

Lithium chloride-catalyzed selective demethylation of aryl methyl ethers under microwave irradiation

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Abstract

A rapid method for the selective cleavage of aryl methyl ether in the lithium chloride-*N,N*-dimethylformamide (LiCl-DMF) system under microwave irradiation has been developed. Effects of substituent, metal salt and solvent on the activity and selectivity in the cleavage reaction have been investigated. It is found that microwave significantly improves the reaction yield and the selectivity of demethylation for electron deficient aromatic methyl ethers. The catalytic mechanism of demethylation by LiCl salt is proposed.

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Keywords: Demethylation; Aryl methyl ethers; Microwave irradiation

1. Introduction

The cleavage of aryl methyl ethers is one of the most fundamental reactions in organic synthesis in the light of its importance for the deprotection of phenols and its involvement in the manufacture of a number of pharmaceuticals, drugs and the other fine chemicals. The reaction is usually caused by acids (including Lewis acids, e.g. AlCl_3 and BBr_3) or bases [1,2]. However, these conditions are not compatible with compounds having acid- or base-sensitive functional groups. Up to now, there are few reports on the procedures for the chemo- and regioselective cleavage of aryl methyl ethers, either by special nucleophilic thiolates or by special Lewis acid. Thus, it is necessary to develop a new and efficient procedure for selective cleavage of aryl methyl ethers in the presence of functional groups with cheap, commercial available reagents under essentially neutral conditions. Lithium chloride is an ideal choice to catalyze the selective cleavage of aryl methyl ethers, but the low activity, unsatisfactory yields and longer reaction time limited its practical application [3,4].

It is well known that microwave irradiation can activate the organic reaction catalyzed by inorganic solids [5–7] and shorten

the reaction time of many organic reactions from hours or days to minutes or even seconds. Microwave has been well recognized as a convenient method for promoting rapid reactions [8,9] with much less energy. Simultaneously, microwave irradiation under milder reaction conditions and using less toxic reagents and solvents offers a further advantage and additional convenience in organic synthesis. Undoubtedly, it is a tendency toward green chemistry. We have exploited the application of microwave in the selective cleavage of aryl methyl ethers in the lithium chloride-*N,N*-dimethylformamide (LiCl-DMF) system.

2. Experimental

2.1. General procedure

The reactions were carried out in MCL-II microwave reactor. Silica gel F254 plates were used for TLC and spots were examined under UV light at 254 nm and developed by an iodine vapor. Flash chromatography was performed on silica gel H. NMR spectra were recorded on Bruker AC-E 200 MHz, Varian Mercury 400 MHz and Bruker Avance 600 MHz spectrometer.

2.2. Reactions

To a solution of aryl methyl ether (1.46 mmol) in anhydrous DMF (4.37 mmol, 0.3 mL), was added LiCl (4.37 mmol, dried).

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Table 1
Product data

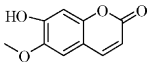
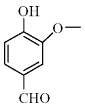
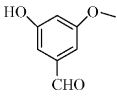
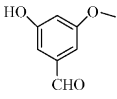
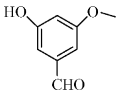
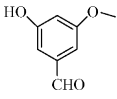
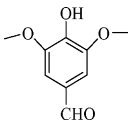
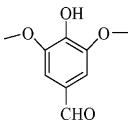
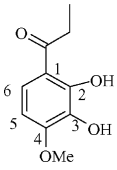
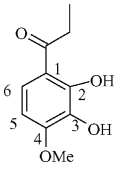
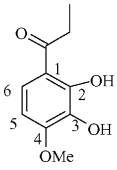
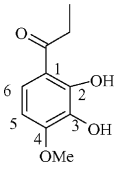
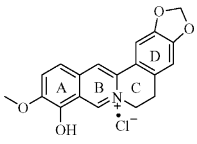
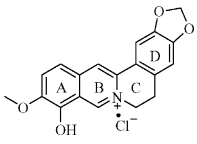
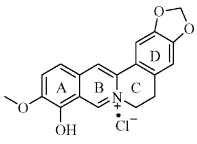
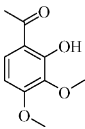
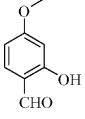
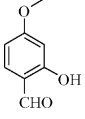
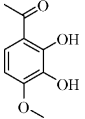
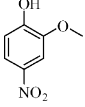
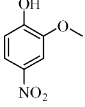
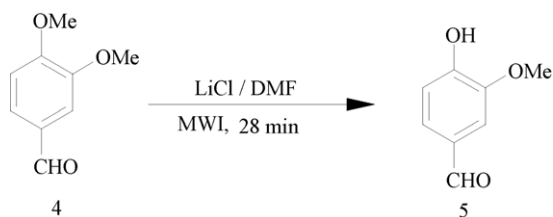
	m.p.	203–205 °C (lit. 204 °C) [10]
	¹ H NMR (CDCl ₃ , 400 MHz)	δ(ppm) 3.88 (s, 3H, –OCH ₃), 6.85(s, 1H, PhO–H), 6.99–7.39(m, 3H, Ph–H), 9.77(s, 1H, –CHO)
	m.p.	80–82 °C (lit. 81–83 °C) [11]
	¹ H NMR (CDCl ₃ , 400 MHz)	δ(ppm) 3.85(s, 3H, –OCH ₃), 5.45(s, 1H, PhO–H), 6.68–7.27(m, 3H, Ph–H), 9.89(s, 1H, –CHO)
	¹³ C NMR (DMSO-d ₆ , 50 MHz)	δ(ppm) 55.6, 105.6, 107.8, 108.9, 138.6, 159.4, 161.2, 193.1
	m.p.	129–130 °C (lit. 128–129 °C) [12]
	¹ H NMR (CDCl ₃ , 400 MHz)	δ(ppm) 3.96(s, 6H, –OCH ₃), 6.38(s, 1H, PhO–H), 7.16(s, 2H, Ph–H), 9.81(s, 1H, –CHO)
	m.p.	112–114 °C (lit. 113–114 °C) [13]
	¹ H NMR (CDCl ₃ , 600 MHz)	δ(ppm) 1.22–1.24(t, 3H, –CH ₃ , <i>J</i> = 7.32), 2.96–2.99(q, 2H, –CH ₂ –, <i>J</i> = 7.26), 3.96(s, 3H, –OCH ₃), 5.53(s, 1H, PhO–H), 6.49–7.36(m, 2H, Ph–H), 12.61(s, 1H, PhO–H)
	¹³ C NMR (CDCl ₃ , 150 MHz)	δ(ppm) 8.4, 31.2, 56.2, 102.8, 114.2, 121.7, 133.5, 150.4, 151.8, 206.2
	NOEDS (CDCl ₃ , 400 MHz)	NOE difference spectroscopy gave NOE correlations from the 5 position proton (δ 6.50, H-5) to 4 position methoxy proton (δ 3.95) and 6 position proton (δ 7.35).
	HRMS (ESI)	<i>m/z</i> (%) for C ₁₀ H ₁₂ O ₄ Na, calcd. 219.0633, found (M+Na) 219.0632
	¹ H NMR (DMSO-d ₆ , 600 MHz)	δ(ppm) 3.09–3.11(t, 2H, –CH ₂ –, <i>J</i> = 6.03), 4.59–4.61(t, 2H, –CH ₂ –, <i>J</i> = 5.97), 3.81(s, 3H, –OCH ₃), 6.12(s, 2H, –OCH ₂ O–), 6.70(s, 1H, PhO–H), 7.01–8.44(m, 5H, Ph–H), 9.35(s, 1H, N=CH–)
	m.p.	245 °C (dec.) (lit. 245 °C dec.) [14]
	NOEDS (DMSO-d ₆ , 400 MHz)	NOE difference spectroscopy gave NOE no correlation from the methoxy proton (δ 3.78) to the 5 position proton (δ 9.35)
	m.p.	74–76 °C (lit. 75–77 °C) [15]
	¹ H NMR (CDCl ₃ , 600 MHz)	δ(ppm) 3.85(s, 3H, –OCH ₃), 6.42–7.43(m, 3H, Ph–H), 9.71(s, 1H, –CHO), 11.48(s, 1H, PhO–H)
	m.p.	39–42 °C (lit. 41–42 °C) [16]
	¹ H NMR (CDCl ₃ , 600 MHz)	δ(ppm) 2.57(s, 3H, –CO–CH ₃), 3.96(s, 3H, –OCH ₃), 5.57(s, 1H, PhO–H), 6.50–7.33(m, 2H, Ph–H), 12.50(s, 1H, PhO–H)
	¹ H NMR (CDCl ₃ , 400 MHz)	δ(ppm) 4.00(s, 3H, –OCH ₃), 6.34(s, 1H, PhO–H), 6.97–7.89(m, 3H, Ph–H)
	m.p.	101–103 °C (lit. 99.5–101.5 °C) [17]

Table 1 (Continued)

	¹ H NMR (CDCl ₃ , 400 MHz)	δ(ppm) 4.01(s, 3H, -OCH ₃), 5.92(s, 1H, PhO-H), 6.90–7.86(m, 3H, Ph-H)
	m.p.	103–105 °C (lit. 104–106 °C) [17]
	¹ H NMR (CDCl ₃ , 400 MHz)	δ(ppm) 3.86(s, 3H, -OCH ₃), 5.71(s, 1H, PhO-H), 6.69–7.07(m, 3H, Ph-H)
	b.p.	95–98 °C (lit. 95–110 °C) [18]



Scheme 1. Demethylation of 3,4-dimethoxybenzaldehyde.

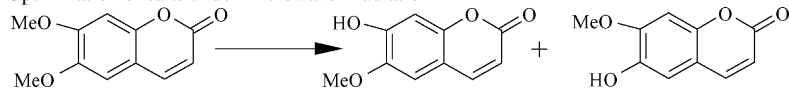
The mixture was irradiated under microwave (545 W, 160 °C) for 5–30 min. On completion of the reaction, as indicated by TLC, 8 mL of diluted HCl (0.1 M) was poured into the reaction mixture at 0 °C, then the solution was filtrated to give the crude product or extracted with ethyl acetate (3 × 10 mL), and the combined solution was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give the crude product. The crude product was purified by recrystallization in 95% ethanol or flash column chromatography of silica gel with petroleum ether/ethyl acetate as eluant to give final product. The products were confirmed by ¹H NMR, ¹³C NMR spectra, NOE difference spectroscopy and HRMS (ESI). The spectra data are summarized in Table 1.

3. Results and discussion

3.1. Solvent effect

First we investigated the solvent effect on the cleavage of aryl methyl ether under microwave irradiation. 6,7-Dimethoxy-2H-1-benzopyran-2-one (compound **1**) as model was irradiated by

Table 2

Optimization of salts under microwave irradiation^a

Entry	Salts ^b	Products	Yield (%)	t (min)
1	NaCl (or NaBr, or KCl, or KBr)	2 and 3 mixture	Trace	30
2	NaI (or KI)	2 and 3 mixture	~70	30
3	CuCl	2 and 3 mixture	Trace	30
4	CuCl ₂ (or CuBr ₂)	2 and 3 mixture	~70	30
5	NH ₄ Cl	–	0	30
6	LiCl	2	73	30

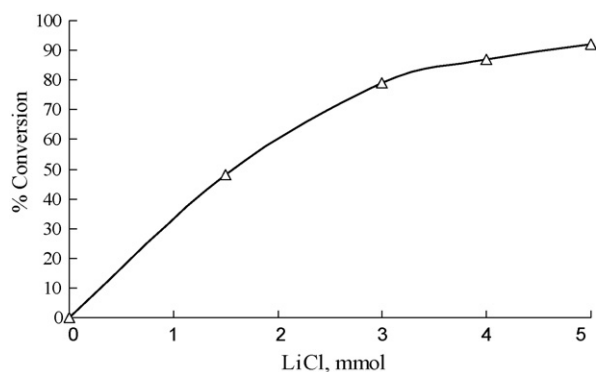
^a DMF as solvent.^b Substrate:salt = 1.46:4.37 (mmol).

Fig. 1. Influence of the amount of lithium chloride on conversion. The reactivity of demethylation increases with the amount of lithium chloride. The demethylation of 3,4-dimethoxybenzaldehyde carried out at 545 W for 28 min of irradiation, using DMF as solvent, 1.5–5 mmol of lithium chloride.

microwave in different solvents with LiCl as promoter. DMF was the most effective for this cleavage, but the reaction hardly proceeded in water, ethyl acetate, declin, xylene, or toluene. The reactions carried out in dimethylsulfoxide (DMSO), tetrahydrofuran (THF), or acetonitrile resulted in formation of trace cleavage products after a long time (1–2 h) under microwave irradiation. The solvent effect on the reaction may be linked with the solubilities of **1** and LiCl in the solvents.

3.2. Effect of salt

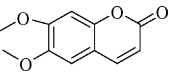
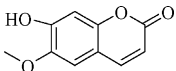
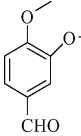
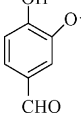
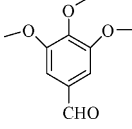
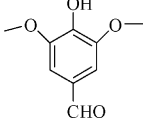
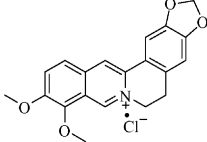
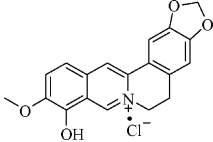
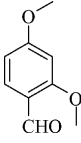
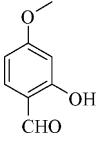
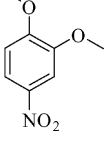
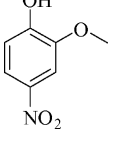
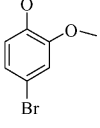
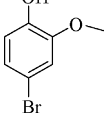
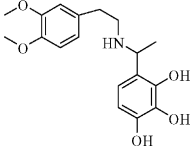
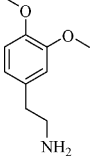
Besides lithium chloride, sodium iodide, sodium chloride, potassium bromide, cuprous chloride, cupric chloride and

ammonia chloride were employed as promoter for the cleavages of **1** in DMF. As shown in Table 2, sodium iodide, potassium iodide, cupric chloride and lithium chloride were effective in promote cleavage reaction. However, interestingly only lithium chloride was found to have regioselectivity for the reaction under similar conditions (Table 2, entry 6). Lithium chloride may form

regioselectively favored transition state or transition state which was attacked regioselectively.

The influence of the amount of salt on the conversion of the demethylation of 3,4-dimethoxybenzaldehyde (Scheme 1) has been studied using 1.5–5 mmol of lithium chloride. Fig. 1 shows the effect of the amount of lithium chloride at 545 W for 28 min

Table 3
Effect of substituent on demethylation of aryl methyl ethers using LiCl-DMF system under microwave irradiation

Entry	Starting material	Products	Yield ^{a,c} (%)	<i>t</i> ^a (min)	Yield ^b (%)	<i>t</i> ^b (h)
1			73	28	35	24
2			81	28	26	22
3			91	10	–	–
4			96	5	–	–
5			68	28	42	22
6			72	20	–	–
7			54	28	–	–
8			<10	30	–	–
9			<10	30	–	–

^a Microwave irradiation.

^b Conventional reflux.

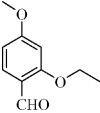
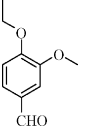
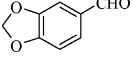
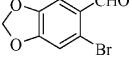
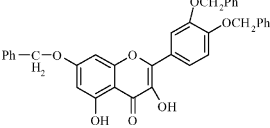
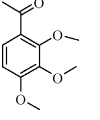
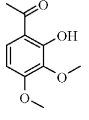
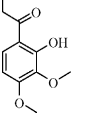
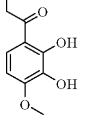
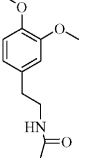
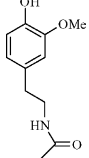
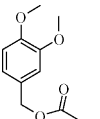
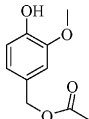
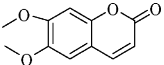
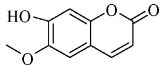
^c Isolated yield.

of irradiation, using DMF as solvent; the reaction rate increases with the amount of lithium chloride.

3.3. Comparison of reactivity between microwave irradiation and traditional heating

The cleavages of a series of aryl methyl ethers in the LiCl-DMF system were investigated under microwave irradiation or by traditional heating. Table 3 demonstrates that just only one methyl group of aryl methyl ethers was removed rapidly under microwave irradiation in moderate to high yields (entries 1–7).

Table 4
Influence of protecting groups on the demethylation of aryl methyl ethers with LiCl-DMF system under microwave irradiation

Entry	Starting material	Products	Yield ^a (%)	t (min)
1		– ^b	0	30
2		– ^b	0	30
3		– ^b	0	30
4		– ^b	0	30
5		– ^b	0	30
6			49	30
7			66	30
8			<10	30
9			~65	5
10			73	28

^a Isolated yield.

^b Only not desired products and only starting materials were recovered after irradiating for 30 min at 545 W.

But demethylation of aryl methyl ethers by conventional refluxing under identical conditions gave lower yields (<42%) after more than 20 h (entries 1, 2, 5 and 8). The results reveal that microwave irradiation has evident advantages of good yields, selectivity and short reaction time over the traditional heating mode.

3.4. Effect of substituent

In Table 3, we notice that the cleavage of these aryl methyl ethers with electron-withdrawing substituent in the *para*-

position results in moderate to high yields (54–96%) (entries 1–7); however, the aryl methyl ethers with electron-donating groups in the *para*-position (entries 8 and 9) gave only trace amount of corresponding phenol products.

3.5. Influence of protecting group

The effect of protecting groups was investigated using several different ethers under strictly identical conditions. When substrates, such as protected ethers with benzyl, ethyl and methylenyl groups were treated with the LiCl-DMF system under microwave irradiation, the activity for deethylation, debenzylation and demethylenylation reactions was low and only starting materials (entries 1–5) were recovered after irradiating for 30 min at 545 W (Table 4). However, Table 4 indicates that only the methyl group was removed in the reaction. Other acid-sensitive and alkali-sensitive groups, such as AcNH (entry 8), AcO (entry 9), and lactone (entry 10) are also unaffected under these reaction conditions. Alkali-sensitive groups, such as CHO (entries 1–4), COCH₂CH₃ (entry 7), Br (entry 4 and Table 3, entry 7) make no difference under identical conditions.

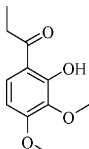
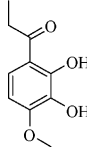
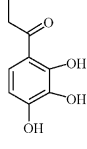
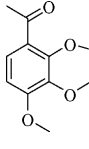
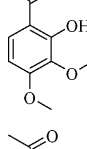
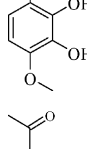
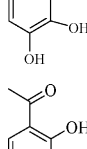
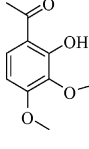
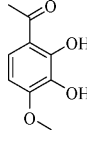
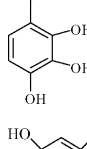


3.6. Reactivity of polymethoxy phenols

In the series of phenols with polysubstituents (Table 5), the reaction time increased to 30 min. The methyl group in the *meta*-position of electron-withdrawing substituents can be removed with the LiCl-DMF system under microwave irradiation and the deprotection rate follows the order *o* > *m* > *p*. The products were identified by ¹H NMR spectra.

3.7. Mechanism of the demethylation reaction

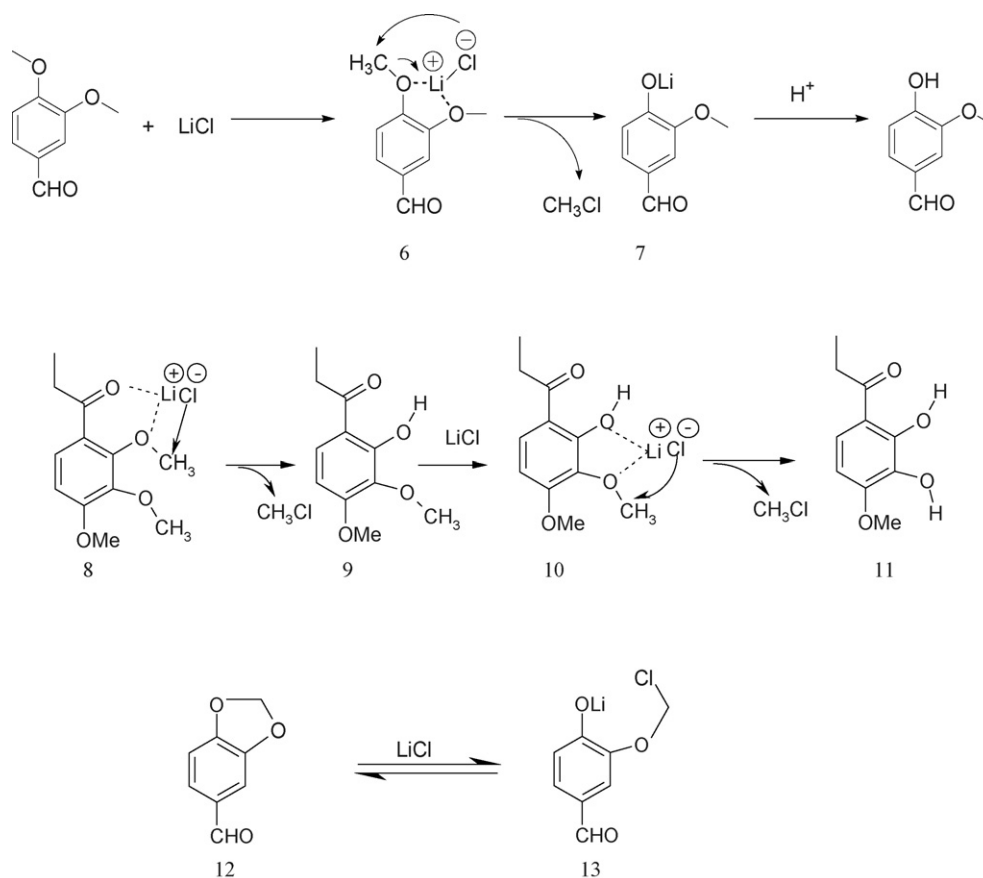
In organic synthesis assisted by microwave, the reactants under microwaves subjected to material-wave interactions leading to thermal effects and non-thermal effects (specific effect). The thermal effect may result from dipolar polarization as a consequence of dipole–dipole interaction of polar molecules with the electromagnetic field. It originates in dissipation of energy as heat, as an outcome of agitation and intermolecular friction of molecules when dipoles change their mutual orientation at each alternation of the electric field at a very high frequency [19]. But traditional heating only causes thermal equilibration via manners of conduction, convection, and radiation. Therefore, the microwave-heated reactions were faster than conventional and their rate enhancement was over one order of magnitude. Concerning the mechanism of the demethylation reaction, specific effect could be considered to be the cause of reactivity and kinetics. Because of the dipolar polarization phenomenon, the greater the polarity of a molecule is, the greater microwave effect will be produced [20]. Hence, the polar transition state is favored under the action of microwave radiation (Scheme 2). The more polar transition state (substituted with an electron-withdrawing group in the *para*-position and *ortho*-position) is more stabilized by dipole–dipole interactions with the electric field and therefore more prone to microwave effects [21].

Table 5
Cleavage of the *meta*-position methoxyl group under microwave irradiation

Entry	Starting material	Products	Yield (%)	<i>t</i> (min)
1			66	30
			Trace	
2			49	30
			26	
			Trace	
3			42	35
			Trace	
4			81	33

LiCl-DMF system.

To gain further insight into the mechanism of the demethylation reaction, we examined the possible course of demethylation reactions under the same reaction condition. These reactions afforded chloromethane (CH₃Cl). CH₃Cl can be detected from the reaction in a boiling state by passing the steam through the tube into another flask into which 10% silver nitrate solution was added. CH₃Cl vapor was absorbed in silver nitrate solution and white precipitate appeared in the solution. We think that the process of demethylation reaction probably occurs by a nucleophilic attack of Li⁺Cl⁻ on the methyl group followed by the release of CH₃Cl (Scheme 2). So the occurrence of this cleavage may be attributed to a nucleophilic attack resulting from the strongly electron-withdrawing effect. The effect of the substituted group makes the cleavage reaction of the substituted ether derivatives



Scheme 2. Proposed mechanism of catalytic dealkylation of aryl ether by LiCl.

with electron-withdrawing group in the *para*-position more rapid and easy. Due to these effects, the selectivity and reactivity are greatly influenced when there are dipole pairs present which specifically help chloride ion in pulling off the leaving group. From charge transfer of the structure in Scheme 2 and formation of ligand of five-member ring with lithium (Scheme 2), we know that the selectivity of catalyzed demethylation follows the order of $o(p) > m$ by lithium chloride, and the protecting group of polysubstituted phenols can be removed and the deprotection rate follows the order $o > m > p$. Therefore, microwave improves the reaction yield and facilitates the selectivity of demethylation of aromatic methyl ethers in the LiCl-DMF system.

The effect of protecting groups on debenzylation, deethylation and demethylenylation reactions were also examined. As shown in Table 4 we have not found the products of debenzylation, deethylation and demethylenylation. We can see with ease that the effect of electronic effect and steric effect from Scheme 2. These effects led to deprotection reaction handicap. The reaction rates were decelerated when these protecting groups are present. Simultaneity benzyl chloride and compound 13 (Scheme 2) would be formed if the reaction is carried out under identical conditions. But benzyl chloride and compound 13 were difficult to release out of the reaction system because of their higher boiling point. In addition, compound 12 could be formed for the easy formation of the stable five-member ring. So the reaction equilibrium could not be overcome, or there was great possibility of the reversible reactions.

4. Conclusion

In summary, we have developed a rapid and mild and efficient procedure for chemo- and regioselective cleavage of aryl methyl ether in the presence of other functional groups by LiCl-DMF under microwave irradiation. The method offers several advantages, such as rapid and mild conditions, simple workup, and moderate to high yields, inexpensive reagents and compatibility with other functional groups. It is an alternative complement for cleavage of aryl methyl ethers with acid- and alkali-sensitive functional groups.

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