Reactions of 2,2',5',2"-Terfuran

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Formylation of 2,2',5',2"-terfuran (**1**) with *N*-methylformanilide and phosphorus oxychloride gave 5-formyl-2,2',5',2"-terfuran (**2**) and 5,5"-diformyl-2,2'5',2"-terfuran (**3**). Reduction of **2** and **3** afforded 5-hydroxymethyl-2,2',5',2"-terfuran (**4**) and 5,5" dihydroxymethyl-2,2',5',2"-terfuran (**5**), respectively. Terfuran **1** reacted with phenylmagnesium bromide to give 5-(phenylhydroxymethyl)-2,2',5',2"-terfuran (**6**), and was carbonated to 5-carboxy 2,2',5',2"-terfuran (**7**) and 5,5"-dicarboxy-2,2',5',2"-terfuran (**8**). Bromination of **1** with *N*-bromosuccinimide gave 5,5"-dibromo 2,2',5',2"-terfuran (**9**).

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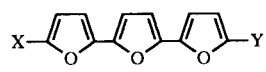
2,2',5',2"-Terthiophene (α-**T**), the sulfur analog of 2,2',5',2"-terfuran (**1**), has been extensively studied because of its phototoxic activity [1,2]. α-**T** is an efficient oxygen generator [3,4,5] and is toxic toward mosquito larvae and other organisms [6,7,8]. The naturally-occurring compound has also been synthesized by various workers [9-16]. Substitution reactions of α-**T** have been reported by Morand and coworkers [17,18] and by Kagan and coworkers [18]. The 5,5"positions on the terthiophene ring system were found to be the most reactive.

In view of the toxicity and chemical reactions of the terthiophene, it was considered worthwhile to synthesize and study the chemistry of 2,2',5',2"-terfuran (**1**), which is not naturally occurring. We are also synthesizing and studying the chemistry of other three-ring systems having a mixture of furan and thiophene rings, specifically 2,2"-dithiophene-2',5'-furan. This paper deals only with the chemistry of **1**. Syntheses of **1** include heating 1,4-difuryl-1,4-butanedione with acetic anhydride and hydrochloric acid [9,19,20], reaction of 2,5-dibromofuran with 2-(tributylstannyl)furan [21], reaction of 2,2'-bifuranyl with furan-2-lithium [22], and reaction of 1,4-di(furyl)but-2-yne-1,4-diol with $Pd_2(dba)_3CHCl_3$,Bu_3P [23]. Spectra (nmr, ir, uv, mass) were obtained and interpreted [9,19-22,24,25].

Ishida and coworkers [21] brominated **1** with *N*-bromosuccinimde and obtained 5,5"-dibromo-2,2',5',2"-terfuran (**9**). Exhaustive bromination with *N*-bromosuccinimide gave 3,3",5,5"-tetrabromo-2,2',5',2"-terfuran and at higher temperatures 3,3',3",4',5,5"-hexabromo-2,2',5',2"-terfuran. The ^{1}H nmr spectra of the bromo compounds were reported. El-Hajj and coworkers [19] synthesized 5,5"-dimethyl-2,2',5',2"-terfuran from (methyl-5"(bifuryl-5',2")-2')-1-pentanedione-1,4, acetic anhydride, and sulfuric acid. 5,5"-Diethyl-2,2',5',2"-terfuran was prepared from furan and ethanol at 140° with ruthenium chloride catalyst [26]. Tetrafuran was synthesized from 2,2'-bifuryl, *n*-butyllithium and cupric chloride [22]. Leung and LeGoff prepared 1,4-bis(5-2,2':5',2"terfuryl)-1,4-butanedione from tetra-*N*-methylsuccinimide, terfuran and *n*-butyllithium [27].

In this laboratory **1** was prepared by the general method of El-Hajj and coworkers [19] from 1,4-difuryl-1,4-butanedione [28]. 5-Formyl-2,2',5',2"-terfuran (**2**) was prepared from **1** and a mixture of *N*-methylformanilide and phosphorus oxychloride by the Vilsmeier-Haack reaction [17]. The monoaldehyde was obtained in 63% yield when the ratio of **1** and the complex *N*-methylformanilidephosphorus oxychloride was 1:1. 5,5"-Diformyl-2,2',5',2"-terfuran (**3**) contaminated the monoaldehyde but could easily be removed by column chromatography. No reaction occurred unless the *N*-methylformanilide and phosphorus oxychloride mixture was stirred until a yellow solid formed. The diformyl derivative **3** was obtained in 81% yield when the ratio of complex to **1** was 3:1. The aldehydes were identified by elemental analysis, ^{1}H nmr, ir, and by the 2,4-dinitrophenylhydrazone of **2**.

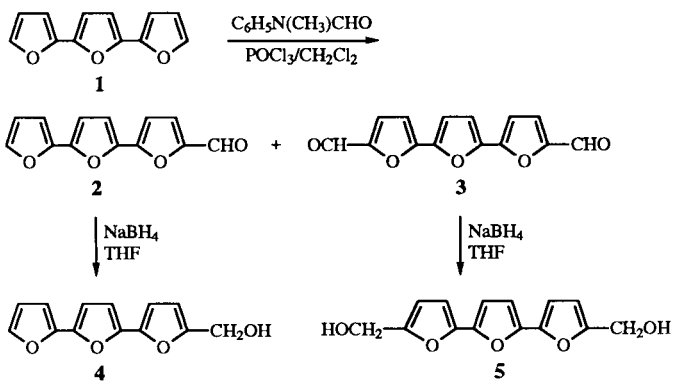
Table 1
Compounds of Terfuran



1, X = H, Y = H
2, X = H, Y = CHO
3, X = CHO, Y = CHO
4, X = H, Y = CH_2OH
5, X = CH_2OH, Y = CH_2OH
6, X = H, Y = $CH(OH)C_6H_5$
7, X = H, Y = COOH
8, X = COOH, Y = COOH
9, X = Br, Y = Br

Reduction of **2** and **3** with sodium borohydride in tetrahydrofuran gave excellent yields of 5-hydroxymethyl-2,2',5',2"-terfuran (**4**) and 5,5"-dihydroxymethyl-2,2',5',2"-terfuran (**5**), respectively. The aldehyde ^{1}H nmr absorption at δ 9.6 disappeared during the reduction of **2** and **3** and was replaced by absorptions of the CH_2 (δ 4.75) and OH (δ 4.3) hydrogens. 5-Formyl-2,2',5',2"-terfuran (**3**) underwent a Grignard reaction with phenylmagnesium bromide to give 5-(phenylhydroxymethyl)-2,2',5',2"-terfuran (**6**).

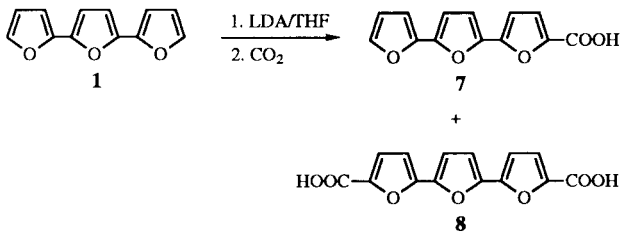
Scheme 1



Carbonylation of **1** was accomplished by preparing lithium diisopropylamine from diisopropylamine and *n*-butyllithium. The amine ion extracted a hydrogen atom from the 5-position of **1**. The resultant carbanion reacted with carbon dioxide ("Dry Ice") to give 5-carboxy-2,2',5',2"-terfuran (**7**). Compound **7** was insoluble in most organic solvents except hot acetone but was soluble in an aqueous sodium hydroxide solution. Infrared, elemental analysis, and solubility in strong base supported the assigned structure. Dicarbonylation of **1** to 5,5"-dicarboxy-2,2',5',2"-terfuran (**8**) was effected by the use of an excess of *n*-butyllithium. The solid product was soluble only in concentrated ammonia and aqueous sodium hydroxide solution. The di-acid was purified by dissolving in aqueous sodium hydroxide and reprecipitating with hydrochloric acid. A distinct melting point could not be obtained because **8** began to decompose at 240°.

It is possible that **8** was contaminated by **7** in the crude product and **7** was lost in the reprecipitation step. It was found independently that when attempts were made to purify **7** by dissolving in sodium hydroxide solution and acidifying no product precipitated.

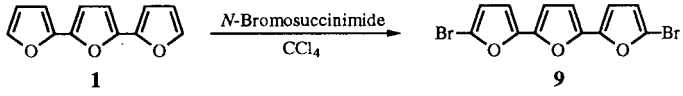
Scheme 2



5,5"-Dibromo-2,2',5',2"-terfuran (**9**) was synthesized from **1** and two moles of *N*-bromosuccinimide [21]. From observation of the changing intensity of the δ 7.47 peak in the ^{1}H nmr spectrum (peak assigned to the 5 and 5" hydrogens) [22] during the reaction, monobromo terfuran and more highly brominated products were probably obtained. These were not isolated and purified. Efforts to isolate pure dibromide were unsuccessful until triethylamine was added to the methylene chloride solution before concentration. In the absence of the triethylamine, the product, when dry, would quickly change to a black resinous material with melting point greater than 400°. Analysis of the resin showed high percentages of bromine. Perhaps the generated hydrogen bromide polymerized the monomeric bromo compounds. It was noted that when triethylamine was added to the methylene chloride solution a small amount of triethylamine hydrobromide precipitated and was filtered off.

Attempts to chlorinate and iodinate with *N*-chlorosuccinimide and *N*-iodosuccinimide were unsuccessful. The *N*-chlorosuccinimide did not react, whereas *N*-iodosuccinimide gave a mixture of products including large amounts of polymeric material which did not melt up to 400°. In most of the reactions of **1** there appeared to be a greater tendency toward polymerization than that reported for the reactions of 2,2',5',2"-terthiophene [17,18].

Scheme 3



EXPERIMENTAL

Terfuran (**1**) was synthesized in this laboratory or was obtained from the Riverside Organic Research Lab, Apakoneta, Ohio. Furfuraldehyde was freshly distilled before use and other chemicals and solvents were commercial grade and used without further purification. Chlorinated solvents were dried over molecular sieves and hydrocarbon and ether solvents were dried over sodium. Reactions were carried out at room temperature unless otherwise stated. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Nicolet 5DXB Fourier Transform Spectrometer and the ^{1}H nmr spectra on a 270 MHz JEOL FT-NMR. Elemental analyses were by the Midwest Microlab, Inc., Indianapolis, Indiana.

1,4-Difuryl-1,4-butanedione.

Using the method of Stetter and Bender [28] the dione was prepared from furfuraldehyde and divinyl sulfone in the presence of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride catalyst. 2,2',5',2"-Terfuran (**1**).

To prepare **1**, 1,4-difuryl-1,4-butanedione was heated with acetic anhydride and hydrochloric acid for 2 days [19]. Extraction with dichloromethane and concentration gave a crude product which was purified by passing through a silica gel column and eluting with hexane. The average yield was 65%, mp 61-62° (lit 63° [19]).

5-Formyl-2,2',5',2"-terfuran (**2**).

A mixture of 0.32 ml (2.7 mmoles) of *N*-methylformanilide and 0.23 ml (2.5 mmoles) of phosphoryl chloride [17] was magnetically stirred under nitrogen until a yellow solid formed (10 minutes). A solution of **1** (500 mg, 2.5 mmoles) in 10 ml of dried dichloromethane was added and the grape-wine solution stirred for 48 hours.. An additional 10 ml of dichloromethane and 50 ml of 2.5*M* hydrochloric acid were added and the mixture stirred for 1 hour. Separation of the layers and further

extraction with 3 x 25 ml of dichloromethane gave an organic layer with some black solid. The latter was filtered off, the organic layer dried over anhydrous magnesium sulfate, and the solvent evaporated *in vacuo* to afford 360 mg (63%) of green-yellow solid, mp 107-110°. Chromotography on silica gel and elution with chloroform gave **2**, mp 114-115°; ^{1}H nmr (deuteriochloroform): δ 6.53 (q, 1H), 6.65-6.82 (m, 3H), 6.98 (d, 1H), 7.3 (d, 1H), 7.47 (d, 1H), 9.6 (s, 1H); ir (potassium bromide): ν max 2884, 1670, 1620 cm^{-1}.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.51. Found: C, 68.10; H, 3.85.

5,5"-Diformyl-2,2',5',2"-terfuran (**3**).

N-Methylformanilide (108 mg, 8.0 mmoles) and phosphoryl chloride (107 mg, 7.0 mmoles) were stirred together under nitrogen for 10 minutes. To the resultant yellow complex was added **1** (500 mg, 2.5 mmoles) in 10 ml of dichloromethane. After 41 hours of stirring the orange solid and solution were added to 50 ml of 2.5*M* hydrochloric acid and stirred for 1 hour. The solid **3** was collected by suction filtration, washed successively with dichloromethane and water, and dried, 520 mg (81%), mp 239-240° dec. Recrystallization from acetone gave product with mp 241-242° dec. The product was insoluble in most organic solvents and only slightly soluble in boiling acetone; ^{1}H nmr (deuteriochloroform): strong peak at δ 9.6 (CHO), missing peak at 7.47; ir (potassium bromide): ν max 2890, 1669,1615 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 65.62; H, 3.13. Found: C, 65.32; H, 3.02.

5-Hydroxymethyl-2,2',5',2"-terfuran (**4**).

Sodium borohydride (45.4 mg, 1.2 mmoles) was added to **2** (228 mg, 1.0 mmole) in 15 ml of dry THF. After 21 hours of stirring the solvent was removed *in vacuo* and 25 ml of water added to the solid. The mixture was acidified with 6*M* hydrochloric acid, and the green solid collected by filtration, washed with water, and dried to give 233 mg (100%) of solid, mp 112-115°. Trituration with petroleum ether afforded 210 mg (91%) of solid mp 114-116°. Recrystallization from ethanol/water gave pure **4**, mp 115-116°; ir (potassium bromide): ν max 3396 (OH), 2924 (CH), 1610 (aromatic ring) cm^{-1}; an absorption at 1670 cm^{-1} was absent.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.67, H, 4.55.

5,5"-Dihydroxymethyl-2,2',5',2"-terfuran (**5**).

A mixture of **3** (250 mg, 0.98 mmole) and sodium borohydride (132 mg, 3.5 mmoles) in 20 ml of dry THF was stirred for 24 hours. The mixture of white solid and solution was concentrated *in vacuo* to give 455 mg of solid to which was added 25 ml of water and enough hydrochloric acid to acidify the mixture. Filtration, washing on the filter with water, and drying gave 209 mg (82%) of white-yellow solid **5**, mp 184-186°. Recrystallization from ethanol/water gave platelets, mp 190-192°. Further recrystallization gave no change in mp; ir (potassium bromide): 3385 (OH), cm^{-1}; a peak at 1669 (C=O) was absent.

Anal. Calcd. for $C_{14}H_{12}O_5$:C, 64.61; H, 4.65. Found: C, 64.28; H, 4.90.

5-(Phenylhydroxymethyl)-2,2',5',2"-terfuran (**6**).

Terfuran monoaldehyde (**2**) (200 mg, 0.87 mmole) was placed in a dry 100-ml round-bottomed 3-necked flask along with 15 ml of THF. Commercial 3*M* (in ether) phenylmagnesium bromide (0.59 ml, 1.76 mmoles) was added and the red mixture stirred at 40-50° for 3 hours under nitrogen. The mixture was hydrolyzed by adding 25 ml of 0.50*M* hydrochloric acid and 15 ml of ether. The separated organic layer was washed with 3 x 15 ml of water, dried over anhydrous magnesium sulfate, and concentrated to a light brown solid, **6**, (205 mg, 77%), mp 124-129°. Recrystallization from benzene/petroleum ether gave a product with mp 153-154°; ir (potassium bromide): ν max 3469 (OH), 3015 (aromatic C-H), 2924 (aliphatic C-H), 1576 and 1605 (aromatic C=C) cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.51; H, 4.58. Found: C, 74.89; H, 4.37.

2,4-Dintrophenylhydrazone of **2**.

A solution (10 ml) of 2,4-dintrophenylhydrazine reagent [29] was added to 228 mg (1.0 mmole) of **2** in 3 ml of ethanol and the mixture shaken. The brown crystals were collected by suction filtration, washed with water on the filter, and dried to give a product (225 mg, 63%), mp 192° dec. Recrystallization from ethanol gave **2**, mp 223-225° dec.

Anal. Calcd. for $C_{19}H_{12}N_4O_7$: C, 55.89; H, 2.93; N, 13.60. Found: C, 55.52; H, 2.80; N, 13.29.

5-Carboxy-2,2',5',2"-terfuran (**7**).

Diisopropylamine (0.35 ml, 2.5 mmoles) was added to a 100-ml round-bottomed 3-necked flask containing 25 ml of dry THF under nitrogen. *n*-Butyllithium (1.0 ml, 2*M* in hexanes, 2.5 mmoles) was added and the mixture stirred 30 minutes at -30 to -50°. Terfuran (**1**) (503 mg, 2.5 mmoles) in 10 ml of THF was added and the mixture stirred an additional 30 minutes. To the creamy thick yellow mixture was added an excess of "Dry Ice" in small portions. The mixture was stirred 30 minutes cold and an additional 1 hour without cooling. Acidification with 3*M* hydrochloric acid followed by concentration of the mixture *in vacuo* gave 585 mg (95%) of yellow solid, mp 188-194° dec. Washing with hexane afforded product, mp 195-196° dec; ir (potassium bromide): ν max 3050-2600, 1673 cm^{-1}. Product **7** was insoluble in methanol, water, chloroform, and acetic acid, but soluble in hot acetone and 5% sodium hydroxide solution.

Anal. Calcd. for $C_{13}H_8O_5$: C, 63.91; H, 3.32. Found: C, 63.70; H, 3.56.

5,5"-Dicarboxy-2,2',5',2"-terfuran (**8**).

To a mixture of 0.35 ml (2.5 mmoles) of diisopropylamine and 1.60 ml (3.7 mmoles) of 2.5*M* *n*-butyllithium in hexanes was added 505 mg (2.5 mmoles) of **1** in 20 ml of dry THF at -30°. "Dry Ice" was added during 15 minutes at -50° with stirring. The thick yellow mixture was allowed to stand at room temperature overnight after which it was reddish-brown. Acidification with 3*M* hydrochloric acid restored the yellow color. The solid was collected by suction filtration, washed with water and then with low-boiling petroleum ether, and dried to provide the product, 426 mg (59%), mp 200-250° dec. A sample was purified by dissolving in 5% sodium hydroxide solution and reprecipitating with hydrochloric acid solution. The dried yellow solid darkened at about 240° and decomposed to a black solid at 300°. It was slightly soluble in boiling acetone and chloroform, soluble in concentrated ammonium hydroxide and sodium hydroxide solutions, but insoluble in water, acetic acid, and concentrated hydrochloric acid; ir (potassium bromide): ν max 2660-3100, 1676 cm^{-1}.

Anal. Calcd. for $C_{14}H_8O_7$: C, 58.34; H, 2.78. Found: C, 58.08; H, 3.02.

5,5"-Dibromo -2,2',5',2"-terfuran (**9**).

N-Bromosuccinimide (752 mg, 4.22 mmoles) and **1** (422 mg, 2.11 mmoles) in 30 ml of dried carbon tetrachloride were stirred for 65 hours. The precipitated succinimide (397 mg, 96%) was filtered off, mp 115-119°. Triethylamine (2 ml) was added to the filtrate and the small amount of precipitate removed by filtration. Concentration *in vacuo* gave 350 mg (46%) of **9**, mp 108-110°. Recrystallization from petroleum ether gave **9**, mp 116-116.5° (lit 115° [21]); ^{1}H-nmr (deuteriochloroform): δ 6.52, 6.50, 6.31; absorption in the δ 7.4 region was not observed.

Anal. Calcd. for $C_{12}H_6Br_2O_3$: C, 40.22; H, 1.68; Br, 44.65. Found: C, 40.11; H, 1.48; Br, 44.47.

Acknowledgements.

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