ACTA CHEMICA SCANDINAVICA 25 (1971) 206–210

Ring Opening Reactions of Dispiro[5.0.5.1.]trideca-1,5,8,12-tetraone

IV.* Reactions with Chloride, Bromide, and Iodide Ions[1]

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Dispiro[5.0.5.1.]trideca-1,5,8,12-tetraone, (*1*), in aprotic solvents readily undergoes rearrangement to the spiro dihydrofuran *3* in the presence of chloride, bromide, and iodide ions. A small amount of the isomer *4* is also formed, except with iodide ions. The suggested mechanism for the rearrangement involves initial nucleophilic ring opening with halide.

When treated with a molar excess of iodide and bromide ions at elevated temperatures, compound *3* is reduced to methylene-bis-1,3-cyclohexanedione. The reverse reaction, oxidative coupling with iodine and bromine, has earlier been described as a procedure of general applicability for preparing derivatives of type *3*. The suggested mechanism for the oxidative coupling involves carbon-halide bond formation. A diradical coupling mechanism is rejected.

Dispiro[5.0.5.1.]trideca-1,5,8,12-tetraone,[2] (*1*), readily undergoes ring opening reactions. Methanol,[3] ethanol,[3] and thiourea [4] add to *1* under mild conditions with preferential attack on the methylene group of the cyclopropyl ring. Formic and acetic acid, on the other hand, exclusively attack one of the spiro carbons.[5] The reactions of *1* with chloride, bromide, and iodide ions have now been studied in some detail.

The experiments have been performed with the free tetraketone *1* or its monohydrate *2*. All ring opening reactions are assumed to proceed *via 1*. Compound *1* can be obtained from *2*, either through cautious short path distillation [2] or more conveniently by treatment with formic acid.[5]

Most of the reactions have been performed in acetonitrile and acetone, in which the nucleophilic tendency of halide ions is far more pronounced than in protic solvents.[6]

* No. III in this series, see Ref. 5.

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When *2* was refluxed in the presence of small amounts of tetramethylammonium chloride in acetonitrile for 48 h, one major and two minor products were formed as shown by TLC. The major product, isolated in 78 % yield, was shown to be the spiro enol ether *3*.[2]

Only one of the minor products was successfully isolated, m.p. 163 – 164°C, < 5 % yield. The mass spectrum gave the peak of highest mass at *m/e* 234, with the composition $C_{13}H_{14}O_4$, which most likely corresponds to the molecular peak. From this evidence, the product was assumed to be isomeric with *3*. The IR and UV spectra of the isomers were similar. IR bands at 1610, 1625, 1695, and 1722 cm^{-1} ($\varepsilon_{1695}/\varepsilon_{1722} \sim 2$) were consistent with the occurrence of a 2,2-disubstituted 1,3-cyclohexanedione ring and an enone system which indicated that the isomer had structure *4*. The NMR spectrum ($CDCl_3$) gave further support for the suggested structure. The methylene protons of the 1,3-cyclohexanedione and the cyclohexenone rings appeared as a poorly resolved multiplet in the region δ 1.6 – 3.0. The methylene protons of the dihydrofuran ring gave rise to a singlet at δ 5.00 (Compare with the methylene bridge protons of *3*, which appear as a triplet at δ 3.19 ($J = 1.8$ cps).)

The mass spectrum of *4*,[3] although related to that of *3*,[7] showed several other prominent peaks, which are of minor importance in the latter spectrum, *e.g.* at *m/e* 179, 189, and 192.

When *2* was treated with lithium bromide in acetonitrile or acetone, it similarly gave *3* as the major product. The minor product *4* was not isolated from the reaction mixture, although TLC revealed the presence of a compound which showed the same properties as *4*.* The reaction of *2* with sodium iodide in acetone also gave *3* as the major product, but gave no sign of *4*.

In order to confirm the assumption that the dehydration of *2* is the rate-determining step in the reaction sequence *2*→*1*→*3*, the free tetraketone *1* was treated with lithium bromide in CD_3COCD_3. The reaction was carried out in an NMR sample tube in the spectrometer at 40°C. The reaction was completed within less than 5 min, even with traces of lithium bromide. The NMR spectrum of the reaction mixture was superimposable on the spectrum of a pure sample of *3* in CD_3COCD_3.

Thus, the overall reaction of *1* in aprotic solvents in the presence of halide ions consists of a rearrangement to the dihydrofuran structure *3*, although in the case of chloride and bromide a simultaneous rearrangement, leading to minor quantities of *4*, is observed.

Due to the pronounced reactivity of *1*, even towards weak nucleophiles, the mechanism for the rearrangements are suggested to involve an initial ring opening with halide ions. The attack occurs mainly on a spiro carbon to give the intermediate *5*, but also to a minor extent (Cl^-, Br^-) on the methylene group of the cyclopropyl ring with formation of *6*. Intramolecular nucleophilic displacement of bromine in *5* and *6* by the enolate oxygen results in the observed products *3* and *4*, respectively.

Attempts to obtain the above rearrangement of *2* with a *molar excess* of iodide in refluxing acetonitrile or acetone were unsuccessful, but resulted

* R_F values for compounds *3* and *4* on silica gel HF in 1,2-dichloroethane-methanol (85:15) were 0.3 and 0.7, respectively.

in the formation of several other products as shown by TLC. Only one of the products was isolated in moderate yield and shown to be methylene-bis-1,3-cyclohexanedione. As expected, the same product was obtained from the rearrangement product *3* under similar conditions. No attempts have so far been made to trap the iodine formed in the reaction in order to increase the yield of methylene-bis-1,3-cyclohexanedione.

The observed reaction is the reverse of a general procedure to prepare cyclic enol ethers of type *3*, as originally described by Radulescu and Georgescu.[8] The authors treated the sodium salts of several 2,2'-alkylidene-bis-1,3-cyclohexanedione derivatives in ether with iodine, and obtained products which were erroneously formulated as cyclopropane derivatives of type *1*.[2,8-11]

A plausible mechanism for the reduction with iodide, outlined in Fig. 1, involves initial nucleophilic ring opening of *3* (formed *in situ* from *1*) with the formation of the reactive intermediate *5*. Nucleophilic displacement on iodine by iodide would give the disodium salt of the observed product. A similar nucleophilic displacement on bromine by iodide evidently takes place, when monobromo derivatives of enols react with iodide.[12]

The reverse, oxidative coupling reaction may formally involve one-electron transfers, followed by a diradical coupling.[13] However, we prefer the alternative mechanism (Fig. 1) with carbon-halide bond formation. No other one-electron

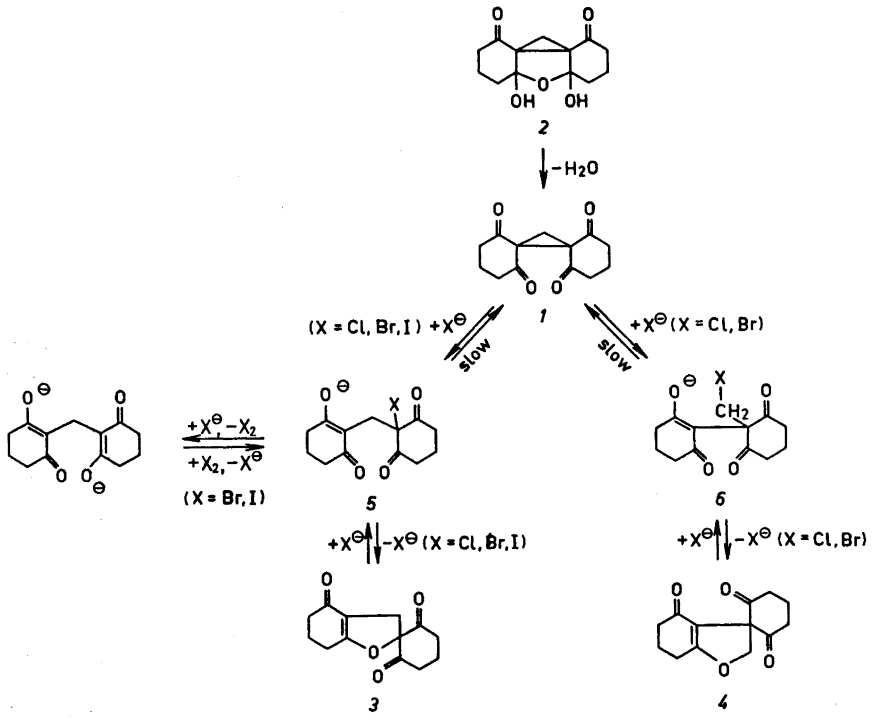

Fig. 1.

transfer reagent with as low an oxidation potential as iodine [$E°(I_2/I^-) = 0.535$ V] has been suggested to give 1,3-cyclohexanedione radicals. Furthermore, it is known [14] that the highest spin density of 1,3-cyclohexanedione radicals is found on the carbon atom, which would favour carbon-carbon coupling. However, when methylene-bis-1,3-cyclohexanedione was treated with iodine and bromine, even in aqueous alcohol systems there was no sign of *1*,[15] while similar treatment with iron(III) hexacyanoferrate(III) [from iron(III) chloride and potassium hexacyanoferrate(III)], suggested to be a one-electron transfer reagent, gave both *1* and *3*.[2]

When *3* was treated with a molar excess of lithium bromide in acetone, the result was similar to that obtained with iodide, as indicated by TLC examination.

EXPERIMENTAL

Conditions and equipment used were those earlier described.[2,3]

Reaction of 2 *with tetramethylammonium chloride; molar ratio* 2:*chloride* = *10:1.* A mixture of *2* (504 mg, 2.0 mmol), tetramethylammonium chloride (23 mg, 0.2 mmol), and acetonitrile (15 ml) was refluxed for 48 h. After filtration and partial removal of the solvent, a little water was added. A crystalline product (51 mg) was obtained, which was recrystallized from isopropyl alcohol, giving *4* (15 mg, 3 %), m.p. 163 – 164°C, mass spectrum $M^+ = 234$ m.u., λ_{max}(EtOH) 265 nm (ε 12 000), ν_{max}(KBr) 1722, 1695 (s), 1625 (s), 1610, 1396, 1188, 1080, 952 cm^{-1}. High resolution mass spectroscopy gave $M^+ = 234.0883$. $C_{13}H_{14}O_4$ requires 234.0892.

The aqueous mother liquor from the isolation of *4* was evaporated to dryness *in vacuo*. Addition of ethyl acetate yielded a crystalline product (365 mg, 78 %) which was sublimed at 0.1 mmHg, 125°C, to give pure *3*, m.p. 138 – 139°C (lit.[2] 138 – 139°C). The NMR and IR spectra were identical with those given by an authentic sample of *3*.

Reaction of 2 *with lithium bromide; molar ratio* 2:*bromide* = *4:1.* A mixture of *2* (504 mg, 2.0 mmol), lithium bromide (43 mg, 0.5 mmol), and acetonitrile (30 ml) was refluxed for 4 h. After filtration and removal of the solvent, a residue was obtained, which crystallized on addition of ethyl acetate to give *3* (329 mg, 70 %). After sublimation at 0.1 mmHg, 125°C, pure *3*, m.p. 138 – 139°C, was obtained.

Reaction of 2 *with sodium iodide; molar ratio* 2:*iodide* = *4:1.* The reaction with iodide was performed in the same way as with bromide. Yield of *3* was 80 %.

Reaction of 2 *with sodium iodide; molar ratio* 2:*iodide* = *1:2.* A mixture of *2* (252 mg, 1.0 mmol), sodium iodide (300 mg, 2.0 mmol), and acetonitrile (10 ml) was refluxed for 15 h. After removal of the solvent, the crystals obtained were treated with water and filtered. The product obtained was crystallized from ethyl acetate to yield methylene-bis-1,3-cyclohexanedione (83 mg, 35 %), m.p. 133 – 134°C (lit.[16] m.p. 132°C). The NMR and IR spectra of the product were identical with those given by an authentic sample.

Reaction of 3 *with sodium iodide; molar ratio* 3:*iodide* = *1:3.1.* A mixture of *3* (as semiketal with methanol, 182 mg, 0.68 mmol), sodium iodide (319 mg, 2.1 mmol), and acetone (30 ml) was refluxed for 3 h. Removal of the solvent gave a crystalline residue, which was treted with water and filtered to yield methylene-bis-1,3-cyclohexanedione (66 mg, 41 %), m.p. 132 – 134°C.

Acknowledgements. The authors are indebted to Mrs. Helena Liedgren for recording the spectra, and to Dr. P. Fredricks for linguistic help. This work has been supported by *Statens Naturvetenskapliga Forskningsråd.*

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Received June 9, 1970.