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A mild and chemoselective method for deprotection of aryl acetates and benzoates under non-hydrolytic condition

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Abstract—Chemoselective deprotection of aryl acetates and benzoates can be achieved under non-hydrolytic condition by treatment with K_2CO_3 in *N*-methyl-2-pyrrolidone (NMP) at 100°C. Selective cleavage of aryl acetates and benzoates take place in the presence of alkyl carboxylates during intramolecular competitions.

Protection/deprotection of functional groups[1] is one of the most inevitable synthetic transformations. In the synthesis of multifunctional targets the necessity of deprotection of a particular functionality in the presence of others is frequently desired. Amongst the many functional groups requiring synthetic manipulation involving deprotection, one often encounters the phenolic hydroxyl group, due to its presence in a variety of biologically active compounds. Thus, the masking of phenolic hydroxyl function is a frequently desirable process in organic synthesis and considering the ease of preparation and the availability of starting materials, phenols are protected as acetates and benzoates. The various methods available for deprotection of aryl acetates/benzoates include the treatment with activated zinc in MeOH,[2] NaHTe in refluxing EtOH,[3] 2-bromo-1,3,2-benzodioxaborole in DCM,[4] $^nBuNH_2$ in benzene,[5] guanidine in EtOH–DCM,[6] *N*-methyl-2-dimethylaminoacetohydroxamic acid in THF/aqueous phosphate buffer,[7] *p*-TsOH on SiO_2 in toluene saturated with water at 80°C,[8] $(^nBu_3Sn)_2O$ in refluxing toluene,[9] Al_2O_3 under microwave irradiation,[10] PPl/CCL in organic solvent,[11] antibody (17E8),[12] cyclodextrine in aqueous DMSO,[13] Bi(III)-mandelate in DMSO at 80–125°C,[14] $Yb(OTf)_3$,[15] and natural kaolinitic clay.[16] However, most of these methods are applicable only to acetates, lack the selectivity between aryl and alkyl esters, and require stringent conditions, longer reaction times, special reagents and apparatus.

The most strategic approach for the deprotection of aryl esters seems to be the nucleophilic attack on the carboxyl group. Recently we have developed an efficient procedure for selective deprotection of aryl ester in the presence of aryl alkyl ether and alkyl ester[17] through in situ generation of thiolate anion in a 'demand based' fashion. Although excellent selectivity was achieved, dealing with thiols is alarming because of their radical generating ability. The susceptibility of thiols for areal oxidation (to form the corresponding disulfides[18]) is also a potential problem with the use of thiols. Thus we felt the need to develop a method for efficient chemoselective deprotection of aryl esters using cheap and easy to handle reagents.

As the carboxyl carbon of an ester is a hard centre, application of the 'Hard Soft Acid Base (HSAB)' principle[19] suggests that hard nucleophiles should preferably react at this site. 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[20] (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).

Carbonate anion is a hard nucleophile and we were attracted by a recent report[21] wherein the intermittently formed monoalkyl carbonate anion has been exploited as a nucleophile for the preparation of mixed alkyl carbonates. Although potassium carbonate in aqueous methanol has been utilised for the deprotection of alkoxymethyl carbonate[22] and alkali metal carbonates/bicarbonates have been employed for peptidic methyl, ethyl and benzyl ester deprotection,[23] however, in these cases it is not certain whether carbonate anion is the effective nucleophile as the reactions are carried out in presence of water and the question of maintenance of chemoselectivity between aryl and alkyl esters remains unaddressed. The sole report available in the literature depicting the use of alkali metal carbonates for cleavage of aryl esters under non-aqueous medium is

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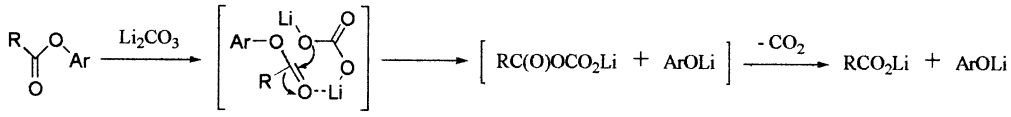


Scheme 1.

Table 1. Reaction of 2-naphthyl benzoate with K_2CO_3 under various conditions

Entry	K_2CO_3[a]	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)[b,c]
1	1.2	NMP	100	3	44
2	1.2	NMP	Reflux	1	72
3	1.2	NMP	Reflux	0.5	69
4	1.6	NMP	100	3	97
5	1.6	NMP	100	3	90[d]
6	1.6	NMP	Reflux	0.5	100
7	1.6	DMPU	100	3	60
8	1.6	DMEU	100	3	55.5
9	1.6	Sulfolane	100	3	83
10	1.6	DMF	100	3	90
11	1.6	DMSO	100	3	33
12	1.6	MeCN	Reflux	3	14
13	1.6	THF	Reflux	3	3
14	1.6	THP	Reflux	3	30
15	1.6	DME	Reflux	3	22

[a] Equivalent amount used with respect to 2-naphthyl benzoate.
[b] Yield of 2-naphthol.
[c] On each occasion the unreacted starting material could be recovered.
[d] Reaction with 2-naphthyl acetate.

from Zaugg[24] wherein phenanthrene diacetate and resorcinol dibenzoate undergo selective cleavage to the corresponding monoacetate or monobenzoate in the presence of a 10% excess of Cs_2CO_3 in either boiling THF (21 h) or boiling DME (10–24 h). The serious drawbacks of this deprotection methodology are the use of costly Cs_2CO_3 and long reaction time. Therefore, we planned to modify the deacetylation/debenzoylation procedure with an aim to carry out the reaction with cheaper reagent and shorter periods.

The reason for using Cs_2CO_3 in the above example was its greater solubility in the employed solvents compared to that of the corresponding potassium salt. As the key step of the reaction is the nucleophilic attack at the carboxyl carbon by the carbonate anion, we felt that activation of the ester carbonyl through co-ordination may facilitate the formation of the tetrahedral intermediate (Scheme 1). Considering the co-ordinating capability of the lithium ion[25] we thought of using Li_2CO_3. The poor solubility of Li_2CO_3 in THF was expected to be overcome by the use of tetrahydropyran (THP).[26] However, when 4-nitrophenyl benzoate and 2-naphthyl acetate were treated with Li_2CO_3 in THP under reflux for 6 and 16 h, respectively, no appreciable amount of debenzoylation or deacetylation was observed. Reaction of 2-naphthyl acetate with Li_2CO_3 in THF in the presence of a stoichiometric amount of TMEDA or 5 mol% of 12-C-4 or TBAI under reflux for 16 h did not result in any deprotection. Use of K_2CO_3 in THF in the presence of 5 mol% separately of TBAI, 18-C-6, PEG 8000 or PEG 4600 under reflux for 16 h also failed to produce any desirable result.

Table 2. Reaction of 2-naphthyl benzoate with various metal carbonates

Entry	Carbonate	Yield (%)[a,b]
1	K_2CO_3	97 (6)[c]
2	Cs_2CO_3	83 (2)[c,d]
3	Rb_2CO_3	99
4	Na_2CO_3	14
5	Li_2CO_3	7
6	$CaCO_3$	7
7	$MgCO_3$	7
8	$BaCO_3$	Nil
9	$SrCO_3$	Nil
10	$ZnCO_3$	32
11	$Bi_2(CO_3)_3$	Nil
12	$La_2(CO_3)_3 \cdot xH_2O$	Nil
13	$Y_2(CO_3)_3 \cdot xH_2O$	Nil

Reactions were carried out by treatment of the ester with 1.6 equiv. of the carbonate in NMP at 100°C for 3 h.
[a] Isolated yield of 2-naphthol.
[b] The unreacted 2-naphthyl benzoate could be recovered on each occasion.
[c] The figures in parenthesis are the yields of the product using the corresponding bicarbonate.
[d] No appreciable amount of deprotecion was observed in carrying out the reaction at room temperature for 4 h.

We planned to use dipolar aprotic solvents as these should specifically solvate the cation generating the 'naked' carbonate anion and enhance the rate of the nucleophilic attack.[27] In order to determine the best operative conditions, 2-naphthyl benzoate was treated with K_2CO_3 under various conditions and the results are summarised in Table 1. Amongst the various dipolar aprotic solvents employed, excellent results are obtained with NMP, DMF and sulfolane whereas DMEU and DMPU provided only moderate yields. Weakly polar ethereal solvents were ineffective. The debenzoylation is best carried out with 1.6 equiv. of K_2CO_3 in NMP either at 100°C for 3 h or under reflux (~200°C) for 30 min.

Various metal carbonates were used in the reaction with

Table 3. Reaction of 2-naphthyl benzoate with various salts of potassium

Entry	K-salt	Yield (%)[a,b]
1	$K_2S_2O_8$	5
2	KSCN	17
3	KNO_3	9
4	K_3PO_4	Nil
5	K_2HPO_4	Nil
6	K_3PO_4	7
7	KH_2PO_4	Nil
8	K_2SO_4	Nil
9	$K_2S_2O_3{\cdot}xH_2O$	Nil

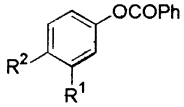
Reactions were carried out by the treatment of the ester with 1.6 equiv. of the K-salt in NMP at 100°C for 3 h.
[a] Isolated yield of 2-naphthol.
[b] The unreacted 2-naphthyl benzoate could be recovered on each occasion.

2-naphthyl benzoate in NMP at 100°C for 3 h and the results are summarised in Table 2. Although Rb_2CO_3 and Cs_2CO_3 provided comparable results, others such as Na_2CO_3, Li_2CO_3, $MgCO_3$, $CaCO_3$, $SrCO_3$, $ZnCO_3$, $Bi_2(CO_3)_3$, $La_2(CO_3)_3$ and $Y_2(CO_3)_3$ were ineffective. No significant amount of debenzoylation could be observed with $KHCO_3$ or $CsHCO_3$.[24] The inefficiency of the bicarbonates may be explained as a result of decrease of nucleophilicity due to hydrogen bonding.

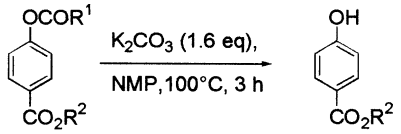
To evaluate the effect of counter anion, other potassium salts, e.g. persulfate, thiocyanate, nitrate, hydrogen phosphates, etc. were also employed and found to be ineffective (Table 3).

Various aryl benzoates were treated with K_2CO_3 (1.6 equiv.) in NMP at 100°C under nitrogen and the results are summarised in Table 4. Chemoselectivity was observed by the fact that methyl ethers do not experience any nucleophilic cleavage (entries 1, 8),[28] no competitive aromatic nucleophilic substitution takes place for substrates bearing halogen atoms (entries 2, 3),[29] and ketone, aldehyde and nitrile functionalities remain unaffected. The chemoselectivity of the process was further tested for substrates

Table 4. Deprotection of various aryl benzoates with K_2CO_3 in NMP

Entry	Aryl benzoate	Yield(%)[a,b]
		
1	R^1=H; R^2=OMe	57 (67)[c]
2	R^1=H; R^2=Cl	93
3	R^1=Me; R^2=Cl	90
4	R^1=H; R^2=OCOPh	86[d]
5	R^1=OCOPh; R^2=H	66[d]
6	R^1=H; R^2=COMe	73
7	R^1=H; R^2=NO_2	72
8	R^1=H; R^2=CHO	75
7	R^1=H; R^2=CN	38 (80)[c]
8	R^1=OMe; R^2=CHO	66

Reactions were carried out by treatment of the ester with 1.6 equiv. of K_2CO_3 in NMP at 100°C for 3 h.
[a] Isolated yield of the corresponding phenol.
[b] The unreacted starting material could be recovered on each occasion.
[c] The figures in parenthesis are the corresponding yields under reflux for 20 min.
[d] The product was isolated through freeze drying.



$R^1 = R^2 = Me$ 92 %
$R^1 = Ph$; $R^2 = Me$ 68 %
$R^1 = Me$; $R^2 = Et$ 62 %
$R^1 = Ph$; $R^2 = Et$ 88 %
$R^1 = Me$; $R^2 = {}^nPr$ 79 %
$R^1 = Ph$; $R^2 = {}^nPr$ 90 %

Scheme 2.

bearing both aryl and alkyl ester functionalities during intramolecular competition (Scheme 2). Excellent level of selectivity was observed in that aryl acetates and aryl benzoates are deprotected selectively in preference to alkyl benzoates.[30]

In conclusion, we have developed an improved and efficient method for selective deprotection of aryl esters under non-hydrolytic conditions using a cheap and easy to handle reagent.

1. Experimental

The esters were either available commercially or prepared following standard procedure.[1] The solvents were distilled before use. K_2CO_3, $BaCO_3$, $MgCO_3$, $SrCO_3$, $K_2S_2O_8$, KNO_3, and KSCN were procured from S.d. Fine Chemicals, India. Li_2CO_3, Na_2CO_3, $CaCO_3$, $KHCO_3$, K_2HPO_4, KH_2PO_4, and K_2SO_4 were procured from Loba Chemie, India. $ZnCO_3$ was purchased from CDH, India. Rb_2CO_3, Cs_2CO_3, $CsHCO_3$, $K_2S_2O_3{\cdot}xH_2O$, KNO_3, K_3PO_4, $Y_2(CO_3)_3{\cdot}xH_2O$ and $La_2(CO_3)_3{\cdot}xH_2O$ were procured from Aldrich, USA. $Bi_2(CO_3)_3$ was procured from Titan Biotech, India.

1.1. General procedure for the deprotection

1.1.1. Representative procedure for deprotection of aryl ester. A mixture of 2-naphthyl benzoate (0.62 g, 2.5 mmol) and K_2CO_3 (0.55 g, 4 mmol) in NMP (2.5 ml) were heated at 100°C for 3 h 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 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, brine (20 ml), dried (Na_2SO_4) and concentrated to afford 2-naphthol (mp=122°C, yield=97%, 350 mg, GC-MS purity=100%), identical (^{1}H NMR, FTIR) with an authentic sample.[31]

GC-MS (*m/z*): 144 (M, 100), 115 (M−CHO, 91), 89 (115-C_2H_2, 19), 63 (89-C_2H_2, 20).

1.1.2. Representative procedure for deprotection of aryl ester in the presence of alkyl ester. A mixture of methyl 4-acetoxy benzoate (0.48 g, 2.5 mmol) and K_2CO_3 (0.55 g,

4 mmol) in NMP (2.5 ml) were heated at 100°C for 3 h 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 dried ($MgSO_4$) and concentrated under vacuo to afford methyl 4-hydroxy benzoate (mp=126°C, yield=92%, 350 mg, GC-MS purity=100%) identical (^{1}H NMR, FTIR) with an authentic sample.[31]

GC-MS (*m*/*z*): 152 (M, 33), 121 (M−OCH_3, 100), 93 (M−CO_2CH_3, 37), 65 (93-CO, 59).

These generalised methods were followed for the remaining substrates and in each occasion the product was found to be identical (^{1}H 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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