PhSH - (Catalytic) KF as an Efficient Protocol for Chemoselective Ester *O*-Alkyl Cleavage under Non-hydrolytic Neutral Condition

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Methyl esters are chemoselectively deprotected by thiophenol in presence of catalytic amount of KF in dry NMP (1-Methyl-2-pyrrolidinone) under non-hydrolytic neutral condition.

Masking of carboxyl function is one of the most frequently desirable transformations in organic synthesis. Carboxylic acids are often protected as methyl esters by virtue of the stability and ease with which methyl esters can be obtained from carboxylic acids or the corresponding acid chlorides. Regeneration of the carboxyl function from the ester is classically accomplished by acidic or basic hydrolysis in protic medium. This procedure has the disadvantage of potential occurrence of side reactions, particularly when multifunctional molecules are involved.[1] Since many molecules of synthetic interest are multifunctional, it is imperative to have protecting groups which can be removed under conditions suitable in presence of other sensitive moieties. A wide range of deprotection methods based on different chemical principles - hydrolysis, photolysis, hydrogenolysis, oxidation and reduction (chemical as well as electrochemical) etc. are now available.[2] Although there are some hydrolytic methods operative under neutral or nearly neutral conditions[3] few are available for non-hydrolytic cleavage of esters under neutral condition.[4]

In this communication we report an efficient method for chemoselective cleavage of methyl esters by PhSH in presence of catalytic amount of KF. Although the strong nucleophilicity of thiolate anions should make them useful reagents for ester *O*-alkyl cleavage the potentiality of these reagents haven't been widely exploited. Thiolates employed for ester *O*-Me cleavage include ^{n}PrSLi,[5] EtSNa[6] and MeSLi.[7] The scope and limitation of the current protocol are summarised in Table 1. In contrast to the reported stoichiometric thiolate protocols reactions are carried out under neutral condition through catalytic *in situ* generation of PhS^- in a 'demand based' fashion under the current observations. The present method has the distinct advantages over the stoichiometric thiolate anion protocols in that it avoids the use of expensive and difficult to handle bases (LiH,[5] NaH[6] and MeLi[7]), use of carcinogenic HMPA[5,7] as solvent, manipulation involved in using the low boiling alkane thiols and extra efforts needed to make the metal hydride bases oil free. It shows wider applications in chemoselective deprotection of esters containing substituent/group susceptible to competitive nucleophilic substitution or reduction. Thus while nucleophilic substitution of phenoxy[6] group is the major reaction with esters bearing this functionality selective ester *O*-Me cleavage takes place for substrates having phenoxy/thiophenoxy group under the current protocol (entries 13, 14). The use of stoichiometric amount of thiolates e.g. $PhCH_2SLi$,[8] MeO_2CCH_2SLi[9] leads to aromatic nucleophilic substitution of nitro group whereas efficient chemoselctive deprotection of ester is achieved following the present method (compare with entries 6-10, 19). Esters bearing chlorine also undergo chemoselective deprotection (entries 4, 5) although stoichiometric thiolates generally lead to aromatic nucleophilic substitution of chlorine.[10] The powerful reducing property of thiolate anion (due to RS^- to $RS^{\cdot}$ transformation[11]) makes the protocols involving stoichiometric use of thiolate reagents inferior to the present method (compare with entries 6-10, 18, 19) due to the reduction of the nitro group[12] and α,β-unsaturated carbonyl compounds.[13] The currently described method also finds its superiority with respect to the recently introduced TBAF.xH_2O - $PhCH_2SH$ system[14] in that it employes only 1 eq. of PhSH and catalytic amount of KF compared to the use of 5 eq. of $PhCH_2SH$ and 5 eq. of the costly reagent TBAF.xH_2O. This method also avoids Michael addition[15] (entries 18, 19). The reactions are best carried out in dry NMP at 190 ^{0}C for 10 min. with lowering of temperature necessiating longer reaction period, however, the reaction temperature has no detrimental effect on either the product or the recovered starting ester. The presence of KF in catalytic amount is necessary since no significant ester cleavage takes place in its absence. Other catalysts found to be effective (*albeit* to a lesser extent) are KHF_2 and NaF. This method works with ethyl and benzyl esters as well (entries 9, 10). While the benzyl esters could be deprotected more readily compared to methyl esters the corresponding ethyl esters were found to be less reactive (compare entries 1-3) indicating the potentiality of this method for selective deprotection amongst various esters.

The effectiveness of this protocol is based on the basicity of the 'naked F^-'[17] (use of KCl, KBr and KI as catalysts afford poor yields with relative efficiencies in the order KF >> KCl > KBr > KI). The net conversion may be realised as an initial proton exchange between F^- and PhSH folllowed by nucleophilic attack at the carbinol carbon of ester by PhS^-. The liberated carboxylate anion undergoes proton exchange with PhSH due to perhaps better solvation of PhS^- in dipolar aprotic solvent[18] compared to that of the carboxylate anion. Activation of the ester through co-ordination of a species $KF(HF)_n$ formed by deprotonation of the thiol may also be envisaged[19] for making the nucleophilic attack by PhS^- more facile (Figure 1).

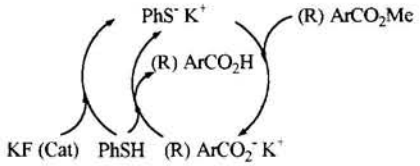
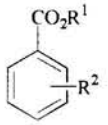
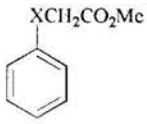
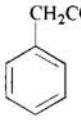
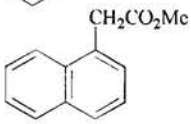
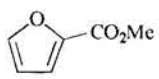
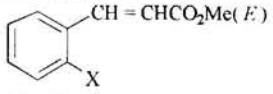


Figure 1. The catalytic cycle for ester cleavage.

In a typical experiment the magnetically stirred mixture of the

ester (5 mmol), PhSH (5 mmol) and KF (10 mol%) in dry NMP (2.5 ml) was heated at 190 °C under N_2 for 10 min. The cold reaction mixture was poured into ice-water, the solid filtered and purified through crystallisation or chromatography (silica gel, eluent 15% hexane-ethyl acetate) to afford the carboxylic acid. Alternatively (for low melting solid or liquid product) the reaction mixture was made alkaline with saturated aq. $NaHCO_3$ and extracted with Et_2O to remove the neutral component. The aqueous extract was acidified with dil. HCl and extracted with Et_2O to afford the crude carboxylic acid which was further purified as usual. The recovered unreacted starting material (wherever applicable) may be recycled without purification ultimately giving the products in virtually quantitative yield.

Table 1. Chemoselective deprotection of *O*-alkyl esters by catalytically *in situ* generated PhS^-

Entry	Ester		Yield (%)
			
1	R^1 = Me	R^2 = H	90
2	R^1 = Et	R^2 = H	60
3	R^1 = Bz	R^2 = H	100[a]
4	R^1 = Me	R^2 = 2-Cl	80
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	62
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[a]
11	R^1 = Me	R^2 = 2-OH	86
12	R^1 = Me	R^2 = 4-OH	55
			
13	X = O		90
14	S		75
			
15			85
			
16			80
			
17			90
			
18	X = H		70
19	NO_2		72

[a] Reactions were carried out for 5 min.

In conclusion we have described here an efficient method for chemoselective cleavage of ester under non-hydrolytic and neutral conditions. Further exploration of this protocol with respect to its regioselectivity for inter- and intra-molecular competitions, mechanistic insight etc. are in progress.

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