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Cyanuric Chloride-Catalyzed One-Pot Synthesis of 4,4'-Epoxydicoumarins

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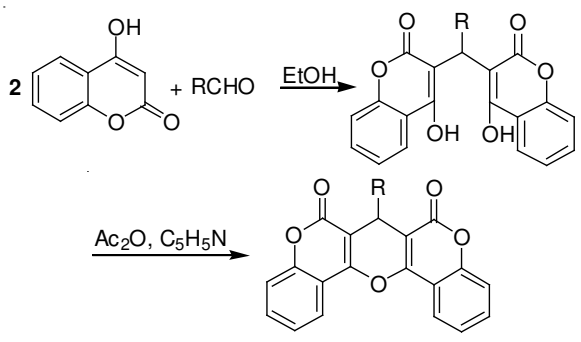
A simple, green and efficient solvent free procedure for the synthesis of 4,4'-epoxydicoumarins from 4-hydroxycoumarin and aldehydes in the presence of catalytic amount of cyanuric chloride at 120 ºC is described. Using this method, 4,4'-epoxydicoumarins were produced in high yields.

Key Words: 4,4'-Epoxydicoumarins, 4-Hydroxycoumarin, Cyanuric chloride, Solvent-free.

INTRODUCTION

4,4'-Epoxydicoumarins are important heterocycles that are known to possess multiple biological activities such as antiplatelet[1], anticoagulant[2], antimicrobial and antioxidant activities[3]. The compounds can be synthesized by a two-step process (**Scheme-I**)[1-3]. However, the method has significant drawbacks such as long reaction times, low yields, harsh reaction conditions, difficult work-up and use of environmentally toxic reagents or media. Thus, there is still need of a simple and general procedure for synthesis of 4,4'-epoxydicoumarins.



Scheme-I

Cyanuric chloride (TCT, Fig. 1) is an inexpensive, easily available reagent of low toxicity and less corrosive than other similar reactants, has been widely used in organic reactions[4]. There is an increasing interest in the use of environmentally benign reagents, conditions and particularly to solvent-free procedures. Avoiding organic solvents during the reactions in organic synthesis leads to a clean, efficient and economical technology[5]. Solvent-free condensation of 4-hydroxycoumarin with carbonyl compounds is scarce in the literature.

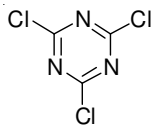
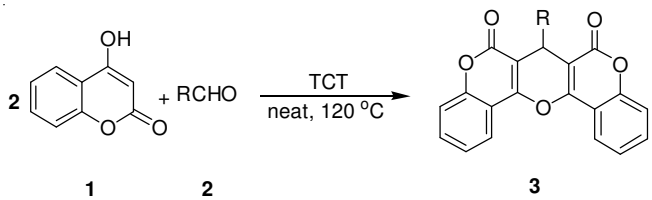


Fig. 1 Structure of cyanuric chloride

Considering the above facts and also an extension of our previous studies on solvent-free organic reactions[6], we report a new and simple cyanuric chloride-promoted synthesis of 4,4'-epoxydicoumarins by reaction of 4-hydroxycoumarin with aromatic aldehydes under solvent-free conditions (**Scheme-II**).



Scheme-II

EXPERIMENTAL

IR spectra were determined on FTS-40 infrared spectrometer; 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.

General procedure for the preparation of 4,4'-epoxydicoumarins: A mixture of 4-hydroxycoumarin (2 mmol), aldehyde (1 mmol), cyanuric chloride (0.05 mmol) and H_2O (2 drops) were mixed and stirred for 5 min at room temperature and then temperature was raised to 120 ºC and maintained for the appropriate time (Table-2). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (20 mL) and stirred for 5 min at 80 ºC. The resulting solid products were collected by filtration and were recrystallized from ethanol. 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 ºC; 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 $C_{25}H_{13}O_5Cl$: 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 ºC; 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 ºC; 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 ºC; 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 ºC; 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 ºC; 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

To optimize reaction conditions, the reaction of benzaldehyde (1 mmol) and 4-hydroxycoumarin (2 mmol) was selected as a model reaction to provide the desired 3,3'-benzylidene-4,4'-epoxydicoumarin. At first, the reaction was examined using various amounts of cyanuric chloride at different temperatures. The results are displayed in Table-1. As Table-1 indicates, higher yield and shorter reaction time were obtained when the reaction was carried out in the presence of 0.05 mmol catalyst at 120 ºC. When reactions were carried out in the absence of catalyst for long period of time (6-8 h), the yield of product was low (< 30 %). Thus, we applied these optimal conditions for all other reactions.

TABLE-1
SYNTHESIS OF 3,3'-BENZYLIDENE-4,4'-EPOXYDICOUMARIN UNDER VARIOUS CONDITIONS

Entry	Cyanuric chloride (mol %)	Temp. (ºC)	Time (h)	Yield (%)[a]
1	0	120	6	<10
2	1	120	4	49
3	2	120	4	57
4	3	120	3	65
5	4	120	2	76
6	4	130	2	78
7	5	50	6	<10
8	5	80	4	32
9	5	90	3	38
10	5	100	2	67
11	5	110	2	78
12	5	120	2	85
13	5	130	2	85
14	5	140	1.5	83
15	6	110	2	79
16	6	120	2	85
17	7	120	2	84
18	8	120	1.5	85

[a]Isolated yield.

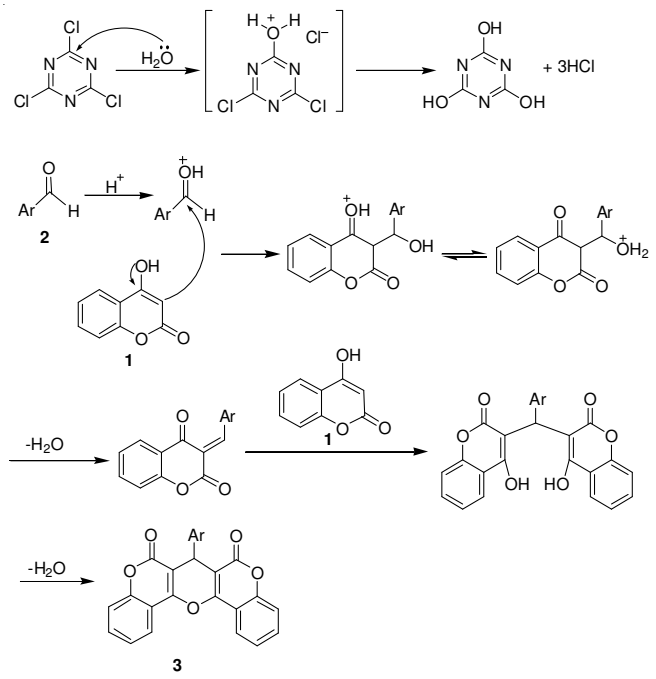
To explore the scope and limitations of this reaction further, we have extended the reaction of 4-hydroxycoumarin **1** with a range of other aromatic aldehydes **2b-g** under similar conditions (5 mol % cyanuric chloride/120 ºC), furnishing the respective 4,4'-epoxydicoumarins **3b-g** in good yields. The optimized results are summarized in Table-2. Good yields were obtained using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents. Aliphatic aldehyde reacted poorly under the same conditions (< 10 %).

TABLE-2
PREPARATION OF 4,4'-EPOXYDICOUMARINS CATALYZED BY CYANURIC CHLORIDE[a]

Entry	R	Time (h)	Product	Yield (%)[b]	m.p. (°C)
1	C_6H_5	2.0	**3a**	85	387-388
2	4-Cl-C_6H_4	1.5	**3b**	89	364-366
3	4-MeO-C_6H_4	2.0	**3c**	81	293-295
4	4-Me-C_6H_4	2.0	**3d**	83	316-317
5	4-NO_2-C_6H_4	2.0	**3e**	92	356-357
6	3-NO_2-C_6H_4	2.5	**3f**	89	348-349
7	4-F-C_6H_4	1.5	**3g**	88	350-352

[a]Reaction conditions: 4-hydroxycoumarin (2 mmol); aldehyde (1 mmol); cyanuric chloride (0.05 mmol); 120 °C; neat; [b]Isolated yield.

HCl generated *in situ*, from cyanuric chloride, efficiently catalyses these reactions, a plausible mechanism is shown in **Scheme-III**. Accordingly, cyanuric chloride (5 mol %) reacts with 'incipient' moisture and releases 3 mol of HCl and cyanuric acid (removable by washing with water) as by-product. The *in situ* generated HCl acts as protic acid to activate the carbonyl oxygen to form the 4,4'-epoxydicoumarins.



Scheme-III

To emphasize the effect of catalyst the model reaction between benzaldehyde (1 mmol) and 4-hydroxycoumarin (2 mmol) was described and different catalysts were subjected to the reaction. All the reactions were run in the same conditions and similar amounts of catalysts (5 mol %) were used. As can be seen in Table-3, satisfactory results were obtained only with cyanuric chloride (entry 7).

TABLE-3
EFFECT OF CATALYSTS ON THE REACTION OF BENZALDEHYDE AND 4-HYDROXYCOUMARIN[a]

Entry	Catalyst	Time (h)	Yield (%)[a]
1	*p*-TsOH	2	69
2	H_2SO_4	4	23
3	$NaHSO_4$	5	62
4	$NaHSO_3$	7	35
5	I_2	2	72
6	$ZnCl_2$	5	52
7	Cyanuric chloride	2	85

[a]Isolated yield

Conclusion

A simple one-step method is developed for the preparation of 4,4'-epoxydicoumarins from the corresponding commercially available of 4-hydroxycoumarin and aromatic aldehydes. The method offers several advantages including high yield of products, short reaction times and ease of work-up procedure.

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