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A Simple Regioselective Demethylation of *p*-Aryl Methyl Ethers Using Aluminum Chloride-Dichloromethane System

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Abstract: Several aryl methyl ethers of phenolic esters and diaryl ketones have been selectively demethylated to their corresponding 4-hydroxy derivatives by using aluminium chloride-dichloromethane system at room temperature in good yields (53–85%).

Keywords: Aryl methyl ethers, regioselectivity, aluminium chloride

INTRODUCTION

Deprotection of phenolic ethers is a frequently encountered synthetic step in the preparation of complex molecules. Mild reagents and efficient protocols for deprotection always benefit a total synthesis of complex natural product. It has been intensively studied[1] due to its importance in organic synthesis,

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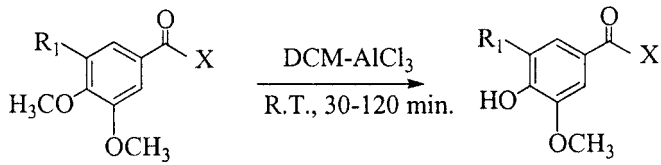
and numerous reagents and methods have been developed.[2–9] Demethylation of phenolic ethers with aluminium chloride[10–12] has been well studied, but the use of this reagent as a regioselective demethylating agent is less explored. In this communication, aluminium chloride-dichloromethane ($AlCl_3$-DCM) system is used for regioselective deprotection of aryl methyl ethers with the limitation of having an ester or a ketone group at *para* position. The process is simple, mild, and completes in a short time.

RESULTS AND DISCUSSION

We found that $AlCl_3$-DCM system could be used for deprotection of *p*-methoxy group in 3,4-dimethoxyphenylbenzoate, 3,4,5-trimethoxyphenylbenzoate, 3,4,5-trimethoxynaphthyl benzoates (Scheme 1 and Table 1, entries 1–4) at room temperature in short time. In these cases all the products were obtained in good yield (59–85%) with a simple workup procedure. This was further successfully extended to a natural product, i.e., reserpine[13,14] (**5a**, Table 1, entry 5). However, the reaction took 2 h to yield (**5b** in 68% yield). This may be due to the lower solubility of reserpine in DCM and/or the bulkier nature of the molecule. We carried out further investigations on several naphthophenone derivatives (Table 1, entries 6 and 7) and here also we observed that the deprotection at *para* position occurred regioselectively. The reaction could not be extended to aryl methyl ethers with free carboxylic acids such as 3,4-dimethoxy benzoic acid/3,4,5-trimethoxybenzoic acid and aryl methyl ethers without any carbonyl group in the aromatic ring.

2,4,5-Trimethoxybenzaldehyde has been selectively demethylated[10] to 3-methoxy, 2,4-dihydroxy benzaldehyde using $AlCl_3$ in ethyl acetate at room

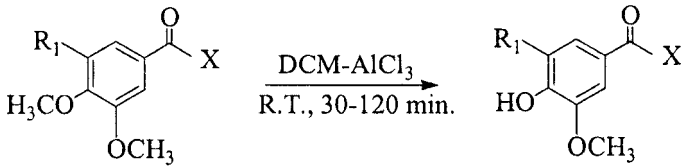


R_1= H/OCH_3 53-85%

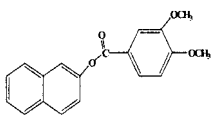
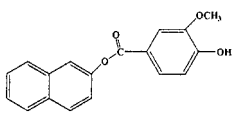
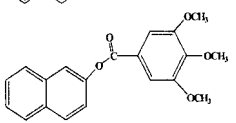
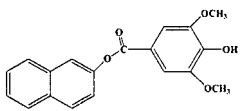
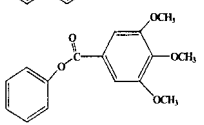
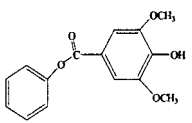
X= Phenyloxy/ 1-naphthyloxy/ 2-naphthyloxy/ 1-Naphthyl,2-ol/ 1-Naphthyl,2-O-acetic acid/Yohimban moiety of Reserpine.

Scheme 1.

Table 1. Deprotection of *p*-aryl methyl ethers in $AlCl_3$-DCM system

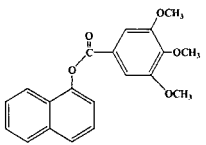
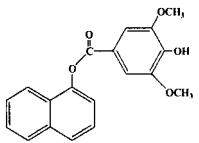
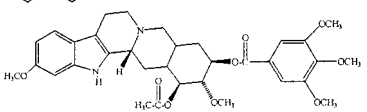
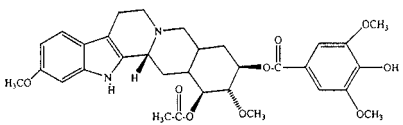
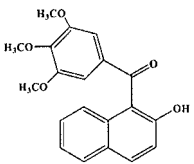
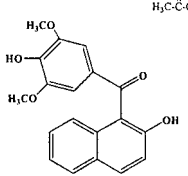
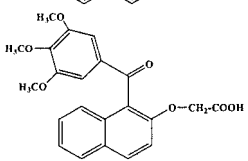
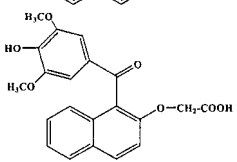


R_1= H/OCH_3 53-85%
X= Aryl/aryloxy

Entry	Substrate (a)	Product (b)	Molar equiv. of $AlCl_3$	Time (min)	Isolated yield (%)
1			7	30	58
2			7	30	85
3			7	40	82

(*continued*)

Table 1. Continued.

Entry	Substrate (a)	Product (b)	Molar equiv. of $AlCl_3$	Time (min)	Isolated yield (%)
4			7	40	73
5			9	120	68
6			7	50	72
7			9	40	53

temperature. Horie et al.[2] selectively demethylated 7-hydroxy-3,5,8-trimethoxy flavones with aluminium bromide in acetonitrile to corresponding 5,7-dihydroxy flavone and 3,7-dihydroxy flavone derivatives. Another demethylation approach was developed by [3,7] in which they have selectively demethylated *o*-methoxy group in 2,3,4,6-tetramethoxy acetophenone moieties by the same system. Mateeva et al.[12] used $AlBr_3$ as demethylation agent in the synthesis of some novel flavonoid derivatives as potential HIV-Integrase inhibitors. In these flavonoids they selectively demethylated 5-methoxy group while the rest of the methoxy groups at 7,3′,4′ and 5′ were intact.

The use of present $AlCl_3$-DCM system was effective to produce exclusively *p*-demethylated product only for the aryl methyl ethers having an ester or a keto groups at *para* position as listed in the Table 1. The deprotection at *p*-position might be facilitated by the electron withdrawing nature of carbonyl group, but the failure of the reaction in case of free carboxylic acids is not clear.

In summary, it has been demonstrated that aluminium chloride in dichloromethane acts as an efficient regioselective demethylating agent for *p*-aryl methyl ethers in phenolic esters and diary1 ketones.

EXPERIMENTAL

All the reactions were monitored on Merck precoated silica gel GF_{254} TLC plates. Compounds were purified on a BUCHI B-688 MPLC system using TLC grade silica gel-H (without binder) as an adsorbent and hexane-ethyl acetate as eluents. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. ^1H & ^{13}C-NMR spectra were recorded on a Bruker-AVANCE DRX-300 MHz spectrometer. TMS was used as an internal standard. Electrospray mass spectra were recorded on MICROMASS QUATTRO II triple quadrupole mass spectrometer after dissolving in methanol. Elemental analysis was carried out on HERAEUS CHN-*O*-RAPID elemental analyzer.

TYPICAL PROCEDURE

To a solution of **6a** (Table 1, entry 6, 100 mg, 0.296 mmol) in dry dichloromethane (20 mL) was added anhydrous aluminium chloride (280 mg, 2.09 mmol). It was stirred for 30 min at room temperature. On completion of the reaction, the reaction mixture was diluted with $CHCl_3$, washed with dil. HCl (5%, 10 mL) and water. The organic layer was dried (Na_2SO_4) and

concentrated. The residue was purified by silica gel chromatography to yield **6b** (69 mg, 72%) as a crystalline solid.[1]

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[1]Selected data for **5a**: ^{1}H NMR (300 MHz $CDCl_3$, TMS): 3.49 (s 3H C-17, OCH_3), 3.79 (s, 6H, 3′ & 5′, OCH_3), 3.81 (s, 3H, C-11, OCH_3), 3.92 (s, 3H, 4′, OCH_3). ^{13}C NMR (75.46 MHz, $CDCl_3$): 16.8 (C-6), 24.2 (C-14), 29.7 (C-19), 32.3 (C-15), 34.0 (C-20), 49.0 (C-21), 51.2 (C-5), 51.6 (C-16), 51.7 (OCH_3 at C-11), 53.7 (C-3), 56.2 (3′ & 5′, OCH_3), 60.80 (4′, OCH_3), 77.8 (C-18), 78.0 (C-17), 95.3 (C-12), 107.0 (C-2′ & 6′), 108.0 (C-7), 108.9 (C-10), 118.9 (C-9), 122.2 (C-8), 125.3 (C-1′), 130.5 (C-2), 136.4 (C-13), 143.0 (C-4′), 152.9 (C-3′ & 5′), 156.2 (C-11), 165.4 (ester carbonyl at C-18), 172.7 (ester carbonyl at C-16); Electrospray Mass: 609 $[M]^+$. Selected data for **5b**: m.p.: oil. Yield: 68% ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 3.52 (s, 3H, C-17, OCH_3), 3.84 (s, 9H, C-11, 3′ & 5′, OCH_3), ^{13}C NMR (75.46 MHz, $CDCl_3$): 51.87 (C-17), 57.7 (3′ & 5′, OCH_3), 60.7 (C-11), 77.4 (C-18), 79.6 (C-17), 106.9 (C-2′ & 6′), 124.9 (C-1′), 138.4 (C-4′), 153.9 (C-3′ & 5′), 155.8 (C-11), 171.6 (ester carbonyl at C-16), 165.3 (ester carbonyl at C-18). Electrospray Mass: 595 $[M]^+$; Selected data for **6a**: m.p.; 138–40°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 3.70 (s, 6H, 3′ & 5′, OCH_3), 3.93 (s, 3H, 4′, OCH_3), 6.90–7.93 (m, 8H, aromatic protons), 10.84 (s, 1H, phenolic OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): 56.63 (3′ & 5′ OCH_3), 61.02 (4′, OCH_3), 108.57–160.47 (aromatic carbons), 198.73 (ketone); Electrospray Mass: 360.9 $[M + Na]^+$, 338.9 $[M + H]^+$; Analysis: $C_{20}H_{18}O_5$, Calcd: C, 71.01%; H, 5.32%. Obsd: C, 71.48%; H, 4.92%. Selected data for **6b**: Yield 69 mg (72%). m.p.: 116–18°C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 3.75 (s, 6H, 3′ & 5′, OCH_3), 6.96–7.94 (m, 8H, aromatic protons), 5.99 (s, 1H, phenolic OH), 10.92 (s, 1H, phenolic OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): 56.33 (3′ & 5′, OCH_3), 107.47–159.79 (aromatic carbons), 198.29 (ketone); Analysis: $C_{19}H_{16}O_5$, Calcd: C, 67.28%; H, 4.94%. Obsd: C, 66.84%; H, 4.69%. Selected data for **7a**: m.p.: 132–35°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 3.74 (s, 6H, 3′ & 5′, OCH_3), 3.92 (s, 3H, 4′, OCH_3), 4.77 (s, 2H, OCH_2), 7.16–7.97 (m, 8H, aromatic); ^{13}C NMR (75.46 MHz, $CDCl_3$): 56.73 (3′ & 5′, OCH_3), 60.86 (4′, OCH_3), 67.17 (OCH_2), 108.85–153.60 (aromatic carbons), 170.39 (-COOH), 196.11 (ketone); Electrospray Mass: 419 $[M + Na]^+$, 397 $[M + H]^+$; Analysis: $C_{22}H_{20}O_7$, Calcd: C, 66.67%; H, 5.05%. Obsd: C, 67.18%; H, 5.39%. Selected data for **7b**: Yield: 53%. m.p.: 109–110°C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 3.80 (s, 6H, 3′ & 5′, OCH_3), (s, 2H, OCH_2), 7.18–7.72 (m, 8H, aromatic protons); ^{13}C NMR (75.46 MHz, $CDCl_3$): 56.62 (3′ & 5′-OCH_3), 67.24 (OCH_2), 109.1–154.42 (aromatic carbons), 170.68 (-COOH), 196.62 (ketone); Analysis: $C_{21}H_{18}O_7$, Calcd: C, 65.97%; H, 4.71%. Obsd: C, 66.43%; H, 4.29%.

REFERENCES

1. Ranu, B. C.; Bhar, S. Dealkylation of ethers. A review. *Organic Preparations and Procedures International* **1996**, *28*, 371–409.
2. Horie, T.; Tsukanyama, M.; Kawamura, Y.; Seno, M. Studies of the selective *O*-alkylation and dealkylation of flavonoids. 10. Selective demethylation of 7-hydroxy-3,5,8-trimethoxy flavones with anhydrous aluminium halide in acetonitrile or ether. *J. Org. Chem.* **1987**, *52* (21), 4702–4709.
3. Horie, T.; Tsukanyama, M.; Kawamura, Y.; Yamamoto, S. Studies of the selective *O*-alkylation & dealkylation of flavonoids IX. A new method for synthesizing 3,5-dihydroxy-7,8-dimethoxy flavones from 3-hydroxy-5,7,8-trimethoxy flavones. *Chem. Pharm. Bull.* **1987**, *35* (11), 4465–4472.
4. Lal, K.; Ghosh, S.; Solomon, R. Hydroxyl-directed regioselective monodemethylation of polymethoxy arenes. *J. Org. Chem.* **1987**, *52* (6), 1072–1078.
5. Breeden, S. W.; Coop, A.; Husbands, S. M.; Lewis, J. W. 6-*O*-Demethylation of the thevinols with lithium aluminium hydride. Selective demethylation of tertiary alkyl methyl ether in the presence of an aryl methyl ether. *Helv. Chim. Acta.* **1999**, *82*, 1978–1980.
6. Piggott, M. J.; Wege, D. Synthesis of ventilone A. *Aust. J. Chem.* **2000**, *53* (9), 749–754.
7. Deville, J. P.; Behar, V. Chelation-controlled selectivity in the clay-catalysed deprotection of phenolic methoxy methyl ethers. *J. Org. Chem.* **2001**, *66* (11), 4097–4098.
8. Younis, Y. M. H. Demethylation of aryl methyl ethers and selective demethylation of pyrones using iodotrimethylsilane. *Int. J. Chem.* **2001**, *11* (2), 75–85.
9. Chakraborti, A. K.; Sharma, L.; Nayak, M. K. Influence of hydrogen bonding in the activation of nucleophiles: PhSH-(catalytic) KF in *N*-methyl-2-pyrrolidone as an efficient protocol for selective cleavage of alkyl/aryl esters and aryl alkyl ethers under nonhydrolytic and neutral conditions. *J. Org. Chem.* **2002**, *67* (8), 2541–2547.
10. Demettenaere, J.; Syngel, K. V.; Markusse, A. P.; Vervisch, S.; Debenedetti, S.; Kimpe, N. D. Synthesis of 6-methoxy-4*H*-1-benzopyran-7-ol, a character donating component of the fragrance of *Wisteria sinensis*. *Tetrahedron* **2002**, *58*, 2163–2166.
11. Learmonth, D. A.; Alves, P. C. Improved method for demethylation of nitrocatechol methyl etheres. *Synth. Commun.* **2002**, *32* (4), 641–649.
12. Mateeva, N. N.; Kode, R. N.; Redda, K. K. Synthesis of novel flavonoid derivatives as potential HIV-Integrase inhibitors. *J. Het. Chem.* **2002**, *39* (6), 1251–1258.
13. Chatterjee, A.; Mukhopadhyay, S.; Shoolery, J. N. ^{13}C Nuclear Magnetic Resonance study of tri-*O*-methyl gallomide a biosynthetic unit of reserpine from *Alstonia venenatia*. *R. Br. Ind. J. Chem.* **1978**, *16B*, 67–68.
14. Lounasmaa, M.; Tolvanen, A. A 400 MHz ^{1}H NMR study of four basic reserpine alkaloids. *Heterocycles* **1985**, *23* (2), 371–375.