Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 7947–7950
Tetrahedron Letters

Montmorillonite KSF-catalyzed one-pot synthesis of hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline derivatives

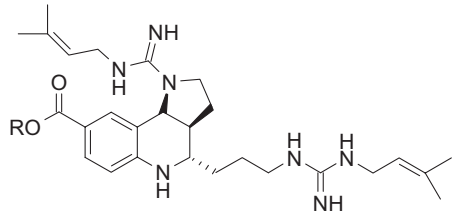
J. S. Yadav,* B. V. Subba Reddy, V. Sunitha, K. Srinivasa Reddy and K. V. S. Ramakrishna

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

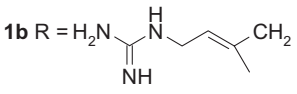
Received 12 March 2004; revised 9 August 2004; accepted 20 August 2004
Available online 11 September 2004

Abstract—Aryl amines react with endocyclic ene-carbamates such as *tert*-butyl 2,3-dihydro-1*H*-1-pyrrolecarboxylate and *tert*-butyl 1,2,3,4-tetrahydro-1-pyridinecarboxylate, on the surface of montmorillonite KSF clay under mild conditions to afford the corresponding 3-aminopropylhexahydropyrrolo[3,2-*c*]quinoline or 4-aminobutyloctahydrobenzo[*h*][1,6]naphthyridine derivatives in excellent yields with moderate diastereoselectivity.

Martinellic acid **1a**, and martinelline **1b** isolated from the roots of the Amazonian plant *Martinella iquitosensis* are the first non-peptide natural product bradykinin receptor antagonists.[1] Martinelline also exhibits potent antibiotic activity against both Gram-positive and Gram-negative bacteria and also has affinity for several G-protein coupled receptors.[2]



1a R = H



1b R = H_2N

Synthetic interest in martinellic acid has recently been stimulated and many new approaches have been developed to construct the hexahydropyrrolo[3,2-*c*]quinoline core structure.[3] A variety of approaches such as inter- and intra-molecular 1,3-dipolar cycloadditions of azomethine ylides, radical cyclizations, transition metal catalyzed cyclizations, and imino-Diels–Alder reactions, have been developed to synthesize the tricyclic core of the martinellines.[4,5] Among these methods, the hetero-Diels–Alder reaction is one of the most straightforward approaches for the synthesis of hexahydropyrroloquinolines.[6] The imino-Diels–Alder reaction of 2-azadienes, derived in situ from aryl amines and endocyclic ene-carbamates provides an easy access to the synthesis of pyrroloquinolines.[7] The advantage of this approach is that all three chiral centers present in the hexahydropyrroloquinoline can be generated in a single-step. However, the development of simple and efficient approaches would widen the scope of this methodology. Furthermore, there are no examples of reactions with six-membered ene-carbamates producing novel octahydrobenzo[*h*][1,6]-naphthyridine of biological and medicinal importance.

In recent years, the use of solid acidic catalysts such as clays and zeolites has attracted significant attention in different areas of organic synthesis.[8] In fact, solid acids are advantageous as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation, thereby making the process economically viable. In many cases, heterogeneous solid acids can be recovered with only minor changes in activity and selectivity so that they can be conveniently used in continuous flow reactions. Among various heterogeneous catalysts, clays are the most attractive because

Keywords: Ene-carbamates; Aryl amines; Hetero-Diels–Alder reaction; Pyrroloquinolines.
* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: yadav@iict.res.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.08.128

of their reusability, environmental compatibility, high selectivity, low cost, non-toxicity, and operational simplicity. Furthermore, clay catalysts make the reaction process quite simple and act as both Brønsted and Lewis acids in their natural and ion-exchanged forms, enabling them to function as efficient catalysts for various organic transformations.[9]

In continuation of our interest on the catalytic application of clays,[10] we wish to highlight our results on the montmorillonite KSF clay promoted 2:1 coupling of endocyclic ene-carbamates with aryl amines to afford hexahydropyrrolo[3,2-*c*]quinoline and octahydrobenzo[*h*][1,6]naphthyridine derivatives. Accordingly, treatment of the *N*-Boc derivative of 2,3-dihydropyrrole with aniline **1** in the presence of montmorillonite KSF afforded 3-aminopropylhexahydropyrroloquinolines **2a** and **3a** in a combined 89% yield (Scheme 1).

The product was obtained as a mixture of *endo*- **2a** and *exo*-isomers **3a** in a ratio of 1:1. The stereochemistry of the products was established by NOE experiments. In product **2a**, the presence of Ha/Hb, Hb/Hc, and Ha/Hc NOE cross peaks indicates that the protons Ha, Hb, and Hc are on the same side of the rings. In the *exo*-isomer **3a**, the six-membered quinoline and five-membered pyrrolidine rings are also *cis*-fused as indicated by the presence of NOE cross peaks between Ha/Hb and Hb/Hc. However, the absence of a NOE cross peak between Ha/Hc indicates that the protons Ha and Hc are on different sides of the rings (Fig. 1). Further, the proposed structures were confirmed by energy minimization calculations.[11]

The diastereomeric ratio was determined from the ^{1}H NMR spectrum of the crude product. The diastereomers **2a** and **3a** could not be separated by column chromatography. The structures were confirmed by ^{1}H NMR in DMSO at 30 °C and characterized by NMR, IR, and FAB mass spectroscopy and also by comparison with authentic compounds. The spectroscopic data of products were identical with data reported in the literature.[7] In a similar manner, various aryl amines underwent reaction with *N*-Boc-protected 2,3-dihydropyrrole to give the corresponding hexahydropyrrolo[3,2-*c*]quinolines (Table 1). In all cases, the reaction proceeded efficiently in THF at room temperature with moderate diastereoselectivity. Furthermore, the six-membered ene-carbamate, that is the *N*-Boc derivative of tetrahydropyridine also underwent cyclization with aryl amines to give 4-aminobutyl octahydrobenzo[*h*][1,6]naphthyridine derivatives (Scheme 2, Table 1).

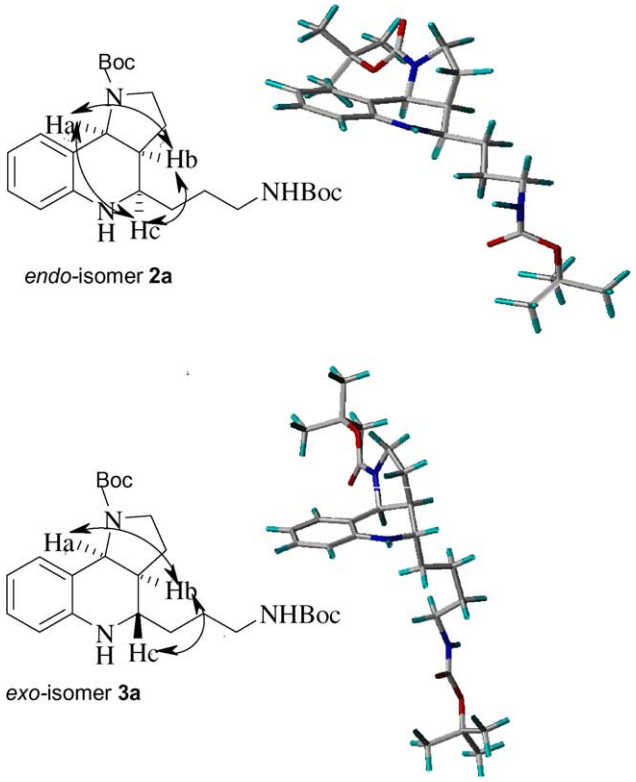
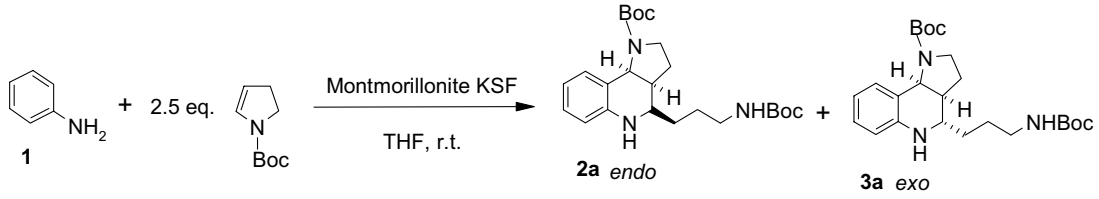


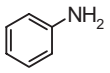
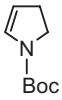
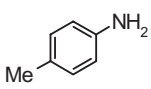
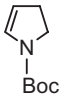
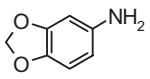
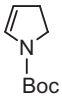
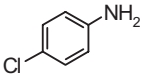
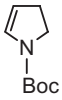
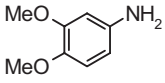
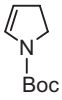
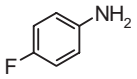
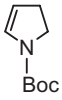
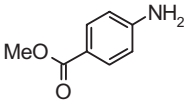
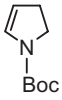
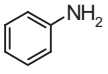
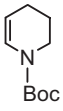
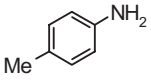
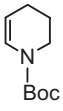
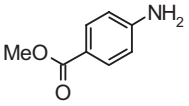
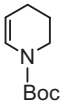
Figure 1. Characteristic NOE's and the energy minimized structures of **2a** and **3a**.

Analogous to five-membered ene-carbamates, reactions of six-membered ene-carbamates with aryl amines also gave the products as a mixture of *exo*- and *endo*-isomers, which could not be separated by column chromatography. Among various solvents such as dichloromethane, acetonitrile, and tetrahydrofuran used for this reaction, THF was found to give the highest *exo*-selectivity. It is worth mentioning that the reactions also proceeded smoothly in water on the surface of montmorillonite KSF. For instance, treatment of aniline with the *N*-Boc-protected 2,3-dihydropyrrole for 3 h in water gave the corresponding hexahydropyrrolo[3,2-*c*]quinoline in 85% yield. However, high *endo*-selectivity was observed in water (90% *endo*-isomer). In the absence of clay, the reaction did not proceed either in water or in THF even after 12 h. This clearly indicates that clay is essential for the success of the reaction. The clay could be recovered by simple filtration and washing with methanol and recycled for use in subsequent reactions (after activation at 120 °C for 4–5 h) with only a gradual decrease in activity; for example, the reaction of aniline with

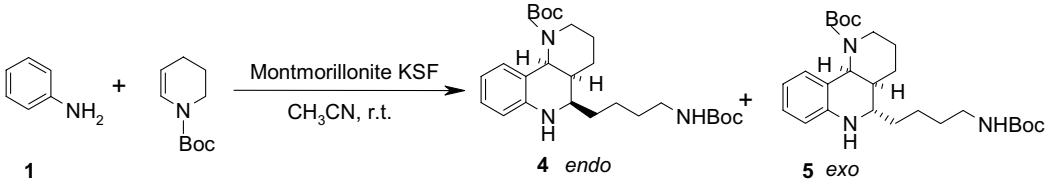


Scheme 1.

Table 1. Montmorillonite KSF-promoted hetero-Diels–Alder reactions

Entry	Aryl amine	Ene-carbamate	Time (h)	Yield (%)[a]	*endo*:*exo*[b]
a			3.0	89	50:50
b			3.5	91	40:60
c			4.0	85	45:55
d			3.5	87	35:65
e			4.0	82	45:55
f			4.5	79	35:65
g			3.5	85	30:70
h			4.5	90	55:45
i			5.0	85	45:55
j			4.5	80	40:60

[a] Yield refers to pure products after chromatography.
[b] Ratio was determined from the ^{1}H NMR spectra of the crude products.



Scheme 2.

N-Boc-2,3-dihydropyrrole under similar conditions afforded 89%, 85%, and 79% yields over three cycles.[12]

In summary, we have described a simple, convenient, and efficient approach for the synthesis of hexahydropyrrolo[3,2-*c*]quinolines and octahydrobenzo[*h*][1,6]-naphthyridine derivatives in a one-pot operation by a 2:1 coupling of ene-carbamates and aryl amines using montmorillonite KSF clay as an inexpensive and environmentally benign catalyst.

Acknowledgements

B.V.S., K.S.R., and V.S. thank CSIR New Delhi for the award of fellowships.

References and notes

1. Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682–6685.
2. Malassene, R.; Sanchez-Bajo, L.; Toupet, L.; Hurvois, J. P.; Moinet, C. *Synlett* **2002**, 1500–1504.
3. Judd, W. R.; Aube, J. *CHEMTRACTS* **2003**, *16*, 105–116.
4. (a) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *2*, 1395; (b) Gurjar, M. K.; Pal, S.; Rama Rao, A. V. *Heterocycles* **1997**, *45*, 231; (c) Kim, S. S.; Cheon, H. G.; Kang, S. K.; Yum, E. K.; Choi, J. K. *Heterocycles* **1998**, *48*, 221.
5. (a) Frank, K. E.; Aube, J. *J. Org. Chem.* **2000**, *65*, 655; (b) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287; (c) Martin, S. F.; Cheavens, T. H. *Tetrahedron Lett.* **1989**, *30*, 7017–7020.
6. (a) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215–1218; (b) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405–9409.
7. (a) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chem. Commun.* **1999**, 651–652; (b) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916.
8. (a) Cornelis, A.; Laszlo, P. *Synlett* **1994**, 155; (b) Sen, S. E.; Smith, S. M.; Sullivan, K. A. *Tetrahedron* **1999**, *55*, 12657.
9. (a) Balogh, M.; Laszlo, P. *Organic Chemistry using Clay*; Springer: New York, 1993; (b) Laszlo, P. *Science* **1987**, *235*, 1473; (c) Laszlo, P. *Pure Appl. Chem.* **1990**, *62*, 2027.
10. (a) Yadav, J. S.; Reddy, B. V. S.; Patil, K. S.; Reddy, P. S. R. *Tetrahedron Lett.* **2002**, *43*, 3853; (b) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Murthy, Ch. V. S. R. *Tetrahedron Lett.* **2001**, *42*, 89; (c) Yadav, J. S.; Reddy, B. V. S.; Madan, Ch. *Synlett* **2001**, 1131.
11. Molecular mechanics calculations were carried out using the SYBYL 6.8 program on a Silicon Graphics O2 workstation.
12. *Typical procedure*: A mixture of the aryl amine (1 mmol), ene-carbamate (2.5 mmol), and montmorillonite KSF clay (1.0 g) in THF (5 mL) was stirred at ambient temperature for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the product was separated by simple filtration and washing with ethyl acetate (2×10 mL). The combined organic extracts were concentrated in vacuo and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate–*n*-hexane (2:8) to afford a mixture of tetrahydroquinoline derivatives **2a** and **3a**. The presence of *endo* and *exo*-isomers are confirmed by ^{1}H NMR in DMSO at 30 °C. Spectroscopic data for selected products IR (KBr): υ 3351, 2945, 1697, 1523, 1251, 1135, 1054, 760 cm^{-1}. ^{1}H NMR (DMSO, 500 MHz) for **2a**: 7.30 (d, 1H, $J = 7.6$ Hz, H-1), 6.87 (m, 1H, H-3), 6.75 (t, 1H, $J = 5.8$ Hz, NH–COOBu-*t*), 6.51 (d, 1H, $J = 8.1$ Hz, H-4), 6.46 (t, 1H, $J = 7.6$ Hz, H-2), 5.81 (br s, 1H, NH), 4.85 (d, 1H, $J = 7.2$ Hz, Ha), 3.33 (m, 2H, H-11), 3.06 (m, 1H, H-b), 2.90 (m, 2H, H-8), 2.28 (m, 1H, H-c), 1.89 (m, 2H, H-10), 1.46 (m, 2H, H-7), 1.39 (m, 2H, H-6), 1.38 (m, 9H, NH–COOBu-*t*), 1.35 (m, 9H, N–COOBu-*t*). ^{1}H NMR ($CDCl_3$ 500 MHz) for **3a**: 7.37 (d, 1H, $J = 7.6$ Hz, H-1), 6.87 (m, 1H, H-3), 6.79 (t, 1H, $J = 5.8$ Hz, NH–COOBu-*t*), 6.55 (d, 1H, $J = 8.1$ Hz, H-4), 6.48 (t, 1H, $J = 7.6$ Hz, H-2), 5.38 (br s, 1H, NH), 5.02 (d, 1H, $J = 7.3$ Hz, Ha), 3.31 (m, 2H, H-11), 3.17 (m, 1H, H-b), 2.96 (m, 2H, H-8), 2.34 (m, 1H, H-c), 1.79 (m, 2H, H-10), 1.46 (m, 2H, H-7), 1.38 (m, 9H, NH–COOBu-*t*) 1.37 (m, 2H, H-6), 1.32 (m, 9H, N–COOBu-*t*). FAB mass: *m*/*z*: 431 M$^+$, 388, 376, 346, 332, 302, 219, 111, 97, 83, 71, 57, 43. HRMS calcd for $C_{24}H_{37}N_3O_4$: 431.2784. Found: 431.2738. The data is given for the mixture as the diastereomers are not well resolved in ^{1}H NMR for **4h/5h**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.04–6.90 (m, 1H), 6.84 (d, 1H, $J = 8.5$ Hz), 6.70–6.55 (m, 1H), 6.42 (d, 1H, $J = 8.5$ Hz), 5.50–5.25 (m, 1H), 4.48 (br s, NH, 1H), 4.06–3.95 (m, 1H), 3.92–3.79 (m, 1H), 3.54–3.43 (m, 1H), 3.22–3.04 (m, 2H), 3.02–2.99 (m, 1H), 2.68–2.40 (m, 1H), 1.92–1.78 (m, 2H), 1.63–1.35 (m, 26H). IR (KBr): υ 3359, 2945, 1697, 1523, 1251, 1135, 1054, 760 cm^{-1}. FAB mass: *m*/*z*: 459 M$^+$, 358, 348, 302, 231, 185, 144, 123, 109, 97, 91, 83, 69, 57. HRMS calcd for $C_{26}H_{41}N_3O_4$: 459.3097. Found: 459.3065.