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Ultrasound-enhanced one-pot synthesis of 3-(Het)arylmethyl-4-hydroxycoumarins in water

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ABSTRACT

3-(Aryl)methyl-4-hydroxycoumarins were produced in good to excellent yields by reaction between 4-hydroxycoumarin and (hetero)aromatic aldehydes in the presence of Hantzsch 1,4-dihydropyridine (HEH) which works as an hydride donor (i.e., in a sequential Knoevenagel–reductive Michael addition). The sonochemical-assisted procedure (method B) provides an improved and accelerated conversion when compared to conventional silent reactions (method A). Experiments carried out according to method B showed that the reaction could be more efficiently run in the absence of organic solvents, at 30–40 °C in open vessel, without the need of an excess HEH and with simplified work-up and separation procedures.

1. Introduction

The ring system of 2*H*-1-benzopyran-2-one (hereafter named coumarin as it belongs to the family of phenylpropanoids) is the core building block of an ever growing number of natural and non-natural derivatives which display an impressive array of biological properties, including anticoagulant [1], photosensitizing [2] and antineoplastic properties [3]. 4-Hydroxycoumarin is an interesting compound found in many plants and particularly known as the natural precursor of dicoumarol a powerful anticoagulant that acts as a vitamin K antagonist [4]. In addition, recent studies in a collaborative effort between chemists and biologists have shown that a number of 3(aryl)methyl-4-hydroxycoumarins **4a-z** show biological activity as potent non-nucleoside RT inhibitors [5], HIV integrase [6] or HIV protease [7] inhibitors, promising characteristics have been identified. On account of these findings, extensive synthetic efforts are under way to produce agents with higher activity, enhanced selectivity, good atom economy and fewer side effects. Although a number of methods to synthesize derivatives **4** are found in the literature [8], the large majority of them fall into two classes: in the first, heterocyclization, in which closing the ring system is the final step [9]; in the second, the 3-substituent is added to 4-hydroxycoumarin **1** itself or one of its derivatives [10] at a later stage. The first strategy is often beset by lengthy sequences, low overall yields and a limited capacity to vary substituents; or it requires starting materials which are not easily accessible. The second one typically relies upon, either the reduction of suitable precursors [e.g., 3-arylidene- **3**, 3-acyl-, 3-(thioalkyl)methylaryl or 3,3′-arylidenebis(coumarin) derivatives **5**] or the alkylation of **1** with benzylic electrophiles (under base catalysis or the Mitsunobu protocol). The major limitation of both these approaches is the additional step required for the preparation of precursors to undergo the reductive step, whereas an inherent lack of selectivity (*O- vs C*-alkylation) was observed in the alkylation step.

Transition-metal-catalyzed reactions have recently been proven to be highly versatile when applied to electrophilic equivalents of **1** [e.g., 3-phenyl iodonium ylide [1] or 3-diazo-benzopyran-2,4(3*H*)dione] [12]. At this stage, the regioselective alkylation of **1** remains an important and actively pursued problem. Accordingly, greater efficiency would be expected in an approach that merges the Knoevenagel reaction with the hydrogenation of the intermediately formed aryliden-1,3-dicarbonyl derivative **3** and a number of these syntheses have capitalized on this tactic [13]. As part of an ongoing project concerned with the development of protocols for the preparation of 3-(het)arylmethyl-4-hydroxycoumarins **4** under mild and environmentally benign conditions, we have developed a single-step alkylation of 1 with (het)aromatic aldehydes and a Hantzsch ester (i.e., 3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydro-

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pyridine) (**6**, HEH) [14,15] using an organocatalytic reductive strategy (Scheme 1). This was successfully carried out and implemented in water under power ultrasound (US) in the presence of *p*-dodecylbenzenesulphonic acid (DBSA) for its surfactant property and the strong Brønsted acidity. Such optimized conditions strongly promoted the reaction, restrain side reactions and facilitates the work-up (Scheme 1).

2. Experimental

2.1. General

All reagents were obtained from commercial sources and used without further purification. 5-Formyl-1,3-dimethyluracil **2r** [16], 2,6-pyridinedicarbaldehyde **2t** [17], Hantzsch's ester (HEH) **6** [18] and 7-diethylamino-4-hydroxycoumarin **7** [19] were prepared according to the literature. 4-Formyl-benzeneboronic **2h** acid was generously supplied by Archimica SpA (Origgio, Italy).

Reactions were monitored by TLC carried out on precoated glass-backed plates Merck 60 F254 (0.25 mm) with UV light, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concd H_2SO_4)-heat as developing agents. Column chromatography was performed under medium pressure using Merck Kieselgel 60 (230–400 mesh).

IR spectra were recorded with a Shimadzu FT-IR 8001 spectrophotometer. Melting points were measured using a Büchi melting point apparatus. Elemental analyses were performed using a Perkin Elmer Series II CHNS/O Analyzer 2400. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.63 MHz) were obtained on a Bruker Avance 400 spectrometer. Chemical shifts (δ) are given in parts per million relative to TMS, coupling constants (J) in Hz. Chemical ionization mass spectra (+ve mode) (CI^+-MS) were performed on a Finnigan-MAT TSQ70 with isobutane as the reactant gas. All reactions, except those involving sonication, were run under nitrogen atmosphere. All sonochemical reactions were performed in a commercially available 120 mL-cavitating tube (Danacamerini, Turin, Italy). This thermostatted high-power probe reactor consists of a thin titanium hollow cylinder lodged in a Delrin® housing that can be cooled by a flow of refrigerated liquid (ethylene glycol/water 1:1) [20]. The transducers consist of high-efficiency prestressed piezoelectric (PZT) rings (planar PZT Morgan Electronics, diameter 50 mm) compressed between two ergal discs. The working frequency is 19.6 kHz, and power can be varied up to a maximum of 300 W (input power).

2.1.1. General procedure under conventional conditions (method A)

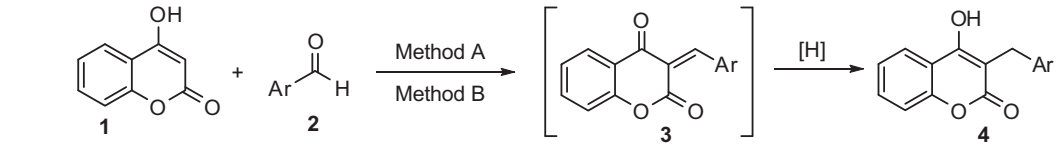
HEH was added, in small portions (up to six) every hour (overall amount:700 mg, 1.5 equiv), to a stirred suspension of 4-hydroxycoumarin **1** (300 mg, 1.85 mmol, 1 equiv), the aldehyde (1 equiv) and *L*-proline (42 mg, 0.2 equiv) in EtOH (50 mL) under nitrogen atmosphere and heated at reflux for 6 h. After cooling, the solvent was removed under reduced pressure, water (50 mL) was added to the residual material and the mixture extracted with EtOAc (2 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The obtained residue was chromatographed on a silica gel column and then recrystallized from the appropriate solvent.

2.1.2. General procedure under sonochemical conditions (method B)

Water (50 mL), 4-hydroxycoumarin **1** (162 mg, 1 equiv), **6** (253 mg, 1 equiv), the aldehyde (1 equiv) and *p*-dodecylbenzenesulphonic acid (~90% purity, technical, Aldrich) (DBSA) (0.1 equiv) were placed in the 120-mL sonochemical reactor that was sealed at the top with a tight stopper and sonicated for 1.5 h (19.6 kHz, 60 W). During the sonication we allowed the temperature to rise from its initial value of 20 °C up to 40 °C. The mixture was then poured into saturated $NaHCO_3$ (25 mL) and stirred vigorously for 30 min. The insoluble material (which was found to be oxidized HEH) was discarded by centrifugation (3500 rpm for 4 min) and the pH of the aqueous layer was adjusted to 4.5 by adding a solution of 10% H_2SO_4 while stirring in an ice-water bath. A precipitate was formed which was collected by vacuum filtration, washed with little cold water, dried and crystallized from the appropriate solvent.

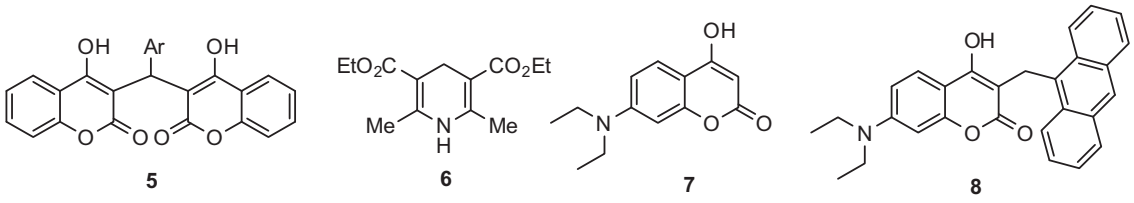
3-Benzyl-4-hydroxy-chromen-2-one **(4a)**. Yellow solid; Mp 207–209 °C; R_f = 0.40 (*n*-hexane-AcOEt, 6:4). ^{1}H NMR (DMSO); δ: 3.37 (bs, 1H, overlapped with water signal), 3.88 (s, 2H), 7.14–7.17 (m, 1H), 7.24–7.25 (m, 4H), 7.34–7.38 (m, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (DMSO);δ: 30.0 (CH_2), 104.9 (C), 117.1 (2CH), 117.3 (C), 124.2 (CH), 124.7 (CH), 126.7 (CH), 128.9 (CH), 129.0 (CH), 132.7 (CH), 119.9 (CH), 140.8 (C), 152.9 (C), 161.7 (C), 163.8 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{16}H_{12}O_3$: 252.3. Found: 253. Analysis calculated for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 77.11; H, 4.94.

3-(2-Bromo-benzyl)-4-hydroxy-chromen-2-one **(4b)**. White solid; Mp 250–251 °C; R_f = 0.38 (*n*-hexane-AcOEt, 6:4). ^{1}H NMR (DMSO); δ: 3.91 (s, 2H), 6.99 (d, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.37–7.42 (m, 2H), 7.62–7.67 (m, 2H), 7.99 (d, *J* = 7.8 Hz, 1H), 11.66 (bs, 1H). ^{13}C NMR (DMSO); δ: 31.1



Method A (unless differently stated): 4-hydroxycoumarin (1 equiv), aldehyde (1 equiv), HEH (1.5 equiv, portionwise), *L*-proline (0.2 equiv), N_2, EtOH, reflux, 6 h.

Method B (unless differently stated): 4-hydroxycoumarin (1 equiv), aldehyde (1 equiv), HEH (1.05 equiv), DBSA (0.1 equiv), open to the atmosphere, H_2O, US (19.6 kHz, 60 W), from r.t. to 40°C, 1.5 h.



Scheme 1. General reaction scheme.

(CH_2), 102.5 (C), 117.0 (C), 117.2 (CH), 124.3 (CH), 124.9 (CH), 125.1 (C), 128.6 (CH), 128.9 (CH), 129.2 (CH), 133.0 (CH), 133.2 (CH), 138.9 (C), 153.1 (C), 162.6 (C), 163.6 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{16}H_{11}BrO_3$: 331.17. Found: 332. Analysis calculated for $C_{16}H_{11}BrO_3$: C, 58.03; H, 3.35%. Found: C, 57.89; H, 3.42.

3-(2-Iodo-benzyl)-4-hydroxy-chromen-2-one **(4c)**. White solid; Mp 240–243 °C; R_f = 0.34 (*n*-hexane-AcOEt 6:4). ^{1}H NMR (DMSO); δ: 3.83 (s, 2H), 6.19 (d, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.36–7.41 (m, 2H), 7.64 (t, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 11.79 (bs, 1H). ^{13}C NMR (DMSO); δ: 35.9 (CH_2), 102.1 (C), 102.5 (C), 116.7 (CH), 116.8 (C), 124.0 (CH), 124.4 (CH), 127.9 (CH), 128.5 (CH), 128.8 (CH), 132.5 (CH), 139.3 (CH), 141.6 (C), 152.8 (C), 162.4 (C), 163.2 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{16}H_{11}O_3I$: 378.2. Found: 379. Analysis calculated for $C_{16}H_{11}O_3I$: C, 50.82; H, 2.93. Found: C, 50.09; H, 2.88.

4-Hydroxy-3-(2-nitro-benzyl)-chromen-2-one **(4d)**. White solid; Mp 244 °C; R_f = 0.46 (*n*-hexane-AcOEt 1:9). ^{1}H NMR (DMSO); δ: 4.05 (s, 2H), 7.32–7.27 (t, *J* = 6.9 Hz, 3H), 7.43–7.41 (t, *J* = 7.8 Hz, 1H), 7.56–7.92 (m, 2H), 7.92–7.90 (d, *J* = 7.8 Hz, 2H). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{16}H_{11}NO_5$: 297.26. Found: 298.

4-Hydroxy-3-(4-nitro-benzyl)-chromen-2-one **(4e)**. Pale yellow solid; Mp 296–297 °C; R_f = 0.20 (*n*-hexane-AcOEt, 6:4). ^{1}H NMR (DMSO); δ: 4.02 (s, 2H), 7.37–7.41 (m, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.64 (t, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 2H), 11.80 (bs, 1H). ^{13}C NMR (DMSO); δ: 30.2 (CH_2), 103.8 (C), 117.0 (C), 117.1 (CH), 124.2 (2CH), 124.3 (CH), 124.8 (CH), 130.2 (2CH), 132.9 (CH), 146.8 (C), 149.1 (C), 153.0 (C), 162.1 (C), 163.7 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{16}H_{11}NO_5$: 297.3. Found: 298. Analysis calculated for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73 N, 4.71%. Found: C, 64.53; H, 3.77; N, 4.81.

3,3′-Dibenzyl-4,4′-dihydroxybis[2*H*-1-benzopyran-2-one] **(4f)**. White solid; Mp 355–356 °C; R_f = 0.56 (Methanol-AcOEt, 3:7). ^{1}H NMR (DMSO); δ: 3.45 (bs, 2H), 3.82 (s, 4H), 7.13 (s, 4H), 7.32–7.36 (m, 4H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.95 (dd, *J* = 1.7 Hz, *J* = 8.4 Hz, 2H). ^{13}C NMR (DMSO); δ: 29.6 ($2CH_2$), 105.1 (2C), 117.0 (4CH), 117.1 (2C), 124.2 (2CH), 124.7 (2CH), 128.8 (2CH), 132.6 (2CH), 138.3 (2C), 152.8 (2C), 161.3 (2C), 163.7 (2C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{26}H_{18}O_6$: 426.4. Found: 427. Analysis calculated for $C_{26}H_{18}O_6$: C, 73.23; H, 4.25%. Found: C, 73.11; H, 4.48.

4-Hydroxy-3-(4-*N*,*N*-dimethylamino-benzyl)-chromen-2-one **(4g)**. Mp 160–162 °C; ^{1}H NMR (DMSO); δ: 2.84 (s, 6H), 3.87 (s, 2H), 6.61 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.38–7.20 (overlapped signals, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{18}H_{17}NO_3$: 295.3. Found: 296. Analysis calculated for $C_{18}H_{17}NO_3$: C, 73,20; H, 5,80; N, 4,74; O, 16,25. Found: C, 73,31; H, 5,73; N, 4,60.

3-(4-Dihydroxyboranyl-benzyl)-4-hydroxy-chromen-2-one **(4h)**. White solid; Mp 231–233 °C; R_f = 0.20 (*n*-hexane-AcOEt 4:6). ^{1}H NMR (DMSO); δ: 3.88 (s, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.34–7.38 (m, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.91 (s, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 11.60 (s, 1H). 7.91 (s, 2H) and 11.60 (s, 1H) disappeared trough an exchange with D_2O. ^{13}C NMR (DMSO); δ: 30.1 (CH_2), 104.7 (C), 117.1 (CH), 117.3 (C), 124.2 (CH), 124.7 (CH), 128.0 (CH), 132.5 (C), 132.7 (2CH), 135.0 (2CH), 142.7 (C), 152.9 (C), 161.7 (C), 163.7 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{16}H_{13}O_5B$: 296.1. Found: 297.

3-[3-(4-Dimethylamino-phenyl)-propyl]-4-hydroxy-chromen-2-one **(4i.1)**. Dark yellow solid; Mp 74–75 °C; R_f = 0.33 (*n*-hexane-AcOEt, 1:1). ^{1}H NMR ($CDCl_3$); δ: 1.87–1.91 (m, 2H), 2.19 (bs, 1H), 2.62–2.67 (m, 4H), 3.00 (s, 6H), 6.98 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.26–7.30 (m, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ: 23.9 (CH_2), 29.9 (CH_2), 35.0 (CH_2), 43.4 ($2CH_3$), 60.9 (C), 105.8 (C), 116.1 (2CH), 116.7 (2CH), 123.7 (CH), 124.3 (CH), 129.9 (CH), 131.8 (CH), 136.1 (C), 146.2 (C), 152.6 (C), 161.1 (C), 165.1 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{20}H_{21}NO_3$: 323.4. Found: 324. Analysis calculated for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.36%. Found: C, 73.95; H, 6.62; N, 4.26.

3-[(E)-3-(4-Dimethylamino-phenyl)-allyl]-4-hydroxy-chromen-2-one **(4i.2)**. Yellow solid; Mp 158–160 °C; R_f = 0.47 (*n*-hexane-AcOEt, 1:1). ^{1}H NMR ($CDCl_3$); δ: 1.30–1.45 (m, 1H), 2.06–2.17 (m, 1H), 2.31–2.36 (m, 1H), 2.69–2.77 (m, 2H), 3.02 (s, 6H), 4.40–4.43 (m, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 6.82 (bs, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.32–7.35 (m, 2H), 7.51 (t, *J* = 8.5. Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ: 20.3 (CH_2), 40.9 ($2CH_3$), 61.8 (C), 80.1 (CH), 101.4 (C), 112.8 (CH), 116.3 (C), 116.9 (CH), 123.0 (CH), 123.3 (CH), 124.1 (CH), 127.7 (CH), 127.9 (CH), 131.7 (CH), 141.4 (CH), 151.1 (C), 152.8 (C), 160.9 (C), 163.6 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{20}H_{19}NO_3$: 321.4. Found: 322. Analysis calculated for $C_{20}H_{19}NO_3$: C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.37; H, 6.02; N, 4.30.

3-(Benzo-1,3-dioxol-5-ylmethyl)-4-hydroxy-chromen-2-one **(4j)**. Pale yellow solid; Mp 217 °C; Rf = 0,52 (*n*-hexane-AcOEt 1:9). ^{1}H NMR (DMSO); δ: 3.82 (s, 2H), 5.93 (s, 2H), 6.76–6.72 (d, *J* = 8 Hz, 1H), 6.82–6.80 (d, *J* = 7.8 Hz, 1H), 6.83 (s, 1H), 7.41–7.36 (m, 2H), 7.64–7.61 (t, *J* = 8.4 Hz, 1H), 8.01–7.98 (d, *J* = 8.1 Hz, 1H). ^{13}C-NMR (DMSO) δ: 28.7 (CH_2), 100.6 (CH_2), 104,6 (2C), 108.0, (CH), 108.7 (CH), 116.2 (CH), 120.8 (CH), 123.3 (CH), 123.9 (CH), 131.9 (CH), 133.5 (C), 145.4 (C), 147.1 (C), 151.9 (C), 160.3 (C), 162.8 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{17}H_{12}O_5$: 296.27. Found: 297; IR (KBr); 3188, 2952, 1730, 1668, 1635, 1485, 1244, 1170, 933, 752 cm^{-1}.

4-Hydroxy-3-(4-hydroxy-3-methoxybenzyl)-chromen-2-one **(4k)**. Yellow-orange solid; Mp 192 °C; Rf = 0.53 (*n*-hexane-AcOEt 1:9). ^{1}H NMR (DMSO); δ: 3.73 (s, 3H), 3.80 (s, 2H), 6.65–6.62 (m, 2H), 6.88 (s, 1H), 7.41–7.36 (m, 2H), 7.98–7.65 (t, *J* = 7.8 Hz, 1H), 8.01–7.98 (d, *J* = 8.0 Hz, 1H), 11.60 (br, 1H). ^{13}C NMR (DMSO); δ: 28.5, 55.6, 104.8, 112.7, 115.2, 116.2, 116.3, 120.1, 123.3, 123.89, 130.5, 131.8, 144.75, 151.9, 160.1. MS (CI) *m/z* $(M + H)^+$ calculated for $C_{17}H_{14}O_5$: 298.3. Found: 299. IR (KBr, cm^{-1}); 3188, 2950, 1728, 1670, 1634, 1510, 1393, 1265, 754.

3-Furan-2-ylmethyl-4-hydroxy-chromen-2-one **(4l)**. Yellow solid; Mp 158–161 °C; R_f = 0.60 (*n*-hexane-AcOEt, 6:4). ^{1}H NMR ($CDCl_3$); δ: 4.07 (s, 2H), 5.95 (bs, 1H), 6.27–6.36 (m, 2H), 7.30–7.38 (m, 3H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.89 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR ($(CD_3)_2CO$); δ: 23.1 (CH_2), 102.2 (C), 107.4 (CH), 111.4 (CH), 116.2 (C), 116.9 (CH), 123.6 (CH), 124.5 (CH), 132.6 (CH), 142.3 (CH), 152.1 (C), 152.8 (C), 161.7 (C), 164.1 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{14}H_{10}O_4$: 242.2. Found: 243. Analysis calculated for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 70.02; H, 4.11.

4-Hydroxy-3-(3*H*-imidazol-4-ylmethyl)-chromen-2-one **(4m)**. Pink solid; Mp 173–174 °C; R_f = 0.32 (Methanol-AcOEt, 3:7). ^{1}H NMR (DMSO); δ: 3.73 (s, 2H), 7.00 (bs, 1H), 7.13–7.20 (m, 4H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.86 (dd, *J* = 1.6 Hz, *J* = 7.4 Hz, 1H), 8.39 (bs, 1H). ^{13}C NMR (DMSO); δ: 21.3 (CH_2), 96.2 (C), 115.5 (CH), 116.5 (CH), 116.7 (CH), 122.6 (C), 123.2 (CH), 125.1 (CH), 131.1 (CH), 136.7 (C), 154.0 (C), 165.0 (C), 171.5 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{13}H_{10}N_2O_3$: 242.2. Found: 243. Analysis calculated for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56%. Found: C, 65.01; H, 4.08; N, 11.77.

4-Hydroxy-3-thiophen-3-ylmethyl-chromen-2-one **(4n)**. Yellow solid; Mp 188–190 °C; R_f = 0.41 (*n*-hexane-AcOEt, 6:4). ^{1}H NMR (DMSO); δ: 3.86 (s, 2H), 7.02 (d, *J* = 5.0 Hz, 1H), 7.14 (m, 1H), 7.34–7.41 (m, 3H), 7.60 (t, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 11.50 (bs, 1H). ^{13}C NMR (DMSO); δ: 25.1 (CH_2), 104.8 (C), 117.0 (CH), 121.7 (CH), 123.5 (C), 124.2 (CH), 124.7 (CH), 129.3 (CH), 132.6 (CH), 140.6 (C), 140.8 (CH), 152.8 (C), 162.1 (C), 166.0 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{14}H_{10}O_3S$: 258.30. Found:

259. Analysis calculated for $C_{14}H_{10}O_3S$: C, 65.10; H, 3.90%. Found: C, 64.97; H, 3.94.

3-Benzofuran-2-ylmethyl-4-hydroxy-chromen-2-one **(4o)**. Yellow solid; Mp 193–194 °C; R_f = 0.20 (*n*-hexane-AcOEt, 7:3), Orange spot Ehrlich. ^{1}H NMR (DMSO); δ: 4.08 (s, 2H), 6.52 (s, 1H), 7.14–7.22 (m, 2H), 7.37–7.41 (m, 2H), 7.48–7.50 (m, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 11.97 (bs, 1H). ^{13}C NMR (DMSO); δ: 24.2 (CH_2), 101.0 (C), 101.1 (C), 103.2 (CH), 111.5 (CH), 117.1 (CH), 121.2 (CH), 123.5 (CH), 124.2 (CH), 124.4 (CH), 124.9 (CH), 129.4 (C), 133.1 (CH), 153.0 (C), 154.9 (C), 157.3 (C), 162.4 (C), 163.4 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{18}H_{12}O_4$: 292.3. Found: 293. Analysis calculated for $C_{18}H_{12}O_4$: C, 73.97; H, 4.14%. Found: C, 74.05; H, 4.10.

4-Hydroxy-3-(1*H*-indol-3-ylmethyl)-chromen-2-one **(4p)**. Pale green solid; Mp 200–201 °C; R_f = 0.42 (*n*-hexane-AcOEt, 1:1). ^{1}H NMR ($(CD_3)_2CO$); δ: 4.10 (s, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.14 (s, 1H), 7.32–7.38 (m, 3H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 9.98 (bs, 1H). ^{13}C NMR ($(CD_3)_2CO$); δ: 20.0 (CH_2), 105.1 (C), 111.5 (CH), 112.7 (C), 116.5 (CH), 116.8 (C), 118.9 (CH), 119.3 (CH), 121.7 (CH), 122.8 (CH), 123.3 (CH), 124.1 (CH), 127.9 (C), 131.9 (CH), 137.2 (C), 153.0 (C), 159.8 (C), 163.1 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{18}H_{13}NO_3$: 291.3. Found: 292. Analysis calculated for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50, N, 4.81. Found: C, 73.98; H, 4.53, N, 4.71.

4-Hydroxy-3-pyridin-2-ylmethyl-chromen-2-one **(4q)**. Yellow solid; Mp 173–174 °C; R_f = 0.20 (*n*-hexane-AcOEt, 1:1), Green spot Ehrlich. ^{1}H NMR ($CDCl_3$); δ: 4.29 (s, 2H), 7.27–7.31 (m, 2H), 7.36 (t, *J* = 5.7 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.87 (t, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.05 (bs, 1H), 8.50 (d, *J* = 5.7 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ: 33.2 (CH_2), 101.5 (C), 115.8 (C), 116.6 (CH), 118.2 (C), 122.9 (CH), 124.1 (CH), 124.2 (CH), 124.3 (CH), 132.1 (CH), 139.8 (CH), 146.3 (CH), 153.1 (C), 160.4 (C), 165.8 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{15}H_{11}NO_3$: 253.3. Found: 254. Analysis calculated for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53%. Found: C, 71.93; H, 4.27; N, 5.59.

5-(4-Hydroxy-2-oxo-2*H*-chromen-3-ylmethyl)-1,3-dimethyl-1*H*-pyrimidine-2,4-dione **(4r)**. Yellow solid; Mp 261–262 °C; R_f = 0.17 (*n*-hexane-AcOEt, 1:1). ^{1}H NMR ($CDCl_3$); δ: 3.42 (s, 3H), 3.46 (s, 3H), 3.57 (s, 2H), 7.28–7.31 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 11.39 (bs, 1H). ^{13}C NMR ($CDCl_3$); δ: 22.6 (CH_2), 29.0 (CH_3), 37.7 (CH_3), 103.4 (C), 110.5 (C), 116.7 (CH), 117.2 (C), 124.3 (CH), 132.2 (CH), 132.3 (CH), 143.0 (CH), 151.3 (C), 152.9 (C), 162.7 (C), 164.6 (C), 167.8 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{16}H_{14}N_2O_5$: 314.30. Found: 315. Analysis calculated for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49%; N, 8.91%. Found: C, 61.07; H, 4.52; N, 8.95.

4-Hydroxy-3-quinolin-2-ylmethyl-chromen-2-one **(4s)**. Yellow solid; Mp 215–216 °C; R_f = 0.27 (*n*-hexane-AcOEt, 1:1). ^{1}H NMR ($CDCl_3$); δ: 4.54 (s, 2H), 7.30–7.41 (m, 2H), 7.51–7.55 (m, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.78 (bs, 1H), 7.84 (t, *J* = 7.3 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 8.20 (t, *J* = 8.0 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ: 33.8 (CH_2), 101.0 (C), 101.1 (C), 116.6 (CH), 118.2 (C), 122.4 (CH), 124.1 (CH), 124.2 (CH), 126.7 (CH), 127.5 (CH), 128.3 (CH), 131.4 (CH), 132.1 (CH), 140.0 (CH), 145.1 (C), 153.2 (C), 161.5 (C), 164.6 (C), 166.2 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{19}H_{13}NO_3$: 303.3. Found: 304. Analysis calculated for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62%. Found: C, 75.11; H, 4.48; N, 4.73.

3,3′-(Pyridinylmethyl)-bis-4-hydroxy-chromen-2-one **(4t.1)**. Brown solid; Mp 152–154 °C; R_f = 0.10 (CH_2Cl_2-MeOH, 8:2). ^{1}H NMR (DMSO); δ: 4.08 (s, 4H), 6.26 (bs, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.90 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (DMSO); δ: 31.7 ($2CH_2$), 100.8 (2C), 116.5 (2CH), 117.4 (2C), 122.3 (2CH), 123.8 (2CH), 124.1 (2CH), 132.4 (2CH), 140.9 (CH), 152.7 (2C), 158.6 (2C), 163.3 (2C), 164.1 (2C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{25}H_{17}NO_6$: 427.4. Found: 428. Analysis calculated for $C_{25}H_{17}NO_6$: C, 70.25; H, 4.01; N, 3.28. Found: C, 70.47; H, 4.12; N, 3.19.

4-Hydroxy-3-ferrocenylmethyl-chromen-2-one **(4u)**. Brown solid; Mp 220–225 °C; R_f = 0.38 (*n*-hexane-AcOEt, 6:4). ^{1}H NMR (DMSO); δ: 3.59 (s, 2H), 4.01–4.20 (m, 9H), 7.33–7.37 (m, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 11.43 (bs, 1H). ^{13}C NMR (DMSO); δ: 24.1 (CH_2), 67.6–69.5 (9CH), 87.8 (C), 106.2 (C), 117.0 (CH), 117.1 (C), 124.1 (CH), 124.7 (CH), 132.6 (CH), 152.7 (C), 160.3 (C), 163.7 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{20}H_{16}FeO_3$: 360.2. Found: 361. Analysis calculated for $C_{20}H_{16}FeO_3$: C, 66.69; H, 4.48. Found: C, 67.06; H, 4.31.

3-Anthracen-9-ylmethyl-4-hydroxy-chromen-2-one **(4v)**. Yellow solid; Mp 272–273 °C; R_f = 0.36 (*n*-hexane-AcOEt, 6:4). ^{1}H NMR (DMSO); δ: 4.83 (s, 2H), 7.08–7.29 (m, 2H), 7.46–7.49 (m, 5H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 8.46 (s, 1H), 8.57 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (DMSO); δ: 33.3 (CH_2), 106.8 (C), 113.7 (CH), 120.0 (C), 120.9 (C), 122.7 (CH), 125.3 (CH) 125.5 (CH), 125.7 (CH), 126.0 (CH), 126.9 (CH), 127.7 (CH), 127.8 (C), 128.2 (CH), 129.3 (CH), 129.5 (CH), 131.3 (C), 131.8 (C), 132.0 (C), 132.1 (C), 132.4 (C), 133.9 (C), 135.4 (CH), 139.9 (CH). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{24}H_{16}O_3$: 352.4. Found: 353. Analysis calculated for $C_{24}H_{16}O_3$: C, 81.80; H, 4.58. Found: C, 81.95; H, 4.46.

4-Hydroxy-3-pyren-1-ylmethyl-chromen-2-one **(4w)**. Pale orange solid; Mp 265–267 °C; R_f = 0.40 (*n*-hexane-AcOEt, 1:1). ^{1}H NMR (DMSO); δ: 4.64 (s, 2H), 7.39–7.44 (m, 2H), 7.66 (t, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 8.04–8.09 (m, 2H), 8.12 (s, 2H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.26–8.31 (m, 3H), 8.60 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (DMSO); δ: 27.8 (CH_2), 104.2 (C), 117.2 (CH), 117.4 (C), 124.3 (CH), 124.5 (CH), 124.8 (CH), 125.0 (C), 125.7 (CH), 125.8 (CH), 125.9 (CH), 126.4 (CH), 127.0 (CH), 127.4 (CH), 128.1 (CH), 128.3 (CH), 129.3 (C), 130.1 (C), 130.8 (C), 131.2 (C), 131.8 (C), 132.9 (CH), 134.5 (C), 153.1 (C), 162.4 (C), 163.9 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{26}H_{16}O_3$: 376.4. Found: 377. Analysis calculated for $C_{26}H_{16}O_3$: C, 82.96; H, 4.28. Found: C, 83.01; H, 4.19.

3-Anthracen-9-ylmethyl-7-diethylamino-4-hydroxy-chromen-2-one **(8)**. Brown solid; Mp 253–257 °C; R_f = 0.53 (*n*-hexane-AcOEt 1:1). ^{1}H NMR (DMSO); δ: 1.06 (t, *J* = 7.0 Hz, 6H), 3.35 (q, *J* = 7.0 Hz, 4H), 4.77 (s, 2H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.59 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 1H), 7.44–7.49 (m, 4H), 7.69 (d, *J* = 9.1 Hz, 1H), 8.03–8.05 (m, 2H), 8.44 (s, 1H), 8.55–8.57 (m, 2H). ^{13}C NMR (DMSO); δ: 13.1 ($2CH_3$), 23.7 (CH_2), 31.5 (C), 44.7 ($2CH_2$), 97.2 (CH), 101.2 (C), 104.7 (C), 109.0 (CH), 124.8 (CH), 125.6 (2CH), 125.9 (2CH), 126.4 (CH), 126.6 (2CH), 129.6 (2CH), 131.1 (C), 132.0 (C), 134.9 (C), 151.0 (C), 155.3 (C), 160.7 (C), 162.2 (C), 164.4 (C). MS (CI) *m/z* $(M + H)^+$ calculated for $C_{28}H_{25}NO_3$: 423.5. Found: 424. Analysis calculated for $C_{28}H_{25}NO_3$: C, 79.41; H, 5.95; N, 3.31. Found: C, 78.93; H, 6.07; N, 3.24.

3. Results and Discussions

The search for new synthetic approaches to highly functionalized derivatives and particularly the development of green methodologies and protocols is a research field of enormous interest and potentially unlimited applications.

The reaction was standardized with **1** and benzaldehyde **2a** and in our feasibility study we initially explored in a wide survey, numerous combinations of hydride and/or hydrogen donors [$NaBH_4$, $NaBH_3(CN)$, $NaBH(OAc)_3$, $Na_2S_2O_4$, HCO_2NH_4, NaH_2PO_2 and Hantzsch dihydropyridine (HEH)], Brønsted/Lewis catalysts [ethylenediammonium diacetate (EDDA), piperidinium diacetate, *L*-proline, $Yb(OTf)_3$], solvents [H_2O, THF, dioxane, MeCN, MeOH and EtOH either neat or mixed with water]. In water as a solvent the presence of a surfactant [Aliquat® 336, sodium dodecyl sul-

Table 1
Formation of 3-(Het)arylmethyl-4-hydroxycoumarins (4a-w) and (8) under two methodologies (thermal and ultrasound).

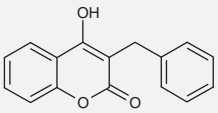
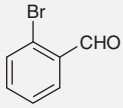
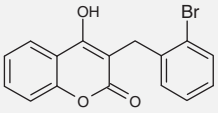
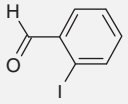
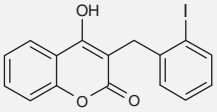
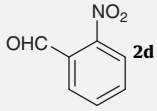
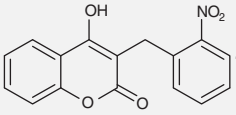
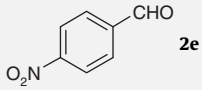
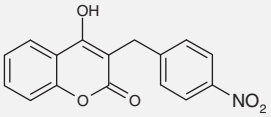
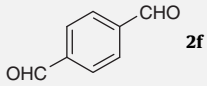
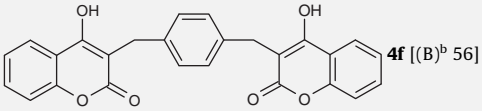
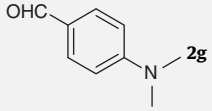
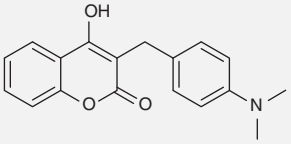
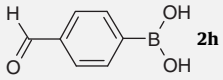
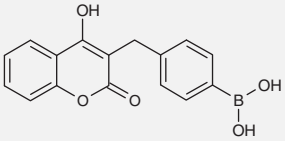
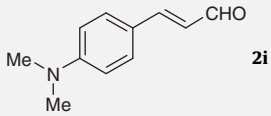
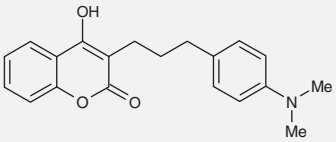
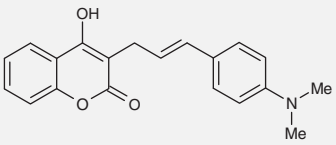
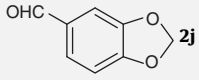
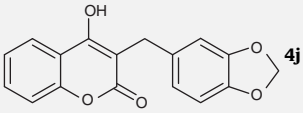
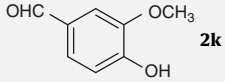
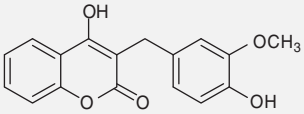
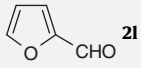
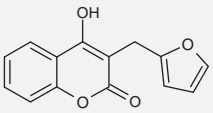
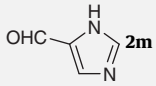
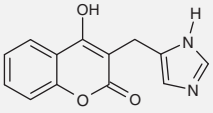
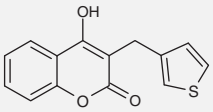
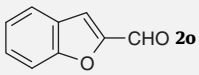
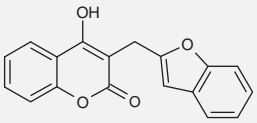
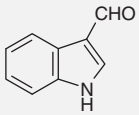
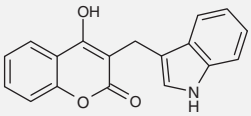
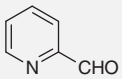
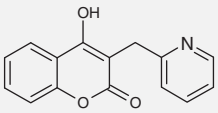
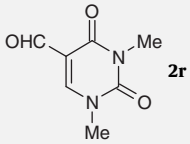
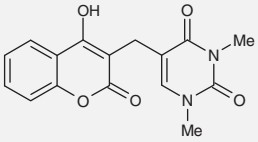
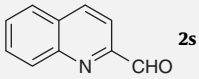
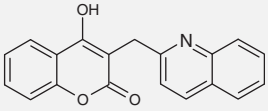
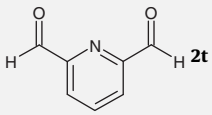
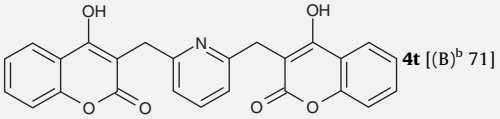
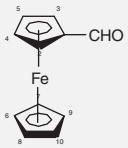
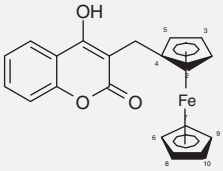
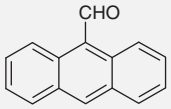
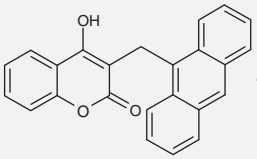
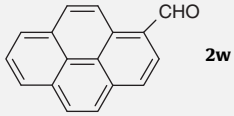
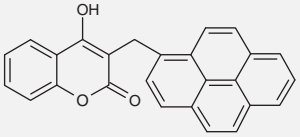
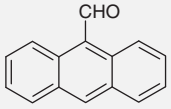
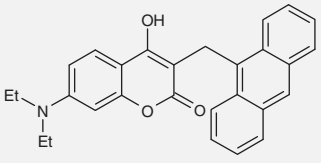
Entry	Aldehyde	Product(s) [Isolated yield(s)%]
1	 **2a**	 **4a** [(A)[a] 62; (B)[b] 88]
2	 **2b**	 **4b** [(A)[a] 58; (B)[b] 73]
3	 **2c**	 **4c** [(B)[b] 69]
4	 **2d**	 **4d** [(A)[a] 58; (B)[b] 67]
5	 **2e**	 **4e** [(A)[a] 80; (B)[b] 87]
6[c]	 **2f**	 **4f** [(B)[b] 56]
7	 **2g**	 **4g** [(A)[a] 82; (B)[b] 77]
8	 **2h**	 **4h** [(B)[b] 54]
9	 **2i**	 **4i.1** [(B)[b] 50]
		 **4i.2** [(B)[b] 27]
10	 **2j**	 **4j** [(A)[a] 60; (B)[b] 65]
11	 **2k**	 **4k** [(A)[a] 54; (B)[b] 63]
12	 **2l**	 **4l** [(B)[b] 74]
13	 **2m**	 **4m** [(B)[b] 88]

Table 1 (*continued*)

Entry	Aldehyde	Product(s) [Isolated yield(s)%]
14	 **2n**	 **4n** [(A)[a] 54; (B)[b] 79]
15	 **2o**	 **4o** [(B)[b] 81]
16	 **2p**	 **4p** [(B)[b] 60]
17	 **2q**	 **4q** [(A)[a] 75; (B)[b] 72]
18	 **2r**	 **4r** [(B)[b] 76]
19	 **2s**	 **4s** [(A)[a] 54; (B)[b] 61]
20[c]	 **2t**	 **4t** [(B)[b] 71]
21	 **2u**	 **4u** [(B)[b] 72]
22	 **2v**	 **4v** [(B)[b] 63]
23	 **2w**	 **4w** [(B)[b] 67]
24[d]	 **2v**	 **8** [(B)[b] 66]

[a]Method A (unless differently stated): 4-hydroxycoumarin (1 equiv), aldehyde (1 equiv), HEH (1.5 equiv, portion wise), *L*-proline (0.2 equiv), N_2, EtOH, reflux, 6 h.
[b]Method B (unless differently stated): 4-hydroxycoumarin (1 equiv), aldehyde (1 equiv), HEH (1.05 equiv), DBSA (0.1 equiv), open to the atmosphere, H_2O, US (19.6 kHz, 60 W), 20 °C → 40 °C, 1.5 h.
[c]4-Hydroxycoumarin/aldehyde = 2:1 ratio.
[d]Obtained as described for method B, starting from 7-dimethylamino-4-hydroxycoumarin (7).

phate, Tween 80 and Triton X-100] in the reaction mixture was evaluated. After considerable experimentation [21], it was decided to use benzaldehyde (1 equiv), 20 mol% of *L*-proline with HEH (1.5 equiv) in EtOH at reflux (6 h) under nitrogen as the preferable set of conditions to afford **4a** (62% isolated yield) (method A, Table 1). The protocol involves the use of **6** (HEH), a dihydropyridine closely

related to NADH, as a safe, easy-to-handle and environmentally benign reagent for the efficient reduction of electrophilic olefins [22–24]. The formation of **4a** under these conditions probably involved the initial electron-hydrogen transfer from HEH to the transient intermediate **3a** followed by proton transfer leading to **4a** and oxidized HEH [25].

However, there are some limitations, including the use of organic solvents, relatively long reaction times, the need of excess HEH and protection under inert atmosphere. This last finding agrees with the well-known proclivity of HEH to undergo oxidation in the presence of air. To partially circumvent this hurdle, HEH was added in four equal portions (1.5 equiv is the overall amount of all the additions) over 6 h at reflux. However, under these conditions, the process was still plagued by a side reaction; the Michael addition of **1** to the transient electron-deficient heterodiene **3a** to give the 3,3′-adduct **5a** in yield range (10–35%) and all attempts to induce the reductive fragmentation of **5a** were unsuccessful.

As a result, attempts to find an alternative approach which does not suffer from the severe drawbacks of the conventional procedures are still very desirable. In previous work we had studied the reactivity of **1** under sonochemical conditions both in anhydrous organic solvents and aqueous media [26]. Accordingly, the versatility of the method and our excellent results prompted us to further experiment with this approach. The literature of the last two decades offers a plethora of synthetic protocols that have been dramatically improved and accelerated by acoustic cavitation in liquid solutions [27]. In particular, reactions in heterogeneous systems (with insoluble reagents or catalysts) benefit most. In this context, organic reactions in water without the use of unfriendly solvents are steadily gaining considerable interest [28]. Water represents the solvent *par excellence* because of its potential advantages in terms of cost, safety, work-up procedure and environmental concerns. Unfortunately, not all reactions are feasible in water: many organic compounds are almost insoluble in water and many reactive intermediates and catalysts are decomposed in water. However, there are also a number of chemical transformations that are not only compatible with water but actually benefit from its unique physical and chemical properties [e.g., high cohesive energy density (c.e.d. = 547 cal/cm^3 at 298 K and P ambient), high dielectric constant and internal pressure, hydrophobic effect] [29]. The concept of reaction 'on water' is now well established [29d]. Water therefore presents different reactivity and selectivity patterns compared with those observed in common organic solvents. The inspiration (and stimulus) for our research came from the pioneering work of Kobayashi on the use of Brønsted acid–surfactant-combined catalysts (BASCs) [30–32], as an efficient system for multi-component C–C bond-forming reactions in water. BASCs composed of a Brønsted acidic group and a hydrophobic moiety [e.g., *p*-dodecylbenzenesulphonic acid (DBSA)] would efficiently catalyze the tandem reductive alkylation process by activating the intermediate heterodiene **3** and by creating effective micro-colloidal dispersions. This favourable catalytic behaviour was well proved by several authors in recent papers [33]. Our own familiarity with US-enhanced synthetic transformations [34] prompted a closer examination of the potential catalytic activity of DBSA as a BASC in water under US irradiation. As we expected, the reaction of **1** with benzaldehyde (1 equiv) and HEH (1.5 equiv) in water at room temperature under the influence of 20 mol% DBSA but without the need of an inert atmosphere turned out to be sluggish (8 h). It gave **4a** in a 64% yield, along with significant amounts (>15%) of the bis-adduct **5a**. In contrast, when these reaction conditions were adopted in conjunction with power US (19.6 kHz, 60 W), an improvement in terms of yields, reaction times and selectivity could be achieved. After some experimentation, we were pleased to see that this reaction went to completion (TLC check) in only 1.5 h at 30 °C (final temperature 40 °C) delivering **4a** in a 88% isolated yield with as little as 1.05 equiv HEH and 10 mol% DBSA (entry 1, method B, Table 1) and only trace (<2%) tandem reductive Knoevenagel–Michael product **5a**. The relatively short time under sonication was enough to promote the reaction completely even without the protection of an inert gas [35].

Spurred on by this finding, we investigated the scope and limitations of the US-enhanced approach using a structurally diverse set of (hetero)aromatic aldehydes (24 examples) under the optimized reaction conditions (method B, Table 1). It was found that all carbonyl partners worked well, the reactions were generally complete within 2 h and the corresponding 3-(het)arylmethyl-4-hydroxycoumarins **4** were produced in fair to excellent yields of. All reported products were characterized by ^{1}H and ^{13}C NMR spectra, mass spectra and elemental analyses. The reaction tolerates a range of substituents (electron-withdrawing and -releasing) on the (hetero)aromatic aldehyde. The presence of a bromine, iodine or dioxoboranyl substituent (entries 2, 3 and 8, respectively) is not problematic, thereby providing a potential handle for further functionalization (e.g., Heck, Stille, Sonogashira and Suzuki–Miyaura reactions) of the corresponding products **4b**, **4c** and **4h**. Similarly, the chemoselectivity of this reaction was uniformly high, irrespective of the potentially reducible functional groups (e.g., nitro) present in the aldehyde partner (entries 4 and 5).

Performing the C–C bond-forming reactions with dialdehydes **2f** and **2t** (**1**:dialdehyde in 2:1 ratio) provided the bis-alkylated adducts **4f** (71%, entry 6) and **4t** (56%, entry 20) along with trace amounts of mono-coupling products (15–20%). A distinct feature of this procedure was that it enabled the synthesis of some heterobenzylic derivatives (i.e., **4l-m**), by employing the commercially available aldehydes (entries 12–15). Attempts to prepare the mentioned derivatives by direct alkylation of **1** were thwarted by the instability [36] of the corresponding heterobenzylic halides. An additional feature is that aldehydes with acid-sensitive substituents (i.e. 2-furyl and 3-indolyl) also provided the desired products **4l** and **4p** (entries 12 and 16, respectively), which exemplified the exceptionally mild nature of this protocol. In addition, more exotic derivatives were also synthesized like ones which include polyaromatic cores (e.g., **4v**, **4w** and **8**). It is worthwhile mentioning that **8** was prepared, starting from 7-diethylamino-4-hydroxycoumarin **7** and 9-anthraldehyde, in a 66% isolated yield (entry 24). The 7-aminocoumarins like **8** which include a freely rotating dialkylamino substitution at the 7-position and a strong electron acceptor at the 3-position (in our case the 9-anthryl subunit) have been actively investigated as laser dyes for the "blue–green" region, NLO chromophores and excellent fluorophores for studying solvation dynamics in homogeneous solutions as well as in organized media [37]. Furthermore, to enlarge the potential utility of these derivatives, we attached a ferrocenyl group to the 3-position of **1** to give **4u** (entry 21). Ferrocene, undergoing a fast and reversible one-electron oxidation at readily accessible redox potentials, might allow us to monitor the binding ability of 4-hydroxycoumarin subunit by cyclic voltammetry (CV) [38,39].

In sharp contrast, aliphatic (enolizable) aldehydes showed different behaviour under identical reaction conditions with **1** leading to complicated mixtures that eluded characterization. As is to be expected, the messy reaction was possibly due to competitive aldol-type self condensation of the aldehyde [40].

Finally, in the case of 4-dimethylaminocinnamaldehyde **2i**, the product arising from the reduction of the C–C double bond, namely **4i.2**, could be isolated (50%) along with the minor product **4i.1** (27%) (entry 9) [41].

4. Conclusion

In conclusion, US may pave the way for an expedient access to a vast array of 3-(het)arylmethyl-4-hydroxycoumarins through a

tandem Knoevenagel–reductive Michael addition reaction that avoids the use of organic solvents, the need to isolate any intermediates as well as troublesome isolation operations which may be caused by side products.

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