A Mild and Chemoselective Dealkylation of Alkyl Aryl Ethers by Cerium(III) Chloride-NaI

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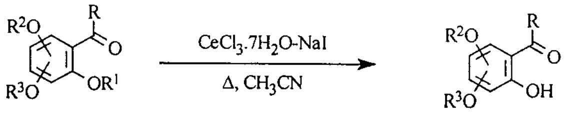
The alkoxy groups present ortho to carbonyl group in alkoxybenzaldehydes are selectively deprotected in high yields leaving other alkoxy groups unaffected by cerium(III) chloride–NaI in refluxing acetonitrile under neutral reaction conditions.

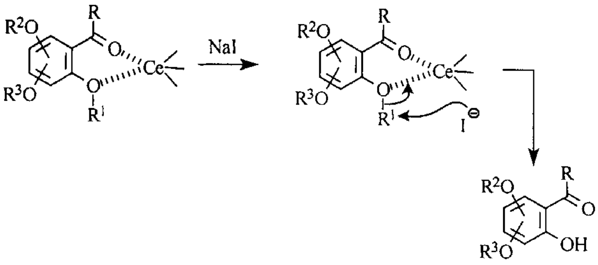
Performing chemoselective transformations of polyfunctional compounds is a challenging problem in organic synthesis. Ethers are frequently used as stable protective groups for the hydroxyl groups in multi-step synthesis of complex natural products like polyketide derived macrolides and polyether antibiotics.[1] Among various ethers, methoxy ethers are the most versatile[2] owing to their ease of formation, inherent stability and a variety of available deprotection methods including nucleophilic[3,4] and Lewis acid promoted cleavages.[5–7] In the nucleophilic cleavage of aryl methyl ethers carrying electron attracting groups, several competing reactions[8] like dehalogenation via nucleophilic aromatic substitution, electrophilic addition of formyl groups and Von Richter reaction by NaCN in DMSO with nitro arylethers etc., are possible that limit the efficiency of the methods. Furthermore reactive Lewis acids such as aluminum and boron halides are found to offer no selectivity and cleave all methoxy groups present in the substrate. In addition, the nucleophilic cleavage of arylmethyl ethers suffer from the use of strong basic conditions, require long reaction times at elevated temperature, incompatibility with other functional groups present in the substrate and the use of highly polar solvents like DMF, HMPA and DMSO which require tedious aqueous work-up. Although, the dealkylation of alkyl aryl ethers has been reported[3] using $MgI_2 \cdot OEt_2$, the procedure is applicable only to the 2,6-dimethoxy benzaldehydes and that is not a general method for aldehydes having various substituents like nitro, acetyl, benzoyl, benzyl, prenyl and ester groups in the aromatic ring. In recent years, lanthanide salts mediated organic reactions[9] have attracted much attention due to low toxicity, ease of handling, low cost of the reagents, stability and recoverability from water. However, the development of new methods with more efficacy, convenient procedures and better yields is of interest.

In continuation of our work towards the total synthesis of Lamellarin alkaloids, we required the chemoselective demethylation of polymethoxy benzaldehydes under mild conditions. Since $AlCl_3$ or BX_3 in the chemoselective demethylation caused the removal of all methoxy groups present in the substrate, herein we report a mild and efficient method for the chemoselective cleavage of methoxy groups located at ortho to carbonyl group leaving other methoxy groups unaffected by cerium(III) chloride–NaI in acetonitrile (Scheme 1).



Scheme 1

The combination of cerium(III) chloride and sodium iodide in refluxing acetonitrile smoothly cleaved methoxy groups located ortho to carbonyl group and leaving other methoxy groups intact. Such selectivity is a highly desirable feature in the cleavage of ethers which offers various beneficial prospects in organic synthesis. The cleavage was effected by cerium chloride through the formation of a six-membered chelate ring.

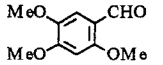
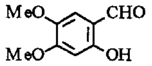
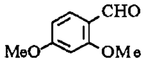
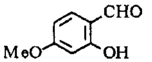
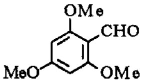
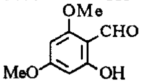
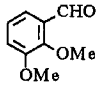
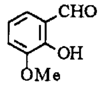
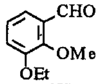
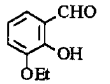
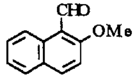
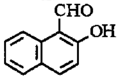
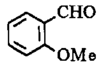
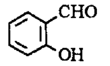
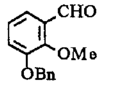
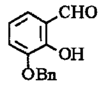
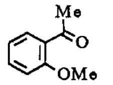
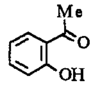
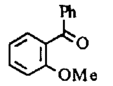
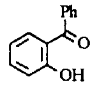
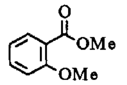
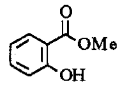
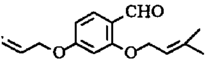
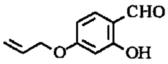
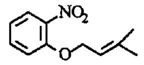
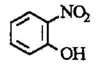
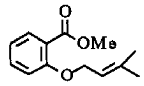
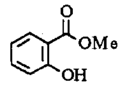
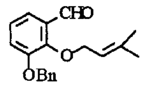
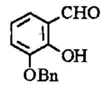


Scheme 2

The cleavage requires longer reaction times when methoxy groups are present either ortho to nitro or ester moieties in place of carbonyl group. Further no cleavage was observed with anisole and di or trimethoxy benzenes. The deprotection was successful only with alkyl aryl ethers carrying formyl, acetyl and ester groups in the aromatic ring. The protocol could be successfully applied for the selective removal of prenyl ethers present ortho to nitro, formyl, acetyl and ester moieties in the molecule. The deprotection of prenyl ethers occurs rapidly in high yields within 2–4 h of reaction time when compared to arylmethyl ethers. The reaction conditions are neither acidic nor basic and afford demethylated products in good yields in reasonable reaction times. The results summarized in Table 1 indicate the scope of the reaction for various polymethoxy benzaldehydes. The cleavage was also effected by 1 eq of anhydrous $CeCl_3$ and 1 eq of NaI in acetonitrile resulting in dealkylated products in comparable yields (68–90%). The reagent system $CeCl_3 \cdot 7H_2O$–NaI was selectively cleaved the alkoxy groups located at ortho carbonyl group without affecting the methoxy, prenyl, benzyl, acetyl, benzoyl and ester groups present in the substrate.

In conclusion, the letter describes the chemoselective dealkylation of alkoxy groups present ortho to formyl, acetyl, benzoyl, methoxycarbonyl and nitro groups in alkyl aryl ethers by cerium(III) chloride–NaI in refluxing acetonitrile. The method offers several advantages like mild reaction conditions, simple experimental / isolation procedures, high chemoselectiv-

Table 1 : Chemo-selective cleavage of alkyl and prenyl ethers by cerium(III) chloride-NaI

Entry	Substrate	Product[a]	Reaction Time / h	Yield / %[b]
1.			8	87
2.			5	75
3.			9	68[c]
4.			7	89
5.			10	86
6.			18	73
7.			15	69
8.			10	85
9.			8	77
10.			12	79
11.			20	67
12.			4	88
13.			3	80
14.			5	87
15.			3	90

[a] All products were characterised by ^{1}H NMR, IR and Mass spectra.
[b] Isolated yields. [c] 2,6-Dihydroxy product was isolated in 15%.

ity and compatibility with various functional groups hence it is useful addition to the existing methods.

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Reference and Notes

1 a) T. W. Greene and P. G. M. Wuts, “Protecting Groups in Organic Synthesis”, 3rd ed. Wiley, New York (1999). b) P. J. Kocienski, “Protecting Groups”; Thieme, Stuttgart (1994).

2 a) V. Bhatt, and Y. Kulkarni, *Synthesis*, **1983**, 249. b) B. C. Ranu and S. Bhar, *Org. Prep. Proced. Int.*, **1996**, 373.

3 S. Yamaguchi, M. Nedachi, H. Yokoyama, and Y. Hiraj, *Tetrahedron Lett.*,**1999**, 40, 7363

4. A. M. Bernard, M. R. Ghiani, P. P. Piras, and A. Rivoldini, *Synthesis*, **1989**, 287.

5 E. G. Paul and P. S .C. Wang, *J. Org. Chem.*, **1979**, 44, 2307.

6 D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc.,C*, **1971**, 40, 2204.

7 J. M. Lansinger, and R. C. Ronald, *Synth. Commun.*, **1979,** 9, 341.

8 a) G. I. Feutrill, and R. N. Mirrington, *Tetrahedron Lett.*, **1970**, 1327. b) G. I. Feutrill, R. N. Mirrington, and R. J. Nichols, *Aust. J. Chem.*, **1973**, 26, 345. c) B. Loubinox, G. Coudert, and G. Guillaumet, *Synthesis*, **1980**, 638. d) J. R. McCarthy, J. L. Moore, and R. J. Cregge, *Tetrahedron Lett.*, **1978**, 5183. e) G. I. Feutrill, and R. N. Mirrington, *J. Chem. Soc., Sect. C*, **1972,** 25, 1719.

9 a) G. A. Molander, *Chem. Rev.*, **92**, 29 (1992). b) D. Bartoli, M. Bosco, and L. Sambri, E. Marcantoni, and F. Nobili, *J. Org. Chem.*, **1997**, 62, 4183.

10 Experimental : A mixture of methyl or prenyl ether (2 mmol), cerium(III) chloride heptahydrate (3 mmol), and sodium iodide (3 mmol) in acetonitrile (10 mL) was stirred under reflux for an appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was diluted with water and extracted twice with ether (2 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting product was purified by column chromatography on silica gel (Aldrich, 100–200 mesh, ethyl acetate–hexane, 2:8) to give the pure hydroxy compound. **2a** (Table 1, Entry 1): mp 104–105 °C. ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3H), 3.95 (s, 3H), 6.4 (s, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 9.8 (s, 1H, -CHO), 11.4 (s, OH). EI MS : *m/z* (%) : 182 (100), 167 (70), 139 (20), 111 (15).