



# Solvent-free synthesis of 3-carboxycoumarins†

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3-Carboxycoumarins, an important class of biologically active compounds, are synthesized in very high yield and in an energy efficient manner, without use of noxious reagents or volatile organic solvents, either by direct reaction of the solid reagents, or in an aqueous slurry. Remarkably, even though the first step in the reaction cascade is a condensation reaction, the reaction proceeds rapidly as a stirred aqueous slurry without application of heat. A reason for this phenomenon is advanced and recycling of the aqueous filtrate post product separation is described. Although the reaction is not 100% atom efficient (1 mole of acetone is evolved for each mole of coumarin produced) it is a significant improvement on previously described methods for the synthesis of such compounds.

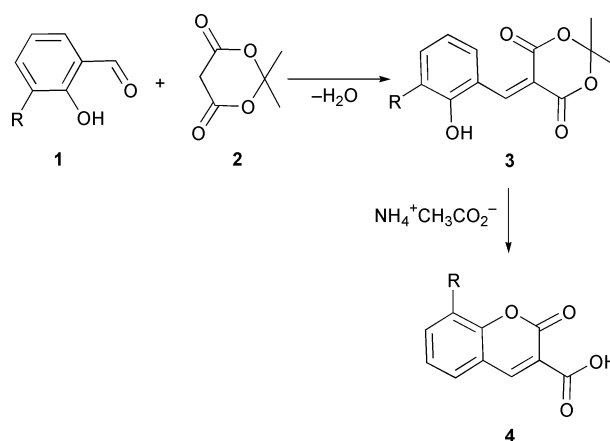
## Introduction

The 1-benzopyran-2-one, or coumarin, subunit appears in a vast range of natural products and, due to the high levels of biological activity exhibited by many such compounds, has been duplicated in numerous synthetic compounds exhibiting pharmaceutical activity. The reaction of active methylene compounds with 2-hydroxybenzaldehydes, an example of the Knoevenagel reaction, has been extensively used as the first step in the synthesis of 3-carboxycoumarins and Knoevenagel himself described the solution phase condensation of 2-hydroxybenzaldehydes with malonic acid more than 100 years ago.<sup>1</sup> Numerous synthetic routes to 3-substituted coumarins from 2-hydroxyarylaldehydes or 2-hydroxyarylketones have been published including syntheses requiring the use of noxious phosphorylating agents such as POCl<sub>3</sub>,<sup>2,3</sup> bases such as piperidine<sup>4</sup> or solvents such as DMF.<sup>5</sup> Recently a 'solid phase' synthesis of substituted 3-carboxycoumarins utilising ethyl malonate tethered to a Wang resin and suspended in pyridine has been described,<sup>6</sup> although reported yields are poor and often significantly less than 50%.

Analysis of the numerous routes to coumarins such as **4** (see Scheme 1) shows that simple, efficient 'green' methodology to this important class of heterocyclic compounds is lacking. Bandgar *et al.* have recently published a one-pot, microwave-mediated synthesis of substituted 3-carboxycoumarins which entails the use of solid catalysts.<sup>7</sup> While this method circumvents the use of noxious acids, bases or solvents it is not solvent-free as the product must be removed from the catalyst by dissolution in a volatile organic solvent and product purification by column chromatography is deemed necessary.

## Results and discussion

We now report the facile synthesis of 3-carboxycoumarins from 2-hydroxybenzaldehydes and Meldrum's acid by a room-temperature solid/solid or solid/liquid reaction with catalytic amounts of ammonium acetate. Quantitative conversion of starting materials is readily achieved without heating and no volatile organic solvents are required, with product purification



Scheme 1 a R = OMe, b R = H.

achieved by an aqueous wash yielding an aqueous solution containing ammonium acetate which may be reused in subsequent reactions. Toda has reported numerous solid/solid reactions<sup>8</sup> and we have recently described solvent-free syntheses of Aldol condensation products<sup>9</sup> and cyclic bowl shaped compounds.<sup>10</sup> The facility with which condensation reactions proceed under these conditions led us to attempt the synthesis of 3-carboxycoumarins in ground mixtures of neat reagents with remarkable results.

Grinding of solid *o*-vanillin **1a** with solid Meldrum's acid **2** leads to the almost quantitative formation of the Knoevenagel

## Green Context

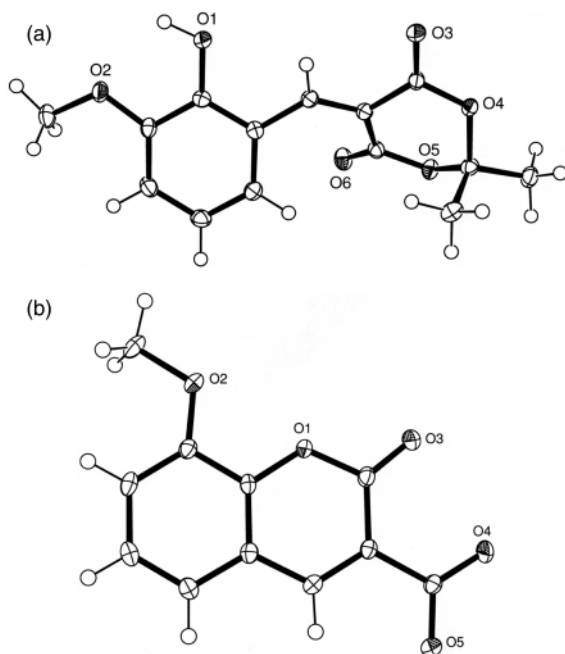
The development of solvent-free reactions is an important step towards simplifying reaction systems and minimising waste. However, most such systems described in the literature require the use of solvents during the isolation stage, thus making the process as a whole solvent-intensive. Here, a solid state (or aqueous slurry) route to coumarins has been developed, which uses a water-soluble catalyst. Reaction takes place readily and efficiently, and the isolation is simply a filtration after suspension in water to remove the catalyst.

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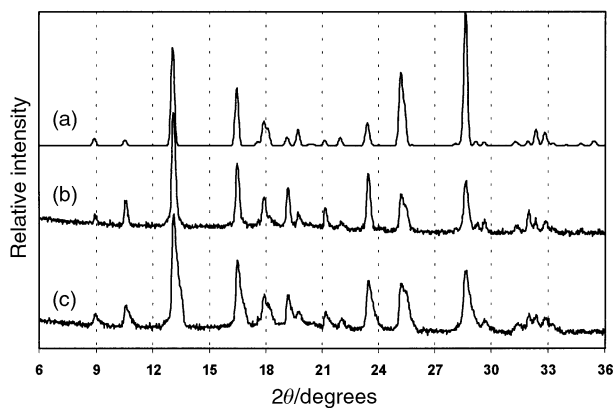
† Electronic supplementary information (ESI) available: cell dimensions vs. temperature of data collection for **4a**. See <http://www.rsc.org/suppdata/gc/b0/b006704k/>

product **3a** while addition of catalytic amounts of ammonium acetate to the mixture of solid reagents results in almost quantitative conversion to **4a** (Scheme 1). Isolation of the product is achieved by slurrying in water followed by filtration and drying.‡ The bright yellow intermediate benzylidene Knoevenagel product **3a** may be isolated from reaction mixtures containing no ammonium acetate. A similar reaction with liquid salicylaldehyde **1b** and Meldrum's acid in the presence of ammonium acetate yields the corresponding coumarin **4b** quantitatively. Grinding of liquid **1b** and solid **2** without catalyst does not, however, lead to significant formation of **3b**.

The unequivocal identification of solid products obtained in solid/solid reactions requires the use of non-solution analytical or spectroscopic methods and to this end molecular structure and geometry of each of the products, **3a**, **4a** and **4b** has been established by single crystal X-ray diffractometry.§ The molecular structures of **3a** and **4a** are illustrated in Fig. 1 and X-ray powder diffraction patterns obtained from solid samples of reaction products were compared with those generated from single crystal data<sup>11</sup> to verify that the reaction had indeed occurred in the solid or slurry forms and the products were not an artifact of analysis. Fig. 2 illustrates the comparison between



**Fig. 1** ORTEP molecular diagrams, with ellipsoids at 50% probability, of (a) benzylidene intermediate **3a** and (b) coumarin product **4a**. The preferred *E*-configuration of the intermediate in the solid state is clear.



**Fig. 2** Comparison between X-ray powder diffraction patterns of coumarin products **4a** produced by solid grinding method (c), aqueous slurry method (b) and the calculated pattern derived from single crystal data (a) and corrected for room-temperature cell dimensions.

the powder pattern generated from single crystal data and solid/solid and slurry reaction products for compound **4a**.¶

Remarkably, in spite of the extremely low aqueous solubility of both Meldrum's acid and the benzaldehyde derivatives used, the reaction may be carried out in an aqueous solution of ammonium acetate, yielding 3-carboxycoumarins of high purity in almost quantitative yield. The aqueous ammonium acetate solution obtained once the solid product is filtered off may be reused in further reactions without detriment to product quality. Alternately the benzylidene intermediate **3a** may be isolated from a reaction mixture containing no catalysts and slurried in aqueous ammonium acetate to yield the same result. The reaction proceeds most rapidly when powdered reagents are added directly to a stirred aqueous solution of ammonium acetate. This holds true even in the reaction with salicylaldehyde **1b** (a viscous liquid) where a separate organic phase is formed upon addition to aqueous ammonium acetate. As the reaction proceeds this oily phase is consumed and a white slurry results.

It is generally accepted that the second step in the Knoevenagel reaction, the 1,2-elimination, is inhibited in protic solvents<sup>12</sup> and this may provide a clue to the increased rate of reaction in aqueous slurry. The benzylidene formed crystallises as the *E*-isomer yet only the *Z*-isomer has the correct orientation for ring closure to the coumarin. If 1,2-elimination is inhibited and hydrolysis of Meldrum's acid and ring closure proceeds once the  $\beta$ -hydroxydiketone is formed, *i.e.* before or concomitantly with 1,2-elimination of water, then, the longer lived the flexible  $\beta$ -hydroxydiketone, the more favourable the conditions for coumarin formation and the more rapid the reaction.

We have demonstrated a convenient, clean and efficient method for the formation of an important class of biologically active compounds that obviates the need for polar aprotic solvents such as DMF or solid acid catalysts and requires no organic solvent or heat. The product is of high purity and waste is minimised.

## Experimental

<sup>1</sup>H NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer in CDCl<sub>3</sub> or d<sub>6</sub>-acetone solution with TMS as reference.

Crystals suitable for single crystal diffractometry were prepared from isolated products by deposition from acetone or acetone–dichloromethane solutions. Data for all structures were collected on an Enraf-Nonius Kappa CCD at 123 K using graphite monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.71073$  Å,  $1^\circ \varphi$  and  $\omega$  scans). Structures were solved by direct methods using the program SHELXS-97<sup>13</sup> and refined by full matrix least squares refinement on  $F^2$  using the programs SHELXL-97<sup>14</sup> and Xseed.<sup>15</sup> Non-hydrogen atoms were refined anisotropically and hydrogen atoms inserted at geometrically determined positions with temperature factors fixed at 1.2 times that of the parent atom except for methyl hydrogen atoms where the temperature factors were constrained to equal 1.5 times that of the parent carbon atom.

## Solvent free reactions

Powdered reagents (1:1 molar ratio) were gently ground together in a mortar and pestle and a catalytic amount of NH<sub>4</sub><sup>+</sup>MeCO<sub>2</sub><sup>-</sup> (0.05–0.15 mol equivalents based on the benzaldehyde derivative) added and the reagents thoroughly mixed by grinding. The resultant sticky mass was allowed to stand, with occasional grinding, overnight or until no starting material was detectable by TLC analysis. The ground mixture underwent a series of colour and consistency changes from white powders to sticky bright yellow material to off-white or

beige solid. After regrinding, the product was suspended in water to dissolve the catalysts, filtered off, washed with water and dried in air.

### Slurry reactions

Powdered reagents (1:1 molar ratio) were stirred in water (*ca.* 10 volumes based on reagent mass) to produce a slurry. A catalytic amount of  $\text{NH}_4^+\text{MeCO}_2^-$  (0.05–0.15 mol equivalents based on the benzaldehyde derivative) was added and the slurry stirred overnight. The resultant white or beige slurry was filtered and the product dried in air. The filtrate was retained for reuse in further reactions.

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### Notes and references

‡  $^1\text{H}$  NMR spectra of coumarins prepared by both slurry and solid/solid methods indicate products of high purity, while **3a** shows traces of coumarin.

§ *Crystal data*: for **3a**:  $\text{C}_{14}\text{H}_{14}\text{O}_6$ ,  $M_r = 278.25$ , triclinic, space group  $P\bar{1}$ ,  $a = 5.9637(2)$ ,  $b = 9.1230(6)$ ,  $c = 12.0646(7)$  Å,  $\alpha = 99.666(3)$ ,  $\beta = 96.329(3)$ ,  $\gamma = 95.837(3)^\circ$ ,  $V = 638.28(6)$  Å<sup>3</sup>,  $Z = 2$ ,  $\mu(\text{Mo-K}\alpha) = 0.114$  mm<sup>-1</sup>. Of 5454 reflections measured, 2985 were unique with 2221 having  $I > 2\sigma(I)$ ,  $R$  indices [ $I > 2\sigma(I)$ ]  $R_1 = 0.0437$ ,  $wR_2 = 0.0673$ , GOF on  $F^2 = 1.037$  for 188 refined parameters and one restraint (OH bond length).

For **4a**:  $\text{C}_{11}\text{H}_8\text{O}_5$ ,  $M_r = 220.17$ , monoclinic, space group  $P2_1/c$ ,  $a = 5.1100(2)$ ,  $b = 19.5292(4)$ ,  $c = 9.4299(3)$  Å,  $\beta = 99.909(2)^\circ$ ,  $V = 927.01(5)$  Å<sup>3</sup>,  $Z = 4$ ,  $\mu(\text{Mo-K}\alpha) = 0.127$  mm<sup>-1</sup>. Of 4155 reflections

measured, 2151 were unique with 1583 having  $I > 2\sigma(I)$ ,  $R$  indices [ $I > 2\sigma(I)$ ]  $R_1 = 0.0437$ ,  $wR_2 = 0.0690$ , GOF on  $F^2 = 1.037$  for 146 refined parameters and zero restraints. The carboxylic acid group is disordered with apparent C–O bond lengths intermediate between expected single and double bond lengths and the largest residual electron density peaks were found at 0.8–0.9 Å from the oxygen atoms suggesting two carboxylic H positions. The carboxylic H-atoms were not included in the model.

For **4b**: colourless, tabular crystals were found to have cell dimensions indistinguishable from those found by Dobson and Gerkin.<sup>16</sup>

CCDC 1048/3. See <http://www.rsc.org/suppdata/gc/b0/b006704k/> for crystallographic files in .cif format.

¶ Single crystal data was collected at 123 K while powder data was collected at 294 K. Measurements of cell dimensions at temperatures between 123 and 293 K indicate distinct anisotropic shrinkage of cell dimensions (ESI†) which are corrected for in the calculated powder pattern.

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