

A novel, tandem construction of C–N and C–C bonds: facile and one-pot transformation of the Baylis–Hillman adducts into 2-benzazepines†

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A novel reaction involving tandem construction of C–N and C–C bonds *via* the simultaneous Ritter and Houben–Hoesch reactions on Baylis–Hillman adducts leading to a convenient, one-pot synthesis of 2-benzazepine derivatives is described. A facile stereoselective transformation of the Baylis–Hillman adducts into (*E*)- and (*Z*)-allyl amides is also presented.

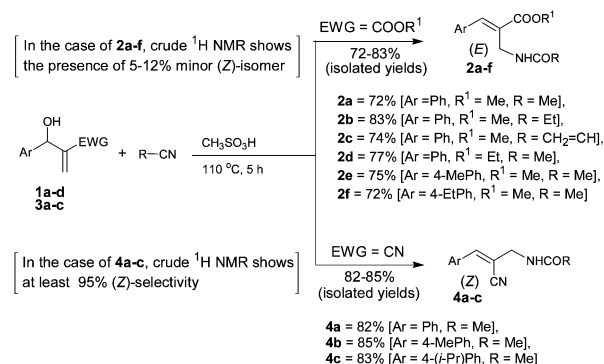
The 2-benzazepine moiety is present in many pharmaceutically active naturally occurring molecules such as galanthamine (one of the most effective current drugs for Alzheimer's disease), lycoramine, narwedine, montanine, coccinine, pancracine, brunsvigine, ribasine, communesin A, communesin B, nomofungin, *etc.*¹ and in fact, several synthetic 2-benzazepines have also been found to exhibit hypotensive, analgesic, antiarrhythmic activity and are also useful for treatment of mental disorders and hypoxia.² Therefore, the development of simple and convenient procedures for the synthesis of 2-benzazepine derivatives continues to be a challenging endeavor in synthetic organic chemistry.^{1a–d,3} In continuation of our interest in the synthesis of heterocyclic molecules using Baylis–Hillman chemistry,⁴ we herein describe a novel reaction involving tandem construction of C–N and C–C bonds *via* the simultaneous Ritter⁵ and Houben–Hoesch⁶ reactions on Baylis–Hillman adducts leading to a convenient, one-pot synthesis of 2-benzazepine derivatives.

The Baylis–Hillman reaction is an emerging atom-economical carbon–carbon bond forming reaction providing densely functionalized molecules whose applications in many organic transformation methodologies have been well documented.^{4,7,8} During our ongoing research program on the synthesis of useful and important heterocyclic molecules,⁴ we required various 2-benzazepine derivatives. We have envisioned that 2-benzazepine derivatives can in principle be obtained from the Baylis–Hillman adducts *via* the construction of a C–N bond through the Ritter reaction with simultaneous construction of a C–C bond through the Houben–Hoesch reaction as there would be a nitrilium ion intermediate (Scheme 1).

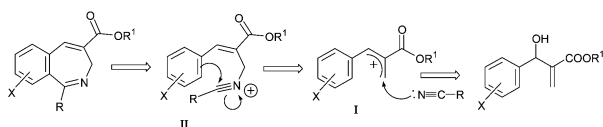
Accordingly, we first selected methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**), the Baylis–Hillman adduct obtained from methyl acrylate and benzaldehyde, as a substrate for performing the Ritter and Houben–Hoesch reactions with acetonitrile in the presence of methanesulfonic acid under various conditions. However this reaction did not proceed to the formation of the desired 2-benzazepine derivative but stopped at the allyl amide stage. The best results were obtained when methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**) (1 mmol) in acetonitrile (5

mL) was treated with methanesulfonic acid (3 mL) at 110 °C for 5 h, thus providing methyl (*E*)-2-acetylaminoethyl-3-phenylprop-2-enoate (**2a**) in 72% isolated yield. We then prepared representative (*E*)-allyl amides (**2b–f**) *via* treatment of various Baylis–Hillman adducts (**1b–d**) with aceto-, propio-, and acrylonitriles (Scheme 2). With a view to understanding the stereochemical directive effects of the cyano group we also examined the reaction of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**3a**) with acetonitrile under similar conditions, which provided (*Z*)-2-acetylaminoethyl-3-phenylprop-2-enitrile (**4a**) in 82% isolated yield. We then successfully transformed a representative class of Baylis–Hillman adducts (**3b, 3c**) into the corresponding (*Z*)-allyl amides (**4b, 4c**) (Scheme 2). This stereochemical reversal from ester group to cyano group is consistent with earlier reports on various transformations of the Baylis–Hillman adducts.⁹

At this stage it occurred to us that the presence of electron donating group(s) on the aromatic ring might help in the construction of the C–C bond (*via* the Houben–Hoesch reaction) after construction of the C–N bond (*via* Ritter reaction) thus leading to the formation of 2-benzazepine derivatives (Scheme 3). Accordingly, we treated ethyl 3-hydroxy-2-methylene-3-(3-methoxyphenyl)propanoate (**1e**), the Baylis–Hillman adduct obtained from ethyl acrylate and 3-methoxybenzaldehyde, with acetonitrile in the presence of methanesulfonic acid under various conditions. We were pleased to isolate the expected 3-aza-2-methyl-5-ethoxycarbonyl-9-methoxybicyclo[5.4.0]undeca-1(7),2,5,8,10-pentaene (**5**) in 55% yield when **1e** (2 mmol) in acetonitrile (5 mL) was

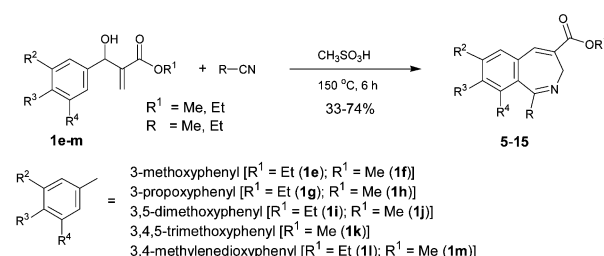


Scheme 2 Stereoselective transformation of Baylis–Hillman adducts into (*E*)-allyl amides (**2a–f**) and (*Z*)-allyl amides (**4a–c**) under Ritter conditions.^{10,11}




Scheme 1 Schematic representation of synthetic strategy for 2-benzazepine derivatives.

† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical, spectral data for all 2-benzazepine derivatives (**5–15**) and allyl amides (**2a–f**, **4a–c**). Stereochemical assignment for **2a–f** and **4a–c**. See <http://www.rsc.org/suppdata/cc/b3/b310550d/>

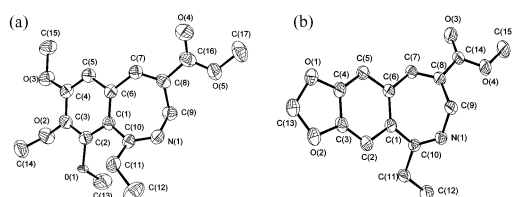


Scheme 3 Facile one-pot synthesis of 2-benzazepine derivatives (**5–15**) involving novel tandem construction of C–N and C–C bonds.¹¹

Table 1 Synthesis of 2-benzazepine derivatives (**5–15**)^a

Alcohol (1e–m)		R ¹ (alkyl)	R (alkyl)	Product (5–15)	Yield (%)
1e	3-(MeO)Ph	Et	Me	5	55
1e	3-(MeO)Ph	Et	Et	6	67
1f	3-(MeO)Ph	Me	Et	7	44
1g	3-(PrO)Ph	Et	Et	8	58
1h	3-(PrO)Ph	Me	Et	9	65
1i	3,5-(MeO) ₂ Ph	Et	Me	10	70
1i	3,5-(MeO) ₂ Ph	Et	Et	11	74
1j	3,5-(MeO) ₂ Ph	Me	Me	12	72
1k	3,4,5-(OMe) ₃ Ph	Me	Et	13	33
1l	3,4-(OCH ₂ O)Ph	Et	Et	14	48
1m	3,4-(OCH ₂ O)Ph	Me	Et	15	46

^a All the reactions were carried out on 2 mmol scale of Baylis–Hillman alcohols (**1e–m**) with methanesulfonic acid in alkanenitriles (5 mL) at 150 °C for 6 h. Yields are of the pure compounds obtained after column chromatography. All the compounds were fully characterized.

**Fig. 1** ORTEP diagrams of (a) **13** and (b) **15**.

treated with methanesulfonic acid (3 mL) at 150 °C for 6 h.¹² We then extended this strategy to representative Baylis–Hillman adducts (**1e–m**) to provide the desired 2-benzazepine derivatives (**6–15**) in moderate to good yields *via* reaction with aceto- and propionitriles (Scheme 3, Table 1). The structures of **13** and **15** were also established by single crystal X-ray crystallography (Fig. 1).¹³

In conclusion, we have developed a novel strategy involving tandem construction of C–N and C–C bonds leading to a convenient one-pot procedure for the synthesis of 2-benzazepine derivatives from the Baylis–Hillman adducts. We have also described the stereoselective transformation of the Baylis–Hillman adducts into (*E*) or (*Z*)-allyl amides, thus demonstrating the efficacy of the Baylis–Hillman adducts as an important source for exploration of new reactions and stereoselective transformation methodologies.

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- See ESI† for *E/Z* of the amides.
- A plausible mechanism for the formation of allyl amides and 2-benzazepines is presented in the ESI†.
- A temperature of 150 °C is necessary as at 110 °C 2-benzazepine (**5**) is not formed. Also in the case of **1a**, even at 150 °C there is no formation of the corresponding 2-benzazepine derivative.
- Crystal data* for **13**: C₁₇H₂₁NO₅; *M*, 319.35; crystal colour, habit: light yellow, rectangular; crystal dimensions, 0.5 × 0.48 × 0.24 mm; crystal system, monoclinic; lattice type, primitive; *a* = 10.669(6), *b* = 13.041(8), *c* = 12.062(9) Å; β = 93.18(5)°; *V* = 1675.6(18) Å³; space group, *P21/a* : *b3* (No. 14); *Z* = 4; μ = 0.093 mm⁻¹; *D*_{calcd} = 1.266 g cm⁻³; *F*₀₀₀ = 680; λ(Mo K_α) = 0.71073 Å; *R* = 0.0569, *wR*² = 0.1845. *Crystal data* for **15**: C₁₅H₁₅NO₄; *M*, 273.28; crystal colour, habit: light yellow, rectangular; crystal dimensions, 0.47 × 0.42 × 0.40 mm; crystal system, monoclinic; lattice type, primitive; *a* = 8.096(5), *b* = 16.436(8), *c* = 10.159(8) Å; β = 98.73(5)°; *V* = 1336.1(15) Å³; space group, *P21/a* : *b3* (No. 14); *Z* = 4; μ = 0.099 mm⁻¹; *D*_{calcd} = 1.359 g cm⁻³; *F*₀₀₀ = 576; λ(Mo K_α) = 0.71073 Å; *R* = 0.0441, *wR*² = 0.1081. CCDC 211673 and 211674. See <http://www.rsc.org/suppdata/cc/b3/b310550d/> for crystallographic data in CIF or other electronic format.