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Ultrasound in fatty acid chemistry: facile dehydrobromination of dibromo fatty esters to acetylenic ester derivatives

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Abstract

Dehydrobromination of dibromo derivatives of olefinic fatty acids was accomplished using KOH in 20% aqueous ethanol under concomitant ultrasonic irradiation (20 kHz) for 30 min at ambient temperature to give the corresponding acetylenic fatty acid derivatives (52–72% yield). Ten different dibromo fatty acid substrates were used. Products include: fatty acids with a terminal or internal acetylenic bond; acetylenic fatty acids containing an additional functional group, such as hydroxy, chloro or azide group. The structures of the products were characterized by infrared and NMR spectroscopy. © 1998 Elsevier Science Ireland Ltd.

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1. Introduction

One of the most thorough investigations conducted on the chemical transformation of olefinic fatty acids to the corresponding acetylenic fatty acids was reported (Gunstone and Hornby, 1969). Their general procedure involved the bromination of an olefinic fatty acid to the dibromo intermediate, which was subsequently dehydrobrominated in the presence of a base to give the requisite acetylenic fatty acid. From their result it appeared that one of the best conditions for the dehydrobromination process was to react the dibromo fatty acid intermediate with 1,5-diazabicyclo(5.4.0)undec-5-ene (DBU) in benzene under reflux for 5 h. For example, 9-octadecynoic acid was obtained in 85% yield from methyl 9,10-dibromostearate, which was derived from methyl oleate. But when we repeated the same reaction under similar conditions as described by Gunstone and Hornby, the average yield of 9-octadecynoic acid obtained was only 15%. Several modifications to the procedure were tried to increase the yield of the product. For instance, by increasing the reflux period of the reaction from 5 to 12 h, the yield was slightly increased to 22%.

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Table 1
Dehydrobromination of dibromo fatty esters with KOH in aqueous ethanol under concomitant ultrasonic irradiation followed by methylation

Substrate	Reaction time (ultrasound) min	Products	Yield %
$CH_2BrCHBr–R^1$	30	$HC\equiv C–R^1$ (**1**)	62
$R^2–CHBrCHBr–R^3$	30	$R^2–C\equiv C–R^3$ (**2**)	52
$R^4–CHOH–CH_2–CHBrCHBr–R^3$	30	$R^4–CHOH–CH_2–C\equiv C–R^3$ (**3**)	66
$R^5–CHBrCHBr–(CH_2)_2CHOH–R^3$	30	$R^5–C\equiv C–(CH_2)_2CHOH–R^3$ (**4**)	72
$R^4–CHCl–CH_2–CHBrCHBr–R^3$	30	$R^4–CHCl–CH_2–C\equiv C–R^3$ (**5**)	65
$R^5–CHBrCHBr–(CH_2)_2CHCl–R^3$	30	$R^5–C\equiv C–(CH_2)_2CHCl–R^3$ (**6**)	69
$R^4–CHN_3–CH_2–CHBrCHBr–R^3$	30	$R^4–CHN_3–CH_2–C\equiv C–R^3$ (**7**)	55
$R^5–CHBrCHBr–(CH_2)_2CHN_3–R^3$	30	$R^5–C\equiv C–(CH_2)_2CHN_3–R^3$ (**8**)	60
$R^4–CHOAc–CH_2–CHBrCHBr–R^3$	30	$R^4–CHOH–CH_2–C\equiv C–R^3$ (**3**)	58
$R^5–CHBrCHBr–(CH_2)_2CHOAc–R^3$	30	$R^5–C\equiv C–(CH_2)_2CHOH–R^3$ (**4**)	65

$R^1 = (CH_2)_8COOCH_3$; $R^2 = CH_3(CH_2)_7$; $R^3 = (CH_2)_7COOCH_3$; $R_4 = CH_3(CH_2)_5$; $R^5 = CH_3(CH_2)_4$; OAc = acetoxy.

The use of higher concentrations of DBU than recommended did not improve the yield (15%) either. Replacing DBU by sodium hydride as the base and substituting benzene with dimethyl sulfoxide as the solvent furnished 9-octadecynoic acid in 30% yield after 16 h of reflux. Adkins and Burks recorded a yield of about 40% of 9-octadecynoic acid, when 9,10-dibromo-octadecanoic acid was refluxed with KOH in amyl alcohol for 10 h (Adkins and Burks, 1967).

Many organic reactions carried out under concomitant ultrasonic irradiation have shown significant increase in the yield of the products formed. We have recently reported the successful application of ultrasound energy in the chemical transformation of long-chain fatty acids and their derivatives (Lie Ken Jie and Kalluri, 1995, 1996; Lie Ken Jie and Lam, 1995, 1996; Lie Ken Jie et al., 1994, 1996, 1997). However, when a mixture of methyl 9,10-dibromooctadecanoate, DBU and benzene was irradiated under ultrasound, no acetylenic derivative was obtained as the starting material was recovered.

In view of our need to obtain acetylenic fatty acid derivatives for chemical and biological studies, we describe in this paper a facile and quick ultrasound-assisted dehydrobromination procedure for long chain olefinic fatty esters to give the corresponding acetylenic derivatives in good yield (52–72%). The results of the various reactions are summarised in Table 1.

2. Materials and methods

10-Undecenoic acid and oleic acid were purchased from Aldrich Chemical (Milwaukee, WI). Ricinoleic acid (12-hydroxy-*cis*-octadecenoic acid) and iso-ricinoleic acid (9-hydroxy-*cis*-12-octadecenoic acid) were isolated from castor oil and from the seed oil of *Wrightia tinctoria*, respectively (Gunstone, 1954). Seeds from *Wrightia tinctoria* were gifts from Prof S.M. Osman, Department of Chemistry, Aligarh Muslim University, India. The corresponding chloro, azido and acetoxy derivatives of methyl ricinoleate and methyl iso-ricinoleate were prepared as described elsewhere (Lie Ken Jie and Cheng, 1995). Infrared (IR) and nuclear magnetic resonance (^1H and ^{13}C NMR) spectroscopy were carried out as described elsewhere (Lie Ken Jie et al., 1994). Ultrasonication was carried out using a 20 kHz ultrasound horn (Sonoreactor, Undatim Ultrasonic, Louvain la Neuve, Belgium) with the reaction mixture contained in a water-jacketed cell (40 mm i.d., 80 mm length).

2.1. General method for the bromination of long-chain unsaturated fatty esters with bromine as exemplified by the bromination of methyl 12-hydroxy-9-cis-octadecenoate

A mixture of methyl 12-hydroxy-9-*cis*-octadecenoate (2.0 g, 6.4 mmol) and diethyl ether (80 ml) was cooled to 0–5°C. A solution of bromine

(3.0 g in 20 ml of diethyl ether) was added slowly to the reaction mixture over 10 min and the reaction mixture stirred for a further 15 min. A solution of sodium thiosulfate (10%, 20 ml) was then added to react with the excess bromine. The ethereal layer was successively washed with water (2×20 ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated to give methyl 12-hydroxy-9,10-dibromo-octadecanoate (3.0 g, 99%), which required no further purification.

2.2. General procedure for the dehydrobromination of long-chain dibromo fatty esters with KOH in aqueous ethanol under ultrasonic irradiation as exemplified by the dehydrobromination of methyl 12-hydroxy-9,10-dibromo-octadecanoate

A mixture of methyl 12-hydroxy-9,10-dibromo-octadecanoate (3.0 g, 6.4 mmol), ethanol (24 ml), water (6 ml) and KOH (5.7 g) was placed in a water-jacketed cell and sonicated for 30 min at 20–25°C. The reaction mixture was acidified with dilute HCl (6 M, 20 ml) and extracted with diethyl ether (3×30 ml). The ethereal extract was washed with water (20 ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated and the residue was refluxed with BF_3-methanol complex (14%, w/w, 5 ml) and absolute methanol (20 ml) for 15 min. Water (50 ml) was added and the reaction mixture was extracted with diethyl ether (3×30 ml). The filtrate was evaporated and silica column chromatographic separation of the residue using a mixture of petroleum ether and diethyl ether (9:1, v/v) as eluent gave pure methyl 12-hydroxy-9-octadecynoate (**3**, 1.3 g, 66%). IR (film) 3450, 1740, 1460, 1360 and 1170 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 0.88 (t, J = 7 Hz, 3H, C*H*$_3$), 1.2–1.6 (m, 20H, C*H*$_2$), 2.04 (s, 1H, CHO*H*), 2.2 (m, 4H, 8-*H* and 11-*H*), 2.30 (t, J = 7 Hz, 2H, 2-*H*), 3.66 (s, 3H, COOC*H*$_3$) and 3.69 (m, 1H, C*H*OH); ^{13}C NMR ($CDCl_3$, δ_C) 14.11 (C-18), 18.72 (C-8), 22.75 (C-17), 24.91 (C-3), 25.66 (C-14), 27.95 (C-11), 28.75 (C-7), 28.86, 29.15, 31.91 (C-16), 34.02 (C-2), 36.21 (C-13), 51.42 (COO*C*H$_3$), 70.37 (C-12, *C*HOH), 78.24 (C-10), 82.41 (C-9) and 174.23 (C-1).

Methyl 10-undecynoate (**1**, 62%) IR (film) 3100, 2970, 2850, 2012, 1740, 1440, 1197 and 760 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 1.2–1.6 (m, 12H, C*H*$_2$), 1.94 (m, 1H, 11-*H*), 2.17 (t, J = 7 Hz, 2H, 9-*H*), 2.30 (t, J = 7.5 Hz, 2H, 2-*H*) and 3.66 (s, 3H, COOC*H*$_3$); ^{13}C NMR ($CDCl_3$, δ_C) 18.41 (C-9), 24.70 (C-3), 28.49–29.03, 34.07 (C-2), 51.42 (COO*C*H$_3$), 68.15 (C-11), 84.67 (C-10) and 174.35 (C-1).

Methyl 9-octadecynoate (**2**, 52% yield) IR(film) 2960, 2850, 1740, 1450, 1120 and 740 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 0.88 (t, J = 7 Hz, 3H, C*H*$_3$), 1.2–1.6 (m, 22H, C*H*$_2$), 2.13 (t, J = 7 Hz. 4H, 8-*H*, 11-*H*), 2.34 (t, J = 7 Hz, 2H, 2-*H*) and 3.66 (s, 3H, COOC*H*$_3$); ^{13}C NMR ($CDCl_3$, δ_C) 14.13 (C-18), 18.74 (C-8), 18.79 (C-11), 22.72 (C-17), 24.78 (C-3), 28.65–29.74, 31.92 (C-16), 34.12 (C-2), 51.43 (COO*C*H$_3$), 80.06 (C-9), 80.37 (C-10) and 174.33 (C-1).

Methyl 9-hydroxy-12-octadecynoate (**4**, 72% yield) IR 3450, 1740, 1435, 1360 and 1170 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 0.88 (t, J = 7 Hz, 3H, C*H*$_3$), 1.2–1.6 (m, 20H, C*H*$_2$), 2.11 (t, J = 6 Hz. 2H, 14-*H*), 2.29 (t, J = 6 Hz, 2H, 11-*H*), 2.33 (t, J = 7 Hz, 2H, 2-*H*), 3.21 (s, br., 1H, CH–O*H*), 3.66 (s, 3H, COOC*H*$_3$) and 3.68 (m, 1H, C*H*OH); ^{13}C NMR ($CDCl_3$, δ_C) 14.05 (C-18), 15.26 (C-11), 18.77 (C-14), 22.32 (C-17), 24.99 (C-3), 25.67 (C-7), 28.91–29,58, 31.17 (C-16), 34.07 (C-2), 36.54 (C-10), 37.39 (C-8), 51.41 (COO*C*H$_3$), 70.72 (C-9, *C*HOH), 79.86 (C-12), 80.64 (C-13) and 174.27 (C-1).

Methyl 12-chloro-9-octadecynoate (**5**, 65% yield); IR (film) 2960, 2850, 1740, 1450, 1197 and 740 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 0.88 (t, J = 7 Hz, 3H, C*H*$_3$), 1.2–1.6 (m, 20H, C*H*$_2$), 2.12 (m, 4H, 8-*H*, 11-*H*), 2.33 (t, J = 7 Hz, 2H, 2-*H*), 3.66 (s, 3H, COOC*H*$_3$) and 4.12 (quintet, 1H, C*H*–Cl); ^{13}C NMR ($CDCl_3$, δ_C) 14.10 (C-18), 18.72 (C-8), 22.62 (C-17), 24.88 (C-3), 25.62 (C-14), 27.75 (C-11), 28.65–29.29, 31.81 (C-16), 34.05 (C-2), 36.01 (C-13), 51.46 (COO*C*H$_3$), 60.19 (C-12, *C*H–Cl), 76.30 (C-10), 83.20 (C-9) and 174.28 (C-1).

Methyl 9-chloro-12-octadecynoate (**6**, 69% yield) IR (film) 2960, 2850, 1740, 1440, 1197 and 780 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 0.88 (t, J = 7 Hz, 3H, C*H*$_3$), 1.2–1.8 (m, 20H, C*H*$_2$), 2.11 (t, J = 6 Hz, 2H, 14-*H*), 2.33 (t, J = 7 Hz, 2H, 2-*H*),

2.35 (t, J = 6 Hz, 2H, 11-*H*), 3.66 (s, 3H, $COOCH_3$) and 4.03 (quintet, 1H, C*H*–Cl); ^{13}C NMR ($CDCl_3$, δ_C) 14.04 (C-18), 16.31 (C-11), 18.72 (C-14), 22.28 (C-17), 24.93 (C-3), 26.40 (C-7), 28.78–29.16, 31.11 (C-16), 34.02 (C-2), 37.81 (C-10), 38.35 (C-8), 51.36 ($COOCH_3$), 62.54 (C-9, *C*H–Cl), 78.48 (C-12), 81.07 (C-13) and 174.05 (C-1).

Methyl 12-azido-9-octadecynoate (**7**, 55% yield) IR (film) 2930, 2850, 2099, 1740, 1440, 1249, 1190 and 1160 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 0.88 (t, J = 7 Hz, 3H, CH_3), 1.2–1.6 (m, 20H, CH_2), 2.32 (t, J = 7 Hz, 2H, 2-*H*), 2.40 (m, 4H, 8-*H*, 11-*H*), 3.38 (m, 1H, C*H*-N_3) and 3.66 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$, δ_C) 14.10 (C-18), 18.74 (C-8), 22.65 (C-17), 24.96 (C-3), 25.15 (C-14), 25.99 (C-11), 28.69–29.10, 31.77 (C-16), 33.55 (C-13), 34.03 (C-2), 51.36 ($COOCH_3$), 61.47 (C-12, *C*H–N_3), 75.72 (C-10), 82.99 (C-9) and 174.09 (C-1).

Methyl 9-azido-12-octadecynoate (**8**, 60% yield) IR (film) 2950, 2850, 2100, 1740, 1440, 1250, 1195 and 760 cm^{-1}; ^1H NMR ($CDCl_3$, δ_H) 0.88 (t, J = 7 Hz, 3H, CH_3), 1.2–1.8 (m, 20H, CH_2), 2.12 (m, 4H, 11-*H*,14-*H*), 2.33 (t, J = 7 Hz, 2H, 2-*H*), 3.44 (quintet, J = 6.5, 2H, C*H*–N_3) and 3.66 (s, 3H, $COOCH_3$); ^{13}C NMR ($CDCl_3$, δ_C) 14.03 (C-18), 15.85 (C-11), 18.71 (C-14), 22.26 (C-17), 24.92 (C-3), 26.02 (C-7), 28.78–29.23, 31.11 (C-16), 33.75 (C-10), 34.03 (C-2), 34.30 (C-8), 51.42 ($COOCH_3$), 61.84 (C-9, *C*H-N_3), 78.52 (C-12), 81.32 (C-13) and 174.18 (C-1).

3. Results and discussion

Our effort to repeat the DBU in benzene (Gunstone and Hornby, 1969) for the dehydrobromination of methyl 9,10-dibromo-octadecanoate resulted in a poor average yield of 15% of the desired acetylenic product. We are unable to explain this low yield product formation, but as a consequence this experience has led us to investigate the use of ultrasound to accelerate the dehydrobromination process. After failing to increase the yield in any significant degree by extending the reflux period or by increasing the amount of the base (DBU), it was also discovered that ultrasound did not have any effect on the dehydrobromination process when benzene was used as the solvent with DBU. An attempt to use sodium hydride as the base in dimethyl sulfoxide under prolonged reflux period (16 h) produced a marginal increase in the production of the acetylenic derivative (30%).

Ultrasound energy is best conducted in solvents such as water and alcohols, due to their polar properties and high dielectric constants. In view of the fact that KOH in amyl alcohol was used (Adkins and Burks, 1967) for the dehydrobromination of dibromo-octadecanoic acid (in about 40% yield), we decided to reinvestigate this method under ultrasonic irradiation. The result under concomitant ultrasonic irradiation (30 min) at 20–25°C produced only 10% of the requisite 9-octadecynoic acid. Despite the low yield in this reaction, the result showed that dehydrobromination could be achieved in a short period (30 min) of ultrasonication at ambient temperature. Following this lead, a study of mixtures of ethanol and water was conducted to search for a suitable solvent system. A serial study of ethanol with different amounts of water was investigated and it was found that KOH in 20% aqueous ethanol provided the optimum condition for the dehydrobromination process.

Ten dibromo fatty ester substrates were prepared and subjected to KOH and aqueous ethanol under concomitant ultrasonic irradiation at 20–25°C for 30 min. The results are summarised in Table 1. The yield of these reactions varied from 52 to 72% and the methyl esters of the resulting acetylenic acids could be readily purified by silica column chromatography. Terminal and internal acetylenic products (compounds **1** and **2**) could be prepared by this quick ultrasound procedure. There was no bond migration of the acetylenic system as determined by the oxidative cleavage of the resulting acetylenic fatty esters, which furnished the corresponding mono- and di-acid moieties as determined by gas liquid chromatography (Lie Ken Jie and Kalluri, 1996).

In the case of methyl 12-chloro-9,10-dibromo and methyl 9-chloro-12,13-dibromo-octadecanoate, the dehydrohalogenation process proceeded exclusively with the elimination of the bromine atoms as expected, while the chloro atom

was retained in the products (compounds **5** and **6**). This observation was confirmed by the NMR spectral results. The dehydrobromination of the azido-dibromo fatty ester substrates proceeded successfully to give the corresponding azido-acetylenic fatty esters (compounds **7** and **8**). However, in the case of the acetoxy-dibromo fatty ester substrates, the presence of the KOH also caused the acetoxy function to be hydrolysed which yielded the hydroxy-acetylenic products (compounds **3** and **4**).

It can be concluded from these results that dehydrobromination of dibromo fatty acid derivatives is readily achieved under ultrasound at ambient temperature when KOH is used as the base in aqueous ethanol.

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References

Adkins, H., Burks, R.E. Jr., 1967. Stearolic acid. Org. Synth. 3, 785–786.

Gunstone, F.D., 1954. The nature of the oxygenated acid present in *Vernonia anthelmintica* (Willd) seed oil. J. Chem. Soc. 1611–1616.

Gunstone, F.D., Hornby, G.M., 1969. The conversion of alkenoic acids to alkynoic acids by bromination–dehydrobromination. Chem. Phys. Lipids 3, 91–97.

Lie Ken Jie, M.S.F., Cheng, K.L., 1995. Nuclear magnetic resonance spectroscopic analysis of homoallylic and bis homoallylic substituted methyl fatty ester derivatives. Lipids 30, 115–120.

Lie Ken Jie, M.S.F., Kalluri, P., 1995. Synthesis of pyrazole fatty ester derivatives in water: a sonochemical approach. J. Chem. Soc. Perkin Trans. 1, 1205–1206.

Lie Ken Jie, M.S.F., Kalluri, P., 1996. Ultrasound-assisted oxidative cleavage of acetylenic and ethylenic bonds in unsaturated fatty esters with potassium permanganate. Lipids 31, 1299–1301.

Lie Ken Jie, M.S.F., Lam, C.K., 1995. Ultrasound assisted epoxidation reaction of long chain unsaturated fatty esters in water. Ultrasonic Sonochem. 2, 11–14.

Lie Ken Jie, M.S.F., Lam, C.K., 1996. Regiospecific oxidation of unsaturated fatty esters with palladium(II) chloride-*p*-benzoquinone: a sonochemical approach. Chem. Phys. Lipids 81, 55–61.

Lie Ken Jie, M.S.F., Pasha, M.K., Ahmad, F., 1996. Ultrasound-assisted synthesis of santalbic acid and a study of triacylglycerol species in *Santalum album* (Linn.) seed oil. Lipids 31, 1083–1089.

Lie Ken Jie, M.S.F., Pasha, M.K., Lam, C.K., 1997. Ultrasonic stimulated oxidation reactions of 2,5-disubstituted C18 furanoid fatty esters. Chem. Phys. Lipids 85, 101–106.

Lie Ken Jie, M.S.F., Syed Rahmatullah, M.S.K., Lam, C.K., Kalluri, P., 1994. Ultrasound in fatty acid chemistry: synthesis of a novel 1-pyrroline fatty ester isomer from methyl ricinoleate. Lipids 29, 889–892.