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Serendipitous Synthesis of 1,1-Bisfuryl-1-[5-(tri-2-furylmethyl)]furylmethane by the Reaction of Tri-2-furylmethane with *n*-Butyllithium[†]

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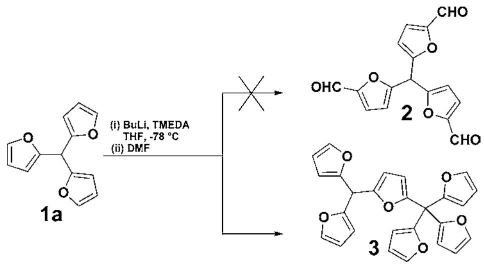
ABSTRACT



In an experiment designed to synthesize the tricarboxaldehyde 2 from tri-2-furylmethane, we observed the serendipitous formation of 1,1-bisfuryl-1-[5-(tri-2-furylmethyl)]furylmethane 3, presumably via the intermediacy of the tri-2-furylmethyl radical.

The fundamental discovery of the triphenylmethyl radical by Gomberg in 1900[1] heralded a new era in organic chemistry. Gomberg's hypothesis of the equilibrium between triphenylmethyl radical and hexaphenylethane captured the imagination of leading organic chemists in the U.S. and Europe who engaged in this new realm of chemistry, viz., free radical chemistry. Although the original hexaphenyl ethane structure assigned for the dimer was wrong, and the correct quinoid structure was suggested by Jacobson as early as 1905,[2] the issue was settled only in 1968 by Nauta, MacLean, and Lankamp, who provided convincing evidence for the quinoid structure of the dimer.[3]

Despite the universal interest shown in the triphenylmethyl radical and its dimer,[3–5] surprisingly, there has been very little work on their heterocyclic analogues. The detection of tri-2-thienyl and tri-3-thienylmethyl radicals by Mangini[6] and the dimerization of the tri-2-thienylmethyl radical, generated by the reduction of the corresponding cation, studied in detail by Nakayama,[7] are noteworthy in this connection. In the context of an ongoing research program in our laboratory that is concerned with the synthesis of furan-based dendrimers, we became interested in the chemistry of tri-2-furyl methane **1a**[8] (Figure 1). In particular, we were intrigued by the possibility of generating a Gomberg-type radical from **1a**, and the results of our efforts are presented in this letter. Our initial plan was to generate the radical from the halo derivatives **1b**–**d** of **1a** by reduction of the carbon–halogen

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[†] This paper is dedicated to Professor Gilbert Stork in honor of his seminal contributions to organic chemistry.

(1) Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757.

(2) Jacobson, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 196.

(3) Lankamp, H.; Nauta, W. Th.; MacLean, C. *Tetrahedron Lett*. **1968**, *47*, 249.

(4) (a) Guthrie, R. D.; Wiesman, G. R. *Chem. Commun*. **1969**, 1316. (b) Staab, A.; Breltschneider, H.; Brunner, H. *Chem. Ber*. **1970**, *103*, 1101. (c) Volz, H.; Lotsch, W.; Schnell, H. W. *Tetrahedron* **1970**, *26*, 5343.

(5) For review of the work in this area, see: McBride, J. M. *Tetrahedron* **1974**, *30*, 2009.

(6) (a) Mangini, A.; Pedulli, G. F.; Tiecco, M. *Tetrahedron Lett*. **1968**, *47*, 4941. (b) Bernardi, F.; Guerra, M.; Pedulli, G. F.; Kurt, M. *Tetrahedron* **1976**, *32*, 951.

(7) Nakayama, J.; Ishii, A.; Yamada, Y.; Sugino, M.; Hoshino M. *Tetrahedron Lett.* **1990**, *31*, 2627.

(8) Prepared by the condensation reaction of furfural and furan in the presence of phosphorous pentoxide, using benzene as the solvent (cf.: Nakayama, J.; Sugino, M.; Ishii, A.; Hoshino, M. *Chem. Lett*. **1992**, 703).

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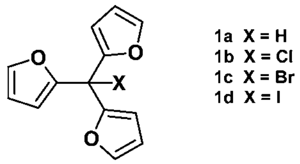
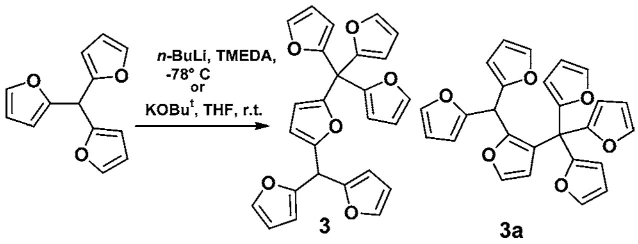


Figure 1. Tri-2-furylmethane and the potential radical precursors.

bond using metals such as Ag or Zn in the manner of Gomberg. This plan, however, was foiled by the difficulty in accessing the halocompounds by a variety of methods.[9]

Contemporaneous with the aforementioned investigations, we were interested in the preparation of the trialdehyde **2** from **1a**. The synthesis of tri-5-formyl-2-thienylmethane from tri-2-thienylmethane by Oda and co-workers appeared attractive in this context.[10] Adopting similar experimental conditions, we performed the following reaction. To a stirred solution of compound **1a** and a catalytic amount of TMEDA in THF kept at −78 °C was added *n*-BuLi (4 equiv). The deep red solution that resulted was stirred for 30 min at −78 °C. DMF (4 equiv) was added to the solution with the expectation of obtaining the trialdehyde **2**. Surprisingly, however, the product obtained in 40% yield (91% considering the recovery of the starting material), as a very pale yellow liquid, was found to be **3** (Scheme 1). Any role for DMF in this reaction can be discounted since **3** was obtained in comparable yields from experiments which excluded DMF. Subsequent experiment showed that **3** could be obtained in 50% yield more conveniently by treating **1a** with KOBu^t (2 equiv) in THF at rt for 30 min.

Scheme 1. Reaction of Tri(2-furyl)methane with *n*-Buli/KOBu^t



The structure of the product **3** was established by spectroscopic analysis. In the proton NMR spectrum of **3** (300 MHz, $CDCl_3$), shown in Figure 3, the methine proton-labeled **a** resonated as a singlet at δ 5.50 ppm. The identity of this proton was discernible from its chemical shift (δ 5.50 ppm) comparable to that of the methine proton (δ 5.52 ppm) of its precursor tri-2-furylmethane **1a**. In both cases, the methine protons were exchangeable with D_2O (KOBu^t, THF, rt, 30 min); no other protons exchanged under these conditions. Proton **f** appeared as a doublet around δ 5.92 ppm, while protons **d**, **e**, and **i** appeared as a multiplet centered at δ 6.01 ppm. Two multiplets centered at δ 6.28 and 6.32 ppm correspond to protons **c** and protons **h**. Protons **b** and **g** resonated as doublets at δ 7.30 and 7.39 ppm, respectively. Satisfactory ^{13}C NMR spectral data and HRMS data were also obtained for **3**.

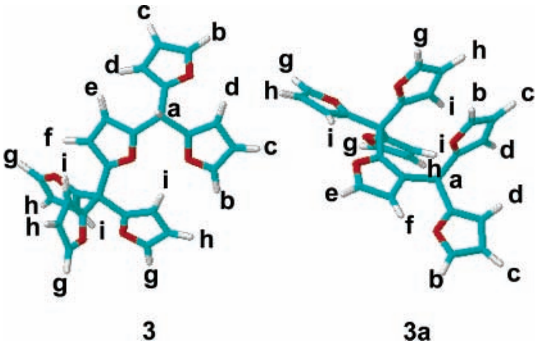


Figure 2. Structural assignment of dimer **3**.

The alternate structure **3a** may be considered for the dimer. However, convincing evidence for its exclusion was obtained from ^{1}H NMR data. In the ^{1}H NMR spectrum, the signals for C-2 protons (labeled **b** and **g**) account for only five protons (agreeable with structure **3**) against the six such protons present in **3a**. Further confirmation of the structure assignment came from a Gradient COSY experiment, which showed correlation between the protons resonating at δ 5.92 and 6.01 ppm. These signals are assignable only to protons labeled **e** and **f** in **3**. It may be noted that HMQC was of not much help in this case, since ^{13}C chemical shift values are very close to each other.

Although no definitive mechanistic pathway can be delineated for the reaction at the present time, the following rationalization may be advanced to account for the formation of the product. The initial event may be considered as the deprotonation of **1a** by *n*-BuLi to generate tri-2-furylmethyl anion.[11] The latter then transfers an electron to a second molecule of **1a** to generate a radical/radical anion pair.[12]

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(9) An attempt to synthesize **1b**, via the Friedel−Craft's reaction of furan with CCl_4 and $AlCl_3$, was unsuccessful. Subsequently, we attempted the preparation of the corresponding cation from **1a** using DDQ, followed by trapping with halide ions. Accessing the desired products **1b**−**d** using this strategy also failed. When we tried the synthesis of the iodo derivative **1d** using NIS in the presence of TFA, the desired product was obtained, albeit in very low yields (cf.: Castanet, A. S.; Colobert, F.; Broutin, P. E. *Tetrahedron Lett.* **2002**, *43*, 5047).

(10) Hiroyaki, K.; Kenji, H.; Hiromichi, N.; Takeshi, K.; Oda, M. *Chem. Lett.* **2003**, *32*, 422.

(11) Deep red color of the solution and exchangeability of the methine hydrogen by deuterium (vide supra) lend credence to this assumption. For the record, furan itself is known to be deprotonated at the 2-position (Gilman, H.; Breur, F. *J. Am. Chem. Soc.* **1934**, *56*, 1123). The situation in **1a** is quite different, and it is not surprising that the deprotonation is occurring exclusively at the sp^3 C−H.

(12) Such electron transfers have been alluded to, in general terms, by Bilevitch et al. Bilevitch, K. A.; Bubnov, N. N.; Okhlobystin, O. Yu. *Tetrahedron Lett.* **1968**, *31*, 3465. Also, addition of electrons to electron-rich systems have precedent in the Birch reduction of phenols, and anilines, under very mild conditions. See: (a) Radlick, P.; Crawford, H. T. *J. Org. Chem.* **1972**, *37*, 1669. (b) Nelson, N. A.; Hsi, R. S. P.; Schuck, J. M.; Khan, L. D. *J. Am. Chem. Soc.* **1960**, *82*, 2573. (c) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956**, *78*, 4604.

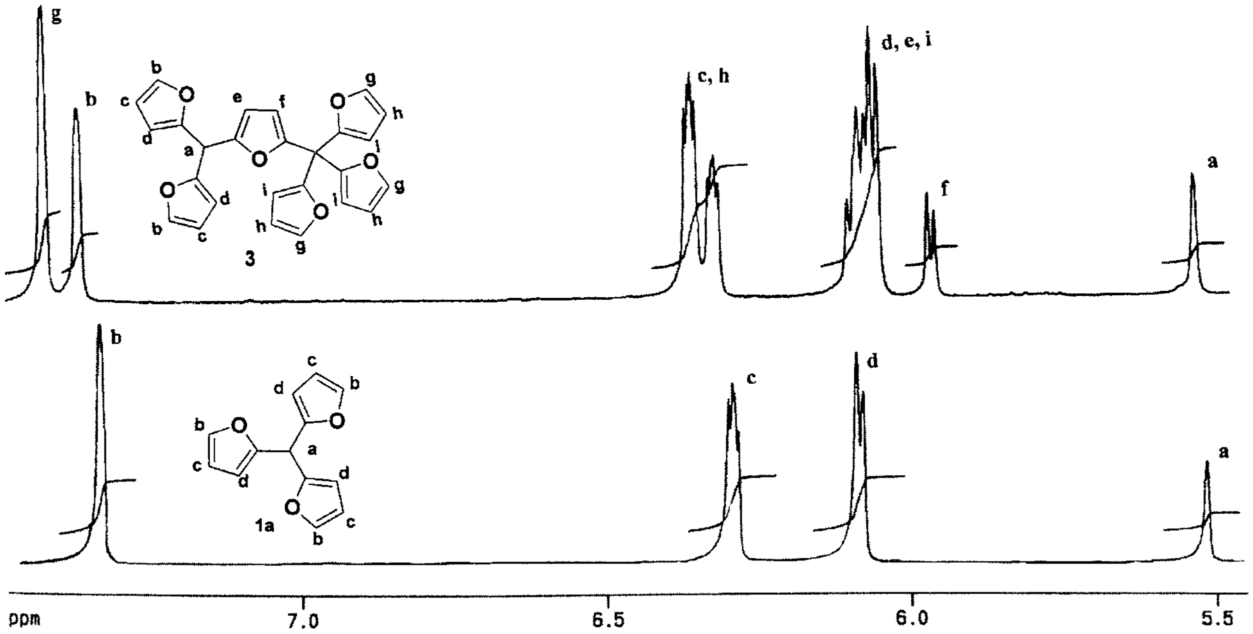
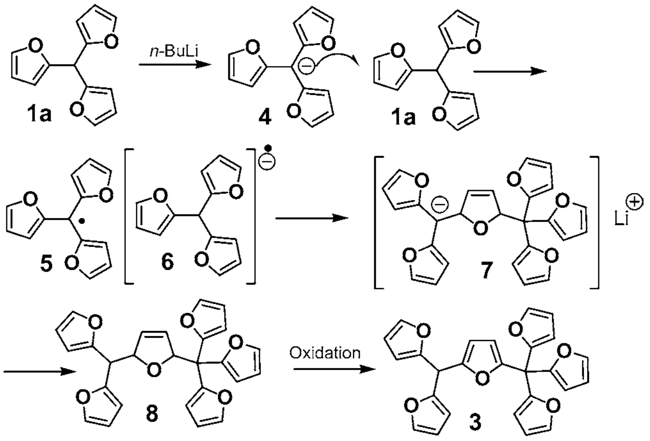


Figure 3. 300 MHz ^{1}H NMR spectrum of **1a** and **3** in $CDCl_3$.

Coupling of the radical and the radical anion leading to a species such as **7** followed by protonation of the latter and subsequent aromatization during workup can conceivably deliver **3** (Scheme 2). Relief of the severe steric strain imposed by the bulky substituents at the 2- and 5-positions of the dihydrofuran **8** may be a crucial factor contributing to its ready aromatization.

Scheme 2. Mechanism



In conclusion, we have uncovered a facile synthesis of 1,1-bisfuryl-1-[5-(tri-2-furylmethyl)]furylmethane from tri-2-furylmethane by the reaction of butyllithium with the latter, presumably via an electron-transfer process. Further work is underway in this area.

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Supporting Information Available: Detailed synthetic procedure and spectroscopic characterization of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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