Synthesis of 10-Methylbenz[e]acephenanthrylene

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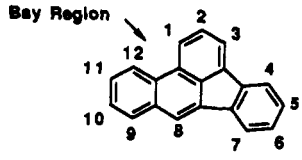
The incomplete pyrolysis of fossil fuels and biomass generates combustion products including polycyclic aromatic hydrocarbons (PAHs). These PAHs induce tumors in experimental animals, and organic extracts of particles from combustion emissions of various sources containing PAHs have been shown to induce genotoxic and carcinogenic effects *in vitro* and *in vivo*.[1-4] The introduction of methyl groups into the nonbenzo bay region positions of PAHs often markedly enhances their potency as carcinogens.[5] The carcinogenic and mutagenic properties of methylated benzofluoranthenes may provide important information about the pathways of metabolic activation of the parent PAH. This is of considerable interest because benz[e]acephenanthrylene (BeA, 1)[6] is one of the most



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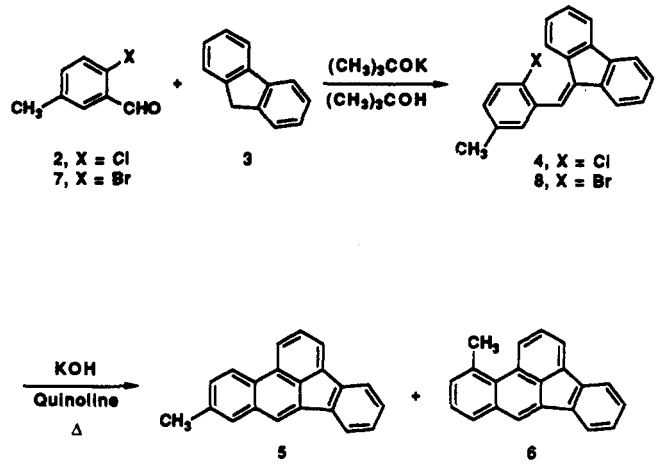
tumorigenic PAHs commonly detected in the environment.[7,8] As part of our continuing effort to develop an understanding of the potential environmental hazard posed by PAHs, we have synthesized 10-methylbenz[e]-acephenanthrylene (5).[8,9] To our knowledge, the synthesis of this compound has never before been reported in the literature.

The starting material for the synthesis of 10-methyl-BeA (Scheme I), 2-chloro-5-methylbenzaldehyde (2), was prepared according to the procedure of Jolad and Rajagopal from 2-chloro-5-methylaniline.[10] Condensation of fluorene (3) and the aldehyde (2) with potassium *tert*-butoxide gave 9-(2-chloro-5-methylbenzylidene)fluorene (4). Treatment of 4 with potassium hydroxide (KOH) and quinoline, a method that has been used for synthesizing 7-methyl-BeA,[11] gave an equal mixture of 10-methyl-BeA

Scheme I

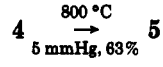


(5) and 12-methyl-BeA (6). The 12-methyl-BeA (6) was identified by comparing the NMR spectra of an authentic sample as well as other data.[11] This mixture proved very difficult to separate, and only small amounts could be purified by chromatography.

In an effort to synthesize 10-methyl-BeA (5) without forming 12-methyl-BeA (6), we synthesized 9-(2-bromo-5-methylbenzylidene)fluorene (8) (Scheme I) using the same method as used for 4.[10] When 8 was treated with KOH and quinoline, again a mixture of 10-methyl-BeA (5) and 12-methyl-BeA (6) was obtained. In an effort to determine if the mixture of 5 and 6 was forming after cyclization, we treated pure 10-methyl-BeA (5) with KOH and quinoline under the reaction conditions. No rearrangement of 5 to 6 had occurred. A method was needed that would yield only the desired 10-methyl-BeA (5).

A high-temperature cyclization using flash vacuum pyrolysis (FVP) had been used by Scott to construct corannulene,[12,13] and this approach seemed to offer a more selective cyclization. Compound 4 was placed in a quartz tube and heated to 800 °C in a tube furnace evacuated to 5 μm and connected to a liquid nitrogen trap. Chromatography of the product gave a good yield of only the desired 10-methyl-BeA (5) (Scheme II). The FVP reaction

Scheme II



was tried with 8 at 900 °C, and again the desired 10-methyl-BeA (5) was formed; however, the yield was lower, and other products were formed.

Scott et al.[13] postulated that the FVP formation of corannulene could be reasonably explained by electrocyclic ring closure followed by aromatization. In the case of either 4 or 8, each can undergo electrocyclic ring closure to give a hexacyclic intermediate, which should spontaneously aromatize to 5 by loss of HCl or HBr, respectively. The KOH–quinoline reaction of either 4 or 8 probably generates an aryne, which reacts to form 5 and 6. It has been found that mixtures of structural isomers will usually be obtained

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if a substituted aryl halide is used to generate the aryne; therefore, the formation of **5** and **6** is not unexpected.[14,15]

Experimental Section

Melting points (uncorrected) were determined on a Mel-Temp melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. Ultraviolet spectra were obtained on a Varian DMS-90. The NMR spectra were recorded on a Varian Gemini 300-MHz spectrophotometer using tetramethylsilane as the internal standard. The NMR multiplicities are reported by use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. A Thermolyne Model 21100 tube furnace was used for the flash pyrolysis. Column chromatography was performed by using E. Merck silica gel 40 (70–230-mesh ASTM). Microanalyses were performed by Desert Analytics, Tucson, AZ.

9-(2-Chloro-5-methylbenzylidene)fluorene (4). To a suspension of 2.69 g (16.2 mmol) of fluorene (**3**) and 1.82 g (16.2 mmol) of potassium *tert*-butoxide in 80 mL of freshly distilled *tert*-butyl alcohol at 40 °C was added 2.50 g (16.2 mmol) of 2-chloro-5-methylbenzaldehyde (**2**). The reaction mixture was stirred at 50 °C for 3 h and then poured into 50 mL of H_2O. The resulting solution was extracted with dichloromethane (CH_2Cl_2), washed with H_2O, dried ($MgSO_4$), and evaporated to give 5.7 g of crude product (**4**). Chromatography on silica gel, eluting with hexane, gave 4.44 g (91%) of the desired product (**5**): ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 7.02–7.80 (m, 1H), 7.13–7.18 (m, 1H), 7.28–7.42 (m, 5H), 7.46–7.49 (m, 1H), 7.59 (s, 1H), 7.69–7.73 (m, 2H), 7.80–7.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.85, 119.65, 119.82, 120.63, 124.20, 124.41, 126.80, 127.14, 128.51, 128.75, 129.48, 130.29, 130.94, 131.89, 135.04, 136.48, 136.52, 137.37, 139.17, 139.38, 141.43. Anal. Calcd for $C_{21}H_{15}Cl$: C, 83.29; H, 4.99. Found: C, 83.09; H, 5.02.

9-(2-Bromo-5-methylbenzylidene)fluorene (8). Following the same procedure as for the synthesis of **4**, 3.27 g (16.2 mmol) of 2-bromo-5-methylbenzaldehyde (**7**) gave 4.00 g (71%) of **8**: ^1H NMR ($CDCl_3$) δ 2.50 (s, 3H), 7.10–7.17 (m, 1H), 7.26–7.48 (m, 5H), 7.57 (s, 1H), 7.62 (d, 1H, J = 4.95 Hz), 7.65 (d, 1H, J = 5.07 Hz), 7.74 (s, 1H), 7.75–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.02, 119.74, 119.93, 120.36, 124.47, 124.65, 126.05, 126.85, 127.15, 128.36, 128.46, 128.82, 131.66, 132.57, 136.14, 136.46, 136.90, 138.19, 139.29, 139.43, 141.45. Anal. Calcd for $C_{21}H_{15}Br$: C, 72.64; H, 4.35. Found: C, 72.56; H, 4.39.

10-Methylbenz[*e*]acephenanthrylene (5) and 12-Methylbenz[*e*]acephenanthrylene (6). A solution of 2.22 g (7.33 mmol) of **4** in 5 mL of freshly distilled quinoline was treated with 4.11 g (73.3 mmol) of KOH and refluxed for 3 h under argon. The mixture was poured onto ice and neutralized with concd H_2SO_4. The solution was extracted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and evaporated. Chromatography on silica gel, eluting with hexane, gave 0.40 g (1.33 mmol) of recovered starting material (**4**). Further elution with 75% hexane/25% benzene gave a 1:1 mixture of **5** and **6** (1.35 mmol, 23%) based on recovered starting material. When the same procedure was tried with **8** the results were identical.

10-Methylbenz[*e*]acephenanthrylene (5). A sample of 1.44 g (4.76 mmol) of **4** was placed in a quartz tube (2.5-cm i.d. × 60 cm) connected to a liquid nitrogen trap and evacuated to 5 μm. The quartz tube was placed in a tube furnace (7-cm i.d. × 35 cm). The material coated the first centimeter (cold zone) of the quartz tube. The tube was then heated to 800 °C (hot zone). A heat lamp was used to distill the material to the hot zone, where pyrolysis occurred. The process was rapid, with most of the material transferring in 10–15 min. The heat lamp was used to complete the transfer of material over a 2-h period. After the tube had cooled to rt, it was opened, and the contents were rinsed out with CH_2Cl_2. Evaporation gave 1.4 g of crude material, which was purified by column chromatography on silica gel, eluting with cyclohexane, to give 0.65 g (2.15 mmol) of recovered starting material (**4**). When the column was washed with 3/1 cyclohexane/benzene, 0.44 g of product **5** was recovered. A 63% yield based on recovered starting material was obtained: mp 144–145 °C; ^1H NMR ($CDCl_3$) δ 2.57 (s, 3H), 7.38–7.42 (m, 2H), 7.49 (dd, 1H, J = 1.82 and 8.36 Hz), 7.72 (dd, 1H, J = 7.13 and 8.12 Hz), 7.80 (s, 1H), 7.88–8.00 (m, 3H), 8.12 (s, 1H), 8.39 (d, 1H, J = 8.25 Hz), 8.52 (d, 1H, J = 8.31 Hz); ^{13}C NMR ($CDCl_3$) δ 21.63, 119.19, 121.35, 121.40, 121.54, 121.91, 123.06, 127.43, 127.67, 128.04, 128.17, 128.62, 128.81, 129.96, 131.89, 134.26, 135.13, 136.61, 137.01, 138.67, 140.77; IR (KBr pellet) 3052, 2916, 1614, 1528, 1462, 1445, 1376, 1239, 1151, 907, 803, 776, 756, 734, 626, 601, 466 cm^{-1}; UV (hexane) λ_{max} 203.3 nm (ϵ 29 481), 223.3 (37 394), 239.2 (36 236), 256.3 (41 158), 282.6 (28 854), 287.6 (28 902), 300.2 (37 394), 341.1 (11 097); EIMS m/z 266 (M^+), 239, 131, 97, 59. Anal. Calcd for $C_{21}H_{14}$. C, 94.70; H, 5.30. Found: C, 94.60; H, 5.36.

Following the same procedure, treatment of 220 mg (1.63 mmol) of **8** at 900 °C yielded 27 mg (30%) of **5** based on recovered starting material (**8**).

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