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A straightforward synthesis of conhydrine by hetero Diels–Alder strategy mediated by microwaves

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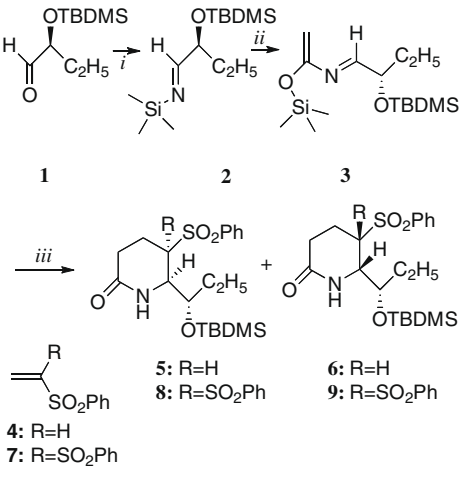
ABSTRACT

Synthesis of optically active conhydrines has been achieved by hetero Diels–Alder cycloaddition assisted by microwaves.

Six-membered nitrogen containing heterocyclic rings, as piperidines, constitute a framework very frequently encountered in natural products. Among them, special attention is paid to piperidines, bearing in α-position of the nitrogen atom an hydroxyalkyl side chain, since they are present, inter alia, in alkaloids[1,2], with important bioactivity. A number of very valuable syntheses of such scaffold, particularly those associated with conhydrines,[3] have been already published but, to our knowledge, very few of them are based on an hetero Diels–Alder strategy.[4–10] In connection with our studies on the preparation and synthetic use of functionalized azabutadiene[11] of type **3**, we became interested in developing a simple and feasible route to 6-hydroxyalkyl-piperidin-2-one synthon, which may be considered the parent of a 2-hydroxylakyl piperidones, thanks to a known protocol for the easy reduction of the δ-lactam functionality.[12] Herein we report our new synthesis of such scaffold and its easy elaboration to conhydrines.[13–30] Our strategic plane involved the use of an optically active azadiene of type **3**, which has been already used by our group in the building-up hetero Diels–Alder adducts.[31] Reaction of **3** with dienophilic vinylsulfone **4** gave the expected aza-Diels–Alder adducts **5** and **6** in poor yields. Since this HDA reaction must be considered of '*normal electron demand*' we anticipated that higher yields could be obtained using the commercially available 1,1-bis(phenylsulfonyl)ethylene moiety **7** as dienophile.[32] Moreover, in the light of the conditions needed for a successful HDA reaction, we felt that the simultaneous use of **MAOS** (**M**icrowave-**A**ssisted **O**rganic **S**ynthesis) (Scheme 1) methodology in achieving the cycloaddition reaction could have a positive effect on the efficiency of the cycloaddition reaction.[33–35] As expected, the reaction of azadiene **3** with sulfone moiety **7** in toluene, under MAOS conditions, furnished the expected HAD-adduct in 82% chemical yields and 50/50 diastereomeric ratio (41% for each diastereoisomer), after flash chromatography [SiO_2/dichloromethane (DCM)/ethyl acetate 70/30]. The stereo assignments of the substituents were demonstrated



Scheme 1. Reagents and conditions: (i) LiHMDSA, TMSCl, hexane; (ii) CH_3COCl, TEA, hexane; (iii) **4** or **7**, MW, toluene.

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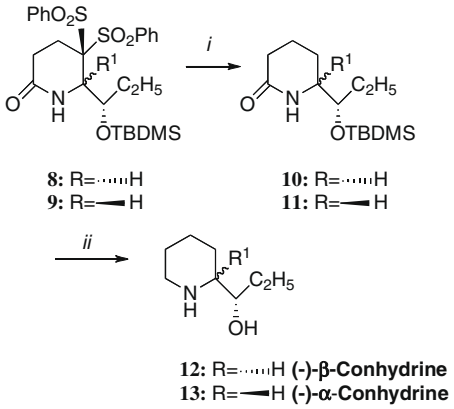

Scheme 2. Reagents and conditions: (i) Na/Hg/MeOH; (ii) LiAlH4, THF/*t*-butylmethyl ether.

by the elaboration of the cyclic adducts **8** and **9** to corresponding conhydrines **12** and **13**, and comparing their chemo-physical properties including analysis of their enantiomeric purity by chiral HPLC (chiracel column) and the optical rotation values (vide infra) with those of well-known authentic compounds. To this aim and in order to demonstrate the synthetic utility of our approach, herein described, the elaboration of the HDA-adducts **8** and **9** to the corresponding conhydrines **12** and **13** in optically pure form was performed through a simple protocol. In detail, treatment of the intermediates **8** and **9** with sodium amalgam in methanol gave rise to the corresponding pyridin-2-ones **10** and **11** in 77% yields. Exhaustive reduction by $LiAlH_4$ furnished the target compounds **12** in 68% and **13** in 74% yields, respectively (Scheme 2).[30]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.039.

References and notes

1. Casiraghi, G.; Zanardi, F.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677–1716.
2. Elbein, A. D.; Molyneux, R. J. *Alkaloids: Chemical and Biological Perspective*; Wiley: New York, 1986.
3. Reynolds, T. *Phytochemistry* **2005**, *66*, 1399–1406.
4. Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553–2581.
5. Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493–3513.
6. Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633–640.
7. Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813.
8. Laschat, S. *Liebigs Ann. Chem.* **1996**, 1–11.
9. Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729.
10. Zhu, W.; Mena, M.; Jnoff, E.; Sun, N.; Pasau, P.; Ghosez, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5880–5883.
11. Panunzio, M.; Vicennati, P.. In *Recent Research Development in Organic Chemistry*; Pandalai, S. G., Ed.; Transworld Research Network: Trivandrum, India, 2002; Vol. 6, pp 683–707.
12. Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387–1394.
13. Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113.
14. Chang, M.-Y.; Kung, Y.-H.; Chen, S.-T. *Tetrahedron* **2006**, *62*, 10843.
15. Chang, M. Y.; Kung, Y. H.; Chen, S. T. *Tetrahedron* **2006**, *62*, 10843–10848.
16. Enders, D.; Nolte, B.; Raabe, G.; Runsink, J. *Tetrahedron: Asymmetry* **2002**, *13*, 285–291.
17. Guerreiro, P.; Ratovelomanana-Vidal, V.; Genet, J. P. *Chirality* **2000**, *12*, 408–410.
18. Jamieson, A. G.; Sutherland, A. *Org. Lett.* **2007**, *9*, 1609–1611.
19. Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3268.
20. Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957.
21. Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2008**, *19*, 1245–1249.
22. Lysenko, I. L.; Bekish, A. V.; Kulinkovich, O. G. *Russ. J. Org. Chem.* **2002**, *38*, 875–879.
23. Masaki, Y.; Imaeda, T.; Nagata, K.; Oda, H.; Ito, A. *Tetrahedron Lett.* **1989**, *30*, 6395–6396.
24. Nagata, K.; Toriizuka, Y.; Itoh, T. *Heterocycles* **2005**, *66*, 107–109.
25. Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 4091.
26. Rodriguez, D.; Pico, A.; Moyano, A. *Tetrahedron Lett.* **2008**, *49*, 6866–6869.
27. Roy, S.; Sharma, A.; Mula, S.; Chattopadhyay, S. *Chem. Eur. J.* **2009**, *15*, 1713–1722.
28. Saikia, P. P.; BaiShya, G.; Goswami, A.; Barua, N. C. *Tetrahedron Lett.* **2008**, *49*, 6508–6511.
29. Srivastava, A. K.; Das, S. K.; Panda, G. *Tetrahedron* **2009**, *65*, 5322–5327.
30. Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358–5361.
31. For the synthesis of the azadiene **3**, the starting aldehyde **1** was prepared, in optically active form, in 73% yield from commercially available α-hydroxy acid according: (a) Ahmed, F.; Al-Mutairi, E. H.; Avery, K. L.; Cullis, P. M.; Primrose, W. U.; Roberts, G. C. K.; Willis, C. L. *Chem. Commun.* **1999**, 2049–2050; See also: (b) Moore, G. C.; Murphy, P. J.; Williams, H. L.; McGownb, A. T.; Smith, N. K. *Tetrahedron* **2007**, *63*, 11771–11780.
32. De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755–6794.
33. Kappe, C. O.; Dallinger, D. *Mol. Divers.* **2009**, *13*, 71–193.
34. Moseley, J. D. *Chim. Oggi-Chem. Today* **2009**, *27*, 6.
35. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.