Tetrahedron Letters No. 44, pp 4201-4204, 1971. Pergamon Press . Printed in Great Britain

THE REFORMATSKY REACTION OF ETHYL *a*-BROMO-ISOBUTYRATE AND BIS (CHLOROMETHYL) ETHER - A COMPLETE PRODUCT STUDY

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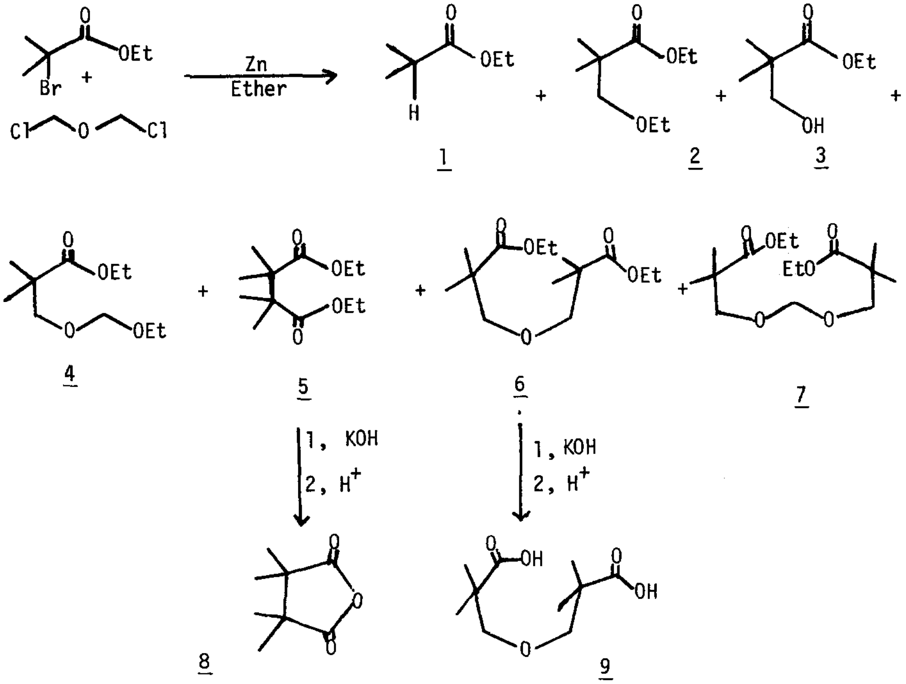
(Received in USA 26 July 1971; Received in UK for publication 6 October 1971)

Recent reports [1,2,3] in the literature on the reactions of organozinc compounds with *a*-chloroethers prompts us to report our results in this area. As part of a synthetic scheme we needed the bis neopentyl substituted ether *6*. A scan of the literature showed no simple procedures have been reported for the synthesis of dineopentyl systems; hence a general synthetic route seemed worth pursuing. Since Reformatsky reagents have been shown to couple with *a*-chloroethers,[3] we decided to attempt the formation of *6* by reacting 2 equivalents of Reformatsky reagent *10*[6] with one equivalent of bis (chloromethyl) ether. Preliminary results indicated some formation of the desired product, so a study of this reaction was undertaken in order to better understand the reaction, thus allowing us to improve the yield of desired product *6*.

Fig. 1



Under improved conditions 6 could be obtained consistently in 55% to 65% yield using ether as the solvent.[9] The other products (Fig. I) were identified after separation by careful fractional distillation by spectral analysis and synthesis.

A typical procedure in which the desired product, 6, is obtained nearly pure by separation as the zinc halide complex is given.

A flask containing 26.2 g (0.4 mol) of powdered zinc metal under N_2 was flame dried. Dried ether, 250 ml, ethyl α-bromo-isobutyrate, 78.0 g (0.4 mol), and a crystal of iodine[4] were added to the flask and the mixture was stirred 3 hrs at 10°. Bis (chloromethyl) ether, 23.0 g (0.2 mol), was added dropwise over 1 hr and the reaction mixture was allowed to warm to 25° while stirring. It was then refluxed for 1 hr and cooled. Hexane, 25 ml, was added and the precipitated zinc halide complex which formed was allowed to settle.

The solvent, which was decanted off of the precipitate, was washed with dil $NaHCO_3$ and H_2O, dried K_2CO_3, filtered and evaporated to give 13 g of a crude oily mixture. Careful distillation of this mixture gave the following products: 3.0 g (88%) 2; bp 28-29°/0.1 mm; ir 1735 cm^{-1}; nmr $\left(^{\mathrm{TMS}}_{\mathrm{CCl_4}}\right)$ δ 1.09(t, 3), 1.10(s, 6), 1.20(t, 3), 3.32(s, 2), 3.40(q, 2), 4.05(q, 2): 1.5 g (3.8%) 4; bp 50-51°/0.1 mm; ir 1740 cm^{-1}; nmr $\left(^{\mathrm{TMS}}_{\mathrm{CCl_4}}\right)$ δ 1.14(s, 6), 1.15(t, 3), 1.21(t, 3), 3.48(s, 2), 3.51(q, 2), 4.10(q, 2), 4.56(s, 2): 6.0 g (13.0%) 5[5]: bp 65-70°/0.1 mm; ir 1725 cm^{-1}; nmr $\left(^{\mathrm{TMS}}_{\mathrm{CCl_4}}\right)$ δ 1.19(s, 12), 1.23(t, 6), 4.09(q, 4). (Hydrolysis of 5 in KOH aqueous ethanol followed by acidification, workup and purification gave tetramethylsuccinic anhydride (8): mp 150-152° (lit 152°)[7]: 2.0 g (3.3%) 7; bp 108-112°/0.1 mm; ir 1735 cm^{-1}; nmr $\left(^{\mathrm{TMS}}_{\mathrm{CCl_4}}\right)$ δ 1.16(s, 12), 1.22(t, 6), 3.46(s, 4), 4.11(q, 4), 4.59(s, 2).

The precipitated complex remaining after decanting the solvent was extracted with ether-water. The ether was washed with dil $NaHCO_3$ and H_2O, dried K_2CO_3, filtered and evaporated to give 39 g crude oily material. Careful distillation of this material gave 5.5 g (18.8%) 3; bp 70-72°/3.0 mm; ir 3520, 1720 cm^{-1}; nmr $\left(^{\mathrm{TMS}}_{\mathrm{CCl_4}}\right)$ δ 1.11(s, 6), 1.21(t, 3), 3.47(s, 2), 3.55 (s, 1, exchanges D_2O), 4.10(q, 2): 30.6 g (56%) 6; bp 73-75°/0.1 mm; ir 1730 cm^{-1}; nmr $\left(^{\mathrm{TMS}}_{\mathrm{CCl_4}}\right)$ δ 1.15(s, 12), 1.26(t, 6), 3.41(s, 4), 4.10(q, 4).

Hydrolysis of diester 6 in KOH aqueous-ethanol followed by acidification, workup and purification gave 96% yield of 2, 2, 6, 6-tetramethyl-4-oxaheptanedioic acid (9); mp 134-5°; ir 3400-2800, 1710 cm^{-1}; nmr $\left(^{\mathrm{TMS}}_{\mathrm{CDCl_3\text{-}pyridine}}\right)$ 1.22(s, 12), 3.60(s, 4).

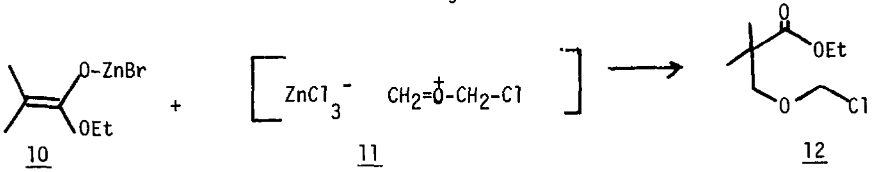
GLC (10% Se 30) analysis showed about 3 g (13.5%) ethyl isobutyrate (1) was also formed in this reaction.

This reaction can also be worked up by adding H_2O to the crude reaction mixture and extracting with ether which is washed, dried, evaporated and the residue carefully distilled; however, we found it difficult to purify the complete mixture by distillation.

When no precautions were taken to keep the reaction dry, little or no 6 was formed and the main products were 1 (25%), 4 (20%) and 7 (27%).

The mechanism for the formation of 6 appears to involve attack of the Reformatsky reagent, 10, on a zinc halide complex of the α-chloroether[10], 11, giving a half alkylated intermediate 12 (figure 2).

Fig. 2

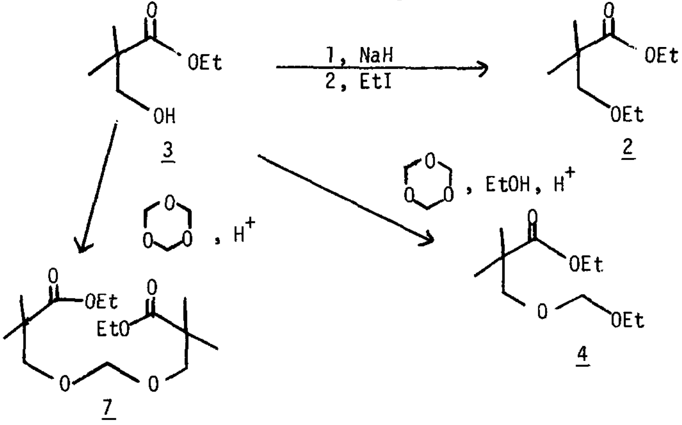


A zinc halide complex of Intermediate 12 could then further react with a second mole of 10 to give 6, or could react with H_2O or EtOH generated as by-products during the reaction to give, after hydrolysis or nucleophilic attack, the other products.

It is also likely that formaldehyde is present in the reaction mixture resulting from the thermal decomposition of the bis chloroether[11]. Product 7 could be formed by reaction of alcohol 3 with formaldehyde. Further work on the scope and mechanism of this reaction is in progress.

Products 2, 3, 4 and 7 have been synthesized according to the following scheme (Fig. 3) and have been shown to be identical to those isolated from the above reaction mixture. A complete report on their syntheses and properties will be presented at a later date.

Fig. 3



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4) Sometimes there was an induction period for this reaction. On occasion it was necessary to heat the mixture to get it started and then cool it to -10°.

5) Only a trace of the normal Reformatsky condensation product of ethyl α-bromo-isobutyrate, ethyl isobutyrisobutyrate[6] was observed. We believe the lewis acid, ZnBrCl, formed during the reaction caused this anomaly. A report on the nature of the condensation products formed during the Reformatsky reaction is forthcoming.

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9) A 66% yield of 6 was recovered when dried dimethoxyethane was used as the solvent. On the other hand, more than 20 products were formed (by glc) when dried THF was used as the solvent; there was no major product. While we do not understand this result, it was repeatable!

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