

Recent Developments in the Synthesis of Fatty Acid Derivatives

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Synthesis of New Oleochemicals: Functionalization of Fatty Compounds Using Radical Reactions

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Introduction

Unsaturated fatty compounds such as oleic acid [**1a**], 10-undecenoic acid [**2a**], petroselinic acid [**3a**], erucic acid [**4a**], and the respective esters, alcohols, and native oils (Fig. 1) are alkenes and contain an electron-rich double bond that can be functionalized in many different ways by reactions with electrophilic reagents. It is therefore remarkable that >90% of oleochemical reactions have been focused on the carboxylic acid functionality and <10% have been reactions of the alkyl chain and the C,C-double bond (1). A review on radical additions to unsaturated fatty compounds that appeared in 1989 (2) quoted only very few C,C-bond-forming reactions giving branched and chain-elongated fatty compounds. Since then, modern preparative radical chemistry has been developing and has been applied also to fat chemistry (3–5). We report here on radical additions of activated haloalkanes such as alkyl 2-haloalkanoates and 2-haloalkanenitriles to unsaturated fatty compounds [**1**]–[**4**] initiated by electron transfer from copper in solvent-free

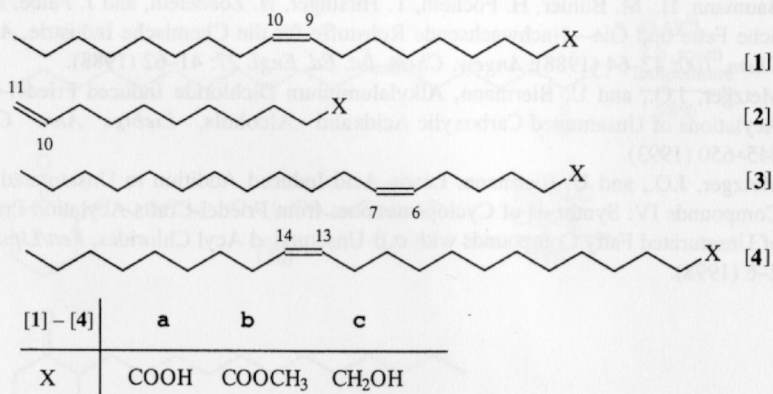


Fig. 1. Unsaturated fatty compounds: oleic acid [**1a**], 10-undecenoic acid [**2a**], petroselinic acid [**3a**], erucic acid [**4a**], and the respective esters [**1b**]–[**4b**] and alcohols [**1c**]–[**4c**].

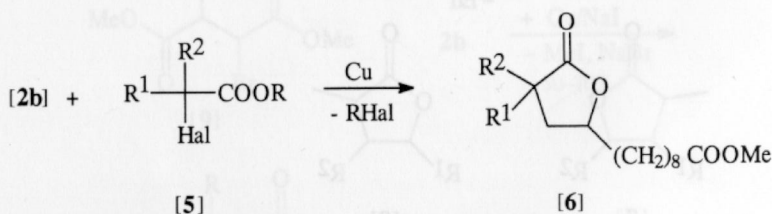
systems. These additions were also carried out with fatty compounds that are hydrogenated in the 2-position to alkenes such as allyl alcohol, vinyl esters, and trimethylsilyl enol ethers.

Radical Additions of Alkyl 2-Haloalkanoates to Unsaturated Fatty Compounds

We reported recently on the radical additions of alkyl 2-iodoalkanoates [5] to alkenes initiated by copper metal in the absence of solvent to give γ -lactones (6,7) (Scheme 1). The reaction procedure is very simple: the alkene, iodo compound, and commercial copper powder are mixed without any pretreatment in a ratio of 1:1.3:1.3 and heated to 100–130°C in an inert atmosphere for some hours. After a simple work-up procedure, the products are obtained analytically pure and in satisfactory yields. Primary (Table 1, entry 1), secondary (entries 2–5), and tertiary (entry 6) alkyl 2-iodoalkanoates [5] have been added to methyl 10-undecenoate [2b].

The alkyl 2-iodoalkanoates [5] can be formed *in situ* from the corresponding bromo compounds, which are more readily available, by the addition of a stoichiometric amount of sodium iodide to the reaction mixture. The products are obtained in high yields, which are similar to those obtained by direct use of the iodo compound (Table 1, entries 2–6). The products can be synthesized without problems on a multigram scale. All of the alkyl 2-haloalkanoates [5] used in this reaction gave the expected radical addition reaction.

Interestingly, the reaction procedure also worked well with methyl oleate [1b], methyl petroselinate [3b], and methyl erucate [4b]. Addition of ethyl 2-iodopropionate [5b] gave the regioisomeric γ -lactones [7] and [8] in good yields and a ratio



Hal = Br, I; R = Me, Et

[5],[6]	a	b	c	d	e	f
R ¹	H	Me	nBu	nC ₁₄ H ₂₉	iPr	Me
R ²	H	H	H	H	H	Me

SCHEME 1. Additions of alkyl 2-haloalkanoates [5] to methyl 10-undecenoate [2b]. Source: Ref. 7.

TABLE 1

Results of the Copper-Initiated Additions of Ethyl 2-Haloalkanoates [5] to Methyl Oleate [1b], Methyl 10-Undecenoate [2b], Methyl Petroselinate [3b], and Methyl Erucate [4b] (Schemes 1 and 2)

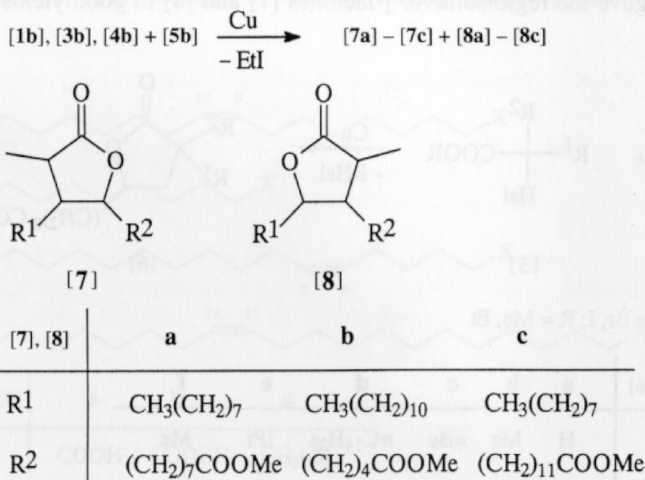
Entry	Alkene	Haloalkane [5]	Product(s)	Yield % ^a
1	2b	a	6a	78
2	2b	b	6b	86 (73)
3	2b	c	6c	73 (70)
4	2b	d	6d	79 (72)
5	2b	e	6e	— (69)
6	2b	f	6f	40 (54)
4	1b	b	7a + 8a ^b	51 (58)
5	3b	b	7b + 8b ^b	49 (60)
6	4b	b	7c + 8c ^b	50 (59)

^aIsolated yield relative to starting alkene obtained with [5] (X = I; R = Et); yield in parentheses was obtained with [5] (X = Br; R = Et) with added NaI.

^bRegioisomeric mixture of products [7] and [8] is ~1:1.

of ~1:1 (Scheme 2). It is remarkable that in these reactions, improved yields of the addition products were obtained by using ethyl 2-bromopropionate [5b] with stoichiometric amounts of sodium iodide added (Table 1, entries 6–8).

We assume that the reaction is initiated by electron transfer from copper to the activated iodoalkane (Fig. 2). The electrophilic radical formed after cleavage of the halide adds to the electron-rich double bond of the alkene, and subsequent iodo abstraction yields a methyl 4-iodoalkanoate that cyclizes to a γ -lactone with elimination of iodo alkane.



SCHEME 2. Additions of ethyl 2-haloalkanoate [5b] to methyl oleate [1b], methyl petroselinate [3b], and methyl erucate [4b].

Source: Ref. 7.

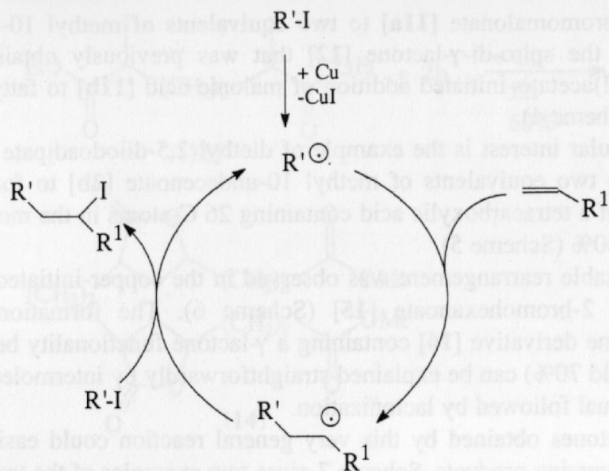
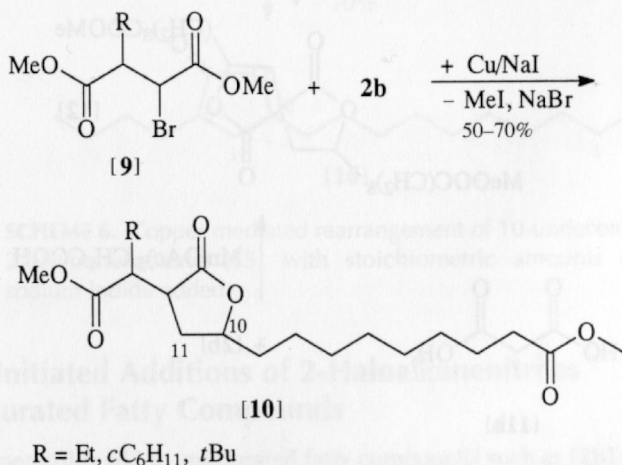


Fig. 2. Mechanism for the copper-initiated addition of activated iodoalkanes to alkenes (R^1-I = alkyl 2-iodoalkanoate **[5]**, 2-iodoalkanenitrile **[18]**; R^1 = alkyl, $(CH_2)_8COOMe$).

Dicarboxylic acid derivatives were reacted as well. Additions of dimethyl 2-alkyl-3-bromosuccinates **[9]** to methyl 10-undecenoate **[2b]** gave new derivatives of tetradecandioic acid with an additional γ -lactone moiety **[10]** (Scheme 3).

Dialkyl bromomalonates, which are strongly activated, were added to alkene **[2b]** initiated by copper in good yields (7). An interesting example is the addition



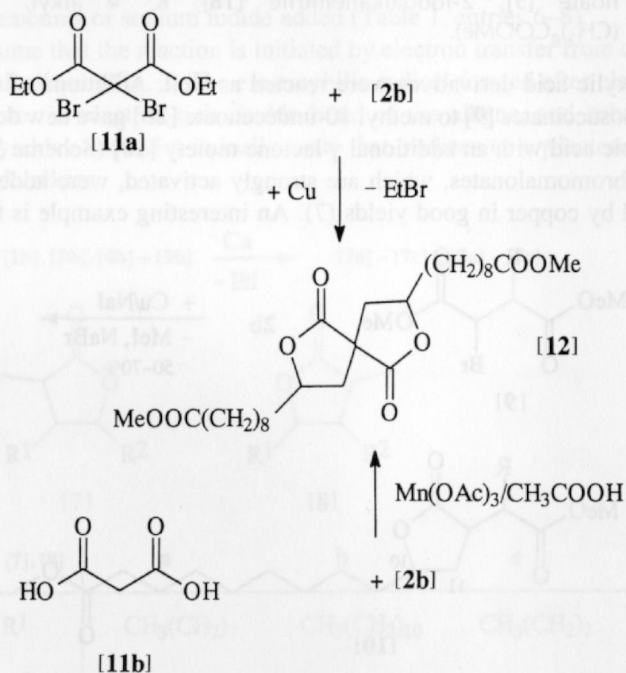
SCHEME 3. Additions of dimethyl 1-alkyl-2-bromo-succinates **[10]** to methyl 10-undecenoate **[2b]** in the presence of stoichiometric amounts of sodium iodide.

of diethyl dibromomalonate [**11a**] to two equivalents of methyl 10-undecenoate [**2b**] to give the spiro-di- γ -lactone [**12**] that was previously obtained also by manganese(III)acetate-initiated addition of malonic acid [**11b**] to fatty compound [**2b**] (8,9) (Scheme 4).

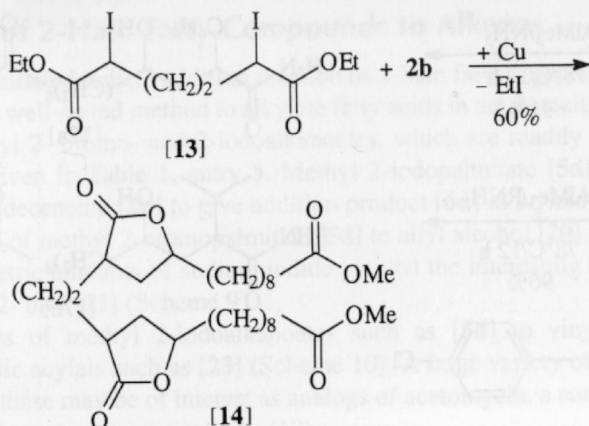
Of particular interest is the example of diethyl 2,5-diiodoadipate [**13**], which was added to two equivalents of methyl 10-undecenoate [**2b**] to form the di- γ -lactone [**14**] of a tetracarboxylic acid containing 26 C-atoms in the molecule chain in a yield of 60% (Scheme 5).

A remarkable rearrangement was observed in the copper-initiated reaction of 10-undecenyl 2-bromohexanoate [**15**] (Scheme 6). The formation of the 1-iodohexadecane derivative [**16**] containing a γ -lactone functionality between C-10 and C-12 (yield 70%) can be explained straightforwardly by intermolecular radical addition as usual followed by lactonization.

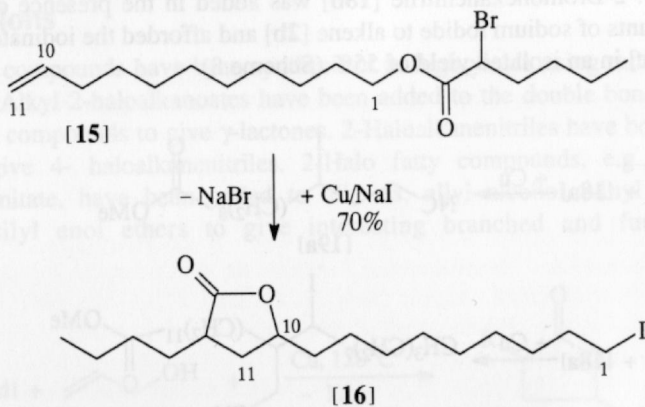
The γ -lactones obtained by this very general reaction could easily be transformed to interesting products. Scheme 7 gives two examples of the transformation of lactones [**6c**] and [**6e**] to diamide [**17a**] and dianilide [**17b**], respectively.



SCHEME 4. Additions of diethyl dibromomalonate [**11a**] initiated by copper powder and of malonic acid [**11b**] initiated by manganese(III)acetate to methyl 10-undecenoate [**2b**] to give spiro-di- γ -lactone [**12**]. Source: Ref. 7.



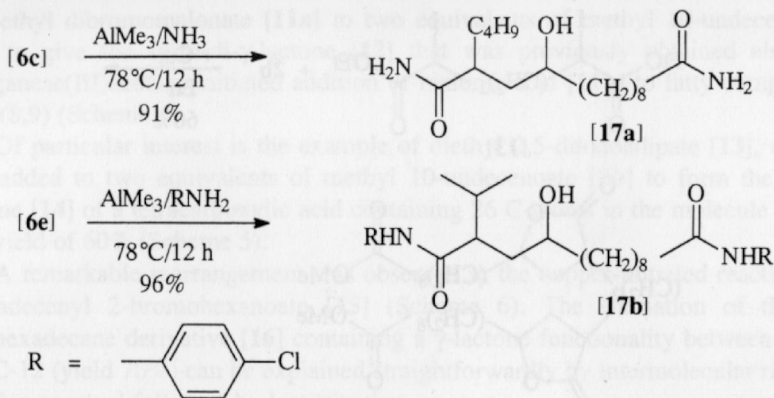
SCHEME 5. Addition of diethyl α,α' -diiodoadipate [13] to two equivalents of methyl 10-undecenoate [2b].
Source: Ref. 7.



SCHEME 6. Copper mediated rearrangement of 10-undecenyl 2-bromohexanoate [15] with stoichiometric amounts of sodium iodide added.

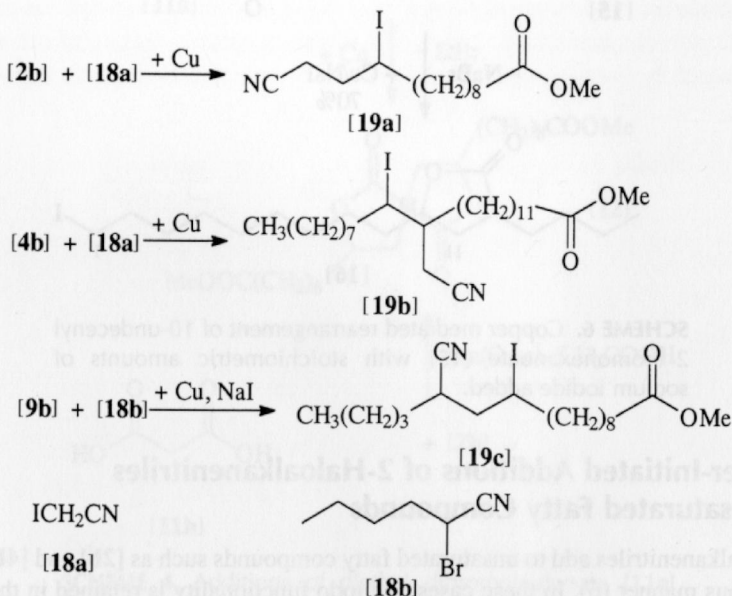
Copper-Initiated Additions of 2-Haloalkanenitriles to Unsaturated Fatty Compounds

2-Haloalkanenitriles add to unsaturated fatty compounds such as [2b] and [4b] in an analogous manner (6). In these cases, the iodo functionality is retained in the addition products, offering interesting possibilities for further transformations. Thus, iodoacetonitrile [18a] was added to methyl 10-undecenoate [2b] and to methyl



SCHEME 7. Transformation of γ -lactones [6c] and [6e] to diamide [17a] and dianilide [17b].

erucate [4b] to give the addition products [19a] and [19b] in yields of 66 and 44%, respectively. 2-Bromohexanenitrile [18b] was added in the presence of stoichiometric amounts of sodium iodide to alkene [2b] and afforded the iodinated addition product [19c] in an isolated yield of 55% (Scheme 8).



SCHEME 8. Additions of 2-haloalkanenitriles to methyl 10-undecenoate [2b] and methyl erucate [4b]. Source: Ref. 7.

Additions of 2-Halo Fatty Compounds to Alkenes

The copper-initiated radical addition reaction of 2-halo fatty compounds to alkenes seems to be a well-suited method to alkylate fatty acids in the 2-position of the alkyl chain *via* alkyl 2-bromo- and 2-iodoalkanoates, which are readily available. One example is given in Table 1, entry 5. Methyl 2-iodopalmitate [5d] was added to methyl 10-undecenoate [2b] to give addition product [6d] in a yield of 79%.

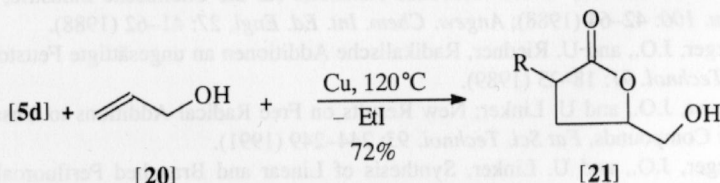
Addition of methyl 2-bromopalmitate [5d] to allyl alcohol [20] in the presence of stoichiometric amounts of sodium iodide yielded the interesting γ -lactone of an octadecan-1,2-diol [21] (Scheme 9).

Additions of methyl 2-iodoalkanoates such as [5d] to vinyl acetate [22] afforded cyclic acylals such as [23] (Scheme 10). A large variety of acylals can be synthesized; these may be of interest as analogs of acetomycin, a natural compound with antibiotic and antitumor activity (10).

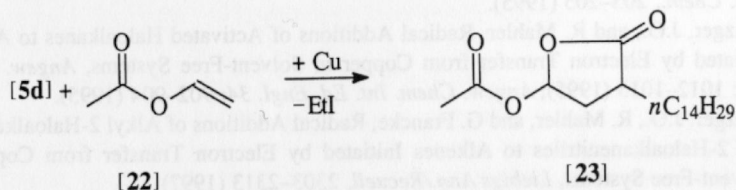
Additions of methyl 2-bromopalmitate [5d] in the presence of sodium iodide to trimethylsilyl enol ethers [24] yielded methyl 2-alkyl-4-oxoalkanoates [25] (Scheme 11).

Conclusions

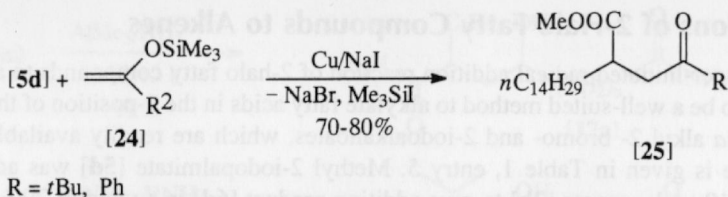
New fatty compounds have been synthesized in high yields using radical addition reactions. Alkyl 2-haloalkanoates have been added to the double bond of unsaturated fatty compounds to give γ -lactones. 2-Haloalkanenitriles have been added as well to give 4-haloalkanenitriles. 2-Halo fatty compounds, e.g., methyl 2-bromopalmitate, have been added to alkenes, allyl alcohol, vinyl esters, and trimethylsilyl enol ethers to give interesting branched and functionalized



SCHEME 9. Addition of methyl 2-iodopalmitate [5d] to allyl alcohol [20].



SCHEME 10. Addition of methyl 2-iodopalmitate [5d] to vinyl acetate [22].



SCHEME 11. Additions of methyl 2-bromopalmitate [5d] to trimethylsilyl enol ethers [24] (R = *t*Bu, Ph).

compounds. Key features of the reaction described here are as follows: no solvent is used, the work-up procedure is simple in comparison to other methods because the copper powder initiator is unproblematic for both work-up and separation, the reagents are used in essentially stoichiometric quantities, the yields are comparably high, even with 1,2-dialkylethenes, the reaction can be performed without problems on a multigram scale, and the initiator can be reused (after total oxidation of the copper, it is readily recovered by reduction).

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