eV, CH_3OH 10.8 eV, and $(CH_3)_2O$ 10.0 eV.[10] In contrast to what could be expected from the trend in the ionization energies the $-\Delta H$ values for adduct formation with $SbCl_5$ as acceptor have been found to decrease in following way: water > methanol > methyl propyl ether. The same order in donor strength between alcohols and ethers has been found with BF_3 as acceptor and using ΔG as a measure of the strength of interaction.[11] In these acceptor molecules the halogen atoms may interact with the groups attached to the donor atom and give rise to steric strains in the adducts and possibly to some extent reduce the donor strength of ethers. It has namely been found that ethers give higher $-\Delta H$ values than alcohols for complex formation with the much weaker acceptor I_2,[12] where steric interactions between donor and acceptor molecules could be expected to be less influential. The data are not, however, conclusive as the influence of the self-association of alcohols seems not to have been taken into account.

It was concluded from qualitative experiments on enthalpies of adduct formation that ethers and ketones showed comparable donor strengths towards $SbCl_5$ and $SnCl_4$ as acceptors.[13] This is confirmed by the results found in this investigation. The $-\Delta H$ values for the ether adducts are, however, slightly higher than for ketone adducts,[14] but the differences are too small to permit any valid conclusions.

Considering the $-\Delta H$ values found for methyl propyl ether and dipropyl ether (18.1 and 17.8 kcal·mole^{-1}, respectively) the value for diethyl ether can be expected to be close to 18.0 kcal·mole^{-1}. A recently reported value[15] of 19.2 kcal·mole^{-1} thus seems to be about 1 kcal·mole^{-1} too high.

Acknowledgement. The author is indebted to Mr. T. Henricsson for help with the preparative work. A grant from the *Faculty of Mathematics and Natural Sciences*, University of Lund, is gratefully acknowledged.

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Received March 23, 1968.

A Simple One-pot Procedure for the Synthesis of Certain Substituted Thiophene Aldehydes and Ketones

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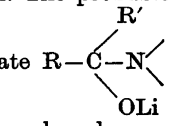
Starting from the dibromothiophenes, various disubstituted thiophenes are available through step-wise halogen-metal interconversion followed by reaction of the bromothienyllithium derivative with an appropriate reagent, provided that the group introduced first does not interfere with the second halogen-metal exchange (for review, *cf.* Ref. 1).

Substituted thiophene aldehydes were prepared by reacting the bromothienyllithium derivative with *N*,*N*-dimethylformamide, protecting the formyl group of the bromothiophene aldehyde formed through acetal formation, followed by a second halogen-metal exchange and reaction with an appropriate reagent. This method was first introduced by Goldfarb *et al.*,[2] who found that the acetals of thiophene aldehydes as well as of thienyl ketones were

stable both in the halogen-metal exchange reaction of bromothiophenes and also in the metalation of thiophenes. This method has been used for the preparation of various thiophene dialdehydes,[3-6] formyl-[7,8] and acetylthiophenecarboxylic acids,[9] formylthiopheneboronic acids,[10,11] and other derivatives.[12]

Not only halogen-metal interchange, but also the metalation reaction can be utilized. Thus metalation of 3-thiophene aldehyde ethylene acetal with butyllithium followed by reaction with CO_2 yielded 3-formyl-2-thiophenecarboxylic acid.[7] Certain dihalothiophenes such as 2,3-dibromo-, 2,5-dibromo-, or 3,4-diiodothiophenes give with excess butyllithium the corresponding dilithiothiophenes, which have been utilized for the preparation of thiophene dialdehydes through the reaction with *N,N*-dimethyl formamide, although in some cases the yields are low.[6]

We have now found that the carbonyl function introduced need not be protected by acetalation. The probable structure of the intermediate  incorporates a "protected" carbonyl group, and in this way a second function (such as boronic acid or carboxyl group) can be inserted in a "one-pot" reaction.

A convenient synthesis of 2-formyl-3-thiophenecarboxylic acid in 40 % yield is thus possible by reacting 2,3-dibromothiophene with 1 equivalent of butyllithium at −70°C followed by reaction with *N,N*-dimethyl formamide. A second equivalent of butyllithium is added and the mixture carbonated. If 2,4-dibromothiophene is the starting material, 2-formyl-4-thiophenecarboxylic acid is obtained. Reacting 3-bromo-2-thienyllithium first with *N,N*-dimethyl formamide followed by an additional equivalent of butyllithium and butylborate yielded 2-formyl-3-thiopheneboronic acid in 35 % yield.

The modified carbonyl function in the intermediate obtained upon reaction of a thienyllithium derivative with *N,N*-dimethyl formamide is also stable towards alkyllithium in refluxing ether. Thus the intermediate obtained upon reaction of 3-thienyllithium with *N,N*-dimethyl formamide was metalated by butyl- or ethyllithium in refluxing ether exclusively in the 2-position. Reaction with carbon dioxide and butylborate yielded 3-formyl-2-thiophenecarboxylic acid and 3-formyl-2-thiopheneboronic acid, respectively, in about 40 % yield.

The purification of the final product is facilitated by its acidic properties. However, it was also possible to obtain, for instance, 3-acetyl-2-formylthiophene by reacting 3-thienyllithium with *N,N*-dimethyl acetamide followed by metalation of the intermediate product with ethyllithium and reaction with *N,N*-dimethyl formamide. Reversing the order of addition of *N,N*-dimethyl acetamide and *N,N*-dimethyl formamide yielded 2-acetyl-3-formylthiophene. The yields of pure products, however, were in both cases rather low (10−20 %).

For the synthesis of formylthiophenecarboxylic acids and formylthiopheneboronic acids the net yield in the "one-pot" procedure is better than in the traditional way, but it is above all highly time-saving. We are further investigating the scope of this method.

Experimental. As an example of the general procedure, the preparations of 2-formyl-3-thiopheneboronic acid and of 3-formyl-2-thiophenecarboxylic acid are given.

2-Formyl-3-thiopheneboronic acid. To 0.33 mole of ethereal ethyllithium cooled to −70°C was added under nitrogen and with vigorous stirring 72.0 g (0.3 mole) of 2,3-dibromothiophene[13] in 200 ml of anhydrous ether. After stirring for 5 min, 23.4 g (0.32 mole) of *N,N*-dimethyl formamide in 75 ml of anhydrous ether was added in a slow stream. The cooling bath was removed and the mixture stirred for 2 h. After cooling to −70°C, 0.36 mole of ethereal ethyllithium was added in a slow stream followed by addition of 97.5 g (0.42 mole) of butylborate in 170 ml of anhydrous ether in one portion. The mixture was stirred for 4 h at −70°C, the cooling bath removed and when the temperature had risen to 0°C the reaction mixture was worked up as described earlier,[10] yielding 26.5 g (57 %) of crude 2-formyl-3-thiopheneboronic acid. Recrystallization from ethanol-water yielded 16.5 g (35 %) of pure 2-formyl-3-thiopheneboronic acid having the same IR-spectrum as an authentic sample.

3-Formyl-2-thiophenecarboxylic acid. A solution of 16.3 g (0.10 mole) of 3-bromothiophene in 50 ml of anhydrous ether was added during a few minutes to 148 ml of a well-stirred ethereal solution of 0.74 N butyllithium cooled to −70°C. After stirring for an additional 15 min, 8.03 g (0.11 mole) of *N,N*-dimethyl formamide was added in one portion and the

reaction mixture allowed to warm to room temperature. After one hour, 172 ml of 0.74 N ethereal butyllithium was added dropwise and the mixture refluxed for 135 min. It was then poured onto solid carbon dioxide covered with ether and worked up in the usual way, yielding 6.9 g (44 %) of 3-formyl-2-thiophenecarboxylic acid having after recrystallization from a benzene-ligroin mixture, the same melting point (130–131°C) and IR-spectrum as an authentic sample.[7]

Acknowledgement. The authors are indebted to Miss Anna-Maj Balsberg for skilful experimental help. A grant from the *Swedish Natural Science Research Council* to S.G. is gratefully acknowledged.

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Received April 2, 1968.

Isoelectric Focusing of α-Crystallin Subunits

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α-Crystallin, isolated from the bovine lens by different techniques, such as isoelectric precipitation, zone electrophoresis or gel chromatography, has a molecular weight of about 800 000.[1-4] On treatment with 7 M urea the molecular weight falls to about 25 000, and the urea-treated material can be separated into several bands by polyacrylamide gel electrophoresis.[5] This demonstrates that the α-crystallin molecule is composed of a large number of subunits. Evidence indicating that several of these subunits differ from each other has recently accumulated.[4,6,7] This problem, however, can be unequivocally solved only by the purification of different subunits and the comparison of their properties. The technique of isoelectric focusing in a pH gradient, developed by Svensson and Vesterberg,[8-11] has been applied to the separation of the α-crystallin subunits, and the results obtained will be reported in this communication.

α-Crystallin was prepared from calf lenses by the method of Mok and Waley.[12] In order to remove residual low molecular weight impurities, 50 mg of this material were dissolved in 7 ml of 0.1 M tris buffer, pH 8.0, containing 0.5 M NaCl, and the solution was passed through a column of Sephadex G 200 (4 × 100 cm) equilibrated with the same buffer. The purified sample was then dialysed against distilled water and lyophilised.

Isoelectric focusing was carried out in an LKB 8102 Electrofocusing Column with a total volume of about 450 ml, following the directions given by Haglund.[13] A stepwise sucrose gradient containing 7 M urea was prepared. The carrier ampholytes forming the pH gradient were also supplied by LKB-Produkter AB, Stockholm, Sweden; they covered the pH range 5–8 and were used at a concentration of 1 %. The α-crystallin sample (about 40 mg) was dissolved in one of the middle fractions of the gradient. It was necessary to perform the experiment at 20°C in order to avoid precipitation of urea or sucrose at the bottom of the column, which otherwise