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Synthesis of asymmetrically disubstituted anthracenes

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ABSTRACT

We have developed synthetic pathways toward differently substituted hydroxyanthracenes (anthrols) with the aim to investigate their photochemical reactivity in dehydration reactions. Although the syntheses of anthracenes substituted at positions 9,10 are well known, reports for the synthesis of anthracenes with different substitution patterns are scarce. Herein we review known and report novel synthetic pathways toward anthrols with substituents at 1,2-, 2,3-, and 2,6- positions. We present two synthetic approaches: (i) building of the anthracene tricyclic fused ring system from the appropriate benzene derivatives, and (ii) reduction of the corresponding anthraquinones.

Reduction of 2-hydroxyanthracene-1-carbaldehyde to the corresponding alcohol yields rather unexpected 1,1′-methylenedianthracen-2-ol, whose proposed mechanism of formation is supported by experimental observations and calculations.

1. Introduction

Anthracene derivatives are the subject of many research areas due to applications arising from their spectroscopic properties and photoreactivity. They are commonly utilized as fluorescent probes,[1] for labeling in biological systems, e.g. as a chemical trap for singlet molecular oxygen in cells[2] or bioimaging.[3] The well known anthracene photodimerization was thoroughly studied in solution,[4] and used to study the reactivity and selectivity in supramolecular complexes.[5] Dimerization in solid state can be used for high-density 3D optical storage memory devices.[6] Furthermore, it has been demonstrated that anthracene derivatives can be used for photoinduced DNA-cleavage,[7] and therefore, they have potential for the use in photochemotherapy.[8,9]

An on-going interest in our group is the photochemical generation of quinone methides (QM) from suitable precursors, and investigation of their biological effects. QMs are common reactive intermediates in chemistry and photochemistry of phenols and phenol-related compounds.[10] Their biological activity arises from their ability to react with proteins and DNA.[11] Since QMs can be photochemically generated from precursor compounds directly in cancer cells, they have a potential for the use in cancer therapy (photochemotherapy).[12] However, for real application in biology and medicine, it is important to develop QM precursors that absorb visible light, which is itself harmless for cells. Our group has studied the mechanisms of QM generation and biological activity of benzene,[13] biphenyl[14] and naphthalene series of QM precursors.[15] However, it was necessary to further increase the chromophore in order to shift the absorption spectrum to the visible region of light, which is harmless for the living cell. That was achieved by introducing the anthracene as a chromophore. Development of anthracene QM precursors, bearing hydroxy and hydroxymethyl groups, required design of new synthetic pathways. For the synthesis of symmetrically disubstituted anthracenes or anthracenes substituted at positions 9,10 many examples can be found in the literature.[16] On the other hand, the syntheses of asymmetrically substituted anthracenes (with two or more different substituents) are scarce, often including a large number of steps and/or suffering from low yields and formation of mixtures which are difficult to separate.[17] Herein we review known and report novel synthetic approaches to 2,3-, 1,2-, and 2,6-substituted anthracene derivatives **1**–**5** (Fig. 1). As will be shown, in some cases these syntheses provided surprising results, which were fully rationalized by additional experiments and calculations.

2. Results and discussion

It is well known that the electrophilic substitution reaction on anthracene occurs at positions 9 and 10, with the highest electron

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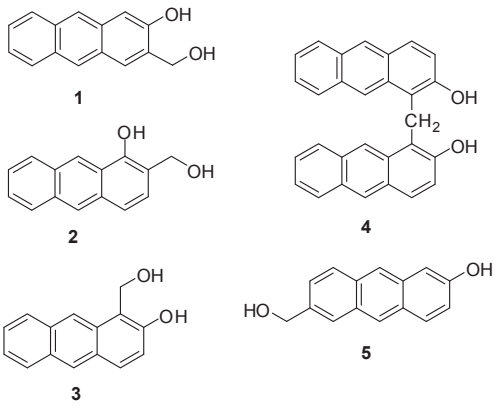

Fig. 1. Target molecules in this work.

density.[18] Thus, anthracene is not a suitable precursor for the synthesis of derivatives unsubstituted at the positions 9 and 10. If 2-anthrol was employed as a precursor, in addition to the positions 9 and 10, the reactions of electrophilic substitution would take place at both *ortho* positions to the hydroxyl group (1 and 3). The separation of anthracene regioisomers is difficult.[17] Consequently, anthracenes substituted at other positions than 9 and 10 are less common and more expensive, since their preparation requires a specific synthetic approach or multi-step synthesis. Two main approaches for the synthesis of anthracene derivatives are usually employed: the first includes building of the tricyclic ring system from some suitable benzene derivatives,[19] whereas the second is based on the synthetic transformation of some appropriately substituted anthraquinone derivatives, in which the fused tricyclic system is already assembled. In our synthetic attempts to obtain 2,6-substituted anthracene **5** we tried both approaches. The second approach, which uses anthraquinone derivatives as precursors, was proven to be better, since it enabled also to access compounds **1**–**4**. An advantage of the anthraquinone precursors in the synthesis is the fact that reactive anthracene 9,10-positions are protected, directing the substitution to one of the outer rings. After the key synthetic steps to introduce the substituents at the desired positions, the keto-groups at the positions 9,10 can be reduced to afford corresponding anthracene derivative. Many methods of anthraquinone reduction were described in the literature (*vide infra*), but, most of them are incompatible with the OH or/and halogen substituents on the anthraquinone, as will be described below.

2.1. Synthesis of 2,3-substituted anthracenes

Synthesis of 3-hydroxyanthracene-2-carbaldehyde, precursor of compound **1**, is already described in the literature, but the reported synthesis results in a very poor yield caused by the difficult separation of 1- and 3-carbaldehyde isomers on 2-anthrol.[17] To avoid these problems, we decided to develop a simple and easily scalable synthesis of 2,3-substituted anthracenes. As a starting material for this synthesis, inexpensive 2-aminoanthraquinone was used that already has the tricyclic fused ring system. It can be easily converted to hydroxy-derivative **6** *via* a known procedure (Scheme 1).[20] Anthraquinone **6** contains the desired structural motif – the hydroxy group at the anthraquinone position 2, with the positions 9 and 10 blocked for the electrophilic substitution. In the next step, the substituent at the anthraquinone position 3 was introduced. Selective iodination of hydroxyanthraquinone **6** at the position 3 is known,[21] and it was reproducible in our hands. However, reduction of iodoanthraquinone to the corresponding anthracene using aluminum powder was non-reproducible and yielded only a small amount of very impure 3-iodo-2-anthrol. Thus, we have developed the approach which uses bromination instead of iodination, since the aromatic bromides are more stable than iodides. Bromination of **6** led to a mixture of bromides **7**–**9**. When the bromination was carried out with a small excess of bromine (1–2 eq.), the reaction was not complete even at prolonged heating to reflux (2 weeks), and significant amount of unwanted isomer **9** was present (10–20%), together with the dibromo derivative **8** (30%). If the reaction was carried out with a large excess of bromine (5 eq.) formation of a 1:1 mixture of bromide **7** and dibromide **8** occurred, which can be separated by column chromatography.[22] Many methods for the reduction of anthraquinones to anthracene derivatives are described in the literature, but in case of bromide **7**, many problems occurred, often yielding some undesired products. We have tried many methods for the reduction of anthraquinone **7** before a simple and successful method was found. The most widely used method for the anthraquinone reduction is the use of refluxing conc. HI.[20,23] In the case of **7**, these severe reaction conditions led to the substitution of the OH-group and bromine with iodine, together with the over-reduction of anthracene, yielding 2,3-diiodo-9,10-dihydroanthracene as the main product. Second often used method for the conversion of anthraquinones to anthracenes is the reduction with zinc dust in ammonia.[24,25] In these conditions, debromination of compound **7** occurred, yielding 2-anthrol in high yield. The typical methods for the reduction of ketone to methylene are Clemensen and Wolff-Kishner reductions. The Clemensen reduction was not applicable on compound **7**, since debromination occurred in the reaction with zinc. In the Wolff-Kishner reduction, **7** was heated first with hydrazine in diglyme, but the corresponding bishydrazone was not formed even after prolonged reflux time, or in triglyme at higher reflux temperature. Therefore, the Wolff-Kishner reduction was not usable in this case, and it also failed on attempt to reduce methylated derivative of **7** (2-OMe instead of 2-OH). Furthermore, the reduction of **7** with $LiAlH_4$ yielded 2-anthrol. The reduction of anthraquinones with $NaBH_4$ is usually carried out in two steps - reduction to anthrone followed by its reduction to anthracene.[26] When the reduction of hydroxyanthraquinones with $NaBH_4$ was carried out in alkaline water it proceeded in one step only.[27] We used the latter method for the reduction of bromide **7** and dibromide **8**. Interestingly, both compounds gave the desired 3-bromo-2-hydroxyanthracene (**10**). Therefore, we tried to perform the reduction with $NaBH_4$ in alkaline aqueous solution (1 M Na_2CO_3) on crude mixture of **7** and **8**, which resulted with **10** as the product in high yield. Under the reduction conditions a selective debromination occurred on the anthracene position 1 in **8**, whereas debromination on the position 3 was insignificant if the reduction was not run longer than 15 min. In this way, **10** was obtained selectively, in high yield (95%) and with high purity (>90%), without a need for chromatographic separation in three consecutive reaction steps.[8a,9] These steps can be carried out on milligram or multigram scale of compounds.

Bromoanthrol **10** was treated with an excess BuLi and the resulting organolithium compound was quenched with DMF. After the hydrolysis of the addition product, aldehyde **11** was obtained in 84% yield. Diol **1** was obtained in high yield after reduction of aldehyde **11** with $NaBH_4$.[8a] The overall yield in the synthetic pathway from **6** to **1** is 77% (4 steps).

2.2. Synthesis of 1,2-substituted anthracenes

Aldehyde **16** was synthesized starting from tetraline according to the known procedure with some modifications, in similar yields (Scheme 2).[28,29] In the first step, tetralin reacted with succinanhydride in the Friedel-Crafts conditions to give keto-acid **12**,[30]