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Investigation on Oxidation of Cyclic Ketones and Synthesis of ω-Bromoalkanoic Acids

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Abstract: Various chain-lengths of ω-bromoalkyl carboxylic acids were synthesized from cyclic ketones of different ring size via the oxidation to ω-hydroxyalkyl carboxylic acids followed by bromine substitution of hydroxyl group. The oxidation was conducted in acidic condition or in alkaline condition followed by treatment with hydrobromic acid to achieve the bromine substitution.

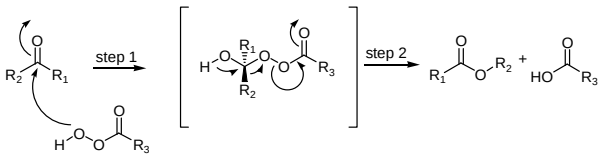
Keywords: cyclic ketones, hydroxyalkanoic acids, bromoalkanoic acids, hydrogen peroxide, and anti-SARS disinfectant.

Introduction

Since we have other applications of various chain-length of ω-bromoalkyl carboxylic acids in the preparation of cosmetic formulations, we chose to synthesize these compounds from cyclic ketones of different ring size via the oxidation to ω-hydroxyalkyl carboxylic acids followed by bromine substitution of hydroxyl group. According to the literature oxidation method [1] used for cyclohexanone, the cyclooctanone failed to afford the desired 8-hydroxyoctanoic acid but to yield 1,8-octanedioic acid instead. Therefore, we decided to examine the oxidation to other ring size of cyclic ketones including 5, 6, 7 and 8 member rings.

In 1899, Baeyer and Villiger [2] were the first one to report the oxidation of cyclic ketone to lactone using the peroxycarboxylic acid. The likely mechanism is believed to be depicted in the Scheme 1. Ever since there were several methods reported in the literature over few decades, however, a systematic study involving the oxidation of 5- to 8-membered ring ketones are lacking. Most methods used less practical reagents, such as pertrifluoroacteic acid, m-chloroperbenzoic acid with trifluoroacteic acid, 1,1,1,3,3,3-hexafluoro-2-propanol with hydrogen peroxide, bis(trimethylsilyl) peroxide with stannic chloride, and a combination of oxygen, benzaldehyde, magnesium oxide and copper [3-7].

Scheme 1. Reaction mechanism of ketone by peroxycarboxylic acid



With our earlier findings which differed from the literature results [1], we decided to undergo further examination of this oxidation

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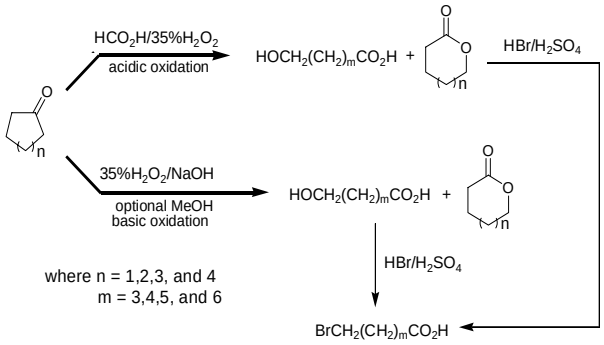
under various conditions as follows. The oxidation was conducted in (1) acidic condition consisting of formic acid and hydrogen peroxide and (2) alkaline condition consisting of aqueous sodium hydroxide, hydrogen peroxide and optional addition of methanol, respectively.

Results and Discussion

As indicated in the previous section, the oxidations were performed under acidic and basic condition for comparison whether one route is superior to the other. The general reaction routes were illustrated in Scheme 2.

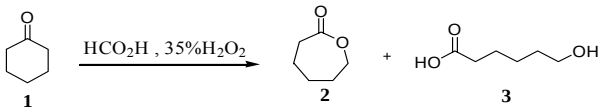
Scheme 2. Routes of reaction



After the oxidation of ketones by either conditions, the intermediate products were further treated with hydobromic acid with sulfuric acid [1] to afford ω-bromoalkyl carboxylic acids. This investigation included the variables, such as (1) reaction temperature, (2) stoichiometry, and (3) reaction time to determine the effect in product formations and yields as well.

Initially, we investigated the various usages of formic acid following the literature method [1]. The results were presented in Table 1.

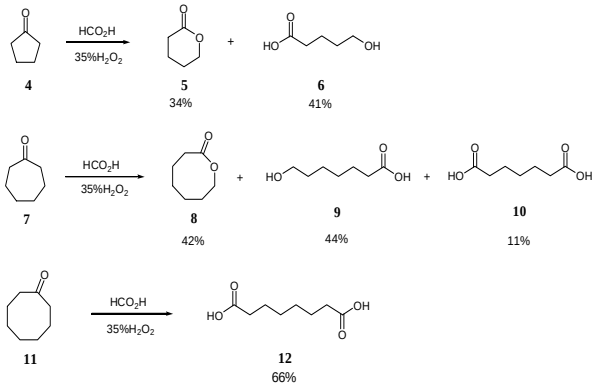
Table 1. Effects of formic acid usage on yield of product(s)



	1	HCO_2H	H_2O_2	2 : 3	Yield 2(%)	Yield 3(%)	Total (%)
Molar ratio	1	3.1	11.2	3.5 : 1	49	12	61
	1	6.2	11.2	2.5 : 1	41	16	57
	1	12.4	11.2	1.1 : 1	58	42	100
	1	24.8	11.2	1: 1.6	33	54	87

Thus, the molar ratio of ketone:formic:hydrogen peroxide at 1:12:11 was selected for other ketones for further investigation. Their results were presented in Scheme 3.

Scheme 3. Yields of oxidation products for other cyclic kentones



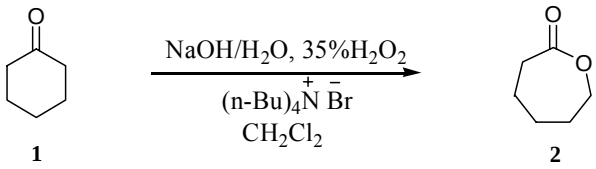
As shown in Scheme 3, the dioic acids, 10 and 12, were produced unexpectedly. As a result, the alternative route should be explored accordingly. Then, the oxidation under basic condition in a two-phase system consisting of aqueous and organic layers in the presence of phase transfer catalyst, tetrabutylammonium bromide, was conducted at various ratios of the reactants. The test results presented in Table 2 indicated no favorable improvement in this two-phase system. Therefore, the next attempt for oxidation was performed in the homogenous basic solution preferably.

Again, cyclohexanone was used for the initial examination for various ratios of reactants. Their test results depicted in Table 3 appeared more favorable than the earlier ones.

The ratio of ketone:NaOH: H_2O_2 at 1:4:4 was chosen for further investigation in other

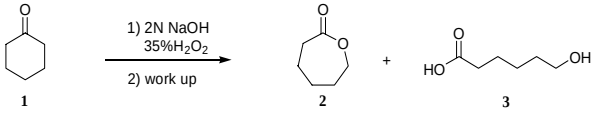
cyclic ketones. As noticed in early trial experiments for cycloheptanone and cyclooctanone, they were not soluble in water. As a result, their yields were disappointed and around 90% of starting materials were recovered. Therefore, methanol was used instead of water to achieve the homogenous system and a significant improvement was obtained. The results of these oxidations were presented in Scheme 4.

Table 2. Results of basic oxidation in phase transfer catalyzed two-phase system



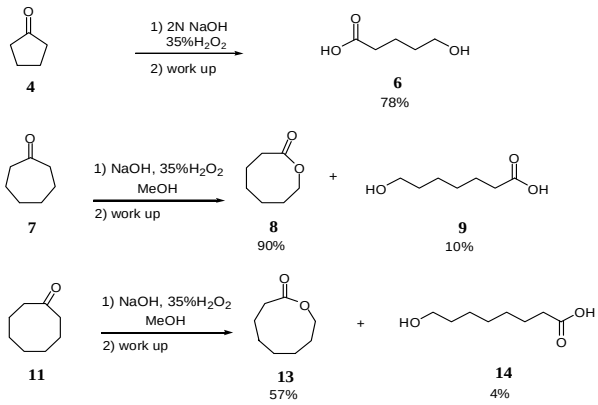
	1	NaOH	H_2O_2	Yield 2(%)
Molar ratio	1	2	2	12
	1	4	4	25
	1	8	8	42
	1	12	12	67

Table 3. Results of basic oxidation in homogenous system

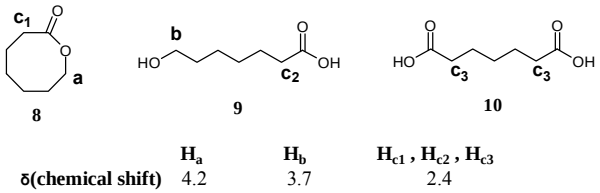


	1	NaOH	H_2O_2	2 : 3	Yield 2	Yield 3	Total
Molar ratio	1	2	4	2 : 1	53%	32%	85%
	1	4	4	1:0	100%	0%	100%

Scheme 4. Results of basic oxidation



It should be noted that the individual yield in a product mixture of lactone 8, and its open forms, 9 and 10 obtained from oxidation of 7 in Scheme 3 could be estimated from the integrals of its ^{1}H NMR spectrum since their chemical shifts of methylene proton next to carbonyl group and oxygen are significantly different. For example, the chemical shifts of relevant mehtylene groups are shown in Figure 1. The molar ratio of 8:9:10 is equal to the integral ratio of H_a:H_b:H_{c3}. Therefore, the yield of each component of products can be determined accordingly.

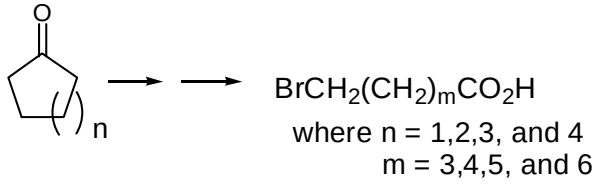


	H_a	H_b	H_{c1} , H_{c2} , H_{c3}
δ(chemical shift)	4.2	3.7	2.4

Figure 1. Chemical shifts of methylene groups in compounds 8, 9 and 10

Since the goal of our study is to prepare various bromoalkanoic acids, it was straight forward in transforming any mixture of lactone and its corresponding open form of hydroxyalkanoic acid to the target product with the treatment of hydrobromic acid and sulfuric acid. Their overall yields from cyclic ketones were summarized in Table 4.

Table 4. Overall yields of the 2-step transformation from cyclic ketones



Ketone	m	Bromoalkanoic acid	Overall Yield (%)
4	3	16	59
1	4	17	64
7	5	18	84
11	6	19	43

During the course of this investigation, the characterization of all products in any reactions was based on the spectral data including ^{1}H NMR and ^{13}C NMR mainly and IR spectra since all of the reaction products have been reported in the literatures.

Conclusion

We have examined three sets of oxidation, one in the acidic solution and the other two in basic solution. Under the basic condition in a homogenous aqueous solution or aqueous methanol, the results appeard to be the best. Particularly, when the starting materials, cycloheptanone and cyclooctanone, are not soluble in water, methanol is used predominately in solution to assure the superior overall results. Then, the oxidation products, lactone and/or its open form, can be readily converted into bromoalkanoic acid without further separation or purification.

It is worth noting that cycloocatnone can selectively afford either dioic acid 12 under acidic oxidation or hydroxyalkanoic acid 14 under basic oxidation. The compound 14 is also known as anti-SARS disinfectant in a spray.

Experimental

NMR spectra were obtained at 200MHz in $CDCl_3$ solvent(unless otherwise noted), and chemical shifts were reported in δ ppm.

Melting points are uncorrected. IR spectra were obtained by Perkin Elmer Paragon 500 and reported in wave number. All raw materials were used as received (unless otherwise noted).

General procedure for preparation for hydroxyalkanoic acids in the acidic solution

A mixture of formic acid (77 mmol) and 35% hydrogen peroxide (70 mmol) was prepared jn 5-10 min. prior to the addition of cyclic ketone. Cyclic ketone (6.2 mmol) was added dropwise at room temperature. After addition, the resulting solution was stirred for 24-hour at ambient temperature. Water (10 mL) was added and the solution was extracted with ethyl acetate (3X10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the product.

Tetrahydro-pyran-2-one (5) [8] & 5-Hydroxy-pentanoic acid (6) [9]

IR (film) cm^{-1}: 3206(OH), 2956(CH_2), 1731(C=O), 1167(C-O); ^{1}H NMR δ : 4.19~4.09 (4H, m), 2.50~2.32(4H, m), 1.74~1.70 (8H, m); Yield: 41%.

Oxepan-2-one (2) [8] & 6-Hydroxy-hexanoic acid (3) [11]

IR (film) cm-1: 3225(OH), 2944(CH_2), 1732(C=O), 1167(C-O); ^{1}H NMR δ : 4.18 (2H, t, J=6.5Hz), 3.67 (2H, t, J=6.4Hz), 2.39 (4H, t, J=6.7Hz), 1.72~1.39 (8H, m); Yield: 58% of 2; 42% of 3.

Oxocan-2-one (8) [13], 7-Hydroxy-heptanoic acid (9) [14] & Heptanedioic acid (10) [15]

IR (film) cm^{-1}: 3215(OH), 2945(CH_2), 1724(C=O), 1462(CH_2), 1414(CH_2), 1194(C-O); ^{1}H NMR δ: 4.16 (4H, t, J=6.6Hz), 3.65 (4H, t, J=6.5Hz), 2.36 (12H, t, J=7.4Hz), 1.96~1.25 (14H, m); Yield: 42% of 8, 44% of 9, 11% of 10.

Octanedioic acid (12) [16]

IR (film) cm^{-1}: 3230(OH), 2928(CH_2), 1700(C=O), 1465(CH_2); ^{1}H NMR δ: 2.92 (br, OH), 2.26 (4H, t, J=7.4Hz), 1.61~1.55 (4H, m), 1.35~1.29 (4H, m); ^{13}C NMR δ: 176.5, 33.6, 28.4, 24.3; mp: 131~133^{0}C (lit[16] mp:138~139^{0}C); Yield: 66%.

General procedure for preparation for

hydroxyalkanoic acids in the basic solution

To a solution of sodium hydroxide (40 mmol) dissolved in water (3.5 mL) at ambient temperature, cyclic ketone (10 mmol) was added. Then, 35% hydrogen peroxide (40 mmol) was dropwise. The resulting solution was stirred for 24-hour at ambient temperature. Water (15 mL) was added and then, 12 N hydrochloric acid was added to give an acidic pH. The solution was extracted with ethyl acetate (3X15 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford product.

5-Hydroxy-pentanoic acid (6)[9]

IR (film) cm^{-1}: 3288(OH), 2925(CH_2), 1715(C=O), 1410(CH_2); ^1H NMR δ : 4.05 (2H, m), 2.42 (2H, m), 1.78~1.69 (4H, m); Yield: 78%.

Oxepan-2-one (2) [8]

IR (film) cm^{-1}: 2945(CH_2), 1714(C=O), 1405(CH_2), 1172(C-O); ^1H NMR δ : 4.03 (2H, t, J=6.3Hz), 2.38 (2H, t, J=7.2Hz), 1.68 (2H, m), 1.43 (4H, m); Yield: 100%.

Oxocan-2-one (8) [13]**, 7-Hydroxy-heptanoic acid (9)** [14]

IR (film) cm^{-1}: 3206(OH), 2933(CH_2), 1714(C=O), 1410(CH_2), 1224(C-O)。
^1H NMR δ: 4.02 (2H, t, J=6.5Hz), 3.66(2H, t, J=6.4Hz), 2.36 (4H, t, J=7.3Hz), 1.68~1.59 (8H, m), 1.48~1.29 (8H, m); Yield: 90% of **8**; 10% of **9**.

Oxonan-2-one (13) [18] **&**
8-Hydroxy-octanoic acid (14) [14]

IR (film) cm^{-1}: 3311(OH), 2934(CH_2), 1712(C=O), 1414(CH_2), 1257(C-O)。
^1H NMR δ: 4.01 (2H, t, J=6.5Hz), 3.65 (2H, t), 2.35 (4H, t, J=7.4Hz), 1.67~1.35 (20H, m); Yield: 57% of 13, 4% of 14.

General procedure for preparation for bromoalkanoic acids

To round-bottom flask, hydroxyalkanoic acid and/or its lactone (4.52 mmol) and 48% hydrobromic acid (6.8 mmol) were charged. 98% sulfuric acid (3.6 mmol) was added drop- wise. The resulting solution was refluxed for 12-hour and allowed to cool to ambient temperature. Water (60mL) was added and extracted with ethyl acetate (3X30mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated on rotary evaporator under vacuum to afford the product.

5-Bromo-pentanoic acid (16) [9]

IR (film) cm^{-1}: 3206(OH), 2964(CH_2), 1732(C=O), 1443(CH_2), 1201(C-O);
^1H NMR δ : 3.43 (2H, t, J=4.3Hz), 2.41 (2H, t, J=7.1Hz),1.97~1.75 (4H, m)。
^{13}C NMR δ : 179.6, 33.0, 32.9, 31.8, 23.1; mp: 38.3~40℃ (lit[9] mp:42.5℃);
Yield: 75-80%.

6-Bromo-hexanoic acid (17) [12]

IR (film) cm^{-1}: 3129(OH), 2941(CH_2), 1714(C=O), 1413(CH_2), 1258(C-O)。
^1H NMR δ: 3.42 (2H, t, J=6.7Hz), 2.39 (2H, t, J=7.2Hz), 1.89 (2H, m), 1.66 (2H, m), 1.51 (2H, m)。^{13}C NMR δ : 179.6, 33.8, 33.3, 32.3, 27.6, 23.8 mp: 33.2~35.1 ℃ (lit[12] mp:31.2~31.8℃) Yield: 64-71%.

7-Bromo-heptanoic acid (18) [17]

IR (film) cm^{-1}: 3210(OH), 2936(CH_2), 1714(C=O), 1410(CH_2), 1254(C-O)。
^1H NMR δ: 3.40 (2H, t, J=6.8Hz), 2.37 (2H, t, J=7.3Hz), 1.83 (2H, m), 1.61 (2H, m), 1.42

(4H, m)。^{13}C NMR δ : 179.6, 33.8, 33.6, 32.5, 28.1, 27.8, 24.4; Yield: 84%

8-Bromo-octanoic acid (19) [19]

IR (film) cm^{-1}: 3110(OH), 2934(CH_2), 1713(C=O), 1412(CH_2), 1244(C-O); ^{1}H NMR δ: 3.40 (2H, t, J=6.7Hz), 2.36 (2H, t, J=7.4Hz), 1.85 (2H, m), 1.64 (2H, m), 1.38(6H, m); ^{13}C NMR δ: 179.9, 33.9, 32.7, 28.8, 28.4, 27.9, 24.5; mp: 34~36℃ (lit[19] mp:34~36℃); Yield: 70%.

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References

[1] Sankaranarayanan, S. and Chattopadhyay, S. 1998. Asymmetric synthesis of a cytotoxic amide of *Telesto riisei Tetrahedron Asymmetry*, 9: 1345-1350.

[2] Plesnicar, B. 1978. *"In Trahanovsky oxidation in organic chemistry"*, Academic Press, New York, Part C: 254-267.

[3] Sager, W. F. and Duckworth, A. 1955. Oxidative ring enlargement of cyclic ketones by peroxytrifluoroacetic acid. *Journal of the American Chemical Society*, 77: 188-190.

[4] Koch, S. S. C. and Chamberlin, A. R. 1989. Modified conditions for efficient Baeyer-Villiger oxidation with m-chloroperoxybenzoic acid. *Synthetic Communications*, 19: 829-833.

[5] Neimann, K. and Neumann, R. 2000. Electrophilic Activation of Hydrogen Peroxide: Selective Oxidation Reactions in Perfluorinated Alcohol Solvents. *Organic Letters*, 2: 2861-2863.

[6] Matsubara, S., Takai, K., and Nozaki, H. 1983. Baeyer-Villiger oxidation with bis(trimethylsilyl) peroxide ($Me_3SiOOSiMe_3$) under assistance of tin(IV) chloride or boron fluoride-ethyl ether complex ($BF_3.OEt_2$). *Bulletin Chemical Society Japanese*, 56: 2029-2032.

[7] Yan, Y. Y., Dong, L. M., Guo, J. P., Huang, M. Y., and Jiang, Y. Y. 1997. Magnesium oxide-supported polytitanazane copper(II) complex catalyzed aerobic Baeyer-Villiger oxidation of ketones and cyclohexanol in the presence of benzaldehyde. *Journal of Macromolecular Science*, 34: 1097-1104.

[8] Hao, X., Yamazaki, O., Yoshida, A., and Nishikido, J. 2003. Green Baeyer-Villiger oxidation with hydrogen peroxide: $Sn[N(SO_2C_8F_{17})_2]_4$ as a highly selective Lewis acid catalyst in a fluorous biphase system. *Green Chemistry,* 5: 524-528.

[9] Aleman, C., Casanovas, J., Zanuy, D., and Hall, H. K. Jr. 2005. Systematic evaluation of the conformational properties of alphaticω-hydroxy acids. *Journal of Organic Chemistry*, 70: 2950-2956.

[10] Olah, G. A., Narang, S. C., and Mehrotra, A. K. 1982. Synthetic methods and reactions; Cleavage of ethanediyl S, S-acetals with iodo (bromo) trimethylsilane/dimethyl sulfoxide. *Synthesis*, 11: 965-966.

[11] Kanemitsu, T., Wong, C. H., and Kanie, O. 2002. Solid-Phase Synthesis of Oligosaccharides and On-Resin Quantitative Monitoring Using Gated Decoupling ^{13}C NMR. *Journal of the American Chemical Society*, 124: 3591-3599.

[12] Zinkevich, E. P., Treboganov, A. D., Genokhova, N. S., Sarycheva, I. K., and Preobrazhenskii, N. A. 1966. Macrocyclic compounds. VII. Synthesis of cyclopentadecanone(exaltone) and pentadecanolide(tibetolide). *Zhurnal Organicheskoi Khimii,* 2: 2028-2031.

[13] Solladie, G., Rubio, A., Carreno, M. C., and Garcia Ruano, J. L.1990. Asymmetric synthesis of orsellinic acid type macrolides: The example of lasiodiplodin. *Tetrahedron. Asymmetry,* 3: 187-198.

[14] W Kenneth, B. and Roy, F. W. 1991. Lactones 2. Enthalpies of hydrolysis, reduction, and formation of the C_4-C_{13} monocyclic lactones. Strain energies and conformations. *Journal of the American Chemical Society,* 113: 7697-7705.

[15] Ruholl, H. and Schaefer, H. J. 1988. Oxidative cleavage of vicinal diols at the nickel hydroxide electrode. *Synthesis*, 1: 54-56.

[16] Habib, R. M., Chiang, C. Y, and Bailey, P. S. 1984. Dicarboxylic acids from ozonnalysis of cycloalkenes. *Journal of Organic Chemistry*, 49: 2780-2784.

[17] Rao, A. V. R., Krishnappa, S., Reddy, K. L. Narasimha, Reddy, K. Ashok, Reddy, and Pulla, S. 1986. Strategy and construction of macrocyclic compounds. VII. Synthesis of the backbone bistetrahydrofuran system for synthesis of rollinicin. *Synthetic Communications*, 16: 1141-1148.

[18] Pawar, D. M., Moody, E. M., and Noe, E. A. 1999. Conformational Study of Oxacyclooctan-2-one by Dynamic NMR Spectroscopy and Computational Methods. *Journal of Organic Chemistry*, 64: 4586-4589.

[19] Ames, D. E., and Islip, P. J. 1961. Syntheses of long-chain acids. II. Synthesis of linoleic acid. *Journal Chemical Society*, 4409-4412.