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A Facile and Practical *p*-Toluenesulfonic Acid Catalyzed Route to Dicoumarols Containing an Aroyl group

Saeed Khodabakhshi,[a,*] Bahador Karami,[b] Khalil Eskandari[b,*] and Alimorad Rashidi[a]

[a]*Nanotechnology Research Center, Research Institute of Petroleum Industry, Tehran, Iran.*

[b]*Department of Chemistry, Yasouj University, P.O. Box 353, Yasouj, 75918-74831, Iran.*

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ABSTRACT

New and known dicoumarols may be efficiently synthesized employing *p*-toluenesulfonic acid (*p*-TSA) as a solid acid catalyst from the reaction of 4-hydroxycoumarin with aryl glyoxal in water. This method offers direct access to structurally diverse coumarin derivatives in moderate to good yields (up to 65%). A total of five new compounds were synthesized.

KEYWORDS

Dicoumarol, *p*-toluenesulfonic acid, aryl glyoxal, 4-hydroxycoumarin.

1. Introduction

Among the analogues of vitamin K antagonists, dicoumarol, which may be considered as bridge substituted dimers of 4-hydroxycoumarin, is a naturally occurring anticoagulant.[1] This compound is used for the prevention and treatment of thrombosis. Furthermore, dicoumarol derivatives exhibit bioactivity as inhibitor of reductases.[2] The chemistry of coumarin derivatives has recently gained much attention from chemists owing to some interesting biological properties.[3–5]

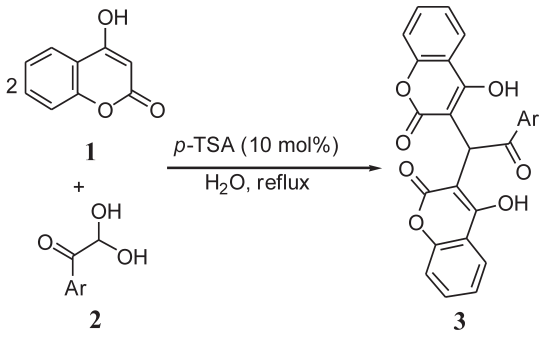
Dicoumarol was firstly discovered in moldy wet sweet-clover hay subsequent to which several methods have been reported for the development of its chemistry and synthesis of derivatives. Traditionally, the most popular strategies towards the synthesis of dicoumarols start from salicylaldehyde and formaldehyde[6] and involve the biosynthesis of dicoumarol using micro-organisms such as *Penicillium jenseni*,[7] or require the Knoevenagel condensation of 4-hydroxycoumarins with carbonyl compounds using several catalysts.[8–10]

For many years, chemical reactions in water have attracted the attention of chemists.[11] From an environmental and economic point of view, water as a solvent or media has many advantages and usually results in excellent efficiency and selectivity.[12] Accordingly, we describe an ecofriendly method for the synthesis of some new and known dicoumarols containing an aryloyl group in water as solvent.

2. Results and Discussion

Recently, we have been involved in studies involving the synthesis of new coumarin derivatives.[13] In this regard, we found that the condensation between 4-hydroxycoumarin (**1**) and aryl glyoxals **2** in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) in water under reflux produces new and known dicoumarols **3** (Scheme 1). *p*-TSA is well known as catalyst because of its advantages, such as low corrosivity, simple handling and it is inexpensive. It has been widely used as an efficient catalyst in several organic reactions.[14–16]

In order to establish the best conditions for the synthesis of **3** using *p*-TSA as catalyst, reaction between 4-hydroxycoumarin (**1**) and phenyl glyoxal was selected as a model. Results indicated that the reaction did not go to completion in the absence of catalyst even after extended reaction times. Higher loadings of catalyst did not afford a marked influence on the product yield nor reaction rate. In another experiment, in order to illustrate the effect of solvent or media on the reaction progress, several different solvents were employed, the results of which are illustrated in Table 1.



Scheme 1
Synthesis of dicoumarols catalyzed by *p*-TSA.

It may be concluded that protonic solvents such as EtOH, MeOH, and H_20 can accelerate the condensation reaction. Finally, it was found that this reaction is enhanced using *p*-TSA (10 mol%) as catalyst under reflux in H_2O in 70 min.

After determining the optimal reaction conditions, attention was focused on the extension of the scope of the method. For this, various aryl glyoxals **2** and 4-hydroxycoumarin (**1**) were reacted. Results are given in Table 2 in which it is apparent that aryl glyoxals, including those bearing electron-poor and electron-rich substituents, were able to undergo this reaction. Compared with a previously reported method which has used AcOH as reaction media,[9] the present method provides environmentally safe conditions using water as solvent and *p*-TSA as catalyst to obtain the desired products with better yields than previous reported. Recently, organic synthesis on water has also been reviewed by Fokin and co-workers.[17] Based on their study, it would appear that this reaction type may be placed in the category of 'on-water' synthetic reactions.

Based on the common mechanistic pathway of the Knoevenagel

* To whom correspondence should be addressed. E-mail: saeidkhm@yahoo.com / khalileskandari@yahoo.com

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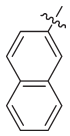
Table 1 Effect of catalyst amount and various solvents on the synthesis of **3a** at reflux temperature.

Entry	Catalyst amount/mol%	Solvent	Time/min	Yield/% *
1	10	MeOH (50 mL)	50	78
2	10	EtOH (50 mL)	45	80
3	10	THF (50 mL)	50	75
4	10	CH_2Cl_2 (50 mL)	120	50
5	10	EtOH/H_2O (1/1) (50 mL)	60	82
6	10	H_2O (50 mL)	70	80
7	–	H_2O (50 mL)	180	30
8	5	H_2O (50 mL)	180	75
9	20	H_2O (50 mL)	50	77

* Values provided are the average of three experiments.

Table 2 Synthesis of dicoumarols using *p*-TSA (10 mol%) under reflux in H_2O

Entry	Ar	Time (min)	Yield/% [a] [Lit.]	Mp/°C [Lit.]
3a	C_6H_5	70	82 (74) [9]	197–199 (200–202) [9]
3b	4-F-C_6H_4	65	78	273–235
3c	4-Br-C_6H_4	70	81 (79) [9]	240–242 (236–238) [9]
3d	4-NO_2-C_6H_4	60	80 (76) [9]	243–245 (240–242) [9]
3e	4-MeO-C_6H_4	55	78	265–267
3f	3-MeO-C_6H_4	75	70	205–207
3g	4-Cl-C_6H_4	70	75	250–252
3h		60	84	255–257

[a] Isolated yields.

and Michael reaction,[18,19] we propose a reasonable mechanism involving the protonic acid-catalyzed reaction of aryl glyoxal **2** with 4-hydroxycoumarin (**1**), as depicted in Scheme 2. Firstly, Knoevenagel condensation between 4-hydroxycoumarin (oxonium ions not depicted in mechanism) and the aryl glyoxal generates the non-isolable α,β-unsaturated carbonyl compound **4**. Attack of the next 4-hydroxycoumarin molecule (**1**) through a Michael-type addition to **4** and subsequent, the enolization of adduct **5**, gives the final product **3**.

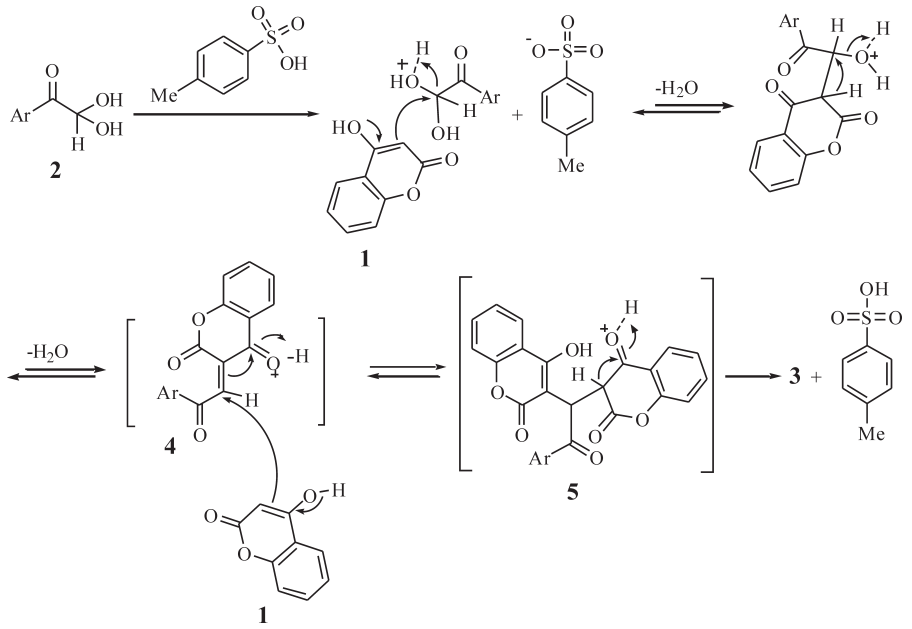
3. Experimental

3.1. General

All chemicals were purchased from Merck and Aldrich. Aryl gloxals were synthesized in accord with our previous method.[20] The reactions were monitored by thin layer chromatography (TLC; silica-gel 60 F_{254}, n-hexane: ethyl acetate). IR spectra were recorded on a FT-IR JASCO-680 and the ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance Ultra Shield spectrometer respectively at 400, 300, 100, and 75 MHz. The Vario EL-III CHNS elemental analyzer from Isfahan Industrial University was used for elemental analysis. The structures and purity of the products were deduced from their IR, elemental analysis, and NMR spectral data.

3.2. Preparation of Dicoumarols 3

A mixture of 4-hydroxycoumarin **1** (20 mmol, 3.2 g), aryl glyoxals **2** (10 mmol) and *p*-TSA (10 mol%) in H_2O (50 mL) was



Scheme 2
Plausible mechanism for *p*-TSA-catalyzed condensation of 4-hydroxycoumarin with aryl glyoxal (H^+ transfers not depicted).

refluxed for an appropriate time mentioned in Table 2. The progress of the reaction was monitored by TLC (EtOAc/hexane, 1:1). After completion, the mixture was poured on ice and the precipitate was filtered and purified by recrystallization from EtOH/THF (2:1). In some cases, column chromatography is needed (EtOAc/hexane, 1:1).

Benzoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3a**): Recrystallized from EtOH/THF (TLC n-hexane:ethyl acetate, 1:1, Rf = 0.12); M.p. 197–199 °C (Lit.[9] 200–202 °C); IR (KBr) ν = 3400–2900, 3073, 1698, 1659, 1618, 1566, 1271, 1100 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.95 (s, 2H), 7.92 (dd, 2H, J_1 = 7.8, J_2 = 2.8 Hz), 7.63–7.58 (m, 2H), 7.43 (d, 2H, J = 7.2 Hz), 7.39–7.31 (m, 7H), 6.31 (s, 1H).

4-Flourobenzoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3b**): Recrystallized from EtOH/THF (TLC n-hexane:ethyl acetate, 1:1, Rf = 0.15);M.p. 235–237 °C; IR (KBr) ν = 3500–3300, 3066, 2887, 1695, 1650, 1619, 1600, 1567, 1271, 1225, 1107 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.15 (s, 2H), 7.89 (dd, 2H, J_1 = 8.2, J_2 = 1.6 Hz), 7.79–7.75 (m, 2H), 7.56–7.50 (m, 2H), 7.33–7.24 (m, 4H), 6.94 (t, 2H, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 192.9, 165.4, 152.4, 133.2, 132.0, 130.7, 130.6, 125.0, 124.5, 116.7, 116.3, 115.9, 115.6, 42.8. Anal. Calcd. for $C_{26}H_{15}FO_7$: C, 68.12; H, 3.30. Found: C, 68.30; H, 3.22.

4-Bromobenzoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3c**): Recrystallized from EtOH/THF (TLC n-hexane:ethyl acetate, 1:1, Rf = 0.11); M.p. 240–242 °C (Lit.[9] 236–238 °C); IR (KBr) ν = 3400–2900, 1711, 1651, 1614, 1564, 1497, 1267, 1099 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.56 (s, 2H), 7.89 (d, 2H, J = 7.6 Hz), 7.59 (t, 2H, J = 7.6 Hz), 7.40–7.29 (m, 6 H), 7.11 (d, 2H), 6.28 (s, 1H).

4-Nitrobenzoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3d**): Recrystallized from EtOH/THF (TLC n-hexane:ethyl acetate, 1:1, Rf = 0.12); M.p. 243–245 °C (Lit.[9] 240–242 °C); IR (KBr) ν = 3400–2900, 2883, 1715, 1650, 1614, 1565, 1518, 1341, 1266, 1102 cm^{-1}; 10.95 (s, 2H), 7.92 (dd, 2H, J_1 = 7.8 Hz, J_2 = 2.8 Hz), 7.63–7.58 (m, 2H), 7.43 (d, 2H, J = 7.2 Hz), 7.39–7.31 (m, 7H), 6.31 (s, 1H).

4-Methoxybenzoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3e**): Purified by column chromatography (EtOAc/hexane, 1:1) (TLC n-hexane:ethyl acetate, 1:1, Rf = 0.16); M.p. 265–267 °C; IR (KBr) ν = 3500 3300, 3076, 2978, 1684, 1650, 1620, 1601, 1571, 1263 $\chi\mu^{-1}$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.22 (s, 2H), 8.00 (dd, 2H, J_1 = 8.2, J_2 = 1.6 Hz), 7.77–7.72 (m, 2H), 7.55–7.49 (m, 2H), 7.32–7.24 (m, 4H), 6.77–6.72 (m, 2H), 6.00 (s, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.1, 165.2, 163.5, 152.4, 133.0, 130.4, 128.3, 124.9, 124.5, 116.6, 116.4, 113.8, 55.4, 42.6. Anal. Calcd. for $C_{27}H_{18}O_8$: C, 68.94; H, 3.86. Found: C, 69.10; H, 3.69.

3-Methoxybenzoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3f**): Purified by column chromatography (EtOAc/hexane, 1:1) (TLC-n-hexane:ethyl acetate, 1:1, Rf = 0.15); M.p. 205–207 °C; IR (KBr) ν = 3500–3300, 1693, 1655, 1619, 1602, 1567, 1273, 1427 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.16 (s, 1H), 8.00 (dd, 2H, J_1 = 8.2, J_2 = 1.6 Hz), 7.55–7.49 (m, 2H), 7.34–7.24 (m, 6H), 7.12 (t, 1H, J = 8.2 Hz), 6.94–6.90 (m, 1H), 6.00 (s, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.2, 165.2, 159.7, 152.4, 136.9, 133.1, 129.4, 125.0, 124.5, 120.2, 120.1, 116.7, 116.4, 112.4, 42.9. Anal. Calcd. for $C_{27}H_{18}O_8$: C, 68.94; H, 3.86. Found: C, 69.06; H, 3.65.

4-Chlorobenzoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3g**): Purified by column chromatography (EtOAc/hexane, 1:1) (TLC n-hexane:ethyl acetate, 1:1, Rf = 0.18); M.p. 250–252 °C; IR (KBr) ν = 3500–3300, 3080, 2884, 1713, 1665, 1650, 1614, 1564, 1266, 1090, 767 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.10 (s, 2H), 7.85 (d, 2H, J = 6.0 Hz), 7.72 (d, 2H, J = 5.2 Hz), 7.62–7.52 (m, 4H), 7.31–7.25 (m, 4H), 6.28 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 196.1, 165.9, 163.3, 152.2, 135.9, 131.6, 131.2, 129.3, 125.9, 123.8, 123.4, 118.0, 115.8, 101.6, 42.9. Anal. Calcd. for $C_{26}H_{15}ClO_7$: C, 65.76; H, 3.18. Found: C, 65.91; H, 3.03.

2-Naphthoyl[bis(4-hydroxycoumarin-3-yl)]methane (**3h**): Recrystallized from EtOH/THF (TLC n-hexane:ethyl acetate, 1:1, Rf = 0.11); M.p. 255–257 °C; IR (KBr) ν = 3550–3300, 1694, 1653, 1617, 1565, 1454, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.24 (s, 2H), 8.27 (s, 1H), 8.01 (dd, 2H, J_1 = 8.2, J_2 = 1.6 Hz), 7.83–7.72 (m, 4H), 7.54–7.43 (m, 4H), 7.33–7.23 (m, 4H), 6.19 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 177.3, 166.6, 163.6, 152.3, 134.4, 134.3, 131.8, 131.5, 129.1, 127.9, 127.5, 126.7, 124.1, 123.9, 123.3, 118.5, 115.7, 101.6, 43.1. Anal. Calcd. for $C_{30}H_{18}O_7$: C, 73.47; H, 3.70. Found: C, 73.68; H, 3.75.

4. Conclusion

An improved route for the synthesis of dicoumarols containing an aryloyl group from simple substrates and *p*-TSA catalyst has been achieved with a very high atom economy for the preparation of pharmaceutically relevant heterocyclic systems. Importantly, use of water as a cheap and clean media for reaction should place this chemistry in the category of Green Chemistry. A total of five new compounds were obtained.

Supplementary material

The ^{1}H and ^{13}C spectra of all the novel compounds are given in the online supplement.

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