Synthesis of Novel 6,6′-Methylene-bis-[3-(2-anilinoacetyl)-4-hydroxycoumarin] Derivatives

Cherkupally Sanjeeva Reddy* and Mekala Raghu

Department of Chemistry, Kakatiya University; Warangal–506 009, India.
Received August 7, 2008; accepted September 17, 2008; published online September 19, 2008

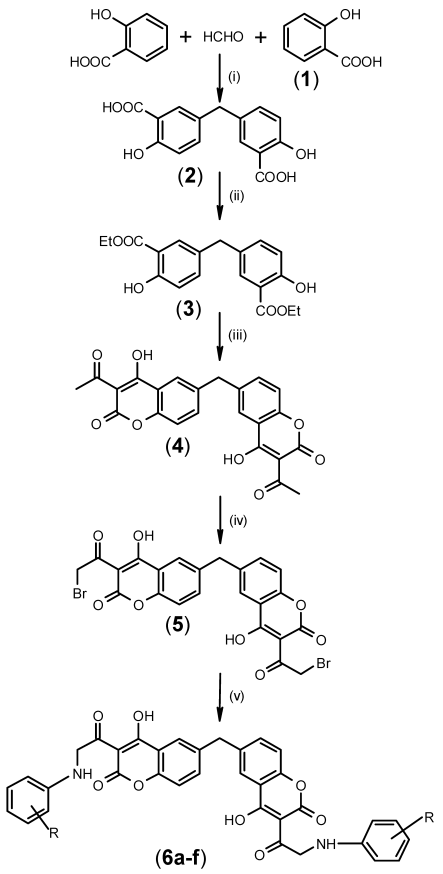
The synthesis of novel 6,6′-methylene-bis-[3-(2-anilinoacetyl)-4-hydroxycoumarin] derivatives 6a—f was achieved in excellent yields from 6,6′-methylene-bis-[3-(2-bromoacetyl)-4-hydroxycoumarin] 5 and various arylamines. 5,5′-Methylene-bis-ethylsalicylate 3 was obtained by the esterfication of 5,5′-methylene-bis-salicylic acid 2 with ethanol, which was in turn obtained from salicylic acid 1 and formaldehyde. Cyclocondensation of 3 with ethyl acetoacetate resulted in 6,6′-methylene-bis-[3-acetyl-4-hydroxycoumarin] 4, which on selective α-bromination with molecular bromine in the presence of montmorillonite K10–$AlCl_3$ catalyst, in chloroform–ethyl acetate binary solvent mixture at room temperature, afforded the compound 5 in excellent yield. All the newly synthesized compounds were characterized by their spectral data.

Key words 4-hydroxycoumarin; selective α-bromination; montmorillonite K10–$AlCl_3$

3-Substituted 4-hydroxycoumarins are a class of fused ring heterocycles which occur widely among natural products and have importance in medicine.[1)] Several natural products with the coumarinic moiety exhibit interesting biological and pharmacological properties such as antibacterial,[2)] anticancer,[3)] and inhibitory of platelet aggregation,[4)] steroid 5α-reductase,[5)] and human immunodeficiency virus (HIV)-1 protease.[6)] Additionally, coumarin derivatives have been used as active components in the formulation of pesticides, and additives in manufacture of pharmaceuticals, foods, cosmetics,[1)] laser dyes and fluorescent markers.[7,8)] Besides functionalized coumarins, polycyclic coumarines such as calanolides,[9)] isolated from *Callophyllum* genus and others, have shown potent anti-HIV (NNRTI) activity. These properties turn coumarins into very interesting targets to organic chemists, and several strategies for their synthesis were developed including Pechmann,[10)] Perkin,[11)] Knoevenagel,[12)] Reformatsky,[13)] Claisen,[14)] Wittig[15,16)] reactions and Flash vacuum pyrolysis.[17)] On the other hand, to the best of our knowledge, there is no report on the synthesis of 6,6′-methylene-bis-[3-(2-anilinoacetyl)-4-hydroxycoumarin] and its derivatives from any of the afore mentioned reactions using any reagent. Therefore, in connection with our research on the design and synthesis of biologically active and pharmacologically important new heterocycles,[18—20)] it was thought worthwhile to synthesize the title compounds with a view to obtain certain new chemical entities with two active pharmacophores in a single molecular frame work for the intensified biological and pharmacological properties. The synthetic route leading to the title compounds is summarized in Chart 1.

For the synthesis of the target compounds **6a**—**f**, the 5,5′-methylene-bis-salicylic acid **2** was prepared in 87% yield by the reaction of salicylic acid **1** with formaldehyde in the presence of sulfuric acid.[21)] Subsequent esterification of compound **2** with ethanol in the presence of a catalytic amount of sulfuric acid at reflux, gave 5,5′-methylene-bis-ethylsalicylate **3** in 84% yield.[18)] The ester **3** on cyclocondensation with ethyl acetoacetate, in the presence of sodium ethoxide in ethanol at reflux, afforded 6,6′-methylene-bis-[3-acetyl-4-hydroxycoumarin] **4** in 88% yield.[18)]

The coumarin **4** on selective α-bromination with molecular bromine, in the presence of montmorillonite K10–$AlCl_3$ catalyst in chloroform–ethyl acetate (1 : 2) binary solvent mixture at room temperature, afforded 6,6′-methylene-bis-[3-(2-bromoacetyl)-4-hydroxycoumarin] **5** in 90% yield.



(i) CH_2O, H_2SO_4, reflux 10 h; (ii) EtOH, H_2SO_4, reflux 3 h; (iii) EAA, EtOH, NaOEt, reflux 3 h; (iv) Br_2, Mont. K10–$AlCl_3$, EtOAc–$CHCl_3$, RT; (v) Arylamine, EtOH, reflux 2—3 h.

R= a) H; b) 3-NO_2; c) 4-NO_2; d) 4-Cl; e) 4-CH_3; f) 4-OCH_3

Chart 1

* To whom correspondence should be addressed. e-mail: chsrkuc@yahoo.co.in

Compound **5** on addition reaction with aniline in ethanol at reflux gave, after purification by column chromatography, the 6,6′-methylene-bis-[3-(2-anilinoacetyl)-4-hydroxycoumarin] **6a** in 88% isolated yield. The generality of this method was extended with various arylamines (Chart 1) and the yields of the products **6b**—**f** were excellent (86—90%) regardless structural variation in arylamine. Chemical structures of all the newly synthesized compounds were confirmed by their IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral analysis.

A heterogenous system consisting of montmorillonite K10 and $AlCl_3$ promotes the side chain bromination of compound **4** with molecular bromine, affording the required product **5** in excellent yield. Montmorillonite K10 and KSF behave as ditopic catalysts containing both acidic and basic sites.[22] The basic sites ascribable to the negative charges dispersed over entire sheets of oxygen atoms[23] and act as proton acceptor in the $AlCl_3$ catalyzed enolization reactions.

The bifunctional array containing montmorillonite K10 and a Lewis acid *i.e.* $AlCl_3$ coordinates and activates the ketone forming the oxonium salt, which due to its electron attracting power of the positively charged oxygen facilitates the removal of an α-proton by the basic sites of montmorillonite (mont.) thereby converting the compound **4** to its aluminium chloride complex of enol form (Chart 2), which reacts rapidly with molecular bromine to give the bromo product **5**.

Side chain bromination reaction was also carried out using various combinations of the catalyst system such as (i) mont. K10–$AlCl_3$, (ii) mont. KSF–$AlCl_3$, (iii) mont. K10, (iv) mont. KSF and (v) $AlCl_3$. The yields (90, 84, 66, 60 and 62% respectively) of the pure bromo product **5** obtained in all these cases indicate that, mont. K10 is the most efficient promoter of the reaction, due to its lower acidity value compared to that of mont. KSF.[22] Using mont. KSF as the catalyst, a 6% fall of yield was observed as compared to that of mont. K10. The yields of the bromo product **5** also indicate that the mixed system of mont. and $AlCl_3$ is an efficient catalyst system than either component alone. In fact mont. promotes the $AlCl_3$ catalyzed enolization of compound **4**, wherein it acts as a proton acceptor and increases the enol content of the compound **4** and hence an increase in the bromo product **5** yield.

Montmorillonite catalyst being water insoluble and stable was simply recovered by filteration after pouring the reaction mixture in water. It was washed with ethyl acetate, then with methanol, air-dried and reused for four times without significant loss of activity, giving the compound **5** in 90, 89, 87 and 85% yield respectively.

The choice of solvent was also critical and had a marked influence on the course of the reaction. Compound **4** did not react with bromine in the presence of montmorillonite K10–$AlCl_3$ at an observable rate in carbon tetrachloride but reacts readily in ethyl acetate and/or chloroform to give the compound **5**, however, better yields were obtained in chloroform–ethyl acetate solvent mixture. In S_N2 bimolecular substitution reaction, the reaction will be faster in dipolar aprotic solvents like ethyl acetate and chloroform than in a neutral solvent such as carbon tetrachloride, resulting in better yield and reduced reaction time. Protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser structures and it is easier for a large anion to be fitted in.[24]

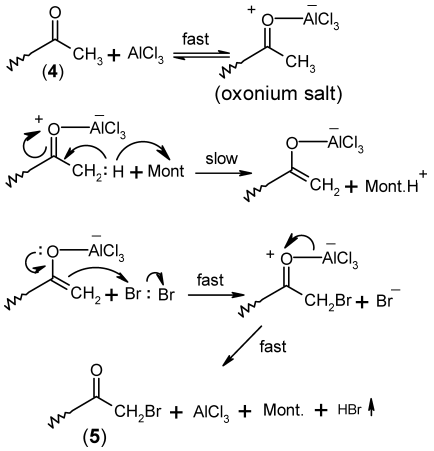


Chart 2

Uchil and Joshi[25] reported the side chain bromination of 2′-hydroxyacetophenone using molecular bromine and heterogenous catalyst system consisting of mont. K10–$AlCl_3$ in ethyl acetate solvent but with low (76%) yield and poor selectivity. 2′,6′-Dihydroxyacetophenone and 2′,3′,4′-trihydroxyacetophenone resulted in nuclear brominated products. However, in the present study, when coumarin **4** was brominated using the same catalyst system in chloroform–ethyl acetate binary solvent mixture, only side chain brominated product **5** was obtained with high (94%) yield and there was no indication of nuclear bromination.

The mixture of ethyl acetate and chloroform (2 : 1) was used for α-bromination of coumarin **4** since preliminary work indicated that this mixed solvent system gave cleaner product than either solvent alone. We thus conclude that the present method using molecular bromine and heterogenous catalyst system such as mont. K10–$AlCl_3$ in chloroform–ethyl acetate binary solvent mixture is the cleanest and the most convenient method for the preparation of 6,6′-methylene-bis-[3-(2-bromoacetyl)-4-hydroxycoumarin] **5**, which is reported for the first time.

Experimental

General All the reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^{1}H-NMR and 100 MHz for ^{13}C-NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Typical Procedure 6,6′-Methylene-bis-[3-(2-bromoacetyl)-4-hydroxycoumarin] (5) A mixture of compound **4** (0.01 mol) in ethyl acetate (10 ml) and anhydrous $AlCl_3$ (5 mg) was stirred at room temperature for 15 min. To this, montmorillonite K10 (100 mg) was added and continued stirring for further 15 min, then bromine (0.02 mol) in chloroform (5 ml) was added dropwise at a slow rate while stirring. After complete addition of bromine, stirring was continued for 30 min and the reaction mixture was poured into 100 ml of cold water. The solid montmorillonite catalyst in the resulting reaction mixture was recovered by filteration and washed with fresh ethyl acetate (10 ml) followed by methanol (20 ml), dried and reused. The methanol and the ethyl acetate washings were combined with the filtrate, transferred to a separating funnel and the organic layer was separated from the aqueous layer. The organic layer was made neutral to pH by vigorous shaking with water and brine solution, separated from the aqueous layer, dried over anhydrous sodium sulphate, and distilled off under reduced pressure. The crude product **5** obtained was purified by recrystallization from ethanol.

6,6′-Methylene-bis-[3-(2-anilinoacetyl)-4-hydroxycoumarin] (6) To a stirred solution of **5** (0.01 mol) in ethanol (20 ml) was added arylamine (0.02 mol) and the mixture was refluxed for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice-cold water. The crude product formed as solid was filtered, dried and subjected to coloumn chromatography over silica gel using 30% EtOAc in hexane as eluent to obtain pure product **6**. A similar procedure was used to prepare the other compounds **6b**—**f**.

5,5′-Methylene-bis-salicylic acid (2) White solid, yield 87%, mp 238—240 °C (dec.). IR (KBr) cm^{-1}: 3410, 3062, 1702. ^{1}H-NMR (DMSO-d_6) δ: 3.99 (2H, s), 6.92 (2H, d, J=9.1 Hz), 7.38 (2H, d, J=9.1 Hz), 7.42 (2H, s), 9.87 (2H, s), 10.90 (2H, s). ^{13}C-NMR δ: 44.7, 111.2, 123.8, 132.6, 133.9, 137.9, 161.3, 176.7. MS m/z: 288 (M^+).

5,5′-Methylene-bis-ethylsalicylate (3) Pink solid, yield 84%, mp 220—222 °C (dec.). IR (KBr) cm^{-1}: 3367, 3062, 1718, 1220. ^{1}H-NMR (DMSO-d_6) δ: 1.41 (6H, t, J=7.2 Hz), 3.94 (2H, s), 4.30 (4H, q, J=7.2 Hz), 7.10—7.76 (6H, m), 11.20 (2H, s). ^{13}C-NMR δ: 16.0, 43.8, 60.3, 113.4, 119.7, 128.3, 130.1, 131.9, 154.1, 170.2. MS m/z: 344 (M^+).

6,6′-Methylene-bis-[(3-acetyl)-4-hydroxycoumarin] (4) Pink solid, yield 88%, mp 118—120 °C. IR (KBr) cm^{-1}: 3438, 3062, 1730, 1685, 1561, 1174. ^{1}H-NMR (DMSO-d_6) δ: 2.32 (6H, s), 4.00 (2H, s), 7.22—7.70 (6H, m), 11.60 (2H, s). ^{13}C-NMR δ: 20.9, 43.6, 101.2, 117.3, 119.1, 121.9, 130.7, 136.2, 149.8, 159.7, 178.3, 184.2. MS m/z: 420 (M^+).

6,6′-Methylene-bis-[3-(2-bromoacetyl)-4-hydroxycoumarin] (5) Red solid, yield 90%, mp 208—210 °C. IR (KBr) cm^{-1}: 3480, 1728, 1680, 1587, 1180, 586. ^{1}H-NMR (DMSO-d_6) δ: 3.92 (2H, s), 4.21 (4H, s), 7.14 (2H, d, J=8.6 Hz), 7.18 (2H, d, J=8.6 Hz), 7.50 (2H, s), 15.07 (2H, s). ^{13}C-NMR δ: 31.9, 43.5, 101.0, 115.8, 118.2, 119.6, 131.4, 136.3, 149.2, 157.6, 182.1, 185.2. MS m/z: 578 (M^+).

6,6′-Methylene-bis-[3-(2-anilinoacetyl)-4-hydroxycoumarin] (6a) Brown solid, yield 88%, mp 168—170 °C. IR (KBr) cm^{-1}: 3451—3359, 1721, 1592, 1468, 1173. ^{1}H-NMR (DMSO-d_6) δ: 3.95 (4H, d), 4.03 (2H, s), 6.73 (4H, d, J=8.3 Hz), 6.83 (6H, m), 7.18 (2H, d, J=8.6 Hz), 7.28 (2H, d, J=8.3 Hz), 7.61 (2H, s), 8.89 (2H, t), 11.29 (2H, s). ^{13}C-NMR δ: 43.5, 47.4, 100.1, 114.0, 115.8, 116.8, 117.2, 118.2, 127.1, 131.4, 136.3, 147.8, 148.0, 156.8, 179.0, 182.3. MS m/z: 602 (M^+).

6,6′-Methylene-bis-[3-(3-nitro-2-anilinoacetyl)-4-hydroxycoumarin] (6b) Yellow solid, yield 87%, mp 138—140 °C. IR (KBr) cm^{-1}: 3450—3354, 1719, 1590, 1518, 1470, 1171. ^{1}H-NMR (DMSO-d_6) δ: 3.95 (4H, d) 4.03 (2H, s), 6.79 (2H, s), 7.09 (2H, m), 7.18 (2H, d, J=8.6 Hz), 7.26 (2H, d J=8.3 Hz), 7.31 (2H, d, J=7.2 Hz), 7.58 (2H, s), 7.73 (2H, d, J=7.1 Hz), 9.06 (2H, t), 11.30 (2H, s). ^{13}C-NMR δ: 43.4, 47.5, 100.1, 109.0, 114.3, 115.8, 117.2, 118.2, 128.1, 131.4, 136.3, 146.4, 148.0, 153.4, 156.8, 179.0, 182.3. MS m/z: 716 (M^+).

6,6′-Methylene-bis-[3-(4-nitro-2-anilinoacetyl)-4-hydroxycoumarin] (6c) Yellow solid, yield 84%, mp 180—181 °C. IR (KBr) cm^{-1}: 3455—3358, 1720, 1593, 1522, 1468, 1168. ^{1}H-NMR (DMSO-d_6) δ: 3.99 (4H, d), 4.03 (2H, s), 6.75 (4H, d, J=7.2 Hz), 7.18 (2H, d, J=8.3 Hz), 7.23 (2H, d, J=7.7 Hz), 7.56 (2H, s), 7.94 (4H, d, J=7.1 Hz), 8.99 (2H, t), 11.41 (2H, s). ^{13}C-NMR δ: 43.4, 47.4, 100.1, 115.8, 117.2, 118.6, 122.8, 131.4, 136.3, 139.1, 148.0, 151.7, 156.8, 179.0, 182.3. MS m/z: 716 (M^+).

6,6′-Methylene-bis-[3-(4-chloro-2-anilinoacetyl)-4-hydroxycoumarin] (6d) Yellow solid, yield 89%, mp 184—186 °C. IR (KBr) cm^{-1}: 3460—3350, 1724, 1560, 1465, 1172. ^{1}H-NMR (DMSO-d_6) δ: 3.99 (4H, d), 4.03 (2H, s), 6.47 (4H, d, J=8.1 Hz), 7.09 (4H, d, J=8.7 Hz), 7.18 (2H, d, J=8.3 Hz), 7.23 (2H, d, J=7.7 Hz), 7.56 (2H, s), 8.99 (2H, t), 11.41 (2H, s). ^{13}C-NMR δ: 43.4, 47.4, 100.1, 115.9, 117.2, 118.2, 119.6, 124.1, 127.8, 131.4, 136.3, 147.5, 148.1, 156.8, 179.1, 182.3. MS m/z: 671 (M^+).

6,6′-Methylene-bis-[3-(4-methyl-2-anilinoacetyl)-4-hydroxycoumarin] (6e) Yellow solid, yield 90%, mp 148—150 °C. IR (KBr) cm^{-1}: 3458—3352, 2872, 1721, 1562, 1464, 1170. ^{1}H-NMR (DMSO-d_6) δ: 2.00 (6H, s), 3.99 (4H, d), 4.03 (2H, s), 6.17 (4H, d, J=7.8 Hz), 6.98 (4H, d, J=8.2 Hz), 7.18 (2H, d, J=8.3 Hz), 7.23 (2H, d, J=7.8 Hz), 7.56 (2H, s), 8.99 (2H, t), 11.41 (2H, s). ^{13}C-NMR δ: 19.5, 43.4, 47.4, 100.1, 115.2, 115.8, 117.2, 118.2, 127.6, 130.6, 131.4, 136.3, 148.0, 148.1, 156.8, 179.0, 182.3. MS m/z: 630 (M^+).

6,6′-Methylene-bis-[3-(4-methoxy-2-anilinoacetyl)-4-hydroxycoumarin] (6f) Yellow solid, yield 87%, mp 132—134 °C. IR (KBr) cm^{-1}: 3450—3360, 2870, 1720, 1565, 1465, 1223, 1175. ^{1}H-NMR (DMSO-d_6) δ: 3.99 (4H, d), 3.82 (6H, s), 4.03 (2H, s), 6.21 (4H, d, J=7.8 Hz), 6.95 (4H, d, J=8.2 Hz), 7.16 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=7.7 Hz), 7.57 (2H, s), 8.97 (2H, t), 11.40 (2H, s). ^{13}C-NMR δ: 19.6, 43.4, 47.4, 100.1, 115.2, 115.9, 117.4, 118.2, 127.7, 130.6, 131.4, 136.3, 148.1, 148.2, 156.7, 179.1, 182.4. MS m/z: 662 (M^+).

Acknowledgement The authors thank the Director, Indian Institute of Chemical Technology, Hyderabad, India for providing the spectral data.

References

1) O'Kennedy R., Thornes R. D., "Coumarins: Biology, Applications and Mode of Action," John Wiley & Sons, Chichester, 1997.
2) Kayser O., Kolodziej H., *Planta Med.*, **63**, 508—510 (1997).
3) Wang C. J., Hsieh Y. J., Chu C. Y., Lin Y. L., Tseng T. H., *Cancer Lett.*, **183**, 163—168 (2002).
4) Cravotto G., Nano G. M., Palmisano G., Tagliapietra S., *Tetrahedron: Asymmetr.*, **12**, 707—709 (2001).
5) Fan G. J., Mar W., Park M. K., Wood C. E., Kim K., Kin S., *Bioorg. Med. Chem. Lett.*, **11**, 2361—2363 (2001).
6) Kirkiacharian S., Thuy D. T., Sicsic S., Bakhchinian R., Kurkjian R., Tonnaire T., *II Farmaco.*, **57**, 703—708 (2002).
7) Zahradnik M., "The Production and Application of Fluorescent Brightening Agents," John Wiley & Sons, New York, 1992.
8) Song A., Wang X., Lam K. S., *Tetrahedron Lett.*, **44**, 1755—1758 (2003).
9) Kashmann Y., Gustafson K. R., Fuller R., Cardellina J. H., McMohan J. B., Currens M. J., Buckheit R. W., Hughes S. H., Cragg G. M., Boyd M. R., *J. Med. Chem.*, **35**, 2735—2743 (1992).
10) Pechmann V. H., Duisberg C., *Chem. Ber.*, **17**, 929—979 (1884).
11) Perkin W. H., Henry W. Sr., *J. Chem. Soc.*, **28**, 10—11 (1875).
12) Jones F., Piermatti O., Pizzo F., *Heterocycles*, **43**, 1257—1266 (1996).
13) Shriner R. L., *Org. React.*, **1**, 15—16 (1942).
14) Cairns N., Harwood L. M., Astles D. P., *J. Chem. Soc., Perkin Trans. I*, **1994**, 3101—3107 (1994).
15) Mali R. S., Tilve S. A., *Synth. Commun.*, **20**, 1781—1791 (1990).
16) Yavari I., Hekmat-Shoar R., Zonouzi A., *Tetrahedron Lett.*, **39**, 2391—2393 (1998).
17) Cartwright G. A., McNab H., *J. Chem. Res.* (*S*), **1997**, 296—300 (1997).
18) Sanjeeva Reddy Ch., Nagaraj A., *J. Heterocycl. Chem.*, **44**, 1357—1362 (2007).
19) Raghu M., Nagaraj A., Sanjeeva Reddy Ch., *J. Heterocycl. Chem.*, **45**, 1115—1120 (2008).
20) Sanjeeva Reddy Ch., Srinivas A., Nagaraj A., *J. Heterocycl. Chem.*, **45**, 999—1003 (2008).
21) Clemenson H., *J. Am. Chem. Soc.*, **33**, 737—741 (1911).
22) Bigi F., Chesini L., Maggi R., Sartori C., *J. Org. Chem.*, **64**, 1033—1037 (1999).
23) Roberts J. D., Caserio M. C., "Basic Principles of Organic Chemistry," 2nd ed., John Wiley & Sons, New York, 1977, p. 739, 743.
24) March J., "Advanced Organic Chemistry," 3rd ed., Wiley Eastern, New Delhi, India, 1992, p. 317.
25) Uchil V. R., Joshi V., *Indian J. Chem.*, **42B**, 408—411 (2003).