A Directed Metalation Approach to 2-Trialkylammoniomethyl-3-(trimethylsilylmethyl)thiophene Iodides: Precursors to 2,3-Bis(methylene)-2,3-dihydrothiophene[1]

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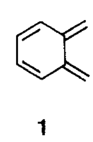
Syntheses of precursors to 2,3-bis(methylene)-2,3-dihydrothiophene (**2**) are described. As key step, a lithiation reaction using secondary carboxamido functionality as directing group is used.

The generation and synthetic utility of 5,6-bis(methylene)-1,3-cyclohexadiene (*o*-quinodimethane, *o*-xylylene, **1**) is well documented in the literature.[4] However, thiophene analogues of **1** have received relatively little attention. Recently several groups including ours have reported the generation of the thiophene analogue **2**.[5-10] A particularly mild generation of **2** has been accomplished by a fluoride ion induced 1,4-elimination process from salt **3**.[9]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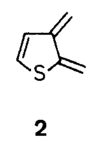
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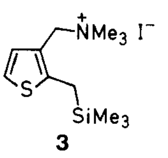

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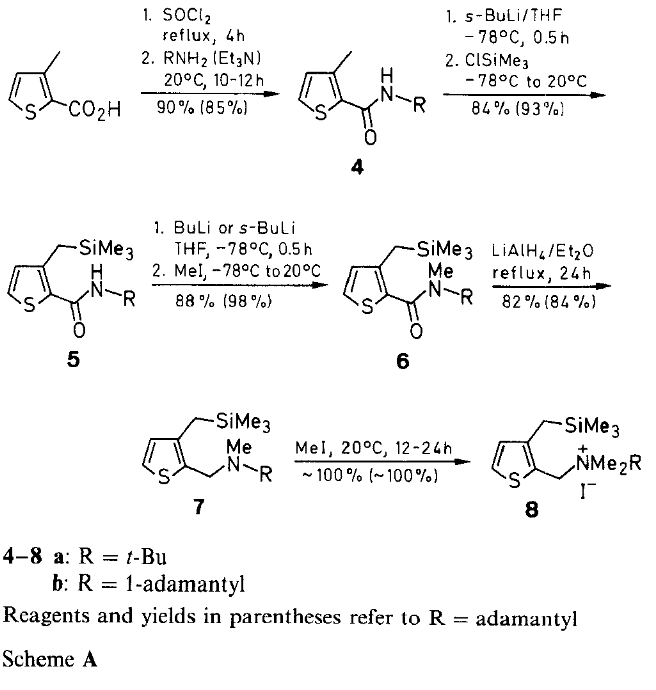
In response to this communication by van Leusen and van den Berg,[9] we are prompted to report the syntheses of 2-trialkylammoniomethyl-3-(trimethylsilylmethyl)thiophene iodides **8**, which have the opposite regiochemical substitution pattern to salt **3**, and which the aforementioned authors reported they had been unable to prepare.[11]

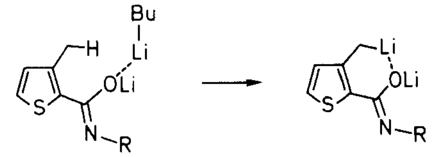
The syntheses of salts **8** commence from commercially available 3-methyl-2-thiophenecarboxylic acid (Scheme A). Conversion to secondary amides **4** is routinely carried out on multigram scale (typically 20 g of acid). Regiospecific lithiation at C-3 methyl group of carboxamides **4** is directed by the amidate anion formed on addition of the first equivalent of organolithium reagent[12] (Scheme **B**).



4–8 a: R = *t*-Bu
b: R = 1-adamantyl

Reagents and yields in parentheses refer to R = adamantyl

Scheme A



Scheme **B**

Subsequent reaction of the dilithio species with chlorotrimethylsilane proceeds smoothly to give **5**. Conversion of silylated secondary amides **5** into the corresponding tertiary amides **6**, reduction to the amines **7**, and finally *N*-alkylation, constitutes a high yielding synthetic procedure [55% (67%) overall from 3-methyl-2-thiophenecarboxylic acid] for the preparation of precursors **8**[13] to 2,3-bis(methylene)-2,3-dihydrothiophene (**1**) (Scheme A).

Further work on the chemistry of **8** will be reported elsewhere.[14]

Product purity was checked by TLC on Merck 10 × 2 cm aluminium-backed plates with an 0.2 mm layer of Kieselgel 60 F_{254}. Flash column chromatography was carried out using Macherey-Nagel MN-Kieselgel 60, and dry flash column chromatography was carried out using Merck Kieselgel 60 H. Solvents were dried and distilled prior to use: Et_2O and THF from sodium/benzophenone; hexane, petroleum ether (PE) (bp 60–80 °C) and CH_3CN from CaH_2. Organolithium reagents were purchased from Lithium Corporation of Europe and from Aldrich Chemical Company, and were standardised prior to use.[15] Melting points were determined on a Köfler block and are uncorrected. Microanalyses were performed in the University of Liverpool Microanalyses Laboratory. ^1H-NMR spectra were recorded, either on a Perkin-Elmer R34 (220 MHz), Bruker WM 250 (250 MHz), or a Jeol JMN-PMX 60 (60 MHz) spectrometer. IR spectra were recorded on Perkin-Elmer 298 and 1720 FT spectrophotometers. Mass spectra were obtained on VG Micromass 7070E and AEI MS 902 mass spectrometers.

2-*tert*-Butylcarboxamido-3-methylthiophene (4a):

3-Methyl-2-thiophenecarboxylic acid (20 g, 0.14 mol) is refluxed with thionyl chloride (ca 100 mL) for 4 h. Excess of thionyl chloride is removed *in vacuo* and the residue is dissolved in CH_2Cl_2 (200 mL). *tert*-Butylamine (20.5 g, 0.28 mol) is added dropwise with the reaction temperature maintained below 10 °C. When addition of the amine is complete, the mixture is stirred at r. t. for 16 h. The solution is washed with water (3 × 30 mL) and separated. The aqueous washings are basified to pH 11 with 40% aq KOH and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts are dried ($MgSO_4$) and evaporated. The crude product is purified by dry flash chromatography (eluent: EtOAc/PE, 1 : 20) to give the pure amide **4a** as a waxy solid; yield: 24.83 g (90%); mp 32–34 °C (Lit.[16] mp 32–34 °C).

IR (film): $\nu = 1640\ cm^{-1}$ (C=O).

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 1.44$ (s, 9H, t-C_4H_9), 2.47 (s, 3H, CH_3), 5.67 (br, 1H, NH), 6.82 (d, 1H, $J = 5.04$ Hz, H-4), 7.16 (d, 1H, $J = 5.04$ Hz, H-5).

MS: $m/z = 197$ (M^+, 24), 149 (38), 125 (100), 69 (25).

2-(1-Adamantylcarboxamido)-3-methylthiophene (4b):

The procedure as described for **4a** can be followed, the only deviation being the mixing of equimolar amounts of acid chloride and 1-adamantanamine in the presence of 1.5 molar equivalents of Et_3N. Purification by recrystallisation from EtOAc/PE gives the pure amide **4b** as white crystals; yield: 85%; mp 123–124 °C.

$C_{16}H_{21}NOS$ calc. C 69.79 H 7.69 N 5.09
(275.4) found 69.69 7.83 5.00

IR (KBr): $\nu = 1620\ cm^{-1}$ (C=O).

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 1.71$ (m, 6$H_{adamantyl}$), 2.09 (m, 9$H_{adamantyl}$), 2.48 (s, 3H, CH_3), 5.97 (br, 1H, NH), 6.85 (d, 1H, $J = 5.02$ Hz, H-4), 7.21 (d, 1H, $J = 5.02$ Hz, H-5).

MS: $m/z = 275$ (M^+, 67), 260 (10), 242 (30), 218 (69), 125 (100).

2-*tert*-Butylcarboxamido-3-(trimethylsilylmethyl)thiophene (5a); Typical Procedure:

To the amide **4a** (4 g, 20.3 mmol) in THF (150 mL) at −78 °C is added s-BuLi (40.6 mmol). The mixture is stirred at −78 °C for 0.5 h, after which time $ClSiMe_3$ (9.02 mL, 71.05 mmol) is added. After stirring at −78 °C for a further 0.25 h, it is then allowed to warm to r.t. THF is removed *in vacuo* and EtOAc (150 mL) and water (20 mL) are added to the residue. The organic phase is washed with water (2 × 20 mL), brine (1 × 20 mL), and dried ($MgSO_4$). Evaporation of the solvent gives the crude product as a dark oil. Purification by bulb-to-bulb distillation affords the pure amide **5a** as a clear liquid; yield: 4.58 g (84%); bp 185 °C/0.13 mbar. On cooling a waxy white solid is obtained; mp 26–28 °C.

$C_{13}H_{23}NOSSi$ calc. C 57.94 H 8.60 N 5.20
(269.5) found 57.92 8.70 4.95

IR (film): $\nu = 1650\ cm^{-1}$ (C=O).

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.44$ [s, 9H, $Si(CH_3)_3$], 1.89 (s, 9H, t-C_4H_9), 3.05 (s, 2H, CH_2), 6.73 (d, 1H, $J = 6.19$ Hz, H-4), 7.17 (d, 1H, $J = 6.19$ HZ, H-5).

MS: $m/z = 269$ (M^+, 19), 212 (33), 73 (100), 57 (22).

5b; yield: 93%; white solid; mp 102–104 °C (PE).

$C_{19}H_{29}NOSSi$ calc. C 65.65 H 8.41 N 4.03
(347.6) found 65.79 8.56 3.91

IR (KBr): $\nu = 1646\ cm^{-1}$(C=O).

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.28$ [s, 9H, $Si(CH_3)_3$], 2.00 (m, 6$H_{adamantyl}$), 2.38 (m, 9$H_{adamantyl}$), 2.86 (s, 2H, CH_2Si), 6.68 (d, 1H, $J = 5.85$ Hz, H-4), 7.12 (d, 1H, $J = 5.85$ Hz, H-5).

MS (70 eV): $m/z = 347$ (M^+, 21), 332 (70), 314 (22), 135 (100), 73 (36).

2-*tert*-Butyl(methyl)carboxamido-3-(trimethylsilylmethyl)thiophene (6a); Typical Procedure:

To the secondary amide **5a** (3.5 g, 13.01 mmol) in THF (100 mL) at −78 °C is added BuLi (13.01 mmol). The mixture is stirred at 78 °C for 0.5 h, after which time MeI (8.10 mL, 0.13 mmol) is added and the mixture is allowed to warm r.t. After stirring for a further 14 h, the THF is removed *in vacuo* and EtOAc (150 mL) and water (20 mL) are added to the residue. The organic phase is washed with water (2 × 10 mL), brine (1 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and subsequent bulb-to-bulb distillation gives the pure tertiary amide **6a** as a clear liquid; yield: 3.24 g (88%); bp 180 °C/0.2 mbar. On cooling a waxy white solid is obtained; mp 52–54 °C.

$C_{14}H_{25}NOSSi$ calc. C 59.31 H 8.89 N 4.94
(283.5) found 58.99 9.11 4.62

IR (film): $\nu = 1630\ cm^{-1}$ (C=O).

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.40$ [s, 9H, $Si(CH_3)_3$], 1.90 (s, 9H, t-C_4H_9), 2.79 (s, 2H, CH_2), 3.42 (s, 3H, NCH_3), 6.66 (d, 1H, $J = 4.83$ Hz, H-4, 7.19 (d, 1H, $J = 4.83$ Hz, H-5).

MS: $m/z = 283$ (M^+, 5), 268 (6), 73 (100), 57 (21).

6b; yield: 98% (the above procedure works best when s-BuLi is used); white solid; mp 107–108 °C (PE).

$C_{20}H_{31}NOSSi$ calc. C 66.43 H 8.64 N 3.87
(361.6) found 66.49 8.78 3.71

IR (KBr): $\nu = 1635\ cm^{-1}$ (C=O).

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.49$ [s, 9H, $Si(CH_3)_3$], 2.23 (m, 6$H_{adamantyl}$), 2.64 (m, 4$H_{adamantyl}$), 2.75 (m, 7H, CH_2Si + 5$H_{adamantyl}$), 3.13 (s, 3H, NCH_3), 6.80 (d, 1H, $J = 4.43$ Hz, H-4), 7.33 (d, 1H, $J = 4.43$ Hz, H-5).

MS: $m/z = 361$ (M^+, 19), 346 (22), 328 (18), 226 (14), 197 (19), 135 (100), 73 (30).

2-*tert*-Butyl(methyl)aminomethyl-3-(trimethylsilylmethyl)thiophene (7a); Typical Procedure:

A solution of tertiary amide **6a** (2.85 g, 10.0 mmol) in Et_2O (35 mL) is added dropwise to a suspension of $LiAlH_4$ (0.77 g, 20.0 mmol) in Et_2O. The mixture is then refluxed for 24 h. After cooling, EtOAc is added until no further effervescence is observed. Water (ca. 10 mL) is added and the slurry is filtered under suction, the residues being repeatedly washed with EtOAc and water (ca 100 mL of a 4:1 mixture). The filtrate is separated, the organic layer washed with water (2 × 20 mL), and dried ($MgSO_4$). Removal of solvent *in vacuo* with subsequent bulb-to-bulb distillation gives the pure amine **7a** as a clear oil; yield: 2.20 g (82%); bp 150 °C/0.13 mbar.

$C_{14}H_{27}NSSi$ calc. C 62.38 H 10.10 N 5.20
(269.5) found 62.05 10.29 4.89

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.27$ [s, 9H, $Si(CH_3)_3$], 1.41 (s, 9H, t-C_4H_9), 2.32 (s, 2H, CH_2Si), 2.45 (s, 3H, NCH_3), 3.82 (s, 2H, CH_2N), 6.64 (d, 1H, $J = 4.87$ Hz, H-4), 7.05 (d, 1H, $J = 4.87$ Hz, H-5).

MS: $m/z = 269$ (M^+, 16), 255 (86), 167 (26), 73 (100).

7b; yield: 84%; decomposes on attempted distillation. The product is obtained as spectroscopially pure oil and can be used directly for the next step.

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.24$ (s, 9H, $Si(CH_3)_3$), 1.80 (m, 6$H_{adamantyl}$), 1.92–2.26 (m, 11H, CH_2Si + 9$H_{adamantyl}$), 2.37 (s, 3H, NCH_3), 3.77 (s, 2H, CH_2N), 6.62 (d, 1H, $J = 4.98$ Hz, H-4), 7.02 (d, 1H, $J = 4.98$ Hz, H-5).

MS: $m/z = 255$ (18), 182 (59), 135 (27), 99 (67), 73 (100).

HRMS: $m/z = 347.2109$ (M^+, 14), $C_{20}H_{33}NSSi$ requires 347.2103.

2-*tert*-Butyl(dimethyl)ammoniomethyl-3-(trimethylsilylmethyl)-thiophene Iodide (8a); Typical Procedure:

Tertiary amine **7a** (2.0 g, 7.43 mmol) is stirred with a large excess of MeI (10 mL) for 12 h, after which time the excess of methyl iodide is removed *in vacuo*. The crude product is washed with PE (3 × 30 mL) to give the salt **8a** yield: 3.05 g (~ 100%) as a pale yellow solid; mp 116–118 °C (dec).

$C_{15}H_{30}INSSi$ calc. C 43.78 H 7.35 N 3.41
(411.5) found 43.71 7.19 3.22

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.33$ [s, 9H, $Si(CH_3)_3$], 2.04 (s, 9H, t-C_4H_9), 2.46 (s, 2H, CH_2Si), 3.37 [s, 6H, $N(CH_3)_2$], 4.85 (s, 2H, CH_2N); 6.80 (d, 1H, $J = 5.43$ Hz, H-4), 7.42 (d, 1H, $J = 5.43$ Hz, H-5).

MS: $m/z = 284$ ($M^+ - I$, 4), 269 (11), 197 (62), 73 (100).

8b; yield: ~ 100%; pale yellow solid; mp 120–122 °C (dec).

$C_{21}H_{36}INSSi$ calc. C 51.52 H 7.41 N 2.86
(489.6) found 51.70 7.42 2.99

^{1}H-NMR ($CDCl_3$/CH_2Cl_2 as internal standard): $\delta = 0.43$ (s, 9H, $Si(CH_3)_3$), 2.18 (m, 6$H_{adamantyl}$), 2.56–2.85 (m, 11H, CH_2Si +

9 $H_{adamantyl}$), 3.45 [s, 6 H, $N(CH_3)_2$], 4.92 (s, 2 H, CH_2N), 6.81 (d, 1 H, $J = 5.04$ Hz, H-4), 7.43 (d, 1 H, $J = 5.04$ Hz, H-5).

MS: $m/z = 362$ ($M^+ - I$, 6), 347 (11), 197 (51), 73 (100).

We thank the S.E.R.C. for financial support and Synthetic Chemicals for a generous gift of 3-methyl-2-thiophenecarboxylic acid.

Received: 23 March 1990; revised: 14 May 1990

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