Preparation of 4-Hydroxy-3-Substituted, 2*H*-1-Benzopyran-2-ones and 2*H*-1-Benzothiopyran-2-ones from Carboxylic Esters and Methyl Salicylates or Methyl Thiosalicylate

Sharon E. Davis, A. Cameron Church, Rebecca C. Tummons and Charles F. Beam*

Department of Chemistry and Biochemistry, College of Charleston, Charleston, South Carolina 29424

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C(α)-Carboxylic acid esters were treated with excess lithium diisopropylamide, condensed with methyl salicylates or methyl thiosalicylate, followed by acid cyclization to either 4-hydroxy-3-substituted, 2*H*-1-benzopyran-2-ones (coumarins), or 2*H*-1-benzothiopyran-2-ones (thiocoumarins).

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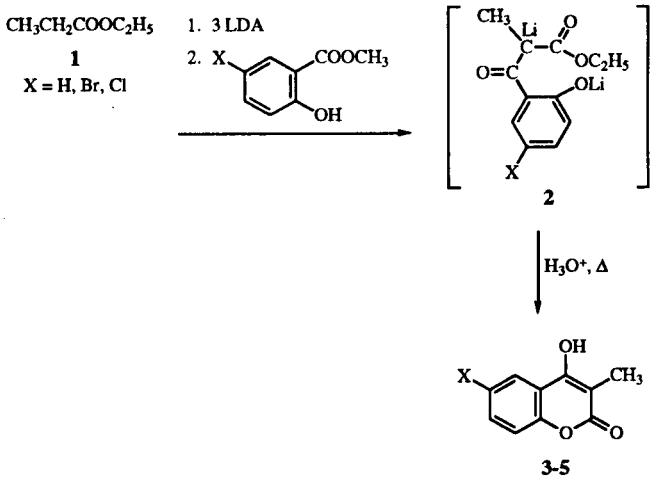
The preparations and importance of 3-substituted, 4-hydroxy-2*H*-1-benzopyran-2-ones, also referred to as coumarins and related materials, are well documented [1]; however, there are fewer reports for the preparation and overall potential of 3-substituted, 4-hydroxy-2*H*-1-benzothiopyran-2-ones [2], also referred to as thiocoumarins. One reaction that has received considerable early and ongoing attention has been the condensation/cyclization of phenols or thiophenols with malonates or related materials. Another reaction related to this report is the intramolecular Claisen cyclization of select acylated salicylic acid esters [3]. Within the past decade or so, several new methods have been reported for the preparation of substituted 4-hydroxycoumarins, which is indicative of the continued interest in these compounds [4].

A major pharmaceutical and pharmacological interest in coumarins has been their anticoagulant [1-5] and vitamin K-like activity [6], in addition to other biological activity [7], and their use in other syntheses [8]. Many of these compounds are those where there is an alkyl or aryl substituent in the 3-position, and an OH or ether linkage in the 4-position. Several of these agents [9], with this particular substitution pattern, available for therapeutic purposes at an earlier time, currently includes coumadin and sometimes dicumarol. The potential for new compounds with this substitution pattern is the central point of this study.

The preliminary results presented indicate direct and regioselective syntheses of various coumarins and thiocoumarins. This initial study has focused on the preparation of 4-hydroxy-3-methylcoumarins (Scheme 1), and 3-alkyl-4-hydroxythiocoumarins (Scheme 2). In each instance an enolate/carbanion type intermediate of a carboxylic acid ester has undergone a Claisen-type condensation with another anion-type substrate of either a salicylate, or a thiosalicylate ester.

Specifically, ethyl propionate **1** was monolithiated with excess lithium diisopropylamide, and condensed with either lithiated methyl salicylate, lithiated methyl 5-bromosalicylate, or lithiated methyl 5-chlorosalicylate to give lithiated intermediates **2** that were cyclized with aqueous acid to

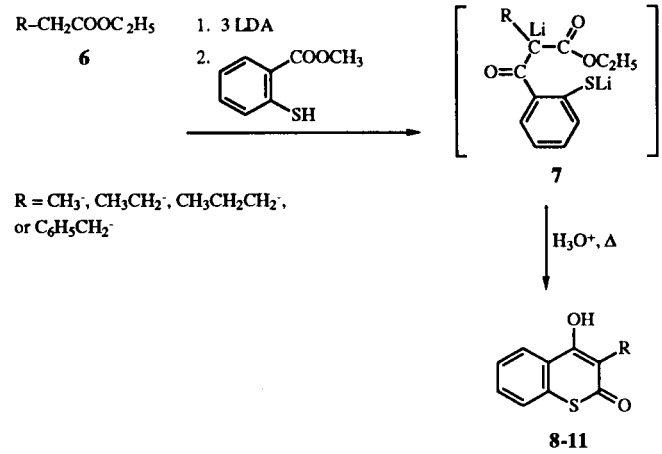
Scheme 1
4-Hydroxy-3-methyl-2*H*-1-benzopyran-2-ones



4-hydroxy-3-methylcoumarins **3** (94% yield), **4** (52% yield), and **5** (40% yield). (Scheme 1) Coumarin **3** is known and coumarins **4** and **5** are new, and they were characterized by absorption spectra, with support from C and H combustion analysis. Also, carboxylic acid ethyl esters **6**, propionate, butyrate, valerate, or hydrocinnamate were monolithiated with excess lithium diisopropylamide, condensed with lithiated methyl thiosalicylate to lithiated intermediates **7** that were acid cyclized to thiocoumarins **8** (27% yield), **9** (68% yield), **10** (50% yield), and **11** (30% yield), respectively. Thiocoumarins **8-10** are known; but the melting points obtained in this study differed by 5° or more with the melting points reported for the same materials. (Scheme 2)

The characterization data obtained for coumarins **3-5** is straightforward, and similar data obtained for thiocoumarins **8-11** is presented with additional commentary. We observed the differences between melting points obtained for **8-10** and those reported [2a] for these compounds, and we also noted some greater differences in melting points reported for the dithio-coumarin analogs of dicumarol [9g] (305° [2j] and 322° [2f]). While the data may suggest different polymorphic crystalline forms, this

Scheme 2
3-Alkyl-4-hydroxy-2*H*-1-benzothiopyran-2-ones



does indicate the desirability for X-ray crystallographic analyses [10], which are already in progress. The proton magnetic resonance spectra are consistent with the assigned structures, and comprehensive studies will also include supplementary spectral information. Another concern was with the infrared carbonyl absorption of the thiolactone for thiocoumarins **8-11**. The limited literature reports [2n,o] indicate such absorptions are found from 1620-1640 cm^{-1}, and those observed in **8-11** were displayed as clearly discernible shoulders, 1630-1633 cm^{-1}, associated with a dominant aromatic absorption at approximately 1600 cm^{-1}.

One of the principal advantages of these regioselective preparations has been the relative ease in purification of products, which are solids, and they are readily crystallized/recrystallized from routine solvents. The yields of compounds reported here ranged from 27-94%, which indicates that this may not necessarily represent the optimum conditions for the preparation of an individual compound, or a well developed general procedure. At this point in the study, it is relatively easy to obtain multigram quantities of the pure products to ensure that enough material is available for characterization and subsequent biological testing [11]. In addition, the products are prepared from readily available starting materials, and a preliminary experimental procedure is straightforward so that someone not necessarily familiar with strong-base procedures can be successful with the reactions.

Initially, we were somewhat surprised to observe how readily some of these carbanion/enolate multiple anion-type systems condensed with lithiated methyl salicylates and lithiated methyl thiosalicylate and other reagents where the electrophilic center (atom) was in a position for diminished reactivity, due to the location of an anion-type nucleophilic group in a resonance position. A longer condensation time appeared to be the major requirement for a successful reaction [12].

Even though there has been extensive research conducted [1,3-6] on the preparation and biological activity of 3-substituted, 4-hydroxycoumarins, we anticipate that many new members of this series will also be prepared. Most of the targeted compounds will have pendant groups in a variety of positions exerting inductive and resonance effects on the products, and they may be difficult to prepare, or inaccessible by traditional procedures. The limited biological screening [2] of 3-substituted, 4-hydroxythiocoumarins has indicated anticoagulant properties, and some of them may be comparable to their oxygen analogs. In addition to a developed syntheses and testing of substituted coumarins and thiocoumarins, absorption and mass spectral studies are also in progress.

EXPERIMENTAL

Melting points were obtained with a Mel-Temp melting point apparatus in open capillary tubes and are uncorrected. Fourier Transform infrared spectra were obtained on a Nicolet Impact 410 or Mattson Polaris FT-IR. Proton magnetic resonance were obtained with a Varian Associates 360L Nuclear Magnetic Resonance Spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane standard [13]. Since 4-OH absorptions were not always clearly distinguishable, integration ratios of aromatic hydrogens with other hydrogens are not included. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888.

General Procedure for the Preparation of Coumarins **3-5** and Thiocoumarins **8-11**.

In a typical reaction, 0.032 mole of lithium diisopropylamide in **35-40** ml anhydrous tetrahydrofuran was treated with 0.010 mole of ester in 25-30 ml tetrahydrofuran at 0°/nitrogen for 30-45 minutes. The methyl salicylates or methyl thiosalicylate (0.011 mole), dissolved in 30-35 ml tetrahydrofuran, were added and condensed with the enolate-carbanion type system for 2-2.25 hours, which was followed by addition of 100 ml of 3*N* hydrochloric acid. The stirred two-phase system was heated under reflux for approximately 15 minutes for cyclizations to coumarins **3-5** and approximately 5 minutes for cyclizations to thiocoumarins **8-11**. The work-up consisted of pouring the mixture into ice water, adding ether (100 ml), neutralizing the mixture with solid sodium bicarbonate, extracting the organic portion with ether (2 x 50 ml), combining organic phases, evaporation, and crystallization/recrystallization. Each of the compounds listed below was recrystallized from ethanol/water.

4-Hydroxy-3-methyl-2*H*-1-benzopyran-2-one **3**.

This compound was obtained in 94% yield, mp 226-229° (lit [14a,b] mp 225-227° and 230°); ir (paraffin oil/potassium bromide): 3161/3167 (OH), 1666/1668 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): δ 2.17 (s, CH_3) and 7.05-8.28 (m, ArH and 4-OH).

6-Bromo-4-hydroxy-3-methyl-2*H*-1-benzopyran-2-one **4**.

This compound was obtained in 52% yield, mp 255-258°; ir (paraffin oil/potassium bromide): 3147/3150 (OH), 1672 shoulder/1716 and 1687 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): δ 2.17 (s, CH_3) and 7.23-8.83 (m, ArH and 4-OH)].

Anal. Calcd. for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77. Found: C, 47.21; H, 2.98.

6-Chloro-4-hydroxy-3-methyl-2*H*-1-benzopyran-2-one **5**.

This compound was obtained in 40% yield, mp 241-244°; ir (paraffin oil/potassium bromide): 3145 shoulder/3182 (OH), 1678/1693 and 1678 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.08 (s, CH_3) and 7.32-8.88 (m, ArH and 4-OH)].

Anal. Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35. Found: C, 56.80; H, 3.44.

4-Hydroxy-3-methyl-2*H*-1-benzothiopyran-2-one **8**.

This compound was prepared in 27% yield, mp 225-228° (lit [2a] mp 220°); ir (potassium bromide): *ca.* 3280 broad (OH), 1633 shoulder (C=O) and 1595 (ArH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.17 (s, CH_3), 7.87-8.17, and 8.63-9.05 (m, ArH and 4-OH)].

Anal. Calcd. for $C_{10}H_8O_2S$: C, 62.48; H, 4.19. Found: C, 62.25; H, 4.35.

3-Ethyl-4-hydroxy-2*H*-1-benzothiopyran-2-one **9**.

This compound was prepared in 68% yield, mp 138-140° (lit [2a] mp 133°); ir (potassium bromide): *ca.* 3280 broad (OH), 1633 shoulder (C=O), and 1601 (ArH) cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): δ 1.10 (t, 3H, CH_3), 2.76 (q, 2H, $-CH_2-$), 7.38-7.68, and 8.55-8.93 (m, ArH and 4-OH).

Anal. Calcd. for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89. Found: C, 64.08; H, 5.01.

4-Hydroxy-3-propyl-2*H*-1-benzothiopyran-2-one **10**.

This compound was prepared in 50% yield, mp 164-166° (lit [2a] mp 172°); ir (potassium bromide): *ca.* 3300 broad (OH), 1630 shoulder (C=O), and 1601 (ArH) cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): δ 1.02 (t, 3H, CH_3-), 2.42-3.08 (m, 2H, $-CH_2-$), 3.38 (t, 2H, $-CH_2-$), 7.62-7.92 and 8.43-8.80 (m, ArH and 4-OH).

Anal. Calcd. for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49. Found: C, 65.14; H, 5.75.

4-Hydroxy-3-phenylmethyl-2*H*-1-benzothiopyran-2-one **11**.

This compound was prepared in 30% yield, mp 167-170°; ir (potassium bromide): *ca.* 3300 broad (OH), 1633 shoulder (C=O), and 1604 (ArH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.22 (s, $-CH_2-$) and 6.98-7.97 (m, ArH and 4-OH).

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51. Found: C, 71.39; H, 4.45.

Acknowledgments.

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REFERENCES AND NOTES

[1] Annually there are many citations dealing with clinical studies and some syntheses of these substituted coumarins. Reviews: [a] J. P. Hepworth, in Comprehensive Heterocyclic Chemistry, Vol **3**, Part **2B**, A. R. Katritzky and C. W. Rees, eds, Board, Pergamon Press, New York, New York, 1984, pp 799-810; [b] R. Livingston, Rodd's Chemistry of Carbon Compounds, S. Coffey, ed, Elsevier, Amsterdam, 1977, Vol **10**, Part E, pp 738, 767, 799, 816, 830, 861, 878, 919-920; [c] S. Wawzonek, Coumarins, Vol **2**, Heterocyclic Compounds, R. C. Elderfield, ed, John Wiley and Sons, New York, New York, 1951; [d] R. D. H. Murray, J. Mendez, S. A. Brown, The Natural Coumarins, John Wiley and Sons, Inc, New York, New York, 1982; [e] M. Darbarwar and V. Sundramurthy, *Synthesis*, 337 (1982); [f] P. M. Dewick, in The Flavanoids: Advances in Research, J. B. Harborne and T. J. Mabry, eds, Chapman and Hall, London, 1982, p 535.

[2a] P. S. Jamkhandi and S. Rajagopal, *Arch. Pharm. (Weinheim)*, **300**, 561 (1967); [b] P. S. Jamkhandi, S. Rajagopal and M. Sirsi, *Indian J. Exp. Biol.*, **6**, 224 (1968); [c] A. Ruwet, C. Draguet and M. Renson, *Bull. Soc. Chim. Belg.*, **79**, 639 (1970); [d] P. S. Jamkhandi and S. Rajagopal, *Indian J. Chem.*, **10**, 1114 (1972); [e] G. M. Vishnyakova, T. V. Smirnova, A. Perina and L. V. Sugrobova, *Izv. Vyssb. Uchebn. Zaved., Khim. Khim.*, **22**, 283 (1979); *Chem. Abstr.*, **91**, 39268x (1979); [f] C. Mentzer, P. Meunier, J. Lecorq, D. Billet and D. Xuong, *Bull. Soc. Chem. France*, **12**, 430 (1945); [g] C. Mentzer and P. Meunier, *Bull. Soc. Chem. Biol.*, **25**, 379 (1943); [h] J. R. Geigy, British Patent 784,281 (1957); *Chem. Abstr.*, **52**, P 6413g (1958); [i] C. Mentzer and A. Ville, J. Favre-Bonvin, *Bull. Soc. Chem. France*, **92** (1963); [j] E. Ziegler and H. Junek, *Monatsh. Chem.*, **86**, 29 (1955); [k] P. S. Jamkhandi and S. Rajagopal, *Monatsh. Chem.*, **94**, 1271 (1963); [l] P. S. Jamkhandi, S. Rajagopal and S. M. Srinivasa, *Indian J. Exp. Biol.*, **6**, 224 (1965); [m] P. S. Jamkhandi and S. Rajagopal, *Monatsh. Chem.*, **97**, 1732 (1966); [n] W. Asker and P. Elnagdi, *J. Prakt. Chem.*, **313**, 715 (1971); [o] J. R. Merchant and G. Martyres, *Indian J. Chem., Sect. B.*, **22B**, 35 (1983); [p] K. C. Majumdar, P. K. Choudhury and A. T. Kahn, *Synth. Commun.*, **19**, 3249 (1989).

[3a] B. S. Wildi, *J. Org. Chem.*, **16**, 407 (1951); [b] M. A. Stahmann, I. Wolf and K. L. Link, *J. Am. Chem. Soc.*, **65**, 2285 (1943).

[4a] D. H. R. Barton, D. M. X. Donnelly, J. P. Finet and P. H. Stenson, *Tetrahedron*, **44**, 6387 (1988); [b] D. H. R. Barton, D. M. X. Donnelly, J. P. Finet and P. J. Guiry, *Tetrahedron Letters*, **30**, 1539 (1989); [c] D. H. R. Barton, D. M. X. Donnelly, J. P. Finet and P. J. Guiry, *J. Chem. Soc., Perkin Trans 1*, 1365 (1992); [d] R. Gandhidasan, S. Neelakatan, P. V. Raman and S. K. Sripathi, *Indian J. Chem., Sect. B*, **27B**, 849 (1988); [e] A. Ogawa, N. Kambe and N. Sonoda, *Synthesis*, 257 (1988); [f] L. D. Sardesai, S. K. Paknikor, R. B. Bates, T. J. Siahoan, V. U. Kane and P. K. Mishra, *Heterocycles*, **26**, 2941 (1987); [g] A. Clerici and O. Porta, *Synthesis*, 99 (1993).

[5a] B. van Zanten and W. T. Nauta, *Arzneim.-Forsch.*, **14**, 29 (1964); [b] R. Labbe-Bois, C. Laruelle and J. J. Godfroid, *J. Med. Chem.*, **18**, 85 (1975); [c] R. G. Bell and P. Stark, *Biochem. Biophys. Res. Commun.*, **72**, 619 (1976); [d] R. B. Silverman, *J. Am. Chem. Soc.*, **103**, 3910 (1981); [e] R. B. Silverman, *J. Am. Chem. Soc.*, **102**, 5421 (1980); [f] P. Ren, P. Y. Stark, R. L. Johnson and R. G. Bell, *J. Pharmacol. Exp. Ther.*, **201**, 541 (1977).

[6a] P. Meunier, C. Mentzer and A. Vinet, *Helv. Chim. Acta*, **29**, 1291 (1946); [b] B. S. Kirkiacharian, A. Rabaron and M. C. Plat, *R. Hebd. Seances Acad. Sci., Ser. C.*, **284**, 697 (1977); *Chem. Abstr.*, **87**, 67488e (1977); [c] P. Briet, J. J. Berlhelon and J. C. Depin, British Patent 1,556, 491 (1980); *Chem. Abstr.*, **94**, P 65472r (1980).

[7a] L. Fontaine, M. Grand, D. Molho and E. Boschetti, *Chim. Ther.*, **2**, 430 (1967); [b] P. R. Andrews, D. J. Craik and J. L. Martin, *J. Med. Chem.*, **27**, 1648 (1984); [c] D. J. Anderson, L. S. Banitt, P. J. W. Strohbach, S. Thaisrivongs, C. -P. Yang and R. C. Thomas, Patent Int. Appl. WO 94 18,188 (1994); *Chem. Abstr.*, **123**, P 285778c (1995); [d] S. Wang, G. W. A. Milne, X. Yan, I. Posey, M. C. Nicklaus, L. Graham and W. G. Rice, *J. Med Chem.*, **39**, 2047 (1996).

[8a] M. A. Chauncey, M. F. Grundor and M. J. Rutherford, *J. Chem. Soc., Chem.Commun.*, 527 (1988); [b] G. Appendino, S. Taglia, G. M. Nano and G. Palmisano, *J. Chem. Soc., Perkin Trans 1*, 2305 (1989).

[9a] Acenocoumarin (acenocoumarol): 4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2*H*-1-benzopyran-2-one; [b] cyclocumarol: 3,4-dihydro-2-methoxy-2-methyl-4-phenyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyan-5-one; [c] dicumarol (dicoumarin): 3,3'-methylene-*bis*[4-hydroxy-2*H*-1-benzopyran-2-one]; [d] tromexan (dicumacyl or B.O.E.A.); 4-hydroxy-α-(4-hydroxy-2-oxo-2*H*-1-benzopyran-3-yl)-2-oxo-2*H*-1-benzopyran-3-acetic acid ethyl ester; [e] phenprocoumon: 4-hydroxy-3-(1-phenylpropyl)-2*H*-1-benzopyran-2-one; [f] coumadin (warfarin): 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-1-benzopyran-2-one; [g] 3,3'-methylene-*bis*[4-hydroxy-2*H*-1-benzothiopyran-2-one].

[10] Collaborative study with Dr. Clyde R. Metz of this department and Dr. William T. Pennington of Clemson University.

[11] Initially, biological screening will be coordinated and performed by Merck and Co., Inc. at several of their research facilities.

[12a] A. M. Huff and C. F. Beam, *J. Heterocyclic Chem.*, **23**, 1343 (1986); [b] M. J. Livingston, M. F. Chick, E. O. Shealy, D. J. Park, T. D. Fulmer and C. F. Beam, *J. Heterocyclic Chem.*, **19**, 215 (1982); [c] C. L. Mazat, C. F. Beam and M. A. Hines, *Synth. Commun.*, **20**, 253 (1990); [d] M. U. Koller, K. L. Peariso, T. S. Guion, S. Studer Martinez and C. F. Beam, *Synth. Commun.*, **25**, 2963 (1995); [e] T. M. Harris, T. P. Murray, C. M. Harris, M. Gumulka, *J. Chem. Soc., Chem. Commun.*, 362 (1974).

[13] High field multi-probe nmr (FT) will be available and performed in this department later in 1997 for inclusion in subsequent reports.

[14a] K. N. Triveda, *J. Sci. Ind. Res. (India)*, **21B**, 402 (1962); [b] Y. Kawase and K. Sakashita, *Bull. Chem. Soc. Japan*, **35**, 1869 (1962).