Glasnik hemičara i tehnologa Bosne i Hercegovine

Bulletin of the Chemists and Technologists of Bosnia and Herzegovina

2012

38

1-4

Print ISSN: 0367-4444
Online ISSN: 2232-7266

UDC: _____

Original Scientific Article

Three novel 4-methylcoumarin derivatives

Ćavar, S.[a], Kovač, F.[b,*]

[a]*University of Sarajevo, Faculty of Science, Department of Chemistry, Zmaja od Bosne 33-35, 71000 Sarajevo, Bosnia and Herzegovina*

[b]*University of Ljubljana, Faculty of Chemistry and Chemical Technology, Aškerčeva 5, 1000 Ljubljana Slovenia*

Article info
Received: 02/11/11
Accepted: 13/01/12

Keywords:
4-methylcoumarins
Pechmann synthesis
Benzoylation

***Corresponding author:**
E-mail: franci.kovac@fkkt.uni-lj.si
franci.kovac@gmail.com;
Phone: 00-386-1-2419-252
Fax: 00-386-1-2419-220

Abstract: Substituted 4-methylcoumarins are synthesized from phenols and ethyl acetoacetate via Pechmann condensation, then, using common method for benzoylation, three novel coumarin derivatives were obtained: 4-methyl-2-oxo-2*H*-chromen-6-yl benzoate (**2a**), 4,5-dimethyl-2-oxo-2*H*-chromen-7-yl benzoate (**2b**), and 4-methyl-2-oxo-2*H*-chromen-7,8-diyl benzoate (**2c**). The structures of novel coumarins were characterized by elemental analysis, GC/MS, NMR, and IR techniques.

INTRODUCTION

Organic compounds containing coumarin moiety (2*H*-1-chromen-2-one) are widely distributed in nature. Coumarin and its derivatives have been essentially found in green plants belonging to the family of Rutaceae and Umbelifferae. These compounds can be obtained from plants by different extraction methods. Many compounds containing 2*H*-1-chromen-2-one subunit exhibit useful and diverse biological activity and find their application in pharmaceuticals, fragrances, agrochemicals and insecticides (Sethna, and Shah, 1945). Due to their physical properties they have also been used as organic scintillators and dispersed fluorescent and laser dies. Therefore, the chemical synthesis of coumarin derivatives is done to fulfill their requirements in numerous applications.

Chemically, coumarins can be synthesized by several synthetic routes such as Pechmann, Perkin, Knoevenagel, Reformatsky and Wittig reactions (Sethna, and Shah, 1945). However, due to simple and relatively inexpensive starting materials, the Pechmann reaction has been widely used for the syntheses of coumarins.

Many coumarins have been found to be effective in scavenging activity against reactive oxygen species such as superoxide radicals, hydroxyl radicals, and inhibit lipid peroxidations (Liu, Yu, and Liu, 1999; Kaneko, Baba, and Matsuo, 2003; Ćavar, Kovač, Maksimović, 2009).

Therefore, these facts have been stimulating to synthesize novel 4-methylcoumarin derivatives.

EXPERIMENTAL

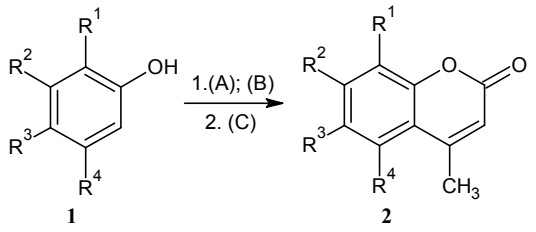
Materials

All chemicals used were purchased from the Sigma-Aldrich chemical company.

Synthesis of 4-methylcoumarin derivatives

The synthesis of coumarins was carried out according to the slightly modified Pechmann method (Russell and Frye, 1941; Vogel, Tatchell, Furnis, et al., 1996; Manhas, Ganguly, Mukherjee, et al., 2006; Kumar, Saini, and Sandhu, 2007; Mandhane, Joshi, Ghawalkar, et al., 2009), which involves the condensation of different phenols with β-keto esters in the presence of acidic condensing agents,

such as concentrated sulphuric acid and anhydrous aluminum chloride. Hydroxy-derivatives of 4-methylcoumarin were benzoylated in order to obtain the corresponding benzoxy-derivatives of 4-methylcoumarin (**2a-c**). Esterification reaction was carried out using benzoyl chloride in basic media (Figure 1)



1 **2**

1a: R^1=R^2=R^4=H, R^3=OH **2a**: R^1=R^2=R^4=H, R^3=OCOPh

1b: R^1=R^4=CH3, R3=H, R^2=OH **2b**: R^1=R^4=CH3, R3=H, R^2=OCOPh

1c: R^1=R^2=OH, R^3=R^4=H **2c**: R^1=R^2= OCOPh, R^3=R^4=H

Figure 1: Pechman synthesis of 4-methylcoumarins.
Reagents and conditions: (A) concentrated sulfuric acid, ethylacetoacetate, 0-10°C, reaction time 60 min; (B) polyphosphoric acid, ethyl acetoacetate, 75-80°C, reaction time 25 min; (C) benzoyl chloride, 5% sodium hydroxide, 25°C, reaction time 30 min.

Spectroscopic analyses of 4-methylcoumarins

Synthesized 4-methylcoumarins were identified by the determination of melting points on Kofler microscope hot stage apparatus (Model No. 220392, Reichert), using elemental analysis on CHN Analyzer (Perkin-Elmer 2400), GC/MS and NMR techniques.

The GC/MS (Hewlett-Packard GC 6890 series II and MSD 6890 series II) conditions were as follows: a fused-silica HP-5 column (5% phenyl methyl siloxane; 30 m x 250 µm x 0.25 µm), carriers gas He (1.1 mL/min), temperature program: 20°C/min from 100°C to 270°C; the injection port temperature was 250°C; detector temperature 280°C. Ionization of the sample components was performed in the EI mode, (70 eV). The NMR spectra were recorded in $CDCl_3$, acetone-d_6 and DMSO-d_6 at 300.13 MHz using Bruker DPX 300 NMR spectrometer. Novel compounds were also characterized by IR spectroscopy, recording the spectra of solid samples in KBr pellets on Perkin-Elmer spectrum BX FTIR system.

RESULTS AND DISCUSSION

The condensation of phenols and acetoacetic ester provided the 4-methylcoumarin and its derivatives. The concentrated sulfuric acid and polyphosphoric acid have been used as the condensing agents.

The yields of obtained 4-methylcoumarins were, in general, very high regardless of the structural variations of phenol substrates (1a-c). Substrates having electron-donating groups in the *para* position to the site of electrophilic substitution, gave maximum yields under mentioned reaction conditions.

The 4-methylcoumarin esters were prepared in high yields using benzoylation as a common method for esterification of organic compounds. In contrast to the Pechmann condensation, there is no correlation to the position of the hydroxy group in the coumarin molecule.

The purity of synthesized 4-methylcoumarins was determined by GC/MS technique. All samples were dissolved in acetone. They showed appreciable purity which was confirmed by elemental analysis. Data obtained from elemental analysis were in agreement with the calculated data. Structural confirmation was done using ^{1}H NMR, ^{13}C NMR and EI mass spectrometric methods.

The ^{1}H NMR spectra showed characteristic chemical shifts: 3-H δ 5.99-6.92, 4-methyl protons at δ 2.15-2.46, and protons from benzenoid part of molecule at δ 6.57-7.65, for all of the synthesized compounds. Benzoxy group attached to the aromatic part of coumarin molecules showed resonance peaks at δ 7.35-8.12. Observed results are in agreement with those found in the literature (Borsche, 1907; Mali and Yadav, 1977; Khan, Saify, Begum, et al., 2003).

The ^{13}C NMR spectra showed characteristic peaks of C-2 at δ 161.39-162.76, C-3 at δ 111.24-115.54, C-4 at δ 152.23-154.62, C-5 at δ 107.92-136.53, C-6 at δ 110.92-156.53, C-7 at δ 115.82-161.74, C-8 at δ 99.57-135.45, C-8a at δ 143.72-156.24, and C-4a at δ 112.28-121.92. Chemical shifts for aromatic carbon atoms were in a wide span due to the resonance influence of electron-acceptor substituent groups attached to the particular carbon atom. Benzoxy group displayed chemical shifts at δ 166.04-167.17 for carbonyl atom and at δ 129.12-133.72 for C-atoms from phenyl-group. Observed results are in agreement with those found in literature (Mital, Gupta, and Jain, 1972; Sojka, 1975; Chang and Floss, 1977).

Finally, the structures of synthesized 4-methylcoumarins were supported by their EI mass spectra. All compounds showed characteristic molecular $[M]^+$ peaks, *m/z* 280 (**2a-b**), and *m/z* 400 (**2c**). Moreover, all examined compounds displayed characteristic fragmentation of coumarin structure, such as $[M - HC=O]^+$. Observed results are in agreement with those found in literature (Desai and Mavani, 1942; Mali and Yadav, 1977, Woods and Sapp, 1962; Khan et al., 2003).

The IR spectra showed characteristic absorption bands for stretching of ester groups (1720 cm^{-1}), and for stretching of lactone C=O group (1680-1700 cm^{-1}). Other significant absorption bands were noted at 2900-3100 cm^{-1} (medium stretching of aromatic C-H bonds), and at 1590 cm^{-1} (weak stretching of aromatic C=C bonds).

Analytical and spectral characteristics of the novel compounds are given below.

4-Methyl-2-oxo-2*H*-chromen-6-yl benzoate; syn: 6-benzoxy-4-methyl-2-oxo-2*H*-chromen (**2a**). Yield 59%. m.p. 110-115°C. Anal. calcd for $C_{17}H_{12}O_4$: C 72.85, H 4.32; found: C 72.48, H 4.47. MS (EI; 70 eV): *m/z* (%) 39 (3), 51 (6), 77 (29), 91 (4), 105 (100), 106 (8), 280 (4). ^{1}H-NMR (300.13 MHz; DMSO-d_6): δ 8.06 (dd, J_1 = 7.9 Hz, J_2 = 2.0 Hz, 2H), 7.72 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.67 (d, J_2 = 2.1 Hz, 1H), 7.46 (dd, J_1 = 8.0 Hz, J_2 = 7.9 Hz, 2H), 7.35 (d, J_1 = 7.6 Hz, 1H), 7.21 (dd, J_1 = 7.6 Hz, J_2 = 2.1 Hz 1H), 6.04 (s, 1H), 2.42 (s, 3H). ^{13}C-NMR (300.13 MHz; $CDCl_3$): δ 167.17, 162.33, 152.99, 151.93, 149.75, 133.63, 130.95, 129.72-129.53, 129.32, 128.87, 120.65, 117.55, 114.90, 113.49, 21.32. IR (ν_{max}/cm^{-1}; KBr): 3060-3100, 1720, 1688, 1480, 1225, 840.

4,5-dimethyl-2-oxo-2*H*-chromen-7-yl benzoate; syn: 7-benzoxy-4-methyl-2-oxo-2*H*-chromen (2b). Yield 72%. m.p. 152-153°C. Anal. calcd for $C_{18}H_{12}O_4$: C 73.46, H 4.79; found: C 74.12, H 5.09. MS (EI; 70 eV): *m/z* (%) 51 (6), 77 (27), 105 (100), 106 (8), 294 (3). ^{1}H-NMR (300.13 MHz; DMSO-d_6): δ 8.02 (dd, J_1 = 7.8 Hz, J_2 = 2.1 Hz, 2H), 7.64 (dd, $_1$ = 7.9 Hz, J_2 = 2.1 Hz, 1H), 7.53 (dd, J_1 = 7.9 Hz, J_2 = 7.8 Hz, 2H), 7.03 (d, J_1 = 2.6 Hz, 1H), 6.76 (d, J_1 = 2.6 Hz, 1H), 5.93

(s, 1H), 2.43 (s, 3H), 2.24 (s, 3H). ^{13}C-NMR (300.13 MHz; $CDCl_3$): δ 167.17, 162.59, 154.63 -153.96, 135.92, 133.63, 130.95, 129.92 -129.53, 129.32-128.97, 117.40, 116.67, 115.56, 105.40, 21.37, 20.73. IR (ν_{max}/cm^{-1}; KBr): 3260, 1816, 1700-1720, 1272, 1224, 696.

4-methyl-2-oxo-2*H*-chromen-7,8-diyl benzoate; syn: 7,8-dibenzoxy-4-methyl-2-oxo-2*H*-chromen (**2c**). Yield 76%. m.p. 139-140°C. Anal. calcd for $C_{18}H_{12}O_4$: C 72.00, H 4.04; found: C 72.11, H 4.03. MS (EI; 70 eV): *m/z* (%) 51 (15), 77 (36), 105 (100), 106 (8), 198 (9). ^{1}H-NMR (300.13 MHz; DMSO-d_6): δ 8.09 – 7.51 (m, 10H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 1H), 2.26 (s, 3H). ^{13}C-NMR (300.13 MHz; $CDCl_3$): δ 166.14, 165.47, 166.49, 153.42, 148.99-148.13, 133.83-133.43, 132.02, 131.15 -130.75, 129.92-129.53, 129.32-128.91, 122.40, 117.75, 117.02, 112.24, 22.09. IR (ν_{max}/cm^{-1}; KBr): 2980, 1700-1720, 1590-1610, 1350-1390, 1000-1015.

CONCLUSIONS

This study presents the synthesis and characterization of three novel 4-methylcoumarin derivatives. After effective Pechman condensation, esterification of 4-methylxoumarins has been performed, and all of coumarin derivatives were obtained in high yields.

REFERENCES

Borsche, W. (1907). 4-Methyl-6-hydroxycoumarin and β-quinoylcrotonic acid. *Chemische Berichte, 40*, 2731-2736.

Chang, C., Floss, H. G. (1977). Carbon-13 magnetic resonance spectroscopy of coumarins. Carbon-13-proton long-range coupling constants. *Journal of Organic Chemistry*, *42*, 1337-1340.

Ćavar, S., Kovač, F., Maksimović, M. (2009) Synthesis and antioxidant activity of selected 4-methylcoumarins. *Food Chemistry, 117*, 135-142.

Desai, R. D., Mavani, C. K. (1942). Heterocyclic compounds. XVI. Coumarins from hydroquinone derivatives. *Proceedings of Indian Academy of Science A*, *15*, 11-15.

Kaneko, T. Baba, N. Matsuo, M. (2003). Protection of coumarins against linoleic acid hydroperoxide-induced cytotoxicity. *Chemico-Biological Interactions*, *142*, 239-254.

Khan, K. M., Saify, Z. S., Begum, S., Noor, F., Khan, M. Z., Hayat, S., Choudhary, M. I., Perveen, S., Atta-Ur-Rahman, Zia-Ullah(2003). Synthesis and biological screening of 7-hydroxy-4-methyl-2*H*-chromen-2-one, 7-hydroxy-4,5-dimethyl-2*H*-chromen-2-one and their some derivatives. *Natural Product Research*, *17*, 115-125.

Kumar, S., Saini, A., Sandhu, J. S. (2007) LiBr-Mediated, solvent free von Pechmann reaction: facile and efficient method for the synthesis of 2*H*-chromen-2-ones. *Archive for Organic Chemistry, ARKIVOC*, *XV*, 18-23.

Liu, Z.-Q., Yu, W., Liu, Z.-L. (1999). Antioxidative and prooxidative effects of coumarin derivatives on free radical initiated and photosensitized peroxidation of human low-density lipoprotein. *Chemistry and Physics of Lipids*, *103*, 125-135.

Mali, R. S., Yadav, V. J. (1977). Convenient synthesis of naturally occurring coumarins, (2-oxo-2H-benzopyrans) and 4-methylcoumarins (4-methyl-2-oxo-2*H*-benzopyrans). *Synthesis*, *7*, 464-465.

Mandhane, P. G., Joshi, R. S., Ghawalkar, A. R., Jadhav, G. R., Gill, C. H. (2009) Ammonium Metavanadate: A Mild and Efficient Catalyst for the Synthesis of Coumarins, *Bull. Korean Chem. Soc., 30*, 2969-72.

Manhas, M. S., Ganguly, S. N., Mukherjee, S., Jain, A. K., Bose, A. K. (2006). Microwave initiated reactions: Pechmann coumarin synthesis, Biginelli reaction, and acylation. *Tetrahedron Letters, 47*, 2423-2425.

Mital, R. L., Gupta, R. R., Jain, S. K. (1972). Proton magnetic resonance of 4-substituted coumarins. *Journal of Chemical Engineering Data*, *17*, 383-384.

Raj, H. G., Parmar, V. S., Jain, S. C., Goel, S., Singh, A., Gupta, K., Rohil, V., Tyagi, Y. K., Jha, H. N., Olsen, C. E., Wengel, Y. (1998). Mechanism of biochemical action of substituted 4-methylbenzopyran-2-ones. Part II: Mechanism-based inhibition of rat liver microsome-mediated aflatoxin B_1–DNA binding by the candidate antimutagen 7,8-diacetoxy-4-methylcoumarin. *Bioorganic and Medicinal Chem*istry, *10*, 1895-1904.

Russell, A., Frye, J. R. (1941). *Organic Synth*eses, *21*, 22-26.

Sethna, S. M. Shah, N. M. (1945). The chemistry of coumarins. *Chemical Reviews, 36*, 1-62.

Sojka, S. A. (1975). Carbon-13 nuclear magnetic resonance spectra of 2*H*-1-chromen-2-ones (coumarins) in chloroform and sulfuric acid. *Journal of Organic Chemistry, 40*, 1175-1178.

Vogel, A. I., Tatchell, A. R., Furnis, B. S., Hannaford, A. J., Smith, P. W. G. (1996). *Vogel's Textbook of Practical Organic Chemistry*. 5th Ed. Prentice Hall.

Woods, L. L.; Sapp, J. (1962). New one-step synthesis of substituted coumarins. *Journal of Organic Chemistry*, *27*, 3703-3705.

Summary/Sažetak

Substituirani 4-metilkumarini su sintetizirani Pechmanovom metodologijom gdje se vrši kondenzacija fenola i etilacetoacetata uz prisustvo jakih kiselina kao katalizatora. Sintetizirani derivati 4-metilkumarina su dalje podvrgnuti benzoiliranju, pri čemu su sintetizirana tri nova derivata kumarina, i to: 4-metil-2-okso-2*H*-hromen-6-il benzoat (**3a**), 4,5-dimetil-2-okso-2*H*-hromen-7-il benzoat (**3b**) i 4-metil-2-okso-2*H*-hromen-7,8-diil benzoat (**3c**). Struktura novih kumarinskih derivata je potvrđena elementarnom analizom uzoraka, te GC/MS, NMR i IR tehnikama.