Tetrahedron Letters No. 43, pp. 3995 - 3998, 1971. Pergamon Press. Printed in Great Britain.

THE HALOGENATION OF LITHIUM ESTER ENOLATES. A CONVENIENT METHOD FOR THE PREPARATION OF ALPHA-IODO AND ALPHA-BROMO ESTERS.

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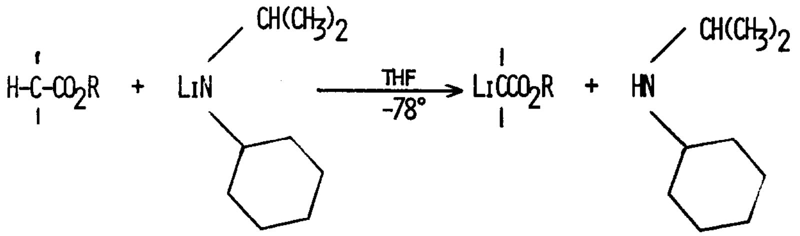
(Received in USA 26 July 1971; received for publication in UK 22 September 1971)

The preparation of alpha-halogenated carboxylic acid derivatives is normally achieved by refluxing the carboxylic acid with halogen and phosphorous trichloride.[1] Alternatively, substituted malonic acids may be brominated and decarboxylated to obtain the corresponding α-bromo acids.[2] Both of these methods require acidic and relatively vigorous reaction conditions. Furthermore, they are not normally applicable to the preparation of iodo derivatives.[3]

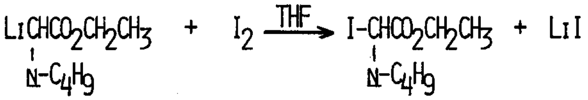
The halogenation of ester enolate anions provides a method for preparing α-halo esters using exceedingly mild and essentially basic reaction conditions. In addition, the reaction is well suited to the preparation of iodo esters.

As previously reported,[4] esters may be converted almost quantitatively to the corresponding lithium enolates by reaction with lithium N-isopropylcyclohexylamide in tetrahydrofuran solution at -78° (I).



(I)

Addition of iodine to a solution of lithio ethyl hexanoate maintained at 20° results in rapid decolorization of the iodine; however, the yield of ethyl 2-iodohexanoate is negligible (<5%). (II).



$$\underset{\text{n-}C_4H_9}{\text{LiCHCO}_2\text{CH}_2\text{CH}_3} + I_2 \xrightarrow{\text{THF}} \underset{\text{n-}C_4H_9}{\text{I-CHCO}_2\text{CH}_2\text{CH}_3} + \text{LiI} \qquad \text{(II)}$$

Apparently, the iodo ester undergoes further reaction when generated in the presence of excess ester enolate. Addition of the enolate solution to a tetrahydrofuran solution of iodine at a temperature of 20° increases the yield to 67%. Finally, a similar sequence conducted at a temperature of −78° produces the iodo ester in almost quantitative yield (95% isolated).

Using the latter technique, a variety of esters was converted to the corresponding α-iodo ester in high yield as illustrated in Table I.

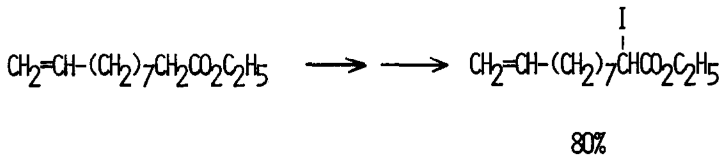
Table 1. The Halogenation of Lithium Ester Enolates.

Ester	Product[a]	Yield, %[b]
Ethyl hexanoate	Ethyl 2-iodohexanoate Ethyl 2-bromohexanoate	(95) (92)
Ethyl isobutyrate	Ethyl 2-iodoisobutyrate Ethyl 2-bromoisovalerate	87 (90)
Ethyl isovalerate	Ethyl 2-iodoisovalerate	97
Ethyl cyclohexane carboxylate	Ethyl 2-iodocyclohexane carboxylate	84
Ethyl undecylenate	Ethyl 2-iodoundecylenate	80

[a] All products were isolated by either distillation or preparative glpc. The identity of products was confirmed by spectral analysis in all cases.

[b] Glpc yields, isolated yields in parentheses.

It is noteworthy that the reaction is applicable to the preparation of unsaturated iodo esters as shown by the results obtained with ethyl undecylenate(III). Finally, a similar procedure



$$CH_2{=}CH{-}(CH_2)_7CH_2CO_2C_2H_5 \longrightarrow \longrightarrow CH_2{=}CH{-}(CH_2)_7\overset{I}{C}HCO_2C_2H_5 \qquad (III)$$

80%

provides a preparation of α-bromo esters as shown by the entries for ethyl hexanoate and ethyl isobutyrate in the table.

The speed and simplicity of the method is illustrated by the following representative procedure for the conversion of ethyl hexanoate into ethyl 2-iodohexanoate. A dry 50 ml round-bottom flask is equipped with a magnetic stirrer, septum inlet, and a mercury bubbler. The flask is flushed with nitrogen and 25 ml of a 1M tetrahydrofuran solution of lithium N-isopropylcyclohexylamide (25 mmol)[4] is injected. The flask is cooled to -78° and 3.6 g (25 mmol) of ethyl hexanoate is added dropwise over a period of 5 minutes. After complete addition, the flask is allowed to reach room temperature and the solution of ester enolate is withdrawn and added dropwise by means of a syringe to a solution of 7.6g of iodine (30 mmol, 20% excess) in 25 ml of tetrahydrofuran maintained at dry-ice temperatures. 5 ml of concentrated hydrochloric acid is then injected and the solution allowed to reach room temperature. The solution is extracted with two 30 ml portions of water containing sufficient sodium thiosulfate to remove the iodine color, dried with magnesium sulfate and subjected to simple vacuum distillation. There was obtained 6.4 g, 95%, of ethyl 2-iodohexanoate, b.p. 112-114°/15mm (lit.[3] b.p. 111-114°/15mm). In some cases, the iodo esters decomposed seriously on attempted distillation. However, products of satisfactory purity, as determined by glpc analysis, could usually be obtained merely by stripping off the solvent under vacuum. The sole contaminant of iodo esters not subjected to distillation was the unconverted starting ester. Consequently, isolation of the iodo esters does not appear necessary for their further utilization in most cases.

α-Halo esters are useful intermediates for the preparation of a wide variety of organic compounds including α-hydroxy and α-amino esters through nucleophilic displacement reactions and β-hydroxy esters via the Reformatsky sequence. The present procedure for the direct halogenation of ester enolates should represent the method of choice for the preparation of many halo esters.

ACKNOWLEDGMENT

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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