Pergamon

Tetrahedron Vol. 50, No. 39, pp. 11533-11540, 1994
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0040-4020/94 $7.00+0.00

0040-4020(94)00712-8

Copper (I) Catalysed Formation of 3-Methoxy-2,5-dimethylthiophene and 3,4-Dimethoxy-2,5-dimethylthiophene

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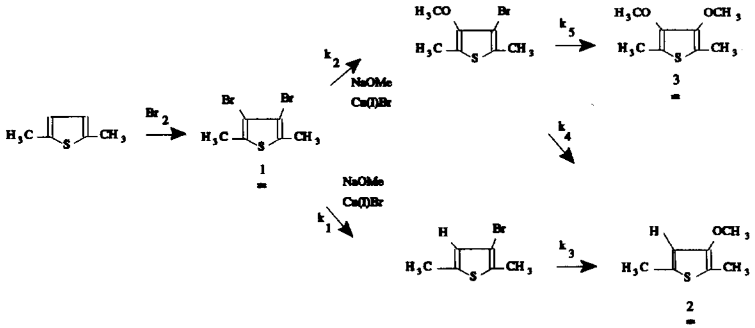
Abstract: 3-Methoxy-2,5-dimethylthiophene and 3,4-dimethoxy-2,5-dimethylthiophene have been prepared from 3,4-dibromo-2,5-dimethylthiophene and sodium methoxide using Cu(I)Br as a catalyst. The influence of some cosolvents and reaction temperature is investigated. Best results are obtained by refluxing in DMF at 125°C for 4 hours. The mixture is easily separated by flash chromatography.

INTRODUCTION

Progress into the applications of the potentially highly conducting poly(2,5-thienylene vinylenes) is hampered by synthetic problems. Particularly thiophene monomers containing electron donating substituents in 3- and 4-position are difficult to obtain. We report here a two-step route (see Fig.1) towards 3,4-dimethoxy-2,5-dimethylthiophene (3) from 3,4-dibromo-2,5-dimethylthiophene (1) which is prepared by direct bromination of 2,5-dimethylthiophene. A side-product, although in this context a very useful one, is 3-methoxy-2,5-dimethylthiophene (2).

Figure 1



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Copper catalysed substitution under homogeneous conditions is nowadays the standard route to convert unactivated aryl bromides (such as 1) into aryl ethers[1-5], but the conversion of heteroaromatic halides is not competely solved yet[1].

RESULTS AND DISCUSSION

3,4-Dibromo-2,5-dimethylthiophene (1) was synthesised by direct bromination of commercial 2,5-dimethylthiophene. To avoid the use of the flammable and toxic compounds carbon disulfide and copper cyanide, we did not follow the procedure of Melles et al[6], but rather adapted that of Paal[7]. When the final crystallisation was performed at low temperature (-18°C) the pure product was obtained in 70% yield.

Direct methoxylation by nucleophilic substitution of non-activated halogen atoms in (hetero-)aromatic compounds requires the heating of the bromides at elevated temperatures with an excess of sodium methoxide in a highly concentrated solution under the catalyc influence of copper(I)bromide. Aalten et al.[2] investigated the mechanism and developed a synthetic procedure for the conversion of aryl bromides, while Keegstra et al.[1] extended the scope of the reaction to inter alia bromothiophenes. Possible competing reactions are hydro-dehalogenation (ArBr → ArH) and Ullman coupling (ArBr → ArAr), both catalysed by copper. Methoxylation is primarily promoted by homogeneous Cu-catalysts (e.g. Cu(I)Br), while dehalogenation and coupling are mainly promoted by heterogeneous Cu-catalysts. Small changes in the experimental conditions often greatly affect the results of these reactions[8]. For example, at higher temperatures Cu(I)Br dispropotionates in hard coordinating solvents into Cu(II) and Cu(0). Although Cu(II) can be reduced back to Cu(I) by methoxide[2], the Cu(0) formed causes an increase in the side reactions. Furthermore, when methanol is used as the only solvent for sodium methoxide and Cu(I)Br, the composition of the mixture changes during the reaction and causes an undesirable decrease in the reflux temperature. Therefore, a cosolvent is often added, which may act as a ligand increasing the solubility of the Cu-catalyst and/or stabilise the Cu(I) oxidation state.

The difference between the procedures of Aalten et al[2] and of Keegstra et al[1] is mainly in the choice of solvent. These studies as well as those of Bacon et al[4,5,8] show that the nature of the solvent is critical, as it may swing the course of the reaction from predominantly methoxy substitution to predominantly dehalogenation. Therefore, we tested four solvents and monitored the reaction by gas chromatography-mass spectrometry. Table 1 summarises the yields together with the retention times.

Table 1. Retention Times (in min.) and Yields (in % given by GC) of Compounds produced by Cu(I)Br Catalysed Methoxylation of 3,4-Dibromo-2,5-dimethylthiophene in Various Solvents at 125°C. X : substituent at C(3); Y : substituent at C(4)
See experimental section for details

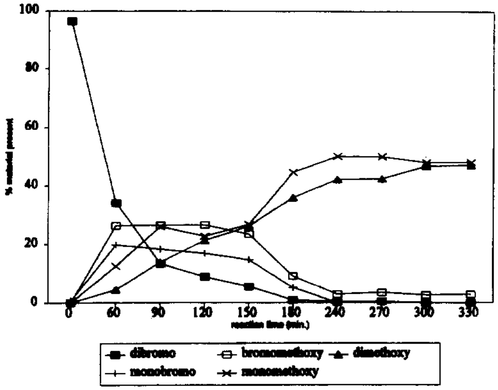
X	Y	Retention time	yield in DMF[a]	DMA	COL	NMP
OCH_3	OCH_3	4.3	48	35	19	0
OCH_3	H	3.3	49	58	57	0
OCH_3	Br	5.5	3	6	24	0
Br	Br	6.8				
Br	H	3.6				

[a] DMF : N,N-dimethylformamide DMA : N,N-dimethylacetamide
COL : 2,4,6-Collidine NMP : N-methyl-2-pyrrolidinone

In contrast to the results of Keegstra et al.[1] on 3,4-dibromothiophene, we observed in N-methyl-2-pyrrolidinone (NMP) no methoxylation of 3,4-dibromo-2,5-dimethylthiophene, only dehalogenation and substitution of bromine by methyl occurred. The latter substitution is probably caused by the thermal instability of NMP at higher temperatures. Furthermore, it shows that N,N-dimethylformamide (DMF) gives the best results. We then tried to decrease the amount of hydrogen transfer (dehalogenation reaction) by changing the reaction temperature. In DMF at 70°C no reaction occured, while at 90°C the rate was low and only monomethoxylation and hydrogen transfer took place. Raising the temperature to 125°C increased the rates and the dimethoxylation yield. The fact that DMF starts to decompose at about 125°C precludes the use of higher temperatures. The use of commercial Cu(I)Br (98% purity), ultrapure (99.999%) or freshly prepared Cu(I)Br had no significant effect. This was expected, because the reaction environment is able to convert Cu(II) to Cu(I).

Fig.2 depicts the conversion of 3,4-dibromo-2,5-dimetylthiophene in DMF versus the reaction time. Inspection of the data (Fig.2) reveals an exponential decrease of the starting product (**1**) and a quasi steady-state of the intermediates 3-bromo-2,5-dimethylthiophene and 3-bromo-4-methoxy-2,5-dimethylthiophene during the 4 hours of the reaction. The steady-state also shows in the quasi-linear increase of the final products (**2** and **3**, Fig.1).

Figure 2



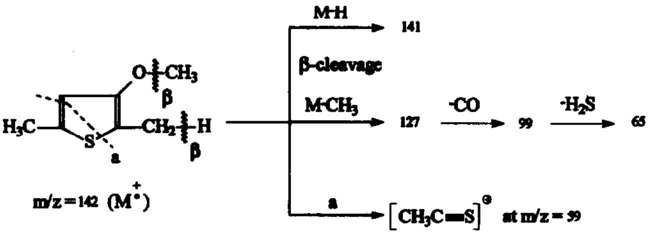
Then, in first approximation, the methoxylation steps proceed at the same rate ($k_2 \approx k_3 \approx k_5$), and so do the dehalogenation steps ($k_1 \approx k_4$). This in turn makes that the methoxylation is about three times faster than the dehalogenation, and rationalises the about equal yields of **2** and **3** (three out of four bromine atoms are replaced by OCH_3 groups and one by hydrogen).

The above results are in the line with observations of Litvak and Shein[9], who found that copper catalysed substitutions are first order in aryl bromide, and who showed a small influence of substituents (Hammet $\rho = 0.48$). The results also agree with those of Keegstra et al[1], who observed similar moderate selectivities with dibromothiophenes.

Finally, the mixture of 3-methoxy-2,5-dimethylthiophene and 3,4-dimethoxy-2,5-dimethylthiophene is easily separated by flash chromatography.

All compounds were fully characterised by IR, ^1H-NMR, ^{13}C-NMR and mass spectrometry (see experimental section for numerical values). Two details may be noted at this point. First, the ^1H-chemical shift of the OCH_3-group increases from 3.68 ppm in 3,4-dimethoxythiophene[1], via 3.74 ppm in 3-methoxy-2,5-dimethylthiophene to 3.80 ppm in 3,4-dimethoxy-2,5-dimethylthiophene. For the corresponding ^{13}C-chemical shifts one finds δ = 56.7 ppm[1], δ = 59.0 ppm and δ = 59.5 ppm, respectively. Such increases probably reflect an increasing rotation of the OCH_3 group out of the thiophene plane[10]. Second, the mass spectra of the 2,5-dimethyl substituted as well as those of the 2,5-unsubstituted derivatives (published in ref.1 without interpretation) follow well esthablished fragmentation patterns[11], as shown in Fig.3. For example, β-fission with respect to the thiophene ring is so dominant over α-fission that loss of CH_3 only occurs from the OCH_3 groups and not from the 2,5-dimethyl groups.

Figure 3



EXPERIMENTAL

Synthesis of 3,4-dibromo-2,5-dimethylthiophene, 1

To a mixture of 10g (0.087 mol) 2,5-dimethylthiophene and 5 ml chloroform, 27.8g (0.174 mol) bromine was added dropwise under vigorous stirring, while the temperature was kept at about 20°C. Next, the mixture was stirred overnight at room temperature, then refluxed for 7 hours, washed with 20 ml 2N sodium hydroxide solution, and under vigorous stirring added dropwise to a solution of 7.3g potassium hydroxide in 15 ml 95% ethanol. After 5 min. the solution was poured into water and the organic layer was separated. This layer, consisting of impure 3,4-dibromo-2,5-dimethylthiophene, was washed with water and dried on calcium chloride. The compound was purified by crystallisation from ethanol at -18°C. The crystals were filtered as cold as possible. Yield : 16.3g (70%); mp. : 44-46°C (litt.[6] : 44-46°C).

IR (cm^{-1}) : 2950 (C-H stretch); 1530 and 1030 (aromatic C=C bending); 1460 and 1376 (C(sp^3)-H bending); 743 (C-Br stretch)

^{1}H-NMR (δ in ppm) : 2.38 (CH_3-group; singlet)

^{13}C-NMR (δ in ppm) : 131.4 (C2); 111.7 (C3); 15.7 (CH_3)

Synthesis of 3-methoxy-2,5-dimethylthiophene and of 3,4-dimethoxy-2,5-dimethyl-thiophene, 2 *and* 3.

Reactions were carried out under a dry, oxygen-free atmosphere using Schlenk techniques[12]. Solvents were dried and destilled prior to use. A 250 ml three-necked round-bottom flask was equipped with a natural rubber septum, a tube for the addition of solids and a reflux condensor with a bubbler on top. To the round-bottom flask were added 10g (0.037 mol) 3,4-dibromo-2,5-dimethylthiophene, 18.5 ml DMF (or any of the other cosolvents), 10 ml methanol and 8g (0.15 mol) sodium methoxide. The mixture was heated to 90°C and 1.06g (0.0074 mol) Cu(I)Br was added through the solids addition tube. Subsequently the temperature was raised to 125°C. After 4.5 hours of reflux, the reaction mixture was poured into 100 ml water, and extracted five times with 25 ml portions of hexane. The hexane fraction was concentrated by rotary evaporation to 40 ml. To this solution was added dropwise 15 ml butyllithium solution (2.5M in hexane), in order to remove any unreacted or incompletely reacted bromothiophenes. After 15 min. of stirring at room temperature, water was added to destroy the excess butyllithium, and the organic layer - now containing only the two methoxylated thiophenes - was subjected to flash chromatography (column length : 7 cm; diameter : 6 cm; packed with TLC grade silica), using cyclohexane/toluene (1/1 v/v) as the eluens. The first fraction (100 ml) contained pure 3-methoxy-2,5-dimethylthiophene (yield : 1.6g , 30%; bp. : 194-196°C/760 mmHg), the second fraction (250 ml) contained pure 3,4-dimethoxy-2,5-dimethylthiophene (yield : 1.9g; 30%; bp.: 148-150°C/760 mmHg).

3-methoxy-2,5-dimethylthiophene
IR (cm^{-1}) : 3100 (aromatic C-H stretch); 2950 (alifatic C-H stretch); 2850 (C-H stretch in ArOMe); 1460 and 1385 ($C(sp^3)$-H bending); 1147 (C-O-C stretch)
^{1}H-NMR (δ in ppm) : 6.46 (H(C4)); 3.74 (OCH_3); 2.36 (CH_3 on C5); 2.20 (CH_3 on C2)
^{13}C-NMR (δ in ppm) : 152.6 (C3); 133.8 (C5); 115.5 (C4); 113.0 (C2); 59.0 (OCH_3); 15.8 (CH_3 on C5); 10.4 (CH_3 on C2)

3,4-dimethoxy-2,5-dimethylthiophene
IR (cm^{-1}) : 2950 (alifatic C-H stretch); 2850 (C-H stretch in ArOMe); 1460 and 1385 ($C(sp^3)$-H bending); 1147 (C-O-C stretch)
^{1}H-NMR (δ in ppm) : 3.80 (OCH_3); 2.23 (CH_3)
^{13}C-NMR (δ in ppm) : 145.0 (C3, C4); 115.5 (C2, C5); 59.5 (OCH_3); 10.4 (CH_3)

Analytical procedures

The methoxylation reaction was monitored by taking samples out of the reaction mixture through a septum with syringe techniques. Each sample (0.5 ml) was added to 2 ml water and extracted with 20 ml pentane. The pentane extract was analysed by gas chromatography on a Packard 438A Gas Chromatograph, using a CP-SIL-8CB column. An Shimadzu CR6A Chromatopac integrator was connected, and the conversion degrees were obtained using the normalised area method. Characterisation of the reaction products was obtained by GC-MS on a Hewlett Packard 5890 (CP-SIL-5 CB column) coupled with a Finnigan Mat (MS). The resulting electron impact (70 eV) spectra are given in table 2.

FT-IR spectra are transmission spectra of the pure liquids taken on a Nicolet 5 DXB FTIR-spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Unity NMR instrument using deuterated chloroform as a solvent and tetramethylsilane as internal standard.

Table 2. Characteristic m/z-Values in Mass Spectra (electron impact, 70 eV).

3-bromo-2,5-dimethylthiophene; retention time 3.6 min.

m/z-values : 192/190 M^+ (a); 191/189 M-H (a); 111 M-Br base peak; 77 M-Br-H_2S; 67; 59 M-HBr-$CH_3C\equiv S$.

3,4-dibromo-2,5-dimethylthiophene; retention time 6.8 min.

m/z-values : 272/270/268 M^+ (b); 271/269/267 M-H (b); 191/189 M-Br (a) base peak; 110 M-2Br; 109 M-HBr-Br;
95/93 CH_2Br; 69; 65 C_5H_5; 59 $CH_3C\equiv S$

3-methoxy-2,5-dimethylthiophene; retention time 3.3 min.

m/z-values : 142 M^+; 141 M-H; 127 M-CH_3; 99 M-CH_3-CO; 65 C_5H_5; 59 $CH_3C\equiv S$ base peak

3,4-dimethoxy-2,5-dimethylthiophene; retention time 4.3 min.

m/z-values : 172 M^+; 171 M-H; 157 M-CH_3; 142 M-2CH_3; 129 M-CH_3-CO; 97 M-CH_3-$CH_3C\equiv S$-H; 95 M-CH_3 CO-H_2S; 75;
59 $CH_3C\equiv S$ base peak

3-bromo-4-methoxy-2,5-dimethylthiophene; retention time 5.5 min.

m/z-values : 222/220 M^+ (a); 221/219 M-H (a); 207/205 M-CH_3 (a); 141 M-Br; 126 M-Br-CH_3; 98 M-Br-CH_3-CO;
67 M-Br-$CH_3C\equiv S$; 59 $CH_3C\equiv S$ base peak

(a) two peaks in ratio 1:1 due to bromine isotope

(b) three peaks in ratio 1:2:1 due to bromine isotope

ACKNOWLEDGEMENTS

L.P. is grateful to the Belgian Institute IWONL for a predoctoral grant. This work was performed with financial support of the Flemish Ministry of Economic Affairs, while parts of this text present the results of the Belgium Programme on Interuniversity Attraction Poles initiated by the Belgian State (Prime Minister's Office) Science Policy Programming. Scientific responsibility, however, is assumed by the authors.

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(*Received in UK* 1 *July* 1994; *revised* 4 *August* 1994; *accepted* 12 *August* 1994)