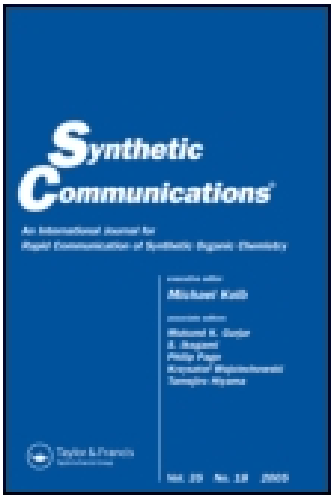

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Efficient Dimeric Esterification of Alcohols with NBS in Water Using L-Proline as Catalyst

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EFFICIENT DIMERIC ESTERIFICATION OF ALCOHOLS WITH NBS IN WATER USING L-PROLINE AS CATALYST

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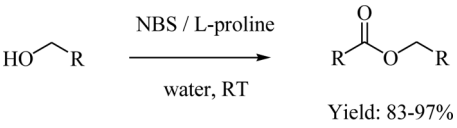
GRAPHICAL ABSTRACT



Abstract *The L-proline-catalyzed oxidation of aliphatic primary alcohols with* N*-bromosuccimide (NBS) in water at room temperature to afford the corresponding dimeric esters in good to excellent yields was described. This pathway of dimeric esterification was proved to be very simple and environmentally friendly.*

Keywords Aliphatic primary alcohols; dimeric esterification; L-proline; NBS; water

INTRODUCTION

Extensive studies on the dimeric esterification of primary alcohols have been carried out over the past 20 years, and numerous methods have been developed. For example, dimeric esterification could be successfully promoted by metal complexes [$Ru_3(CO)_{12}$,[1] $RuH_2(Ph_3P)_4$,[2,3] $PdCl_2$,[4,5] $Pd(OAc)_2$,[6] $PhCH_2N^+Me_3Br_4^-MoO$ [7] and $[IrCl(coe)_2]_2$[8]], chromic acids ($Na_2Cr_2O_7/H_2SO_4$[9] and PCC/Al_2O_3[10]), oxoammonium salt in combination with pyridine,[11] molecular iodine,[12] and brominated reagents [$Br_2/KBrO_3$,[13] $NaBrO_2/CH_3COOH$,[14] $NaBrO_3/HBr$,[15] pyridinium hydrobromide perbromide (PHPB)[16] and others.[17–20]]. However, most of these pathways still have several drawbacks from both environmental and operational points of view, such as employment of toxic and expensive metal complexes as catalysts, use of volatile organic compounds as solvents, poor yields, and requirements for an anhydrous environment, strong oxidative conditions, high temperature, long reaction times or inert gases. Thus there is still demand for simple and clean oxidation procedures.

As the use of *N*-bromosuccinimide (NBS) is more convenient and safe in organic synthesis than bromine, NBS is typically used for bromination.[21–23] In addition, NBS/additives have received considerable attention for oxidation of

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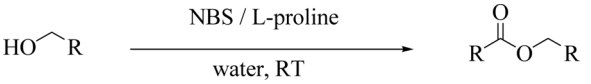
alcohols to the corresponding aldehydes or ketones, such as NBS/β-cyclodextrin,[24] NBS/cobalt(II) acetylacetonate,[25] NBS/NH_4Cl,[26] NBS/H_2O_2,[27] and so on. However, NBS used for the dimeric esterification of primary alcohols has rarely been described. Therefore, it is meaningful to develop dimeric esterification of primary alcohols using NBS as an effective oxidizing agent, which is a simple and green procedure.

Recently, organocatalysis using small molecules has generated great interest in organic synthesis.[28–31] Among many organocatalysts, L-proline is very important because it is commercially available and inexpensive and could serve as an efficient catalyst for a range of quintessential reactions, such as the asymmetric Aldol,[32,33] Mannich,[34,35] Michael,[36,37] α-oxidation,[38–40] Diels–Alder,[41,42] multicomponent Biginelli,[43,44] and Knoevenagel-type reactions.[45–48] Herein, to establish more simple and safe reaction conditions, we have used NBS in the dimeric esterification. To the best of our knowledge, this is the first successful example of efficient dimeric esterification of aliphatic primary alcohols in water with NBS as oxidant and L-proline as catalyst (Scheme 1).

Initially, the esterification of n-pentanol (2 mmol) was carried out with NBS (1 equiv.) in the presence of L-proline (0.8 mmol) in water (4 ml) at room temperature, and the corresponding pentyl pentanoate was obtained in 67% yield in 2 h (Table 1, entry 1). This reaction was used as a model to evaluate the effect of catalyst and oxidant loading on the reaction. The results were described in Table 1. In Table 1, it was exciting to observed that when 0.2 m mol L-proline was used as catalyst and 2 equiv. NBS was used as oxidant, in 1 h the corresponding dimeric ester could be obtained in 97% yield (Table 1, entry 10). Based on those experimental results in Table 1, we could conclude that both the concentration of Br_2, which was generated from NBS, and the reaction time have effects on the yields of the products. Moreover, different organic solvents were further tested as reaction media, and the results showed that no reaction took place in solvents such as Et_2O, dimethylsulfoxide (DMSO), and CH_3CH_2OH, while poor yields of dimeric ester were obtained in CH_3COCH_3, CH_2Cl_2, and CH_3CN. Obviously, water was the best solvent for the reaction.

The efficiency of the L-proline reagent compared to various primary or secondary amines catalysts was also examined (Table 2). This study found that the corresponding dimeric ester could be obtained in good yield in the presence of any catalyst in Table 2. However, L-proline was a more efficient and superior catalyst (entry 4) than other catalysts with respect to yield of the desired ester in comparison. To show the effect of L-proline for esterification, the reaction was carried out without L-proline and no reaction took place (Table 2, entry 1). L-Proline was consequently ascertained to be essential for the esterification of n-pentanol with NBS in water.



Scheme 1. Dimeric esterification of aliphatic primary alcohols with NBS using L-proline as catalyst.

Table 1. L-Proline catalyzed oxidation of n-pentanol

Entry	NBS (equiv.)	L-proline (mol%)	Solvent	Time (h)	Yield[a] (%)
1	1.0	20	H_2O	2.0	67
2	0.5	20	H_2O	2.0	31
3	1.5	20	H_2O	2.0	84
4	2.0	20	H_2O	2.0	93
5	2.5	20	H_2O	2.0	93
6	2.0	0	H_2O	2.0	0
7	2.0	5	H_2O	2.0	89
8	2.0	10	H_2O	2.0	95
9	2.0	40	H_2O	2.0	88
10	2.0	60	H_2O	2.0	90
11	2.0	10	H_2O	0.5	92
12	2.0	10	H_2O	1.0	97
13	2.0	10	H_2O	1.5	95
14	2.0	10	H_2O	2.5	95
15	2.0	10	Et_2O	4.0	0
16	2.0	10	CH_3COCH_3	4.0	7[b]
17	2.0	10	CH_2Cl_2	4.0	18[b]
18	2.0	10	CH_3CN	4.0	38[b]
19	2.0	10	DMSO	4.0	0
20	2.0	10	CH_3CH_2OH	4.0	0

Note. Reaction conditions: n-pentanol, 2 mmol; solvent, 4 ml; at room temperature. A variety of conditions to get pentyl pentanoate were investigated including the reaction times, solvents, and L-proline and NBS loading.

[a]Isolated yield.

[b]Yield determined by GC.

Based on these optimized conditions, several aliphatic primary alcohols with NBS utilizing L-proline in water at room temperature were examined. All reactions were completed within 1–3 h, as indicated in Table 3. From the results in Table 3, we could see that higher aliphatic primary alcohols underwent oxidation smoothly to give the corresponding dimeric esters in excellent yields and high purity without

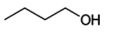
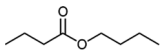
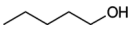
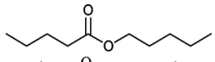
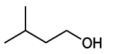
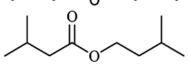
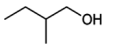
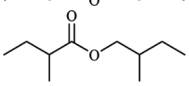
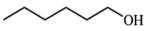
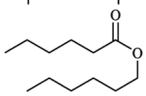
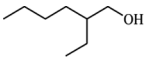
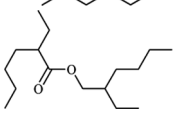
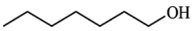
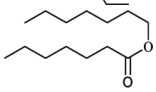
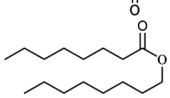
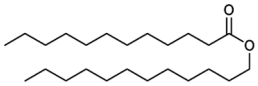
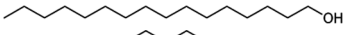
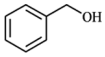
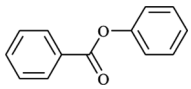
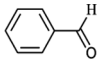
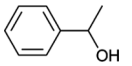
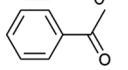
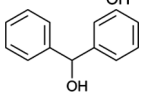
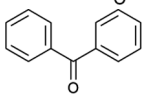
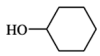
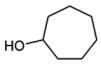
Table 2. Effect of catalysts on pentyl pentanoate yield

Entry	Catalyst	Yield[a] (%)
1	No catalyst	0
2	Pyrrolidine	79
3	Piperidine	88
4	L-proline	97
5	L-alanine	83
6	D-valine	86
7	L-lysine	90
8	L-aspartic acid	87
9	L-cystine	86

Note. Reaction conditions: n-pentanol, 2 mmol; NBS, 4 mmol; catalyst, 0.2 mmol; water, 4 ml; at room temperature; and 1 h.

[a]Isolated yield.

Table 3. L-Proline-catalyzed oxidation of alcohols using NBS as oxidant

Entry	Reagent	Product	Time (h)	Yield[a] (%)
1			3.0	90
2			1.0	97
3			2.0	85
4			3.0	92
5			1.0	94
6			1.0	95
7			1.0	97
8			3.0	94
9			3.0	99
10		—	24	—
11			2.0	Trace
			2.0	83
12			2.0	84
13			4.0	91
14			1.0	83
15			1.0	91

Note. Reaction conditions: alcohols, 2.0 mmol; NBS, 4.0 mmol; L-proline, 0.2 mmol; water, 4 ml; and at room temperature.

[a]Isolated yield.

further purification by column chromatography (Table 3, entries 2 and 5–9). 1-Hexadecanol, however, could not react very well for a long time, which may be because the 1-hexadecanol was solid and totally insoluble in water, and thus could not be brought into contact with the reaction medium very well (Table 3, entry 10).

Moreover, branched aliphatic primary alcohols such as 3-methyl-1-butanol and 2-methyl-1-butanol were also oxidatively dimerized to the corresponding esters in good yields accompanied by a small amount of free fatty acids (Table 3, entries 3 and 4). However, oxidation of benzyl alcohol gave a negligible extent of benzyl benzoate under identical conditions; instead, the corresponding benzaldehyde and some monobromo benzaldehydes were obtained (Table 3, entries 11).[14] On the other hand, secondary alcohols could also participate in the reaction to afford good yields of the corresponding carbonyl compounds, which were in accordance with previous reports (Table 3, entries 12–15).[4,16,18]

In conclusion, we have developed a green and efficient method for the dimeric esterification of various primary alcohols with NBS using a catalytic amount of L-proline as catalyst in water at room temperature. The important advantages of this procedure are as follows: (a) operational simplicity, (b) eliminating toxic organic solvents as reaction medium, (c) mild reaction conditions, (d) short reaction time, (e) good to excellent yields without further purification by column chromatography, and (f) employment of a catalytic amount of inexpensive and easily accessible catalyst.

EXPERIMENTAL

Most of the organic chemical substrates are commercially available and purchased from Alfa Aesar. Infrared radiation (IR) spectra were recorded on an Nexus 470 Fourier transform (FT)–IR spectrophotometer, and ^{1}H NMR data were recorded on an Advance DMX 500-MHz spectrometer in $CDCl_3$ solution using tetramethylsilane (TMS) as internal standard.

General Reaction Protocol

In a typical experiment, alcohol (2 mmol), NBS (4 mmol), and water were (4 ml) added a round-bottomed flask (25 ml). Then, L-proline (0.2 mmol) was added, and the reaction mixture was stirred at room temperature. After the reaction was completed, the mixture was quenched with 0.5 M aqueous $Na_2S_2O_3$ (3–5 ml) and extracted with Et_2O three times (3×5 ml). The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the product was purified by column chromatography if necessary (n-hexane/ethyl acetate).

Spectral (IR and ^{1}H NMR) Data of Some Representative Compounds

Butyl butyrate (Table 3, Entry 1). IR: 1473, 1724 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ [t, J(H,H) = 7.2 Hz, 6H, $-CH_3$], 1.3 (m, 2H, $-CH_2$), 1.4 (m, 2H, $-CH_2$), 1.6 (m, 2H, $-CH_2$), 2.3 [t, J(H, H) = 7.3 Hz, 2H, $-CH_2$], 4.1 ppm [t, J(H,H) = 6.6 Hz, 2H, $-CH_2$].

Pentyl pentanoate (Table 3, Entry 2). IR: 1467, 1739 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ [t, J(H,H) = 6.4 Hz, 6H, $-CH_3$], 1.3 (m, 6H, $-CH_2$), 1.6 (m, 4H, $-CH_2$), 2.3 [t, J(H, H) = 7.5 Hz, 2H, $-CH_2$], 4.0 ppm [t, J(H,H) = 6.8 Hz, 2H, $-CH_2$].

3-Methyl-1-butyl 3-methylbutanoate (Table 3, Entry 3). IR: 1467, 1738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ (m, 12H, $-CH_3$), 1.1 (m, 2H, $-CH_2$), 1.5 (m, 1H, $-CH_2$), 1.6 (m, 1H, $-CH$), 2.1 [d, 2H, J(H, H) = 3.5 Hz, $-CH_2$], 4.1 ppm [t, J(H, H) = 6.9 Hz, 2H, $-CH_2$].

2-Methyl-1-butyl 2-methylbutanoate (Table 3, Entry 4). IR: 1463, 1737 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ (m, 9H, $-CH_3$), 1.2 (m, 5H, $-CH_2$ and $-CH_3$), 1.5 (m, 2H, $-CH_2$), 1.7 (m, 1H, $-CH_2$), 2.4 (m, 1H, $-CH_2$), 3.9 (m, 1H, $-CH_2$), 4.0 ppm (m, 1H, $-CH_2$).

Hexyl hexanoate (Table 3, Entry 5). IR: 1467, 1739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ [t, J(H, H) = 7.9 Hz, 6H, $-CH_3$], 1.3 (m, 10H, $-CH_2$), 1.6 (m, 4H, $-CH_2$), 2.3 [t, J(H, H) = 7.5 Hz, 2H, $-CH_2$], 4.1 ppm [t, J(H, H) = 6.7 Hz, 2H, $-CH_2$].

2-Ethylhexyl 2-ethylhexanoate (Table 3, Entry 6). IR: 1462, 1735 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ (m, 12H, $-CH_3$), 1.3 (m, 12H, $-CH_2$), 1.4 (m, 4H, $-CH_2$), 1.6 (m, 1H, $-CH$), 2.3 (m, 1H, $-CH$), 4.0 ppm [d, J(H, H) = 5.70 Hz, 2H, $-CH_2$].

Heptyl heptanoate (Table 3, Entry 7). IR: 1467, 1739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ [t, J(H, H) = 6.7 Hz, 6H, $-CH_3$], 1.3 (m, 14H, $-CH_2$), 1.6 (m, 4H, $-CH_2$), 2.3 [t, J(H, H) = 7.5 Hz, 2H, $-CH_2$], 4.1 ppm [t, J(H, H) = 6.7 Hz, 2H, $-CH_2$].

Octyl octanoate (Table 3, Entry 8). IR: 1467, 1739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ (t, J(H, H) = 6.4 Hz, 6H, $-CH_3$), 1.3 (m, 18H, $-CH_2$), 1.6 (m, 4H, $-CH_2$), 2.3 [t, J(H, H) = 7.5 Hz, 2H, $-CH_2$], 4.1 ppm [t, J(H, H) = 6.7 Hz, 2H, $-CH_2$].

Dodecyl dodecanoate (Table 3, Entry 9). IR: 1466, 1740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.9$ [t, J(H, H) = 6.9 Hz, 6H, $-CH_3$], 1.3 (m, 34H, $-CH_2$), 1.6 (m, 4H, $-CH_2$), 2.3 [t, J(H, H) = 7.5 Hz, 2H, $-CH_2$], 4.1 ppm [t, J(H, H) = 6.7 Hz, 2H, $-CH_2$].

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