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SYNTHESIS OF 2-ALKOXY-7-METHYLANTHRACENES USING DIRECTED ORTHO METALATION OF 4-METHYL-N-PHENYLBENZAMIDE

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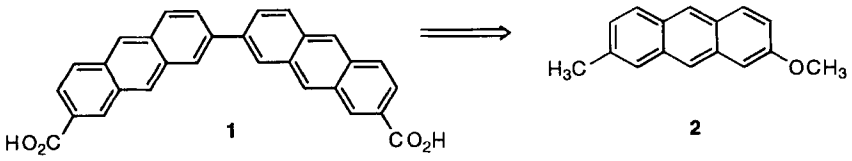
Abstract: *An efficient synthesis of 2-alkoxy-7-methylanthracenes using ortho metalation chemistry is described.*

A common strategy used to mimic a discontinuous region on a protein surface is to covalently link together two or more of the remote peptide fragments using a spacer molecule. In connection with a project to develop peptide mimics, we required a hydrophobic spacer molecule capable of holding two amino acid residues with a separation of approximately 18 Å between the α-carbons. Molecular modeling studies convinced us that a 2,2'-bianthryl-7,7'-dicarboxylic acid (**1**) would be a



1 **2**

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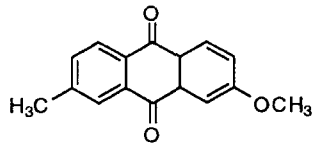
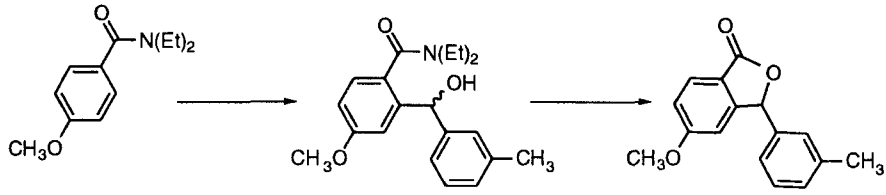
suitable spacer.[1] Retrosynthetic analysis identified 2-methoxy-7-methylanthracene (**2**) as a useful precursor to the proposed bianthryl spacer molecule. Although no synthetic references to **2** were found in the literature, there was one reference to the synthesis of the corresponding anthraquinone(**3**).[2] Since there are a number of methods reported for the reduction of anthraquinones to anthracenes[3], we chose to use this approach.



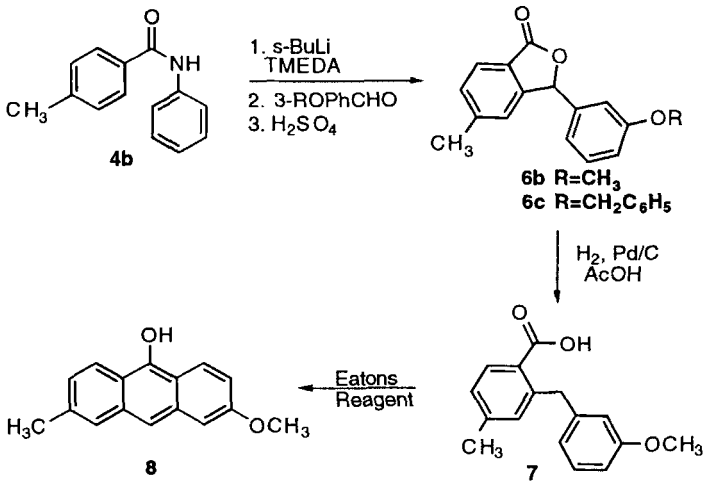
3

The literature synthesis[2] of **3** utilized a directed ortho metalation strategy[3] starting with the N,N-diethylbenzamide, **4a**. In repeating this work, we confirmed the low yield of the phthalide, **6a**[5], presumably due to the resistance of the hydroxy N,N-diethylamide, **5a**, to hydrolysis. We



4a **5a** **6a**

thought that the yield could be improved by replacing the N,N-diethyl amide with a N-phenylamide. Townsend *et al.*[6] in their synthesis of averufin, a methoxy-containing anthraquinone, found that the hydroxy N-phenyl amide intermediate could not be isolated due to the facile cyclization to the phthalide. We also chose to have the methoxy group in the benzaldehyde ring since a *meta*-methoxy group may make the aldehyde slightly more reactive due to inductive effects.



When the dianion of **4b** was reacted with *m*-anisaldehyde we obtained a quantitative yield of crude hydroxy amide. After hydrolysis with dilute sulfuric acid, the lactone **6b** was isolated in 79% overall yield which is a significant improvement over the diethylamide route.[5] The reaction worked equally well with *m*-benzyloxybenzaldehyde to afford the benzyloxylactone **6c** in 62% yield. Catalytic reduction of **6b** with 5% Pd/C at 60° in acetic acid generated the *o*-benzyl-benzoic acid **7** in 94% yield. Cyclization to the anthranol **8** was accomplished in modest yield using Eaton's reagent (phosphorus pentoxide, 7.5 wt % solution in methanesulfonic acid). In our hands, the more routinely used cyclodehydrating reagents trifluoroacetic anhydride or polyphosphoric acid gave less satisfactory results. Finally, reduction of **8** to the anthracene **2** was effected using $NaBH_4$ in refluxing ethanol. We were unable to obtain satisfactory combustion analysis of the anthracene **2** due presumably to facile air oxidation to the anthraquinone **3**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H (300 MHz) NMR spectra were

recorded in $CDCl_3$ solutions on a General Electric QE300 spectrometer. Chemical shifts are expressed in parts per million downfield from internal TMS. High-resolution mass spectra (HRMS) were recorded and elemental analyses were determined at FMC Corporation, Analytical Services Department. All reagents and solvents were used as received from commercial suppliers

3-(3'-Methoxyphenyl)-5-methyl-1(3H)-isobenzofuranone (6b)

A solution of 15 g (71 mmol) of 4-methyl-N-phenylbenzamide, 21 ml (142 mmol) of TMEDA and 300 ml of anhydrous THF was cooled to -78°C under N_2 . To this clear solution was added dropwise 109 ml (142 mmol) of 1.3 M *sec*-butyllithium in cyclohexane at a rate to maintain the reaction temperature at -70°C(±5°). After the addition, the reaction mixture was stirred at -78°C for 1 h then a solution of 10.4 ml (11.6 g, 85 mmol) of *m*-anisaldehyde in 50 ml of anhydrous THF was added dropwise, again maintaining the reaction temperature at -70°C(±5°). After an additional 1 h stirring at -78°C, the mixture was allowed to warm to room temperature then quenched with 10% aqueous NH_4Cl. The mixture was extracted with diethyl ether, washed with brine, dried over anhydrous magnesium sulfate, and evaporated to afford a quantitative yield of the crude hydroxyamide as an oil which was essentially homogeneous by tlc (CH_2Cl_2). The crude hydroxyamide was dissolved in 500 ml of THF then 100 ml of 10% aqueous H_2SO_4 was added. After stirring for 1 h at room temperature, the THF was removed and the residue was extracted with diethyl ether, washed with brine, dried over $MgSO_4$, and concentrated. The crude oil was chromatographed (CH_2Cl_2) on silica gel to afford 14.2 g (79%) of a white solid, mp 67-68 C°. ^1H NMR δ 2.43 (s,3H), 3.75 (s,3H), 6.30 (s,1H), 6.78 (s,1H), 6.89 (m,2H), 7.12 (s,1H), 7.31 (q,2H), 7.82 (d,1H). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.73; H, 5.52.

3-(3'-Benzyloxyphenyl)-5-methyl-1(3H)-isobenzofuranone (6c)

Prepared as in **6b** from 0.1 mol of 4-methyl-N-phenylbenzamide, 0.2 mol of TMEDA, 0.2 mol of 1.3 M *sec*-butyllithium, and 0.1 mol of *m*-benzyloxy-

benzaldehyde to afford 20.5 g (62%) of a tan solid, mp 177-178 C°. ^{1}H NMR δ 2.43 (s,3H), 5.04 (s,2H), 6.31 (s,1H), 6.86 (t,1H), 6.96 (m,2H), 7.09 (s,1H), 7.27-7.41 (m,7H), 7.83 (d,1H). Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.78; H, 5.27.

2-(3-Methoxyphenyl)methyl-4-methylbenzoic acid (7)

A solution of 12.6 g (50 mmol)of **6b** and 300 ml of glacial acetic acid was hydrogenated over 3 g of 5% Pd/C at 2 atm H_2 at 60°C. After 4 h, the catalyst was filtered and the solvent removed to afford 12 g (94%) of solid. An analytical sample was obtained by recrystalization from heptane; mp 134 -135 C°. ^{1}H NMR δ 2.36 (s,3H), 3.77 (s,3H), 4.43 (s,2H), 6.76 (m,3H), 7.05 (s,1H), 7.17 (m,2H), 8.00 (d,1H). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.15; H, 6.32.

2-Methoxy-7-methyl-9-anthranol (8)

To 50 ml of Eaton's reagent (phosphorus pentoxide, 7.5 wt % solution in methanesulfonic acid) cooled on an ice bath was added 12.2 g (50 mmol) of **7**. The mixture was warmed to room temperature and stirred for 3 h, then poured into ice. The gummy residue gradually turned into a granular solid which was filtered and recrystalized from heptane/ethyl acetate to afford 5.7 g (50 %) of a yellow solid, mp 133-134 C°. IR (KBr) 1643, 1602 cm^{-1}. ^{1}H NMR δ 2.43 (s,3H), 3.89 (s,3H), 4.27 (s,2H), 6.88 (d,1H), 6.99 (dd,1H), 7.25 (m,3H), 8.27 (dd,2H). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.94; H, 5.67.

2-Methoxy-7-methylanthracene (2)

To a solution of 3.4 g (14.3 mmol) of **8**, 50 ml of THF and 50 ml of ethanol was added 0.34 g (9 mmol) of $NaBH_4$. The mixture was heated at reflux for 1 h, cooled, then quenched by the slow addition of 25 ml of 10% aqueous HCl. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, concentrated and the residue was recrystalized from ethyl acetate to afford 1.5 g (48%) of a yellow solid, mp 135 -136 C°. ^{1}H NMR δ 2.55

(s,3H), 3.92 (s,3H), 7.19 (m,3H), 7.70 (s,1H), 7.87 (d,2H), 8.17 (s,1H), 8.30 (s,1H). HRMS for $C_{16}H_{14}O$, calcd. 222.1045, found 222.1046.

References and Notes

1. Molecular modeling studies conducted using SYBYL software purchased from TRIPOS Inc., St. Louis, MO. The TRIPOS force field was employed for all molecular mechanics and dynamic annealing experiments.
2. Kelly, T. R. and Parekh, N. D. *J. Org. Chem.* **1982**, 47, 5009.
3. Tius, M. A.; Gomez-Galeno, J.; Gu, X. Q. and Zaidi, J. H. *J. Am. Chem. Soc.* **1991**, 113, 5775, and references cited within.
4. For a recent review see; Snieckus, V. *Chem. Rev.* **1990**, 90, 879.
5. An overall yield of 10.5%was obtained in going from **3a** to **5a**.
6. Townsend, C. A.; Christensen, S. B. and Davis, S. G. *J. Chem. Soc. Perkin Trans. I* **1988**, 839.

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