Influence of Hydrogen Bonding in the Activation of Nucleophiles: PhSH−(Catalytic) KF in *N*-Methyl-2-pyrrolidone as an Efficient Protocol for Selective Cleavage of Alkyl/Aryl Esters and Aryl Alkyl Ethers under Nonhydrolytic and Neutral Conditions†

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The nucleophilicity of arenethiols can be augmented via hydrogen bonding with 'naked' halide anion. The activity of the halide anions follow the order $F^- \gg Cl^- \sim Br^- \sim I^-$ and is dependent on the countercation ($Bu_4N \sim Cs \sim K > Na \gg Li$). The solvent plays an important role in nucleophilic activation as well as regeneration of the effective nucleophile (e.g. ArS^-) and those with high dielectric constant, high molecular polarizability, high donor number (DN), and low acceptor number (AN) are the most effective. Selective deprotection of alkyl/aryl esters and aryl alkyl ethers can be achieved under nonhydrolytic and neutral conditions by the treatment with thiophenol in 1-methyl-2-pyrrolidone (NMP) in the presence of a catalytic amount of KF. Aryl esters are selectively deprotected in the presence of alkyl esters and alkyl methyl ethers during intramolecular competitions.

Introduction

Protection/deprotection of phenolic and carboxylic acid functionalities are frequently desirable transformations in organic synthesis. Considering the ease of preparation and the availability of starting materials, phenols are protected as their acyl and methyl ether derivatives[1,2] while the carboxylic acids are often protected as methyl esters.[1,3] Hydrolytic deprotection of esters are among the simplest and most common of all laboratory reactions and normally accomplished by heating the esters in either aqueous acid or base.[4] However, due to the poor nucleophilic property of H_2O/OH^-, the harsh treatment required for the hydrolytic cleavage is not compatible with multifunctional substrates (particularly those with acid or alkali labile groups). Since the introduction of PhS^- by Sheehan et al.[5] and EtS^- by Feutril and Mirrington,[6] as effective nucleophiles for deprotection of alkyl esters and aryl alkyl ethers, respectively, alkali metal thiolates have been the reagents of choice for functional group transformations requiring nucleophilic cleavage.[7] However, all of these methods require stoichiometric amounts of the desired thiolate anion for the expected conversion to take place and suffer from one or more of the disadvantages such as the (i) use of expensive and difficult to handle bases (e.g. LiH,[8] NaH,[9] and MeLi[10]), (ii) extra efforts needed to make the metal hydride bases oil free, (iii) manipulation involved in using the low boiling thiols, (iv) use of stringent reaction condition such as the requirement of heating in sealed tube,[7g,f] (v) use of carcinogenic HMPA[8,10] as solvent, (vi) competitive side reactions such as the aromatic nucleophilic substitution of the nitro[11]/chloro[12] groups, reduction of the nitro[7g,f]/α,β-unsaturated carbonyl[13] functionalities and Michael addition to α,β-unsaturated carbonyl groups.[14]

Recently we have developed efficient methods for in situ generation of arenethiolate anions in a "demand-

† Dedicated to Prof. S. V. Kessar on the occasion of his 70th birthday.

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(1) (a) Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: New York, 1994. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(2) Basak (née Nandi), A.; Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett*. **1998**, *39*, 4883 and the references therein.

(3) Chakraborti, A. K.; Basak (née Nandi), A.; Grover, V. *J. Org. Chem*. **1999**, *64*, 8014 and the references therein.

(4) McMurry, J. *Org. React*. **1977**, *24*, 187.

(5) Sheehan, J. C.; Daves, Jr., G. D. *J. Org. Chem*. **1964**, *29*, 2006.

(6) Feutril, G. I.; Mirrington, R. N. *Tetrahedron Lett*. **1970**, 1327.

(7) For references on ester cleavage: (a) E. Haslam, *Tetrahedron* **1980**, *36*, 2409. (b) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691. (c) Wallace, O. B.; Springer, D. M. *Tetrahedron Lett*. **1998**, *39*, 2693. For references on ether cleavage: (d) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (e) Tiecco, M. *Synthesis* **1988** 749. (f) Hwu, J. R.; Wong, F. F.; Shiao, M.-J. *J. Org. Chem*. **1992** *57*, 5254. (g) Shiao, M.-J.; Lai, L.-L.; Ku, W.-S.; Lin, P.-Y.; Hwu, J. R. *J. Org. Chem*. **1993**, *58*, 4742. (h) Dodge, J. A.; Stocksdale, M. G.; Fahey, K. J.; Jones, C. D. *J. Org. Chem*. **1995**, *60*, 739. (i) Ranu, B. C.; Bhar, S. *Org. Prep. Proc. Int*. **1996**, *28*, 371. (j) Huffman, J. W.; Yu, S.; Showalter, V.; Abood, M. E.; Wiley, J. L.; Compton, D. R.; Martin, R.; Bramblett, R. D.; Reggio, P. H. *J. Med. Chem*. **1996**, *39*, 3875. (k) Pinchart, A.; Dallaire, C.; Bierbeek, A. V.; Gingras, M. *Tetrahedron Lett*. **1999**, *40*, 5479.

(8) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett*. **1970**, 4459.

(9) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem*. **1972**, *25*, 1731.

(10) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett*. **1977**, 3859.

(11) (a) Cogolli, P.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem*. **1979**, *44*, 2636. (b) Kornblum, N.; Cheng, L.; Krebber, R. C.; Kestner, M. V.; Newton, B. N.; Pinnick, H. W.; Smith, R. G.; Wade, P. A. *J. Org. Chem*. **1976**, *41*, 1560. (c) Beck, J. R. *J. Org. Chem*. **1973**, *38*, 4086.

(12) Caruso, A. J.; Colley, A. M.; Bryant, G. L. *J. Org. Chem*. **1991**, *56*, 862 and references therein.

(13) Meissner, J. W. G.; van dar Laan, A. C.; Pandit, U. K. *Tetrahedron Lett*. **1994**, *35*, 2757.

(14) (a) Niyazymbetov, M. E.; Laikhter, A. L.; Semenov, V. V.; Evans, D. H. *Tetrahedron Lett*. **1994**, *35*, 3037. (b) Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem*. **1995**, *60*, 6188. (c) Ito, A.; Konishi, K.; Aida, T. *Tetrahedron Lett*. **1996**, *37*, 2585.

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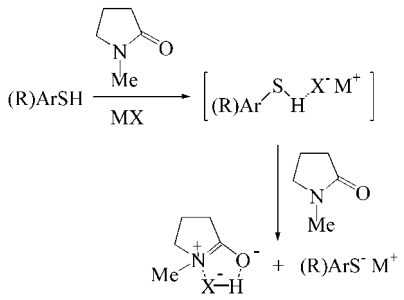
Scheme 1



based" fashion by the reaction of the thiols in the presence of catalytic quantities of a base for chemoselective deprotection of aryl alkyl ethers,[15] alkyl esters,[16] and aryl esters.[17] In a preliminary communication we reported that the use of PhSH in the presence of a catalytic amount of KF in NMP constitutes an efficient protocol for chemoselective deprotection of alkyl esters under nonhydrolytic and neutral conditions.[18] We describe herein the scope and limitations of this protocol so as to achieve efficient methods for chemoselective and nonhydrolytic cleavage of aryl alkyl ethers, aryl esters, and selective deprotection of aryl esters in the presence of alkyl esters and aryl alkyl ethers.

Results and Discussion

To make the "demand-based" in situ generation of the thiolate anion effective under neutral conditions, we presumed that the use of an alkali metal halide in aprotic polar solvent would liberate the "naked" halide anion[19] which in turn would be involved in strong hydrogen bonding[20] with the thiol group and ultimately generate the thiolate anion due to its relatively greater stabilization[21] in aprotic polar medium compared to that of the halide anion. The liberated HX may be entrapped by the solvent through hydrogen bond formation (Scheme 1). The efficiency of the protocol should be dependent on the specific "solvent anion" interaction, and in this regard we further reasoned that the proton abstraction ability of the halide anion should be controlled by a combined effect of the (i) dielectric constant of the solvent, (ii) size of the countercation, (iii) relative activity of the free halide anion, (iv) DN and AN of the solvent,[22] and (v) molecular polarizability of the solvent.

To test this hypothesis, methyl benzoate was treated with PhSH in the presence of 10 mol % of alkali metal halides in NMP, and the results are summarized in Table 1. Among the halides derived from a particular countercation, the catalytic activity follows the order F ≫ Cl ∼ Br ∼ I. The effect of the countercation was revealed by the fact that fluorides with large cationic size such as KF, CsF, and $^{n}Bu_4NF$ were the most effective catalysts highlighting the significance of the dissociation of the halides. The poor results with Me_3PhCH_2NF and Me_4NF (entries 21 and 22, Table 1) is further implication of the role of the size of the cation. Excellent results, albeit to a lesser extent, could be obtained by the use of NaF, but no appreciable catalytic influence was exhibited by LiF. Among the bifluorides, although KHF_2 afforded very good results, NH_4HF_2 was not effective. A moderate results were obtained on using KF/Al_2O_3.[23] The reaction is best carried out by the treatment of the ester with 1 equiv of PhSH in the presence of 10 mol % of KF[24] in NMP under reflux for 5−10 min. Reactions carried out at lower temperature required longer time and afforded lower yields (compare the results of entries 1, 5, and 8 with those of entries 18, 19, and 20, respectively, Table 1); however, the higher operational reaction temperature has no detrimental effect on either the products or the unreacted starting materials.

The effect of the solvent was studied during the reaction of methyl benzoate with 1 equiv of PhSH in the presence of 10 mol % of KF in various solvents (Table 2). The solvent plays a dual role in the (i) ionization of the

Table 1. The Effect of Temperature and Alkali Metal Halides on the Cleavage of Methyl Benzoate by Thiophenol in NMP[a]

entry	MX[b]	temp (°C)	time (min)	yield[c,d,e,f] (%)
1	$^{n}Bu_4NF$	reflux	10	92
2	$^{n}Bu_4NCl$	reflux	10	nil
3	$^{n}Bu_4NBr$	reflux	10	nil
4	$^{n}Bu_4NI$	reflux	10	nil
5	CsF	reflux	10	89
6	CsCl	reflux	10	53
7	CsI	reflux	10	30
8	KF	reflux	10	90 (5)
9	KF/Al_2O_3	reflux	10	50
10	KCl	reflux	10	25
11	KBr	reflux	10	15
12	KI	reflux	10	15
13	NaF	reflux	10	82 (3)
14	NaCl	reflux	10	20
15	NaBr	reflux	10	20
16	NaI	reflux	10	20
17	LiF	reflux	10	23
18	$^{n}Bu_4NF$	100	60	67
19	CsF	100	60	26
20	KF	100	60	24
21	Me_3PhCH_2NF	reflux	10	10
22	Me_4NF	reflux	10	40
23	NH_4F	reflux	10	nil
24	KHF_2	reflux	10	70 (0)
25	NH_4HF_2	reflux	10	15
26	KOAc	reflux	10	60 (9)
27	LiOAc	reflux	10	19
28	KOCOPh	reflux	10	70
29	None	reflux	10	nil

[a] The ester (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 10 mol % of the halide. [b] The commercially available hydrate of the tetralkylammonium fluorides were used. [c] Isolated yield of benzoic acid. [d] The ^1H NMR spectra of the products were in full agreement with the literature.[41] [e] The unreacted ester could be recovered. [f] The figure in parentheses refers to the yield of benzoic acid obtained by the use of stoichiometric quantities of the salt in the absence of PhSH.

(15) Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett*. **1997**, *38*, 8749.
(16) Sharma, L.; Nayak, M. K.; Chakraborti, A. K. *Tetrahedron* **1999**, *55*, 9595.
(17) Chakraborti, A. K.; Nayak, M. K.; Sharma, L. *J. Org. Chem*. **1999**, *64*, 8027.
(18) Nayak, M. K.; Chakraborti, A. K. *Chemistry Lett*. **1998**, 297.
(19) (a) Cox, D. P.; Terpinsky, J.; Lawrynowicz, W. *J. Org. Chem*. **1984**, *49*, 3216. (b) Clark, J. H.; Smith, D. *Tetrahedron Lett*. **1985**, *26*, 2233. (c) Mori, Y.; Harada, K.; Morishima, N.; Zen, S. *Chem. Pharm. Bull*. **1993**, *41*, 755.
(20) (a) Clark, J. H.; Miller, J. M. *J. Am. Chem. Soc*. **1977** *99*, 498. (b) Clark, J. H. *Chem. Rev*. **1980**, *80*, 429.
(21) Parker, A. J. *Chem. Rev*. **1969**, *69*, 1.
(22) Gutmann, V. *The Donor−Acceptor Approach to Molecular Interactions*; Plenum: New York, 1978.
(23) (a) Clark, J. H.; Cork, D. G.; Robertson, M. S. *Chemistry Lett*. **1983**, 1145. (b) Villemin, D.; Ricard, M. *Tetrahedron Lett*. **1984**, *25*, 1059. (c) Kabalka, G. W.; Pagni, R. M. *Tetrahedron* **1997**, *53*, 7999.
(24) Although the use of CsF and TBAF afforded comparable or better results than that of the use of KF, we preferred to use KF as it is less hygroscopic and appreciably cheaper.

Table 2. The Effect of Solvents on the Cleavage of Methyl Benzoate in the Presence of KF[a]

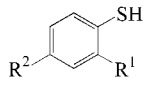
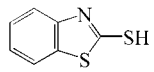
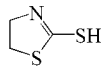
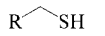
entry	solvent	temp (°C)[b]	yield (%)[c,d,e,f]
1	NMP	202	90
2	DMPU	146/44 mmHg	93
3	DMEU	106/17 mmHg	87
4	HMPA	235	90
5	formamide	210	20
6	DMF	153	70
7	DEF	176	96 (nil)
8	DMSO	189	40
9	DMA	166	99
10	DEA	182	98 (nil)
11	sulfolane	285	30
12	toluene	110	nil[g]

[a] The ester (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 10 mol % of KF in the respective solvent under heating at a bath temp of 210 °C (except for entry 12) for 10 min. [b] Bp of the respective solvents. [c] Isolated yield of benzoic acid. [d] The ^{1}H NMR spectra of the products were in full agreement with the literature.[41] [e] The unreacted ester could be recovered. [f] The figure in the parentheses corresponds to the yield obtained for reaction carried out at 100 °C for 60 min. [g] The reaction was carried out for 60 min in the presence of 10 mol % of 18-C-6.

metal salt and (ii) activation/destabilization of the halide anion. The higher the dielectric constant, molecular polarizability, and DN of a solvent the better will be its interaction with the cation resulting in the generation of the "naked" anion. On the other hand, solvents with lower AN should have minimum stabilizing interaction with the halide anion, thus making it more active. It is these combined effects that make HMPA, NMP, DMA, DMPU, DEF, DEA, and DMEU (dielectric constants 29.6−37.8, DNs 38.8−27.3, molecular polarizabilities 18.8−9.65, and ANs 10.6−13.6) as effective solvents for the desired transformation to take place. The poor results obtained with formamide, DMSO, and DMF may be the result of higher ANs (39.8, 19.8, and 16.0, respectively), enabling them to stabilize the halide anion, thereby making it less active despite of the higher dielectric constants (109.5, 48.9, and 36.7, respectively) compared to that of the above-mentioned solvents. The lower molecular polarizabilities (4.219, 7.91, and 7.97, respectively) of formamide, DMSO, and DMF may also be the reason for their relatively inferior ability to ionize the salts. The poor results with sulfolane may be due to its low DN (14.8), making it least effective in interacting with the cation. The overall effectiveness of NMP and the solvents alike compared to that of DMSO may be due to the (i) weaker solvation of small inorganic ions in NMP forcing the small halide anion to disperse its charge through hydrogen bonding with the sulfhydryl group and (ii) better solvation of highly delocalized anion making the generation of the thiolate anion facile.[25]

The effect of thiol on the ester deprotection was evaluated by the reaction of methyl benzoate with various aromatic and aliphatic thiols in the presence of 10 mol % of KF in NMP under reflux for 10 min (Table 3). The reactivity of the arenethiols was found to be dependent on the substitutent. The deprotection could be best carried out with PhSH; substituted thiophenols afforded moderate to good yields. 2-Thiazoline-2-thiol and 2-benzothiazolethiol led to inferior results, and aliphatic thiols were found to be ineffective.

Table 3. The Effect of Thiols on the Cleavage of Methyl Benzoate in the Presence of KF in NMP[a]

entry	thiol	yield (%)[b,c,d]
		
1	$R^1 = R^2 = H$	90
2	$R^1 = H$; $R^2 = Me$	58
3	$R^1 = H$; $R^2 = OMe$	42
4	$R^1 = H$; $R^2 = NH_2$	43
5	$R^1 = NH_2$; $R^2 = H$	62
6		39
7		29
		
8	R = Ph	59
9	R = Me	Nil

[a] The ester (2.5 mmol) was treated with 1 equiv of the thiol in the presence of 10 mol % of KF in NMP under reflux for 10 min. [b] Isolated yield of benzoic acid. [c] The ^{1}H NMR spectra of the products were in full agreement with the literature.[41] [d] The unreacted ester could be recovered.

The generality of the protocol was established during the reaction with various alkyl esters (Table 4). Excellent chemoselectivity was observed such that substrates bearing nitro group or chlorine atom did not suffer any competitive aromatic nucleophilic substitution (entries 4−10 and 19, Table 4). Methyl phenoxyacetate (entry 13, Table 4) underwent smooth *O*-Me cleavage without any competitive nucleophilic displacement of the phenoxy group.[9,26] No competitive reduction of the nitro group (entries 6−10 and 19, Table 4) and the α,β-unsaturated esters (entries 18 and 19, Table 4) were observed despite the known SET propensity of thiolate anions.[27] α,β-Unsaturated esters did not undergo Michael addition (entries 18 and 19, Table 4). This method is superior to the recently introduced TBAF·xH$_2$O−PhCH$_2$SH system[28] in that it employs only 1 equiv of PhSH and catalytic amount of KF compared to the use of 5 equiv of PhCH$_2$-SH and 5 equiv of costly and difficult to handle (highly hygroscopic) TBAF·xH$_2$O.

The 'demand-based' in situ generation of the thiophenolate anion may be explained by the catalytic cycle (Scheme 2). An initial proton exchange (path a) between the thiol and the F^- liberates the thiolate anion[29] which in turn reacts with the ester at its *O*-alkyl carbon (path b) liberating the carboxylate anion. The isolation of thioanisole (see Experimental Section) in the neutral component of the reaction mixture obtained from the

(25) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem*. **1980**, *45*, 3305.

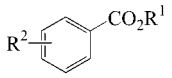
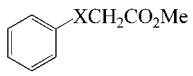
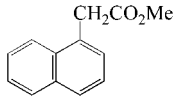
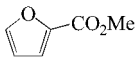
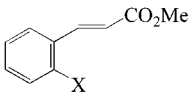
(26) (a) Cogoli, P.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem*. **1979**, *44*, 2636. (b) Cogoli, P.; Mailo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem*. **1979**, *44*, 2642.

(27) (a) Ashby, E. C.; Park, W.-S.; Goel, A. B.; Su, W. Y.; *J. Org. Chem*. **1985**, *50*, 5184. (b) Surdhar, P. S.; Armstrong, D. A. *J. Phys. Chem*. **1986**, *90*, 5915.

(28) Ueki, M.; Aoki, H.; Katoh, T. *Tetrahedron Lett*. **1993**, *34*, 2783.

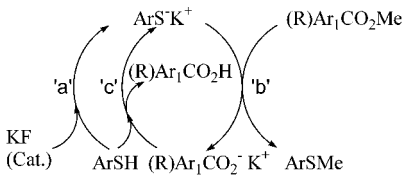
(29) (a) Sharma, R. K.; Fry, J. L. *J. Org. Chem*. **1983**, *48*, 2112. (b) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. *J. Am. Chem. Soc*. **1990**, *112*, 7619.

Table 4. Chemoselective Deprotection of *O*-Alkyl Esters by Catalytically in Situ Generated PhS^- [a]

entry	ester	yield (%)[b,c,d]
		
1	R^1 = Me; R^2 = H	90
2	R^1 = Et; R^2 = H	60[e]
3	R^1 = Bz; R^2 = H	100[e,f]
4	R^1 = Me; R^2 = 2-Cl	80[g]
5	R^1 = Me; R^2 = 4-Cl	80
6	R^1 = Me; R^2 = 2- NO_2	60
7	R^1 = Me; R^2 = 4- NO_2	60
8	R^1 = Me; R^2 = 3- NO_2	70
9	R^1 = Et; R^2 = 4- NO_2	50
10	R^1 = Bz; R^2 = 4- NO_2	65[e]
11	R^1 = Me; R^2 = 2- OH	86
12	R^1 = Me; R^2 = 4- OH	55
		
13	X = O	90
14	X = S	75
15	X = Nil	85
16		80
17		90[g]
		
18	X = H	70
19	X = NO_2	72

[a] The ester (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 10 mol % of KF in NMP under reflux for 10 min. [b] Isolated yield of the corresponding acid. [c] The ^{1}H NMR spectra of the products were in full agreement with the literature.[41] [d] The unreacted ester could be recovered. [e] Reactions carried out in the presence of CsF and TBAF in place of KF afforded 30% and 45% yields, respectively. [f] The reaction was carried out for 5 min. [g] The ^{1}H NMR spectra of the products were in full agreement with the literature.[42]

Scheme 2



reaction of methyl benzoate with PhSH justifies the possibility of *O*-alkyl cleavage. The relative rate of reaction (as indicated by the time and yield) following the order $PhCH_2$ > Me > Et, as a result of the influence of steric and electronic factors on the transition state for nucleophilic substitution at a saturated carbon further indicates that the ester cleavage proceeds by a nucleophilic attack at the *O*-alkyl group (compare entries 1−3, Table 4). The possibility of nucleophilic attack by the thiol itself may be ruled out by the fact that no appreciable amount of ester deprotection was observed in the absence of KF (entry 29, Table 1). The inefficiency of the chloride, bromide, and iodide in promoting the initial proton exchange with the thiol is a result of their less destabilizing interaction compared to that of the fluoride in dipolar aprotic medium. As the polarizability of the halide anion follows the order $F^- \ll Cl^- < Br^- < I^-$ it would be expected that the F^- should be the least stabilized by its interaction with the polarizable NMP.[21] Thus, F^- should be the most reactive in NMP. The effect of the countercation of the fluoride salts may be explained by the relative rate of dissociation to generate the free F^-. LiF being the least dissociated, was found to possess very little catalytic activity.[30] The lesser catalytic effect of KHF_2 compared to that of KF is in conformity with the fact that the increase in the degree of protonation (e.g. F^-, HF^-, and $H_2F_3^-$) decreases the global reactivity[31] whereas the ineffectiveness of NH_4HF_2 may be the result of the increased degree of protonation in association with the "suicidal" hydrogen bonding of the fluoride anion with NH_4^+ (resulting in catalyst poisoning). That the effective nucleophilic species is the thiolate anion is proved by the fact that no significant amount of ester cleavage takes place by the use of stoichiometric amount of KF, NaF, and KHF_2 in the absence of thiol (entries 8, 13, and 24, respectively, Table 1). The liberated carboxylate anion undergoes proton exchange with the thiol (path c) to generate the thiolate anion and maintains the catalytic cycle. The rather unusual proton exchange between carboxylate anion and thiol [i.e. carboxylic acids are in general stronger acids than thiols, $pK_{a\ (water)}$: ArSH = 6−8; $PhCO_2H$ = 4.19][32] may be explained by the leveling effect and the better stabilization of carboxylate anion in dipolar aprotic medium.[21] The pK_a values of uncharged carboxylic acids increase dramatically in aprotic polar solvents.[33] For example, the $pK_{a(water)}$ values of 7.15 and 4.75, respectively, of 4-nitrophenol and acetic acid are changed to 10.4 and 11.6, respectively, in DMSO.[34] Since in DMSO there is a possibility for hydrogen bond formation, through the oxyanionic site, with the OH of the acid, the leveling effect is expected to be more pronounced in NMP and is exemplified by the fact that the pK_a of 4-nitrophenol is 12.5 in NMP.[35] On the other hand, the extent of interaction of the anion with the solvent should depend on the mutual polarizability of the anion and the solvent. The greater polarizability of NMP compared to that of other aprotic polar solvents (except that of HMPA) should enable it to interact better with the polarizable

(30) Winstein, S.; Savendoff, L.; Smith, S.; Stevens, I.; Gall, J. *Tetrahedron Lett.* **1960**, 24.

(31) (a) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1989**, *54*, 328. (b) Cousseau, J.; Albert, P. *J. Org. Chem.* **1989**, *54*, 5380. (c) Seto, H.; Qian, Z.; Yioshioka, H.; Uchibori, Y.; Umeno, M. *Chem. Lett.* **1991**, 1185.

(32) Weast, R. C. Ed. *Handbook of Chemistry and Physics*, 57th ed.; 1985; CRC: Boca Raton, p D150−152.

(33) Kolthoff, I. M.; Chantooni, M. K., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 3843.

(34) Sarjeant, E. P.; Dempsey, B. *Ionization Cosntants of Organic Acids in aqueous Solutions*; Pergamon Press: Oxford, 1979.

(35) Kreshkov, A. P.; Gurvich, Y. A.; Galpern, G. M.; Kryuchkova, N. F. *Zh. Anal. Khim.* **1972**, *27*, 1166.

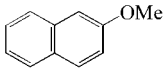
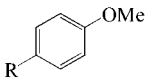
thiolate anion than with the carboxylate anion (the charge dispersal of various anions decreases in the order $PhS^- \gg 4\text{-}NO_2\text{-}C_6H_4O^- > PhO^- > AcO^- > MeO^-$).[36] Thus, the leveling effect coupled with the phenomenon of anion solvent interaction should make the proton exchange between the carboxylate anion and the thiol feasible. The importance of proton exchange between the thiol and the carboxylate anion is supported by the facts that an appreciable amount of ester cleavage takes place by the use of 10 mol % each of KOAc and KOCOPh instead of KF (entries 26 and 28, Table 1). The poor catalytic activity of LiOAc (entry 27, Table 1) may be explained as a result of sluggishness of initial proton exchange with the thiol due to the poor dissociation of LiOAc. The lack of ester cleavage by using stoichiometric amount of KOAc in the absence of any thiol is further proof of the involvement of thiolate anion as the effective nucleophile. The inferior results obtained with some substituted thiophenols may be associated with their less acidic character compared to that of PhSH. In the case of aminothiophenols, the effect of hydrogen bonding involving the thiolate anion and the amino group (thereby reducing the nucleophilic property of the thiolate anion) may also cause the reduced activity of these thiols (entries 4 and 5, Table 3). The decreased nucleophilicity of the anions derived from 2-thioazoline-2-thiol and 2-benzothiazolethiol, due to resonance, explains the poor results obtained with these thiols (entries 6 and 7, Table 3). The inferior results obtained with aliphatic thiols (entries 8 and 9, Table 3) further emphasizes the involvement of proton exchange between the carboxylate anion and the thiol (pK_a: EtSH 10.6). Activation of the ester through coordination of a species $KF(HF)_n$ formed by deprotonation of the thiol[37] may be ruled out by the fact that KHF_2 afforded inferior result compared to that of KF.

To find out whether this *O*-Me cleavage applies to the deprotection of aryl methyl ethers, 2-naphthyl methyl ether was treated with 1 equiv of PhSH separately in the presence of 10 mol % of each of KF, CsF, and Bu_4NF in NMP under various conditions (Table 5). The best results were obtained with KF by heating under reflux for 60 min. To claim this ether cleavage protocol as a generalized procedure, various aryl methyl ethers were subjected to deprotection. The excellent results obtained without any competitive reduction, Michael-type addition or aromatic nucleophilic substitution demonstrated the chemoselectivity. The catalytic effect of KF in generating the thiolate anion as the effective nucleophile in a "demand-based" fashion is suggested in Scheme 3. Initial proton exchange between ArSH and KF, via hydrogen bonding with the F^-, generates ArS^- (path a). Nucleophilic attack by the ArS^- on the methyl carbon of the ether liberates the ArO^- (path b). The better charge dispersal of ArS^-, compared to that of ArO^- in NMP,[21] assists the proton exchange between ArSH and ArO^- to regenerate PhS^- (path c). The detection (GCMS) of the formation of PhSMe (see Experimental Section) during the reaction of 2-naphthyl methyl ether with PhSH in the presence of KF provides support for the involvement of the nucleophilic attack by ArS^- in path b.

While extending this protocol to the cleavage of aryl esters, we reasoned that as the cleavage of the aryl esters should involve a nucleophilic attack on the carbonyl carbon as compared to that on a saturated carbon it would be expected that the deprotection of aryl esters might be carried out under milder conditions. 2-Naphthyl benzoate was subjected to the treatment with PhSH in the presence of 10 mol % of KF in NMP under various conditions (Table 6). Excellent results were obtained by heating under reflux for 15 min or at 100 °C for 60 min (entries 1−4, Table 6). Efficient deprotection of 2-naphthyl acetate was also achieved (entry 5, Table 6). However, poor results were obtained with 2-naphthyl tosylate (entries 6 and 7, Table 6).

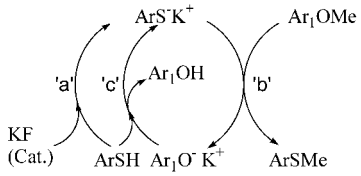
The overall transformations involved during the deprotection of the aryl esters are illustrated in Scheme 4. The thiolate anion, generated via the initial proton exchange with the F^- (path a), undergoes a nucleophilic attack on the ester carbonyl group followed by elimination of the aryloxide anion (path b). The suggested nucleophilic attack on the carbonyl functionality by the thiolate anion is supported by the detection/isolation of PhCOSPh (GCMS) in the neutral component of the reaction mixture obtained by the reaction of 2-naphthyl benzoate with PhSH in the presence of KF (see Experimental Section). The liberated aryloxide anion in turn should be involved in proton exchange with PhSH to regenerate $PhS.^-$

Table 5. Chemoselective Deprotection of Aryl Methyl Ethers by Catalytically in Situ Generated PhS^- [a]

entry	ether	yield (%)[b,c,d,e]
1		80 (Nil)[f,g,h]
2	 R = NO_2	70
3	R = COMe	82
4	R = CHO	79
5	R = HC=CHPh (*trans*)	86
6	R = HC=CHCOPh (*trans*)	68[i]
7	R = COHC=CHPh (*trans*)	54[j]

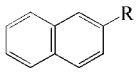
[a] The ether (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 10 mol % of KF in NMP under reflux for 60 min. [b] Isolated yield of the corresponding phenol. [c] The ^1H NMR spectra of the products were in full agreement with the literature.[41] [d] The unreacted ether could be recovered. [e] The figure in parentheses refers to the yield of 2-naphthol obtained by the use of stoichiometric quantities of KF in the absence of PhSH. [f] The reaction carried out in the presence of 10 mol % of CsF instead of KF afforded 70% yield. [g] No ether cleavage took place when the reaction was carried out in the presence of 10 mol % of Bu_4NF instead of KF. [h] No ether cleavage took place in the absence of KF. [i] The mp and spectral data (IR, ^1H NMR, and MS) of the product were in full agreement with the literature.[43] [j] The mp and spectral data (IR, ^1H NMR, and MS) of the product were in full agreement with the literature.[42]

Scheme 3



(36) C. K. Ingold *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca; 1953, Ch. 7.
(37) Albanese, D.; Landini, D.; Penso, M. *Synthesis* **1994**, 34.

Table 6. The Effect of Temperature and Time on the Deprotection of 2-Naphthyl Esters by PhSH in the Presence of KF in NMP[a]

entry	ester	temp (°C)	time (min)	yield[b,c,d,e] (%)
				
1	R = OCOPh	Reflux	30	92
2	R = OCOPh	Reflux	15	88
3	R = OCOPh	100	60	80 (Nil)
4	R = OCOPh	100	30	63
5	R = OAc	100	60	78
6	R = OTs	100	180	44
7	R = OTs	100	30	43

[a] The ester (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 10 mol % of KF in NMP. [b] Isolated yield of 2-naphthol. [c] The ^{1}H NMR spectra of the products were in full agreement with the literature.[41] [d] The unreacted ester could be recovered. [e] The figure in parentheses refers to the yield of 2-naphthol obtained by the use of stoichiometric quantities of the salt in the absence of PhSH.

Scheme 4

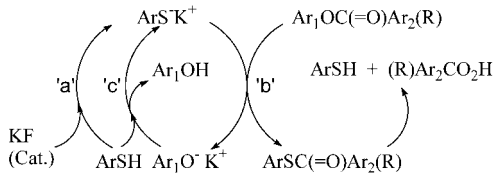
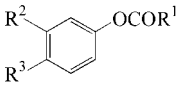


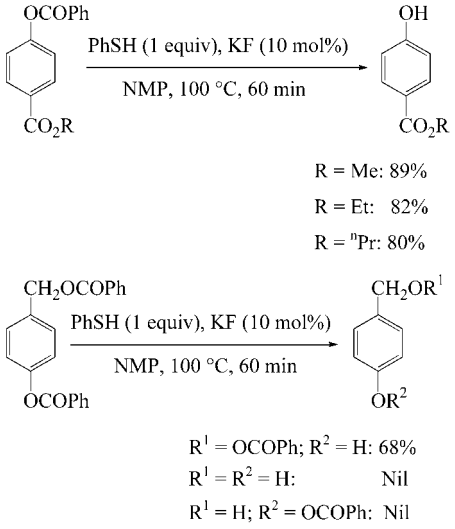
Table 7. Deprotection of Aryl Esters by PhSH in the Presence of KF in NMP[a]

entry	ester	yield(%)[b,c,d]
		
1	R^1 = Ph, R^2 = H, R^3 = COMe	98
2	R^1 = Ph, R^2 = H, R^3 = CHO	78
3	R^1 = Ph, R^2 = H, R^3 = CN	85
4	R^1 = Ph, R^2 = H, R^3 = NO_2	80
5	R^1 = Ph, R^2 = Me, R^3 = Cl	80
6	R^1 = Ph, R^2 = OMe, R^3 = CHO	95[e]
7	R^1 = Me, R^2 = OMe, R^3 = CHO	90[e]

[a] The ester (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 10 mol % of KF in NMP at 100 °C for 60 min. [b] Isolated yield of the corresponding phenol. [c] The ^{1}H NMR spectra of the products were in full agreement with the literature.[41] [d] The unreacted ester could be recovered. [e] The products corresponding to the methyl ether cleavage were not formed.

To claim this transformation as a general methodology for deprotection of aryl esters, we subjected the benzoate derivative of various substituted phenols to this reaction system; the results are summarized in Table 7. Excellent results were obtained for substrates bearing keto, formyl, cyano, and chloro groups. No competitive reactions such as aromatic nucleophilic substitution of the nitro/chloro groups, reduction of the nitro/keto/formyl groups, and

Scheme 5



nucleophilic addition to the keto/formyl/cyano groups could be observed. As exemplified by the higher product yields, the faster deprotection of substrates bearing electron-withdrawing groups is the manifestation of better stabilization of the corresponding phenolate anion compared to that of 2-naphthoxide anion (vide infra). The results of entries 6 and 7, Table 7, exemplify the chemoselective deprotection of aryl esters in the presence of aryl methyl ethers during intramolecular competitions.

The relative charge dispersal order in dipolar aprotic medium of various anions, e.g. $PhS^- \gg 4\text{-}NO_2{-}C_6H_4O^- > PhO^- > AcO^- > MeO^-$,[21] suggests that an aryloxide anion should be a better leaving group than a carboxylate anion in NMP. Thus, the relative values of leaving group property of ArO^- and $(R)ArCO_2^-$ in NMP imply that selective cleavage of the aryl ester is expected to take place during competitions between aryl and alkyl esters. To test this hypothesis, we subjected each of methyl 4-benzoyloxybenzoate, ethyl 4-benzoyloxybenzoate, and propyl 4-benzoyloxybenzoate, respectively, to treatment with 1 equiv of PhSH in the presence of 10 mol % of KF (Scheme 5). Selective deprotection of the benzoyloxy group took place affording methyl 4-hydroxybenzoate, ethyl 4-hydroxybenzoate, and propyl 4-hydroxybenzoate in 89, 82, and 80% yields, respectively; no product corresponding to the cleavage of the alkoxycarbonyl group could be detected (GCMS). The chemoselective deprotection of aryl ester over alkyl ester was further exemplified during the treatment of 4-benzoyloxybenzyl benzoate with 1 equiv of PhSH in the presence of 10 mol % of KF (Scheme 5) wherein 4-hydroxybenzyl benzoate[38] could be was in 68% yield as the only product. Similar selectivity could be observed with 2-benzoyloxybenzyl benzoate; however, the poor yield (40%) of 2-hydroxybenzyl benzoate[39] as the sole product may due to the steric hindrance of the ortho substituent.

Conclusions

Nucleophilicity of arenethiols is increased through hydrogen bonding with "naked" fluoride anion present

(38) Greenaway, W.; May, J.; Scaysbrook, T.; Whatley, F. R. *Z. Naturforsch., C: Biosci*. **1991**, *46*, 111; *Chem. Abstr*. **1991**, *115*, 68768e.
(39) Yongfang, S.; Jialiang, L.; Shanquing, N.; Shuangsheng, W. *Lin. Hua. Yu. Gong*. **1990**, *10*, 256; *Chem. Abstr*. **1991**, *115*, 78593h.

in a catalytic amounts in the presence of dipolar aprotic solvents with high dielectric constant, high molecular polarizability, high DN, and low AN. Chemoselective deprotection of alkyl/aryl esters and aryl alkyl ethers are carried out by thiophenol in the presence of catalytic quantities of KF under nonhydrolytic and neutral conditions via a "demand-based" in situ generation of thiolate anion. No competitive aromatic/aliphatic nucleophilic substitution, reduction and Michael addition could be observed for substrates susceptible to undergo such side reactions. Aryl esters could be deprotected selectively in the presence of alkyl esters and aryl methyl ethers during intramolecular competitions.

Experimental Section

The esters studied were either available commercially or prepared by standard procedures.[2,40] The solvents were distilled before use. DMA, DMPU, DMEU, DEF, DEA, DMSO, sulfolane, formamide, PhSH, 4-Me-C_6H_4SH, 4-MeO-C_6H_4SH, 4-NH_2−C_6H_4SH, 2-NH_2-C_6H_4SH, $PhCH_2SH$, EtSH, 2-mercaptobenzthiazole, 2-mercaptothiazoline, LiOAc, CsF, LiF, TBAF·xH_2O, $Me_4NF·4H_2O$, $Me_3PhCH_2NF·xH_2O$, and NH_4HF_2 were purchased from Aldrich, St. L. KF, KHF_2, NaF, KCl, KBr, KI, NaCl, NaBr, NaI, NH_4Cl, KOAc, KOCOPh, DMF, and NMP were procured from S. d. Fine chemicals, India.

The ^{1}H NMR and IR spectra of the following compounds were in complete agreement with those of the authentic samples: benzoic acid, 2-chlorobenzoic acid, 4-chlorobenzoic acid, 2-nitrobenzoic acid, 4-nitrobenzoic acid, 3-nitrobenzoic acid, 2-hydroxybenzoic acid, 4-hydroxybenzoic acid, phenoxyacetic acid, thiophenoxyacetic acid, phenylacetic acid, 1-naphthylacetic acid, 2-furoic acid, cinnamic acid, 2-nitrocinnamic acid, 2-naphthol, 4-nitrophenol, 4-hydroxyacetophenone, 4-hydroxybenzaldehyde, 4-cyanophenol, 4-chloro-3-methylphenol, 4-hydroxy-3-methoxybenzaldehyde, methyl 4-hydroxybenzoate, ethyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate, (Aldrich), *trans*-4-hydroxystilbene (Acros Organics), *trans*-4-hydroxychalcone, *trans*-4′-hydroxychalcone (Lancaster).

General Procedure for Deprotection. Example of the General Procedure Deprotection of Alkyl Esters. A mixture of methyl benzoate (0.34 g, 2.5 mmol), PhSH (0.27 g, 2.5 mmol), and KF (15 mg, 0.25 mmol, 10 mol %) in NMP (2.5 mL) were heated under reflux for 10 min under N_2. The cold reaction mixture was diluted with saturated aqueous $NaHCO_3$ (25 mL) and extracted with Et_2O (2 % 20 mL) to separate the neutral component (the GCMS of these combined ethereal extracts showed the presence of PhSMe supporting the nucleophilic attack at the carbinol carbon). The aqueous part was acidified (6 M HCl) with ice-cooling and extracted with Et_2O (3 % 20 mL) to afford the product (274.5 mg, 90%) which was in full agreement with mp and spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of benzoic acid.

This generalized method was followed for the remaining substrates, and on each occasion the product was found to be in full agreement with the spectral data (^{1}H NMR, FTIR, and GCMS) of an authentic sample. In most cases the product was isolated in pure form and, whenever required, purification was accomplished through crystallization (EtOAc−hexane) or chromatography (silica gel, eluent 15% EtOAc−hexane).

Representative Procedure for Deprotection of an Aryl Alkyl Ether. A mixture of 2-methoxynaphthalene (395.5 mg, 2.5 mmol), PhSH (0.27 g, 2.5 mmol), and KF (15 mg, 0.25 mmol, 10 mol %) in NMP (2.5 mL) were heated under reflux for 60 min under N_2. The cooled reaction mixture was made alkaline with 5% aqueous NaOH (25 mL) and extracted with Et_2O (3 × 15 mL) to separate any neutral component (GCMS of these combined ethereal extracts showed the presence of PhSMe). The aqueous part was acidified in the cold (ice bath) with 6 N HCl and extracted with Et_2O (3 × 15 mL). The combined Et_2O extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under vacuo to afford a brown solid which on passing through a column of silica gel (230−400, 1 g) and elution with 5% EtOAc−hexane (200 mL) afforded the product (288 mg, 80%) which was in full agreement with mp and spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of 2-naphthol.

Representative Procedure for Deprotection of an Aryl Ester. A mixture of 2-naphthyl benzoate (0.62 g, 2.5 mmol) and KF (15 mg, 0.25 mmol, 10 mol %) in NMP (2.5 mL) were heated under reflux for 30 min under N_2. The cold reaction mixture was diluted with 5% aqueous NaOH (10 mL) and extracted with Et_2O (3 × 20 mL) to separate any neutral component (the GCMS results showed the presence of PhSCOPh indicating the nucleophilic attack at the carbonyl carbon of the substrate). The aqueous layer was acidified with ice-cooling (6 M HCl) and extracted with Et_2O (3 × 20 mL). The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ (2 % 20 mL) to separate the liberated benzoic acid and brine (20 mL), dried (Na_2SO_4), and concentrated to afford 2-naphthol (332 mg, 92%) which was in full agreement with mp and spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of 2-naphthol. 2-Naphthol (289 mg, 80%) could be obtained by carrying out the reaction at 100 °C for 60 min.

Representative Procedure for Deprotection of an Aryl Ester in the Presence of an Alkyl Ester. A mixture of methyl 4-benzoyloxybenzoate (0.64 g, 2.5 mmol) and KF (15 mg, 0.25 mmol, 10 mol %) in NMP (2.5 mL) were heated at 100 °C for 60 min under N_2. The cold reaction mixture was diluted with 2% aqueous NaOH (10 mL) and extracted with Et_2O (3 × 20 mL) to separate any neutral component. The aqueous layer was acidified with ice-cooling (6 M HCl) and extracted with Et_2O (3 × 20 mL). The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) to separate the liberated benzoic acid, and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the product (339 mg, 89%) which was in full agreement with mp and spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of methyl 4-hydroxybenzoate.

This generalized method was followed for ethyl 4-benzoyloxybenzoate and propyl 4-benzoyloxybenzoate and in each occasion the product was found to be in full agreement with the spectral data (IR, ^{1}H NMR and GCMS) of an authentic sample. In most cases the product was isolated in pure form or, when required, purification was accomplished through crystallization (EtOAc−hexane) or chromatography (silica gel, eluent 15% EtOAc−hexane).

Acknowledgment. L.S. thanks CSIR, New Delhi, for award of senior research fellowship.

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(40) Furniss, B. R.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman: London, 1996.

(41) Pouchart, C. J.; Jacqlynn, B. *The Aldrich Libraray of ^{13}C and ^1H FT NMR Spectra*, 1st ed.; Aldrich Chemical Co. Inc.: Milwaukee, 1993; vol. II.

(42) Cirovic, M. M. *Properties of Organic Compounds*; CRC Press Inc.: Boca Raton, 1996; POC-personal ed., version 5.1.

(43) Hseih, H.-K.; Lee, T.-H.; Wang, J.-P.; Wang, J.-J.; Lin, C.-N. *Pharmacol. Res.* **1998**, *15*, 39.