Synthesis of Long-Chain (E)-3-Alkenoic Acids by the Knoevenagel Condensation of Aliphatic Aldehydes with Malonic Acid

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Knoevenagel condensation of aliphatic aldehydes with malonic acid in equimolar ratio in triethylamine, which served the dual purpose of the solvent as well as the base, gave alkenoic acids in 80–88% yield as determined by acid values of the products and by gas-liquid chromatography with methyl heptadecanoate as the internal standard. The alkenoic acids were converted to methyl esters, purified by column chromatography and characterized by proton nuclear magnetic resonance, infrared and mass spectral analyses. The spectral data clearly established that the acids formed were (E)-3-alkenoic acids. The purified methyl esters were also subjected to the oxymercuration-demercuration reaction, and the mass spectra of the resulting methoxy esters confirmed the exclusive formation of 3-alkenoic acids.

KEY WORDS: Aliphatic aldehydes, (E)-3-alkenoic acids, Knoevenagel condensation, malonic acid, triethylamine.

Long-chain 3-alkenoic acids are useful intermediates for the synthesis of a variety of organic compounds and are synthesized by various methods (1–6). The simplest method for synthesis of (E)-2-alkenoic acid is the Knoevenagel condensation of an aldehyde with malonic acid by means of an organic base such as pyridine. The Linstead modification (7) of the Knoevenagel condensation, in which triethanolamine or other tertiary amines are used, gives modest yields of 3-alkenoic acids. Corey (8,9) postulated the possibility of orienting the Knoevenagel condensation for the synthesis of Δ2- or Δ3-unsaturated acids in a predictable way by modifying the base strength and the polarity of the medium. 3-Alkenoic acids of high stereochemical purity were prepared by Ragoussis (10) in good yields by reacting various aliphatic aldehydes with a three-molar excess of malonic acid and with piperidinium acetate as a base in xylene. The present communication pertains to the synthesis and spectral studies of a series of (E)-3-alkenoic acids of high purity that were obtained in good yields by the Knoevenagel condensation of various aliphatic aldehydes with malonic acid in equimolar ratio by using triethylamine, which served as a base, as well as a solvent.

EXPERIMENTAL PROCEDURES

Materials and methods. The long-chain primary alcohols were purchased from Fluka Chemie (Buchs, Switzerland). Triethylamine and malonic acid of laboratory reagent grade were purchased from Loba Chemie (Bombay, India) and Alchem Laboratories (Bombay, India), respectively. Pyridinium chlorochromate (PCC) was prepared in the laboratory and used for the oxidation of alcohols (11). Other chemicals and solvents used were of analytical grade.

Infrared (IR) spectra were recorded in CS_2 solution in a Shimadzu IR-470 unit (Shimadzu, Japan) with a 0.2-mm NaCl cell. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in $CDCl_3$ solution in a Jeol FX 90Q spectrometer (JEOL Ltd., Japan) with tetramethylsilane as internal standard. Mass spectra were recorded in a V.G. Micromass 7070 H unit (VG Analytical Ltd., Manchester, United Kingdom). Gas-liquid chromatography (GLC) was carried out in an HP 5840 A unit (Hewlett-Packard, Palo Alto, CA) equipped with a data processor, hydrogen flame ionization detector (FID) and a glass column (1.8 m × 6 mm) packed with 5% SE-30 Gas Chrom Q (100–120 mesh). The injection port and detector were maintained at 270 and 300°C, respectively. The column temperature was programmed from 100 to 250°C at the rate of 10°C/min. The flow rate of carrier gas, nitrogen, was 30 mL/min.

Octanal. A 1-L, round-bottom flask, equipped with a reflux condenser, a mechanical stirrer and a nitrogen inlet, was charged with anhydrous dichloromethane (300 mL) and PCC (65 g, 0.3 mole). One-octanol (25 g, 0.2 mole), in one portion, was added to this stirred suspension, and stirring was continued for 2 h under nitrogen atmosphere. Anhydrous diethyl ether (300 mL) was then added, and supernatant liquid was decanted from the black gum. The residue was washed with anhydrous diethyl ether (3 × 100 mL), and the combined solution was filtered through a pad of Celite. Concentration of the filtrate and distillation of the residue gave octanal (b.p. 63–65°C at 11 mm Hg pressure; 18 g; 75% yield).

3-Decenoic acid. Malonic acid (6.1 g, 58.5 mmoles) was dissolved in triethylamine (8.9 g, 87.8 mmoles) in a 100-mL, round-bottom flask fitted with a magnetic stirring bar, a reflux condenser, a dropping funnel and a nitrogen inlet tube. Octanal (7.5 g, 58.5 mmoles) was added slowly over a period of 0.5 h under continuous stirring at room temperature (25°C). The contents were then heated to 80°C and maintained at this temperature for 3 h. The product was then acidified with dilute HCl and extracted with diethyl ether. The ether extracts were thoroughly washed with distilled water and dried over anhydrous sodium sulfate. The product (9.32 g) was obtained by removal of the solvent with a rotary evaporator. The acid value of the product was found to be 298 (calculated 330). The yield (83.7%) of the acid was found on the basis of determined and calculated acid values. The crude product was converted to methyl ester by treating with methanol containing sulfuric acid (2%), followed by usual work-up. The yield of 3-decenoic acid as methyl ester was calculated also by GLC on an SE-30 column with methyl heptadecanoate (17:0) as internal standard. The crude methyl ester was purified by silica gel (60–120 mesh) column chromatography with hexane/diethyl ether (96:4, vol/vol) as eluting solvent. The purity of methyl ester, as determined by GLC, was 95%. The purified methyl ester was characterized by ^{1}H-NMR, mass and IR spectral analyses, and the *trans* content was determined according to the AOCS method (12). ^{1}H-NMR ($CDCl_3$, δ): 5.57–5.37,

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TABLE 1

Yields of (E)-3-Alkenoic Acids

3-Alkenoic acid	Acid value		% Yield	
	Determined	Calculated	Based on acid value of the product[a]	Based on gas-liquid chromatography data
3-Nonenoic acid	319	360.0	84.0	86.2
3-Decenoic acid	298	330.0	83.7	84.0
3-Undecenoic acid	262	304.9	80.5	82.1
3-Dodecenoic acid	235	283.3	88.4	88.0
3-Tetradecenoic acid	212	248.0	81.8	80.0
3-hexadecenoic acid	183	220.6	82.2	80.2
3-Octadecenoic acid	156	198.9	78.1	79.5

[a] After making corrections for the saturated acid (*ca.* 4%) formed due to oxidation of the aldehyde during reaction.

m (2H, C*H*=C*H*); 3.72, *s* (3H, OCH_3); 2.97, *d* (2H, CH=CH-CH_2-C=O); 2.12-1.81, *m* (2H, -CH_2-C=C); 1.25, *bs* (8H, -(CH_2)$_4$-); 0.85, *t* (3H, -CH_3). Mass, *m/z* (relative intensity, %): 184 (M^+, 10.4), 152 (M-32, 66.6), 110 (M-MLRF, 100), 96 (54.1), 74 (MLRF, 47.9). IR (neat, cm^{-1}): 1740, 1660, 970.

The purified esters were subjected to the oxymercuration reaction by means of mercuric acetate in methanol followed by reduction with $NaBH_4$ (13). The resulting methoxy ester was purified by thin-layer chromatography with silica gel G and hexane/diethyl ether (80:20, vol/vol) and analyzed by mass spectrometry. Mass, *m/z* (relative intensity, %): 216 (M^+, absent), 201 (M-15, 16), 131 (100), 71 (70).

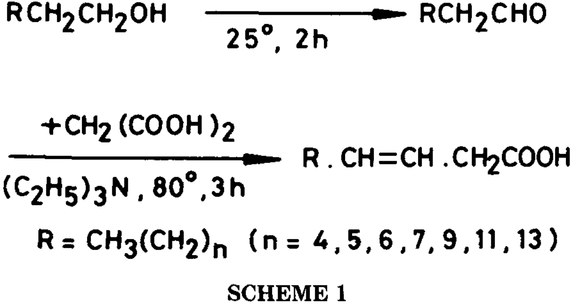
In a similar way, 3-nonenoic, 3-undecenoic, 3-dodecenoic, 3-tetradecenoic, 3-hexadecenoic and 3-octadecenoic acids were prepared from suitable aldehydes and malonic acid in the presence of triethylamine, and they were also analyzed. The results are given in Table 1.

RESULTS AND DISCUSSION

The present synthesis of (E)-3-alkenoic acids is outlined in Scheme 1. Heptanal, octanal, nonanal, decanal, dodecanal, tetradecanal and hexadecanal were prepared from the corresponding alcohols by the PCC oxidation method. These aldehydes were reacted with malonic acid in the presence of the triethylamine in the molar ratio of 1:1:1.5, respectively. The yields of 3-alkenoic acids were calculated on the basis of acid values of the total products and from GLC data. The response factors of different purified alkenoic acid esters in comparison with 17:0 ranged from 0.9 to 1.0. The individual responses of the purified esters were used for the analysis of crude esters. The yields of the alkenoic acids, determined on the basis of the acid values of the total reaction products and by GLC, are in fair agreement and ranged from 80–88% (Table 1).

The ^{1}H-NMR spectra of the alkenoic esters, apart from other signals, showed a doublet at 3.0 δ for methylene-group protons, which are flanked by the carbonyl function of the ester group and by the olefinic group, indicating that the acids formed were 3-alkenoic acids. The mass spectra of all esters showed a clear molecular ion of intensity ranging from 10–15%, with respect to the base peak. The mass spectra also showed peaks corresponding to the loss of MeOH, the McLafferty rearrangement fragment (MLRF) and other characteristic fragments of a normal aliphatic ester. Loss of MLRF from the molecular ion as a neutral species resulted in a terminal acetylenic ion radical in all esters with varying intensities (75–100%), as shown in Figure 1. The presence of this acetylenic ion radical appears to be a characteristic feature of 3-olefinic esters, which is not observed in other olefinic esters.

The mass spectra of all the purified methoxy esters showed a base peak at *m/e* 131, which could be formed by the homolytic cleavage of the bond between the carbon bearing the methoxy group and the carbon of the alkyl chain, leaving the charge on the hetero atom as explained in Figure 2. This confirms the exclusive formation of 4-methoxy derivatives. It is also reported in the literature (13) that 3-alkenoic esters, when subjected to oxymercuration reaction, yield 4-methoxy derivatives up to an extent



SCHEME 1

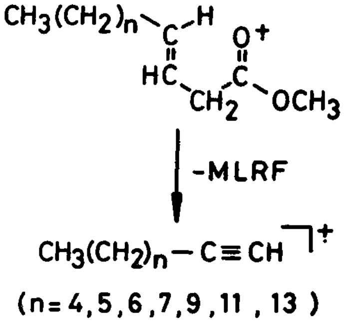


FIG. 1. Mass spectral fragmentation of (E)-3-alkenoic acid methyl esters.

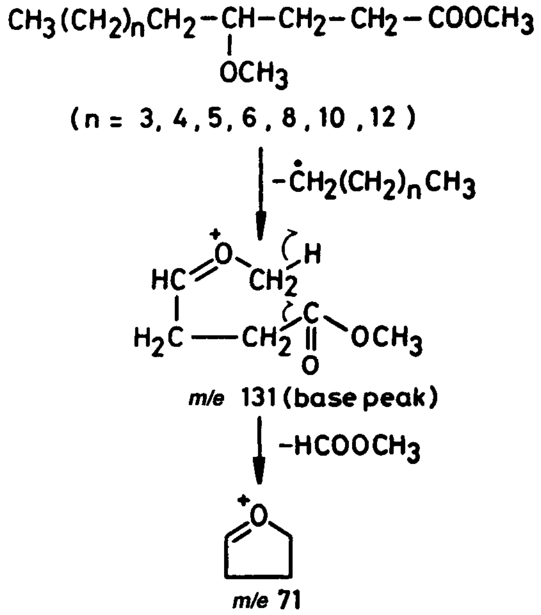


FIG. 2. Mass spectral fragmentation of methoxy derivatives of (E)-3-alkenoic acid methyl esters.

of about 90%. The base peak at *m/e* 131 loses methyl formate to afford an intense ion at *m/e* 71 (relative abundance is ⩾70% in all cases), as shown in Figure 2. The above data showed the formation of 4-methoxy esters, confirming the original acids to be 3-alkenoic acids. The IR spectra of 3-alkenoic acid esters showed bands at 1740 and 1660 cm^{-1} due to the presence of C=O and C=C groups. The presence of a strong band at 970 cm^{-1} showed formation of *trans* unsaturation. The *trans* content in various esters ranged from 90–95% in comparison with methyl elaidate (12).

In the present work, use of triethylamine as a base as well as solvent and equimolar ratios of malonic acid and aldehydes yields (E)-3-alkenoic acids in good amounts, ranging from 80–88%. The presented synthesis avoids the use of large molar excess of expensive malonic acid. The reaction conditions are easily attained, and only a simple work-up is required to obtain the product.

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