Pergamon

*Tetrahedron Letters*, Vol. 35, No. 17, pp. 2763-2766, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0374-7

# Synthesis of γ-Haloesters and γ-Ketoesters by Homolytic Addition of Carbon Radicals Generated by α-Haloesters and Triethylborane to Alkenes and Silyl Enol Ethers.

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*Abstract*: An efficient synthesis of γ-haloesters has been achieved, under very mild conditions, by addition of electrophilic carbon radicals $\cdot CH(R)CO_2Et$ (R=H, Me, $CO_2Et$) generated by $XCH(R)CO_2Et$ (X=Br, I) / $BEt_3$ / air in DMSO to alkenes and cycloalkenes. The synthesis of γ-ketoesters is also possible when silyl enol ethers are used as the substrates.

The free radical additions of α-haloesters to alkenes have been the object of many investigations, since these reactions lead to γ-haloesters, useful intermediates for the synthesis of γ-lactones[1,2] which are precursors of a number of biologically active compounds.[2,3]

We now wish to report that these additions can be performed, under very mild conditions, when α-iodo or α-bromoesters are reacted with the appropriate alkenes under air and in the presence of $BEt_3$. When a silyl enol ether is used as the alkene, the same procedure can provide us with an efficient method for the synthesis of γ-ketoesters.

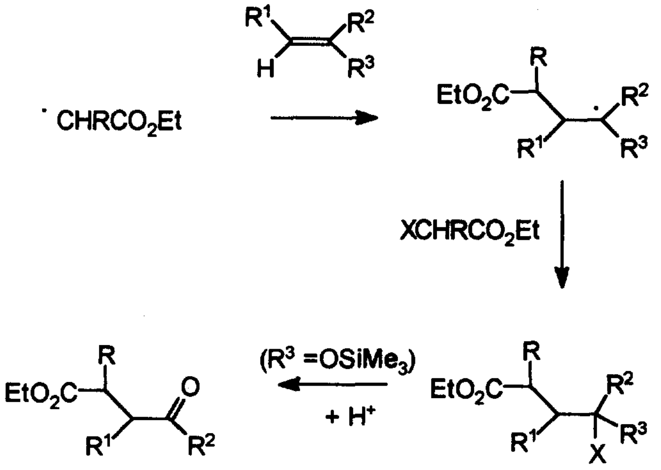
$$Et^{\cdot} + O_2 \longrightarrow EtO_2^{\cdot}$$

$$EtO_2^{\cdot} + Et_3B \longrightarrow EtO_2BEt_2 + Et^{\cdot}$$

$$Et^{\cdot} + XCHRCO_2Et \longleftrightarrow EtX + {}^{\cdot}CHRCO_2Et$$

Scheme 1

Under the above conditions, the radical $\cdot CHRCO_2Et$ (R= H, Me, $CO_2Et$) is generated (Scheme 1, X= I, Br).[4,5] Attack of the radical to the alkene ensues and the products (γ-haloesters or γ-ketoesters) form as described in Scheme 2 ($R^1$= H; alkyl; $R^2$= alkyl; $R^3$= H, $OSiMe_3$). The results are displayed in the Table.



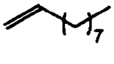
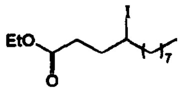
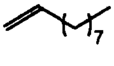
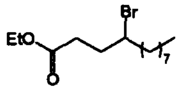
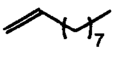
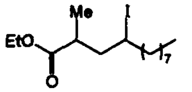
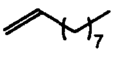
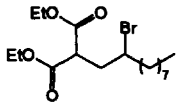
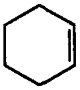
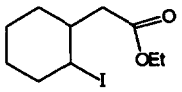
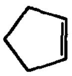
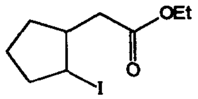
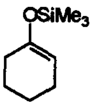
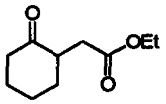
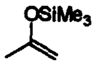
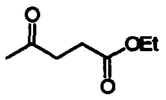
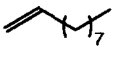
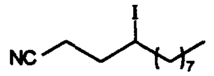
**Scheme 2**

The yields range from fair to good and are certainly comparable with those of other procedures. Better yields are observed with α-iodoesters than with α-bromoesters (compare entries 1 and 2). Interestingly, even though the reaction involves attack of the carbon radical to a non terminal double bond, fair yields are obtained with cyclic alkenes such as cyclohexene (entry 5) and cyclopentene (entry 6). This represents a simple route to the synthetically important 2-iodocyclohexane- and 2-iodocyclopentane acetic acids.[6] Both the cyclic substrates afford a mixture of *cis* and *trans* isomers. With cyclohexene the two isomers can be separated by column chromatography, while this has not been possible with cyclopentene. A mixture of two diastereoisomers has also been obtained in the addition of ethyl α-iodopropionate to 1-decene (entry 3).

When a bromomalonate is used as the α-bromoester, a much more efficient reaction occurs (compare entry 4 with entry 2), leading to a β-bromomalonate, which is a versatile starting compound for the construction of functionalized malonates.[7]

With silyl enol ethers as the subtrates (entries 7, 8), γ-ketoesters are formed when the reaction mixture, after work up, is stirred for 2 min with HCl 2N. Very probably, an addition product first forms that undergoes fast acid-catalyzed decomposition to a γ-ketoester. The yields in γ-ketoester are good with 1-trimethylsilyloxypropene, but less satisfactory with 1-trimethylsilyloxycyclohexene; this is reasonable since in the latter case an internal double bond is involved.

**Table.** Addition of Haloesters to Alkenes and Silyl Enol Ethers in DMSO in the presence of Triethylborane.

| Entry | Alkene | α-Haloester | [Alkene]/ [α-Haloester] | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  | $ICH_2CO_2Et$ | 3/1 |  | 90[b] |
| 2 |  | $BrCH_2CO_2Et$ | 1/3 |  | 65[c] |
| 3 |  | $ICH(CH_3)CO_2Et$ | 10/1 |  | 54[d] |
| 4 |  | $BrCH(CO_2Et)_2$ | 2/1 |  | 89[e] |
| 5 |  | $ICH_2CO_2Et$ | 10/1 |  | 48[f] |
| 6 |  | $ICH_2CO_2Et$ | 14/1 |  | 54[g] |
| 7 |  | $ICH_2CO_2Et$ | 2.5/1 |  | 35[h,i] |
| 8 |  | $ICH_2CO_2Et$ | 2.5/1 |  | 66[h] |
| 9 |  | $ICH_2CN$ | 10/1 |  | 51 |

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[a] yields of isolated product with respect to the radical source. All products have been identified by GC-MS and NMR methods (comparison with literature data). [b] the yield is 54% when the reaction is carried out in THF. [c] yield with respect to the alkene. [d] an approximately 1:1 mixture of the two diastereoisomers was obtained (determined by GC). [e] the yield is 78% when the reaction is carried out in hexane. [f] an approximately 1:1 mixture of the two diastereoisomers (*cis* and *trans*) was obtained (determined by GC). [g] an approximately 1.5:1 mixture of the two diastereoisomers was obtained (determined by GC). [h] after the usual workup the reaction mixture was stirred for 2 min with HCl 2N. [i] The unreacted substrate was not recoverable because it was converted in cyclohexanone.

The last notation is that γ-iodonitriles can be obtained using iodoacetonitrile as the radical source (entry 9).

**General procedure for the addition reactions.** A 1.0 M solution of $BEt_3$ in hexane (1 ml) was added, at room temperature, to an open-air stirred mixture of the alkene and the alkyl halide (1.0 mmol) in 5 ml of DMSO (or hexane or THF). When the halide was ethyl bromoacetate, four further additions of $BEt_3$ (1 ml), every 30 min, were necessary to consume all the halide. The mixture was then diluted with brine and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and evaporated. When THF or hexane were used as solvent, the reaction mixture was evaporated without any further workup. The products were then isolated by column chromatography (silica-gel, pentane-diethyl ether) and characterized as the corresponding lactones (obtained by cyclization in refluxing NaOH)[1] or by GC-MS and NMR (comparison with literature data).

**Acknowledgements.** This work was carried out into the framework of the Progetto Finalizzato CNR Chimica Fine.

## References and Notes

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(*Received in UK* 24 *January* 1994; *revised* 15 *February* 1994; *accepted* 18 *February* 1994)