A General Synthetic Method for 2-Substituted Anthracenes

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Dedicated to Professor Manfred Regitz on the occasion of his 60th birthday

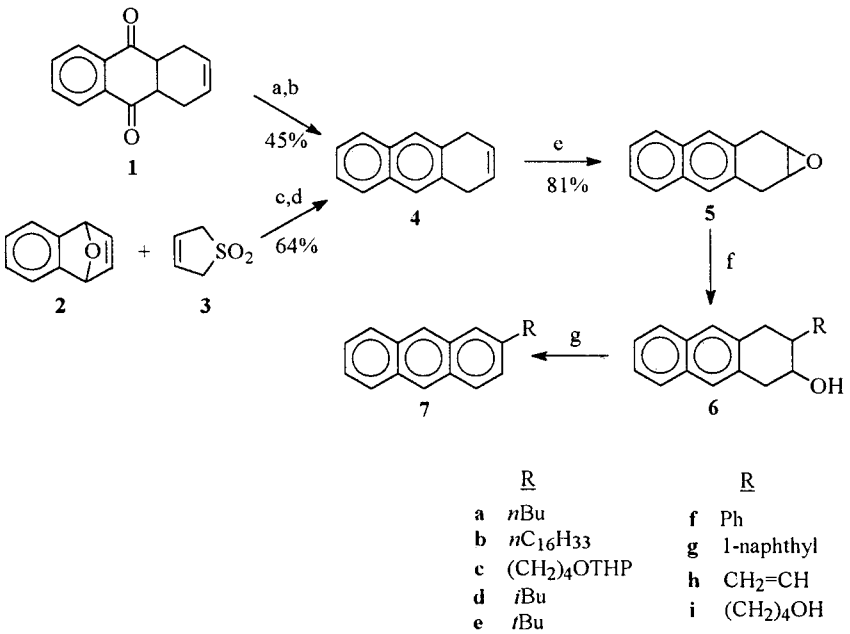
Anthracenes bearing a primary alkyl, ω-hydroxyalkyl, aryl or vinyl substituent at the 2-position are conveniently prepared by a copper-catalyzed Grignard reaction on 2,3-epoxy-1,2,3,4-tetrahydroanthracene, followed by dehydration – dehydrogenation of the resulting alcohols with tetrachloro-1,2-benzoquinone (*o*-chloranil).

Direct alkylation and acylation of anthracene is known to occur preferentially at the 9 or 9 and 10 positions, and only under specific conditions have 2-substituted derivatives been obtained.[1] Therefore, 2-substituted anthracenes are normally prepared by a multistep procedure starting from phthalic anhydride and a monosubstituted benzene; a sequence comprising an inter- and intramolecular Friedel–Crafts acylation and reduction of the intermediate anthraquinone.[2] This classical method, however, suffers from several disadvantages such as the rather drastic reaction conditions which preclude the introduction of sensitive functions in the side chain, and the poor solubility of the intermediates in most organic solvents makes their purification and characterization difficult.

We have now devised a new method for obtaining 2-substituted anthracenes which is more general and also superior to the one mentioned above because it operates under milder conditions and involves intermediates that are well soluble. It also allows the incorporation of functional groups in the side chain.

Our approach is outlined in Scheme 1 and uses 2,3-epoxy-1,2,3,4-tetrahydroanthracene **(5)** as a key synthetic intermediate. This compound is readily prepared by *m*-chloroperbenzoic acid (MCPBA) epoxidation of 1,4-dihydroanthracene **(4)**, which itself is available either from tetrahydroanthraquinone **(1)**,[3] or from 1,4-epoxy-1,4-dihydronaphthalene **(2)** and 2,5-dihydrothiophene 1,1-dioxide **(3)**.[4] The latter method proved to be the most convenient for producing large quantities of **4** (> 10 g).

Nucleophilic ring opening of the epoxide **5** with organometallic reagents furnished the secondary alcohols **6**. The reactions were performed under a variety of conditions and the results are summarized in Table 1. Whereas the Grignard reagents gave the alcohols in only moderate yields (entries 1, 6 and 12), considerable improvement was achieved by adding 10% of copper(I) iodide[5] and by using an excess of combined organometallic reagent (compare entries 2 and 3, and 13 and 14). A 6-fold excess of reagent is sufficient since more equivalents did not give much higher yields (compare entries 3 and 4). Organolithium/copper reagents can also be used but are not superior to the copper-catalyzed Grignard reagents (compare entries 3 and 5, and 14 and 15).



R		R	
a	*n*Bu	**f**	Ph
b	$nC_{16}H_{33}$	**g**	1-naphthyl
c	$(CH_2)_4OTHP$	**h**	CH_2=CH
d	*i*Bu	**i**	$(CH_2)_4OH$
e	*t*Bu		

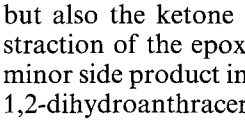
Scheme 1. a) $NaBH_4$/EtOH, r.t., 2h; b) HCl, reflux; c) toluene, 145 °C/autoclave, 36h; d) HCl/MeOH, reflux, 15h; e) MCPBA/$CHCl_3$, r.t. overnight; f) RMet (see Table 1); g) o-chloranil/toluene, 110 °C, overnight (see Table 2).

Table 1. Reactions of Epoxide **5** with Organometallic Reagents

Entry	Product	R	Met[a]	Ratio of **6**: RMet	Yield[b] (%)
1	**6a**	Bu	MgBr	1:2	40
2			MgBr/CuI	1:1	12
3			MgBr/CuI	1:6	67
4			MgBr/CuI	1:12	70
5			Li/CuI	1:5	47
6	**6b**	$C_{16}H_{33}$	MgBr	1:2.5	32
7			MgBr/CuI	1:6	73
8	**6c**	$(CH_2)_4OTHP$[c]	MgCl/CuI	1:2.5	80
9			MgCl/CuI	1:6	84
10	**6d**	*i*-Bu	MgBr/CuI	1:6	40[d]
11	**6e**	*t*-Bu	MgBr/CuI	1:6	0
12	**6f**	Ph	MgBr	1:2	50
13			MgBr/CuI	1:1	40
14			MgBr/CuI	1:3	84
15			Li/CuI	1:2.5	87
16	**6g**	1-naphthyl	MgBr/CuI	1:4.5	56
17	**6h**	vinyl	MgBr/CuI	1:6	62[e]

[a] MgBr/CuI refers to 10% CuI added to the Grignard reagent; Li/CuI refers to 50% CuI added to the organolithium reagent.
[b] Yields isolated after chromatographic purification and corresponding to *trans* structures unless otherwise indicated.
[c] THP = tetrahydropyran-2-yl.
[d] Isolated as a 48 : 52 *cis-trans* mixture.
[e] Isolated as a 56 : 44 *cis-trans* mixture.

From Table 1 we also note that *tert*-butylmagnesium cuprate failed to give any of the alcohol **6e** (entry 11); instead *trans*-2-bromo-3-hydroxy-1,2,3,4-tetrahydroanthracene **(8)** was obtained (20%) and much of the starting epoxide was recovered (35%). The less bulky isobutylmagnesium cuprate produced the alcohol **6d** (entry 10), but also the ketone **9** (15%) as a result of proton abstraction of the epoxide by the nucleophile. A common minor side product in all the experiments was 2-hydroxy-1,2-dihydroanthracene **(10)** (5–10%).



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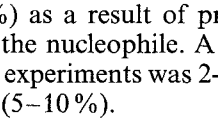

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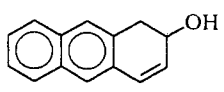

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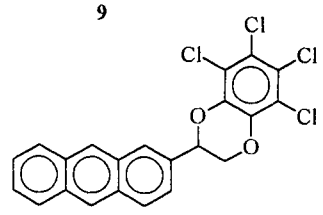

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The secondary alcohols thus obtained were found by ^{1}H NMR spectroscopy to have the expected *trans*-configuration ($J_{a,a}$ = 10 Hz), except for R = isobutyl and vinyl (entries 10 and 17) where *cis-trans* mixtures of the alcohols **6d** and **6h** were isolated in ratios of 48:52 and 56:44% respectively. The mechanism of formation of the *cis*-isomers is uncertain, but may involve the intermediacy of radicals generated by the copper(I) catalyst.

The final step in our reaction sequence (Scheme 1) is the conversion of the alcohols **6** into the 2-substituted anthracenes **7**. For this purpose two quinones, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and tetrachloro-1,2-benzoquinone (*o*-chloranil),[6] in a two-fold excess were treated with the alcohols **6** in refluxing toluene; the results are summarized in Table 2. It is apparent that *o*-chloranil is the best choice, since DDQ was only effective for the phenyl and 1-naphthyl substituted alcohols **6f** and **6g**, and even then gave the anthracenes **7f, g** in lower yields. Both reagents failed to convert the compound **6d** into the anthracene derivative **7d**; only decomposition products were observed. In the reaction of compound **6h** with *o*-chloranil, the dioxin **11** was produced as byproduct and its yield depended on the amount of reagent used (20% and 52% for one and two equivalents of *o*-chloranil). Here, the best result was obtained when *p*-chloranil was used as the dehydration/dehydrogenation reagent, affording 2-vinylanthracene **(7h)** in 61% yield. This compound has previously been prepared by a multistep procedure and is of interest for the synthesis of high molecular weight polymers.[7]

2,3-Epoxy-1,2,3,4-tetrahydroanthracene (5):
A mixture of 1,4-epoxy-1,4-dihydronaphthalene (**2**; 5.6 g, 38.9 mmol), 2,5-dihydrothiophene 1,1-dioxide (**3**; 5.8 g, 49 mmol) and $NaHCO_3$ (1 g) in toluene (50 mL) was heated in a steel autoclave at 145°C for 36 h. After cooling, the precipitate was filtered and washed with toluene (2 × 30 mL). The filtrate and combined extracts were evaporated in vacuo, and the resulting oil was chromatographed on silica gel with $CHCl_3$ as the eluent to give 9,10-epoxy-1,4,4a,9,9a,10-hexahydroanthracene (5.43 g, 70%); mp 64–65°C (Lit.[4a] mp 64–66°C). This compound was treated with concentrated HCl (12.5 mL) in refluxing MeOH (125 mL) for 15 h. After cooling, the crystalline compound **4** was collected and washed with MeOH (4.46 g, 91%); mp 151°C (Lit.[4a] mp 151–153°C).

A solution of compound **4** (4.46 g, 24.8 mmol) in $CHCl_3$ (100 mL) was treated with MCPBA (5.7 g, 31 mmol) and stirred overnight at r. t. The precipitated *m*-chlorobenzoic acid was filtered, the filtrate evaporated, and the resulting residue chromatographed on silica gel with $CHCl_3$ as the eluent to give epoxide **5** as a colourless solid (3.9 g, 81%); mp 159–160°C.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.34 and 3.50 (4H, 2d, ^2J = 17 Hz), 3.52–3.56 (2H, m), 7.3–7.4 (2H, m), 7.51 (2H, br s), and 7.15–7.25 (2H, m).

Table 2. Conversion of the Alcohols **6** into the Anthracenes **7**

Product	R	Yield (%)[a]	
		DDQ Method	*o*-Chloranil Method
7a	Bu	0	61
7b	$C_{16}H_{33}$	0	63
7d	*i*-Bu	0	0
7f	Ph	44	68
7g	1-naphthyl	53	74
7h	vinyl	0	40[b]
7i	$(CH_2)_4OH$[c]	–	40

[a] The reactions were carried out with 2 equiv of quinone, except for **7h** (1 equiv).
[b] With 2 equiv of *p*-chloranil the yield was 61%.
[c] This compound was obtained from **6c** after conversion into **7c** followed by deprotection of the THP ether with HCl.

^{13}C NMR ($CDCl_3$): δ = 30.2 (CH_2), 51.6 (CHO, $^1J_{CH}$ = 177 Hz), 125.3, 127.0, and 127.5 (CH_{arom}), 130.5, 132.6 (C_{arom}).

MS (EI, 70 eV): m/z = 196 ($M^{\cdot+}$, 100), 178 ($M^{\cdot+} - H_2O$, 16), 165 (72), 152 (30).

$C_{14}H_{12}O$	calc.	C 85.68	H6.16
(196.3)	found	85.51	6.22

3-Hydroxy-2-phenyl-1,2,3,4-tetrahydroanthracene (6f); Typical Procedure:

Method A (Met = MgBr): A solution of phenylmagnesium bromide, prepared from bromobenzene (1.57 g, 10 mmol), Mg turnings (0.24 g, 10 mmol) and a few crystals of I_2 in anhyd. Et_2O (30 mL) under N_2 atmosphere, was cooled to 0 °C and treated with epoxide **5** (0.98 g, 5 mmol) in anhyd. THF (10 mL). The mixture was stirred overnight at r.t. and poured into ice-water (300 mL) containing NH_4Cl (5 g). After extraction with Et_2O (3 × 100 mL), the combined extracts were dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel with $CHCl_3/Et_2O$ (3:1) as the eluent to give alcohol **6f** (0.7 g, 50%).

Method B (Met = MgBr/CuI): A solution of phenylmagnesium bromide, prepared from bromobenzene (4.71 g, 30 mmol), Mg turnings (0.72 g, 30 mmol) and a few crystals of I_2 in anhyd. THF (35 mL) under N_2 atmosphere, was cooled to − 15 °C and treated with a suspension of CuI (0.57 g, 3 mmol) in anhyd. THF (15 mL). After stirring for 5 min, epoxide **5** (2 g, 10 mmol) was added and the mixture was stirred for 24 h at r.t. The reaction mixture was worked up as in Method A to give alcohol **6f** (2.3 g, 84%).

Method C (Met = Li/CuI): A benzene/Et_2O solution (3:1, 6.4 mL) of PhLi (12.8 mmol) was injected with a syringe into a suspension of CuI (1.21 g, 6.4 mmol) in Et_2O (25 mL) at − 10 °C. After stirring for 20 min at this temperature, a solution of epoxide **5** (0.9 g, 4.6 mmol) in Et_2O (50 mL) was added dropwise over 30 min. The mixture was stirred at 0 °C for 1 h and worked up as in Method A to give alcohol **6f** (1.1 g, 87%); mp 118–119 °C (from pentane/Et_2O).

IR (KBr): ν = 3578, 3547 cm^{-1} (m, OH).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.8 (1 H, br s, OH), 3.045 (1 H, td, $^3J_{aa}$ = 10, $^3J_{ae}$ = 5.5 Hz, H-2), 3.08 (1 H, dd, ^2J = 17, $^3J_{aa}$ = 10 Hz, H-4), 3.22 (1 H, dd, ^2J = 17, $^3J_{aa}$ = 10 Hz, H-1), 3.32 (1 H, dd, ^2J = 17, $^3J_{ae}$ = 5.5 Hz, H-1), 3.46 (1 H, dd, ^2J = 17, $^3J_{ae}$ = 5.5 Hz, H-4), 4.27 (1 H, td, $^3J_{aa}$ = 10, $^3J_{aa}$ = 10, $^3J_{ae}$ = 5.5 Hz, H-3), 7.25–7.42 (7 H, m), 7.55, 7.63 (2 H, 2 s), 7.70–7.77 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 36.9, 38.0 (C-1 and/or C-4), 49.5 (C-2), 71.6 (C-3), 125.3, 125.4, 126.1, 127.0, 127.1, 127.2, 128.0, 129.0 (CH_{arom}), 132.2 (× 2), 133.4, 134.2, 141.9 (C_{arom}).

MS (EI, 70 eV): m/z = 274 ($M^{\cdot+}$, 1), 196 ($M^{\cdot+}$ − Ph − H, 100), 181 (15), 178 (196 − H_2O, 42), 165 (64), 152 (178 − C_2H_2, 25), 63 (17), 51 ($C_4H_3^+$, 13).

$C_{20}H_{18}O$	calc.	C 87.56	H 6.61
(274.4)	found	87.38	6.50

The following alcohols were similarly prepared (see Table 1 for methods and yields): **6a** (mp 89–90 °C), **6b** (mp 79–80 °C), **6c** (oil), **6d** (as a 48:52 *cis-trans* mixture), **6g** (mp 180 °C) and **6h** (as a 56:44 *cis-trans* mixture).

2-Phenylanthracene (7f); Typical Procedure:

A solution of alcohol **6f** (260 mg, 0.95 mmol) and *o*-chloranil (469 mg, 1.9 mmol) in toluene (50 mL) was refluxed overnight under N_2 atmosphere. After evaporation of the solvent, the residue was chromatographed on silica gel with hexane/$CHCl_3$ (1:1) as the eluent to give anthracene **7f** as colorless crystals (165 mg, 68%); mp 207–208 °C (Lit.[8] mp 208–209 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.55 (5 H, m, C_6H_5), 7.72–7.80 (3 H, m), 7.97–8.04 (2 H, m), 8.07 (1 H, d, ^3J = 8 Hz, H-4), 8.20 (1 H, m, H-1), 8.43 and 8.47 (2 H, 2 s, H-9, 10).

^{13}C NMR ($CDCl_3$): δ = 125.4, 125.5, 125.6, 125.7, 126.0, 126.6, 127.4, 128.2, 128.3, 128.8, 128.9 (CH_{arom}), 131.0, 132.0 (× 2), 132.2, 137.9, 141.0 (C_{arom}).

MS (EI, 70 eV): m/z = 254 ($M^{\cdot+}$, 100).

The following anthracenes were similarly prepared (see Table 2): **7a** (mp 115–117 °C), **7b** (mp 96–97 °C), **7g** (mp 67–68 °C), **7h** (mp 213–214 °C, Lit.[7] mp 211 °C), **7i** (mp 115–117 °C) prepared by refluxing **7c** with HCl in MeOH for 2 h.

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(1) Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1979; Vol. 3, Part H, p 24.
(2) Bayer, O. *Methoden der Organischen Chemie (Houben–Weyl)* VII/3c; Thieme: Stuttgart, 1979, p 46.
(3) Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2212.
(4) (a) Müller, P.; Rey, M. *Helv. Chim. Acta* **1982**, *65*, 1157.
(b) Lin, C.T.; Chou, T.C. *Synthesis* **1988**, 628.
(5) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503.
(6) Jackman, L.M. *Adv. Org. Chem.* **1960**, *2*, 329.
Fu, P.P.; Harvey, R.G. *Chem. Rev.* **1978**, *78*, 317.
(7) Stolka, M.; Yanus, J.F.; Pearson, J.M. *Macromolecules* **1976**, *9*, 710 and 719.
(8) Lang, K.F.; Buffleb, H. *Chem. Ber.* **1961**, *94*, 1075.