Facile One-Pot Two-Step Hydroxylation of Alkyl Halides and Alkyl Sulfonates *via* Acetate Intermediates

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Hydroxylation of primary and secondary alkyl halides and alkyl sulfonates was readily achieved by one-pot two-step reaction under mild condition. Less reactive chloride and secondary mesylate functionalities were also transformed to hydroxide group in high yields. When 5% water-containing DMSO solvent was used, catalytic cycle of two-step hydroxylation smoothly proceeded in the presence of catalytic amount of acetate anion.

Key Words : Acetoxylation, One-pot two-step hydroxylation, Alkyl halides, Alkyl sulfonate, Alkyl acetate

Introduction

Facile functional group transformations in both forward and backward way are essential tools for successful journey to the multi-step organic synthesis.[1] It is also as an important individual chemical reaction as carbon-carbon bond formation. Hydroxyl group is one of the most common and useful functionality because of its versatile convertible property to other functional groups as well as biological interest. Among several methods for the preparation of hydroxyl group in literature,[2] hydroxylation of alkyl halides and alkyl sulfonates is the representative transformation reaction. Although the simple displacement of halides and sulfonates with alkali metal hydroxide has been mainly employed, undesired elimination product was also produced considerably due to β-proton abstraction by hydroxide anion, acting as a base. Especially, the hydroxylation of secondary halides and sulfonates produce the eliminated olefin as a major product. Furthermore, since that reaction requires harsh conditions in high pH aqueous media under reflux for several hours, other chemical bonds can be broken or epimerized. Therefore, a variety of mild reagents and reaction conditions have been attempted to avoid these disadvantages.[3] Recently, our group reported the hydroxylation of alkyl halides in neutral ionic liquids, which enhance the nucleophilicity of water molecule.[4] However, that method is practically unfavorable because very extended reaction time is required for the reaction completion maintaining high temperature (110 °C).

Sometimes, two-step hydroxylation was attempted by using either formate[5] or acetate[6] as an oxygen nucleophile that has only nucleophilicity with reduced basicity. The resulting ester bonds were hydrolyzed to give corresponding alcohols using appropriate bases. However, that procedure needed two separate individual steps, high temperature, and excess of base. In addition, hydroxylation of alkyl chloride was still unsuccessful. Thus, from practical and environmental point of view, a systematic study for efficient hydroxylation is still demanded to overcome these synthetic limitations by using simple reagents and reasonable reaction conditions. In this paper, we report very facile one-pot two-step hydroxylation using ubiquitously abundant reagents in organic chemistry laboratory under mild condition.

As we needed an efficient transformation of alkyl sulfonates to alkyl hydroxide, we carefully searched for a suitable reaction conditions. Intriguingly, this reaction was found to be not as simple as expected. As a result of literature study, it was also found that there were few references on systematic investigation of hydroxylation of alkyl halides and alkyl sulfonates.[4] Unlike direct hydroxylation with alkali metal hydroxide, two-step reaction constituted of acetoxylation and hydrolysis was thought to be reliable. Acetoxylation of alkyl halides[7] with acetate anion and hydrolysis of ester bond are both well-known reactions carried out under mild condition. Therefore, we attempted to combine these two reactions into one-pot synthesis for experimental convenience.

Acetoxylation of alkyl halide and hydrolysis of alkyl acetate were investigated separately. Table 1 shows the results of the acetoxylation of 2-(3-bromopropoxy)naphthalene (**1**) with 1.5 equiv of two different acetates *e.g.* potassium acetate and tetraethylammonium acetate (TEAOAc) in several polar solvents such as DMSO, MeOH, DMF, and CH_3CN. The reaction using TEAOAc was faster than potassium acetate, probably due to better solubility and higher nucleophilicity of TEAOAc, and the acetoxylation in more polar aprotic solvent proceeded faster. DMSO was found to be the best solvent of choice. For in situ hydrolysis of corresponding acetate intermediate **2**, additional six reactions were performed in H_2O/DMSO cosolvent (5, 10, and 20% v/v of H_2O) using potassium acetate or TEAOAc because H_2O is required to hydrolyze acetate intermediate. However, the rate of the reaction was decreased as water amount was increased, regardless of kind of acetate. As expected, all cases in Figure 1 afforded no eliminated product.

Hydrolysis of alkyl acetate **2** was examined using 1.5 equiv of six different oxygen bases, K_2CO_3, Cs_2CO_3, LiOH,

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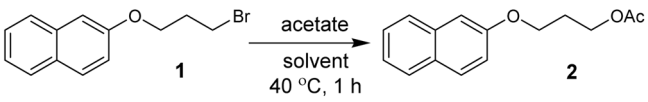
Table 1. Acetoxylation of Alkyl Bromide in Various Solvents[a]



entry	acetate	solvent	time (h)	% conversion[b]
1	KOAc	DMSO	1.0	97
2	KOAc	MeOH	1.0	0
3	KOAc	DMF	1.0	68
4	KOAc	CH_3CN	1.0	1
5	KOAc	DMSO/H_2O (50 μL)	1.0	94
6	KOAc	DMSO/H_2O (100 μL)	1.0	77
7	KOAc	DMSO/H_2O (200 μL)	1.0	68
8	TEAOAc	DMSO	0.5	100
9	TEAOAc	MeOH	1.0	
10	TEAOAc	DMF	0.5	100
11	TEAOAc	CH_3CN	1.0	89
12	TEAOAc	DMSO/H_2O (50 μL)	1.0	100
13	TEAOAc	DMSO/H_2O (100 μL)	1.0	90
14	TEAOAc	DMSO/H_2O (200μL)	1.0	41

[a]All reactions were carried out on a 0.1 mmol scale of **1** using KOAc (0.15 mmol) or TEAOAc (0.15 mmol) in seven different solvents (1.0 mL). [b]% Conversion yield was determined by HPLC integration.

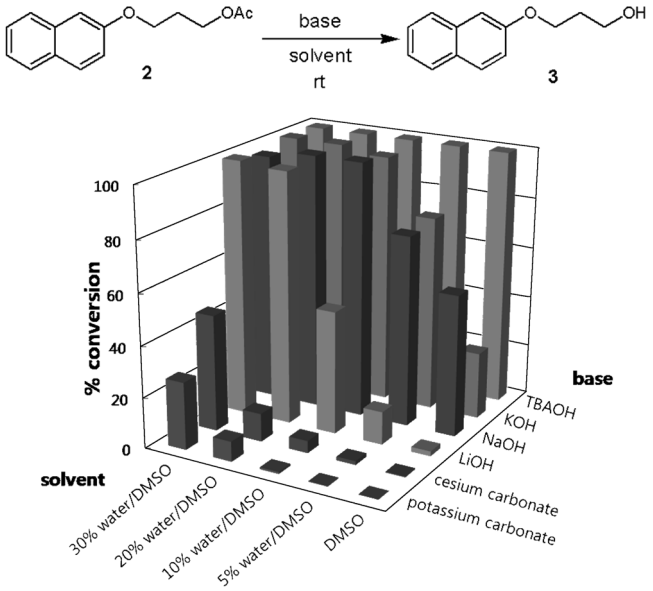
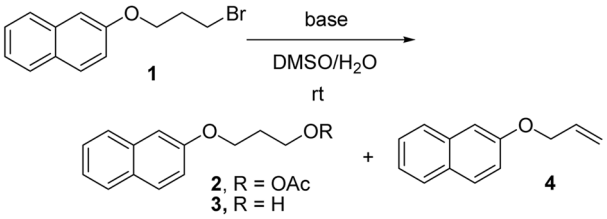


Figure 1. Hydrolysis of alkyl acetates. All reactions were carried out on a 0.1 mmol scale of **2** using six different bases (0.15 mmol) in anhydrous DMSO (1 mL) or aqueous DMSO (1 mL) at room temperature for 1 h (carbonates) or 30 min (hydroxides). % Conversion was determined by HPLC integration.

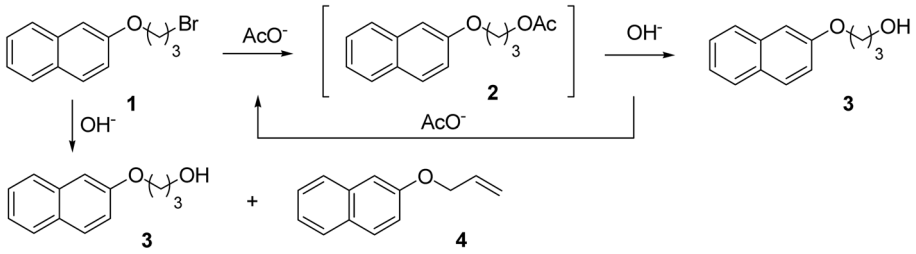
NaOH, KOH, and tetrabutylammonium hydroxide (TBAOH) in anhydrous and four different aqueous DMSO solvents (5, 10, 20, and 30% v/v of H_2O) as shown in Figure 1. All reactions were carried out at room temperature for 1 h (carbonates) or 30 min (hydroxides). In contrast to that water impeded acetoxylation of alkyl bromide **1** in the first step, water enabled all bases to be soluble to some extent in solvents and to enhance hydrolysis reaction in the second step. Two weak bases, K_2CO_3 and Cs_2CO_3, showed low reactivity to give 0-27% and 0-46% conversion after 1 h, respectively. Meanwhile, three alkali metal hydroxides provided better conversion in the order of Na > K > Li. The reaction with TBAOH was completed within 30 min even in anhydrous DMSO solvent, probably because TBAOH contains 60% water. As a consequence of above two experiments, we found that anhydrous DMSO is the best solvent for acetoxylation while aqueous DMSO shows the better performance in hydrolysis reaction. Since we found the optimal condition for each steps, the combined one-pot synthesis was examined in 10% H_2O/DMSO solvent (Table 2). In addition, for comparison with direct hydroxylation, six different oxygen bases were used without acetate (entries 1-6 in Table 2). Carbonate bases (K_2CO_3 and Cs_2CO_3) gave only 2 and 4% of product **3** after 3 h, respectively. LiOH was less reactive than other hydroxides, providing only 4% of product including 6% of olefin **4** (entry 4 in Table 2). When using other hydroxides such as NaOH, KOH, and TBAOH, starting molecule disappeared completely after 3 h at room temperature. However, eliminated compound was obtained as a major product. After examination of direct hydroxylation using single bases, we also tested two-step hydroxylation using several combinations of potassium acetate and hydroxides, which were added together. While LiOH/KOAc

Table 2. Hydroxylation of Alky Bromide using Various Bases in One-Pot[a]



entry	base/acetate	DMSO/H_2O	time (h)	yield (%)[b]			
				1	**2**	**3**	**4**
1[c]	K_2CO_3/–	9/1	3	98		2	–
2[c]	Cs_2CO_3/–	9/1	3	96		4	–
3[c]	LiOH/–	9/1	3	90		4	6
4[c]	NaOH/–	9/1	3	–		25	75
5[c]	KOH/–	9/1	3	–		35	65
6[c]	TBAOH/–	9/1	3	–		34	66
7[d]	LiOH/KOAc	9/1	3	37	5	52	6
8[d]	NaOH/KOAc	9/1	3	13	1	39	47
9[d]	KOH/KOAc	9/1	3	1	–	37	62
10[d]	TBAOH/KOAc	9/1	3	–	–	37	63
11[e]	TEAOAc, KOH	10/3[f]	0.5/0.5[g]	–		100	–
12[e]	KOAc, KOH	10/3[f]	2.5/0.5[g]	–		100	–

[a]Ten reactions (entries 1-10) were carried out on a 0.1 mmol scale of **1** in 1.0 mL of 10% H_2O/DMSO solvent. [b]% Conversion was determined by HPLC integration. [c]1.5 equiv of base was used. [d]Hydroxide (1.5 equiv) and acetate (1.5 equiv) were added together. [e]Acetate (1.5 equiv) was added first, hydroxide (1.5 equiv) was added after completion of acetoxylation. [f]DMSO (1 mL) was used for acetoxylation, and aqueous 0.33 M KOH (0.3 mL) was added for hydrolysis. [g]Reaction time for acetoxylation/hydrolysis.



Scheme 1. Catalytic Hydroxylation of Alkyl Bromide Using Potassium Acetate.

exhibited enhanced reactivity and selectivity, compared to using only LiOH, other three examples such as NaOH/KOAc, KOH/KOAc, and TBAOH/KOAc showed almost the same results as obtained by using only hydroxide bases. Unfortunately, in 10% aqueous DMSO solvent, direct hydroxylation or elimination by hydroxide proceeds faster than acetoxylation by potassium acetate.

Finally, we tried stepwise one-pot two-step reaction (entries 11, 12 in Table 2). In the first step with either TEAOAc or KOAc, acetoxylation was completed in 0.5 and 2.5 h, respectively. Subsequent hydrolysis was performed by adding 0.3 mL of aqueous 0.33 M KOH solution to give a quantitative conversion to alcohol compound **3** within 0.5 h at room temperature.

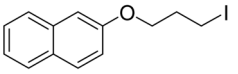
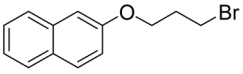
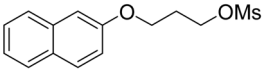
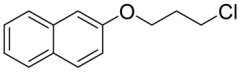
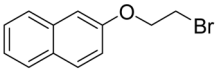
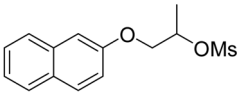
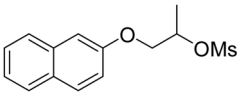
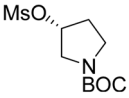
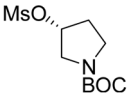
On the basis of mechanism, we thought that acetate anion could be regenerated after hydrolysis and reused for the next acetoxylation as shown in Scheme 1. Additional reactions using LiOH (1.5 equiv) and various equiv (0.1-1.5 equiv) of KOAc were carried out in 5% aqueous DMSO solvent. When using 0.2 equiv of KOAc, 18% of product **3** was yielded with 11% of acetate **2** and 4% of olefin **4** after 6 h (for detail, see supporting information). We could observe the catalytic performance of acetate. However, the reaction proceeded very slowly (after 6 h, 67% of starting molecule remained) to require more extended periods of time for reaction completion.

The hydroxylation of various primary, secondary and cyclic halides or mesylate was performed in a stepwise manner based on previously described reaction condition (entries 11, 12 in Table 2). Acetoxylation was monitored by TLC every 30 min. After insuring that starting molecule disappeared completely, aqueous KOH solution was added for hydrolysis of alkyl acetate, where a preheated solution was cooled to room temperature before adding aqueous KOH solution. While acetoxylations were carried out at variable temperature and for different time depending on the lability of leaving groups, all hydrolyses were performed under the same condition, at room temperature for 30 min.

As expected, alkyl iodide was quickly converted to alkyl acetate within 1.5 h at room temperature. Subsequent treatment with aqueous KOH solution gave alcohol **3** in 98% yield (entry 1 in Table 3). In case of alkyl bromide, it took 2.5 h for complete acetoxylation, and slightly less reactive alkyl mesylate required somewhat elevated temperature (40 °C). It is noteworthy that hydroxylation of less reactive alkyl chloride could be achieved by employing our procedure to afford **3** in 92% yield, although more elevated temperature (50 °C) and longer reaction time (7.5 h) was required for acetoxylation. Compared to other published methods for the hydroxylation of alkyl chloride, our condition is considerably faster and milder. In entry 5, 2-(2-naphtoxy)ethyl bromide was treated under the same condition. Generally, bromo compound having ethylene carbon chain tends to be easily eliminated in direct hydroxylation reaction, providing the corresponding olefin compound.

Using our procedure, the bromo compound was exclusively converted to alcohol in 84% yield. Moreover, the two-step hydroxylation of sterically hindered secondary propyl mesylate afforded 89% of alcohol without formation of

Table 3. Hydroxylation of Various Alkyl Halides and Sulfonates[a]

entry	compound	temp (°C)	time (h)[b]	yield (%)[c]
1		rt	1.5/0.5	98
2		rt	2.5/0.5	96
3		40	2.5/0.5	94
4[d]		50	7.5/0.5	92
5		rt	3.5/0.5	84
6		70	5.0/0.5	89
7[d]		70	3.0/0.5	92
8		100	9.5/0.5	65
9[d]		80	3.5/0.5	96

[a]Unless otherwise noted, all reactions were carried out on a 2.0 mmol scale using KOAc (3.0 mmol) and KOH (3.0 mmol) in DMSO (30 mL) and water (9 mL). [b]Reaction time for acetoxylation/hydrolysis. [c]Isolated yield. [d]TEAOAc (3.0 mmol) was used instead of KOAc.

olefins (entry 6 in Table 3), although the reaction was slightly slower than entry 5 due to steric hindrance and less reactive leaving group. When TEAOAc was used instead of KOAc for the same substrate (entry 7 in Table 3), the acetoxylation was completed about 2-fold faster than entry 6. In addition, much less reactive secondary cyclic mesylate was also transformed to the corresponding acetate in spite of that trace amount of olefin was observed (entry 8 in Table 3). As a matter of course, TEAOAc could allow this reaction at lower temperature in shorter time, and subsequent hydrolysis provided 96% of product without formation of olefins. In addition, BOC moiety of pyrrolidine compound was not damaged under this condition.

In summary, we described the selective and mild hydroxylation of alkyl halides and alkyl sulfonates *via* alkyl acetates intermediate by using stoichiometric amount of acetate and hydroxide from practical point of view. This procedure requires no purification step between acetoxylation and hydrolysis by means of employing DMSO solvent in both reactions. This mild one-pot two-step reaction condition is generally applicable to most alkyl halides and sulfonates regardless of the lability of leaving groups, giving rise to alcohol compound in high yield without formation of side-products.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification unless otherwise stated. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed with Merck Silica gel F-254 glass-backed plates. Visualization on TLC was monitored by UV light or phosphomolybdic acid indicator. ^{1}H and ^{13}C NMR spectra were recorded using both Varian Gemini-2000 (200 MHz) and Varian UNITY-INOVA 400 (400 MHz) and calibrated using residual undeuterated solvent or tetramethylsilane as an internal reference. High performance liquid chromatography (HPLC) was performed using a Gilson system: 321 HPLC pump, 151-UV/VIS monitor. HPLC Conditions: (econosil, RP-C18, 250 mm × 4.6 mm) at the flow-rate of 1 mL/min eluting with CH_3CN/H_2O (70/30). Mass spectra were obtained on VK Quattro II GC-MS/MS spectrometer.

General Procedure for the Preparation of 2-(3-Hydroxypropoxy)naphthalene (Entry 2 in Table 3). A mixture of 2-(3-bromopropoxy)naphthalene (**1**, 530 mg, 2.0 mmol) and KOAc (294 mg, 3.0 mmol) was well suspended in DMSO (30 mL) at room temperature. After the completion of acetoxylation on TLC (2.5 h), aqueous 0.33 M KOH (9 mL, 3.0 mmol) was added to the reaction mixture and stirred at room temperature. After 30 min, the reaction mixture was diluted with water (20 mL) and brine solution (200 mL). The organic compounds were extracted with EtOAc (20 mL × 3) from aqueous phase. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by flash column chromatography (40% EtOAc/hexane) to give 2-(3-hydroxypropoxy)naphthalene (3, 387 mg, 96%) as a white solid.

3-(2-Naphthyloxy)propyl Acetate (2). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.70 (d, 1H, J = 7.6 Hz), 7.67 (d, 2H, J = 8.8 Hz), 7.39 (td, 1H, J = 7.6 Hz, 1.2 Hz), 7.28 (td, 1H, J = 7.6 Hz, 1.6 Hz), 7.10 (dd, 1H, J = 9.0 Hz, 2.2 Hz), 7.06 (d, 1H, J = 2.8 Hz), 4.24 (t, 2H, J = 6.4 Hz), 4.04 (t, 2H, J = 6.2 Hz), 2.12-2.06 (m, 2H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.6, 156.4, 134.2, 129.1, 128.7, 127.4, 126.4, 126.1, 123.4, 118.6, 106.3, 64.1, 61.1, 28.4, 20.8; MS (EI) m/z 244 [M^+], 144, 127, 115, 101 (100); HRMS (EI) m/z $C_{15}H_{16}O_3$ calcd: 244.1099; found: 244.1099.

2-(3-Hydroxypropoxy)naphthalene (Entry 1 in Table 3). CAS No. 7598-29-0; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.81-7.73 (m, 3H), 7.52-7.33 (m, 2H), 7.20-7.14 (m, 2H), 4.20 (t, 2H, J = 5.9 Hz), 3.89 (t, 2H, J = 6.1 Hz), 2.44 (s, 1H), 2.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.6, 134.4, 129.3, 128.9, 127.5, 126.6, 126.3, 123.5, 118.9, 106.6, 65.4, 60.1, 31.8; MS (FAB) m/z 203 [M+H]$^+$.

2-(2-Hydroxyethoxy)naphthalene (Entry 5 in Table 3). CAS No. 93-20-9, commercially available; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.81-7.72 (m, 3H), 7.50-7.32 (m, 2H), 7.21-7.16 (m, 2H), 4.20 (t, 2H, J = 4.6 Hz), 4.03 (t, 2H, J = 4.4 Hz), 2.37 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.9, 134.4, 129.5, 129.1, 127.6, 126.7, 126.4, 123.7, 118.7, 106.8, 69.1, 61.4; MS (FAB) m/z 189 [M+H]$^+$ (100), 149, 144, 115.

2-(2-Hydroxypropoxy)naphthalene (Entries 6 and 7 in Table 3). CAS No. 108298-91-5, commercially available; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.79-7.68 (m, 3H), 7.47-7.28 (m, 2H), 7.18-7.06 (m, 2H), 4.31-4.15 (m, 1H), 4.01 (dd, 1H, J = 9.3, 3.1 Hz), 3.88 (dd, 1H, J = 9.1, 7.7 Hz), 2.52 (brs, 1H), 1.30 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.4, 134.4, 129.4, 129.1, 127.6, 126.7, 126.4, 123.7, 118.6, 106.9, 73.2, 66.2, 18.8; MS (FAB) m/z 203[M+H]$^+$ (100), 185, 144, 115.

***N*-*tert*-Butoxycarbonyl-(*R*)-(−)-pyrrolidin-3-ol (Entries 8 and 9 in Table 3).** CAS No. 101469-92-5, commercially available; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.31 (m, 2H), 3.85 (brs, 1H), 3.30 (m, 4H), 1.84 (m, 2H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.7, 79.2, 70.0, 53.9, 43.4, 33.3, 28.3; MS (EI) m/z 188 [M+H]$^+$, 154, 132, 114.

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