Synthesis of Tetrakis(2-furyl)methane

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The parent tetrakis(2-furyl)methane is first synthesized using aromatic nucleophilic substitution on 2-chlorofurans as a key reaction. X-ray analysis reveals the shortest bond length between the central methane carbon and furyl *ipso*-carbons among known tetraarylmethanes. Successful tetrabromination and tetralithiation promise its high synthetic utility.

Although tetraphenylmethane and its derivatives have recently been attracting intense renewed interest from the view points of crystal engineering and material science,[1] tetrakis(heteroaryl)methanes have been little explored. In view of higher functionality of heterocyclic aromatic compounds than benzene, tetrakis(heteroaryl)methanes would be compounds of potential interest. The reason for their absence may be ascribed to their synthetic difficulty. Under these circumstances, we had begun to explore their synthesis and recently reported the first syntheses of tetrakis(2-thienyl)methane **1** and tetrakis(2-pyridyl)methane **2**.[2,3] One of other fundamental members is tetrakis(2-furyl)methane **3** which would be a versatile synthon for novel three-dimensional molecules based on tetrafurylmethane because furan can be easily functionalized by either aromatic electrophilic substitution or lithiation-functionalization at 2-(or 5-)position. Although its derivatives have been briefly described,[4,5] the parent compound **3** has remained unknown. Here we report the first synthesis, structure and some chemistry of **3**.

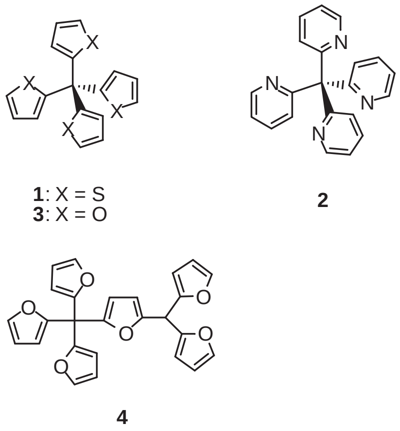
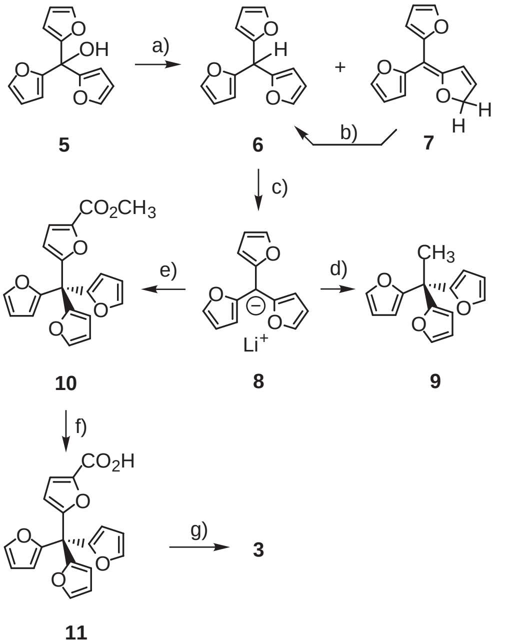


Chart 1.

Recently, Nair and co-workers reported serendipitous formation of a tetrafurylmethane derivative **4** by the reaction of tris(2-furyl)methane **6** with *n*-BuLi.[5] We had considered **6** to be a key synthetic intermediate for **3** and synthesized **6** in a different way from Nair's: reduction of tris(2-thienyl)methyl alcohol **5**, prepared by the reaction of methyl 2-furancarboxylate with two equivalents of 2-furyllithium in THF (96% yield), with $LiAlH_4 \cdot AlCl_3$[6] under controlled conditions[7] afforded about 2:1 mixture (^1H NMR) of reduction products **6** and **7** in up to 80% yield. Although compounds **6** and **7** were hardly separable, treatment of the mixture with KOH in methanol at room temperature effected the isomerization of **7** to **6** to give nearly pure **6**[8] (78% yield after distillation).



Scheme 1. Synthesis of tetrafurylmethane **3** and derivatives: a) 1.2 equiv. $LiAlH_4$–$AlCl_3$/ether, rt, 2 h, 80%; b) 10% KOH/MeOH, rt, 16 h; c) 1.1 equiv. *n*-BuLi– cat. *i*-Pr_2NH/DME, −70 °C, 30 min; d) CH_3I, rt, 1 h, 97% from **6**; e) methyl 5-chloro-2-furancarboxylate/DME, −70–−40 °C, 1 h, 34%; f) 10% NaOH/MeOH, rt, 15 h, 84%; g) Cu powder/quinoline, 180 °C, 2 h, 87%.

Tris(2-furyl)methyl anion **8** turned out to be considerably less stable than tris(2-thienyl)methyl anion[9] that is fairly stable in THF at room temperature. Treatment of **6** with *n*-BuLi in the presence of a small amount of diisopropylamine (ca. 0.1 equiv.) at −70 °C followed by addition of excess methyl iodide and warming up to −20 °C afforded 1,1,1-tris(2-furyl)ethane **9** in 90% yield. However, when the red solution of **8** was first warmed up to 0 °C, the solution turned blackish and addition of methyl iodide resulted in poor yield of **9** (16%). In spite of the stability problem, **8** was found to react with 2-chlorofuran derivatives having electron-withdrawing groups at 5-position: addition of methyl 5-chlorofuran-2-carboxylate[10] (1.0 equiv.) to a THF solution of **8** at −70 °C followed by warming up to −40 °C afforded the desired product **10** though the yield was poor (6–10%). Use of *tert*-butyl ester improved the yield slightly (12%). Better yield (22–32% for the methyl ester) was obtained

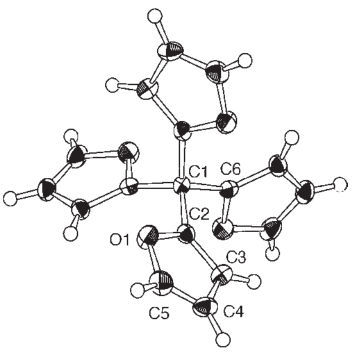


Figure 1. ORTEP drawing of tetrafurylmethane **3**. Selected bond lengths [Å] and angles [°]: C1–C2, 1.517(2); C2–C3, 1.347(2); C3–C4, 1.431(2); C4–C5, 1.331(2); O1–C2, 1.370(2); O1–C5, 1.375(2); C2–C1–C6, 106.83(9); C1–C2–C3, 135.0(1); C2–C3–C4, 106.5(1); C3–C4–C5, 106.5(1); C4–C5–O1, 110.7(1); C2–O1–C5, 106.07(10).

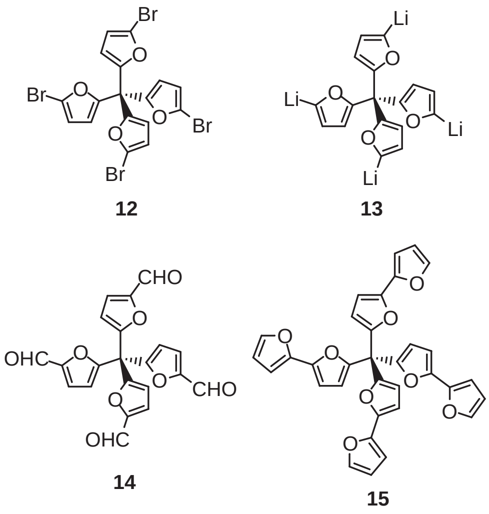


Chart 2.

by change of solvent from THF to DME.[11] Alkaline hydrolysis of **10** in methanol at room temperature gave carboxylic acid **11** (84%) and decarboxylation of **11** by heating at 180 °C in quinoline in the presence of Cu-powder furnished tetrakis(2-furyl)methane **3**[8] as a stable, colorless, and crystalline compound (87%).

Figure 1 shows X-ray structure of **3**.[12] The 2-furyl groups take an alternate up-and-down conformation similar to **1** and **2**. Notably, the bond lengths around the central methane carbon (Cα–C*ipso* = 1.514 Å in average) are shortest among typical tetraarylmethanes (1.524 Å in tetrakis(5-bromo-2-thienyl)methane;[2a] 1.543 Å in **2**,[3a] and 1.553 Å in tetraphenylmethane[13]), probably due to the smallest steric bulkiness of furan.

Reaction of **3** with *N*-bromosuccinimide (NBS) (4.2 equiv.) in DMF at room temperature afforded tetrabromide **12** in 75% yield. Treatment of **12** with *n*-BuLi (6 equiv.) at −40 °C in THF generated tetralithio compound **13** and its reaction with DMF furnished tetraformyl derivative **14** in 76% yield. Compound **14** was also obtained through direct tetralithiation of **3** with *t*-BuLi (10 equiv.) in THF (56%). The Suzuki coupling[14] of **12** with 2-furanboric acid gave tetrakis[2-(5,2′-bifuryl)]methane **15**[8] in 95% yield.

Thus, tetrakis(2-furyl)methane **3** would be a versatile synthon for the synthesis of tetrafurylmethane-based, three-dimensional, novel molecules of physicochemical interest. Improvement of the total yield and further chemistry of **3** are in progress.

References and Notes

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7 Use of excess $LiAlH_4$ over $AlCl_3$ (more than 2:1 molar ratio) at 0 °C gave successful results. Appreciable decomposition of materials occurred with 1:1 ratio of $LiAlH_4 \cdot AlCl_3$.

8 Selected physical and spectroscopic data for **3**, **6**, and **15**. **3**: colorless prisms; mp 130–130.4 °C; MS(EI) m/z (rel. intensity) 280 (M^+, 39%), 251 [$(M\text{-}CHO)^+$, 44%], 213 [$(M\text{-}C_4H_3O)^+$, 20%]; ^1H NMR (270 MHz, $CDCl_3$) δ 7.43 (dd, $J = 1.8$, 1.0 Hz, 4H), 6.36 (dd, $J = 3.3$, 1.8 Hz, 4H), 6.06 (dd, $J = 3.3$, 1.0 Hz, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 152.57, 142.25, 110.22, 108.79, 48.83; UV (cyclohexane) λ_{max} 219 nm ($\log \varepsilon = 4.43$); Found: C, 72.69; H, 4.26%. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32%; **6**: colorless oil; bp 85 °C (0.4 mmHg); ^1H NMR (270 MHz, $CDCl_3$) δ 7.36 (dd, $J = 1.8$, 0.8 Hz, 3H), 6.33 (dd, $J = 3.3$, 1.8 Hz, 3H), 6.12 (dt, $J = 3.3$, 0.8 Hz, 3H), 5.54 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 151.68, 141.80, 110.20, 107.16, 38.91; **15**: colorless prisms; mp 200–201 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.38 (dd, $J = 1.9$, 0.7 Hz, 4H), 6.52 (d, $J = 3.4$ Hz, 4H), 6.48 (dd, $J = 3.5$, 0.7 Hz, 4H), 6.41 (dd, $J = 3.5$, 1.9 Hz, 4H), 6.23 (d, $J = 3.4$ Hz, 4H); ^{13}C NMR (67.8 MHz. $CDCl_3$) δ 151.12, 146.38, 146.32, 141.65, 111.25, 111.07, 105.68, 105.28, 49.22; UV (CH_3CN) λ_{max} 305 ($\log \varepsilon = 4.68$), 291 (4.81), 284 (4.78) nm.

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11 In view of our results on the synthesis of **1** and **2**, use of 5-cyano-2-chlorofuran or methyl 5-fluorofuran-2-carboxylate as a substrate would improve the yield of substitution products.

12 Crystal data for **3** ($C_{17}H_{12}O_4$): $M_r = 280.28$, tetragonal, space group $P4_12_12$, $a = 8.301(1)$ Å, $c = 19.719(4)$ Å, $V = 1358.7(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.370\ g\,cm^{-1}$, Mo K$\alpha$ ($\lambda = 0.71075$ Å), $2\theta_{max} = 55.0°$; 8950 measured reflections, 970 unique, $R_{int} = 0.037$, $R = 0.032$ (1255 data, $I > 2\sigma(I)$), $R_w = 0.072$, GOF = 0.91, CCDC 26518.

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