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Tin–Copper Couple. A New Reagent for Selective Debromination of Activated Dibromides

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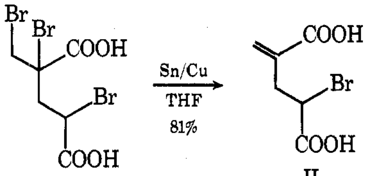
Received June 14, 1976

We wished to prepare the α-methylene-γ-bromoglutaric acid II. Attempts to accomplish this from the known[1] γ-methyleneglutamic acid by diazotization in the presence of sodium bromide[2] were frustrated by persistent lactone formation. As an alternative, the selective debromination of the tribromide I was explored. The latter is readily prepared by Hell–Volhard–Zelinsky bromination of α-methyleneglutaryl chloride.



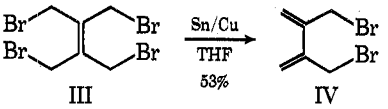
I II

Of the many possible reagents appropriate for the reductive removal of vicinal dibromides,[3] zinc–copper couple[4] was chosen for this purpose. Tetrahydrofuran was used as solvent in order to avoid lactone formation to whatever extent possible.

Attempts to carry out the desired reduction with zinc–copper couple led in every case to substantial overreduction, with production of starting α-methyleneglutaric acid (60%). A lesser amount (40%) of the desired monobromide II was also observed. It seemed reasonable to suppose, since tin has a lower reduction potential than zinc, that improved selectivity might be realized if the reduction could be induced to proceed with tin[5] instead of with zinc.

We have found that the bromoglutarate II can be prepared in 81% yield (recrystallized) from the tribromide I using tin–copper couple in tetrahydrofuran. In the total crude product approximately 3% of the fully reduced α-methyleneglutaric acid can be detected by NMR.[9] This impurity is readily removed by one crystallization from chloroform–ethyl acetate. An interesting feature of this reduction is the requirement of only 0.5 mol of tin–copper couple for complete reaction. This facet has not been explored further. However, it appears that Sn(II) is also sufficiently reactive to promote elimination of such active dibromides and that a further refinement in selectivity might be realized using the latter as a reagent.

Tin–copper couple reacts very slowly, if at all, with 1,2-dibromoethane. On this limited basis, it appears that unactivated dibromides will be relatively unreactive toward this reagent. By contrast, the tin–copper reagent quite effectively reduced tetrakis(bromomethyl)ethylene (III) to the labile dibromide IV.[6]



III IV

Because of its simplicity and ready availability, the tin–copper couple reagent may serve, in favorable instances, as an alternative to electrochemical reduction as it is used to select among several readily reduced functional groups.

Experimental Section

α-Methyleneglutaryl Chloride.[7] α-Methyleneglutaric acid (5.76 g, 0.04 mol) was carefully mixed with phosphorus pentachloride (18.35 g, 0.09 mol) in a round-bottom flask. A vigorous reaction began immediately, and the reaction mixture became liquid. When the initial exothermic part of the reaction had subsided, the mixture was heated at 110–115 °C for 15 min. Phosphorus oxychloride was removed by distillation under aspirator vacuum. The liquid remaining was distilled through a 14-cm Vigreux column yielding 6.15 g (85%), bp 84–86 °C (2 mm), of a colorless liquid: infrared (neat) 5.59 and 5.78 μ; NMR (CCl_4) one-proton vinyl singlet at δ 6.6, one-proton vinyl singlet at δ 6.2, and two two-proton aliphatic multiplets at δ 3.2 and 2.8.

α-Bromomethyl-α,γ-dibromoglutaric Acid (I). Dry bromine (5.65 ml, 0.11 mol) was added dropwise to α-methyleneglutaryl chloride (9.05 g, 0.05 mol) with stirring at room temperature. When the addition was complete (ca. 30 min), the reaction mixture was heated in an oil bath at 80–85 °C for 14 h. The reaction mixture was allowed to cool to room temperature, then transferred to a large watchglass for slow hydrolysis in the air. After 36 h a solid mass was formed. It was collected and washed with 15 ml of chloroform yielding 5.85 g (71%) of the desired tribromo diacid I, mp 148–152 °C. One crystallization from a mixture of chloroform–ethyl acetate (2:1) yielded 5.52 g (67%) of white solid, mp 153–155 °C. The melting point was not improved by further crystallization. Infrared (KBr) 5.81 μ; NMR (acetone-d_6) two-proton broad singlet at δ 9.7, one-proton quartet (H_γ, $J_{\beta\gamma} = 4.4$, $J_{\beta'\gamma} = 7$ Hz) at δ 4.67, two-proton bromomethyl singlet at δ 4.25, one-proton quartet (H_β, $J_{\beta\gamma} = 7$, $J_{\beta\beta'} = 17$ Hz) at δ 3.57, and a one-proton quartet ($H_{\beta'}$, $J_{\beta'\gamma} = 4.4$, $J_{\beta\beta'} = 17$ Hz) at δ 2.78. At 250 MHz the singlet at δ 4.25 is split further into an AB quartet ($J = 12$ Hz).

Anal. Calcd for $C_6H_7O_4Br_3$: C, 18.81; H, 1.82; Br, 62.63. Found: C, 19.04; H, 1.90; Br, 62.58.

Tin–Copper Couple. The procedure of Le Goff,[4] developed for the preparation of zinc–copper couple, was followed. Thirty mesh granular tin (3.5 g, 0.0295 mol, Mallinckrodt) was added to a hot solution of cupric acetate monohydrate (0.050 g, 0.0025 mol) in acetic acid (25 ml). The mixture was stirred and shaken until the blue color of the cupric acetate was no longer evident (ca. 3 min). The acetic acid was decanted and the reddish tin–copper couple washed with two 15-ml portions of acetic acid followed by three 20-ml portions of ether. The tin–copper couple was used freshly prepared and was kept covered with ether.

α-Methylene-γ-bromoglutaric Acid (II). A solution of α-bromomethyl-α,γ-dibromoglutaric acid (I, 3.83 g, 0.01 mol) in dry tetrahydrofuran (6 ml), freshly distilled from $LiAlH_4$, was stirred magnetically with freshly prepared tin–copper couple (0.590 g, 0.005 mol) for 1 h. The precipitated tin bromide was removed by filtration and washed with carbon tetrachloride. Removal of the solvent from the filtrate and addition of chloroform to the concentrate afforded 1.92 g (86%) of white, crystalline α-methylene-γ-bromoglutaric acid (II), mp 133–136 °C. Crystallization from a 2:1 mixture of chloroform–ethyl acetate yielded 1.80 g (81%) of the pure bromo acid II: mp 136–137 °C; infrared (KBr) 5.81, 5.92, and 6.13 μ; NMR (acetone-d_6) two-proton, broad carboxylic acid singlet at δ 8.83, one-proton vinyl singlet at δ 6.33, one-proton vinyl doublet ($J = 1$ Hz) at δ 5.83, one-proton bromomethylene triplet (H_γ, $J_{\beta\gamma} = J_{\beta'\gamma} = 7$ Hz) at δ 4.60, allylic one-proton quartet (H_β, $J_{\beta\beta'} = 14$, $J_{\beta\gamma} = 7$ Hz) at δ 3.25, and allylic one-proton quartet ($H_{\beta'}$, $J_{\beta\beta'} = 14$, $J_{\beta'\gamma} = 7$ Hz) at γ 2.83. The NMR spectrum of the total crude product shows approximately 3% of the fully reduced α-methyleneglutaric acid, which is easily removed in the crystallization step.

Anal. Calcd for $C_6H_7O_4Br$: C, 32.30; H, 3.14; Br, 35.84. Found: C, 32.41; H, 3.28; Br, 35.67.

2,3-Bis(bromomethyl)-1,3-butadiene (IV). Tetrakis(bromomethyl)ethylene (III) was prepared according to Cope and Kagan,[8] NMR ($CDCl_3$) singlet at δ 4.18. A solution of the tetrabromide III (50 g, 0.125 mol) in 300 ml of tetrahydrofuran was stirred for 48 h in the refrigerator (4 °C) with 250 g (2.106 mol) of freshly prepared tin–copper couple. The progress of the reaction was conveniently followed in the same solvent using NMR. The bromomethyl protons of IV are shifted to slightly higher field than those of the starting material III. When the reaction was judged to be complete, it was filtered and the solvent was removed on the rotary evaporator at room temperature. The resulting yellow solid was triturated repeatedly with six 50-ml portions of ether yielding 25 g of solid after evaporation of the ether. This substance was then triturated several times with *n*-pentane with very brief heating on the steam bath each time, followed by filtration. Evaporation of the combined filtrates yielded 22 g of a solid. A white fibrous substance was removed in the filtration step. Finally, the product was dissolved in *n*-pentane with gentle warming and allowed to crystallize overnight in the freezer (−20 °C) yielding 16 g of slightly tan, crystalline dibromide IV, mp 57–58 °C (resolidifies to a fibrous gel soon after melting). The dibromide IV exhibits a very clean NMR spectrum ($CDCl_3$): two-proton vinyl singlet at δ 6.03, two-proton vinyl singlet at δ 5.97, and four-proton bromomethyl singlet at δ 4.15.

Acknowledgment. This work was generously supported by the Institute for General Medical Sciences of the National Institutes of Health through Grant GM 19906 01.

Registry No.—I, 60239-16-9; II, 60239-17-0; III, 30432-16-7; IV, 18214-55-6; α-methyleneglutaryl chloride, 32287-80-2; α-methyleneglutaric acid, 3621-79-2; Sn/Cu, 12735-84-1.

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(9) Use of copper powder alone (tetrahydrofuran, 12 h, 25 °C) yielded a small amount of the desired bromide II (5%) together with a comparable amount of unwanted lactone. The bulk of the material was unreacted tribromide I. The reaction was only marginally improved at 60 °C.

Substitution and Elimination Reactions of Steroid Tertiary C-17 Trifluoroacetates

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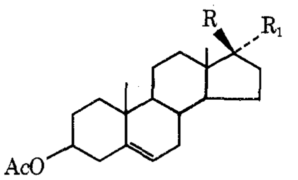
Received June 15, 1976

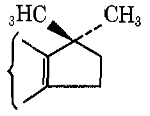
Although solvolytic reactions in the steroid field are of long established synthetic and mechanistic interest,[1] the use of a tertiary trifluoroacetoxy substituent as a leaving group has received relatively little attention. Just and Di Tullio reported briefly that the ethanolysis of 3α-methylcholest-5-en-3β-yl trifluoroacetate (**5**) resulted merely in the recovery of the starting 3β-alcohol (**5a**).[2] Work in other fields suggested, nevertheless, that tertiary trifluoroacetates react in uncatalyzed (neutral) hydrolyses by an alkyl–oxygen fission path or a mechanism which involves both SN and $B_{Ac}2$ routes.[3] Prompted by these results we have examined the solvolytic behavior of 17α-methylandrost-5-ene-3β,17β-diol 3-acetate 17-trifluoroacetate (**1**)[4] and its epimer at C-17 (**1a**), both readily available from the corresponding tertiary alcohols **1b** and **1c**.

Results and Discussion

When **1** and **1a** were solvolyzed in refluxing methanol in the presence of sodium acetate, the following major products were formed. The less polar fractions after chromatography consisted essentially of 17,17-dimethyl-18-norandrosta-5,13-dien-3β-yl acetate (**2**)[5] and a mixture of 17-methyleneandrost-5-en-3β-yl acetate (**3**)[6] and 17-methylandrosta-5,16-dien-3β-yl acetate (**4**)[7] which could not be separated. The other products were, in order of elution, the 17α-methoxy-17β-methylandrost-5-en-3β-yl acetate (**1d**), and (from 1 only) the 17β-alcohol **1b**.[8]



1, R = $OCOCF_3$; R_1 = CH_3
1a, R = CH_3; R_1 = $OCOCF_3$
b, R = OH; R_1 = CH_3
c, R = CH_3; R_1 = OH
d, R = CH_3; R_1 = OCH_3
e, R = CH_3; R_1 = OC_2H_5
f, R = CH_3; R_1 = N_3
g, R = CH_3; R_1 = $NHCOCH_3$



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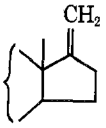

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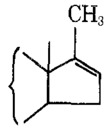

4

The structure of the methyl ether **1d** was deduced on the basis of analytical and spectral data and by comparison of the C-5 saturated analogue[9] with an authentic sample.[10]

In Table I the yields of the products resulting from the two methanolyses are compared. The enhancement of the elimination path for the quasi-axial 17α-trifluoroacetate **1a** has analogy in the solvolyses of several secondary sulfonate esters.[11] The major product **4** should derive from a rapid trans quasi-diaxial elimination with the 16β proton. In both cases the unrearranged elimination products are accompanied by the rearranged Δ^{13} olefin **2**, which is the usual product from a C-17 carbonium ion.[5] The replacement reaction by alkyl–oxygen fission, though proceeding by unimolecular heterolysis (SN1),[12] leads, whatever the substrate, to the 17α-methoxy derivative **1d**, a result which probably depends on the steric opposition of the 13-methyl group to β-attack by the solvent.

Methanolysis of **1** in the absence of a buffer gave the expected enhancement of the rearranged Δ^{13} olefin **2** at the expense of the 17β-alcohol **1b** (only traces).

Turning next to the solvolysis in ethanol, the 17α-ethoxy derivative **1e**[13] was obtained in 11% yield from **1** in the presence of sodium acetate, together with the usual elimination products (52% yield), and the 17β-alcohol **1b** (25% yield).

This result differed considerably from that reported by Just and Di Tullio for **5**[2] but a reexamination of the ethanolysis of **5** showed that, in addition to a 78% yield of the starting alcohol **5a**, only an 8% yield of a hydrocarbon mixture containing both 3-methylcholesta-3,5-diene (**6**)[14] and 3-methylenecholest-5-ene (**7**)[14] and a 9% yield of 3β-ethoxy-3α-methylcholest-5-ene (**5b**)[14] were formed.

As to the aprotic solvents, when dimethyl sulfoxide was used, in the presence of sodium acetate, the decomposition of **1** and **1a** to the elimination products strongly preponderated, as can be seen from Table I. For **1**, the olefin composition observed appears to minimize the possible intervention of a preliminary SN2 substitution of the trifluoroacetoxy group by the solvent (which is more nucleophilic than AcO^- anion) to give an axial *O*-alkyl sulfonium salt,[15] since this would