection of aromatic methyl ethers has previously been performed with pyridine hydrochloride, KO^tBu and crown ether and with lithium iodide and solid supports. These methods were either not fast enough and/or the used reagents did not lend themselves well to the handling constraints of fluorine-18 and carbon-11 chemistry. Monomodal microwave heating is used to speed up the cleavage of methylphenyl ethers with methanesulfonic acid ($\text{CH}_3\text{SO}_3\text{H}$) (Scheme 7). Since $\text{CH}_3\text{SO}_3\text{H}$ is very polar, it would be expected to interact strongly with the oscillating electromagnetic field^[8].

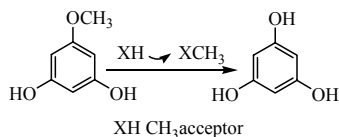


Scheme 7

3. Biological technology

DeWeed et al. had reported that anaerobic bacteria could demethylate phenyl methyl ethers by O-demethylation in 1988. Berman and Frazer found in *Acetobacterium woodii* cell extracts, ATP and tetrahydrofolate (H_4folate) were necessary for the air-sensitive demethylation reaction in 1992. In 1993, Stupperich and Konle found that in *Sporomusa ovata* cell extracts, demethylation was corrinoid-dependent and needed reductive activation by Ti^{3+} and ATP and yielded $\text{CH}_3\text{-H}_4\text{folate}$ (Scheme 8). In *clostridium*

thermoaceticum cell extracts, syringate was demethylated by an oxygen-insensitive, corrinoid-independent, ATP-consuming enzyme yielding CH₃-H₄folate^[9].



Scheme 8

Desulfotobacterium hafniense and *Desulfotobacterium* sp strain PCE-S grew under anoxic conditions with a variety of phenyl methyl ethers as electron donors in combination with fumarate as electron acceptor. The phenyl methyl ethers were *O*-demethylated to the corresponding phenol compounds. *O*-demethylation occurred with CO₂ as electron acceptor. One molar phenyl methyl ether R-O-CH₃ was *O*-demethylated to R-OH and 3 molar fumarates reduced to succinate^[10].

4 Conclusions

Methods for demethylating reaction of methyl ethers have been developed. Chemical method seems to be simple, but they usually bring about other structural or stereochemical change. Microwave-assisted method is simple, high yielding and selective. We should put more attention on it. Compared to the two methods before, biological technology brings us a new way for demethylation. It is the transferring of CH₃ in essential. Because biological technology is more selective than chemical methods and microwave -assisted method, it deserves more attention.

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