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A New Abbreviated Synthesis of 5-Methylchrysene and its 2-Hydroxy- and 8-Hydroxy Derivatives

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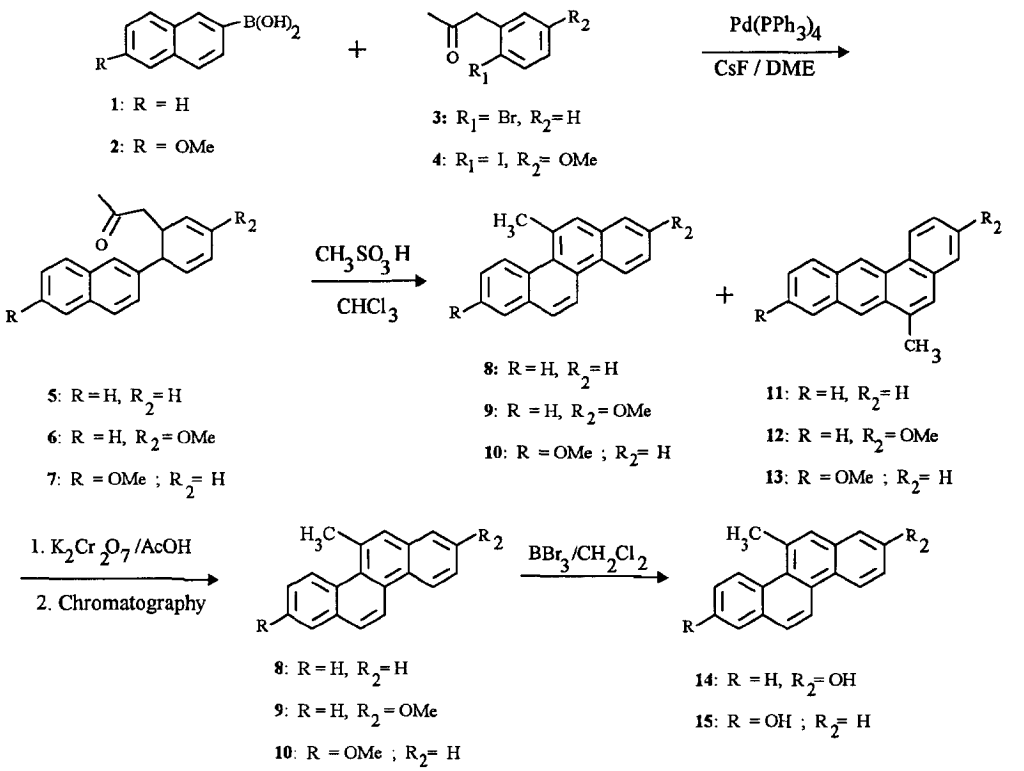
Abstract: The Suzuki reaction has been applied to provide a highly abbreviated synthesis of 5-methylchrysene and its 2-hydroxy- and 8-hydroxy derivatives from easily accessible starting materials.

Efficient synthesis of methyl substituted polynuclear aromatic hydrocarbons (PAHs) and their phenolic, dihydrodiol, and diol epoxide derivatives remains a challenging problem to many organic chemists. Only a few of these compounds are available commercially, and even those are very expensive and in short supply. The availability of these compounds in a timely manner is crucial to understanding why methyl substitution, especially, in the 'bay-region' often results in the formation of potent carcinogens.[1] Therefore, it is important that an efficient synthesis of methyl substituted PAHs and their metabolites be developed. These metabolites, especially, bay-region diol epoxides are useful precursors in the synthesis of various authentic mononucleotide, oligonucleotide or DNA adducts which are critically needed in order to further elucidate the mechanism of PAH-induced carcinogenesis at the molecular genetic level.[2] Often such studies are hampered because of the current availability of these diol epoxides in sufficient amounts by time-consuming, complex procedures.

The pioneering discovery of the Suzuki reaction[3] has set a foundation for the synthetic development of PAHs and their highly functionalized derivatives.[4,5] This reaction entails the transition metal catalyzed cross coupling of aryl boronic acid with aryl halides or aryl trifilates to produce unsymmetrical biaryls. These unsymmetrical, appropriately substituted biaryls which are generally produced in moderate to high yields from the readily available reactants can be used in the synthesis of a variety of PAHs and their substituted derivatives.[4,5] The coupling reactions are generally carried out under aqueous basic conditions which are in many cases not entirely compatible with the functional group present in the desired reactants.

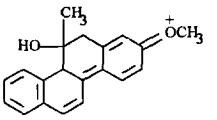
Recently, Wright *et al.*[6] modified the Suzuki reaction that allowed boronic acid coupling reactions to occur rapidly in high yield under essentially non-basic conditions in aprotic solvents which were compatible with many sensitive functional groups in the reactants or products. Such an increased versatility of the Suzuki reaction prompted us to develop a novel and highly convergent approach for the synthesis of 5-methylchrysene (**8**) and its 2-hydroxy- (**14**) and 8-hydroxy- (**15**) derivatives (Scheme 1). The phenolic compounds **14** and **15** are valuable intermediates for the synthesis of various dihydrodiols and diol epoxides of 5-methylchrysene (**5**).[7,8]

Scheme 1



Coupling of 2-naphthalene boronic acid (**1**) or its 6-methoxy- derivative **2** with readily available 2-bromophenylacetone (**3**)[9] or 2-iodo-5-methoxyphenylacetone (**4**)[10] in the presence of cesium fluoride and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) produced the corresponding 2-(2-acetonylphenyl)naphthalenes (**5** - **7**) in 55-98% yield. Boronic acids **1** and **2** were conveniently obtained in large quantities from the corresponding Grignard reagent.[3] The ^{1}H NMR spectra of various 2-(2-acetonylphenyl)naphthalenes (**5** - **7**) were consistent with their corresponding structures.[11] Cyclodehydration of these 2-(2-acetonylphenyl)naphthalenes (**5** - **7**) with methanesulfonic acid in dry chloroform at room temperature took place quantitatively; however, the reaction was non-regiospecific and produced a mixture of 5-methylchrysenes (**8-10**) and the corresponding 6-methylbenz[a]anthracenes (**11-13**) as indicated by ^{1}H NMR. The regiospecificity of the cyclodehydration reaction depended upon the starting ketone. Thus, **6** produced 8-methoxy-5-methylchrysene (**9**) with nearly 90% regiospecificity. In contrast, ketones **5** and **7** produced 5-methylchrysene (**8**) and 2-methoxy-5-methylchrysene (**10**) with only 50% and 33% regiospecificities, respectively. The trace amount of **12** from **9** was removed by fractional recrystallization from ethanol to produce pure **9** in 80-85% yield as colorless crystals which had spectral and chromatographic properties

identical to those of the authentic standard.[13] The formation of **9** with high regioselectivity appears to be due to electronic effects and can be explained on the basis that theoretically the positive charge of the transient carbocation can be delocalized more efficiently at the methoxy oxygen when the cyclization occurs at the C-1 rather than at the C-3 of the naphthalene moiety (see structures **16** and **17**). However, the non-regiospecific formation of **8** and **10** is predominantly due to steric effects because under similar conditions 2-(6-methoxy-2-



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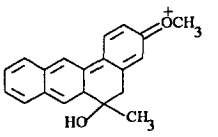

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naphthyl)phenylacetaldehyde produced exclusively 2-methoxychrysene in quantitative yield.[14]

Several attempts using tlc were made to separate 5-methylchrysene (**8**) or 2-methoxy-5-methylchrysene (**10**) from the corresponding benz[a]anthracene derivatives **11** or **13** but these were unsuccessful. Previous studies have shown that benz[a]anthracene derivatives were easily oxidizable to benz[a]anthra-7,12-quinones by chromic acid,[15] presumably because of high electron density in the meso-positions (L-region). Since the chrysene nucleus does not have an electron-rich meso-position, there is a possibility that chrysene derivatives could be relatively more stable to such oxidizing agents under mild conditions. Thus a solution of the mixture of **8** and **11**, or **10** and **13** in acetic acid was briefly treated with potassium dichromate, and the resulting product was chromatographed on dry column grade silica gel. The elution of the column with hexane produced pure **8** or **10** in 30-45% yield based on the ketones **5** and **7**. Only a minor loss of chrysene derivative (~ 5% of original) was noted during the treatment of the mixture with potassium dichromate in acetic acid. Demethylation of **9** and **10** was carried out as described earlier.[12] However, the present study indicated that by using 50% molar excess of BBr_3, demethylation proceeds with greater than 90% yield.

In a typical procedure, a mixture of naphthalene-2-boronic acid **1** (10 mmole), 2-bromophenylacetone **3** (9 mmole), cesium fluoride (20 mmole), and tetrakis(triphenylphosphine)palladium(0) (0.3 mmole, 3 mole percent) in 25 mL of dry 1,2-dimethoxyethane (DME) was refluxed under argon. The reaction, monitored by tlc (silica gel, 10% EtOAc-hexane), was generally complete within 2-3 hr. The usual work-up of the reaction mixture and column chromatography of the crude product on dry column grade silica gel using 10% ethyl acetate-hexane as a developing solvent produced 2-(2-acetonylphenyl)naphthalene (**5**) as an oil in 55-60% yield. A solution of **5** (1.0 g) in 100 mL of 10% methanesulfonic acid in dry chloroform (v/v) was stirred at room temperature for 1 hr. The reaction mixture was partitioned between ice-cold ethyl acetate and water. After washing the organic phase with 5% NaOH and water successively, it was dried and concentrated to produce 0.9 g of a 1:1 mixture of 5-methylchrysene (**8**) and 6-methylbenz[a]anthracene (**11**). This mixture was dissolved in 50 ml of warm acetic acid, and then stirred with 1.0 g of potassium dichromate for 10 min. The work-up of the reaction mixture gave a reddish semisolid residue which was chromatographed on dry

column grade silica gel. The elution of the column with hexane gave a colorless product which was recrystallized from EtOH to yield 420 mg (45%) of pure 5-methylchrysene (**8**), mp 116-17 °C (Lit.[7] mp 115-17 °C). In a similar manner, **9** [mp 149-50 °C (lit.[12] mp 148-50 °C)] and **10** [mp 149-50 °C (lit.[12] mp 147-48 °C)] were obtained from **3** and **4** in overall 84% and 18% yields, respectively. Stirring of **9** and **10** with a 50% molar excess of BBr_3 at 0 °C for 5 hr, under argon, and the usual work-up[12] of the mixture produced the corresponding phenols, 8-hydroxy-5-methylchrysene (**14**), mp 191-93 °C (lit.[8] mp 196.5-97.0 °C) and 2-hydroxy-5-methylchrysene (**15**), mp 191-92 °C (lit.[12] mp 186-87 °C), in 90-95% yields.

In summary, the present study describes an application of the Suzuki reaction leading to a highly abbreviated synthesis 5-methylchrysene and its 2- and 8-hydroxy- derivatives. Studies on the application of the Suzuki reaction to the synthesis of other PAHs and their derivatives are currently in progress. **Acknowledgement** is made to the United States Environmental Protection Agency (R 823874-01-0) for financial support of this work.

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11. 400 MHz ^{1}H NMR spectrum of **5** (Acetone-d_6): δ 1.95 (s, 3 H, $COCH_3$), 3.80 (s, 2 H, CH_2CO), 7.28-8.00 (m, 11 H, ArH); **6** (Acetone-d_6): δ 1.99 (s, 3 H, $COCH_3$), 3.78 (s, 2 H, CH_2CO), 3.86 (s, 3 H, OCH_3), 6.89-8.25 (m, 10 H, ArH); **7** (Acetone-d_6): δ 1.96 (s, 3 H, $COCH_3$), 3.80 (s, 2 H, CH_2CO), 3.95 (s, 3 H, OCH_3), 7.20-7.93 (m, 10 H, ArH).
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