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PHOTOCHEMICAL SYNTHESIS OF CHRYSENOLS

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ABSTRACT

Chrysenols are formed together with other metabolites when chrysene is metabolized in living organisms. The principal metabolites are needed as pure compounds for reference materials and standards to study various aspects of this metabolism. In this study the 1-, 2-, 3-, and 4-chrysenols have been made in pure form by photochemical ring closure of [(methoxyphenyl)vinyl]naphthalene to the methoxychrysenes followed by deprotection, and purification of the chrysenols. The method may be applied to make the single pure compounds in high yields.

INTRODUCTION

Although chrysene is among the less carcinogenic PAHs, their metabolites are of interest. Chrysene has been proposed as a biomarker for monitoring the exposure of marine life to pollutants from both onshore industry and the offshore oil industry (1). This synthetic work was initiated by the need of reference materials for this kind of research (2). In fish chrysene is rapidly transformed into its metabolites, and among these are 1-,2- ,3- and 4-chrysenols.

The first systematic work to obtain the various chrysenols was reported by Cook and Schoental as early as 1945 (3). Note that they used different numbering of the substituents than the current IUPAC nomenclature. Later a lot of work was done to prepare some of the regioisomers reflecting the improvement of synthetic methods along the way.

Direct oxidation of chrysene gives reaction mainly in the K-region (5- and 6-position) (4). Thus the skeleton has to be assembled while the functionality is in place. This has been done by assembling a partly saturated skeleton and then oxidizing the compound down to the chrysene (5, 6, 7) or by assembling aromatic rings by a Suzuki cross coupling reaction (8). The ring system may be made by a photochemical cyclization with iodide (9, 10, 11)

What appears to be the shortest way to the functionalized chrysene skeleton consists of a Wittig-type reaction to connect a naphthalene unit with a benzene ring through a double bond followed by the photochemical cyclization to give the chrysene ring system. This method has been used by a number of groups (9, 11, 12, 13, 14, 15) to obtain different substituted chrysenes, and appears to have become the standard way for making substituted chrysenes. We decided to use the same approach while trying to improve on the actual reactions.

RESULTS AND DISCUSSION

The synthetic route is shown in Figure 1. We decided to do the Wittig-reaction from the Wittig-salts of methoxybenzyl chlorides and 1-naphthaldehyde, as chlorides are less expensive and should be reactive enough (12). The methoxybenzyl chlorides were mixed with 1.1 eq. triphenylphosphine and stirred under N_2 at 120 °C for two days. The solvent was removed under reduced pressure and the remaining solids washed 5 times with diethyl ether. We obtained the Wittig-salts of 2-methoxybenzyl chloride (92%), 3-methoxybenzyl chloride (82%) and 4-methoxybenzyl chloride (94%). The Wittig-salts were reacted with 1-naphthaldehyde under phase-transfer conditions (12, 15) with 50% NaOH in CH_2Cl_2 at room temperature for 1-3 days. The reactions were practically quantitative for all compounds. The NMR signals of the olefinic hydrogens showed a 1:1 E/Z-ratio for all 3 compounds.

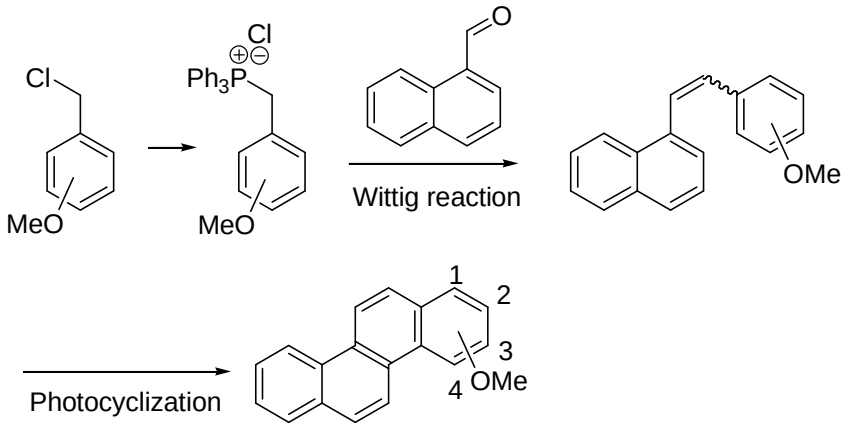

Figure 1. Synthesis of the 1-, 2-, 3-, and 4-chrysenols

This is less selectivity than reported for similar compounds (12, 13), but the E/Z-ratio is of no importance in that further reactions of the E/Z-isomers gives the same photoproduct.

Photochemical oxidative cyclization with oxygen present gives low yields for compounds with methoxy groups, which appear to further oxidize. Liu et al. (16) developed a method where stoichiometric amounts of iodine were used as oxidant. Stoichiometric amounts of iodine make it possible to use an inert atmosphere. The intermediates will isomerize on the double bond and annulate into the chrysene skeleton. Left unattended the formed HI will reduce the stilbene double bond and give byproducts. Adding propylene oxide to consume the formed HI improves the yields. The less toxic butylene oxide works as well as propylene oxide (15). Due to safety restrictions on benzene toluene was used as solvent. This worked as well as and even slightly faster than the reaction in benzene. In solvents degassed by ultrasound and an inert atmosphere no byproducts were formed. Increasing the concentration of the reaction mixture from 3 mM up to 15 mM worked well, but a 25 mM solution gave traces of byproducts. The reaction times required were less than proportionate to the increased concentrations.

Thus, 1-[2-(2-methoxy-phenyl)-vinyl]-naphthalene gave pure 1-methoxychrysene (**1**) in 59% yield after recrystallization from toluene, while 1-[2-(4-methoxy-phenyl)-vinyl]-naphthalene gave pure 3-methoxychrysene (**3**) in 42% yield after recrystallization from heptane. These yields can be substantially improved by flash chromatography, but these compounds are rather cumbersome to purify, at least on silica gel, due to low solubility in the eluent and poor separation from large band broadening.

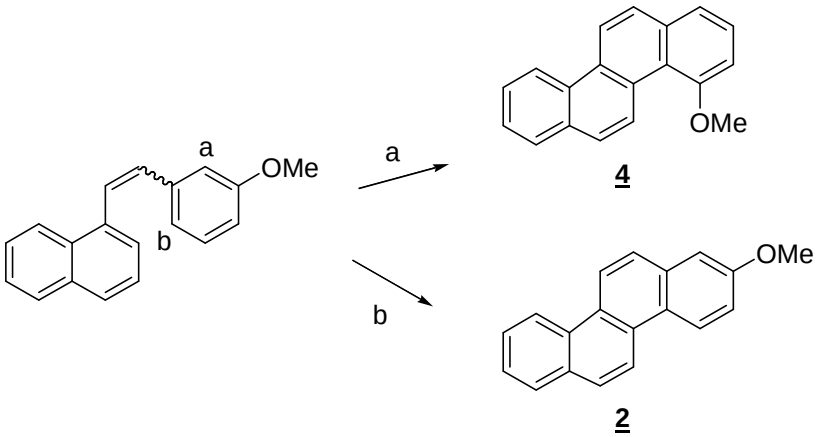

Figure 2. With both *o*-positions free, the *m*-methoxylated benzylnaphthyletane gives two different products.

The meta-substituted 1-[2-(3-methoxyphenyl)vinyl]naphthalene gives different products from the two reactive positions (Figure 2), resulting in 2-methoxychrysene (**2**) and 4-methoxychrysene (**4**) in a 1:1 mixture (Measured on HPLC). Olsen and Pruett (11) got **2** and **4** in a 1:3 ratio with iodine in cyclohexane under inert atmosphere, but without any epoxide). Recrystallization of the mixture from acetone gave 40% of pure **2**. The mother liquid was purified by flash chromatography to yield 40% of **4**. Chromatography of **4** is also less cumbersome than for the other compounds.

Deprotections of methoxy-PAHs are usually done with BBr_3. This procedure is reported to be practically quantitative for **3** (13). Among the many other methods of cleaving a methoxy group on an aromatic ring, a method using potassium in THF (17) got our attention. The method is simple and was reported to give phenol from methoxybenzene in 94 % yield. The reaction follows a radical mechanism and probably forms a radical anion. The outcome, demethylation or demethoxylation, varies with the reaction conditions. THF was reported to promote demethylation while less polar solvents promote demethoxylation. The radicals are later quenched in ethanol to give the products.

Table 1. Deprotection of methoxygroups to chrysenols

	K		**BBr_3**	
	Yield	Purity	Yield	Purity
1-Chrysenol (**5**)	62 %	>90 %	96 %	~90 %
2-Chrysenol (**6**)	73 %	>95 %	93 %	> 99 %
3-Chrysenol (**7**)	60 %	>90 %	58 % [a)]	> 98 %
4-Chrysenol (**8**)	62 %	>90 %	96 %	~90 %

[a)] Mechanical losses. Seidel (13) reported 99% for the same reaction

Our results are shown in Table 1. The potassium reaction gave substantial amounts of chrysene together with the chrysenols **5**, **6**, **7** and **8**. The BBr_3- reaction was also more sluggish than reported by others. Sometimes it had to be left overnight at room temperature to achieve high yields. The product was still often contaminated with unreacted starting materials. Sublimation removed colored impurities but our principal contaminants remained. Attempts at recrystallization didn't improve the purity either. As mentioned before, flash chromatography on silica gel of these compounds was cumbersome. Small differences in retention times between product and impurities made it difficult to obtain pure compounds. The chrysenols, particularly **8**, are also prone to oxidation by extended handling in air.

To further purify **5** and **8** the hydroxy-group had to be protected. Silyl-protective groups are known to enhance the mobility of compounds on silica gel. Acidic deprotection should also allow the groups to be easily removed without much workup. Based on half-lives in acidic conditions of silyl-groups on creosol (18) the TBDMS-group appeared to balance chromatographic stability and ease of removal.

Silylation with TBDMSCl and imidazole in DMF gave pure 1-*t*-butyldimethylsilanoxychrysene (**9**) in 82% yield from **5** and 4-*t*-butyldimethylsilanoxychrysene (**10**) in 70% yield from **8** after purification by flash chromatography. The protective group of **9** was removed with HCl in methanol at 40 °C for two days. Upon cooling the product precipitated and could be filtered off to yield 85% of the pure **5**.

Deprotection of **10** was more cumbersome as the compound didn't dissolve in methanol. In ethanol the reaction took 5 days and the product had to be precipitated with water. The product contained 10% of unreacted **10**. But these compounds were easily separated by flash chromatography. By exclusion of air in the column and solvents a 70% yield of pure **8** was obtained.

ACKNOWLEDGEMENTS

The compounds obtained in this work are commercially available as standards from Chiron AS (www.chiron.no)

EXPERIMENTAL

The photochemical reactions were performed in a Photochemical Reactors Ltd. 400 W medium pressure Mercury-lamp in a 2 L quartz immersion well reactor fitted with a no. 3408 glass filter sleeve. Silica gel Silice 60A C.C. 40-43 μm from SDS were used for Flash chromatography. Melting points were obtained in sealed capillary tubes on a Stuart Scientific melting point apparatus SMP3. Nmr-spectra were measured on a Varian Mercury 300MHz instrument with tetramethylsilane as internal reference. Purity of compounds and composition of mixtures were analyzed on a VYDAC reverse phase C18 column in a Thermo separation products spectra system HPLC with a UV1000 detector adjusted to 254 nm. Eluents used were acetonitrile and a 0.05 M ammonium acetate water buffer at pH 4,0.

Wittig-salts - general procedure

A mixture of *o*-, *m*- or *p*-methoxybenzyl chloride (18 mmol) and triphenylphosphine (18 mmol) in toluene (18 ml) was stirred under nitrogen at 120 °C for two days. The solvent was then removed under reduced pressure and the remaining solids washed with diethyl ether (5x20 mL). The Wittig-salt remained as a white powder in 82-94 % yield.

Wittig reaction – general procedure

The Wittig salt (16.6 mmol) was mixed with 1-naphthaldehyde (13.8 mmol) in DCM (120 mL) and added 50% aqueous NaOH (12 mL). The mixture was vigorously stirred at room temperature under nitrogen for 1 day for the *o*- and *p*-substituted compounds. The *m*-substituted compound required 3 days. The reaction mixture was washed with water (300 mL). The water phase was extracted with DCM (100 mL). The combined DCM-phases were dried with $MgSO_4$ and concentrated under reduced pressure. The remaining oil was purified by flash chromatography on silica gel (Heptane: Ethyl acetate 9:1) to give 97-99 % of the stilbenes as thick colorless oil.

Photochemical cyclization – general procedure

The photo reactor was flushed with N_2 and charged with [(methoxyphenyl)vinyl] naphthalene (1 eq.), iodine (1.1 eq.), 1, 2-epoxybutane (30 eq.) and degassed toluene (1.2 L). The toluene was degassed by ultrasound for 10 min. under N_2 atmosphere. The reaction was irradiated until the color of iodine disappeared (1.5 – 6 hours depending on concentration). The reaction mixture was concentrated under reduced pressure to about 400 mL, washed with 10% $Na_2S_2O_3$ (100 mL) and brine (100 mL), dried with $MgSO_4$ and evaporated to dryness. The pure products were obtained by recrystallization.

*1-Methoxychrysene (**1**):*

After 1.5 h of irradiation 1-[2-(2-methoxyphenyl)-vinyl]-naphthalene (0.973 g, 3.74 mmol) gave 0.570 g (59%) of **1** as leaf-formed white crystals upon crystallization from toluene. Melting point 186-187 °C. Lit.: 185-186 °C (19), 188-190 °C (20)
^{1}H-nmr (acetone-d_6) δ: 4.11 (s, 3H), 7.18 (d, J=7.8 Hz, 1H), 7.65-7.79 (m, 3H), 8.07-8.11 (m, 2H), 8.48 (d, J=9.0 Hz, 2H), 8.83 (d, J=8.7 Hz, 1H), 8.86 (d, J=9.3 Hz, 1H), 8.94 (dd, J= 8.8, 0.9 Hz, 1H)

*2-Methoxychrysene (**2**) and 4-Methoxychrysene (**4**)*:

After 4 h of irradiation 1-[2-(3-methoxyphenyl)-vinyl]-naphthalene (3.75 g, 14.4 mmol) gave a mixture of **2** and **4** in a 1:1 ratio (measured by HPLC). The crude mixture was recrystallized from hot acetone and pure **2** filtered off. The filtrate was concentrated and recrystallized once more to obtain a total of 1.54 g of **2** as a white powder. The filtrate was concentrated and purified by flash chromatography (Heptane: Ethyl acetate 7:1) to obtain 1.41 g of **4** for a combined yield of 80%.

2: Melting point 251.5-252.5 °C. Lit.: 250-251 °C (3), 251-252 °C (11), 246-247 °C (8)
^{1}H-nmr (acetone-d_6) δ: 4.00 (s, 3H), 7.38 (dd, J=9.3, 3.0 Hz, 1H), 7.53 (d, J=2.7 Hz, 1H), 7.62-7.76 (m, 2H), 8.03-8.09 (m, 3H), 8.77-8.54 (m, 3H), 8.89 (d, J=8.4 Hz, 1H)

4: Melting point 113-114 °C. Lit.: 102-103 °C (3), 102-104 °C (11)
^{1}H-nmr (acetone-d_6)δ: 4.18 (s, 3H), 7.31 (dd, J=7.5, 1.2 Hz, 1H), 7.57-7.74 (m, 4H), 8.00-8.06 (m, 3H), 8.88 (d, J=8.7 Hz, 1H), 8.89(d, J=8.4 Hz, 1H), 9.81 (d, J=9.3 Hz, 1H)

*3-Methoxychrysene (**3**):*

After 6 h of irradiation 1-[2-(4-methoxyphenyl)-vinyl]-naphthalene (3.75 g, 14.4 mmol) gave 1.56 g (42%) of **3** as white crystals upon double recrystallization from heptane. Melting point 146-147.5 °C. Lit.: 145-146 °C (9), 147.5-148.5 °C (21)
^{1}H-nmr (acetone-d_6) δ: 4.09 (s, 3H), 7.33 (dd, J=8.7, 2.4 Hz, 1H), 7.64-7.77 (m, 2H), 7.98-8.08 (m, 4H), 8.30 (d, J=2.7 Hz, 1H), 8.71 (d, J=8.7 Hz, 1H), 8.84 (d, J=8.7 Hz, 1H), 8.90 (d, J=7.8 Hz, 1H)

Deprotection with potassium – general procedure

To methoxychrysene (1 mmol) in dry THF (30 mL) was added potassium (3 eq.) and refluxed under N_2 for 4 h. The black solution was allowed to reach room temperature before it was poured into cold ethanol (50 mL) under stirring. To the mixture was added 0.1 M HCl (25 mL) and brine (25 mL) before it was extracted with DCM (3x50 mL). The combined DCM-phases were dried with $MgSO_4$ and concentrated under reduced pressure. The products were purified by flash chromatography (Heptane: Ethyl acetate from 3:1 to 9:1).

Deprotection with BBr_3 – general procedure

Methoxychrysene (7 mmol) in DCM (125 mL) was stirred under N_2 at -25 °C and added 1.0 M BBr_3 in DCM (1.3 eq.) After 30 min. the reaction was allowed to reach room temperature and stirred for another 4 h. The reaction mixture was then poured over crushed ice (400 mL). When the ice was melted the mixture was diluted with DCM (300 mL) and 0.1 M NaOH (200 mL) and extracted. The water phase (including undissolved matter) was extracted with ethyl acetate (200 mL). The combined organic phases was washed with water (300 mL) and brine (300 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield the crude product.

*2-Chrysenol (**6**)*

The crude product after deprotection of 90% pure **2** (1,2950 g, 5,017 mmol) with BBr_3 was sublimed at 175 °C, $2x10^{-3}$ mBar, to remove coloured impurities, and subsequently purified by flash chromatography (Heptane: Ethyl acetate 3:1-1:1) to yield 1.0210 g (93% when subtracting impurities in starting material) of off-white powder (>99% pure on HPLC). The solids have to be completely dry before contact with air to avoid discolouration. Melting point: Decomposes at 284-287 °C in a sealed capillary tube. Lit: 273-275 °C (3), 265-267 °C (5).
^{1}H-nmr (acetone-d_6) δ: 7,36 (dd, J=2.7, 9.0 Hz, 1H), 7.42(d, J=2.7 Hz, 1H), 7.60-7.75(m, 2H), 7.94(d, J=8.7Hz, 1H), 8.03-8.07(m, 2H), 8.75-8.80(m, 3H), 8.86(d, J=8.4 Hz, 1H), 8.87(s, OH)

*3-Chrysenol (**7**)*

Crude **(3)** (1.5644 g, 6.006 mmol) was, after reaction with BBr_3 (and mechanical losses), sublimed at 190 °C, $2x10^{-3}$ mBar and subsequently purified by flash chromatography (Heptane: Ethyl acetate 4:1) to yield 0.8533 g (58%) of **7** (>98 % pure on HPLC) together with 14% recovered **3**. Melting point: Decomposes at 268-270 °C in a sealed capillary tube. Lit: 271-273 °C (21)
^{1}H-nmr (acetone-d_6) δ: 7.30 (dd, J=9.0, 2.5 Hz, 1H), 7.63-7.75 (m, 2H), 7.94-8.06 (m, 4H), 8.23 (d, J= 2.1 Hz, 1H), 8.64 (d, J=8.7 Hz, 1H), 8.67 (d, J=8.4 Hz, 1H), 8.86 (s, OH), 8.88 (d, J=8.7 Hz, 1H)

Purification by silylation – desilylation

*1-tert-Butyldimethylsilanoxychrysene (**9**)*

Crude **1** (1.8519g, 7.17 mmol) gave upon deprotection with BBr_3 a crude solid (1.7895 g, 7.3247 mmol). This solid and imidazole (1.4960 g, 21.97 mmol) was dissolved in DMF (20 mL) under N_2 at room temperature and added 1.0M TBDMSCl in THF (11.0 mL, 11.0 mmol). The mixture was stirred overnight and then diluted with ethyl acetate (200 mL) and washed with water (100 mL). The water phase was extracted with ethyl acetate (100 mL). The combined organic phases was washed with brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (Petroleum ether: Ethyl acetate 19:1-9:1) to yield 2.1400 g (82%) of pure **9**. Melting point: 159-161 °C
^{1}H-nmr (acetone-d_6) δ: 0.37(s, 6H), 1.16(s, 9H), 7.18(dd, J=0.9, 6.9 Hz, 1H), 7.60-7.79(m, 3H), 8.07-8.12(m, 2H), 8.46(d, J=9.3 Hz, 1H), 8.54(d, J=8.7 Hz, 1H), 8.84(d, J=8.7 Hz, 1H), 8.88(d, J=9.3 Hz, 1H), 8.94(d, J= 8.4 Hz, 1H)

*1-Chrysenol (**5**)*

The solution of **9** (1.4603 g, 4.073 mmol) in degassed methanol (100 mL) was added 6.0 M HCl (15 mL) under N_2. After stirring at 40°C for 2 days, the mixture was cooled on an ice bath and filtered under N_2. The solids were dried under reduced pressure to yield 0.8420 g (85%) of **5** as a white powder (Pure on HPLC). Melting point: Does not decompose below 350 °C in a sealed capillary tube. Litt: 281-283 °C (5), decompose at 278-280°C (7)
^{1}H-nmr (acetone-d_6) δ: 7.14(d, J= 7.5 Hz, 1H), 7.56(dd, J= 7.8, 8.1 Hz, 1H), 7.65-7.79(m, 2H), 8.07-8.10(m, 2H), 8.40 (d, J=8.4 Hz, 1H), 8.51 (d, J=9.3 Hz, 1H), 8.81(d, J=3.9 Hz, 1H), 8.84(d, J=3.9 Hz, 1H), 8.94(d, J=8.4 Hz, 1H), 9.20 (broad s, OH) In fair agreement with literature data (7).

*4-tert-Butyldimethylsilanoxychrysene (**10**)*

Crude **8** (0.2793 g, 1.143 mmol) from deprotection with BBr_3, and imidazole (0.234 g, 3.44 mmol) was dissolved in DMF (5 mL) under N_2 and added 1.0 M TBDMSCl in THF (1.7 mL, 1.7 mmol) and stirred at room temperature overnight. To the mixture was added ethyl acetate (50 mL) and extracted with water (30 mL). The water phase was extracted with ethyl acetate (15 mL). The combined organic phases was washed with brine (15 mL) concentrated and purified by flash chromatography (Petroleum ether: Ethyl acetate 19:1) to yield 0.2879 g (70%) of **10** as a pale yellow solid. Melting point: 147-149 °C
^{1}H-NMR($CDCl_3$) δ: 0.37 (s, 6H), 1.11(s, 9H), 7.28(dd, J=0.9, 7.8 Hz, 1H), 7.55(t, J=7.8 Hz, 1H), 7.64-7.76(m, 3H), 8.00-8.08(m, 3H), 8.86(d, J=8.7 Hz, 1H), 8.92(d, J=8.4 Hz, 1H), 9.85 (d, J=9.0 Hz, 1H)

*4-Chrysenol (**8**)*

To a solution of **10** (0.1608 g, 0.448 mmol) in degassed ethanol (10 mL) under N_2 was added 6.0 M HCl (1.5 mL). The mixture was stirred at 40°C for 3 days under N_2, cooled on an ice bath, added degassed water (20 mL) and stirred for 1 h before filtration under N_2. The solids were dried in vacuo, but contained 10% starting material. The compound were put on top of a dry packed flashcolumn and eluted with degassed solvents under N_2 (Petroleum ether: Ethyl acetate 4:1) and yielded 0.096 g (88%) of **8** as a white powder (Pure on HPLC). Melting point: 172-172.5 °C in a sealed capillary tube. Litt: 152-153 °C (3)
^{1}H-nmr (acetone-d_6) δ: 7,26 (dd, J=7.5, 1.5 Hz, 1H), 7.48(t, J=8.1 Hz, 1H), 7.58-7.75(m, 3H), 8.01-8.06(m, 3H), 8.86(d, J=9.0 Hz, 1H), 8.92(dd, J=8.1, 0.6 Hz, 1H), 9.64(s, OH), 10.00(dd, J=9.6, 2.1 Hz, 1H)

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