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2-(Diethylamino)ethanethiol, a New Reagent for the Odorless Deprotection of Aromatic Methyl Ethers

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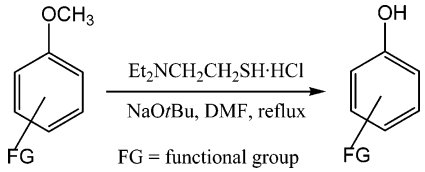
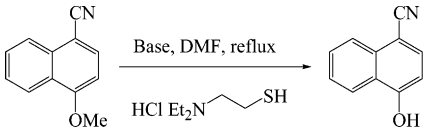


A new reagent for the deprotection of aromatic methyl ethers, 2-(diethylamino)ethanethiol, is reported. This compound, commercially available as its HCl salt, affords the corresponding phenols in good to excellent yields on a wide variety of substrates. A clear advantage of this method over the use of more common thiols, such as ethanethiol, is the easy extraction of both the deprotecting reagent and the byproduct 2-(diethylamino)ethyl methyl sulfide into the aqueous phase by quenching with dilute acid, which allows an essentially odorless workup.

Protecting groups have found widespread use in the area of organic synthesis, and they are especially important during the preparation of complex molecules. Among the most important ones are the protecting groups for phenols since, because of the reactivity of this functional group, it is often necessary to temporarily shut it down. Currently, a very wide variety of groups are at the disposal of the organic chemist to accomplish this goal. Methyl ethers, both aliphatic and aromatic, are one of them, but sometimes a major drawback is their robustness as well as the difficulty that their cleavage entails. Aromatic methyl ethers are more easily cleaved than their aliphatic counterparts but, despite the numerous methods to perform this transformation,[1] there still is a need for new and practical methodologies to perform the task.

During the development of an important active pharmaceutical in our laboratories, we had the need to demethylate a highly functionalized intermediate to afford the corresponding phenol. Given this and the large amounts of material that had to be prepared for further studies, a search for an economical method that gave good yields and acceptable purity and avoided extensive purification was undertaken. The initial route called for the use of 3 equiv of LiI in 2,4,6-collidine at 160 °C.[2] The reaction worked well on a small scale but, upon scaling up, tended to be more sluggish and generated more impurities. Also, the workup was difficult because of the high viscosity of the mixture upon cooling. The use of $AlCl_3$/EtSH,[3] BBr_3,[4] Cl_3MeSi/NaI,[5] and TMSI[6] gave either decomposition or mostly unreacted methyl ether. However, when a combination of NaH and ethanethiol in refluxing *N*,*N*-dimethylformamide (DMF) was tested,[7] complete conversion to the phenol in good yields (80−90%) and reasonable purity (80−85%) was observed after 1 h. Unfortunately, the foul smell that evolved during the workup and its presence in the phenol product clearly undermined the practicality of this methodology. A search to find more user-friendly alternatives to ethanethiol that maintained its performance was then carried out. The HCl salt of 2-(diethylamino)-ethanethiol fulfilled these requirements. This compound, readily available from commercial sources at a reasonable cost, effected the deprotection of our substrate in 76% yield on small-scale

TABLE 1. Influence of Base on the Demethylation of 4-Methoxy-1-naphthonitrile in DMF at Reflux



base	yield (%)
NaO*t*-Bu	91
KO*t*-Bu	86
NaH	76
$LiNH_2$	78
NaOH (50%)	65

TABLE 2. Influence of Solvent on the Demethylation of 4-Methoxy-1-naphthonitrile with NaO*t*-Bu as Base

solvent	yield (%)
DMF[a]	91
NMP[a]	88
THF[b]	36
DMSO[a]	23

[a] Reactions run at 150 °C. [b] Reaction run at reflux.

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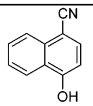
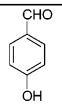
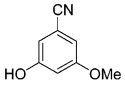
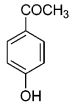
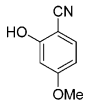
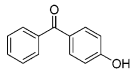
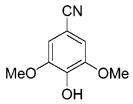
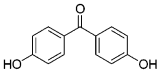
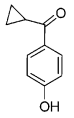
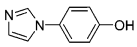
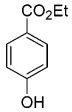
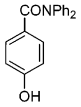
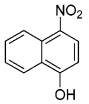
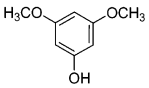
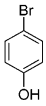
TABLE 3. Aryl Methyl Ether Deprotection through the Use of 2-(Diethylamino)ethanethiol Hydrochloride[a]

Entry	Product	Reaction time (h)	Equivalents of thiol	Yield (%)	Entry	Product	Reaction time (h)	Equivalents of thiol	Yield (%)
1		0.5	1.2	91	11		0.3	1.2	70
2		3	1.2	80	12		1	1.2	86
3		0.25	1.2	78[b]	13		1	1.2	91
4		0.8	1.2	67	14		2	2.4	92
5		1	1.2	56	15		1	1.2	44
6		0.3	1.2	14	16		2	1.2	78
7		1	1.2	69	17		0.75	2	79
8		0.5	1.2	58	18		0.15	1.2	67
9		0.5	1.2	80	19		2	1.2	84
10		3	1.2	97					

[a] All experiments were run on a 5 mmol scale in refluxing *N*,*N*-dimethylformamide (0.5 M in substrate) under a nitrogen atmosphere with NaO*t*-Bu as base. The amount of base was 2.1 times the number of equivalents of 2-(diethylamino)ethanethiol HCl. The yields refer to isolated yields after column chromatography and/or recrystallization. All products gave satisfactory analytical data. [a] The *p*-demethylated phenol was obtained in 18% yield as the minor product.

experiments (10−20 mmol) in 1 h in refluxing DMF with 1.2 equiv of NaH as base. Since NaH was not considered amenable for the large-scale synthesis of our target molecule, a number of alternative bases were explored. Thus, lithium amide gave similar results (78%), whereas the use of sodium *tert*-butoxide consistently gave the best yields (85−90%). The use of other solvents such as 1-methyl-2-pyrrolidinone (NMP) or *N*,*N*-dimethylacetamide did not have any appreciable effect on the process and worked equally well. When the reactions were complete, the addition of 1 N HCl allowed for the extraction of the excess deprotecting agent as well as its methylated byproduct from the reaction into the aqueous phase through the formation of their HCl salts. This avoided the stench that had been previously encountered when ethanethiol was used.

A literature search revealed that 2-(diethylamino)ethanethiol had never been reported as a demethylating agent and, in view of the promising results obtained on our substrate, we decided to further investigate its potential. We first focused on the determination of the optimal reaction conditions. Thus, taking 4-methoxy-1-naphthonitrile as our substrate, we studied the influence of the base on the outcome of the reaction. The results are summarized in Table 1.

Although good yields were obtained with all the bases that were tried, alkoxides and, in particular, sodium *tert*-butoxide proved to be the bases of choice.

In a similar fashion, we tested the influence of the solvent on the outcome of the reaction when sodium *tert*-butoxide was used as base. The results are summarized in Table 2.

Both DMF and NMP proved superior to either THF or DMSO, with the former giving a slightly better yield. The lower yield in THF is most likely due to the low boiling point of this solvent, whereas the acidity of DMSO may play an unexpected role leading to low conversions.

In view of the results shown above, the NaO*t*-Bu/DMF combination was tried on a number of aromatic methyl ethers. The results are summarized in Table 3. This methodology works well in the presence of a broad variety of functional groups. Electron-withdrawing groups on the ring clearly facilitate the transformation and usually led to shorter reaction times, as has been previously reported.[8]

Thus, cyano (entries 1, 3, and 4), aldehyde (entry 11), and nitro (entry 18) groups gave very fast conversions, while the presence of less electronegative groups such as keto (entries 12 and 13), imidazolyl (entry 16), or dimethoxy (entry 19) required longer reaction times.

The substitution pattern on the ring plays an important role on the outcome of the reaction and, when both ortho and para positions relative to the electron-withdrawing group are available for deprotection, the former undergoes the transformation preferentially (entry 3). On the other hand, when both meta and para positions compete, the latter reacts exclusively (entry 4), which agrees with what is expected on the basis of the electronics of the ring. When several methoxy groups are present on the ring in equivalent positions, the amount of thiol can be controlled to selectively accomplish mono- or bisdeprotection, as is shown in entries 2, 14, and 19. This selectivity is further enhanced by the fact that once the first deprotection has taken place, the ring becomes more electron-rich and additional demethylation is disfavored. It is worth highlighting that compounds with relatively acidic protons can be deprotected under these conditions in fair to excellent yields, such as the ketones in entries 12 and 15. When the ester group is present (entries 5, 6, and 7), low to fair yields are obtained. The yield for entry 6, where meta-substitution is present, was especially low, even after attempts to optimize the reaction conditions. As a side reaction, the formation of the byproduct from the attack of the thiolate species on the carbonyl group to give the corresponding thioester was observed. Several substrates with the carboxylic acid functionality were also tested, but no reaction was observed due to the precipitation of their sodium or lithium salts, when LiO*t*-Bu was used as base, in the reaction medium.

The major limitation for this methodology has to do with the absence of electron-withdrawing groups on the ring; thus, 2-methoxynaphthalene gave incomplete reaction even after prolonged reaction times (up to 7 h at reflux) and a large excess of thiol (up to 4 equiv). Also, compounds with triple bonds ([(3-methoxyphenyl)ethynyl]trimethylsilane), with very acidic hydrogens (*p*-anisamide), or more heavily functionalized (4-chloro-3-nitroanisole) gave decomposition. 4-Fluoroanisole also gave partial decomposition together with some product resulting from the nucleophilic aromatic substitution of the fluorine atom by the thiol, while 4-methoxychalcone gave a complex mixture of products where the known fact that thiols can give rise to radical processes may have played a significant role.[9]

In conclusion, a useful demethylation protocol for aromatic methyl ethers has been developed that is compatible with an extensive range of functional groups on the aromatic ring and that circumvents the smell problems associated with the use of ethanethiol. This methodology can be useful to both discovery and process chemists as a practical way to have access to phenols.

Experimental Section

The following experimental procedure to prepare 4-hydroxy-1-naphthonitrile (entry 1) is representative: An oven-dried, 50-mL, round-bottomed flask equipped with a magnetic stirrer and under a nitrogen atmosphere was charged with 2-(diethylamino)ethanethiol HCl (1.28 g, 7.5 mmol). *N*,*N*-dimethylformamide (10 mL) was added via syringe, and the flask was cooled in an ice water bath. When the internal temperature was below 5 °C, solid NaO*t*-Bu (1.54 g, 16.1 mmol) was added in one portion After 5 min, the cooling bath was removed, and the white suspension was allowed to warm to ambient temperature. After 15 min, 4-methoxy-1-naphthonitrile was added in one portion, and the contents of the flask were heated to reflux for 30 min. TLC analysis (hexanes/ethyl acetate 1/1 as mobile phase) and mass spectrometry analyses showed complete reaction. The mixture was allowed to cool to ambient temperature, and the flask was placed in an ice water bath. 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 × 25 mL), and the combined organic extracts were washed with water (3 × 10 mL) and saturated brine (10 mL) and dried over $MgSO_4$. The solvent was removed under vacuum to give a brown solid that was chromatographed (hexanes/ethyl acetate 1/1 as mobile phase) to give 0.77 g (91%) of 4-hydroxy-1-naphthonitrile as a white solid: mp 176−180 °C. IR: 3350, 3104, 2229, 2217, 1577, 1520, 1384, 1353, 1221, 821, 754 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 11.46 (s, 1 H), 8.22−8.24 (d, 1 H, J = 7.99 Hz), 7.92−7.97 (m, 2 H), 7.70−7.74 (ddd, 1 H, J = 8.33, 6.97, 1.27 Hz), 7.56−7.61 (ddd, 1 H, J = 8.29, 6.92, 1.17 Hz), 6.94−6.96 (d, 1 H, J = 8.19 Hz). MS m/z = 168 $(M - H)^+$. Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28. Found: C, 77.83; H, 4.28; N, 8.23.

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Supporting Information Available: Synthetic procedure and complete characterization data for entries 2 through 19 in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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