Efficient and Chemoselective Access to 3-(Chloromethyl)coumarins via Direct Cyclisation of Unprotected Baylis–Hillman Adducts

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Abstract: Reaction of substituted 2-hydroxybenzaldehydes with t-butyl acrylate in the presence of DABCO has been shown to afford isolable Baylis–Hillman adducts, acid-catalysed cyclisation of which affords the corresponding 3-(chloromethyl)coumarins directly and in high yield.

Key words: heterocycles, synthesis, coumarins, 2H-1-benzopyran-2-ones, Baylis–Hillman reaction

The coumarin nucleus is well represented in natural products, and in a variety of pharmacologically active compounds. Recently reported examples include: coumarin-7-xylosides, as oral anti-thrombotic agents; synthetic analogues of the naturally-occurring anti-bacterial, novobiocin and clorobiocin; and khellactone derivatives as potential HIV-1 inhibitors. Various syntheses of coumarin derivatives have been developed and, in recent communications, we have reported the application of Baylis–Hillman methodology in the preparation of 3-substituted coumarins.

The major challenge in this approach has been to achieve regioselective cyclisation since the somewhat elusive, unprotected analogues (considered to act as pivotal intermediates) tend to cyclise directly to form complex mixtures of chromene and coumarin derivatives. Initially, attention was given to the use of protecting groups to obtain coumarins chemoselectively, and O-benzylated 2-hydroxybenzaldehydes were successfully used as substrates, permitting isolation of the corresponding Baylis–Hillman adducts. Cyclisation to the chromenes via conjugate addition (Path I; Scheme 1) was prevented by nucleophilic interception of the electrophilic vinylic centre through the addition of either an amine (benzylamine or piperidine) or a halogeno acid. Subsequent removal of the O-benzyl protecting group and cyclisation via acyl substitution then afforded the 3-substituted coumarins. We now report an application of Baylis–Hillman methodology in which 3-(chloromethyl)coumarins are produced chemoselectively without any recourse to the use of protecting groups.

Scheme 1

Scheme 2
When salicylaldehyde 1a was reacted with \( t \)-butyl acrylate 11 in the presence of DABCO, the Baylis–Hillman adduct 12a was obtained as a surprisingly stable and isolable product (Scheme 3). In order to explore its potential to undergo direct cyclisation to chromene or coumarin products, the adduct 12a was treated with DABCO in CDCl\(_3\). \(^1\) \(^1\)H NMR analysis of the reaction mixture, however, revealed that the adduct 12a had, in fact, reverted to the precursors 1a and 11, confirming the possibility of retro-Baylis–Hillman processes. The adduct 12a was then heated in refluxing acetic acid to afford a 1:2 mixture of the chromene-2-carboxylic ester 13 and the 3-(acetoxy-methyl)coumarin 14, supporting the assumption that such adducts can provide access to chromene and coumarin derivatives – albeit under acidic conditions! Formation of the acetoxy derivative 14 is attributed to addition of acetic acid either prior to or following cyclisation of the adduct 12a, as outlined in Scheme 4. However, when the adduct 12a was treated with hydrochloric acid in refluxing acetic acid for one hour, the 3-(chloromethyl)coumarin 10a was obtained in 98% yield! Surprisingly, use of hydriodic acid (instead of hydrochloric acid) and a mixture of acetic acid and acetic anhydride (as solvent) gave the 3-iodomethyl analogue 9a in only 17% yield.

Given the success of these preliminary results, a series of 2-hydroxybenzaldehydes (1b,e,f) was reacted with \( t \)-butyl acrylate 11 in the presence of DABCO to afford the corresponding Baylis–Hillman adducts 12b,e,f, in yields ranging from 41–66%. Reaction of these adducts with hydrochloric acid in refluxing acetic acid then afforded the 3-(chloromethyl)coumarins 10b,c,e,f in excellent yield (86–98%). The reaction presumably involves initial conjugate addition of HCl (or HI) to the \( \alpha,\beta \)-unsaturated ester moiety prior to acid-catalysed lactonisation, thus inhibiting formation of chromenes as competition products.

In summary, stable salicylaldehyde-derived Baylis–Hillman adducts have been isolated and cyclised under acidic conditions to produce 3-(chloromethyl)coumarins chemoselectively, in high yield and without the need to use any protecting groups.

NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at 303 K in CDCl\(_3\), and calibrated using solvent signals. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 spectrometer. Low-resolution (EI) mass spectra were obtained on a Finnigan GCQ mass spectrometer and high-resolution (EI) mass spectra on a VG70-SEQ Micromass double-focusing magnetic sector spectrometer (Cape Technikon Mass Spectrometry Unit).

Full characterisation of the 3-(halomethyl)coumarins 9 and 10, prepared in this study, has been reported previously.\(^6\)\(^7\) The general synthetic procedures are illustrated by the following examples.

**tert-Butyl 3-Hydroxy-3-(2-hydroxyphenyl)-2-methyleneponoate (12a)**

A mixture of salicylaldehyde 1a (98%; 1.0 mL, 9.2 mmol), \( t \)-butyl acrylate 11 (2.1 mL, 23 mmol) and DABCO (0.86 g, 7.7 mmol) in CDCl\(_3\) (3 mL) was stirred in a stoppered reaction flask for 14 d. The mixture was concentrated in vacuo to give a dark brown oil, which was purified using flash chromatography (hexane–EtOAc, 4:1) to afford 12a (0.95 g, 41%) as a colourless oil which later crystallised; mp 108–110 °C.

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**Scheme 3**

**Scheme 4**

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Conc. HCl (4 mL) was added to a solution of 3-(Iodomethyl)coumarin (9a) 7 in HOAc (2 mL). The mixture was boiled under reflux for 2 h, allowed to cool to r.t. and then poured into ice-cooled H2O (10 mL). Stirring for ca. 30 min gave a precipitate, which was filtered off and washed with hexane to afford 10a as a grey solid (0.39 g, 98%).

HRMS: m/z (%): 232 (M+, 47.6), 131 (100).

1H NMR (400 MHz, CDCl3): δ = 1.51 [9 H, s, C(CH3)3], 4.29 (1 H, d, J = 3.0 Hz, OCH3), 6.85–7.20 (4 H, series of m, ArH), 8.09 (1 H, s, ArOH).

13C NMR (100 MHz, CDCl3): δ = 78.0 [C(CH3)3], 112.6, 119.5, 121.6, 124.1, 127.8, 129.6, 142.0, 143.8 and 147.1 (C=CH2 and ArC), 166.2 (C=O).

MS (EI): m/z (%) = 232 (M+, 47.6), 131 (100).

HRMS: m/z calc’d for C13H10O4: 218.05797; found: 218.05791; m/z calc’d for C13H10O5, 280.13107; found: 280.13073.

**tetr-Butyl 2H-1-Chromene-3-carboxylate 13 and 3-(acetoxymethyl)coumarin (14)**

A mixture of 52 mg, 0.21 mmol) in HOAc (12 mL) was boiled under reflux for 6 h. H2O (10 mL) was added to the cooled solution and the resulting mixture was extracted with CHCl3. The organic solution was dried over anhyd Na2SO4, filtered and evaporated in vacuo to afford a yellow solid, which was purified using preparative layer chromatography (CHCl3:hexane, 3:1) to afford 13 and 14.

**tetr-Butyl 2H-1-chromene-3-carboxylic acid 13**

Pale-yellow oil; yield: 50 mg, 38%.

1H NMR (400 MHz, CDCl3): δ = 1.53 [9 H, s, C(CH3)3], 4.94 (2 H, d, J = 0.8 Hz, CH2), 6.82 (1 H, d, J = 8.0 Hz, ArH), 6.86–7.23 (3 H, series of m, ArH), 7.32 (1 H, s, 4-H).

13C NMR (100 MHz, CDCl3): δ = 78.0 [C(CH3)3], 64.6 (CH2), 81.2 [C(CH3)2], 116.0, 121.1, 121.6, 124.3, 128.7, 131.6, 132.5 and 155.0 (ArC), 163.9 (CeO).

MS (EI): m/z (%): 232 (M+, 47.6), 131 (100).

HRMS: m/z calc’d for C14H16O3: 232.04641; found, 232.04643.

**tetr-Butyl 3-(3-Ethoxy-2-hydroxyphenyl)-3-hydroxy-2-methyleprenopanoate (12c)**

Pale-yellow crystals; yield: 1.65g, 56%.

HRMS: m/z (%): 276 (M+, 18.2), 220 (100).

**tetr-Butyl 3-(5-Bromo-2-hydroxyphenyl)-3-hydroxy-2-methyleprenopanoate (12f)**

White crystals; yield: 1.70g, 41%; mp 186–188 °C.

HRMS: m/z (%) = 328 [M+ (79 Br2), 3.7], 211 (100).

**tetr-Butyl 3-(3,5-Dibromo-2-hydroxyphenyl)-3-hydroxy-2-methyleprenopanoate (12f)**

White crystals; yield: 2.07g, 66%; mp 186–188 °C.

1H NMR (400 MHz, CDCl3): δ = 1.51 [9 H, s, C(CH3)3], 4.26 (1 H, br s, OH), 5.56 and 6.26 (2 H, 2 x s, C=CH2), 6.79 (1 H, d, J = 8.7 Hz, ArH), 7.09 (1 H, d, J = 2.1 Hz, ArH), 7.28 (1 H, dd, J = 2.1 and 8.7 Hz, ArH), 8.18 (1 H, br s, ArOH).

13C NMR (100 MHz, CDCl3): δ = 76.0 [C(CH3)3], 64.5 (OCH2CH3), 69.4 (CHOH), 81.5 [C(CH3)2], 111.3, 119.5, 119.6, 125.1, 126.6, 142.2, 143.6 and 146.1 (C=CH2 and ArC), 166.1 (CeO).

MS (EI): m/z (%): 294 (M+, 18.2), 220 (100).

HRMS: m/z calc’d for C17H17O5, 294.14672; found, 294.14688.

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**References**


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(8) In our own studies unprotected Baylis–Hillman adducts of this type have only been isolated as minor products in reactions of protected substrates.


(14) Nominal m/z values from HRMS analysis.