Pergamon

Tetrahedron Letters 43 (2002) 1573–1575

TETRAHEDRON LETTERS

Bismuth(III) chloride-catalyzed intramolecular hetero-Diels–Alder reactions: a novel synthesis of hexahydrodibenzo[*b*,*h*][1,6]naphthyridines†

Gowravaram Sabitha,* E. Venkata Reddy, Ch. Maruthi and J. S. Yadav

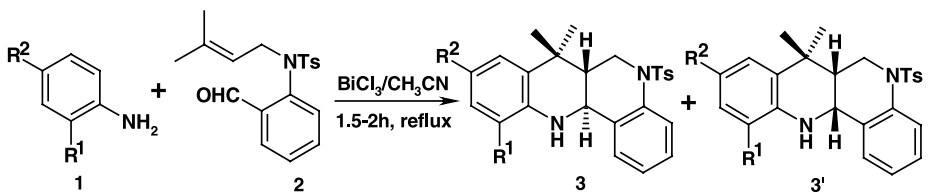
Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 25 October 2001; revised 11 December 2001; accepted 20 December 2001

Abstract—$BiCl_3$ efficiently catalyzed the intramolecular hetero-Diels–Alder reactions of aldimines generated in situ from aromatic amines and the *N*-allyl derivative of *o*-aminobenzaldehyde in refluxing acetonitrile to afford a novel class of hexahydrodibenzo[*b*,*h*][1,6]naphthyridine derivatives. The products are isolated as mixtures of *trans* and *cis* diastereoisomers in a 1:1 ratio, in good to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

The hetero-Diels–Alder reaction is one of the most powerful methods for the synthesis of nitrogen heterocycles[1] and gives access to many building blocks.[2] This strategy offers a powerful solution to many problems in complex natural product synthesis.[3] Tetrahydroquinoline derivatives constitute an important class of natural products displaying a wide range of interesting biological activities.[4] The synthesis of these derivatives has been studied extensively in solution[5] as well as on solid phase[6] using [4+2] cycloaddition reactions. Recently bismuth(III) derivatives[7] have emerged as efficient catalysts in various organic transformations of interest because of their friendly ecological behavior. In continuation of our interest in intramolecular hetero-Diels–Alder reactions,[8] we herein report highly efficient $BiCl_3$-catalyzed [4+2] cycloaddition reactions of anilines with the *N*-allyl derivative of *o*-aminobenzaldehyde, containing an electron rich olefin substituent, for the synthesis of a novel class of nitrogen heterocyclic compounds, hexahydrodibenzo[*b*,*h*][1,6]naphthyridine derivatives (Scheme 1).

Treatment of aniline **1a** with the *N*-allyl derivative of *o*-aminobenzaldehyde **2**[9] in the presence of 10 mol% $BiCl_3$ in refluxing acetonitrile resulted in the formation of a mixture of two products **3a** and **3a′**[10] as *trans* and *cis* diastereoisomers in a 1:1 ratio in 94% yield. The reaction was completed in 2 h, as indicated by TLC by in situ generation of the imine, followed by an intramolecular [4+2] cycloaddition reaction to afford the products. Although it can be considered as the product that would result from a Diels–Alder reaction, the stepwise mechanism might actually be operating. The ratio of the products was determined by isolating the two isomers in pure form using silica gel column chromatography and the stereochemistry of the products was based on coupling constants in their ^1H NMR spectra and NOE difference experiments. In compound **3a**, the H-6a proton appeared as a td at δ 1.50, its coupling with the H-12a and H-6′ protons resulting in a triplet with a large J value ($J = 10.5$ Hz), which again splits into a doublet with a small J value ($J = 3.9$ Hz) by coupling to the nearby H-6 proton.



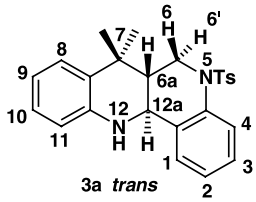
Scheme 1.

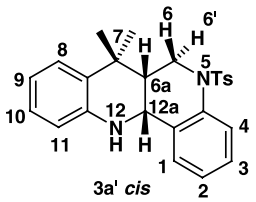
Keywords: hetero-Diels–Alder reactions; bismuth(III) chloride; hexahydrodibenzonaphthyridines.

* Corresponding author.

† IICT communication No. 01X12.

PII: S0040-4039(02)00018-7





This clearly indicated the axial positions of the H-6a and H-12a protons and hence the *trans* ring fusion. Whereas in compound **3a**′ the H-6a proton appeared as a dt at δ 1.55, its coupling with the H-6′ proton resulting in a doublet with a large J value ($J=12.8$ Hz) which is split into a triplet with a small J value ($J=2.6$ Hz) by coupling with the H-12a and H-6 protons which are in equatorial positions. This represents a *cis* fusion at the ring junction. Moreover, in the *trans* fused isomer **3a**, the H-12a proton appears as a doublet at δ 3.95 with a large J value due to vicinal coupling with the axial H-6a proton ($J_{12a,6a}=10.5$ Hz). The large vicinal coupling was taken as strong evidence for the *trans* ring fusion, which was further confirmed by a weak NOE peak between H-6a and H-12a in compound **3a**. In *cis* isomer **3a**′, the doublet due to the H-12a proton appeared at δ 4.30 with a small J value resulting from vicinal coupling with an equatorial H-6a proton ($J_{12a,6a}=2.6$ Hz). The *cis* configuration of H-6a and H-12a in compound **3a**′ was also confirmed by a strong NOE peak between them.

Under similar conditions, several aromatic amines **1b–i** were treated with the *N*-allyl derivative **2** to illustrate the novelty of the present strategy for the synthesis of the title compounds and the results are summarized in Table 1. Although Lewis acids such as $ZnCl_2$, $FeCl_3$, $ZrCl_4$, $AlCl_3$ and $BF_3{\cdot}OEt_2$ have been found to promote the intramolecular hetero-Diels–Alder reaction, more than stoichiometric amounts of the acids were required. The reaction times were also too long with moderate yields, whereas the $BiCl_3$-catalyzed reaction is more effective by overcoming the above-mentioned drawbacks.

In summary, a novel, mild and highly efficient method for the synthesis of hexahydrodibenzo[*b*,*h*][1,6]-naphthyridine derivatives has been developed that relies on an intramolecular [4+2] cycloaddition reaction of an imine derived in situ from an *o*-aminobenzaldehyde derivative with aromatic amines.

Acknowledgements

E.V.R. and Ch.M. thank CSIR, New Delhi for the award of Fellowships.

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Table 1. $BiCl_3$-catalyzed synthesis of hexahydrodibenzo[*b*,*h*][1,6]naphthyridines[a,b]

Entry	Substrate (amine)	R^1	R^2	Time (h)	Overall yield[c] **3** and **3**′ (%)
1	**1a**	H	H	2	94
2	**1b**	CH_3	H	2	92
3	**1c**	Br	CH_3	1.5	94
4	**1d**	H	OCH_3	2	90
5	**1e**	H	Cl	1.5	96
6	**1f**	H	F	1.5	93
7	**1g**	OH	H	2	90
8	**1h**	H	CH_3	1.5	92
9	**1i**	1-Naphthyl	Amine	1.5	94

[a] All reactions were conducted in refluxing acetonitrile using 10 mol% $BiCl_3$.
[b] The products were characterized by MS, IR, ^1H and ^{13}C NMR spectra.
[c] Yield refers to the 1:1 mixture of product diastereoisomers isolated after column chromatography.

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9. The construction of precursor **2** was achieved from methyl anthranilate by tosylation (82%), followed by prenylation (74%) of the amine group and a two-step procedure involving reduction with LAH (83%) followed by oxidation using IBX (90%) of the ester group in an overall yield of 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H, -CH_3), 1.60 (s, 3H, -CH_3), 2.45 (s, 3H, -CH_3), 3.80–3.90 (m, 1H, N-CH_2), 4.40–4.60 (m, 1H, N-CH_2), 5.05–5.10 (m, 1H, -CH=C-), 6.75 (d, 1H, J=8.3 Hz, ArH), 7.25 (d, 2H, J=8.3 Hz, ArH), 7.40–7.50 (m, 2H, ArH), 7.55 (d, 2H, J=8.3 Hz, ArH), 7.95 (d, 1H, J=8.3 Hz, ArH), 10.25 (s, 1H, -CHO).
10. **General procedure**: $BiCl_3$ (10 mol%) was added to a mixture of aniline **1** (1 mmol) and the *N*-allyl derivative of *o*-amino benzaldehyde **2** (1.1 mmol) in 5 mL of acetonitrile. The reaction mixture was stirred at acetonitrile reflux temperature for 1.5–2 h. On completion, as indicated by TLC, the reaction mixture was quenched with dilute HCl and extracted with ethyl acetate. The organic layer was washed with a $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product was chromatographed on silica gel (EtOAc/hexane, 3:97) to afford **3** and **3′** in 90–96% yield. Selected analytical data for compound **3a** (*trans*): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 3H, -CH_3), 1.30 (s, 3H, -CH_3), 1.50 (td, 1H, J=10.5, 3.9 Hz, H-6a), 2.30 (s, 3H, -CH_3), 3.40 (dd, 1H, J=13.2, 10.5 Hz, H-6′), 3.95 (d, J=10.5 Hz, H-12a), 4.35 (dd, 1H, J=13.2, 3.9 Hz, H-6), 6.50 (d, 1H, J=7.9 Hz, ArH), 6.65 (t, 1H, J=7.9 Hz, ArH), 6.95 (t, 1H, J=7.9 Hz, ArH), 7.05–7.35 (m, 6H, ArH), 7.45 (d, 2H, J=7.9 Hz, ArH), 7.95 (d, 1H, J=7.9 Hz, ArH). MS (m/e): 418 (M^+). Selected analytical data for compound **3′a** (*cis*): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (s, 3H, -CH_3), 1.40 (s, 3H, -CH_3), 1.55 (dt, 1H, J=12.8, 2.6 Hz, H-6a), 2.40 (s, 3H, -CH_3), 3.10 (t, 1H, J=12.8 Hz, H-6′), 4.10 (dd, 1H, J=12.8, 3.8 Hz, H-6), 4.30 (d, 1H, J=2.6 Hz, H-12a), 6.05 (d, 1H, J=7.7 Hz, ArH), 6.60 (t, 1H, J=7.7 Hz, ArH), 6.90 (t, 1H, J=7.7 Hz, ArH), 7.05–7.45 (m, 8H, ArH), 7.95 (d, 1H, J=7.7 Hz, ArH). MS (m/e): 418 (M^+).