

Synthesis of 3,4-bis(2,5-dimethyl-3-thienyl)furan-2,5-dione from mucobromic acid

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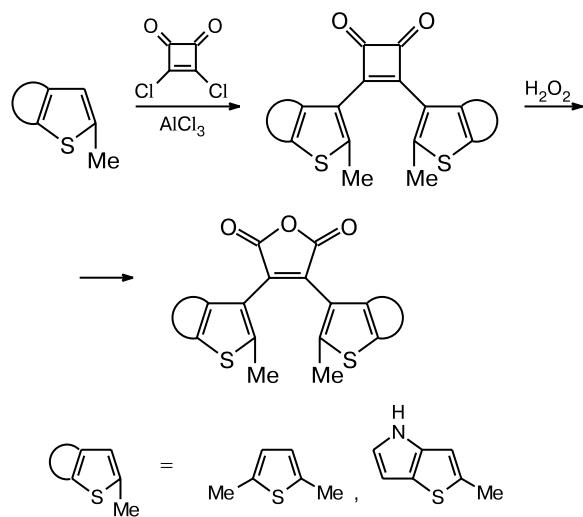
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Palladium-catalyzed cross-coupling between 2,5-dimethyl-3-thienylboronic and mucobromic acids under phase-transfer catalysis (PTC) conditions gave the expected 3,4-bis(2,5-dimethyl-3-thienyl)-5-hydroxyfuran-2-one in 32% yield. The by-product was 2,2',5,5'-tetramethyl-3,3'-bithiophene. The oxidation of the obtained hemiacetal with potassium permanganate under PTC conditions afforded 3,4-bis(2,5-dimethyl-3-thienyl)furan-2,5-dione in high yield.

Key words: Suzuki reaction, cross-coupling, boronic acids, palladium complexes, mucobromic acid, thiophene, phase-transfer catalysis.

Earlier,^{1–3} a convenient method for the synthesis of photochromic thienyl or thienopyrrolyl derivatives of maleic anhydride was developed in our laboratory. The key step of the process is the reaction of substituted thiophene with 3,4-dichlorocyclobutene-1,2-dione (Scheme 1). The reaction product is then oxidized with peroxide hydrogen into 3,4-bis(hetaryl)furan-2,5-dione in a virtually stoichiometric yield.

Scheme 1

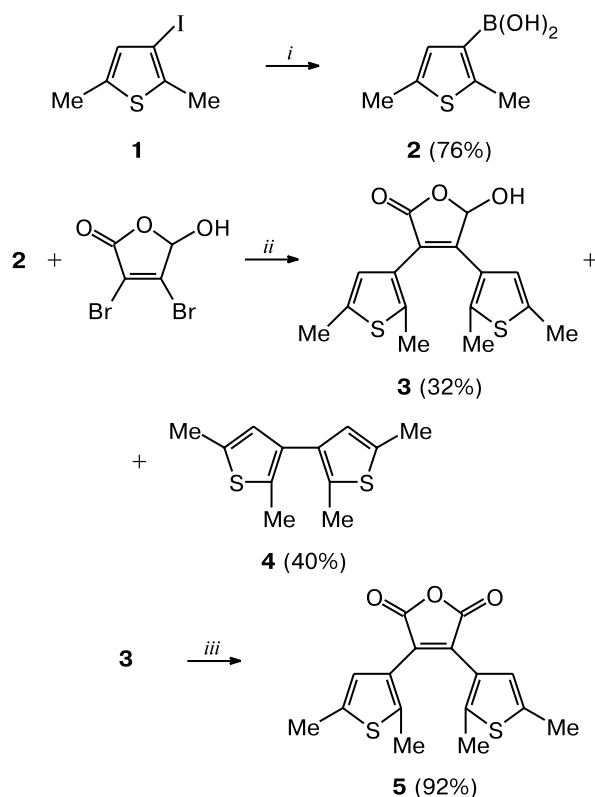


In the present communication, an alternative route to furandione derivatives is proposed.

Cross-coupling of aromatic and heterocyclic boronic acids with aryl and alkenyl halides and triflates (Suzuki reaction⁴) catalyzed by palladium complexes is known to

be a versatile method for C—C bond formation and find a wide application in organic synthesis. Recently,⁵ it was

Scheme 2



Reagents and conditions: *i.* 1) BuⁿLi; 2) B(OBu)₃. *ii.* Pd(Ph₃P)₄, C₆H₅Me—H₂O, CsF, BnEt₃NCl. *iii.* KMnO₄, C₆H₆—H₂O, BnEt₃NCl.

demonstrated that derivatives of mucochloric and mucobromic acids can successfully be used in cross-coupling reactions with various substituted phenylboronic acids under phase-transfer catalysis (PTC) conditions to give the corresponding substituted α,β -unsaturated γ -butyrolactones. Taking into account that mucochloric and mucobromic acids are inexpensive and easily accessible compounds, we found it attractive to apply this approach to the synthesis of the aforementioned photochromic derivatives of maleic anhydride.

3,4-Bis(2,5-dimethyl-3-thienyl)furan-2,5-dione (**5**) was synthesized in three steps (Scheme 2). 2,5-Dimethyl-3-thienylboronic acid (**2**) was obtained in 76% yield by the reaction of 3-iodo-2,5-dimethylthiophene (**1**) with Bu^nLi in THF at -78°C and then with tributyl borate. Commercially accessible mucobromic acid was used as a substrate.

The cross-coupling gave compound **3** in a moderate yield. However, considerable amounts of 2,2',5,5'-tetramethyl-3,3'-bithiophene (**4**) were also obtained. Replacement of $\text{Pd}(\text{Ph}_3\text{P})_4$ by $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ did not change the ratio between the reaction products. The final step, namely, the oxidation of hemiacetal **3**, proceeds under PTC conditions without any complications to give 3,4-bis(2,5-dimethyl-3-thienyl)furan-2,5-dione (**5**) in high yield.

Experimental

Melting points were determined on a Boetius instrument. ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) in CDCl_3 . Mass spectra were recorded on a Finnigan MAT instrument (EI, 70 eV). The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC using Merck 60 F_{254} plates.

2,5-Dimethyl-3-thienylboronic acid (2). A 1.3 M solution of Bu^nLi (18 mL) in hexane was added at -78°C in an atmosphere of argon to a solution of 3-iodo-2,5-dimethylthiophene⁶ (**1**) (3 mL, 5.4 g, 22 mmol) in 50 mL of THF. The reaction mixture was stirred at this temperature for 30 min and tributyl borate (9.1 mL) was added in one portion. Stirring was continued at -78°C for an additional 1 h and the mixture was allowed to warm for ~ 12 h. Upon cooling to 0°C , MeOH (5 mL) was added and the reaction mixture was concentrated in a rotary evaporator so that the bath temperature was no higher than 50°C . Ether (50 mL) and an ice-cooled mixture of conc. HCl (4 mL) and water (26 mL) were added and the reaction mixture was stirred for 1 h. The organic layer was separated and organic material was extracted from the aqueous phase with ether. The combined organic phases were washed with water and 5% NaOH (4×20 mL). The alkaline solution was washed with ether, cooled with ice to -5°C , and acidified, while stirring, with conc. HCl (9 mL). The precipitate of boronic acid **2** was filtered off, washed with a small amount of water, and dried in a desiccator. The yield of compound **2** was 2.67 g (76%), m.p. $180\text{--}183^\circ\text{C}$. Found (%): C, 52.32; H, 5.23; S, 23.50. $\text{C}_{18}\text{H}_{21}\text{B}_3\text{O}_3\text{S}_3$. Calculated (%): C, 52.22; H, 5.11; S, 23.23. According to ^1H NMR and MS data, this compound exists as a cyclic trimeric an-

hydride. ^1H NMR, δ : 2.45, 2.82 (both s, 3 H each, Me); 7.09 (s, 1 H, H arom.). MS, m/z (I_{rel} (%)): 416 [$\text{M} + 3$] (16), 415 [$\text{M} + 2$] (18), 414 [$\text{M} + 1$] (65), 413 [M]⁺ (48), 137 (100), 111 (95).

3,4-Bis(2,5-dimethyl-3-thienyl)-5-hydroxyfuran-2-one (3) and 2,2',5,5'-tetramethyl-3,3'-bithiophene (4). A stirred mixture of mucobromic acid (0.258 g, 1 mmol), boronic acid **2** (0.467 g, 3 mmol), $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.06 g, 5 mol.%), CsF (0.608 g, 4 mmol), and BnEt_3NCl (0.01 g) was refluxed under argon for 4 h in a mixture of degassed toluene (10 mL) and distilled and degassed water (10 mL). A solution of NH_4Cl (80 mL) was added and the product was extracted with AcOEt (3×50 mL). The organic phase was washed with brine and concentrated. The residue was chromatographed on SiO_2 with a gradient from hexane to hexane–AcOEt (3 : 1) to give hemiacetal **3** (0.103 g, 32%) and bithiophene **4** (0.133 g, 40%).

Compound 3. Found (%): C, 59.82; H, 5.17; S, 20.18. $\text{C}_{16}\text{H}_{16}\text{O}_3\text{S}_2$. Calculated (%): C, 59.97; H, 5.03; S, 20.01. ^1H NMR, δ : 1.92, 2.40 (both s, 6 H each, Me); 4.05 (s, 1 H, OH); 6.35 (s, 1 H); 6.66, 6.72 (both s, 1 H each, H arom.). MS, m/z (I_{rel} (%)): 322 [$\text{M} + 2$] (1), 321 [$\text{M} + 1$] (8), 320 [M]⁺ (100), 275 (59), 245 (35), 112 (90).

Compound 4. Found (%): C, 65.02; H, 6.37; S, 28.65. $\text{C}_{12}\text{H}_{14}\text{S}_2$. Calculated (%): C, 64.81; H, 6.34; S, 28.83. ^1H NMR, δ : 2.29, 2.45 (both s, 6 H each, Me); 6.53 (s, 2 H, H arom.). MS, m/z (I_{rel} (%)): 223 [$\text{M} + 1$] (7), 222 [M]⁺ (36), 207 (20), 189 (13), 128 (17), 71 (100).

3,4-Bis(2,5-dimethyl-3-thienyl)furan-2,5-dione (5). Hemiacetal **3** (0.1 g, 3 mmol), KMnO_4 (0.1 g, 6.3 mmol), and BnEt_3NCl (0.02 g) in a stirred mixture of benzene (5 mL) and water (5 mL) were heated under argon at 60°C until the starting reagent **3** disappeared (5 h, TLC data). The organic layer was separated and the product from the aqueous layer was extracted with benzene. The organic phases were combined and concentrated. The residue was chromatographed on a plate in hexane–AcOEt (6 : 1) to give dione **5** (91 mg, 92%). The constants of compound **5** are identical with the literature data.¹

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