Bromination of ketones with the systems H_2O_2—LiBr—Ce^{III} and H_2O_2—LiBr—Ce^{IV}

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A new method for the synthesis of α-bromoketones was suggested. The C_5—C_{11} linear and branched ketones in the reaction with the systems H_2O_2—LiBr—Ce^{III} and H_2O_2—LiBr—Ce^{IV} in acetonitrile were brominated at α-position. The reaction is highly selective.

Key words: bromination, ketones, bromo ketones, hydrogen peroxide, lithium bromide, oxidation, cerium(III) nitrate, cerium(IV) ammonium nitrate.

Halogenation processes take one of the central places in organic synthesis, are widely represented in chemical laboratory practice, are used in industry. Besides traditional technique of halogenation with aggressive, toxic, and frequently inconvenient in handling chlorine, bromine, and iodine, other methods using milder halogenating agents are developed. Halogenation with such agents is most often used for compounds containing carbon—carbon multiple bonds, aromatic rings, and activated methyl and methylene groups. Hydrohalic acids and their Li, Na, and K salts in the combination with oxidants serve as the source of halogen. Hydrogen peroxide is especially efficient in the role of the oxidant (see review[1] and references sited therein). *tert*-Butyl peroxide,[2—4] a complex of hydrogen peroxide with urea,[5] and oxone[6,7] were also used. Among other oxidant, ceric ammonium nitrate (CAN) successfully used in many reactions of organic synthesis, including bromination reactions, also attracted the attention.[8] Thus, alkenes, cycloalkenes, alkenylarenes add bromine upon the action of CAN and KBr to be converted to the corresponding vicinal dibromides. Methyl 2,3-dibromo-3-phenylpropionate was obtained from methyl cinnamate[9]. Cinnamic acid itself under similar conditions decarboxylates to be converted to β-bromostyrene, no addition of bromine is observed in this case.[10] The solid-phase reactions of β-arylacrylic acids with CAN—LiBr also lead to β-bromostyrenes.[11] Alkylaromatic hydrocarbons undergo bromination in this oxidation system at the side chain,[12] whereas activated aromatic compounds are reacted at the aromatic ring.[13] In the cited works, CAN was exclusively used as a stoichiometric oxidant.

In the present work, we report the results on the bromination of aliphatic ketones upon the action of the oxidative systems H_2O_2—LiBr—$Ce(NH_4)_2(NO_3)_6$ (CAN) and H_2O_2—LiBr—$Ce(NO_3)_3 \cdot 6H_2O$ (cerium nitrate (CN)). The purpose of the work was to develop a new approach in the use of cerium salts in organic reactions, where the Ce^{IV} and Ce^{III} salt performed the function of the redox catalyst in the combination with the stoichiometric oxidant, hydrogen peroxide. We effected this approach for the first time in the oxidation of alkanols to esters by the system H_2O_2—LiBr—Ce^{III} (see Ref. 14) and in the bromination of alkenols to vicinal dibromoalkanols.[15] This approach resulted in the decrease of the consumption of expensive and not quite convenient (because of the high molecular weight) oxidant CAN, replacing it with the environmentally friendly and chip hydrogen peroxide.

The bromination of ketones was performed using three modifications: with the stoichiometric amount of CAN with respect to the ketone (procedure *A*), with the catalytic amount of CAN in the combination with H_2O_2 (procedure *B*), and with the catalytic amount of CN in the combination with H_2O_2 (procedure *C*). Bromine involved in the bromination reaction was generated from LiBr upon the action of Ce^{IV}. The Ce^{III} salt used as the starting reagent (or formed from Ce^{IV} in the course of the reaction) was oxidized by hydrogen peroxide to Ce^{IV}. Thus, several oxidation-reduction cycles were subsequently repeated involving Ce^{IV} salt as the redox catalyst in the bromination process (Scheme 1). The steps of this cycle we described in the preceding publications.[14,16,17]

Scheme 1

$$Ce^{IV} \xrightarrow{Br^-} Ce^{III} \xrightarrow{H_2O_2} Ce^{IV}$$

Hydrogen bromide formed in the bromination reaction together with α-bromoketone was oxidized by hydrogen peroxide and Ce^{IV} salt to bromine. Under the optimal

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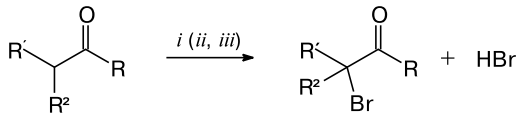
conditions, the conversion of LiBr and the yields of α-bromoketones were close to the quantitative.

Six C_5—C_{11} linear and branched ketones (**1a—f**) were chosen as the objects of our studies (Scheme 2, Tables 1 and 2).

Scheme 2



1a—f **2a—f**

i. CAN, LiBr (*A*); *ii*. CAN_{cat}, H_2O_2, LiBr (*B*); *iii*. CN_{cat}, H_2O_2, LiBr (*C*)

a: R = Et, R′ = H, R″ = Me; **b:** R = Pr, R′ = H, R″ = Et; **c:** R = Bu, R′ = H, R″ = Pr; **d:** R = Am, R′ = H, R″ = Bu; **e:** R = Bu^t, R′ = R″ = H; **f:** R = Pr^i, R′ = R″ = Me

Dibutylketone (**1c**) was chosen as a model compound to study the dependence of the conversion and the yields of 4-bromononan-5-one (**2c**) from the procedure of bromination (*A*, *B*, *C*) and the ratio of reagents (see Table 1). The selection of the bromination conditions was considerably determined by the purpose to obtain high yields of α-bromoketones with the high conversion of the starting reagents and simple experimental procedure, *i.e.*, the purpose to develop a procedure easily adapted for the use in the preparative syntheses.

Table 1. Bromination of ketone **1c** by the system H_2O_2—LiBr—Ce^{III}/Ce^{IV}[a]

Entry	Molar ratio **1c** : Ce : LiBr : H_2O_2 : H_2SO_4	Ce^{III}/Ce^{IV}	Conversion of **1c**	Yield[b] of **2c**
			%	
1	1 : 0 : 1 : 0 : 1	—	—	—
2	1 : 0 : 1 : 10 : 1	—	—	—
	Procedure *A*			
3	1 : 2.5 : 1 : 0 : 0	Ce^{IV}	50	45
4	1 : 2.5 : 1 : 0 : 0.1	Ce^{IV}	73	73
5	1 : 2.5 : 1 : 0 : 0.2	Ce^{IV}	98	95
6	1 : 2.5 : 1 (HBr) : 0 : 0	Ce^{IV}	90	85
	Procedure *B*			
7	1 : 0.3 : 1 : 5 : 0	Ce^{IV}	45	45
8	1 : 0.3 : 1 : 10 : 0	Ce^{IV}	75	73
9	1 : 0.3 : 1 : 10 : 0.1	Ce^{IV}	75	75
10	1 : 0.3 : 1 : 10 : 0.2	Ce^{IV}	92	90
11	1 : 0.3 : 1 : 5 : 0.2	Ce^{IV}	60	60
12	1 : 0.2 : 1 : 10 : 0.2	Ce^{IV}	56	56
	Procedure *C*			
13	1 : 0.3 : 1 : 10 : 0.2	Ce^{III}	78	75

[a] Reaction conditions: **1c** (1 mmol), CH_3CN (10 mL), 65—70 °C, 5—6 h (procedure *A*) or 10—12 h (procedures *B* and *C*), Ce^{III} is $Ce(NO_3)_3 \cdot 6H_2O$, Ce^{IV} is $Ce(NH_4)_2(NO_3)_6$.
[b] Calculated based on the amount of ketone **1c** taken for the reaction.

Table 2. Bromination of ketones **1a—f** by the system H_2O_2—LiBr—Ce^{III}/Ce^{IV}[a]

Ketone **1a—f**	Procedure	Conversion of **1a—f** (%)	Product	Yield[b] of **2a—f** (%)
EtCOEt (**1a**)	*A*	99	EtCOCHBrMe (**2a**)	97
1a	*B*	97	**2a**	96
1a	*C*	96	**2a**	95
PrCOPr (**1b**)	*A*	95	PrCOCHBrEt (**2b**)	92
1b	*B*	93	**2b**	90
1b	*C*	93	**2b**	89
BuCOBu (**2c**)	*A*	98	BuCOCHBrPr (**2c**)	95
2c	*B*	92	**2c**	90
2c	*C*	78	**2c**	75
AmCO C_5H_{11} (**1d**)	*A*	95	AmCOCHBrBu (**2d**)	93
1d	*B*	93	**2d**	90
1d	*C*	65	**2d**	65
Bu^tCOMe (**1e**)	*A*	95	Bu^tCOCH$_2$Br (**2e**)	94
1e	*B*	97	**2e**	95
1e	*C*	96	**2e**	95
Pr^iCOPr^i (**1f**)	*A*	85	Pr^iCOCBrMe$_2$ (**2f**)	83
1f	*B*	63	**2f**	60
1f	*C*	45	**2f**	40

[a] Reaction conditions: **1a—f** (1 mmol), the molar ratio **1** : Ce^{IV} : LiBr : H_2O_2 : H_2SO_4 = 1 : 2.5 : 1 : 0 : 0.2 (*A*), **1** : Ce^{IV} : LiBr : H_2O_2 : H_2SO_4 = 1 : 0.3 : 1 : 10 : 0.2 (*B*), **1** : Ce^{III} : LiBr : H_2O_2 : H_2SO_4 = 1 : 0.3 : 1 : 10 : 0.2 (*C*), CH_3CN (10 mL), 65—70 °C, 5—6 h and 10—12 h (procedure *A* and procedure *B*, respectively), 10—12 h (procedure *C*), Ce^{III} is $Ce(NO_3)_3 \cdot 6H_2O$, Ce^{IV} is $Ce(NH_4)_2(NO_3)_6$.
[b] Calculated based on the amount of ketones **1a—f** taken for the reaction.

Procedure *A* (stoichiometric amount of CAN, see Table 1, entries *3—6*). In the absence of CAN, lithium bromide cannot generate bromine upon the action of only H_2O_2 or only H_2SO_4, thus failing to cause the bromination reaction of ketone **1c** (entries *1*, *2*). At the molar ratio **1c** : CAN : LiBr = 1 : 2.5 : 1, the conversion of **1c** and the yield of bromoketone **2c** were 50 and 45%, respectively. When sulfuric acid was added to the oxidation system in the amount of 0.2 mol per 1 mol of LiBr, these values increased almost twofold (entries *3—5*). The effect of sulfuric acid is primarily explained by the increase in the oxidative efficiency of CAN in the acidic medium.[18] Moreover, the reaction of sulfuric acid with LiBr leads to the formation of hydrogen bromide, from which bromine is generated more readily upon the action of CAN than from LiBr. In fact, when LiBr was replaced by

HBr, both the conversion **1c** and the yield of **2c** were increased (entry *6*).

Procedure *B* (catalytic amount of CAN, see Table 1, entries *7—12*). At the molar ratio **1c** : CAN : LiBr : H_2O_2 = = 1 : 0.3 : 1 : 10, the index conversion of **1c**/yield of **2c** did not exceed 75/73%. Like in the procedure *A*, the introduction of 0.2 mol of H_2SO_4 per 1 mol of LiBr to the oxidation system leads to the increase in the conversion of ketone **1c** and the yield of bromoketone **2c** to 92 and 90%, respectively. A decrease in the amount of any of three components of the oxidation system, either sulfuric acid to 0.1 mol, or CAN to 0.2 mol, or H_2O_2 to 5 mol, resulted in the decrease of both the conversion of **1c** and the yield of **2c** (see Table 1, entries *9*, *11*, *12*).

Procedure *C* (catalytic amount of CN, see Table 1, entry *13*). Cerium nitrate as compared to CAN is less efficient in the role of the redox catalyst in the bromination reactions of ketones. At the molar ratio **1c** : Ce : LiBr : H_2O_2 : H_2SO_4 equal to 1 : 0.3 : 1 : 10 : 0.2, the conversion of **1c** and the yield of **2c** were 78 and 75%, respectively, that is 15% lower than in procedures *A* and *B*.

Ketones **1a**,**b**,**d—f** were brominated under the optimal conditions found for ketone **1c** (see Table 2). The use of procedures *A* and *B* resulted in the close indices of conversion of ketones **1a—f** (86—98%) and the yields of α-bromoketones **2a—f** (83—96%). Virtually the same results were also obtained for diethyl (**1a**), dipropyl (**1b**). and *tert*-butyl methyl ketone (**1e**) in the procedure *C*. However, procedure *C* has proved less efficient with respect to the three symmetric ketones **1c**,**d**,**f** containing butyl, pentyl, or isopropyl group sterically more hindered for the attack by bromine. Ketone **1f** was also harder to brominate than other ketones using procedures *A* and *B*. The reason is that bromine not only brominates ketones, but also facilitates a catalytic decomposition of hydrogen peroxide. As a result, the conversion of ketones to α-bromoketones decreases because of the decreased amount of H_2O_2 involved in this process. This is especially pronounced in the cases of ketones **1c**,**d**,**f**. At the same time, the yield of all the α-bromoketones **2a—f** (without exception) calculated based on the consumed in the reaction ketones **1a—f** remained similarly high and reached >95%, *i.e.*, the reaction proceeded with high selectivity.

In conclusion, without use of bromine or hydrogen bromide the reaction of ketones with the systems H_2O_2—LiBr—Ce^{III} and H_2O_2—LiBr—Ce^{IV} can be used for the solution of the problem of preparative synthesis of α-bromoketones.

Experimental

Reaction mixtures were analyzed by GLC on a LKhM-80 chromatograph with the flame-ionizing detector and analytical metal columns 2000×3 mm with 5% SE-30 and 5% FFAP on Chromaton N-AW-HMDS (0.16—0.20 mm). The yields of products were determined using an internal standard (pentan-2-one and hexan-2-one) with allowance for the experimentally found correction coefficients. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer under standard conditions in $CDCl_3$. Reaction products were isolated by column chromatography (silica gel L 40/100 μm, eluent heptane—ethyl acetate). The starting ketones (pentan-3-one, heptan-4-one, nonan-5-one, undecan-6-one, 2,4-dimethylhexan-3-one, 3,3-dimethylbutan-2-one), ceric ammonium nitrate $(Ce(NH_4)_2(NO_3)_6)$, cerium(III) nitrate hexahydrate $(Ce(NO_3)_3 \cdot 6H_2O)$, and hydrogen peroxide (35% aqueous solution)) were commercially available from Acros and were used without additional purification. Acetonitrile (pure grade) was distilled before use. Lithium bromide (pure grade) was calcined before use.

Bromination of ketones 1a—f by the system CAN—LiBr in MeCN (general procedure). A mixture of ketone **1**, CAN, and LiBr (for ratios of reagents, see Tables 1 and 2) in MeCN (10 mL) was vigorously stirred on a magnetic stirrer at 65—70 °C until the oxidant was completely converted (the change of the color from orange to light yellow). The reaction time was 5—6 h. The reaction mixture was extracted with diethyl ether (3×20 mL), the combined extracts were washed with $NaHCO_3$ and water, and dried with $MgSO_4$, the solvent was evaporated. The product yields and the conversion of ketones **1** were determined by GLC using an internal standard (see Tables 1 and 2). The reaction products were isolated by column chromatography.

Bromination of ketones by the systems H_2O_2—LiBr—Ce^{III} or H_2O_2—LiBr—Ce^{IV} in MeCN (general procedure). A solution of 35% aqueous H_2O_2 in MeCN (5 mL) was added in portions (by 0.2—0.3 mL) to a solution of ketone **1**, LiBr, and Ce^{III} or Ce^{IV} salt in MeCN (5 mL) at 65—70 °C with vigorous stirring over 10—12 h (for the ratio of reagents, see in Table 2). In the case of Ce^{IV}, an orange color appeared immediately after mixing ketone **1**, LiBr, and Ce^{IV}, which disappeared in 20—30 min. In the case of Ce^{III}, the color appeared after addition of the first portion of the H_2O_2 solution and disappeared also in 20—30 min. Each subsequent portion of H_2O_2 was added after discoloration of the reaction mixture . After all peroxide was added, the reaction mixture was cooled, extracted with diethyl ether (3×20 mL), washed with aq. $NaHCO_3$ and water, and dried with $MgSO_4$. The yield of the products was determined by GLC using an internal standard (see Table 2). The reaction products were isolated by column chromatography.

2-Bromopentan-3-one (2a) (*cf.* Ref. 17). ^{1}H NMR, δ: 1.09 (t, 3 H, CH_3, J = 7.3 Hz); 1.72 (d, 3 H, C<u>H</u>$_3$CHBr, J = 7.0); 2.59 (m, 2 H, CH_2); 4.40 (m, 1 H, CHBr). ^{13}C NMR, δ: 8.18 (CH_3); 20.15 (<u>C</u>H$_3$CHBr); 31.96 (CH_2); 47.31 (CHBr); 205.07 (CO).

3-Bromoheptan-4-one (2b) (*cf.* Ref. 17). ^{1}H NMR, δ: 0.91 (t, 3 H, CH_3, J = 7.0 Hz); 1.04 (t, 3 H, CH_3, J = 7.0 Hz); 1.60 (m, 2 H, CH_2); 1.97 (m, 2 H, C<u>H</u>$_2$Br); 2.35 (t, 2 H, C<u>H</u>$_2$CO, J = 7.3 Hz); 4.16 (t, 1 H, CHBr, J = 6.9 Hz). ^{13}C NMR, δ,: 11.97 (CH_3); 13.68 (CH_3); 17.30 (CH_2); 26.88 (<u>C</u>H$_2$Br); 40.91 (<u>C</u>H$_2$CO); 55.47 (CHBr); 204.16 (CO).

4-Bromononan-5-one (2c) (*cf.* Ref. 17). ^{1}H NMR, δ: 0.87 (t, 3 H, CH_3, J = 6.4 Hz); 0.94 (t, 3 H, CH_3, J = 6.4 Hz); 1.36 (m, 2 H, CH_2); 1.47 (m, 2 H, CH_2); 1.59 (m, 2 H, CH_2); 1.92 (m, 2 H, CH_2CHBr); 2.65 (t, 2 H, CH_2CO, J = 7.0 Hz); 4.24 (t, 1 H, CHBr, J = 7.1 Hz). ^{13}C NMR, δ: 13.29 (CH_3); 13.77 (CH_3); 20.61 (CH_2); 22.19 (CH_2); 25.99 (CH_2); 34.58 (<u>C</u>H$_2$CHBr); 42.70 (<u>C</u>H$_2$CO); 53.52 (CHBr); 204.34 (CO).

5-Bromoundecan-6-one (2d) (*cf.* Ref. 19). ^{1}H NMR, δ: 0.85 (t, 3 H, CH_3, J = 6.4 Hz); 0.93 (t, 3 H, CH_3, J = 6.4 Hz); 1.26—1.61 (m, 10 H, 5 CH_2); 1.92 (m, 2 H, C$\underline{H}_2$CHBr); 2.51 (t, 2 H, CH_2CO, J = 7.1 Hz); 4.2 (t, 1 H, CHBr, J = 7.0 Hz). ^{13}C NMR, δ: 13.71 (CH_3), 13.79 (CH_3), 22.05 (CH_2), 23.55 (CH_2), 29.40 (CH_2), 31.15 (CH_2), 34.28 ($\underline{C}H_2CHBr$), 42.65 ($\underline{C}H_2CO$), 53.68 (CHBr), 204.19 (CO).

1-Bromo-3,3-dimethylbutan-2-one (2e) (*cf.* Ref. 17). ^{1}H NMR, δ: 1.23 (s, 9 H, CH_3); 4.17 (s, 2 H, C$\underline{H}_2$BrCO). ^{13}C NMR, δ: 26.77 (3 CH_3), 31.64 (CH_2Br), 44.29 ($\underline{C}(CH_3)_3$), 206.19 (CO).

2-Bromo-2,4-dimethylpentan-3-one (2f) (*cf.* Ref. 17). ^{1}H NMR, δ: 1.28 (d, 6 H, 2 CH_3, J = 6.8 Hz); 1.82 (s, 6 H, 2 CH_3); 3.40 (m, 1 H, C$\underline{H}$CO). ^{13}C NMR, δ: 18.60 (CH_3), 18.67 (CH_3), 29.39 (CH_3), 29.42 (CH_3), 34.63 ($\underline{C}H(CH_3)_2$), 64.65 ($\underline{C}Br(CH_3)_2$), 210.02 (CO).

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