

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

Deevi Basavaiah* and Tummanapalli Satyanarayana

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

Received (in Cambridge, UK) 2nd September 2003, Accepted 12th November 2003

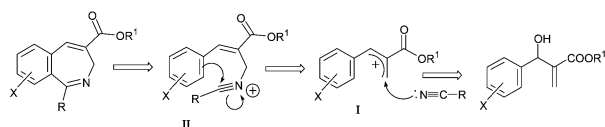
First published as an Advance Article on the web 28th November 2003

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

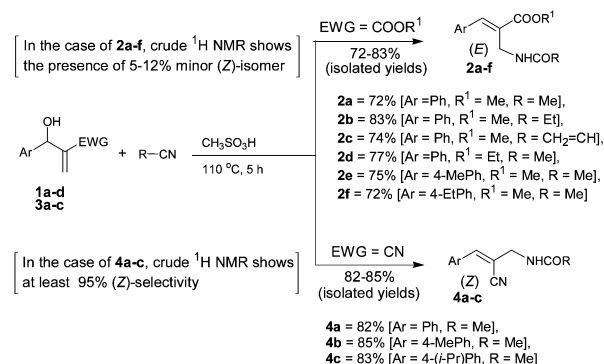


Scheme 1 Schematic representation of synthetic strategy for 2-benzazepine derivatives.

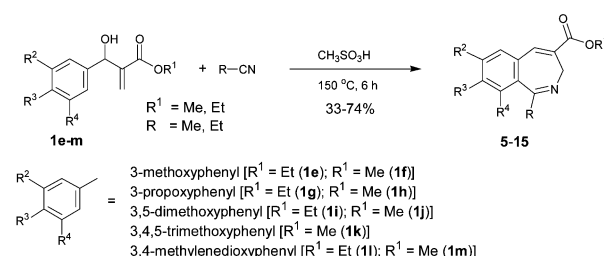
† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical, spectral data for all 2-benzazepine derivatives (**5–15**) and allyl amides (**2a–f**, **4a–c**). Stereochemical assignment for **2a–f** and **4a–c**. See <http://www.rsc.org/suppdata/cc/b3/b310550d/>

mL) was treated with methanesulfonic acid (3 mL) at 110 °C for 5 h, thus providing methyl (*2E*)-2-acetylaminomethyl-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 (*2Z*)-2-acetylaminomethyl-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-ethoxy-carbonyl-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}

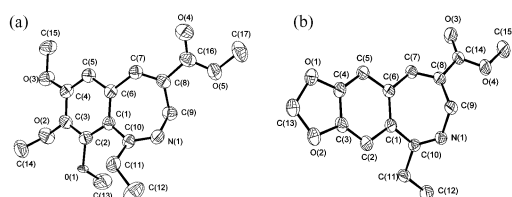


Scheme 3 Facile one-pot synthesis of 2-benzazepine derivatives (**5–15**) involving novel tandem construction of C–N and C–C bonds.¹¹

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.

We thank DST (New Delhi) for funding this project. We thank UGC (New Delhi) for recognizing our University of Hyderabad as a “University with Potential for Excellence (UPE)” and generous funding and also for a Special Assistance Program in Organic Chemistry in the School of Chemistry. TS thanks UGC (New Delhi) for his research fellowship. We also thank the National Single Crystal X-ray Facility in our School of Chemistry funded by DST (New Delhi). We thank Professor T. P. Radhakrishnan for helpful discussions regarding X-ray crystal structures.

Notes and references

- (a) J. A. May, R. K. Zeidan and B. M. Stoltz, *Tetrahedron Lett.*, 2003, **44**, 1203; (b) C. Guillou, J.-L. Beunard, E. Gras and C. Thal, *Angew. Chem., Int. Ed.*, 2001, **40**, 4745; (c) C.-K. Sha, A.-W. Hong and C.-M. Huang, *Org. Lett.*, 2001, **3**, 2177; (d) J. Jin and S. M. Weinreb, *J. Am. Chem. Soc.*, 1997, **119**, 2050; (e) J. M. Boente, L. Castedo, R. Cuadros, J. M. Saa, R. Suau, A. Perales, M. Martinez-Ripoll and J. Fayos, *Tetrahedron Lett.*, 1983, **24**, 2029.
- (a) R. E. Johnson and C. A. Busacca (Sterling drug, Inc.), *US Pat.* 5,098,901; *Chem. Abstr.*, 1992, **117**, 7949j; (b) P. Croisier and L. Rodriguez (UCB S. A.), *Ger. Offen.* 2,733,868 and 2,733,869; *Chem. Abstr.*, 1978, **88**, 152455g and 152456h; (c) J. A. Meschino (McNeil

Laboratories, Inc.), *US Pat.* 3,894,072; *Chem. Abstr.*, 1975, **83**, 114031e; (d) J. A. Meschino (McNeil Laboratories, Inc.), *US Pat.* 3,828,096; *Chem. Abstr.*, 1974, **81**, 136001f; (e) J. A. Meschino (McNeil Laboratories, Inc.), *US Pat.* 3,483,186; *Chem. Abstr.*, 1970, **72**, 121383x; (f) H. Fujimura and M. Hori (Takeda Chemical Industries, Ltd.), *US Pat.* 3,409,607; *Chem. Abstr.*, 1969, **70**, 77827c.

- (a) A. Kamimura, Y. Taguchi, Y. Omata and M. Hagihara, *J. Org. Chem.*, 2003, **68**, 4996; (b) M. Nyerges, A. Viranyi, A. Pinter and L. Toke, *Tetrahedron Lett.*, 2003, **44**, 793; (c) J. C. Martins, K. V. Rompaey, G. Wittman, C. Tomboly, G. Toth, N. De Kimpe and D. Tourwe, *J. Org. Chem.*, 2001, **66**, 2884; (d) R. Gamez-Montano, M. I. Chavez, G. Roussi and R. Cruz-Almanza, *Tetrahedron Lett.*, 2001, **42**, 9; (e) L. Ollero, L. Castedo and D. Dominguez, *Tetrahedron Lett.*, 1998, **39**, 1413; (f) A. G. Griesbeck and H. Mauder, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 73; (g) R. A. Holton, M. P. Sibi and W. S. Murphy, *J. Am. Chem. Soc.*, 1988, **110**, 314.
- (a) D. Basavaiah and A. J. Rao, *Chem. Commun.*, 2003, 604; (b) D. Basavaiah and T. Satyanarayana, *Tetrahedron Lett.*, 2002, **43**, 4301; (c) D. Basavaiah and T. Satyanarayana, *Org. Lett.*, 2001, **3**, 3619; (d) D. Basavaiah, M. Bakthadoss and S. Pandiaraju, *Chem. Commun.*, 1998, 1639.
- (a) R. Bishop, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 6, p. 261; (b) L. I. Krimen and D. J. Cota, *Org. React.*, 1969, **17**, 213; (c) K. V. Emelen, T. D. Wit, G. J. Hoornaert and F. Compennolle, *Org. Lett.*, 2000, **2**, 3083.
- (a) K. Hoesch, *Ber. Dtsch. Chem. Ges.*, 1915, **48**, 1122; (b) J. Houben, *Ber. Dtsch. Chem. Ges.*, 1926, **59**, 2878; (c) P. E. Spoerri and A. S. DuBois, *Org. React.*, 1949, **5**, 387; (d) W. Ruske, in *Freidel–Crafts and Related Reactions*, ed. G. A. Olah, Wiley-Interscience, New York, 1964, vol. III, part I, ch. 32; (e) M. Yato, T. Ohwada and K. Shudo, *J. Am. Chem. Soc.*, 1991, **113**, 691; (f) Y. Sato, M. Yato, T. Ohwada, S. Saito and K. Shudo, *J. Am. Chem. Soc.*, 1995, **117**, 3037; (g) R. Kawecki, A. P. Mazurek, L. Kozerski and J. K. Maurin, *Synthesis*, 1999, 751.
- (a) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811; (b) E. Ciganek, in *Organic Reactions*, ed. L. A. Paquette, John Wiley & Sons, New York, 1997, vol 51, p. 201; (c) D. Basavaiah, P. Dharna Rao and R. Suguna Hyma, *Tetrahedron*, 1996, **52**, 8001; (d) S. E. Drewes and G. H. P. Roos, *Tetrahedron*, 1988, **44**, 4653.
- (a) V. K. Aggarwal, I. Emme and S. Y. Fulford, *J. Org. Chem.*, 2003, **68**, 692; (b) K.-S. Yang, W.-D. Lee, J.-F. Pan and K. Chen, *J. Org. Chem.*, 2003, **68**, 915; (c) W. P. Almeida and F. Coelho, *Tetrahedron Lett.*, 2003, **44**, 937; (d) H. Kraiem, M. I. Abdullah and H. Amri, *Tetrahedron Lett.*, 2003, **44**, 553; (e) M. Shi and Y.-M. Xu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4507; (f) C. Yu and L. Hu, *J. Org. Chem.*, 2002, **67**, 219; (g) L.-C. Wang, A. L. Luis, K. Agapiou, H.-Y. Jang and M. J. Krische, *J. Am. Chem. Soc.*, 2002, **124**, 2402; (h) S. A. Frank, D. J. Mergott and W. R. Roush, *J. Am. Chem. Soc.*, 2002, **124**, 2404; (i) R. Racker, K. Döring and O. Reiser, *J. Org. Chem.*, 2000, **65**, 6932; (j) G. Li, J. Gao, X. Wei II and M. Enright, *Org. Lett.*, 2000, **2**, 617; (k) A. G. M. Barrett, A. S. Cook and A. Kamimura, *Chem. Commun.*, 1998, 2533.
- (a) D. Basavaiah and P. K. S. Sarma, *Chem. Commun.*, 1992, 955; (b) D. Basavaiah, M. Krishnamacharyulu, R. Suguna Hyma and S. Pandiaraju, *Tetrahedron Lett.*, 1997, **38**, 2141; (c) H. J. Lee, M. R. Seong and J. N. Kim, *Tetrahedron Lett.*, 1998, **39**, 6223.
- 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.