Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Available online: 27 Apr 2009

To cite this article: Xiujie Ji, Bowen Cheng, Jun Song, Chao Liu & Yufei Wang (2009): Nitro-Group-Directed Selective Dealkylation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:11, 2053-2057

To link to this article: http://dx.doi.org/10.1080/00397910802633439

Synthetic Communications®, 39: 2053–2057, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802633439

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Nitro-Group–Directed Selective Dealkylation

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Abstract: Nitro-substituted phenolic ethers were successfully selectively dealkylated. The directing effect of the nitro group is supported by the excellent regioselectivities and good yields. These reactions demonstrate that the complexation of $AlCl_3$ with the phenolic nitro group is stronger than with the phenolic ether alone. The mechanism for the selective dealkylation directed by the nitro group is proposed.

Keywords: $AlCl_3$, complexation, nitro group, selective dealkylation

It has long been found that heteroatoms with lone pairs can complex with Lewis acids. Stable complexes are often obtained when the heteroatoms are nitrogen and oxygen.[1] Nitro is a fundamental functional group in organic chemistry. We have reported that $AlCl_3$ coordinates more strongly to the oxygen in the nitro group and in the neigh'boring ester group than it does to an isolated phenolic ester.[2] We believe that this directing effect of the nitro group can be taken advantage of in organic synthesis such as selective dealkylation. To prove further the existence

Received October 12, 2008.
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Table 1. Selective dealkylation of 1,4-dialkoxy-2-nitrobenzene using $AlCl_3$

1 **2**

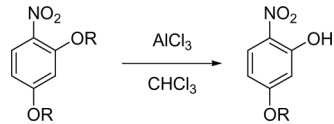
Entry	Product	R	$AlCl_3$ (eq.)	Temp. (°C)	Time (h)	Yield (%)[a]	Mp (°C)
1	**2a**	Bn	1.0	0	0.5	87	154–156 (156–158[4])
2	**2b**	i-Pr	1.0	0	1.5	96	42–44 (42–44[5])
3	**2c**	Me	2.0	60	2.5	93	74–75 (78–79[6])
4	**2d**	Et	1.5	60	1.5	87	80–82 (81–81.5[7])
5	**2e**	n-Bu	1.5	60	1.0	96	Yellow oil

[a]Yield of isolated product.

of this effect as well as to use this effect in organic synthesis prompted us to carry out the following research.

The substrates, 1,4-dialkoxy-2-nitrobenzene and 1,5-dialkoxy-2-nitrobenzene, were made by dialkylation of the hydroquinone and resorcinol using the corresponding alkyl halides under basic condition followed by nitration using $Cu(NO_3)_2$ and Ac_2O.[3] Substrates were treated with $AlCl_3$ in anhydrous chloroform. Dialkylated nitro hydroquinones and dialkylated nitro resorcinols were all successfully and selectively dealkylated in good yields and at good reaction rates (Tables 1 and 2).

Table 2. Selective dealkylation of 1,5-dialkoxy-2-nitrobenzene using $AlCl_3$



3 **4**

Entry	Product	R	$AlCl_3$ (eq.)	Temp. (°C)	Time (h)	Yield (%)[a]	Mp (°C)
6	**4a**	Bn	1.0	0	0.5	90	94–96 (96–97[8])
7	**4b**	i-Pr	1.0	0	1.0	94	44 (44[9])
8	**4c**	Me	1.5	60	1.5	93	92 (95[10])
9	**4d**	Et	1.5	60	1.5	93	76–78 (79[11])
10	**4e**	n-Bu	1.5	60	1.0	96	43–44 (43–44[12])

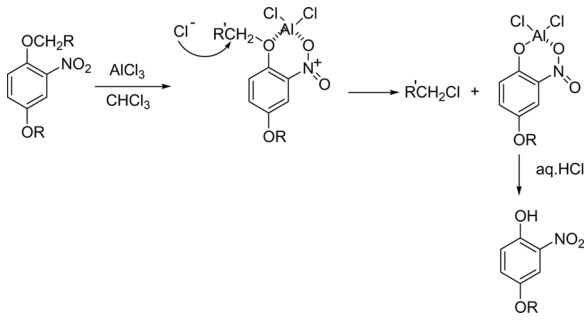
The $AlCl_3$ use ranged from 1 to 2 eq. For selective dealkylation of benzyl and isopropyl groups, the reaction temperatures were 0°C and 60°C for methyl and primary alkyl groups. These results suggest that the nitro oxygen and the ether oxygen both complex with $AlCl_3$. This makes the alkyl group susceptible to attack by a chloride anion to form RX (Scheme 1). We carried out gas chromatography–mass spectrometric (GC-MS) and GC anlysis and found that BnCl was formed in 81% yield. This type of deprotection has been catalyzed by trifluroaceticacid (TFA),[3] LiCl,[13] and LiI[14] under harsh conditions (e.g., in refluxing quinoline).[14]

From the result listed in Tables 1 and 2, we can see that the benzyl cation is the most stable one and the dealkylation is the fastest. The secondary group (isopropyl) is the second fastest. The primary alkyl group and methyl group are roughly at the same dealkylation rate because the methyl group is less hindered but the primary cation is more stabilized. Accordingly, the following mechanism is proposed (Scheme 1).

Most of the dealkylated compounds such as 4-methoxy-2-nitrophenol are useful intermediates for dye stuffs,[14] calcium ion indicators,[15] antibacterial and antitumor medications,[16] anti-inflammatories, and allergy inhibitors.[17]

In conclusion, we have provided evidence that the complexation of $AlCl_3$ with the phenolic nitro group is stronger than that with the phenolic ether alone. This type of complexation has led to an efficient and convenient selective dealkylation of dialkylated nitrohydroqinone and nitroresorcinol.

All the products are fully characterized spectroscopically, and their infrared (IR; 3250–3430 cm^{-1}) and ^1H NMR (10–10.5 ppm) spectra display typical intramolecular hydrogen bonding.



Scheme 1. Proposed reaction mechanism of selective dealkylation using $AlCl_3$.

EXPERIMENTAL

Typical Procedure of Selective Dealkylation

The substrate **1** (1 mmol) was dissolved in anhydrous chloroform (30 mL) and cooled to 0°C. After aluminum chloride (1.0 to 2.0 eq) was added in portions within 5 min, the reaction was kept at 0°C or refluxed (as indicated in Tables 1 and 2). Upon addition of $AlCl_3$, the reaction solution became red. Thin-layer chromatography (TLC) monitored the reaction. When the substrate disappeared, the reaction was cooled to rt, and reaction mixture was treated with 10% aq. HCl, extracted with dichloromethane (40 mL × 3), dried with Na_2SO_4, and concentrated. The residue was purified by crystallization or flash-column chromatography.

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