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TIN-FREE REDUCTIVE PHOTOCHEMICAL CARBOXYMETHYLATION OF OLEFINS WITH α-ALKYLTHIOACETATES

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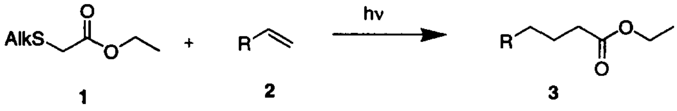
Abstract. An efficient tin-free reductive photochemical carboxymethylation of olefins with α-alkylthioacetates is developed, which (a) is an experimentally simple technique furnishing substituted derivatives of fatty acids in moderate to good yields, (b) is compatible with polar/protic functional groups and solvents, (c) does not require a special reducing reagent, (d) is fairly insensitive to the presence of dissolved oxygen and, generally, does not require degassing prior to irradiation. The critical feature of the mechanism is the "reluctance" of short-lived $MeS^{\bullet}$ to group-transfer, resulting in hydrogen abstraction from the media. © 1997 Elsevier Science Ltd.

Carbon-carbon bond formation via the radical addition across the olefinic double bond is becoming a frequently used tool in organic synthesis,[1] with intramolecular cyclizations of α-halogen carbonyl compounds in the presence of a radical initiator and alkyltin hydride being the technique of choice. Organoselenium/sulfur groups are also employed in such reactions in place of a halogen.[2] Generally, a radical-initiated addition/cyclization is either accompanied by X-group transfer or terminated by hydrogen abstraction. Various alkyltin hydrides, mainly Bu_3SnH, are most commonly employed in radical chain reactions to carry out the reductive radical alkylations. The difficulties frequently encountered in the removal of organotin residues from the reaction products often make this approach less attractive. Another point is that the ratio of radical addition rates and the rates of radical quenching by the tin hydride sometimes prevent *inter*molecular use of this reaction.

We now report a novel, "tin-free", reductive photochemical carboxymethylation of olefins, which (a) is an experimentally simple technique furnishing substituted derivatives of fatty acids in moderate to good yields, (b) is compatible with polar/protic functional groups (e.g. hydroxy) and polar/protic solvents (e.g. aqueous ethanol), (c) does not require a special reducing reagent, (d) is fairly insensitive to the presence of dissolved oxygen and, generally, does not require degassing prior to irradiation.

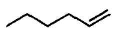
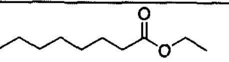
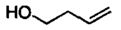
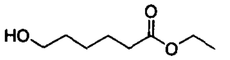
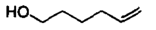
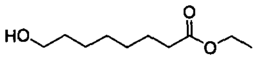
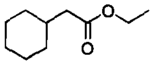
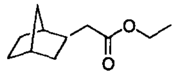
We found that when ethyl α-(methylthio)acetate is irradiated in the presence of an alkene the following reaction takes place (see Table 1 for details).



Scheme 1

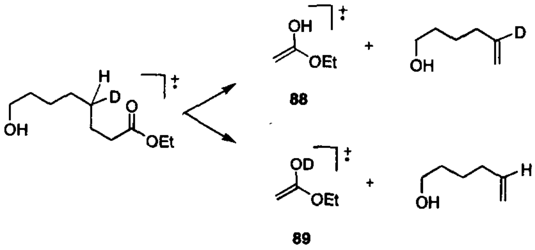
Unfiltered UV irradiation of a medium-pressure Hanovia lamp was used.[3] As it follows from the analysis of the reaction yields, the reaction is clearly more efficient in cases of terminal olefins which is in keeping with the radical character of the process.

Table 1. **Tin-free Photochemical Carboxymethylation of Olefins with MeSCH$_2$COOEt (1)**

Entry	Olefin, 2	Product, 3	Solvent	%, yield^a
1	 **2a**	 **3a**	Acetonitrile	70
			Methanol	64
			80% aq. Ethanol	63
2	 **2b**	 **3b**	Acetonitrile	84
			Methanol	76
			100% Ethanol	66
			80% aq. Ethanol	71
3	 **2c**	 **3c**	Acetonitrile	90
			Methanol	73
			80% aq. Ethanol	68
4	 **2d**	 **3d**	Acetonitrile	21
			Methanol	16
			80% aq. Ethanol	16
5	 **2e**	 **3e**	Acetonitrile	45
			Methanol	48
			80% aq. Ethanol	55

^{a} *optimized yields as determined by calibrated GC; 0.05 M MeSCH$_2$COOEt, 0.25 M olefin; 2.5 hr irradiation*

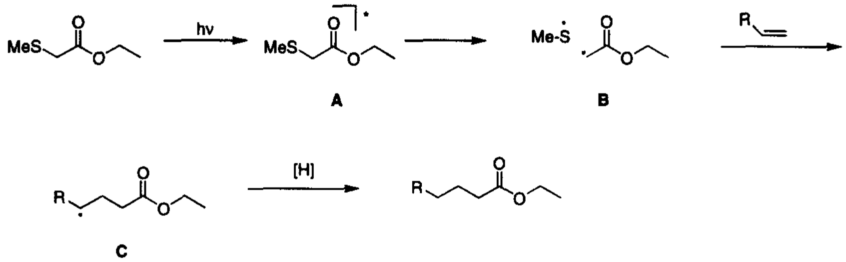
The absence of the MeS-transfer product is confirmed by GC-MS analysis of all reaction mixtures (the confidence level is $\leq 0.5\%$). It was not immediately clear whether MeS$^{\bullet}$ can serve as a hydrogen donor itself further facilitating the reduction, or if the slower rate of the MeS-transfer (as compared with, e.g., PhS-transfer) allows for more efficient hydrogen abstraction from the media. A deuterated ethyl (methyl-d$_3$-thio)acetate (**1-d$_3$**) was synthesized[4] to test whether the methylthio group can deliver a hydrogen atom at the final step of the reaction. Its reaction with several olefins showed no deuterium incorporation in the product (NMR and MS monitoring). For example, the reaction of the deuterated acetate **1-d$_3$** with 5-hexenol furnished ethyl 8-hydroxyoctanoate **3c**. The following fragments in its mass spectrum confirmed that no deuterium was incorporated: 143 (M -EtO), 115 (M -COOEt), 101 (M -CH$_2$COOEt). The 100 % peak in the spectrum, *m/e* = 88, is a product of McLafferty rearrangement. If there were any deuterium incorporation at the position 4 of **3c** we would observe the abundance of peak 89 grow at the expense of peak 88. This was not the experimental finding, in fact, there was no difference in mass spectra of the octanoate **3c** obtained from undeuterated or deuterated ethyl methylthioacetate.



Scheme 2

Solvent participation as a hydrogen donor was examined by carrying out the irradiations in deuterated acetonitrile-d$_3$ and methanol-d$_4$. MS analysis of the products showed no more than 10 % incorporation of deuterium in cases when excess olefin was used. Optimization of reaction conditions, namely, the concentration and the initial ratio α-(alkylthio)acetate/olefin, revealed that the maximum yields were reached when the olefin was used in a 4 to 5-fold excess. All the above led us to the conclusion that it is the olefin which serves as a primary source of hydrogen under those conditions. A rationale of the reaction mechanism is presented in Scheme 3. It was also found that in cases when the olefin to methylthioacetate ratio was low the percentage of deuterium incorporated into the final product from deuterated solvent increased considerably. Thus, the reaction in methanol-d$_3$ using only 1:1 ratio of **1** and 5-hexenol (**2c**) gave hydroxyoctanoate, **3c**, which had in its mass spectrum two McLafferty fragmentation peaks, 88 (no deuterium) and 89 (mono-deuterated) of equal abundance. (see Scheme 2). This indicates that at low concentrations of olefin the solvent can serve as hydrogen donor at the final step of the reaction.

GC-MS monitoring of the reaction mixture showed the products of MeS$^{\bullet}$ addition to olefin to be the major by-products. When we used t-BuS-CH$_2$COOEt (**4**)[5] in place of **1**, the amount of AlkS$^{\bullet}$ addition to olefin is reduced and di-*tert*-butyl disulfide is detected in the reaction mixture.[6] Another important observation was that in all these reactions we did not observe any detectable amount of ethyl acetate, indicating that the rate of addition of $^{\bullet}$CH$_2$COOEt to olefins is much greater than that of hydrogen abstraction. Another explanation for the absence of ethyl acetate would be a non-dissociative mechanism whereby an excited state **A** (Scheme 3) is being directly attacked by the olefin in a bimolecular



Scheme 3. Proposed mechanism

fashion. To test this we carried out the following competition experiment. A mixture of equimolar amounts of the methylthio- and *tert*-butylthiosubstituted acetates (**1** and **4** respectively) was irradiated in the presence of 5-hexenol **2c** and the relative rates of disappearance of **1** and **4** were monitored by GC at low and high conversions using a small amount of dodecane as an internal standard. It was found that the rate of disappearance of α-(methylthio)acetate **1** (k_{Me}) was only about 50 percent higher than the rate of disappearance of α-(*tert*-butylthio)acetate **4** (k_{tBu}). Due to considerable steric hindrance introduced by the *tert*-butyl group one would expect the k_{Me}/k_{tBu} ratio to be several orders of magnitude greater if the rate-limiting step were a bimolecular reaction.

Fluorescence quenching experiments showed that the olefin does not quench the emission from the excited **1**. This would also indicate that the operating mechanism is dissociative as depicted on Scheme 3, not bimolecular.

We also examined the effect of oxygen on this reaction. Table 2 shows the relative quantum yields of product formation for degassed and non-degassed reactions of $MeSCH_2COOEt$ with 5-hexenol and 3-butenol. At low and medium conversions (~ 5-20 %) the quantum yields of degassed reactions are only by a factor of 1.1-1.3 higher than the corresponding quantum yields of oxygenated samples.

Table 2. Effect of Oxygen on the Addition of Ethyl (Methylthio)acetate[a]

Entry	Olefin	Conversion	$\Phi_{degassed}/\Phi_{Oxygen}$ [b]
1	5-hexenol	4.5 %	1.26 ± 0.09
2		19.3 %	1.15 ± 0.04
3	3-butenol	5.2 %	1.22 ± 0.08
4		24.7 %	1.11 ± 0.05

[a] reaction of 0.05 *M* CH_3SCH_2COOEt and 0.25 *M* olefin in CH_3OH; [b] degassed samples were prepared by 4 freeze-thaw cycles, oxygenated samples were prepared by bubbling O_2 through the solution for 5 min at 20 °C

Analysis of the literature indicates that whenever PhS(e)-substitution is used in a similar radical process, PhS(e) transfer is competing successfully with the reduction at the last stage of the reaction (see, e.g. [2d]). Radical addition of diethyl (2-phenylseleno)-propanedioate to olefins is *quantitatively* a PhSe-transfer reaction,[2b] and in the presence of carbon monoxide the group transfer carbonylation is observed.[7] A quantitative study on rate constants for chalcogen group transfers by Curran et al.[8] shows that the rate of MeS transfer in comparable systems is anywhere from three-fold to an order of magnitude smaller than that of PhS. It is conceivable that in our case the failure of AlkylS-group to transfer makes the chain mechanism ineffective. This would also be in keeping with our observation of the low oxygen sensitivity for this process. Thus the most probable (non-chain) mechanism includes a simple photochemical homolysis followed by the addition and, finally, hydrogen abstraction.[9]

After Peter Wagner's study[10] on charge-transfer interactions in triplet keto-sulfides we did consider a possibility of intramolecular electron-transfer in triplet ethyl α-(methylthio)acetate. It appears from the reaction outcome, however, that the C-S bond cleavage mechanism is not critical for understanding the overall reaction. Whether or not this cleavage occurs directly from a singlet excited state of the alkylthio-substituted ester or it is a triplet state/charge-transfer intermediate which is the immediate precursor of the radical pair, does not change the fact that it is the radical species $^{\bullet}CH_2COOEt$ which performs the addition. Relatively low sensitivity of the reaction to the presence of oxygen which is known to quench triplets would also indicate that in this particular reaction triplet ^{3}**1** is not of significant importance.

We also tested α-alkylthio-substituted *acetamides* in the photochemical addition reaction. The yields of products of such photochemical amidomethylation of olefins ranged from 60% to 80% (as long as we did not use a N-monoalkyl substituted acetamide, which caused unacceptably low yields of the products). For example, irradiation of N,N-dimethyl α-(methylthio)acetamide, $MeS\text{-}CH_2C(O)NMe_2$,[11] in the presence of **2a** (or **2b-c,e**) gave N,N-dimethylamides of octanoic, 6-hydroxyhexanoic, 8-hydroxyoctanoic, and 1-(2-norbornyl)acetic acids respectively.

Carboxymethylations in the presence of trialkylphosphite. We also employed trimethylphosphite as a sulfur scavenger and obtained the same products of carboxymethylation **3a-e**. The yields, based on $MeSCH_2COOEt$, were slightly (5 to 10 %) lower than reported in the Table 1 for the reactions in the absence of $P(OMe)_3$. However, the olefin in this case is not "wasted" via the $MeS^{\bullet}$ addition.[12]

In summary, reductive photochemical carboxy/amidomethylation of olefins with α-(alkylthio)acetates/amides is an efficient and experimentally simple technique allowing synthesis of substituted fatty esters/amides in a tin-free environment.

Acknowledgment. We thank Professor Eric Block, SUNY Albany, for useful discussion and suggestions.

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3. *General procedure for irradiations.* Most irradiations were carried out in the presence of air. In cases when degassing was needed, 4-5 freeze-thaw cycles with nitrogen purging was employed to remove oxygen. Solution of 0.05 *M* ethyl α-(alkylthio)acetate (or alkylthio-acetamide) and 0.25 *M* olefin in appropriate solvent was irradiated in a quartz flask for 2-2.5 hours at 18-20 °C. The resulting solution was examined by GC-MS. The product yields were determined by GC analysis against the curve calibrated with standard ethyl alkanoates (or amides).
4. *Deuterated ethyl methylthioacetate (**1-d₃**).* 57 mg (2.5 mmol) of sodium was dissolved in 2 mL of absolute ethanol and 275 μl (2.5 mmol) of ethyl mercaptoacetate was added at 20 °C. After 5 min. 1 g (7 mmol) of CD_3I was added to the resulting solution of sodium thiolate. The reaction tube was sealed (Teflon screw-cap) and heated at 50 °C for 1 hour. The resulting solution was poured into 5 mL of 10 % aqueous solution of $Na_2S_2O_3$, extracted with ether (2 x 10 mL) and dried over Na_2SO_4. Removal of solvent in vacuum gave 260 mg of CD_3SCH_2COOEt (76 %) as a colorless oil. ^{1}NMR ($CDCl_3$) δ 4.20 (q, J = 7.15 Hz, 2H), 3.24 (s, 2H), 1.30 (t, J = 7.15 Hz, 3H); (the peak of CH_3 group at 2.2 ppm as seen in undeuterated **1** was clearly absent in **1-d₃**); MS (*m/e*): 137 (M^+), 89, 64. For comparison, MS of CH_3SCH_2COOEt (*m/e*): 134 (M^+), 88, 61. In deuterated **1-d₃** peak-134 is also present at the abundance level of 600, whereas the abundance of peak-137 is approximately $5 \cdot 10^6$.
5. *Ethyl (tert-butylthio)acetate (4).* 115 mg (5 mmol) of sodium was dissolved in 10 mL of absolute ethanol and 450 mg (5 mmol) of *tert*-butyl thiol was added at 20 °C. After 10 min. 0.62 g (5 mmol) of ethyl chloroacetate was added to the resulting solution. Immediately, a white cloud of sodium chloride precipitation was observed. The reaction was stirred for 30 min at 20 °C. The resulting solution was diluted with 20 mL of water, extracted with ether (2 x 20 mL) and dried over Na_2SO_4. Solvent removal and column purification on silica gel, ethyl acetate - hexane 1:6, gave 0.7 g of **4** (80 %) as a faintly yellow liquid. ^{1}H NMR ($CDCl_3$) δ 4.19 (q, J = 7.15 Hz, 2H), 3.29 (s, 2H), 1.34 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H); MS (*m/e*) 176 (M^+), 120, 103, 87, 74, 57, 41.
6. After running several carboxymethylation experiments with *tert*-butyl derivative **4** we found no justification of using it in place of commercially available methylthioacetate **1**. The yields as determined by calibrated GC were within 5-10 % for both reactants.
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10. Wagner, P. J.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 3057.
11. *N,N-Dimethyl α-(methylthio)acetamide (5).* α-(Methylthio)acetyl chloride was generated by reacting 1 g (9.4 mmol) commercially available (Aldrich) α-(methylthio)acetic acid with 3.4 g (28.3 mmol) of thionyl chloride in 3 mL of dry ether. After 30 min of stirring at about 35 °C the reaction mixture was cooled down, the solvent and excess thionyl chloride was removed with rotary evaporator to give 1.08 g (92 %) of α-(methylthio)acetyl chloride as a yellowish oil. ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 2H), 2.24 (s, 3H). A flow of dimethylamine (gas) was slowly passed through the ice-bath cooled solution of 0.3 g (2.4 mmol) α-(methylthio)acetyl chloride in 10 mL dry ether causing abundant precipitation of white crystalline hydrochloride. After precipitation stopped, the solution was stirred for additional 15 min and dimethylamine hydrochloride was filtered off. Evaporation of the ether and purification by flash column chromatography on silica gel, ethyl acetate-hexane, 1:3, gave 0.262 g (82 %) of **5** as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 2H), 3.08 (s, 3H), 2.98 (s, 3H), 2.21 (s, 3H) which is in agreement with previously reported data: Tamura, Y.; Maeda, H.; Choi, H. D.; Ishibashi, H. *Synth. Commun.* **1982**, 56.
12. In view of this result, we examined the possibility of employing diethyl thiobis(acetate), $S(CH_2COOEt)_2$, in the presence of $P(OMe)_3$ in a hope to utilize both CH_2COOEt moieties. To our disappointment, the yields of products of monocarboxymethylation (**3a-e**) were never above 48% as calculated based on used thiobis(acetate). Although a simple explanation that only one $^{\bullet}CH_2COOEt$ reactive radical is generated in this case is possible, our rationale (based on GC-MS analysis) is that other reaction channels become available, such as dimerization of radicals **C** (Scheme 3) and *di*carboxymethylation of the olefin.

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