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EDTA-catalyzed fast and efficient eco-friendly synthesis of dicoumarol derivatives in water

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ABSTRACT

EDTA-Catalyzed a simple, fast and efficient eco-friendly green protocol for the synthesis of dicoumarol derivatives in excellent yields in water at room temperature. This EDTA-catalyzed aqueous reactions of 4-hydroxycoumarin and various aldehydes avoids the use of expansive, corrosive, toxic solvents and provides several advantages such as short reaction time and scalable green synthesis.

Key words: Dicoumarols, 4-Hydroxycoumarin, Aldehydes, EDTA-catalyzed, Aqueous media, Green Chemistry.

INTRODUCTION

Coumarin compounds have gained the remarkable importance due to their widespread biological activities and also additives to food, cosmetics, and optical brightening agents [1]. Coumarin ring system is one of the most important substructure found in a large number of natural products and pharmacologically active compounds such as antibiotics [2] and antitumor drugs [3]. Coumarin derivatives have recently revealed new biological activities with interesting potential in therapeutic application besides their traditional employment as anticoagulant and sustaining agents [4, 5]. Among the systems studied, the 3,3'-benzylidene bis(4-hydroxycoumarin-3-yl)toluene has been tested as a HIV integrase inhibitor and has shown significant activity [6, 7] and it was found that the minimum active pharmacophore consisted of a coumarin dimer containing an aryl substituent on the central linker methylene [6, 8]. The addition of 4- and 7-hydroxy substituents in the coumarin rings improved the potency of the compounds.

Due to their great importance, many synthetic strategies have been developed. Recently, there are several methods reported in the literature for the synthesis of dicoumarols from 4-hydroxycoumarin and aldehydes in presence of different catalysts such as AcOH [9], $MnCl_2$ [10], ionic liquid [11], silica-supported preyssler nanoparticles [12], phosphotungstic acid [13], heteropolyacids [14], HCl [15], tetrabutylammonium bromide (TBAB) [16], silica gel [17], montmorillonite-KF [18], H_2SO_4 [19], molecular iodine [20], piperidine [21] and phase transfer catalyst TEBA [22]. However, these methods require prolonged reaction time and exotic reaction condition and some of these procedures require the use of toxic organic solvents, expensive catalysts and tedious workup. Thus, the development of a new method for the synthesis of dicoumarol derivatives would be highly desirable.

In recent years, synthetic chemists are challenged to consider more environmentally friendly methods for generation of the desired target molecules. Among the 12 principles of green chemistry, the desire for to utilize ‘‘safer solvents’’ and to ‘‘design for energy efficiency’’ can be considered 2 key principles of relevance to synthetic chemists [23]. Because of the toxic and volatile nature of many organic solvents, water as a reaction medium was considered a very promising and attractive substitute for volatile organic solvents and was widely used in the green chemistry area since Breslow [24], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in 1980s. There has been growing recognition that water is an attractive medium for many organic reactions, resulting in less expensive, less

dangerous, and environmentally friendly reactions, such as Diels–Alder reactions [25], Claisen rearrangement reactions [26], Reformatsky reactions [27], and pinacol-coupling reactions [28].

Presently, EDTA (ethylene diamine tetraacetic acid) have gained special attention as catalyst in organic synthesis because many advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness and eco-friendly nature. To the best of our knowledge, there is no report of the application of EDTA catalyst for the synthesis of dicoumarol derivatives in aqueous media, and we hope that this will be a very useful, simple, fast and scalable green protocol for the preparation of dicoumarol derivatives in water.

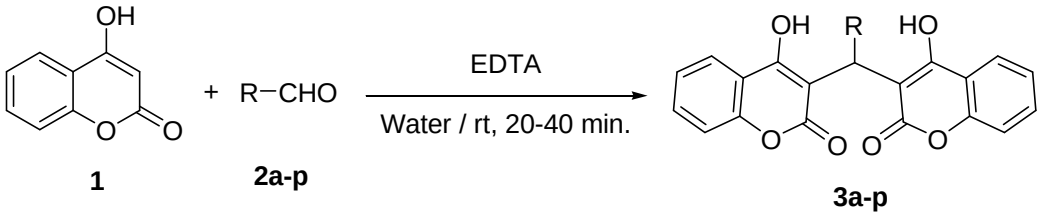
EXPERIMENTAL SECTION

All reagents and solvents were of the highest commercial quality purchased from Aldrich & Merk and were used without further purification. ^{1}H NMR spectra were recorded on a Bruker AC 400 (^{1}H NMR, 400 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm, δ). Infrared Spectra (IR) was recorded on JASCO IR-A-302 Spectrometer. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106 Italy. Purities of assayed compounds are, in all cases, greater than 96%, as determined by reverse-phase HPLC analysis. Thin layer chromatography (TLC) was performed on pre-coated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by, UV at 254 and 365 nm, followed by iodine vapors. Melting points were determined on a *Kofler* hot-stage apparatus and are uncorrected.

Synthesis

General procedure for the synthesis of dicoumarol derivatives (**3a-p**): A mixture of 4-hydroxycoumarin (**1**) (2 mmol) and aromatic/heteroaromatic aldehydes (**2a-p**) (1 mmol) in 15 mL of water was added EDTA-catalyst (10 mol%) and stirred at room temperature for the appropriate time mentioned in Table 1. The completion of reaction was monitored by Thin Layer Chromatography system. After completion of the reaction, the solid products were collected by filtration methods and washed with hot water. Finally the products were recrystallized from ethanol to give the desired pure products (**3a-p**).

Table 1. EDTA-catalyzed synthesis of dicoumarol derivatives (3a-p) in water[a]



Entry	R	Product	Time (min)	Yield (%)
1	C_6H_5	**3a**	30	96
2	4-$CH_3OC_6H_4$	**3b**	25	93
3	4-ClC_6H_4	**3c**	25	95
4	4-HOC_6H_4	**3d**	30	94
5	2-$NO_2C_6H_4$	**3e**	25	90
6	2-C_5H_4N	**3f**	30	85
7	2-C_4H_3O	**3g**	25	90
8	2,5-$(OCH_3)_2C_6H_3$	**3h**	20	98
9	4-$N(CH_3)_2C_6H_4$	**3i**	20	96
10	H	**3j**	40	85
11	CH_3	**3k**	35	80
12	2-OHC_6H_4	**3l**	25	92
13	3-ClC_6H_4	**3m**	20	94
14	-CH=CH-C_6H_5	**3n**	30	93
15	1-Naphthyl	**3o**	25	90
16	2,4,5-$(OCH_3)_3C_6H_2$	**3p**	20	98

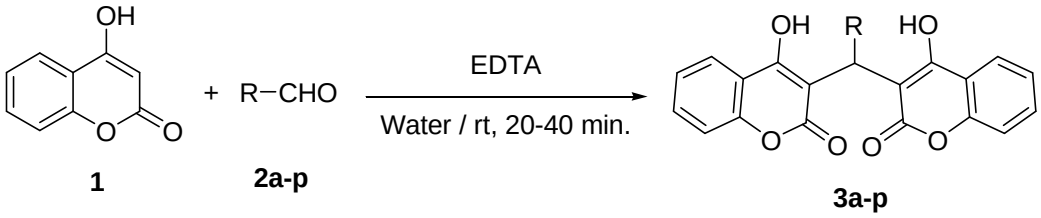
[a]Reaction conditions: EDTA (10 mol %), 4-hydroxycoumarin (2.0 mmol); Benzaldehyde (1.0 mmol); 15 mL water at RT.

All synthesized compounds were characterized with ^{1}H-NMR and mass spectrometry. Also the melting points recorded were compared with the corresponding literature melting points and found to be matching.

RESULTS AND DISCUSSION

In this paper, we wish to report a EDTA-catalyzed green approach for the synthesis of dicoumarol derivatives in water at room temperature (Scheme 1). In our initial study, 4-hydroxycoumarin was reacted with benzaldehyde in the presence of NH_4OAc in water solution under refluxing temperature for 1 h and the expected product was

obtained in 85% yield (Table 2, entry 6). The use of other catalysts (Table 2, entries 1-5) does not improved the yields even after several hours in water under reflux conditions. However, excellent yield was achieved when the reaction was carried out in presence of EDTA in water at room temperature and the reaction was completed within 30 min affording the desired product in 96% yield (Table 2, entry 7).



Scheme 1. EDTA Catalyzed Synthesis of Dicoumarol Derivatives in Water.

Table 2. Evaluation of catalytic activity of different catalysts for the synthesis of dicoumarol (3a) in water

Entry	Catalyst	Mol (%)	Time	Yield (%)
1	AcOH	10	[a] 5 h	80
2	I_2	10	[a] 4 h	75
3	pTSA	10	[a] 10 h	65
4	NH_4Cl	10	[a] 10 h	60
5	LiBr	10	[a] 3 h	70
6	NH_4OAc	10	[a] 1 h	85
7	**EDTA**	**10**	**[b] 30 min**	**96**

[a]Reaction conditions: 4-hydroxycoumarin (2.0 mmol); Benzaldehyde (1.0 mmol); Catalyst (10 mol%); in water (15 mL) under reflux conditions.
[b]Reaction conditions: 4-hydroxycoumarin (2.0 mmol); Benzaldehyde (1.0 mmol); Catalyst (10 mol%); in water (15 mL) at RT.

In order to optimize the EDTA-catalyzed reactions, we have evaluate the reaction of 4-hydroxycoumarin and benzaldehyde to afford **3a** in various other organic solvents such as CH_3OH, dichloromethane and CH_3CN at room temperature for 24 h, and percentage of yields are very poor with compare to the water-mediated green protocol (Table 2, entry 7).

This observations encouraged us to expand the scope and generality of this standardized EDTA-catalyzed reaction methodology in Water, a range of dicoumarol derivatives **3a-p** were synthesized starting from 4-hydroxycoumarin and various aldehydes (Scheme 1 and Table 1, entries 1-16) in presence of EDTA in water at room temperature. The method was found to be equally effective for the condensation of 4-hydroxycoumarin with aromatic aldehydes bearing electron-withdrawing (**3c, 3e**) as well as electron-donating (**3b, 3p**) substituents and heteroaromatic aldehydes (**3f** and **3g**) are summarized in Table 1. The yields obtained for dicoumarol derivatives (**3a-p**) were good to excellent and were in the range of the 80-98% (Table 1, entries 1-16).

Spectral characterization data

Compound **3a**: White solid (Yield: 96%); Mp: 229–232 ^oC; ^1H-NMR ($CDCl_3$) δ: 6.23 (s, 1H, CH), 7.23–8.11 (m, 13H, Ar-H), 11.31 (s, 1H, OH), 11.54 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 36.23, 105.69, 116.64, 124.40, 124.87, 126.48, 126.89, 128.64, 132.83, 135.23, 152.54; IR (KBr) ν: 3423, 3034, 1675, 1612, 1562, 1494, 1443, 1349, 758 cm^{-1}; Anal. calcd. for $C_{25}H_{16}O_6$: C, 72.81; H, 3.91. Found: C, 72.79; H, 3.86.

Compound **3b**: White solid (Yield: 93%); Mp: 246–249 ^oC; ^1H-NMR ($CDCl_3$) δ: 3.83 (s, 3H, CH_3O), 6.05 (s, 1H, CH), 6.85–8.05 (m, 12H, Ar-H), 11.32 (s, 1H, OH), 11.53 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 35.53, 54.26, 114.06, 116.63, 124.42, 124.84, 126.93, 127.63, 132.78, 158.43, 135.23, 152.54; IR (KBr) ν: 3453, 3072, 1673, 1614, 1562, 1505, 1454, 1353, 1306, 1254, 765 cm^{-1}; Anal. calcd. for $C_{26}H_{18}O_7$: C, 70.58; H, 4.10. Found: C, 70.64; H, 4.13.

Compound **3c**: White solid (Yield: 95%); Mp: 257–260 ^oC; ^1H-NMR ($CDCl_3$) δ: 6.03 (s, 1H, CH), 7.15–8.11 (m, 12H, Ar-H), 11.32 (s, 1H, OH), 11.56 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 35.73, 103.73, 105.29, 116.63, 124.42, 124.93, 127.86, 128.83, 132.75, 133.93, 152.54, 164.63, 166.84, 169.23; IR (KBr) ν: 3425, 3068, 1675, 1613, 1560, 1494, 1489, 1443, 1349, 1274, 1213, 763 cm^{-1}; Anal. calcd. for $C_{26}H_{15}ClO_6$: C, 67.20; H, 3.38. Found: C, 67.28; H, 3.42.

Compound **3d**: White solid (Yield: 94%); Mp: 220–223 ^oC; ^1H-NMR ($CDCl_3$) δ: 6.22 (s, 1H, CH), 7.03–8.16 (m, 12H, Ar-H), 9.82 (s, 1H, OH), 11.32 (s, 1H, OH), 11.53 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 36.26, 106.12, 116.63, 124.45, 125.07, 126.48, 127.12, 128.64, 132.85, 135.26, 152.53; IR (KBr) ν: 3340, 3035, 1670, 1607, 1562, 1493, 1443, 1349, 763 cm^{-1}; Anal. calcd. for $C_{25}H_{16}O_7$: C, 70.09; H, 3.76. Found: C, 70.14; H, 3.79.

Compound **3e**: Yellow solid (Yield: 90%); Mp: 234–236 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.53 (s, 1H, CH), 7.26–8.34 (m, 12H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ: 35.56, 114.06, 116.67, 123.38, 124.84, 126.86, 127.63, 133.18, 158.46, 135.22, 153.14; IR (KBr) ν: 3035, 1660, 1614, 1530, 1505, 1348, 1306, 765 cm^{-1}; Anal. calcd. for $C_{25}H_{15}NO_8$: C, 65.65; H, 3.31; N, 3.06. Found: C, 65.72; H, 3.34; N, 2.98.

Compound **3f**: brown solid (Yield: 85%); Mp: 323–326 °C; ^{1}H-NMR (DMSO-d_6) δ: 6.33 (s, 1H, CH), 6.60 (d, *J*=2.1 Hz, 2H), 6.67 (dd, *J*=8.6, *J*=2.2 Hz, 2H), 7.59 (d, *J*=8.7 Hz, 2H), 7.88 (dd, *J*=8.1, *J*=5.7 Hz, 1H), 8.25 (d, *J*=8.0 Hz, 1H), 8.53 (s, 1H), 8.66 (d, *J*=5.6 Hz, 1H), 10.20 (s, 2H, OH); IR (KBr) ν: 3450, 3179, 1685, 1613, 1560, 1404, 760 cm^{-1}; Anal. calcd. for $C_{24}H_{15}NO_6$: C, 69.73; H, 3.66; N, 3.39. Found: C, 69.76; H, 3.73; N, 3.42.

Compound **3g**: Black solid (Yield: 90%); Mp: 200–203 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.08 (s, 1H, CH), 6.34–6.57 (m, 3H, Furyl-H), 7.32–8.30 (m, 8H, Ar-H), 11.37 (s, 1H, OH), 11.54 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 36.25, 104.69, 115.63, 124.83, 126.89, 128.62, 132.85, 135.00, 152.53; IR (KBr) ν: 3034, 1658, 1602, 1562, 1494, 1349, 768 cm^{-1}; Anal. calcd. for $C_{23}H_{14}O_7$: C, 68.66; H, 3.51. Found: C, 68.63; H, 3.48.

Compound **3h**: White solid (Yield: 98%); Mp: 264–267 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.69 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.13 (s, 1H, CH), 6.74–8.12 (m, 11H, Ar-H), 11.34 (s, 1H, OH), 11.59 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 35.73, 55.84, 56. 03, 110.49, 111.34, 116.64, 118.93, 124.40, 124.86, 127.53, 132.89, 148.10, 149.23, 152.43; IR (KBr) ν: 3436, 3075, 1673, 1612, 1562, 1513, 1450, 1353, 1307, 1254, 765 cm^{-1}; Anal. calcd. for $C_{27}H_{20}O_8$: C, 68.43; H, 4.25. Found: C, 68.39; H, 4.23.

Compound **3i**: White solid (Yield: 96%); Mp: 213–216 °C; ^{1}H-NMR (DMSO-d_6) δ: 3.23 (s, 6H, $2CH_3$), 6.34 (s, 1H, CH), 7.23–7.86 (m, 12H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 36.43, 103.69, 116.14, 120.10, 123.46, 124.57, 128.62, 131.64, 141.23, 153.10, 164.93, 167.94; IR (KBr) ν: 3424, 3083, 1665, 1610, 1562, 1523, 1446, 1350, 1305, 763 cm^{-1}; Anal. calcd. for $C_{27}H_{21}NO_6$: C, 71.20; H, 4.65; N, 3.08. Found: C, 71.16; H, 4.64; N, 3.03.

Compound **3j**: white solid (Yield: 85%); Mp: 272–275 °C; ^{1}H-NMR (DMSO-d_6) δ: 3.94 (s, 2H, CH_2), 7.20 (td, 2H, *J*=7.8, *J*=2.1 Hz, H-6/6'), 7.33 (d, 2H, *J*=7.8 Hz, H-8/8'), 7.56 (td, 2H, *J*=7.8, *J*=2.0 Hz, H-7/7'), 7.95 (d, 2H, *J*=7.8 Hz, H-5/5'); IR (KBr) ν: 3647, 3064, 1650, 1596, 1565, 1453, 1344, 765 cm^{-1}; Anal. calcd. for $C_{19}H_{12}O_6$: C, 67.86; H, 3.60. Found: C, 67.89; H, 3.64.

Compound **3k**: white solid (Yield: 80%); Mp: 173–176 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.43 (d, 3H, *J*=5.6 Hz, CH_3), 4.32 (s, 1H, CH-11), 7.25 (td, 2H, *J*=7.8, *J*=2.5 Hz, H-6/6'), 7.33 (d, 2H, *J*=7.8 Hz, H-8/8'), 7.41 (td, 2H, *J*=2.3 Hz, H-7/7'), 7.72 (d, 2H, *J*=7.8 Hz, H-5/5'); IR (KBr) ν: 3643, 3059, 1654, 1586, 1563, 1443, 758 cm^{-1}; Anal. calcd. for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03. Found: C, 68.53; H, 3.96.

Compound **3l**: Yellow solid (Yield: 92%); Mp: 252–254 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.43 (s, 1H, CH), 7.14–8.13 (m, 12H, Ar-H), 8.60 (s, 1H, OH), 11.28 (s, 1H, OH), 11.56 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 36.13, 105.73, 116.64, 124.47, 124.85, 126.46, 127.14, 128.64, 133.82, 135.24, 152.57; IR (KBr) ν: 3423, 3035, 1675, 1613, 1564, 1496, 1443, 1347, 765 cm^{-1}; Anal. calcd. for $C_{25}H_{16}O_7$: C, 70.09; H, 3.76. Found: C, 70.13; H, 3.79.

Compound **3m**: white solid (Yield: 94%); Mp: 213–216 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.06 (s, 1H, CH), 7.16–8.14 (m, 12H, Ar-H), 11.32 (s, 1H, OH), 11.58 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 35.75, 103.76, 105.30, 117.23, 124.42, 124.93, 128.06, 128.83, 132.72, 131.25, 152.53, 164.68, 167.03, 169.24; IR (KBr) ν: 3423, 3065, 1670, 1614, 1565, 1493, 1443, 1350, 1275, 765 cm^{-1}; Anal. calcd. for $C_{25}H_{15}ClO_6$: C, 67.20; H, 3.38. Found: C, 67.26; H, 3.43.

Compound **3n**: Pale yellow solid (Yield: 93%); Mp: 227–230 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.53 (s, 1H, CH), 6.61 (d, 1H, CH), 6.72 (d, 1H, CH), 7.13–8.14 (m, 12H, Ar-H), 11.31 (s, 1H, OH), 11.54 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 36.25, 96. 73, 97.52, 106.68, 116.65, 124.40, 124.89, 126.58, 127.84, 128.64, 132.83, 135.26, 152.53; IR (KBr) ν: 3323, 3034, 3026, 1723, 1672, 1614, 1562, 1443, 1349, 766 cm^{-1}; Anal. calcd. for $C_{27}H_{18}O_6$: C, 73.97; H, 4.14. Found: C, 73.88; H, 4.09.

Compound **3o**: Yellow solid (Yield: 90%); Mp: 245–248 °C; ^{1}H-NMR (DMSO-d_6) δ: 6.74 (s, 1H, CH), 7.24–7.32 (m, 5H, Ar-H), 7.35–7.41 (m, 4H, Ar-H), 7.48–7.56 (m, 3H, Ar-H), 7.72 (d, 1H, *J*=8.8 Hz), 7.83 (d, 2H, *J*=8.8 Hz, CH); ^{13}C-NMR (DMSO-d_6) δ: 36.23, 106.68, 117.14, 124.40, 124.87, 126.48, 126.89, 127.32, 128.64, 130.16, 132.14, 132.83, 135.23, 152.54; IR (KBr) ν: 3424, 3060, 2973, 1656, 1603, 1562, 1443, 1349, 764 cm^{-1}; Anal. calcd. for $C_{29}H_{18}O_6$: C, 75.32; H, 3.92. Found: C, 75.26; H, 3.89.

Compound **3p**: White solid (Yield: 98%); Mp: 270–273 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.68 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3. 92 (s, 3H, CH_3), 6.14 (s, 1H, CH), 6.73–8.14 (m, 10H, Ar-H), 11.33 (s, 1H, OH), 11.56 (s, 1H, OH); ^{13}C-

NMR ($CDCl_3$) δ: 35.73, 55.84, 56. 03, 56.73, 110.48, 112.36, 116.67, 118.94, 124.43, 125.26, 127.59, 132.86, 147.93, 149.24, 152.46; IR (KBr) ν: 3435, 3074, 1670, 1613, 1564, 1513, 1452, 1353, 1313, 1256, 765 cm^{-1}; Anal. calcd. for $C_{28}H_{22}O_9$: C, 66.93; H, 4.41. Found: C, 66.98; H, 4.43.

CONCLUSION

In conclusion, we have developed EDTA-catalyzed simple, fast and efficient eco-friendly synthetic green protocol in water at room temperature and the present methodology was superior to the literature methods in terms of scalable green synthesis in water.

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