Synthesis of fluorescent compound, 7-Hydroxy-4-methyl-2*H*-chroman-2-one via Pechmann condensation of citric acid and resorcinol

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Abstract

In an attempt to synthesize a coumarin-based chemosensor, 7-hydroxy-4-methyl-2H-chroman-2-one was unexpectedly obtained. The compound was characterized based on spectrometry UV/Vis and emission, FTIR, ^{1}H-NMR, ^{13}C-NMR and MS. The compound was acquired from Pechmann condensation of citric acid and resorcinol with a 24% chemical yield.

The product was a yellowish-brown solid which has melting point of 187.6-188.8°C, λ_{max} UV/visible, λ_{em} (λ_{ex}=300 nm) in MeCN; 318, and 380 nm respectively. The product was plausibly formed due to the partial decarboxylation of citric acid in concentrated sulfuric acid before the reaction with resorcinol. The synthetic pathway is relatively new and can potentially be employed as an alternative method for synthesis of the compound.

Keywords: Fluorescent, 7-hydroxy-4-methyl-2H-chroman-2-one, Pechmann, decarboxylation.

Introduction

The development of small molecules behaving as chemical sensors was progressively explored during the past three decades.[1-5] Coumarins, with benzopyrone skeleton,[6] have been widely applied in those fields, in addition to fluorescent dyes,[7-9] medicine,[10-12] biology[13] and photoremovable protecting groups.[14] This is attributable to their properties of high quantum yields of fluorescence, large Stokes shift, remarkable photo-stability, and less toxicity.[15] The synthetic method of benzopyran-2-one system of coumarin has been reported in various approaches including via condensation of Knovenagel,[16,17] Pechmann,[18-21] Perkin,[22,23] Wittig[24] etc.

The Pechmann reaction which involves condensation of phenol and its derivatives with β-keto esters over dehydrating agents, has found the most well-known use in the synthesis of coumarins.[19] The reaction is one-pot synthesis with sequential reaction of electrophilic aromatic substitution followed by transesterification and a final dehydration.[21] Some by-products of the reaction were observed as chromones, diarylglutamic acids and their anhydrides, and dilactones.[25]

In an attempt to synthesize a coumarin-based chemosensor described by García-Beltrán et al,[26] we report here the unexpected synthesis of 7-hydroxy-4-methyl-2H-chroman-2-one 1 resulting from Pechmann condensation of resorsinol 3 and citric acid 4 in concentrated sulfuric acid. The structure of the product 1 was characterized based on the spectroscopic method. The synthetic pathway of compound 1 from the related precursors has not been reported in our prior work and could be an alternative method for the synthesis of 1.

Material and Methods

The reagents and solvents of Proanalysis grade were employed, or they were purified using standard procedures. All glassware was oven-dried prior to use. ^{1}H and ^{13}C NMR spectra were recorded on Agilent 500 MHz and 126 MHz spectrometers respectively in acetone-d_6. The NMR signals were referenced to the residual peak of the (major) solvent. The deuterated solvents were stored over activated 3 Å molecular sieves (8–12 mesh) under dry N_2. UV absorption spectra and the molar absorption coefficients were then measured on a Shimadzu 8400 UV-vis spectrometer with matched 1.0 cm quartz cells. Emission spectra were recorded on an automated Fluorescence Agilent G9800A spectrometer in 1.0 cm quartz fluorescence cuvettes, at 25°C.

The sample concentration was adjusted to preserve the absorbance below 0.1 at λ_{max}. Each sample was measured five times, and the spectra were averaged. Infra-red spectra were obtained on Perkin Elmer FTIR with potassium bromide (KBr) pellets. Relative masses were obtained using Mass Spectroscopy MS-TQD (Tandem Quadrupole Detector) in negative ion mode. The melting points were determined on a non-calibrated Mettler Toledo digital melting point apparatus in open-end capillary tubes.

Synthesis of 7-hydroxy-4-methyl-2*H*-croman-2-one (1): The synthetic protocol is based on the procedure reported by García-Beltrán et al.[26] Citric acid monohydrate 4 (19 g, 90 mmol) was dissolved in a two neck round bottom flask with 60 mL of 98% sulfuric acid at 0 °C. The temperature of solution 4 was increased gradually up to 40 °C to diminish the effervescent for 1.5 h. The solution of 4 was then cooled at 5°C. Resorcinol 3 (10 g, 90 mmol) was dissolved in a beaker glass independently with 70 mL of 98% sulfuric acid at 0 °C, and mixed with a solution of 4 while maintaining the temperature of the reaction at 5°C.

The reaction mixture was stirred at room temperature for 48 h and then poured into 300 g of crushed ice. The precipitated

solid was filtered out, dissolved in saturated sodium bicarbonate, and then extracted with ethyl acetate.

The organic layer was dried over sodium sulfate anhydrate and filtered. The solvent was removed under reduced pressure to obtain a yellowish brown solid. Yield: 244 mg (24%). M.P. 187.8─188.8 °C. UV/Vis spectra in acetonitrile ($1.52─2.84 \times 10^{-4}$ mol dm^{-3}): λ_{max}/nm (ε/mol^{-1} dm^{-3} cm^{-1}): 318 (7538). Emission Spectra in acetonitrile (~ 6×10^{-6} mol dm^{-3}): λ_{ex}/nm; 300, λ_{em}/nm; 380, in 1N sodium hydroxide ($A_{\lambda\ max} < 0.1$): λ_{ex}/nm; 280, λ_{em}/nm; 563. IR Spectrum (KBr): *v*/cm^{-1}; 3468 (─OH), 3112 (C─H sp^2), 2921 (C─H sp^3), 1668 (C=O), 1604 (C=C alkene), 1452 (C=C aromatic), 1076 (C─O─C ester). ^{1}H-NMR (500 MHz, Acetone-d_6): δH/ppm = 9.39 (b.*s*, 1H, H-12); 7.61 (*d*, *J*=8.7 Hz, 1H, H-8); 6.86 (*dd*, *J*=8.7, 2.4 Hz, 1H, H-6); 6.74 (*d*, *J*=2.4 Hz, 1H, H-5); 6.08 (*d*, *J*=1.0 Hz, 1H, H-3); 2.41 (*d*, J=1.1 Hz, 3H, H-11). ^{13}C-NMR (125 MHz, Acetone-d_6): δC/ppm = (161.78, C-2); (160.98, C-7); (156.31, C-9); (153.80, C-4); (127.28, C-5); (113.63, C-6); (113.43, C-3); (111.80, C-10); (103.27, C-8); (18.52, C-11). MS (ES^-) *m/z*: $[M-H]^-$ calculated for $C_{10}H_8O_3$ 175.16; found 175.37.

Results and Discussion

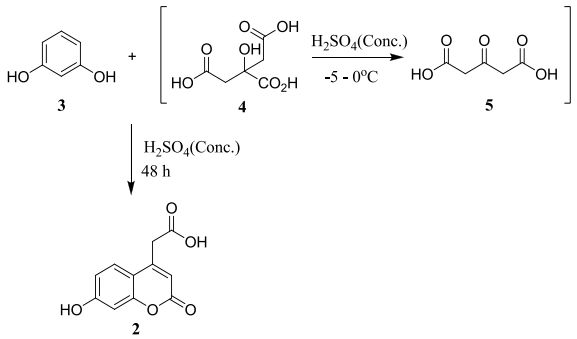
The reaction course of 3 and 4 over the condensing agent of concentrated sulfuric acid produced a 24% chemical yield of 7-hydroxy-4-methyl-2*H*-croman-2-one 1 in addition to product 2 as reported by García-Beltrán et al[26] (Scheme 1 and 2). The melting point of 1 was found to be in the range of 187.8─188.8°C which is still in the range of pure compound (0.5─1°C).[27] In fact, the measured melting point was slightly different from the reported one (185─186 °C)[28]; 194─195°C,[29] which might be due to an uncorrected apparatus. Compound 1 demonstrated strong absorption maximum (λ_{maks}) in acetonitrile at 318 nm. The maximum of 1 was in agreement with the typical spectrum of benzopyran-2-one skeleton which corresponds to conjugated diene and benzenoid system.

The compound 1 also showed emission maximum (λ_{em}) in acetonitrile at 380 nm with λ_{ex} 300 nm and shifted bathochromically to 563 nm with λ_{ex} 280 nm in 1 N sodium hydroxide (Figure 1). The increase of emission band intensity of 1 in basic condition pH > 10 was also reported by Flasik et al[30] related to the anionic form of phenolic moiety of the compound. In general, the emission band of coumarin and its derivatives should lie in the range 380─488 nm.[31]

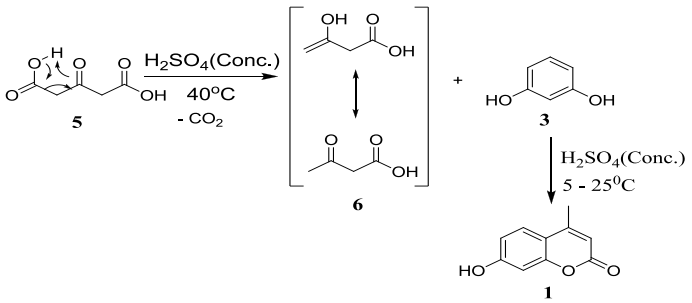
Based on IR spectrum (Table 1), a typical strong absorption of saturated lactone was indicated by a stretching vibration of C=O at 1668 cm^{-1} and C=C alkene at 1604 cm^{-1}. This finding was also confirmed by the characteristic band of C-O-C ester at 1076 cm^{-1}. On the other side, a week stretching vibration at 3112 and 1452 cm^{-1} appeared as a sign of aromatic C─H and C=C consecutively. A broad band at 3468 cm^{-1} was assigned to the stretching vibration of phenolic moiety. According to ^{1}H-NMR spectrum (Figure 2, Table 2), there were a total of six proton signals. A moiety of –OH at C-7 was detected as broad singlet at 9.39 ppm. A $–CH_3$ moiety at position C-4 was confirmed by a signal at 2.41 ppm. Three aromatic protons appeared at 6.74-7.61 ppm, while a double bond proton C-3 in the lactone ring was observed at 6.08 ppm.

The evidence of ^{1}H-NMR was emphasized by ^{13}C-NMR (Figure 3 and Table 4). A methyl carbon at position C-11 was found at 18.52 ppm. A saturated lactone ring was assigned with the signals of C=C (C-3 and C-4) at 113.43 and 153.80 ppm and a signal of C-2 (C=O) at 161.78 ppm. Aromatic CH was observed at chemical shift 103.27-127.28 ppm, while the three aromatic tersier carbons C-10, C-9, and C-7 appeared at 111.80, 156.31, and 160.98 ppm respectively. Typical spectra and number of signals are in agreement with the literature which was reported in DMSO-d_6 (Table 3 and 4). Finally, the elucidation of compound 1 was confirmed by mass spectrum. The molecular ion peak with *m/z*: $[M-H]^-$ of 175.37 was found clearly in the spectrum.

It can be supposed that the formation of compound 1 from the corresponding starting material was plausibly due to the partial decarboxylation of precursor 4. In 1925, Adams et al[32] observed the formation of acetonedicarboxylate 5 from citric acid 4 in concentrated sulfuric acid at -5 – 0 °C. In this case, a course of the reaction leads to the formation of 2 in the presence of resorcinol (Scheme 1).[26] Since the temperature of the citric acid solution increased gradually up to 40 °C, further decarboxylation of 5 should take place and eventually form acetone and carbon dioxide.[33]



Scheme 1: Pechmann condensation of 3 and 4 in concentrated sulfuric acid



Scheme 2: Plausible reaction mechanism of 1 from 3 and decarboxylated product of 5 in concentrated sulfuric acid.

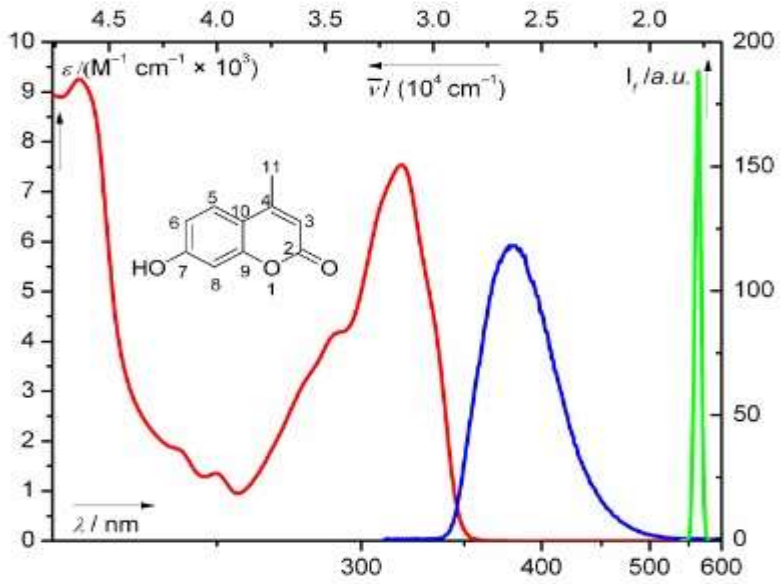


Figure 1: Absorbance spectrum; λ_{maks} 318 nm (---) in acetonitrile, emission spectrum; λ_{ex} 300 nm, λ_{em} 380 nm (---) in acetonitrile, λ_{ex} 280 nm, λ_{em} 563 nm (---) in 1 N sodium hydroxide

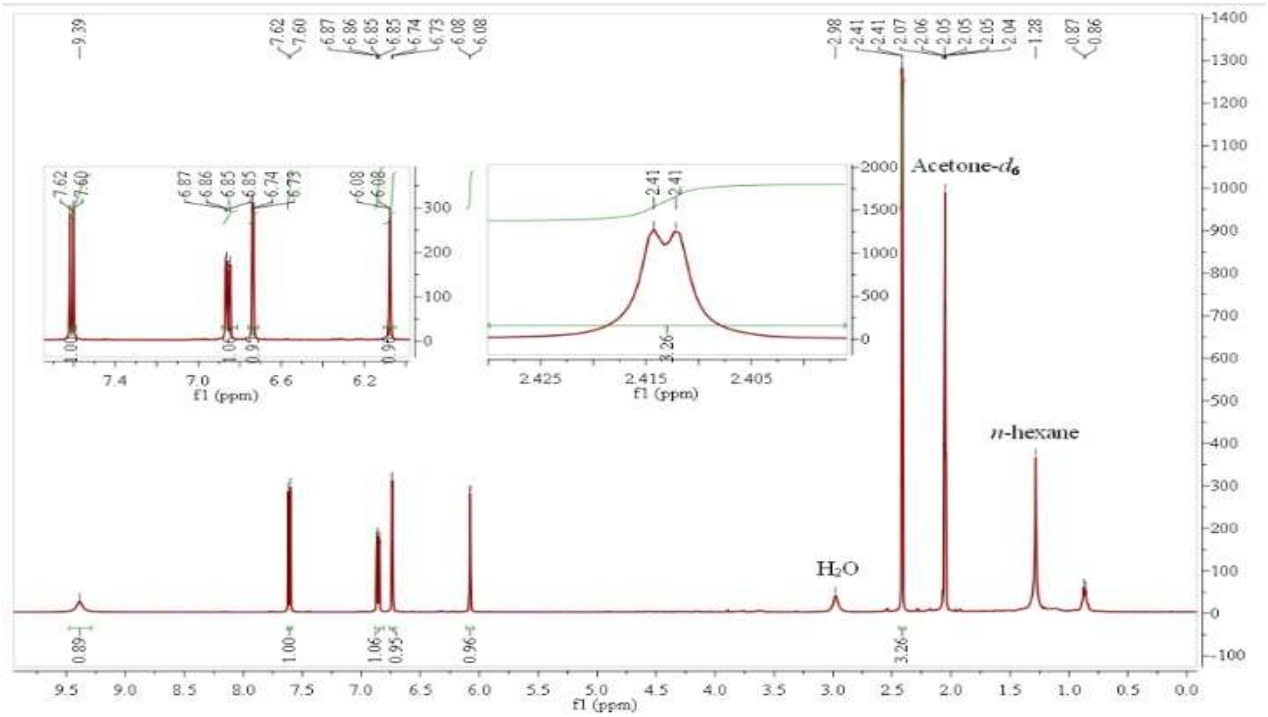


Figure 2: ^{1}H-NMR spectrum of 7-hydroxy-4-methyl-2*H*-croman-2-one 1 in acetone-d_6 (500 MHz)

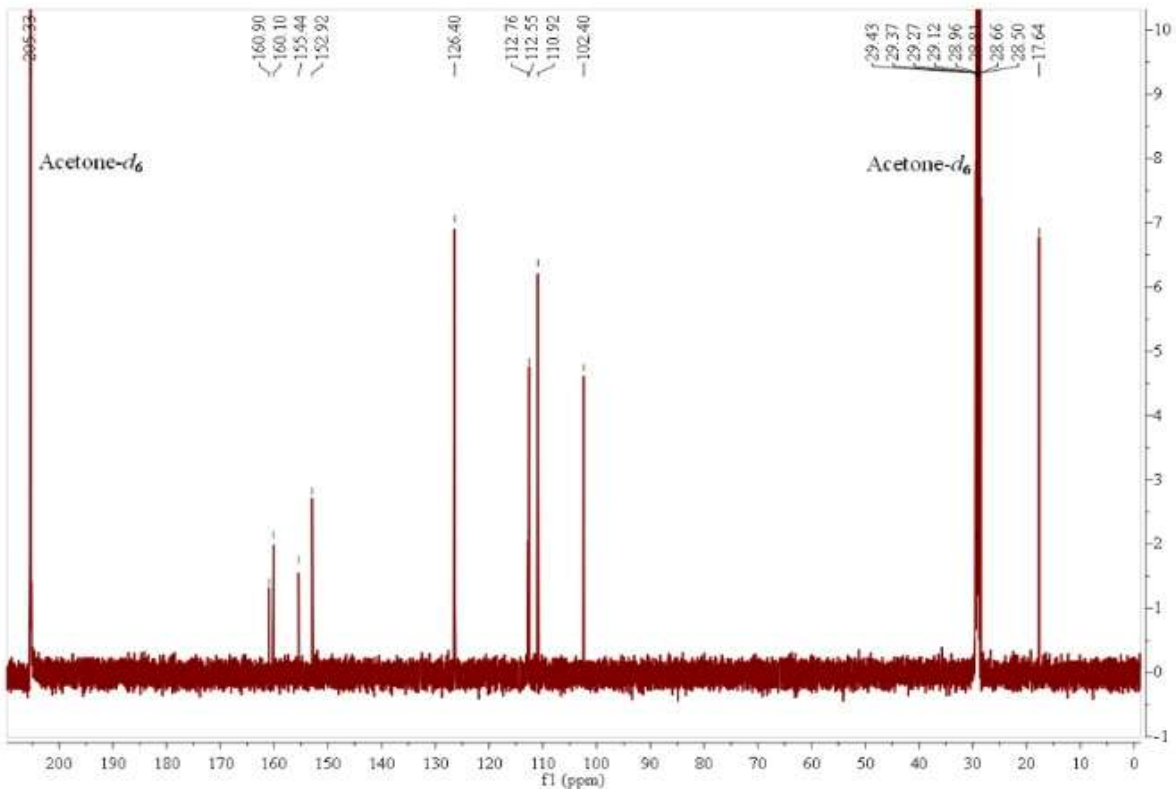


Figure 3: ^{13}C-NMR spectrum of 7-hydroxy-4-methyl-2*H*-croman-2-one 1 in acetone-d_6 (126 MHz)

Table 1
Summary of infrared absorbance spectrum of 1 in KBr pellets

S.N.	Type of Functional group	$\overline{\nu}$ (cm^{-1})	Intensity	Band
1	Stretching O─H	3468	Week	Broad
2	Stretching aromatic C─H	3112	Week	Broad
3	Stretching C─H Sp^3	2921	Strong	Sharp
4	Stretching C=O	1668	Strong	Sharp
5	Stretching alkene C=C	1604	Medium	Sharp
6	Stretching aromatic C=C	1452	Medium	Sharp
7	Stretching ester C-O-C	1076	Week	Broad

Table 2
^{1}H-NMR data of 7-hydroxy-4-methyl-2*H*-croman-2-one 1 in acetone-d_6 (126 MHz)

S.N.	δH (ppm)	Integration	No. proton	Multiplicity	Type of Proton
1	2.41	3.38	3H	Doublet (J=1.1 Hz)	H-11
2	6.08	0.96	1H	Doublet (J=1.0 Hz)	H-3
3	6.74	0.90	1H	Doublet (J= 2.4 Hz)	H-5
4	6.86	1.06	1H	Doublet doublet (J=8.7 Hz; (J=2.4 Hz))	H-6
5	7.61	1.00	1H	Doublet (J=8.7 Hz)	H-8
6	9.39	1.00	1H	Singlet	H-12

Table 3
^{1}H-NMR data of 7-hydroxy-4-methyl-2*H*-croman-2-one 1 in DMSO-d_6 (300 MHz) reported by Schroll et al.[34]

S.N.	δH (ppm)	No. proton	Multiplicity
1	2.35	3H	Doublet (*J* = 1.1 Hz)
2	6.12	1H	Doublet (*J* = 1.1 Hz)
3	6.70	1H	Doublet (*J* = 2.4 Hz)
4	6.79	1H	Doublet doublet (*J* = 8.7, 2.4 Hz)
5	7.58	1H	Doublet (*J*=8.7 Hz)
6	10.52	1H	Singlet

Table 4
^{13}C-NMR data of 7-hydroxy-4-methyl-2*H*-croman-2-one 1 versus reported data by Schroll et al.[34]

Compound 1 (Literature) (75 MHz, DMSO-d_6)	Compound 1 (Experiment) (126 MHz, Acetone- d_6)	Type of carbon
δC (ppm)	δC (ppm)	
18.0	18.52	C-11
102.1	103.27	C-8
110.1	111.80	C-10
111.9	113.43	C-3
112.7	113.63	C-6
126.5	127.28	C-5
153.4	153.80	C-4
154.7	156.31	C-9
160.2	160.98	C-7
161.0	161.78	C-2

Srivastava et al[28] and Schroll et al[34] demonstrated that compound 1 is composed of resorcinol and ethylaceto acetate in the presence of sulfuric acid. Therefore, compound 5 most probably undergoes further partial decarboxylation to form acetoacetic acid 6 prior to the reaction with 3 at a given temperature (40°C) (Scheme 2). As partial decarboxylation of 4 in the presence of sulfuric acid was temperature dependent, the formation of 1 from the related precursors might be optimized under careful reaction conditions.

Conclusion

7-hydroxy-4-methyl-2H-chroman-2-one 1 was produced unexpectedly via Pechmann condensation as a 24% chemical yield. The product was conceivably formed due to the partial decarboxylation of citric acid in concentrated sulfuric acid, prior to the reaction with resorcinol. The synthetic pathway is relatively new and potentially used as an alternative method for synthesis of the compound.

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