Organic Chemistry

Synthesis of ω- and (ω − 1)-acetylenic acids from five-, six-, or seven-membered cycloalkanones

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A convenient method for the synthesis of ω- and (ω − 1)-acetylenic acids involves free-radical oxidative scission of cycloalkanones containing five-, six, or seven-membered cycles to give the corresponding ω-olefinic acids followed by bromination of the latter and subsequent dehydrobromination under the action of alkalis.

Key words: 4-pentynoic acid, synthesis from cyclopentanone; 4-hexynoic acid, synthesis from cyclohexanone; 5-hexynoic acid, synthesis from cyclohexanone; 5-heptynoic acid, synthesis from cycloheptanone; 6-heptynoic acid, synthesis from cycloheptanone; 4,5-dibromopentanoic acid, dehydrobromination; 5,6-dibromohexanoic acid, dehydrobromination; 6,7-dibromoheptanoic acid, dehydrobromination.

Recently,[1] we have found that the results of dehydrobromination of 5,6-dibromohexanoic acid (**1b**) with alkali metal hydroxides depend substantially on the nature of alkali metal. Thus, the reactions with LiOH or NaOH smoothly afforded 5-hexynoic acid (**2b**), whereas the reaction with KOH was accompanied by intense isomerization of this acid into 4-hexynoic acid. The aim of the present study was to synthesize ω- and (ω − 1)-acetylenic acids from the corresponding five-, six-, and seven-membered cycloalkanones taking into account the above-mentioned effect.

Results and Discussion

ω-Acetylenic carboxylic acids are the useful starting compounds in the syntheses of compounds containing triple and *Z*-double bonds or other functional fragments separated from the carboxyl group by several (1—4) methylene groups. Among these are many natural unsaturated acids,[2] eicosanoids, oxylipins, and enzyme inhibitors of their biosynthesis[3] as well as other natural compounds.[4] Although the syntheses of the above-mentioned acetylenic acids have been described in many studies,[5—13] these procedures are either multistage or inconvenient. Hence, the development of a simple preparative procedure for their synthesis is still a topical problem.

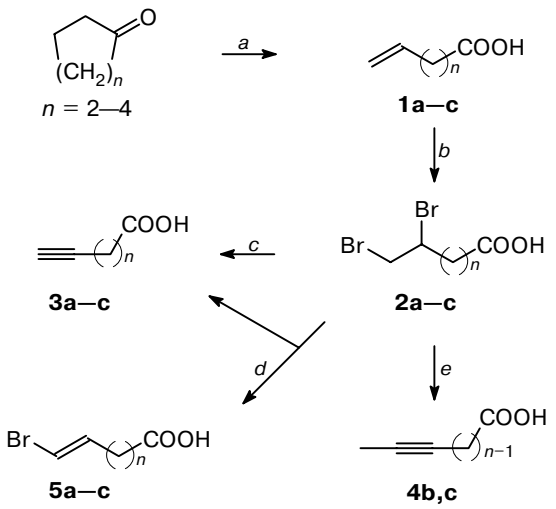
The syntheses of ω- and (ω − 1)-acetylenic acids from the corresponding five-, six-, and seven-membered cycloalkanones were performed according to Scheme 1. ω-Alkenoic acids (**1a—c**) are rather readily accessible. 5-Hexenoic acid (**1b**) and 6-heptenoic acid (**1c**) were prepared according to a known procedure[14] by the reactions of C_6- and C_7-cycloalkanones, respectively, with hydrogen peroxide (0.5 mol-equiv.) and Fe^{II} and Cu^{II} sulfates (the yields were 22—24%).*

* Hereinafter, unless otherwise stated, the yields are given with respect to the ketone introduced into the reaction without regard for its excess and partial recovery from the reaction.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 797—801, May, 2001.

1066-5285/01/5005-833 $25.00

Scheme 1



n = 2 (**a**), 3 (**b**), 4 (**c**)

Reagents and conditions: *a*) H_2O_2, $CuSO_4$, $FeSO_4$; *b*) Br_2, CH_2Cl_2, −40 °C; *c*) $NaNH_2$, NH_3, −33 °C; *d*) NaOH, PEG-2000, 80 °C; *e*) KOH, PEG-2000, 120 °C.

4-Pentenoic acid (**1a**) was obtained from cyclopentanone only in 8% yield due to the low conversion of the latter. Besides, acid **1a** thus obtained contained up to 12% of *n*-pentanoic acid due to competitive detachment of the H atom from cyclopentanone under the action of carboxybutyl radicals. The use of 2 moles of hydrogen peroxide per mole of cyclopentanone resulted in an increase in the yield of acid **1a** to 12% with a simultaneous decrease in the amount of *n*-pentanoic acid to 8%.

Oxidative decyclization of the ketones used was not accompanied by essential side processes (except for that considered above) so that the yields of acids **1a—c** reached 65% with respect to the consumed ketone.[14,15] Acid **1a**, which was most difficult to prepare by the method under consideration, can also be synthesized according to an alternative two-stage procedure involving C-allylation of diethyl malonate with allyl acetate catalyzed by palladium complexes[16] followed by decomposition of the malonate fragment.[17]

Bromination of alkenoic acids **1a—c** proceeded smoothly due to which dibromoacids **2a—c** obtained in virtually quantitative yields can be used in the subsequent stage without additional purification. We studied double dehydrobromination of dibromoacids **2a—c** under the action of NaOH and KOH (Table 1). In all experiments with hydroxides, aqueous solutions containing poly(ethylene glycol) with the molecular weight of 2000 (PEG-2000) were used. Previously, it has been demonstrated[1] that the addition of PEG-2000 is favorable for dehydrobromination. For comparison, sodium amide in liquid ammonia was used as the standard reagent for the synthesis of acetylenes from 1,2-dibromides.[13]

As in the case of dibromoacid **2b** reported previously,[1] dehydrobromination of dibromoacids **2a,c** with NaOH proceeded under rather mild conditions (80 °C). Complete elimination of the second HBr molecule occurred only in the case of formation of two (out of three) intermediate isomeric bromoolefinic acids, *viz.*, ω-bromo-(*Z*)- and (ω − 1)-bromo-(ω − 1)-alkenoic acids (see Table 1, runs *1*, *4*, and *8*). Under the conditions used, both dehydrobromination of ω-bromo-(*E*)-(ω − 1)-alkenoic acids (**5a—c**), which cannot undergo *trans*-elimination, and subsequent conversions of the resulting ω-acetylenic acids **3a—c** into (ω − 1)-isomers **4a—c** proceeded to only a small extent. Dehydrobromination of the highest homolog **2c** (see Table 1, runs *8* and *9*), which unexpectedly required the larger

Table 1. Reaction conditions and results of dehydrobromination of dibromoacids **2a—c**

Run	Compound	*n*	Reaction conditions				Composition of the products (%)[a]			Total yield (%)
			Base	[PEG-2000] (%)	*T*/°C	τ/h	**3**	**4**	**5**	
1	**2a**	2	NaOH	5	80	8	62	3	35[b]	88
2	**2a**	2	KOH	8	120	8	—	—	—	86[c]
3	**2a**	2	$NaNH_2$	—	−33	1.5	100	—	—	69
4	**2b**	3	NaOH	8	82	8	57	1	39	91
5	**2b**	3	KOH	13	120	8	—	100	—	92
6	**2b**	3	KOH	—	120	8	—	100	—	87
7	**2b**	3	$NaNH_2$	—	−33	1.5	100	—	—	65
8	**2c**	4	NaOH	8	80	8	24	<0.5	48[d]	—[e]
9	**2c**	4	NaOH	8	80	16	61	4	35	89
10	**2c**	4	KOH	17	120	8	—	100	—	85
11	**2c**	4	$NaNH_2$	—	−33	1.5	100	—	—	63

[a] Data from GLC analysis.
[b] An additional amount (0.6%) of the corresponding (*Z*) isomer was found by GLC.
[c] A mixture of oligomeric unsaturated acids.
[d] An additional amount (28%) of the corresponding (*Z*) isomer was found by GLC.
[e] The yield was not determined.

Table 2. Chemical shifts in the ^{1}H NMR spectra (200.13 MHz, $CDCl_3$) of the compounds synthesized

Compound	δ						
	H(1)	H(2)	H(3)	H(4)	H(5)	H(6)	H(7)
2a	11.35 (br.s)	1.94—2.16 (m, 1 H); 2.47—2.77 (m, 3 H)		4.26 (br.t)	3.64 (t, A); 3.90 (dd, B)	—	—
2b*	11.5 (br.s)	2.44 (t)	1.70—2.36 (m)		4.17 (dddd)	3.63 (t, A); 3.86 (dd, B)	—
2c	10.7 (br.s)	2.44 (t)	1.40—2.30 (m)			4.17 (m)	3.63 (t, A); 3.87 (dd, B)
3a	11.44 (br.s)	2.55 (t)	2.46 (t)	—	1.98 (t)	—	—
3b*	11.62 (br.s)	2.48 (t)	2.01 (m)	2.29 (m)	—	1.98 (t)	—
3c	11.8 (br.s)	2.35 (t)	1.55 (quint)	1.70 (quint)	2.17 (br.t)	—	1.96 (t)
4b	11.45 (br.s)	2.55 (m)	2.45 (m)	—	—	1.76 (t)	—
4c	11.8 (br.s)	2.48 (t)	1.74 (m)	2.19 (m)	—	—	2.19 (m)
5a	10.83 (br.s)	2.31—2.57 (m)		6.20 (m)		—	—
5b*	11.72 (br.s)	2.36 (t)	1.76 (quint)	2.13 (q)	5.97—6.24 (m)		—
5c	11.2 (br.s)	2.38 (t)	1.47 (quint)	1.65 (quint)	2.07 (q)	5.98—6.27 (m)	

* The data published in the literature[1] are given for comparison.

reaction time, is characterized by the same regularities. The resulting mixtures of acetylenic (**3a—c**) and bromoolefinic acids (**5a—c**) can be readily separated by fractionation *in vacuo* giving rise to ω-acetylenic acids **3a—c** in 49—61% yields. The conventional procedure for dehydrobromination involving sodium amide, which is experimentally less convenient, afforded the same acids **3a—c** in slightly higher yields (63—69%, see Table 1, runs *3*, *7*, and *11*).

Dehydrobromination of dibromoacids **2a—c** with KOH was carried out under more severe conditions (120 °C) so as to complete the conversion of bromoalkenoic acids **5a—c**, which were difficult to dehydrobrominate. In this case, intermediate ω-acetylenic acids **3a—c** were completely isomerized to the corresponding (ω − 1)-isomers **4b,c**. As a result, dibromides **2b,c** were converted into the corresponding (ω − 1)-acetylenic acids **4b,c** in high yields (see Table 1, runs *5*, *6*, and *10*). Apparently, this is the best procedure for their preparation. However, we failed to synthesize acid **4a** by this method (see Table 1, run *2*) because isomerization of acid **3a** under the reaction conditions proceeded by a different mechanism specific to this acid.[8]

To summarize, a divergent and experimentally simple procedure for the synthesis of ω- and (ω − 1)-(C_5—C_7)-acetylenic acids starting from five-, six-, and seven-membered cycloalkanones was developed based on the difference in the behavior of NaOH and KOH as reagents for dehydrobromination of ω- and (ω − 1)-dibromoacids.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument (200.13 and 50.32 MHz, respectively). The GLC analysis was carried out on an LKhM-80MD instrument equipped with a flame ionization detector and a column (3 m×3 mm) with the 6% SE-30 phase on Chromosorb W (60—80 mesh) using nitrogen as the carrier gas (30 mL min^{-1}). The melting points were determined on a Kofler instrument.

We used PEG-2000 (98% purity) purchased from Austrowaren Wien Laboratoriums Reagentien. The starting alkenoic acids **1a**, b.p. 86—87 °C (14 Torr), **1b**, b.p. 93—95 °C (12 Torr), and **1c**, b.p. 116—118 °C (12 Torr), were prepared according to a procedure reported previously[14]* (the results were discussed above).

Dibromoacids 2a—c (general procedure). An equimolar amount of a solution of Br_2 (80 g, 0.5 mol) in CH_2Cl_2 (100 mL) was added with intense stirring to a solution of alkenoic acid **1a—c** (0.5 mol) in CH_2Cl_2 (200 mL) at −40 °C for 1 h. The reaction mixture was stirred at this temperature for 0.5 h and then concentrated *in vacuo*. The residue was recrystallized from hexane. The spectral data for these products are given in Tables 2—4.

4,5-Dibromopentanoic acid (2a) was prepared from acid **1a** containing 11% of *n*-pentanoic acid in 82% yield (with respect to acid **1a**), m.p. 55—57 °C (see Ref. 5). Found (%): C, 23.61; H, 3.14; Br, 61.89. $C_5H_8Br_2O_2$. Calculated (%): C, 23.10; H, 3.10; Br, 61.49.

5,6-Dibromohexanoic acid (2b). The yield and physicochemical characteristics have been reported previously.[1]

6,7-Dibromoheptanoic acid (2c). The yield was 89%, m.p. 29 °C. Found (%): C, 28.98; H, 4.03; Br, 55.93. $C_7H_{12}Br_2O_2$. Calculated (%): C, 29.19; H, 4.20; Br, 55.49.

Dehydrobromination of dibromoacids 2a—c with aqueous solutions of sodium and potassium hydroxides (general procedure). A solution of dibromoacid **2** in a 10 *M* aqueous solution of NaOH or KOH containing 10 mol of alkali per mole of acid **2** with the addition of PEG-2000 (up to 5—15% by weight) was vigorously stirred (the conditions are listed in Table 1). The reaction mixture was diluted with an equal volume of water and

* ***Caution:*** Note that regeneration of the excess ketones according to a procedure described previously[14] should be carried out only after thorough removal of all peroxide compounds, including rather stable dialkyl peroxides. When these rules were not met, an explosion occurred at the beginning of distillation of ketone.

Table 3. Spin-spin coupling constants of the compounds synthesized

Compound	*J*/Hz			
	H(2)—H(3)	H(3)—H(4)	H(4)—H(5)	Other
2a	—	9.6	9.6 ($4—5^A$), 5.1 ($4—5^B$)	9.6 ($6^A—6^B$)
2b*	6.7	—	2.9 ($4^A—5$), 8.7 ($4^B—5$)	10.2 ($6^A—6^B$)
2c	6.6	—	—	10.2 ($6^A—6^B$)
3a	6.6	—	—	2.3 (3—5)
3b*	7.5	—	—	2.0 (4—6)
3c	7.2	7.2	7.2	—
4b	—	—	—	1.8 (5—7)
4c	7.1	—	—	—
5b*	7.7	7.7	7.7	—
5c	7.5	7.5	7.5	—

Note. The H(5)—H(6) spin-spin coupling constants for compounds **2b** and **5c** are 10.2 ($5—6^A$), 4.4 ($5—6^B$), and 7.5 Hz, respectively. The H(6)—H(7) spin-spin coupling constants for compound **2c** are 10.2 ($5—6^A$) and 4.8 ($5—6^B$).
* The data published in the literature[1] are given for comparison.

acidified with concentrated HCl to pH 2. The solution was extracted with ether. The extract was dried with anhydrous $MgSO_4$ and concentrated. The resulting oily or crystalline residues (2—3 mg) were methylated with an ethereal solution of CH_2N_2 and analyzed by GLC and NMR spectroscopy (see Tables 2—4). The procedures used for the preparative isolation are included in Table 1 along with the characteristics of the final products.

4-Pentynoic (3a) and 5-bromopent-4(*E*)-enoic (5a) acids. Acid **3a** and bromoacid **5a** were isolated from the reaction mixture obtained in run *1* (see Table 1) by fractionation *in vacuo*. The yield of **3a** was 51%, b.p. 94—95 °C (10 Torr), m.p. 54—56 °C (see Ref. 5). The yield of **5a** was 18%, b.p. 65—68 °C (1 Torr), m.p. 52—53 °C. Redistillation (1 Torr) of the distillation residue in a flask afforded a higher-boiling distillate (3% by weight) consisting (according to the ^{13}C NMR spectrum) of bromoacid **5a** and its (*Z*) isomer in a ratio of 4 : 1.

5-Hexynoic (3b) and 6-bromohex-5(*E*)-enoic (5b) acids (see Table 1, run *4*). The yield and physicochemical characteristics have been reported previously.[1]

4-Hexynoic acid (4b). The crystalline substance obtained in runs *5* and *6* (see Table 1) was in fact chromatographically pure acid **4b**; the yields were 92 and 87%, respectively, m.p. 102—103 °C (from aqueous MeOH) (Refs. 8 and 11).

6-Heptynoic (3c)[6] and 7-bromohept-6(*E*)-enoic (5c) acids. According to the data from GLC analysis (the column temperature was 135 °C, the evaporator temperature was 250 °C; the retention times of methyl esters of **3c** and **5c** were 4.05 and 18.0 min, respectively), the mixture obtained in run *8* (see Table 1) contained a substantial amount of methyl ester of (6*Z*)-**5c** (the retention time was 13.2 min). The mixture was heated until ester of **5c** completely disappeared (run *9*). Fractionation of the resulting mixture afforded acid **3c** with 95% purity in 61% yield, b.p. 130—132 °C (14 Torr) (lit data:[6] m.p. 18—20 °C), and bromoacid **5c**, b.p. 128—131 °C (1 Torr), m.p. 40—42 °C. Found (%): C, 40.94; H, 6.01; Br, 38.01. $C_7H_{11}BrO_2$. Calculated (%): C, 40.60; H, 5.35; Br, 38.59.

5-Heptynoic acid (4c). The crystalline substance obtained in run *10* (see Table 1) was in fact chromatographically pure acid **4c**, the yield was 85%, m.p. 37—39 °C (from aqueous MeOH; Ref. 8).

Dehydrobromination of dibromoacids 2a—c with sodium amide (see Table 1, runs *3*, *7*, and *11*). A solution of dibromoacid **2** in ether (1.33 *M*) was added with vigorous stirring to a 2 *M* suspension of $NaNH_2$ in liquid NH_3, which was prepared *in situ* from metallic Na, at −33 °C for 30 min. The viscous suspension was stirred at this temperature for 15 min. Ammonia was evaporated and one-half of the volume of water was added with caution to the solid residue heated to 20 °C. The resulting solution was acidified with concentrated HCl to pH 2 at 0 °C and extracted with ether. The extract was washed with water, dried with $MgSO_4$, and concentrated. Vacuum distillation of the residue afforded acid **3**; the yields are given in Table 1; the physicochemical characteristics are listed above.

Table 4. ^{13}C NMR spectra (50.32 MHz, $CDCl_3$, δ) of the compounds synthesized

Compound	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)
2a	178.86	31.56	31.04	51.16	35.75	—	—
2b[a]	179.66	33.08	21.94	35.14[b]	51.90	35.85[b]	
2c	180.04	33.79	23.79	26.25	35.61	52.38	36.10
3a	178.25	33.08	13.92	82.10	69.28	—	—
3b[a]	179.80	32.73	23.38	17.84	83.07	69.40	—
3c	180.24	33.51	23.63	27.66	18.06	83.76	68.76
4b	178.82	33.82	14.41	76.65[b]	76.91[b]	3.45	—
4c	180.03	32.77	23.75	17.99	76.52[b]	77.62[b]	3.24
5a	178.79	32.88	27.76	135.43	106.19	—	—
(4*Z*)-**5a**[c]	178.79	32.34	24.79	132.36	109.44	—	—
5b[a]	179.97	33.01	23.35	32.04	136.63	105.38	—
(5*Z*)-**5b**[a,d]	173.26	33.07	23.21	28.85	133.51	108.58	—
5c	180.07	33.70	23.85	27.86	32.45	137.34	104.64

[a] The data published in the literature[1] are given for comparison.
[b] These data in the rows can be interchanged.
[c] The data were obtained from the spectrum of a mixture of (4*Z*)-**5a** and **5a**.
[d] The corresponding methyl ester.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 99-03-33053) and by the Russian Federation Government Program "Leading Scientific Schools" (Project No. 00-15-97328).

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Received October 9, 2000;
in revised form December 22, 2000