An Organic Synthesis Laboratory Exercise: Preparation of 2-Methoxyanthracene

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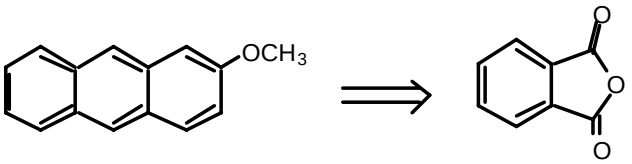
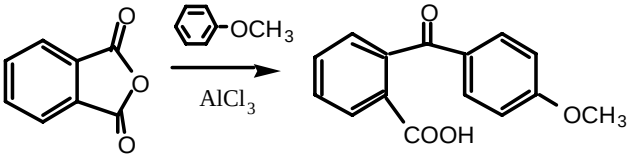
Abstract: 2-Methoxyanthracene (*target*), a non-natural polycyclic aromatic compound, was obtained from the commercially available phthalic anhydride (*starting material*) through familiar reactions but a new approach.

The objective of this laboratory exercise is for students in the undergraduate laboratory courses to profit from the opportunity to demonstrate in practice some of the organic synthesis concepts that they have previously learned, and to develop the combined practical skills of an organic chemist.

The Friedel–Crafts acylation is one of the important reactions in aromatic substitution chemistry and has been used to illustrate the synthesis of new molecules, the use of alternative catalysts [1] and the study of an organic reaction mechanism [2]. In particular, these reactions have already been used for the direct synthesis of anthraquinones and related compounds [3–9].



target starting material

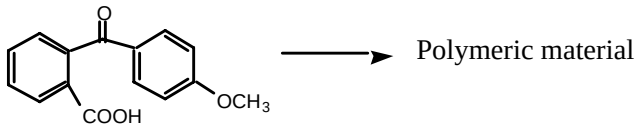


1 2

The first step of this synthesis starts with phthalic anhydride, an excess of anisole (used also as solvent), and a Lewis acid catalyst such as aluminum chloride that reacts with both the acid and carbonyl functions of the carboxylic acid group, giving a complex salt of 2-(4-methoxy)benzoyl benzoic acid. Then, the complex is decomposed by hydrolysis affording exclusively compound **2** with the expected regioselectivity.

Suggested discussion with the students: Elaborate on the regioselectivity found in the previous reaction.

According to the literature, the tricyclic systems and many larger fused ring systems are often made, through a cyclodehydration process, from substrates containing one of the acyl groups on a ring. However, all our attempts to produce the cyclization to the desired 2-methoxyanthraquinone, through the reported procedures, using the usual catalysts such as polyphosphoric or sulfuric acids [10] failed, and produced only the polymerization of the starting material.



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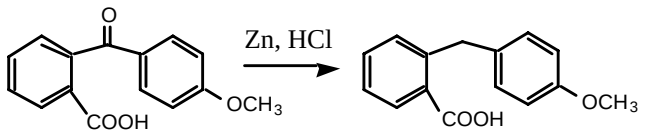
Suggested discussion with the students: Why does compound **2** not undergo the cyclization reaction? At this point, it is convenient to analyze the geometric requirements for the ring closure versus the directing groups effects on the reaction outcome. Also, elaborate on the cyclization (intramolecular) versus polymerization (intermolecular) preferences.

The fact that the intermolecular reaction was preferred to the expected intramolecular cyclization forced us to seek an alternative route that incorporates **3** as new key intermediate. To accomplish this we had to eliminate the bridge carbonyl of **2** by treatment under Clemmensen´s conditions [11, 12].

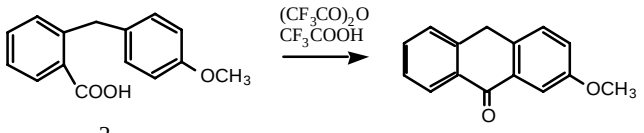


2 3

Suggested discussion with the students: Again, analyze the directing groups' effects on compound 3.

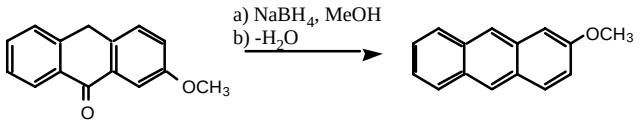
On treatment with trifluoroacetic anhydride [12], the carboxylic acid **3** furnished the unsymmetrically substituted anthrone **4.** This compound exists as a keto–enol equilibrium (tautomeric mixture) in solution, as corroborated by NMR spectroscopy [7]. A solution of this compound is fluorescent green in color: it absorbs at 268 nm (λ_{max}), and upon excitation at 280 nm produces fluorescence at 530 nm.

Finally, the transformation of anthrone **4** to the substituted anthracene **5** (fluorescent blue solution) requires the removal of the carbonyl group, using an heterogeneous alcoholic sodium borohydride reduction, and subsequent dehydration [7]



3 4

to afford 2-methoxyanthracene **5** in good yield. The fluorescence emission measurements show two bands of fluorescence at 418 and 438 nm upon excitation at 262 nm.



4 5

The present project describes a simple four-step synthetic sequence for the preparation of a substituted anthracene derivative via an anthrone intermediate. We believe that this laboratory exercise provides the students with the opportunity to explore the following techniques and concepts:

1) Two Friedel–Crafts reactions: an intermolecular acylation to yield a ketone (**1** → **2**), and an intramolecular ring closure (**3** → **4**).

2) The effects and influences of ortho–para directing groups versus the geometric factors in the Friedel–Crafts cyclization.

3) The application of two deoxygenation reactions according to the required transformation of functional groups: a Clemmensen reduction (**2** → **3**), and the use of sodium borohydride followed by acid-promoted dehydration to demonstrate that aromatization favored the process leading to a substituted anthracene (**4** → **5**).

4) An example of the tautomeric equilibrium of the anthrones, the unsymmetrically substituted **4**, which is analyzed by NMR techniques.

Experimental

The students should be able to perform the experiment under the supervision of a laboratory instructor and assistants in five 4–5 hour laboratory sessions using equipment and reagents available in a typical organic chemistry instructional laboratory.

Safety Precautions. All the experiments must be carried out in a hood avoiding skin and eye contact with reagents and products by wearing rubber gloves and eye protection. We always recommend reading the labels of all the chemical reagents and consult the *Merck Index* for the reagent properties and safety precautions before using them.

Equipment. Complete set of glassware**,** mechanical and magnetic stirring units**,** vacuum desiccator**,** rotary evaporator**,** melting point apparatus, and infrared and NMR spectrometers.

Materials. This experiment requires hydrochloric acid, sodium sulfate, sodium hydrogen carbonate, hexane, ethyl ether, dichloromethane, toluene, and ethyl acetate (all practical grades); methyl alcohol (pro analysis), silica gel 60 F_{254} TLC aluminum sheets (20 × 20 cm), and silica gel 60 for thin layer chromatography (used for flash column chromatography). Reagents (with CAS Registry numbers): phthalic anhydride 99% [85-44-9], anisole [100-66-3], aluminum chloride [7476-70-0], zinc powder [7440-66-6], trifluoroacetic acid [74-05-1], trifluoroacetic anhydride [407-25-0], and sodium borohydride [16940-66-2].

The Supporting Material (46rc1897.pdf) contains the complete description of all procedures and the compound characterizations including melting points, yields, as well as IR, and ^{1}H and ^{13}C NMR spectra, along with the UV–visible absorption spectra and fluorescence measurements of compounds **4** and **5**.

Conclusions

The preparation of 2-methoxyanthracene (an intermediate to 2-anthrol) was carried out in four steps with an overall yield of 41%. Each of the solid crystalline products was analyzed and characterized by a combination of TLC, IR, NMR, and melting-point range determination. The fluorescent compounds **4** and **5** could also be used for further UV and fluorescent spectroscopic studies [13].

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