Selective Deprotection of Aryl Acetates, Benzoates, Pivalates, and Tosylates under Nonhydrolytic and Virtually Neutral Conditions†

Asit K. Chakraborti,*,‡,§ Mrinal K. Nayak,§ and Lalima Sharma‡

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S. A. S. Nagar 160 062, India, and Department of Chemistry, The University of Burdwan, Burdwan 713 104, India

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Deprotection of functional groups[1] is one of the most important and widely carried out synthetic transformations in preparative organic chemistry. In the synthesis of multifunctional molecules, the problem regularly arises that a given functional group has to be deprotected in the presence of others. Of the many methods available for protection of phenolic hydroxyl group, esters have still retained a position of prominence due to their ease of formation as their rich choices of a whole array of different esters such as acetates, benzoates, pivalates, and sulfonates. The methods available for deprotection of aryl acetates involve treatment with Zn−MeOH,[1a] $LiBH_4$,[1a] *p*-TsOH−SiO_2−H_2O,[1a] BBTO,[2] NaHTe,[3] borohydride-exchanged resin,[4] Al_2O_3/μw,[5] metal complexes,[6] enzymes,[7] metalloenzymes,[8] antibodies,[9] and cyclodextrin[10] and micelle-catalyzed saponification.[11] Deprotection of aryl benzoates is carried out by treatment with acids,[1a] bases,[1a] and NaHTe,[3] and the scanty choices left for depivalylation include alkaline hydrolysis[1a] or irradiation under microwave.[5] The limited options available for cleavage of aryl sulfonates are treatment with aqueous alkali,[1a] PhLi/PhMgBr,[1a] and reducing agents.[1a,12] However, these methods suffer from the disadvantages of harsh reaction conditions, use of costly reagents, and not always being effective for multifunctional substrates.

Table 1. Effect of Thiol, Base, Solvent, and Temperature on Deprotection of 2-Naphthyl Benzoate

entry	thiol	base[a]	solvent	*T* (°C)	time (min)	yield (%)
1	PhSH	K_2CO_3	NMP	reflux	15	96
2	PhSH	Nil	NMP	reflux	60	trace
3	Nil	K_2CO_3	NMP	reflux	60	trace
4	PhSH	K_2CO_3	NMP	100	180	20
5	PhSH	K_2CO_3	DMPU	200	15	95
6	PhSH	K_2CO_3	HMPA	200	15	98
7	PhSH	K_2CO_3	DMEU	200	15	80
8	PhSH	K_2CO_3	sulfolane	reflux	15	70
9	PhSH	K_2CO_3	DMF	reflux	15	88
10	4-MeC_6H_4SH	K_2CO_3	NMP	reflux	15	95
11	2-$NH_2C_6H_4SH$	K_2CO_3	NMP	reflux	5	95
12	2-$NH_2C_6H_4SH$	K_2CO_3	NMP	100	45	100
13	2-$NH_2C_6H_4SH$	K_2CO_3	NMP	rt	360	trace
14	EtSH	K_2CO_3	NMP	reflux	60	trace

[a] Used in catalytic amount (5 mol %).

We report herein that aromatic thiols (e.g., PhSH, 4-MeC_6H_4SH, and 2-$NH_2C_6H_4SH$) in the presence of a catalytic amount of K_2CO_3 in dipolar aprotic solvents constitute an efficient protocol for selective cleavage of aryl ester (Table 1). The deprotection was carried out by heating the reaction mixture at 200 °C in DMPU, DMEU (1,3-dimethyl-2-imidazolidinone), HMPA, and sulfolane or under reflux in NMP and DMF for 5−15 min. With 2-NH_2-C_6H_4SH, the deprotection could be carried out at 100 °C although a longer time was required. Both K_2CO_3 and the thiol are essential for deprotection to take place. The results of deprotection of several aryl acetates, benzoates, pivalates, and tosylates in the presence of chloro, nitro, aldehyde, and acetyl groups are summarized in Table 2. Excellent chemoselectivity was observed for substrates bearing nitro and chloro groups (entries 1, 3, 6−8, 14, and 17) wherein selective deprotection of aryl esters took place without any competitive aromatic nucleophilic substitution of the nitro[13] or chloro[14] groups or reduction of the nitro[15] group despite the known SET property of thiolate anions.[16]

The reaction may be thought to proceed as depicted in Scheme 1. The proton exchange between K_2CO_3 and the thiol (path a) generates ArS^-. Nucleophilic attack by ArS^- at the ester carbonyl (path b) liberates ArO^-, which in turn undergoes proton exchange (path c) with ArSH to replenish the thiolate anion. This "demand-based" in situ generation of ArS^- as the effective nucleophile makes the method highly chemoselective. The importance of the use of NMP as solvent may be realized through the efficient proton exchange (path c) between ArSH and the liberated ArO^- during which the equilibrium [ArSH + ArO^- = ArS^- + ArOH] is shifted to the right as a result of better solvation of ArS^- compared to that of ArO^-.[17] The lack

* To whom correspondence should be addressed. Fax: +91-(0)172-677185. E-mail: niper@chd.nic.in.

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‡ National Institute of Pharmaceutical Education and Research.

§ The University of Burdwan.

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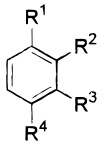
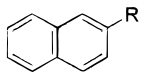
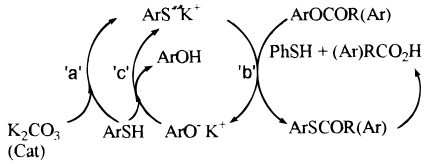
Table 2. Chemoselective Deprotection of Aryl Acetates, Benzoates, Pivalates, and Tosylates[a]

Entry	Aryl Ester	Method A		Method B	
		Time (min)	Yield (%)	Time (min)	Yield (%)
					
1	R^1 = OAc; R^2 = R^3 = H; R^4 = Cl	15	96	30	90
2	R^1 = OAc; R^2 = R^4 = Cl; R^3 = H	15	92		
3	R^1 = OAc; R^2 = R^3 = H; R^4 = NO_2	15	88		
4	R^1 = OAc; R^2 = R^3 = H; R^4 = COMe	15	80		
5	R^1 = OAc; R^2 = R^3 = H; R^4 = CN	15	100	30	100
6	R^1 = OBz; R^2 = R^3 = H; R^4 = Cl	15	90	45	95
7	R^1 = OBz; R^2 = R^4 = Cl; R^3 = H	15	74		
8	R^1 = OBz; R^2 = R^3 = H; R^4 = NO_2	15	85	30	80
9	R^1 = OBz; R^2 = R^3 = H; R^4 = COMe	15	85		
10	R^1 = OBz; R^2 = R^4 = H; R^3 = CHO	15	90		
11	R^1 = OBz; R^2 = R^3 = H; R^4 = CN	15	100	30	90
12	R^1 = OPiv; R^2 = R^3 = H; R^4 = CN	15	90	90	100
13	R^1 = OPiv; R^2 = R^3 = H; R^4 = COMe	15	82		
14	R^1 = OPiv; R^2 = H; R^3 = Me; R^4 = Cl	30	70	120	98
15	R^1 = OTs; R^2 = R^3 = H; R^4 = CN	60	79		
16	R^1 = OTs; R^2 = R^3 = H; R^4 = COMe	60	60		
17	R^1 = OTs; R^2 = H; R^3 = Me; R^4 = Cl	60	95		
					
18	R = OAc	15	91	30	85
19	R = OBz	30	90	45	100
20	R = OPiv	60	83	120	100
21	R = OTs	60	70		

[a] Method A: PhSH (1 equiv), K_2CO_3 (5 mol %), NMP, reflux. Method B: 2-$NH_2C_6H_4SH$ (1 equiv), K_2CO_3 (5 mol %), NMP, 100 °C.

Scheme 1



of proton exchange between EtSH and ArO^-, due to the weaker acidic property of EtSH compared to that of ArOH [pK_a/EtSH = 10.6; ArOH = 8−11], makes the use of EtSH ineffective (Table 1, entry 14) and thus highlights the crucial role of path c. The nucleophilic attack (path b) of the in situ generated ArS^- on the ester via a tetrahedral mechanism[18] is anticipated by the detection of PhSCOPh,[19] PhSCOMe, PhSCOBu^t, and PhSTs during the progress of the reactions (GCMS) of 2-naphthyl benzoate, 2-naphthyl acetate, 2-naphthyl pivalate, and 2-naphthyl tosylate, respectively, with PhSH as well as their isolation in the neutral component after workup.[20]

Furthermore, high selectivity was observed in the competitive deprotection of aryl methyl ether[21] vs aryl ester; acetate vs benzoate, pivalate, or tosylate and benzoate vs pivalate and tosylate (Scheme 2). Thus, during the intermolecular competition between 2-methoxynaphthalene and 2-naphthyl acetate, a 4:96 selectivity was observed in favor of acetate deprotection. Selective (80−95%) deacetylation was also observed during the competitions of 2-naphthyl acetate vs 2-naphthyl benzoate, 2-naphthyl pivalate, and 2-naphthyl tosylate. Selectivities of 80:20 and 70:30 in favor of debenzoylation were observed in the competition between 2-naphthyl benzoate vs 2-naphthyl pivalate and 2-naphthyl benzoate vs 2-naphthyl tosylate, respectively. The origin of these selectivities may well be conceived to be due to the different extent of steric requirement in the respective transition state for S_N2 attack by ArS^-.

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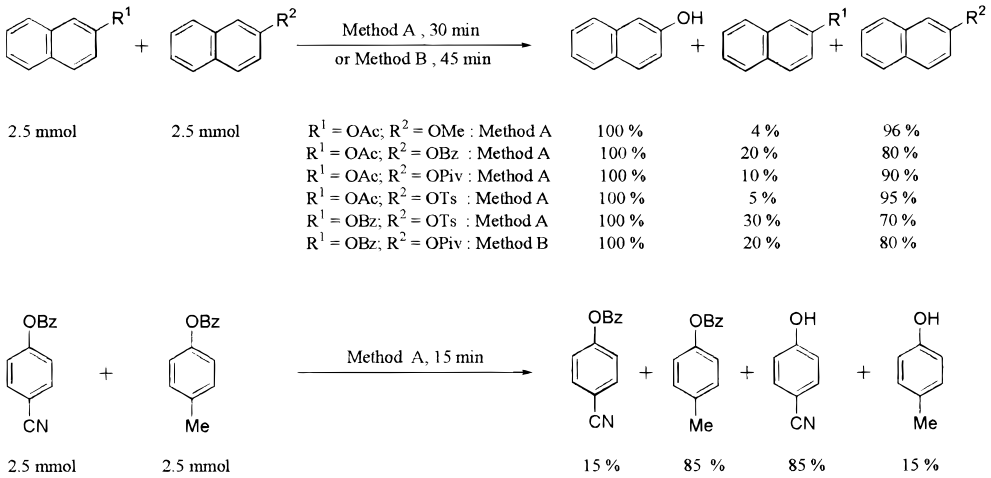
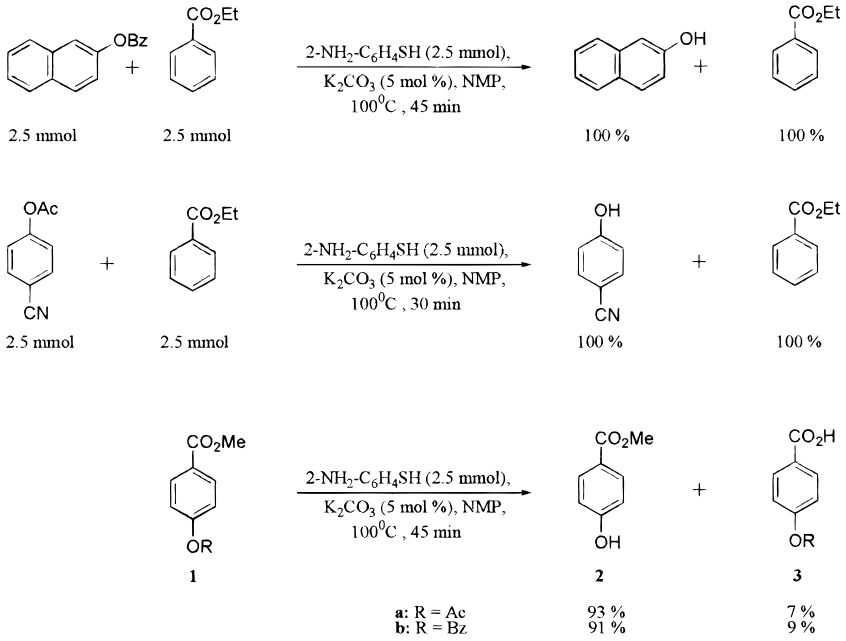
(19) The thioesters RCOSPh produced undergo partial hydrolysis during workup liberating PhSH, which is oxidized to PhSSPh and the corresponding carboxylic acids ($PhCO_2H$ could be isolated in case of debenzoylation reactions).

Scheme 2[a]



[a] Method A: PhSH (2.5 mmol), K_2CO_3 (5 mol %), NMP, reflux. Method B: 2-$NH_2C_6H_4SH$ (2.5 mmol), K_2CO_3 (5 mol %), NMP, 100 °C.

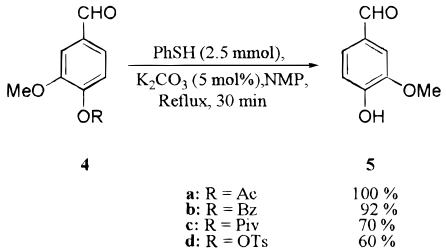
Scheme 3



A careful examination of Table 2 reveals that substrates bearing strong electron-withdrawing groups are deprotected at a faster rate than that of those without such substitution (compare entries 19 and 20 with 8−11 and 12−13, respectively). This difference in rate of reaction could be exploited in achieving selective deprotection, and in the competition between 4-cyanophenyl benzoate and (4-methyl)phenyl benzoate a 85:15 selectivity was observed in favor of the former.

Excellent selectivities were observed during the inter- and intramolecular competition between aryl esters and alkyl esters[22] (Scheme 3). Thus, 2-naphthyl benzoate and 4-cyanophenyl acetate experienced selective deprotection over ethyl benzoate. During intramolecular competitions, selective deprotection of the acetate or the benzoate over that of the methyl ester took place when methyl 4-acetoxybenzoate and methyl 4-benzoyloxybenzoate were treated with 2-$NH_2C_6H_4SH$.

Scheme 4



Selective deprotection of the aryl ester took place in the intramolecular competitions between aryl methyl ether and aryl acetate, benzoate, pivalate, or tosylate during which the aryl methyl ether remained unaffected[23] (Scheme 4).

In conclusion, we have described herein an extremely efficient deprotection protocol of various aryl esters under

(20) Deprotection of acetates, benzoates, and pivalates with 2-$NH_2C_6H_4SH$ resulted in the isolation of 2-methyl benzothiazoline, 2-phenylbenzothiazoline, and 2-*tert*-butylbenzothiazoline, respectively, in the isolated neutral component, confirming the involvement of the tetrahedral mechanism.

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easily operative conditions. The high selectivity arising due to the "demand-based" generation of the nucleophile will enable the method to be applicable for multifunctional substrates as exemplified in Schemes 3 and 4. Although thiolates are popular reagents for deprotection of aryl alkyl ethers[21] and alkyl esters,[22] to our knowledge this is the first report of exploiting PhS^-, or thiolate anion in general, for deprotection of aryl acetates, benzoates, pivalates, and sulfonates.

Experimental Section

General Methods. The aryl esters were either available commercially or prepared by standard procedures.[1] Solvents were distilled before use. The PhSH, 4-MeC_6H_4SH, 2-$NH_2C_6H_4$-SH, and EtSH were purchased from E. Merck, Germany. Analytical grade anhydrous K_2CO_3 from S. d. fine chemicals, India, was used for all reactions.

General Procedure for Deprotection. Representative Procedure. Method A. A mixture of 2-naphthyl benzoate (620.00 mg, 2.5 mmol), PhSH (275 mg, 0.256 mL, 2.5 mmol), and K_2CO_3 (17.25 mg, 0.125 mmol, 5 mol %) in NMP (2.5 mL) was heated under reflux for 30 min under nitrogen. The cooled reaction mixture was made alkaline with 5% aqueous NaOH (25 mL) and extracted with Et_2O (2 × 15 mL) to separate any neutral component (GCMS of these combined ethereal extracts showed the presence of PhCOSPh and PhSSPh). 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 saturated aqueous $NaHCO_3$ (2 × 15 mL) to separate any benzoic acid formed as a result of partial hydrolysis of PhCOSPh and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a light yellow solid that on passing through a column of silica gel (230−400, 1 g) and elution with 5% EtOAc−hexane (200 mL) afforded the product (324 mg, 90%), which was in full agreement with spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of 2-naphthol.

Method B. A mixture of 2-naphthyl benzoate (620.00 mg, 2.5 mmol), 2-$NH_2C_6H_4SH$ (312 mg, 0.267 mL, 2.5 mmol), and K_2CO_3 (17.25 mg, 0.125 mmol, 5 mol %) in NMP (2.5 mL) was heated at 100 °C for 45 min under nitrogen. The cooled reaction mixture was worked up as above to afford 2-naphthol (360 mg, 100%). The neutral component showed the presence of 2-phenylbenzothiazoline (GCMS).

Selective Deprotection in Intermolecular Competition Following Method A. A mixture of 2-naphthyl benzoate (620 mg. 2.5 mmol), 2-naphthyl acetate (465 mg, 2.5 mmol), PhSH (275 mg, 0.256 mL, 2.5 mmol), and K_2CO_3 (17.25 mg, 0.125 mmol, 5 mol %) in NMP (2.5 mL) was heated under reflux for 15 min under nitrogen. The cooled reaction mixture was worked up as above. The neutral component on being subjected to GCMS analysis was found to contain unreacted 2-naphthyl acetate and 2-naphthyl benzoate in a ratio of 4:96 indicating selective cleavage of the acetate. The phenolic product was isolated as usual and was found to contain 2-naphthol (360 mg, 100%).[24] Other intermolecular competitive deprotections were carried in a similar fashion, and the neutral component was subjected to GCMS analysis in each case.

Selective Deprotection in Intermolecular Competition Following Method B. A mixture of 2-naphthyl benzoate (620 mg. 2.5 mmol), 2-naphthyl pivalate (570 mg, 2.5 mmol), 2-$NH_2C_6H_4SH$ (312 mg, 0.267 mL, 2.5 mmol), and K_2CO_3 (17.25 mg, 0.125 mmol, 5 mol %) in NMP (2.5 mL) was heated at 100 °C for 45 min under nitrogen. The cooled reaction mixture was worked up as above. The neutral component on being subjected to GCMS analysis was found to contain unreacted 2-naphthyl benzoate and 2-naphthyl pivalate in a ratio of 20:80 indicating selective cleavage of the benzoate. The phenolic product was isolated as usual and was found to contain 2-naphthol (360 mg, 100%).[24] Other intermolecular competitive deprotections were carried out in a similar fashion, and the neutral component was subjected to GCMS analysis in each case.

Selective Deprotection in Intramolecular Competition between Alkyl and Aryl Esters. A mixture of methyl 4-acetoxybenzoate (**1a**) (485 mg, 2.5 mmol), 2-$NH_2C_6H_4SH$ (312 mg, 0.267 mL, 2.5 mmol), and K_2CO_3 (17.25 mg, 0.125 mmol, 5 mol %) in NMP (2.5 mL) was heated at 100 °C for 45 min under nitrogen. After usual workup and purification, the phenolic product **2** was isolated (353.4 mg, 93%) and was in full agreement with spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of methyl 4-hydroxybenzoate. The carboxylic acid product **3a** was isolated (31.5 mg, 7%) and was in full agreement with spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of 4-acetoxybenzoic acid. Deprotection of the corresponding benzoate (**1b**) in an analogous manner resulted **2** and **3b** in 91 and 9% yields, respectively.

Selective Deprotection in Intramolecular Competition between Aryl Methyl Ether and Aryl Esters. A mixture of 4-acetoxy-3-methoxybenzaldehyde (**4a**) (485 mg, 2.5 mmol), PhSH (275 mg, 0.256 mL, 2.5 mmol), and K_2CO_3 (17.25 mg, 0.125 mmol, 5 mol %) in dry NMP (2.5 mL) was heated under reflux for 30 min under nitrogen. After usual workup and purification, the phenolic product **2** was isolated (380 mg, 100%) and was in full agreement with spectral data (IR, ^{1}H NMR, and GCMS) of an authentic sample of vanillin. Deprotection of the corresponding benzoate (**4b**), pivalate (**4c**), and tosylate (**4d**) in an analogous manner resulted **5** in 92, 70 and 60% yields, respectively.

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(23) The isolated neutral component did not show any PhSMe in the GCMS.

(24) The yield has been measured with respect to the starting aryl thiol.