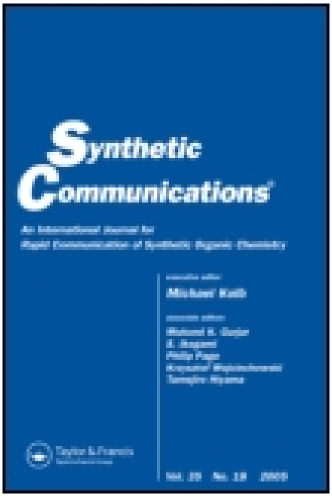

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Improved Synthesis of Tetrakis(2-thienyl)methane

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ABSTRACT

An improved synthesis of tetrakis(2-thienyl)methanes, where an aromatic nucleophilic substitution is the key reaction for the introduction of the fourth 2-thienyl group, has been developed, thus, reaction of tris(2-thienyl)methyl anion with 2-fluoro-5-cyanothiophene smoothly proceeded to give (5-cyano-2-thienyl)-tris(2-thienyl)methane in good yield. Alkaline hydrolysis of the cyano group to carboxylic acid followed by decarboxylation at 180°C in quinoline in the presence of copper(I) oxide afforded the parent tetrakis(2-thienyl)methane in 50% total yield from the trithienylmethane.

Key Words: Tetrakis(heteroaryl)methanes; Tetrakis(2-thienyl)methane; Aromatic nucleophilic substitution; Decyanation.

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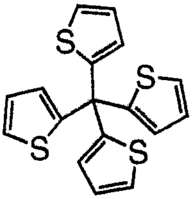
We recently reported the first synthesis of tetrakis(2-thienyl)methane (**1**) by the application of butadiyne-thiophene transformation.[1] In view of easy functionalization of thiophene at 2-(or 5)-position either by aromatic electrophilic substitutions or lithiation-functionalizations as well as the synthetic equivalency of thiophene with a tetramethylene unit by Raney-nickel reduction, compound **1** would be a versatile synthon for novel three-dimensional molecules of structural and physicochemical interest. However, the total yield of **1** was poor, and yield improvement was needed for development of its chemistry. More recently, we reported the synthesis of tetrakis (2-pyridyl)methane (**2**)[2] by the reaction of tris(2-pyridyl)methyl anion with 2-chloropyridine (52% yield). Later, we found that the yield can be further improved up to 93% by use of 2-fluoropyridine in place of 2-chloropyridine.[3] A key to the successful synthesis of **2** is high reactivity of 2-halopyridines toward aromatic nucleophilic substitutions. In contrast to the electron-poor nature of pyridine, however, thiophene is one of the electron-rich aromatic heterocyclic compounds, and therefore, aromatic nucleophilic substitution is not practical for 2-halothiophenes. However, 2-halothiophenes having an electron-withdrawing group at 5-position become more susceptible to aromatic nucleophilic substitutions.[4] We now report an improved and practical synthesis of **1** based on the aromatic nucleophilic substitution of 2-halopthiophenes.



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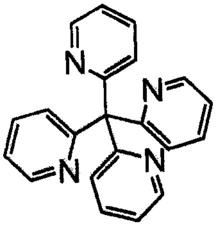
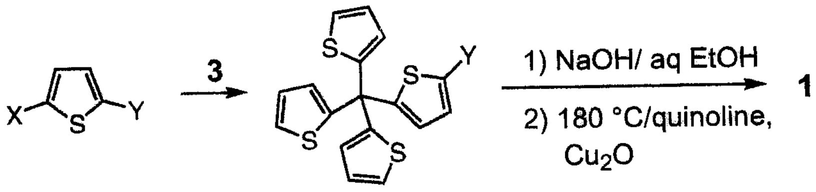


2

We at first examined the reaction of tris(2-thienyl)methyl anion **3**[5] with 2-chlorothiophene **4** and 2,5-dichlorothiophene **5** under several conditions. Although **4** did not give **1** at all, **5** gave the substitution product **6** under a drastic condition (reflux in xylene for 24 hr) in poor yield of 4% (Scheme 1). Next examined was 2-chloro-5-nitrothiophene **7**: the reaction of **3** with **7** in THF gave the dimeric material **8** in 27% yield as only isolable product. The formation of **8** indicates the occurrence of single electron transfer (SET) from **3** to **7**, generating tris(2-thienyl)methyl radical of which dimerization has been reported (Scheme 2).[6] Thus, it turned out that the



5: X = Y = Cl
9a: X = Cl; Y = CN
9b: X = F; Y = CN

6: Y = Cl
10: Y = CN

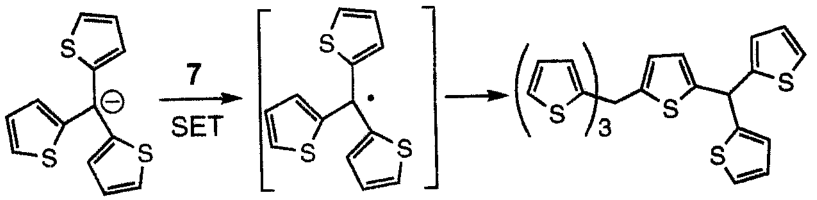
Scheme 1.

chloro group is too weak and the nitro group is too strong as electron-withdrawing substituents for the present purpose.

Taking these results into account, we chose cyano group as a potentially promising substituent. The reaction of **3** with 2-chloro-5-cyanothiophene **9a** proceeded in THF at room temperature and the desired (5-cyano-2-thienyl)-tris(2-thienyl)methane **10** was obtained in moderate yields (Scheme 1). However, this reaction suffered from the poor reproducibility and the yield varied from 4% to 48% under similar conditions.

Finally, 2-fluoro-5-cyanothiophene **9b** was found to be the best substrate: the reaction of **3** with **9b** smoothly proceeded in THF at −78°C to give **10** in 78% yield. Alkaline hydrolysis of the cyano group of **10** gave the corresponding carboxylic acid **11** and subsequent decarboxylation by heating the crude **11** at 180°C in quinoline in the presence of copper(I) oxide afforded the parent compound **1** in 65% yield from **10**.

Thus, tetrakis(2-thienyl)methane (**1**) is now available in gram quantity, and its chemistry and application to the synthesis of novel three-dimensional molecules are in progress.



3

8

Scheme 2.

EXPERIMENTAL

Materials

Tris(2-thienyl)methane,[5] 2-chloro-5-nitrothiophene (**5**),[7] 5-chlorothiophene-2-carbonitrile (**9a**),[8] and 5-fluorothiophene-2-carbonitrile (**9b**)[9] were prepared according to literature. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl before use. Butyllithium in hexane solution, copper(I) oxide, and quinoline were all commercially available and used without further purification. The structure of **6** was determined by mass spectral and ^{1}H NMR analyses.

Procedure

(5-Chloro-2-thienyl)-tris(2-thienyl)methane (**6**)

To a solution of 524 mg (2.0 mmol) of tris(2-thienyl)methane in THF (10 mL) was added dropwise a 1.4 M solution of butyllithium (1.4 mL, 2.0 mmol) over 5 min at −70°C under nitrogen atmosphere. The red suspension of anion **3** was stirred at room temperature for an hour. Dry xylene (15 mL) and **5** (1.1 mL, 10 mmol) were added, and the mixture was heated at 90°C to remove THF by distillation and then heated at refluxing temperature of xylene for 24 hr. After cooling, the reaction mixture was added with 50 mL of water and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by column chromatography on silica gel eluted with hexane–ethyl acetate (10 : 1 v/v) to give 30 mg (4%) of **8**: colorless crystals; mp 92–93°C (hexane); EIMS (rel intensity) m/z 378 (M$^+$; ^{35}Cl, 100), 380 (M$^+$; ^{37}Cl, 56), 343 ([M−Cl]$^+$, 58); ^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 6.79 (d, $J = 4.1$ Hz, 1H, Th-3′H), 6.82 (d, $J = 4.1$ Hz, 1H, Th-4′H), 6.99 (dd, $J = 5.1$, 3.5 Hz, 3H, Th-4H), 7.07 (dd, $J = 3.5$, 1.4 Hz, 3H, Th-3H), 7.25 (dd, $J = 5.1$, 1.4 Hz, 3H, Th-5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ/ppm 53.34 (central-C), 125.48 (Th-5C), 125.57 (Th-3′C), 126.50 (Th-4C), 126.89 (Th-4′C), 127.89 (Th-3C), 129.94 (Th-5′C), 151.05 (Th-2′C), 151.81 (Th-2C); UV-vis (CH_2Cl_2) λ_{max} (log ε) 228sh (4.33), 241 (4.43); Anal. Calcd for $C_{17}H_{11}ClS_4$: C, 53.88; H, 2.93. Found: C, 53.83; H, 3.14.

(5-Cyano-2-thienyl)-tris(2-thienyl)methane (**10**)

A solution of **3**, generated by the treatment of tris(2-thienyl)methane (1.05 g, 4.0 mmol) in THF (20 mL) with 1.4 M solution of butyllithium in hexane (2.8 mL, 4.0 mmol) at −78°C then rt for an hour, was added dropwise to a solution of **9b** (0.51 g, 4.0 mmol) in THF (20 mL) at −78°C. After stirring for 2 hr, 50 mL of water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by column chromatography on silica gel eluted with hexane–ethyl acetate (15 : 1 v/v) to give 1.14 g (78%) of **10**: colorless needles; mp 131–132°C (hexane–ethyl acetate); EIMS (rel intensity) m/z 369 (M^+, 100), 286 ($[M-Th]^+$, 20); ^1H NMR (500 MHz, $CDCl_3$) δ/ppm 7.01 (dd, $J = 5.2$, 3.7 Hz, 3H, Th-4H), 7.06 (dd, $J = 3.7$, 1.2 Hz, 3H, Th-3H), 7.11 (d, $J = 4.0$ Hz, 1H, Th-3′H), 7.28 (dd, $J = 5.2$, 1.2 Hz, 3H, Th-5H), 7.51 (d, $J = 4.0$ Hz, 1H, Th-4′H); ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm 53.39 (central-C), 109.36 (Th-5′C), 114.08 (CN), 125.89 (Th-5C), 126.69 (Th-4C), 128.03 (Th-3′C), 128.14 (Th-3C), 136.96 (Th-4′C), 150.95 (Th-2C), 160.97 (Th-2′C); IR (KBr disk) ν/cm^{-1} 2220 (CN); UV-vis (CH_2Cl_2) λ_{max} (log ε) 240 (4.44), 272 (4.14); Anal. Calcd for $C_{18}H_{11}NS_4$: C, 58.50; H, 3.00; N, 3.79. Found: C, 58.35; H, 2.86; N, 3.82.

Tetrakis(2-thienyl)methane (**1**)

A mixture of **10** (1.71 g, 4.6 mmol), ethanol (75 mL), and 10% NaOHaq (60 mL) was heated at reflux for 3 hr. After cooling, the reaction mixture was neutralized with 2M HClaq and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. Filtration and concentration gave the crude 5-(tris(2-thienyl)methyl)-2-thiophenecarboxylic acid (**12**) (1.73 g, 96%) that was used for further reaction without purification. A suspension of the crude **12** (0.50 g, 1.3 mmol), Quinoline (5 mL), and copper(I) oxide (46 mg, 0.32 mmol) was heated at 180°C for 2 hr. After cooling, solids were removed by filtration through a pad of celite and washed with ethyl acetate thoroughly. The filtrate and washings were combined and washed with water, 2M HCl aq, water, and brine and then dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by column chromatography on silica gel eluted with hexane–ethyl acetate (10 : 1 v/v) to give 290 mg (65%) of **1**: colorless crystals; mp 171–172°C (hexane–ethyl acetate); EIMS (rel intensity) m/z 344 (M^+, 41), 261 ($[M-Th]^+$, 27), 178 ($[M-2Th]^+$, 37); ^1H-NMR (500 MHz, $CDCl_3$) δ/ppm 6.98 (dd, $J = 5.2$, 3.7 Hz, 4H, Th-4H), 7.07 (dd, $J = 3.7$, 1.2 Hz, 4H, Th-3H), 7.23 (dd, $J = 5.2$, 1.2 Hz, 4H, Th-5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ/ppm 53.19 (central-C), 125.22 (Th-5C), 126.37 (Th-4C), 127.79 (Th-3C), 152.67 (Th-2C); UV-vis (CH_2Cl_2) λ_{max} (log ε) 228sh (4.36), 240 (4.46); Anal. Calcd for $C_{17}H_{12}S_4$: C, 59.26; H, 3.51. Found: C, 59.11; H, 3.52.

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