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SYNTHESIS OF NOVEL HIGHLY SOLUBLE *N*-(3,5-DI-*TERT*-BUTYLBENZYL)-MONOPYRROLO-TETRATHIAFULVALENE DERIVATIVES

Andreas Denhof, Jens Cordes, and Vladimir A. Azov
Department of Chemistry, University of Bremen, Bremen, Germany

Abstract *Highly soluble bis-(2-cyanoethyl)-protected derivative (**11**) of monopyrrolo-tetrathiafulvalene containing a bulky 3,5-di-tert-butylbenzyl solubilizing group has been synthesized and characterized. It was successfully employed to prepare two aromatic conjugates of monopyrrolo-tetrathiafulvalenes (TTFs) and is proposed to be used for preparation of TTF-containing molecular tweezers.*

Keywords Molecular recognition; molecular tweezers; pyrrolo-tetrathiafulvalenes; tetrathiafulvalenes; thiolates

INTRODUCTION

Tetrathiafulvalenes[1] (commonly known as TTFs, **1**; Figure 1) represent one of the most widely studied heterocyclic systems. Initially, research focus was concentrated on their application in the field of organic electronics.[2] Later, due to the strong electron-donating capabilities of tetrathiafulfalenes and the possibility of reversible stepwise oxidation, they have found use in many other areas of chemistry,[1,3] where their unique electrochemical properties are of an interest. In supramoleculrar chemistry, tetrathiafulvalenes have been elegantly employed for molecular recognition of electron-deficient viologen-based macrocycles and served as molecular motors in various interlocked architectures,[4] triggering reversible positional displacement of supramolecular components upon oxidation/reduction.[5]

Previously we have reported the synthesis and characterization of bis-TTF molecular tweezers[6] **2**, which comprised aromatic backbone connected to two tetrathiafulvalene arms via semi-rigid eight-membered dithia rings (Figure 1). Molecular tweezers are know as efficient guest binders, able to sandwich flat, electron-deficient guest molecules in between their arms.[7] Use of tetrathiafulvalene arms should afford the possibility to switch reversibly between the binding (ground) and nonbinding (oxidized) states of the receptors. In addition, the redox-driven large-scale switching between two profoundly different conformations[6a] suggests their use for the construction of molecular machines.

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Address correspondence to Vladimir Azov, Department of Chemistry, University of Bremen, Leobener Strasse NW 2C, D-28359 Bremen, Germany. E-mail: vazov@uni-bremen.de

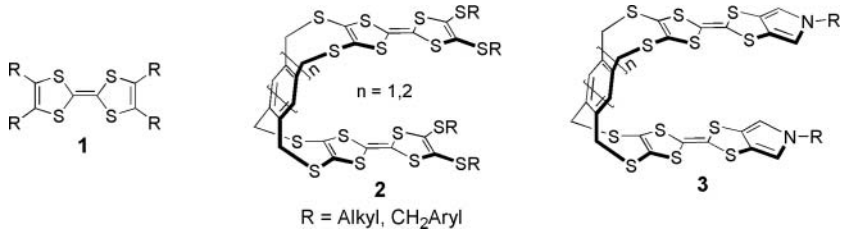


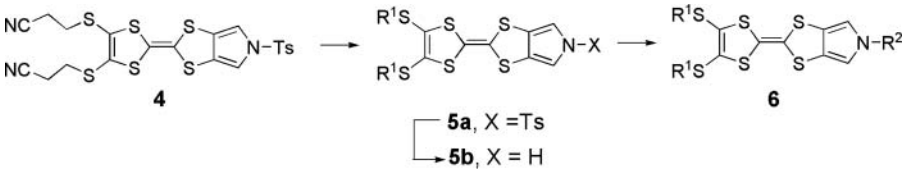
Figure 1 Structures of tetrathiafulvalene **1** and bis-TTF molecular tweezers **2** and **3**.

In this article, we report the synthesis of highly soluble bis-(2-cyanoethyl)-protected monopyrrolo-tetrathiafulvalene derivative and two model monopyrrolo-tetrathiafulvalenes, which were prepared in order to test the new synthetic strategy aimed for construction of molecular tweezers with monopyrrolo-TTF arms.

RESULTS AND DISCUSSION

As reported,[6b] initial binding studies have demonstrated affinity of the bis-TTF tweezers to electron-poor organic guests. The binding was relatively weak, which was due to the poor electron-donating properties of the tetrathioalkyl-tetrathiafulvalenes. Pyrrolo-TTFs[8] are known to have lower oxidation potentials as well as more extended π-systems, which significantly improve their binding ability in comparison to tetrathioalkyl-TTFs.[9] Monopyrrolo-tetrathiafulvalenes have been successfully employed before for the synthesis of molecular belts[10] and tweezer-like architectures,[11] which were proved to be efficient binders of electron-deficient species. Thus, we considered monopyrrolo-TTFs with large solubilizing groups as possible arms for molecular tweezers **3** (Figure 1).

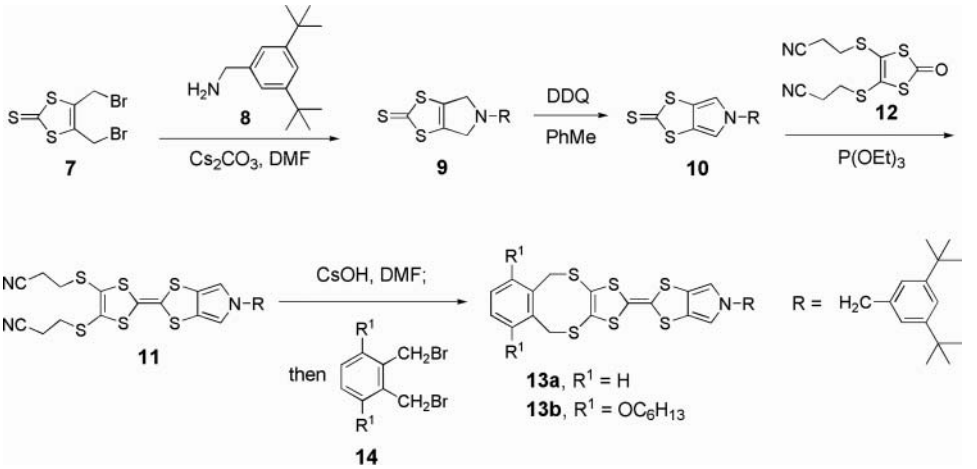
The common synthetic methodology[8] for the preparation of asymmetric monopyrrolo-tetrathiafulvalene derivatives employs the building block **4** (Scheme 1), containing tosyl and two cyanoethyl protective groups, as a key intermediate. First, the side containing cyanoethyl protective groups is substituted using conventional thiolate chemistry[12] giving **5a**, and then the substitution on the tosylated side of the monopyrrolo-TTF is carried out in a two-step sequence affording the target compound **6**.



Scheme 1 Common methodology for the preparation of monopyrrolo-tetrathiafulvalene derivatives.

We decided to modify this methodology due to the expected poor solubility of the intermediate molecular tweezers without large solubilizing groups. Thus, we have chosen to install the bulky 3,5-di-*tert*-butylbenzyl moiety during the earlier synthetic steps to render high solubility to the synthetic intermediates and target compounds.

The synthesis started with dibromo-derivative **7**,[8a] which was treated with 3,5-di-*tert*-butylbenzylamine **8**[13] under the basic conditions, followed by the oxidation of the intermediate **9** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford dithiolo[4,5]pyrrole-2-thione **10** (Scheme 2). The key intermediate, bis(2-cyanoethylthio)tetrathiafulvalene **11**, was prepared in a phosphite-mediated coupling of thione **10** and oxo-derivative **12**[12] using triethylphosphite as a coupling agent. This step required stepwise addition of compound **12** to avoid excessive homo-coupling of **12** with the formation of the nondesired symmetric tetrakis(2-cyanoethylthio)tetrathiafulvalene. Two mono-TTF aromatic derivatives **13a**,**b** have been synthesized in reaction of TTF dithiolates,[12] which were generated in situ from 2,3-bis(2-cyanoethylthio)tetrathiafulvalene **11**, with aromatic methylene bromides **14a** and **14b**.[14] Three new tetrathiafulvalene derivatives **11** and **13a**,**b** represent bright yellow crystals or slowly crystallizing syrups, which are relatively prone to oxidation on air in a solution. Synthesis and characterization of bis-moopyrrolo-TTF molecular tweezers **3** should follow.[15]



Scheme 2 Synthesis of the tetrathiafulvalene derivatives **11** and **13a**,**b**.

To conclude, the synthesis of the bis-cyanoethylprotected monopyrrolo-tetrathiafulvalene **11** has been performed, and the first monopyrrolo-TTF derivatives with the aromatic backbone **13a**,**b** have been prepared, paving the way for the synthesis of bis-monopyrrolo-TTF molecular tweezers **3**.

EXPERIMENTAL

All experiments were carried out under inert atmosphere. When necessary, solvent degassing was performed using two to three freeze–pump–thaw cycles. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ with a Bruker Avance DPX-200 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane using the residual $CHCl_3$ peak as internal reference (7.26 ppm for ^1H, 77.23 ppm for ^{13}C). Melting points were determined using capillary melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) and R_f

values were determined using 0.2-mm silica gel F-254 TLC cards. Flash chromatography (FC) was carried out using 230–440 mesh (particle size 36–70 μm) silica gel.

5-(3,5-Di-*tert*-butylbenzyl)-5,6-dihydro-4*H*-1,3-dithiolo[4,5-*c*]pyrolle-2-thione (9)

Solution of dibromide **7** (2.87 g, 8.97 mmol) in tetrahydrofuran (THF)/MeCN (1:2, 30 mL) was added to the hot mixture of amine **8** (1.96 g, 8.93 mmol) and Cs_2CO_3 (11.7 g, 36 mmol) in THF/MeCN (1:2, 60 mL) over a period of 10 min. The reaction mixture was stirred with reflux for 1 h. Then the solvent was removed, the brown residue was dissolved in CH_2Cl_2 and washed with brine, and the organic phase was dried ($MgSO_4$). FC (CH_2Cl_2/PE, 1:1) afforded 2.64 g (78%, 7.0 mmol) of the yellow crystalline product **9**. $R_f = 0.55$ (CH_2Cl_2). Mp 145–147°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.33$ (s, 18H, *CH*$_3$), 3.87 (s, 4H, *CH*$_2$), 3.94 (s, 2H, *CH*$_2$), 7.17 (d, $J = 1.8$ Hz, 2H, *Aryl-H*), 7.34 ppm (t, $J = 1.8$ Hz, 1H, *Aryl-H*). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 31.72$, 35.02, 57.54, 61.16, 121.71, 122.85, 137.18, 139.04, 151.25 ppm. HR-EI-MS (70 eV): $m/z = 377.12800$ (M^+, $C_{20}H_{27}NS_3^+$, Calcd. 377.13057).

5-(3,5-Di-*tert*-butylbenzyl)-5*H*-1,3-dithiolo[4,5-*c*]pyrolle-2-thione (10)

A mixture of compound **9** (2.64 g, 6.99 mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (1.74 g, 7.67 mmol) was refluxed in dry toluene (50 mL) for 1 h. The precipitate was removed by filtration and the filtrate was washed with 10% NaOH. The organic phase was dried ($MgSO_4$) and concentrated to a dark brown oil. FC (CH_2Cl_2/PE, 2:3) afforded 2.10 g (80%, 5.59 mmol) of yellow crystalline **10**. $R_f = 0.29$ (CH_2Cl_2/PE, 2:3). Mp 171–175°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.30$ (s, 18H, *CH*$_3$), 5.10 (s, 2H, *CH*$_2$), 6.73 (s, 2H, *CH*-N), 7.01 (d, $J = 1.8$ Hz, 2H, *Aryl-H*), 7.40 ppm (t, $J = 1.8$ Hz, 1H, *Aryl-H*). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 31.62$, 35.08, 55.31, 112.69, 114.18, 122.01, 122.60, 135.68, 151.85, 196.94 ppm. HR-EI-MS (70 eV): $m/z = 375.11458$ (M^+, $C_{20}H_{25}NS_3^+$, Calcd. 375.11492).

2-[4,5-Bis(2-cyanoethylthio)-1,3-dithiol-2-ylidene]-5-(3,5-di-*tert*-butylbenzyl)-5H-1,3-dithiolo[4,5-*c*]pyrrole (11)

Suspension of compounds **10** (0.399 g, 1.06 mmol) and **12** (0.33 g, 1.14 mol) in freshly distilled $P(OEt)_3$ (10 mL) was heated up to 110°C and then two additional portions of **12** (0.33 g, 1.14 mmol) were added at intervals of 30 min. After anadditional 30 min $P(OEt)_3$ was removed by distillation in vacuum and the product **11** was purified by FC (CH_2Cl_2) to give 194 mg (30%, 0.315 mmol) of the bright yellow crystalline product. $R_f = 0.35$ (CH_2Cl_2). Mp 151–154°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.30$ (s, 18H, *CH*$_3$), 2.73 (t, $J = 7.0$ Hz, 4H, *CH*$_2$), 3.08 (t, $J = 7.0$ Hz, 4H, *CH*$_2$), 4.97 (s, 2H, *Aryl-CH*$_2$), 6.52 (s, 2H, *CH*-N), 7.01 (d, $J = 1.8$ Hz, 2H, *Aryl-H*), 7.38 ppm (t, $J = 1.8$ Hz, 1H, *Aryl-H*). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.05$, 31.44, 31.61, 35.04, 55.34, 107.00, 113.17, 117.68, 118.76, 121.97, 122.42, 124.82, 127.87, 135.93, 151.69 ppm. IR (KBr): $\nu = 2252$ cm^{-1} (CN). UV/Vis (CH_2Cl_2): λ_{max} (ε) = 329 nm (18,750 dm^3 mol^{-1} cm^{-1}). HR-EI-MS (70 eV): $m/z = 615.09914$ (M^+, $C_{29}H_{33}N_3S_6^+$, Calcd. 615.09988).

Compounds 13a,b, General Procedure

To a degassed chilled solution of **11** (50 mg, 0.081 mmol) in dimethylformamide (DMF) (3 mL) 1 M CsOH/MeOH solution (0.17 mL, 0.17 mmol) was added; the mixture was stirred for 15 min at rt and then the aromatic bromide **14** (0.080 mmol) was added in THF (1 mL) upon chilling to 0°C. The mixture was stirred for 90 min and allowed to warm to rt. The solvent was removed under vacuum and the product **13** was purified by FC (CH_2Cl_2/C_6H_{12}, 1:3).

Compound 13a. Yield 30 mg (61%, 0.049 mmol) of yellow-orange slowly crystallizing syrup. R_f = 0.29 (CH_2Cl_2/C_6H_{12}, 1:3). Mp 140–143°C. ^{1}H NMR (200 MHz, $CHCl_3$): δ = 1.27 (s, 18H, *CH*$_3$), 4.26 (s, 4H, *CH*$_2$-S), 4.92 (s, 2H, *CH*$_2$-N), 6.43 (s, 2H, *CH*-N), 6.96 (d, J = 2 Hz, 2H, *Aryl-H*), 7.18–7.31 (m, 4H, *Aryl-H*), 7.34 ppm (t, J = 2.0 Hz, 1H, *Aryl-H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.62, 35.04, 38.65, 55.20, 110.84, 113.00, 119.10, 120.98, 121.87, 122.31, 128.85, 130.11, 130.76, 134.80, 136.11, 151.64 ppm. HR-EI-MS (70 eV): m/z = 611.09326 (M^+, $C_{31}H_{33}NS_6^+$, Calcd. 611.09373).

Compound 13b. Yield 26 mg (39%, 0.032 mmol) of yellow-orange slowly crystallizing oil. R_f = 0.27 (CH_2Cl_2/C_6H_{12}, 1:3). Mp 114–115°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.93 (t, J = 6.4 Hz, 6H, *CH*$_3$), 1.28 (s, 18H, *CH*$_3$), 1.24–1.60 (m, 12H, (*CH*$_2$)$_3$CH$_3$), 1.73–1.86 (m, 4H, *CH*$_2$CH$_2$O), 3.95 (t, J = 6.4 Hz, 4H, *CH*$_2$-O), 4.33 (s, 4H, *CH*$_2$-S), 4.93 (s, 2H, *CH*$_2$-N), 6.45 (s, 2H, *CH*-N), 6.78 (s, 2H, *Aryl-H*), 6.97 (d, J = 1.8 Hz, 2H, *Aryl-H*), 7.35 ppm (t, J = 1.8 Hz, 1H, *Aryl-H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 14.35, 22.90, 26.09, 29.63, 31.62, 31.79, 31.89, 35.05, 55.21, 69.50, 111.69, 112.53, 112.98, 119.19, 120.57, 121.86, 122.31, 125.23, 130.76, 136.15, 150.75, 151.64 ppm. HR-EI-MS (70 eV): m/z = 811.27066 (M^+, $C_{43}H_{57}NO_2S_6^+$, Calcd. 811.27136).

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15. The results will be reported elsewhere, together with electrochemical and binding properties of the reported compounds.