Lithiation of a Pyrrolo-Annulated Tetrathiafulvalene

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Received 3 June 2004

Abstract: Mono- and bis-lithiations of N-tosyl monopyrrolo-tetrathiafulvalene provide novel methods for the introduction of substituents, such as alkyl and halogens, into the 4- and 6-positions of monopyrrolo-tetrathiafulvalenes.

Key words: carbanions, halogenation, organometallic, pyrrole, tetrathiafulvalene

Derivatives of tetrathiafulvalene1 (TTF, 1, Figure 1) have received much interest during the past three decades on account of their unique redox properties and their ability to form electrically conducting materials. In the past years, there has been a growing interest in utilizing TTF derivatives as the redox active component in molecular, macromolecular, and supramolecular systems. The progress in molecular, macromolecular, and supramolecular TTF chemistry has been revolutionized by an ongoing development of new TTF building blocks and has transformed complicated TTF systems such as cyclophanes,2 chemical sensors,3 catalysts,4 shuttles/switches,5 and devices6 from chemical curiosities into a vibrant area of modern-day research. Recently, two of us developed an efficient synthesis of monopyrrolo[3,4-d]tetrathiafulvalene (MPTTF) derivatives 2 (Figure 1) using a nonclassical and simple pyrrole synthesis.7 On account of effective N- and S-alkylations, it has been possible to functionalize (Figure 2a) the MPTTF unit in the 5-, 4-, and 5′-positions and several cyclophanes,8 and amphiphilic bistable [2]rotaxanes9 have been prepared from MPTTF building blocks. However, functionalization of the 4- and 6-positions (Figure 2b) in MPTTF derivatives have until now virtually been unexplored, except for a few examples involving preparation of TTF-porphyrins10,11 and TTF-calix[4]pyrroles.12 It therefore appeared interesting to unleash this potential.

N-Sulfonylpyrroles are less electron-rich, and hence easier to handle than the parent unprotected pyrroles and can be deprotonated at the 2-position with different lithium bases affording C2-lithiated pyrroles.12 Subsequent

Figure 1 Molecular formulas of TTF 1 and MPTTF 2

Figure 2 Different types of functionalization of MPTTF derivatives, a) in the 5-, 4′- and 5′-positions and b) in the 4- and 6-positions.

quenching with a variety of electrophiles leads to 2-substituted pyrroles in variable yields.13 Since N-sulfonyl-MPTTF derivatives – in the shape of N-tosyl-MPTTF derivatives – are now easily available, we chose to use 2-[4,5-bis(propylthio)-1,3-dithiole-2-yliden]-5-tosyl-(1,3)-dithiole[4,5-c]pyrrole (3) as the building block for our investigations and we present here a general method for the functionalization of the 4- and 6-positions in N-tosyl-MPTTF derivatives.

Deprotonation of the MPTTF derivative 3, in its 4-position, was carried out by addition of 1.1 equivalents of lithium diisopropylamide14 (LDA) to a THF solution of 3. This procedure produced (Scheme 1) almost exclusively the monolithiated MPTTF derivative 4 as evidenced by the formation (Scheme 2) of the monomethyl MPTTF derivative 6 in 86% yield after quenching the solution with iodomethane (MeI). Treatment of the monolithiated MPTTF derivative 4 with other electrophiles, such as cyanogen bromide (CNBr), N-bromosuccinimide (NBS), or iodine (I2) gave (Scheme 2) the monohalogenated products 7 and 8 in 50–59% yields.

Scheme 1
In addition to monolithiation, bis-lithiation of 3 could also be carried out as illustrated in Scheme 1. Addition of 3.0 equivalents of LDA to a THF solution of 3 produced the bis-lithiated MPTTF derivative 5, which subsequently was reacted (Scheme 3) with either MeI, CNBr, or I₂ affording the bis-methylated product 9 and bis-halogenated products 10 and 11 in moderate to excellent yields (56–88%).

Although the monolithiated derivative 4 could be reacted with NBS to afford (Scheme 2) the monobrominated derivative 7, addition of NBS to the bis-lithiated derivative 5 failed completely to give any bis-brominated product. Surprisingly, treatment of the bis-lithiated MPTTF derivative 5 with acetone gave (Scheme 3) the monosubstituted product 12 as the major product (70%) and only traces of the expected bis-substituted product was obtained. This observation can most likely be accounted for by a competing acid-base reaction occurring in solution between the acidic α-hydrogens in acetone and the bis-lithiated MPTTF derivative 5.

All new compounds described herein were characterized by ¹H and ¹³C NMR spectroscopy, high-resolution mass spectrometry and in some cases also elemental analyses as listed in the experimental section.

In conclusion, we have developed an effective method for the preparation of 4- and 6-substituted N-tosyl-MPTTF derivatives and demonstrated that functionalization can be carried out selectively in the 4-position by treatment of the N-tosyl-MPTTF derivative 3 with one equiv. LDA followed by addition of different electrophiles. Some of the compounds described herein are appealing as starting material for the preparation of TTF polypyrroles (i.e., 10 and 11) or TTF-calix[n]pyrroles (i.e., 12). Work is currently aimed in these directions.

All reactions were carried out under a dry argon atmosphere in an oven-dried round-bottomed flask. Chemicals were purchased from commercial sources and were used as received except compound 3 and N-benzylbenzamide, which were prepared according to literature procedures. NBS was recrystallized from H₂O and dried in vacuum over Siccapent, while LDA solutions were titrated immediately prior to use using N-benzylbenzamide. Solvents were dried according to literature procedures. TLC was carried out using aluminum sheets precoated with silica gel 60 F₂₅₄ (Merck 5554). The plates were inspected under UV light (254 nm) and, if required, developed in I₂ vapor. Column chromatography was carried out using silica gel 60F (Merck 9385, 0.040–0.063 mm). Melting points were determined on a Büchi melting point apparatus and are uncorrected.

1H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on a Gemini-300BB instrument, using TMS or the residual solvent as the internal standard which were assigned on the basis of Nudelman. Fourier transform matrix-assisted laser-desorption/ionization mass spectrometry (FT-MALDI-MS) was performed on an IonSpec 4.7 tesla Ultima Fourier Transform mass spectrometer, utilizing a 2,5-dihydroxybenzoic acid (DHP) matrix. Microanalyses were performed by the Atlantic Microlab, Inc., Atlanta, Georgia, USA.

2-[4,5-Bis(propylthio)-1,3-dithiol-2-ylidene]-4-methyl-5-tosyl-(1,3)-dithiolo[4,5-c]pyrrole (6)

Compound 3 (109 mg, 200 μmol) was dissolved in anhyd THF (4 mL) under argon in an oven dried 5 mL one-necked round-bottomed flask fitted with a rubber septum. The clear yellow solution was cooled (acetone/dry ice) to –78 °C before a LDA solution (1.49 M in hexanes, 208 μmol, 1.05 equiv) was added by means of an oven-dried Hamilton syringe. The reaction mixture was stirred for 30 min at –78 °C and MeI (125 μL, 285 mg, 2008 μmol, 10 equiv) was added in one portion. The mixture was stirred for 1 h at –78 °C, whereupon the cooling bath was removed and the reaction was allowed to warm to r.t. The mixture was then poured into
sat. aq solution of NH₄Cl (25 mL). The mixture was extracted with CH₂Cl₂ (3 × 25 mL) and the combined organic phases were washed with H₂O (25 mL) and dried (MgSO₄). Evaporation of the solvent gave a yellow solid, which was purified by column chromatography (300 mL SiO₂, ɵ = 5 cm, eluent: CH₂Cl₂). The yellow band (Rₗ 0.75) was collected and the solvent was evaporated to give the product as a yellow solid, which contained small amounts of 3; yield: 96 mg (86%); mp 103–106 °C.

1H NMR (CDCl₃/TMS): δ = 1.00 (t, 3 H, J = 7.3 Hz), 1.01 (t, 3 H, J = 7.3 Hz), 1.65 (sextet, 2 H, J = 7.3 Hz), 2.26 (s, 2 H, J = 4.2 Hz), 2.42 (s, 3 H), 2.78 (t, 2 H, J = 7.3 Hz), 2.79 (t, 2 H, J = 8.3 Hz), 7.67 (d, 2 H, J = 8.3 Hz).

13C NMR (CDCl₃/TMS): δ = 13.3 (two overlapping lines), 13.6, 21.8, 23.2 (two overlapping lines), 38.3 (two overlapping lines), 112.0, 115.3, 116.2, 120.8, 124.3, 125.9, 127.0, 127.5, 127.6, 130.3, 135.7, 145.4.

FT-MALDI-MS: m/z (%) = 582 (MNa⁺, 1), 559 (M⁺, 31), 405 (M⁺ – Ts, 100).

FT-MALDI-HRMS: m/z calc'd for MNa⁺: 581.98922; found: 581.98911; m/z calc'd for M⁺: 558.9930; found: 558.9894.

2-[4,5-Bis(propylthio)-1,3-dithiol-2-ylidene]-4-bromo-5-tosyl-(1,3)-dithiolo[4,5-c]pyrrole (7)

Method A, Using CNBr: Compound 3 (103 mg, 188 µmol) was dissolved in anhyd THF (4 mL) under argon in an oven dried 10 mL round-bottomed flask and cooled (acetone/dry ice) to –78 °C, before a LDA solution (1.62 M in hexanes, 286 µmol, 1.2 equiv) was added. The reaction mixture was then stirred for 30 min at –78 °C and CNBr (31 mg, 300 µmol, 1.6 equiv) dissolved in anhyd THF (2 mL) was transferred to the mixture by means of a syringe. Upon addition, the color changed from yellow/orange to dark orange. Stirring was continued for additional 30 min at –78 °C. Subsequently, the cooling bath was removed and the mixture was stirred for 1 h at r.t. The mixture was then poured into H₂O (40 mL) and Na₂SO₄ (1.7 g) was added. The resulting mixture was stirred for 10 min before it was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were washed with H₂O (25 mL) and dried (MgSO₄). Evaporation of the solvent gave a brown solid, which was purified by column chromatography (300 mL SiO₂, ɵ = 2.5 cm, eluent: CH₂Cl₂–cyclohexane, 1:4) The first yellow band (Rₗ 0.35 eluent: CH₂Cl₂–cyclohexane, 1:1) was collected and evaporation of the solvent gave 8 as a yellow oil; yield: 67 mg (50%).

1H NMR (CDCl₃/TMS): δ = 1.00 (t, 3 H, J = 7.3 Hz), 1.01 (t, 3 H, J = 7.3 Hz), 1.65 (sextet, 2 H, J = 7.3 Hz), 2.26 (s, 2 H, J = 7.3 Hz), 2.43 (s, 3 H), 2.78 (t, 2 H, J = 7.3 Hz), 2.79 (t, 2 H, J = 8.3 Hz), 7.23 (s, 1 H), 7.32 (d, 2 H, J = 8.5 Hz), 7.79 (d, 2 H, J = 8.5 Hz).

13C NMR (CDCl₃/TMS): δ = 13.3 (two overlapping lines), 21.9, 23.3 (two overlapping lines), 38.4 (two overlapping lines), 91.2, 114.1, 114.6, 116.8, 125.3, 127.6, 127.8, 127.9, 130.2, 130.6, 134.7, 146.0.

FT-MALDI-MS: m/z (%) = 623 (M⁺, 10), 545 (M⁺ – Br, 13), 469 (M⁺ – Ts, 75).

FT-MALDI-HRMS: m/z calc'd for MNa⁺: 645.8777; found: 645.8743; m/z calc'd for M⁺: 622.8873; found: 622.8860.

2-[4,5-Bis(propylthio)-1,3-dithiol-2-ylidene]-4-iodo-5-tosyl-(1,3)-dithiolo[4,5-c]pyrrole (8)

Compound 3 (109 mg, 200 µmol) was dissolved in anhyd THF (4 mL) under argon in an oven dried 10 mL one necked round-bottomed flask fitted with a rubber septum. The clear yellow solution was cooled (acetone/dry ice) to –78 °C before a LDA solution (1.23 M in hexanes, 220 µmol, 1.1 equiv) was added by means of an oven dried Hamilton syringe. The reaction mixture was stirred for 30 min at –78 °C, whereupon I₂ (72 mg, 284 µmol, 1.4 equiv) was added in one portion. The mixture was stirred for 5 h at –78 °C before the reaction was allowed to warm to r.t. over 1 h. The mixture was then poured into H₂O (40 mL) and Na₂SO₄ (1.7 g) was added. The resulting mixture was stirred for 10 min before it was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic phases were washed with H₂O (25 mL) and dried (MgSO₄). Evaporation of the solvent gave a brown solid, which was purified by column chromatography (300 mL SiO₂, ɵ = 2.5 cm, eluent: CH₂Cl₂–cyclohexane, 1:4) The yellow band (Rₗ 0.3, eluent: CH₂Cl₂–cyclohexane, 1:1) was collected and evaporation of the solvent gave 9 as a yellow oil; yield: 22 mg (5%).

1H NMR (CDCl₃/TMS): δ = 1.00 (t, 3 H, J = 7.3 Hz), 1.01 (t, 3 H, J = 7.3 Hz), 1.65 (sextet, 2 H, J = 7.3 Hz), 2.26 (s, 2 H, J = 7.3 Hz), 2.43 (s, 3 H), 2.78 (t, 2 H, J = 7.3 Hz), 7.31 (d, 2 H, J = 8.4 Hz), 7.33 (s, 1 H), 7.79 (d, 2 H, J = 8.4 Hz).

13C NMR (CDCl₃/TMS): δ = 13.3 (two overlapping lines), 21.9, 23.3 (two overlapping lines), 38.4 (two overlapping lines), 53.8, 112.9, 116.5, 117.1, 125.7, 127.6, 127.8, 128.0, 130.2, 134.7, 138.6, 145.9.

FT-MALDI-MS: m/z (%) = 694 (MNa⁺, 3), 671 (M⁺, 18), 517 (M⁺ – Ts, 100).

FT-MALDI-HRMS: m/z calc'd for MNa⁺: 693.8632; found: 693.8632; m/z calc'd for M⁺: 670.8740; found: 670.8757.

Anal. Calc'd for C₃₂H₂₈INO₇S₇: C, 37.55; H, 2.94; N, 1.88; S, 33.41. Found: C, 37.65; H, 2.38; N, 2.05; S, 33.12.

2-[4,5-Bis(propylthio)-1,3-dithiol-2-ylidene]-4,6-dimethyl-5-tosyl-(1,3)-dithiolo[4,5-c]pyrrole (9)

Compound 3 (125 mg, 229 µmol) was dissolved in anhyd THF (4 mL) under argon in an oven dried 10 mL round-bottomed flask fitted with a rubber septum. The yellow solution was cooled (acetone/dry ice) to –78 °C, before a LDA solution (1.62 M in hexanes, 680 µmol, 3.0 equiv) was added by means of an oven dried Hamilton syringe. Stirring was continued at –78 °C for 30 min before MeI (200 µL, 3213 µmol, 14 equiv) was added in one portion. Stirring was continued for additional 30 min at –78 °C. Subsequently, the cooling bath was removed and the solution was allowed to reach r.t. before it was poured into sat. aq solution of NH₄Cl (25 mL). The solution was extracted with CH₂Cl₂ (2 × 25 mL), whereupon the combined organic phases were washed with sat. aq solution of NH₄Cl (2 × 25 mL) and dried (MgSO₄). Evaporation of the solvent followed by column chromatography (170 mL SiO₂, ɵ = 6 cm, eluent: CH₂Cl₂) gave a yellow band (Rₗ 0.75) which was collected.
The solvent was removed in vacuo yielding a yellow oil. Recrystallization from CHCl₃-MeOH gave as long yellow needles; yield: 116 mg (88%); mp 106–107 °C.

1H NMR (CDCl₃/TMS): δ = 1.00 (t, 6 H, J = 7.3 Hz), 1.65 (sextet, 4 H, J = 7.3 Hz), 2.34 (s, 6 H), 2.42 (s, 3 H), 2.78 (t, 4 H, J = 7.3 Hz), 2.79 (d, 2 H, J = 8.7 Hz), 2.75 (d, 2 H, J = 8.7 Hz). 13C NMR (CDCl₃/TMS): δ = 13.3, 15.6, 21.8, 23.3, 38.4, 115.3, 115.5, 121.6, 124.2, 126.4, 127.6, 130.1, 133.0, 136.7, 145.1.

FT-MALDI-MS: m/z (%) = 573 (M⁺, 11), 419 (M⁺–H₂O – Ts, 100).

FT-MALDI-HRMS: m/z calc for M⁺: 573.0081; found: 573.0086.

1H NMR (CDCl₃/TMS): δ = 1.01 (t, 6 H, J = 7.3 Hz), 1.65 (sextet, 4 H, J = 7.3 Hz), 2.44 (s, 3 H), 2.78 (t, 4 H, J = 7.3 Hz), 3.23 (d, 2 H, J = 8.7 Hz), 3.25 (d, 2 H, J = 8.4 Hz).

13C NMR (DMSO-d₆/TMS): δ = 13.3, 21.8, 23.2, 38.0, 63.0, 108.6, 116.9, 127.4, 127.6, 131.1, 134.5, 137.4, 146.9.

FT-MALDI-MS: m/z (%) = 797 (M⁺, 3), 671 (M⁺–I, 25), 643 (M⁺–Ts, 100), 517 (M⁺–Ts – I, 22).

FT-MALDI-HRMS: m/z calc for M⁺: 796.7701; found: 796.7715.

Anal. Calc'd for C₂₃H₂₇NO₂S₇: C, 48.13; H, 4.74; N, 2.44; S, 13.3, 15.6, 21.8, 23.2, 38.0, 63.0, 108.6, 116.9, 127.4, 127.6, 131.1, 134.5, 137.4, 146.9.

The combined organic phases were washed with H₂O (25 mL), dried (MgSO₄), and subsequently concentrated in vacuo. The resulting residue was purified by column chromatography (400 mL SiO₂, ɔ = 5 cm, eluent: CHCl₃-MeOH). The orange band (Rf 0.7) was collected and evaporated of the solvent gave the title compound 11 as an orange solid; yield: 115 mg (81%); mp 118.5–119.5 °C.

1H NMR (CDCl₃/TMS): δ = 1.01 (t, 6 H, J = 7.4 Hz), 1.65 (sextet, 4 H, J = 7.3 Hz), 2.44 (s, 3 H), 2.78 (t, 4 H, J = 7.3 Hz), 3.23 (d, 2 H, J = 8.7 Hz), 3.25 (d, 2 H, J = 8.4 Hz).

13C NMR (CDCl₃/TMS): δ = 13.3, 21.8, 23.2, 38.0, 63.0, 108.6, 116.9, 127.4, 127.6, 131.1, 134.5, 137.4, 146.9.

FT-MALDI-MS: m/z (%) = 797 (M⁺, 3), 671 (M⁺–I, 25), 643 (M⁺–Ts, 100), 517 (M⁺–Ts – I, 22).

Acknowledgment

We gratefully acknowledge financial support from the Carlsberg-fondet and the Danish Natural Science Research Council (SNF, projects #21-03-0317 and #21-02-0414).

Synthesis 2004, No. 15, 2555–2559 © Thieme Stuttgart · New York

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References


(8) (a) H NMR spectroscopy revealed that the isolated product contained ca. 5% of 3.