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

Manickam Bakthadoss *, Nagappan Sivakumar, Govindan Sivakumar, Gandhi Murugan

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, Tamil Nadu, India

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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.

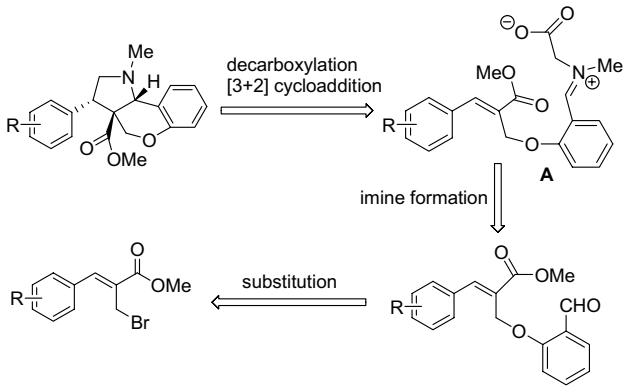
Keywords: Baylis–Hillman reaction; Intramolecular [3+2]cycloaddition; Azomethine ylides; 1,3-Dipolar cycloaddition; Tricyclic compounds

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.

* Corresponding author. Tel.: +91 44 22202812; fax: +91 44 22352494.
E-mail address: bhakthadoss@yahoo.com (M. Bakthadoss).

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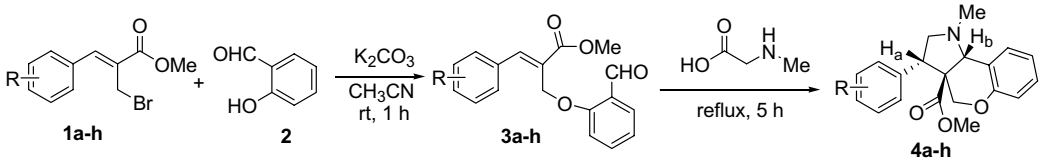


Scheme 2. R = H, 4-Me, 4-Et, 4-^{i}Pr, 4-F, 2-Cl, 3-Cl, 4-Cl.

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).

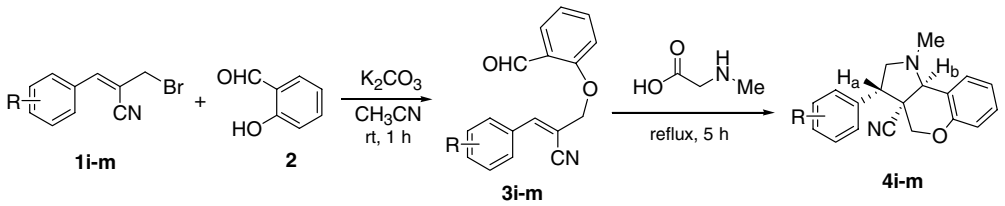
Encouraged by this result, we prepared a variety of methyl (2*E*)-2-((2-formylphenoxy)methyl)-3-arylacrylates (**3b**–**h**). The treatment of compounds **3b**–**h** with sarcosine led successfully to the desired fused tricyclic compounds **4b**–**h** in 65–92% yields (Scheme 2). The results are summarized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

acrylonitrile, we prepared precursors **3i–m** from the corresponding bromo compounds **1i–m** in very good yields. The cyano compounds **3i–m** were treated with sarcosine at reflux to provide the corresponding fused tricyclic compounds **4i–m** in very good yields (81–95%) possessing a nitrile functionality in the angular position (Scheme 3, Table 1). The results are summarized in Table 1.

It is very important to mention here that the reaction is highly regio and stereoselective as evidenced by NMR spectral data and X-ray crystal data analyses. The negative charge generated on the methylene carbon attached to the nitrogen atom after the decarboxylation of the acid moiety in intermediate **A** (see Scheme 1) forms a bond intramolecularly with the electrophilic carbon at the β-position of the α,β-unsaturated ester/cyano moiety in the same molecule rather than forming a bond at the α-position. If the negative charge on the methylene carbon, after decarboxylation, formed a bond at the α-position of the α,β-unsaturated ester/cyano moiety in the same molecule, then the product would have been the other regioisomer which is a bicyclic compound, **5** in the case of an ester as the starting material and **6** in the case of the nitrile as the starting material (Fig. 1). Furthermore, if regioisomers **5** and **6** had been formed, there would be two doublets corresponding to the H_x and H_y protons in the ^{1}H NMR spectrum (these were not observed in any of the cases). The ^{1}H NMR spectrum of compound **4a** showed a triplet for the H_a proton at δ 2.96 and a singlet for the H_b proton at δ 3.63. The CH_2 protons adjacent to oxygen in the six-membered ring appeared as two doublets at δ 4.02 and δ 3.66 (partially merged with the H_b proton). The nitrogen-attached CH_2 protons in the five-membered ring appeared as two doublets of doublets at δ 3.76 (partially merged with the ester methyl protons) and δ 3.38. The NCH_3 protons appeared as a singlet at δ 2.54. We also further confirmed the structures and the stereochemistry of **4f** and **4l** (Figs. 2 and 3) by single-crystal X-ray analysis.[20]

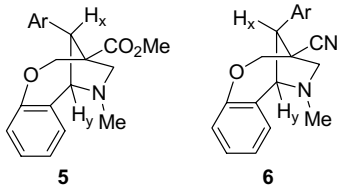


Fig. 1.

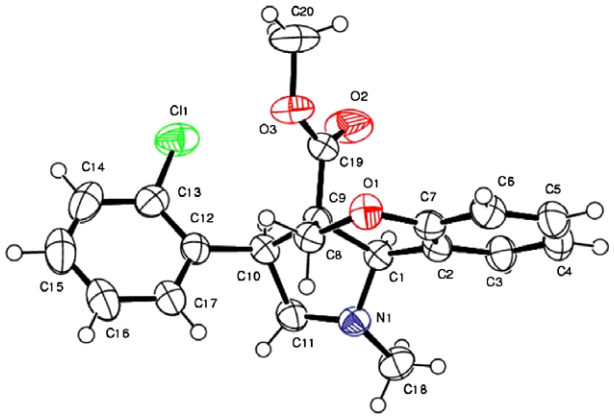


Fig. 2. ORTEP diagram of **4f**.

The X-ray crystal structure of compound **4l** showed that the relative stereochemistry of the cyanide group and aryl group in the vicinal positions was in cis orientation whereas in the crystal structure of compound **4f**, the ester group and aryl group in the vicinal positions were not in the cis orientation. The cyanide group and H_b proton in **4l** were cis and similarly in the crystal structure **4f**, the ester group and H_b proton were also in the cis orientation (Figs. 2 and 3).

In conclusion, we have developed a simple and novel protocol for the facile transformation of Baylis–Hillman bromides into an interesting class of functionalized tricyclic chromeno[4,3-*b*]pyrrolidines with high regio- and stereoselectivity.

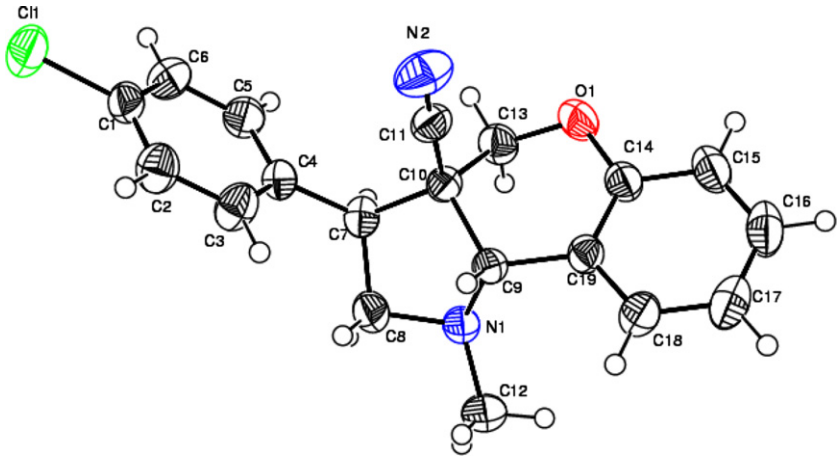


Fig. 3. ORTEP diagram of **4l**.

Acknowledgements

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20. The X-ray crystal structure data of **4f** and **4l** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 659316 (**4f**), CCDC 659165 (**4l**).
21. *Typical experimental procedure*: *Methyl 1,2,3,3a,4,9b-hexahydro-1-methyl-3-phenylchromeno[4,3-b]pyrrole-3a-carboxytate* (**4a**): A mixture of methyl (2*E*)-2-(2-formylphenoxy)methyl-3-phenylacrylate (**3a**) (2 mmol, 0.592 g) and sarcosine (2 mmol, 0.178 g) in acetonitrile (8 mL) was refluxed for 5 h. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated and the resulting crude mass was diluted with water (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified by column chromatography on silica gel (Acme 100–200 mesh), using ethyl acetate–hexanes (1:9) to afford the pure methyl 1,2,3,3a,4,9b-hexahydro-1-methyl-3-phenylchromeno[4,3-*b*]pyrrole-3a-carboxytate (**4a**) as a colourless solid in 91% yield.
Compound **4a**: mp 112–114 °C; IR (KBr): 3036, 2956, 2846, 1738 cm^{-1}; ^1H NMR: δ 2.54 (s, 3H), 2.96 (t, 1H, $J = 9.9$ Hz), 3.38 (dd, 1H, $J = 3.0$, 10.2 Hz), 3.63 (s, 1H), 3.66 (d, 1H, $J = 11.0$ Hz); 3.72 (s, 3H), 3.76 (dd, 1H, $J = 3.0$, 10.2 Hz), 4.02 (d, 1H, $J = 11.0$ Hz), 6.82–6.94 (m, 2H), 7.14–7.33 (m, 7H); ^{13}C NMR: δ 39.79, 48.50, 52.04, 52.37, 60.80, 65.81, 66.99, 116.92, 119.71, 120.02, 127.21, 128.25, 128.82, 129.02, 131.38, 138.02, 154.47, 173.82. MS (*m*/*z*): 324 (M^++1). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.74; H, 6.33; N, 4.60.
Compound **4i**: mp 102–104 °C; IR (KBr): 3033, 2920, 2850, 2237 cm^{-1}; ^1H NMR: δ 2.58 (s, 3H), 2.88 (t, 1H, $J = 9.6$ Hz), 3.25 (dd, 1H, $J = 7.5$, 9.6 Hz), 3.50 (dd, 1H, $J = 7.5$, 9.6 Hz), 3.63 (s, 1H), 4.25 (s, 2H), 6.95–7.04 (m, 2H), 7.20–7.46 (m, 7H); ^{13}C NMR: δ 39.56, 46.03, 48.19, 61.82, 67.10, 67.70, 117.71, 118.76, 118.86, 121.29, 128.28, 128.85, 128.93, 129.83, 131.02, 137.47, 153.95. MS (*m*/*z*): 291 (M^++1). Anal. Calcd for $C_{19}H_{18}N_2O_1$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.30; H, 6.09; N, 9.21.