Notes

Approaches to Anthracyclines: Efficient Syntheses of Substituted Naphthylacetonitriles[1]

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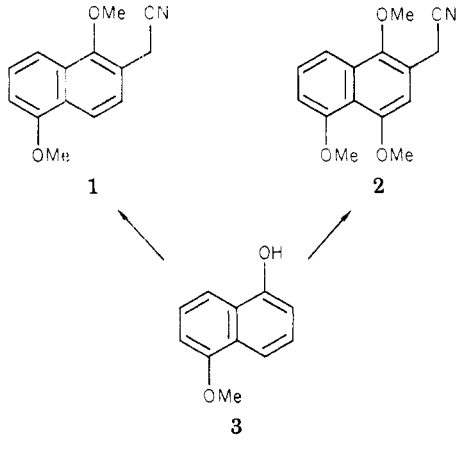
The potential of the three-step, regiospecific annelative quinone synthesis as a practical route to anthracycline intermediates[2,3] depends on the availability of naphthylacetonitriles **1** and **2** (or synthetic equivalents). Previous

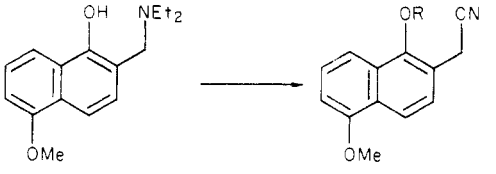


syntheses of these compounds were based on the introduction of an allyl side chain to 5-methoxy-1-naphthol (**3**) via Claisen rearrangement followed by modification of the side chain.

As we felt that these sequences were too long and because we desired better overall yields, we have investigated the use of more direct methods of introducing the cyanomethyl substituent ortho to the phenolic hydroxyl. We are now pleased to report improved routes to naphthalenes **1** and **2**. Both syntheses are based on the Mannich reaction of phenols[4] and incorporate a modified procedure for the conversion of benzylamines to benzyl cyanides.

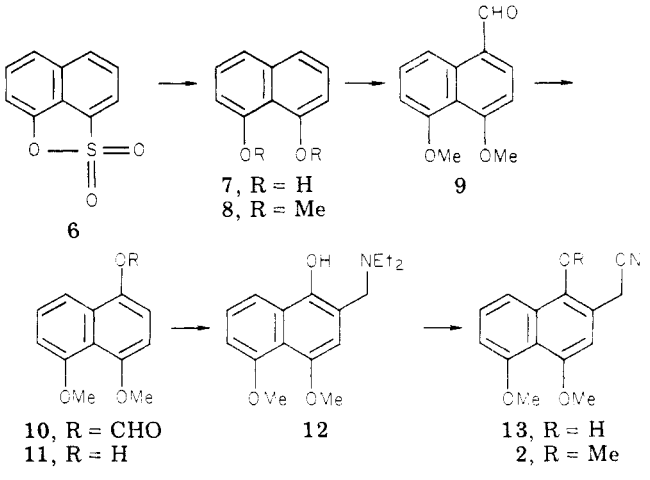
C. W. Ours and co-workers[5] reported the capricious reaction of *o*- and *p*-hydroxybenzylamines with potassium cyanide at 110–130 °C in dimethylformamide (DMF) to give the corresponding phenylacetonitriles; they postulated quinone methide intermediates for this transformation. When we subjected naphthol **4**[6] prepared from 5-methoxy-1-naphthol (**3**),[7] diethylamine, and formaldehyde to these reaction conditions, we isolated a complex mixture.

However, a very clean nitrile **5** could be recovered when naphthol **4** was treated with potassium cyanide complexed with 1 equiv of 18-crown-6 in dimethylformamide. (With less than 1 equiv of crown ether, or with crown ether in benzene, the product was contaminated by a number of byproducts.)



For our purposes, neither phenol **4** nor nitrile **5** was isolated. The Mannich reaction followed by treatment with potassium cyanide 18-crown-6 in DMF and direct alkylation of the phenolic hydroxyl of nitrile **5** with methyl iodide gave nitrile **1**. This three-step, one-pot sequence converted naphthol **3** to nitrile **1** in 70% yield.

Preparation of naphthalene **2** by an analogous introduction of the side chain required phenol **11**. This was



prepared from sultone **6**.[8] Treatment with KOH (melt) gave diol **7**[9] which was methylated in workup with dimethyl sulfate to give 1,8-dimethoxynaphthalene (**8**) in 50% yield. Vilsmeier reaction of naphthalene **8** gave aldehyde **9**[10] in 85% yield; Baeyer–Villiger oxidation of aldehyde **9** with *p*-nitroperoxybenzoic acid[11] gave formate **10** which was hydrolyzed without purification to give the desired naphthol **11** in 70% yield.

(1) Portions of this work were reported at the Joint Meeting of the American Chemical Society and the Chemical Society of Japan, Honolulu, HI, April 2–6, 1979.
(2) K. A. Parker and J. L. Kallmerten, *Tetrahedron Lett.*, 1197 (1979).
(3) A. S. Kende, J. Rizzi, and J. Riemer, *Tetrahedron Lett.*, 1201 (1979).
(4) A review on the Mannich reaction refers to many examples in which one reactant is a phenol: F. F. Blicke, *Org. React.*, 1, 304–341 (1942).
(5) J. H. Short, D. A. Dunnigan, and C. W. Ours, *Tetrahedron Lett.*, **29**, 1931 (1973).
(6) The procedure of J. H. Burckhalter and Robert J. Seiwald, *J. Org. Chem.*, **24**, 445 (1959), was followed.
(7) O. Fischer and C. Bauer, *J. Prakt. Chem.*, **94**, 13 (1916). See also ref 2, footnote 13.
(8) We are indebted to the Verona Division of the Mobay Corporation for a generous gift of 8-hydroxy-1-sulfonic acid γ-sultone (**6**). We have prepared this compound by the procedure of Erdmann (ref 9). In our hands, the yielf from 8-amino-1-naphthalenesulfonic acid, a readily available dyestuff intermediate (still inexpensive), is 92° (see Experimental Section).
(9) H. Erdmann, *Justus Liebigs Ann. Chem.*, **247** 345 (1888).
(10) Ng. Ph. Buu-Hoi and D. Lavit, *J. Chem. Soc.*, 2412 (1956).
(11) This reagent, Aldrich technical grade, contains about 15% of methyl *p*-nitrobenzoate which is eventually removed from the product by trituration (see Experimental Section).

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Naphthol **11** underwent the Mannich reaction with formaldehyde and diethylamine to give the Mannich base **12**; treatment with potassium cyanide and 1 equiv of 18-crown-6 gave nitrile **13**, which was methylated directly to give the target naphthylacetonitrile **2** in 67% yield (from naphthol **11**).

Each of the routes described relies on a readily available and inexpensive starting material and can easily be carried out on a preparative scale. Increased accessibility to naphthalenes **1** and **2** significantly increases the potential of the annelative quinone synthesis[2,3] as a practical approach to anthracyclines.

Experimental Section

Solvents and reagents were routinely distilled before use. Infrared spectra were recorded on a Perkin-Elmer 257 grating infrared spectrometer. Nuclear magnetic resonance spectra were run on a Varian A-60 A instrument with tetramethylsilane as an internal standard. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Silica gel (70–230 mesh) for chromatography was obtained from E. Merck. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory.

5-Methoxy-2-[(*N*,*N*-diethylamino)methyl]-1-naphthol (4). A solution of 964 mg (5.54 mmol) of 5-methoxy-1-naphthol and 116 mg (5.54 mmol) of paraformaldehyde in 3.24 g (44.3 mol) of diethylamine was stirred under nitrogen at 70 °C for 2.5 h. Excess diethylamine was removed under reduced pressure to leave a pale yellow oil: IR (film) 1595, 1505, 1405, 1255, and 1065 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 6 H), 2.66 (q, J = 7.5 Hz, 4 H), 3.75 (s, 2H), 3.88 (s, 3 H), 6.68–7.95 (m, 5 H), 11.46 (br s, 1 H).

(1,5-Dimethoxynapth-2-yl)acetonitrile (1). Naphthol **4**, prepared as above, was dissolved in 7 mL of dry DMF and the solution was degassed. To this were added 1.46 g (5.54 mmol) of 18-crown-6 and 0.54 g (8.3 mmol) of KCN. The reaction mixture was stirred at 70 °C for 1.5 h. Then 1.53 g of anhydrous K_2CO_3 and 3.26 g (16.6 mmol) of methyl iodide were added. After 2.5 h at 70 °C, the reaction mixture was cooled to room temperature and 50 mL of water was added. The resulting mixture was extracted twice with ether and the combined ether solution was washed several times with water and dried over $MgSO_4$. Concentration gave a light brown oil which was subjected to column chromatography on silica gel. Elution with 10:90 ether/benzene afforded 1.006 g of a gray-white solid, which distilled at 160 °C (0.1 mm) to afford 0.88 g (70%) of white crystals, mp 60–61 °C. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.74; H, 5.84; N, 5.97.

1,8-Naphthalenesultone (6). The method of Erdmann[9] was modified. A 71-g sample (0.318 mol) of 8-amino-1-naphthalenesulfonic acid was suspended in 300 mL of 13% aqueous HCl in a 2-L beaker. To this was added dropwise a solution of 40 g of $NaNO_2$ in 200 mL of water. The addition required 0.5 h and the reaction mixture was stirred for an additional 0.5 h after addition was complete. Then the reaction mixture was heated on the steam bath for 1 h; it was necessary to monitor the heating so that the reaction mixture did not froth out of the beaker. Then the reaction mixture was allowed to cool to room temperature and filtered. The precipitate was washed thoroughly with water and then air-dried. A chloroform solution of this material was decolorized with activated charcoal and concentrated. When the solution was cooled, needles formed. Filtration gave 60 g (92%) of the sultone, mp 155 °C (lit.[8] 155 °C).

1,8-Dimethoxynaphthalene (8). A 2-neck, 1-L, round-bottom flask fitted with a nitrogen inlet and containing 102 g (1.82 mol) of KOH and a magnetic stirring bar was heated until the KOH melted (~250–255 °C). Then 30 g (0.146 mol) of sultone **6** was added in small portions so that mixing was thorough. (When most of the sultone had been added, the reaction mixture became semisolid and the stirrer stopped; therefore stirring was accomplished with a spatula until addition was complete.) Addition required 1 h; the reaction mixture was heated for an additional 45 min with occasional stirring. Then it was allowed to cool to 100 °C and 300 mL of water was added (carefully). The resulting mixture was heated until all solid had dissolved and then cooled in an ice bath.

To this solution, stirred at 0 °C, was added 70 mL of dimethyl sulfate (in small portions over 1 h); after the solution was stirred at room temperature for an additional 3 h, the precipitate was isolated by filtration and washed thoroughly with water. The filtrate was treated with an additional 15 mL of dimethyl sulfate added at room temperature in portions over 3 h. Additional precipitate was isolated by filtration and washed with water. The combined precipitate (a pale dirty green in color) was air-dried. Sublimation at 150 °C (1 mm) gave white crystals which were recrystallized from ethanol to give 13.7 g (50%) of white leaflets, mp 156–157 °C (lit.[10] 157 °C).

4,5-Dimethoxy-1-naphthaldehyde (9). The method of Buu-Hoi and Lavit[10] converted 9.4 g of 1,8-dimethoxynaphthalene to aldehyde **9**, mp 94–95 °C (lit. 95 °C), in 85% yield after recrystallization from ethanol.

4,5-Dimethoxy-1-naphthyl Formate (10). To a stirred suspension of 8.8 g (64 mmol) of K_2CO_3 in 150 mL of ethyl acetate under nitrogen was added 6.88 g (31.8 mmol) of aldehyde **9**. Then 8.75 g of *p*-nitroperoxybenzoic acid[11] was added in portions.

After 3 h of stirring at room temperature, TLC showed no remaining starting material; the reaction mixture was washed with water, 1% Na_2SO_3 solution, saturated bicarbonate, and again water. The organic solution was dried over $MgSO_4$ and concentrated. The residue was triturated with 15 mL of ether and the resulting crystals were washed with 10 mL of ether. After air-drying, 5.87 g (79%) of light-brown crystals, mp 126–127 °C, remained; this material was used for the preparation of phenol **11**.

Recrystallization from chloroform gave colorless needles: mp 164 °C; IR (KBr) 2805, 1740, 1420, 1380, and 1275 cm^{-1}; NMR (acetone-d_6) δ 3.90 (s, 6 H), 6.80–7.50 (m, 5 H), and 8.64 (s, 1 H). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.05; H, 5.24.

4,5-Dimethoxy-1-naphthol (11). A 5.85 g sample of formate **10** was suspended under nitrogen in 80 mL of deoxygenated methanol. A solution of 3 g of KOH in 20 mL of water was added dropwise to the stirred suspension. Afer 0.5 h, 100 mL of water was added and the solution was acidified with 10% HCl. The resulting gray-white precipitate was isolated by filtration, washed with water, air-dried, and recrystallized from chloroform to give 4.5 g (88%) of white needles: mp 164 °C; IR (KBr) 3400, 1470, 1460, 1390, 1370 cm^{-1}; NMR (acetone-d_6) δ 3.81 (s, 3 H), 3.90 (s, 3 H), 7.0–8.16 (m, 5 H).

4,5-Dimethoxy-2-[(*N*,*N*-diethylamino)methyl]-1-naphthol (12). A solution of 2.00 g (9.80 mmol) of phenol **11** and 296 mg (9.87 mmol) of paraformaldehyde in 5.7 g (78 mmol) of diethylamine was stirred under argon at 70 °C for 2 h. Excess diethylamine was removed under reduced pressure, leaving a light-brown oil: IR (film) 1590, 1500, 1450, 1250, and 1065 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, J = 7 Hz, 6 H), 2.65 (q, J = 7 Hz, 4 H), 3.84 (s, 2 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 6.58 (s, 1 H), 6.79–7.99 (m, 3 H), and 10.4 (br s, 1 H).

(1,4,5-Trimethoxynaphth-2-yl)acetonitrile (2). The amine described above was dissolved in 10 mL of DMF; the resulting solution was thoroughly degassed and the reaction vessel was flushed with argon. Then 2.56 g (9.70 mmol) of 18-crown-6 and 920 mg of KCN (14.1 mmol) were added, and the reaction mixture was stirred at 70 °C for 1 h during which it became dark brown in color. Then 676 mg (4.9 mmol) of anhydrous K_2CO_3 was added; this was followed by 1.04 g (7.35 mmol) of methyl iodide and the reaction mixture was stirred for another 1.5 h at 70 °C. After cooling to room temperature the reaction mixture was partitioned between ether and water. The organic solution was washed several times with water, dried over $MgSO_4$, and decolorized with activated charcoal. Concentration afforded 2.16 g of a light orange-brown solid which was recrystallized from ethyl acetate–cyclohexane to give 1.70 g (67%) of a sand-colored solid: mp 113–114 °C (lit.[3] 110–111 °C); IR (KBr) 2260, 1605, 1590, 1395, 1270, and 1075 cm^{-1}; NMR ($CDCl_3$) δ 3.85 (s, 2 H), 3.94 (s, 9 H), and 6.78–7.75 (m, 4 H).

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Registry No. 1, 71742-31-9; 2, 71611-77-3; 3, 3588-80-5; 4, 72659-47-3; 6, 83-31-8; 8, 10075-66-8; 9, 72659-48-4; 10, 72659-49-5; 11, 61836-40-6; 12, 72659-50-8; 8-amino-1-naphthalenesulfonic acid, 82-75-7.

Azlactone Oxidation

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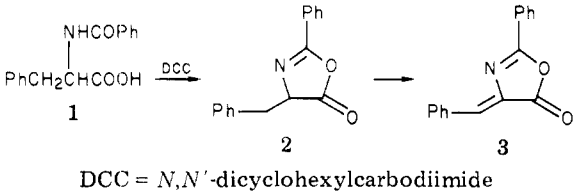
In our investigations into the synthesis of dehydropeptides, we saw at least two logical approaches: i.e., (1) the synthesis of dehydroamino acid derivatives followed by coupling of both the carboxyl and amino functions with other amino acids[1] and (2) the synthesis of dehydrodipeptides by direct oxidation[2] followed by coupling into the desired sequence. We have chosen to concentrate on the latter approach because it obviates the low-yield coupling of an activated amino acid derivative with an enamine nitrogen atom which is required in the first approach. Consequently, we have studied in some detail the oxidation of the carboxyl terminal amino acid of several dipeptides[2] and during these studies have used several *N*-benzoyl amino acids (e.g., 1) as models for the oxidation. We found



1 2 3

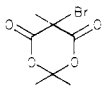
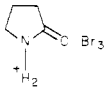
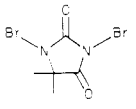
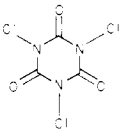
DCC = *N,N'*-dicyclohexylcarbodiimide

no reagent which would oxidize the acyl amino acid **1** itself, but azlactonization increased the susceptibility of the system to halogenation, to enolization and, consequently, to oxidation. This paper reports the results of a rather extensive investigation of the oxidation of several azlactones of the type **2**.

Azlactones have been previously halogenated[3] at the 4-position, albeit in low yields, for various purposes in the past. Initially we attempted to halogenate **2** by using bromine,[3a] *N*-bromosuccinimide (NBS), 2-pyrrolidinone hydrotribromide (PHT),[4] trichloroisocyanuric acid (TCIC),[5] isopropylidene 2-bromo-2-methylmalonate (Trost's reagent),[6] 1,3-dibromo-5,5-dimethylhydantoin (dibromantin),[7] and sulfuryl chloride.[3b] In most cases the reaction was carried out in carbon tetrachloride solution in the presence of solid potassium carbonate as proton acceptor. Table I shows the yields of **3** obtained by this halogenation–dehydrohalogenation method. In order to determine the possible effect of ring substituents on the yield of unsaturated azlactone, we prepared *N*-(*p*-methoxybenzoyl)- and *N*-(*p*-nitrobenzoyl)phenylalanine and oxidized them with a dibromantin/K_2CO_3 mixture. Yields of 47 and 54% of the 2-*p*-methoxyphenyl and 2-*p*-nitrophenyl azlactones, respectively, were obtained. The difference between these yields and that obtained from the unsubstituted compound appeared insignificant and indicated that electronic factors were unimportant in this reaction sequence.

Table I

$$2 \xrightarrow[CCl_4/K_2CO_3]{(O)} 3$$

reagent	yield, %[a]
Br_2	52[b]
SO_2Cl_2	43
 (NBS)	36[c]
 (Trost)	29
 (PHT)	47[d]
 (dibromantin)	54[e]
	44[f]

[a] Isolated yield. [b] 100-W bulb irradiation. [c] LiCl/$LiCO_3$/DMF used for the elimination. [d] THF used as solvent. [e] 100-W bulb and $(PhCO)_2O_2$. [f] Trace of $(PhCO)_2O_2$ added.

Table II

$2 \longrightarrow 3$

reagent	yield, %[a]	reagent	yield, %[a]
SeO_2/Ac_2O	55	$Pd(OAc)_2$[b]	23
$PhSeCl/H_2O_2$	28	DDQ/collidine[b]	31
t-BuOCl/K_2CO_3/Δ	66		

[a] Isolated yield. [b] Determined by quantitative high-pressure LC.

Table III

$4 \longrightarrow 3$

reagent	yield, %[a]	reagent	yield, %[a]
Br_2/K_2CO_3	62	DDQ	75
$Pd(OAc)_2$	24[b]		

[a] Isolated. [b] Determined by liquid chromatography.

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