

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

Lalima Sharma^a, Mrinal K. Nayak^b and Asit K. Chakraborti^{a,b,*}

^aDepartment of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S. A. S. Nagar 160 062, India. Fax: +91-(0)172-677185. E. Mail: niper@chd.nic.in.

^bDepartment of Chemistry, Burdwan University, Burdwan 713 104, India.

Received 9 March 1999; revised 18 May 1999; accepted 3 June 1999

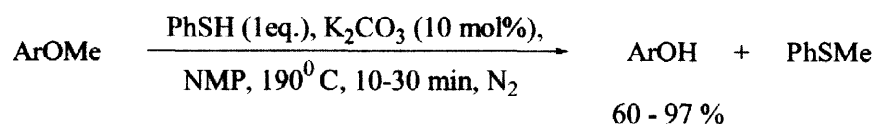
Abstract: Chemoselective deprotection of methyl esters can be achieved under non-hydrolytic and virtually neutral conditions by treatment with thiophenol in *N*-methyl-2-pyrrolidone (NMP) in the presence of a catalytic amount of K₂CO₃. © 1999 Elsevier Science Ltd. All rights reserved.

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)' theory¹ 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 base² (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 anion⁴ 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, AlCl₃-EtSH, AlCl₃-R₂S, AlI₃, MgBr₂, MgI₂ 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, Na₂CS₃ and Na₂S for the deprotection of cyanomethyl esters and NaSCH₂CH₂SNa has been employed for the deprotection

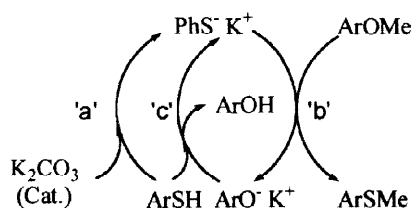
of 2-haloethyl esters.³ Deprotection of carboxamidomethyl esters with $\text{LiSCH}_2\text{CH}_2\text{OH}$ has been exploited as handle in polystyrene based peptide synthesis.⁶ In all of these protocols the thiolate reagents are used in a stoichiometric amount or more. The strong reducing property of the thiolate anion⁷ (due to RS^- to RS^\cdot conversion⁸) 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 reported⁹ a method for aryl methyl ether cleavage with PhSH in presence of catalytic amount of K_2CO_3 in NMP at 190°C :



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.* $pK_a(\text{water})$: $\text{ArSH} = 6-8$ and $\text{PhCO}_2\text{H} = 4.19$]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 NMP¹² decreases in the order $\text{PhS}^- \gg \text{AcO}^-$ implicating greater interaction of PhS^- with NMP. Hence the levelling effect and the better stabilisation of PhS^- compared to that of $(\text{R})\text{ArCO}_2^-$ 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-C₆H₄SH or 2-NH₂-C₆H₄SH at 190°C in the presence of a catalytic amount of K₂CO₃ 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.

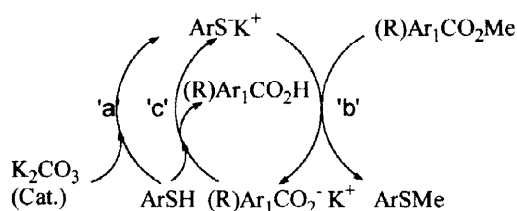
Entry	Thiol	Base ^a	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	PhSH	K ₂ CO ₃	NMP	190	10	100
2	PhSH	K ₂ CO ₃	NMP	110	60	35
3	PhSH	K ₂ CO ₃	NMP	RT	480	Trace
4	PhSH	Nil	NMP	190	60	Trace
5	Nil	K ₂ CO ₃	NMP	190	60	Trace
6	PhSH	KOAc	NMP	190	10	60
7	PhSH	KOCOPh	NMP	190	10	70
8	PhSH	Li ₂ CO ₃	NMP	190	10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

^aUsed 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, NO₂ etc.), reduction (*e.g.* NO₂, 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-C₆H₄SH or

2-NH₂-C₆H₄SH) 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 substitution of the halogen atom¹³ or the nitro group¹⁴ (Table 2, Entries 2-5). Methyl phenoxyacetate and methyl thiophenoxyacetate do not experience substitution of the phenoxy or thiophenoxy groups¹⁵ (Table 2, Entries 8,9). No reduction of the nitro group¹⁶ or α,β -unsaturated double bond¹⁷ 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 addition¹⁸ 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 K₂CO₃ (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).

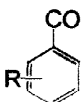
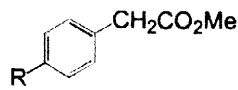
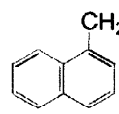
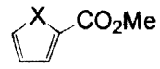
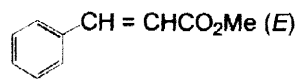
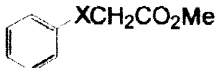
Scheme 2



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 K₂CO₃ 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-C₆H₄SMe and 2-NH₂-C₆H₄SMe 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		100	10		95
2	R = 2-Cl	75	11	R = OMe	80
3	R = 4-Cl	75	12		90
4	R = 2-NO ₂	65	13		100
5	R = 4-NO ₂	60	14	X = S	75
6	R = 2-OH	83	15		86
7	R = 4-OMe	85			
8		80			
9	X = S	72			

EXPERIMENTAL

The esters were available commercially. The solvents were distilled before use. PhSH, 4-Me-C₆H₄SH and EtSH and 2-NH₂-C₆H₄SH were purchased from E. Merck, Germany. KOAc, KOCOPh and K₂CO₃ 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 K₂CO₃ (0.02 g, 5 mol%) in NMP (2.5 ml) were heated at 190°C for 10 mins under N₂. The cold reaction mixture was diluted with saturated aqueous NaHCO₃ (25 ml) and extracted with Et₂O (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 Et₂O (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).

REFERENCES AND NOTE

† NIPER Communication No. 36

- Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. Hudson, R. F. *Coord. Chem. Rev.* **1966**, *89*. Saville, B. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 928. Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*,

1827. Pearson, R. G.; Songstad, J. *J. Org. Chem.* **1967**, *32*, 2899. Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 512. Pearson, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 7684. Pearson, R. G. *J. Org. Chem.* **1989**, *54*, 1423. Pearson, R. G. *Acc. Chem. Res.* **1993**, *26*, 250.
2. McMurry, J. *Org. React.* **1977**, *24*, 187.
 3. E. Haslam, *Tetrahedron* **1980**, *36*, 2409. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 2nd Edt. **1991**. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691. Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: New York, **1994**.
 4. Mascaretti, O. A. *Aldrichimica Acta* **1993**, *26*, 47. Harmon, K. M.; Southworth, B. A.; Wilson, K. E.; Keefe, P. K. *J. Org. Chem.* **1993**, *58*, 7294.
 5. Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1996**, *37*, 5229. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *J. Chem. Soc., Perkin Trans. I* **1996**, 995. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *J. Org. Chem.* **1994**, *59*, 7259. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1991**, *32*, 4239. Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1988**, *29*, 6893.
 6. Shekhani, M. S.; Grubler, G.; Echner, H.; Voelter, W. *Tetrahedron Lett.* **1991**, *31*, 339.
 7. Ashby, E. C.; Park, W. -S.; Goel, A. B.; Su, W. Y.; *J. Org. Chem.*, **1985**, *50*, 5184.
 8. Surdhar, P. S.; Armstrong, D. A. *J. Phys. Chem.* **1986**, *90*, 5915.
 9. Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.*, **1997**, *38*, 8749.
 10. Weast, R. C. Ed. *Handbook of Chemistry and Physics*; 57th Edn; CRC:Ohio. 1985; pp. D 150-152.
 11. Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.*, **1967**, *89*, 2960.
 12. Parker, A. J. *Chem. Rev.*, **1969**, *69*, 1.
 13. Caruso, A. J.; Colley, A. M.; Bryant, G. L. *J. Org. Chem.* **1991**, *56*, 862 and references cited therein.
 14. 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. Beck, J. R. *J. Org. Chem.* **1973**, *38*, 4086.
 15. Cogoli, P.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1979**, *44*, 2636. Cogoli, P.; Mailo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1979**, *44*, 2642. Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1731.
 16. Hwu, J. R.; Wong, F. F.; Shiao, M. -J. *J. Org. Chem.* **1992**, *57*, 5254. Shiao, M. -J.; Lai, L. -L.; Ku, W. -S.; Lin, P. -Y.; Hwu, J. R. *J. Org. Chem.* **1993**, *58*, 4742.
 17. Meissner, J. W. G.; van der Laan, A. C.; Pandit, U. K. *Tetrahedron Lett.*, **1994**, *35*, 2757.
 18. Niyazymbetov, M. E.; Laikhter, A. L.; Semenov, V. V.; Evans, H. D. *Tetrahedron Lett.*, **1994**, *35*, 3037. Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem.* **1996**, *60*, 6188. Ito, A.; Konishi, K.; Aida, T. *Tetrahedron Lett.*, **1996**, *37*, 2585.
 19. Sears, P. G.; Wolford, R. K.; Dawson, L. R. *J. Electrochem. Soc.* **1956**, *103*, 633.