Regioselectivity in the Alkaline Thiolate Deprotection of Aryl Methyl Ethers

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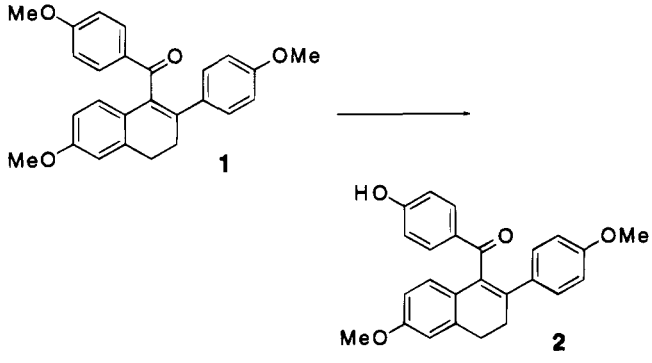
The masking of the phenol moiety as its methyl ether is a ubiquitous protective group tactic[1] in organic synthesis. While such functionality provides excellent protection against a variety of reagents and experimental conditions, harsh reaction protocols (e.g., refluxing HBr[2]) have been historically required to liberate the parent phenol. This is due, in large part, to the inherent chemical stability of this particular ether linkage. This caveat has contributed to the development of numerous phenol protecting groups which can be readily removed under a diverse array of mild and selective conditions.[1] Alternatively, and in complimentary fashion, a wide variety of reagents have been developed to cleave the aryl methyl ether bond under less stringent reaction conditions.[3] In particular, the use of sodium ethanethiolate (EtSNa) in dimethylformamide, introduced in 1970 by Feutrill and Mirrington,[4] has gained general acceptance in this capacity. Despite the widespread popularity of this protocol, we were surprised to find relatively few examples of regioselective demethylation using this method.[5,6] To address this issue, we have systematically investigated the use of alkyl thiolate anions to deprotect aryl methyl ethers in a regiocontrolled manner.

Our initial interest in this area stemmed from the need for multigram quantities of phenol **2** as a key intermediate for structure–activity studies in our anti-estrogen research.[7] We envisioned **2** could be prepared by selective deprotection of a trimethoxy precursor, such as **1**,



in which O-demethylation of the 4-aroyl ether would presumably occur in preference to the two remaining ether moieties. Initially, a variety of protocols were screened for this purpose including protic acids (HBr[2], pyridinium salts[8]), Lewis acids (BBr_3,[9] $AlCl_3$/EtSH[10]), and iodotrimethylsilane.[11] In all cases, unsatisfactory mixtures of demethylated products were obtained. As a result of these unsuccessful attempts, we became interested in a report by Koutek[12] in which rate differences were observed in the EtSNa demethylation of substituted anisole derivatives. In particular, Koutek observed dramatic rate enhancements in this process when electron-withdrawing groups were present on the anisole ring. Given this precedent, it seemed possible the electron deficient nature of the aroyl group would lend itself to selective removal of the desired methyl ether moiety. From a practical standpoint, however, the experimental protocol employed by Koutek required high temperatures (autoclave, 190 °C) and long reaction times to affect demethylation. As these conditions were not amenable to the quantities of **2** required, we elected to employ the Feutrill and Mirrington modification[4] of this reaction in which DMF is advantageously exploited as the reaction medium. Thus, when trimethoxydihydronaphthalene **1** was subjected to these modified conditions (sodium ethanethiol in DMF at 100 °C for 0.5 h) a single product was obtained. NOE studies on the purified material indicated demethylation occurred exclusively at the desired position leaving the remaining methoxy groups entirely intact.[13]

In order to define the scope and limitation of this regioselective cleavage, a variety of multifunctionalized substrates were subsequently investigated (Table 1). Examination of the results reveals a distinct trend in which the methyl ether moiety *para* to the carbonyl reacts in preference to other nonactivated aryl positions.[14] In addition, these conditions appear specific regardless of whether the substrate possesses two or three methoxy groups (e.g., compare entry 1 or 2 with entry 3) and whether these groups are on the same or different

(1) See: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; p 145. Also: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.

(2) Burwell, R. L. *Chem. Rev.* **1954**, *54*, 615.

(3) (a). Meerwein, H. In *Houben-Weyl*, 4th ed.; Georg Thieme Verlag: Stuttgart, 1965; Vol. VI, p 143. (b) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (c) Evers, M. *Chemica Script.* **1986**, *26*, 585. (d) Tiecco, M. *Synthesis* **1988**, 749.

(4) (a) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, *16*, 1327. (b) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1719, 1731.

(5) See: (a) Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Tetrahedron* **1982**, *38*, 3687. (b) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548. (c) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 1831. For selective demethylations aided by neighboring group participation see: Cannon, J. R.; Feutrill, G.; Wong, L. C. H. *Aust. J. Chem.* **1983**, *36*, 2572. Lal, K.; Ghosh, S.; Salomon, R. G. *J. Org. Chem.* **1987**, *52*, 1072. Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon *J. Am. Chem. Soc.* **1986**, *108*, 1311. Also, monodemethylation of symmetrically disubstituted aryl ethers are well documented: For example, see ref 5c and: Rao, K. V.; Kuo, H.-S. *J. Heterocycl. Chem.* **1979** *16*, 1241.

(6) For the use of sodium *p*-thiocresolate/HMPT in this capacity see: (a) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191. (b) Loubinoux, B.; Coudert, G.; Guillaumet, G. *Synthesis* **1980**, 8, 638. For use of selenolate anions (sodium benzylselenide) in the regioselective deprotection of di- or trimethoxyaryl substrates see: Ahmed, R.; Saa, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228.

(7) Jones, C. D.; Blaszczak, L. C.; Goettel, M. E.; Suarez, T.; Crowell, T. A.; Mabry, T. E.; Ruenitz, P. C.; Srivatsan, V. *J. Med. Chem.* **1992**, *35*, 931.

(8) Sheehan, J. C.; Erman, W. F.; Cuickshank, P. A. *J. Am. Chem. Soc.* **1957**, *79*, 147.

(9) Mc Omie, J. F. W.; West, D. E. *Organic Syntheses;* Wiley: New York, 1973; Collect. Vol V, p 412.

(10) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057.

(11) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

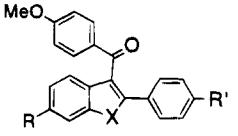
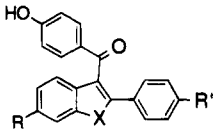
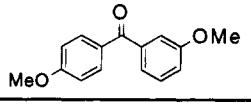
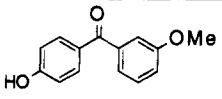
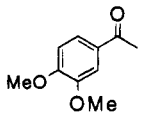
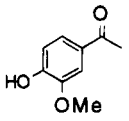
(12) Koutek, B.; Setinek, K. *Collect. Czech. Chem. Commun.* **1968**, *33*, 866.

(13) Upon irradiation of the individual methoxy groups, NOE's were observed at the 5,7 and 3',5' protons indicating ether functionality at the desired 6- and 4'-positions, respectively. Regiochemical assignments for the remaining cases (Table 1) were determined by similar NOE experiments with the exception of entries 6 and 7 which were compared to authentic samples of the monophenols prepared *via* independent means.

(14) Rapoport has observed similar results with this reagent in a 1,4-disubstituted naphthalene system. See: Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.

0022-3263/95/1960-0739$09.00/0

Table 1. Regioselectivity in the Thiolate-Mediated Demethylation of Aryl Methyl Ethers

entry	ether	phenol	conditions[a]	yield (%)
				
	X / R / R'			
1	CH_2CH_2 / MeO / H		1.5 eq.[b], 0.5 h, 85 °C	87
2	CH_2CH_2 / H / MeO		1.5 eq., 3.5 h, 80 °C	83
3	CH_2CH_2 / MeO / MeO		1.3 eq., 0.5 h, 100 °C	77
4	O / MeO / MeO		1.5 eq., 4.0 h, 80 °C	75
5	NEt / MeO / MeO		2.0 eq., 6.0 h, 85 °C	54
6			1.5 eq., 3.5 h, 80 °C	80[c]
7			1.5 eq., 3.5 h, 80 °C	60[d]

[a] Expressed in terms of EtSNa equivalents, reaction time, and temperature. [b] EtSLi employed. [c] 4% of the *meta* monodeprotected product was isolated. [d] The remainder of the material was unreacted starting material.

aromatic rings.[15] Moreover, a variety of aromatic frameworks (furan, indole, naphthalene, dihydronaphthalene, and aceto- and benzophenone) appear amenable to this protocol.[16] In terms of the thiol counterion, we have found the lithium salt to be as effective as sodium (for example, a 73% yield was obtained for entry 3, Table 1, when EtSLi was employed), although the commercial availability of the latter makes it significantly more appealing as a practical reagent. As expected, longer reaction times, elevated temperatures, and excess thiolate all result in deterioration of the observed selectivity. Significantly, a moderate degree of chemoselectivity has also been observed in the presence of other phenolic protecting groups, such as methoxymethyl (MOM) and benzyl.[17]

Given the apparent role electronic factors play in the selectivity of this process, we became interested in studying this phenomenon in more detail. In particular, we wanted to examine the relationship between the electronic character of the aryl methyl ether and the efficacy of the reaction (gauged by yield). Thus, a representative spectrum of electron-rich and -deficient anisole derivatives were individually subjected to identical EtSNa reaction conditions (80 °C, DMF, 3.5 h).[19] As shown in Table 2, comparison of the Hammet constant (σ) for each substituent with the corresponding yield of

Table 2. Substitutent Effects in the EtSNa Demethylation of Substituted Anisole Derivatives

entry	ArOMe	σ_p or σ_m[18]	yield (%)
1	*p*-CN	0.70	89
2	*p*-NO_2	0.81	81
3	*p*-$COCH_3$	0.47	77
4	*p*-Br	0.26	43
5	*p*-Cl	0.24	27
6	*m*-$COCH_3$	0.36	18
7	*p*-F	0.15	13
8	H	0	10
9	*p*-Ph	0.05	9
10	*p*-OMe	−0.12	<5[a]
11	*p*-Et	−0.13	<5[a]
12	*p*-Me	−0.14	<5[a]
13	*p*-$CH(Me)_2$		<5[a]

[a] Determined by ^{1}H-NMR (300 MHz) of the crude reaction mixture.

the reaction indicates an apparent correlation between these two indexes; *i.e.*, electron-withdrawing groups such as cyano, nitro, and acetyl provide good yields of demethylated product whereas neutral or electron-releasing substituents (methyl, ethyl, methoxy) are appreciably less effective (<5%).[20] The significance of the carbonyl moiety is evident by comparison of entries 3 and 11 (Table 2) in which replacement of the acetyl carbonyl with dihydro (C=O to CH_2) results in a drastic reduction in yield from 77 to <5%. The relative position of the electron-withdrawing group also plays a key role in determining reactivity; *i.e.*, the demethylation of *p*-acetophenone proceeds with 4-fold efficacy relative to its *meta* compliment (77 vs 18%, respectively). These observations are entirely consistent with the reaction kinetics observed by Koutek[21] and further demonstrate the importance of substituent effects in the cleavage of aryl methyl ethers.[22]

In summary, sodium ethanethiolate in DMF provides a convenient and regioselective method for the O-demethylation of aryl methyl ethers substituted by electron-

(15) It is surprising to note that in entries 2–5 (Table 1) cleavage of the 2-(4-methoxyphenyl) ether is not observed; *i.e.*, the phenolate derived from reaction of this methoxy group can be delocalized to the ketone as a consequence of its *para* vinylogous nature. Presumably, the steric requirements for such charge delocalization, in which all three aromatic rings are constrained to lie in the same plane, are prohibitive.

(16) All products exhibited satisfactory spectral characteristics (^{1}H- and ^{13}C-NMR, IR, elemental analysis, and/or mass spectrum) for the assigned structure.

(17) Competition studies employing 4,4'-benzophenone derivatives differentially substituted with either benzyl or MOM and methyl ether functionality revealed a 2-fold preference for cleavage of the methyl ether moiety. As expected, silyl protecting groups were cleaved under these conditions.

(18) Values of σ_p and σ_m were obtained from: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; Part A, p 201.

(19) We elected not to explore substrates with *ortho* methoxy groups to eliminate possible misinterpretation of the results due to inherent steric factors.

(20) In all cases, the remainder of the material balance was unreacted ether.

(21) Koutek has demonstrated relative rate enhancements in the EtSNa/EtOH (190 °C) deprotection of anisoles substituted with electron-withdrawing substituents such as CHO or acetyl. See ref 12.

(22) Contrary to previous reports (see ref 4), competing nucleophilic aromatic substitution by the thiolate anion is not observed.

withdrawing groups. Electronic factors appear to control the observed selectivity; *i.e.*, methyl ethers *para* to the electron-withdrawing functionality react preferentially with the thiol anion. In addition, substituent effects indicate a relationship between the Hammet constant and the efficacy of the reaction, with more electron-poor species providing higher yields of demethylated product. It is also apparent that a variety of these substituents (NO_2, CN, acetyl) provide useful yields of deprotected product, thereby providing additional synthetic utility to this general method.

Experimental Section[23]

Representative Procedure for the Regioselective Deprotection of Aryl Methyl Ethers: (4-Hydroxyphenyl)[3,4-dihydro-6-methoxy-2-(4-methoxyphenyl)-1-naphthalenyl]-methanone (Table 1, Entry 3). To a solution of **1**[7] (40.0 g, 100 mmol) stirring in DMF (500 mL) at room temperature was added sodium ethanethiol (11.0 g, 130 mmol).[24] The mixture was heated to 100 °C and after 0.5 h, the reaction mixture was allowed to cool to room temperature and then concentrated. The resulting crude material was partitioned between $CHCl_3$ and saturated aqueous ammonium chloride. The mixture was treated with 1 N HCl to acidic pH and the organic portion collected. The extract was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The resulting brown oil was purified by filtration through a short bed of silica gel (hexanes to 30% hexanes/ethyl acetate gradient) to give 30 g (77%) of the desired product as a yellow foam: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.16 (m, 2H), 6.85 (d, 1H, J = 8.0 Hz), 6.77 (s, 1H), 6.65 (m, 5H), 6.11 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.00 (m, 2H), 2.77 (m, 2H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 201.1, 162.4, 159.7, 159.6, 137.5, 137.2, 134.6, 134.2, 133.3, 130.6, 129.6, 127.6, 127.2, 116.5, 114.7, 114.5, 112.3, 56.2, 56.0, 30.7, 29.6; IR ($CHCl_3$) 3401, 1642, 1601 cm^{-1}; MS (FD) *m/e* 386 (M^+). EA calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74. Found: C, 77.46; H, 5.91.

(4-Hydroxyphenyl)[3,4-dihydro-6-methoxy-2-phenyl-1-naphthalenyl]methanone (Table 1, entry 1): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.6 Hz), 7.15–7.18 (m, 2H), 7.05–7.18 (m, 3H), 6.86 (d, 1H, J = 8.6 Hz), 6.78 (d, 1H, J = 2.7 Hz), 6.60–6.70 (m, 3H), 6.23 (br s, 1H), 3.78 (s, 3H), 2.95–3.05 (m, 2H), 2.75–2.85 (m, 2H); MS (FD) *m/e* 356 (M^+). EA calcd for $C_{24}H_{20}O_3$: C, 80.87; H, 5.66. Found: C, 80.66; H, 5.48.

(4-Hydroxyphenyl)[3,4-dihydro-2-(4-methoxyphenyl)-1-naphthalenyl]methanone (Table 1, entry 2): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 8.9 Hz), 6.91–7.24 (m, 6H), 6.66–6.71 (m, 4H), 3.71 (s, 3H), 3.03 (t, 2H, J = 8.4 Hz), 2.77 (t, 2H, J = 8.1 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 199.2, 160.6, 158.3, 138.2, 134.0, 133.5, 132.9, 132.8, 131.8, 129.9, 128.1, 127.0, 126.8, 126.2, 124.4, 114.9, 113.0, 54.5, 29.4, 27.7; IR ($CHCl_3$) 3271, 1600 cm^{-1}; MS (FD) *m/e* 356 (M^+). EA calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found: C, 80.60; H, 5.33.

(4-Hydroxyphenyl)[6-methoxy-2-(4-methoxyphenyl)benzo[*b*]furan-3-yl]methanone (Table 1, entry 4): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 2H, J = 8.6 Hz), 7.61 (d, 2H, J = 8.7 Hz), 7.34 (d, 1H, J = 8.6 Hz), 7.07 (d, 1H, J = 2.2 Hz), 6.74–6.88 (m, 5H), 3.87 (s, 3H), 3.79 (s, 3H); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ 190.9, 163.6, 161.1, 159.2, 155.4, 155.1, 133.2, 129.8, 129.6, 122.7, 122.5, 121.7, 116.4, 115.6, 115.2, 113.7, 97.0, 56.7, 56.3; IR ($CHCl_3$) 3279, 3014, 1603 cm^{-1}; MS (FD) *m/e* 374 (M^+).

(4-Hydroxyphenyl)[*N*-ethyl-6-methoxy-2-(4-methoxyphenyl)-3-indolyl]methanone (Table 1, entry 5): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 1H, J = 8.7 Hz), 7.47 (d, 2H, J = 8.6 Hz), 7.18 (d, 2H, J = 8.6 Hz), 6.88–6.91 (m, 2H), 6.79 (d, 2H, J = −8.6 Hz), 6.57 (d, 2H, J = 8.6 Hz), 4.08 (q, 2H, J = 7.2 Hz), 3.91 (s, 3H), 3.76 (s, 3H), 1.29 (t, 3H, J = 7.2 Hz); IR ($CHCl_3$) 3126, 1612 cm^{-1}; MS (FD) *m/e* 401 (M^+). EA calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N 3.49. Found: C, 75.00; H, 5.73; N, 3.50.

4′-Hydroxy-3-methoxybenzophenone (Table 1, entry 6): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.69 (d, 2H, J = 9 Hz), 7.43–7.48 (m, 1H), 7.18–7.22 (m, 3H), 6.90 (d, 2H, J = 9 Hz), 3.81 (s, 3H); IR ($CHCl_3$) 3277, 1646, 1598; MS (FD) *m/z* 228 (M^+). EA calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.83; H, 5.32.

4′-Hydroxy-4-methoxybenzophenone (Table 1, entry 7): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 9 Hz), 7.70 (d, 2H, J = 9 Hz), 6.96 (d, 2H, J = 9 Hz), 6.92 (d, 2H, J = 9 Hz), 3.88 (s, 3H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 194.4, 162.4, 161.3, 132.2, 131.9, 130.7, 129.1, 114.97, 113.2, 55.2; IR ($CHCl_3$) 3272, 1643, 1605; MS (FD) *m/e* 228 (M^+). EA calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.42; H, 5.35.

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(23) For general experimental information see: Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. Sodium ethanethiolate and anhydrous DMF were purchased from Aldrich Chemical Co.

(24) All manipulations involving sodium ethanethiol were carried out in a well-ventilated hood owing to the strong odor of this reagent and the thiol byproduct of the reaction (methyl ethyl sulfide).