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The Baylis–Hillman Acetates as a Valuable Source for One-Pot Multistep Synthesis: A Facile Synthesis of Functionalized Tri-/Tetracyclic Frameworks Containing Azocine Moiety

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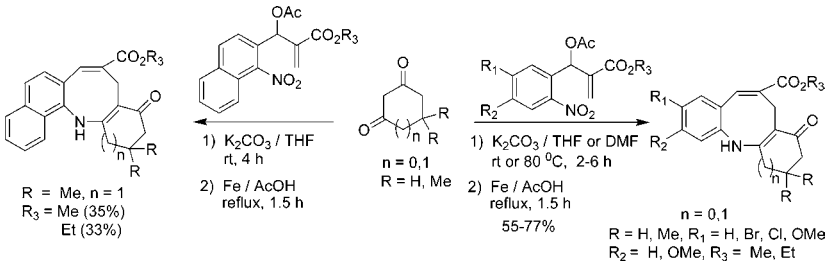
ABSTRACT



The Baylis-Hillman acetates have been conveniently transformed into tri-/tetracyclic heterocyclic frameworks containing an important azocine moiety via one-pot multistep protocol involving alkylation, reduction, and cyclization sequence.

The synthesis of medium sized rings, in particular eight- and nine-membered rings, has been and continues to be a challenging and fascinating endeavor in synthetic chemistry, because unfavorable entropic and enthalpic factors prevent the adaptation of traditional methods of ring formation.[1] An eight-membered nitrogen heterocyclic framework (particularly azocines and benzfused azocines) occupies a special place in the history of nitrogen heterocycles because of the presence of this moiety in various biologically active molecules possessing antihypertensive,[2a] herbicidal,[2b] antidepressant,[2c] analgesic,[2d] antitussive,[2e] and/or anthelmintic[2e] activities. Some dibenzazocine derivatives are known to be inhibitors of 17β-hydroxysteroid dehydrogenase type 3.[2f] Owing to these remarkable biological activities of azocines and benzfused azocines there has been increasing interest in the development of easy and simple methodologies/strategies for the synthesis of these molecules.[1b,3]

In continuation of our interest in the synthesis of heterocyclic molecules[4] we report a simple one-pot multistep protocol for facile transformation of the Baylis−Hillman (BH) acetates into tri-/tetracyclic heterocyclic frameworks containing an important azocine moiety following the reaction sequence involving alkylation, reduction, and cyclization.

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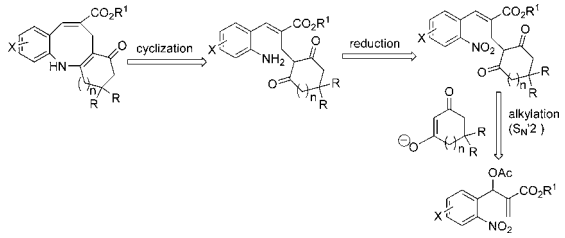
In recent years the Baylis−Hillman reaction has become a powerful and useful synthetic tool for the atom-economical construction of a C−C bond involving the coupling of the α-position of activated alkene with an electrophile under the influence of a catalyst/catalytical system providing densely functionalized molecules whose applications in various organic transformation methodologies have been well documented in the literature.[5−7]

We have recently developed an interesting one-pot synthetic protocol for transforming Baylis−Hillman adducts, derived from various 2-nitrobenzaldehydes and acyclic/cyclic enones into substituted quinolines,[8a] tetrahydroacridines,[8b] cyclopenta[*b*]quinolines,[8b] and 3-benzoylquinolines[8c] using Fe/AcOH for the in situ reduction of a nitro group into an amino group as a key step. On the basis of this experience we envisioned that Baylis−Hillman acetates[4e,i,9] can be in principly transformed into tri-/tetracyclic heterocyclic derivatives containing azocine moiety through an appropriate synthetic strategy. After considering some retrosynthetic strategies we arrived at the plan as shown in Scheme 1, which

Scheme 1. Retrosynthetic Strategy for the Synthesis of Azocine Frameworks



involves an alkylation ($S_N'2$), reduction, and cyclization sequence to provide the desired azocine moiety.

Accordingly, we first selected ethyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**1a**), acetate of the Baylis−Hillman alcohol, obtained via the reaction between 2-nitrobenzaldehyde and ethyl acrylate, as a substrate for treatment with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**2a**) with a view to obtain 2-aza-5,5-dimethyl-10-ethoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,-16-pentaen-7-one (**3**) in a one-pot multistep protocol. Best results were obtained when we treated BH acetate **1a** (1 mmol) with 5,5-dimethyl-1,3-cyclohexanedione **2a** (1 mmol) in the presence of K_2CO_3 (1 mmol) in THF (1 mL) at room temperature for 2 h followed by the treatment of resulting product (obtained after removal of THF under reduced pressure) with Fe/AcOH (5 mL) at reflux temperature for 1.5 h, thus providing 2-aza-5,5-dimethyl-10-ethoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,16-pentaen-7-one (**3**) in 62% isolated yield after the usual workup followed by column chromatography (Table 1, entry 1). Structure of this molecule was further established by single-crystal X-ray data (see Figure 1).[10]

To examine the generality of this strategy, we have prepared representative Baylis−Hillman acetates (**1b**−**f**) from the corresponding alcohols (derived from selected 2-nitrobenzaldehydes and alkyl acrylates) and subjected them to this synthetic sequence (with **2a** and cyclohexane-1,3-dione **2b** as nucleophiles**)** to provide the desired hexahydrodibenz[*b*,*g*]azocine derivatives (**4**−**12**) in 56−77% isolated yields (Table 1, entries 2−10). We have also further confirmed the structure of molecule **12** (see Figure 1) by single-crystal X-ray data.[10]

To understand the generality[11] of this reaction and also to synthesize tricyclic molecules with a 6-8-5-ring system, we employed 1,3-cyclopentanedione (**2c**) as a nucleophile. Thus the reaction of 1,3-cyclopentanedione (**2c**) with **1b** and **1d** followed by reduction and cyclization using Fe/AcOH

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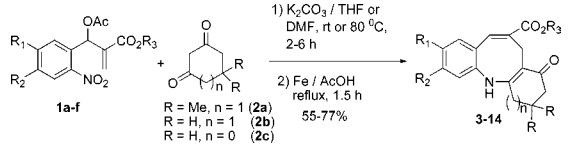
(10) Detailed X-ray crystallographic data is available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. for compounds **3** (CCDC no. 622201), **12** (CCDC no. 622202), **13** (CCDC no. 643665), and **15** (CCDC no. 622203).

Table 1. Synthesis of Tricyclic Framework Containing Azocine Moiety via the Reaction of **1a**−**f** with **2a**, **2b**,[a] or **2c**[b,12]



entry	acetate	R_1	R_2	R_3	dione	product[c]	yield(%)
1	**1a**	H	H	Et	**2a**	**3**[d]	62
2	**1b**	H	H	Me	**2a**	**4**	68
3	**1c**	Br	H	Me	**2a**	**5**	63
4	**1d**	Cl	H	Me	**2a**	**6**	57
5	**1e**	OMe	OMe	Me	**2a**	**7**	59
6	**1f**	OMe	OMe	Et	**2a**	**8**	64
7	**1b**	H	H	Me	**2b**	**9**	77
8	**1c**	Br	H	Me	**2b**	**10**	66
9	**1d**	Cl	H	Me	**2b**	**11**	56
10	**1e**	OMe	OMe	Me	**2b**	**12**[d]	62
11	**1b**	H	H	Me	**2c**	**13**[d]	64
12	**1d**	Cl	H	Me	**2c**	**14**	55

[a] All reactions were carried out on 1 mmol scale of Baylis−Hillman acetate (**1a**−**f**) with 1 mmol of cyclicdione **2a** or **2b** in the presence of K_2CO_3 (1 mmol) in THF at room temperature for 2 h (in the case of **2a**) and 6 h (in the case of **2b**) followed by reductive cyclization. [b] Reaction was carried out at 80 °C for 4 h in DMF followed by reductive cyclization. [c] All compounds were fully characterized (see Supporting Information). [d] Structure of these molecules were further confirmed by single-crystal X-ray data (see Supporting Information).[10]

provided the desired tricyclic molecules **13** and **14** (containing 6-8-5-ring system) in 64% and 55% isolated yields (Table 1 entries 11 and 12) respectively. We have also confirmed the structure of molecule **13** (see Figure 2) by single-crystal X-ray data.[10]

To examine the potential of this strategy for synthesis of tetracyclic framework containing azocine moiety we have subjected methyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**1g**) and ethyl 3- acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**1h**) (prepared from the corresponding Baylis−Hillman alcohols, which were obtained via the reaction of 1-nitro-2-naphthaldehyde with methyl acrylate and ethyl acrylate respectively) to this strategy. The required azocine derivatives 2-aza-19, 19-dimethyl-14-methoxycarbonyltetracyclo[14.4.0.0.^{3,12}0^{4,9}]eicosa-1(16),3,5,7,9,11,13-heptaen-17-one (**15**)[13] and 2-aza-19,19-dimethyl-14-ethoxycarbonyltetracyclo[14.4.0.0.^{3,12}0^{4,9}]eicosa-

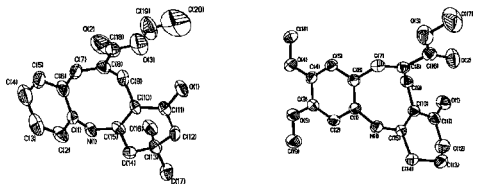


Figure 1. ORTEP diagrams of compounds **3** and **12** (hydrogen atoms were omitted for clarity).

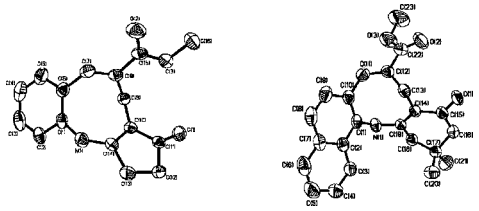
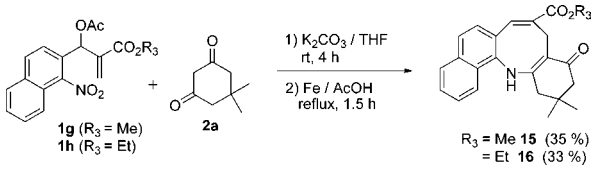


Figure 2. ORTEP diagrams of compounds **13** and **15** (hydrogen atoms were omitted for clarity).

1(16),3,5,7,9,11,13-heptaen-17-one (**16**) were obtained in 35% and 33% isolated yields respectively (Scheme 2). We have also further confirmed the structure of the molecule

Scheme 2. Synthesis of Tetracyclic Framework Containing Azocine Moiety via the Reaction of **1g**, **1h** with **2a**



15 by single-crystal X-ray data (see Figure 2).[10] Although the yields are not that high, these results certainly indicate the importance of our strategy for providing the tetracyclic ring system containing azocine framework in a simple one-pot multistep process.

A plausible mechanism for this transformation (taking **1b** as the Baylis−Hillman acetate and **2a** as the alkylating agent as a model case) is presented in Scheme 3 (for simplified mechanism see Supporting Information).

Interesting Observations in NMR Spectra. We have noticed an interesting observation regarding the appearance of *gem*-dimethyl protons/carbons in NMR spectra for compounds **3**−**8**, **15**, and **16**. The *gem*-dimethyl protons in compounds **3**−**8** appeared as singlet in the region δ 1.01−1.03 while in the case of compounds **15** and **16** they appeared as singlets at δ 1.10 and 1.11, respectively, in ^{1}H NMR spectra at room temperature. In the ^{13}C NMR spectrum at room temperature *gem*-dimethyl carbons appeared as a small peak in the region δ 27.86−28.06 in the case of compounds

(11) We have also examined the applicability of acyclic dione, that is, 2,4-pentanedione as a nucleophile. Thus the treatment of BH acetate (**1b**) with 2,4-pentanedione in the presence of K_2CO_3 provided the trisubstituted alkene in 57% isolated yield as a mixture of *E*/*Z* isomers (*E*/*Z* = 78:22) [cyclicdiones provide very minor amounts of (*Z*)-isomer (<5%)]. Subsequent treatment of this trisubstituted alkene (containing *E*/*Z* isomers) with Fe/AcOH at reflux temperature did not provide the expected azocine moiety but resulted in the formation of 6-(2-aminophenyl)-5-methoxycarbonyl-hexan-2-one (reduced and mono deacetylated product) and the corresponding pure (*E*)-isomer was obtained after crystallization.

(12) These reactions were carried out in DMF because in THF these were very sluggish probably because of solubility problems.

(13) To examine whether the reaction was more facile and the yield of **15** would be higher using a stepwise method, we also isolated the trisubstituted alkene in 73% yield after the usual workup followed by column chromatography. Subsequent treatment of trisubstituted alkene with Fe/AcOH at reflux temperature for 1.5 h provided the desired tetracyclic azocine moiety **15** in 51% isolated yield (37% overall yield).

Scheme 3. Plausible Mechanism

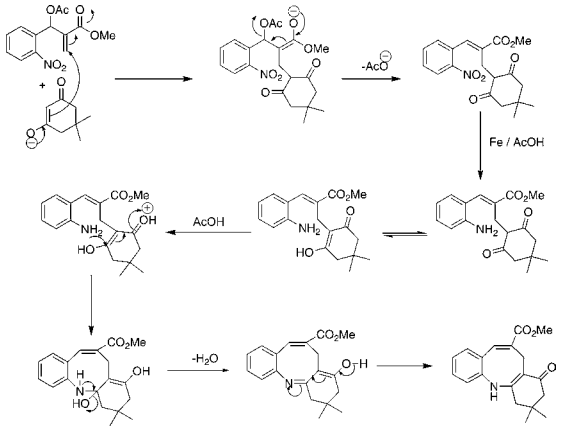
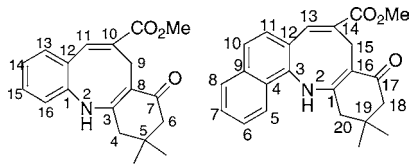


Table 2. Appearance and Chemical Shift Values of *gem*-Dimethyl Protons/Carbons in ^{1}H and ^{13}C NMR Spectra at Room Temperature and −30 °C



4 **15**

^{1}H NMR	rt	δ 1.02 (s)	δ 1.10 (s)
	−30 °C	δ 0.96 (s) and 1.05 (s)	δ 1.01 (s) and 1.15 (s)
^{13}C NMR	rt	δ 27.86	δ 28.40
	−30 °C	δ 25.84 and 29.83	δ 25.86 and 29.95

3−**8** while in compounds **15** and **16** similar carbons appeared as a broad peak at δ 28.40 and 27.38, respectively, with low intensity in comparison with that of quaternary carbon (further confirmed by DEPT 135 and a hetero COSY experiment in the case of compound **4**) at room temperature. This interesting appearance of *gem*-dimethyl carbons in the ^{13}C NMR spectra at room temperature led us to examine the NMR spectra at low temperatures to understand the conformational rigidity/flexibility. We have selected two compounds (**4** and **15**) for the study at low temperature. The *gem*-dimethyl protons (which appeared as singlet at room temperature) appeared as two singlets in the ^{1}H NMR spectra at −30 °C and *gem*-dimethyl carbons (which appeared as a small/broad peak at room temperature) appeared as two peaks in the ^{13}C NMR spectra at −30 °C in both compounds **4** and **15 (**Table 2).

We have also observed an interesting splitting pattern for three methylene groups at C-4, C-6, and C-9 (for compound **4**) and at C-15, C-18, and C-20 (for compound **15**) in the ^{1}H NMR spectrum from room temperature to −30 °C and −40 °C for compound **4** and to −30 °C for compound **15** (for further details see Supporting Information). From these observations it appears that these compounds have conformational rigidity at low temperature, while at room temperature there may be conformational flexibility that resulted in broadening of the signals.

In conclusion, we have developed a facile, convenient synthesis of functionalized tri/tetracyclic frameworks containing an important azocine moiety thus demonstrating the applications of the Baylis−Hillman adducts as valuable source for one-pot multistep protocol for synthesis of important and useful structural frameworks.

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Supporting Information Available: Experimental procedures (with all spectral data and ORTEP diagrams), ^{1}H and ^{13}C NMR spectra of all compounds **3**−**16**, DEPT 135, NMR spectra for compounds **4** and **15** at −30/−40 °C, CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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