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Highly regio- and stereoselective synthesis of tricyclic frameworks using Baylis–Hillman derivatives

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Abstract

A simple and convenient synthetic route for the synthesis of tricyclic chromeno[4,3-*b*]pyrrolidine frameworks using Baylis–Hillman bromides involving in situ formation of an imine, decarboxylation and a [3+2] cycloaddition sequence is described.

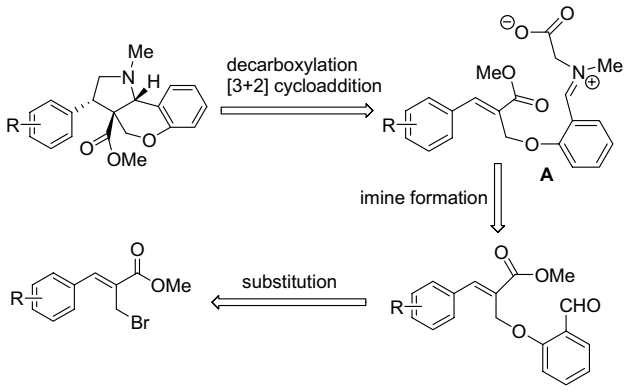
Keywords: Baylis–Hillman reaction; Intramolecular [3+2]cycloaddition; Azomethine ylides; 1,3-Dipolar cycloaddition; Tricyclic compounds

The Baylis–Hillman reaction is an atom economical, green and simple reaction which provides densely functionalized molecules.[1–4] As a result, Baylis–Hillman adducts have become valuable sources for making cyclic frameworks, especially tricyclic compounds containing heteroatoms.[5–7] The abundance of oxygen- and nitrogen-containing cyclic compounds in pharmaceuticals and agrochemicals continues to ensure that they are important synthetic targets for organic chemists.[8–10]

Concerted [3+2] cycloaddition of azomethine ylides is a powerful tool for the construction of various types of complex polyheterocyclic frameworks.[11–14] In recent years the azomethine ylide has gained a vital place in the field of heterocyclic chemistry as it serves as an important building block for the construction of nitrogen-containing five-membered heterocycles, which are often an integral part of many natural products and bioactive molecules.

In continuation of our interest in the field of Baylis–Hillman chemistry,[15–17] we herein report a simple and convenient route for the synthesis of tricyclic chromeno [4,3-*b*]pyrrolidine frameworks from Baylis–Hillman bromides involving substitution followed by in situ formation of an imine, decarboxylation and a [3+2] cycloaddition sequence as shown in the retrosynthetic strategy described in Scheme 1. This type of tricyclic chromeno[4,3-*b*]pyrrolidine framework is known as a non-competitive antagonists of the muscular nicotine receptor.[18] Moreover, a similar tricyclic skeleton is present in martinelline,[19] a natural product isolated from *Martinella iquitosensis*.

Baylis–Hillman adducts have been utilized for the synthesis of various heterocyclic compounds.[1–4] An efficient and short synthesis of complex organic molecules is a challenging task for organic chemists. To date Baylis–Hillman



Scheme 1. Retrosynthetic strategy for the synthesis of tricyclic frameworks.

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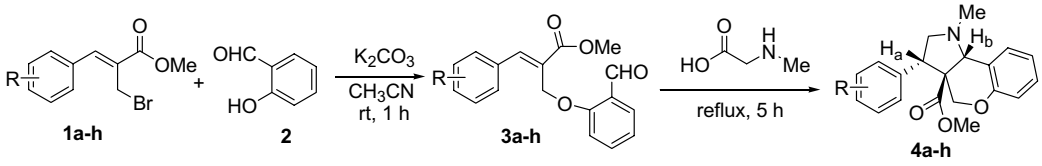


Scheme 2. R = H, 4-Me, 4-Et, 4-^{i}Pr, 4-F, 2-Cl, 3-Cl, 4-Cl.

bromides have not been utilized for the synthesis of fused tricyclic chromeno frameworks via [3+2] cycloaddition. We envisaged that the *O*-allylic salicylaldehyde derivatives prepared from Baylis–Hillman bromides would be suitable precursors for the synthesis of substituted tricyclic frameworks containing a pyrrolidine unit via a key [3+2] cycloaddition reaction using sarcosine according to the retrosynthetic strategy shown below.

To demonstrate our approach, we first selected methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**), a bromo derivative of the Baylis–Hillman (BH) adduct obtained via the reaction of benzaldehyde and methyl acrylate, as the starting material for the generation of the required precursor (**3a**) with a view to obtain the desired tricyclic chromeno pyrrolidine compounds. The best results were obtained when BH bromide **1a** was treated with salicylaldehyde in the presence of K_2CO_3 in acetonitrile for 1 h at room temperature to provide **3a** in 95% yield.

Reaction of **3a** and sarcosine without any catalyst in acetonitrile for 5 h at reflux provided successfully the desired tricyclic chromeno[4,3-*b*]pyrrolidine **4a** in very good yield (91%) after work up followed by column chromatography. Compound **4a** was characterized by IR, ^{1}H, ^{13}C NMR and mass spectral data and by elemental analysis (Scheme 2 and Table 1).

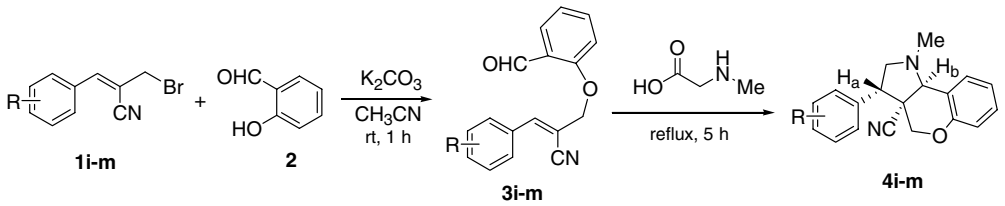
Encouraged by this result, we prepared a variety of methyl (2*E*)-2-((2-formylphenoxy)methyl)-3-arylacrylates (**3b**–**h**). The treatment of compounds **3b**–**h** with sarcosine led successfully to the desired fused tricyclic compounds **4b**–**h** in 65–92% yields (Scheme 2). The results are summarized in Table 1.

To examine further the generality of the reaction and its applicability to the Baylis–Hillman bromides derived from

Table 1
Synthesis of fused tricyclic compounds from Baylis–Hillman derivatives **1a**–**m**[21]

Allyl bromide	R	Intermediate[a,b]	Yield[c] (%)	Product[b,d]	Yield[c] (%)
1a (CO_2Me)	H	**3a**	95	**4a**	91
1b (CO_2Me)	4-Me	**3b**	87	**4b**	72
1c (CO_2Me)	4-Et	**3c**	97	**4c**	68
1d (CO_2Me)	4-^{i}Pr	**3d**	88	**4d**	69
1e (CO_2Me)	4-F	**3e**	92	**4e**	65
1f (CO_2Me)	2-Cl	**3f**	90	**4f**	92
1g (CO_2Me)	3-Cl	**3g**	90	**4g**	72
1h (CO_2Me)	4-Cl	**3h**	79	**4h**	70
1i (CN)	H	**3i**	88	**4i**	81
1j (CN)	3,4-Dimethoxy	**3j**	84	**4j**	90
1k (CN)	3-Cl	**3k**	85	**4k**	87
1l (CN)	4-Cl	**3l**	91	**4l**[e]	95
1m (CN)	2,4-Dichloro	**3m**	93	**4m**	90

[a] All reactions were carried out using 4 mmol of bromo compound **1a**–**m** and 2-hydroxybenzaldehyde (4 mmol) in 15 mL of CH_3CN in the presence of K_2CO_3 (4 mmol) at room temperature for 1 h.
[b] All products gave satisfactory IR, ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), mass spectral data and elemental analyses.
[c] Yields of the pure products (**3a**–**m** and **4a**–**m**) obtained after column chromatography (silica gel, (**3a**–**m**) 5% EtOAc in hexanes, (**4a**–**m**) 10% EtOAc in hexanes).
[d] All reactions were carried out using 2 mmol of intermediates **3a**–**m** with sarcosine (2 mmol) in 8 mL of CH_3CN under reflux for 5 h.
[e] Structures were further confirmed by single-crystal X-ray analyses.



Scheme 3. R = H, 3,4-di-OMe, 3-Cl, 4-Cl, 2,4-di-Cl.