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Radical Additions of Activated Haloalkanes to Alkenes Initiated by Electron Transfer from Copper in Solvent-Free Systems**

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*Dedicated to Professor Hansjörg Sinn
on the occasion of his 65th birthday*

The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.^[1] The time has now come for ecological factors to be considered in the development of synthetic procedures and for them to play an important role in the assessment of the quality of any new synthesis. Within this context, the reduced use of ecologically suspect solvents is of considerable significance. Thus the radical bromination of alkylarenes in supercritical carbon dioxide has been reported recently.^[2] The polymerization of neat methacrylate is an important example of a solvent-free industrial process.^[3]

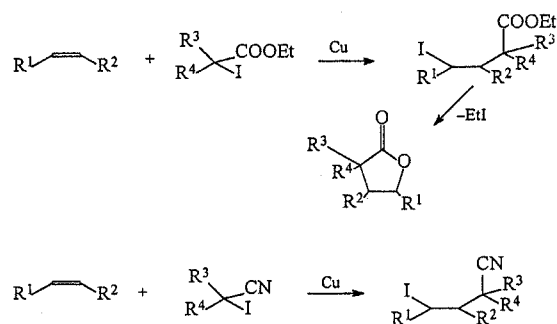
For some time now intermolecular radical addition reactions have been powerful tools in preparative organic chemistry,^[4] but the most widely used methods have a number of ecological disadvantages for widespread industrial use. This applies particularly to the frequently used organotin compounds.^[5, 6] Transi-

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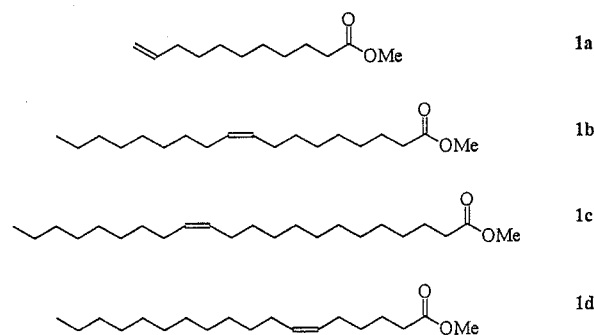
tion metal complexes and salts that initiate radical reactions by electron transfer processes^[7] offer a viable alternative. Thus ethyl trichloroacetate and other compounds similarly activated by electron-withdrawing substituents may be induced to undergo radical addition to alkenes by copper(I) chloride^[8] in acetonitrile, $[\text{RuCl}_2(\text{PPh}_3)_3]$,^[9] $[\text{CpMo}(\text{CO})_3]_2$,^[10] $[\text{CpFe}(\text{CO})_2]_2$,^[10] and $[\text{Co}_2(\text{CO})_8]$ ^[10] in benzene and, in the latter example, without solvent.^[10] These initiators,^[11] as well as $[\text{Pd}(\text{PPh}_3)_4]$ ^[12] in benzene and $[\text{Cu}(\text{bpy})\text{Cl}]$ in dichloromethane or 1,2-dichloroethane,^[13] have been used successfully for the radical cyclization of esters of a number of suitable unsaturated α -halocarboxylic acids. Methyl α -iodo-(*Z*)-6-octadecenoate has been cyclized to cyclopentanecarboxylic acids by metallic silver in methanol.^[14] Metallic copper has been used in the Ullmann reaction for the synthesis of diaryls from aryl halides,^[15] and bromomalonodinitrile^[16] and 2,2-dibromo-1,3-diones^[17] have undergone addition to alkenes in benzene in the presence of copper as an initiator.

We now report the first radical addition of alkyl α -iodocarboxylates and α -iodoalkanenitriles to alkenes in the absence of solvent initiated by electron transfer from copper metal (Scheme 1). The alkenes most frequently used were the esters of



Scheme 1. Cu-catalyzed addition of alkyl α -iodocarboxylates and α -iodoalkanenitriles to alkenes. $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{H}, \text{alkyl}, (\text{CH}_2)_n, \text{COOMe}$.

unsaturated carboxylic acids such as methyl 10-undecenoate (**1a**), methyl (*Z*)-9-octadecenoate (**1b**), methyl (*Z*)-13-docosenoate (**1c**), and methyl (*Z*)-6-octadecenoate (**1d**), which are of considerable interest as renewable raw materials.^[18]



The reaction procedure is very simple: the alkene, iodo compound, and commercial copper powder are mixed without any pretreatment and heated at 100–130 °C in an inert atmosphere. After a simple workup procedure, the products are obtained analytically pure in satisfactory yields (Table 1).

The addition of alkyl 2-iodocarboxylates to 1-alkenes affords γ -lactones in high yields (entries 1, 2, 3b). The more readily

Table 1. Results of the copper-initiated addition of alkyl 2-halocarboxylates and 2-haloalkanenitriles to alkenes **1a–d**.

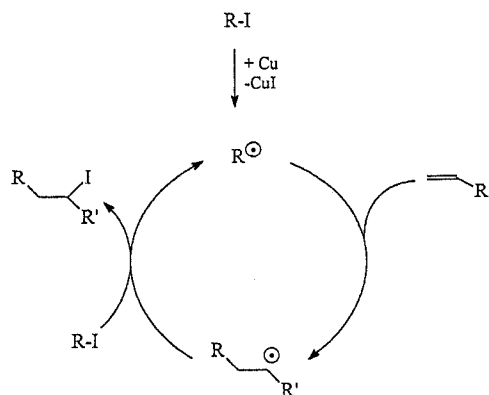
Entry	Alkene	Haloalkane	Product[a]	Yield [%]
1	1a	ethyl iodoacetate		70[b]
2	1a	methyl 2-iodopalmitate		79[b]
3a	1a	ethyl 2-bromobutyrate		41[b]
3b	1a	ethyl 2-iodobutyrate		80[b]
3c	1a	ethyl 2-bromobutyrate, NaI		72[b]
4	1a	diethyl 2-bromo-2-methylmalonate		87[b]
5	1a	ethyl 2-bromo-2-methylpropionate, NaI		54[b]
6	1a	methyl 2-bromohexanoate, NaI		70[b]
7	1a	dimethyl 2-bromo-3-tert-butylsuccinate, NaI		73[c]
8	1a	diethyl 2,5-diiodoadipate		60[c, e]
9	1b	ethyl 2-iodopropionate		51[b, d]
10	1d	ethyl 2-bromopropionate, NaI		60[b, d, f]
11	1a	2-bromohexanenitrile, NaI		55[b]
12	1c	iodoacetonitrile		44[b, d]

[a] All products were fully characterized by ¹H NMR and ¹³C NMR spectroscopy and by mass spectrometry. [b] Isolated yield relative to starting alkene. [c] Isolated yield relative to starting haloalkane. [d] Regioisomeric mixture, ca. 1:1. [e] α (**1a**): α (iodoalkane) = 6:1. [f] The analogous additions of **1b** and **1c** gave the corresponding products in 58 and 59% yield, respectively.

available alkyl 2-bromocarboxylates also undergo copper-initiated addition to alkenes (entries 3a, 4). High yields are achieved with the more strongly activated alkyl bromomalonates (entry 4), however, yields from reaction with alkyl 2-bromomonocarboxylates (entry 3a) are much lower than with the corresponding iodo compounds (entry 3b). If the iodo derivative is formed from the corresponding bromo compound in situ by the addition of a stoichiometric amount of sodium iodide to the reaction mixture (entries 3c, 5–7), the products are obtained in high yields, similar to those obtained by direct use of the iodo derivatives. In this way primary, secondary, and tertiary alkyl 2-halocarboxylates were added to 1-alkenes. Of particular interest is the example of diethyl 2,5-diiodoadipate, which adds to two equivalents of **1a** to form a di- γ -lactone (entry 8). Radical addition to 1,2-dialkylethenes with extended alkyl groups such as methyl (*Z*)-9-octadecenoate (**1b**) using traditional methods frequently provides the products in only poor yields.^[4] Thus in the benzoyl peroxide initiated addition of ethyl bromoacetate (in a tenfold excess) to methyl (*Z*)-9-octadecenoate the product is obtained in only 10% yield.^[19] Moreover, using several variants of the tin procedure we were still unable to achieve satisfactory additions.^[20] In contrast, with

copper initiation we were able to achieve yields in excess of 50% without any difficulty (entries 9, 10), which could be improved by very slow addition of the halo compound. 2-Iodo- and 2-bromoalkanenitriles add to 1-alkenes such as **1a** and to 1,2-dialkylethenes such as **1c** in an analogous manner (entries 11, 12). In these cases, the iodo functionality is retained, offering interesting possibilities for further transformations.

The reaction is initiated by electron transfer from copper to the activated haloalkane (Scheme 2). The electrophilic radical



Scheme 2. Mechanism for the Cu-initiated addition of iodoalkanes to alkenes. RI = alkyl 2-iodocarboxylates, 2-iodoalkanenitriles. R' = alkyl, (CH₂)_nCOOMe.

formed after cleavage of the halide adds to the electron-rich double bond of the alkene, and subsequent halogen abstraction affords the product, which in the case of alkyl 2-halocarboxylates cyclizes to a γ -lactone. About 30% of the copper is oxidized to copper(I) iodide during the reaction and about 20% of the haloalkane is reduced by halogen-hydrogen exchange. It is thus a radical chain reaction with a relatively short chain length. The C-I bond must be activated by an electron-withdrawing substituent. Iodine transfer onto the adduct radical by 1,3-induction is only slightly diastereoselective; the ratio of diastereoisomers is typically *cis/trans* = 1.5/1 (entry 2). The same stereoisomeric ratio was also obtained in the corresponding benzoyl peroxide initiated addition^[22] and in Curran's iodine transfer method.^[23] This confirms that like in these two reactions, the iodoalkane is also the iodine donor in the copper-initiated addition (Scheme 2). When the reaction is carried out with a bromoalkane and sodium iodide, the corresponding iodoalkane is formed as the intermediate, which was confirmed by gas chromatography. Key features of the reaction described here: no solvent is used, the workup procedure is simple in comparison to other methods since the copper powder initiator is unproblematic for workup and separation,^[24] the reagents are used in essentially stoichiometric quantities, the yields are comparably high, even with 1,2-dialkylethenes, and the initiator can be reused (after total oxidation of the copper it is readily recovered by reduction).

Experimental Procedure

General method: A 50 mL, two-necked flask equipped with a magnetic stirrer, reflux condenser, and a gas inlet tube was charged with 1.3 equiv of iodoalkane, 1 equiv of alkene, and 1.3 equiv of copper powder (purum, Merck). The mixture was heated with constant stirring at 130 °C in an inert atmosphere [28]. The reaction was monitored by thin-layer chromatography and was usually complete within 3–7 h. The product was isolated by distillation; alternatively, the reaction mixture

was taken up into diethyl ether and after removal of the copper salts by filtration and evaporation of the solvent on a rotary evaporator, the product was isolated by Kugelrohr distillation and recrystallization or flash chromatography.

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- [28] We used a small excess of copper, whereby the reaction rate is increased. About 30% of the copper is oxidized during the reaction. The copper/copper iodide mixture can be reused twice as an initiator. The use of 1.3 equivalents of copper appears high from an ecological viewpoint, even though one batch can be used three times. With respect to both price and weight, however, the amount of copper used is low in comparison to that of the metal complexes mentioned in the text [9–13] such as [Pd(PPh₃)₄]. Furthermore, while the separation and recovery of homogeneous catalysts is often difficult if not impossible, that of the copper in our reactions is straightforward. Even the reaction temperature of 130 °C is ecologically acceptable when one considers that foods are cooked at about this temperature.