Dealkylation of Activated Alkyl Aryl Ethers Using Lithium Chloride in Dimethylformamide

Angela M. Bernard, M. Rossella Ghiani, Pier Paolo Piras,* Antonio Rivoldini

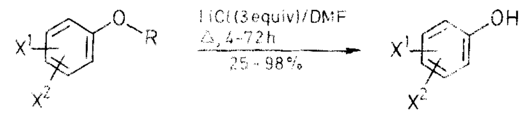
Istituto di Chimica Farmaceutica, Tossicologica ed Applicata, Università di Cagliari, Via Ospedale 72, I-09100 Cagliari, Italy

Alkyl aryl ethers having electron-withdrawing substituents in the *ortho* or *para* positions are easily cleaved with lithium chloride in dimethylformamide.

Studying the stereochemistry of the dealkoxycarbonylation of some dimethyl arylmethylenepropanedioates[1] using chloride ion, we observed ether cleavage[2] to varying extents when a methoxy group was present in the *ortho* position of the aromatic ring. A literature search revealed that the use of halide ion in ether cleavage has received scant attention[3] in spite of the fact that this reaction can be carried out under essentially neutral conditions. Only lithium iodide in collidine or pyridine was used to cleave methyl aryl ethers and ethyl or methyl aryl ethers containing intramolecular hydrogen bonds.[4,5]

The cleavage of ethers is usually carried out with acids;[6] however, attention has also been devoted to the use of nucleophilic reagents,[3,7] in particular sodium[8-10] and lithium[11] alkanethiolate reagents. Ethoxyphenols[12] may be obtained by the selective cleavage of the methoxy group in ethoxymethoxyarenes using lithium diphenylphosphide; thus, for example, 4-ethoxy-3-hydroxybenzaldehyde may be obtained from 4-ethoxy-3-methoxybenzaldehyde.[13]

In the nucleophilic cleavage of alkyl aryl ethers carrying electron-attracting groups, several competing reactions are possible that limit the efficiency of the method: halogen atoms can be removed via nucleophilic aromatic substitution[8-10] when using thiolates in dimethylformamide, whereas formyl groups can undergo electrophilic addition by the sodium salt of *N*-methylaniline in the presence of hexamethylphosphoric triamide.[14] Further, treatment of alkyl nitroaryl ethers with sodium cyanide in dimethyl sulfoxide failed to give clean ether cleavage[15] because of the occurrence of the von Richter reaction. We now report the use of lithium chloride in dimethylformamide for the cleavage of alkyl aryl ethers carrying formyl, ester, or nitro groups. The reactions were carried out using a 3:1 molecular ratio of lithium chloride/ether in boiling dimethylformamide for reaction times of 4-72 hours (Tables 1 and 2). Ethoxy and even isopropoxy groups were easily cleaved when they were *ortho* to a nitro group. When an aldehydic or an ester carbonyl group were present the cleavage required longer reaction times but the yields were reasonably good. The methoxycarbonyl function does not survive these reaction conditions but undergoes demethylation to the carboxy group. Halogen atoms do not interfere, at least in the examined cases; they undergo nucleophilic substitution only to a very limited extent.



1a-u **2a-u**

The benzodioxole ring appears to remain unaffected under our experimental conditions, but we cannot exclude a ring opening-ring closure equilibrium.

Table 1. Cleavage of Alkyl Aryl Ethers **1a–q** with LiCl in DMF

Ether[a]	R	X¹	X²	Reaction Time (h)	Yield[b] (%)	Phenol[c]	mp (°C) or bp (°C)/Torr	
							found	reported
1a	Me	2-NO_2	H	6	98 (92)[17]	**2a**	44	45[18]
1b	Me	3-NO_2	H	6	50	**2b**	95	96[18]
1c	Me	4-NO_2	H	24	98 (92)[19]	**2c**	115	114[18]
1d	Et	2-NO_2	H	22	90	**2a**	44	45[18]
1e	*i*-Pr	2-NO_2	H	24	35	**2a**	44	45[18]
1f	$PhCH_2$	2-NO_2	H	22	98[d]	**2a**	44	45[18]
1g	Et	4-NO_2	H	24	10	**2c**	112	114[18]
1h	Me	2-NO_2	4-Br	4	95[e]	**2h**	90	89[23]
1i	Me	2-Br	H	72	67[f] (81)[20]	**2i**	90/14	194–195/760[18]
1j	Me	2-Cl	H	72	55 (80)[17]	**2j**	63/14	175–176/760[18]
1k	Me	2-CHO	H	22	70 (48)[21]	**2k**	83/13	196.5/760[18]
1l	Et	2-CHO	H	22	25	**2k**	83/13	196.5/760[18]
1m	*i*-Pr	2-CHO	H	22	5	**2k**	83/13	196.5/760[18]
1n	Me	2-CO_2Me	H	22	90[g] (89)[14]	**2n**	161	159[18]
1o	CH_2CO_2Me	2-Me	H	22	5[h]	**2o**	188/760	191 5/760[18]

[a] Except for **1h**[16], ethers **1** were either commercially available (Aldrich Chemie) or easily prepared from the corresponding phenols.

[b] Yield of isolated product. In brackets, reported yields.

[c] Identified by NMR spectrometry and by comparison of the physical properties with those of authentic samples.

[d] Benzyl chloride yield was isolated in almost quantitative from the material insoluble in aqueous sodium hydroxide.

[e] Traces of 4-chloro-2-nitro-phenol were detected.

[f] 2-Chlorophenol was detected in 6% yield.

[g] Salicylic acid was the only isolated product.

[h] 2-Methylphenoxyacetic acid was recovered in 90% yield.

Table 2. Cleavage of Di- and Trimethoxybenzenes **1p–r** and of Dimethoxybenzaldehydes **1s–u** with LiCl in DMF

Ether[a]	R	X¹	X²	Reaction Time (h)	Yield[b] (%)	Relative Content (%) of Isomer[c]	Phenol	X¹	X²	mp (°C) or bp (°C)/Torr	
										found	reported
1p	Me	2-OMe	H	25	8	– (90)[22]	**2p**	2-OMe	H	92/14	106.5/24[18]
1q	Me	3-OMe	H	25	7	– (89)[22]	**2q**	3-OMe	H	124/10	244.3/760[18]
1r	Me	2-OMe	3-OMe	48	60 (60)[22]	75[d] (30)[22]	**2r**	2-OMe	6-OMe	55	55–56[18]
						12 (30)[22]	**2r′**	2-OMe	3-OMe	121/12	124–125/17[18]
1s	Me	2-CHO	6-OMe	22	98	–	**2s**	2-CHO	6-OMe	43	42–43[24]
1t	Me	2-CHO	5-OMe	22	70	60	**2t**	2-CHO	5-OMe	40	41–42[25]
						40	**2t′**	3-OMe	4-OMe	152	153[26]
1u	Me	4-CHO	2-OMe	22	61	44[e]	**2u**	2-OMe	4-CHO	80	81–82[18]
						42	**2u′**	2-OMe	5-CHO	115	116[18]

[a] All ethers and phenols except for **2t′**[26] were purchased from Aldrich-Chemie, Germany.

[b] Yield of isolated product or mixture of isomers. In brackets: reported yield.

[c] Determined by GLG; in brackets: reported percentages. The products were also separated by column chromatography (silica gel, light petroleum/Et_2O, 3 : 1) and compared with authentic samples.

[d] 3-Methoxy-1,2-dihydroxybenzene was present in 13% yield.

[e] 3,4-Dihydroxybenzaldehyde was detected in 14% yield.

Practically no reaction was observed with anisol and the methylanisols. Dimethoxybenzenes are cleaved only to a very low degree, whereas 1,2,3-trimethoxybenzene undergoes cleavage at the central methoxy group with high selectivity (75%). One methoxy group of dimethoxybenzaldehydes is easily cleaved, whereas the tendency for bis-demethylations is very limited.

Since some of the drawbacks of the nucleophilic reagents mentioned above are not observed and because of the neutral reaction conditions and the low cost of the reagent, the use of lithium chloride will be particularly attractive for the cleavage of activated alkyl aryl ethers.

2-Hydroxy-3-methoxybenzaldehyde (2s); Typical Procedure:

2,3-Dimethoxybenzaldehyde (**1s**; 1.0 g, 6 mmol) and LiCl (0.76 g, 18 mmol) are heated in boiling DMF (10 mL), the reaction being monitored by GLC (2 m SE-30 packed column). When the starting material has disappeared (22 h), 10% aqueous NaOH (30 mL) is added, the solution is washed with Et_2O (2 × 25 mL), then acidified with 10% aqueous HCl (50 mL), and extracted with Et_2O (2 × 25 mL). The organic phase is washed with brine (30 mL), dried (Na_2SO_4), and concentrated in a rotavapor; yield: 0.88 g (98%); mp 42 °C; mixture mp with a commercial sample (Aldrich): 42 °C.

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