ORGANIC LETTERS

2004
Vol. 6, No. 22
4133–4136

Efficient and Simple $NaBH_4$ Reduction of Esters at Cationic Micellar Surface

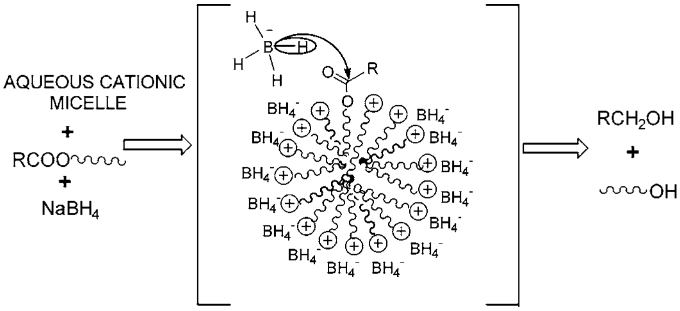
Debapratim Das, Sangita Roy, and Prasanta Kumar Das*

Department of Biological Chemistry, Indian Association for the Cultivation of Science
Jadavpur, Kolkata 700 032, India

bcpkd@iacs.res.in

Received September 16, 2004

ABSTRACT



A simple, efficacious, and biocompatible methodology for reducing esters with sodium borohydride at an aqueous cationic micellar surface under ambient conditions has been developed. The present method holds promise for future use in selective functional group reduction and stereocontrolled alcohol synthesis.

A simple and efficient methodology for sodium borohydride reduction of esters at an aqueous cationic micellar surface has been developed. The simplicity of use, low cost, mild nature, and high chemoselectivity are some of the distinct features that make $NaBH_4$ one of the most popular reducing agents used in industries.[1] Usually, $NaBH_4$ reduces aldehydes, ketones, and imines. However, it fails to reduce other functionalities, including amides, acids, nitro, nitriles, olefins, and esters under ambient conditions.[1] The suboptimal electrophilicity of the ester carbonyl group due to the resonance stabilization by heteroatom inhibits ester reduction by $NaBH_4$.[2] Although strong reductants such as lithium aluminum hydride are capable of reducing esters, they can hardly be used for chemoselective conversions of molecules containing multiple reducible groups.[1,2]

Esters have been reduced with $NaBH_4$ in reaction conditions including high temperature, higher equivalence of $NaBH_4$, presence of coreagent, or different positive counterion of reductant, etc., or by changing the structure of the esters.[3] Such modifications clearly limit the wider applications of $NaBH_4$ to reduce esters. Ester molecules possessing α or β substitutions (hydroxyl/oxo/amino and/or electron-withdrawing groups) have been reduced by $NaBH_4$ plausibly through intramolecular hydride transfer due to complex formation between boron and the heteroatoms.[3h−k] The requirement of such additional functional groups further limits the broad applicability of $NaBH_4$.

Interestingly, self-organized aggregates such as aqueous micellar media can bind the otherwise insoluble organic substrates by incorporating their hydrophobic part in the micellar interior and exposing their polar part at the water–micelle interface.[4] Moreover, they offer a clean and viable alternative to traditional methods of accomplishing organic

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[1] Brown, H. C. *Hydroboration*; W. A. Benjamin, Inc: New York, 1962.

[2] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; Part A.

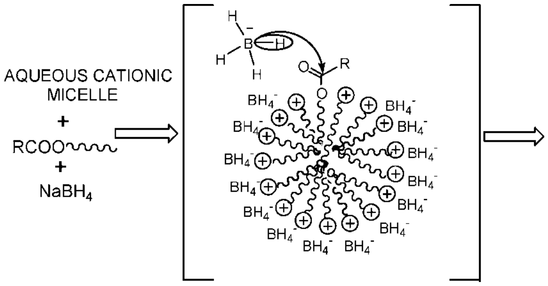
[3] (a) Brown, M. S.; Rapoport, H. *J. Org. Chem.* **1963**, *28*, 3261. (b) Santaniello, E.; Ferraboschi, P.; Sozzani, P. *J. Org. Chem.* **1981**, *46*, 4584. (c) Guida, W. C.; Entreken, E. E.; Guida, A. R. *J. Org. Chem.* **1996**, *61*, 3024. (d) Kokotos, G.; Noula, C. *J. Org. Chem.* **1989**, *54*, 6994. (e) Bhanu Prasad, A. S.; Kanth, B.; Periasamy, M. *Tetrahedron Lett.* **1992**, *48*, 4623. (f) Ranu, B. C. *Synlett* **1993**, 855. (g) Suri, J. T.; Vu, T.; Hernandez, A.; Congdon, J.; Singaram, B. *Tetrahedron Lett.* **2002**, *43*, 3649. (h) Dalla, V.; Cotelle, P.; Catteau, J. P. *Tetrahedron Lett.* **1997**, *38*, 1577. (i) Dalla, V.; Catteau, J. P.; Pale, P. *Tetrahedron Lett.* **1999**, *40*, 5193. (j) Correa, I. R., Jr.; Moran, J. S. *Tetrahedron* **1999**, *55*, 14221. (k) Patra, A.; Batra, S.; Bhaduri, A. P. *Synlett* **2003**, 1611.

10.1021/ol0481176 CCC: $27.50

transformations with the prospect of executing enantioselection through use of appropriate chiral surfactants.[4,5] The intrinsic solubilization ability of micelles provides a discrete reaction site at the microheterogeneous interface by bringing the reacting molecules in close proximity. Hence, the local interfacial concentrations of reactants get enhanced compared to their stoichiometric concentration.[4] The energy of activation is lowered presumably due to increased collisions between such interfacially concentrated reactants (interfacial thickness being within the range of a few Ångstroms).

Herein, we have developed a simple method to reduce esters using only sodium borohydride under ambient conditions in aqueous self-aggregates of cationic surfactants (Scheme 1) obviating the need of any aforementioned modifications. A series of ester molecules with varied hydrophilic−lipophilic balance (HLB) were reduced by $NaBH_4$ in the aqueous micelles of cationic surfactants (Scheme 2) exploiting the propinquity of both reactants (Scheme 1).

Scheme 1



Scheme 2

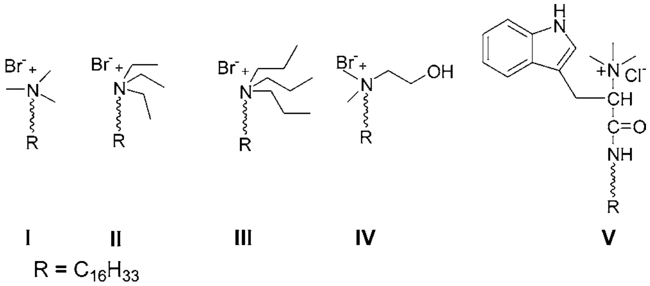
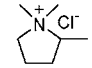
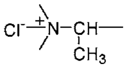


Table 1. $NaBH_4$ Reduction of Esters (RCOOR′) in CTAB Micelle

entry	R-	R′-	yield[a](%)
1	Ph-	$-C_6H_{13}$	27
2	*m*-NO_2-Ph-	$-C_6H_{13}$	65
3	*p*-NO_2-Ph-	$-C_6H_{13}$	84
4	*o*-HO-Ph-	$-C_6H_{13}$	47
5	*p*-CH_3CONH-Ph-	$-C_6H_{13}$	14
6	*o*-Cl-Ph-	$-C_6H_{13}$	15
7	1-Naphthyl-CH_2-	$-C_6H_{13}$	80
8	1-Naphthyl-CH_2-	*p*-NO_2-Ph-	45
9	9-Anthracene-	*p*-NO_2-Ph-	25[b]
10		$-C_{16}H_{13}$	69[b]
11		$-C_{16}H_{33}$	83[b]

[a] Unless otherwise mentioned, yields were calculated from the HPLC peak area of the alcohols using HPLC methods. [b] Isolated yield.

Initially, we have employed the $NaBH_4$ reduction for *n*-hexylbenzoate (Table 1, entry 1) in aqueous cetyltrimethylammonium bromide (CTAB, **I**) micelle,[6] which yielded 27% benzyl alcohol (yields were calculated from the observed HPLC peak areas of the alcohols). To investigate the necessity of surfactant assemblies in ester reduction, *n*-hexylbenzoate was reduced in the aqueous solution of varying CTAB concentration (0−100 mM) keeping all other parameters identical. The chemical yields of benzyl alcohol were 4.5, 15, 26, and 27% in 1 mM (critical micelle concentration), 10 mM, 50 mM, and 100 mM CTAB, respectively. While in pure aqueous or in submicellar (0.1 mM CTAB) solution, no reduction was observed. Thus, the yield was increased with surfactant concentration and became asymptotic in nature above 50 mM. To ensure maximum conversion, all reductions were performed in 100 mM micellar solutions.

The HLB of a substrate determines its solubilization site within the micellar aggregates. The absence of any hydrophilic moiety in *n*-hexylbenzoate presumably leads to a deeper penetration of ester within the hydrocarbon-like core of micelles (water can penetrate within the micelles even up to the first seven carbon atoms[7]), thereby reducing the

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(5) (a) Brown, J. M.; Bunton, C. A. *Chem. Commun.* **1974**, 969. (b) Diego-Castro, M. J.; Hailes, H. C. *Chem. Commun.* **1998**, 1549. (c) Zhang, Y.; Wu, W. *Tetrahedron: Asymmetry* **1997**, *8*, 3575. (d) Perez-Juste, J.; Hollfelder, F.; Kerby, A. J.; Engberts, J. B. F. N. *Org. Lett.* **2000**, *2*, 127. (e) Sato, A.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 2217.

(6) Briefly, in a typical experiment, the reduction of esters was carried out in aqueous CTAB (100 mM) micelle using 10 mM esters and 40 mM $NaBH_4$ at room temperature for ∼4−6 h. Aqueous sodium perchlorate (1.1 equiv with respect to surfactant concentration) solution was added to precipitate out the surfactant molecule as its perchlorate salt and filtered, and the residue was washed thoroughly with water followed by a small amount of ether. The filtrate and the washing were extracted with ether, and the ether part was dried over anhydrous sodium sulfate and concentrated. The concentrated material was taken in 2-propanol/ethanol and diluted with the mobile phase prior to injecting into a HPLC column. The detailed procedure is given in Supporting Information.

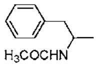
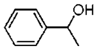
access of ester group to the reductant BH_4^- ions. Keeping this view in mind, we have introduced polar substitutions (Table 1, entries 2−6) in the benzene ring and, as expected, a notable (47-84%) yield increase was observed in the case of −OH- and $-NO_2$-substituted esters (Table 1, entries 2−4). In contrast, a significant decrease in yield was observed for $-NHCOCH_3$- and −Cl-substituted esters (Table 1, entries 5 and 6), where hydrophobicity plays the dominant role. To confirm further that the observed reduction is micelle-mediated, *n*-hexyl-*p*-nitrobenzoate, being the highest reducible substrate, was reduced in varying concentrations of CTAB solutions in a manner similar to that discussed for *n*-hexylbenzoate. Here also, reduction was not observed in pure aqueous or submicellar solution and maximum conversion was obtained at ≥50 mM (see Supporting Information).

To ascertain the role of HLB on the reaction yield, further investigations were carried out using esters containing extended aromatic rings such as naphthalene and anthracene (Table 1, entries 7−9). The yield (80%) was very promising in the case of *n*-hexyl ester of α-naphthylacetic acid (Table 1, entry 7). In accord with the previous observation,[4d,e] the high conversion might be due to the interaction between the naphthalene π-system and the cationic headgroup. Furthermore, the presence of the *n*-hexyl chain probably provides flexibility to the molecule, allowing better accessibility of the ester group to the BH_4^- ions. The yields were modest for *p*-nitrophenyl ester of α-naphthylacetic acid and anthracene-9-carboxylic acid (Table 1, entries 8 and 9) possibly due to constrained orientation of the molecules diverting the ester group away from the interface.

Toward studying the scope of the present method, aliphatic esters containing two different surfactants (Table 1, entry 10, 11) were comicellized with CTAB as a cosurfactant and reduced by $NaBH_4$. Significant yields (69 and 83%, respectively) were obtained. The present method was also found to be useful for reducing ester groups with excellent functional group selectivity. For instance, selective reduction of ester group for $-NO_2$ and $-NHCOCH_3$ substrates (Table 1, entries 2, 3, and 5) is not possible using lithium aluminum hydride and also no ester reduction with $NaBH_4$ was observed in a simple methanol−water solvent mixture. In accordance with the above perception, we have tried to reduce a particular ester moiety selectively in a diester substrate, namely, benzyl-*p*-nitrophenylsuccinate with varying HLB of the two ester functionalities. The reduction of benzyl *p*-nitrophenyl succinate produced 71% *p*-nitrophenol, while only 27% of the benzyl ester was found to be reduced, showing 44% selectivity toward *p*-nitrophenyl ester.

The efficiency of the ester reduction was significantly improved (Table 2, entries 1−5) in the aqueous cationic micelles of three different surfactants (Scheme 2, **II**−**IV**) containing bulkier headgroups. The increase in the size of polar head enhances the second-order rate constants possibly due to the greater electrostatic interaction between the substrates and headgroups. Disruption of the hydration shell of halide counterions by a bulkier headgroup might have led to the easier access of BH_4^- ions to esters.[4c−f] The yields for *n*-hexyl benzoate and *n*-hexyl *o*-chlorobenzoate reduction were increased by at least 2- and 3-fold in the micelles of the surfactants **II** and **III**, respectively, compared to that in the CTAB system. The highest yield (92%) was obtained using surfactant **IV** (Table 2, entry 5), where that hydroxyl group at the polar head may further increase the interaction between BH_4^- ions and esters presumably via hydrogen bonding interactions.

Table 2. $NaBH_4$ Reduction of Esters (RCOOR′) in Aqueous Micelle

entry	R-	R′-	surfactant	yield (%)[a]	ee (%)
1	Ph-	$-C_6H_{13}$	**II**	48	-
2	Ph-	$-C_6H_{13}$	**III**	63	-
3	*o*-Cl-Ph-	$-C_6H_{13}$	**II**	41	-
4	*o*-Cl-Ph-	$-C_6H_{13}$	**III**	51	-
5	*o*-Cl-Ph-	$-C_6H_{13}$	**IV**	92	-
6		$-C_6H_{13}$	**V**[b]	41	43(*S*)
7		$-C_6H_{13}$	**V**[b]	11	11(*R*)

[a] See footnote a in Table 1. [b] Concentration of **V** = 5 mM; aqueous solution of **V** was not isotropic in higher concentration. Proportionately, concentrations of ester and $NaBH_4$ were 0.5 and 2 mM, respectively.

Much attention is being given to the search for routes for synthesizing enantiopure products because of the growing demand for optically pure materials in chemical and pharmaceutical industries.[8] To this end, the present methodology was adopted to reduce DL-pairs of esters (Table 2, entries 6 and 7) in aqueous chiral micelle of surfactant **V** (Scheme 2) containing L-tryptophan as a polar head. The chiral interface was found to induce a notable enantioselectivity (43% (*S*) and 11% (*R*) ee, respectively) during the formation of corresponding alcohols.[9] This initial finding supports the notion that the present method holds promise for future exploitation in the area of enantioselective alcohol synthesis.

To summarize, we have developed an efficient and simple method of reducing esters under ambient conditions using $NaBH_4$ at a cationic micellar surface. In addition to being applicable for reducing simple aromatic or aliphatic ester molecules, the present method holds promise for future use in selective functional group reduction and stereocontrolled alcohol synthesis.

Acknowledgment. D.P.D. and S.R. acknowledge Council of Scientific and Industrial Research, India, for Junior Research Fellowships, and P.K.D. is thankful to Department of Science and Technology, Government of India, for

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(8) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2003.

(9) Racemic 2-acetamido-3-phenylpropanol and 2-hydroxy-1-phenylethanol were isolated using the CTAB micellar-assisted $NaBH_4$ reduction of the corresponding esters. Lithium aluminium hydride reduction of these esters was not successful for preparing the alcohols.

financial assistance. We thank Antara Dasgupta for helpful discussion.

Supporting Information Available: Experimental procedures, syntheses of esters, alcohols, and surfactants, characterization of compounds, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0481176