An expedient, cost effective large scale synthesis of tetrathiafulvalene

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TTF is synthesized (85% yield) in two steps from 4,5-bis(benzoylthio)-1,3-dithiole-2-thione and isolated in high purity without the use of chromatography.

The donor molecule tetrathiafulvalene (TTF, **1**) and its derivatives have been the most intensely studied sulfur heterocycles in the past two decades[1] owing to their role in the development of organic metals and superconductors. A number of new syntheses of TTF and key intermediates have been developed[2–7] in part due to the high cost of TTF from commercial sources. More recently, the use of TTF as a primary precursor to extended organic metals,[8–10] Langmuir–Blodgett (LB) films[11,12] and additionally as the principal building block in supramolecular architectures[13–15] requiring bulk quantities of TTF has prompted the development of more cost-effective syntheses.[16,17]

Recently we had reported a novel non-coupling route to TTF from 4,5-bis(benzoylthio)-1,3-dithiole-2-thione (**2**).[17] The initial step involves the formation of tetrathianaphthalene (TTN, **3**) from ethylene tetrathiolate (**4**) and *cis*-1,2-dichloroethylene. Compound **3** is then smoothly rearranged into TTF (yield 75%) upon deprotonation with LDA.[18,19] It has been noted by other researchers that the procedure although facile, has two drawbacks: (1) *cis*-1,2-dichloroethylene is somewhat expensive[16] and (2) the use of LDA is restrictive for bulk syntheses of TTF.[20] We now report two important refinements to this procedure: (1) an inexpensive mixture of *cis*- and *trans*-1,2-dichloroethylene can be used to make TTN, and (2) TTN is easily rearranged irreversibly and quantitatively into TTF upon deprotonation with KO[t]Bu (Scheme 1).
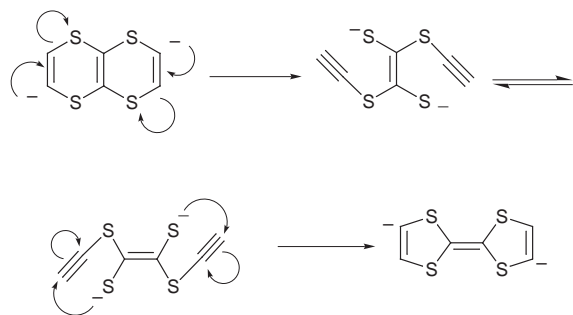

Scheme 1
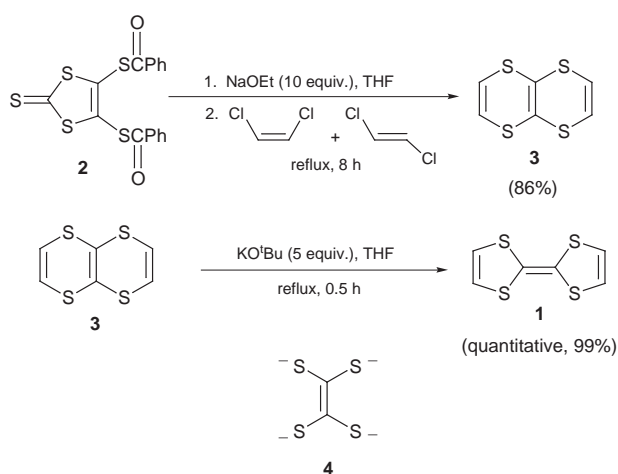
In order to synthesize TTN in a more cost efficient manner, a close examination of the mechanism for the formation of **3** reveals that the product is not formed from **4** as a result of simple nucleophilic displacements of chlorine from *cis*-1,2-dichloroethylene, but as a result of an elimination–addition mechanism.[21–25] Pioneering research by Truce has shown that *cis*-1,2-dichloroethylene readily reacts with nucleophilic agents such as sodium benzenethiolate, sodium toluene-*p*-thiolate and

sodium 2-methylpropane-2-thiolate, while *trans*-1,2-dichloroethylene when treated likewise, is recovered unchanged.[21–25] The mechanism is also applicable to the herein reported synthesis of TTN which involves two intramolecular elimination–addition processes (Scheme 2).

Scheme 2
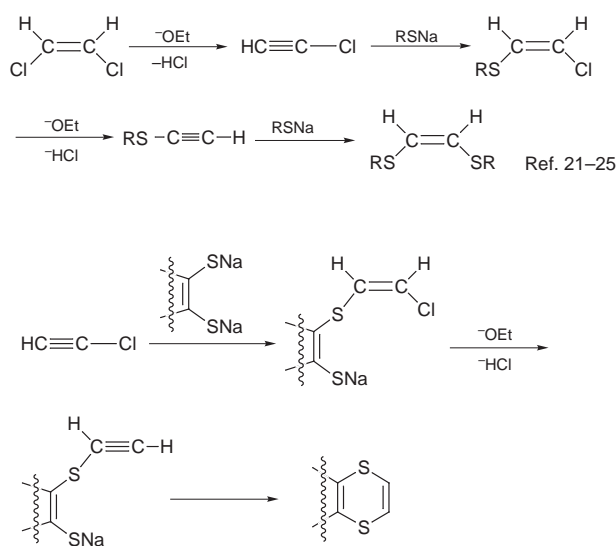
The more readily dehydrohalogenated *cis*-1,2-dichloroethylene in the presence of sodium ethoxide smoothly adds to **4**. On the other hand, attempts to react *trans*-1,2-dichloroethylene with **4** resulted in recovered starting materials. Beyond being mechanistically intriguing, this demonstrates that **3** can be easily synthesized from **2**, excess sodium ethoxide and a mixture of *cis*- and *trans*-isomers of 1,2-dichloroethylene. Mixtures of *cis*- and *trans*-1,2-dichloroethylene are available in bulk from several sources at a cost substantially less than that of pure *cis*-1,2-dichloroethylene. Provided that two moles of *cis*-1,2-dichloroethylene are available for every mole of **2**, the presence of the *trans* isomer during the reaction does not hinder the production of **3**. Quite surprising is the fact that TTF is not directly formed in this reaction, but we have found that TTN can easily be converted quantitatively into TTF with KO[t]Bu in THF after 3 days at room temperature, or under gentle reflux in 0.5 h. This marks a substantial improvement in yield and practically over deprotonation with LDA.[17–19] It is important to note that the transformation can be easily monitored by TLC. Although TTF and TTN are isomers and their R_f values are similar (0.56 and 0.67 for TTF and TTN, respectively, on silica plates with CCl_4 as eluent), TTF decomposes within seconds on drying the developed silica plate, aiding in identification (*i.e.* the plate develops itself in this respect). We have determined that TTN requires two molar equivalents of KO[t]Bu for full conversion into TTF. This synthesis lends additional credence to a proposed deprotonation and rearrangement mechanism of **3** into **1** (Scheme 3).[18,19]

After refluxing for more extended periods with additional KO[t]Bu, it becomes apparent that the transformation from TTN

Scheme 3

to TTF is essentially (thermodynamically) irreversible. Calculations have shown that TTF is more stable than both the chair and boat configurations of TTN[26–28] by 1.7 kcal mol^{-1} and 5.4 kcal mol^{-1} respectively at the 6-31G*-MP2 level.[28]

During the synthesis of TTN, there is strong evidence for the formation of **4**. Nucleophilic attack of **2** from two equivalents of sodium ethoxide produces the 1,3-dithiole-2-thioxo-4,5-dithiolate dianion **5** and two equivalents of ethyl benzoate at room temperature in only a few minutes. Indeed **5** is routinely used to produce 4,5-ethylenedithio-1,3-dithiole-2-thione **6** in high yield (87%).[29] Reaction of **5** with *cis*-1,2-dichloroethylene produces 4,5-vinylenedithio-1,3-dithiole-2-thione **7** in only 10–15% yield after 24 hours.[30] Attempts to improve this yield under more rigorous conditions (temperature, solvent) have failed in our hands. Compound **7** has been produced by other means by various researchers.[31–33] Compound **5** is converted into **4** and one equivalent of diethyl thiocarbonate upon nucleophilic attack from two equivalents of sodium ethoxide requiring higher temperature and longer reaction times (65 °C, 6 h) than the thioester cleavage of **2** (Scheme 4).
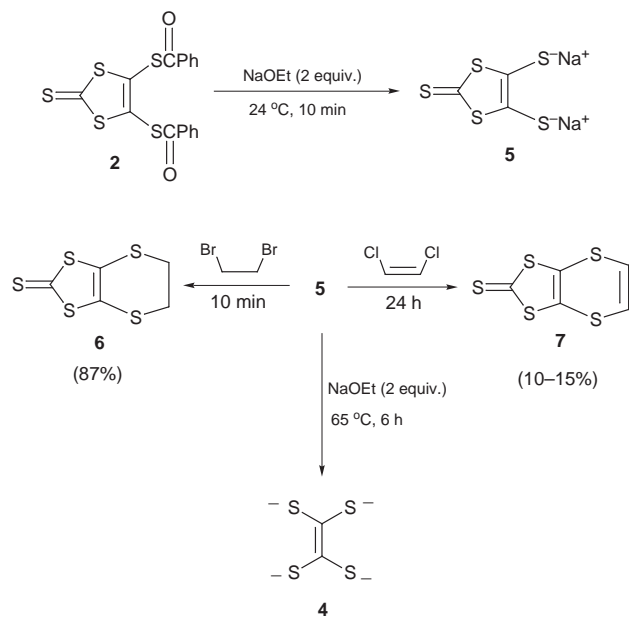
Scheme 4

In order to convert **4** into TTN, additional sodium ethoxide is needed for the dehydrohalogenation of *cis*-1,2-dichloroethylene. A large excess of NaOEt (10 equiv.) is used to ensure a complete conversion. It should be noted here that chloroacetylene is highly combustible. Likewise, more than the required two equivalents of KO^{t}Bu (5 equiv.) are used for the conversion of TTN into TTF. It is noteworthy that although sodium ethoxide is a good nucleophile, its pK_a of 16.00 is not high enough to deprotonate and rearrange TTN into TTF, whereas KO^{t}Bu with pK_a = 18.00 is sufficient. As one can envision, **2** can be converted into TTF in a one pot reaction

after the formation of TTN when KO^{t}Bu and NaOEt (ethanol free) are present; however, due to the presence of large amounts of ethyl benzoate, diethyl thiocarbonate and sodium chloride by-products, much higher yields are obtained when TTN is first isolated and then converted into TTF.

In conclusion, herein we show a practical, inexpensive large scale synthesis of tetrathiafulvalene.

Experimental

1,4,5,8-Tetrathianaphthalene 3
EtOH (400 ml) was added to a three-necked 2000 ml round-bottomed flask equipped with a stirring bar, one 1000 ml pressure equalizing funnel, one stopper and a reflux column all under N$_2$. Fresh sodium (18.4 g, 800 mmol) was added portionwise slowly to the EtOH through the unstoppered hole. After all of the sodium had reacted, 500 ml of THF was charged into the flask. 4,5-Bis(benzoylthio)-1,3-dithiole-2-thione (**2**) (32.48 g, 80 mmol, modified literature procedure[29]) was dissolved in 600 ml of THF and added to the additional funnel, and 1,2-dichloroethylene (46 ml, 600 mmol of a 30% *cis* and 70% *trans* mixture, *i.e.* 180 mmol of *cis*) was added with mixing to the addition funnel. The resultant solution was then added dropwise over an 8 h period to the sodium ethoxide solution under gentle reflux with stirring. *Note*: *chloroacetylene is highly combustible*.

Compound **2** turned red upon reaction with the alkoxide solution, and the whole reaction mixture turned yellow accompanied by a large amount of precipitate after allowing the reaction to reflux gently overnight. After cooling, 300 ml of water was added, dissolving the precipitate (NaCl) and turning the solution a purple color. After transferring the solution to a one-necked flask, the THF (and some of the water) was removed by rotary evaporation to give a light brown-yellow solid. The solid was then dissolved in 500 ml of dichloromethane and transferred with the excess water to a separatory funnel. The organic layer was washed with additional water (3 × 300 ml), dried with anhydrous MgSO$_4$, filtered through a plug of silica and concentrated to give a yellow solid. The product was recrystallized from cyclohexane–hexane (5:3) to give yellow–orange crystals. Yield: 14.06 g (86%), mp 125–127 °C (lit.,[34] mp 125–126 °C); δ_H(CDCl$_3$–SiMe$_4$) 6.45 (s, 4H); δ_C(CDCl$_3$–SiMe$_4$) 118.70 (s, int. C=C), 125.39 (s, ext. C=C); *m/z* 204 (M$^+$).

Tetrathiafulvalene 1
TTN (10 g, 48.93 mmol), KO^{t}Bu (28 g, 249.51 mmol) and 300 ml of THF were charged into a 500 ml round-bottomed flask with a stirring bar and reflux column under N$_2$. The solution was gently stirred and refluxed for 0.5 h until all the TTN had converted into TTF as evidenced by TLC. The reaction solution was then concentrated by rotary evaporation and the residue was dissolved in 400 ml of dichloromethane and 100 ml of water, transferred to a separatory funnel and the organic layer was washed with additional water (3 × 300 ml), dried with anhydrous MgSO$_4$ and condensed to give an orange–yellow crystalline product. Yield: 9.88 g (99%), mp 118–120 °C (lit.,[16] mp 119 °C); δ_H(CDCl$_3$–SiMe$_4$) 6.32 (s, 4H); δ_C(CDCl$_3$–SiMe$_4$) 110.10 (s, int. C=C), 119.06 (s, ext. C=C); *m/z* 204 (M$^+$).

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