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P_2O_5/SiO_2 as a New, Efficient and Reusable Catalyst for Preparation of 4,4′-Epoxydicoumarins Under Solvent-free Conditions

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Abstract: An efficient solvent-free procedure for the preparation of 4,4′-epoxydicoumarins via the ondensation of 4-hydroxycoumarin with aldehydes in the presence of catalytic amount of phosphorus pentoxide/silica gel at 110 °C is described. The advantages of this method are generality, high yields, short reaction times, ease of product isolation, low cost and ecologically friendly.

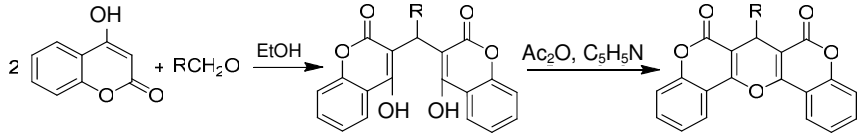
Keywords: 4,4′-Epoxydicoumarins, 4-Hydroxycoumarin, P_2O_5/SiO_2, Solvent-free

Introduction

The development of simple, efficient and general synthetic methods forwidely used organic compounds fromreadily available reagents is one of the major challenges in organic synthesis. Recently, a variety of reports regarding synthetic studies on 4,4′-epoxydicoumarin derivatives has been presented, as these compounds were documented to exhibit a wide range of biological activities[1-3]. The compounds can be synthesized by a two-step process (Scheme 1). However, the method has not been entirely satisfactory, with disadvantages such as low yields, long reaction times, harsh reaction conditions and toxic reagents or media. Therefore, to avoid these limitations, the discovery of a new and efficient process for the synthesis of epoxydicoumarins is of prime interest.

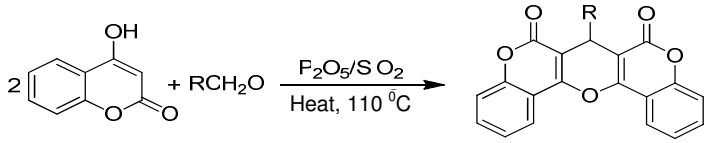
Phosphorus pentoxide/silica gel (P_2O_5/SiO_2) is inexpensive, green, commercially available and heterogeneous catalytic system which has been used in several organic transformations, such as synthesis of *N*-sulfonyl imines[4], condensation of indoles with carbonyl compounds[5], esterification[6], oxidation of sulfides to sulfoxides[7], schmidt reaction[8], Fries rearrangement[9], direct sulfonylation of aromatic rings[10], oxime preparation[11], conversion of aldehydes to acylals[12], selective deprotection of 1,1-diacetals[13] and acetalization of carbonyl compounds[14].

Solvent-free organic reactions have been applied as useful protocol in organic synthesis. Solvent-free conditions often lead to shorter reaction times, increased yields, easier workup, matches with green chemistry protocols and may enhance the regio- and stereoselectivity of reactions[15].



Scheme 1

Considering the above facts and also in extension of our previous studies on green organic synthesis[16], herein we report an efficient, green and simple method for the synthesis of 4,4′-epoxydicoumarins by the condensation of 4-hydroxycoumarin with aldehydes in the presence of catalytic amount of P_2O_5/SiO_2 at 110 ºC under solvent-free conditions (Scheme 2).



Scheme 2

Experimental

NMR spectra were determined on Bruker AV-400 spectrometer at room temperature using TMS as internal standard, coupling constants (*J*) were measured in Hz; Elemental analysis were performed by a Vario-III elemental analyzer; Melting points were determined on a XT-4 binocular microscope and were uncorrected; COmmercially available reagents were used throughout without further purification unless otherwise stated.

Preparation of P_2O_5/SiO_2 catalytic system

A mixture of SiO_2 (2 g) and P_2O_5 (1 mmol, 0.142 g) was ground vigorously to give P_2O_5/SiO_2 catalytic system as a white powder (2.142 g).

*General procedure for synthesis of **3***

To a mixture of compounds consisting of aldehyde (1 mmol)and 4-hydroxycoumarin (2 mmol) in a 10 mL round-bottomed flask connected to a reflux condenser was added P_2O_5/SiO_2 (1.07 g) and the resulting mixture was stirred in an oil-bath (110 °C) for the times reported in Table 3. Afterward, the reaction mixture was cooled to room temperature and was suspended in warm $CHCl_3$ (50 mL), filtered and the filtrate was washed with saturated solution of Na_2CO_3 (2×50 mL) and water (2×50 mL) and dried with $MgSO_4$. The solvent was evaporated and the crude product was purified by recrystallization from ethyl alcohol. Due to very low solubility of the products **3a, 3h**, we cannot report the ^{13}C NMR data for these products.

3,3′-Benzylidene-4,4′-epoxydicoumarin **(3a)**

White powder, m.p. 386-388 ^oC; IR (cm^{-1}): 1730, 1718, 1666, 1609, 1456, 1365, 1336, 1178, 1062, 1042, 888, 766, 713; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.11 (d, 2H, J = 8.0 Hz), 7.69-7.64 (m, 2H), 7.50-7.40 (m, 8H), 7.24-7.20 (m, 1H), 5.19 (s, 1H); Anal. calcd for $C_{25}H_{14}O_5$: C 76.14, H 3.58; found: C 76.20, H 3.52.

3,3′-(4-Chlorobenzylidene)-4,4′-epoxydicoumarin **(3b)**

White powder, m.p. 364-365 °C; IR (cm^{-1}): 1730, 1667, 1611, 1488, 1456, 1368, 1216, 1180, 1058, 1015, 889, 763; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.12 (d, 2H, J = 7.6 Hz), 8.02-7.98 (m, 2H), 7.90-7.87 (m, 2H), 7.69 (t, 2H, J = 7.2 Hz), 7.52-7.34 (m, 4H), 5.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.0, 153.6, 152.8, 139.5, 132.9, 130.3, 128.7, 124.7, 122.3, 117.2, 113.3, 105.9, 34.4; Anal. calcd for $C_{25}H_{13}ClO_5$: C 70.02, H 3.06; found: C 70.13, H 3.00.

3,3′-(4-Methoxybenzylidene)-4,4′-epoxydicoumarin **(3c)**

White powder, m.p. 293-295 °C; IR (cm^{-1}): 1732, 1668, 1610, 1520, 1482, 1366, 1253, 1178, 1045, 889, 768; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.11 (d, 2H, J = 8.0 Hz),7.68-7.62 (m, 2H), 7.49-7.37 (m, 6H), 6.88-6.81 (m, 2H), 5.13 (s, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.1, 159.0, 153.3, 152.7, 133.2, 132.7, 130.0, 124.5, 124.3, 122.3, 117.1, 113.9, 113.5, 106.5, 55.2, 34.1; Anal. calcd for $C_{26}H_{16}O_6$: C 73.58, H 3.80; found: C 73.62, H 3.75.

3,3′-(4-Methybenzylidene)-4,4′-epoxydicoumarin **(3d)**

White powder, m.p. 293-295 °C; IR (cm^{-1}): 1740, 1667, 1609, 1469, 1365, 1284, 1177, 1063, 887, 767; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.11 (d, 2H, J = 8.0 Hz),7.68-7.64 (m, 2H), 7.49-7.34 (m, 6H), 7.10 (d, 2H, J = 8.0 Hz), 5.15 (s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.1, 153.4, 152.7, 138.1, 137.4, 132.7, 129.2, 128.7, 124.5, 122.3, 117.1, 113.5, 106.5, 34.5, 21.1; Anal. calcd for $C_{26}H_{16}O_5$: C 76.46, H 3.95; found: C 76.53, H 4.02..

3,3′-(4-Nitrobenzylidene)-4,4′-epoxydicoumarin **(3e)**

White powder, m.p. 356-358 °C; IR (cm^{-1}): 1726, 1668, 1610, 1511, 1456, 1368, 1348, 1180, 1069, 889, 763; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.18-8.13 (m, 4H), 7.73-7.65 (m, 4H), 7.51 (t, 2H, J = 7.6 Hz), 7.44 (t, 2H, J = 8.4 Hz), 5.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.9, 154.0, 152.8, 148.0, 147.3, 133.3, 130.0, 124.9, 123.7, 122.5, 117.3, 113.0, 105.0, 35.1; Anal. calcd for $C_{25}H_{13}NO_7$: C 68.34, H 2.98, N 3.19; found: C 68.29, H 3.00, N 3.14.

3,3′-(3-Nitrobenzylidene)-4,4′-epoxydicoumarin **(3f)**

White powder, m.p. 348-349 °C; IR (cm^{-1}): 1723, 1668, 1610, 1530, 1456, 1366, 1306, 1243, 1180, 1063, 888, 758, 717; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.16-8.11 (m, 4H), 8.03 (d, 1H, J = 7.6 Hz), 7.71 (t, 2H, J = 7.6 Hz), 7.55-7.50 (m, 3H), 7.44 (d, 2H, J = 8.4 Hz), 5.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.0, 154.1, 152.9, 148.5, 143.1, 136.3, 133.3, 129.3, 124.9, 123.1, 122.9, 122.6, 117.3, 113.1, 105.0, 35.0; Anal. calcd for $C_{25}H_{13}NO_7$: C 68.34, H 2.98, N 3.19; found: C 68.25, H 3.04, N 3.11.

3,3′-(4-Florobenzylidene)-4,4′-epoxydicoumarin **(3g)**

White powder, m.p. 352-354 °C; IR (cm^{-1}): 1725, 1667, 1609, 1532, 1457, 1367, 1221, 1179, 1061, 888, 761, 560; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.12-8.10 (m, 2H), 7.70-7.65 (m, 2H), 7.50-7.41 (m, 6H), 6.98 (t, 2H, J = 8.8 Hz), 5.16 (s, 1H); Anal. calcd for $C_{25}H_{13}FO_5$: C 72.82, H 3.18; found: C 72.78, H 3.20.

Results and Discussion

In order to get the best experimental reaction condition, the reaction of 4-hydroxycoumarin **1** and benzaldehyde **2a** (in 2:1 molar ratio) in the presence of 50 mol% of P_2O_5/SiO_2 under solvent-free conditions has been considered as a standard model reaction. We have investigated the model reaction at ambient temperature, and we did not get the product.

(Table 1, Entry 1). In the next step, we carried out the reaction at 80 ºC, 90 ºC, 100 ºC, 110 ºC, 120 ºC and 130 ºC, the best result was obtained at 110 ºC and the product was obtained within 1.5 min in 86% yield (Table 1, Entry 5).

Table 1. Temperature optimization for the synthesis of 3,3′-benzylidene-4,4′-epoxydicoumarin[a]

Entry	Temperature / °C	Time/ h	Yield/ %[b]
1	25	4	0
2	80	2.5	35
3	90	2.5	52
4	100	2	76
5	110	1.5	86
6	120	1.5	86
7	130	1.5	85

[a] *Reaction conditions: 4-hydroxycoumarin (2 mmol); benzaldehyde (1 mmol); P_2O_5/SiO_2 (0.5 mmol); neat.* [b]*Isolated yield*

To determine the appropriate concentration of the catalyst P_2O_5/SiO_2, we investigated the model reaction at different concentrations of catalyst like 0, 10, 20, 30, 40, 50, 60, 70 and 80 mol% under solvent-free conditions. The product formed in 0, 59, 64, 69, 79, 86, 86, 85 and 84% yield respectively. This indicates that 50 mol% of P_2O_5/SiO_2 is sufficient for the best result (Table 2, Entry 6). The model reaction was also tested in the presence of only P_2O_5 or only SiO_2 at 110 °C under solvent-free conditions; however, these reagents were not efficient separately. P_2O_5 afforded the product in 56% yield after 3 h and SiO_2 gave the product in 34 % after 6 h (Table 2, entries 10 and 11). Thus, it is necessary to support P_2O_5 on SiO_2.

Table 2. The amounts of catalyst optimization for the synthesis of 3,3′-benzylidene- 4,4′-epoxydicoumarin[a]

Entry	Catalyst	Time/ min	Yield/ %[b]
1	0	6	<10
2	P_2O_5/SiO_2, 0.1 mmol	3	68
3	P_2O_5/SiO_2, 0.2 mmol	2	80
4	P_2O_5/SiO_2, 0.3 mmol	2	0
5	P_2O_5/SiO_2, 0.4 mmol	1.5	46
6	P_2O_5/SiO_2, 0.5 mmol	1.5	57
7	P_2O_5/SiO_2, 0.6 mmol	1.5	78
8	P_2O_5/SiO_2, 0.7 mmol	1.5	96
9	P_2O_5/SiO_2, 0.8 mmol	1.5	95
10	P_2O_5, 0.5 mmol	3	56
11	SiO_2, 1 g	6	34

[a]*Reaction conditions: 4-hydroxycoumarin (2 mmol); benzaldehyde (1 mmol); 110 °C ; neat.* [b]*Isolated yield*

After optimization of the reaction conditions, the reaction was examined with structurally diverse aldehydes and 4-hydroxycoumarin. The results are summarized in Table 3. As it is clear from Table 3, all reaction proceeded efficiently and the desired epoxydicoumarins were produced in high to excellent yields. Various substituted aryl aldehydes were used for the synthesis of epoxydicoumarin having different substituents such as -Cl, -F, $-NO_2$, -Me, -OMe. It was found that; electron donating substituent requires longer time whereas electron withdrawing substituent requires shorter time for the completion of reaction.

Table 3. Preparation of 4,4′-epoxydicoumarins catalyzed by P_2O_5/SiO_2[a]

Entry	R	Time/ h	Product	Yield/ %[b]	m.p. / °C
1	C_6H_5	1.5	**3a**	86 (84, 80, 76)[c]	387-388
2	4-Cl-C_6H_4	1	**3b**	88	364-366
3	4-MeO-C_6H_4	2.5	**3c**	84	293-295
4	4-Me-C_6H_4	2	**3d**	82	316-317
5	4-NO_2-C_6H_4	1	**3e**	89	356-357
6	3-NO_2-C_6H_4	1.5	**3f**	87	348-349
7	4-F-C_6H_4	1	**3g**	91	350-352

[a]Reaction conditions: 4-hydroxycoumarin (2 mmol); aldehyde (1 mmol); P_2O_5/SiO_2 (0.5 mol); 110 °C; neat. [b]Isolated yield. [c]Yields after three times of catalyst recovery

P_2O_5/SiO_2 is immiscible with non-polar organic compounds or solvents. Thus, the recovery of catalyst is convenient when a non-polar solvent is used as a medium. In this protocol, P_2O_5/SiO_2 is a heterogeneous acid catalyst. Because it is insoluble in the reaction medium, (CH_2Cl_2). The catalyst was recovered after reaction by simple filtration. To rule out the possibility of catalyst leaching, the activity of the recovered catalyst in each reaction was investigated carefully. The experimental results revealed that P_2O_5/SiO_2 could be recovered in more than 85% of the cases. In the synthesis of 3,3′-benzylidene-4,4′-epoxydicoumarin, the catalyst could be reused for three times without significant loss of activity (Table 3, entry 1).

In order to show the merit of P_2O_5/SiO_2 in comparison with other catalysts used for the similar reaction, we have tabulated some of the results in Table 4. As it is evidence from the results, P_2O_5/SiO_2 found to be effective catalyst for the synthesis of 4,4′-epoxydicoumarins.

Table 4. Effect of catalysts on the reaction of benzaldehyde and 4-hydroxycoumarin[a]

Entry	Catalyst	Time/ h	Yield/ %[b]
1	*p*-TsOH	2	72
2	H_2SO4	4	25
3	H_3PO_4	5	18
4	PPA_3	7	29
5	I_2	2	73
6	$ZnCl_2$	5	56
7	P_2O_5/SiO_2	1.5	86

[a] Reaction conditions: 4-hydroxycoumarin (2 mmol); benzaldehyde (1 mmol); Catalyst (0.5 mmol); 110 °C; neat. [b]Isolated yield

Conclusion

In conclusion, P_2O_5/SiO_2 is an easily available, inexpensive, efficient and safe catalyst for the synthesis of epoxydicoumarins from various aryl aldehydes in the presence of catalytic amount of P_2O_5/SiO_2 at 110 ºC under solvent-free conditions. The remarkable advantages offered by this method are simple experimental procedure, solvent-free reaction conditions, short reaction times, high yields and easiness of product isolations.

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