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

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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 (α-quinodimethane, α-xylene, 1) is well documented in the literature. 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

![Image](image)

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-thiophencarboxylic acid (Scheme A). Conversion to secondary amides 4 is routinely carried out on multigram scale (typically 20 g of acid). Regional specific lithiation at C-3 methyl group of carboxamides 4 is directed by the amidate anion formed on addition of the first equivalent of organolithium reagent¹² (Scheme B).

![Image](image)

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-thiophencarboxylic acid] for the preparation of precursors 8¹³ 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 F₂₅₄. 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: Et₂O and THF from sodium/benzophenone; hexane, petroleum ether (PE) (bp 60–80°C) and CH₂CN from CaH₂. 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 Kofler block and are uncorrected. Microanalyses were performed in the University of Liverpool Microanalyses Laboratory.¹¹¹-H NMR spectra were recorded, either on a Perkin–Elmer R34 (220 MHz), Bruker WM 250 (250 MHz), or a Jeol JNM–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-thiophencarboxylic 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 CH₂Cl₂ (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 CH₂Cl₂ (2 × 50 mL). The combined organic extracts are dried (MgSO₄) 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): ν = 1640 cm⁻¹ (C=O).

Reagents and yields in parentheses refer to R = adamantyl

Scheme A
2-(1-Adamantylcarboxamido)-3-methylthiophene (4b): The procedure as described for 4a can be followed, but only deviation being the mixing of equimolar amounts of acid chloride and 1-adamantamidine in the presence of 1.5 molar equivalents of Et$_3$N. Purification by recrystallisation from EtOAc/PE gives the pure amide 4b as white crystals; yield: 85%; mp 123–124°C. C$_{24}$H$_{32}$NOSi calc. C 79.61, H 6.97, N 5.09 (275.4) found 79.61 7.01 5.00 IR (KBr): ν = 1620 cm$^{-1}$ (C=O).

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 CI$_3$SiMe$_2$ (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 x 20 mL), brine (1 x 20 mL), and dried (MgSO$_4$). Evaporation of the solvent gives the pure 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 solid is obtained; mp 26–28°C. C$_{31}$H$_{35}$NOSi calc. C 75.94 H 8.60 N 5.20 (269.5) found 75.92 8.70 4.95 IR (film): ν = 1630 cm$^{-1}$ (C=O).

2-Tert-Butyl(1-adamantyl)aminomethyl-3-(trimethylsilylmethyl)thiophene (7a); Typical Procedure:
A solution of tertiary amide 6a (2.85 g, 10.0 mmol) in Et$_2$O (35 mL) is added dropwise to a suspension of LiAlH$_4$ (0.77 g, 20.0 mmol) in Et$_2$O. 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 x 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.

2-Tert-Butyl(1-adamantyl)aminomethyl-3-(trimethylsilylmethyl)thiophene (7a)
9H$_{\text{ adamantane}}$, 3.45 [s, 6 H, N(CH$_2$)$_3$], 4.92 (s, 2 H, CH$_2$N), 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$^+$ - 1, 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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(4) For a recent review, see:
(11) 2-(Diethyl(methyl)ammoniomethyl)-3-(trimethylsilylmethyl)-thiophenene iodide has been independently prepared from 3-methyl-2-thiophene-carboxylic acid by a somewhat different approach to that described in this paper. van Leusen, A.M.; van den Berg, K.J., personal communication, 1990. Submitted for publication to Rec. Trav. Chim. Pays-Bas.
(12) For an account of amidate anion directed lithiation at C-3 in thiophenes, see:
(13) For a similar approach to 1, see:
(14) Plant, A.; Chadwick, D.J. unpublished results.