Efficient and Simple NaBH₄ Reduction of Esters at Cationic Micellar Surface

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Supporting Information

General: HPLC grade solvents were purchased from Qualigens, and SpectroChem, India. Alcohol formation in ester reduction was confirmed with the pure alcohols (either procured from Aldrich Chemical Co. or synthesized). Silica gel of 60-120 mesh from SRL, India was used for the column chromatography and thin layer chromatography was performed on Merck precoated silica gel 60-F₂₅₄ plates. Amberlyst A-26 chloride ion exchange resin was obtained from BDH, UK. All other reagents and solvents were purchased from SRL, India. ¹H NMR spectra were recorded on AVANCE 300MHz (BRUKER) spectrometer. Chemical shifts are reported in ppm, using TMS for ¹H NMR as internal standard. High Performance Liquid Chromatography (HPLC) was performed in SHIMADZU-LC10-AT liquid chromatograph.

Methods:

Syntheses of Esters: The ester molecules were prepared following the usual *N*, *N*-dicyclohexylcarbodiimide (DCC) coupling of the corresponding acid and the alcohol in presence of 4-*N,N*-(dimethylamino)pyridine (DMAP). In brief, the acid (1 equivalent) was coupled with the alcohol (1 equivalent) in the presence of 1.1 equivalent of both DMAP and DCC in dry DCM under nitrogen atmosphere at ice-salt temperature and allowing the mixture to reach the room temperature. After overnight stirring, the reaction mixture was filtered and the concentrated filtrate was extracted with ether. The ether part was washed with water and dried over anhydrous sodium sulphate. Ether was concentrated in a rotary evaporator and the desired product was purified through a silica gel (60-120 mesh) column chromatography with acetone/hexane solvent mixture as elutant. In case of *N*-acetylated esters, precursor amines were acetylated prior to DCC coupling.

Synthesis of Benzyl-*p*-nitrophenyl-succinate (diester): The hemi-ester of succinic acid was prepared following the procedure described earlier.¹ Briefly, succinic anhydride (1g, 10 mmol)

was stirred at room temperature with benzyl alcohol (0.89g, 8.3 mmol) and DMAP (1.01g, 8.3 mmol) in dry DCM for 18 hrs. The reaction mixture was then basified with 5% sodium carbonate aqueous solution. The aqueous layer was and acidified with 1N HCl solution and extracted with ethylacetate. The ethylacetate part was washed with brine to neutrality; dried over sodium sulphate and concentrated to get benzyl hemi succinate. The diester was then prepared from this monoester with *p*-nitrophenol following DCC coupling method mentioned above.

Syntheses of alcohols: *para*-Acetamidobenzylalcohol, 2-Acetamido-3-phenylpropanol, and 2-Hydroxy-1-phenylethanol were isolated using the CTAB-micellar assisted NaBH₄ reduction (discussed later) of the corresponding *n*-hexyl esters.

Synthesis of [2-(1H-Indole-3-yl)-1-hexadecylcarbamoyl-ethyl-trimethyl-ammonium chloride (Scheme 2. V): Boc-protected L-tryptophan was coupled with *N*-Hexadecylamine using the procedure mentioned above (DCC-coupling) and the Boc-protected amide thus obtained were then subjected to deprotection by Trifluoroacetic acid (TFA, 4 equivalent) in dry DCM . After 2hrs of stirring, solvents were removed on a rotary evaporator and the mixture was taken in ethyl acetate. The EtOAc part was thoroughly washed with aqueous 10% sodium carbonate solution followed by brine to neutrality. The organic part was dried over anhydrous sodium sulphate and concentrated to get the corresponding amine. Thus the produced amine (1 equivalent) was quartanized with excess iodomethane using 2.2 equivalent anhydrous potassium carbonate and catalytic amount of 18-crown-6-ether in dry DMF for one and half hrs. The reaction mixture was taken in ethyl acetate and washed with aqueous thiosulphate solution and water, respectively. The concentrated ethyl acetate part was crystallized from methanol/ether to obtain solid quartanized iodide, which was subjected to ion exchange on Amberlyst A-26 chloride ion exchange resin column to get the pure chloride (**V**).

Syntheses of *N*-Hexadecyl *N*, *N*, *N*-triethylammonium Bromide (Scheme 2, **II**), ***N*-Hexadecyl *N*, *N*, *N*-tripropylammonium Bromide** (Scheme 2, **III**) and ***N*-Hexadecyl *N,N*-dimethyl *N*-(2-hydroxyethyl)ammonium Bromide**(Scheme 2, **IV**): **II** and **III** were prepared using the procedure mentioned in the literature,² while **IV** was synthesized following the recently published protocol.³ The elemental analysis data as well the ¹H NMR data were with good agreement with the reported values.

Syntheses of and (1-Hexadecyloxycarbonyl-ethyl)-trimethyl-ammonium chloride and 2-Hexadecyloxycarbonyl-1,1-dimethyl-pyrrolidinium chloride (reducible substrates of Table 1, entry 10, 11): These compounds were synthesized following exactly the procedure used for **V**, except *n*-hexadecanol was used instead of *n*-hexadecylamine. During permethylation to synthesize 2-Hexadecyloxycarbonyl-1,1-dimethyl-pyrrolidinium chloride, 1.1 equivalent of potassium carbonate was used.

¹H NMR (300MHz, CDCl₃) and Elemental Analysis of the Synthesized Compounds:

***n*-Hexylbenzoate:** δ = 0.89 (t, *J* = 6.99 Hz, 3H), 1.50 – 1.31 (m, 6H), 1.89 – 1.73 (m, 2H), 4.32 (t, *J* = 6 Hz, 2H), 7.44 (dd, *J* = 6.69, 6.33 Hz, 1H), 7.54 (d, *J* = 2.55 Hz, 2H), 8.05 (dd, *J* = 6.99, 3.18 Hz, 2H). E.A: calculated for C₁₃H₁₈O₂: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.61.

***n*-Hexyl *m*-nitrobenzoate:** δ = 0.93 (t, *J* = 6.6 Hz, 3H), 1.46-1.25 (m, 6H), 1.84 - 1.75 (m, 2H), 4.37(t, *J* = 6.9 Hz, 2H), 7.65 (dd, *J* = 7.8 Hz, 8.1 Hz, 1H), 8.42-8.32 (m, 2H), 8.85(s,1H). E.A: calculated for C₁₃H₁₇NO₄: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.51; H, 6.90; N, 5.55.

***n*-Hexyl *p*-nitrobenzoate:** δ = 0.90 (t, *J* = 6.6 Hz, 3H), 1.47-1.24 (m, 6H), 1.81-1.73 (m, 2H), 4.36 (t, *J* = 6.6 Hz, 2H), 8.20 (dd, *J* = 6.7Hz, 3.8 Hz, 2H), 8.27 (dd, *J* = 8 Hz, 3.8 Hz, 2H). E.A: calculated for C₁₃H₁₇NO₄: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.34; H, 6.70; N, 5.49.

***n*-Hexyl *o*-hydroxybenzoate** : $\delta = 0.90$ (t, $J = 5.7$ Hz, 3H), 1.47 – 1.3 (m, 6H), 1.82 – 1.73 (m, 2H), 4.34 (t, $J = 6.6$ Hz, 2H), 6.88 (d, $J = 9$ Hz, 1H), 6.99 (dd, $J = 8.1, 8.4$ Hz, 1H), 7.45 (dd, $J = 7.2, 8.4$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H). E.A: calculated for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.16; H, 8.09.

***n*-Hexyl *p*-acetamidobenzoate** : $\delta = 0.83$ (t, $J = 6.9$ Hz, 3H), 1.39 – 1.04 (m, 6H), 1.59 – 1.39 (m, 2H), 2.14 (s, 3H), 4.24 (t, $J = 6.66$ Hz, 2H), 7.53 (d, $J = 8.42$ Hz, 2H), 7.94 (d, $J = 6.93$ Hz, 2H). E.A: calculated for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.25; H, 8.25; N, 5.41.

***n*-Hexyl *o*-chlorobenzoate**: $\delta = 0.80$ (t, $J = 6.6$ Hz, 3H), 1.42-1.18 (m, 6H), 1.64-1.73 (m, 2H), 4.26 (t, $J = 6.69$ Hz, 2H), 7.26-7.20 (m, 1H), 7.38 - 7.30 (m, 2H), 7.73 (d, $J = 7.6$ Hz, 1H). E.A: calculated for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.12. Found: C, 65.05; H, 6.98.

***n*-Hexyl-2-(1-naphthyl)-ethanoate** : $\delta = 0.85$ (t, $J = 6.9$ Hz, 3H), 1.22 (m, 6H), 1.57 (m, 2H), 4.08 (m, 4H), 7.5 – 7.26 (m, 4H), 7.82 (dd, $J = 6.54, 2.85$ Hz, 1H), 7.86 (dd, $J = 7.47, 1.89$ Hz, 1H), 8.01 (d, $J = 7.98$ Hz, 1H). E.A: calculated for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.62; H, 8.09.

***p*-Nitrophenyl-2-(1-naphthyl)-ethanoate** : $\delta = 4.05$ (s, 2H), 7.53 – 7.41 (m, 7H), 7.78 (d, $J = 6.7, 1H$), 7.84 (d, $J = 7.5$ Hz, 1H), 8.0 (d, $J = 8.13, 2H$). E.A: calculated for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 69.96; H, 4.16; N, 4.44.

***p*-Nitrophenyl-anthracene-9-carboxylate** : $\delta = 7.54 – 7.68$ (m, 6H), 8.12 (d, $J = 8.34$ Hz, 2H), 8.23 (d, $J = 8.67$ Hz, 2H), 8.44 (d, $J = 8.67$ Hz, 2H), 8.66 (s, 1H). E.A: calculated for $C_{21}H_{13}NO_4$: C, 73.46; H, 3.82; N, 4.08. Found: C, 73.20; H, 3.96; N, 3.99.

Benzyl-*p*-nitrophenylsuccinate : δ = 2.82 (t, J = 4.56, 2H), 2.92 (t, J = 2.34, 2H), 5.17 (s, 2H), 7.3 (m, 5H), 8.25 (dd, J = 7.14, 3.13 Hz, 2H). E.A: calculated for C₁₇H₁₅NO₆: C, 62.00; H, 4.59; N, 4.25. Found: C, 62.38; H, 4.68; N, 4.16.

2-Hexadecyloxycarbonyl-1,1-dimethyl-pyrrolidinium chloride: δ = 0.88 (t, J = 6.6 Hz, 3H), 1.33 – 1.18 (m, 28H), 1.70- 1.63 (br, 4H), 3.19 (s, 3H), 3.74 (s, 3H), 3.88 (m, 2H), 4.27 – 4.17 (m, 2H), 5.44 (t, J = 9.6 Hz, 1H). E.A: calculated for C₂₃H₄₆ClNO₂: C, 68.37; H, 11.47; N, 3.47. Found: C, 68.71; H, 11.35; N, 3.61.

(1-Hexadecyloxycarbonyl-ethyl)-trimethyl-ammonium chloride : δ = 0.88 (t, J = 5.58, 3H), 1.33 – 1.18 (m, 28H), 1.75 (m, 3H), 3.59 (s, 9H), 4.27 – 4.19 (br, 2H), 4.87 (q, J = 7.17 Hz, 1H). E.A: calculated for C₂₂H₄₆ClNO₂: C, 67.40; H, 11.83; N, 3.57. Found: C, 67.31; H, 11.65; N, 3.45.

***n*-Hexyl-2-acetamido-3-phenylpropionate** : δ = 0.73 (t, J = 6.9 Hz, 3H), 1.16 – 1.09 (br, 6H), 1.48 – 1.39 (br, 2H), 1.82 (s, 3H), 2.95 (d, J = 3.9 Hz, 2H), 3.98 – 3.89 (m, 2H), 4.72 (m, 1H), 6.95 (m, 3H), 7.14 (m, 2H). E.A: calculated for C₁₇H₂₅NO₃: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.88; H, 8.45; N, 4.68.

***n*-Hexyl-2-hydroxy-2-phenyl-ethanoate** : δ = 0.77 (t, J = 6.9 Hz, 3H), 1.25 – 1.12 (m, 6H), 1.53 – 1.45 (m, 2H), 3.43 (d, J = 5.7 Hz, ½ H), 4.08 (t, J = 6.6 Hz, 2H), 5.09 (d, J = 5.7 Hz, ½ H), 7.36 – 7.21 (m, 5H). E.A: calculated for C₁₄H₂₀O₃: C, 71.16; H, 8.53. Found: C, 71.48; H, 8.40.

***p*-Acetamido-benzylalcohol** : δ = 2.1 (s, 3H), 4.58 (s, 2H), 7.25(d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H). E.A: calculated for C₉H₁₁NO₂: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.21; H, 6.86; N, 8.33.

2-Acetamido-3-phenylpropanol : δ = 1.89 (s, 3H), 2.8 (d, J = 7.2 Hz, 2H), 3.64-3.5 (m, 2H), 4.09 (m, 1H), 7.26 – 7.29 (m, 5H). E.A: calculated for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.15; H, 7.63; N, 7.38.

2-Hydroxy-1-phenylethanol : (br, 2H), 4.78 (br, 1H), 7.31-7.19 (m, 5H). E.A: calculated for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.28; H, 7.50.

[2-(1H-Indole-3-yl)-1-hexadecylcarbamoyl-ethyl-trimethyl-ammonium chloride (Scheme 2, V): δ = 0.83(t, 3H), 0.97-1.32 (br, 26H), 1.66-1.73(br, 2H), 2.82-2.91 (m, 2H), 3.28 (s, 3H), 3.20 – 3.24 (m, 2H), 3.31(s, 9H), 5.60(br, 1H), 7.01-7.06(br, 1H), 7.29-7.31(d, 2H), 7.41(d, 1H), 7.48-7.51(d, 1H). E.A: calculated for $C_{29}H_{51}N_3OCl$: C, 70.62; H, 10.42; N, 8.52. Found : C, 70.43; H, 10.66; N, 8.42. $[\alpha]_D^{25} = -29.27^\circ$ (MeOH).

Micelle Mediated Reduction of Esters With $NaBH_4$ (Detailed Procedure): In a typical experiment, to a 100 mM aqueous micellar solution (5mL) required amount of the ester substrate dissolved in 50 μ L HPLC grade acetonitrile, was added to reach the substrate concentration 10 mM. After 10 min. of stirring, $NaBH_4$ (7.6 mg, 40 mM) was added to the reaction mixture and was allowed to stir at room temperature for 4-6 hrs. Aqueous solution of sodium perchlorate (1.1 equivalent with respect to the concentration of the surfactant) was added to the reaction mixture to precipitate out the surfactant as their perchlorate salt. The reaction mixture was filtered and the solid residue was washed with water (5 mL) and ether (1mL). The filtrate was then thoroughly extracted with ether and the ether part was dried over anhydrous sodium sulphate followed by concentrated on a rotary evaporator. The concentrated material was taken either in HPLC grade isopropanol or ethanol according to the requirement. This solution was then diluted with the proper solvent (mobile phase of the HPLC) to the desired concentration and injected into HPLC.

A 20 μ l sample loop was used for the injection of the product mixtures. Depending upon the situation, the reaction mixtures were diluted in the concentration range 10^{-4} to 10^{-2} M. The yield of the reactions was calculated from the product alcohol peak areas obtained from the chromatograms using the previously prepared calibration equations of the pure alcohols. The pure alcohols, purchased or synthesized, were previously injected into HPLC in the similar concentration range to obtain the calibration equations. The detailed information of the HPLC data, including calibration equation, peak area, retention time, mobile phase are given in Table S2.

In the cases of *p*-nitrophenyl esters (Table 1, entry 8, 9, 12) and for the aliphatic esters (Table 1, entry 10, 11), the reaction mixtures after the usual workup were subjected to column chromatography (60 – 120 mesh silica gel) for the purification of the alcohols. The product alcohols (*p*-nitrophenol and *n*-hexadecanol) were isolated by eluting the column with acetone/hexane solvent mixture. The reported yields are the isolated yields in all these cases.

In case of the asymmetric ester reduction (Table 2, entry 6,7) the 5mM surfactant (V) concentration used since the aqueous solution of the surfactant is anisotropic at higher concentration. Since the surfactant concentration become lower, proportionally the concentrations of substrate and NaBH₄ were also lowered to keep the concentration ratio surfactant: substrate: NaBH₄ :: 5: 0.5 : 2.

The isomers of 2-hydroxy 1-phenyl ethanol was identified by injecting the pure *R* isomer in CHIRALCEL-ODH column. The isomers of 2-acetamido-3-phenyl propanol were assigned conventionally since the *R* isomer comes prior to the *S* isomer.in CHIRALCEL-OD H column in all instances.

HPLC Chromatograms of the Reaction Mixtures of the Micelle Assisted Reduction of *n*-hexyl Benzoate and *n*-hexyl *p*-nitrobenzoate Using Varying CTAB Concentration (mobile phase: 10% *i*PrOH in Hexane, λ : 254nm, Column: μ -Porasil (Waters) 4.6 mm i.d. $\times$ 250 mm normal phase, and flow rate: 0.5mL/min. Peak area and chemical yields have been mentioned in Table S1.):

HPLC Chromatograms of the Pure Esters, Pure Product Alcohols, and Reaction Mixtures (Unless otherwise mentioned, μ -Porasil (Waters) 4.6 mm i.d. $\times$ 250 mm normal phase column has been used. For the synthesized esters, mobile phase: hexane/2-propanol 90/10, v/v; λ = 254nm (unless otherwise mentioned); flow rate: 0.5 mL/min , for other cases the values are mentioned in Table S 2.):

Table S1. HPLC Calibration Equation of the Pure Product Alcohols and Peak Area, and Chemical Yield of the Micelle Mediated Reduction of *n*-hexyl benzoate and *n*-hexyl *p*-nitrobenzoate Using Varying Concentration of CTAB.

Ester	[CTAB] mM	Calibration equation of the corresponding alcohol Area (μ V) =	Injection concentration of alcohols	Peak Area of the corresponding alcohol (μ V)	% Yield
<i>n</i> -hexylbenzoate	0(aqueous)	$3 \times 10^8 [\text{alcohol}] \text{M} - 5723$	1mM	-	-
	00.1		1mM	-	-
	1		1mM	8055	4.5
	10		1mM	41872	15
	50		1mM	72971	26
	100		1mM	74810	27
<i>n</i> -hexyl <i>p</i> -nitrobenzoate	0(aqueous)	$1.26 \times 10^{10} [\text{alcohol}] \text{M} + 17614$	0.1mM	-	-
	00.1		0.1mM	-	-
	10		0.1mM	1211344	54
	50		0.2mM	2207912	86
	100		0.1mM	1080910	84

Table S2. HPLC Mobile Phase, Injection Concentration for the Alcohols, Calibration Equation , Peak Area, and Yield of Micelle Mediated Reduction^a

Product alcohol	Table/Entry	λ (nm)	Mobile Phase	Injection Conc. (mM)	Calibration Equation Area (μV) =	Correlation Coefficient	Peak Area (μV)	% Yield
benzyl alcohol	Table 1/1		10% ⁱ PrOH in Hexane	1.0	$3 \times 10^8 [\text{alcohol}] \text{M} - 5723$	0.997	74810	27
	Table 2/1	254	"	1.0	"		136798	37
	Table 2/2		"	1.0	"		183280	48
	Table 1/12		5% ⁱ PrOH in Hexane	0.1	$3.84 \times 10^9 [\text{alcohol}] \text{M} - 1877$		101803	27
<i>m</i> -nitro benzylalcohol	Table 1/ 2	254	10% ⁱ PrOH in Hexane	0.1	$1.29 \times 10^{10} [\text{alcohol}] \text{M} - 27455$	0.999	813565	65
	Table 1/ 3	254	10% ⁱ PrOH in Hexane	0.1	$1.26 \times 10^{10} [\text{alcohol}] \text{M} + 17614$	0.998	1080910	84
<i>o</i> -hydroxy benzylalcohol	Table 1/ 4	275	10% EtOH in Hexane	1.0	$4.12 \times 10^9 [\text{alcohol}] \text{M} + 82760$	0.999	2006150	47
	Table 1/ 5	254	10% EtOH in Hexane	1.0	$5.15 \times 10^{10} [\text{alcohol}] \text{M} + 1.8 \times 10^6$	0.998	7325964	14
<i>o</i> -chloro benzylalcohol	Table 1/6		10% ⁱ PrOH in Hexane	1.0	$4.36 \times 10^8 [\text{alcohol}] \text{M} + 3369$	0.999	66963	15
	Table 2/ 3	264	"	1.0	"		181094	41
	Table 2/ 4		"	1.0	"		227621	51
	Table 2/ 5		"	1.0	"		402916	92
1-naphthalene ethanol	Table 1/ 7	254	10% ⁱ PrOH in Hexane	0.1			2644862	80
	Table 1/ 8		"	0.1	$3.34 \times 10^{10} [\text{alcohol}] \text{M} + 9388$	0.999	1502888	45
2-acetamido-3-phenyl propanol ^b	Table 2/ 6 ^c	254	2.5 % ⁱ PrOH in Hexane	1.25 (R) 1.25 (S)	$8 \times 10^8 [\text{alcohol}] \text{M} + 3669.4$ $1 \times 10^9 [\text{alcohol}] \text{M} - 11071$	0.999 0.994	122453(11.9%) 355910(29.3%)	41
	Table 2/7 ^c	254	5% EtOH in Hexane	1.25 (R) 1.25 (S)	$9.15 \times 10^8 [\text{alcohol}] \text{M} - 1803.3$ $9.08 \times 10^8 [\text{alcohol}] \text{M} + 2170.6$	0.999 0.999	63521(5.71%) 54169 (4.57%)	11

^a Injections were made in $\mu\text{Porasil } 4.6 \text{ mm i.d.} \times 250 \text{ mm column}$ and the flow rate was 0.5 mL/min.

^b Injections were done in CHIRALCEL OD-H, 4.6 mm i.d. $\times$ 250 mm, DAICEL CHEMICAL INDUSTRIES, LTD column.

^c Concentration of V, ester, and NaBH₄ were 5, 0.5, 2 mM respectively, since the aqueous solution of V was not isotropic at higher concentration.

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