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Copper(I) Halide Catalysed Synthesis of Alkyl Aryl and Alkyl Heteroaryl Ethers

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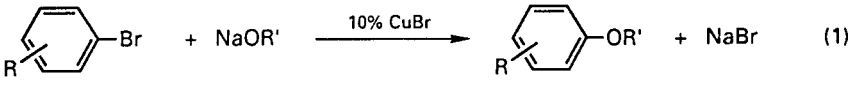
Abstract: A number of alkyl aryl and alkyl heteroaryl ethers have been prepared from (hetero) aryl halides (mainly bromides) and sodium alkoxides, using copper(I)bromide as a catalyst. The influence of the main solvent, the halogen atom, reaction temperature and the presence of oxygen upon the rate and selectivity has been studied. Furthermore the decomposition of the catalyst and the reduction of the aryl halide are studied.

INTRODUCTION

In contrast to palladium[1] and nickel[2] complexes, copper compounds are capable of catalysing the displacement of bromine and iodine in non-activated aryl and heteroaryl halides by alkoxides (equation 1).[3,4,5]



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A well known example is the Ullmann synthesis of diaryl ethers.[6,7] Applying copper catalysis McKillop *et al.* succeeded in displacing the three bromine atoms in 1,3,5-tribromobenzene by methoxy groups.[8]

Bacon described the substitution of bromine and iodine by methoxide and ethoxide in a number of aryl halides by heating the aromatic compounds with an excess of alkoxide in collidine in the presence of copper(I) iodide.[9] Under these homogeneous conditions substitution occurred to a high extent, but the reaction times were long. Under heterogeneous conditions, using copper(I) oxide as a catalyst, reduction to the arene was the main reaction. Gronowitz[10] and Sicé[11] used methanol as solvent and CuBr or Cu_2O as a catalyst for the preparation of 3-methoxy- and 2-methoxythiophene, respectively. Complete conversion required prolonged heating under reflux.

The mechanism of the copper(I) catalysed alkoxylation has been studied extensively.[12,13] The present investigation was undertaken to obtain information about the scope and limitations of the copper(I) catalysed ether synthesis and to find attractive preparative conditions for this reaction.

RESULTS AND DISCUSSION

Scope of the reaction with bromobenzene and 1-bromonaphthalene

As an extension of the investigations of Aalten *et al.*,[13] who optimized the conversion of bromobenzene into anisole, we tested their conditions for the reactions of bromobenzene and some other aryl bromides with

various alkoxides. Some had already been performed by Bacon *et al.*[9] Although in our conversions the amount of catalyst was less than one third of those used by Bacon, our reactions were generally finished within a few hours, with variable selectivities. Our results with bromobenzene are summarized in table 1.

In several reactions we observed formation of elementary copper, which we assumed to be due to decomposition of the catalyst. This assumption was supported by the fact that the catalytic activity gradually disappeared. This was found also by Aalten *et al.*, who stirred copper(I) bromide and sodium methoxide in dimethylformamide (DMF) overnight at 110°C and observed that the catalytic activity had disappeared.[13] The rate of this catalyst deactivation appeared to be nucleophile dependent: using ethoxide [run 4], *n*-propoxide [5,6], *neo*-pentoxide [11], allyl alkoxide [14,15], or the alkoxide from $HOC_2H_4OCH_3$ [17, 18], the formation of Cu(0) proceeded faster than in the reactions with methoxide [1], *n*-butoxide [7], *n*-pentoxide [8], *tert*-butoxide [12], or the alkoxide of $HOC_2H_4N(CH_3)_2$ [19], where it was observed only in the final stage of the reaction. In some cases the copper(0) formation could be delayed and the result improved by omission of the polar co-solvent. Under those conditions, however, the reaction was considerably slower (compare run [1] and [2]). In other experiments the result could be improved by the use of more catalyst.

In the substitution with ethoxide the quality of the base appeared to be very important [3,4]. When for the substitution of bromobenzene the brown, commercially available sodium ethoxide was used, no reaction occurred, whereas the conversion with the freshly prepared base proceeded quite successfully. If the reaction was *not* carried out under nitrogen, it stopped after some time. Addition of a fresh amount of catalyst was necessary to re-start the reaction. When the reaction with sodium *methoxide* was carried out under air, the colour of the reaction mixture changed into blue, due to the formation of Cu(II), but the rate and selectivity of the reaction were not influenced.

The reaction proceeded also smoothly with alkoxides having longer carbon chains [5,7,8], while the reaction rate or the selectivity decreased in the case of $NaOCH(CH_3)_2$, $NaOC(CH_3)_3$, and $NaOCH_2C(CH_3)_3$ [9-12].

From the reaction with the unsaturated alkoxides [13-15] no substitution products could be isolated. In the case of propargylic alcohol this was caused by the instability of the alkoxide, which decomposed before the substrate and the catalyst had been introduced. With allyl alkoxide formation of Cu(0) was observed within 1 h, while the aimed product was not formed. This result is not easily understood. It might be related to formation of a 1:1 complex of allyl alcohol and Cu(I), influencing the stability of the catalyst.[14] In the absence of a polar solvent some substitution product was formed, but benzene was the major product (compare the discussion below).

The sodium salts of $HOCH_2CF_3$ [16] and $HOC_2H_4N(CH_3)_2$ [19] reacted smoothly and highly selectively.[15] The reaction of $NaOC_2H_4OCH_3$ [17,18], however, proceeded much less selectively and formation of Cu(0) was observed. The selectivity could be improved by using 14 mol% of copper(I) bromide. The substitution with $NaOC_2H_4SC_2H_5$ proceeded rather slowly, though the selectivity was satisfactory. During the first two hours no Cu(0) was observed, making it unlikely that the low rate is caused by decomposition of the catalyst. The low reactivity may be rather the consequence of a strong complexation of the catalyst by sulfur, resulting in a inactivation. Peters[16] made similar observations during the CuBr catalysed reaction of aryl halides with thiolates.

Using the mono-alkoxide of ethanediol the catalyst underwent a rapid decomposition and no substitution product could be isolated [21].

1-Bromonaphthalene and sodium methoxide [22] reacted smoothly under the standard conditions (NMP as co-solvent, 10 mol% catalyst) giving 1-methoxynaphthalene in an excellent yield (92%). Bacon used 50 % catalyst for the same conversion in refluxing collidine.

Table 1 - Reactivity and Selectivity in the Reaction of Bromobenzene with Alkoxide[a]

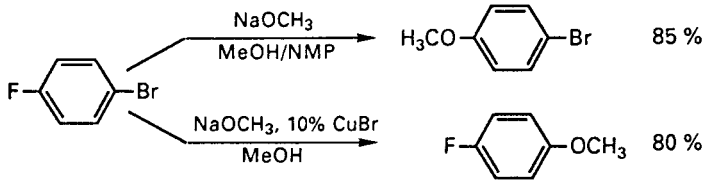
run	alkoxide	co-solvent[b]	time (hr)	conversion (%)	selectivity (%)[c]	isolated yield (%)	remarks
1	$NaOCH_3$	DMF	0.5	100	100	95	d
2	$NaOCH_3$	e	3	100	100		f
3	$NaOC_2H_5$	NMP	1	0			g
4	$NaOC_2H_5$	NMP	0.75	100	99	93	h
5	NaO *n*-C_3H_7	NMP	1	100	74		
6	NaO *n*-C_3H_7	e	0.5	18	100		
			16	62	64		
7	NaO *n*-C_4H_9	NMP	1	97	95	85	
8	NaO *n*-C_5H_{11}	NMP	0.5	100	85	75	
9	NaO *i*-C_3H_7	NMP	1.5	57	74		
10	NaO *i*-C_3H_7	NMP	3.5	90	90	70	i
11	$NaOCH_2$ *t*-C_4H_9	NMP	2	85	20		
12	NaO *t*-C_4H_9	NMP	1	2	100		
13	$NaOCH_2C{\equiv}CH$	NMP					j
14	$NaOCH_2CH{=}CH_2$	NMP	1	34	0		k
15	$NaOCH_2CH{=}CH_2$	e	1	30	33		k
16	$NaOCH_2CF_3$	NMP	0.75	100	99	85	
17	$NaOC_2H_4OCH_3$	NMP	2	99	64		
18	$NaOC_2H_4OCH_3$	NMP	2	100	99	85	i
19	$NaOC_2H_4N(CH_3)_2$	NMP	1.5	100	98	80	
20	$NaOC_2H_4SC_2H_5$	NMP	2	50	94		k
21	$NaOC_2H_4OH$	NMP	1	50	0		
22	$NaOCH_3$	NMP	0.5	100	99	92	l

a: amount of CuBr generally 10%, starting temperature: 110°C. Base concentration: 4.6 M; b: NMP = 1-methyl-2-pyrrolidinone; c: benzene was the only side-product; d: ref. 13. e: the alcohol corresponding to the alkoxide was the only solvent used. Base concentration: 10 M. Starting temperature: ~ 100°C (reflux); f: bromobenzene was added after 18 h of reflux (97°C), concentration of NaOMe in MeOH: 8,6 M; g: commercially available NaOEt was used; h: NaOEt freshly prepared, 12 mol% CuBr was used; i: 14 mol % catalyst was used; j: vigorous decomposition of the alkoxide at 80°C; k: prepared from the alcohol with a suspension of NaH in diethyl ether, followed by distillative removal of the diethyl ether; l: 1-bromonaphthalene was used as the substrate.

Catalysed and non-catalysed substitutions with p-bromofluorobenzene

Reaction of *p*-bromofluorobenzene with a large (200 mol%) excess of sodium methoxide under the standard reaction conditions gave not only the expected *p*-fluoromethoxybenzene, but also some *p*-dimethoxybenzene. This finding led us to suspect that a subsequent, *non-catalysed* substitution of fluorine had occurred. All text-books on organic chemistry suggest that non-catalysed substitution of fluorine by an S_NAr mechanism requires the presence of an activating group, such as NO_2, in *ortho* or *para*-position of fluorine. A literature search revealed that there are very few examples of nucleophilic displacements with unactivated aromatic fluorides. Cram *et al.*[17] mentioned the conversion of *o*-fluorotoluene into *o*-cresol under the influence of potassium *tert.*-butoxide in dimethylsulphoxide (DMSO) while more recently the successful nucleophilic substitution of fluorine in a number of unactivated aryl fluorides by alkylthio-groups was published.[18]

Our discovery gave rise to a separate investigation resulting in optimal conditions for a very selective non-catalysed substitution of fluorine. Fluorine substitution could be prevented by omission of the polar non-protic solvent, which is indispensible for the S_NAr-substitution (eq. 2).

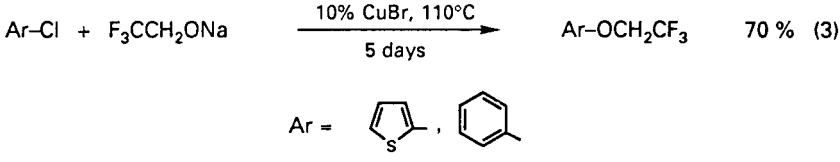


(2)

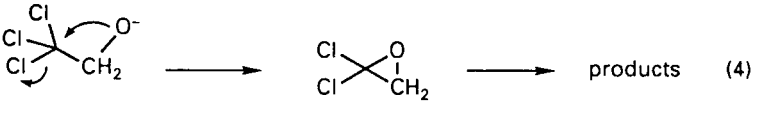
Chlorine substitution

Aalten *et al.*[13] described unsuccessful attempts to substitute chlorine in chlorobenzene by methoxide in the presence of copper(I) bromide using NMP as co-solvent. The main products they observed were Cu(0) and benzene.

The finding that solvents like DMF and NMP gave rise to a faster decomposition of the catalyst (*vide supra*), led us to carry out the reaction with chlorobenzene in methanol as the only solvent. Using a high concentration of sodium methoxide we succeeded in attaining a fully selective conversion of chlorobenzene. The maximum of 20% conversion was reached after 24 h heating under reflux. The termination of the reaction in this stage is undoubtedly due to decomposition of the catalyst (Cu(0) was observed).



Prolonged heating of chlorobenzene and 2-chlorothiophene with the lesser reactive sodium 2,2,2-trifluoroethanolate in the corresponding alcohol did result in complete substitution of the chlorine atom (eq. 3). In these cases no elementary copper was formed. Attempts to carry out a substitution with sodium 2,2,2-trichloroethanolate were not successful. At elevated temperatures a vigorous reaction of the alkoxide occurred, even in absence of the substrate and the catalyst. Possibly this decomposition is initiated by an intramolecular reaction (eq. 4).



(4)

Unfortunately the chlorine substitution could not be extended to other oxygen nucleophiles because of the catalyst decomposition described. Attempts to regenerate the catalyst carrying out the reaction under oxygen or N_2O, or bubbling the oxidizing gas through the solution were unsuccessful, *i. e.* copper(0) was not oxidized. This is probably due to the low reactivity of the clustered copper species.

Substitutions with heteroaryl halides

The favourable experience with the polar co-solvents in the substitution with aromatic bromides (*vide supra*, compare ref. 13) led us to apply these solvents also in the alkoxylation of heteroaromatic halides.

The results appeared to depend strongly upon the nature of the heteroaromatic substrate. Whereas the reactions of 3-bromothiophene, 2- and 3-bromopyridine with sodium methoxide in NMP as the main solvent gave the methyl ethers with a high selectivity and mostly in good yields (table 3), poor selectivities were observed in the cases of 2-bromofuran, 2-bromothiophene and a number of dibromothiophenes. Using these substrates reductive dehalogenation was the main reaction. In order to arrive at optimal preparative conditions for the copper-catalysed methoxylation of these substrates a series of experiments was carried out (table 2). The substitution with 2-bromothiophene was used as the model reaction.[19]

Table 2 - Copper(I) bromide catalysed reaction of 2-bromothiophene with sodium methoxide Influence of reaction conditions on the substitution/reduction ratio

run	[$NaOCH_3$] (mol/l)	co-solvent or additive (mL)	starting Temp. (°C)	time (hr)	conversion (%)	selectivity (%)[a]	remarks
1	4.6	NMP (12.5)	110	0.5	100	30	b, c, d
2	4.6	DMF (12.5)	110	1	68	44	b, d, e
3	4.6	DMI[h] (12.5)	110	1	100	55	b, f
4	4.6	NMP (12.5)	110	2	100	0	g
5	4.6	DMSO(12.5)	110	5 min.	24	0	g
6	4.6	TMSu[h](12.5)	110	6	100	73	d
7	8.6	PBu_3 10%	97	6	88	60	d
8	4.6	dioxane(12.5)	97	6	93	88	d
9	8.6	-	97	1	37	92	d
				2	62	92	
				6	100	92	
10	4.6	*t*.-BuOH (12.5)	98	18	100	92	d

a: percentage of desired product. Thiophene observed as side-product; b: Cu(0) observed; c: vigorous reaction. d: greyish or blue reaction mixture; e: $(CH_3)_2NC(O)OCH_3$ observed in the reaction mixture; f: brown reaction mixture; g: no catalyst used; h: TMSu: Tetramethylenesulfone, DMI: dimethylimidizolidone.

As may be concluded from these experiments, 2-bromothiophene is much more reduction-responsive than bromobenzene. This appeared particularly when the substitutions were carried out in the presence of the (co-) solvents DMF, NMP, DMI [Runs 1-3]. The reduction in these solvents occurred even in the absence of the catalyst [4,5]. With other co-solvents or additives the selectivities were somewhat better, but the reaction rate was much lower [6-8]. The highest selectivities were obtained with methanol or *tert*.-butylalcohol as the solvent [9-10]. While a satisfactory rate of conversion could be attained using a high alkoxide concentration (10 M.) and temperatures in the region of 100°C, the catalytic system did not undergo decomposition to metallic copper within the reaction period.

This investigation resulted in efficient procedures for 2- and 3-methoxythiophene (table 3 [1,3,4]). In a similar way 2- and 3-ethoxythiophene were obtained by treatment of the substrate with a very concentrated solution of freshly prepared $NaOC_2H_5$ in ethanol, though here more CuBr (15 mol%) was needed [2,5]. As was described above, it was essential to maintain an atmosphere of inert gas. Even 3-(*i*-propoxy)thiophene [6] could be prepared. For a complete conversion, however, a high starting temperature and prolonged heating were necessary before the reaction was completed. As in the case of chlorobenzene we were not able to

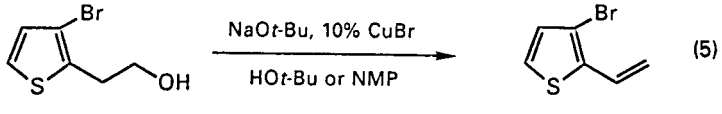
substitute the chlorine of 2-chlorothiophene completely by methoxide. When the reaction mixture was heated under reflux overnight, the catalyst had decomposed and the reaction had stopped. The use of an alkoxide with an electron-deficient oxygen led to selective substitution, as is described above (eq. 3).

Table 3 - Substitutions with heteroaromatic halides.

run	substrate	base	co-solvent	start. temp. (°C)	time (hr)	conversion (%)	selectivity[a] (%)	isol. yield (%)	remarks
1	2-bromothiophene	NaOMe	-	97	6	100	92	83	
2	2-bromothiophene	NaOEt	-	103	2.5	100	92	83	b, c
3	3-bromothiophene	NaOMe	DMF	110	0.5	100	98	88	
4	3-bromothiophene	NaOMe	-	97	5	100	97		
5	3-bromothiophene	NaOEt	DMF	110	1	100	98	94	c
6	3-bromothiophene	NaO*i*-Pr	DMF	112	8	100	99	80	b
7	2-chlorothiophene	NaOMe	-	97	22	44	84		b, c, e
8	2-bromofuran	NaOMe	NMP	110	1	100	0		
9	2-bromofuran	NaOMe	-	90	3	100	96	60	d
10	2-bromofuran	NaOEt	-	90	5	100		30	b, c
11	2-bromo-1-methyl-pyrrole	NaOMe	-	97	2	100	>90	75	
12	2,3-dibromothiophene	NaOMe	-	97	6	98	34		f
13	2,4-dibromothiophene	NaOMe	-	97	6	90	64	47	f, g
14	2,5-dibromothiophene	NaOMe	-	97	6	97	61	49	f
15	3,4-dibromothiophene	NaOMe	-	97	6	100	87	74	f
16	3,4-dibromothiophene	NaOMe	DMF	110	1	100	35		f
17	3-bromo-2-(2-hydroxy-ethyl) thiophene	NaO*t*-Bu	HO*t*-Bu	90	24	62	35		h
18	2-bromopyridine	NaOMe	NMP	110	0.25	100	99	80	i
19	3-bromopyridine	NaOMe	NMP	110	6	100	100		i
20	3-bromopyridine	NaOMe	NMP	110	1	100	100	40	
21	2-chloropyridine	NaOMe	NMP	110	0.25	100	99	70	i
22	2-chloropyridine	NaOEt	NMP	110	0.5	100	98	85	i
23	3-chloropyridine	NaOMe	NMP	110	1	36	92		
					8	98	75		

a: Reduction was the only side-process; b: Cu(0) observed; c: 15% CuBr used d: low yield probably due to volatility of the product; e: reaction had stopped; f: both bromine atoms were substituted; g: substitution with ethoxide has been described before: yield: 18% (ref. 20); i: no catalyst was used.

We have also tried to use this method for an intramolecular coupling [17, eq. 5]. However, instead of the aimed process a side-reaction occurred leading to the formation of 3-bromo-2-ethenylthiophene.[21]

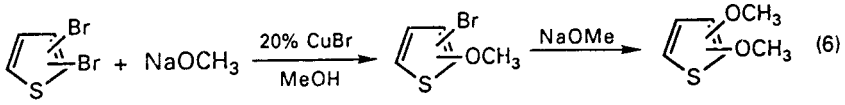


(62%) (5)

2-Bromofuran underwent extensive reduction in the reaction with $NaOCH_3$ in NMP as the main solvent [8], but the reaction in methanol was highly selective and the volatile 2-methoxyfuran could be isolated in a reasonable yield [9]. The ethyl ether could be obtained in only ~30% yield using 15% CuBr [10]. In this reaction formation of zerovalent copper was observed in the dark-brown reaction mixture. Hitherto these products were prepared by a three-step procedure via 5-bromo-2-furoate, since direct substitution of halogen in 2-bromo and 2-iodofuran had proceeded unsuccessfully.[22]

2-Bromo-1-methylpyrrole gave the corresponding methyl ether in a good yield [11], when treated with sodium methoxide in methanol. The preparation of this compound via decarboxylation of the corresponding 2-methoxy-3-carboxylic acid has been described once before.[23]

Of the four dibromothiophenes (eq. 6) the 3,4-isomer [15] gave the highest yield of the corresponding dimethoxy derivative, when the reactions were carried out with a very concentrated (10 M.) solution of sodium methoxide using 20 mol% of CuBr (10 mol% per bromine). Application of DMF or NMP as co-solvents gave rise to a low selectivity [16], though a good selectivity was expected, corresponding to the result with 3-bromothiophene. As already has been observed,[24] the other dibromothiophenes appeared to be more reduction-responsive.



The selectivity in the reaction with 2,3-dibromothiophene was low [12], even when it was carried out in methanol as the only solvent. The reaction of 2,4-dibromothiophene [13] with $NaOCH_3$ in methanol was monitored with GLC. An accumulation of 2-methoxy-4-bromothiophene was noticed after about half an hour. This intermediate product could be isolated in ~35% yield when the reaction was terminated after this period.[25] The primary substitution of the bromine atom in the 2-position is very remarkable, since the reaction of 3-bromothiophene proceeds faster than that of 2-bromothiophene (compare [1] and [4]).

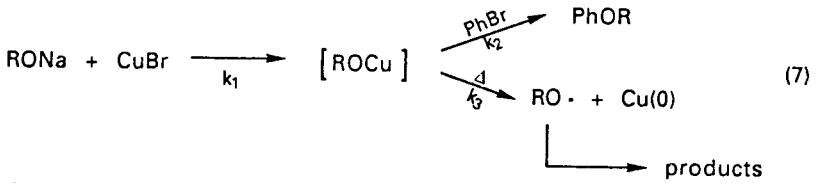
The bromine atom in the 2-position was not only substituted more easily, but it appeared to be also more reduction-responsive. When 2,4-dibromothiophene was exposed to methoxide, considerable amounts of 3-methoxythiophene (up to 25%) were formed, whereas 2-methoxythiophene was formed as a minor component (~4%). Such differences in selectivity had already been noticed by Bacon *et al.* [26]

Of the substrates investigated halopyridines were found to be the most reactive. Their conversion was also possible in the absence of a catalyst. This can be easily understood, since these reactions can proceed via a different pathway.[27] 2-Bromopyridine completely reacted within 15 minutes [18] (compare also refs. 24 and 28). 3-Bromopyridine was converted to 3-methoxypyridine, a well-known flavour compound. This reaction could also be carried out without a catalyst though it proceeded more slowly [19]. For this reaction the co-solvent NMP appeared to be necessary. DMSO cannot be applied successfully as is described in the literature.[29] When 10% of catalyst was added the reaction was complete within 1 h [20]. Also the chloropyridines appeared to be more reactive than the other (hetero)aromatic chlorides. 2-Chloropyridine was converted in 15 minutes without a catalyst [21]. With sodium *ethoxide* the reaction was somewhat slower, but the expected ethyl ether could be obtained in a good yield [22]. For the conversion of 3-chloropyridine into 3-methoxypyridine 8 hours were needed. Using 10% of CuBr a 75% selectivity was obtained [23].

Formation of the catalytic species, its stability and decomposition

We propose that in the copper(I) halide catalysed alkoxylation a copper(I) alkoxide is formed first (compare ref. 30). This compound is believed to be the actual catalyst. It can decompose into elementary

copper and an alkoxy-radical (eq. 7).[30] The rate of decomposition depends upon electron density on the oxygen and upon the concentration of the copper(I) bromide. A high electron density or a high concentration give rise to a faster decomposition.



(7)

These conclusions are based on the following experiments, in which the stability of the copper alkoxides was investigated more in depth by stirring copper(I) bromide (5 mmol on 75 mmol of the base) at 90°C in a 4 M solution of several alkoxides with the corresponding alcohols as the solvent (table 4).

Table 4 - Decomposition of copper(I) alkoxides

CuOR/HOR R =	polarity of alcohol (ref. 31)	decomposition of the catalyst
CH_3	5.1	36-48 h
CH_2CH_3	4.3	< 2 h
$CH_2CH_2CH_3$	4.0	< 2 h
$(CH_2)_3CH_3$	3.9	~ 6 h
$CH(CH_3)_2$	3.9	~ 6 h
CH_2CF_3		> 120 h

After a period, indicated in the table formation of Cu(0) was observed and no substitution occurred upon introduction of bromobenzene afterwards. Applying $NaOCH_3$ or $NaOCH_2CF_3$ as the base, we found a higher stability of the catalyst ($CuOCH_3$, $CuOCH_2CF_3$ respectively) than in the case of the other alkoxides investigated. These two copper(I) alkoxides both have a lower electron-density on the oxygen. The higher stability might therefore be explained by a less easy electron-transfer from the alkoxide to the copper atom, which occurs during the decomposition reaction (eq. 7, k_3).

The faster decomposition of copper(I) ethoxide and *n*-propoxide, compared to copper(I) butoxide and *i*-propoxide cannot be explained on the basis of electron-density, but might be caused by differences in copper(I) bromide concentration in the corresponding alcohols (compare the polarities in table 4). The influence of the copper bromide concentration on the decomposition rate might appear from experiments in which $NaOCH_3$ and CuBr were mixed in methanol in the presence of a polar solvent, such as NMP, DMF, DMSO, or DMI (*vide supra*) or a coordinating compound, such as triphenylphosphine or lithium bromide: Copper(0) formation then was visible at a much earlier stage (after 6 h, compare table 4). We suggest that the higher copper(I) bromide concentration increases the rate of the catalyst formation (eq. 7, k_1). This results in a higher copper alkoxide concentration and therefore in a faster decomposition.

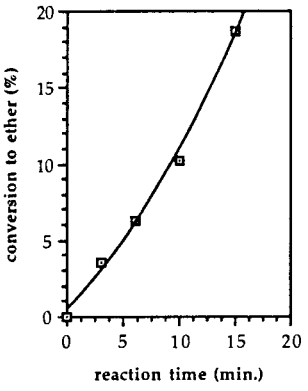


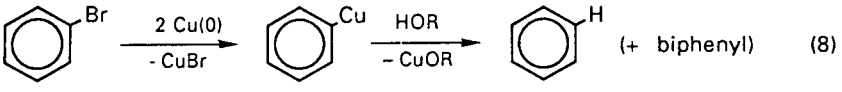
Figure 1

Additional support was found during the methoxylation of chlorobenzene. Whereas the mixture of copper(I) bromide and sodium methoxide in methanol had shown to give copper(0) only after 36 h (table 4), in the presence of chlorobenzene this mixture showed the decomposition product within 18 h. When the catalyst was heated with toluene instead of chlorobenzene, no Cu(0) was formed. However, the presence of anisole caused a decomposition of the catalyst within 18 h. This observation can be explained by coordination of anisole to copper(I) bromide (comparable to the additives and polar solvents mentioned above), thus increasing its concentration.

This anisole induced increase of the copper(I) bromide (and thus the copper(I) alkoxide) concentration also appeared at the start of the copper(I) bromide catalysed reaction of bromobenzene and sodium methoxide in methanol. When this initial period was monitored by GLC a slight increase of the rate with the time was observed (figure 1).

Influence of copper(0) on the reduction of the substrate

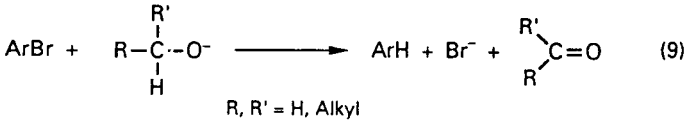
We noticed that the decomposition of the catalyst was often accompanied by a decrease in the selectivity of the reaction, *i. e.* more reductive dehalogenation of the substrate took place. Addition of the substrate *after* the decomposition of the catalyst, as described above, thus gave benzene and traces of biphenyl. This may be the result of a reaction between the *in situ* formed Cu(0) and the aryl halide, leading to an arylcopper species, which subsequently decomposes (eq. 8).[32] When 2-bromobenzene was heated with commercial copper powder substantial amounts of benzene were formed.



As we described above, 2-bromothiophene appeared more sensitive to the reductive dehalogenation. It occurred very rapidly in the presence of a polar co-solvent, even in absence of the catalyst (table 2). These observations suggest an additional mechanism.

We have ascertained that this conversion into thiophene is not accompanied by the formation of 3,4-dibromothiophene, which shows that this is not caused by a base-catalysed halogen dance (compare ref.

33). Bacon explained similar observations with aryl halides as a redox reaction (eq. 9).[34] This assumption was supported by isolation of small amounts of the expected ketones.



The formation of ketones, however, was also observed as a result of the decomposition of copper alkoxides.[30] This and the different results obtained with and without co-solvent, prompted us to do additional research to get more insight in the mechanism of the reduction reaction. A number of experiments were carried out with methanol-d_1 and sodium methoxide-d_3/methanol-d_3, among others. The results are summarized in table 5.

Table 5 - Reduction reaction

run	solvent	catalyst	time (h.)	thiophene (%)	deuterium ratio[a] d_0	d_1	d_2	d_3	total D-%[b]	remarks
1	CH_3OH	-	6	0	-	-	-	-	-	c
2	NMP/CH_3OD	-	1	15	39	43	18	-	20	
3	NMP/CD_3OH	-	1	1	23	38	28	11	32	d
4	CH_3OD	10 % CuBr	6	8	16	45	38	3	31	e
5	CD_3OH	10 % CuBr	6	< 1	90	10	-	-	3	f

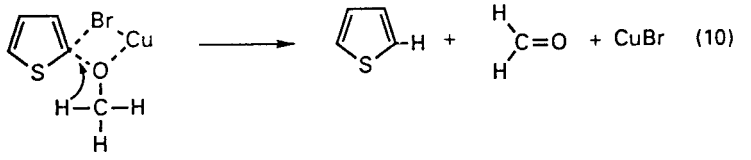
a: The product mixtures were analysed by mass-spectroscopy, the position of the deuterium atoms was not determined; b: total D/H ratio in thiophene formed, calculated from d_0, d_1, d_2, and d_3; c: neither substitution nor reduction took place; d: 4% thiophene formed in 1 h (compare table 2, [4]); e: total D pct bromothiophene 27% f: total D pct. bromothiophene ~ 5%.

Analysis of the reaction mixtures showed the presence of mono-, di, tri- and non-deuterated thiophene. We suggest that this is caused by a base-catalysed hydrogen/deuterium exchange reaction,[35,36] which is discussed in more detail in the cited articles.[37]

In spite of this camouflaging effect some striking observations could be made: (i) no reduction took place in the absence of co-solvent and catalyst (run [1]), (ii) when CD_3ONa/CD_3OH was used only small amounts of reduction product were formed (compare [2] and [3], and [4] and [5]), and (iii) using this base in the absence of the co-solvent gave a low deuterium/hydrogen ratio of the thiophene formed [5].

The small amount of thiophene formed, when using CD_3ONa/CD_3OH in the presence of NMP, probably due to the isotope effect, shows that most of the protons transferred come from the α-carbon atom of the alcohol or the alkoxide. This lends further evidence to the mechanism of Bacon *et al.* (eq. 9).[34] In absence of the co-solvent, however, this mechanism is not plausible since no thiophene (nor methoxythiophene) is formed in absence of the catalyst. This shows that the catalytic species participates in the reduction process under these conditions.

The copper-mediated mechanism as proposed for reduction of bromobenzene (eq. 8), however, is not likely either for certain reasons. Firstly, during the reaction with 2-bromothiophene no Cu(0) was observed, which is necessary for the formation of the arylcopper species (eq. 8). Secondly the reaction of the arylcopper species with the alcohol is supposed to occur by abstraction of a hydroxyl proton of the alcohol and not by a transfer of the protons attached to the carbon (see exp. [5]). Therefore, we propose a copper-mediated reduction process as is depicted in equation 10.



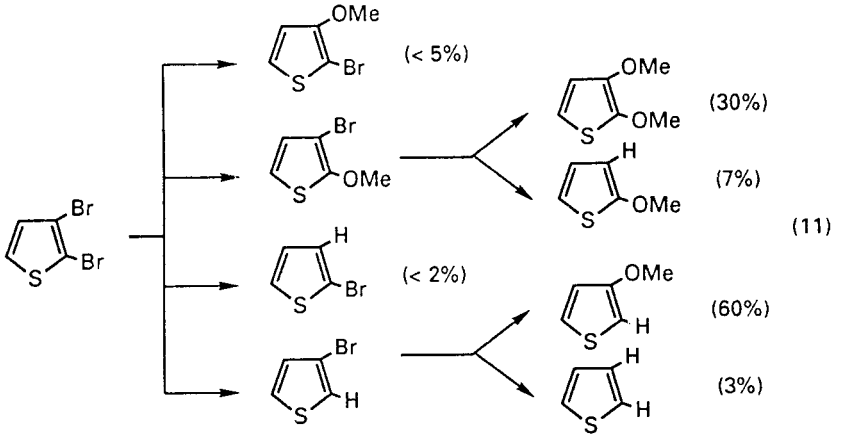
(10)

Dibromothiophenes appeared to be even more sensitive to the reduction process than 2-bromothiophene (table 6). Such substrate dependent selectivities have been noticed before by Bacon *et al.* [38] They showed that *ortho* methoxy groups in the case of bromobenzenes gave a decrease in the selectivity of the reaction. Our results with the dibromothiophenes show that the selectivity is also lowered by an α-sulfur atom (compare [12-14]) and by an *ortho* bromine.

Table 6 - Selectivities of dibromothiophenes in methanol

Substrate	Selectivity
2-bromothiophene	92
2,3-dibromothiophene	34
2,4-dibromothiophene	64
2,5-dibromothiophene	61
3,4-dibromothiophene	87

Although it was not possible for most of the dibromothiophenes to distinguish whether the reduction took place before or after the substitution of the second bromine atom more information was obtained by using 2,3-dibromothiophene. In the reaction of this compound with methoxide 3-methoxythiophene was detected as the predominant side-product (60%). This product can be formed only by reduction of the dibromo compound followed by a substitution, as depicted in eq. 11. The substitution of the bromine atom in the 3-position only occurred to a minor extent, as was also expected because of the higher reactivity of the 2-position (*vide supra*).



(11)

EXPERIMENTAL PART

General: In all reactions an atmosphere of inert gas (N_2) was maintained. Solvents were dried, and distilled prior to use and as all reagents stored under nitrogen. All chemicals were commercially available, unless stated otherwise. 2-Bromothiophene,[39] 2,3-dibromothiophene,[40] 2,5-dibromothiophene,[39] 2-bromofuran,[41] 2-bromo-*N*-methylpyrrole,[42] 3-Bromothiophene,[43] 2,4-dibromothiophene,[44] and 3,4-dibromothiophene[43] were prepared as described in literature. 3-Bromo-2-(2-hydroxyethyl)thiophene was prepared via a modified literature method[45] as described below.

Analysis: Reactions were monitored by taking samples of the reaction mixture through a serum cap with syringe techniques. The samples were added to a v/v 1/1 mixture of water and diethyl ether. The organic layer was analysed quantitatively by GLC on a Pye Unicam 104 gas chromatograph using a capillary silica-coated column or, in the case of the dibromothiophenes, a 10% Apiezon column. GC-MS analysis was carried out on a Varian E-4 mass spectrometer or a Kratos GC-MS combination (tables 5 and 8). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer (^1H: 200 MHz, ^{13}C: 50 MHz) using deuterio chloroform as a solvent and internal standard, unless mentioned otherwise. The spectral data are collected in table 7.

Preparation of 3-bromo-2-(2-hydroxyethyl)thiophene (eq. 5): A 500-mL three-necked round-bottomed flask, equipped with a thermometer, and a mechanical stirrer, was charged with 12 g (0.12 mol) of diisopropyl amine and 70 mL of tetrahydrofuran. To this mixture 70 mL (0.11 mol) of *n*-butyllithium in hexane was added at -20 to -30°C, after which 16.3 g (0.10 mol) of 3-bromothiophene was introduced over 5 min. The temperature was allowed to rise to 0°C. At this temperature 5.28 g (0.14 mol) of ethylene oxide in 25 mL of diethyl ether was added. The temperature was slowly raised to 20°C. The mixture was stirred for 45 min, after which a 10% HCl (aq) solution was added slowly with occasional cooling. The layers were separated and the aqueous layer was extracted with five 50 mL-portions of diethyl ether. The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The product was isolated by distillation. Yield: 15.7 g (76%), bp.: 110°C/0.5 mm Hg, n_D^{20}: 1.5994.

Procedure for GLC-monitored experiments, in the presence of a co-solvent (specific information is given in the tables): In a 100-mL three-necked round-bottomed flask, equipped with a thermometer, a reflux condenser, and a rubber septum, 1.7 g of sodium (75 mmol) was dissolved under heating in an excess of the alcohol mentioned. After the dissolution of the sodium the solvent was evaporated and the solid was powdered under inert gas. (In the case of methanol commercially available sodium methoxide was used.) The solid was suspended in 12.5 ml of the co-solvent and 3.8 mL of the alcohol mentioned in the tables. Subsequently 50 mmol of the aryl halide and 0.71 g copper(I) bromide (10 mol%) were added and the reaction mixture was brought to reflux, to a maximum of 110°C, under magnetic stirring. During the experiment the internal temperature dropped due to the conversion of sodium methoxide. The reaction was monitored by GLC every hour for a period of 6 hours.

Procedure for GLC-monitored experiments using PBu_3 (table 2): In a 100-mL three-necked round-bottomed flask, equipped with a thermometer, a reflux condenser, and a rubber septum, 1.7 g of sodium (75 mmol) was dissolved under heating in an excess of the alcohol mentioned. After the disappearance of the sodium the solvent was evaporated and the solid was powdered under inert gas. (In the case of methanol commercially available sodium methoxide was used.) The solid was then suspended in 8.7 mL of methanol. Subsequently 10 mol% tributylphosphine, 50 mmol of the aryl halide, and 0.71 g copper(I) bromide (10 mol%) were added

and the reaction mixture was heated to reflux, to a maximum of 110°C, under magnetic stirring. For further operations see above.

Procedure for GLC-monitored experiments without the use of a co-solvent (specific information is given in the tables): In a 100-mL three-necked round-bottomed flask, equipped with a thermometer, a reflux condenser, and a septum, 1.7 g of sodium (75 mmol) was dissolved under heating in an excess of the alcohol mentioned. After the disappearance of the sodium the solvent was evaporated and the solid was powdered under inert gas. (In the case of methanol commercially available sodium methoxide was used.) The solid was then suspended in 7.5 mL of the alcohol mentioned in the tables. Subsequently 50 mmol of the aryl halide and 0.71 g copper(I) bromide (10 mol%) were added and the reaction mixture was heated to reflux, under magnetic stirring. For further operations see above.

Procedure for experiments with methanol or methanol-d_1(for specific information see table 5): In a 100-mL three-necked round-bottomed flask, equipped with a thermometer and a reflux condenser, 4.1 g (75 mmol) of sodium methoxide was dissolved in 7.5 mL methanol [exp 1], 7.5 mL methanol-d_1 [exp 4], or in 3.8 mL methanol-d_1 and 12.5 mL NMP [exp 2]. The mixture was heated to reflux [1,4] or 110°C [2] after which 8.2 g (50 mmol) of 2-bromothiophene and 0.71 g (5 mmol) CuBr [exp. 4] were added. After the mentioned period the reaction mixture was cooled down and analysed by mass-spectroscopy (with exception of exp 1).

Procedure for experiments using sodium methoxide-d_3 and methanol-d_3 (specific information in table 5): In a 100-mL three-necked round-bottomed flask, equipped with a thermometer and a reflux condenser, 1.7 g (75 mmol) of sodium was dissolved in 7.5 mL methanol-d_3 under heating. After the sodium had reacted (in exp. 3) 12.5 mL of NMP was added and 3.7 mL of the alcohol were distilled off. The reaction mixture was heated to reflux [5] or 110°C [3] after which 8.2 g (50 mmol) of 2-bromothiophene, and 0.71 g (5 mmol) CuBr [exp. 5] was added. After the mentioned period the mixture was cooled and analysed by mass-spectroscopy.

Preparative experiments:
In these experiments the reactions were not monitored. The information about the reaction times were obtained from the GLC-monitored experiments described above.
Work-up: After the conversion was complete the reaction mixture was cooled to room temperature and 100 ml of an aqueous solution of 5 g sodium cyanide was added under vigorous stirring. The aqueous layer was extracted with pentane (5x30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was distilled off. The product was isolated by distillation.

i-Propoxybenzene: In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 3.45 g (150 mmol) of sodium was dissolved in 19.1 mL of *i*-propanol under magnetic stirring. After the sodium had reacted the mixture was homogenized by adding 25 mL of NMP. Subsequently 15.7 g (100 mmol) of bromobenzene was added, the mixture was heated and the reaction was started by the addition of 1.44 g (10 mmol) of copper(I) bromide. After 3.5 hours the reaction had finished and the product was isolated via the usual work-up. Yield: 70%, bp.: 110 °C/20 mm Hg (compare ref. 46)

Ethoxybenzene: The preparation of ethoxybenzene was carried out as described for *i*-propoxybenzene, using 16.4 mL of ethanol and 12 mol% of the catalyst. The reaction had finished in 0.75 h. Yield: 93%, bp.: 53-55 °C/20 mm Hg (compare ref. 46).

n-Butoxybenzene: The preparation of *n*-butoxybenzene was carried out as described for *i*-propoxybenzene. In this case 21.3 mL of *n*-butanol was used. The reaction had finished in 1 h. Yield: 85%, bp.: 68-69 °C/2 mm Hg (compare ref. 46).

n-Pentoxybenzene: The preparation of *n*-pentoxybenzene was carried out as described for *i*-propoxybenzene, using 23.9 mL of *n*-pentanol to prepare a 4.6 M pentoxide-solution in pentanol/NMP. The reaction had finished in 0.5 hour. Yield: 75%, bp.: 79 °C/2 mm Hg.

(2,2,2-Trifluoroethoxy)benzene: 2,2,2-Trifluoroethoxybenzene was prepared as *i*-propoxybenzene using 14.1 mL of 2,2,2-trifluoroethanol. The reaction had finished in 0.5 hours. Yield: 85%, bp.: 50 °C/15 mm Hg.

(2-Methoxyethoxy)benzene: The preparation of (2-methoxyethoxy)benzene was carried out as described for *i*-propoxybenzene. In this case 19.4 mL of 2-methoxyethanol and 16 mol% of the catalyst was used. The reaction had finished in 2 hours. Yield: 85%, bp.: 69-70 °C/0.5 mm Hg, n_D^{20}: 1.5097.

(2-(Dimethylamino)ethoxy)benzene: The preparation of (2-(dimethylamino)ethoxy)benzene was carried out as described for *i*-propoxybenzene, using 22.7 mL of 2-dimethylaminoethanol. The reaction had finished in 1.5 hours. Yield: 80%, bp.: 66-68 °C/0.7 mm Hg, n_D^{20}: 1.5268.

1-Methoxynaphthalene: In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 8.1 g (150 mmol) of sodium methoxide was suspended in 7.6 mL of methanol under magnetic stirring. The mixture was homogenized with 25 mL of NMP. Subsequently 20.7 g (100 mmol) of 1-bromonaphthalene and 1.44 g (10 mmol) copper(I) bromide were added after which the reaction mixture was immediately heated to 110°C. After 0.5 hour the reaction had finished and the product was isolated via the usual work-up. Yield: 92%, bp.: 135-137 °C/12 mm Hg (compare ref. 9).

p-Fluoromethoxybenzene: In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 8.1 g (150 mmol) of sodium methoxide was dissolved in 15 mL of methanol under heating and magnetic stirring. Subsequently 26.5 g (100 mmol) of *p*-bromofluorobenzene and 1.44 g (10 mmol) of copper(I) bromide were added to the warm solution after which the reaction mixture was heated under reflux for 4 h. The product was isolated via the usual work-up. Yield: 80%, bp.: 47 °C/15 mm Hg.

p-Methoxybromobenzene: p-Methoxybromobenzene was obtained from *p*-bromofluorobenzene as described for 1-methoxynaphthalene in absence of a catalyst. Yield: 85%, bp.: 102 °C/15 mm.

Methoxybenzene from chlorobenzene: Methoxybenzene was prepared as described for *p*-fluoromethoxybenzene using 11.3 g (100 mmol) of chlorobenzene and 20 mmol of CuBr. After 24 h. the reaction had stopped and a 20% conversion was reached without formation of any side-product.

(2,2,2-Trifluoroethoxy)benzene from chlorobenzene: The preparation of (2,2,2-trifluoroethoxy)benzene was carried out as described under *p*-fluoromethoxybenzene using 14.1 mL of 2,2,2-trifluoroethanol. The reaction was stopped after 5 days of heating under reflux, when a conversion of 90% had been reached. The product was isolated after the usual work-up. Yield: 70%, bp.: 50 °C/15 mm Hg.

2-(2,2,2-Trifluoroethoxy)thiophene from 2-chlorothiophene: As described under *p*-fluoromethoxybenzene using 14.1 mL of 2,2,2-trifluoroethanol. The reaction was stopped after 5 days of heating under reflux, when a conversion of 85% had been reached. The product was isolated after the usual work-up. Yield: 70%, bp.: 67 °C/30 mm Hg.

2-Methoxythiophene: In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 8.1 g (150 mmol) of sodium methoxide was suspended in 15 mL of methanol. To this mixture 16.3 g 2-bromothiophene (100 mmol) and 1.44 g copper(I) bromide (10 mmol) were successively added. The reaction mixture was heated under gentle reflux with magnetic stirring. After 6 hours the reaction had finished and the usual work-up was carried out. Yield: 83%, bp.: 90°C/100 mm Hg, (compare ref. 11), n_D^{20}: 1,5262.

2-Ethoxythiophene: In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 3.5 g (150 mmol) sodium was dissolved under heating in 30 mL of ethanol (100%, oxygen free). After all sodium had disappeared the solvent was removed and the white/grey solid was pulverized under N_2. To this powder 10 mL of ethanol and 16.3 g (100 mmol) of 2-bromothiophene were added. The reaction mixture was heated to reflux (103°C) and 1.44 g (10 mmol) CuBr was added. After 3 h the reaction was finished and the product was isolated via the usual work-up. Yield: 83%, bp.: 68 °C/16 mm Hg.

3-Methoxythiophene (with co-solvent): As described under 1-methoxynaphthalene. Yield: 88%, bp.: 81-82°C/ 65 mm Hg (compare ref. 10).

3-Methoxythiophene: (without co-solvent): As described under 2-methoxythiophene. Yield: 82%.

3-Ethoxythiophene: In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 3.5 g (150 mmol) sodium was dissolved under heating in 30 mL of ethanol (100%, oxygen free). After all sodium had reacted the solvent was removed *in vacuo*. The remaining solid was dissolved in 20 mL of DMF. The solution was heated to 110°C after which 12.2 g (75 mmol) of 3-bromothiophene and 1.1 g (7.5 mmol) copper(I) bromide were added. After 1 hour the reaction had finished and the product was isolated via the usual work-up. Yield: 94%, bp.: 62-63°C/18 mm Hg.

3-i-Propoxythiophene: In a 250-mL three-necked flask, equipped with a thermometer and a reflux condenser, 3.5 g (150 mmol) sodium was dissolved in 100 mL of *i*-propyl alcohol. After the sodium had disappeared 20 mL of DMF was added and 60 mL of the solvent was distilled off so that the temperature of the reaction mixture could rise to 112°C. Successively 16.3 g (100 mmol) of 3-bromothiophene and 1.44 g CuBr were added. After 8 h the reaction had finished and the product was isolated following the usual work-up. Yield: 80%, bp.: 83 °C/0.7 mm Hg.

2-Methoxyfuran: 2-Methoxyfuran was obtained as described for 2-methoxythiophene. Yield: 60%, bp.: 110-111 °C (compare ref. 47).

2-Ethoxyfuran: 2-Ethoxyfuran was obtained as described for 2-ethoxythiophene. Yield: 30%, bp.: 125-126 (compare ref. 47).

N-Methyl-2-methoxypyrrole: *N*-Methyl-2-methoxypyrrole was prepared as described for 2-methoxythiophene. Yield: 75%, bp.: 120°C (compare ref. 23).

2,4-, 2,5-, and 3,4-Dimethoxythiophene: In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 8.1 g (150 mmol) of sodium methoxide was suspended in 15 mL of methanol under magnetic stirring. Subsequently 12.1 g (50 mmol) of the dibromothiophene and 1.44 g (10 mmol) copper(I) bromide were added and the reaction mixture was heated to reflux immediately. After 6 h the reaction mixture was cooled down and the product was isolated using the work-up described above. 2,4-dimethoxythiophene: yield: 47%, bp.: 99 °C/20 mm Hg, n_D^{20} = 1.5252; 2,5-dimethoxythiophene: yield: 49%, bp. : 89-90 °C/20 mm Hg (compare ref. 48), n_D^{23} = 1.5190; 3,4-dimethoxythiophene: yield: 74%, bp.: 105 °C/20 mm Hg (compare ref. 49), n_D^{20} = 1.5409.
When in the reaction of 2,4-dibromothiophene 1 eq. of sodium methoxide and 10% of CuBr was used, 4-bromo-2-methoxythiophene could be isolated after heating overnight at 80°C (usual work-up). Yield: 35%, bp.: 92-107 °C/30 mm Hg.

Reaction of 3-bromo-2-(2-hydroxyethyl)thiophene (eq. 5): In a 100-mL three-necked flask, equipped with a thermometer, a reflux condenser, and a septum, 50 mmol of the substrate and 50 mmol NaO*t*-Bu were suspended in 15 mL of *t*-BuOH. The mixture was heated to 90°C and 10 mmol of CuBr (20%) was added. The mixture was stirred 24 h at the 90°C. After this period the mixture was neutralized with a 10% HCl (aq) solution. GLC showed that 35% of the aimed product and 65% of the eliminated product was formed. The latter was isolated in a 62% yield. Bp.: 82-84°C/22 mm Hg, n_D^{20}: 1.6051.

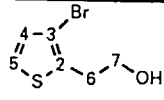
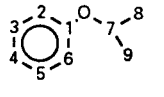
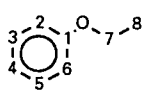
2-Methoxypyridine: In a 100-mL three-necked flask, equipped with a thermometer and a reflux condenser, 8.1 g (150 mmol) of sodium methoxide was suspended in 7 mL of methanol and 32 mL of NMP. After the reaction mixture was heated to 90°C, 11.3 g (100 mmol) of 2-chloropyridine or 15.8 g (100 mmol) of 2-bromopyridine was added. A vigorous reaction took place, causing an increase of the temperature of more than 30°C. The external heating was removed until the temperature had dropped to 110°C. After 15 min the reaction was complete. The product was isolated by the usual work-up. Yield: 80%, bp.: 142°C.

2-Ethoxypyridine: 2-Ethoxypyridine was prepared as described for 3-ethoxythiophene using 11.3 g (100 mmol) of 2-chloropyridine, in absence of CuBr. Reaction time 0.5 h., yield: 85%, bp.: 50°C/15 mm Hg.

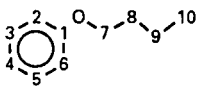
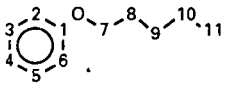
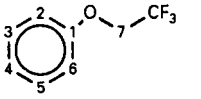
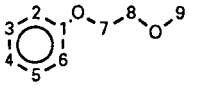
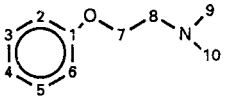
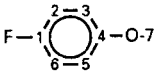
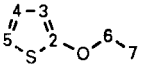
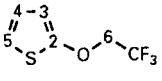
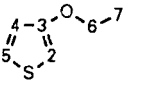
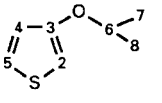
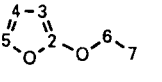
3-Methoxypyridine (without catalyst): 3-Methoxypyridine was prepared from 3-bromopyridine during 6 h, as described under 2-methoxypyridine. Yield: 40%, bp.: 65°C/15 mm Hg.

3-Methoxypyridine (with CuBr): 3-Methoxypyridine was also prepared as described for 1-methoxy-naphthalene. Yield: 35%.

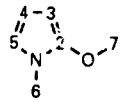
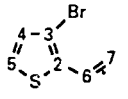
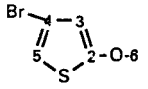
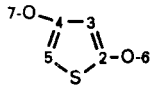
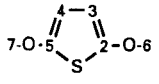
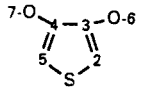
Table 7 - NMR data.

compound	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
	2.99 (2H^6, t), 3.79 (2H^7, t), 6.91 (H^3, d), 7.13 (H^4, d); $^3J_{6,7}$: 6.6 Hz, $^3J_{4,5}$: 5.3 Hz.	32.2 (C^6), 61.9 (C^7), 109.4 (C^3), 123.8 (C^5), 129.7 (C^4), 143.8 (C^2).
	1.43 (6H^{8,9}, d), 4.62 (H^7, h), 6.98-7.04 (H^{2,4,6}, m), 7.33-7.39 (H^{3,5}, m); $^3J_{7,8}$: 6.1 Hz.	21.9 (C^{8,9}), 69.5 (C^7), 115.8 (C^{2,6}), 120.4 (C^4), 129.3 (C^{3,5}), 157.8 (C^1) (compare ref. 50).
	1.45 (3H^{10}, t), 4.04 (2H^9, q), 6.97-6.92 (3H^{2,4,6}, m), 7.34-7.30 (2H^{3,5}, m); $^3J_{9,10}$: 7.0 Hz.	Ref. 50, 51.

(table 7 continued)

	0.89 ($3H^{10}$,t), 1.3-1.5 ($2H^{9}$,m), 1.6-1.78 ($2H^{8}$, m), 3.82 ($2H^{7}$,t), 6.77-6.9 ($3H^{2,4,6}$, m), 7.12-7.24 ($2H^{3,5}$, m); $^{3}J_{9,10}$: 4.5 Hz, $^{3}J_{7,8}$: 6.4 Hz.	Ref. 52.
	1.07 ($3H^{11}$,m), 1.53 ($4H^{9,10}$,m), 1.89 ($2H^{8}$,m), 4.05 ($2H^{7}$,m), 7.05 ($3H^{2,4,6}$,m), 7.39 ($2H^{3,5}$, dd); $^{3}J_{10,11}$: 6.9 Hz, $^{3}J_{7,8}$: 6.5 Hz, $^{4}J_{7,9}$: 1.9 Hz.	13.9 (C^{11}), 22.4 (C^{10}), 28.2 (C^{8}), 28.9 (C^{9}), 67.8 (C^{7}), 114.4 ($2C^{2,6}$), 120.4 (C^{4}), 129.3 ($2C^{3,5}$), 159.0 (C^{1}).
	4.28 ($2H^{7}$,q), 6.90-6.96 ($2H^{3,5}$,m), 7.05 (H^{4},tt), 7.28-7.37 ($2H^{2,6}$, m); $^{3}J_{H,F}$: 8.2 Hz, $^{3}J_{3,4}$: 7.3 Hz, $^{4}J_{2,4}$: 1 Hz.	65.7 (C^{8},q), 114.8 ($C^{2,6}$), 122.4 (C^{4}), 123.4 (CF_3,q), 129.7($C^{3,5}$), 157.3(C^{1}); $^{1}J_{CF}$: 276.3 Hz, $^{2}J_{CF}$: 35.4 Hz.
	3.45($3H^{9}$, s), 3.73 ($2H^{8}$, m), 4.10 ($2H^{8}$, m), 6.93-7.03 ($3H^{2,4,6}$, m), 7.26-7.36 ($2H^{3,5}$, m); $^{3}J_{7,8}$: 4.7 Hz.	58.7 (C^{9}), 66.8 (C^{7}), 70.7 (C^{8}), 114.2 ($C^{2,6}$), 120.5 (C^{4}), 129.1 ($C^{3,5}$), 158.5 (C^{1}).
	2.29 ($6H^{9,10}$, s), 2.67 ($2H^{8}$, t) , 4.00 ($2H^{7}$, t), 6.85-6.95 ($3H^{2,4,6}$, m), 7.18-7.28 ($2H^{3,5}$, m); J_{78} = 5.8 Hz.	45.6 ($C^{9,10}$), 58.0 (C^{8}), 65.6 (C^{7}) 114.2 ($C^{1,5}$), 120.3 (C^{3}), 129.0 ($C^{2,4}$) 158.5 (C^{6}).
1-methoxynaphthalene	Ref. 53.	Ref. 54.
	3.78 ($3H^{7}$), 6.87 ($2H^{3,5}$, m), 7.02 ($2H^{2,6}$, m); $^{3}J_{2,3}$: 9.3 Hz, $^{3}J_{CF}$: 8.2 Hz, $^{4}J_{CF}$: 4.3 Hz (See also ref. 55).[b]	55.3 (C^{7}), 114,7 ($C^{2,6}$,d), 115.6 ($C^{3,5}$,d), 155.7 (C^{4}), 157.2 (C^{1}); $^{1}J_{CF}$: 237.6 Hz, $^{2}J_{CF}$: 23.0 Hz, $^{3}J_{CF}$: 7.9 Hz (see also ref. 56).[b]
4-bromoanisole	Ref. 57.	Ref. 56.
2-methoxythiophene	Ref. 58.	Ref. 59.
	1.39 ($3H^{7}$, t), 3.97 ($2H^{6}$, q), 6.07 (H^{3},dd), 6.39 (H^{5},dd), 6.60 (H^{4}, dd); $^{3}J_{6,7}$:7.1 Hz, $^{3}J_{3,5}$:1.6 Hz, $^{3}J_{4,5}$:5.7 Hz, $^{4}J_{3,4}$:4.0 Hz[c] (also ref. 60).	
	4.39 ($2H^{6}$, q), 6.39 (H^{3}, dd), 6.69 (H^{5}, dd), 6.78 (H^{4}, dd); $^{3}J_{HF}$: 8.1 Hz, $^{3}J_{3,4}$: 3.8 Hz, $^{3}J_{4,5}$: 5.8 Hz, $^{4}J_{3,5}$: 1.5 Hz.	70.4 (C^{6}, q), 107.4 (C^{3}), 114.2 (C^{5}), 122.8 (CF_3, q), 124.6 (C^{4}), 163.5 (C^{2}); $^{1}J_{CF}$: 278 Hz, $^{2}J_{CF}$: 35.6 Hz.
3-methoxythiophene	Ref. 58.	Ref. 59.
	1.42 ($3H^{7}$, t), 4.03 ($2H^{6}$, q), 6.25 (H^{2}, dd), 6.78 (H^{4}, dd), 7.18 (H^{5}, dd); $^{4}J_{2,4}$: 1.55 Hz, $J_{2,5}$: 3.12 Hz, $^{3}J_{4,5}$: 5.24 Hz, $^{3}J_{6,7}$:7.0 Hz.[b]	14.7 (C^{7}), 65.6 (C^{6}), 97.0 (C^{2}), 119.4 (C^{4}), 124.5 (C^{5}), 157.8 (C^{3}).[b]
	1.32 ($6H^{7,8}$,d), 4.30, (H^{6},hept), 6.07 (H^{2},dd), 6.59 (H^{4},dd),7.01 (H^{5}, dd); $^{3}J_{6,(7,8)}$:6.1 Hz, $^{3}J_{3,4}$:1.6 Hz, $^{3}J_{4,5}$:5.2 Hz, $^{4}J_{3,5}$:3.4 Hz.[c]	
2-methoxyfuran	Ref. 61.	Ref. 62.
	1.36 ($3H^{7}$, t), 4.04 ($2H^{6}$, q), 5.12 (H^{3}, dd), 6.23 (H^{4}, dd), 6.85 (H^{5}, dd); $^{3}J_{6,7}$: 7.1 Hz, $^{3}J_{3,4}$: 3.2 Hz, $^{3}J_{4,5}$: 2.2 Hz, $^{4}J_{3,5}$: 1.1 Hz.	14.4 (C^{7}), 66.7 (C^{6}), 80.2 (C^{3}), 110.8 (C^{4}), 132.4 (C^{5}), 160.8 (C^{2}).

(table 7 continued)

	3.51 (3H^6, s), 3.90 (3H^7, s), 5.34 (H^3, dd), 6.06 (H^4, dd), 6.26 (H^5, dd); $^3J_{3,4}$:3.3, $^3J_{4,5}$: 3.5 Hz, $^4J_{3,5}$: 2 Hz.[b]	30.8 (C^6), 57.3 (C^7), 82.4 (C^3), 104.6 (C^4), 113.2 (C^5), 148.1(C^2).
	5.27 (H^7, d), 5.65 (H^7, d), 6.90 (H^6, td), 6.94 (H^4, d), 7.19 (H^5, dd); $^3J_{4,5}$: 5.4 Hz, $^3J_{5,6}$: 3 Hz, $^3J_{6,7}$: 11 Hz, $^3J_{6,7}$: 17.6 Hz	110.4 (C^3), 115.3 (C^7), 124.0 (C^4), 128.2 (C^5), 130.4 (C^6), 137.1 (C^2).
	3.8 (3H^6, s), 6.04 (H^5, d), 6.38 (H^3, d); $J_{2,4}$: 2 Hz[c] (compare ref. 25).	59.9 (C^6), 106.4 (C^3), 106.9 (C^4), 108.6 (C^5), 166.0 (C^2).
	3.74 (3H^7, s), 3.83 (3H^6,s), 5.43 (H^3, d), 5.94 (H^5, d); $J_{2,4}$: 2.1 Hz.	56.0 (C^7), 59.3 (C^6), 81.9 (C^5), 97.0 (C^3), 154.8 (C^4), 164.4 (C^2).
	3.81 (6H^{6,7}, s), 5.81 (2H^{3,4}, s).	60.7 (C^{6,7}), 101.5 (C^{3,4}), 155.4 (C^{2,5}).
	3.68 (6H^{6,7}, s), 6.04 (2H^{2,5},s).[c]	56.7(C^{6,7}), 95.7 (C^{2,5}), 147.1 (C^{3,4}).
2-methoxypyridine	Ref. 63.	Ref. 63.
3-methoxypyridine	Ref. 63.	Ref. 63.

a: interpretation of based upon coupling constants; b: spectrum recorded in $CDCl_3$, on a Bruker AC300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz).; c: spectrum recorded in CCl_4 (2% TMS) on a Varian EM360 spectrometer (^{1}H: 60 MHz).

Table 8 - Mass Spectra of products.

Compound:	*m/e* (% of base peak) The 5 peaks with highest intensity.
2-methoxythiophene	114 (M$^+$, 100), 99 (77), 55 (26), 71 (22), 45 (15).
3-methoxythiophene	114 (M$^+$, 100), 99 (83), 45 (22), 84 (15), 73 (8).
2,4-dimethoxythiophene	144 (M$^+$, 100), 129 (92), 69 (27), 101 (19), 45 (18).
2,5-dimethoxythiophene	129 (100), 144 (M$^+$, 53), 101 (23), 69 (16), 85 (11).
3,4-dimethoxythiophene	144 (M$^+$, 100), 129 (57), 101 (18), 45 (14), 86 (11).
4-bromo-2-methoxythiophene	194/192 (M$^+$, 100)[a], 179/177 (64), 45 (52), 83 (22), 69 (21).
3-bromo-2-ethenylthiophene	190/188 (M$^+$, 100)[a], 109 (100), 65 (30), 45 (20), 39 (14).
2-methoxyfuran	98 (M$^+$, 100), 83 (84), 55 (27), 27 (11), 29 (8).
(2-thioethoxyethoxy)benzene	89 (100), 61 (46), 123 (22), 125 (17), 65 (15)[b].

a: two peaks in 1/1 ratio due to bromine isotope; b: M$^+$ ion: 182.

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