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Free Radical Addition of 2-Bromoalkanoic Acids to Alkenes

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The benzoyl peroxide-catalyzed reaction of 2-bromoalkanoic acids such as bromoacetic, 2-bromopropionic, and 2-bromobutyric acid with 1-alkenes was found to proceed through the addition of the C–Br bond across the double bond followed by cyclization affording 4-alkanolides in good yields.

There has been considerable interest in the construction of γ-butyrolactone skeleton, since γ-butyrolactones act as precursors for biologically active α,β-butenolides[1] or 2-methylene-4-alkanolides,[2] and are sometimes used for flavor and additive for foods.[3]

Although a variety of synthetic methods for the construction of γ-butyrolactone skeleton have been reported,[4] we present in this paper a convenient method for the construction of γ-butyrolactone structure which is easily accomplished by the reaction of a 2-bromoalkanoic acid with simple alkenes in the presence of benzoyl peroxide.[5]

Experimental

Boiling points are uncorrected. GLC analysis was performed on an Ohkura Model 802 instrument equipped with a thermal conductivity detector and 6 mmϕ×1—2 m columns packed with Celite 545AW (60—80 mesh) coated with Silicone DCQF-1 (20%). The yields determined by GLC were corrected with thermal conductivity coefficients. IR spectra were recorded on a Jasco A 102 spectrophotometer, and ^{1}H NMR spectra were obtained on a Varian Associate Model EM-360 spectrometer. Chemical shifts(δ) are given in ppm relative to tetramethylsilane as an internal standard. Abbreviations for multiplicity are t; triplet and m; multiplet. Di-*t*-butyl peroxide[6] and the ruthenium(II) complex[7] were prepared according to literature directions. Benzoyl peroxide (BPO), 2,2′-azobisisobutyronitrile (AIBN), copper(I) chloride, bromoacetic acid, 2-bromopropionic acid, and 2-bromobutyric acid were commercially available and used without further purification. Alkenes were purchased commercially and distilled from calcium hydride prior to use. Known 4-alkanolides obtained in the present work were identified by comparing their physical properties with those of an authentic sample, and for the new compounds, structural determination was made by elementary analysis as well as spectral analysis. All of the physical data for the new compounds are compiled in Table 3.

BPO-, DTBP-, and AIBN-Catalyzed Reactions Were Carried Out as Follows. To a refluxing mixture of bromoacetic acid (12 mmol), 1-octene (10 mmol), and benzene (15 ml) was added with stirring a solution of a catalyst (1—2 mmol) in benzene (15 ml) during 1 h under nitrogen. After the addition was completed, the resulting mixture was refluxed for additional 5—15 h and then subjected to GLC analysis.

CuCl-Catalyzed Reaction. A mixture of bromoacetic acid (12 mmol), 1-octene (10 mmol), acetonitrile (4 ml), and copper(I) chloride (0.6 mmol) was introduced into a glass ampoule. The mixture was degassed through several freeze-evacuate-thaw cycles prior to sealing in vacuo. Then, the sealed ampoule was kept at 80 °C for 12 h. GLC analysis of the resulting mixture disclosed that the expected γ-butyrolactone (**3**) was not produced at all. The starting materials were recovered.

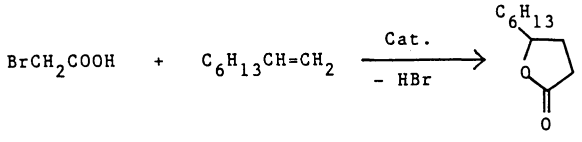
$RuCl_2(PPh_3)_3$-Catalyzed Reaction. A mixture of bromoacetic acid (12 mmol), 1-octene (10 mmol), and the ruthenium(II) complex (0.18 mmol) was heated at reflux for 10 h under argon. GLC analysis of the resulting mixture showed that the alkene was consumed in 41% and the lactone (**3**) was formed in 30% yield.

A Typical Example for the Synthesis of 4-Alkanolides. 2-Methyl-4-nonanolide (7): To a refluxing mixture of 2-bromopropionic acid (19.6 g, 128 mmol), 1-heptene (9.8 g, 100 mmol), and benzene (30 ml) was added with stirring a solution of BPO (3.6 g, 15 mmol) in benzene (45 ml) during 1 h under nitrogen. The reflux was further continued for additional 9 h. The resulting mixture was washed with water and dried with magnesium sulfate. Distillation of the mixture gave 13.0 g (78% yield) of **7**.

Results and Discussion

Initially, catalytic activity of several catalysts such as benzoyl peroxide, di-*t*-butyl peroxide, azobisiso-

Table 1. Comparison of Catalysts for the Construction of γ-Butyrolactone[a)]



Catalyst/mol%[b)]	Conditions	Conv./%[c)]	Yield/%[d)]
BPO (10)	80 °C, 6 h	77	77
DTBP (20)	130 °C, 16 h	85	29
AIBN (10)	80 °C, 9 h	0	0
CuCl (6)	80 °C, 12 h	0	0
Ru (II)	130 °C, 10 h	41	30

a) A 1.2 : 1 mixture of bromoacetic acid and 1-octene was used. b) Based on the alkene charged. c) Conversion of 1-octene. d) Determined by GLC. Based on the alkene charged.

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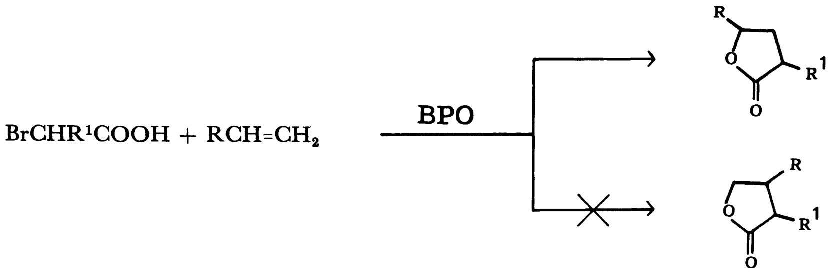
butyronitrile, copper(I) chloride, and dichlorotris(triphenylphosphine)ruthenium(II) complex toward the reaction of bromoacetic acid with 1-octene was investigated. The results are summarized in Table 1 which shows that benzoyl peroxide is the most favorable catalyst. BPO-catalyzed reactions of 2-bromoalkanoic acids (bromoacetic, 2-bromopropionic, and 2-bromobutyric acid) with some 1-alkenes were carried out, the results being shown in Table 2. As is clearly seen from the Table, the reaction of bromoacetic acid with 1-alkenes afforded the corresponding γ-butyrolactones in 65—77% yields. In each reaction, a small amount of debrominated carboxylic acid (2—3% yield) was produced as a by-product, but γ-butyrolactones could be readily isolated by means of simple fractional distillation. Similarly, the reactions of 2-bromopropionic and 2-bromobutyric acid with 1-alkenes gave the corresponding 2-methyl- or 2-ethyl-4-alkanolides in 50—80% yields.

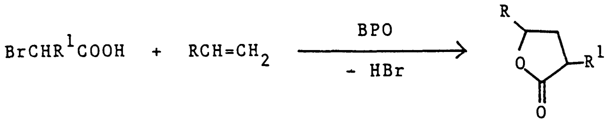
In these reactions, the Markownikoff-type products, $RCH(OOCHBrR^1)CH_3$, were not detected to any appreciable extent. In all cases the γ-butyrolactones thus obtained possess an alkyl group in the γ-position only (Eq. 1).



(1)

The observed regioselectivity is in accord with the finding of Kharasch et al. that carbon–carbon bond formation in the reaction of bromoacetic acid with 1-hexene takes place exclusively on the terminal carbon atom of the alkene under free radical conditions (vide post, Eq. 9).[8] In the reaction of 2-bromopropionic and 2-bromobutyric acid with 1-alkenes, the formation of two geometrical isomers (cis

Table 2. Yields and Boiling Points of γ-Butyrolactones[a]



Alkene	Acid[R¹]	Product[R]	Yield/%[b]	Bp(°C/mmHg)	No.
1-Hexene	H	C_4H_9	68(65)	82/2.5	[1][c]
1-Heptene	H	C_5H_{11}	71(69)	100/0.12	[2][d]
1-Octene	H	C_6H_{13}	74(68)	97/0.6	[3][e]
1-Nonene	H	C_7H_{15}	70(58)	129/3	[4][f]
1-Decene	H	C_8H_{17}	77(54)	111/0.35	[5][c]
1-Hexene	CH_3	C_4H_9	64	81/0.12	[6][g]
1-Heptene	CH_3	C_5H_{11}	80(78)	83/0.2	[7][h]
1-Octene	CH_3	C_6H_{13}	79(45)	100/1	[8][e]
1-Nonene	CH_3	C_7H_{15}	78(53)	100/0.3	[9]
1-Decene	CH_3	C_8H_{17}	72(63)	111/0.3	[10][i]
1-Hexene	CH_2CH_3	C_4H_9	60(54)	107/6	[11]
1-Heptene	CH_2CH_3	C_5H_{11}	72(50)	90/0.15	[12]
1-Octene	CH_2CH_3	C_6H_{13}	50	109/0.3	[13][e]
1-Nonene	CH_2CH_3	C_7H_{15}	67(53)	110/0.3	[14]
1-Decene	CH_2CH_3	C_8H_{17}	73(45)	119/0.3	[15]

a) To a refluxing 1.2 : 1 benzene solution of a 2-bromoalkanoic acid and an alkene was added with stirring a solution of BPO(0.1 equiv) in benzene during 1 h. Then, the mixture was heated for 5—9 h. b) Determined by GLC. In parentheses are shown isolated yields. c) See Ref. 10). d) See Ref. 11). e) See Ref. 12). f) See Ref. 13). g) See Ref. 14). h) See Ref. 15). i) See Ref. 16).

Table 3. Physical Properties of New γ-Butyrolactones

Lactone No.	IR($\nu_{C=O}$)	^{1}H NMR (δ, ppm)	Elemental Analysis[a] C	H
[9]	1775	4.26(m, 1H, -O-C-H), 2.33(m, 3H, =CHH, -COC$\underline{H}$(CH$_3$)-), 1.15(m, 15H, -(CH$_2$)$_6$-, -COCH(C$\underline{H}_3$)-), 0.92(t, 3H, -CH$_3$)	73.11 (72.68	11.29 11.18)
[11]	1770	4.22(m, 1H, -O-C-H), 2.27(m, 3H, =CHH, -COC$\underline{H}$(CH$_2$-CH$_3$)-), 1.57(m, 8H, -(CH$_2$)$_3$-, -COCH(C$\underline{H}_2$CH$_3$)-), 0.87(m, 6H, -CH$_3$, -COCH(CH$_2$C$\underline{H}_3$)-)	70.55 (70.55	10.66 10.66)
[12]	1770	4.17(m, 1H, -O-C-H), 2.25(m, 3H, =CHH, -COC$\underline{H}$(CH$_2$-CH$_3$)-), 1.54(m, 10H, -(CH$_2$)$_4$-, -COCH(C$\underline{H}_2$CH$_3$)-), 0.93(m, 6H, -COCH(CH$_2$C$\underline{H}_3$), -CH$_3$)	71.36 (71.70	11.01 10.94)
[14]	1770	4.34(m, 1H, -O-C-H), 2.33(m, 3H, =CHH, -COC$\underline{H}$(CH$_2$-CH$_3$)-), 1.62(m, 14H, -(CH$_2$)$_6$-, -COCH(C$\underline{H}_2$CH$_3$)-), 1.00(m, 6H, -COCH(CH$_2$C$\underline{H}_3$)-, -CH$_3$)	73.75 (73.54	11.34 11.39)
[15]	1770	4.23(m, 1H, -O-C-H), 2.27(m, 3H, =CHH, -COC$\underline{H}$(CH$_2$-CH$_3$)-), 1.57(m, 16H, -(CH$_2$)$_7$-, -COCH(C$\underline{H}_2$CH$_3$)-), 0.91(m, 6H, -COCH(CH$_2$C$\underline{H}_3$)-, -CH$_3$)	74.05 (74.29	11.54 11.58)

a) In parentheses are shown calculated values.

and trans) is possible. For example, ^{13}C NMR analysis revealed 2-methyl-4-octanolide (**6**) thus obtained to be a mixture of two geometrical isomers,[9] although isomer ratio was not ultimately determined.

A plausible pathway leading to γ-butyrolactone involves the free radical addition of a 2-bromoalkanoic acid to an alkene through the rupture of the C–Br bond to give the expected 1 : 1 adduct followed by subsequent cyclization. Thus, the formation of the 4-bromoalkanoic acid [**C**] is simply explained in terms of a free-radical chain process, involving the two chain-carrying species [**A**] and [**B**] (Eqs. 5 and 6).

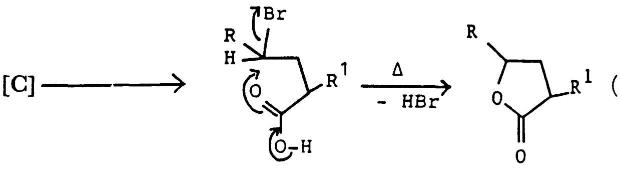
$$\mathrm{BPO} \longrightarrow 2\,\mathrm{PhCOO}\cdot \qquad (2)$$

$$\mathrm{PhCOO}\cdot \longrightarrow \mathrm{Ph}\cdot + \mathrm{CO_2} \qquad (3)$$

$$\mathrm{Ph}\cdot + \mathrm{BrCHR^1COOH} \longrightarrow \mathrm{PhBr} + \underset{[\mathrm{A}]}{\cdot\mathrm{CHR^1COOH}} \qquad (4)$$

$$[\mathrm{A}] + \mathrm{RCH{=}CH_2} \longrightarrow \underset{[\mathrm{B}]}{\mathrm{R\underset{\cdot}{C}HCH_2CHR^1COOH}} \qquad (5)$$

$$[\mathrm{B}] + \mathrm{BrCHR^1COOH} \longrightarrow \mathrm{RCHBrCH_2CHR^1COOH} + [\mathrm{A}] \qquad (6)$$
$$[\mathrm{C}]$$



(7)

Ring closure of the adduct [**C**] with liberation of hydrogen bromide can be most conveniently interpreted by the intramolecular nucleophilic substitution (Eq. 7). Formation of the debrominated adducts is elucidated in terms of the attack of [**B**] on the labile allylic hydrogens in 1-alkenes, HS, (Eq. 8).


$$[\mathrm{B}] + \mathrm{HS} \longrightarrow \mathrm{R\underset{\displaystyle H}{\underset{|}{C}}HCH_2CHR^1COOH} + \cdot\mathrm{S} \qquad (8)$$

In fact, Kharasch et al.[8] reported that the photolysis of bromoacetic acid in excess 1-hexene yielded octanoic acid in 80% yield (Eq. 9).

$$\mathrm{BrCH_2COOH} + \mathrm{C_4H_9CH{=}CH_2} \xrightarrow{h\nu} \mathrm{C_7H_{15}COOH} \qquad (9)$$

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