Reductive Cyclization of a Functionalized 1,1′-Bianthraquinone

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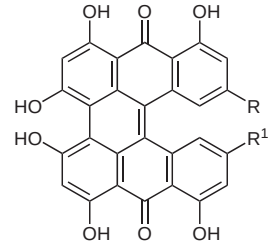
Received 23 May 2005

In memoriam Professor Dr. Dr. E.h. Hans Brockmann (1903–1988).

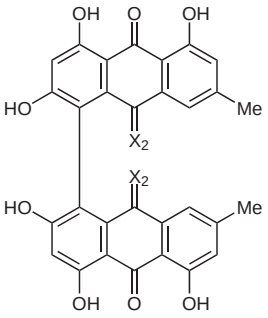
Abstract: Reductive cyclization of 2,2′-dimethoxymethyl-[1,1′-bianthracene]-9,9′,10,10′-tetrone with Cu powder in concentrated sulfuric acid yields helianthrone with partially reduced side chain.

Key words: ring closure, reduction, cyclization, fused-ring systems

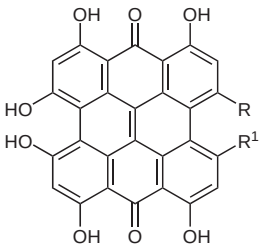
Quinoid natural products possessing a helianthrone (dibenzo[*a*,*o*]perylene-7,16-dione) or a *meso*-naphthodianthrone (phenanthro[1,10,9,8-opqra]perylene-7,14-dione) skeleton are interesting photodynamic compounds and synthetic photosensitizers. Irradiation of helianthrones with visible light leads to the formation of semiquinone radicals and reactive oxygen species.[1–4] Helianthrones are easily photooxidized to form the corresponding *meso*-naphthodianthrones. Typical natural compounds are e.g. the protohypericins (**1**). Both **1** and hypericins **2a**,**b** (Figure 1) have been isolated from *Hypericum spp*.;[5–9] **2a** has been prepared biomimetically via **1a** from **3b**, emodin-9-anthrone or emodin by phenol oxidation in basic medium followed by photooxidation.[10]



1a protohypericin, R, R^1 = Me
b protopseudohypericin, R^1 = CH_2OH, R = Me



3a skyrin, X_2 = O
b penicilliopsin, X = H

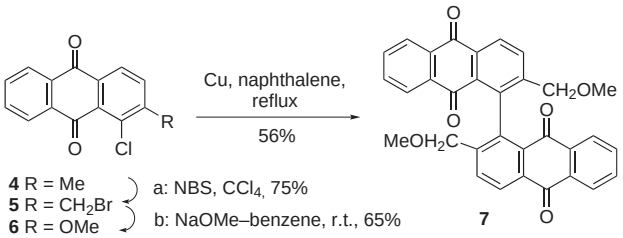


2a hypericin, R, R^1 = Me
b pseudohypericin, R^1 = CH_2OH, R = Me
c cyclopseudohypericin, R–R^1 = CH=CH

Figure 1

SYNLETT 2005, No. 12, pp 1905–1906
Advanced online publication: 07.07.2005
DOI: 10.1055/s-2005-871943; Art ID: G13205ST

This method cannot easily be applied to the synthesis of **1b** or **2b** from side chain oxidized emodins due to the instability of **1b** and **2b**, respectively, in alkaline solutions. On the other hand, **2b** forms cyclopseudohypericin (**2c**) upon photolysis in concentrated sulfuric acid.[9] In order to have access to compounds of type **1b** we investigated the reductive cyclization of 1,1′-bianthraquinones and applied the method of R. Scholl et al.[11–13] to compound **7**.

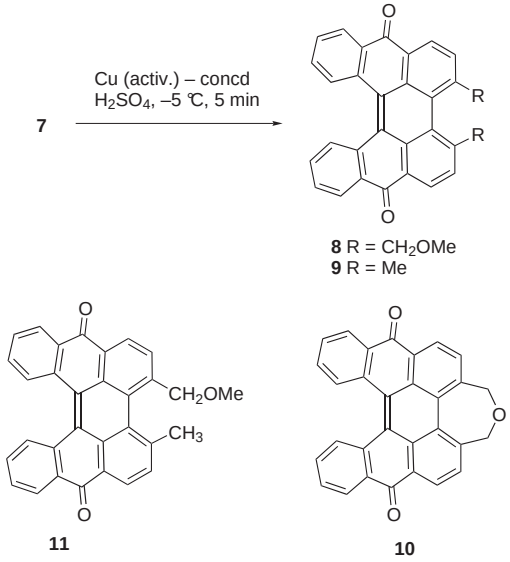


Scheme 1

The bianthraquinone **7** was prepared by a straight forward sequence: bromination of **4** in tetrachloromethane gave the bromomethyl compound **5** in good yield (75%).[14] The bromine atom was replaced by a methoxy group with sodium methoxide in MeOH at room temperature to yield **6** (65%).[15] Ullmann reaction[16] (activated Cu powder in naphthalene at 235 °C, 3 h) gave the functionalized 1,1′-bianthraquinone **7** (56%, Scheme 1). Surprisingly, the reductive cyclization of **7** using activated Cu powder in concentrated sulfuric acid at –5 °C was very fast but we obtained not the expected helianthrone **8** but a mixture of compound **11** and the oxepine **10** instead (Scheme 2).[17] Longer exposure of **7** to Cu powder in concentrated sulfuric acid resulted in the formation of **9**. Helianthrone **11** shows in the ^{1}H NMR spectrum an AB spin system (J_{AB} = 12 Hz) for the diastereotopic hydrogens of the CH_2O group. The ^{1}H NMR spectrum of **1b** shows a similar pattern.[6]

An AB spin system (J_{AB} = 12 Hz) is observed for the methylene groups of the 2,7-dihydrooxepin moiety of **10**, and it indicates the non equivalence of the hydrogens of the CH_2 groups next to the chiral helianthrone chromophore.

The cyclization of **7** with Cu powder in glacial acetic acid–HCl (concd) at room temperature[13] to form helianthrone **8** failed. Compounds **1a** and **2a** cannot be made from skyrin (**3a**) since it is reductively cleaved to form emodin [both in sulfuric acid (concd) and glacial acetic acid–HCl (concd)].



Scheme 2

Acknowledgment

We thank the BASF AG, Ludwigshafen, Germany, for chemicals.

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(15) **Preparation of Compound 6.**
To a solution of **5** (18.00 g, 53.6 mmol) in toluene (700 mL) was added with stirring a freshly prepared solution of NaOMe [Na (4.00 g, 173 mmol) and MeOH (200 mL)] at r.t. The red reaction mixture was diluted with H_2O after 3 h, the organic phase was separated, washed with H_2O until neutral, dried (Na_2SO_4), and filtered over Al_2O_3 (neutral). Elution with toluene gave a yellow filtrate, which was concentrated to yield 10.00 g (65%) of yellow crystals, mp 180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30–7.70 (m, 5 H), 4.75 (s, 2 H, C*H*$_2$), 3.61 (s, 3 H, O*Me*). Anal. Calcd for $C_{16}H_{11}O_3Cl$ (286.7): Cl, 12.4. Found: Cl, 12.62.
(16) (a) Fanta, P. E. *Synthesis* **1974**, 9. (b) **Preparation of Compound 7.**
Activation of Cu-powder: commercially available Cu powder (Merck, Darmstadt, Germany) was treated in glacial acetic acid at r.t. for 10 min. The mixture was filtered and the filter cake washed with H_2O until neutral. The treatment was repeated and the activated Cu was finally washed with acetone and dried in vacuo at r.t. and stored under an atmosphere of argon. Activated Cu powder was introduced into a melt of **6** (10.00 g, 34.9 mmol) in naphthalene (14 g) with stirring. The reaction mixture was kept at 235 °C for 3 h, cooled to r.t. and the crashed cake was extracted with $CHCl_3$. The filtered solution was concentrated and the residue dissolved in toluene (20 mL). This solution was adsorbed on silica gel. Elution with toluene gave after the fast removing of naphthalene a yellow filtrate which was concentrated to give 6.00 g of crude **7**. The crude product was crystallized from hot EtOH to yield 5.00 g (56%), yellow plates, mp 226–227 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.572–8.545 (d, *J* = 8 Hz, 1 H), 8.344–8.316 (dd, *J* = 0.9, 7.6 Hz, 1 H), 8.102–8.076 (d, *J* = 8 Hz, 1 H), 7.999–7.970 (dd, *J* = 1.0, 7.6 Hz, 1 H), 7.796–7.741 (ddd, *J* = 1.0, 7.6, 7.3 Hz, 1 H), 7.714–7.659 (ddd, *J* = 1.0, 7.5, 7.6 Hz, 1 H), 3.40 (s, 2 H, C*H*$_2$), 3.17 (s, 3 H, C*H*$_3$). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 183.85 (s), 183.50 (s), 142.81 (s), 139.94 (s), 134.32 (s), 134.30 (d), 134.08 (d), 133.33 (s), 133.29 (d), 130.75 (s), 127.53 (d), 127.47 (d), 127.12 (d), 72.03 (t), 58.89 (q). MS: *m/z* (%) = 502 (8)[M]$^+$, 470 (100), 409 (30), 383 (20). IR (KBr): 1668 cm^{-1} (C=O). UV (EtOH): λ_{max} (log ε) = 254 nm (4.53), 336 (3.62). Anal. Calcd for $C_{32}H_{22}O_6$ (502.5): C, 76.48; H, 4.41. Found: C, 76.62; H, 4.39.
(17) **Preparation of Compounds 10 and 11.**
To the dark brown solution of **7** (1.01 g, 20 mmol) in concd H_2SO_4 (60 mL) at –5 °C was added Cu powder (5 g) with stirring in the dark. Soon, the solution became green. The reaction mixture was poured on ice (200 g) after 5 min. The precipitate was filtered off, washed with H_2O until neutral and dissolved in $CHCl_3$. The organic solution was dried (Na_2SO_4) and concentrated, and the brown residue (1.00 g) was dissolved in benzene (50 mL). The crude product was chromatographed on silica gel in the dark to avoid photocyclization. Elution with benzene gave 0.150 g (18%) **10** (eluted first) and 0.100 g (11%) **11**.
Compound **10**: red needles, mp >240 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.84 (d, *J* = 7.6 Hz, 2 H), 8.47 (d, *J* = 8 Hz, 2 H), 7.96 (dd, *J* = 8.2, 7.8 Hz, 4 H), 7.57 (dd, *J* = 8.2, 6.9 Hz, 2 H), 7.39 (dd, *J* = 7.5, 7.0 Hz, 2 H), 5.06 and 4.52 (AB, J_{AB} = 12.0 Hz, 4 H, -C*H*$_2$-O-). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 184.1 (s), 141.8 (s), 137.1 (s), 133.1 (d), 132.4 (s), 131.9 (d), 131.7 (s), 131.0 (s), 130.0 (d), 129.7 (d), 129.1 (d), 129.0 (s), 128.0 (d), 127.5 (s), 70.61 (t). MS: *m/z* (%) = 424 (51)[M]$^+$, 395 (20), 236 (35), 28 (100). UV (EtOH): λ_{max} (log ε) = 457 nm (3.75), 353 (3.46), 316 (3.39), 236 (4.19). Anal. Calcd for $C_{31}H_{20}O_3$ (424.4): C, 84.89; H, 3.80. Found: C, 84.48; H, 3.77.
Compound **11**: red needles, mp >240 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85–7.33 (m, 12 H), 5.05 and 4.50 (AB, J_{AB} = 12 Hz, 2 H, -C*H*$_2$-O-), 3.13 (s, 3 H, OMe), 2.63 (s, 3 H, Me). MS: *m/z* (%) = 440 (60)[M]$^+$, 407 (60), 28 (100). Anal. Calcd for $C_{30}H_{16}O_3$ (440.5): C, 84.53; H, 4.58. Found: C, 84.70; H, 4.43.