Oleochemical Manufacture and Applications

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9 New chemistry of oils and fats
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9.1 Introduction

In the search for sustainable chemistry, considerable importance is being attached to renewable raw materials that exploit the synthetic capabilities of nature [1, 2]. Oils and fats of vegetable and animal origin make up the greatest proportion of renewable raw materials currently consumed in the chemical industry, since they offer possibilities for applications which can be rarely met by petrochemistry. The extent of the use of natural oils and fats in chemistry was summarized in 1988 [3] in the statement:

‘More than 90% of oleochemical reactions have been those occurring at the fatty acid carboxy group, while less than 10% have involved transformations of the alkyl chain. However, future progress will be along the lines of these latter types of reactions with their potential for considerably extending the range of compounds obtainable from oils and fats.’

Recently, modern synthetic methods have been applied extensively to fatty compounds for the selective functionalization of the alkyl chain [4, 5]. Radical, electrophilic, nucleophilic, pericyclic and transition metal catalyzed additions to the C—C double bond of, for example, oleic acid as the prototype of a readily accessible, unsaturated fatty acid have led to a large number of novel fatty compounds from which interesting properties are expected. Functionalization of C-H bonds in the alkyl chain is also feasible with remarkable selectivity.

9.2 Reactions of unsaturated fatty compounds

Fatty materials can be processed industrially from vegetable oils in such purity that they may be used for further chemical conversions and for the synthesis of chemically pure compounds. Predominantly, oleic acid (1a), petroselinic acid (2a), erucic acid (3a), linoleic acid (4a), and linolenic acid (5a) have been used in the syntheses described below (figure 9.1). Ricinoleic acid (6a) carries an additional hydroxyl group which is useful in stereo- and regioselective syntheses. By pyrolysis of 6b and subsequent hydrolysis, 10-undecenoic acid (7a), an o-unsaturated carboxylic acid, is obtained [3], which is very useful for selective reactions. Santalbic acid (8a), containing a conjugated enyne system, is
Figure 9.1 Starting materials for the synthesis of novel fatty acids: Oleic acid (1a), petroselinic acid (2a), erucic acid (3a), linoleic acid (4a), linolenic acid (5a), ricinoleic acid (6a), 10-undecenoic acid (7a), santalbic acid (8a), cis-9,10-epoxyoctadecanoic acid (11a), cis-9,10; cis-12,13-bisepoxyoctadecanoic acid (12a); cis-9,10; cis-12,13; cis-15,16-trisepoxyoctadecanoic acid 13a, the respective methyl esters 1b–8b, 11b–13b and alcohols 1c–8c, 11c–13c, methyl 12-oxooctadec-10-enoate (9) and 9-oxo-10-undecenoic acid (10).
the main fatty acid in the seed oil of sandal wood and is a substrate well suited for regioselective functionalization of the alkyl chain [6]. The synthesis of methyl santalbate (8b) can be carried out in an ultrasound-assisted five-step reaction sequence from 6b. It is obtained as a mixture with its (Z)-isomer [7]. Methyl ricinoleate (6b) may be oxidized to methyl 12-oxooleate (9) [8]. Oxidation of methyl 10-undecenoate (7b) by SeO2/iBuOOH followed by dehydrogenation gives the ω-unsaturated enone 10 [8b].

The epoxides 11–13, the synthesis of which has been greatly improved recently [4, 5], are commercially available as reactive fatty compounds (see section 9.4).

9.2.1 Olefin metathesis

Transition metal catalyzed olefin metathesis is a well-established process in petrochemistry and industrial polymer chemistry. The conversion of unsaturated fatty acid esters needs special catalysts that tolerate functional groups [4]. Warwel and co-workers developed in the past few years new and effective heterogeneous boron modified rhenium oxide catalysts such as B2O3·Re2O7 on Al2O3·SiO2 + SnBu4 and CH3ReO3 + B2O3·Al2O3·SiO2 for this purpose [9–13]. Co-metathesis of, for example, methyl oleate (1b) and ethylene afforded methyl 9-decenoate (14) and 1-decene (scheme 9.1). Methyl 13-tetradecenoate was obtained by co-metathesis of methyl erucate (3b) and ethylene [13]. Methyl-trioxorhenium [14] and Ru-carbene complexes (Grubbs catalysts) [15] are also suitable catalysts for the metathesis of unsaturated fatty compounds. The ω-unsaturated fatty ester 14 was transesterified with ethyleneglycol and 1, 4-butanediol, respectively, to give ω,ω′-diunsaturated diester 15 that could be copolymerized effectively with ethylene using a cationic palladium catalyst to give partially cross-linked and branched, high molecular weight polymers (scheme 9.2) [16].

9.2.2 Radical additions

Radical additions to unsaturated fatty compounds such as oleic acid (1a) were reviewed in 1989 [17]. We report here on more recent results.

$$\text{(1b)} + \text{H}_2\text{C}=\text{CH}_2 \xrightarrow{\text{[cat.]}} \text{20°C, 25–50 bar, 5–20 h} \xrightarrow{\text{9}} \text{(CH}_2\text{)}_2\text{CO}_2\text{Me} + \text{H}_2\text{C}=\text{CHC}_8\text{H}_{17}$$

**Scheme 9.1** Co-metathesis of methyl oleate (1b) and ethylene yielding methyl 9-decenoate (14) and 1-decene. The ester 1b used (from high-oleic sunflower seed oil) was 87% pure, the conversions and selectivities each > 90%, and the yields of 14 were > 80% [13].
Scheme 9.2 Transesterification of the ω-unsaturated fatty ester 14 with ethyleneglycol and 1,4-butandiol, respectively, to give ω, ω'-diunsaturated diester 15 [16].

9.2.2.1 Manganese(III) acetate initiated additions

The oxidation of enolizable compounds such as acetic acid, malonic acid and acetone with manganese(III) acetate is a well-known method for the generation of electrophilic C-centered radicals which can be added to electron rich alkenes [18]. The regeneration of manganese(III) acetate is possible by anodic oxidation [19]. Addition of malonic acid to methyl oleate (1b) gave the regioisomeric γ-lactones 16 (scheme 9.3) [20].

The corresponding reaction of methyl 10-undecenoate (7b) afforded the spiro-di-γ-lactones 17 (scheme 9.4) [21, 22]. Additions of acetic acid,

\[
(1b) + \begin{array}{c}
\text{CO}_2\text{H} \\
\text{CO}_2\text{H}
\end{array}
\xrightarrow{\text{Mn(OAc)}_3/\text{KOAc}/\text{HOAc}}
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{CO}_2\text{H}
\end{array}
\]

Scheme 9.3 Manganese(III) acetate induced radical addition of malonic acid to methyl oleate (1b) with formation of the regioisomeric γ-lactones 16 [20, 21].

\[
(7b) + \begin{array}{c}
\text{CO}_2\text{H} \\
\text{CO}_2\text{H}
\end{array}
\xrightarrow{\text{Mn(OAc)}_3/\text{KOAc}/\text{HOAc}}
\begin{array}{c}
\text{MeO}_2\text{C} \\
\text{CO}_2\text{Me}
\end{array}
\]

Scheme 9.4 Manganese(III) acetate induced radical addition of malonic acid to methyl 10-undecenoate (7b) with formation of the spiro-di-γ-lactone 17 (mixture of diastereomers) [21].
monomethyl malonate and cyanoacetic acid to the fatty acid esters 1b and 7b also yielded the corresponding γ-lactones. Unfortunately higher carboxylic acids cannot be oxidized to radicals with manganese(III) acetate and added to alkenes [19, 20].

The addition of acetone to methyl oleate (1b) resulted in formation of the regioisomeric 9- and 10-acetonyloctadecanoic acid methyl esters (18) in a yield of 44% (scheme 9.5a). Methyl 13-oxotetradecanoate (19) was obtained in the corresponding reaction with methyl 10-undecenoate (7b) (scheme 9.5c) [20].

\[
\text{Scheme 9.5 Manganese(III) acetate—generated in situ from KMnO}_4\text{, and catalytic amounts of Mn(OAc)}_2\text{—induced radical addition of acetone to methyl oleate (1b) with formation of a) methyl 9(10)-acetonyloctadecanoate 18. b) In the presence of copper(II) acetate the regioisomeric methyl 9(10)-acetonyloctadecanoates 20 were obtained. c) Addition of acetone to methyl 10-undecenoate (7b) gave the linear 13-oxotetradecanoic acid methyl ester (19) [20, 21].}
\]
Addition of stoichiometric amounts of copper(II) acetate (a reagent used for the oxidation of nucleophilic radicals) to the reaction mixture gave two regiosomeric \((E)\)-configured alkenes with high stereoselectivity. The addition of acetone, for example, to \(C_9\) of methyl olate \((1b)\) afforded the \textit{trans}-double bond at \(C_{10}\) while addition to \(C_{10}\) gave the \textit{trans}-double bond at \(C_8\) \((20)\) (scheme 9.5b). This addition–elimination reaction is of importance because it allows an alkylation with retention of the double bond \([20, 21]\).

9.2.2.2 \textit{Solvent-free, copper-initiated additions of 2-halocarboxylates}

Higher carboxylic acids can be added in a very general reaction to unsaturated fatty compounds as their \(\alpha\)-haloesters initiated by electron transfer from copper \([23–26]\). The addition of 2-iodocarboxylates, for example, methyl 2-iodopropanoate \((21)\), to \(7b\) gave the \(\gamma\)-lactone \(22\) in high yields (scheme 9.6). The reaction procedure is very simple. Additions of primary, secondary and tertiary 2-haloesters such as \(21\) to fatty acid esters such as \(1b, 2b, 3b\) and \(7b\) were carried out, to give the corresponding \(\gamma\)-lactones (such as \(22)\). 2-Iodocarboxylates can be obtained \textit{in situ} from the readily available bromo compounds by addition of a stoichiometric amount of sodium iodide.

Diethyl bromomalonates were added to \(7b\) to give \(\gamma\)-lactones \(24\) in good yields in a copper-initiated reaction without addition of sodium iodide. The addition of, for example, diethyl 2-bromo-2-methylmalonate \((23)\) afforded \(\gamma\)-lactone \(24\) in 87% yield (scheme 9.7). The corresponding reaction with a dimethyl 2-bromo-3-alkylsuccinate such as \(25\) gave the addition product \(26\) in 50% yield (scheme 9.8) \([26]\).

The reaction of diethyl 2,5-diiodoadipate \((27a)\) with two equivalents of \(7b\) occurred by formation of di-\(\gamma\)-lactone \(28a\) in 60% yield. The corresponding reaction of diethyl 2,9-dibromosebacate \((27b)\) was carried out by addition of
Scheme 9.8 Copper-initiated addition of ethyl 2-bromo-3-ethylsuccinate (25) to methyl 10-undecenoate (7b) in the presence of sodium iodide [26].

Scheme 9.9 Reaction of diethyl α,α'-diiodoalkanedioates 27 with two equivalents of methyl 10-undecenoate (7b) to give bis-γ-lactones 28 [23, 24].

sodium iodide and afforded the homologous di-γ-lactone 28b (scheme 9.9). The γ-lactones are good candidates for interesting follow-up reactions [26].

9.2.2.3 Additions of 2-haloalkanenitriles initiated by electron transfer from copper in solvent-free systems

2-Iodo- and 2-bromoalkanenitriles can be added to unsaturated fatty compounds in an analogous fashion to the addition of alkyl 2-haloalkanoates [24, 25]. The iodo functionality is preserved in the adduct molecule and can be used for interesting follow-up reactions. The addition of iodoacetonitrile (29a) to 7b gave 12-cyano-10-iodododecanoic acid methyl ester (30a) in 66% yield (scheme 9.10). Reaction of 7b and 2-bromohexanenitrile (29b) with added sodium iodide yielded the iodinated addition product 30b. The regioisomeric adducts 30c were formed by addition of iodoacetonitrile (29a) to methyl erucate (3b).

9.2.2.4 Additions of perfluoroalkyl iodides

Perfluoroalkyl iodides can be added to methyl 10-undecenoate (7b), methyl oleate (1b) or methyl petroselinate (2b) with good to very good yields when the reaction is initiated by electron transfer from metals such as finely divided silver [27], copper powder [28], or lead with a catalytic amount of copper(II) acetate [28]. Perfluoroalkylated fatty compounds are of interest because of their surfactant properties [29].

Addition of perfluoroalkyl iodides to 7b gave product 31, which can be reacted regioselectively with potassium hydroxide in methanol to give the corresponding linear unsaturated perfluoroalkylated carboxylic acids 32 in high
Scheme 9.10 Copper-initiated addition of iodoacetanitrile (29a) and 2-bromohexanenitrile (29b) to methyl 10-undecenoate (7b) and methyl erucate (3b) [24].

Scheme 9.11 Synthesis of 11-perfluoroalkyl-10-undecenoic acid (32) by regioselective elimination of HI from addition product 31 obtained by addition of perfluoroalkyl iodides to methyl 10-undecenoate (7b) [27].

yields (scheme 9.11) [27]. Perfluoroalkyl-1, ω-diiodides 33 were added to 7b using the initiator system Pb/Cu(OAc)$_2$ in methanol. The diaddition product 34 was obtained in high yield. Catalytic hydrogenation afforded the long-chain dicarboxylic dimethyl esters 35, containing a central perfluoroalkyl unit (scheme 9.12) [28].

9.2.2.5 Thermal additions of alkanes

The alkylation of ω-unsaturated fatty compounds such as methyl 10-undecenoate (7b) can be carried out by a thermally initiated radical addition reaction—the ane reaction—with alkanes. Addition of cyclohexane to 7b yielded methyl 11-cyclohexylundecanoate. Remarkably, thermoacidophilic bacteria such as *Alicyclobacillus acidocaldarius* produce a series of ω-cyclohexyl fatty acids of which ω-cyclohexylundecanoic acid is the most abundant [30]. In a similar reaction heptane gave regioisomeric mixtures of alkyl branched methyl C$_{18}$ alkanoates (14% methyl stearate; 49% methyl 12-methylheptadecanoate; 25% methyl 12-ethylhexadecanoate; 12% 12-propylpentadecanoate) and toluene afforded 12-phenyldodecanoate [31].
9.2.2.6 Addition of α-bromo-tetra-acetylglucose to methyl 9-oxo-10-undecenoate

In the presence of zinc and vitamin B$_{12}$ α-bromo-tetra-acetylglucose (36) was added to methyl 9-oxo-10-undecenoate (10), a polarity reversed unsaturated fatty compound. The product C-glucopyranoside (37) was formed with 77% yield and in a ratio of the α- and β-anomers of 13:1 (scheme 9.13) [8].

Scheme 9.13 Radical addition of α-bromo-tetra-acetylglucose (36) to methyl 9-oxo-10-undecenoate (10). The ratio of the anomers was $[α$-37] : $[β$-37] = 13 : 1 [8].

9.2.3 Lewis acid induced cationic additions

Ritter reactions with nitriles giving products equivalent to the formal addition of amides to the double bond of unsaturated fatty compounds have been reviewed quite recently [32, 33].
9.2.3.1 Ethylaluminium sesquichloride induced alkylation
with alkyl chloroformates

Alkylated fatty acids have interesting properties [34], such as good ‘spreadability’, good emolliency, low viscosity, low pour points and good oxidative and hydrolytic stability. An effective synthesis of these products is therefore important [3]. Isostearic acid, a commercially available product used in cosmetics and lubricants shows many desirable characteristics [35], but commercial isostearic acid is not a pure compound; it consists of a wide-ranging mixture of substances including 13.9% cyclic and 5.6% aromatic fatty compounds [36]. Isostearic acid is formed as a by-product in the montmorillonite-induced dimerization process of oleic acid. Recently a new method for the alkylation of alkenes was described, using alkyl chloroformates in the presence of alkyl aluminium halides [37].

Oleic acid (1a) was treated with isopropyl chloroformate (38) mediated by ethylaluminium sesquichloride yielding 73% of a mixture of 9- and 10-isopropylloctadecanoic acid (39) (scheme 9.14). Methyl ricinoleate (6b) afforded 60% of methyl 12-hydroxyoctadecanoate isopropylated at the 9- and 10-positions. The isopropylation of 1-alkenes such as 7a had to be carried out in the presence of triethylsilane, an effective hydride donor.

The isopropylation of methyl santalbate (8b) afforded a mixture of addition products 40 and 41 in 54% yield [6]. The main product was the isopropylated allenic fatty acid methyl ester 41 (scheme 9.15). The formation of 40 and 41 can be rationalized assuming regioselective addition of the isopropyl cation to C\(_9\) of 8b, giving the resonance-stabilized intermediate, which can be trapped by hydride transfer from triethylsilane to give 41 as the 1,4-addition product and 40 as the 1,2-addition product.

The alkylation has been applied to native oils such as sunflower oil to give the isopropylated oil with low iodine value, low acid number, and a low pour point.

![Scheme 9.14](image-url)

Scheme 9.14 Ethylaluminium sesquichloride induced reaction of oleic acid (1a) with isopropyl chloroformate (38) [37].
Scheme 9.15 Ethylaluminium sesquichloride induced reaction of methyl santalbate \((8b)\) with isopropyl chloroformate \((38)\). The allenic fatty compound \((41)\) was obtained by \(1,4\)-addition as main product. The formation of the minor product \((40)\) occurred by \(1,2\)-addition \([6]\).

9.2.3.2 Lewis acid induced additions of aldehydes and acetics
The ene reaction of formaldehyde and alkenes is a suitable method for the synthesis of primary homoallylic alcohols, especially in the presence of alkylaluminium halides \([38, 39]\). The dimethylaluminium chloride \((\text{Me}_2\text{AlCl})\)-induced reaction of \(7a\) and paraformaldehyde yielded 12-hydroxy-9-dodecenoic acid \((42)\) as a mixture of the \((E)\)- and \((Z)\)-stereoisomers in a ratio of 4:1 (scheme 9.16) \([40]\). It is of interest that \((Z)-42\) induces wound healing of tissue damage in soybeans by stimulation of callus formation at the damaged site \([41]\). The corresponding reaction of oleic acid \((1a)\) gave a regioisomeric mixture \((1:1)\) of the branched homoallylic alcohols 9- and 10-hydroxymethyl-10(8)-octadecenoic acid \((43)\). The products were formed with high stereoselectivity as pure \((E)\)-adducts. The addition of paraformaldehyde to ricinoleic acid \((6a)\) occurred with high regioselectivity to position \(C_{10}\) of the molecule chain. The optically active homoallylic alcohol \((44)\) (yield \(68\%\)) was obtained as a diastereomeric mixture in a ratio of 1:2:1 \([42]\).

Additions of formaldehyde to the fatty acid esters \(1b-3b\) and \(7b\) afforded the corresponding branched and long-chain addition products in the presence of the stronger Lewis acid ethylaluminium dichloride \((\text{EtAlCl}_2)\). Ene reactions of formaldehyde and native oils gave the corresponding di- and trifunctionalized triacylglycerols \([42]\). The Lewis acid induced ene reaction of jojoba oil and formaldehyde afforded a mixture of 1:1- and 1:2-adducts \([43]\). \(\omega\)-Hydroxycarboxylic acids are of interest as polyester components.
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\[
(7a) + (\text{CH}_2\text{O})_n
\]

1. Me\textsubscript{2}AlCl, CH\textsubscript{2}Cl\textsubscript{2}, 2h, r.t.
2. H\textsubscript{2}O

\[
\text{HO}\begin{array}{c}
\text{10} \\
\end{array}\begin{array}{c}
\text{9} \\
\end{array}\begin{array}{c}
\text{CO}_2\text{H} \\
\end{array}
\text{(E)-42}
\]

\[
\text{[\text{(E)}]:[\text{(Z)}] = 4:1}
\]

\[
\begin{array}{c}
\text{11} \\
\end{array}\begin{array}{c}
\text{10} \\
\end{array}\begin{array}{c}
\text{OH} \\
\end{array}\begin{array}{c}
\text{CO}_2\text{H} \\
\end{array}
\]

\[
\begin{array}{c}
\text{(43)} \\
\end{array}
\]

\[
\text{OH} \begin{array}{c}
\text{8} \\
\end{array}\begin{array}{c}
\text{9} \\
\end{array}\begin{array}{c}
\text{CO}_2\text{H} \\
\end{array}
\]

\[
\begin{array}{c}
\text{OH} \\
\end{array}\begin{array}{c}
\text{10} \\
\end{array}\begin{array}{c}
\text{11} \\
\end{array}\begin{array}{c}
\text{OH} \\
\end{array}
\]

\[
\text{(44)}
\]

Scheme 9.16  Dimethylaluminium chloride induced addition of paraformaldehyde to 10-undecenoic acid (7a) to give homoallylic alcohol 42 [(E):(Z) = 4:1]. The corresponding additions to oleic acid (1a) and ricinoleic acid (6a) gave homoallylic alcohols 43 (regioisomeric mixture) and 44 (diastereomeric mixture) [40].

The synthesis of homoallylic ethers can be carried out by EtAlCl\textsubscript{2} induced reactions of unsaturated fatty compounds with acetals [44]. The homoallylic ethers 46a–d were obtained in 48–70% yield by reactions of 7b with the dimethyl acetalts 45a–d. The products were formed as stereoisomeric mixtures in a ratio of [(E)]:[(Z)] ≈ 6:1 (scheme 9.17) [44]. The respective reactions of methyl oleate (1b) and, for example, acetal 45a gave two regioisomeric branched (E)-configured homoallylic ethers such as 47.

Additions of formaldehyde and higher aldehydes to unsaturated fatty compounds in the presence of AlCl\textsubscript{3} gave the corresponding alkyl 4-chlorotetrahydropyrans with high selectivity and in good yields [45]. The reaction of two equivalents of formaldehyde with methyl oleate (1b), for example, yielded 86% of the 3,5-dialkyl 4-chlorotetrahydropyrans 48 as a regioisomeric (ratio 1:1) and diastereomeric mixture (scheme 9.18). The 3-alkyl 4-chlorotetrahydropyrans 49 (yield: 73%) was formed in the corresponding reaction with methyl 10-undecenoate (7b). The addition of one equivalent of formaldehyde to methyl ricinoleate (6b) took place by cyclization with the hydroxy group at C\textsubscript{12} and elimination of H\textsubscript{2}O to give the 2,5-dialkyl 4-chlorotetrahydropyrans 50 as a diastereomeric mixture. The analogous reaction of 7b and pentanal afforded the 2,3,6-trialkyl 4-chlorotetrahydropyrans 51 (scheme 9.18). Variation of the alkene, on the one hand, and the carbonyl compound, on the other, leads to a broad range of alkyl chlorotetrahydropyrans.
Scheme 9.17 Ethylaluminium dichloride induced reaction of methyl 10-undecenoate (7b) with dimethyl acetals 45 affording homoallylic ethers 46. Homoallylic ether 47 was obtained in the corresponding reaction of methyl oleate (1b) and formaldehyde dimethyl acetal 45a as a mixture of two regioisomers [44].

Scheme 9.18 AlCl₃-induced addition of two equivalents of paraformaldehyde to methyl oleate (1b) to give 4-chlorotetrahydropyrans 48 (mixture of two regioisomers). 4-Chlorotetrahydropyrans 49 and 50 were obtained in the corresponding reactions with methyl 10-undecenoate (7b) and methyl ricinoleate (6b). Addition of pentanal to 7b afforded the addition product 51 [45].
Furthermore, the addition of formaldehyde to unsaturated fatty compounds could be induced by Lewis acids such as ruthenium trichloride, hexachloroplatinum acid, boron trifluoride and tin tetrachloride to give mainly 1:1- and 1:2-adducts of formaldehyde [46]. The SnCl₄-induced reaction of oleic acid ethyl ester with glyoxylic acid ethyl ester or mesoxalic acid ethyl ester [EtO₂CCOCO₂Et] proceeds with good results yielding the corresponding 1:1-adducts [47].

The hydrosilylation of 1-alkenes such as methyl 10-undecenoate (7b) was optimized using a hexachloroplatinum acid catalyst. A single-phase hydrosilylation is possible as well as a reaction in a biphasic system [48].

9.2.3.3  Alkylaluminium chloride induced Friedel–Crafts acylations

The Friedel–Crafts acylation is an interesting and versatile method for the functionalization of unsaturated fatty compounds [49,50]. The EtAlCl₂-induced acylation of oleic acid (1a) can be carried out with acyl chlorides derived from acetic, heptanoic, hexadecanoic as well as cyclopropanoic, benzoic and thiophene-2-carboxylic acid chlorides (1a:52:EtAlCl₂ = 1:1:2) giving the corresponding β,γ-unsaturated ketocarboxylic acids 53 as pure (E) adducts in yields of 40–58% (scheme 9.19) [50]. The products were obtained as mixtures of regioisomers in a ratio of approximately 1:1. Δ9-12-ketoalkenoic acids such as 54a and 54b were formed by acylation reactions of 7a with acyl chlorides. The stereoisomeric mixtures ([/[(E)]:[/[(Z)]] ≈ 3:1) were isolated in yields of 50–60% (table 9.1).

\[
\begin{align*}
\text{(1a)} & \quad + \quad \text{O} \\
& \quad R \quad \text{Cl} \quad (52) \\
\quad 40–58\% & \quad 1. \text{EtAlCl}_2, \text{CH}_2\text{Cl}_2, \text{24 h, r.t.} \\
& \quad 2. \text{H}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{O} \\
& \quad \text{11} \quad \text{10} \quad \text{OH} \\
\text{(53) & \quad + \quad \text{regioisomer}} \\
\end{align*}
\]

\[
\begin{array}{cccccccc}
\text{(52), (53)} & \text{a} & \text{b} & \text{c} & \text{d} & \text{e} & \text{f} & \text{g} \\
\text{R} & \text{Me} & n\text{C}_9\text{H}_{13} & n\text{C}_{15}\text{H}_{31} & c\text{C}_5\text{H}_5 & \text{Ph} & \text{Thiophene} & \text{Me} \\
\end{array}
\]

**Scheme 9.19** Ethylaluminium dichloride induced Friedel–Crafts acylations of oleic acid (1a) with acyl chlorides 52a–g gave the unsaturated regioisomeric oxocarboxylic acids 53a–g [49].
Table 9.1 Syntheses of $\beta,\gamma$-unsaturated ketones: ethylaluminium dichloride induced Friedel–Crafts acylations of 10-undecenoic acid (7a) and oleic acid (1a)$^a$ [49]

<table>
<thead>
<tr>
<th>No</th>
<th>Alkene</th>
<th>Acylation agent</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(7a)</td>
<td>(52a)</td>
<td><img src="image1" alt="Image" /></td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>(7a)</td>
<td>(52g)</td>
<td><img src="image2" alt="Image" /></td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>(7a)</td>
<td>(55a)</td>
<td><img src="image3" alt="Image" /></td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>(7a)</td>
<td>(55b)</td>
<td><img src="image4" alt="Image" /></td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>(1a)</td>
<td>(55b)</td>
<td><img src="image5" alt="Image" /></td>
<td>49</td>
</tr>
</tbody>
</table>

$^a$reaction conditions: alkene:acylation agent:EtAlCl$_2$ = 1:1:2, CH$_2$Cl$_2$, r.t., 2 h.

$^b$[(E)]:[(Z)] $\approx$ 3:1.

$^c$after recrystallization the pure (E)-adduct was obtained.

$^d$ratio of regioisomers 1:1.

The addition products 53g and 54b are suitable substrates for Nazarov reactions [51]. The Nazarov cyclization of, for example, 53g was carried out by heating for 2 h in a mixture of phosphoric acid and formic acid or by modified reaction conditions in the presence of montmorillonit K10 (scheme 9.20). The reaction was quantitative and gave the cyclopentenone derivative 58 as a mixture of regioisomers. Catalytic hydrogenation afforded the corresponding cyclopentanone derivative 59 [51].

The acylation of methyl santalbate (8b) with heptanoyl chloride (52b) induced by Me$_2$AlCl gave, after a reaction time of 45 min, regioselectively the allenic fatty compound 60 (scheme 9.21) in 66% yield as a diastereomeric mixture [6]. Fatty acid derivatives with an allenic system are known to have interesting properties [52] and in special cases they have been used as substrates in the synthesis of new fatty compounds (see section 9.4) [53].

The intramolecular reaction of petroselinic acid chloride and EtAlCl$_2$ took place by cyclization with high regio- and stereoselectivity to give a cyclohexanone derivative with an exocyclic (E)-configured double bond [49b, 50].
Scheme 9.20 Nazarov cyclization of allyl vinyl ketone 53g followed by hydrogenation of the cyclopentenones 58 to give the regioisomeric cyclopentanones 59. 53g was obtained by Friedel–Crafts acylation of methyl oleate (1b) with crotonic acid chloride (52g) [51].

\[
\text{H}_2\text{PO}_4/\text{HCOOH, 3 h, 80°C}
\]

or K10, CHCl₃, 4 h, 60°C

\[
\text{H}_2, \text{Pd/C, CH}_2\text{Cl}_2
\]

\[
\begin{align*}
\text{(58)} & \quad + \\
\text{(59)}
\end{align*}
\]

\[
\text{H}_2\text{PO}_4/\text{HCOOH, 3 h, 80°C}
\]

\[
\text{or K10, CHCl}_3, 4 \text{ h, 60°C}
\]

\[
\text{H}_2, \text{Pd/C, CH}_2\text{Cl}_2
\]

\[
\begin{align*}
\text{(58)} & \quad + \\
\text{(59)}
\end{align*}
\]

(8b) + (52b)

\[
\text{66%}
\]

1. \(\text{Me}_3\text{AlCl, CH}_2\text{Cl}_2\), r.t.

2. \(\text{H}_2\text{O}\)

\[
\begin{align*}
\text{Cl}\_\text{CH}_-\text{CH}_-\text{C}=\text{C}(\text{CH}_2)\_\text{CH}_3
\end{align*}
\]

\[
\text{(60)}
\]

\[
R^1 = (\text{CH}_2)\_5\text{CH}_3; R^2 = (\text{CH}_2)\_2\text{CO}_2\text{Me}
\]

Scheme 9.21 Regioselective acylation of methyl santalbate (8b) with heptanoyl chloride (52b), induced by dimethylaluminium chloride to give the allenic compound 60 [6].

9.2.4 Nucleophilic additions to reversed-polarity unsaturated fatty acids

Additions to the double bond of unsaturated fatty acids mainly occur with electrophiles, radicals, or in pericyclic reactions. Totally new coupling possibilities arise when the polarity of the electron rich double bond is reversed to an electron poor double bond. In this way, a number of nucleophiles may be coupled to the double bond by Michael additions. Michael acceptors derived from fats such as the enone fatty ester 10 can be prepared in different ways: by SeO₂ oxidation of unsaturated fatty compounds [54], by photo-oxygenation
with singlet oxygen [54] (see section 9.3.2) or by oxidation of the hydroxy group of methyl ricinoleate (6b) to give 9a and conjugation of the double bond yields enone 61 [55]. Furthermore nucleophiles may be inserted by anodic change of the polarity of the double bond to give a radical cation [56, 57] or by palladium catalyzed reactions of fatty allyl carbonates [58].

9.2.4.1 Nucleophilic additions of carbanions to enone fatty acids [55]
Dimethyl malonate (62) and ethyl acetoacetate (63) were added to methyl (E)-12-oxo-10-octadecenoate (61) to give the adducts 64 and 65, respectively, in good yields. 65 was formed from the primary Michael adduct by subsequent aldol condensation/decarboxylation leading to a cyclohexenone which is integrated in the molecule chain of the fatty acid. 1,4-Additions of nitroalkanes 66a−c to 61 gave the adducts 67a−e (scheme 9.22) [55]. By the Nef reaction [59] γ-nitroketones such as 67b were converted into 1,4-dicarbonyl compounds 68. The wide synthetic potential of these substances is pointed out in the production of pyrrole 69 and furan 70 derivatives by Paal–Knorr syntheses (scheme 9.23a) [55, 60]. Pyrrolidine fatty acids such as 71 were obtained by reductive cyclization of the nitroalkane adducts 67a (scheme 9.23b). Compound

\[
\begin{align*}
\text{a)} & \quad \text{CH}_3\text{(CH}_2)_5\text{CH}_{12} \text{-(CH}_2)_6\text{CO}_2\text{Me} + \text{MeO}_2\text{CO}_2\text{Me} \\
& \quad \text{(61)} + \text{(62)} \\
& \quad \text{NaOMe} \rightarrow \text{(64)} \\
& \quad 90\% \\

\text{b)} & \quad (61) + \text{EtO}_2\text{CO}_2\text{Et} \\
& \quad \text{(63)} \\
& \quad \text{NaOMe} \rightarrow \text{(65)} \\
& \quad 96\% \\

\text{c)} & \quad (61) + \text{R}^1\text{R}^2\text{CHNO}_2 \\
& \quad \text{(66)} \\
& \quad \text{NaOMe, MeOH} \rightarrow \text{(67)} \\
& \quad 81−83\% \\

\begin{array}{c|ccc}
66, 67 & a & b & c \\
\text{R}^1 & H & \text{Me} & \text{Me} \\
\text{R}^2 & H & \text{H} & \text{Me} \\
\end{array}
\]

Scheme 9.22 Michael addition of a) malonate 62, b) ethyl acetoacetate 63 and c) nitroalkanes 66a−c to the enone fatty acid ester 61 [55].
Scheme 9.23  a) Nef reaction of γ-nitroketone $67b$ to 1,4-diketone $68$ with following reaction to pyrrole derivative $69$ and furan derivative $70$. b) Reductive cyclization of γ-nitroketone $67a$ giving pyrrolidine derivative $71$ [55].

$71$ was also synthezised from methyl ricinoleate $6b$ by reaction with sodium azide [61].

Aromatic aldehydes $72$ can be added by Stetter reaction [62] to the enone $61$ by reversal of polarity with cyanide ions (scheme 9.24a). In this way, benzoyl-$73a$ (yield: 44%) and 3-pyridinoyl fatty acid derivatives $73b$ (yield: 84%) were obtained by simple reaction procedure [55]. Analogous additions were carried out to methyl 9-oxo-10-undecenoate $10$ to give 12-aryl-substituted methyl dodecanoates $74a$–$d$ (scheme 9.24b) [8]. The synthesis of the fatty acid methyl

Scheme 9.24  Additions of aromatic and heteroaromatic aldehydes $72$ to a) enone $61$ [55] and to b) enone $10$ [8] to give the aryl-substituted 1,4-diketo fatty acid ester $73$ and $74$, respectively.
ester with an integrated γ-lactone 76 (see also section 9.2.2.2) was carried out by 1,4-addition of hydrogen cyanide to 61 followed by saponification of the nitrile to give the fatty acid methyl ester 75 and selective reduction of the keto functionality (scheme 9.25a) [55].

The Michael-acceptor 10 was reacted with nucleophiles in the same way as enone 61 (scheme 9.25b). 1,4-Addition of hydrogen cyanide, hydrolysis of the nitrile and esterification gave dimethyl 4-oxo-dodecandioate (77) [8]. 77 has already been used as an intermediate for the syntheses of prostaglandins [63, 64]. Other methods are known for the synthesis of 77 [65] but these methods require more reaction steps and more expensive reagents.

Mukayama reactions of enone 61 with silyl enolethers and ketene acetals gave many interesting fatty compounds [58].

Scheme 9.25 Addition of hydrogen cyanide to enone fatty acid esters a) 61 [55] and b) 10 [8], followed by saponification of the nitrile to give the 4-keto carboxylic acids 75 and 77, respectively. Reduction of 75 gave the γ-lactone 76.

9.2.4.2 Cathodic hydrodimerization of enone fatty acids
The hydrodimerization of α,β-unsaturated carbonyl compounds and nitriles to give 1,6-dicarbonyl compounds and 1,6-dinitriles, respectively, can be carried out by a cathodic [66] or chemical reductive [67] method. The electrochemical method is used technically in the hydrodimerization of acrylonitrile to give adipodinitrile and is a part of the nylon (6,6)-synthesis [68]. The cathodic hydrodimerization of enone fatty ester 10 yielded the C_{22} diketodiester 78 (scheme 9.26) [8].
Scheme 9.26 Electrochemical hydrodimerization of enone fatty acid methyl ester 10 to give the diketoester 78 [8].

9.3 Reactions of saturated fatty compounds

9.3.1 Radical C—C coupling

9.3.1.1 Oxidative coupling of anions of fatty acids
Carbon-carbon coupling, with the concurrent formation of symmetrical products, may be achieved by the dimerization of two radicals. Radicals may be formed selectively under mild conditions in high concentrations by the oxidation of anionic precursors. Unsaturated fatty acids possess several sites with comparably high C-H acidities which are suitable for anionization: a) the 11-CH-bond of methyl 12-oxo-oleate (9) has a pK_α-value of about 13; b) the CH-bond in α-position to the ester functionality has a pK_α-value of 24; and c) that of the 11-CH-bond of methyl linoleate (4b) of approximately 37.

For radical α,α’-dimerization fatty acid methyl esters such as 7b were anionized with lithium disopropylamide (LDA) in tetrahydrofuran (THF) LDA in THF and oxidatively coupled with copper(I) bromide to 2,3-dialkylsuccinic diesters. The dimeric products were obtained in yields of 56–73% [4, 55a].

Linoleic acid (4a) was deprotonated with the Schlosser base BuLi/H-BuOK [69] and the anion was trapped with CO_2. Because of deprotonation as well at C_2 as at C_11 a 1:1-mixture of di- and tricarboxylic acids was obtained (yield: 78%). In the corresponding reaction of linoleic alcohol (4c) deprotonation at C_2 did not take place and a regioisomeric mixture of ω-hydroxy carboxylic acids 79 was obtained in 90% yield (scheme 9.27). Cyclization of 79 using

1. nBuLi/KOrBu
2. CO_2
3. H+/H_2O

Scheme 9.27 Synthesis of ω-hydroxy carboxylic acid 79 (regioisomeric mixture) by deprotonation of linoleic alcohol (4c) and addition of CO_2 followed by cyclization to macrolides 80 (isomeric mixture) [70b].
the dilution method with dicyclohexylcarbo-diimide (DCC) gave 80 and regioisomeric macrolides in 68% yield [70b].

Methyl 12-oxo-oleate (9) was anionized with t-BuOK in THF at −78°C and coupled with CuCl$_2$ in dimethyl formamide (DMF) to give the dimers 81a–c. The three regioisomers were statistically formed in a ratio of 1:2:1 (scheme 9.28) [70b].

The dimerization of 17-octadecyn-1-ol (82a) could be carried out with oxygen in the presence of one equivalent of copper(I) ions and one equivalent of diamine with formation of hexatriaconta-17,19-diene-1,36-diol 83a in a yield of 94% [71]. Using 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) as base the reaction time could be shortened compared to the analogous reaction with tetramethylethyl-enediamine (TMEDA). Ester 82b was dimerized in the same way with DBU to product 83b (yield: 96%) (scheme 9.29).

9.3.1.2 Radical C—C coupling of halide fatty acids with activated olefins

Reductive alkylations of C—C double bonds activated by electron withdrawing substituents can be carried out in radical reactions with alkyl halides and

\[
(\text{81a})
\]

\[
(\text{81b})
\]

\[
(\text{81c})
\]

Scheme 9.28 Dimerization of methyl 12-oxo-oleate (9) to give the regioisomeric dimers 81a–c ([81a]:[81b]:[81c]=1:2:1) [70b].

\[
\text{cat. CuCl, DBU Pyridine, O}_2, 8 \text{h} \quad 96\%
\]

\[
X(\text{CH}_2)_{15}C\equiv C\equiv C(\text{CH}_2)_{15}X
\]

\[
(\text{82a}), (\text{82b})
\]

\[
(\text{83a}), (\text{83b})
\]

Scheme 9.29 Oxidative dimerization of 17-octadecyn-1-ol (82a) and methyl 17-octadecynoate (82b) to give the diynes 83a and 83b, respectively [71].
tributyltin hydride [72–74a]. A mixture of methyl 9- and 10-iodostearate (84) was obtained from methyl oleate (1b) and HI by phase transfer catalysis. 84 was reacted with 0.2 equivalent of tributyltin hydride, sodium borohydride and 10 equivalents of activated olefin such as acrylonitrile (85a) and methyl acrylate (85b) to give the adducts 86a and 86b in good yields. In an alternative way the reductive addition can be carried out with zinc and vitamin B12 as catalyst to avoid the toxic tin compound [72, 74a]. Several activated olefins were used and the adducts 86a–c were obtained in good yields (scheme 9.30) [74b].

The anodic homo- and heterocoupling of fatty acids (Kolbe electrolysis) has been used by Schäfer to synthesize many interesting compounds and was reviewed quite recently [75, 76].

![Scheme 9.30: Reductive alkylation of activated olefins 85a–c with methyl 9(10)-iodostearate (84) to the adducts 86a–c [74b].](image)

**Scheme 9.30** Reductive alkylation of activated olefins 85a–c with methyl 9(10)-iodostearate (84) to the adducts 86a–c [74b].

### 9.3.2 Functionalizations of C–H bonds

#### 9.3.2.1 Oxidations of nonactivated C–H bonds

Nonactivated C–H bonds may be functionalized chemically [77] or enzymatically [78]. Particularly important, but yet to be solved satisfactorily, is the regioselectivity of C–H functionalization. Remarkable results were obtained in chlorination reactions [79, 80] especially by photochemical gas phase chlorination of fatty acids [81], and in hydroxylations with amine oxides [8a]. Electrochemical oxidation of terminal C–H bonds proceed with satisfactory regioselectivity [77, 80].

#### 9.3.2.2 Oxidations of allylic C–H bonds

Allylic C–H bonds can be oxidized by a great variety of oxidizing reagents. The allylic oxidation of 1b and 7b with SeO2/tBuOOH [8, 54] is possible but
more favourable is the corresponding reaction of, for example, 1b with singlet oxygen to give a hydroperoxide which is reduced to the corresponding allylic alcohol [54]. In the presence of acetic anhydride and pyridine methyl oleate (1b) can be directly oxidized with singlet oxygen to the regioisomeric mixture of the corresponding α,β-unsaturated ketones 61a, regioisomers of the ketone 61 (scheme 9.31) [54, 58].

9.4 Heterocyclic fatty compounds

Heterocyclic fatty compounds are of increasing interest, since the lipophilic alkyl chain in combination with a heterocyclic moiety is expected to possess promising biological properties. Aziridines are alkylating agents and therefore well known as antitumour agents and chemosterilants, for example [82]. Some 1,5-dialkyltetrazoles are used as analeptics affecting the central nervous system [83]. In 5-substituted tetrazole compounds the tetrazole ring is isosteric with the carboxylic acid group and of comparable acidity. Hence for all biologically active molecules possessing a carboxylic acid group there is a theoretical nitrogen analogue possessing a tetrazole moiety [83]. Tetrazole analogues of fatty acid ethers are substrates for N-myristoyl-transferase and its coenzyme and show antiviral (including HIV) and antifungal activity [84]. Studies on 1,3,4-oxadiazole fatty acid derivatives are not well known although 1,3,4-oxadiazoles in general have a wide variety of uses, particularly as biologically active compounds in medicine and in agriculture [85]. Latest developments including heterocycles on novel long-chain fatty compounds [86] and the synthesis of special fatty acids [87] have been reviewed recently. The synthesis of various fatty compounds containing heterocyclic functionalities have been already mentioned.

9.4.1 O- and S-Heterocyclic fatty acids

Epoxy fatty compounds are the most important fatty heterocycles, having industrial applications as PVC stabilizers and in photochemical cationic curing [88], [89] and synthetic applications as reactants for transformation into further interesting fatty heterocycles. The epoxidation of unsaturated fatty acids has been reviewed recently [90]. Crown ethers derived from unsaturated fatty acids, such as 1a, 2a and 7a were obtained by reacting the corresponding epoxy
derivatives (e.g. 11b) under Lewis acid catalysis with tri-, tetra- or pentaethylenylene glycol followed by tosylation of the hydroxy function, cyclization with alkali hydroxides and saponification of the methyl esters 87a–c (scheme 9.32a) [91]. In this context, it is most interesting that fatty acid-oligo(ethylene glycol) esters have been shown to form ion channels in lipid membranes. The ion channel formers were prepared in a two-step sequence. Monobenzyl ethers, obtained by Williamson reaction of tetra- or pentaethylenylene glycol with benzyl bromide, were esterified with different fatty acids to the corresponding oligo(ethylene glycol) fatty ester 88a–d (scheme 9.32b) [92].

With regard to the pharmacological significance of 2,5-disubstituted furanoid compounds an efficient synthetic method for the preparation of furan 90 has been developed. This method involves conversion of methyl (Z)-9,10-epoxy-12-oxo-octadecanoate (89) (from 6b via chromic acid oxidation to 9b and m-chloroperbenzoic acid epoxidation [93]) with ammonium azide, generated in situ from sodium azide and ammonium chloride in aqueous ethanol (scheme 9.33a) [94]. Introduction of either one or two methyl groups into the

Scheme 9.32  a) Conversion of methyl epoxysestearate 11b to crown ethers 87a–c [91]. b) Oligo(ethylene glycol) fatty esters 88a–d, active as ion channel formers in lipid membranes [92].

Scheme 9.33  a) 2,5-Disubstituted furan 90 by reaction of methyl (Z)-9,10-epoxy-12-oxo-octadecanoate (89) with ammonium azide [94]. b) Ultrasound-assisted Simmons–Smith reaction of furan 90 to form tricyclo derivative 91 [98].
furan ring of a 2,5-disubstituted C₁₈ furan fatty acid is possible [95, 96]. A phenyl substituent at the 3- or 4-position of the furan ring was introduced via 89 as a key intermediate [97]. Ultrasound-assisted Simmons–Smith reaction involving zinc and diiodomethane in 1,2-dimethoxyethane provides a unique method for the cyclopropanation of olefinic bonds in fatty acids and also in triacylglycerols as substrates which also can contain hydroxy groups. Furan 90 was reacted in this manner to form a novel tricyclo derivative 91 (scheme 9.33b) [98].

A number of epithio C₁₈ fatty esters (e.g. 92) resulted in the conversion of the corresponding epoxy fatty esters 6b, 11b or 12b with dimethylthioformamide and trifluoroacetic acid in dichloroethane (scheme 9.34) [99].

### 9.4.2 Nitrogen-containing fatty acid derivatives

Reaction of the nitrone generated in situ by lead tetraacetate oxidation of 3-amino-2-methyl-4-oxoquinazoline with various fatty esters (i.e. 1b, 6b and 10b) furnished the corresponding aziridine derivatives (e.g. 93) in about 50% yield (scheme 9.35) [100]. Treatment of methyl epoxystearate 11b with sodium azide and ammonium chloride gave a regioisomeric mixture of methyl 9,10(10, 9)-azidohydroxystearate (94) and reaction with triphenylphosphine afforded the corresponding aziridine 95 [101]. Starting from diepoxide 12b and triepoxide 13b the methylene-interrupted bisaziridine 96 and trisaziridine 97 were obtained respectively (scheme 9.36) [102]. Both compounds showed considerable cytotoxic, antimicrobial and neuroprotective activity as well as a significant antitumour promoting effect. Azetidine 98 was obtained by treatment of methyl 10-azido-12-hydroxystearate with triphenylphosphine [101].

![Scheme 9.35](image-url)
Isomers of 1-pyrrole fatty methyl esters 99 and 100 were derived from methyl ricinoleate 6b and iso-ricinoleate, respectively (figure 9.2) [61, 103]. The physical properties of a large number of N-substituted pyrrolinium and pyrrolidine derivatives obtained from 1-pyrrole fatty methyl ester were studied [104, 105]. An efficient method has been developed for the preparation of pyrazole and pyridazine fatty ester derivatives. Reaction of methyl 10, 12-dioxostearate (101) (from 6b [106]) and hydrazines in water at 60°C with ultrasound gave pyrazole derivatives 102 in high yields (scheme 9.37) [106]. The latter compound 102 could also be obtained from a novel C18 keto-allenic ester methyl 12-oxo-9,10-oxadienoate (prepared from 6b) by reaction with hydrazone, methylydrazine and phenylhydrazine and ultrasound [53].

Numerous 5-alkyltetrazoles 104 have been prepared starting from fatty nitriles 103 by reaction with sodium azide in the presence of triethylamine.
Scheme 9.37 Synthesis of pyrazole derivatives 102 by reaction of 10,12-dioxostearate 101 and hydrazines with ultrasound [106].

hydrochloride in toluene. The tetrazoles can be converted nearly quantitatively to 5-alkyl-2-methyl-1,3,4-oxadiazoles 105 by refluxing with acetic anhydride (scheme 9.38). Dinitriles could easily be converted in the same manner to bistetrazoles and bisoxadiazoles [107]. Reaction of methyl 9(10)-ketostearate (106) (from 11b [108]) with sodium azide and titanium(IV) chloride in acetonitrile gave a novel 1,5-disubstituted tetrazole derivative 107 (scheme 9.39) [107]. Oxazolines such as 108 have been obtained by conversion of epoxide 11b with nitriles in the presence of boron trifluoride etherate (scheme 9.40) [107].

Scheme 9.38 Preparation of 5-alkyltetrazoles 104 from fatty nitriles 103 by reaction with sodium azide in the presence of triethylamine hydrochloride in toluene and subsequent reaction with acetic anhydride to form 5-alkyl 2-methyl-1,3,4-oxadiazoles 105 [107].

Scheme 9.39 Reaction of methyl 9(10)-ketostearate 106 with sodium azide and titanium(IV) chloride in acetonitrile to 1,5-disubstituted tetrazole derivative 107 [107].

Scheme 9.40 Oxazoline 108 was obtained by conversion of epoxide 11b with acetonitrile in the presence of boron trifluoride etherate [107].
Scheme 9.41 Formation of oxazolidine 109 by hydrogenation of methyl 9,10-azidohydroxystearate 94 and reaction with paraformaldehyde in methanol [107].

Scheme 9.42 Methyl 9(10)-hydroxy-10(9)-oxostearate 110 was converted with (i) formamide to imidazole 111 and (ii) formamide in the presence of sulfuric acid to oxazole derivative 112. Reaction with ammonium thiocyanate in dioxan (iii) yielded an imidazolinethione 113 [107].

Hydrogenation of methyl 9,10-azidohydroxystearate (94) furnished the corresponding amino alcohol. The latter was reacted with aldehydes such as paraformaldehyde in methanol to give oxazolidines such as 109 (scheme 9.41) [107]. Another useful precursor, methyl 9(10)-hydroxy-10(9)-oxostearate (110) (obtained by dimethyl sulfoxide (DMSO) oxidation of epoxide 11b in the presence of boron trifluoride etherate [109]) was converted to imidazole 111 with formamide, to oxazole derivative 112 with formamide in the presence of sulfuric acid, and to imidazolinethione 113 with ammonium thiocyanate in dioxan (scheme 9.42) [107]. Variation of the amide allows access to a great variety of substituted oxazole and imidazole derivatives.

References


