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A Mild and Chemoselective Method for Ester *O* - Alkyl Cleavage using *in situ* Generated Potassium Thiophenoxide from Catalytic Quantities of Base.

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Abstract: Chemoselective deprotection of methyl esters can be achieved under non-hydrolytic and virtually neutral conditions by treatment with thiophenol in N-methyl-2-pyrrolidone (NMP) in the presence of a catalytic amount of K_2CO_3.

Masking of a carboxyl function is a frequently desirable transformation in organic synthesis and considering the ease of preparation and the availability of starting materials, carboxylic acids are often protected as their methyl esters. A carboxylic ester possesses a hard centre (carboxyl carbon) and a soft centre (carbinol carbon). Applying the principle of 'Hard Soft Acid Base (HSAB)' theory[1] hard nucleophiles are expected to attack the carboxyl carbon and soft nucleophiles the carbinol carbon. Hydrolytic deprotections of the ester are amongst the simplest and most common of all laboratory reactions and are normally accomplished by heating the ester in either aqueous acid or base[2] (hard-hard interaction). However, in most of these cases, the harsh treatment required for these hydrolytic cleavages are not compatible with multifunctional substrates (particularly those with acid or alkali labile groups) and under these circumstances the cleavage should be performed through the nucleophilic attack at the carbinol carbon which generally adopts relatively milder conditions.

A number of methods for the deprotection of esters are available based on the HSAB concept.[3] Hard nucleophilic reagents include 'naked' fluoride anion[4] and the recently introduced bis(tributyltin) oxide (BBTO).[5] Amongst the soft nucleophilic species used for the deprotection of ester are PhS^-, RS^-, $PhSe^-$, HSe^-, HTe^- anions.[3] The combination of hard acid and soft nucleophile includes TMSI, $AlCl_3$-EtSH, $AlCl_3$-R_2S, AlI_3, $MgBr_2$, MgI_2 and catechol boron bromide.[3] Considering the cost of the reagent, reaction time involved and the ease of operation, the nucleophilic attack at the carbinol carbon by thiolate reagents seems to be the most attractive proposition. Thus PhSNa, EtSNa and ^nPrSLi have been used for the deprotection of methyl esters, Na_2CS_3 and Na_2S for the deprotection of cyanomethyl esters and $NaSCH_2CH_2SNa$ has been employed for the deprotection

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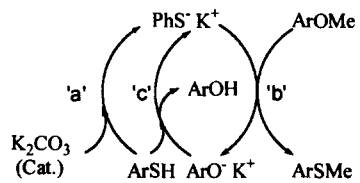
of 2-haloethyl esters.[3] Deprotection of carboxamidomethyl esters with $LiSCH_2CH_2OH$ has been exploited as handle in polystyrene based peptide synthesis.[6] In all of these protocols the thiolate reagents are used in a stoichiometric amount or more. The strong reducing property of the thiolate anion[7] (due to RS^- to $RS^{\cdot}$ conversion[8]) makes them unsuitable for deprotection of esters incorporating nitro groups and/or α,β-unsaturation. The stoichiometric thiolate protocols are also not compatible with methyl esters of chlorobenzoic, nitrobenzoic, phenoxyacetic and thiophenoxyacetic acids due to the nucleophilic substitution of chloro, nitro, phenoxy and thiophenoxy groups.

Earlier we have reported[9] a method for aryl methyl ether cleavage with PhSH in presence of catalytic amount of K_2CO_3 in NMP at 190°C :

$$\text{ArOMe} \xrightarrow[\text{NMP, } 190^0\text{C, 10-30 min, } N_2]{\text{PhSH (1eq.), } K_2CO_3 \text{ (10 mol\%),}} \underset{60\text{ - }97\ \%}{\text{ArOH}} + \text{PhSMe}$$

The reaction proceeded *via* nucleophilic attack of PhS^- (path 'b') generated *in situ* in catalytic amount through proton exchange between PhSH and K_2CO_3 (path 'a'). The proton exchange between the liberated ArO^- and PhSH (path 'c'), by virtue of higher acidity of PhSH compared to that of phenols, led to the regeneration of PhS^- in a 'demand-based' fashion (Scheme 1).

Scheme 1



We planned to extend this protocol for the cleavage of methyl esters. However, it may be thought that with the carboxylic acids, in general, being stronger acids than aryl thiols [*e.g.* $pK_{a\ (water)}$: ArSH = 6-8 and $PhCO_2H$ = 4.19][10] the proton exchange between the liberated $ArCO_2^-$ and PhSH may not be feasible. However, the pK_a of an acid is influenced by the solvent (*e.g.* acetic acid has pK_a values of 4.75 and 11.6 in water and DMSO respectively).[11] Thus there is a levelling effect of the acid strength in organic solvents. The charge dispersal in NMP[12] decreases in the order PhS^- >>AcO^- implicating greater interaction of PhS^- with NMP. Hence the levelling effect and the better stabilisation of PhS^- compared to that of $(R)ArCO_2^-$ in NMP should make the proton exchange between the carboxylate anion and PhSH feasible.

In order to test this hypothesis methyl benzoate was subjected to non-hydrolytic deprotection using various thiols, bases and solvents under different conditions and the results are summarised in Table 1. As evidenced from these studies the reaction could be best carried out by treatment of the ester with an equivalent amounts of PhSH, 4-Me-C_6H_4SH or 2-NH_2-C_6H_4SH at 190°C in the presence of a catalytic amount of K_2CO_3 using NMP, DMPU, DMEU and HMPA as solvents. Carrying out the reactions at lower temperatures resulted in poor yields of the product (Table 1, Entries 2,3). Both the base and the aryl thiol are required for deprotection of the methyl ester as no significant ester cleavage took place in the absence of the base (Table 1, Entry 4) or PhSH (Table 1, Entry 5).

Table 1. Effect of the Thiol, Base, Solvent and Temperature on Non-hydrolytic Cleavage of Methyl benzoate.

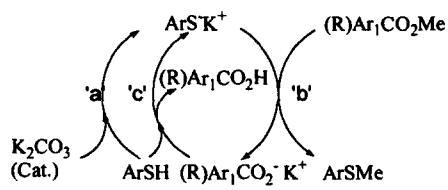
Entry	Thiol	Base[a]	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	PhSH	K_2CO_3	NMP	190	10	100
2	PhSH	K_2CO_3	NMP	110	60	35
3	PhSH	K_2CO_3	NMP	RT	480	Trace
4	PhSH	Nil	NMP	190	60	Trace
5	Nil	K_2CO_3	NMP	190	60	Trace
6	PhSH	KOAc	NMP	190	10	60
7	PhSH	KOCOPh	NMP	190	10	70
8	PhSH	Li_2CO_3	NMP	190	10	43
9	EtSH	K_2CO_3	NMP	190	10	Trace
10	4-Me-C_6H_4SH	K_2CO_3	NMP	190	10	85
11	2-NH_2-C_6H_4SH	K_2CO_3	NMP	190	10	100
12	PhSH	K_2CO_3	DMPU	190	10	100
13	PhSH	K_2CO_3	DMEU	190	10	100
14	PhSH	K_2CO_3	HMPA	190	10	100
15	PhSH	K_2CO_3	Sulfolane	190	10	70
16	PhSH	K_2CO_3	DMF	Reflux	10	54

[a]Used in 5 mol% with respect to methyl benzoate.

The chemoselectivity of this non-hydrolytic ester cleavage was next tested using various aryl and alkyl esters bearing functional groups which are susceptible to nucleophilic substitution (*e.g.* Cl, NO_2 etc.), reduction (*e.g.* NO_2, α,β-unsaturated carbonyl) or conjugate addition (*e.g.* α,β-unsaturated carbonyl) and the results are summarised in Table 2. Although the reaction could also be carried out using other thiols (*e.g.* 4-Me-C_6H_4SH or

2-NH_2-C_6H_4SH) and solvents (*e.g.* DMPU, DMEU or HMPA) we preferred to use the PhSH-NMP combination considering the lower prices of PhSH and NMP compared to those of other thiols and solvents. It is evident from Table 2 that the chemoselective deprotection of the methyl ester takes place for aromatic substrates containing halogen atoms or nitro group without the competitive aromatic nucleophilic substition of the halogen atom[13] or the nitro group[14] (Table 2, Entries 2-5). Methyl phenoxyacetate and methyl thiophenoxyacetate do not experience substitition of the phenoxy or thiophenoxy groups[15] (Table 2, Entries 8,9). No reduction of the nitro group[16] or α,β-unsaturated double bond[17] takes place under this protocol (Table 2, Entries 4, 5, 15). Excellent chemoselectivity was also observed during the deprotection of the methyl ester of an α,β-unsaturated acid (Table 2, Entry 15) wherein no competitive Michael addition[18] of PhS^-K^+ was observed. Esters having aromatic methoxyl functionality (Table 2, Entries 7,11) underwent selective ester cleavage without competitive aryl methyl cleavage.[9] The overall transformation, as visualised, may involve a nucleophilic attack on the carbinol carbon by the thiophenolate anion (path 'b'), generated *in situ* as a result of proton exchange between K_2CO_3 (present in catalytic amount) and PhSH (path 'a'). The liberated carboxylate anion in turn abstracts a proton from PhSH (path 'c') to replenish PhS^- and establishes the catalytic cycle (Scheme 2).

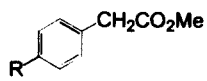
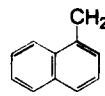
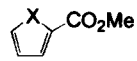
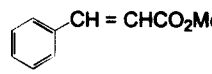
Scheme 2



The efficacy of the process depends upon the proton exchange between the liberated carboxylate anion and the thiophenol (*i.e. in situ* generation of the effective nucleophilic species PhS^- in a demand based fashion) perhaps due to better solvation of PhS^- compared to that of the carboxylate anion in the dipolar aprotic solvent.[19] In this regard it has been found that replacement of PhSH by EtSH (Table 1, Entry 9) under these condition does not lead to any significant deprotection of the ester as EtSH (pK_a 10.6) is much less acidic than PhSH, thereby making it unable to exchange a proton with any liberated carboxylate anion. Use of KOAc or KOCOPh (Table 1, Entries 6,7) as catalysts instead of K_2CO_3 provided good results supporting the proton exchange between the carboxylate anion and PhSH. That the deprotection takes place through nucleophilic attack of ArS^- on the carbinol carbon was supported by the isolation of PhSMe, 4-Me-C_6H_4SMe and 2-NH_2-C_6H_4SMe from the product mixture (see experimental).

In conclusion, we have developed a method for chemoselective deprotection of methyl esters under non-hydrolytic and virtually neutral conditions applicable to multifunctional substrates.

Table 2. Chemoselective Deprotection of Methyl Esters by PhS^-, *via* its *in situ* Generation in Catalytic Amount.

Entry	Ester	Yield (%)	Entry	Ester	Yield (%)
					
1	R = H	100	10	R = H	95
2	R = 2-Cl	75	11	R = OMe	80
3	R = 4-Cl	75			
4	R = 2-NO_2	65	12		90
5	R = 4-NO_2	60			
6	R = 2-OH	83	13	X = O	100
7	R = 4-OMe	85	14	X = S	75
					
8	X = O	80	15		86
9	X = S	72			

EXPERIMENTAL

The esters were available commercially. The solvents were distilled before use. PhSH, 4-Me-C_6H_4SH and EtSH and 2-NH_2-C_6H_4SH were purchased from E. Merck, Germany. KOAc, KOCOPh and K_2CO_3 used were procured from S. d. Fine chemicals, India.

General procedure for the deprotection of methyl esters

A mixture of methyl benzoate (0.34 g, 2.5 mmol), PhSH (0.27 g, 2.5 mmol) and K_2CO_3 (0.02 g, 5 mol%) in NMP (2.5 ml) were heated at 190°C for 10 mins under N_2. The cold reaction mixture was diluted with saturated aqueous $NaHCO_3$ (25 ml) and extracted with Et_2O (2 x 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 with ice-cooling (6M HCl) and extracted with Et_2O (3 x 20 ml) to afford benzoic acid (yield = 100%, 305 mg).

This generalised method was followed for the remaining substrates and in each occasion the product was found to be identical (^1H NMR, FTIR and GCMS) with an authentic sample. In most of the cases the product was isolated in pure form and whenever required purification was accomplished through crystallisation (EtOAc-hexane) or chromatography (silica gel, eluent 15% EtOAc-hexane).

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