We thank Kjeld Schaumburg for the measurement of the PMR spectra and for his helpful comments on them.

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Received July 30, 1969.

On the Halogen-Metal Exchange Reaction between 2-Bromo-3-iodothiophene and Ethyllithium

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Halogen-metal exchange between bromothiophenes and ethyllithium derivatives is a very rapid reaction even at −70°C.[1] It is also known that 2-positioned bromine exchanges much more rapidly than 3-positioned bromine. For instance, this is demonstrated in the halogen-metal exchange reaction between 2,3-dibromothiophene or 2,4-dibromothiophene with butyllithium at −70°C in which case only the α-halogen is exchanged.[1] It is also well-known, from the classical investigations of Wittig *et al.* and Gilman *et al.* that iodides react more rapidly than bromides (for review, *cf.* Ref. 2). Therefore we were interested in studying the halogen exchange reaction of 2-bromo-3-iodothiophene with ethyllithium in order to find out which factor would be the most important.

The study of halogen-metal exchange with this substrate is also of interest in connection with the question of the existence of dehydrothiophene. One of us has earlier pointed out the high stability of *ortho* bromo-thienyllithium derivatives such as 3-bromo-2-thienyllithium.[3] In contrast to *ortho* bromophenyllithium [4] these compounds showed no tendency to split out lithium bromide to give dehydrothiophenes.

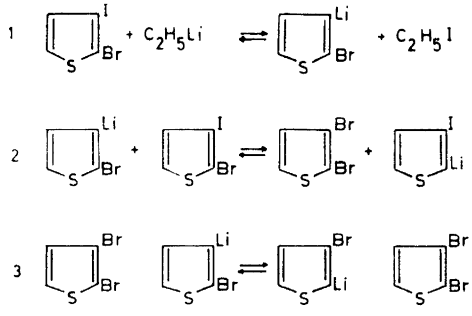
It was also found that 3-fluoro-2-thienyllithium, obtained through metalation of 3-fluorothiophene was stable and no dehydrothiophene could be intercepted with furan.[5] Nor could the Grignard route from 3-fluoro-2-bromothiophene be used for the production of 2,3-dehydrothiophene.

A recent paper by Wittig and Rings describes extensive work to prove the intermediate formation of dehydrothiophene.[6] They used 3-bromo-2-thienyllithium and 2,5-diphenyl-4-iodo-3-thienyllithium as well as similar mercury compounds such as bis[3-iodo-2-thienyl]mercury as substrates. However, no evidence for the intermediate formation of dehydrothiophene was obtained. Reinecke and Adickes[7] have shown that the ciné-substitution, which occurs in the reaction of 2-bromothiophene with potassium amide in liquid ammonia does not proceed *via* a dehydrothiophene but occurs through a series of transbrominations similar to those observed by Gronowitz and coworkers in the reaction of 3-bromothiophene and the dibromothiophenes with butyllithium.[1] We therefore hoped that, if 2-bromo-3-thienyllithium was formed in the halogen-metal exchange reaction, this certainly should constitute the most suitable intermediate hitherto studied for the production of 2,3-dehydrothiophene.

2-Bromo-3-iodothiophene (b.p. 106−109°C/10 mm Hg, τ_{4or5}=2.83 ppm, τ_{5or4}=3.09 ppm J_{45}=5.6 cps) was obtained in 83 % yield through reaction of 3-iodothiophene with *N*-bromosuccinimide in acetic acid.

Adding an ethereal solution of 2-bromo-3-iodothiophene to a 10 % excess of ethereal ethyllithium at −70°C, controlling the temperature below −60°C, yielded upon reaction with ethanol, 20 % 3-iodothiophene, 55 % 3-bromothiophene, 5 % 2-bromothiophene, and 20 % 2,3-dibromothiophene. Carbonation of the reaction mixture yielded an acid mixture, which was esterified with diazomethane and analysed gas-chromatographically. The analysis indicated the formation of 26 % of methyl 3-iodo-2-thiophenecarboxylate, 71 % 3-bromo-2-thiophenecarboxylate, and 3 % 2-bromo-3-thiophenecarboxylate. This indicates that the simple halothiophenes (except 2,3-dibromothiophene) obtained upon hydrolysis exist as lithiated derivatives. It would be attractive to

explain the formation of 3-bromo-2-thienyllithium by the splitting off of lithium bromide from initially formed 2-bromo-3-thienyllithium followed by addition in the reverse more natural sense. However, all attempts to catch the intermediate 2,3-dehydrothiophene with furan failed. Therefore it seems more likely that the initially formed 2-bromo-3-thienyllithium undergoes a series of rapid halogen-metal exchange reactions even at −70°C leading to the thermodynamically most stable lithium derivative, as observed earlier for 4-bromo-3-thienyllithium and 4-bromo-2-thienyllithium.[1] The following transformations can for instance be envisaged:



That 2,3-dibromothiophene is obtained as such and not as its lithium derivative is in accordance with earlier results which showed that 2,3-dibromothiophene is not metalated at such a low temperature.

It was hoped that the rearrangement of the primary halogen-metal exchange product could be slowed down by keeping the temperature below −100°C. This was found to be the case. Using a 50 % excess of ethyllithium and keeping the temperature during the addition below −100°C yielded after hydrolyses 95 % of 2-bromothiophene, 5 % of 3-bromothiophene, and trace amounts (less than 1 %) of 3-iodothiophene and 2,3-dibromothiophene. Analyses of the methyl esters, prepared as described above, showed the formation of 84 % methyl 2-bromo-3-thiophenecarboxylate, 5 % 3-bromo-2-thiophenecarboxylate and 11 % 3-iodo-2-thiophenecarboxylate. The dry ice has to be added carefully in order to avoid a rise in temperature. Through recrystallisation of the carbonation product pure 2-bromo-3-thiophenecarboxylic acid (m.p. 178−179°C, $\tau_{4 \text{ or } 5} = 2.46$ ppm, $\tau_{5 \text{ or } 4} = 2.59$ ppm, $J_{45} = 5.8$ cps. Literature value [6] m.p. 178−179°C) could be obtained in 46 % yield. Halogen-metal exchange between 2-bromo-3-iodothiophene and ethyllithium at −110°C is thus a preparatively usable route for the preparation of 2-bromo-3-thienylsubstituted compounds. If only a 10 % excess of ethyllithium was used at −110°C the amount of 3-iodo-2-thienyllithium as well as of 3-bromo-2-thienyllithium increases and 2,3-dibromothiophene appears. This indicates that 3-iodo-2-thienyllithium is not formed by direct halogen-metal exchange with ethyllithium, but in step 2 of the above reaction scheme.

We also found that using large excess (200 %) of ethyllithium at −70°C suppressed the rearrangement of 2-bromo-3-thienyllithium and decreased the amount of 3-iodo-2-thienyllithium and 3-bromo-2-thienyllithium formed. However, the total yield of halothienyllithium derivatives diminishes due to the formation of dilithiated product as evidenced by the formation of thiophene upon hydrolysis. We are continuing our investigation of the halogen-metal interconversion with mixed dihalothiophenes.

The gas chromatographic analyses were carried out on a Perkin-Elmer 900 gas chromatograph using 2 m × 1/8" NPGS (5 %) column on Chromosorb W (80−100 mesh) and 2 m × 1/8" silicon grease (DC 710) column. For the NPGS column the temperature, when analysing the protonated products, was programmed from 60 to 200°C with an increase of 13°C/min and an initial period of 2 min. The carbonated and esterified products were analysed on the NPGS column with the temperature programmed from 90−200°C with an increase of 13°C/min. When using the DC 710 column the temperature was held constant at 180°C. For analysis the different peaks were calibrated with known amounts.

Acknowledgements. Grants from the *Swedish Natural Science Research Council* (to S.G.) and from the *Faculty of Science of the University of Lund* (to B.H.) are gratefully acknowledged.

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Received August 9, 1969.