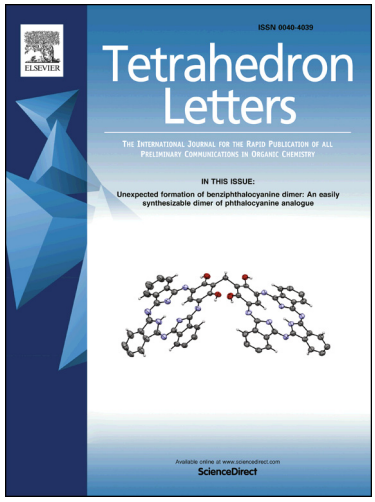

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Synthesis and structure of 2-substituted pyrene-derived scaffolds

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ABSTRACT

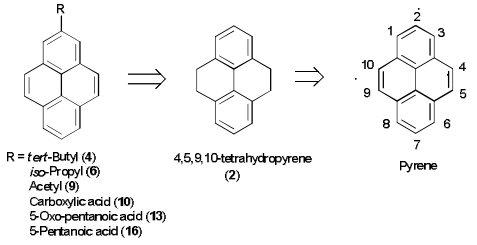
Pyrenes bear a propensity to form fluorescent excimers, and thus this chromophore is often found in sensors and fluorescent probes. 2-Functionalized pyrenes are of particular interest, however the preparation of these scaffolds is not trivial, involving synthetic routes that require 4,5,9,10-tetrahydropyrene as a key intermediate. Herein, the development and optimization of routes for the synthesis of 2-functionalized pyrene-derived building blocks, with potential to be used as tags in the preparation of fluorescent probes, is described. Additionally, the crystal structures of ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate and 2-acetyl-4,5,9,10-tetrahydropyrene revealed distinct conformations of the saturated tetrahydropyrene rings.

1. Introduction

Pyrenes are polycyclic aromatic systems that can undergo stacking by π-π interactions, with a propensity to form fluorescent excimers in solution and the solid state,[1] and with a high carrier mobility.[2] As such, the pyrene chromophore is often applied in sensors[3] or fluorescent probes. Pyrene-based probes have attracted considerable attention in recent decades[7] due to excellent spectroscopic properties, such as unusually long lifetimes of fluorescence vibronic band structure[8] and emission showing a strong dependence on solvent polarity (Ham effect).[9] For example, pyrene-based tags have been linked to lipids,[4] proteins or nucleic acids,[5,6] in order to build probes tailored to specific applications in biological studies.

It has been shown that variations in the substitution pattern of the pyrene ring and/or in the chemical nature of substituents enables control over the molecular architecture, and thus the molecular packing. This is especially relevant for some applications, for instance if pyrene-based semiconductors are envisaged.[10] As such, reliable synthetic methodologies for pyrene substitution are important, and must keep pace with molecular design.

However, the regioselective synthesis of certain pyrene derivatives is not trivial. While direct electrophilic aromatic substitution of the pyrene system occurs almost exclusively at the electron-rich 1, 3, 6 and 8 positions[11] (Scheme 1), direct substitution at positions 2 and 7 is known to take place only after prior *tert*-butylation at the 2-position. In this case, the unfavorable steric interactions induced by the bulky *tert*-butyl group hinder substitution at positions 1, 3, 6 and 8.[12] It has recently been demonstrated that the iridium-catalyzed borylation of pyrene allows the direct synthesis of a wide variety of pyrene derivatives substituted at the 2- or 2,7-positions.[13] Since pyrene derivatives functionalized at positions 2 and 7 are of particular interest due their useful properties,[14] alternative synthetic strategies for their preparation have been developed. One such strategy requires an indirect pathway, involving 4,5,9,10-tetrahydropyrene **2** as a crucial intermediate.[15]



Scheme 1. Retrosynthetic approach towards 2-functionalized pyrenes.

Herein, we describe the preparation of 2-functionalized pyrene scaffolds using 4,5,9,10-tetrahydropyrene **2** as an intermediate (Scheme 1). Pyrenes functionalized at the 2-position are interesting because they retain the long axis of symmetry, displaying a unique range of photophysical properties that differ from those of the 1-substituted analogues. Our work resulted in the synthesis and characterization of 2-functionalized pyrene derivatives bearing functionalities that enable the easy tagging of bio-molecules, for instance through an ester or amide linkage, for application to the preparation of fluorescent probes for biological studies. Additionally, the crystal structures of ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate **11** and

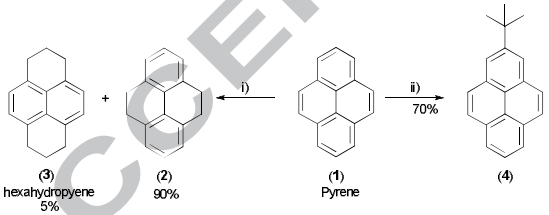
2-acetyl-4,5,9,10-tetrahydropyrene **7** are disclosed and discussed.

2. Results and Discussion

Synthesis of 4,5,9,10-tetrahydropyrene 2 and 2-(*tert*-butyl)pyrene 4

Our route towards 2-functionalized pyrenes began with the partial reduction of pyrene **1** to 4,5,9,10-tetrahydropyrene **2** (Scheme 2) prior to electrophilic aromatic substitution at position 2. 4,5,9,10-Tetrahydropyrene **2** was obtained *via* the Pd-catalysed hydrogenation of pyrene (H_2, 10% Pd/C, THF:MeOH (1:5), 10 Bar, 7 d, 90 ºC) using an adapted literature procedure.[11,12] In this reduction, a mixture of THF:MeOH as the solvent proved to be better than the previously used EtOAc.[11] This reaction proved to be quite sensitive to the amount of pyrene present in the reactor; upon increasing the amount of pyrene, complete reduction to 4,5,9,10-tetrahydropyrene **2** could not be achieved, possibly due to the excess substrate poisoning the catalyst surface. Additionally, commercially available pyrene had to be purified by column chromatography and carefully recrystallised prior to reduction, in order to avoid the formation of a mixture of desired compound **2** and hexahydropyrene **3**. Upon adjusting the reaction conditions (solvent and amount of compound introduced into the reactor), it was possible to form the desired product **2** in 90% yield. The reduction of pyrene under Birch conditions[14] with lithium as reducing agent, was also attempted, however this was unsuccessful. Additionally, this approach would not form 4,5,9,10-tetrahydropyrene **2** directly, and Pd/C catalysed dehydrogenation would therefore be necessary.

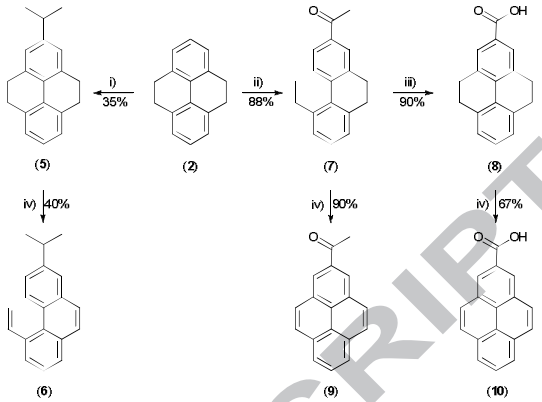
The *tert*-butylation of pyrene is known to be directed to the 2-position;[15] in our hands the preparation of 2-(*tert*-butyl)pyrene **4** was achieved in good yields *via* Friedel-Crafts alkylation, thus demonstrating that the introduction of bulky substituents can be achieved without prior reduction (Scheme 2). This compound is relevant because in future work we aim to determine the non-specific effects on membrane enzymology by evaluating the activity and stability of a reconstituted ionic pump based on bilayers of phospholipid/mixed cholesterol liposomes. Compounds **4** and **5** will be used in this study.



Scheme 2. Reduction of pyrene **1** and the preparation of 2-*tert*-butyl pyrene **4**. Reagents and conditions: i) H_2/Pd(C) (0.65 eq.), THF/MeOH (1:5), 10 bar, 80 ºC, 7 d; ii) $AlCl_3$ (1.2 eq.), *tert*-butyl chloride (1.1 eq.), CS_2, -10 ºC, 36 h.

Preparation of 2-substituted pyrenes from 4,5,9,10-tetrahydropyrene 2

With 4,5,9,10-tetrahydropyrene **2** in hand, we proceeded with the preparation of 2-functionalized derivatives. Friedel-Crafts alkylation of **2** using 1-chloropropane and $AlCl_3$ as a catalyst afforded compound **5** (Scheme 3), which was then converted into 2-isopropyl pyrene **6** upon aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Compound **6** proved to be photolabile; exposure to visible light for a week led to extensive photodegradation.

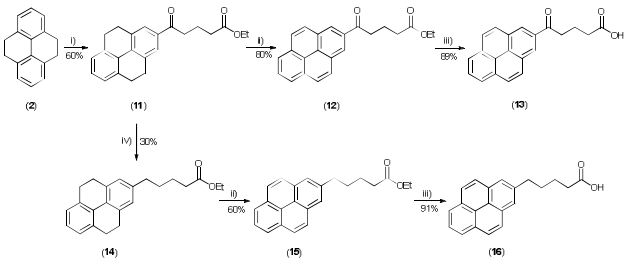


Scheme 3. Preparation of 2-substituted pyrenes from 4,5,9,10-tetrahydropyrene **2**. Reagents and conditions: i) 1-chloropropane (1.1 eq.), $AlCl_3$ (1.2 eq.), CS_2, -10 ºC, 36 h; ii) AcCl (1.1 eq.), $AlCl_3$ (1.2 eq.), CS_2, -10 ºC, 2 d; iii) Br_2 (6.73 eq.), NaOH (18 eq.), 1,4-dioxane, H_2O, 16 h; iv) DDQ (2.1 eq.), THF, reflux, 2 d.

Friedel-Crafts acylation of **2** using acetyl chloride, $AlCl_3$ as catalyst, and carbon disulfide (CS_2) as solvent, afforded crystals of 2-acetyl-4,5,9,10-tetrahydropyrene **7** whose structure was determined by single-crystal X-ray diffraction. Friedel-Crafts reactions (alkylation and acylation) are known to be sensitive to the solvent used; while CS_2 leads to monoacylation, CH_2Cl_2 affords the deacylated products.[13] The reaction conditions were carefully tuned and gratifyingly selectivity could be achieved by using only a slight excess of the alkylating or acylating reagent (1-chloropropane or acetyl chloride) in cold CS_2.

The dehydrogenation of **7** was achieved using a modified literature procedure.[14] Compound **7** was converted by haloform oxidation to the corresponding carboxylic acid **8**, using bromine in 1,4-dioxane and NaOH.[16] Compound **8** was then aromatized with DDQ to afford the target pyrene 2-carboxylic acid **10** (Scheme 3).

In order to obtain 2-substituted pyrenes with a longer aliphatic chain, thus increasing the flexibility of the system, pyrene derivative **12** was prepared from 4,5,9,10-tetrahydropyrene. Friedel-Crafts acylation, using $AlCl_3$ and ethyl glutaryl chloride in CS_2, smoothly afforded the monosubstitution product in good yield. The crystal structure of **11** was determined by single X-ray diffraction. This compound proved to be a versatile intermediate for expanding the library of 2-substituted pyrenes. Dehydrogenation of **11** with DDQ yielded ethyl 2-pyrene-5-oxopentanoate **12**, which was then hydrolyzed to carboxylic acid **13**. Compound **14** was obtained from compound **11** through a Clemmensen-type reduction using Zn and HCl in EtOH and subsequently oxidized with DDQ to give ethyl 2-pyrenepentanoate **15**. Hydrolysis of **15** gave the corresponding carboxylic acid **16** in excellent yields (Scheme 4).



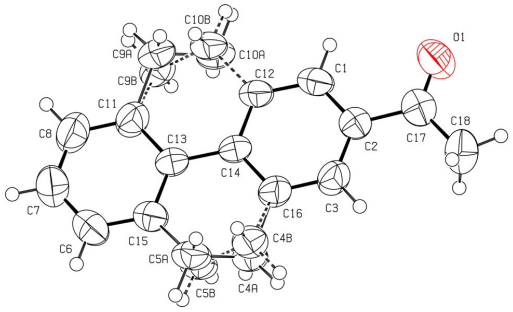
Scheme 4. Preparation of 2-substituted pyrenes from ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate **11**. Reagents and conditions: i) ethyl glutaryl chloride (1.1 eq.), $AlCl_3$ (1.2 eq.), CS_2, -10 ºC, 2 d; ii) DDQ (2.1 eq.), THF, reflux, 2 d; iii) KOH (3.44 eq.), MeOH, H_2O, 50 ºC, 1 d; iv) Zn (23 eq.), EtOH, HCl (37%), 3 d.

Molecular geometry of 2-acetyl-4,5,9,10-tetrahydropyrene 7 and ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate 11

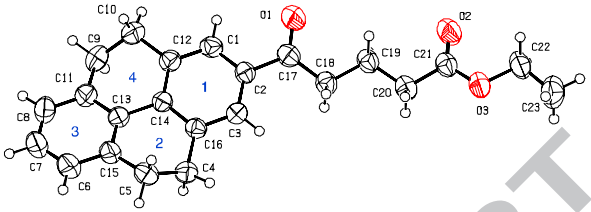
The molecules of 2-acetyl-4,5,9,10-tetrahydropyrene **7** exist in the crystal in two alternate conformations, A and B (see Fig. 1), each having a probability close to 50% of sharing the crystallographic sites. The saturated rings possess half-chair conformations. In monomeric compound **7** the dihedral angle between the least-squares planes of the two aromatic rings is only 2.55(11)˚. The acetyl group is almost coplanar with the aromatic ring, as shown by the small value of the C1-C2-C17-O1 torsion angle of -1.0(2)˚. The oxygen atom of the acetyl group acts as an acceptor of the methyl group proton of a neighbouring molecule, this being the most relevant intramolecular interaction contributing to crystal cohesion in addition to those of Cg…Cg types.

In the crystal phase of ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate **11**, the tetrahydropyrene moiety has an approximate C_2 symmetry axis running through the C13—C14 bond. The molecule is slightly twisted as the two aromatic rings (labelled **1** and **3** in Fig. 1) form a dihedral angle of 16.57(5)˚. The two other rings (2 and 4) have close to a screw-boat conformation, with average puckering amplitude and angles[18] calculated along the reference C9-C10 and C4-C5 bonds of Q=0.452(4) Å, θ=114.6(3)˚ and φ= 209.0(5)˚. Bond lengths and angles within the molecule have values close to the average tabulated values.

Additional crystallographic data for compounds **7** and **11** and a more in depth discussion of the crystal structures are provided as supplementary information.



2-Acetyl-4,5,9,10-tetrahydropyrene **7**



Ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate **11**

Figure 1. ORTEPII plot of compounds **7** and **11** showing the anisotropic displacement ellipsoids drawn at the 50% probability level and the atomic and ring numbering schemes.

3. Conclusion

Easy access to 2-functionalized pyrenes is relevant because these scaffolds retain the long axis of symmetry, displaying a unique range of photophysical properties that differ from those of the 1-substituted analogues. Synthetic routes for the conversion of pyrene into 2-functionalized pyrenes, using 4,5,9,10-tetrahydropyrene **2** as an intermediate, resulted in the synthesis and characterization of various 2-functionalized pyrene derivatives bearing functional groups that may enable easy tagging of bio-molecules, for instance through an ester or amide linkage, for the preparation of fluorescent probes for biological studies. The crystal structures of two intermediate compounds, ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate **11** and 2-acetyl-4,5,9,10-tetrahydropyrene **7**, were also investigated, revealing distinct conformations of the saturated tetrahydropyrene rings. It is hoped that the information reported herein regarding the synthesis and crystal data will help encourage the incorporation of 2-pyrene derivatives into existing and novel pyrene based applications and hopefully make their use as popular as the substituted 1-substituted derivatives.

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Supplementary Material

Experimental details for the synthesis and characterization of compounds, single crystal X-ray structures, crystallographic analysis, supramolecular organization of ethyl 4,5,9,10-tetrahydro-2-pyrene-5-oxopentanoate, **11** and experimental details of the crystallographic studies, as well as selected NMR and MALDI-TOF spectra, are included as supporting information.

Synthesis and structure of 2-substituted pyrene-derived scaffolds useful as fluorescent tags

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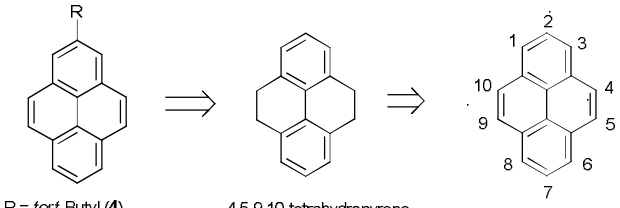
Highlights

- We report the optimised synthesis of key 2-functionalized pyrene building blocks.
- The compounds may be used as tags in the preparation of fluorescent probes.
- Crystal structures of tetrahydropyrene and 2-acetyl-tetrahydropyrene are disclosed.
- We report the crystal structure of ethyl tetrahydro-2-pyrene-5-oxopentanoate (ETPO).
- ETPO is a key block for access to ester- or amide-bridged fluorescent probes.



R = *tert*-Butyl (**4**)
iso-Propyl (**6**)
Acetyl (**9**)
Carboxylic acid (**10**)
5-Oxo-pentanoic acid (**13**)
5-Pentanoic acid (**16**)

4,5,9,10-tetrahydropyrene (**2**)

Pyrene