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Nickel-Catalysed Electrochemical Coupling of 2- and 3-Bromothiophene with Alkyl and Alkenyl Halides

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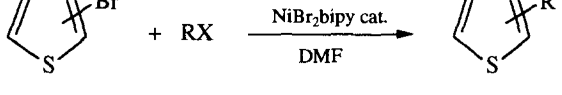
Abstract: 2- or 3-bromothiophene are efficiently coupled with activated alkyl chlorides (α-chloroesters, α-chloroketones, α-chloronitriles), benzyl chloride or vinyl halides, in a one step electrochemical reaction, using the sacrificial anode process and catalysis by $NiBr_2$-2,2'-bipyridine (bipy). © 1997 Elsevier Science Ltd.

3-Substituted thiophenes are very useful compounds for both the material and pharmaceutical fields.[1] For instance, they are used to prepare electronic conductive 3-substituted polythiophenes whose properties are strongly dependent on the nature of the functional group at position 3.[2] 3-Substituted thiophenes can be obtained by coupling between 3-thienyl organometallics and various organic halides in the presence of transition metal complexes as catalysts. However, these organometallics are very difficult to obtain from 3-bromothiophene. Thus 3-bromothiophene reacts with Rieke manganese[3] to form 3-thienylmanganese but not with Rieke zinc or magnesium.[4] 3-Lithiothiophene has been prepared from 3-bromothiophene by classical metal-halogen exchange in ethers at -70 °C,[5] or in a 10/1 hexane-THF mixture at -40 °C.[6] However, except in this last solvent, 3-lithiothiophene is unstable above -70 °C, and isomerises into 2-lithiothiophene in polar medium. In addition, it can not be used in coupling with organic halides bearing reactive electron-withdrawing groups. 3-Alkylthiophene can also be easily obtained by coupling between bromothiophene and Grignard reagents catalyzed by $NiCl_2$(dppp),[7] but this procedure can not be used for introducing electrophilic functionnal groups.

We have already described[8] the one-step electrochemical preparation of 3-thienylzinc bromide from 3-bromothiophene *via* nickel catalysis, and its palladium-catalysed coupling with aryl halides. In this paper we report on the nickel-catalysed electroreductive coupling of 2- and 3-bromothiophene with activated alkyl halides such as α-chloroesters, α-chloroketones, benzyl chloride and with vinyl halides (eq 1), using the sacrificial anode process.

equation 1



The general reaction conditions for this reaction were derived from those used for the electrochemical cross-coupling between aryl halides and activated alkyl halides,[9] *i.e.* DMF as the solvent, NBu_4BF_4 as the

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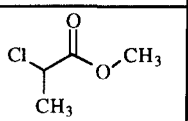
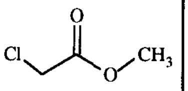
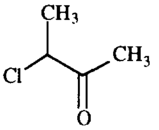
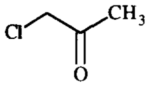
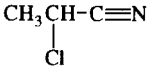
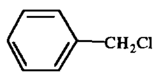
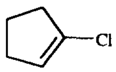
supporting electrolyte, aluminium rod and nickel foam as the anode and the cathode respectively, 10% of $NiBr_2bipy$ as catalyst. However, to obtain the highest efficiency in this coupling reaction, it had been necessary to finely adjust the other experimental parameters. Thus for all 2- or 3-bromothiophene - RX systems, the best results were obtained at room temperature instead of 60 °C and at current intensity lower than 0.2 A (corresponding to 10 mA/cm^2 of current density). Except for the coupling of 3-bromothiophene with alkenyl chlorides, which can be carried out by electrolysis of an equimolar mixture of the two halides, it was necessary to start the electrolysis with a mixture of the bromothiophene and 0.05 to 0.2 eq of RX and then add progressively RX during the electrolysis.

Results are given in Table 1 for reactions involving 3-bromothiophene.

Table 1
Ni-catalysed coupling of 3-bromothiophene with activated alkyl halides.

entry	RX	initial composition of the solution (mmol Br-thiophene/mmol RX)	mmol of RX added during electrolysis	isolated yield[a]% in coupling product
1		10/1.7	13,3	59%
2		10/0.6	18,4	62%
3		10/1	19	43%
4		10/0.6	13.4	40%
5	 $\underset{\displaystyle Cl}{CH_3\overset{}{C}H}\text{-}C{\equiv}N$	10/0.7	19.3	41%
6		10/2	8	75%
7	$CH_3\text{-}CH{=}C(CH_3)Cl$ Z/E = 66/34	7/7	0	70% Z/E = 17/83
8		10/12	0	76%
9	$CH_3\text{-}CH{=}C(CH_3)Br$ Z/E = 25/75	10/2	14	80% Z/E = 7/93

a) isolated yields, based on initial 3-bromothiophene; spectroscopic data for all products were in agreement with the given structures

The general procedure is as follows: in an undivided electrolysis cell fitted with a nickel-sponge cathode (20 cm^2) and an aluminium rod (1 cm diameter) anode, were introduced 40 mL of DMF, 0.6 mmol of NBu_4BF_4, 1 mmol of $NiBr_2bipy$, 2- or 3-bromothiophene (10 mmol), and part of RX (see table 1). Reactions were performed at room temperature, at constant current intensity of 0.15 to 0.2 A until the bromothiophene was totally consumed (2 to 4F/mol). Apart from reactions involving vinyl chlorides (Table 1, entries 7,8) RX was added to the solution during the electrolysis *via* a syringe pump at a rate of 2 - 2.5 mmol/h. Reactions were monitored by GC analysis. The solution was then quenched with 2N HCl and extracted with diethylether. Pure products were isolated by silica-gel column chromatography with pentane/diethylether as eluent.

Chemical yields in 3-substituted products are moderate to good. No isomer at position 2 was detected. For alkyl chlorides activated by an electron withdrawing group (Table 1, entries 1 - 6), the mechanism is probably the same as the one we have described previously for their coupling with aryl halides,[9,10] and can be schematised as in Scheme 1, where T stands for the thienyl moiety.

Scheme 1

$$Ni^{(II)} + 2e^- + 3\text{-Br-T} \xrightarrow{-1,1\ V/ECS} 3\text{-BrNi-T} \qquad (1)$$

$$3\text{-BrNi-T} + e^- \longrightarrow 3\text{-Ni-T} + Br^- \qquad (2)$$

$$3\text{-Ni-T} + RX \longrightarrow 3\text{-R-T} + Ni^{(I)} + X^- \qquad (3)$$

The reaction of $Ni^{(0)}$ with RX can be minimised by use of excess of 3-Br-T *versus* RX. However this reaction can not be completely suppressed and part of RX is consumed to form R-R or RH. In the third step of the mechanism, RX reacts more rapidly than 3-Br-T.

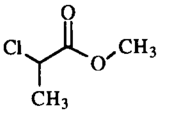
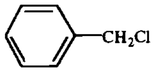
Alkenylation of 3-bromothiophene can also be performed this way. With alkenyl chloride (Table 1, entries 7,8), the reactions were conducted stoichiometrically, *i. e.* without having to use the slow addition procedure. A faster reaction of alkenyl chlorides with $Ni^{(0)}$ as compared to 3-Br-T[11] may be explained this behaviour: this would mean that the reaction sequence would be the opposite to the one given in Scheme 1. However this remains to be proved. With the more reactive bromo derivative (Table 1, entry 9), which also dimerise readily, the slow addition and use of excess of it were required. No systematic study of the stereoselectivity was attempted so far, but the reactions with 2-halo-2-butene (Table 1, entries 7,9) led mainly to the more stable isomer.

Table 2 gives the results obtained with 2-bromothiophene. The procedure was the same as for 3-bromothiophene.

2-Bromothiophene is more reactive than 3-bromothiophene toward $Ni^{(0)}$bipy and gives lower yields in cross-coupling product. This may be due to the occurrence of a more rapid reaction of 2-Ni-T with 2-Br-T than the reaction of 3-Ni-T with 3-Br-T.[12]

A large part of RX should be present at the beginning of the reaction to avoid the formation of 2,2'-bi-thiophene (table 2, entries 1 - 2). In the case of vinylbromide, $Ni^{(0)}$ reacts simultaneously with the two halides and thus 2,2'-bithiophene, vinyl-vinyl and the 2-vinylthiophene are formed.

Table 2
Ni-catalysed coupling of 2-bromothiophene with activated alkyl halides.

entry	RX	initial composition of the solution (mmol Br-thiophene/mmol RX)	mmol of RX added during electrolysis	isolated yield[a]% in coupling product
1		10/10	7	37%
2		10/10	3	56%
3	CH_3-CH=C(CH_3)Br Z/E = 25/75	10/10	5	55% Z/E = 9/91

a) isolated yields, based on initial 2-bromothiophene; spectroscopic data for all products are in agreement with the given structures

In conclusion various substituted thiophenes, especially 3-substituted thiophenes, can be prepared in good yields in one step by a very simple electrochemical method.

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12 Electroanalytical study under current investigation.

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