On the Reaction of Methoxide Ion with Bromoiodothiophenes

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The reaction of 3-bromo-2-iodothiophene with sodium methoxide in methanol, pyridine or hexamethylphosphoric triamide and the same reaction of 4-bromo-2-iodo- and 4-bromo-3-iodothiophene in pyridine led to a halogen-dance, giving the same mixture of 3-bromothiophene, bromo-iodothiophenes, diiodo-bromothiophenes and triiodo-bromothiophenes. The reaction of all three isomeric bromo-iodothiophenes with sodium methoxide in methanol in the presence of cupric oxide gave 4-bromo-2-methoxythiophene.

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Introduction.

The copper-promoted reaction of 2- and 3-bromo- and iodothiophenes with sodium methoxide in methanol (1,2) gives the corresponding methoxythiophenes. The scope and limitations of these reactions have not been investigated. Some simple substituted methoxythiophenes have also been obtained by the alkylation of hydroxythiophene systems applying ion-pair extraction methods. However, some problems are caused by the instability of the hydroxythiophene systems and the ambident nature of the derived anion (3).

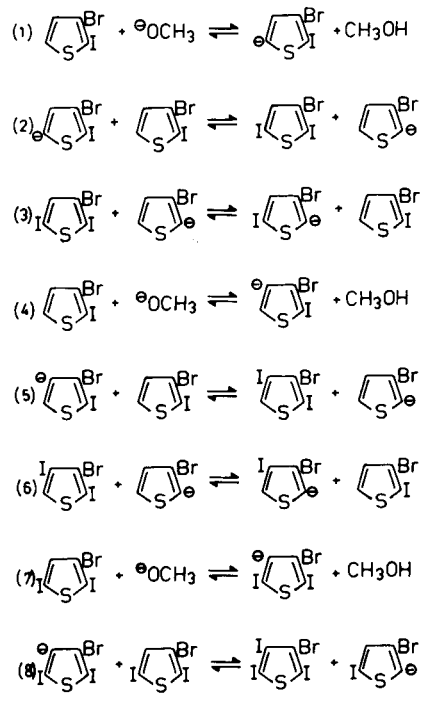
In connection with attempts to prepare 2,5-dimethoxythiophene through the copper-promoted reaction of 2,5-dibromothiophene with sodium methoxide in methanol, Baker, *et al.*, (4), discovered a few years ago that only a low yield of 2-bromo-5-methoxythiophene was formed and that di-, tri- and tetrabromothiophenes readily underwent partial debromination when treated with sodium alkoxides in dimethyl sulfoxide.

In work on the preparation of some potentially physiologically active thiophene derivatives, we also needed some halo-substituted methoxythiophenes, and investigated in this connection the reaction of some bromoiodothiophenes with sodium methoxide in various solvents and with or without copper-promotion.

Results and discussion.

Refluxing 3-bromo-2-iodothiophene with sodium methoxide in methanol for 72 hours led, according to vpc-mass spectrometry, to a complex mixture consisting of 32% 3-bromothiophene, 5% 4-bromo-2-iodothiophene, 8% 3-bromo-2-iodothiophene, 32% 3-bromo-4-iodothiophene, 14% of a bromodiiodothiophene, 4% bromotriiodothiophene and 5% unidentified products. All compounds except the diiodo and triiodo derivatives were identified by comparison with authentic samples.

The same mixture was formed when 3-bromo-2-iodothiophene was reacted with sodium methoxide for 72 hours at room temperature in pyridine or in hexamethylphosphoric triamide. The reaction in pyridine was followed as a function of time, and the results are given in Table 1. Already after 2 minutes, large amounts of 4-bromo-2-iodothiophene, 3-bromothiophene and 3-bromodiiodothiophenes are observed. The former compound decreases with time, while large amounts of 3-bromo-4-iodothiophene appear. The rearrangement was even faster in hexamethylphosphoric triamide. The same composition of halothiophenes as mentioned above was obtained when 4-bromo-2-iodothiophene was reacted with sodium methoxide in pyridine for 72 hours at 20° or 3-bromo-4-iodothiophene with the same reagent for 72 hours at 60°. We also followed the reaction of 4-bromo-2-iodothiophene with time and found rapid isomerisation to 3-bromo-2-iodothiophene, followed by the slow formation of 3-bromo-



Scheme 1

0022-152X/80/010171-04$02.25

Table 1

Halogen-migration of 3-bromo-2-iodothiophene with sodium methoxide in pyridine. Relative distribution in percents (not calibrated).

Time \ Compound							Not identified
2 minutes	22	34	26	0	16		4
60 minutes	27	25	16	10	18		5
24 hours	31	10	6	31	18		4
72 hours	32	8	5	32	14	4	5

4-iodothiophene, until equilibrium was reached after about 72 hours.

The reaction of these bromo-iodothiophenes is very reminiscent of the base-catalyzed halogen-dance studied in detail in the benzene series by Bunnett, *et al.*, (5,6), who especially studied the mechanism of the reversible isomerisation of 1,2,4-tribromobenzene to 1,3,5-tribromobenzene (7) catalyzed by potassium *t*-butoxide in *N,N*-dimethylformamide or hexamethylphosphoric triamide. They also found that this isomerisation required co-catalysis by 1,2,3,5-tetrabromobenzene (8). A similar mechanism could be suggested for the halogen-dance of the bromo-iodothiophenes (Scheme 1). Equations 1-3 illustrate the rapid isomerisation of 3-bromo-2-iodothiophene to 4-bromo-2-iodothiophene, for which 3-bromo-2,5-diiodothiophene acts as a co-catalyst. The slow isomerisation to 3-bromo-4-iodothiophene could occur through slow β-carbanion formation (equation 4), followed by the halogen-exchange reactions (equation 5) and (equation 6), in which case 3-bromo-2,4-diiodothiophene is the co-catalyst. Furthermore, metalation of 3-bromo-2,5-diiodothiophene followed by halogen-metal exchange can explain the formation of triiodo-bromothiophene (equation 7) and (equation 8).

Similar mechanistic schemes have previously been suggested to account for the rearrangements occurring in the reaction of 3-bromothiophene and dibromothiophenes with butyllithium (9). Similar mechanisms have also been suggested for the halogen-dance observed in the reaction of α-bromothiophenes with potassium amide in liquid ammonia, which has been developed into a useful method for the synthesis of 3-bromothiophenes (10-12). Besides halogen rearrangement and disproportionation, *cine* amination was also observed.

When 3-bromo-2-iodothiophene was reacted in pyridine or hexamethylphosphoric triamide with sodium methoxide in the presence of cupric oxide, the same results as above were obtained, and no methoxythiophenes could be detected. In methanol, however, the reaction proceeded differently, and 4-bromo-2-methoxythiophene was obtained in 15-25% isolated yield from all three bromo-iodothiophenes. The only major by-product was 3-bromothiophene. It seems that only 4-bromo-2-iodothiophene, of all the bromoiodothiophenes in equilibrium due to the halogen-dance, is trapped by copper-promoted nucleophilic substitution. In spite of the low yield, the copper-promoted reaction of the easily available 3-bromo-2-iodothiophene with sodium methoxide constitutes a useful method for the preparation of 4-bromo-2-methoxythiophene.

We have also investigated the copper-promoted reaction with two other 2-iodothiophenes. With 2-bromo-5-iodothiophene a complex mixture of over ten different compounds was obtained, and was therefore not further investigated. 2-Chloro-5-iodothiophene gave after 72 hours of reaction unreacted starting material, 25% of 2-chlorothiophene and about 20% of 2-chloro-5-methoxythiophene, according to glc analysis. The latter compound was identified by comparison with an authentic sample obtained by *N*-chlorosuccinimide chlorination of 2-methoxythiophene. 4-Bromo-2-iodothiophene and 3-bromo-4-iodothiophene were conveniently prepared from the corresponding dibromo compounds through halogen-metal exchange at $-70°$, followed by reaction with iodine.

EXPERIMENTAL

Reactions between Iodothiophenes and Sodium Methoxide.

A. 3-Bromo-2-iodothiophene.

a) In Methanol.

A solution of sodium methoxide prepared from 1.38 g. (0.060 mole) of sodium in 20 ml. of anhydrous methanol was added to 5.78 g. (0.020 mole) of 3-bromo-2-iodothiophene (13). The mixture was stirred and gently refluxed for 72 hours and then poured into two volumes of cold water and extracted with ether. The organic phase was washed with water, dried and the ether evaporated. The nmr spectrum (hexadeuterioacetone) of the crude product showed lines only in the aromatic region. A combined glc-ms analysis (OV25, 3%, 1.5 m, 70-250°, 10°/minute) of the crude mixture gave the following results, where relative distribution and retention time in minutes are given in parentheses and peaks smaller than 3% were not examined. 3-Bromothiophene, 32% (2.5); 4-bromo-2-iodothiophene, 5% (8.7); 3-bromo-2-iodothiophene, 8% (9.3); 3-bromo-4-iodo-

thiophene, 32% (9.8); bromodiiodothiophene, 14% (15.7); bromotriiodothiophene, 4% (20.6); and unidentified products, 5%. No attempts were made to isolate any of the components. All compounds except the diiodo- and triiodothiophenes were identified by comparison with authentic material. Calibration with starting material showed that the absolute yield was also about 8% of 3-bromo-2-iodothiophene.

b) In Pyridine.

To a solution of 2.89 g. (0.010 mole) of 3-bromo-2-iodothiophene (10) in 10 ml. of anhydrous pyridine, 1.62 g. (0.030 mole) of sodium methoxide was added. Samples were analyzed after 2 minutes, 1 hour and 24 hours. After 72 hours, the product distribution had stabilized, and after work-up, the same composition as described above was obtained. Addition of 0.398 g. (0.005 mole) of cupric oxide did not change the product distribution.

c) In Hexamethylphosphoric Triamide.

Sodium methoxide, prepared from 0.69 g. (0.030 mole) of sodium in 5.0 ml. of anhydrous methanol, was added to 2.89 g. (0.010 mole) of 3-bromo-2-iodothiophene (10) in 15 ml. of hexamethylphosphoric triamide. A sample taken after 2 minutes showed the same composition as the one obtained after 1 hour in pyridine. After 72 hours at room temperature, the product was worked up giving the same distribution as described above. Addition of 0.398 g. (0.005 mole) of cupric oxide did not change the product distribution.

B. 4-Bromo-2-iodothiophene.

To a solution of 2.89 g. (0.010 mole) of 4-bromo-2-iodothiophene in 10 ml. of anhydrous pyridine, 1.62 g. (0.030 mole) of dry sodium methoxide was added. Samples were analyzed after 2 minutes, 1 hour and 24 hours. Work-up after 72 hours at room temperature gave the same product distribution as described for 3-bromo-2-iodothiophene.

C. 3-Bromo-4-iodothiophene.

A mixture of 0.289 g. (0.0010 mole) of 3-bromo-4-iodothiophene in 1.0 ml. of anhydrous pyridine and 0.162 g. (0.0030 mole) of dry sodium methoxide gave, after stirring at 60° for 72 hours and work-up, the same product distribution as 3-bromo-2-iodothiophene.

Reactions Between Iodothiophenes and Sodium Methoxide in the Presence of Cupric Oxide in Methanol.

A. 3-Bromo-2-iodothiophene.

To 43.35 g. (0.150 mole) of 3-bromo-2-iodothiophene (13) and 5.97 g. (0.075 mole) of cupric oxide, a solution of sodium methoxide prepared from 10.35 g. (0.45 mole) of sodium and 150 ml. of anhydrous methanol was added and the mixture refluxed with stirring. After 20 hours, 10% of the starting material was still present. After 30 hours, the mixture was filtered and poured into two volumes of cold water and extracted with ether. The combined organic phases were washed with water, dried over magnesium sulfate and the ether evaporated. The two main components in the crude product, 3-bromothiophene and 4-bromo-2-methoxythiophene, were separated by distillation *in vacuo* in the presence of potassium carbonate, yielding 7.3 g. (25%) of 4-bromo-2-methoxythiophene, b.p. 56-59°/5 mm; nmr (deuteriochloroform): δ 6.47 (1, d, H5, $J_{3,5}$ = 1.6 Hz), 6.13 (1, d, H3, $J_{3,5}$ = 1.6 Hz), 3.83 (3, s, OCH_3); ms: m/e (%): M^+ 194/192 (81/81), M^+-CH_3 179/177 (100/100), M^+-CH_3-CO 151/149 (44/44).

Anal. Calcd. for C_5H_5BrOS (193.1): C, 31.11; H, 2.61; Br, 41.39. Found: C, 31.24; H, 2.64; Br, 41.17.

B. 4-Bromo-2-iodothiophene.

Refluxing 2.89 g. (0.010 mole) of 4-bromo-2-iodothiophene, 0.030 mole of sodium methoxide and 0.398 g. (0.0050 mole) of cupric oxide in 10 ml. of anhydrous methanol led to a mixture of 3-bromothiophene and 4-bromo-2-methoxythiophene, as in the reaction with 3-bromo-2-iodothiophene.

C. 3-Bromo-4-iodothiophene.

A mixture of 14.45 g. (0.050 mole) of 3-bromo-4-iodothiophene, 2.00 g. (0.025 mole) of cupric oxide, and sodium methoxide prepared from 3.45 g. (0.150 mole) of sodium and 50 ml. of anhydrous methanol, was refluxed with stirring. Glc analysis after 30 hours showed that 40% of the starting material remained. After 72 hours, the mixture was worked up as described above, yielding a mixture of 3-bromothiophene and 4-bromo-2-methoxythiophene. Fractional distillation in the presence of potassium carbonate yielded 1.40 g. (15%) of 4-bromo-2-methoxythiophene, b.p. 54-59°/4.5 mm, with the same spectral data as the sample described above.

D. 2-Bromo-5-iodothiophene.

To 2.89 g. (0.010 mole) of 2-bromo-5-iodothiophene (13), 0.398 g. (0.0050 mole) of cupric oxide and a solution of sodium methoxide, prepared from 0.69 g. (0.030 mole) of sodium in 10 ml. of anhydrous methanol were added. After reflux for 72 hours the mixture was worked up. Glc-mass analysis of the crude product indicated the presence of more than ten components. However, neither bromomethoxy- nor iodomethoxythiophenes could be detected.

E. 2-Chloro-5-iodothiophene.

A mixture of 245 mg. (1.0 mmole) of 2-chloro-5-iodothiophene (13), 40 mg. (0.50 mmole) of cupric oxide, and sodium methoxide prepared from 69 mg. (3.0 mmoles) of sodium in 1.0 ml. of anhydrous methanol was refluxed for 72 hours. Glc-ms analysis of the crude product after the usual work-up indicated that the product consisted of approximately 55% 2-chloro-5-iodothiophene, 25% 2-chlorothiophene and 20% 2-chloro-5-methoxythiophene, which was identified by comparison of retention time and ms with that of an authentic sample. No iodothiophene derivative except the starting material could be found.

Preparation of Starting Material.

4-Bromo-2-iodothiophene.

To 4.84 g. (0.020 mole) of 2,4-dibromothiophene (14) in 100 ml. of anhydrous ether cooled to −70°, 15.1 ml. (0.022 mole) of butyllithium in hexane was added under nitrogen with stirring at such a rate that the temperature was kept below −60°. After stirring for an additional 25 minutes, a solution of 5.08 g. (0.020 mole) of iodine in ether was added, keeping the temperature below −60°. The cooling bath was removed, and after the temperature had reached 0°, the reaction mixture was poured into water. The aqueous phase was extracted with ether and the combined ether phases were washed with water, sodium thiosulfate solution and dried over magnesium sulfate. Distillation *in vacuo* gave 4.00 g. (69%) of 4-bromo-2-iodothiophene, b.p. 70-80°/1.0 mm; nmr (deuteriochloroform): δ 7.19 (1, d, H3 or H5, $J_{3,5}$ = 1.4 Hz), 7.08 (1, d, H5 or H3, $J_{3,5}$ = 1.4 Hz); ms: m/e (%): M^+ 290/288 (100/100), M^+-I 163/161 (22/22).

Anal. Calcd. for C_4H_2BrIS (288.9): C, 16.63; H, 0.70; S, 11.10. Found: C, 16.74; H, 0.79; S, 10.90.

3-Bromo-4-iodothiophene.

From 73.3 ml. (0.11 mole) of butyllithium in hexane, 24.2 g. (0.10 mole) of 3,4-dibromothiophene (15) in 300 ml. of anhydrous ether and 27.9 g. (0.11 mole) of iodine in ether, following the procedure given above, 19.2 g. (67%) of 3-bromo-4-iodothiophene, b.p. 107-110°/3.5 mm, was obtained; nmr (deuteriochloroform): δ 7.42 (1, d, H2 or H5, $J_{2,5}$ = 3.4 Hz), 7.22 (1, d, H5 or H2, $J_{2,5}$ = 3.4 Hz); ms: m/e (%): M^+ 290/288 (100/100), M^+-I 163/161 (15/15).

Anal. Calcd. for C_4H_2BrIS (288.9): C, 16.63; H, 0.70; S, 11.10. Found: C, 16.78; H, 0.84; S, 10.90.

I. 2-Chloro-5-methoxythiophene.

To 16.0 g. (0.140 mole) of 2-methoxythiophene (1) in 200 ml. of glacial acetic acid, 18.7 g. (0.140 mole) of *N*-chlorosuccinimide was added in one portion with stirring. After two hours, the red reaction mixture was poured into an ice-cold solution of 150 g. of sodium hydroxide in 1 ℓ of water. After three extractions with ether, the combined organic phases were washed with 20% sodium chloride solution, dried over magnesium

sulfate and evaporated. Distillation at reduced pressure gave 17.5 g. (84%) of 2-chloro-5-methoxythiophene as a light-yellow liquid, b.p. 83-86°/48 mm; nmr (deuteriochloroform): δ 6.50 (1, d, H3, $J_{3,4}$ = 4.1 Hz), 5.93 (1, d, H4, $J_{3,4}$ = 4.1 Hz), 3.80 (3, s, OCH_3); ms: m/e (%): M^+ 150/148 (37/100), M^+-CH_3 135/133 (32/88), M^+-CH_3-CO 107/105 (32/88).

Anal. Calcd. for C_5H_5ClOS (148.6): C, 40.41; H, 3.39. Found: C, 40.27; H, 3.40.

Mass spectra were recorded on an LKB 900 mass spectrometer. Gas chromatographic analyses were performed with a Varian 1400 gas chromatograph equipped with a flame ionization detector. Nmr spectra were obtained with a Varian A-60 spectrometer.

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