A Selective Synthesis of 4-Bromo-2-furancarboxaldehyde and its Pinacolborane Derivative

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A selective synthesis of ethylene acetal of 4-bromo-2-furancarboxaldehyde (**4**) and its pinacolborane derivative (**5**) is described. The synthesis was carried out using 2-furancarboxaldehyde (**1**) that was brominated to 4,5-dibromo-2-furancarboxaldehyde (**2**) in an emulsion of aluminum chloride and methylene chloride. The product was isolated, protected as ethylene acetal, and selectively debrominated to the ethylene acetal of 4-bromo-2-furancarboxaldehyde (**4**) in one step. This moiety was reacted with pinacolborane to give a reactive reagent of Suzuki coupling.

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Introduction.

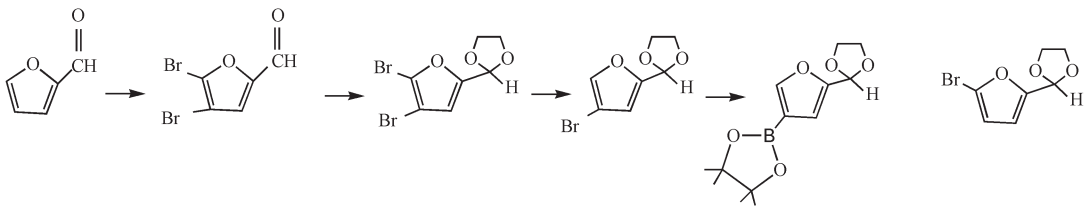
Ethylene acetal of 4-bromo-2-furancarboxaldehyde (**4**) is the starting material for the synthesis of important biologically active compounds such as the cardioactive cardenolide steroids [1-6]. The pinacolborane derivative (**5**) of the above mentioned material could be used to synthesize these cardioactive steroids in a Suzuki reaction with enol triflates [7-8]. In the process of its synthesis, several new bromofuran derivatives have to be synthesized in a multiple step synthesis and each step can be tedious and time consuming. In previous reports methyl 2-furancarboxylate or 2-furancarboxaldehyde were used as starting materials that were subjected to bromination with two equivalents of bromine either in a solvent or solely in the presence of aluminum chloride to give 4,5-dibromofuran derivative [9-11]. This was further debrominated at low temperature. The 4-bromo-2-furancarboxaldehyde derivative was also prepared from 2,3-dibromo-2-furancarboxaldehyde by bromination to 2,3,4-tribromo-2-furancarboxaldehyde followed by two consecutive debrominations with *n*-butyllithium at –70 °C, including a substitution with a hydrogen atom and one with *N,N*-diethylformamide that produced the desired product [9]. In attempt to repeat, the reported procedures we experienced very low yields and low reproducibility, probably because some of the details were omitted from the experimental procedures, leading to extensive polymerization. 4-Bromo-2-furancarboxaldehyde (**4**) is also commercially available but its purchase has two shortcomings. First is its high price and second is its tendency to polymerize even when kept in the freezer under nitrogen, giving it a short shelf life. 2-Furancarboxaldehyde on the other hand is very cheap and the whole synthesis can be done in less than a week in scales of tens of grams. Here, we report a fast, simple, and reproducible procedure to synthesize the ethylene acetal of the 4-bromo-2-furancarboxaldehyde (**4**) and its pinacolborane derivative (**5**) that can be used in Suzuki reactions.

Results and Discussion.

The aim of our study was to develop a practical synthesis of ethylene acetal of 4-bromo-2-furancarboxaldehyde (**4**) and its pinacolborane derivative (**5**). Attempts to repeat the reported procedures that synthesized the 4,5-dibromo-2-furancarboxaldehyde (**2**) through a solvent-less method followed by debromination at (-70 °C), produced unsatisfactory results as low yields and a mixture of two isomers (4-bromo-2-furancarboxaldehyde and 5-bromo-2-furancarboxaldehyde, up to 50%). The separation of the two isomers by distillation at low pressure proved to be very difficult and not practical.

Changes in the reaction conditions as solvent, temperature or length of the reaction, caused only a small change in composition of the product, with little effect on the total yield. Close examination revealed that one of the main fac-

Scheme



1 2 3 4 5 6

tors that contributed to low yield was the occurrence of a polymerization reaction with formation of a black tar. In order to minimize polymerization, the addition of 2-furancarboxaldehyde (**1**) was divided in two steps. First, the 2-furancarboxaldehyde (**1**) was added to the ice cold and mechanically stirred aluminum chloride in a small volume of methylene chloride till a homogeneous mixture of the complex of the aluminum chloride and the 2-furancarboxaldehyde (**1**) was formed. The rest of the 2-furancarboxaldehyde (**1**) was added in additional 40 minutes and the mixture was left to cool down in an ice bath. Further, the bromine was added during the next 2 hours. Any attempts to speed up the bromine addition ended in the production of larger amount of black tar. Attempts to purify the product by distillation at low pressure also produced low yields due to polymerization. In order to avoid polymerization during the purification process, the 4,5-dibromo-2-furancarboxaldehyde (**2**) was first protected as ethylene acetal and the distillation process was replaced by flash chromatography on silica gel.

The debromination process with *n*-butyllithium was carried out at a temperature of –45 to –55 °C because the reaction at lower temperatures (-65 to –75 °C), caused the formation of the unwanted 5-bromo-2-furancarboxaldehyde isomer (**6**). In other words, at a low temperature (-70 °C) the elimination of the 4-bromo atom is as fast as the elimination of the 5-bromo atom producing an equal mixture of the two isomers. In contrast, at higher temperatures (-45 to –55 °C) only the 5-bromo elimination takes place to give the desired 4-bromo-2-furancarboxaldehyde isomer (**4**) exclusively (Table 1). When we consider a plausible mechanism, we must take into account the fact that this is not a simple case of a kinetic and thermodynamic controlled reaction. The reaction is not reversible and once a certain product mixture is formed, it will not change due to time/temperature changes. The bromine in the C5 position is the more hindered among of the two, therefore the lithium-halogen exchange on the C5 position requires a higher temperature in order to take place. At lower temperatures the bromine atom in the C4 position is equally reactive, creating up to an equal mixture of the two products.

The Suzuki boronate derivative was synthesized by a variation of the reported procedure [13]. The reagents were heated for 6 hours at 80 °C due to the low reactivity of the hetero aromatic bromides in formation of the sp^2 - sp^3 bond. Reflux of the toluene was found to decrease the reaction yield - again due to polymerization. The Suzuki reaction uses milder conditions when compared with the condensation of ethylene acetal of 4-bromo-2-furancarboxaldehyde and the 17-ketosteroids in the presence of *n*-butyllithium. Such mild conditions are of great interest in condensation of 17-ketosteroids that contain a 14β-hydroxy group that has been shown to be important in the structure-activity relationship of cardioactive steroids towards Na/K ATPase.

EXPERIMENTAL

2-Furancarboxaldehyde, bromine, *n*-butyllithium, aluminum chloride, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, benzene, ethylene glycol, $PdCl_2(pph_3)_2$ and silica gel (Merck, 230-400 mesh, 60Å) were purchased from Aldrich Chemical, (Milwaukee, IL). All the solvents were purchased from Frutarom Israel. The 2-furancarboxaldehyde was distilled prior to use (95-96 °C at 10 mm Hg). The mass (electron impact ionization) spectra were measured with a TRACE GC/MS (Finnigan, ThermoQuest, San Jose, CA) operating at 70eV and with the ion source heated at 200 °C. The nmr measurements were performed with a Varian T 300 spectrometer in deuteriochloroform.

4,5-Dibromo-2-furancarboxaldehyde (**2**).

To mechanically stirred aluminum chloride (90 g, 680 mmols) and cooled on ice, a solution of 2-furancarboxaldehyde (**1**) (13.5 g, 141 mmols) in methylene chloride (16 mL) was added slowly over a period of 20 minutes. An additional (16.5 g, 172 mmols) of 2-furancarboxaldehyde was added to the mixture over a period of 40 minutes. Bromine (120 g, 750 mmols) was added dropwise for 2 hours and the mixture was left stirring overnight at room temperature. The reaction mixture was cooled on an ice bath and ice was added slowly over a period of 1 hour. After the exothermic reaction stopped, brine (500 mL) and 30% diethyl ether in hexane (800 mL) was added with continuous stirring until all the solid material was dissolved. The organic phase was separated and the solvent removed at low pressure. Co-evaporation with dry benzene (50 mL) yielded 60 g of crude 4,5-dibromo-2-furancarboxaldehyde (yield: 75%). The product was further reacted with ethylene glycol without purification since attempts to distill the 4,5-dibromo-2-furancarboxaldehyde yielded in a black polymer; ^{1}H nmr: δ = 9.48 (s, 1H, CHO), 7.22 ppm (s, 1H, C3-H); ^{13}C nmr: δ = 105.16 (C3), 131.67 (C2), 123.86 (C4), 153.82 (C1), 176.21 ppm (C5); ms: m/z (%): 252 (50 $M^{+\cdot}$), 254 (100), 256 (50).

Table 1

Temperature	-70 to -78 °C	-60 to -70 °C	-50 to -60 °C	-45 to -55 °C
4-bromo-2-furancarboxaldehyde	50%	65%	78%	100%

2-(4,5-Dibromo-2-furanyl)-[1,3]-dioxolane (**3**).

Crude 4,5-dibromo-2-furancarboxaldehyde (**2**) (60 g, 0.23 mols) was dissolved in benzene (300 mL), mixed with ethylene glycol (70 g, 1.12 mols), concentrated sulfuric acid (2 mL) and boiled overnight in a Dean Stark apparatus (10 mL of water was released). Half of the solvent was removed at reduced pressure and replaced with 20% diethyl ether in hexane (200 mL). The

solution was washed twice with saturated sodium bicarbonate solution (200 mL) and twice with brine (200 mL). The organic phase was separated and the solvent evaporated under reduced pressure. The dark oil was dissolved in hexane and purified by flash chromatography on silica gel by elution with hexane. Evaporation of the solvent yielded 55 g of an orange oil (yield: 81%) that was submitted to debromination without additional purification; ^{1}H nmr: δ = 6.49 (s, 1H, C3-H), 5.83 (s, 1H, CHO), 4.05 ppm (m, 4H, CH_2CH_2); ^{13}C nmr: δ = 65.32 (2*CH_2 acetal), 102.29 (C3), 113.75 (C5), 113.92 (C2), 123.73 (C4), 153.84 ppm (C1); ms: m/z (%): 296 (50, $M^{+\cdot}$), 298 (100), 300 (50).

The volume of the benzene was reduced to the minimum because all the attempts to replace it with other solvents for safety reasons failed to give the desired product.

2-(4-Bromo-2-furanyl)-[1,3]dioxolane (**4**).

Ethylene acetal of 4,5-dibromo-2-furancarboxaldehyde (**3**) (22 g, 74 mmols) was dissolved in freshly distilled anhydrous tetrahydrofuran (60 mL) and cooled to –50 °C under nitrogen. *n*-Butyllithium 1.6 *M* in hexane (33 mL, 74 mmols) was added to the stirred solution while maintaining a temperature of –45 ºC to –55 °C. The solution was left to warm up to 0 °C and then kept at that temperature for 30 minutes on ice. The solution was cooled to -20 °C and cold water (20 mL) was added slowly followed by diethyl ether (50 mL). The ethereal solution was separated and washed with 1 *M* hydrochloric acid and water. After evaporation of the solvent, the product was redissolved in hexane (100 mL) and filtered through a plug of silica gel. Evaporation of the hexane at low pressure yielded in 12 g (yield: 74%) of a yellow oily product. NMR measurements showed that the products is composed of 100% ethylene acetal of 4-bromo-2-furancarboxaldehyde (**4**) free of ethylene acetal of 5-bromo-2-furancarboxaldehyde (**6**); ^{1}H nmr: δ = 7.41 (s, 1H, C5-H), 6.50 (s, 1H, C3-H), 5.82 (s, 1H, C2-H), 4.1 ppm (m, 4H, CH_2CH_2); ^{13}C nmr: δ = 65.21 (2*CH_2 acetal), 97.27 (C3), 111.83 (C2), 111.9 (C5), 141.45 (C4), 152.83 ppm (C1); ms: m/z (%): 218 (100, $M^{+\cdot}$), 220 (100).

2-(5-[1,3]Dioxolan-2-yl-furan-3-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**5**).

Ethylene acetal of 4-bromo-2-furancarboxaldehyde (510 mg, 2.32 mmols) was dissolved in dry toluene (5 mL) and palladium(II) chloride $(pph_3)_2$ (51 mg, 0.07 mmols), triethylamine (1 mL, 7.14 mmols) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.52 mL, 3.55 mmols) were added under nitrogen and the reaction was stirred at 80 °C for 6 hours. The reaction was stopped by adding water. The toluene was evaporated and the product was extracted with methylene chloride. The organic phase was washed with water, dried over anhydrous sodium sulfate and evaporated to give a brown oil which after undergoing flash chromatography with 20% diethyl ether in hexane gave 370 mg (yield: 60%); ^{1}H nmr: δ = 7.78 (s, 1H, C2-H), 6.61 (s, 1H, C4-H), 5.87 (s, 1H, CHO), 4.1 (m, 4H CH_2CH_2), 1.3 ppm (m, 12H, 4*CH_3); ms: m/z (%): 266 (46, $M^{+\cdot}$).

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