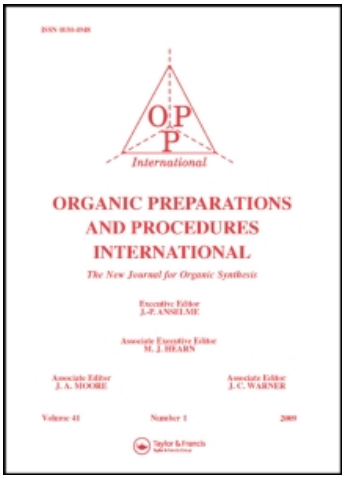


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

NITRO DERIVATIVES OF BENZOCOUMARINS. KEY INTERMEDIATES IN THE SYNTHESIS OF BENZOCOUMARIN-BASED FLUORESCENT REAGENTS FOR BIOLOGICAL APPLICATIONS

Jun-Rui Yang[a]; Carol A. Lambert[a]; Margaret E. Langmuir[a]; Richard Laura[a]
[a] Covalent Associates, Inc., Woburn, MA

To cite this Article Yang, Jun-Rui , Lambert, Carol A. , Langmuir, Margaret E. and Laura, Richard(1991) 'NITRO DERIVATIVES OF BENZOCOUMARINS. KEY INTERMEDIATES IN THE SYNTHESIS OF BENZOCOUMARIN-BASED FLUORESCENT REAGENTS FOR BIOLOGICAL APPLICATIONS', Organic Preparations and Procedures International, 23: 5, 621 — 626
To link to this Article: DOI: 10.1080/00304949109457914
URL: http://dx.doi.org/10.1080/00304949109457914

ORGANIC PREPARATIONS AND PROCEDURES INT., 23 (5), 621-626 (1991)

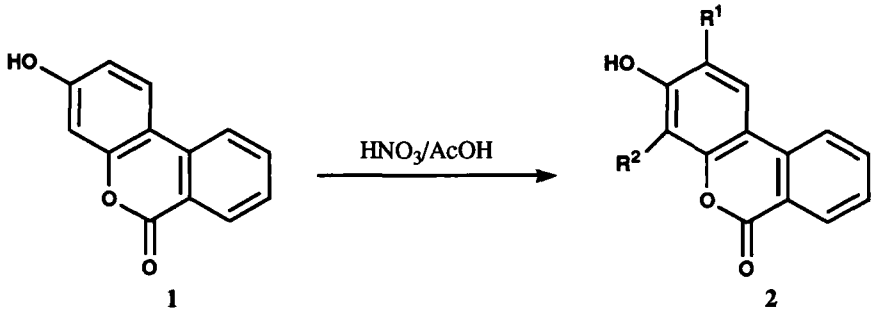
NITRO DERIVATIVES OF BENZOCOUMARINS. KEY INTERMEDIATES IN THE SYNTHESIS OF BENZOCOUMARIN BASED FLUORESCENT REAGENTS FOR BIOLOGICAL APPLICATIONS

Jun-Rui Yang*, Carol A. Lambert, Margaret E. Langmuir and Richard Laura

Covalent Associates, Inc.
52 Dragon Court, Woburn, MA 01801

Many benzocoumarins fluoresce efficiently. They have found wide application as laser dyes,[1] labeling reagents for acidic substances,[2] brighteners for synthetic fibers,[3] and inhibitors of tumors induced by carcinogens.[4] Some benzocoumarin compounds have antiarrhythmic, platelet-antiaggregating and local anesthetic activity.[5] Thus, interest in biological applications of benzocoumarins and their derivatives is growing continually. In efforts to develop fluorescent thiol reagents[6] and cytosolic Ca^{2+} indicators based on benzocoumarins (also known as dibenzopyranones and naphthopyranones), we required nitro derivatives of these pyranones. Nitronaphthopyranones and their simpler analogs, nitrocoumarins, are themselves of biological interest.[7] However, the literature on these nitro compounds is very limited. We report herein the preparation of several new nitronaphthopyranones and nitrodibenzopyranones, as well as different synthetic strategies leading to them.

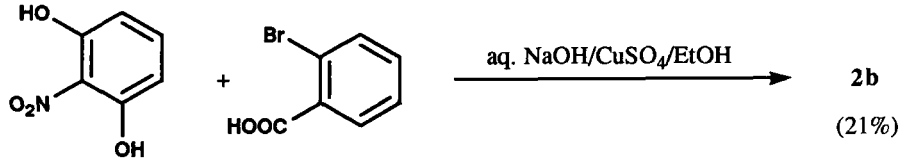
Fluorescent dibenzopyranones or naphthopyranones often contain auxochromes such as hydroxy or methoxy groups. When used as the precursor for the nitration reaction, the aromatic ring is activated toward electrophilic substitution, often resulting in isomeric mixtures and dinitro compounds. For instance, when 3-hydroxydibenzopyranone **1**[8] was treated with one equivalent of nitric acid overnight at room temperature, a mixture of three compounds **2a**, **2b**, and **2c** was obtained.



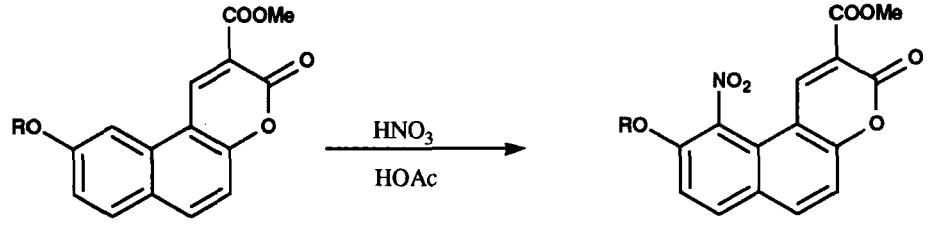
1 **2**

a) $R^1 = NO_2$, $R^2 = H$ b) $R^1 = H$, $R^2 = NO_2$ c) $R^1 = R^2 = NO_2$

Although the mixture was separable by chromatography, the separation was very tedious. By using 1.5 equivalent of nitric acid and extending the reaction time to 65 hours, we obtained a mixture containing only **2a** and **2c**. This mixture can be easily separated by chromatography on silica. In order to avoid the isomeric mixture resulting from the nitration of the corresponding hydroxydibenzocoumarin, it seemed logical to use a starting material bearing a nitro group at the appropriate position before the pyranone ring closure. This idea was tested for the synthesis of compound **2b**. The Hurtley condensation[9] between 2-nitroresorcinol and 2-bromobenzoic acid in the presence of copper (II) sulfate gave **2b** in moderate yield.

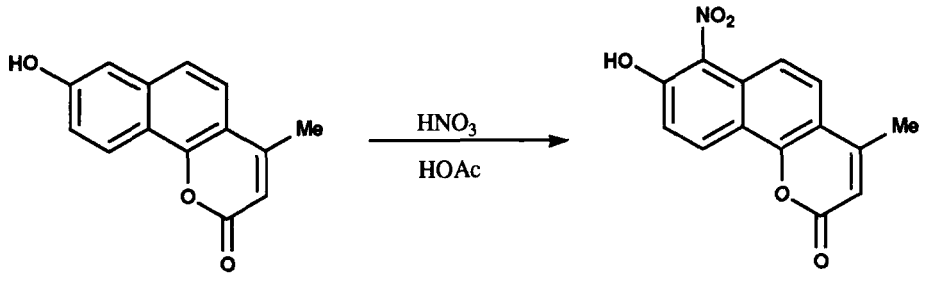


3 **4**

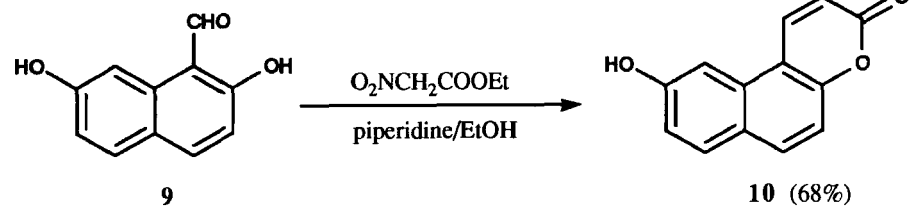


5 **6**

a) R = H b) R = Me



7 **8** (47%)



9 **10** (68%)

The success of this reaction now extends the scope of the Hurtley condensation[9] as this is the first example in which the resorcinol reactant has an electron-withdrawing substituent.

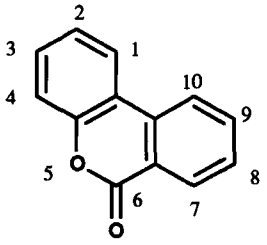
Unlike the hydroxydibenzopyranone in which both positions *ortho* to the hydroxy group are similarly activated, the α-position of hydroxynaphthopyranones is more susceptible to electrophilic substitution than the β-position. This makes it possible to achieve selective nitration using an appropriate nitrating reagent which recognizes the subtle difference in reactivity at those positions. In fact, as we have reported earlier,[6] the reaction of **5a** with nitric acid in acetic acid at room temperature for 6 hours gave only one nitration product **6a**. Under similar conditions, **7**[10] was treated with nitric acid to afford **8** exclusively. Again in compound **7**, the 7-position is the only α-position activated by an *ortho* hydroxy group. The nitration of **5b** was carried out under reflux overnight. A single product **6b** was isolated. The higher temperature and longer reaction time required for **5b** compared to **5a** were expected by the change of the substituent from a hydroxy to a methoxy group.

For compound **10**, since the nitro group is not *ortho* to the hydroxy substituent, direct nitration is not suitable. Dauzonne and Royer have reported a one-step preparation of 3-nitrocoumarins,[11] the benzopyranone analogs of **10**. In their work, the condensation of methyl nitroacetate with salicylaldehydes in toluene, catalyzed by diethylammonium chloride and aided by azeotropic removal of water in a Dean-Stark water trap, gave 3-nitrocoumarins in good yields after refluxing up to 120 hours. In an independent study, Chaurasia and Kauffman obtained a substituted 3-nitrocoumarin through the reaction of ethyl nitroacetate and a substituted salicylaldehyde in the presence of piperidinium acetate;[12] the by-product water was removed by allowing the refluxing solvent to pass through 4Å molecular sieves in a Soxhlet extractor. However, we found that the condensation of ethyl nitroacetate with 2,7-dihydroxy-1-naphthaldehyde[13] in ethanol using piperidine as catalyst provided compound **10** in 68% yield after refluxing for only 4 hours. There was no need to remove water to drive the reaction forward in this case. Although further investigation is required to establish the utility and scope of this reaction, the method does offer a more efficient and convenient alternative to the existing preparations of 3-nitrocoumarins.

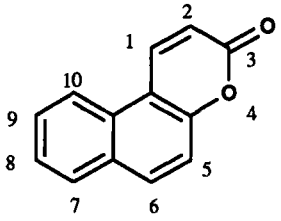
EXPERIMENTAL SECTION

Melting points are uncorrected and were measured on a MEL-TEMP capillary melting point apparatus. IR spectra were recorded on an IBM FT/32 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian XL-300 spectrometer using TMS as an internal standard. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA). The IUPAC numbering system used in naming the compounds and making the ^{1}H NMR assignments is shown below.

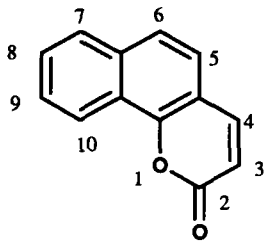
3-Hydroxy-2-nitro-6*H*-dibenzo[*b,d*]pyran-6-one (2a) and 3-hydroxy-2,4-di-nitro-6*H*-dibenzo[*b,d*]pyran-6-one (2c).- To a suspension of **1** (1.06 g, 5.0 mmol)[8] in glacial acetic acid (25 mL) was added conc. nitric acid (0.5 mL, 7.5 mmol). The mixture was stirred at room temperature for 65 hrs before the addition of water (25 mL). The precipitated product was collected, washed with



6*H*-Dibenzo[*b*,*d*]pyran-6-one



3*H*-Naphtho[2,1-*b*]pyran-3-one



2*H*-Naphtho[1,2-*b*]pyran-2-one

water thoroughly, and dried to give a mixture of **2a** and **2c**. The two compounds could be easily separated by column chromatography on silica gel. Elution with methylene chloride yielded 0.60 g (47%) of **2a**, mp. 285-286°. IR (KBr): 3430, 1744, 1634 cm^{-1}. ^1H NMR (DMSO-d_6): δ 11.82 (br s, 1H, -OH), 8.92 (d, 1H, J = 2.0 Hz, H_1), 8.45 (d, 1H, J = 7.9 Hz, H_7), 8.23 (d, 1H, J = 7.9 Hz, H_{10}), 7.95 (t, 1H, J = 7.9 Hz, H_9), 7.68 (t, 1H, J = 7.9 Hz, H_8), 7.05 (d, 1H, J = 2.0 Hz, H_4).

Anal. Calcd. for $C_{13}H_7NO_5$: C, 60.71; H, 2.74; N, 5.45 Found: C, 60.68; H, 2.78; N, 5.45

Elution with acetone then gave 0.70 g (46%) of **2c**, mp. >340°. IR (KBr): 3424, 1757, 1628, 1539 cm^{-1}. ^1H NMR (DMSO-d_6)[14]: δ 8.66 (s, 1H, H_1), 8.09 (d, 2H, J = 7.9 Hz, H_7 and H_{10}), 7.82 (t, 1H, J = 7.9 Hz, H_9), 7.45 (t, 1H, J = 7.9 Hz, H_8).

Anal. Calcd. for $C_{13}H_6N_2O_7$: C, 51.67; H, 2.00; N, 9.27. Found: C, 51.81; H, 2.06; N, 9.29

3-Hydroxy-4-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (2b).- To a solution of commercially available 2-nitroresorcinol (**3**, 0.85 g, 5.5 mmol) and 2-bromobenzoic acid (**4**, 1.01 g, 5.0 mmol) in ethanol (20 mL) was added a solution of sodium hydroxide (0.40 g, 1.0 mmol) in water (0.5 mL), followed by copper(II) sulfate (0.06 g, 0.25 mmol). The resulting mixture was refluxed for 5 hrs, and the solvent was removed. The residue was washed with ether twice, then dissolved in water (30 mL), and acidified with dilute hydrochloric acid. The precipitate formed was collected and recrystallized from acetone/water to provide 0.27 g (21%) of **2b**, mp. 267-268°. IR (KBr): 3229, 1701, 1624, 1535 cm^{-1}. ^1H NMR (DMSO-d_6): δ 11.94 (br s, 1H, -OH), 8.33 (d, 1H, J = 8.6 Hz, H_1), 8.28 (d, 1H, J = 7.9 Hz, H_7), 8.18 (d, 1H, J = 7.9 Hz, H_{10}), 7.93 (t, 1H, J = 7.9 Hz, H_9), 7.62 (t, 1H, J = 7.9 Hz, H_8), 7.08 (d, 1H, J = 8.6 Hz, H_2).

Anal. Calcd. for $C_{13}H_7NO_5$: C, 60.71; H, 2.74; N, 5.45. Found: C, 60.62; H, 2.85; N, 5.38

2-Carbomethoxy-9-hydroxy-10-nitro-3*H*-naphtho[2,1-*b*]pyran-3-one (6a). Typical Procedure.- To a suspension of **5a** (2.68 g, 10 mmol)[6] in glacial acetic acid (20 mL), was added conc. nitric acid (0.75 mL, 12 mmol). After stirring at room temperature for 6 hrs, the reaction was quenched by addition of water (80 mL). The precipitate was collected and washed with water thoroughly.

Recrystallization from dimethylformamide/acetonitrile yielded 2.87 g (91%) of **6a**, mp. 247-249°, lit.[6] mp. 247-249°. IR (KBr): 3252, 1763, 1725, 1698 cm^{-1}. ^1H NMR (DMSO-d_6)[14]: δ 8.59 (s, 1H, H_1), 8.34 (d, 1H, J = 9.2 Hz, H_6 or H_7), 8.16 (d, 1H, J = 9.2 Hz, H_6 or H_7), 7.50 (d, 1H, J = 8.9 Hz, H_5 or H_8), 7.43 (d, 1H, J = 8.9 Hz, H_5 or H_8), 3.85 (s, 3H, -OC$\underline{H}_3$).

2-Carbomethoxy-9-methoxy-10-nitro-3*H*-naphtho[2,1-*b*]pyran-3-one (6b).- Compound **6b** was prepared from **5b**[6] according to the typical procedure for **6a**, except that the reaction mixture was refluxed for 24 hrs. Recrystallization from dimethylformamide yielded **6b** (66%), mp. 314-315° (dec), lit.[6] mp. 314-314.5° (dec). IR (KBr): 1771, 1557, 1524 cm^{-1}. ^1H NMR (DMSO-d_6)[14]: δ 8.63 (s, 1H, H_1), 8.47 (d, 1H, J = 8.7 Hz, H_6 or H_7), 8.41 (d, 1H, J = 8.8 Hz, H_6 or H_7), 7.84 (d, 1H, J = 8.7 Hz, H_5 or H_8), 7.63 (d, 1H, J = 8.8 Hz, H_5 or H_8), 4.10 (s, 3H, -OC$\underline{H}_3$), 3.86 (s, 3H, -OC$\underline{H}_3$).

8-Hydroxy-4-methyl-7-nitro-2*H*-naphtho[1,2-*b*]pyran-2-one (8).- Compound **8** was prepared from **7**[10] according to the typical procedure for **6a**, except that the reaction mixture was stirred at room temperature for 3 hrs. Recrystallization from dimethylformamide/acetone gave **8** (47%), mp. 269-270° (dec). IR (KBr): 3085, 1705, 1636, 1522 cm^{-1}. ^1H NMR (DMSO-d_6)[14]: δ 8.27 (d, 1H, J = 8.9 Hz, H_5 or H_{10}), 7.73 (d, 1H, J = 9.2 Hz, H_5 or H_{10}), 7.42 (d, 1H, J = 8.9 Hz, H_6 or H_9), 7.30 (d, 1H, J = 9.2 Hz, H_6 or H_9), 6.40 (s, 1H, H_3), 2.46 (s, 3H, -C$\underline{H}_3$).
Anal. Calcd. for $C_{14}H_9NO_5$: C, 62.00; H, 3.34; N, 5.16. Found: C, 62.28; H, 3.40; N, 4.88

9-Hydroxy-2-nitro-3*H*-naphtho[2,1-*b*]pyran-3-one (10).- A solution containing 2,7-dihydroxy-1-naphthaldehyde[13] **9** (0.94 g, 5.0 mmol), ethyl nitroacetate (0.70 g, 5.25 mmol), piperidine (0.06 mL), and ethanol (5.0 mL) was refluxed under nitrogen for 4 hrs and then cooled. The precipitate was collected and washed with ethanol three times. Recrystallization from dimethylformamide yielded 0.87 g (68%) of **10**, mp. 323-324°. IR (KBr): 3386, 1742, 1622, 1563 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.47 (br s, 1H, -O$\underline{H}$), 9.43 (s, 1H, H_1), 8.18 (d, 1H, J = 9.2 Hz, H_6), 7.86 (d, 1H, J = 8.8 Hz, H_7), 7.63 (d, 1H, J = 2.1 Hz, H_{10}), 7.26 (d, 1H, J = 9.2 Hz, H_5), 7.17 (d of d, 1H, J = 8.8, 2.1 Hz, H_8).
Anal. Calcd. for $C_{13}H_7NO_5$: C, 60.71; H, 2.74; N, 5.45. Found: C, 60.65; H, 2.77; N, 5.46

Acknowledgment.- This work was partially supported by NIH Grant No. 1 R43 GM38982-01 and NIH Contract No. N43-AM-6-2279.

REFERENCES

1. M. Nakashima, R. C. Clapp, and J. A. Sousa, *Nature Phys. Sci.*, **245**, 124 (1973).

2. K. Ito and J. Maruyama, *Chem. Pharm. Bull., Japan*, **34**, 390 (1986).

3. N. K. Chodankar, S. D. Joshi, S. Sequeria, and S. Seshadri, *Indian J. Chem.*, **26B**, 427 (1987).

4. R. G. Harvey, C. Cortez, T. P. Ananthanarayan, and S. Schmolka, *J. Org. Chem.*, **53**, 3936 (1988).

5. A. Bargagna, M. Longobardi, E. Mariani, P. Schenone, S. Russo, S. Vitagliano, V. DeNovellis, and E. Marmo, *Farmaco. Ed. Sci.*, **43**, 857; *C. A.*, **110**, 165785n (1988).

6. J.-R. Yang and M. E. Langmuir, *J. Heterocyclic Chem.*, In press.

7. D. Dauzonne and R. Royer, *Eur. J. Med. Chem.-Chim. Ther.*, **19**, 477 (1984); *C. A.*, **102**, 78677v (1985).

8. J. P. Devlin, *Can. J. Chem.*, **53**, 343 (1975).

9. K. A. Cirigottis, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **27**, 2209 (1974).

10. O. S. Wolfbeis, *Monatsh. Chem.*, **109**, 1413 (1978).

11. D. Dauzonne and R. Royer, *Synthesis*, 836 (1983).

12. C. S. Chaurasia and J. M. Kauffman, *J. Heterocyclic Chem.*, **27**, 727 (1990).

13. O. S. Wolfbeis and H. Junek, *Z. Naturforsch.*, **34B**, 283 (1979).

14. When DMSO-d_6 contains trace amount of water, no signal for -O<u>H</u> can be detected above 10 ppm.

(Received May 20, 1991; in revised form July 9, 1991)