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SHORT COMMUNICATION

SYNTHESIS AND ANTIOXIDANT ACTIVITY OF NOVEL 8-FORMYL-4-SUBSTITUED COUMARINS

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ABSTRACT. 4-Methyl-8-formyl- and 4-phenyl-8-formyl coumarins have been synthesized by Pechmann reaction using oxalic acid catalyst for the first time. 4-Propyl-7-hydroxy-, and 4-methyl-7-methoxy coumarins have also been accomplished by this catalyst for the first time. They have been characterizated by IR, ^{1}H-NMR, ^{13}C-NMR, mass and elemental analysis. Furthermore, the obtained coumarins were compared according to antioxidant activity by DPPH method.

KEY WORDS: Coumarin, Antioxidant activity, DPPH method

INTRODUCTION

Coumarin is a phytochemical [1] isolated from various plants especially tonka bean (*Dipteryx odorata*), vanilla grass (*Anthoxanthum odoratum*), sweet woodruff (*Galium odoratum*), mullein (*Verbascum* spp.), sweet grass (*Hierochloe odorata*), cassia cinnamon (*Cinnamomum aromaticum*) and sweet clover (*Fabaceae* spp.). Coumarin derivatives have long been recognised to possess anticoagulant [2], antibacterial [3], antifungal [4], antitumour and antioxidant activities [5]. The coumarin derivatives have different characteristic, depending on the variety and place of functional groups. Therefore, the studies on coumarin still remain in different sectors.

Coumarins have been synthesized by several methods including Pechmann [6], Perkin [7], Knoevenegal [8], Reformatsky [9] and Wittig reactions [10]. However, the Pechmann reaction is the most widely applied for the synthesis of coumarins due to simple reaction conditions and good yields.

Nowadays, antioxidants have become one of the major areas of scientific research. Antioxidants are extensively studied for their capacity to protect organisms and cells from damage that is induced by oxidative stress. Scientists in many different disciplines have become more interested in new compounds, either synthesized or obtained from natural sources that could provide active components to prevent or reduce the impact of oxidative stress on cells [11].

Herein, we synthesized two new coumarin derivatives which are 4-phenyl-8-formyl coumarin and 4-methyl-8-formyl coumarin which has three literatures about biologically activity but not about preparation, and three other coumarins (4-propyl-7-hydroxy-, 4-methyl-7-hydroxy- and 4-methyl-7-methoxy coumarin) and we compared them according to antioxidant activity by DPPH method. 4-Methyl-7-methoxy coumarin demonstrated the best antioxidant activity.

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EXPERIMENTAL

Chemicals. All applied chemicals and reagents were purchased from the Merck Chemical Company.

Syntheses of coumarin derivatives. A mixture of phenol (10 mmol), β-keto esters (10 mmol) and oxalic acid (10 mol%) was heated to 80 ^{o}C till completion of the reaction (monitored using TLC). Then, the reaction mixture was cooled to room temperature, and it was poured in ice-water mixture and stirred for 10 min. The precipitated product was collected by filtration, washed with water and dried. The product obtained was recrystallized from appropriate solvent (like ethanol) to afford corresponding pure coumarin product [12]. All synthesized coumarin derivatives were characterized using IR (Mattson-1000 FTIR spectrometer), NMR (Varian Unity INOVA 500 spectrometer), Mass (Thermo Finnigan LCQ Advantage Max LC/MS/MS Spectrometer), elemental analysis (Thermo Finnigan Flash EA 1112 Series Elemental Analyser) and melting point (Buchi B-540).

Sample preparation. Stock solutions of synthesized coumarins were prepared in ethanol in concentration 0.1 mol/L. Ascorbic acid, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) and NDGA (nordihydroguairetic acid) were used as standard controls for antioxidant testing and they were prepared in same concentration as tested coumarins.

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity. 1,1-Diphenyl-2-picrylhydrazyl radical was used for determination of free radical scavenging activity of the synthesized compounds by modified method of Brand-Williams [13]. The concentrations of the tested samples ranged from 0.10 to 0.0001 mol/L. A portion of the sample solution (200 µL) was mixed with 3.0 mL of 5.25 x 10^{-5} mol/L DPPH in absolute ethanol. After 30 min at room temperature the absorbance was recorded at 517 nm using a Jenway 6105 UV/Vis spectrophotometer. All experiments were carried out in triplicate.

The radical-scavenging activity of the tested samples, exhibited as percentage inhibition of DPPH, was calculated according to the formula IC (%) = $[(A_0\text{-}A)/A_0]$ [14]. A is the absorbance value of the tested sample and A_0 is the absorbance value of blank sample. Percent inhibition was plotted against concentration, and the equation for the line was used to obtain the IC_{50} value. A lower IC_{50} value indicates greater antioxidant activity.

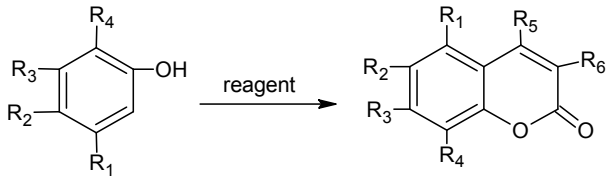
*4-Methyl-8-formyl coumarin (**7**)*. White solid; yield 45%; m.p.: 91.1-91.8 ^{o}C; IR (KBr): ν 1746, 1684, 1615, 1215; ^{1}H-NMR (500 MHz, DMSO): δ 2.4-2.5 (s, -C<u>H</u>$_3$, 3H), 7.36-7.46 (m, Ar-H, 2H), 7.69-7.75 (t, Ar-H, J = 8.7 Hz, 1H), 7.85-7.88 (d, Ar-H, J = 7.8 Hz, 1H), 8.6-8.65 (s, -C<u>H</u>O, 1H); ^{13}C-NMR (125.66 MHz, DMSO): δ 196.7 (1C, Ar-<u>C</u>HO), 159.2 (1C, coumarin C=O), 155.01, 148.07, 135.44, 131.32 (4C, Ar-C), 125.76, 124.66, 118.49, 116.64 (4C, vinyl-<u>C</u>H and Ar-<u>C</u>H), 30.42(1C, <u>C</u>H$_3$); MS (EI) m/z: 89, 101, 118, 131, 145, 160, 173, <u>188</u>; anal. calcd. for $C_{11}H_8O_3$: C, 70.20; H, 4.30; found C, 70.09; H, 4.59.

*4-Phenyl-8-formyl coumarin (**8**)*. White solid; yield 52%; m.p.: 133.8-134.7 ^{o}C, IR (KBr): ν 1715, 1661, 1615, 1246; ^{1}H-NMR (500 MHz, CDCl$_3$): δ 7.3 (t, Ar-H, 1H. J = 7.3 Hz), 7.42 (t, Ar-H, 3H, J = 7.8 Hz), 7.5-7.6 (m, Ar-H, 3H), 7.82 (d, Ar-H, 1H, J = 8.3 Hz), 7.88 (d, Ar-H, 1H, J = 8.3 Hz), 8.0 (s, -C<u>H</u>O, 1H); APT (125.66 MHz, CDCI$_3$) : δ 191.8, 145.57, 145.55, 134.04, 133.82, 129.82, 129.41, 128.83, 125.2, 117.21 (10C, -<u>C</u>HO, vinyl-<u>C</u>H and Ar-<u>C</u>H), 156.6, 155.4, 146.3, 136.5, 127.36, 118.44 (6C, coumarin C=O ve Ar-C); MS (EI) m/z: 77, <u>105</u>, 145, 173, 178, 194, 207, 221, 250; anal. calcd. for $C_{11}H_8O_3$: C,76.80; H,4.00; found C,76.76; H, 4.49.

RESULTS AND DISCUSSION

The coumarins were synthesized by well-known Pechmann condensation. Oxalic acid preferred as catalyst because of easy available and low-priced. Furthermore oxalic acid is the only possible compound containing two carboxylic acid groups joined directly, and hence it is a strong organic acid.

Considering the importance of green chemistry, the solvent free reaction conditions are the advantageous aspect of the present method, since it avoids the use of environmental hazardous and toxic solvents. Synthetic routes are outlined in Scheme 1.



1: $R_1 = R_2 = R_4 = H$; $R_3 = OH$ **4 (1,a):** $R_5 = C_3H_7$; $R_3 = OH$; $R_4 = R_2 = R_1 = R_6 = H$
2: $R_1 = R_2 = R_4 = H$; $R_3 = OCH_3$ **5 (1,b):** $R_5 = CH_3$; $R_3 = OH$; $R_4 = R_2 = R_1 = R_6 = H$
3: $R_1 = R_2 = R_3 = H$; $R_4 = CHO$ **6 (2,b):** $R_5 = CH_3$; $R_3 = OCH_3$; $R_4 = R_2 = R_1 = R_6 = H$
7 (3,b): $R_5 = CH_3$; $R_4 = CHO$; $R_3 = R_2 = R_1 = R_6 = H$
8 (3,c): $R_5 = C_6H_5$; $R_4 = CHO$; $R_3 = R_2 = R_1 = R_6 = H$

Scheme 1. Syntheses of coumarins by using oxalic acid catalyst. Reagents: **a**: ethylbutrylacetoacetate, **b**: ethylacetoacetate, **c**: ethylbenzoylacetoacetate.

Pechmann reaction was applied different phenols bearing either electron-donating or electron-drawing substituents. Reaction times, conditions and yields shown differences (Table 1). It was shown that the phenols which have electron-donating substituent easily react.

Herein, 4-methyl-8-formyl- (**7**) and 4-phenyl-8-formyl coumarin (**8**) have been synthesized by Pechmann reaction using oxalic acid catalyst for the first time. And also 4-propyl-7-hydroxy- (**4**), and 4-methyl-7-methoxy coumarin (**6**) have been accomplished by this catalyst for the first time.

Table 1. Reaction conditions and yields of synthesized coumarins.

Entry	Compound	Phenol (mmol)	β-ketoester (mmol)	Yield (%)	Time
1	**4**	10	10	55	80 min
2	**5**	10	20	50	50 min
3	**6**	10	12	45	45 min
4	**7**	10	10	45	8 h
5	**8**	10	10	52	9 h

The model of scavenging the stable DPPH radical is a widely used method to evaluate the free radical scavenging ability of various samples. DPPH is a stable nitrogen-centered free radical the color of which changes from violet to yellow upon reduction by either the process of hydrogen- or electron-donation. IC_{50} values denote the concentration of sample, which is required to scavenge 50% of DPPH free radicals [15].

Antioxidant activities of synthesized coumarins and standards are compared by DPPH method in Table 2. The coumarins which have electron-donating substituent show more antioxidant activity.

Table 2. Antioxidant activities synthesized coumarins and standards.

Entry	Compound	Antioxidant activity (IC_{50})
1	4-Propyl-7-hydroxy coumarin **(4)**	0.252 ± 0.0086
2	4-Methyl-8-formyl coumarin **(7)**	2.31 ± 0.092
3	4-Methyl-7-hydroxy coumarin **(5)**	1.29 ± 0.38 (7.45 ± 0.16) [16]*
4	4-Methyl-7-methoxy coumarin **(6)**	0.184 ± 0.0018 (14.70 ± 0.15) [16]*
5	4-Phenyl-8-formyl coumarin **(8)**	No activity
6	Ascorbic acid	0.0511 ± 0.000012
7	NDGA	0.055 ± 0.00005
8	BHA	0.052 ± 0.00005
9	BHT	0.0551 ± 0.0001

*IC_{50} x 10^3 mol/L.

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