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1-Decanethiol, a new reagent for the odorless deprotection of aryl methyl ethers

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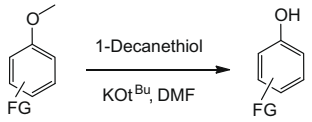
ABSTRACT

1-Decanethiol has been found to be an excellent reagent for the deprotection of aryl methyl ethers. This newly developed protocol afforded the corresponding phenols in good to excellent yields. A clear advantage of 1-decanethiol over the more commonly used thiols is the easy extraction of both the deprotecting reagent and the reaction byproduct into the aqueous phase, which allows an essentially odorless work-up.

1. Introduction

Protecting groups have found widespread use in the area of organic synthesis, and they are especially important during the synthesis of complex organic molecules. The protection of alcohols and phenols is most important, because of the reactivity of these functional groups, it is often needed to temporarily shut down their functionality. Currently, a wide range of protecting groups is at the disposal of organic chemists to accomplish this goal. Methyl ethers of both aliphatic and aromatic moieties are one of them, but a major drawback involved in this is their robustness and the difficulties encountered during their cleavage. Aromatic methyl ethers are more easily cleaved than their aliphatic counterparts but, despite the numerous methods,[1] nucleophilic[2] and reductive[3] cleavages are used to perform this transformation. The use of $AlCl_3$/EtSH,[4] BBr_3,[5] Cl_3MeSi/NaI,[6] and TMSI[7] gives either decomposition or mostly unreacted methyl ether. However, NaH/EtSH[8] shows good results, but the foul smell that evolves during the work-up and its presence in the phenol product clearly undermines the practicality of this methodology. The use of 2-(diethylamino)ethanethiol has the drawback that the aryl compound being protected requires an electron-withdrawing group for good conversion.[9]

Researchers have made various attempts to replace volatile thiols with alkanethiols whose alkyl chains are longer than C8.[10] The longer chain alkanethiols are considered essentially odorless compounds due to their higher boiling points. By keeping this in view,



FG = Cl, Br, NH_2, OMe, CHO, C=O, COOH, CN, C=C-CN

Scheme 1. Deprotection of aryl methyl ethers.

Table 1
Screening of bases[a]

Base	Equivalent	Yield[b] (%)
NaOH	3	81
KOH	3	80
LiOH	2.5	82
NaOMe	3	78
KOt^{Bu}	1.5	83

[a] Reaction conditions: 1-Chloro-4-methoxybenzene, 1-decanthiol (1.5 equiv), DMF, 110 °C.
[b] Isolated yields.

Table 2
Screening of solvents[a]

Solvent	Temperature (°C)	Yield[b] (%)
THF	65	0
DMSO	140	60
NMP	180	65
DMF	110	83

[a] Reaction conditions: 1-Chloro-4-methoxybenzene, 1-decanthiol (1.5 equiv), KOt^{Bu} (1.5 equiv).
[b] Isolated yields.

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Table 3
Reactions of aryl methyl ethers with 1-decanethiol[a]

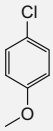
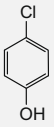
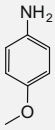
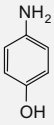
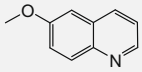
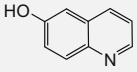
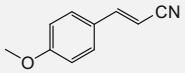
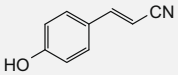
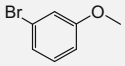
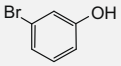
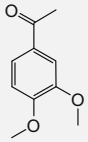
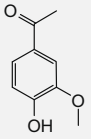
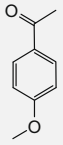
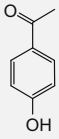
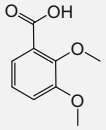
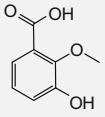
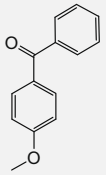
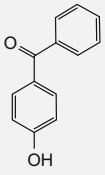
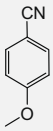
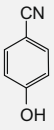
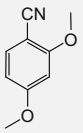
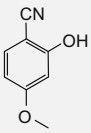
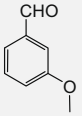
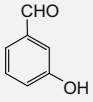
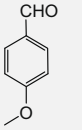
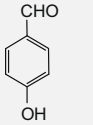
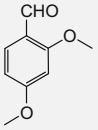
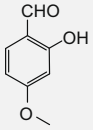
Entry	Aryl methyl ether	Product	Thiol (equiv)	Time (min)	Yield[b] (%)	Mp/Bp (°C)
1			1.5	120	83	99–100[c]
2			1.5	120	82	174–175[c]
3			2.0	180	75	122–124[c]
4			2.0	180	95	120–124[c]
5			2.0	180	85	171–174[c]
6			2.0	180	94	358–360[c]
7			1.5	180	94	138–140
8			1.5	120	95	234–236[c]
9			4.0	120	60	114–116[c]
10			4.0	150	90	146–149[c]
11			1.5	120	38	150–152
12			4.0	240	90	150–155[c]
13			1.5	60	95	78–80
14			1.2	60	92	169–172

Table 3 (*continued*)

Entry	Aryl methyl ether	Product	Thiol (equiv)	Time (min)	Yield[b] (%)	Mp/Bp (°C)
15			4.0	180	45	238–240[c]
16			1.5	30	75	296–299[c]
17			1.5	120	44	116–120[c]

[a] Reaction conditions: Aryl methyl ether, KO*t*^{Bu} (1.5 equiv), DMF, 110 °C.
[b] Isolated yields.
[c] Boiling point.

we decided to use 1-decanethiol for the deprotection of aryl methyl ethers, as it is commercially available and inexpensive compared to other higher chain alkanethiols. A clear advantage of 1-decanethiol over the use of more common thiols, such as methyl thiol, ethanethiol, propanethiol, isopropyl thiol, *n*-butyl thiol, 2-(diethylamino)ethanethiolhydrogen chloride, thiophenol, *p*-thiocresol, and sodium sulfide, is the easy extraction of both the deprotecting reagent and the reaction byproduct, decanethiol methyl sulfide. This byproduct is highly soluble in all non polar solvents, such as heptane, hexane, and cyclohexane, which allow an essentially odorless work-up.

In continuation of our interest in the development of new synthetic methodologies,[11] herein we report a simple and efficient method for the deprotection of aryl methyl ethers by using commercially available reagent 1-decanethiol in the presence of KO*t*^{Bu} base (Scheme 1). This protocol represents the first literature report on the use of 1-decanethiol as a new reagent for the deprotection of aryl methyl ethers involving classical demethylation chemistry.

In order to achieve an optimized reaction condition, the deprotection of 1-chloro-4-methoxybenzene in the presence of 1-decanethiol was considered as a standard model reaction. During this study, we investigated various bases such as NaOH,[12] KOH, LiOH, NaOMe, and KO*t*^{Bu} for the model reaction. It was observed that the use of KO*t*^{Bu} afforded the product in higher yield (83%) using only 1.5 equiv amount (Table 1) whereas other bases required to be used in more equivalence.

To find the suitable solvent for this transformation, various polar aprotic solvents such as THF, DMSO, NMP, and DMF were tested for the model reaction using KO*t*^{Bu} as a base (Table 2). THF was found to be ineffective for complete conversion of reactant into the product even after 4 h at the boiling temperature. In DMSO and NMP, the reaction proceeded well but the yield of the desired product was low (60% and 65%, respectively). Finally, DMF proved to be more effective than other solvents in terms of product yield (83%) and also required the lower temperature. Hence we decided to use DMF as the most suitable reaction solvent. (Table 2).

In order to establish the generality of optimized reaction conditions, various substituted aryl methyl ethers were subjected to demethylation in the presence of 1-decanthiol (Table 3). The substrates containing electron-donating groups showed lower reactivities (Table 3, entries 3, 4, and 5) while very fast conversions were observed for those with electron-withdrawing groups (Table 3, entries 1, 2, 8, 13, and 14). Substitutions at the *ortho*-position and the *para*-position seemed to be electronically equivalent, as very similar results were obtained for these substrates (Table 3, entries 9, 10, and 11). The poly-substituted ether substrate (Table 3, entries 9, 11, 14, and 17) behaved quite differently showing the preferential mono-demethylation. The reaction was compatible for various substituents such as Br, Cl, NH_2, OMe, CHO, COOH, CN, and C≡C–CN. All these functionalities remain unaffected under the experimental conditions.

The reaction was proposed to proceed via the in situ generation of thiolate anion by KO*t*^{Bu} followed by nucleophilic substitution on aryl methyl ether to get the desired product.

As demonstrated above with a simple compound, this newly developed protocol could also be utilized in the mass production of pharmaceutically interesting compounds. For example, Lasofoxifene,[13] an estrogen receptor modulator, and dihydrexidine,[14] a dopamine receptor agonist, contain phenolic moieties in their structures and they could be procured by the cleavage of the aryl methyl ether precursors using this method.

The formation of products was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectroscopic analytical techniques.[15]

2. Conclusion

In conclusion, a practical demethylation method using 1-dacanethiol has been developed. Several advantages over previous methods reported in the literature include (i) essentially odorless conditions during the reaction and work-up, (ii) in situ generation of the reactive thiolate, thereby simplifying the operation, and (iii) excellent chemical yields for a wide range of substrates. This methodology can be useful to both discovery and process chemists as a practical way to have an access to phenols.

Acknowledgment

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15. *Experimental*

Materials and instruments: All solvents and reagents were purchased from the suppliers and used without further purification. Organic solutions were concentrated under reduced pressure. Thin layer chromatography was performed on Merck pre-coated Silica Gel $60F_{254}$ plates. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The mass spectra were recorded on Shimadzu LC–MS-QP 800 LC–MS and AB-4000 Q-trap LC–MS/MS. Melting points were obtained by using the open capillary method and are uncorrected.

Typical procedure: An oven-dried, 50 mL, round-bottomed flask equipped with a magnetic stirrer and nitrogen atmosphere was charged with 1-decanethiol (2.7 g, 0.0112 mol). *N*,*N*-dimethylformamide (10 mL) was added to the reaction mass and the flask was cooled to 5–10 °C. When the internal temperature was below 10 °C, solid KOt^{Bu} (1.26 g, 0.0112 mol) was added in one portion after 10 min, the reaction mass was allowed to warm to 20–25 °C. After 15 min, 4-methoxy-benzonitrile (Table 3, entry 13) (1.0 g, 0.0075 mol) was added in one portion and the reaction mass was heated to 110 °C for 60 min. TLC analysis (hexanes/ethyl acetate 1:1 as mobile phase) showed complete reaction. The mixture was allowed to cool to 20–25 °C and then poured into ice water (25 mL).To the flask was added 1 N HCl dropwise to bring the pH to 1 followed by the addition of water (25 mL). The aqueous phase was extracted with ethyl acetate (3×20 mL), and the combined organic extracts were washed with (2×20 mL) saturated brine and dried over Na_2SO_4. The solvent was removed under vacuum to give a free flowing solid. To this solid was added 20 mL heptane and stirred for 60 min. The solid obtained was filtered out and washed with 10 mL heptane to give 0.77 g (94%) of 4-hydroxy-benzonitrile as a white solid.

All experiments were run on a 1.0 g scale using *N*,*N*-dimethylformamide under a nitrogen atmosphere with KOt^{Bu} as a base at 100–110 °C. The yields refer to isolated yields after column chromatography and/or recrystallization. All products gave satisfactory analytical data. Identification of products was carried out by ^{1}HNMR, ^{13}CNMR, and mass spectroscopic data.

Characterization data

4-Chlorophenol (Table 3, entry 1): boiling point 99–100 °C (Sigma–Aldrich-100 °C); ^1H NMR (DMSO-d_6, δ ppm): 9.8 (s, 1H, –OH), 7.17 (d, 2H, ArH, J = 8.8 Hz), 6.76 (d, 2H, ArH, J = 8.8 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 117.2, 125.1, 130.0, 155.1; MS (m/z): 127 [M^+-1].

2-Chlorophenol (Table 3, entry 2), boiling point 174–175 °C (Sigma–Aldrich-175–176 °C); ^1H NMR (DMSO-d_6, δ ppm): 9.8 (s, 1H, –OH), 7.16 (d, 2H, ArH, J = 8.8 Hz), 6.76 (d, 2H, ArH, J = 8.8 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 115.6, 121.3, 122.0, 128.1, 130.5, 152.9; MS (m/z): 127 [M^+-1].

4-Aminophenol (Table 3, entry 3), boiling point 122–124 °C (Sigma–Aldrich-120–124 °C); ^1H NMR (DMSO-d_6, δ ppm): 8.32 (s, 1H, –OH), 6.47 (d, 2H, ArH, J = 8.6 Hz), 6.44 (d, 2H, ArH, J = 8.2 Hz), 4.3 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, δ ppm): 116.6, 116.9, 138.4, 150.0; MS (m/z): 110 [M^++1].

3-Aminophenol (Table 3, entry 4), boiling point 120–124 °C (Sigma–Aldrich-120–124 °C); ^1H NMR (DMSO-d_6, δ ppm): 8.8 (s, 1H, –OH), 6.76 (d, 1H, ArH, J = 8.1 Hz), 5.98 (d, 2H, ArH, J = 8.3 Hz), 5.91 (d, 1H, ArH, J = 8.1 Hz), 4.83 (s, 2H, $-NH_2$); ^{13}C NMR (DMSO-d_6, δ ppm): 102.8, 106.2, 107.0, 130.6, 147.4, 158.1; MS (m/z): 110 [M^++1].

2-Aminophenol (Table 3, entry 5), boiling point 171–174 °C (Sigma–Aldrich-170–175 °C); ^1H NMR (DMSO-d_6, δ ppm): 8.8 (s, 1H, –OH), 6.62 (d, 2H, ArH, J = 8.3 Hz), 6.37 (d, 2H, ArH, J = 8.1 Hz), 4.42(s, 2H, $-NH_2$); ^{13}C NMR (DMSO-d_6, δ ppm): 116.6, 118.7, 121.4, 137.8, 145.8; MS (m/z): 110 [M^++1].

Quinolin-6-ol (Table 3, entry 6), boiling point 358–360 °C (Sigma–Aldrich-360 °C); ^1H NMR (DMSO-d_6, δ ppm): 10.10 (s, 1H, –OH), 8.63 (d, 1H, ArH, J = 8.6 Hz), 8.12 (d, 1H, ArH, J = 8.2 Hz), 7.84 (d, 1H, ArH, J = 8.6 Hz), 7.36 (d, 1H, ArH, J = 8.6 Hz), 7.30 (d, 1H, ArH, J = 8.6 Hz), 7.28 (d, 1H, ArH, J = 8.6 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 110.6, 120.2, 121.8, 127.3, 131.4, 134.7, 143.3, 147.7, 154.5; MS (m/z): 146 [M^++1].

(2Z)-3-(4-Hydroxyphenyl)prop-2-ene nitrile (Table 3, entry 7), melting point 138–140 °C (Sigma–Aldrich-138–139 °C); ^1H NMR (DMSO-d_6, δ ppm): 10.10 (s, 1H, –OH), 7.53 (d, 2H, ArH, J = 8.8 Hz), 7.48(d, 1H, –CH, J = 16.8 Hz), (6.79 (d, 2H, ArH, J = 8.8 Hz), 6.13 (d, 1H, -CH, J = 16.8 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 94.5, 115.9, 117.6, 126.1, 129.4, 149.9, 154.4; MS (m/z): 146 [M^++1].

3-Bromophenol (Table 3, entry 8), boiling point 234–236 °C (Sigma–Aldrich-236 °C); ^1H NMR (DMSO-d_6, δ ppm): 9.97 (s, 1H, –OH), 7.22(m, 1H, ArH), 7.01 (m, 2H, ArH), 7.016.85 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 114.4, 119.4, 123.0, 124.4, 130.8, 156.2; MS (m/z): 173 [M^++1].

1-(4-Hydroxy-3-methoxyphenyl) ethanone (Table 3, entry 9), boiling point 114–116 °C (Sigma–Aldrich-112–115 °C); ^1H NMR (DMSO-d_6, δ ppm): 9.74 (s, 1H, –OH), 6.71 (d, 1H, ArH, J = 8.2 Hz), 7.32 (d, 1H, ArH, J = 8.0 Hz), 7.31 (d, 1H, ArH, J = 2.1 Hz), 3.81 (s, 3H, $-OCH_3$), 2.48 (s, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6, δ ppm): 26.1, 56.0, 111.2, 113.9, 124.2, 130.4, 146.7, 150.6, 197.1; MS (m/z): 167 [M^++1].

1-(4-Hydroxyphenyl) ethanone (Table 3, entry 10), boiling point 146–149 °C (Sigma–Aldrich-147–148 °C); ^1H NMR (DMSO-d_6, δ ppm): 10.34 (s, 1H, –OH), 7.82 (d, 2H, ArH, J = 8.4 Hz), 6.84 (d, 2H, ArH, J = 8.8 Hz), 2.45 (s, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6, δ ppm): 26.1, 56.0, 111.2, 113.9, 124.2, 130.4, 146.7, 150.6, 197.1; MS (m/z): 137 [M^++1].

3-Hydroxy 2-methoxy benzoic acid (Table 3, entry 11), melting point 150–152 °C (Sigma–Aldrich-151–152 °C); ^1H NMR (DMSO-d_6, δ ppm): 14 (s, 1H, –COOH), 11.9 (s, 1H, –OH), 7.46 (d, 2H, ArH, J = 8.0 Hz), 6.98 (d, 2H, ArH, J = 8.2 Hz), 7.13 (d, 2H, ArH, J = 8.0 Hz), 3.81 (s, 3H, $-OCH_3$); ^{13}C NMR (DMSO-d_6, δ ppm): 61.8, 119.1, 121.6, 123.2, 147.7, 149.4, 167.4; MS (m/z): 169 [M^++1].

(4-Hydroxy phenyl) (phenyl) methanone (Table 3, entry 12), boiling point 150–155 °C (Sigma–Aldrich-150–160 °C); ^1H NMR (DMSO-d_6, δ ppm): 10.42 (s, 1H, –OH), 7.66–7.60 (m, 5H, ArH), 7.52 (d, 2H, ArH, J = 8.4 Hz), 6.99 (d, 2H, ArH, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6, δ ppm); 115.2, 129.6, 129.6, 131.7, 132.6, 131.8, 138.1, 161.5, 195.6; MS (m/z): 199 [M^++1].

4-Hydroxy benzonitrile (Table 3, entry 13), melting point 78–80 °C (Sigma–Aldrich-78–81 °C); ^1H NMR (DMSO-d_6, δ ppm): 10.6 (s, 1H, –OH), 7.63 (dd, 2H, ArH, J = 6.4 Hz, J = 9.2 Hz), 6.90 (dd, 2H, ArH, J = 4.4 Hz, J = 6.8 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 103.6, 116.2, 118.8, 133.4160.7; MS (m/z): 120 [M^++1].

2-Hydroxy 4-methoxy benzonitrile (Table 3, entry 14), melting point 169–172 °C (Sigma–Aldrich-169–171 °C); ^1H NMR (DMSO-d_6, δ ppm): 7.49 (s, 1H, –OH), 6.52 (m, 2H, ArH,), 3.74 (s, 3H, $-OCH_3$); ^{13}C NMR (DMSO-d_6, δ ppm); 55.5, 92.9, 100.6, 108.2, 63.8; MS (m/z): 150 [M^++1].

3-Hydroxy benzaldehyde (Table 3, entry 15), boiling point 230–240 °C (Sigma–Aldrich-240 °C); ^1H NMR (DMSO-d_6, δ ppm): 10.1 (s, 1H, –CHO), 7.50–7.11 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, δ ppm); 116.5, 123.2, 131.4, 139.4, 159.4, 194.8; MS (m/z): 123 [M^++1].

4-Hydroxy benzaldehyde (Table 3, entry 16), boiling point 296–299 °C (Sigma–Aldrich-310 °C); ^1H NMR (DMSO-d_6, δ ppm): 9.77 (s, 1H, –OH), 7.76 (m, 2H, ArH, 6.93 (m, 2H, ArH,); ^{13}C NMR (DMSO-d_6, δ ppm); 116.7, 129.8, 133.0, 163.2, 191.6; MS (m/z): 123 [M^++1].

2-Hydroxy-4-methoxy benzaldehyde (Table 3, entry 17), boiling point 116–120 °C (Sigma–Aldrich-116–126 °C); ^1H NMR (DMSO-d_6, δ ppm): 10.11 (s, 1H, –OH), 7.57 (d, 2H, ArH, J = 8.0 Hz), 6.48 (m, 2H), 3.83 (s, 3H, $-OCH_3$); ^{13}C NMR (DMSO-d_6, δ ppm): 61.8, 119.2, 121.7, 123.3, 147.8, 149.5, 167.5; MS (m/z): 153 [M^++1].