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Practical Demethylation of Aryl Methyl Ethers using an Odorless Thiol Reagent

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A highly practical method for demethylation of aryl methyl ethers employing a long-chain thiol has been developed. Under the conditions described herein, clean and fast conversions to the desired phenolic compounds have been achieved with a broad range of substrates. Unlike other thiolate-mediated methods, this newly developed protocol features *in-situ* generation of sodium alkylthiolate using NaOH, and is almost free from foul smells and potentially harmful gases. It therefore provides an attractive option for the demethylation of aryl methyl ethers.

Key words: Demethylation, Aryl methyl ether, Long-chain thiol, *In-situ* generation of alkylthiolate

INTRODUCTION

During our search for pharmaceutically active compounds, we encountered difficulties in the demethylation of aryl methyl ethers, especially when the scale of the reaction was greater. Although a plethora of methods have been documented (Weissman and Zewge, 2005; Wuts and Greene, 2006), most of these are not applicable to large scale syntheses. For example, BBr_3, perhaps the most popular reagent for the reaction, is not a viable option for mass production due to its high cost, the necessity of the use of special equipment and precautions for handling. Other reagents such as BCl_3, TMSI, and $AlCl_3$/EtSH suffer from similar problems, and often give unsatisfactory results. Hydrohalo acids, especially HBr, are sometimes chosen when the functional groups of the substrate are compatible with the harsh reaction conditions. Even under these stringent conditions, the result is often incomplete demethylation, probably due to the poor solubility of the organic substrates. An alternative method that has proved to be effective is the use of sulfide nucleophiles. Sodium sulfide (NaSH) and sodium thioethoxide (NaSEt) have been used for the last couple of decades (Newman *et al*., 1976; Dodge *et al*., 1995). Small aliphatic thiols such as ethanethiol combined with alkali hydride have been successfully employed in a great number of cases described in the literature (Nakatani *et al*., 2002; Ko *et al*., 2007). However, the foul smells and toxic gases that arise during the reaction and work-up greatly diminish their practicality for large scale synthesis. Nevertheless, the often reported efficiency of the sulfide-mediated reaction and the author's own experience gave us reason to be confident about this type of reaction. The issue remained of how the process could be made more user-friendly and suitable to large scale reactions. In this context, the recent publication by Magano and coworkers is notable as they have reported 'odorless demethylation' using water-soluble thiol (Magano *et al*., 2006). They utilized 2-(diethylamino)ethanethiol, which was deprotonated with NaO^{t}Bu to generate sulfide nucleophiles. During an acidic aqueous work-up, the sulfur-containing compounds were extracted into the aqueous phase, thereby almost completely removing odorous compounds from the product. Although a large range of substrates were tested successfully, this novel reagent has a major drawback, as indicated by the author, that aryl compounds require an electron-withdrawing group for good conversion. With the above information in mind, we searched for less odorous thiols which could be used practically both at the laboratory scale and the industrial scale.

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MATERIALS AND METHODS

General considerations

Aryl methyl ethers, 1-dodecanethiol, bases, and dried

solvents were obtained from commercial sources and used without further purification. All reactions were carried out under nitrogen. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 500 instrument with chemical shifts reported in ppm relative to residual solvent peak or TMS as the internal standard. Gas chromatography analyses were performed on a Hewlett Packard 6890 instrument with HP-1 capillary column and mass spectra were recorded by HP 5973 MSD with EI (electron impact) as the ionization method.

General procedure for demethylation

Aryl methyl ether (2.0 mmol) and NaOH (240 mg, 6.0 mmol) were put in a resealable tube. The tube was evacuated and backfilled with N_2. Anhydrous NMP (2 mL) was added to the reaction mixture followed by 1-dodecanethiol (719 mL, 3.0 mmol). The reaction mixture was stirred at 130°C until the aryl methyl ether was consumed as determined by TLC or GC analysis. After the reaction mixture was allowed to cool to room temperature, it was acidified with 1 N HCl (*ca*. 10 mL) and diluted with EtOAc. The aqueous phase was extracted with EtOAc (15 mL×2) and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash column chromatography (EtOAc:Hexane) afforded the analytically pure desired product.

1-Naphthol (Table III, entry 1)
Yield 98%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.20-8.15 (m, 1 H), 7.82-7.79 (m, 1 H), 7.51-7.46 (m, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.30 (dd, *J* = 8.0, 8.0 Hz, 1 H), 6.80 (d, 8.0 Hz, 1 H), 5.34 (s, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 151.6, 135.0, 127.9, 126.7, 126.1, 125.5, 124.6, 121.8, 120.9, 108.9. MS (EI) m/z 144 (M^+).

2-Naphthol (Table III, entry 2)
Yield 98%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2 H), 7.67 (d, J = 8.5 Hz, 1 H), 7.44-7.41 (m, 1 H), 7.34-7.31 (m, 1 H), 7.14 (d, J = 2.5 Hz, 1 H), 7.10 (dd, *J* = 8.5, 2.5 Hz, 1 H), 5.10 (s, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.6, 134.8, 130.1, 129.2, 128.0, 126.8, 126.6, 123.9, 118.0, 109.7. MS (EI) m/z 144 (M^+).

4-Phenylphenol (Table III, entry 3)
Yield 98%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2 H), 7.49-7.46 (m, 2 H), 7.43-7.40 (m, 2 H), 7.32-7.29 (m, 1 H), 6.92-6.89 (m, 1 H), 5.10 (s, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 155.3, 141.0, 134.2, 129.0, 128.7, 127.0, 126.9, 115.9. MS (EI) m/z 170 (M^+).

2'-Hydroxyacetophenone (Table III, entry 4)
Yield 96%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 12.27 (s, 1 H), 7.74 (ddd, *J* = 7.9, 2.5, 1.5 Hz, 1 H), 7.50-7.46 (m, 1 H), 6.98 (ddd, *J* = 8.3, 2.5, 1.5 Hz, 1 H), 6.93-6.89 (m, 1 H), 2.64 (s, 3 H). ^{13}C-NMR(125 MHz,$CDCl_3$) δ 204.8, 162.6, 136.7, 131.0, 120.0, 119.2, 118.7, 26.9. MS (EI) m/z 136 (M^+).

3'-Hydroxyacetophenone (Table III, entry 5)
Yield 74%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* =1.5, 3.0 Hz, 1 H), 7.51 (ddd, *J* = 1.0, 1.0, 7.5 Hz, 1 H), 7.34 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.11 (ddd, *J* = 1.0, 2.5, 8.0 Hz, 1 H), 6.05 (bs, 1 H), 2.61 (s, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 200.0, 156.7, 138.5, 130.2, 121.3, 121.1, 114.9, 27.1. MS (EI) m/z 136 (M^+).

4'-Hydroxyacetophenone (Table III, entry 6)
Yield 99%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.66 (bs, 1 H), 2.59 (s, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 198.9, 161.7, 131.5, 129.8, 115.8, 26.6. MS (EI) m/z 136 (M^+).

4-Bromophenol (Table III, entry 7)
Yield 99%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 6.72 (d, 8.5 Hz, 2H), 5.73 (bs, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 155.0, 132.7, 117.5, 113.0. MS (EI) m/z 172 (M^+).

3-Bromophenol (Table III, entry 8)
Yield 97%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 8.0, 8.0, 1 H), 7.08-7.05 (m, 1 H), 7.02 (dd, *J* = 2.0, 2.0 Hz, 1 H), 6.78-6.76 (m, 1 H), 5.24 (s, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 156.6, 131.1, 124.2, 123.0, 119.1, 114.5. MS (EI) m/z 172 (M^+).

Ethyl-4-hydroxybenzoate (Table III, entry 9)
Yield 45%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 2 H), 6.88 (d, *J* = 7.75, 2H), 6.51 (bs, 1 H), 4.36 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.2, 160.5, 132.2, 122.8, 115.5, 61.2, 14.6. MS (EI) m/z 166 (M^+).

4-Hydroxybenzaldehyde (Table III, entry 10)
Yield 56%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1 H), 7.82 (d, *J* = 9.0 Hz, 2 H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.22 (bs, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 191.5, 162.0, 132.8, 130.0, 116.3. MS (EI) m/z 121 (M^+).

4-Cyanophenol (Table III, entry 11)
Yield 93%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 9.0 Hz, 2 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 6.31 (bs, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.6, 134.6, 119.6, 116.8, 103.0. MS (EI) m/z 119 (M^+).

α,α,α-Trifluoro-*m*-cresol (Table III, entry 12)
Yield 88%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 7.11 (s, 1 H), 7.03 (dd, *J* = 8.0, 2.5 Hz, 1 H), 5.39 (bs, 1 H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 155.7, 132.3 (q, *J* = 32.0 Hz), 130.6, 124.0 (q, *J* = 270 Hz), 119.1 (d, *J* =1.4 Hz), 118.0 (d, *J* = 4.1 Hz), 112.6 (d, *J* = 4.3 Hz). MS (EI) m/z 162 (M^+).

3,5-Dimethoxyphenol (Table III, entry 13)
Yield 92%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, *J* = 2.0, 2.0 Hz, 1 H), 6.05 (d, *J* = 2.0 Hz, 2 H), 5.86 (bs, 1 H), 3.75 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 161.8, 157.7, 94.6, 93.4, 55.6. MS (EI) m/z 154 (M^+).

4-*i*-Propylphenol (Table III, entry 14)
Yield 75%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 5.15 (bs, 1 H), 2.91-2.83 (septet, *J* = 7.0 Hz, 1 H), 1.24 (d, *J* = 7.0 Hz, 6 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.7, 141.5, 127.7, 115.3, 33.5, 24.5. MS (EI) m/z 136 (M^+).

2,6-Di-*i*-propylphenol (Table III, entry 15)
Yield 93%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 2 H), 6.94 (dd, *J* = 7.5, 7.5 Hz, 1 H), 4.84 (s, 1 H), 3.20 (septet, *J* = 7.0 Hz, 2 H), 1.30 (d, *J* = 7.0 Hz, 12 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 150.2, 133.8, 123.7, 120.9, 27.4, 23.0. MS (EI) m/z 178 (M^+).

RESULTS AND DISCUSSION

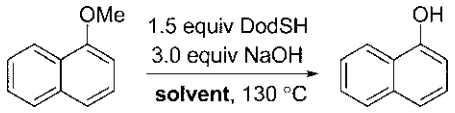
We began with searching for less-odorous thiols that are readily available from commercial sources at reasonable cost. Attempts to replace volatile thiols with alkanethiols whose alkyl chains are longer than C8 have been documented (Node *et al*., 2001; Frey *et al*., 2003; Nishide *et al*., 2004). However, alkanethiols having more than 12 carbons are considered essentially odorless compounds due to their high boiling points (cf. 1-dodecanethiol: 266-283°C) (Node *et al*., 2001; Nishide *et al*., 2004). Only 1-dodecanethiol was found to be supplied by various sources inexpensively and in large quantities, whereas alkanethiols whose chain-lengths are longer than C12 are too expensive for the practical use. Thus, we chose 1-dodecanethiol (abbreviated as DodSH in all the following tables) as the odorless reagent for use in development of appropiate demethylation conditions.

From the mechanistic point of view, thiolate-mediated demethylation can be considered a simple S_N2 substitution of the aryl methyl ether by a thiolate anion. In many precedents reported in the literature, the thiolate nucleophiles were prepared in advance using strong bases such as NaH, NaO^{t}Bu, and NaOMe (Nakatani *et al*., 2002; Ko *et al*., 2007). However, these bases are not very suitable for large scale synthesis; for example, NaH is notorious for its capricious reactivity, in the main due to evolution of H_2 during deprotonation. Therefore, we envisioned that *in-situ* generation of thiolate nucleophiles with more amenable bases would be highly efficient in terms of both ease of operation and scale-up.

To find suitable solvents for the transformation, the polar aprotic solvents, DMSO, DMF, NMP, 1,4-dioxane, and THF, were tested using 1-methoxynaphthalene as the substrate and NaOH as the base (Table I). 1,4-dioxane and THF were ineffective for complete conversion into the product after 3 h at the boiling temperature of the reaction mixtures. In DMSO, the starting material was almost consumed, but unidentified by-products were also detected after 3 h at 130°C. When the NaOH solution in DMSO was heated for 3 h in the absence of 1-methoxynaphthalene, an unpleasant odor was released and similar by-products were detected, suggesting that DMSO is not compatible with bases such as NaOH at an elevated temperature. When DMF and NMP were compared, NMP proved to be more effective than DMF in terms of reaction conversion.

Once we determined that NMP was the most suitable reaction solvent, we turned our attention to screening for the base (Table II). In successful transformation, 1-dodecanethiol (cf. pKa~11) is assumed to be first deprotonated

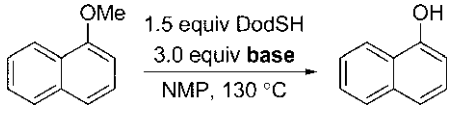
Table I. Solvent effect



solvent	conversion (%)[a]	yield (%)[b]
THF[c]	0	0
Dioxane[d]	5	5
DMF	45	45
NMP	100	99
DMSO	100	84

[a,b] GC conversion and GC yield.
[c] Reaction was run at 65°C.
[d] Reaction was run at 100°C

Table II. Base effect



base	conversion (%)[a]	yield (%)[b]
NaOH	100	99
LiOH	63	62
KOH	92	90
NaOMe	100	99
KO^{t}Bu	100	99

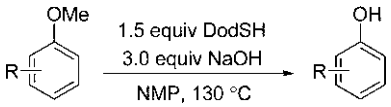
[a,b] GC conversion and GC yield.

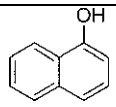
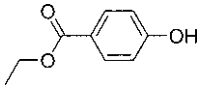
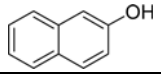
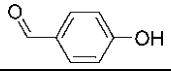
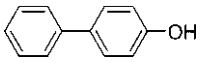
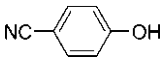
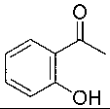
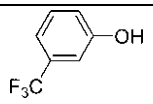
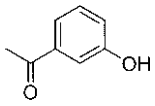
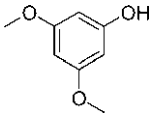
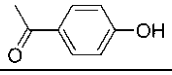
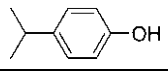
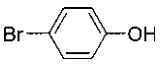
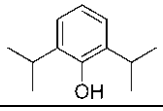
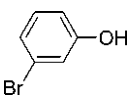
to the corresponding thiolate by a suitable base. As stated above, we thought that more conventional inorganic bases such as NaOH, LiOH, and KOH would be beneficial to the simple operation and scalability of this transformation. With this idea in mind, we tested five bases: NaOH, LiOH, KOH, NaOMe, and KO^{t}Bu. While the reactions with LiOH and KOH were incomplete, NaOH, NaOMe, and KO^{t}Bu were equally effective with the result of a clean conversion to 1-naphthol. Considering its cost and ease of handling, it was obvious that NaOH should be chosen as the base.

Under the conditions above, a reaction temperature lower than 130°C resulted in a prolonged completion reaction time and a reaction temperature of below 100°C was essentially unproductive. Although each substrate may need optimization because of its functional groups, we decided to set the reaction temperature at 130°C in order to achieve a general protocol applicable to a wide range of compounds.

Table III summarizes the results of the demethylation reactions of aryl methyl ether substrates at the 2 mmol scale using the reaction protocol developed, and shows good to excellent reaction yields. The results demonstrate the generality of the reaction protocol, as many functional groups are compatible under the reaction conditions. However, substrates with functional groups such as esters and aldehydes afforded the desired products only at a moderate yield (Table III, entries 9 and 10). In case of the substrate with an ester group, the major by-product was identified as the hydrolyzed product, 4-methoxyl benzoic acid, whereas the substrate with an aldehyde group seemed to be decomposed under the reaction conditions. Attempts to optimize the reaction conditions were not fruitful: varying base (LiOH, NaOH, and KO^{t}Bu), solvents (DMSO, NMP, and DMF), temperature (100-130°C), and amount of base essentially made no difference. Such compounds having functional groups vulnerable to the basic conditions may need acidic reaction conditions in order to achieve better results. Not surprisingly, the reactivities of methyl aryl ethers concur well with a nucleophilic substitution mechanism. Compounds lacking electron-

Table III. Demethylation of aryl methyl ether using DodSH[a]



Entry	Product (ArOH)	Reaction time	Yield[b]	Entry	Product (ArOH)	Reaction time	Yield[b]
1		2 h	99%	9		10 min	45%
2		2 h	98%	10		10 min	56%
3		3 h	99%	11		15 min	93%
4		15 min	96%	12		15 min	88%
5		30 min	74%	13		1 h 30 min	92%
6		15 min	99%	14		6 h	75%
7		15 min	99%	15		6 h	93%
8		15 min	97%				

[a]Reaction conditions: aryl methyl ether (2.0 mmol, 1.0 equiv), 1.5 equiv of 1-dodecanethiol, 3.0 equiv of NaOH in NMP (1.0 mL per mmol of aryl methyl ether).
[b]Isolated yields of > 95% purity as determined by GC and ^{1}H-NMR.

withdrawing groups show lower reactivities (Table III, entries 1, 2, 3, 13, 14 and 15), while very fast conversions were observed for those with electron-withdrawing groups (Table III, entries 4-12). The substitution position on the aromatic ring also affects the demethylation reaction: substitutions at the ortho-position and the para-position seem to be electronically equivalent, as very similar results were obtained for substrates in entries 4 and 6, while the meta-substituted substrate in entry 5 behaved quite differently. Consistent with Magano's result showing the preferential mono-demethylation of trimethoxybenzene, a similar selectivity was observed using the developed protocol (Table III, entry 13). Furthermore, the sterically hindered aryl methyl ether 2,6-di-*i*-propyl anisole was well transformed to its corresponding phenol at an excellent yield (Table III, entry 15).

A larger scale synthesis of 1-naphthol from 1-methoxynaphtalene was carried out as a representative example to demonstrate the scalability of the demethylation protocol. 1-Methoxynaphthalene (63.3 g, 0.400 mol), 1-dodecanethiol (121 g, 0.598 mol), sodium hydroxide (48.0 g, 1.20 mol), and NMP (200 mL) were added under an N_2 atmosphere, to a 500 mL round bottomed flask equipped with a magnetic stirring bar. The reaction mixture was heated for 2 h at 130°C, when the TLC analysis showed the complete conversion of 1-methoxynaphthalene to 1-naphthol. The reaction mixture was poured into ice water (300 mL), and 6 N HCl (220 mL) was added slowly in a cooling bath, to bring the pH of the mixture to below 3. Most of the product was precipitated at this stage. The precipitated product was collected by filtration, and was rinsed with hexanes (100 mL). The product was further purified by recrystallization from EtOAc/hexanes to yield 52.4 g (91%).

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, an estrogen receptor modulator (Renaud *et al.*, 2005) and Dihydrexidine, a dopamine receptor agonist (Fernandes *et al*., 2006) contain phenolic moieties in their structures, and they could be procured by the cleavage of the aryl methyl ether precursors using this method.

In conclusion, a practical demethylation method using 1-dodacanethiol has been developed. Several advantages over previous methods reported in the literature include: (i) essentially odorless conditions during the reaction and work-up, (ii) avoidance of inconvenient bases such as NaH and NaOMe with the use of NaOH, (iii) *in-situ* generation of the reactive thiolate, thereby simplifying the operation, and (iv) excellent chemical yields for a broad range of substrates. A larger scale synthesis of 1-naphthol has been successfully carried out following the developed protocol, thereby demonstrating its utility for application to mass production.

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REFERENCES

Dodge, J. A., Stocksdale, M. G., Fahey, K. J., and Jones, C. D., Regioselectivity in the alkaline thiolate deprotection of aryl methyl ethers. *J. Org. Chem*., 60, 739-741 (1995).

Fernandes, P. B., Mailman, R. B., and Nichols, D. E., Preparation of hexahydrobenzo-phenanthridines as dopamine receptor agonists for treatment of pulmonary edema. PCT Int. Appl., WO 2006012640 (2006).

Frey, L. F., Marcantonio, K. M., Chen, C. Y., Wallace, D. J., Murry, J. A., Tan, L., Chen, W., Dolling, U. H., and Grabowski, E. J. J., Practical synthesis of a highly functionalized thiazole ketone. *Tetrahedron*, 59, 6363-6373 (2003).

Ko, H. M., Lee, D. G., Kim, M. A., Kim, H. J., Park, J., Lah, M. S., and Lee, E., Total synthesis of (-)-blepharocalyxin D. *Org. Lett.*, 9, 141-144 (2007).

Magano, J., Chen, M. H., and Clark, J. D., Nussbaumer, T., 2-(Diethylamino)ethanethiol, a new reagent for the odorless deprotection of aromatic methyl ethers. *J. Org. Chem.*, 71, 7103-7105 (2006).

Nakatani, M., Nakamura, M., Suzuki, A., Inoue, M., and Katoh, T., A new strategy toward the total synthesis of stachyflin, a potent anti-influenza a virus agent: Concise route to the tetracyclic core structure. *Org. Lett.*, 4, 4483-4486 (2002).

Newman, M. S., Sankaran, V., and Olson, D. R., Phenolic and ketonic tautomers in polycyclic aromatic hydrocarbons. *J. Am. Chem. Soc.*, 98, 3237-3242 (1976).

Nishide, K., Ohsugi, S., Miyamoto, T., Kumar, K., and Node, M., Development of odorless thiols and sulfides and their applications to organic synthesis. *Monstshefte fûr chime.*, 135, 189-200 (2004).

Node, M., Kumar, K., Nishide, K., Ohsugi, S-. I., and Miyamoto, T., Odorless substitutes for foul-smelling thiols: syntheses and applications. *Tetrahedron Lett.*, 42, 9207-9210 (2001).

Renaud, J., Bischoff, S. F., Buhl, T., Floersheim, P., Fournier, B., Geiser, M., Halleux, C., Kallen, J., Keller, H., and Ramage, P., Selective estrogen receptor modulators with conformationally restricted side chains. Synthesis and structure-activity relationship of ERα-Selective tetrahydroisoquinoline ligands. *J. Med. Chem.*, 48, 364-379 (2005).

Weissman, S. A. and Zewge, D., Recent advances in ether dealkylation. *Tetrahedron*, 61, 7833-7863 (2005).

Wuts, P. G. M. and Greene, T. W., Protective Groups in Organic Synthesis, John Wiley & Sons, Hoboken, NJ, pp. 370-382 (2007).