Ozonolysis of Olefins, II[1]; Linseed Oil as a Renewable Resource for Alkyl 3,3-Dialkoxypropanoates

Martin Mittelbach,* Norbert Poklukar

Institute for Organic Chemistry, Karl-Franzens-Universität, Graz, Heinrichstraße 28, A-8010 Graz, Austria

A new approach to the synthesis of alkyl 3,3-dialkoxypropanoates, which are important intermediates in organic synthesis, starting from fatty acid esters is described. Thus, ozonolysis of methyl linoleate and methyl linolenate in alcoholic hydrogen chloride affords a reaction mixture, from out of which the alkyl 3,3-dialkoxypropanoates can be isolated by fractional distillation in 60–65% yield. Even linseed oil, which contains high amounts of linolic and linolenic acid, can be used as starting material, after conversion into the methyl esters by methanolysis. Byproducts of the ozonolysis can be oxidized to the corresponding carboxylic acids which are valuable intermediates in oleochemistry.

Alkyl 3,3-dialkoxypropanoates (**3**) are protected derivatives of the unstable esters of formylacetic (malonaldehydic) acid and important intermediates for the synthesis of heterocyclic compounds such as coumarins,[2] isoxazoles,[3] porphyrins,[4,5] and thiadiazines.[6] Further, ethyl 3,3-diethoxypropanoate (**3b**) is used as starting material for the preparation of antihypertensives,[7] cephalosporins,[8] alkaloids,[8] spermine metabolites,[9] and photographic sensitizers.[10] For further applications of the commercially available compounds **3b** see Lit.[11]

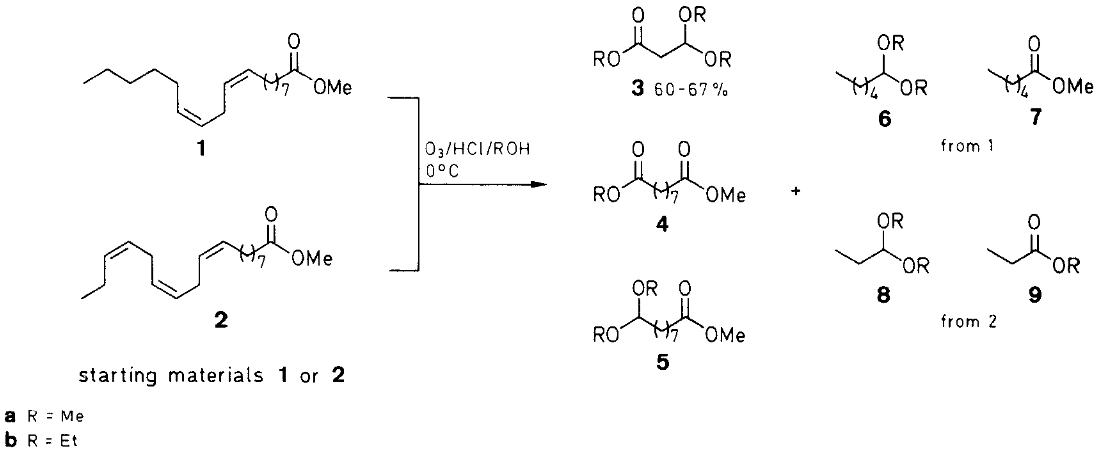
Due to the importance of compounds **3**, numerous methods for their preparation have been published. In the first reported synthesis of **3b**, ethyl formate and ethyl acetate were condensed to ethyl formylacetate which was then acetalized to **3b**.[12] Other preparations of **3b** consist of the addition of tetrachloromethane to ethyl vinyl ether,[13] or the reaction of acetylene with diethyl carbonate in the presence of sodium ethoxide.[14] Compound **3b** has also been obtained by a modified Reformatsky reaction involving triethylorthoformate and ethyl bromoacetate.[9] Other approaches started from ethyl 3-ethoxyacrylate,[15] ethyl propynoate,[16] ketene,[17] ethene[18] and substituted ethenes,[19] 1,3-dioxane derivatives,[20] hydroxyacrylates,[21] or aminopropanoates.[22] All these methods are multistep syntheses, requiring either expensive starting materials and reagents, or giving poor overall yields. Recently, the haloform reaction of 4-alkoxy-1,1,1-trichloro-3-buten-2-ones was reported to give alkyl 3,3-dialkoxypropanoates in good yields.[23]

We describe here a novel strategy for the synthesis of compounds **3** starting from renewable, natural polyunsaturated fatty acids, which possess the structural element $(CH{=}CHCH_2)_n$ ($n \geq 2$).

Ozonolysis of methyl linoleate (**1**) or methyl linolenate (**2**) in alcoholic hydrogen chloride gave C_3 and C_9 fragments (and also C_6 fragments from **1**). Surprisingly, the bifunctional C_3 fragments consisted mainly of esters **3** and only minor amounts of dialkyl malonate and 1,1,3,3-tetraalkoxypropane; this fact has also been observed in the ozonolysis of the model compound 1,4-cyclohexadiene.[1] The other main products were the C_9 compounds dialkyl nonanedioates **4a,b** and alkyl 9,9-dialkoxynonanoates **5a,b** which were obtained in a combined yield of 90%. In addition 1,1-dialkoxyhexanes **6** and alkyl hexanoates **7** were formed in the case of **1** and 1,1-dialkoxypropanes **8** and alkyl propanoates **9** in the case of **2**. From the ozonolysis mixture, the product **3** could be separated by fractional distillation in 61–67% yield with a purity of 97–98%.

Linseed oil, which contains high amounts of polyunsaturated fatty acids, can also be used as starting material. It is converted into the methyl esters by methanolysis,[24] then ozonized to give ester **3a** which is isolated in 60% yield by fractional distillation (purity: 97%). Further oxidation of the byproducts with ozone according to Lit.[25] affords a mixture of practically useful methyl esters, which may be separated by distillation. Another method is the oxidation of the various distillation fractions with a mixture of hydrogen peroxide and formic acid;[26] this affords the corresponding acids, mainly azelaic acid, a valuable intermediate for the synthesis of polymers and plasticizers.

Methyl linoleate (**1**) and methyl linolenate (**2**) were purchased from Aldrich Chemical Co. and were of 99% purity. Linseed oil was of local provenance; the fatty acid composition was analyzed by GC: palmitic acid 6.3%, stearic acid 3.4%, oleic acid 17.5%, linoleic acid 17.0%, linolenic acid 55.5%.



The different reaction products in the ozonolysis mixture were identified either by comparison with authentic samples or by GC/MS using a Hewlett Packard MSD instrument, the ratio of the products being determined by FID detection.

Methyl 3,3-Dimethoxypropanoate (3a) by Ozonolysis of Methyl Linoleate (1):

Methyl linoleate (**1**; 5.5 g, 18.7 mmol) is treated with a 1 M solution of HCl in MeOH (100 mL) and then ozonized with a 4–5 vol% O_3/O_2 mixture at 0 °C, until formation of I_2 is observed in a KI solution, which is connected to the reaction vessel. Nitrogen is bubbled through the mixture for 5 min. The mixture is then slowly heated to reflux temperature und refluxed until all peroxides have been destroyed (ca. 30 min). The solution is neutralized with solid $NaHCO_3$, filtered, and evaporated under reduced pressure. The resultant oil is dissolved in CH_2Cl_2 (20 mL), this solution is dried (Na_2SO_4), and the solvent is evaporated. The residue is distilled through a short Vigreux column to give **3a**; yield: 1.7 g (61 %); bp 79–80 °C/26 mbar (Lit.[23] bp 66–67 °C/14 mbar).

Relative peak area of the components formed by ozonization is determined by GC: dimethyl malonate 0.01, methyl 3,3-dimethoxypropanoate (**3a**) 1.0, 1,1,3,3-tetramethoxypropane 0.05, 1,1-dimethoxyhexane (**6a**) 0.7, methyl hexanoate (**7a**) 0.4, methyl 9,9-dimethoxynonanoate (**5a**) 1.8, and dimethyl nonanedioate (**4a**) 1.5.

Ethyl 3,3-Diethoxypropanoate (3b) by Ozonolysis of Methyl Linolenate (2):

The analogous ozonolysis of methyl linolenate (**2**; 5.26 g, 18.0 mmol) in dry EtOH (150 mL) gives **3b**; yield: 4.6 g (67 %); bp 102–105 °C/26 mbar (Lit.[23] bp 92–95 °C/14 mbar).

Relative peak area of the ozonolysis mixture: diethyl malonate 0.016, ethyl 3,3-diethoxypropanoate (**3b**): 1.0, 1,1,3,3-tetraethoxypropane 0.011, methyl 9,9-diethoxynonanoate (**5b**) 0.46, methyl ethyl nonanedioate (**4b**) 0.56.

Methyl 3,3-Dimethoxypropanoate (3a) by Ozonolysis of Methyl Esters from Linseed Oil:

Methyl esters from linseed oil (20.0 g), prepared by methanolysis of linseed oil,[24] are ozonized in a 1 M solution of HCl in MeOH (160 mL) described for **1** to give **3a**; yield: 7.5 g (60 %); bp 78–79 °C/26 mbar.

Relative peak area of the components of the ozonolysis mixture (without consideration of methyl palmitate and methyl stearate): dimethyl malonate 0.03, methyl 3,3-dimethoxypropanoate (**3a**) 1.0, 1,1,3,3-tetramethoxypropane 0.01, 1,1-dimethoxyhexane (**6**) 0.1, methyl hexanoate (**7a**) 0.09, 1,1-dimethoxynonane 0.24, methyl nonanoate 0.21, methyl 9,9-dimethoxynonanoate (**5a**) 1.18, dimethyl nonanedioate (**4a**) 1.01.

This work was supported by the Jubiläumsfonds der Österreichischen Nationalbank, Projekt Nr. 2573.

Received: 11 August 1989; revised: 29 September 1989

(1) Mittelbach, M.; Poklukar, N.; Junek, H.; Ozonolyse von Olefinen, I; *Liebigs Ann. Chem.* **1990**, in press.

(2) Crosby, D.G.; Berthold, R.V. *J. Org. Chem.* **1962**, *27*, 3083.

(3) Kusumi, T.; Chang, C.C.; Wheeler, M.; Kubo, I.; Nakamishi, K. *Tetrahedron Lett.* **1981**, *22*, 3451.

(4) Collman, J.P.; Chong, A.O.; Jameson, G.B.; Oakley, R.T.; Rose, E.; Schmittou, E.R.; Ibers, J.A. *J. Am. Chem. Soc.* **1981**, *103*, 516.

(5) Lecas-Nawrocka, A.; Levisalles, J.; Mariacher, C.; Renko, Z.; Rose, E. *Can. J. Chem.* **1984**, *62*, 2054.

(6) Goya, P.; Stud, M. *J. Heterocycl. Chem.* **1978**, *15*, 253.

(7) Witkowski, J.T.; Czarniecki, M.F. *US Patent* 4634689 (1985), Schering Corp.; *C.A.* **1987**, *106*, 120067.

(8) Montavon, M.; Reiner, R. *US Patent* 4348518 (1974), Hoffmann-La Roche, Inc.; *C.A.* **1983**, *98*, 71813.

(9) Israel, M.; Zoll, E.C.; Muhammad, N.; Modest, E.J. *J. Med. Chem.* **1973**, *16*, 1.

(10) Cumming, W. *US Patent* 4634773 (1983), Polaroid Corp.; *C.A.* **1987**, *106*, 139831.

(11) Merck Schuchardt INFO 87-13.

(12) Elvain, S.M.; Clarke, R.L. *J. Am. Chem. Soc.* **1947**, *69*, 2657.

(13) Holy, A. *Coll. Czech. Chem. Commun.* **1974**, *39*, 3177.

(14) Croxall, W.J.; Schneider, H.J. *J. Am. Chem. Soc.* **1949**, *71*, 1257.

(15) Croxall, W.J.; Van Hook, J.O.; Luckenbaugh, R. *J. Am. Chem. Soc.* **1949**, *71*, 2736.

(16) Bertz, S.H.; Dabbagh, G.; Cotte, P. *J. Org. Chem.* **1982**, *47*, 2216.

(17) Gresham, W.F. *US Patent* 2449471 (1946), E.I. duPont de Nemours & Co.; *C.A.* **1949**, *43*, 1055.

(18) *Japanese Patent* 5821636 (1981), Ube Industries, Ltd.; *C.A.* **1983**, *99*, 21952.

(19) Fuchigami, T.; Urata, H.; Murata, A. *Japanese Patent* 6289642 (1985), Sagami Chemical Research Center; *C.A.* **1987**, *107*, 153937.

(20) Iwataki, I. *Japanese Patent* 79103823 (1978), Nippon Soda Co., Ltd.; *C.A.* **1980**, *92*, 93910.

(21) Von Itter, F.A.; Vogt, W. *German Patent (DOS)* 3641605 (1986), Huels Troisdorf AG; *C.A.* **1988**, *109*, 230303.

(22) Torii, S.; Iguchi, T.; Kubota, M. *Japanese Patent* 60156643 (1984), Osaka Yuki Kagaku Kogyo Co., Ltd.; *C.A.* **1986**, *104*, 50563.

(23) Tietze, L.F.; Meier, H.; Voß, E. *Synthesis* **1988**, 274.

(24) Mittelbach, M.; Andreae, F.; Junek, H. *Austrian Patent* 386222 (1988).

(25) Sebedio, J.L.; Ratnayake, W.M.N.; Ackman, R.G. *Chem. Phys. Lipids* **1984**, *35*, 21.

(26) Ackman, R., Retson, M.; Gallay, L.; Vandenheuvel, F. *Can. J. Chem.* **1961**, *39*, 1956.