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o-DIRECTED LITHIATION OF ACYLATED HYDROXYTHIOPHENES

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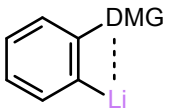
Abstract – *O*-Carbamates derived from 2-hydroxy- and 3-hydroxy-thiophenes generated *o*-directed carbanions, which were transformed to the corresponding methyl sulfides and methyl and trimethylsilyl substituted thiophenes.

Dedicated to Professor Viktoras Sniečkus, an eminent organic chemist and initiator of *Balticum Organicum Syntheticum* (*BOS*), in occasion of his 77th birthday

Directed ortho-metalation (DoM) is one of the most powerful strategies for the synthesis of polysubstituted aromatics.[1] Victor Snieckus was one of the pioneers for employing DoM[2] and its more powerful analog – directed remote metalation (DreM)[3] as the tools in the hands of organic chemists. For the synthesis of furocoumarins,[4] both methods are employed together.

In general, the DoM comprises the deprotonation of a site *ortho*- to a heteroatom-containing directing metalation group (DMG) by a strong base, an alkyllithium reagent, leading to the ortho-lithiated species **A**. Among the most synthetically useful DMGs[1] are tertiary amides[5] and *O*-carbamates.[6]

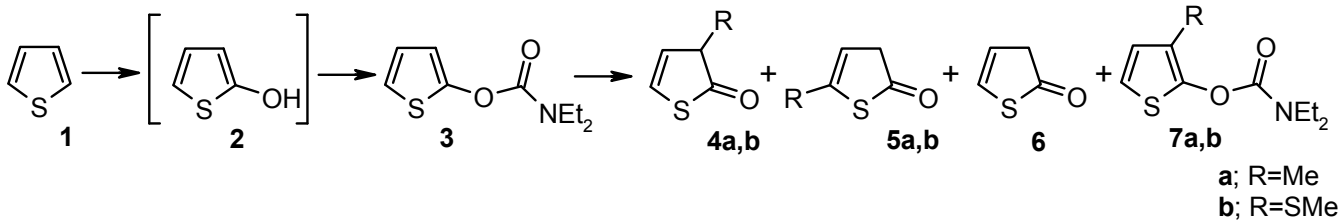


A

The main synthetic potential of DoM reaction is shown on substituted arene *O*-carbamates (benzenes and naphthalenes). Only limited publications are shown for functionalisation of nitrogen heterocycles: pyridines.[7] Deprotonation of unsubstituted thiophenes is going preferentially in 2-position and is reviewed,[8] but functionalized and substituted thiophenes had a lack of information about the directions of lithiation reaction.

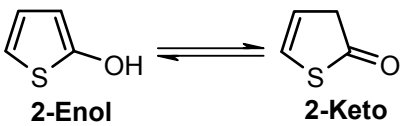
At the same time, some alternatives for functionalisation of thiophenes are known: new C-N bond formation in Buchwald-Hartwig coupling[9] by employing anilines with electron-donating and electron-accepting substituents and β-selective C-H bond arylation of thiophenes with iodoarenes.[10] To the best of our knowledge, there are no systematic deprotonation studies of hydroxythiophenes.

Substituted hydroxythiophenes are good analogs of aromatic compounds as starting materials for new anticancer drug synthesis. Our synthetic aims are connected with functionalized thiophenes as starting materials, keeping the oxygen functionality in thiophene ring, for the synthesis of new heterocyclic systems. Therefore we have used the corresponding *O*-carbamates **3** and **10** prepared from 2-hydroxythiophene **2** (Scheme 1) and 3-hydroxythiophene **9** (Scheme 2) as starting materials for directed *ortho*-lithiation reactions. Better yield (77%) of 2-*O*-carbamate **3** was obtained starting from isolated 2-hydroxythiophene **2**.



Scheme 1

Acetylation of thiophenes **2** and **9** turns to be sluggish because tautomerism of hydroxythiophenes.[11] At the same time there are obvious differences in the tautomerisation process. Thus, ketonization of 2-hydroxybenzothiophenes is 40 times faster than of 3-hydroxybenzothiophenes.[11] Recently the first systematic study of the properties (general stability, tautomerism and NMR spectroscopic parameters) of 3-hydroxythiophene **9** was published.[12] 2-Hydroxythiophene in $CDCl_3$ solution exists in keto form **2-Keto** completely, and therefore acylation reaction was performed in DMF. At the same time, 3-hydroxythiophene in $CDCl_3$ solution exists in **2-Keto** and **2-Enol** form equilibria 74:26.[12]

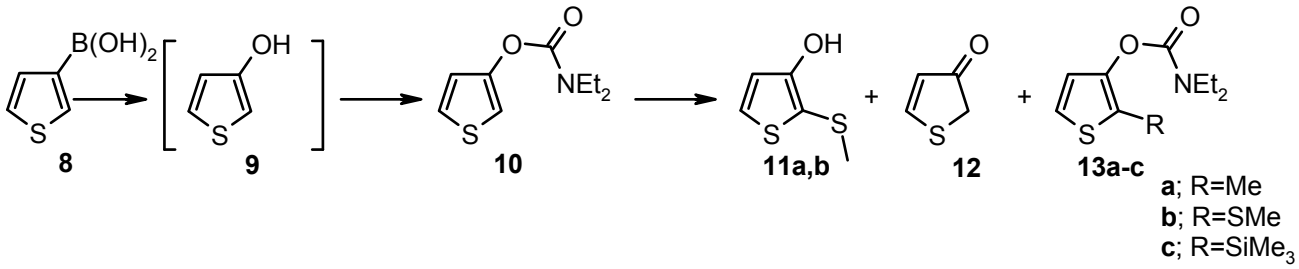


Reaction conditions for lithiation of aryl *O*-carbamates are very important, because higher temperatures are used for the Fries rearrangement of aryl *O*-carbamates.[13] Therefore we have tried to use for thiophene

derivatives standard lithiation conditions applied for *o*-directed metallation of aromatic compounds - with *s*-BuLi at -78 ^{o}C and checked also other lithiation procedures. At the beginning we have deprotonated carbamate **3** with freshly prepared LDA. In all the experiments at -78 °C and at -4 °C, after quenching with MeI as an electrophile only starting materials with some impurities were isolated. Further deprotonation of carbamate **3** with 1.5 eq. of *n*-BuLi in the presence of 1.5 eq. of TMEDA at -8 °C and -30 °C gave a mixture of products, however no more starting material remained. At -78 °C reaction is going more under control and only two products were obtained – deacylation product **6** in the keto- form and 3-methylthiophene **7a** in ratio 40:60 detected after ^{1}H NMR. These results lead us to a conclusion, that even at -78 °C deacylation happens and product **6** is out of expected DoM reaction.

Reaction with *s*-BuLi and TMEDA did not support DoM reaction and only 5-deprotonation as well as deacylation of *O*-carbamate occurred. Thus, obtained compound **5b** exists in a keto form with a characteristic chemical shifts for 3-CH_2 protons: 4.06 as a doublet with J = 3.2 Hz. No *ortho*-directed lithiation products were observed in the case of methylthiolation agent dimethyl disulfide used as an electrofile in the reaction.

Thus, all deprotonation agents (LDA, *n*-BuLi, *s*-BuLi) used in our experiments for substrate **3** partly cleaved *O*-carbamate functionality, and only low yields of *o*-directed lithiation products were obtained. DoM was observed only with *n*-BuLi as a base, but *s*-BuLi deprotonated only 5-position of thiophene ring.



Scheme 2

Simple 3-hydroxythiophenes[14] are often very sensitive and air-unstable and exist in two tautomeric forms. The ratio of keto- and enol-forms depend on the solvent used in the experimental conditions,[12] and simple 3-hydroxythiophenes can react in 2-position. Therefore we have used thiophene *O*-carbamates **3** and **10** as starting materials for two reasons – to investigate *ortho*-directing power of *O*-dimethylcarbamate lithiation directing group and to avoid hydroxythiophene tautomerism. After analysis of results for substrate **3**, we turned to use *n*-BuLi + TMEDA for the 3-hydroxy analog **10** deprotonation studies. First experiments showed that carbamate **10** did not deprotonate with *n*-BuLi at -78 °C, therefore we

performed reactions at higher temperatures. Thus, reaction of carbamate **10** with 1.1 eq. of *n*-BuLi and 1.1.eq. of TMEDA at -30 °C and quenching of obtained carbanion with MeI, two products were obtained – expected 2-methylthiophene **13a** (68%) and deacylated ketone **12** (17%). Quenching of obtained *o*-lithiation directed carbanion with dimethyldisulfide gave 2 products – 2-methylthiothiophenes **11b** (33%) and **13b** (37%). Only TMS-Cl as an electrophile gave 2-TMS thiophene **13c** as a sole product in 38% yield. Increase of the reaction temperature to 0 °C, did not improve the yields of target thiophenes **13a-c**. Moreover, reaction mixtures became more complicated, because of the side reactions - Fries rearrangement and *O*-carbamate deacylation.

Thus, *O*-carbamates derived from 2-hydroxy- and 3-hydroxythiophenes in contrary to the corresponding benzene derivatives[1] generated *o*-directed carbanions only with *n*-BuLi and TMEDA at -78 °C and -30 °C, correspondingly. These generated carbanions were transformed to the corresponding methyl sulfides, methyl and trimethylsilyl substituted thiophenes in moderate yields.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury plus 400 (400 MHz) spectrometer, internal standard was TMS (solvent $CDCl_3$). The ^{13}C NMR spectra were recorded on a Varian Mercury plus 400 (400 MHz) spectrometer, internal standard was $CHCl_3$ (δ 77.0 ppm). TLC was carried out on DC Alufolien plates of Kieselgel 60. Column chromatography was carried out on Kieselgel (Acros), 0.023 – 0.070 mm, pore diameter ca 6 nm. Dichloromethane was distilled from CaH_2. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from Na/benzophenone. Thiophene and thiophen-3-ylboronic acid were purchased from Acros. 2-Hydroxythiophene **1** was prepared after the patent procedure.[15]

2-Diethylcarbamoyloxythiophene (3)

To an ethereal solution (6 mL) of thiophene (0.96 mL, 11.9 mmol) was added *n*-BuLi (1.8M solution in hexanes, 6.6 mL, 11.9 mmol) at room temperature and stirred for 40 min. Then reaction mixture was cooled to -78 ^{o}C and triethylborate (2.92 mL, 16.6 mmol) was added and stirred at -78 °C for 2 h. The cold bath was removed and 30% aqueous H_2O_2 (3.0 mL) was added dropwise at -50 °C and reaction mixture was allowed reflux. After addition the solution was allowed to reflux for additional 30 min. Reaction mixture was acidified with 6N HCl to pH=1. The resulted mixture was extracted with Et_2O (3x10 mL) and combined ethereal solution was washed with 10% aqueous ferrous ammonium sulfate solution (10 mL), washed with water (10 mL), and dried over Na_2SO_4. Et_2O was removed by heating to 42 °C (with no vaccum). Thiophen-2-ol as an orange ethereal solution was used immediately in the next reaction. To the obtained thiophen-2-ol solution was added anhydrous DMF (10 mL) and DABCO (1.85 g, 16.5 mmol) and stirred for 30 min at room temperature. Diethylcarbamoyl chloride (2.10 mL, 16.5

mmol) was added and dark solution was stirred for 17 h. The reaction was quenched with water (50 mL), extracted with EtOAc (3x15 mL), combined EtOAc solution was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (eluent 1:9 EtOAc – petroleum ether) to yield 2-diethylcarbamoyloxythiophene (1.12 g, 51%) as a yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16-1.28 (m, 6H), 3.34-3.46 (m, 4H), 6.62 (dd, *J* = 1.7, 3.7 Hz, 1H), 6.79 (dd, *J* = 3.7, 5.8 Hz, 1H), 6.83 (dd, *J* = 1.7, 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.19, 14.13, 41.92, 42.53, 112.43, 117.49, 123.11, 152.66, 153.33.

5-Methylthio-3*H*-thiophen-2-one (5b)

TMEDA (0.15 mL, 0.98 mmol) was dissolved in dry THF (2 mL) and cooled to -78 °C, *s*-BuLi (1.3 M solution in cyclohexane, 0.75 mL, 0.98 mmol) was added and stirred for 1 h at -78 °C. Then 2-diethylcarbamoyloxythiophene (**3)** (0.13 g, 0.65 mmol) solution in dry THF (2 mL) was added dropwise and reaction mixture was stirred at -78 °C for 2 h. Me_2S_2 (87 μL, 0.98 mmol) was added at -78 °C and stirred for 40 min and the reaction mixture was allowed to warm to room temperature and then stirred overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), extracted with EtOAc (3x10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent 1:4 EtOAc – petroleum ether) to yield 5-methylthio-3*H*-thiophen-2-one (29 mg, 31%) as a slightly yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.06 (d, *J* = 3.2 Hz, 2H), 6.87 (d, *J* = 3.2 Hz, 1H).

3-Methyl-2-diethylcarbamoyloxythiophene (7a)

TMEDA (0.11 mL, 0.75 mmol) was dissolved in dry THF (2 mL) and cooled to -78 °C, *n*-BuLi (1.8 M solution in hexanes, 0.42 mL, 0.75 mmol) was added and stirred for 40 min at -78 °C. Then 2-diethylcarbamoyloxythiophene (**3**; 0.10 g, 0.50 mmol) solution in dry THF (1 mL) was added dropwise and reaction mixture was stirred at -78 °C for 2 h. MeI (50 μL, 0.75 mmol) solution in the dry THF (0.3 mL) was added at -78 °C and stirred for 40 min and the reaction mixture was allowed to warm to room temperature and stirred overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), extracted with EtOAc (3x10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent 1:9 EtOAc – petroleum ether) to yield 3-methyl-2-diethylcarbamoyloxythiophene (12 mg, 11%) as a slightly yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 2.11 (s, 3H), 3.40 (q, *J* = 7.0 Hz, 2H), 3.44 (q, *J* = 7.0 Hz, 2H), 6.66 (d, *J* = 5.8 Hz, 1H), 6.78 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.85, 13.27, 14.10, 41.99, 42.58, 116.32, 122.13, 126.22, 146.96, 152.75.

3-Diethylcarbamoyloxythiophene (10)

To an ethereal solution (10 mL) of thiophen-3-ylboronic acid (0.50 g, 3.91 mmol) was added 10% aqueous H_2O_2 (3.0 mL) and the reaction mixture was refluxed for 2 h and the layers were separated. The aqueous layer was extracted with Et_2O (2x5 mL) and combined ethereal solution was washed with 10% aqueous ferrous ammonium sulfate solution (10 mL), washed with water (10 mL), and dried over Na_2SO_4. Et_2O was removed by heating to 42 °C (with no vaccum). Thiophen-3-ol[16] (**9**) as an orange ethereal solution was used immediately in the next reaction. To the obtained thiophen-3-ol Et_2O solution was added anhydrous DMF (5.0 mL) and DABCO (0.44 g, 3.91 mmol) and stirred for 1 h at room temperature. Diethylcarbamoyl chloride (0.53 g, 3.91 mmol) was added and dark solution was stirred for 1 h. After completion of the reaction, it was quenched with water (10 mL), extracted with EtOAc (3x5 mL), combined EtOAc solution was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (eluent 1:9 EtOAc – petroleum ether) to yield 3-diethylcarbamoyloxythiophene (0.41 g, 53%) as a colorless liquid.

IR (neat) 1721, 2975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15-1.30 (m, 6H), 3.33-3.47 (m, 4H), 6.93 (dd, J = 1.4, 5.3 Hz, 1H), 7.02 (dd, J = 1.4, 3.4 Hz, 1H), 7.21 (dd, J = 3.4, 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.30, 14.16, 41.89, 42.28, 109.97, 121.72, 123.78, 147.98, 153.48.

2-Methyl-3-diethylcarbamoyloxythiophene (13a)

TMEDA (66 µL, 0.44 mmol) was dissolved in dry THF (1.5 mL) and cooled to -30 °C. *n*-BuLi (1.8 M solution in hexanes, 0.25 mL, 0.44 mmol) was added and stirred for 10 min at -30 °C before 3-ethylcarbamoyloxythiophene (**10**; 80 mg, 0.40 mmol) solution in dry THF (0.5 mL) was added dropwise and reaction mixture was stirred at -30 °C for 2 h. MeI (28 µL, 0.44 mmol) solution in dry THF (0.2 mL) was added to the generated thiophene carbanion. After 1 h at -30 °C reaction mixture was allowed to reach room temperature in 40 min, and quenched with saturated aqueous NH_4Cl (5 mL), extracted with EtOAc (3x5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent 1:9 EtOAc – petroleum ether) to yield 2-methyl-3-diethylcarbamoyloxythiophene (40 mg, 47%) as light yellow liquid.

IR (neat) 1718, 2975 cm^{-1}; H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 6H), 3.40 (m, 4H), 2.29 (s, 3H), 6.84 (d, J = 5.4 Hz, 1H), 6.98 (d, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.09, 13.30, 14.14, 41.89, 42.31, 119.84, 122.34, 123.66, 144.13, 153.62.

2-Methylthio-3-hydroxythiophene (11b) and 2-methylthio-3-diethylcarbamoyloxythiophene (13b)

TMEDA (0.7 mL, 0.44 mmol) was dissolved in dry THF (10 mL) and cooled to -30 °C. *n*-BuLi (1.8 M

solution in hexanes, 2.5 mL, 4.42 mmol) was added and stirred for 10 min at -30 °C before 3-ethylcarbamoyloxythiophene (**10**; 0.80 g, 4.01 mmol) solution in dry THF (1.0 mL) was added dropwise and reaction mixture was stirred at -30 °C for 2 h. Me_2S_2 (0.4 mL, 4.42 mmol) was added to the generated thiophene carbanion. After 1 h at -30 °C reaction mixture was allowed to reach room temperature overnight, and quenched with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (3x10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent CH_2Cl_2) to yield 2-methylthio-3-diethylcarbamoyloxythiophene **13b** (0.37 g, 37%) as a slightly yellow liquid and 2-methylthio-3-hydroxythiophene **11b** (0.20 g, 34%) as a light liquid.

11b: IR (neat) 1535, 2920, 3429 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 5.89 (s, 1H), 6.74 (d, *J* = 5.8 Hz, 1H), 7.22 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR δ 22.09, 107.26, 118.05, 127.67, 156.56.

13b: IR (neat) 1732, 2932 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 3.39 (q, *J* = 7.0 Hz, 2H), 3.47 (q, *J* = 7.0 Hz, 2H), 6.96 (d, *J* = 5.8 Hz, 1H), 7.24 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.32, 14.13, 21.16, 42.16, 42.43, 121.38, 122.90, 125.69, 149.56, 153.25.

2-Trimethylsilyl-3-diethylcarbamoyloxythiophene (13c)

TMEDA (83 μL, 0.55 mmol) was dissolved in dry THF (1.5 mL) and cooled to -30 °C. *n*-BuLi (1.8 M solution in hexanes, 0.31 mL, 0.55 mmol) was added and stirred for 10 min at -30 °C before 3-ethylcarbamoyloxythiophene (**10**; 100 mg, 0.50 mmol) solution in dry THF (0.5 mL) was added dropwise and reaction mixture was stirred at -30 °C for 2 h. MeSiCl (70 μL, 0.55 mmol) solution in dry THF (0.2 mL) was added to the generated thiophene carbanion. After 1 h at -30 °C reactions mixture was allowed to reach room temperature in 40 min, and was quenched with saturated aqueous NH_4Cl (5 mL), extracted with EtOAc (3x5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent 1:9 EtOAc – petroleum ether) to yield 2-trimethylsilyl-3-diethylcarbamoyloxythiophene (51 mg, 38%) as a light liquid.

IR (neat) 1723, 2973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 3.38 (q, *J* = 7.1 Hz, 2H), 3.44 (q, *J* = 7.0 Hz, 2H), 7.00 (d, *J* = 5.0 Hz, 1H), 7.42 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -0.53, 13.26, 14.18, 41.63, 42.04, 122.75, 123.67, 128.91, 153.73, 153.84.

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