A Practical Synthesis of 2,6-Dicarboxyfluorenone†

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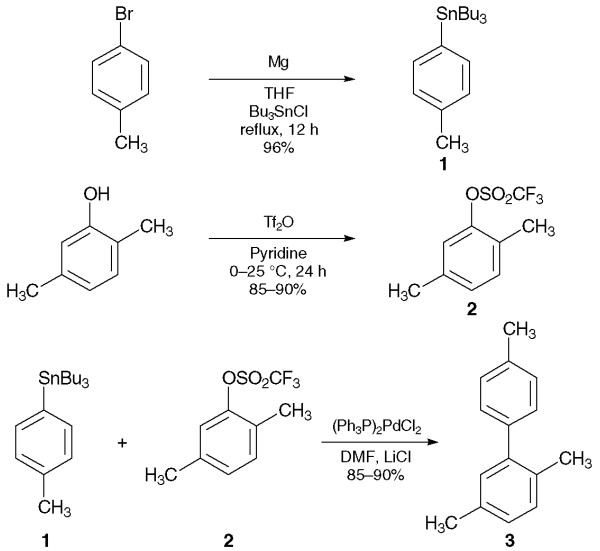
Herein, we report a new and efficient method for the large scale synthesis of 2,6-dicarboxyfluorenone **5** in 95% yield using 0.01 mol% of bis(triphenylphosphine)palladium(II) chloride, $(PPh_3)_2$ $PdCl_2$, as a catalyst, starting with the reaction of 2,5-dimethylbromobenzene and 4-bromotoluene to give 2,4,5-trimethylbiphenyl **3**, followed by oxidation and then cyclization.

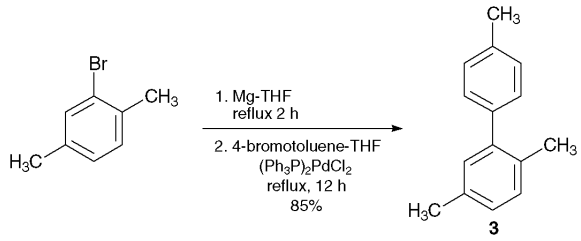
The synthesis of 2,6-dicarboxyfluorenone **5**, a potentially useful compound in the synthesis of polymers and dendrimers with asymmetric structures was undertaken. A practical synthesis for the large scale (*ca.* 500 g) preparation of this material has been developed. The preparation of biphenyl derived structures *via* the palladium-catalyzed cross-coupling reaction of appropriately substituted precursors has emerged as a powerful tool in organic synthesis. For example, the coupling[1–4] of organostannanes with aryl triflates is an important method for the formation of carbon–carbon bonds (Scheme 1).

The cross coupling reaction[1a] was conducted in dimethylformamide with bis(triphenylphosphine)palladium(II) chloride, $(PPh_3)_2PdCl_2$ (4 mol%), as catalyst to give **3** in 85–90% yield. Careful monitoring of the reaction revealed that lower catalyst quantities were ineffective and the reaction did not proceed below 140 °C. The reaction required an excess of tributyl(4-methylphenyl)stannane **1** and additional treatment with ethyl acetate and potassium fluoride was necessary to remove the tin byproduct. This method was inefficient for a large scale synthesis because high temperatures were required, the turnover of the catalyst was poor and purification was tedious.

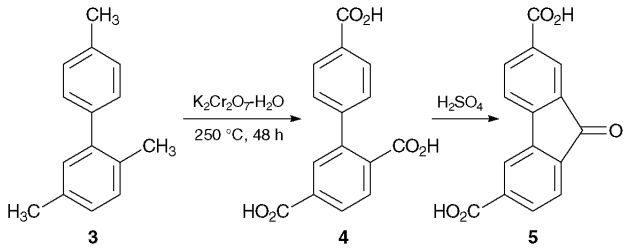
We developed a more efficient route to **3**, shown in Scheme 2. We synthesized **3** in 85% yield *in situ* using $(PPh_3)_2PdCl_2$ (0.01 mol%) as a catalyst in tetrahydrofuran.[3]



Scheme 1 THF = tetrahydrofuran; Tf = CF_3SO_2; DMF = dimethylformamide



Scheme 2



Scheme 3

The major impurity (<2%) 4,4′-dimethylbiphenyl was removed by crystallization after distillation.

Subsequent oxidation[5] of 2,4′,5-trimethylbiphenyl **3** gave 2,4,5-tricarboxybiphenyl (**4**, 70–80% yield) followed by cyclization with sulfuric acid to give 2,6-dicarboxyfluorenone **5** (95% yield, Scheme 3).

Thus, this new method offers an efficient synthesis of 2,6-dicarboxyfluorenone *via* a palladium-catalyzed cross coupling reaction. Advantages of this methodology include high chemical yields, easy purification and a short synthetic sequence.§

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§Spectral data: *tributyl(4-methylphenyl)stannane* **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (9H, m), 1.1 (6H, m), 1.4 (6H, m), 1.6 (6H, m), 2.5 (3H, d, *J* 8.1 Hz), 7.23 (2H, d, *J* 8.1 Hz), 7.45 (2H, d, *J* 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 9.5, 13.7, 21.4, 29.1, 128.9, 136.5, 137.5, 137.8. MS *m*/*z* (relative intensity) 313 (83), 285 (75), 235 (96), 177 (100), 121 (25), 57 (8).

2,5-*Dimethylphenyl trifluoromethanesulfonate* **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.56 (3H, s), 2.58 (3H, s), 7.27–7.42 (2H, m), 7.51–7.54 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 15.9, 20.8, 116.5, 121.6, 128.9, 131.8, 137.9, 148.3, 149.6. MS *m*/*z* (relative intensity) 254 (100), 175 (26), 121 (100), 91 (91), 77 (91).

2,4′,5-*Trimethylbiphenyl* **3**: ^{1}H (300 MHz, $CDCl_3$) δ_H 2.58 (3H, s), 2.66 (3H, s), 2.70 (3H, s), 7.30–7.60 (7H, m). ^{13}C (75 MHz, $CDCl_3$) δ_c 9.64, 13.90, 14.10, 126.74, 127.75, 128.61, 129.03, 129.34, 130.20, 130.60, 132.15, 133.82, 134.98, 136.0, 141.84. MS *m*/*z* (relative intensity) 196 (88), 181 (100), 166 (72), 153 (24), 76 (12).

2,4,5-*Tricarboxybiphenyl* **4**: ^{13}C NMR (75 MHz, [$^2H_6$] DMSO) δ_c 126.96, 128.44, 129.08, 129.92, 130.72, 132.96, 136.04, 140.10, 144.46, 166.36, 167.03, 168.61.

2,6-*Dicarboxyfluorenone* **5**: ^{1}H NMR (300 MHz, [$^2H_6$] DMSO) δ_H 7.5 (1H, m), 7.8 (2H, d, *J* 8.1 Hz), 7.9 (1H, d, *J* 8.1 Hz), 8.0 (1H, m), 8.1 (1H, d, *J* 8.1 Hz). ^{13}C NMR (75 MHz, [$^2H_6$] DMSO) δ_c 122.01, 122.52, 127.39, 129.72, 130.27, 131.85, 132.33, 133.75, 136.96, 137.16, 143.29, 147.16, 166.5, 166.9, 191.63.

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