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PREPARATION AND SOME TRANSFORMATIONS OF LITHIUM-SUBSTITUTED ACETALS OF THE THIOPHENE SERIES

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Some reactions of lithium-substituted acetals of the thiophene series are studied. It is shown that in reaction of some lithium thiophenes with 1-halogenopropynes there is an exchange reaction leading to the halogen atom being replaced by a lithium atom.

When studying the conditions for preparing organometallic compounds containing an acetylated carbonyl group, certain authors [1, 2] pointed out that use of such compounds in synthesis opens up new possibilities. In this connection it is to be borne in mind that the presence of two active reaction centers in molecules of acetals containing metal substituents often gives rise to low stability of the latter. Magnesium and lithium substituted acetals are usually prepared from the corresponding halogenoacetals, the direction of the reaction being controlled by the number of atoms between the halogen and the acetal group, and of course by the reaction conditions. Substituted acetals in which the metal is on the alpha or beta carbon atom are usually unstable [1, 3], and with compounds where the acetal and organometallic group are far apart, stability largely depends on the kind of solvent used. When reaction is carried out in diethyl ether [1], simple ethers are observed to be formed instead of magnesium substituted ketals, but use of tetrahydrofuran makes it possible to obtain such ketals in good yields. This change in the course of the reaction is explained by the authors [1] as being due to a difference in basicity, and to the solvents differing in their capacity to form complexes with the organometallic compounds. Tetrahydrofuran shows that capacity to a greater extent than does ether.

The importance of solvent in formation of acetals of metal-substituted aldehydes is further illustrated by comparing the following facts. A paper [4] related an unsuccessful attempt to replace the bromine in p-bromobenzaldehyde ethyleneacetal by magnesium or lithium, but two years later a method of preparing magnesium or lithiumbenzaldehyde acetals was patented [5]. The difference between the experiments was that the American authors ran the reaction in ether, while the authors of the patent used tetrahydrofuran.

Papers [6-12] from the heterocyclic compounds laboratory of the Institute of Organic Chemistry, AS USSR, describe the preparation and synthetic use of lithium-substituted acetals and ketals of the thiophene series. Unlike acetals of magnesium-substituted thiophene, aldehydes are readily accessible, since they are obtained by simply adding an ether solution of butyl lithium to a solution of an alpha-unsubstituted halogenoacetal or acetal of the thiophene series.

From the results given in the papers mentioned [6-12] it is evident that acetalation is a sufficiently adequate defence for the carbonyl group under conditions of direct metallation of the thiophene ring with butyllithium, or replacement of a bromine atom in the thiophene ring by lithium.

The present paper is concerned with further investigation of the properties of lithium substituted acetals of the thiophene series.

Comparing the two routes for preparing lithium-substituted acetals of the thiophene series, direct metallation of thiophene-2-aldehyde diethylacetal, and replacement of the bromine in 5-bromo-thiophene-2-aldehyde diethylacetal, the present authors confirmed that the second route gives much higher yields of the desired products. The yield of 5-lithiumthiophene-2-aldehyde diethylacetal was found from the amount of 5-formylthiophene-2-carboxylic acid, obtained from the organolithium compound in the usual way.

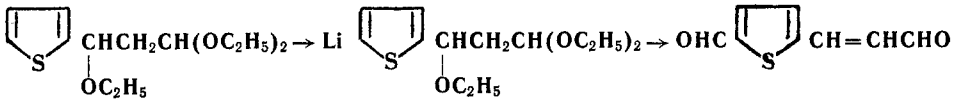
Thiophene-2-aldehyde dimethylacetal, like its diethylacetal, gives, on treatment with butyllithium under the conditions previously described [8], 5-lithiumthiophene-2-aldehyde dimethylacetal, which like the diethylacetal, gives thiophene-2, 4-dialdehyde when further treated with dimethylformamide.

Under the same conditions the readily accessible and stable thiophene-2-aldehyde behaves anomalously. From the product of reaction of its acetal with butyllithium it was not possible, using the appropriate reactants, to obtain comparable amounts of pure aldehydo acid, dialdehyde, and aldehydosulfide. Under certain conditions a considerable part of the initial ethyleneacetal was recovered unchanged, while under other conditions marked gum formation was observed. This is all the more remarkable in view of reported results [13] that thiophene-3-aldehyde ethyleneacetal metallates normally at position 2. This anomalous behavior of thiophene-2-aldehyde may be connected with butyllithium coordinating at the oxygen atoms of the acetal group, and not at the sulfur atom of the thiophene ring. At present, however, experimental data for or against this view are still lacking.

The greater stability of 2-acetothienone diethylketal as compared with its ethylene ketal was turned to account in preparing 5-bromo-2-acetothienone by treating 2-acetothienone ethyleneketal in pyridine with bromine. There acetala-

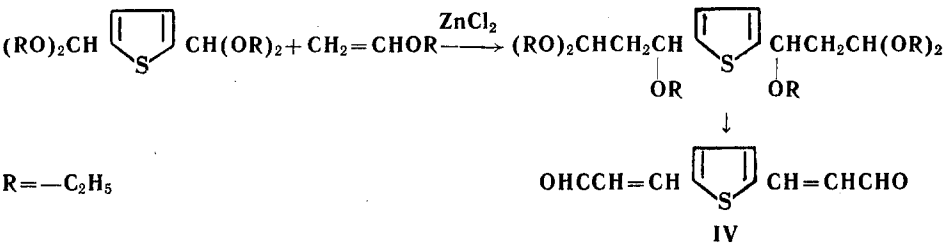
tion of the carbonyl functional group enables the halogen to be introduced at position 5 in the ring, while blocking it with excess aluminum chloride [14] enables halogen to enter position 4.

The condensation product I from thiophene-2-aldehyde diethylacetal and vinylethyl ether when treated with butyllithium also gives the lithium derivative II, and by treating the latter with dimethylformamide, followed by saponification, it can be converted into 5-formyl-2-(β-formylvinyl) thiophene (III).



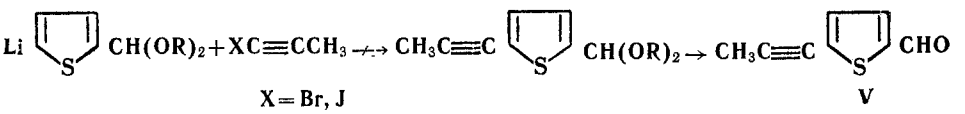
I II III

An attempt to synthesize symmetrical 2,5-bis(β-formylvinyl) thiophene (IV) by condensing thiophene-2, 5-dialdehyde with acetaldehyde, failed. However, the desired compound could be obtained in high yield from thiophene-2, 5-dialdehyde



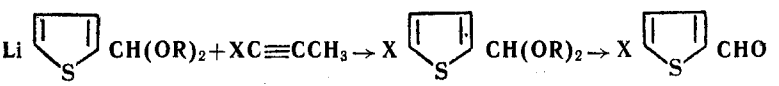
IV

Thiophene derivatives with an aldehyde group and substituents containing acetylenic linkages have attracted the attention of workers in recent years. Such compounds occur naturally, the simplest of them being 5-formyl-2-propynylthiophene (V) (junipal), which is a metabolic product of Daedalena juniperia Murr. [15], a mushroom which breaks down wood. An attempt was made to synthesize that compound by the following route



X = Br, J V

but it proceeded in a different direction, the corresponding halogenated acetal VI being formed



VI

Halogen-substituted acetals of the thiophene series can be prepared in high yield by that method. 5-Bromothiophene-2-aldehyde diethylacetal (VI, X=Br) was also prepared from 5-bromo-2-aldehyde.

Experimental

Thiophene-2, 5-dialdehyde (from 5-lithiumthiophene-2-aldehyde dimethylacetal). Thiophene-2-aldehyde dimethylacetal was prepared by refluxing 20.1 g (0.18 mole) thiophene-2-aldehyde and 29.1 g tetramethoxysilane with a solution of 0.8 g crystalline orthophosphoric acid in 20 ml dry methanol, the product being worked up in just the same way as when preparing thiophene-2-aldehyde diethylacetal [16]. Yield 22.8 g (80%) bp 73° (10 mm), n_D^{20} 1.5100. 22.8 g (0.144 mole) of the acetal thus prepared and 10.2 g (0.16 mole) butyllithium in ether gave a solution of 5-lithiumthiophene-2-aldehyde dimethylacetal, and this, after treating with 22 g (0.3 mole) dimethylformamide in the way previously described [8], gave 12.9 g (45%) thiophene-2, 5-dialdehyde dimethylacetal, bp 143-148° (11 mm), n_D^{20} 1.5385. Saponification of that compound with aqueous alcoholic hydrogen chloride gave thiophene-2, 5-dialdehyde, mp 114-114.5°, mixed mp with an authentic specimen [8] undepressed.

5-Formyl-2-(β-formylvinyl) thiophene (III). 0.5 ml 10% solution of anhydrous zinc chloride in glacial acetic acid was added to 15.9 g (85 mmole) thiophene-2,-aldehyde diethylacetal, and after mixing, 6.2 g (86 mmole) vinylethyl ether was added at 20°. After 10 min the temperature was raised to 55°, and the mixture kept for an hour longer at

50°-55°. After cooling, the reaction products were poured into a mixture of 30 ml 10% KOH solution and 40 ml ether. The ether layer was separated off, washed with water, and dried. Distillation gave 14.6 g (65%) β-(2-thienyl)-β-ethoxypropionaldehyde diethylacetal (I), bp 127-129° (6 mm), n_D^{20} 1.4790. Treatment with a hydrochloric acid solution of 2, 4-dinitrophenylhydrazine gave 2-(β-formylvinyl) thiophene 2, 4-dinitrophenylhydrazone mp 137-138°. Found: N 17.67; 17.42%. Calculated for $C_{13}H_{10}N_4O_2S$: N 17.59%.

β-'5-Lithiumthienyl-2)-β-ethoxypropionaldehyde (II) in ether solution was prepared from 9.5 g (37 mmole) I and 2.6 g (41 mmole) butyllithium in ether, and to it was added, at −20°, a solution of 7 ml dimethylformamide in 20 ml ether, after which the mixture was refluxed for 20 min on a steam bath. After decomposing with water, the ether solution was washed with water and dried over potash. Distillation gave 6.4 g of an oil, bp 160-165° (4 mm), n_D^{20} 1.5066, which was saponified by refluxing for 30 min with a mixture of equal volumes of concentrated hydrochloric acid and alcohol; on cooling there crystallized out 2.2 g (37%) III, mp 120° . After recrystallizing from alcohol it had mp 120.5-121° . Found: C 58.21, 58.16; H 3.70, 3.70; S 19.23, 19.34%. Calculated for $C_8H_6O_2S$: C 57.80; H 3.67; S 19.31%.

2, 5-Bis(β-formylvinyl) thiophene (IV). One g phosphoric anhydride in 20 ml absolute alcohol was added to a solution of 7.2 g (51 mmole) thiophene-2, 5-dialdehyde in 30.1 g (145 mmole) orthosilicic ester. The mixture was refluxed for 4 hr, cooled, and treated with a concentrated sodium hydroxide solution. The organic layer was extracted with ether, washed with water, then a few times with sodium hydroxide solution, and finally with water again. After drying over potash and removing the ether, the residue was distilled under reduced pressure. Yield 12.0 g (81%)thiophene-2, 5-dialdehyde bisdiethylacetal, bp 115-116° (2 mm), n_D^{20} 1.4782.

Twenty drops of a 10% solution of anhydrous zinc chloride in glacial acetic acid were added to a mixture of 10.8 g (38 mmole) of the above acetal and 5.4 g (75 mmole) vinylethyl ether, and the whole stirred from time to time over 2 hr. Heating and darkening took place. The reaction mixture was held at 60-70°, and worked up for the reaction product in the way described above. Distillation gave a 12.2 g fraction bp 175-186° (2 mm), n_D^{20} 1.4700. Thirty min. refluxing of this material with concentrated hydrochloric acid-alcohol saponified it to 5.4 g (76%) IV mp 180°. After recrystallizing from alcohol-benzene it had mp 184° . Found: C 62.07, 62.12; H 4.45, 4.28; S 16.46, 16.37%. Calculated for $C_8H_{10}O_2S$; C 62.44; H 4.21; S 16.69%.

Action of 1-halogenopropynes-1 on 5-lithiumthiophene-2-aldehyde diethylacetal.

1) 5-Iodothiophene-2-aldehyde. 28 g (0.17 mmole) 1-iodopropyne-1* in 50 ml ether was added to an ether solution of 5-lithiumthiophene-2-aldehyde diethylacetal [obtained from 28.0 g (0.15 mole) 2-thiophene-2-aldehyde and 10.2 g (0.16 mole) butyllithium in ether] maintained at −40°. The mixture was then brought to room temperature, and after 3 hr decomposed with water. The ether was evaporated off, and the residue vacuum distilled. Yield 32.8 g (70%) 5-iodothiophene-2-aldehyde diethylacetal bp 144-147° (10 mm), n_D^{20} 1.5660. Saponification of 5.9 g (19 mmole) of this acetal with aqueous-alcoholic hydrogen chloride followed by crystallization gave 4.3 g (95%) 5-iodothiophene-2-aldehyde mp 56° , unchanged by recrystallizing from heptane. Found: C 25.24, 25.45; H 1.16, 1.10%. Calculated for C_5H_3IOS: C 25.24; H 1.26%.

2) 5-Bromothiophene-2-aldehyde diethylacetal. 40 ml of a 30% toluene solution of 1-bromopropyne-1** was added to an ether solution of 5-lithiumthiophene-2-aldehyde diethylacetal [from 18.6 g (0.1 mole) thiophene-2-aldehyde diethylacetal and 6.4 g (0.1 mole) butyllithium] at −10° . Next day the mixture was refluxed for 4 hr, after which it was decomposed with water. The ether solution was washed, and dried over potash. After removing the ether, the residue was vacuum-distilled. Yield 17.3 g (65%) 5-bromo-thiophene-2-aldehyde diethylacetal bp 124-128° (9 mm), n_D^{20} 1.5274. Saponification of this acetal gave 5-bromothiophene-2-aldehyde 112-113° (13 mm), n_D^{20} 1.6330. The literature [19] gives bp 80-83° (2 mm). Semicarbazone mp 200-201°, mixed mp with an authentic specimen undepressed.

Acetalation of 27.6 g (0.145 mole) 5-bromothiophene-2-aldehyde [19] using 32.0 g (0.153 mole) orthosilicic ester and 30 ml 10% alcoholic solution of phosphoric anhydride as catalyst, gave 32 g (94%) 5-bromothiophene-2-aldehyde diethylacetal bp 119-121° (8 mm), n_D^{20} 1.5210. Found: Br 30.28, 30.15%. Calculated for $C_9H_{13}BrO_2S$: Br 30.13%. Aldehyde semicarbazone mp 200-201°.

2-Acetothienone ethyleneketal. 1 ml 70% perchloric acid was carefully added dropwise to a mixture of 37.4 g (0.45 mole) thiophene and 70 ml acetic anhydride which was stirred and cooled to 20-30°. The mixture was held for 2 hr at room temperature, and then poured into cold water. The oil which separated was separated off, the aqueous solution neutralized with alkali, and then extracted with benzene. The separated oil was added to the benzene solution, and the resultant solution washed with dilute alkali and water. 34 g (0.55 mole) ethylene glycol and 0.8 g p-toluenesulfonic acid were added to the solution (350 ml), and the whole refluxed for 20 hr, using an arrangement for drawing off the

* Prepared in 33% yield, n_D^{20} 1.5440, by the method given in [17].

** Prepared by the method of [18]; the concentration in toluene was found by gas-liquid chromatography.

water. The benzene solution was treated with a methanol solution of sodium methoxide, washed with water, and dried over magnesium sulfate. The residue remaining after distilling off the benzene was vacuum-distilled. Yield 43.9 g (58% on the thiophene) 2-acetothienone ethyleneketal, bp 94-95° (13 mm), n_D^{20} 1.5320. The product solidified on cooling. MP 36-37° (from hexane). Found: C 56.58, 56.46; H 6.00, 5.95; S 18.96, 19.04%. Calculated for $C_8H_{10}O_2S$: C 56.44; H 5.93; S 18.86%.

5-Bromo-2-acetothienone ethyleneketal. A solution of 25.6 g (0.16 mole) bromine in 25 ml chloroform was dropped into a mixture of 27.2 g (0.16 mole) 2-acetothienone ethyleneketal, 35 ml chloroform, and 40 ml pyridine and held at −5°. On standing for 1 hr at 0-15° the mixture darkened. The solution was poured into water, the chloroform layer separated off, washed with water, and dried over magnesium sulfate. After distilling off the chloroform there remained 23.7 g dark liquid, which was distilled to give 11.8 g of a fraction bp 90-98° (11 mm) n_D^{20} 1.5540, and 8.4 g of a fraction bp 122-125° (11 mm), which immediately crystallized. A further 3.3 g crystalline material was obtained by repeated distillation of the first fraction. Total yield 11.7 g (29%) mp 66-67° (from heptane). Found: 38.78, 38.67; H 3.62, 3.57%. Calculated for $C_8H_9BrO_2S$: C 38.56; H 3.65%.

5-Bromo-2-acetothienone. A solution of 2.1 g (8.4 mmole) 5-bromo-2-acetothienone ethyleneketal in 15 ml alcohol was refluxed for 1 hr with 10 ml dilute (1 : 1) hydrochloric acid. After cooling, the precipitate was filtered off and washed, to give 1.53 g (93%) 5-bromo-2-acetothienone mp 94-95°, which after repeated recrystallization from alcohol had mp 95-96°, mixed mp with an authentic specimen undepressed.

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