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# SYNTHESIS of 2,5-BIS-(ETHYNYL)FURAN DERIVATIVES FROM 2,5-FURANDICARBOXALDEHYDE

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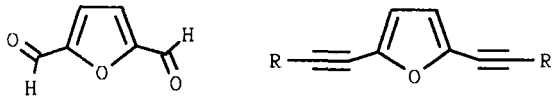
A synthesis of the title compounds has been accomplished by conversion of 2,5-furandicarboxaldehyde to the dilithium salt of 2,5-bis-(ethynyl)furan followed by reaction with electrophiles.

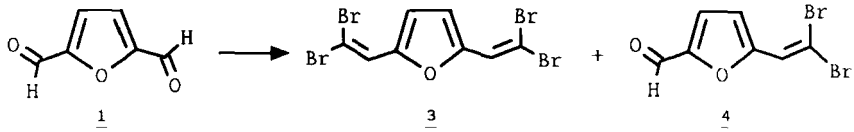
2,5-Furandicarboxaldehyde **1**, a compound isolated from the biomass,[1] constitutes an interesting synthon for the preparation of a wide variety of compounds with industrial and biological properties.[2] Within our interest in the transformation of **1** into synthetically useful functionalized furan derivatives,[3] we have undertaken its conversion into 2,5-bis-(ethylidene)-furan derivatives **2** (Figure **1**).

For this proposal, the Corey and Fuchs' reaction[4] provides an useful procedure for the one carbon homologation of aldehydes into alkynes *via* the



1 2

Figure 1



1 3 4

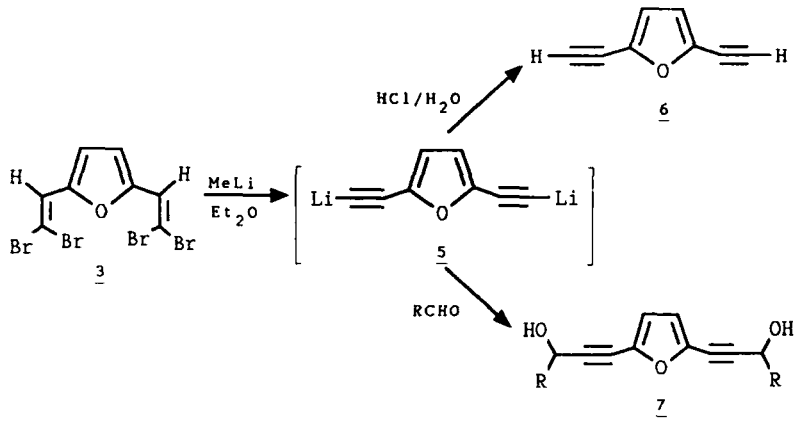
Scheme 1



corresponding dibromo olefin, which constitutes an appealing possibility for the transformation in hand due to its previously tested applicability to furfural.[5]

Treatment of **1** with six equivalents of the carbon tetrabromide - triphenylphosphine - zinc dust reagent under standard Corey and Fuchs' conditions[4] gave rise, after 15 min reaction, to the bromo olefins **3** and **4** in 65% and 35% isolated yield respectively (Scheme **1**).

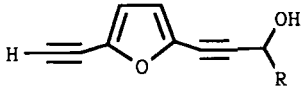
Compound **3** reacts with 4 equivalents of MeLi in $Et_2O$ at -78°C for 1 h and then 25°C for 1 h to afford, after hydrolysis of the *in situ* generated dilithium intermediate **5** with 5% HCl solution, 2,5-bis-(ethynyl)-furan **6** in 70% isolated yield; whereas reaction of **5**, generated from the bromo olefin **3** with BuLi in THF




Scheme 2

solution, with an excess of aromatic and aliphatic aldehydes, gave rise to the otherwise difficult to prepare propargyl alcohol derivatives **7** (Scheme **2**). Yields in pure, isolated products after column chromatography on silica gel were between 40 and 55%.

It has to be pointed out that in all cases much aldehyde was recovered unchanged, and the corresponding alkyl or benzyl alcohol appeared as the major by-product. Noteworthy, the presence of benzyl alcohol and benzoic acid has also been observed in the reaction of sodium acetylide with benzaldehyde in liquid ammonia.[6]



8

a) R = $C_6H_5$; b) R = p-$NO_2$-$C_6H_4$
c) R = p-Br-$C_6H_4$

Figure 2



Several attempts were made in order to improve the yields in ethynylcarbinols **7** taking the reaction with p-nitrobenzaldehyde as a model example and varying the base or the solvent. Thus, a deleterious effect was observed by replacement of BuLi by MeLi or PhLi in THF. On the other hand, using BuLi as base and DME as solvent, only p-nitrobenzyl alcohol was recovered together with unchanged starting aldehyde. However, the same result as with THF was achieved when $Et_2O$ was used as reaction medium. Finally, no reaction was observed either in THF or $Et_2O$ in the presence of DMPU or TMEDA as cosolvents.

An interesting case of monofunctionalization of **6** was observed in 1,4-dioxane at room temperature. In this case, compound **8b** was obtained (40%) together with **7b**. This result was extended to the synthesis of compounds **8a,c** (Figure **2**).

Other attempts to raise the yields of compounds **7** and **8**, were made by transformation of the dilithium

intermediate **5** into the corresponding organomagnesium and organocerium reagents by *in situ* reactions with anhydrous $MgCl_2$ or anhydrous $CeCl_3$ prior to the introduction of the aldehyde. In both cases no reaction was observed.

Finally, it is worth to be mentioned that attempts of direct formation of the Grignard derivative by reaction of **3** with magnesium turnings in THF or $Et_2O$ was unsuccessful, either following previously described procedures for dibromo olefins[7] or by the entrainment method with 1,2-dibromoethane.[8]

## Experimental

### Reaction of 2,5-Furandicarboxaldehyde 1 with the Carbon Tetrachloride - Triphenyphosphine - Zinc Dust Reagent.

**2,2-bis-(dibromovinyl)furan 3**

(2.83 g, 65%), m.p. 73-75 °C (hexane) ; $\nu_{max}$ ($CCl_4$) 1730 $cm^{-1}$ ($CH=CBr_2$vs); $\delta_H$ ($CDCl_3$) 6.91 (2H, s, Furan), and 7.3 (2H, s, $CH=CBr_2$); $\delta_C$ ($CDCl_3$) 88.77 ($CBr_2$), 113.27 (Furan C-3), 125.84 (=CH), and 149.51 (Furan C-2)

**5-(2,2-dibromovinyl)-2-furancarboxaldehyde 4** (0.98 g, 35%), m.p. 94-96 °C (hexane-ethyl acetate) ; $\nu_{max}$ ($CCl_4$) 1700 ($CH=CBr_2$vs) and 1650 $cm^{-1}$ (CHO); $\delta_H$ ($CDCl_3$) 7.15, 7.17 (1H, d, J 3.9 Hz, Furan 4-H), 7.28, 7.29 (1H, d, J 3.9 Hz, Furan 3-H); 7.52 (1H, s, $CH=CBr_2$); and 9.66 (1H, s, CHO); $\delta_C$ ($CDCl_3$) 94.11 ($CBr_2$), 113.15 (Furan C-4), 121.89 (Furan C-3), 125.78 (=CH), 151.33 (Furan C-5), 154.42 (Furan C-2), and 177.55 (CHO).

**2,5-bis-(Ethylidene)furan 6.**

(40 mg, 70%), b.p. 70 °C/690 Torr (Kugelrohr distillation); $\nu_{max}$ (neat) 2230 $cm^{-1}$ (C≡C); $\delta_H$ ($CDCl_3$) 3.88 (2H, s, C≡C-H), and 6.59 (2H, s, Furan); $\delta_C$ ($CDCl_3$) 65.83 (C≡CH), 82.28 (C≡CH), 116.77 (Furan C-3), and 136.85 (Furan C-2).

**Synthesis of 3'-Substituted 2,5-bis-(3-Hydroxy-1-propynyl)furans 7. General Procedure.**

A solution of **3** (218 mg, 0.5 mmol) in THF (20 ml) at -78 °C was treated with a 1.6 M solution of BuLi in hexane (1.5 ml, 2.4 mmol). After being stirred for 1 h at -78 °C, the reaction mixture was warmed to 25 °C and maintained for 1.5 h at that temperature. The mixture was cooled to -78 °C and the corresponding aldehyde (1.2 mmol) in THF (1 ml) was dropwise added. The temperature was slowly raised up to 25 °C and the mixture was stirred for 2 h longer. The solution was

hydrolized with 5% HCl solution (20 ml) and extracted with chloroform. The combined extracts were washed with aqueous sodium hydrogen carbonate, sodium bisulphite, and water. After drying on magnesium sulphate, the solvent was evaporated under reduced pressure. The resultant product was purified by column chromatography on silica gel with hexane-ethyl acetate (2:3) as the eluant for compounds **7a-c** and (4:1) for **7d**.

**2,5-bis-(3-Hydroxy-3-phenyl-1-propynyl)furan 7a.**

(75 mg, 45%); $\nu_{max.}(CCl_4)$ 3300 (OH) and 2200 $cm^{-1}$ (C≡C); $\delta_H(CDCl_3)$ 5.66 (2H, s, CH-C≡C), 6.56 (2H, s, Furan), 7.26-7.40 (6H, m, Phenyl 3-H and 4-H), and 7.53, 7.55 (4H, d, J 7.1 Hz, Phenyl 2-H); $\delta_C(CDCl_3)$ 64.98 (CHOH), 93.63 (C≡C-CHOH), 98.56 (C≡C-Furan), 116.61 (Furan C-3), 124.65, 128.65, 128.75 (Phenyl C-2, C-3, and C-4), 136.96 (Furan C-2), and 139.64 (Phenyl C-1).

**2,5-bis-[3-Hydroxy-3-(p-nitrophenyl)-1-propynyl]furan 7b.**

(85 mg, 40%); $\nu_{max.}(CCl_4)$ 3320 (OH) and 2210 $cm^{-1}$ (C≡C); $\delta_H(CDCl_3)$ 5.80 (2H, s, CH-C≡C), 6.61 (2H, s, Furan), 7.72, 7.75 (4H, d, J 8.4 Hz, Aryl 3-H), and 8.22, 8.25 (4H, d, J 8.4 Hz, Aryl 2-H); $\delta_C(CDCl_3)$ 63.85 (CHOH), 92.61 (C≡C-CHOH), 98.55 (C≡C-Furan), 117.19 (Furan C-3), 123 90 (Aryl C-3), 127.34 (Aryl C-2),

136.73 (Furan C-5), and 146.24 and 146.26 (Aryl C-1 and C-4).

**2,5-bis-[3-(p-Bromophenyl)-3-hydroxy-1-propynyl)furan 7c.**

(95 mg, 40%); $\nu_{max.}(CCl_4)$ 3310 (OH) and 2200 $cm^{-1}$ (C≡C); $\delta_H(CDCl_3)$ 5.64 (2H, s, CH-C≡C), 6.57 (2H, s, Furan), 7.33, 7.36 (4H, d, J 8.4 Hz, Aryl 3-H), and 7.47, 7.49 (4H, d, J 8.4 Hz, Aryl 2-H); $\delta_C(CDCl_3)$ 64.14 (CHOH), 93.18 (C≡C-CHOH), 98.57 (C≡C-Furan), 116.93 (Furan C-3), 122.38 (Aryl C-4), 129.45 (Aryl C-2), 132.26 (Aryl C-3), 136.58 (Furan C-2), and 138.12 (Aryl C-1).

**2,5-bis-(4-Ethyl-3-hydroxy-1-hexynyl)furan 7d.**

(90 mg, 55%); $\nu_{max}(CCl_4)$ 3350 (OH) and 2220 $cm^{-1}$ (C≡C); $\delta_H(CDCl_3)$ 0.92-0.98 (12H, m, Me), 1.47-1.55 (10H, m, $CH(CH_2)_2$, 4.61 (s, 2H, CH-C≡C), and 6.51 (s, 2H, Furan); $\delta_C(CDCl_3)$ 11.44, 11.59 (Me), 21.87, 22.00 ($CH_2$), 47.32 ($CH(CH_2)_2$), 65.19 (CHOH), 94.32 (C≡C-CHOH), 98.58 (C≡C-Furan), 116.08 (Furan C-3), and 136.99 (Furan C-2).

**Synthesis of 2-(3-Aryl-3-Hydroxy-1-propynyl)-5-ethynyl-furans 8. General Procedure.**

A solution of **3** (218 mg, 0.5 mmol) in 1,4-dioxane (20 ml) at 5 °C was treated with a 1.6 M solution of BuLi

in hexane (1.5 ml, 2.4 mmol). After being stirred for 5 min at 5 °C, the reaction mixture was warmed to 25 °C and maintained for 1.5 h at that temperature. The mixture was cooled to 0 °C and the corresponding aldehyde (1.2 mmol) in THF (1 ml) was dropwise added. The temperature was slowly raised up to 25 °C and the mixture was stirred for 2 h longer. The solution was hydrolized with 5% HCl solution (20 ml) and extracted with chloroform. The combined extracts were washed with aqueous sodium hydrogen carbonate, sodium bisulphite, and water. After drying on magnesium sulfate, the solvente was evaporated under reduced pressure. The resultant product was purified by column chromatography on silica gel with hexane-ethyl acetate (2:3) as eluant.

**2-(3-Hydroxy-3-phenyl-1-propynyl)-5-ethynylfuran 8a.** (45 mg, 40%); $\nu_{max}(CCl_4)$ 3340 (OH), 2220 $cm^{-1}$ (C≡C); $\delta_H(CDCl_3)$ 3.39 (1H, s, C≡C-H), 5.67 (1H, s, C≡C-CH), 6.55-6.57 (2H, dd, J 3.4 Hz, Furan), 7.25-7.41 (4H, m, Phenyl 3-H and 4-H), and 7.54, 7.56 (1H, d, J 7.2 Hz, Phenyl H-2); $\delta_C(CDCl_3)$ 64.54 (CHOH), 66.02 (HC≡C-Furan), 82.73 (C≡C-H), 93.72 (C≡C-CH), 98.94 (C≡C-Furan), 116.44 and 116.56 (Furan C-3 and C-4), 126.58, 128.64, and 128.76 (Phenyl C-2, C-3, and C-4), 136.85 and 136.94 (Furan C-2 and C-5), and 140.01 (Phenyl C-1).

**2-[3-Hydroxy-3-(p-nitrophenyl)-1-propynyl]-5-ethynyl-furan 8b.**

(60 mg, 46%); $\nu_{max.}(CCl_4)$ 3350 (OH), and 2210 $cm^{-1}$ (C≡C); $\delta_H(CDCl_3)$ 3.40 (1H, s, C≡C-H), 5.79 (1H, s, C≡C-CH), 6.59-6.62 (2H, dd, J 3.6 Hz, Furan), 7.73-7.76 (2H, d, J 8.7 Hz, Aryl H-3), and 8.24-8.27 (2H, d, J 8.7 Hz, Aryl H-2); $\delta_C(CDCl_3)$ 63.91 (CHOH), 65.95 (HC≡C-Furan), 82.68 (C≡C-H), 93.74 (C≡C-CHOH), 99.36 (C-C≡C-Furan), 116.96 and 117.01 (Furan C-3 and C-4), 123.92 (Aryl C-3), 127.39 (Aryl C-2), 136.75 and 136.80 (Furan C-2 and C-5), and 146.25 (Aryl C-1 and C-4).

**2-[3-(p-Bromophenyl)-3-hydroxy-1-propynyl]-5-ethynyl-furan 8c.**

(50 mg, 35%); $\nu_{max.}(CCl_4)$ 3340 (OH) and 2225 $cm^{-1}$ (C≡C); $\delta_H(CDCl_3)$ 3.39 (1H, s, C≡C-H), 5.65 (1H, s, C≡C-CH), 6.56-6.58 (2H, dd, J 3.5 Hz, Furan), 7.34-7.37 (2H, d, J 8.4 Hz, Aryl H-3), and 7.48-7.50 (2H, d, J 8.4 Hz, Aryl H-2); $\delta_C(CDCl_3)$ 64.14 (CHOH), 65.85 (C≡C-H), 82.38 (HC≡C-Furan), 93.18 (C≡C-CHOH), 98.54 (C-C≡C-Furan), 116.93 and 116.99 (Furan C-3 and C-4), 122.39 (Aryl C-4), 129.48 (Aryl C-2), 132.29 (Aryl C-3), 136.58, 136.62 and 138.12 (Aryl C-1, Furyl C-2 and C-5).

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