New and efficient access to 3-substituted 2,5-dibromothiophenes. Consecutive nickel-catalyzed electrochemical conversion to thienylzinc species

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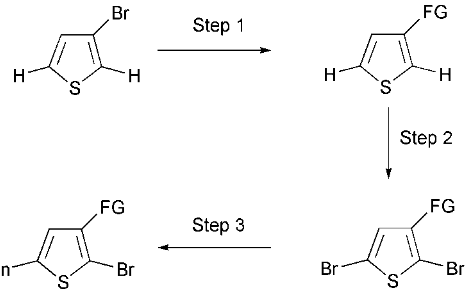
We have achieved the stepwise synthesis of 3-substituted thienylzinc reagents using both electrochemical methods and an original bromination procedure. For several compounds 3-bromothiophene was the starting substrate, which was functionalized according to recently developed electrochemical procedures. The nickel-catalyzed electrochemical reduction of the resulting 3-substituted 2,5-dibromothiophenes in the presence of zinc salts allowed the formation of monothienylzinc species in good yields. The selectivity of this reaction is discussed within the context of the electrochemical synthesis of regioregular polythiophenes.

3-Functionalized thiophenes have found applications as precursors in the synthesis of pharmaceutical, agrochemical and cosmetic products,[1] as well as monomers in the synthesis of polythiophenes.[2] In the latter field, the design of polymer backbones bearing a wide variety of functional groups together with well defined chemical and electronic properties requires: (i) the synthesis of 3-substituted thiophene monomers, sometimes through complex and multiple step procedures,[1] and (ii) a polymerization method that has good functional group compatibility; in this context, the classical oxidative polymerization methods cannot be extended to monomers bearing strong electron-withdrawing or donating groups,[2] although the use of oligomeric precursors has recently allowed this obstacle to be circumvented.[3] Several recent developments in the organometallic chemistry of 3-bromothiophene have provided its functionalization by aryl groups in mild conditions, through the chemical[4] or electrochemical[5] formation of 3-thienylzinc species. Electrosynthetic one-step methods have also been developed in our group in order to carry out the synthesis of thiophenes substituted by benzyl, alkenyl and activated alkyl groups in the 3 position.[6]

Alternative polymerization methods have been developed, also based on the synthesis of intermediate organometallic reagents, providing better control of both the conjugation length and the regioregularity of the resulting polymer.[7] In this context, zerovalent nickel complexes were found to undergo fast oxidative addition to 2,5-dibromothiophene to yield a monothienylnickel intermediate that underwent polymerization upon repeated cathodic cycling.[8,9] Yamamoto *et al.* used stoichiometric amounts of a Ni(0) precursor to achieve the preparative scale polymerization of 2,5-dihalothiophenes.[10] The selective synthesis of 5-(bromozincio)-2-bromothiophenes from the corresponding 3-alkyl-2,5-dibromothiophenes has been carried out by Chen and Rieke and these thienylzinc intermediates were found to undergo quantitative polymerization with Pd or Ni catalysts.[11] This procedure was found to yield a high proportion of regioregular HT–HT linkages (HT = head-to-tail) with Ni catalysts. This method has been extended to thiophenes bearing thioalkyl and aryl groups.[12,13] Regioregular poly-3-octylthiophene has recently been obtained from thienylborane derivatives under Suzuki coupling conditions.[14]

It appears that organometallic chemistry provides powerful methods for the functionalization of both the α and β positions of the thiophene ring, allowing the formation of a wide range of 3-substituted monomers together with control of the polymer structure.

The present work deals with the electrochemical stepwise synthesis of 3-substituted thienylzinc species under mild conditions shown in Scheme 1. This work is aimed at providing the simplest access to 3-substituted thienylzinc species with the greatest variety of groups in the 3 position. Step 1 was achieved for several 3-substituted thiophenes using electrochemical procedures recently developed in our group.[5,6] The bromination method (step 2) and the consecutive conversion to thienylzinc species (step 3) were carried out with electrochemical methods that are presented in this paper.



Scheme 1

Experimental

Reagents and methods

N,*N*-Dimethylformamide (DMF), used as solvent, was purchased from SDS (Peypin, France; analytical grade) and used without further purification. Dichloromethane was purchased from SDS and distilled over calcium hydride. 3-Methylthiophene, 2,5-dichloro-3-acetylthiophene and 2,5-dibromothiophene were purchased from Acros or Aldrich Chemicals and used without further purification. 3-Hexylthiophene was prepared by dropwise addition of 3-bromothiophene to a solution of 1-hexylmagnesium bromide in anhydrous diethyl ether.

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^{1}H-NMR (δ relative to TMS) and ^{13}C-NMR (δ relative to TMS) spectra were recorded on a Brucker AC200 NMR spectrometer ($CDCl_3$ solution); mass spectra were measured on a Finnigan GC/MS ITD 800 spectrometer.

Typical bromination procedure

The bromination of 3-substituted thiophenes was achieved using the following procedure. To 40 cm^3 of freshly distilled dichloromethane was added 20 mmol of 3-substituted thiophene, 2 mmol (10 mol%) of tetrabutylammonium bromide and 10 mmol (50 mol%) of methanol. The solution was stirred at room temperature and 40 mmol (2 equiv.) of Br_2 dissolved in dichloromethane (40 cm^3) was added dropwise to the solution. HBr was neutralized afterwards by adding excess triethylamine. After addition of water (100 cm^3), the organic phase was extracted and dried over anhydrous magnesium sulfate. Dichloromethane was then removed by evaporation and the product (2,5-dibromo-3-substituted thiophene) was purified on a silica column using either pentane or pentane–ether (95 : 5) as eluent.

2,5-Dibromo-3-methylthiophene. Initial hydrogenated product: 20 mmol (1.96 g); isolated brominated product: 18 mmol (4.6 g, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.72 (s, 1H), 2.2 (s, 3H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 131.65, 109.93, 108.16, 14.94. MS (EI) *m*/*z* (%): 258 $[M + 2]^+$ (49); 257 $[M + 1]^+$ (15); 256 $[M]^+$ (100); 177 (64); 96 (55); 81 (19); 69 (36).

2,5-Dibromo-3-hexylthiophene. Initial hydrogenated product: 20 mmol (3.36 g); isolated brominated product: 19 mmol (6.19 g, 95%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.66 (s, 1H), 2.40 (t, $J = 7.54$, 2H), 1.43 (m, 2H), 1.19 (m, 6H), 0.78 (t, $J = 6.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 142.74, 130.70, 110.08, 107.70, 31.34, 29.26, 28.56, 22.33, 13.83. MS (EI) *m*/*z* (%): 328 $[M + 2]^+$ (34); 327 $[M + 1]^+$ (12); 326 $[M]^+$ (70); 255 (72); 246 (13); 177 (100); 165 (21).

(2,5-Dibromothiophen-3-yl)acetic acid ethyl ester. Initial hydrogenated product: 20 mmol (3.4 g); isolated brominated product: 18.6 mmol (6.1 g, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.8 (s, 1H), 4.15 (q, $J = 7$, 2H), 3.55 (s, 2H), 1.13 (t, $J = 7$ Hz, 3H). MS (EI) *m*/*z* (%): 316 $[M - 15 + 2]^+$ (46); 314 $[M - 15 + 1]^+$ (81); 312 $[M - 15 - 1]^+$ (41); 257 (57); 255 (100); 253 (44); 235 (93); 233 (87); 205 (9) 176 (13); 154 (11); 95 (7).

2-(2,5-Dibromothiophen-3-yl)propionic acid methyl ester. Initial hydrogenated product: 20 mmol (3.4 g); isolated brominated product: 18.6 mmol (6.11 g, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.84 (s, 1H), 3.78 (q, $J = 7.1$, 1H), 3.60 (s, 3H), 1.32 (d, $J = 7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 173.06, 140.26, 135.44, 128.97, 110.99, 51.98, 39.70, 17.55. MS (EI) *m*/*z* (%): 330 $[M + 2]^+$ (40); 329 $[M + 1]^+$ (14); 328 $[M]^+$ (76); 257 (54); 255 (100); 249 (52); 183; 115; 67.

3-Benzyl-2,5-dibromothiophene. Initial hydrogenated product: 20 mmol (3.48 g); isolated brominated product: 17 mmol (5.65 g, 85%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.18–7.05 (m, 5H), 6.55 (s, 1H), 3.74 (s, 2H). MS (EI) *m*/*z* (%): 334 $[M + 2]^+$ (28); 332 $[M]^+$ (59); 330 $[M - 2]^+$ (27); 253 (39); 251 (35); 172 (100); 127 (85).

2,5-Dibromo-3-phenylthiophene. Initial hydrogenated product: 20 mmol (3.2 g); isolated brominated product: 19 mmol (6.05 g, 95%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.42–7.38 (m, 5 H), 7.4 (s, 1H). MS (EI) *m*/*z* (%): 318 $[M]^+$ (100).

4-(2,5-Dibromothiophen-3-yl)benzoic acid ethyl ester. Initial hydrogenated product: 20 mmol (4.64 g); isolated brominated product: 18 mmol (7 g, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.02 (d, $J = 8.2$, 2H), 7.49 (d, $J = 8.34$, 2H), 6.96 (s, 1H), 4.32 (q, $J = 7.2$, 2H), 1.33 (t, $J = 7.12$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 166.35, 138.04, 131.18, 129.72, 129.49, 128.21, 111.52, 108.47, 60.87, 14.13. MS (EI) *m*/*z* (%): 396 $[M + 4]^+$ (22); 394 $[M + 2]^+$ (54); 392 $[M]^+$ (55); 390 $[M - 2]^+$ (17); 337 (20); 335 (62); 333 (61); 331 (20); 315 (52); 313 (100); 254 (11); 234 (5); 173 (5); 94 (4).

Electrosynthesis of thienylzinc reagents: typical procedure

The electrochemical conversion of 2,5-dibromo-3-substituted thiophenes to the corresponding thienylzinc species has been carried out at 263 K in an undivided cell fitted with a zinc sacrificial anode and a nickel foam cathode. A description of the cell is reported in ref. 15. The DMF (50 cm^3) solution contained 1.5 mmol of tetrabutylamonium tetrafluoroborate as supporting electrolyte, 5 mmol of 2,5-dibromo-3-substituted thiophene, 0.5 mmol of $NiBr_2$bpy (bpy = 2,2′-bipyridine) catalyst (10 mol%) and 2 mmol of $ZnBr_2$. The electrolysis was carried out at a constant current density of 0.1 A (*ca.* 1.5–3 mA cm^{-2}) and the potential of the cathode was monitored *vs.* a calomel saturated electrode during the reaction. The electrolysis was stopped after total consumption of the original 2,5-dibromo-3-substituted thiophene, that is, at a charge corresponding to 2 Faradays per mol of 2,5-dibromo-3-substituted thiophene (*ca.* 1000 C for 5 mmol of original substrate).

The formation of the thienylzinc species was revealed through iodination of aliquots of the solution (0.2 mL) under argon atmosphere, which gives the iodinated analog of the thienylzinc species. Excess I_2 was therefore removed by addition of 1 mL of a saturated sodium thiosulfate aqueous solution. The organic products were extracted with 2 mL Et_2O and analyzed by GC-MS, calibrated using undecane as an internal standard in the DMF solution. Products were also identified by ^{1}H-NMR on a Brucker spectrometer (200 MHz).

Hydrolysis and iodination products

The products arising from either hydrolysis or iodination of the thienylzinc species reported in Table 1 have been "fully" analyzed only for the three examples reported below; as gas chromatography allowed for the fast identification and the determination of the balance between the regioisomers (*i.e.* two distinct peaks); the relative proportions reported in Table 1 were determined only through GC measurements for other species.

2-Bromo-3-methylthiophene. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.05 (d, $J = 5.5$, 1H), 6.67 (d, $J = 5.5$ Hz, 1H), 2.09 (s, 3H). MS (EI) *m*/*z* (%): 178 $[M + 2]^+$ (58); 177 $[M + 1]^+$ (20); 176 $[M]^+$ (55); 97 (100); 69 (17); 53 (16).

2-Bromo-5-iodo-3-methylthiophene. MS (EI) *m*/*z* (%): 305 $[M + 2]^+$ (7); 304 $[M + 1]^+$ (95); 303 $[M]^+$ (11); 302 $[M - 1]^+$ (100); 223 (41); 96 (18).

2-Bromo-3-hexylthiophene. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.02 (d, $J = 5.7$, 1H), 6.628 (d, $J = 5.7$, 2H), 2.4 (t, $J = 7.4$, 2H), 1.4 (m, 2H), 1–1.3 (m, 6H), 0.78 (t, $J = 7.1$ Hz, 3H). MS (EI) *m*/*z* (%): 248 $[M + 1]^+$ (39); 246 $[M - 1]^+$ (38); 205 (11); 178 (20); 177 (53); 176 (21); 175 (43); 167 (39); 100 (11); 98 (99); 97 (100).

2-Bromo-5-iodo-3-hexylthiophene. MS (EI) *m*/*z* (%): 374 $[M]^+$ (100); 372 $[M - 2]^+$ (68); 305 (16); 304 (39); 303 (63); 302 (47); 301 (38); 293 (14); 225 (35); 223 (100); 168 (15); 166 (79); 165 (17); 164 (22); 162 (18); 138 (14); 137 (32).

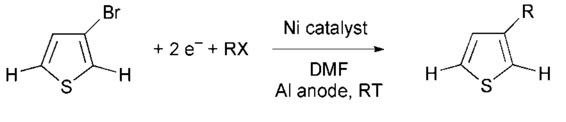
(5-Bromothiophen-3-yl)acetic acid ethyl ester + (2-bromothiophen-3-yl)acetic acid ethyl ester. 5 : **2** = 70 : 30. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: [7.14 (d, $J = 5.6$, **5**) and 6.85 (d, $J = 5.6$,

5) 1H], [6.95 (s, **2**) and 6.92 (s, **2**), 1H], 4.14–4.02 (m, 2H, **2** + **5**), [3.53 (s, **5**) and 3.48 (s, **2**), 2H], 1.18 (t, $J = 7.1$ Hz, 3H, **2** + **5**). MS (EI) m/z (%): 250 $[M + 1]^+$ (25); 248 $[M - 1]^+$ (29); 177 (71); 175 (65); 170 (10); 169 (100); 141 (37); 96 (13).

Results and discussion

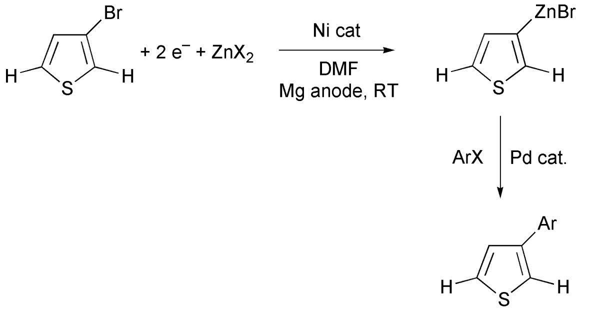
Functionalization of 3-bromothiophene

As mentioned in the introduction, only a few 3-substituted thiophenes are commercially available, due to the difficulty in activating the 3 position of the thiophene ring. For this purpose, we have used two methods, recently developed in our group, to carry out the preparation of some complex 3-alkyl and 3-benzyl thiophenes[6] or 3-aryl thiophenes.[5] The first procedure consists of a one-step electrochemical coupling of 3-bromothiophene with activated alkyl halides or benzyl halides according to:



R = $-CH(Me)CO_2Me$, $-CH_2Ph$

The functionalization of 3-bromothiophene with aryl groups has been carried out through a two-step procedure involving a 3-thienylzinc species:

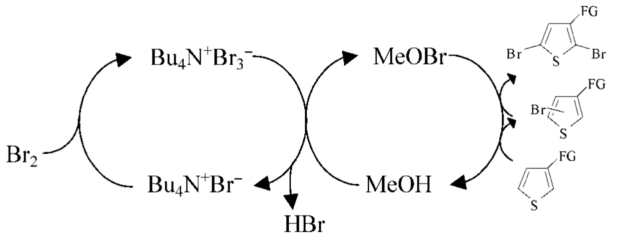


ArX = BrC_6H_4 , 4-$BrC_6H_4CO_2Et$

The 3-substituted thiophenes prepared by both methods are obtained in 50–80% yields, comparable to those already reported.[5,6]

Bromination of 3-substituted thiophenes in the 2 and 5 positions

We first used classical bromination methods[16] reported for thiophenes, using either molecular Br_2 or NBS. In our hands, and from our 3-substituted thiophene precursors, they led to a mixture of the corresponding 5-bromothiophenes and 2,5-dibromothiophenes. We undertook to use a bromination procedure initially developed for anilines,[17] based on the use of catalytic amounts of Bu_4NBr and MeOH, together with stoichiometric amounts of Br_2 in CH_2Cl_2 as solvent. This method allows the stepwise bromination of the 2 and 5 positions of the thiophene ring in excellent yields. A catalytic process is proposed (Scheme 2), similar to that reported for anilines.

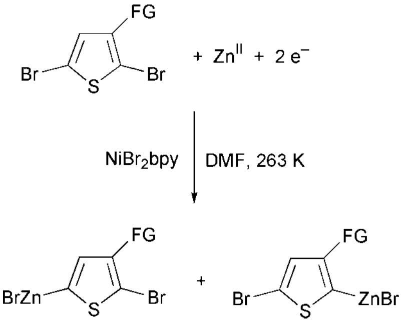


Scheme 2

The resulting 2,5-dibromo-3-substituted thiophenes were identified by ^{1}H-NMR and mass spectrometry. The yields (85–95%) are generally excellent and this method provides a straightforward access to dibrominated thiophenes at room temperature. However, the method failed in brominating thiophenes substituted either with cyano or vinyl groups. In the former case, bromination was not achieved, whereas in the latter case the vinyl position was also brominated.

Electrochemical conversion to thienylzinc species

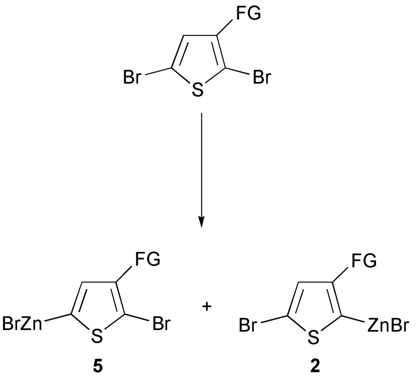
The electrochemical conversion of 2,5-dibromo-3-substituted thiophenes to the corresponding thienylzinc species has been carried out in DMF at 263 K in an undivided cell fitted with a zinc sacrificial anode using catalytic amounts of $NiBr_2bpy$ catalyst. The overall reaction is:



The results are reported in Table 1. The yields are moderate to excellent. Polymerization takes place as a side reaction using 2,5-dibromothiophene as substrate (entry 1). As a matter of fact, in most cases the yields are affected by the formation of the corresponding oligo/polythiophenes. 2,5-Dichloro-3-acetylthiophene (entry 9) is also converted into 2-chloro-3-acetylthiophene (*ca.* 20%). For all other substrates, only traces of hydrogenated products were detected.

A typical evolution of the the substrate and product quantities as a function of electrolysis time is reported in Fig. 1 for

Table 1 Yields and regioselectivity for the conversion of 3-substituted-2,5-dihalothiophenes into thienylzinc species



Entry	FG	Overall yield[a] of **2** + **5** (%)	Regioselectivity[b] **5** : **2**
1	–H	30	—
2	$-CH_3$	75	100 : 0
3	$-n\text{-}C_6H_{13}$	76	100 : 0
4	$-CH_2CO_2Et$	90	70 : 30
5	$-CH(CH_3)CO_2Me$	80	60 : 40
6	$-CH_2C_6H_5$	60	80 : 20
7	$-C_6H_5$	65	70 : 30
8	$-p\text{-}C_6H_4CO_2Et$	45	72 : 28
9	–C(O)Me	45	100 : 0

[a] Yields calculated from GC experiments using an internal standard. [b] Evaluated from both GC and ^{1}H NMR experiments. See text for details.

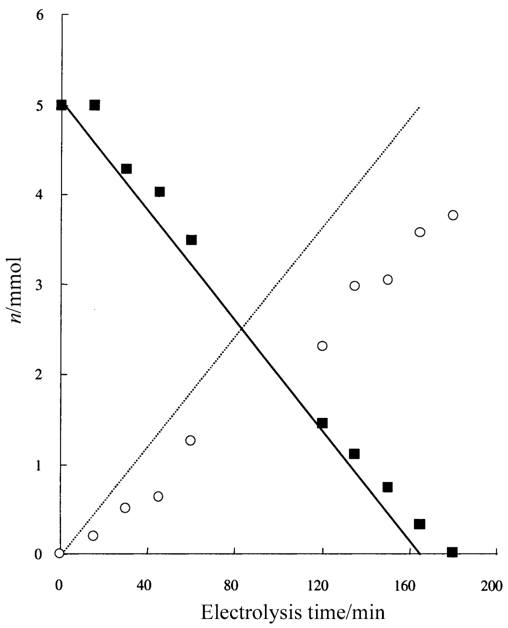
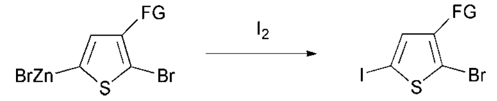


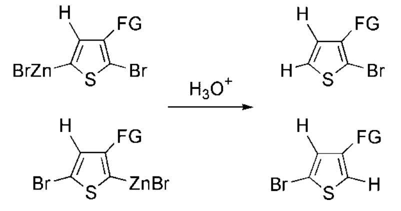
Fig. 1 Evolution of the quantities of 2,5-dibromo-3-hexylthiophene (■) and 2-bromo-5-iodo-3-hexylthiophene (○) as a function of electrolysis time. The solid lines are the theoretical 100% Faradaic consumption (——) and formation (···).

2,5-dibromo-3-hexylthiophene (entry 3). The formation of the thienylzinc species is revealed by quantitative iodination of aliquots of the solution according to:



The consumption of 2,5-dibromo-3-hexylthiophene follows the expected theoretical 2 Faradays per mol slope during the major part of the electrolysis. However, the formation of the corresponding organozinc species takes out from the ideal 100% slope, corresponding to the oligo/polymerization of the thienylzinc species in the presence of nickel salts. Moreover, if the electrolysis is carried out at room temperature, the yield decreases from 76 to 60% for the same substrate (entry 3) and a suspension of brown solid particles is observed at the end of the electrolysis. Rieke's thienylzinc reagents were found to undergo quantitative polymerization in THF in the presence of $NiCl_2$dppe as catalyst.[11] In DMF, the same species remains stable over several hours and this may explain the low proportion of polymer formed.

We have also studied the regioselectivity of the reaction by gas chromatography and ^{1}H-NMR after complete hydrolysis of the DMF solutions. Two thienylzinc regioisomers lead to different hydrolysis products:



The difference between the ^{1}H-NMR coupling constants of aromatic protons for both hydrolyzed species allows the assignment of the signals in the aromatic region and therefore the balance between the regioisomers. These relative proportions were confirmed by two distinct GC signals during the electrolysis.

The main product obtained is generally the 3-substituted 2-bromo-5-(bromozincio)thiophene. The regioisomer, 3-substituted 5-bromo-2-(bromozincio)thiophene, is formed in appreciable amounts for entries 4–8. For entries 4 and 5 the zinc atom could be coordinated by the ester group if located in the 2 position. With phenyl or benzyl groups (entries 6–8) the proportion remains unexplained. Chen and Rieke reported a similar proportion for the phenyl-substituted thiophene in THF.[11] This electrochemical method allows a higher regioselectivity for a thiophene ring substituted with a hexyl group compared to the previously reported ratio of 70 : 30.[11]

The formation of 2,5-di(bromozincio)thiophenes is never observed in significant yields ($<5\%$), even if the electrolysis is continued to a charge corresponding to 4 Faradays per mol. This electrosynthetic process does not allow the consecutive and quantitative insertion of zinc at the second carbon–halogen bond of the thiophene ring.

Conclusion

The synthesis of 3-substituted monothienylzinc species has been achieved using both electrochemical methods and an original and selective bromination method. The very mild and simple conditions used in this stepwise synthesis allow the functionalization of thiophene with a wide variety of groups. Such versatile and selective access to original 3-substituted thienylzinc reagents is of great interest in the further preparation of regioregular 3-substituted polythiophenes.

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