

## Synthesis of Benzene Derivatives via Deoxygenation by Low Valent Titanium<sup>1</sup>

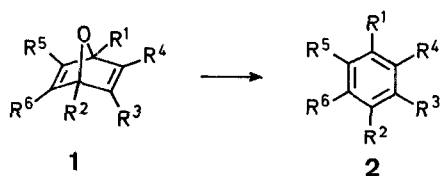
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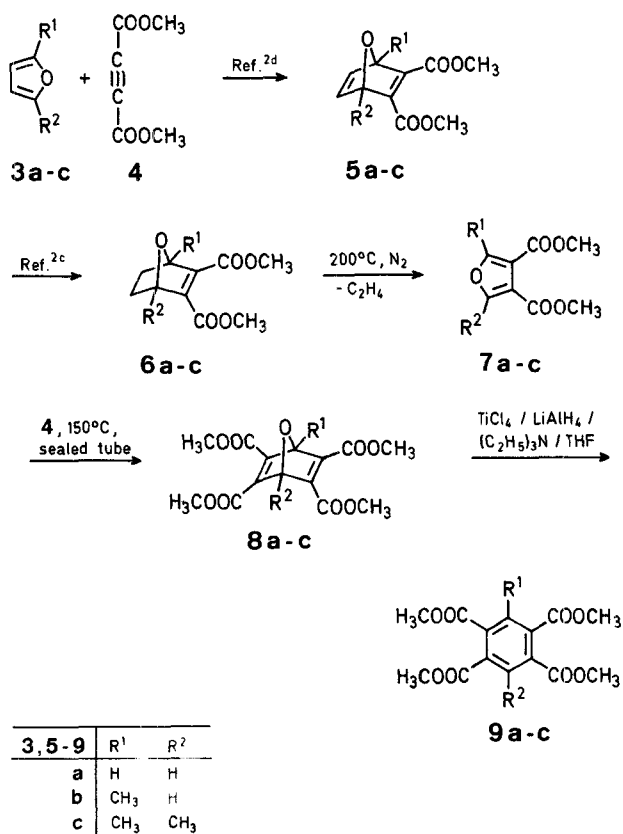
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Extrusion of the oxygen atom from the 7-oxabicyclo[2.2.1]hepta-2,5-diene system **1** has recently emerged as a powerful tool in the synthesis of arene derivatives **2**<sup>1,2</sup>. Though the reagents involved in this reaction are generally applicable only to limited number of examples, the results so far disclosed from the laboratories of Hart<sup>3</sup> as well as ours<sup>2c,d</sup> have led to the conclusion that low valent titanium may be the reagent of choice.

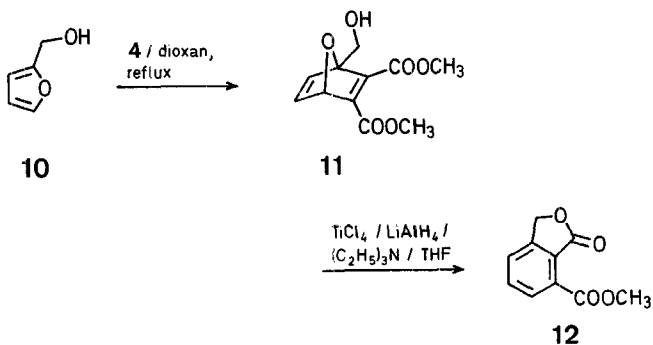


In order to demonstrate the versatility of low valent titanium in the deoxygenation of the system **1**, we now report further examples for the preparation of arene derivatives containing ester, lactone, and trifluoromethyl groups.

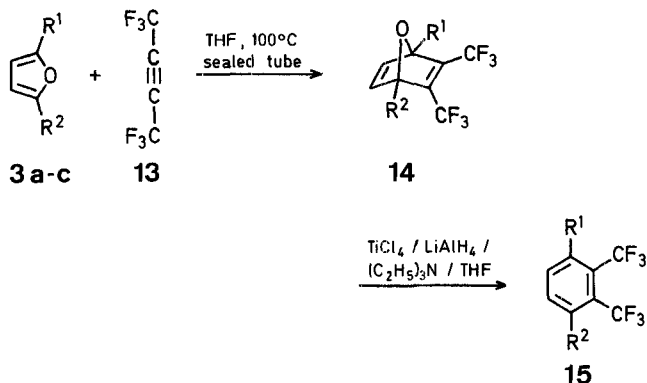
The endoxides **5a-c**<sup>2d</sup> are readily available through Diels-Alder cycloaddition between furans **3a-c** and dimethyl acetylenedicarboxylate (**4**)<sup>4</sup>. The hydrogenation of **5a-c** over Pd-C provides **6a-c**<sup>2c</sup>. Extrusion of the ethylene bridges from **6a-c** is achieved at 200 °C yielding the furandicarboxylates **7a**<sup>5</sup>, **7b**<sup>6</sup>, and **7c**<sup>7</sup>. Cycloaddition of **4** to compounds **7a-c** gives the endoxides **8a-c**. In the last step the endoxides **8a-c** are subjected to low valent titanium deoxygenation reaction affording the benzenetetracarboxylates **9a**<sup>8</sup>, **9b**<sup>9</sup>, and **9c**<sup>10</sup>.



The structure of the Diels-Alder adduct between furfuryl alcohol (**10**) and maleic anhydride was recently reinvestigated and a tricyclic lactone-carboxylic acid structure established<sup>11</sup>. This adduct can be converted to useful phthalides<sup>12</sup>. Similarly, the oxygen-bridged alcohol **11**, obtained by cycloaddition of dimethyl acetylenedicarboxylate to **10**, can be transformed to the phthalide **12**<sup>13</sup> by treatment with low valent titanium.



The furans **3a-c** also react readily with perfluoro-2-butyne (**13**)<sup>14</sup> to furnish the endoxides **14a-c**. Upon treatment with low valent titanium, only **14a**<sup>15</sup> and **14b** can be deoxygenated to the corresponding benzene derivatives **15a**<sup>16</sup> and **15b**. It is assumed that similar treatment of **14c** results in a retro-Diels-Alder reaction followed by complicated cyclizations<sup>17</sup>.



| 3, 14, 15 | R <sup>1</sup>  | R <sup>2</sup>  |
|-----------|-----------------|-----------------|
| a         | H               | H               |
| b         | CH <sub>3</sub> | H               |
| c         | CH <sub>3</sub> | CH <sub>3</sub> |

#### Dimethyl Furandicarboxylates **7**; General Procedure:

The endoxide **6** (0.02 mol) is heated at 200 °C under nitrogen until evolution of ethylene ceases. The resultant mixture is distilled under reduced pressure to give the product **7**. Furans **7a** and **7c** solidify immediately after distillation (Table).

#### Tetramethyl 7-Oxabicyclo[2.2.1]hepta-2,5-diene-2,3,5,6-tetracarboxylate (**8a**):

The furan **7a** (0.17 g, 0.8 mmol) and dimethyl acetylenedicarboxylate (**4**; 0.68 g, 5 mmol) are heated at 150 °C in a sealed tube for 17 h. Then excess **4** is removed under reduced pressure. The residue is chromatographed on preparative silica gel plates (ethyl acetate/hexane, 1:2) to give the product **8a**; yield: 0.11 g; which is recrystallized from methanol (Table).

#### Tetramethyl 1-Methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3,5,6-tetracarboxylate (**8b**):

The furan **7b** (5.1 g, 25 mmol) and reagent **4** (4.4 g, 30 mmol) are heated at 150 °C in a sealed tube for 17 h. The resulting mixture is chromatographed on a silica gel column (ethyl acetate/hexane, 1:2) to give the product **8b**; yield: 7 g; which is recrystallized from methanol (Table).

#### Tetramethyl 1,4-Dimethyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3,5,6-tetracarboxylate (**8c**):

The furan **7c** (0.16 g, 0.7 mmol) and reagent **4** (0.41 g, 2 mmol) are heated at 150 °C in a sealed tube for 17 h. Excess **4** is then removed under reduced pressure and the residue is chromatographed on preparative silica gel plates (ethyl acetate/hexane, 1:2) to give the product **8c**; yield: 0.12 g; which is recrystallized from methanol (Table).

#### Tetramethyl Benzene-1,2,4,5-tetracarboxylate (**9a**):

Tetrahydrofuran (10 ml) is added to titanium(IV) chloride (1 ml, 8 mmol) at 0 °C with stirring under nitrogen. Lithium aluminium hydride (27.59 mg, 0.7 mmol) and triethylamine (0.163 g, 1.6 mmol) are added separately to the above suspension. The mixture is then stirred at reflux at 65 °C for 15 min. The mixture is allowed to cool to room temperature and the endoxide **8a** (85 mg, 0.26 mmol) added. The resulting mixture is stirred at room temperature for 40 h, at 50 °C for 1 h, and at reflux for 2 h. It is allowed to cool, poured into water (40 ml) and extracted with dichloromethane (3 × 50 ml). The dichloromethane solution is dried with magnesium sulfate and evaporated. The residue is chromatographed on preparative silica gel plates (ethyl acetate/hexane, 1:1) to give the product **9a**; yield: 47 mg; which is recrystallized from ethanol (Table).

Table. Compounds 7, 8, 9, 12, 14 and 15 prepared

| Product | Yield [%] | b.p. [°C]/torr;<br>m.p. [°C] | Molecular Formula <sup>a</sup><br>or Lit. Data                      | M.S.<br><i>m/e</i> (M <sup>+</sup> (M <sup>+</sup> )) | <sup>1</sup> H-N.M.R.<br>(CDCl <sub>3</sub> /TMS <sub>int</sub> )<br>δ [ppm] | <sup>19</sup> F-N.M.R.<br>(CCl <sub>4</sub> /CF <sub>3</sub> COOH <sub>ext</sub> )<br>δ [ppm] |
|---------|-----------|------------------------------|---|---|--|---|
| 7a      | 60        | 41–43°                       | 46 <sup>5</sup>   | 184   | 3.90 (s, 6H); 7.90 (s, 2H)   | –   |
| 7b      | 87        | 84–86°/0.5                   | 82–86°/1 <sup>6</sup>   | 198   | 2.46 (s, 3H); 3.75 (s, 3H);<br>3.77 (s, 3H); 7.60 (s, 1H)                    | –   |
| 7c      | 94        | 154–156°/25;<br>59–62°       | 62–63° <sup>7</sup>   | 212   | 2.40 (s, 6H); 3.80 (s, 6H)   | –   |
| 8a      | 44        | 100–104°                     | C <sub>14</sub> H <sub>14</sub> O <sub>9</sub> (326.3)              | 326   | 3.80 (s, 12H); 5.73 (s, 2H)  | –   |
| 8b      | 80        | 90–91°                       | C <sub>15</sub> H <sub>16</sub> O <sub>9</sub> (340.3)              | 340   | 1.76 (s, 3H); 3.75 (s, 6H);<br>3.77 (s, 6H); 5.66 (s, 1H)                    | –   |
| 8c      | 46        | 71–72°                       | C <sub>16</sub> H <sub>18</sub> O <sub>9</sub> (354.3)              | 354   | 1.80 (s, 6H); 3.76 (s, 12H)  | –   |
| 9a      | 59        | 144–146°                     | 146 <sup>8</sup>  | 310   | 3.90 (s, 12H); 8.03 (s, 2H)  | –   |
| 9b      | 50        | 127–129°                     | C <sub>15</sub> H <sub>16</sub> O <sub>8</sub> (324.3) <sup>b</sup> | 324   | 2.30 (s, 3H); 3.95 (s, 6H);<br>3.97 (s, 6H); 8.50 (s, 1H)                    | –   |
| 9c      | 30        | 141–144°                     | 142–143° <sup>10</sup>  | 338   | 2.33 (s, 6H); 3.86 (s, 12H)  | –   |
| 12      | 91        | 106–108°                     | 106–108° <sup>13</sup>  | 192   | 3.90 (s, 3H); 5.30 (s, 2H);<br>7.76 (m, 3H)                                  | –   |
| 14a     | 88        | 119–122°/760                 | 100–126°/760 <sup>15</sup>  | 230   | 5.70 (s, 2H); 7.35 (s, 2H) <sup>c</sup>                                      | +14 (s, 6F)   |
| 14b     | 83        | 118–120°/760                 | C <sub>9</sub> H <sub>6</sub> F <sub>6</sub> O (244.1)              | 244   | 1.85 (s, 3H); 5.55 (s, 1H);<br>7.10 (m, 2H) <sup>c</sup>                     | +13 (s, 3F);<br>+14 (s, 3F)   |
| 14c     | 51        | 130–132°/760                 | C <sub>10</sub> H <sub>8</sub> F <sub>6</sub> O (258.2)             | 258   | 1.78 (s, 6H); 6.93 (s, 2H) <sup>c</sup>                                      | +15 (s, 6F)   |
| 15a     | 60        | 82–85°/760                   |   | 214   | 7.80 (m, 4H) <sup>c,16</sup>   | +19 (s, 6F)   |
| 15b     | 73        | 124–126°/760                 | C <sub>9</sub> H <sub>6</sub> F <sub>6</sub> (228.1)                | 228   | 2.63 (s, 3H); 7.50 (m, 3H) <sup>c</sup>                                      | +21 (m, 3F);<br>+23 (m, 3F)   |

<sup>a</sup> Satisfactory microanalyses obtained: C ± 0.37, H ± 0.17; exception: **8b**, C → C – 0.5.

<sup>b</sup> Ref.<sup>9</sup>, m.p. 103–104°C

<sup>c</sup> Solvents: CCl<sub>4</sub>/TMS<sub>int</sub>.

#### Tetramethyl 3-Methylbenzene-1,2,4,5-tetracarboxylate (9b):

Tetrahydrofuran (10 ml) is added to titanium(IV) chloride (1.5 ml, 12 mmol) at 0°C with stirring under nitrogen. Lithium aluminium hydride (0.11 g, 3 mmol) and triethylamine (0.169 g, 1.6 mmol) are added separately to the above suspension. The mixture is stirred and refluxed at 65°C for 15 min. Then it is allowed to cool to room temperature. The endoxide **8b** (0.92 g, 2 mmol) is added. The mixture is stirred at room temperature for 17 h and then poured into water (40 ml). The mixture is extracted with dichloromethane (3 × 50 ml), the extract is dried with magnesium sulfate, and evaporated. Recrystallization of the residue from methanol gives the product **9b**; yield: 0.43 g (Table).

#### Tetramethyl 3,6-Dimethylbenzene-1,2,4,5-tetracarboxylate (9c):

Tetrahydrofuran (10 ml) is added to titanium(IV) chloride (1 ml, 8 mmol) at 0°C with stirring under nitrogen. Lithium aluminium hydride (67 mg, 1.7 mmol) and triethylamine (0.13 g, 1.3 mmol) are added. The mixture is stirred and refluxed at 65°C for 15 min. Then it is allowed to cool to room temperature. The endoxide **8c** (0.25 g, 0.7 mmol) is added. The mixture is stirred at room temperature for 15 h, at 40°C for 2 h, and finally at reflux for 33 h. It is allowed to cool and poured into water (50 ml). The resulting mixture is extracted with dichloromethane (3 × 50 ml), the extract is dried with magnesium sulfate and evaporated. The residue is chromatographed on preparative silica gel plates (ethyl acetate/hexane, 1:3) to give the product **9c**; yield: 68 mg; which is recrystallized from methanol (Table).

#### Methoxycarbonylphthalide (12):

A mixture of furfuryl alcohol (**10**; 0.998 g, 0.01 mol), reagent **4** (1.47 g, 0.01 mol), and dioxan (4 ml) is refluxed at 110°C for 1.5 h and allowed to stand at room temperature overnight. Dioxan is removed and the residue is distilled under reduced pressure to afford dimethyl 1-hydroxymethyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**11**); yield: 1.973 g (81%). The alcohol **11** is purified by a second reduced pressure distillation; b.p. 160°C/0.75 torr; and should be used directly for the deoxygenation reaction.

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>/TMS): δ = 2.75 (s, 1H); 3.79 (s, 3H); 3.81 (s, 3H); 4.23 (s, 2H); 5.63 (d, 1H, *J* = 2 Hz); 7.10 ppm (m, 2H).

M.S.: *m/e* = 240 (M<sup>+</sup>).

Tetrahydrofuran (10 ml) is added to titanium(IV) chloride (1 ml, 8 mmol) at 0°C with stirring under nitrogen. Then lithium aluminium hydride (91.4 mg, 2 mmol) and triethylamine (0.16 g, 1 mmol) are added. The mixture is stirred and refluxed at 65°C for 15 min. Then it is allowed to cool to room temperature. The endoxide **11** (79 mg, 0.3 mmol) is added, the mixture is stirred at room temperature for 17 h and is then poured into water (50 ml). The resulting mixture is extracted with dichloromethane (3 × 50 ml), the extract is dried with magnesium sulfate, and evaporated. The residue is recrystallized from methanol to give the phthalide **12**; yield: 49 mg (Table).

#### Perfluoro-2-butyne (13)<sup>14</sup>:

Antimony pentachloride (105.75 g, 0.35 mol) and freshly dried powder antimony trifluoride (130 g, 0.73 mol) are placed in a 3-necked round-bottomed flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a condenser connected to a cooled receiving flask. Hexachloro-1,3-butadiene (83.25 g, 0.32 mol) is added dropwise during 1 h with heating at 140–160°C, during which time, the product boiling below 70°C is collected. After all the reactant has been added, the temperature is increased to 200°C until no product distills. The collected product is again steam-distilled and the distillate is washed successively with 20% aqueous hydrochloric acid (300 ml), 0.5 normal aqueous sodium hydroxide (300 ml), and water until neutral. It is then dried with calcium chloride and redistilled to give 2,3-dichlorohexafluoro-2-butyne; yield: 47.5 g (66%); b.p. 64–66°C/atmospheric pressure (Ref.<sup>14</sup>, b.p. 66–68°C).

A 250 ml 3-necked round-bottomed flask is fitted with mechanical stirrer, pressure-equalizing dropping funnel, and a cold trap which is connected to a Dry Ice/acetone cooled receiver. Freshly activated zinc (55 g) and acetic anhydride (64 ml) are placed in the flask, which is heated to 140°C with an oil bath. A small amount of Dry Ice is placed in the cold trap. A solution of 2,3-dichloro-hexafluoro-2-butyne (63 g, 0.32 mol) in acetic anhydride (42 ml) is added dropwise during 45 min, during which time volatile product collects in the cooled receiver. The reaction is continued for 10 h until no product distills. The collected distillate is fractionally redistilled at low temperature to give perfluoro-2-butyne; yield: 28.5 g (62.3%); b.p. –24°C (Ref.<sup>14</sup>, b.p. –24°C).

### 2,3-Bis[trifluoromethyl]-7-oxabicyclo[2.2.1]hepta-2,5-dienes 14a-c:

Perfluoro-2-butyne (7 g, 43 mmol), 3a-c (40 mmol), and tetrahydrofuran (8 ml) are transferred to a sealed tube (100 ml), which is heated to 100°C for 6 h. Then the sealed tube is opened, the solvent is removed on a rotary evaporator, and the residue is distilled to give 14a-c as colorless liquids (Table).

### 1,2-Bis[trifluoromethyl]benzene (15a):

Titanium(IV) chloride (20 ml) is transferred to a 250 ml 3-necked round-bottomed flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a reflux condenser under nitrogen. Tetrahydrofuran (20 ml) is added, carefully with external cooling by an ice/water bath. Lithium aluminium hydride (1.5 g) in tetrahydrofuran (20 ml) is added followed by a solution of triethylamine (1.2 g) in tetrahydrofuran (5 ml). The ice/water bath is removed and the mixture is heated to reflux for 30 min until all the yellow precipitate disappears. The mixture is then allowed to cool to room temperature. A solution of the endoxide 14a (2.1 g) in tetrahydrofuran (20 ml) is added dropwise during 30 min. The mixture is stirred for 26 h, after that it is cooled by an ice/water bath and water (200 ml) is added to decompose the reaction mixture, followed by 20% aqueous potassium carbonate (600 ml). The aqueous solution is extracted with dichloromethane (2 × 200 ml), the extract washed with water (3 × 200 ml), and dried with magnesium sulfate. Dichloromethane is removed by distillation at atmospheric pressure and the residue is again distilled. The fraction boiling between 82–85°C is collected (4.5 g). It is further purified by G.L.C. (Shanghai Gas Chromatograph Model 102G, oxaperfluoroalkylene-triazine polymer/silica gel column, column temperature 120°C, inlet temperature 145°C) to give 15a; yield: 1.17 g (60%); retention time 9 min 45 sec.

Another major peak with retention time 7 min 39 sec, possibly due to triethylamine, was not isolated and identified (Table).

### 2,3-Bis[trifluoromethyl]toluene (15b):

Titanium(IV) chloride (20 ml) is transferred to a 250 ml 3-necked round-bottomed flask fitted with a mechanical stirrer, a pressure-equalizing funnel, and a reflux condenser under nitrogen. Tetrahydrofuran (20 ml) is added with external cooling by an ice water bath. Lithium aluminium hydride (1.46 g) in tetrahydrofuran (20 ml) is added followed by a solution of triethylamine (1.25 g) in tetrahydrofuran (5 ml). The mixture is refluxed for 30 min and then allowed to cool to room temperature. The endoxide 14b (2 g) in tetrahydrofuran (20 ml) is added dropwise during 30 min. The reaction mixture is stirred at room temperature under nitrogen for 23 h and then cooled externally by an ice/water bath. Water (100 ml) and 20% aqueous potassium carbonate (600 ml) are added successively to the mixture. The aqueous mixture is extracted with dichloromethane (3 × 200 ml), the organic extracts are washed with water (3 × 200 ml), and dried with magnesium sulfate. The solvents are distilled at atmospheric pressure and the residue is distilled again.

The material boiling at 124–126°C is collected (3.29 g) and subjected to further purification by G.L.C. (Shanghai Gas Chromatograph Model 102G, oxaperfluoroalkylene-triazine polymer/silica gel column, column temperature 120°C, inlet temperature 145°C) to give 15b; yield: 1.34 g, (73%); retention time 12 min 42 sec (Table). Another major peak with retention time 6 min 18 sec, possibly due to triethylamine, was not isolated and identified.

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