Organic Chemistry

Practical synthesis of hex-5-ynoic acid from cyclohexanone

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Hex-5-ynoic acid, a multipurpose synthon, was synthesized in three steps starting from cyclohexanone by bromination—dehydrobromination of the intermediate hex-5-enoic acid.

Key words: hex-5-ynoic acid, synthesis from cyclohexanone; hex-5-enoic acid, bromination; 5,6-dibromohexanoic acid, dehydrobromination; 6-bromohex-5-enoic acids, stereoisomers; 6-bromohex-5(*E*)-enoic acid; hex-4-ynoic acid.

Aliphatic alkynoic acids with a terminal triple bond, especially hex-5-ynoic acid (**1**), find wide application as synthons for biologically active metabolites of polyunsaturated fatty acids, namely, arachidonic, bishomo-γ-linolenic, eicosa-5,8,11,14,17-pentaenoic, and analogous C_{18} acids. These metabolites include prostaglandins, leucotrienes, hepoxylins, other oxylipins,[1] and other natural products.[2]

The known methods for the synthesis of hex-5-ynoic acid (**1**) *via* not easily available hex-5-ynenitrile[2,3] or hex-5-yn-1-ol[4] are based on multi-step cumbersome procedures. Quite recently, acid **1** has become a commercially available although expensive preparation.[5] Since increasing the accessibility of this valuable synthon remains a topical task, we have developed a three-step method for the synthesis of acid **1** from cyclohexanone.

The first step is the known[6] decyclization of cyclohexanone to give hex-5-enoic acid (**2**) on treatment with hydrogen peroxide in the presence of Fe^{II} and Cu^{II} sulfates (Scheme 1). According to the procedure described in our previous publication,[6b] alkenoic acid **2** is formed in 44% yield.

Bromination of the double bond in alkenoic acid **2** occurs smoothly to give dibrominated acid **3** in a high yield (93.5%).[7] The final step, double dehydrobromination of dibrominated acid **3** with the generation of a triple bond, proved to be more complex.

When a 60% aqueous solution of KOH was used, the first dehydrobromination occurs even at 20 °C to give a mixture of all three possible vinyl bromides, namely, 5-bromohex-5-enoic acid (**4**) and stereoisomeric 6-bromohex-5-enoic acids ((*E*)-**5**, (*Z*)-**5**), in 44 : 32 : 24 ratio (Table 1, entry *1*). The composition of the product mixture and the structures of the components were established by GLC analysis, one-dimensional ^1H and ^{13}C NMR spectra, and two-dimensional H/H and H/C COSY procedures (see Experimental). An increase in the temperature to 82 °C induces the second dehydrobromination, which is selective for two intermediate bromovinyl acids that are able to undergo *trans*-elimination, namely, acids **4** and (*Z*)-**5** (see Table 1, entry *2*). Under these conditions, the formation of the terminal alkynoic acid **1** is accompanied by its partial isomerization to hex-4-ynoic acid (**6**) (this type of

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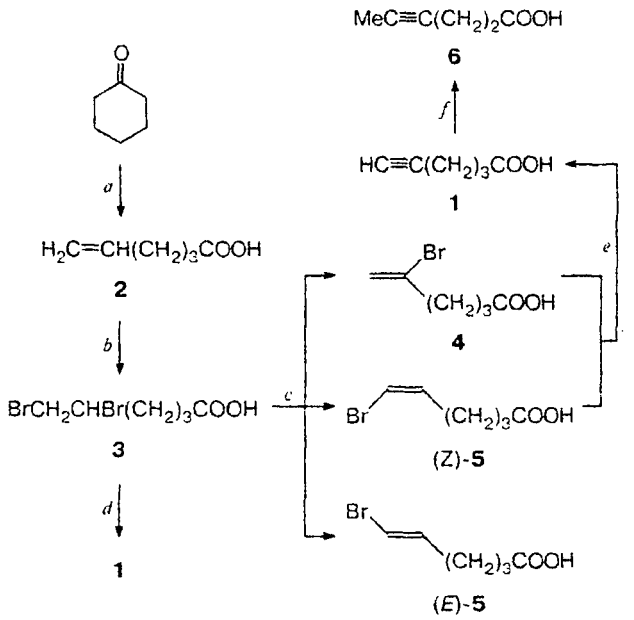
Scheme 1



Reagents and conditions: *a*. H_2O_2, $CuSO_4$, $FeSO_4$. *b*. Br_2, CH_2Cl_2, −40 °C. *c*. KOH (or LiOH or NaOH), PEG, 20 °C. *d*. $NaNH_2$, NH_3, −33 °C. *e*. KOH (or LiOH or NaOH), PEG, 82—100 °C. *f*. KOH, PEG, 82—100 °C.

isomerization is known[8]). Since separation of isomeric alkynoic acids **1** and **6** is difficult, it was necessary to alter the ratio of the rates of the successive dehydrobromination and isomerization reactions.

The attempts to accelerate dehydrobromination by the addition of various polyethylene glycols (PEG) (as recommended in the literature[9]) or 15-crown-5 were successful only to some extent: the content of the isomerization product, acid **6**, actually decreased but only to 3—7% (see Table 1, entries *3*—*5* and *8*), and it sharply increased on attempts to involve the slowly reacting bromo acid (*E*)-**5** in dehydrobromination by increasing the temperature to 100 °C (see entries *6* and *7*). The content of isomer **6** was diminished to an acceptable level (1%) when KOH was replaced by LiOH or NaOH (see entries *9* and *10*). These two hydroxides do not accelerate dehydrobromination but appear to retard isomerization of acid **1**. The isomerization can be completely suppressed by using sodium amide in liquid ammonia as the base (this is a standard procedure for the synthesis of terminal alkynoic acids from dibromides, see Ref. 10 and Table 1, entry *11*). In this case, owing to the stabilization of the terminal position of the triple bond in acid **1** by the irreversible (under the reaction conditions) formation of the acetylenide, bromo acid (*E*)-**5** can undergo dehydrobromination without the formation of detectable amounts of isomeric acid **6**.

It should be noted that some of the reported melting points of the compounds in question were not confirmed in our study. Thus acids **1** and **3** were described[4b,7] as compounds crystalline at 20 °C and acid (*E*)-**5** was described as an oil.[7] In our hands, repeatedly obtained and thoroughly purified samples of acids **1** and **3** (see Experimental) and a commercial sample of acid **1**[5] crystallized only at temperatures below 20 °C, whereas acid (*E*)-**5** had a melting point of 38—40 °C. The reasons for these discrepancies are unknown.

Preparative-scale synthesis of hex-5-ynoic acid (**1**) was studied in the conditions of entries *10* and *11* (see Table 1). In the former experiment, products **1** and (*E*)-**5** were separated by fractional distillation *in vacuo*; these compounds were isolated in 49 and 19.6% yields, respectively. The latter case, in which freshly prepared sodium amide in liquid ammonia was used in dehydrobromination, is much less convenient from the

Table 1. Dehydrobromination of 5,6-dibromohexanoic acid **3**

Entry	Reaction conditions				Product ratio[a] (%)				
	base	catalyst	temperature/°C	time/h	**1**	**4**	(*E*)-**5**	(*Z*)-**5**	**6**
1	KOH[b]	—	20	8	2	44	32	24	—
2	KOH	—	82	12	52	—	30	—	18
3	KOH	PEG-400	82	8	43	—	53	—	4
4	KOH	PEG-600	82	12	69	—	34	—	7
5	KOH	PEG-2000	82	8	60	—	36	—	4
6	KOH	PEG-2000	92	8	62	—	20	—	18
7	KOH	PEG-2000	100	12	35	—	33	—	32
8	KOH	15-Crown-5	82	8	50	—	47	—	3
9	LiOH[c]	PEG-2000	82	8	55	—	41	3	1
10	NaOH[d]	PEG-2000	82	8	57	—	39	3	1
11	$NaNH_2$[e]	PEG-2000	−33→25	1.5	100	—	—	—	—

[a] According to GLC analysis.
[b] A 60% aqueous solution.
[c] A 13% aqueous solution.
[d] A 45% aqueous solution.
[e] A solution in liquid NH_3.

practical viewpoint but it gives acid **1** in 70% yield. Thus, the methods developed in this work secure the preparation of hex-5-ynoic acid from cyclohexanone in three steps in overall yields of 20—31%.

Experimental

IR spectra were recorded on a IR-75 spectrometer. NMR spectra were run in $CDCl_3$ on Bruker AC-200 (200.13 MHz for ^1H and 50.32 MHz for ^{13}C) and DRX-500 (500.13 MHz for ^1H and 125.77 MHz for ^{13}C) instruments. The signals were assigned using H/H and C/C COSY procedures. GLC analyses were performed on an LKhM-8MD instrument with a flame ionization detector and a column (3 m × 3 mm) with 6% SE-30 on Chromosorb W (60—80 mesh) using nitrogen (30 mL min^{-1}) as the carrier gas. Melting points were determined by immersing the thermometer bulb into a melting substance.

Polyethylene glycols produced by Austrowaren Wien Laboratoriums Reagentien and Lancaster 15-crown-5 were used in the study.

5,6-Dibromohexanoic acid (3). A solution of Br_2 (80 g, 0.5 mol) in CH_2Cl_2 (100 mL) was added at −40 °C with vigorous stirring over a period of 1 h to a solution of hex-5-enoic acid **2** (57.0 g, 0.5 mol) in CH_2Cl_2 (200 mL). The mixture was stirred at the same temperature for an additional 0.5 h. Evaporation of the solvent *in vacuo* gave 128.0 g (93.5%) of dibromide **3** as an orange-yellow oil crystallizing at −20 °C. The product was used in the next step without additional purification. Recrystallization from hexane at −20 °C gave large white needles with m.p. 16—18 °C (which did not change upon repeated crystallizations) (lit data[7]: m.p. 45 °C); the crystals melted to give a colorless oil with a purity of >99% according to the ^{13}C NMR spectrum. Found (%): C, 26.55; H, 3.67; Br, 58.03. $C_6H_{10}Br_2O_2$. Calculated (%): C, 26.31; H, 3.68; Br, 58.33. IR (CCl_4), ν/cm^{-1}: 938 (C—Br); 1700 (C=O); 2550—3100 (OH). ^1H NMR ($CDCl_3$), δ: 1.70—2.06, 2.13—2.36 (both m, 3 H and 1 H, $C(3)H_2$, $C(4)H_2$); 2.44 (t, 2 H, $C(2)H_2$, J = 6.7 Hz); 3.63 (t, 1 H, H(6A), J = 10.2 Hz); 3.86 (dd, 1 H, H(6B), J = 4.4 and 10.2 Hz); 4.17 (dddd, 1 H, H(5), J = 2.9, 4.4, 8.7, and 10.2 Hz); 11.5 (br.s, 1 H, OH). ^{13}C NMR, δ: 21.94 (C(3)); 33.08 (C(2)); 35.14 (C(4)); 35.85 (CH_2Br); 51.90 (CHBr); 179.66 (C=O).

Dehydrobromination of dibromo acid 3 by aqueous solutions of hydroxides (general procedure). A solution of dibromo acid **3** (6.0 g, 22 mmol) in 60% aqueous KOH (12 mL, 120 mmol) (or the corresponding solution of LiOH or NaOH) was vigorously stirred under conditions specified in Table 1. The reaction mixture was diluted with water (20 mL) and acidified with concentrated HCl to pH 2. The solution was extracted with ether (4×25 mL), and the extract was dried with anhydrous $MgSO_4$ and concentrated. The resulting oily mixtures of products were methylated with an ethereal solution of CH_2N_2 and analyzed by GLC and NMR. The results are presented in Table 1.

Methyl esters (ME) of bromohex-5-enoic acids 4, (*E*)-5, and (*Z*)-5 were prepared as a mixture in 90% yield under conditions of entry *1* (see Table 1) upon methylation of the crude product mixture with an ethereal solution of CH_2N_2. Individual NMR spectra were extracted from the spectra of the mixture. ME of **4**: GLC retention time (RT) 8.0 min. ^1H NMR, δ: 1.84 (quint, 2 H, $C(3)H_2$, J = 7.3 Hz); 2.28 (t, 2 H, $C(2)H_2$, J = 7.3 Hz); 2.42 (t, 2 H, $C(4)H_2$, J = 7.2 Hz); 3.63 (s, 3 H, OMe); 5.37, 5.54 (both s, each 1 H, CH_2=). ^{13}C NMR, δ: 22.84 (C(3)); 32.18 (C(2)); 40.29 (C(4)); 51.34 (OMe); 117.17 (CH_2=); 133.17 (CBr=); 173.26 (C=O). ME of (*E*)-**5**: RT 10.0 min. ^1H NMR, δ: 1.71 (quint, 2 H, $C(3)H_2$, J = 7.4 Hz); 2.06 (q, 2 H, $C(4)H_2$, J = 7.3 Hz); 2.29 (t, 2 H, $C(2)H_2$, J = 7.4 Hz); 3.63 (s, 3 H, OMe); 6.03 (d, 1 H, H(6), J = 13.7 Hz); 6.11 (dt, 1 H, H(5), J = 13.7 and 6.9 Hz). ^{13}C NMR, δ: 23.56 (C(3)); 32.02 (C(4)); 32.86 (C(2)); 51.34 (OMe); 105.04 (CHBr=); 136.70 (CH=); 173.38 (C=O). ME of (*Z*)-**5**: RT 9.3 min. ^1H NMR, δ: 1.70 (quint, 2 H, $C(3)H_2$, J = 7.4 Hz); 2.20 (q, 2 H, $C(4)H_2$, J = 7.4 Hz); 2.28 (t, 2 H, $C(2)H_2$, J = 7.4 Hz); 3.63 (s, 3 H, OMe); 6.03 (q, 1 H, H(5), J = 7.0 Hz); 6.15 (d, 1 H, H(6), J = 7.0 Hz). ^{13}C NMR, δ: 23.21 (C(3)); 28.85 (C(4)); 33.07 (C(2)); 51.34 (OMe); 108.58 (CHBr=); 133.51 (CH=); 173.26 (C=O).

Hex-5-ynoic acid (1) and 6-bromohex-5(*E*)-enoic acid ((*E*)-5). ***A.*** A mixture of crude dibromo acid **3** (54.8 g, 0.2 mol), a 40% aqueous solution of NaOH (120 mL, 1.1 mol), and PEG-2000 (10 g) was stirred at 80 °C for 8 h. After cooling, the solution was diluted with water (120 mL), acidified by concentrated HCl to pH 2, and extracted with ether (4×75 mL). The dried ($MgSO_4$) extract was concentrated and the residual oil (24 g) was fractionated *in vacuo* to give 11.0 g (49.0%) of hexynoic acid **1** of 96% purity, b.p. 112—114 °C (12 Torr) (other characteristics are given below), and 7.57 g (19.6%) of bromo acid (*E*)-**5**, b.p. 96—98 °C (1 Torr), m.p. 38—40 °C after crystallization in the receiving flask (lit data[7]: oil). Found (%): C, 37.53; H, 4.88; Br, 41.72. $C_6H_9BrO_2$. Calculated (%): C, 37.33; H, 4.70; Br, 41.39. ^1H NMR, δ: 1.76 (quint, 2 H, $C(3)H_2$, J = 7.7 Hz); 2.13 (q, 2 H, $C(4)H_2$, J = 7.7 Hz); 2.36 (t, 2 H, $C(2)H_2$, J = 7.7 Hz); 5.97—6.24 (m, 2 H, CH=CH); 11.72 (s, 1 H, COOH). ^{13}C NMR, δ: 23.35 (C(3)); 32.04 (C(4)); 33.01 (C(2)); 105.38 (CHBr=); 136.63 (CH=); 179.97 (C=O).

B. A solution of crude dibromo acid **3** (from 0.4 mol of hex-5-enoic acid **2**) in Et_2O (300 mL) was added with vigorous stirring at −33 °C over a period of 30 min to a suspension of $NaNH_2$ prepared from Na (46 g, 2 mol) in 1 L of liquid NH_3, and the suspension was stirred at the same temperature for an additional 15 min. The cooling bath was removed and the mixture was allowed to warm to 25 °C over a period of 1 h; after that, water (500 mL) was carefully added. The resulting solution was acidified to pH 2 by the addition of concentrated HCl at 0 °C and extracted with ether (4×150 mL). The extract was washed with water (2×70 mL), dried with $MgSO_4$, and concentrated, and the residue was distilled *in vacuo* to give 31.0 g (70%) of acid **1** as a colorless liquid crystallizing at −20 °C, b.p. 97—100 °C (5 Torr), n_D^{21} 1.4474 (lit data: m.p. −8 °C, b.p. 106 °C (9 Torr), n_D^{17} 1.4500[3a]; m.p. 41—43.5 °C[4b]). IR (liquid film), ν/cm^{-1}: 1710 (C=O); 2115 (C≡C); 2550—3100 (OH); 3300 (≡C—H). ^1H NMR, δ: 1.98 (t, 1 H, ≡C—H, J = 2 Hz); 2.01 (m, 2 H, $C(3)H_2$); 2.29 (m, 2 H, $C(4)H_2$); 2.48 (t, 2 H, $C(2)H_2$, J = 7.5 Hz); 11.62 (br.s, 1 H, COOH). ^{13}C NMR, δ: 17.84 (C(4)); 23.38 (C(3)); 32.73 (C(2)); 69.40 (C(6)); 83.07 (C(5)); 179.8 (C=O).

Hex-4-ynoic acid (6). Acid **6** crystallized off on storage from the crude reaction product (before methylation with CH_2N_2) obtained according to entry *7* (see Table 1) and was filtered off and recrystallized. Colorless needles, m.p. 96.5 °C (from hexane) (lit data: m.p. 95—96 °C[11]; 100—101 °C[8]). IR (CCl_4), ν/cm^{-1}: 934, 1710 (C=O); 2550—3100 (OH). ^1H NMR, δ: 1.65 (br.s, 3 H, $C(6)H_3$); 2.44 (m, 4 H, $C(2)H_2C(3)H_2$); 11.14 (br.s, 1 H, COOH). ^{13}C NMR, δ: 3.43 (C(6)); 14.99 (C(3)); 33.88 (C(2)); 76.64, 76.90 (C(4), C(5)); 178.74 (C=O). These spectra are identical to those of an authentic sample.[11]

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