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A novel Birch reduction of aromatic compounds using aqueous titanium trichloride: anions of *trans*-10b,10c-dimethyl-2,7,10b,10c-tetrahydropyrene

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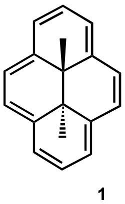
Abstract—The Birch reduction of 10b,10c-dimethyl-10b,10c-dihydropyrene **1** and anthracene could be predicted on the basis of their reduction potentials and achieved readily with aqueous titanium trichloride in near quantitative yields. Controlled reduction of a nitro group could be achieved under these conditions with the aromatic hydrocarbon remaining intact. The anion derived from the hexane obtained from reduction of **1** provided synthetic routes to derivatives of **1** inaccessible from direct substitution reactions of **1**. Oxidative dimerization of the anion led to the formation of a series of interesting products. © 2003 Elsevier Science Ltd. All rights reserved.

The applications of McMurry's reagents involving low-valent titanium species in reduction and reductive coupling reactions of numerous organic functional groups are well documented.[1] Unlike the low-valent titanium species which are usually generated in situ, the Ti(III) ion is commercially available as titanium trichloride in aqueous solution. The Ti(III) ion is a mild reducing agent at a low pH, but the reducing power of the Ti(III)/Ti(IV) system is strongly pH dependent and increases markedly in strongly basic medium.[2] In an acidic solution, $E=(0.100–0.1182\text{pH}+0.0591)\log[\text{TiO}^{2+}/\text{Ti}^{3+}]$ where Ti(IV) is present as soluble TiO^{2+}. In a basic medium, $E=(0.029–0.2364\text{pH}–0.0591)\log[\text{Ti}^{3+}]$ where insoluble TiO_2 is formed, and the reducing power of the Ti(III)/Ti(IV) system could in fact be more negative than −2.5 V.[3] 10b,10c-Dimethyl-10b,10c-dihydropyrene **1** and its derivatives form the most extensively studied family of aromatic annulenes.[4] Its reduction to the hexaene **2** is generally effected by a Birch reduction of **1**[5] or reduction of the quinone **3** by a mixture of lithium aluminum hydride and aluminum chloride.[6] These reactions however have to be carried out in anhydrous conditions and at a low temperature (−78°C). The yield of **2** is only moderate (about 50%). It was reported that the first reduction potential of **1** is −2.22 V in DMF.[7] Thus reduction of **1** to give **2** could, in principle, be achieved by Ti(III) under certain conditions. Although hexaene **2** was used as a non-aromatic model in the numerous studies of the diatropicity of **1** and its derivatives,[4] its chemical properties have rarely been investigated. In this paper we wish to report a simple Birch-like reduction of **1** to **2** by titanium trichloride and the chemical behavior of the monoanion and dianion derived from **2**.



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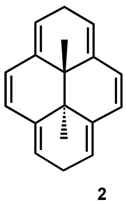

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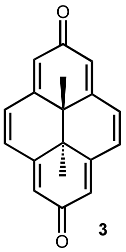

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Treatment of **1** with commercially available aqueous titanium trichloride (about 15% in 10% HCl) in THF at room temperature did not result in any reaction. Progressive addition of NaOH indicated a gradual increase in the formation of **2** on the basis of TLC analyses. When the reaction was carried out in a strongly basic

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Keywords: titanium trichloride; Birch reduction; dihydropyrene; anion; oxidative coupling.

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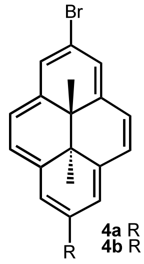
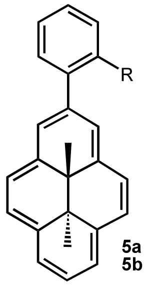
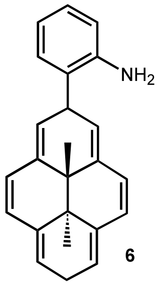
medium using THF/CH_3OH (1:1 v/v) as a mixed solvent system, a quantitative yield of **2** was isolated after 30 min of reaction time.[†] To the best of our knowledge this is the first example to show that titanium chloride reduces an aromatic hydrocarbon directly in a Birch-like manner. The presence of CH_3OH seemed to improve the solubility of NaOH in the solvent system and also serve as a good hydrogen donor.


4a R = H
4b R = Br


5a R = NO_2
5b R = NH_2


6

The reaction was exothermic and proceeded rapidly at room temperature but at 0°C product formation was, however, very slow. This allowed a qualitative study of the relative ease of reducing the dihyropyrene and other organic functional groups. When 2-bromo- or 2,7-dibromodihydropyrene (**4a** and **4b**, respectively) was reacted with Ti(III) under similar conditions, the bromo function was removed[8] cleanly in addition to the reduction of the dihydropyrene even at 0°C. The hexaene **2** was isolated in near quantitative yield in both cases. At 0°C selective reduction of the nitro group[9] in compound **5a** could however be achieved to afford the amine **5b** in an 87% yield.[‡] When an excess of titanium trichloride was used and the reaction mixture was allowed to warm up by the exothermic nature of the reaction, the aminohexaene **6** was isolated in a 95% yield.[§]

The reduction potential of anthracene was reported to be −2.50 V.[10] Treatment of anthracene with Ti(III) under similar conditions afforded 9,10-dihydroanthracene in a 95% isolated yield. The Ti(III) system may thus be a useful reducing reagent for Birch-type reduction of selected aromatic compounds under mild conditions, in particular the relatively more reactive (less stable) non-benzenoid annulenes.

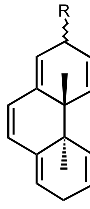
The reaction mechanism of a classical Birch reduction involves a direct electron transfer from the metal.[11] It is known that aqueous titanium trichloride can also act as an electron transfer reagent.[12] In an aqueous solution, the Ti(III) ion may exist as different complexed cations. The cation $Ti(H_2O)_6^{3+}$ is believed to be responsible for electron-transfer reactions.[13] When fluoride ions were added to an aqueous solution of titanium trichloride, the initially observed purple color due to the presence of $Ti(H_2O)_6^{3+}$ was replaced by a persistent green color attributed to the formation of the TiF_6^{3-} anion.[14] In this work, there was no product formation when the reaction was carried out in the absence of NaOH. When an excess of NaOH was present, a colorless solution was observed. It may be proposed that in a strongly basic medium the initial $Ti(H_2O)_6^{3+}$ ions could be converted to a series of $Ti(H_2O)_{6\text{-}x}(OH)_x^{3\text{-}x}$ complex ions which are responsible for the reduction of **1** to **2** via electron transfer processes.

Treatment of **2** with an excess of LDA at −70°C resulted in a dark blue solution which was quenched instantly by addition of an excess of methyl iodide. Chromatography on neutral alumina led to the isolation of two major fractions. Eluted first was believed to be a mixture of **1** and 2-methylhexane **7a** which could not be further separated by chromatography. When treated with DDQ this mixture however, afforded **1** and 2-formyldihydropyrene **8a**.[5] The second major fraction isolated from the reaction of **2** and excess LDA was a mixture of the diastereoisomers of 2,7-dimethylhexane **9**. Conversion of a mixture of **9** to 2,7-diformyldihydropyrene **10**[15] could also be achieved by oxidation with DDQ. The above observations clearly indicated the initial formation of the mono anion and dianion from **2**. Similar results were obtained when **2** was treated with *n*-BuLi followed by quenching with methyl iodide. It was however impossible to drive the initial reaction to form the dianion alone even when a large excess of base was used. Decomposition reactions seemed to compete and resulted in a complicated mixture of products.

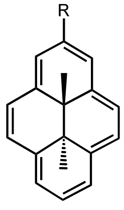
[†] A mixture of NaOH (2.2 g, 54 mmol) and **1** (300 mg, 1.3 mmol) in THF/CH_3OH (50 mL each) was stirred for 5 min and then aqueous titanium trichloride (8.0 mL, 7.8 mmol; 15% in 10% hydrochloric acid) was added. The mixture became warm and after 0.5 h the solution was poured into ice/water (250 mL). The mixture was extracted with CH_2Cl_2 (3×60 mL). The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on neutral alumina using hexane as eluant to afford compound **2** (300 mg, 99%); mp 168–170°C (lit.[5] 168–170°C).

[‡] A mixture of **5a** (20 mg, 0.057 mmol) and NaOH (0.8 g, 20 mmol) in THF/CH_3OH (12 mL each) was stirred until all NaOH dissolved, and then cooled in an ice bath. Aqueous titanium trichloride (0.6 mL, 0.58 mmol; 15% in 10% hydrochloric acid) was added dropwise to the mixture. After 0.5 h the solution was poured into ice-water and extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on a neutral alumina column using hexane/CH_2Cl_2 (1:1 v/v) as eluant to give **5b** as a yellow oil (25 mg, 87%): ^1H NMR δ 8.86 (s, 2H), 8.62, 8.58 (AB, 4H, $J=7.7$ Hz), 8.52 (d, 2H, $J=7.7$ Hz), 8.01 (t, 1H, $J=7.6$ Hz), 7.78–7.98 (m, 2H), 6.99–7.13 (m, 2H), 3.86 (br s, 2H), −3.99, −4.02 (s, 6H); λ_{max} (hexane) 496 (ε 8500), 388 (33800), 346 (66600) nm; MS *m*/*z*: 323 (M^+, 30), 308 (100), 293 (90); M_r calcd for $C_{24}H_{21}N$: 323.1674. Found: 323.1681. Anal. calcd for $C_{24}H_{21}N$: C, 89.12; H, 6.54. Found: C, 88.76; H, 6.59.

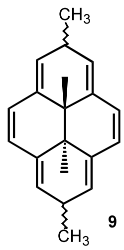
[§] The procedure was similar to that used for reduction of **1**. Compound **6** was isolated as a mixture of two isomers: mp 190–194°C; ^1H NMR δ 7.05–7.09 (m, 2H), 6.72–6.75 (m, 1H), 6.65 (d, 1H, $J=7.3$ Hz), 5.98, 6.05 (AB, 4H, $J=9.6$ Hz), 5.75 (t, 2H, $J=3.8$ Hz), 5.72 (d, 2H, $J=2.0$ Hz), 4.27 (br s, 1H), 3.84 (br s, 2H), 2.98–3.00 (m, 2H), 1.056, 1.054 (s, 6H); MS *m*/*z*: 325 (M^+, 30), 308 (100), 293 (64); M_r calcd for $C_{24}H_{23}N$: 325.1830. Found: 325.1817. Anal. calcd for $C_{24}H_{23}N$: C, 88.57; H, 7.12. Found: C, 88.35; H, 7.06.



7a R = CH_3
7b R = $Si(CH_3)_3$



8a R = CHO
8b R = $Si(CH_3)_3$



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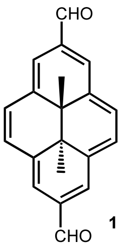
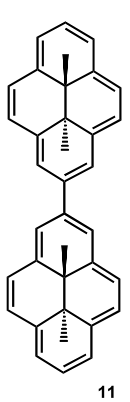


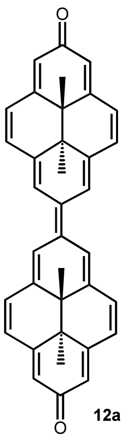
10

The dihydropyrene **1** is known to react readily with electrophiles to yield a series of 2-substituted derivatives.[5] There are however some functional groups, for example, the trimethylsilyl group[¶] that cannot be introduced directly via electrophilic substitutions. Knowing that oxidation of the hexane **2** to **1** could be achieved cleanly,[5,15] the controlled formation of the mono anion from **2** could be a useful and complementary synthetic route to mono-substituted derivatives of **1**. When the hexaene **2** was treated with 1 equiv. of *n*-BuLi at −78°C followed by quenching the very intensely blue solution with an excess of $(CH_3)_3SiCl$, the 2-trimethylsilylhexane **7b** was isolated as light yellow crystals in an 85% yield after chromatography.[‖] Oxidation of **7b** by DDQ in dry benzene at 0°C afforded the desired 2-trimethylsilyldihydropyrene **8b** in a 97% yield. Compound **8b** was isolated as dark green crystals and its electronic spectrum is very similar to that of the parent **1**.[18] This suggests that the trimethylsilyl group does not induce any appreciable conjugation effect on the macroring. The chemical shifts of the internal methyl protons in **8b**, observed at δ −4.18 and −4.21, respectively, are also similar to that of the parent **1** (δ −4.25).[6] Thus the bulky trimethylsilyl group does not seem to impose any significant steric or electronic effect on the diatropicity (ring current) of the dihydropyrene.

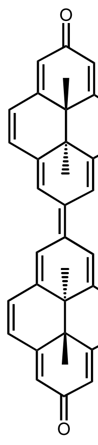
An attempt was made to study the stability of the anion of **2** under prolonged reaction times. Thus treatment of **2** with NaOH in thoroughly degassed THF/CH_3OH for 24 h at room temperature merely returned the starting material. Repeating the reaction with exposure to air for 10 h, however, resulted in the isolation of dihydropyrene **1** (34%), bis(dihydropyrenyl) **11** (24%) and bis(dihydropyrenyl)dione **12** (10%).[**] When a similar reaction was carried out by bubbling oxygen into the solution, a similar mixture of **1** (40%), **11** (8%) and **12** (48%) was obtained within 1 h. The above results clearly indicate an initial oxidative coupling of the anion of **2** to yield the intermediate **13** although all our attempts in the isolation of **13** failed. Autoxidation (dimerization) of organic anions is well documented.[20] Two subsequent, consecutive oxidation reactions would have led to the formation of **11** followed by dione **12**. This was supported by the fact that doing the reaction under oxygen decreased the yield of **11** with a corresponding increase in that of **12**. Due to restricted rotation at the central bridging carbon–carbon double bond in **12**, the molecule exists as two rigid geometric isomers **12a** and **12b**. This was clearly supported by its ^1H NMR spectrum H1,3,10,12 were observed as two singlets at δ 7.06 and 7.07 while the internal methyl protons appeared as two sets of singlets at δ 1.26/1.27 and 1.09/1.10, respectively. Chemically, compound **12** was reduced by a mixture of lithium aluminum hydride and aluminum chloride to afford **11** in a 76% yield.[††]



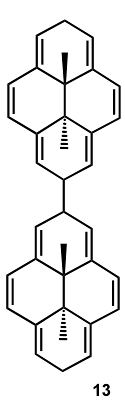
11



12a



12b



13

[¶] The trimethylsilyl group could undergo iododesilylation[16] and the aryl iodide could be used in aryl–aryl coupling reactions in the synthesis of novel aromatic compounds.[17]

[‖] A solution of **2** (50 mg, 0.214 mmol) in THF (25 mL) was cooled to −78°C. *n*-BuLi (5 mL, 1.5 M solution in hexane) was added slowly under nitrogen. The mixture was stirred for 45 min and $(CH_3)_3SiCl$ (1 mL) was added dropwise. The solution was brought to 0°C over 2 h and ice-water (20 mL) was added. The organic layer was separated, washed with water, dried, and concentrated. The residue was chromatographed on silica gel using hexane as eluant to give **7b** (55 mg, 85%): mp 172–176°C; ^1H NMR δ 5.93, 5.87 (AB, 4H, $J=9.6$ Hz), 5.6 (m, 2H), 5.58 (d, 2H, $J=2.8$ Hz), 3.0 (m, 2H), 2.6 (m, 1H), 1.04, 1.01 (s, 6H), 0.06 (s, 9H); MS *m/z* 306 (M^+, 42), 259 (45), 217 (78), 202 (90), 73 (100). A solution of **7b** (31 mg, 0.1 mmol) in benzene (40 mL) was cooled to 0°C and DDQ (65 mg) was added. The mixture was stirred for 20 min and ice-water (40 mL) was added. The organic layer was washed, dried, and evaporated. The residue was chromatographed on silica gel using hexane as eluant to give **8b** (29 mg, 97%): mp 187–189°C; ^1H NMR δ 8.73 (s, 2H), 8.62 (s, 4H), 8.57 (d, 2H, $J=7.7$ Hz), 8.10 (t, 1H, $J=7.7$ Hz), 0.57 (s, 9H), −4.18, −4.21 (s, 6H); λ_{max} (hexane) 478 (ε 15900), 380 (57300), 338 (94800) nm; MS *m/z* 304 (M^+, 35), 259 (40), 217 (55), 202 (66), 73 (100). Anal. calcd for $C_{21}H_{24}Si$: C, 82.83; H, 7.94. Found: C, 82.53; H, 7.81.

[**] A mixture of **2** (120 mg, 0.43 mmol) and NaOH (3 g, 75 mmol) in THF/CH_3OH (40 mL each) was stirred for 24 h with exposure to air. The solution was then poured into ice-water and extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on silica gel using hexane as eluant. Eluted first was **1** (40 mg, 34%). Eluted next was **11** (28 mg, 24%): mp 196-198°C (lit.[19] 195–199°C). Changing the eluant to CH_2Cl_2/CH_3COCH_3 (10:1 v/v) eluted **12** (12 mg, 10%) as a mixture of two isomers: mp 196–204°C; ^1H NMR δ 7.06, 7.07 (s, 4 H), 6.39, 6.59 (AB, 8H, $J=9.4$ Hz), 6.27 (br s, 4H), 1.26, 1.27 (s, 6H), 1.09, 1.10 (s, 6H); λ_{max} (hexane) 560 (ε 85400), 526 (59300), 304 (40900), 268 (46700); MS *m/z*: 492 (M^+, 56), 477 (78), 462 (100), 376 (40), 187 (65); Anal. calcd for $C_{36}H_{28}O_2$: C, 87.78; H, 5.73. Found: C, 87.33; H, 5.50.

[††] $LiAlH_4$ (10 mg, 0.26 mmol) was added to a solution of **12** (20 mg, 0.04 mmol) in THF (40 mL) followed by $AlCl_3$ (ca. 6 mg). The mixture was heated at reflux for 1 h, and then 10% HCl (10 mL) was added to quench the reaction and the solvent was evaporated. The solid residue was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with water, 10% aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was chromatographed on silica gel using hexane as eluant to give **11** (14 mg, 76%).

In conclusion, a very efficient Birch-like reduction for the conversion of dihydropyrene **1** to bis-triene **2** was achieved with Ti(III). This could be applicable to other aromatic systems within the appropriate range of reduction potentials. The mono-anion and dianion derived from bis-triene **2** could serve as synthetic precursors to substituted derivatives of **1** inaccessible through normal electrophilic substitutions.

Acknowledgements

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