The Baylis-Hillman entrée to heterocyclic systems — the Rhodes contribution

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This review focuses on applications of the Baylis-Hillman reaction in the synthesis of various heterocyclic products, which include indolizines, chromenes, thiochromenes, coumarins and quinolines. Attention is also given to the mechanistic implications and the elaboration of various products to afford compounds with medicinal potential.

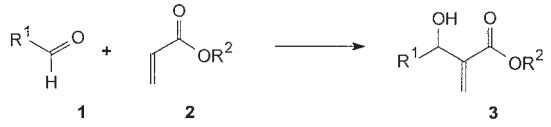
Simply stated, organic synthesis may be viewed as the construction of target molecules by forming carbon–carbon bonds between appropriate structural fragments (synthons). In the Baylis-Hillman reaction,[1] first reported in the patent literature in 1972,[2] multi-functional products (**3**) are obtained by reacting aldehydes (**1**) with activated alkenes (**2**) in the presence of a tertiary amine catalyst, typically 1,4-diazabicyclo[2.2.2]octane (DABCO) (Scheme 1). In an even earlier report, Morita *et al.*[3] had described the use of tertiary phosphine catalysts in similar transformations and, consequently, in his review of the Baylis-Hillman reaction,[4] Ciganek has suggested that the reaction should be known as the 'Morita-Baylis-Hillman' reaction.

In our own research at Rhodes during the last fifteen years, attention has been given to exploring both the mechanistic basis and potential applications of this important reaction, which has now achieved 'text-book' status![29] While generally easily executed, Baylis-Hillman reactions can be exceedingly slow — in some cases requiring several weeks to afford reasonable yields. Use of highly reactive pyridinecarbaldehydes [e.g. (**4**)] as substrates results in significant rate acceleration,[5] permitting kinetic data to be collected in a matter of hours. The resulting data provided the basis for the first reported kinetic-mechanistic study of the reaction[6] — a reaction in which formation of the zwitterionic species (**7**) (Scheme 2) is considered to be rate-determining. While collapse of this intermediate could, in principle, follow either E2 or $E1_{CB}$ pathways, the latter appears to be supported by computational results (manuscript in preparation).

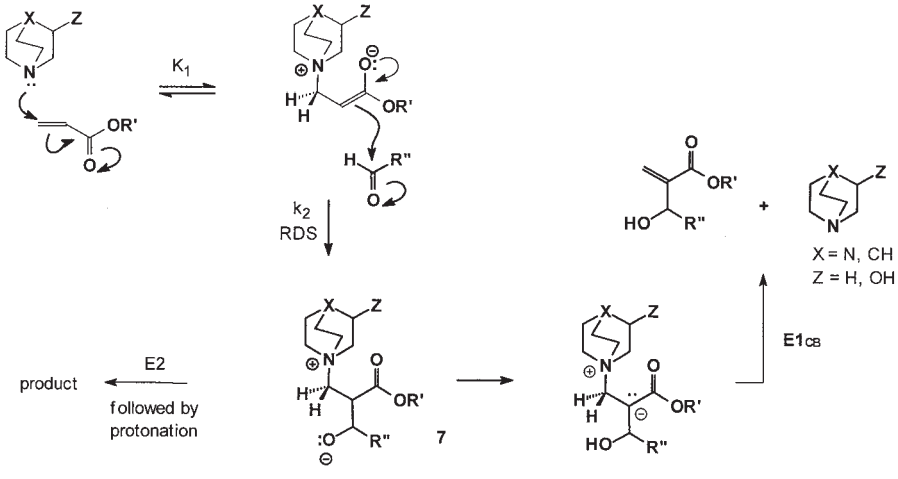
Serendipity often plays a significant role in scientific discovery and, in our own research, served to introduce us to the potential of the Baylis-Hillman reaction in the construction of benzannulated heterocyclic products. Attempted distillation of a *liquid* Baylis-Hillman adduct of type (**5**) afforded, unexpectedly, colourless *crystals*, subsequent analysis of which indicated the formation of the indolizine (**6**) via thermal cyclization of the corresponding adduct (**5**) (Scheme 3).[7] The generality of this approach to indolizines was demonstrated,[8] prompting us to explore the formation of other benzannulated heterocycles, such as the chromenes (**9**), via similar cyclization of Baylis-Hillman adducts generated using 2-hydroxybenzaldehyde precursors (**8**) (Fig. 1). In an initial attempt to exploit this approach,[9] the novel, crystalline coumarin derivative (**10**) (Scheme 4) was isolated in low yield. In subsequent studies,[10,11] however, careful chromatographic separation of the product mixtures afforded representative examples of no less than eight classes of chromene and coumarin derivatives, reflecting a cascade of competing and consecutive transformations (Fig. 2).

While these results clearly indicated the *potential* of the Baylis-Hillman reaction in the construction of heterocyclic systems, it was equally apparent that several questions needed to be addressed if the method was to be synthetically useful. For example: Could the regioselectivity of cyclization be controlled to afford *either* chromenes (Path I; Fig. 2) *or* coumarins (Path II) *chemoselectively*? Could the yields be improved? Could the method be extended to include the preparation of nitrogen- and sulphur-containing analogues? Could the putative intermediacy of the Baylis-Hillman adducts (**11**) be confirmed?

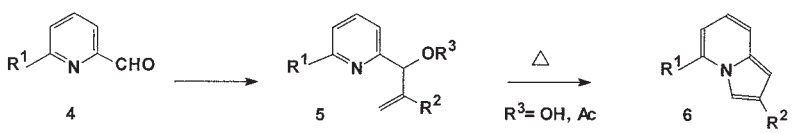
The *chemoselective* synthesis of the chromene derivatives (**14**) was successfully achieved using activated alkenes (**12**) (such as vinyl ketones, sulphones or sulphonates) in which the activating



Scheme 1



Scheme 2



Scheme 3

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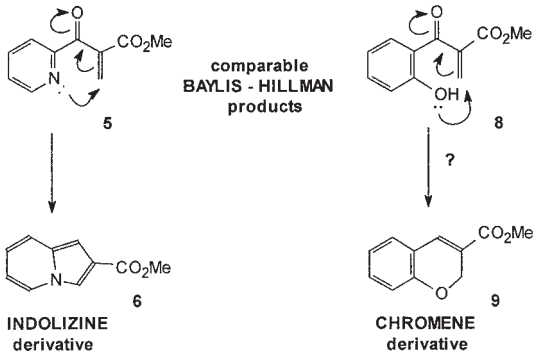
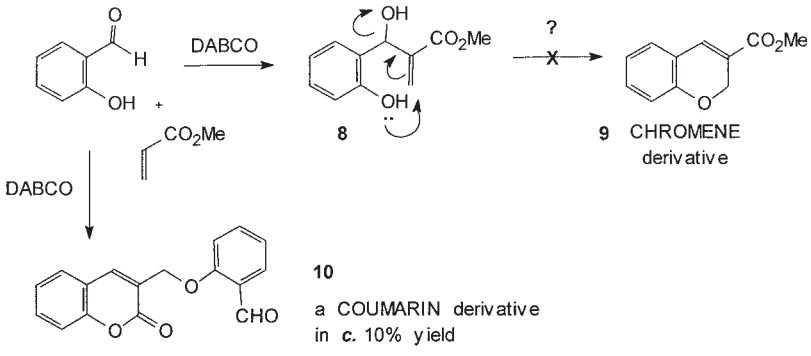


Fig. 1. Putative cyclization to chromene derivatives.



Scheme 4

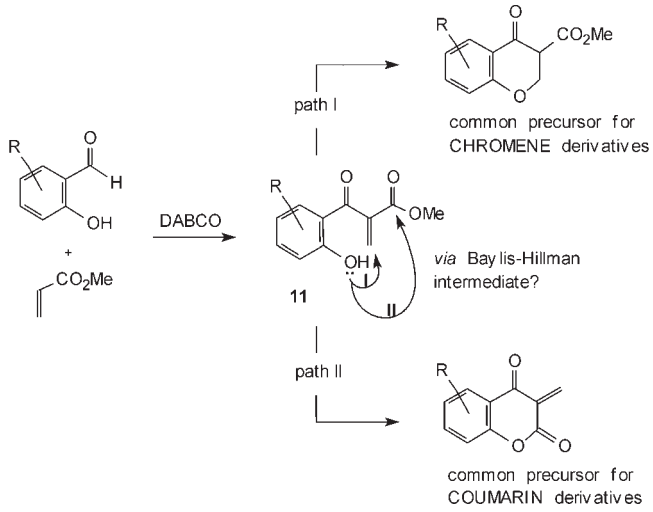
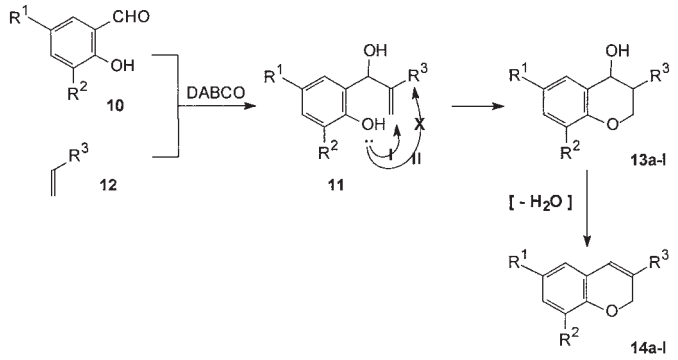
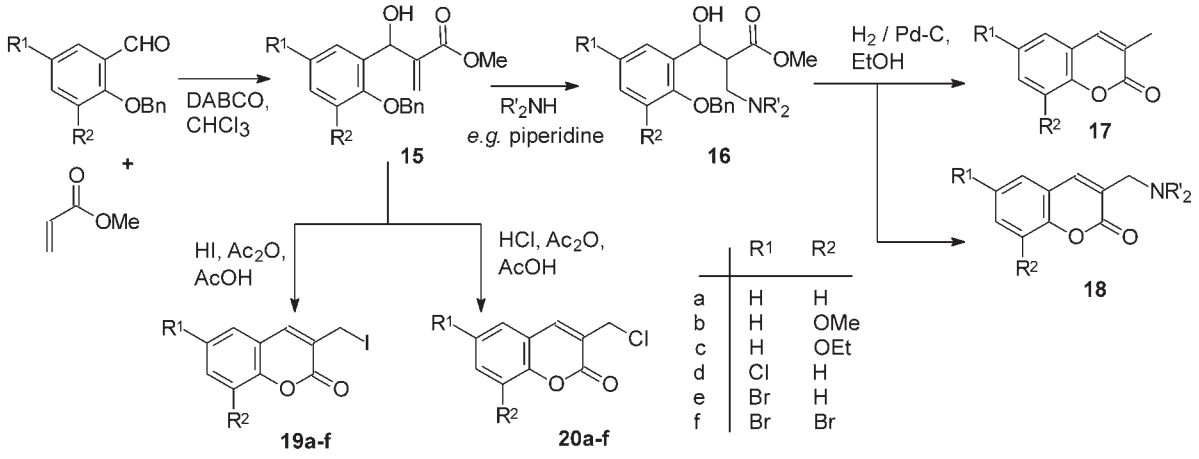


Fig. 2



Scheme 5

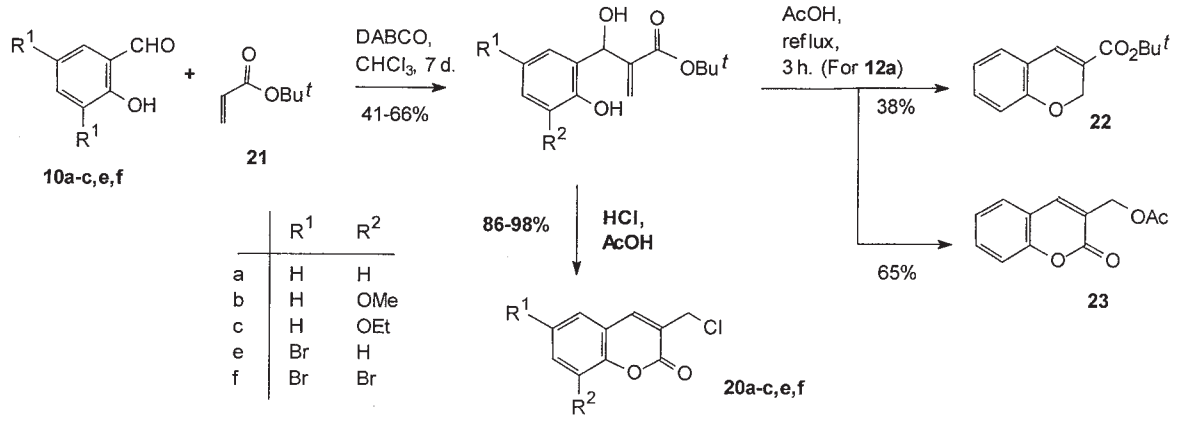


	R1	R2
a	H	H
b	H	OMe
c	H	OEt
d	Cl	H
e	Br	H
f	Br	Br

Scheme 6

group (R^3) effectively inhibits cyclization via the acyl substitution pathway (Path II; Scheme 5).[12,13] Application of the Baylis-Hillman method to the preparation of coumarin derivatives, however, required inhibition of the conjugate addition pathway (Path I), and several approaches to this problem were investigated. In the first (extending work reported by Drewes *et al.*[30]), the nucleophilicity of the phenolic oxygen was masked by *O*-benzylation and the electrophilicity of the C–C double bond by nucleophilic interception using an amine (piperidine or benzylamine; Scheme 6).[14] Debenzylation of the protected intermediates (**16**) then afforded the coumarin derivatives (**17**) and (**18**). In an alternative but mechanistically similar approach, the halogen acids, HI or HCl, were used to effect the nucleophilic interception and debenzylation steps consecutively, in one pot, affording the 3-halogenomethyl derivatives, (**19**) and (**20**), respectively.[15] In an even simpler approach (Scheme 7), use of *tert*-butyl acrylate (**21**) as the activated alkene permitted convenient,[19] direct access to the coumarin derivatives (**20**), (**22**) and (**23**), without recourse to the use of *any* protecting group strategies!

In principle, the direct formation of chromene and coumarin derivatives from unprotected 2-hydroxybenzaldehydes could occur via the alternative pathways B and C, rather than the Baylis-Hillman pathway A — as illustrated in Fig. 3. We have, however, obtained and reported substantial evidence for the intermediacy of Baylis-Hillman



Scheme 7

adducts in these reactions.[17]

Extension of the general method to the preparation of the sulphur-containing thiochromene analogues (**26**) (Scheme 8) was facilitated by the spontaneous formation of the disulphide (**25**) during oxidation of the hydroxymethyl precursor (**24**) — a 'self protection' that effectively masks the nucleophilic thiol group. Baylis-Hillman reactions of the disulphide dicarbaldehyde (**24**), using 1,6-diazabicyclo[4.4.0]undecane (DBU) as the nucleophilic catalyst, afforded the required products (**26**) directly and in good yield. Somewhat surprisingly, but most conveniently, the reaction conditions permit *in situ* reduction of the disulfide moiety and consequent cyclization to the required thiochromenes (**26**).[18]

2-Aminobenzaldehydes would seem, at first sight, to be obvious Baylis-Hillman precursors for the construction of quinolines (nitrogen-containing analogues); they are, however, relatively inaccessible. Moreover, the 2-amino group is expected to decrease the electrophilicity of the aldehyde carbonyl group, thus inhibiting reactivity under Baylis-Hillman conditions. Consequently, 2-nitrobenzaldehydes were explored as activated alternatives, subsequent reduction of the nitro group being expected to permit cyclization of the resulting amine. As expected, reaction of 2-nitrobenzaldehyde (**27**) with activated alkenes [(**28**); Scheme 9] provided access to the corresponding Baylis-Hillman adducts (**29**). The regioselectivity of cyclization following reduction, however, appears to depend on the nature of substituent 'R' in the activated alkene (**28**). Thus, acrylic esters (R = OMe, OEt) appear to favour cyclization via acyl substitution to give 2-quinolones [e.g. (**30**), (**32**)–(**34**)], whereas, vinyl ketones [(**28**); e.g. R = Me] favour cyclization via nucleophilic addition, *in situ* dehydration affording quinoline *N*-oxides [e.g. (**31**)] or quinolines directly.[19]

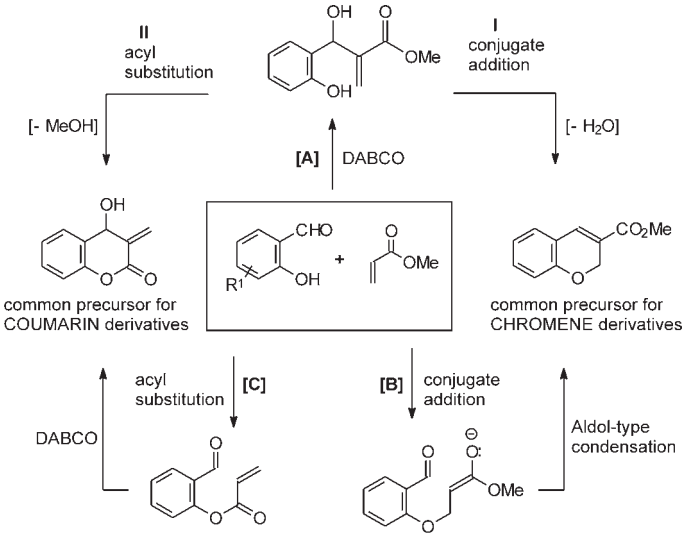
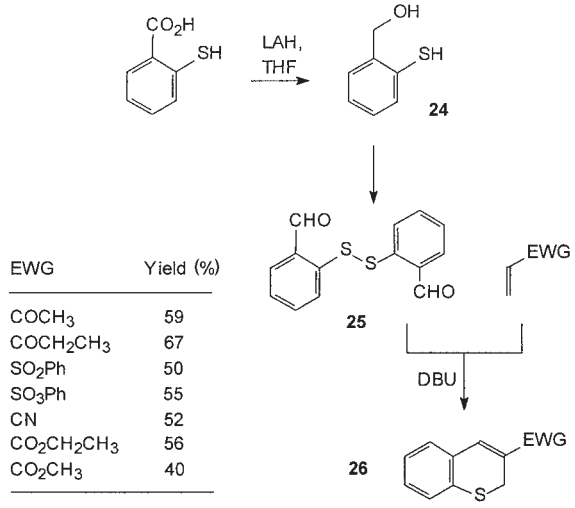


Fig. 3. Possible pathways to chromene and coumarin derivatives.



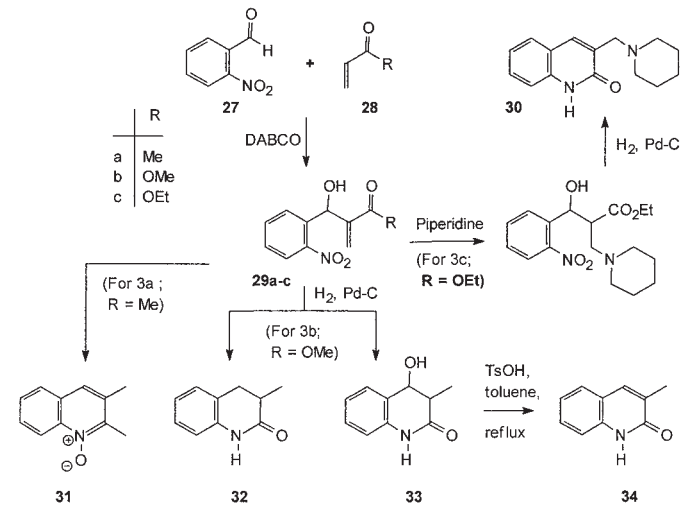
Scheme 8

The quinoline nucleus is present in quinine and in many synthetic anti-malarial agents, while indolizines, in addition to exhibiting various pharmacological effects, have found use as dyes, photographic sensitizers and fabric brighteners.[20,21] The oxygenated systems, coumarins and chromenes, are widely distributed in nature, with many of them showing interesting biological activity.[22,23] In this general context, the development of novel synthetic approaches to medicinally and technologically useful compounds has obvious relevance.

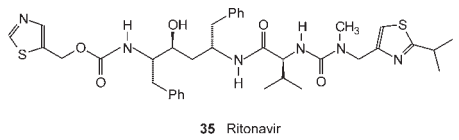
We have also begun to explore specific Baylis-Hillman-derived compounds as potential HIV-1 protease and integrase inhibitors. Particular attention has been given to the preparation of analogues of ritonavir (**35**), one of a number HIV-1 protease inhibitors in clinical use.[24,25] On binding to the enzyme active site, such compounds block access by endogenous substrates, thus inhibiting enzyme function critical for viral replication. Our initial approach has been to prepare analogues (such as the chromene-derived system (**37**) illustrated in Scheme 10), in which Baylis-Hillman-derived heterocycles are attached to the

amino termini of the hydroxyethylene dipeptide isostere (**36**),[26] present in ritonavir. A range of such analogues, containing chromone or Baylis-Hillman-derived chromene, thiochromene and coumarin systems, has been prepared.[27] Results from *in silico* enzyme-docking studies and *in vitro* enzyme-inhibition assays indicate the potential of some of these compounds to act as HIV-1 protease inhibitors.[28] Current research in this area is focused on developing structurally simpler (and, hence, synthetically more accessible) Baylis-Hillman-derived heterocyclic products as HIV-1 protease and integrase inhibitors (V. Pakhade and D.M. Molefe, unpubl. obs.).

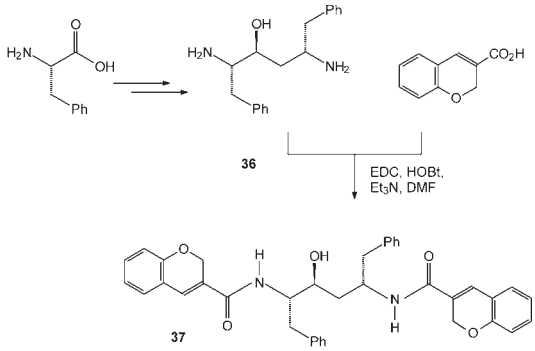
Without the much-appreciated contributions of the colleagues and research students whose names appear in the reference section, there would have been nothing to report! The generous financial support of the National Research Foundation, the Medical Research Council and Rhodes University is also gratefully acknowledged.



Scheme 9



35 Ritonavir



Scheme 10

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