On the Grignard Reaction of 2-Bromo-3-iodo- and 3-Bromo-2-chlorothiophene

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2-Bromo-3-iodo- and 3-bromo-2-chlorothiophene react with magnesium in the presence of 1,2-dibromoethane to give 2-halo-3-thiophene magnesium halide which opens a useful route to 2,3-disubstituted thiophenes having an electron-withdrawing group in the 3-position.

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It has recently been shown that 2-bromo-3-iodothiophene undergoes halogen-metal exchange with alkyllithium derivatives at -100° in the 3-position (1,2). The 2-bromo-3-thienyllithium thus formed is extremely unstable and rearranges on standing at this temperature and even faster at -70°, through a complex series of halogen-metal exchanges and metalations to the thermodynamically more stable 3-bromo-2-thienyllithium (1,2). On the other hand, 2-chloro-3-thienyllithium formed from 3-bromo-2-chlorothiophene by halogen-metal exchange was reasonably stable at -70°, but rearranged at room temperature to a complex mixture containing 5-chloro-2-thienyllithium and 3-bromo-2-chloro-5-thienyllithium (2). Another complication which has been observed with certain 3-thienyllithium derivatives at room temperature is ring-opening to lithium enynethiolates (3,4). It was noticed, however, that the corresponding Grignard reagents did not ring-open (3).

We were therefore interested in finding out which Grignard reagent is formed from a mixed dihalothiophene with the more reactive halogen in the β-position and have hitherto studied the behaviour of 2-bromo-3-iodothiophene and 3-bromo-2-chlorothiophene. The mechanism and effect of substituents on the direct formation of Grignard reagents and on halogen-lithium exchange are different (5) and therefore a priori the same results as in the halogen-metal exchange cannot be expected. It should perhaps also be stressed that *ortho*-halothienyllithium and *ortho*-halothienylmagnesium reagents in contrast to the corresponding benzene derivatives are stable and do not form dehydro intermediates (2).

The reactions of the mixed dihalothiophenes with magnesium were carried out by the entrainment technique (6,7) with a 9-fold excess of ethylene dibromide. The latter is a very useful entrainer as no Grignard reagent but only magnesium bromide and ethylene are formed (8). The mechanism of the entrainment Grignard reaction probably does not differ very much from the normal formation of Grignard reagents. The function of the entrainer is to keep the magnesium surface clean and reactive (8,9). In principle it has been shown that 2-bromothiophenes undergo halogen-magnesium exchange with ethylmagnesium bromide (5,9), but that this route is not of importance under entrainment conditions (9). This mechanistic route is, in any case, hardly possible with ethylene bromide as an entrainer. Reaction of 2-bromo-3-iodothiophene and ethylene dibromide in the approximate porportion of 1:9 with magnesium gave after reaction with carbon dioxide, 2-bromo-3-thiophenecarboxylic acid in 80% yield. In order to avoid formation of *bis* Grignard reagents, an excess of magnesium was not used.

Upon reaction of the Grignard reagent with *N,N*-dimethylformamide, 2-bromo-3-thiophenecarbaldehyde was obtained in 60% yield. It is thus obvious that the 3-iodo reacts faster than the 2-bromo substituent and that the 2-bromo-3-thiophenemagnesium iodide formed is stable under the reaction conditions used. Similarly, the reaction of 3-bromo-2-chlorothiophene and ethylene bromide with magnesium gave 2-chloro-3-thiophenemagnesium bromide, which with carbon dioxide and *N,N*-dimethylformamide gave 2-chloro-3-thiophenecarboxylic acid and 2-chloro-3-thiophenecarbaldehyde, respectively.

These results open a useful preparative route to 2,3-disubstituted thiophenes having an electron-withdrawing group in the 3-position, as electrophilic substitution of 3-thiophenecarboxylic acid and 3-thiophenecarbaldehyde occurs in the 5-position.

Previously, 2-bromo-3-thiophenecarboxylic acid and the corresponding aldehyde have been prepared by bromination of 3-methylthiophene followed by oxidation of the methyl group (10). The chloro derivatives have been obtained in a similar manner (10) and from 3-bromo-2-chlorothiophene by exchange with butyllithium at -70°,

followed by carbon dioxide treatment or *N,N*-dimethyldimethylformamide, respectively (11).

EXPERIMENTAL

2-Bromo-3-thiophenecarboxylic Acid.

To 30.2 g. (1.24 moles) of magnesium covered with 100 ml. of anhydrous ether in the usual Grignard apparatus, about 50 ml. of a solution of 227 g. (1.22 moles) of ethylene bromide in 300 ml. of anhydrous ether was added until the Grignard reaction started. The residual ethylene dibromide solution was mixed with 57.8 g. (0.20 mole) of 2-bromo-3-iodothiophene (1) and added dropwise during about two hours, at such a rate that the mixture refluxed. After the addition was completed the mixture was refluxed for an hour, cooled and poured onto crushed carbon dioxide covered with ether. When the temperature of the reaction mixture had risen to about 0°, 2 *N* hydrochloric acid was added. The ether phase was separated and the aqueous phase extracted several times with ether. The combined ether phases were extracted with several portions of 2 *N* sodium hydroxide solution and the combined aqueous phases acidified with 2 *N* hydrochloric acid precipitating 33.7 g. (81%) of the title compound, m.p. 176-178° after recrystallization from 40% aqueous ethanol, literature value (1,10) m.p. 178-179°; pmr (DMSO-d_6): δ 7.20 [d (J = 5.7 Hz), 1H, H_4], δ 7.78 [d (J = 5.7 Hz), 1H, H_5].

2-Chloro-3-thiophenecarboxylic Acid.

Applying the same procedure as described above to 3.45 g. (0.142 mole) of magnesium, 26.0 g. (0.138 mole) of ethylene dibromide and 6.6 g. (0.033 mole) of 2-chloro-3-bromothiophene (11) gave 3.3 g. (87%) of the title compound, m.p. 161-163° after recrystallization from aqueous ethanol, literature value (10) m.p. 163°; pmr (DMSO-d_6): δ 7.25 [d (J = 5.9 Hz), 1H, H_4], δ 7.55 [d (J = 5.9 Hz), 1H, H_5].

2-Bromo-3-thiophenecarbaldehyde.

The Grignard reagent solution was preapred as described above from 25.0 g. (1.02 moles) of magnesium, 178.5 g. (0.95 mole) of ethylene dibromide, 28.9 g. (0.10 moles) of 2-bromo-3-iodothiophene and the appropriate amounts of anhydrous ether. After refluxing for 3 hours, 20 g. (0.27 mole) of anhydrous *N,N*-dimethylformamide in 25 ml. of ether was added and the mixture refluxed for an additional 2-3 hours. After cooling in ice-water, 200 ml. of 2 *N* hydrochloric acid was added dropwise and the mixture stirred for 1 hour. The ether phase was separated and the aqueous phase extracted several times with ether. The combined ether phases were washed with sodium carbonate solution and water, dried over magnesium sulphate and fractionated to give 11.5 g. (60%) of the title compound, b.p. 98-102°/11 mm Hg; pmr (perdeuterioacetone): δ 7.21 [q (J = 5.8 Hz and 0.4 Hz), 1H, H_4], δ 7.73 [q (J = 5.8 Hz and 0.8 Hz), 1H, H5], δ 9.92 [q (J = 0.8 Hz and 0.4 Hz), 1H, CHO]. This sample had the same spectral data as an authentic sample.

2-Chloro-3-thiophenecarbaldehyde.

Applying the same procedure as described above to 25.0 g. (1.02 moles) of magnesium, 178.5 g. (0.95 mole) of ethylene dibromide, 19.7 g. (0.10 mole) of 3-bromo-2-chlorothiophene (11), 20.0 g. (0.27 mole) of *N,N*-dimethylformamide and the appropriate amounts of anhydrous ether, yielded 4.8 g. (33%) of 2-chloro-3-thiophenecarbaldehyde, b.p. 88-90°/10 mm Hg; literature value (11) b.p. 60-62°/0.1 mm Hg; pmr (deuteriochloroform): δ 7.02 [q (J = 5.9 Hz and 0.7 Hz), 1H, H_5], δ 7.42 [d (J = 5.9 Hz), 1H, H_4], δ 10.02 [d (J = 0.7 Hz), 1H, CHO].

The ir spectra were recorded on a Perkin-Elmer 257 Grating Infrared Spectrophotometer and the nmr spectra on a Varian A60 spectrometer.

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