Microwave-Assisted Cleavage of Aryl Methyl Ethers with Lithium Thioethoxide (LiSEt)

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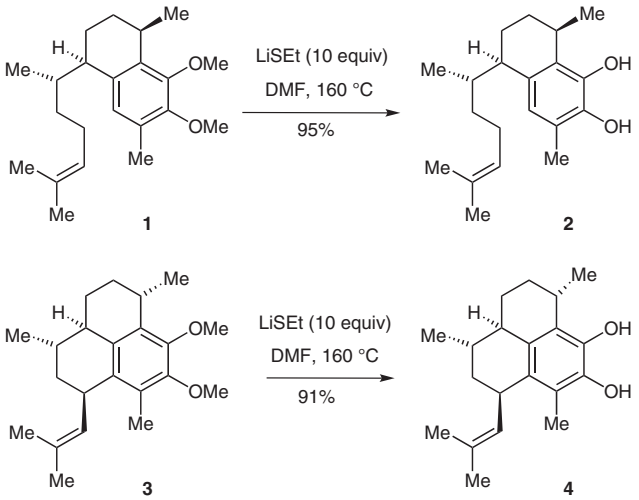
Abstract: Lithium thioethoxide (LiSEt), a white solid easily prepared from EtSH and *n*-BuLi in hexane, was identified as a highly efficient reagent for the cleavage (*O*-demethylation) of aryl methyl ethers, i.e. methyl-protected phenols. Of particular synthetic value are applications in the double deprotection of 1,2-dimethoxyarenes (to give catechols) and in the selective monodeprotection of di- and trimethoxyarenes. The thermal reactions, which are usually performed in DMF as a solvent, can be greatly accelerated through microwave irradiation. In this case, the monodemethylated products are usually formed in high (80–99%) yield within only 15 minutes.

Key words: lithium, thioethanolate, phenol protecting groups, microwave irradiation, S_N2 reactions, demethylation

Amongst phenol protecting groups, the simple methyl group still occupies a particular place due to its unrivalled properties, especially in terms of stability and compatibility with various reaction conditions.[1] Many important natural products possess one or more phenol functionalities and, occasionally, aromatic hydroxyl and methoxy groups occur site-by-site within the same molecule or even at the same aromatic ring (partly *O*-methylated polyphenols).[2] Therefore, the availability of efficient methods for the chemo- and regioselective cleavage of aryl methyl ethers is of significant importance for organic synthesis. All reagents used for the *O*-demethylation of methoxyarenes exploit a S_N2-type reaction at the methyl group and can be divided into two groups. The first group comprises reagents which preliminary act as Brønsted or Lewis acids to activate the oxygen atom as a leaving group [e.g. HBr (48%),[3] TMSI,[4] TMSCl–NaI,[5] BBr_3,[6] BBr_3·Me_2S,[7] BCl_3,[8] BI_3,[9] BF_3·Et_2O,[10] $AlCl_3$,[11] $AlBr_3$,[12] 9-I-9-BBN,[13] MgI_2[14]]. The second group spans nonacidic but strongly nucleophilic reagents such as NaSEt,[15] NaSPr,[16] sodium benzylselenide,[17] sodium *p*-thiocresolate,[18] LiCl–DMF,[19] MeMgI,[20] LiI–quinoline,[21] LiI–collidine,[22] NaCN–DMSO,[23] lithium diphenylphosphide,[24] Na_2S–NMP,[25] MeSLi,[26] *n*-BuSLi,[27] Me_3SiSNa[28] or imidazolium or pyridinium salt based ionic liquids.[29] Also, combinations of an acidic and a nucleophilic reagent have been successfully employed ($MeSO_3H$–methionine,[30] $AlBr_3$–EtSH,[31] $AlBr_3$–NaI,[32] and $AlCl_3$–EtSH[33]).

Recently, in the course of our research program on the total synthesis of the pseudopterosins, helioporins and related bioactive diterpenes,[34] we faced unexpected problems concerning the deprotection (double demethylation) of veratrol derivatives such as **1** and **3** to the corresponding catechols. However, while several of the common reagents only gave very unsatisfactory yields (due to incomplete conversion and/or acid-catalyzed side reactions) we succeeded in achieving such transformations in a very clean fashion by heating the substrates with an excess of lithium thioethoxide (LiSEt) in DMF at 160 °C for three hours (Scheme 1).[35] It is interesting to note that the corresponding sodium salt (NaSEt)[15] was not reactive enough under comparable conditions, and a mixture consisting mainly of monodemethylated compounds was formed in this case.



Scheme 1 Application of the LiSEt-mediated *O*-methyl cleavage in the total synthesis of pseudopterosin-related diterpenes

Another interesting application of LiSEt we came across in our laboratory is the selective conversion of the trimethoxystilbene **5** (resveratrol trimethyl ether)[36] into pinostilbene (**6a**). In this case, two out of three methoxy groups were cleaved with a remarkable high efficiency if the reaction was stopped after two hours (Scheme 2).[37] Only after prolonged reaction times (e.g. 15 h) significant amounts of the fully deprotected product **6b** (resveratrol) were formed.

An additional advantage of LiSEt, which has prompted us to apply it repeatedly as a reagent of choice for the cleavage of aryl methyl ethers, is its ease of preparation and handling. By simply injecting ethanethiol (EtSH) into a solution of *n*-BuLi in anhydrous hexane and subsequent

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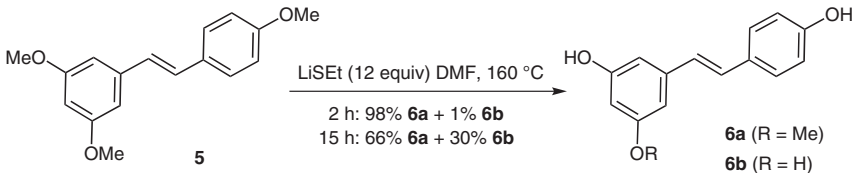
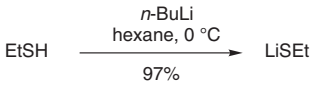


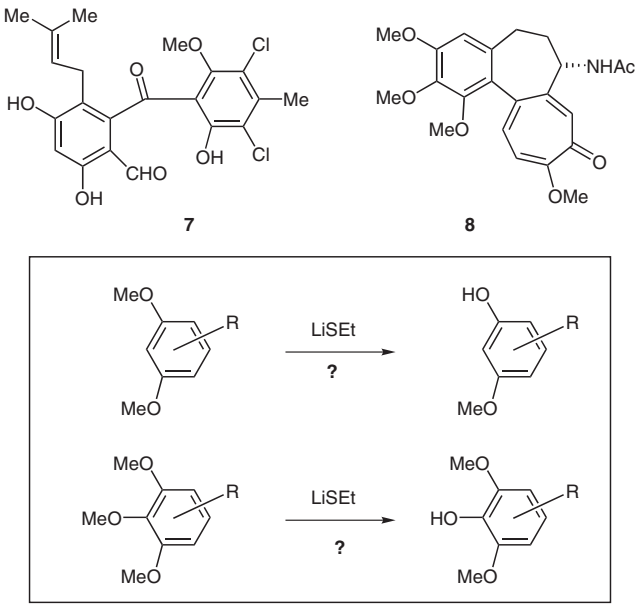
Scheme 2 Selective conversion of *O*-permethylated resveratrol (**5**) into pinostilbene (**6a**) by LiSEt



Scheme 3 Preparation of LiSEt

removal of all volatiles in vacuo, LiSEt is obtained as a white powder, which might be stored under argon at room temperature for several months without loss of quality (Scheme 3). The only drawback of LiSEt (which it shares with several of its competitors) is a rather bad smell. Thus all operations should be performed in a well-ventilated hood.

In the course of our research program aiming at the synthesis of structural analogues of pestalone (**7**),[38] colchicine (**8**)[39] and other relevant oxy-substituted aromatic compounds, we became interested in the question whether LiSEt is a (generally) suitable reagent for the selective monodeprotection of 1,3-dimethoxy- and 1,2,3-trimethoxyarenes (Scheme 4).[40] Because the established reaction conditions are quite harsh (DMF, 160 °C), we were also intrigued by the possibility to perform such reactions under milder conditions using microwave assistance.[41,42] We here present the results of a study showing that LiSEt is indeed a remarkably efficient reagent for such transformations, which can also be significantly accelerated by microwave irradiation.



Scheme 4 Motivation of the present study: Possible use of LiSEt for selective *O*-demethylation reactions

The results of various experiments, mainly employing commercially available di- and trimethoxyarenes, are summarized in Table 1. Reactions were performed in such a fashion that a solution of the substrate and LiSEt (usually 2 equiv) in DMF was heated either in an oil bath or in a microwave reactor. After extractive aqueous workup the products were purified by chromatography and characterized by standard spectroscopic techniques.

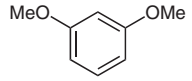
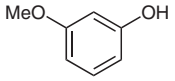
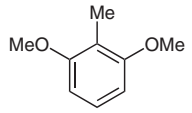
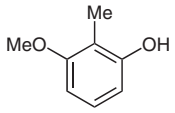
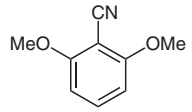
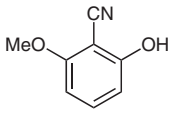
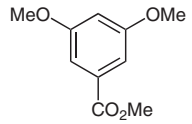
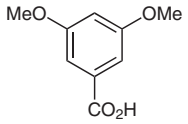
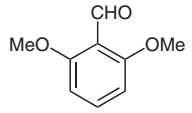
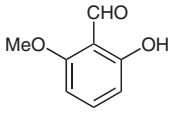
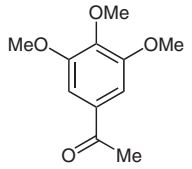
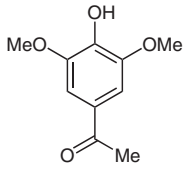
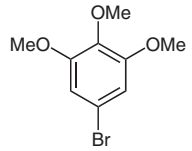
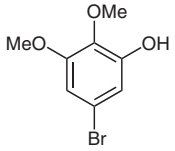
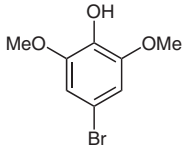
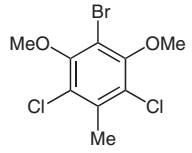
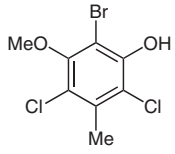
We started with simple 1,3-dimethoxybenzene (**9**) which under classical heating at 160 °C for four hours afforded the monodeprotected product **10** in 74% isolated yield. Prolonging the reaction time had no beneficial effect due to competing decomposition processes. However, we were glad to find that a fast and efficient reaction occurred under microwave irradiation, and the desired 3-methoxyphenol (**10**) was obtained in 90% yield after only 15 minutes at 135 °C (Table 1, entry 1). In a similar manner, 1,3-dimethoxy-2-methylbenzene (**11**) gave the monodemethylated product **12** in 92% yield (entry 2).

We next investigated the tolerance of the protocol towards some relevant functional groups. The mono-*O*-demethylation of 2,6-dimethoxybenzonitrile (**13**) to the phenol **14** in 81% yield demonstrates that a cyano group is well tolerated, at least if the amount of LiSEt is reduced to 1.2 equivalents (entry 3). Interestingly, both methoxy groups stayed completely unscathed when the ester **15** was employed as a substrate, under both classical and microwave conditions (entry 4). In this case, the ester functionality was selectively attacked, and the carboxylic acid **16** was obtained in more or less quantitative yield. This suggests that the procedure also represents a simple and efficient protocol for the cleavage of methyl esters in a nonaqueous medium.

The attempt to convert 2,6-dimethoxybenzaldehyde (**17**) with LiSEt to the corresponding salicylic aldehyde **18** failed (entry 5). In this case, a mixture of compounds was formed, probably resulting from nucleophilic attack of the thiolate at the carbonyl group and subsequent processes. The (labile) primary thiosemiacetal could be detected by GC–MS analysis in the crude product mixture.

To probe the applicability of the protocol also for the selective demethylation of 1,2,3-trimethoxyarenes, we next studied the acetophenone **19** as a substrate (entry 6). Even without microwave assistance, this substrate reacted smoothly already at 100 °C to give the phenol **20** in 90% yield after three hours. Nevertheless, microwave irradiation again led to an increase in both rate and yield. The (regio-) selective cleavage of the central methoxy group, as reflected by the symmetry of the product, is certainly sup-

Table 1 Results of Various LiSEt-Mediated Demethylation Reactions of Di- and Trimethoxyarenes According to Scheme 4[a]

Entry	Substrate	Product		Classical heating		Microwave reactor	
				Conditions	Yield	Conditions	Yield
1	 **9**	 **10**		165 °C, 4 h	74%	135 °C, 15 min	90%
2	 **11**	 **12**		–	–	150 °C, 20 min	92%
3	 **13**	 **14**		–	–	100 °C, 15 min (1.2 equiv LiSEt)	81%
4	 **15**	 **16**		r.t., 19 h	99%	100 °C, 10 min	95%
5	 **17**	 **18**		165 °C, 3 h	<5%	100 °C, 15 min	<5%
6	 **19**	 **20**		100 °C, 3 h	90%	70 °C, 15 min	95%
7	 **21**	 **22a**	 **22b**	165 °C, 3 h	39% (**22a**)	135 °C, 15 min	58% (**22a**) 37% (**22b**)
8	 **23**	 **24**		r.t., 1 h	92%	50 °C, 5 min	99%

[a] Unless otherwise stated, reactions were performed using LiSEt (2 equiv) in DMF (ca. 5 mL/mmol of substrate). Yields refer to isolated compounds.

ported electronically by the acetyl substituent in *para* position. This is in accordance with the fact that the bromo analogue **21** reacted much slower and with less pronounced regioselectivity (entry 7). Nevertheless, under microwave irradiation a satisfying conversion was observed and the unsymmetrical monodemethylation product **22a** was obtained in at least 58% yield as the major isomer besides 37% of the symmetrical isomer **22b**.

Finally, we probed the use of LiSEt for the synthesis of compound **24**, i.e. the eastern building block for the synthesis of pestalone (**7**).[38] Starting from the highly substituted arene **23** we were pleased to find that reaction with LiSEt in DMF already occurred under very mild conditions (r.t.), certainly as a result of the electron-withdrawing effects of the chlorine substituents at the arene. Within only one hour the desired product **24** was obtained in 92% yield (entry 8), and under microwave assistance, the reac-

tion proceeded within five minutes to give the phenol **24** in 99% yield. This result, which could be easily reproduced on a gram scale, opens a direct and much more efficient access to the eastern building block of pestalone, which previously had to be prepared by methylation of a mono-MOM-protected intermediate.

In conclusion, we have shown that LiSEt in DMF represents a highly efficient, non-acidic reaction system both for the double deprotection of 1,2-dimethoxyarenes (veratrol derivatives) and for the selective monodemethylation of dimethoxy- and trimethoxyarenes.[43] In combination with microwave irradiation products are obtained under relatively mild conditions in high yield and often within minutes. The operationally convenient methodology is compatible with a spectrum of relevant functional groups (olefins, nitriles, ketones, alcohols) and therefore well suited for application in natural products synthesis.

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(43) DMF (99.8%, Fluka) was stored over molecular sieves. GC–MS measurements were carried out on an Agilent HP6890 instrument with MS detector 5937 N using an Optima 1 MS (Macherey–Nagel) 30 m × 0.25 mm capillary column with H_2 as carrier gas. NMR data were measured on Bruker DPX 300 and AC 250 instruments. Chemical shifts (δ) are given in ppm relative to the solvent reference as the internal standard. Reactions under microwave irradiation were performed in a CEM Discover instrument (300 W) in glass tubes with temperature and pressure control.

Preparation of the Reagent (LiSEt): In a dry 500-mL Schlenk flask a solution of *n*-BuLi (1.3 M) in hexane (120 mL, 160 mmol) was diluted with hexane (150 mL) under an argon atmosphere. The solution was cooled to 0 °C and under rapid stirring EtSH (200 mmol, 1.25 equiv, 15 mL) was added dropwise, whereupon a white precipitate formed. The reaction mixture was stirred at 0 °C for 10 min and at r.t. for 30 min. After removal of the solvent (always ensuring inert conditions) the residue was dried in vacuo to give LiSEt as a white solid (10.6 g, 156 mmol, 97%). The product was stored under argon at ambient temperature. C_2H_5SLi; M = 68.06 g/mol. ^{1}H NMR (250 MHz, DMSO): δ = 1.06 (t, ^3J = 7.2 Hz, 3 H, H2), 2.27 (q, ^3J = 7.3 Hz, 2 H, H1).

General Procedure: The substrate (0.6 mmol, 1 equiv) and LiSEt (1.2 mmol, 2 equiv) were weighed into the reaction vessel (either a Schlenk tube or a microwave reactor), which was then evacuated and flushed with argon three times before DMF (5 mL) was added and the reaction mixture was heated/irradiated as specified in Table 1. Reactions were monitored by TLC and/or GC–MS. For workup, the mixture was cooled to r.t. and partitioned between 2 N aq HCl (5 mL) and MTBE (5 mL). The aqueous layer was re-extracted with MTBE (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a pad of silica and solvents were evaporated. The residue was flash chromatographed on silica gel with *c*-hexane–EtOAc (4:1).

3-Methoxyphenol (10): colorless oil. ^{1}H NMR ($CDCl_3$): δ = 3.76 (s, 3 H), 5.03 (br s, 1 H), 6.40–6.43, 6.46–6.50 (m, 3 H), 7.09–7.14 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 55.3 (q), 101.5, 106.4, 107.9 (3 × d), 130.1 (d), 156.7 (s), 160.9 (s). HRMS (EI, 70 eV): *m*/*z* calcd for $C_7H_8O_2$: 124.0524; found: 124.053.

3-Methoxy-2-methylphenol (12): white solid; mp 42–43 °C. ^{1}H NMR ($CDCl_3$): δ = 2.11 (s, 3 H), 3.81 (s, 3 H), 4.80 (s, 1 H), 6.44 (d, ^3J = 8.5 Hz, 1 H), 6.47 (d, ^3J = 8.5 Hz, 1 H), 7.02 (ψt, ^3J = 8.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 7.9 (q), 55.6 (q), 103.0 (d), 108.0 (d), 112.1 (s), 126.4 (d), 154.3 (q), 158.6 (q). HRMS (EI, 70 eV): *m*/*z* calcd for $C_8H_{10}O_2$: 138.0681; found: 138.068.

2-Hydroxy-6-methoxybenzonitrile (14): white solid; mp 163–164 °C. ^{1}H NMR (CD_3OD): δ = 3.87 (s, 3 H), 6.50 (d, ^3J = 8.4 Hz, 1 H), 6.52 (d, ^3J = 8.4 Hz, 1 H), 7.34 (ψt, ^3J = 8.5 Hz, 1 H). ^{13}C NMR (CD_3OD): δ = 56.7 (q), 90.6 (s), 102.9 (d), 109.0 (d), 115.4 (s), 136.1 (d), 163.0 (s), 163.9 (s). IR (ATR): 3220 (br m), 2230 (s), 1607 (s), 1594 (s), 1476 (s) cm^{-1}. HRMS (EI, 70 eV): *m*/*z* calcd for $C_8H_7NO_2$: 149.0477; found: 149.047.

3,5-Dimethoxybenzoic acid (16): GC–MS and NMR data matched those of an authentic(commercial) sample.

1-(4-Hydroxy-3,5-dimethoxyphenyl)ethanone (20): colorless oil. ^{1}H NMR ($CDCl_3$): δ = 2.54 (s, 3 H), 3.92 (s, 6 H), 6.03 (br s, 1 H), 7.22 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ = 26.2 (q), 56.4 (q), 105.7 (d), 128.8 (s), 139.7 (s), 146.7 (s), 200.3 (s). IR (ATR): 3350 (br m), 1728 (s) cm^{-1}. HRMS: *m*/*z* calcd for $C_{10}H_{12}O_4$: 196.0736; found: 196.074.

5-Bromo-2,3-dimethoxyphenol (22a): white solid; mp 68–70 °C. ^{1}H NMR ($CDCl_3$): δ = 3.82 (s, 3 H), 3.85 (s, 3 H), 5.83 (br s, 1 H), 6.59 (d, ^4J = 2.1 Hz, 1 H), 6.75 (d, ^4J = 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 56.5 (q), 60.9 (q), 107.9 (d), 111.6 (d), 116.4 (s), 134.8 (s), 149.9 (s), 152.8 (s). MS (EI, 70 eV; isotope pattern reflected a molecule with one bromine atom): *m*/*z* (%) = 234 (95) [M]$^+$, 232 (100) [M]$^+$, 219 (95), 217 (97), 191 (46), 189 (55), 173 (29), 171 (31), 110 (14), 67 (41). HRMS: *m*/*z* calcd for $C_8H_9O_3{}^{79}Br$: 231.9735; found: 231.974.

4-Bromo-2,6-dimethoxyphenol (22b): white solid; mp 90–92 °C. ^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 6 H), 5.42 (br s, 1 H), 6.70 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ = 56.4 (q), 108.4 (d),

111.04 (s), 138.9 (s), 147.5 (s). MS (EI, 70 eV; isotope pattern reflected a molecule with one Br atom): *m*/*z* (%) = 234 (93) $[M]^+$, 232 (100) $[M]^+$, 219 (37), 217 (41), 191 (27), 189 (30), 176 (16), 174 (16), 110 (13), 67 (19), 50 (16). HRMS: *m*/*z* calcd for $C_8H_9{}^{79}BrO_3$: 231.9735; found: 231.974.

2-Bromo-4,6-dichloro-3-methoxy-5-methylphenol (24): white solid; mp 128 °C. ^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 3 H), 3.85 (s, 3 H), 5.91 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 18.1 (q), 60.6 (q), 103.7 (s), 117.0 (s), 121.2 (s), 134.9 (s), 148.0 (s), 152.5 (s). MS (EI, 70 eV; isotope pattern reflected a molecule with one Br and two Cl atoms): *m*/*z* (%) = 290 (6) $[M]^+$, 288 (44) $[M]^+$, 286 (100) $[M]^+$, 284 (63) $[M]^+$, 273 (14), 271 (31), 269 (20), 245 (23), 243 (56), 241 (34), 179 (15), 177 (14). HRMS: *m*/*z* calcd for $C_8H_7O_2{}^{79}Br^{35}Cl_2$: 283.9006; found: 283.901.