Intramolecular Hetero-*Diels–Alder* Reactions Catalyzed by $BiCl_3$: Stereoselective Synthesis of Benzo-Annelated Decahydrofuro[3,2-*h*][1,6]-naphthyridine Derivatives

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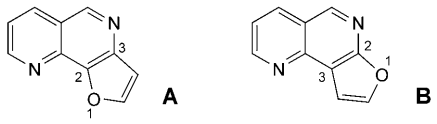
A novel, efficient synthesis of a series of functionalized, benzo-annelated decahydrofuro[3,2-*h*][1,6]naphthyridine derivatives **3** has been achieved. The protocol is based on the intramolecular hetero-*Diels–Alder* (IMHDA) reaction of *in situ* formed imines derived from an *N*-prenylated sugar aldehyde **1** and different aromatic amines **2** in the presence of bismuth(III) chloride as catalyst. The reactions could be run under very mild conditions at room temperature, and were complete within 30 min, affording exclusively and stereoselectively the corresponding *trans*-fused products **3** in good-to-excellent yields (*Table*).

Introduction. – The *Diels–Alder* reaction with its myriad applications has enabled the construction of complex molecules and afforded numerous unparalleled solutions to a diverse range of synthetic puzzles provided by nature in the form of natural products. Over recent years, intramolecular hetero-*Diels–Alder* (IMHDA) reactions have found wide application in numerous reactions of prominence in organic synthesis because of their economical and stereocontrolled nature in the synthesis of polycyclic skeletons [1] [2]. These reactions allow the formation of two or more rings at once at the expense of sequential chemical transformations.

We have reported [3] several $BiCl_3$-catalyzed IMHDA reactions of imines derived from *O*-, *N*-, and *S*-prenyl derivatives of aldehydes and anilines. However, there is no single report on IMHDA reactions using *N*-prenylated sugar aldehydes derived from D-glucose and amines. One possible target structure of such reactions is furo[3,2-*h*][1,6]naphthyridine (**A**), a rare and basically non-investigated heterocyclic systems, in contrast to the isomeric furo[2,3-*h*][1,6]naphthyridine skeleton (**B**), which can be readily made by *Smiles* rearrangement followed by cyclization [4]. These [2,3-*h*][1,6]naphthyridine derivatives have shown relaxation activity against tracheal muscular contraction induced by carbamylcholine chloride.

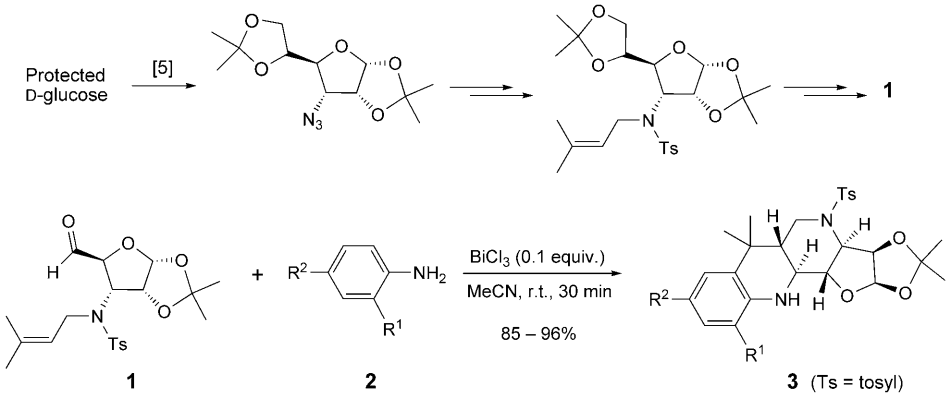
In the present work, we introduce a novel, stereoselective method for the preparation of a series of complex, tetra- or pentacyclic furo[3,2-*h*][1,6]naphthyridine derivatives from anilines or naphthalene-1-amine and a simple sugar derivative.

Results and Discussion. – The crucial building block in the synthesis of furo[3,2-*h*][1,6]naphthyridines was the *N*-prenylated, protected sugar aldehyde **1**, which can



be readily prepared from D-glucose (*Scheme*). When **1** was reacted with 4-bromo-2-methylaniline (**2a**) in the presence of 10 mol-% of $BiCl_3$ as catalyst in MeCN, compound **3a** was obtained as a single stereoisomer in 96% yield (*Table*). The reaction was complete within 30 min, as indicated by TLC. Mechanistically, the process starts with *in situ* generation of the corresponding imine, followed by an intramolecular [4+2] cycloaddition to afford the product. Although compound **3a** could result from a concerted *Diels–Alder* reaction, a stepwise mechanism might actually be operating.

Scheme



When other amines were used, the IMHDA reaction was similarly stereoselective, affording only *trans*-fused products **3**. Their configuration was derived by means of in-depth NMR experiments. ^{1}H,^{1}H-NMR coupling constants and characteristic NOEs were used to derive the proposed structures, which were additionally supported by minimum-energy calculations.

In the case of **3a**, the NMR couplings J(3b,11b), J(11b,11a), J(11a,5a), J(5a,5$_{ax}$), and J(5a,5$_{eq}$), with values of 9.7, 10.0, 11.3, 11.6, and 3.9 Hz, respectively, suggested a chair conformation for the six-membered *B*-ring (*Figure*). Further, NOEs between H–C(3b) and H$_{ax}$–C(5)[1]), as well as between H–C(5a) and H–C(11b) confirmed a $^{3b}C_{5a}$ chair conformation, H–C(3b), H–C(11a), and H$_{ax}$–C(5) being on one side of the ring, and H–C(11b) and H–C(5a) on the other. These observations are in accord with *trans*-fused rings *B* and *C*, and rings *A* and *B*, respectively. Finally, NOEs between H–C(12a) and H–C(3b), and between H–C(3b) and H–C(3a) indicated that these H-atoms are on the same side of the fused furan ring in **3a**, confirming inversion of configuration at C(3b).

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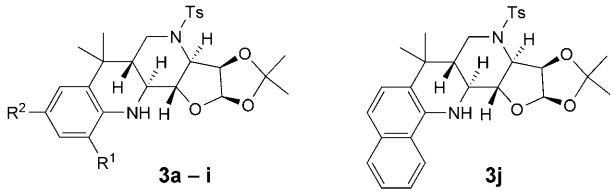
[1]) H$_{ax}$–C(5) corresponds to the axial (*pro-R*) H-atom.

Table. *Substituents, Isolated Yields, and Optical Rotations of the Prepared Benzo-Annelated Decahydrofuro[3,2-h][1,6]naphthyridines* **3a**–**j**



No.	R^1	R^2	Yield [%]	$[\alpha]_D^{25}$ ($c=0.5$, $CHCl_3$)
3a	Me	Br	96	+61.6
3b	H	Cl	94	+43.9
3c	Me	H	85	+54.8[a])
3d	H	F	94	+83.8
3e	H	MeO	86	+46.9[a])
3f	H	H	88	+43.2[b])
3g	MeO_2C	H	93	+78.1
3h	MeO	H	85	+66.2
3i	F	F	96	+60.4
3j[c])			90	+64.8

[a]) $c=1.0$ ($CHCl_3$). [b]) $c=1.5$ ($CHCl_3$). [c]) Reaction performed with naphtalen-1-amine.

In the IMHDA reaction between **1** and different aromatic amines (such as 2-methylaniline, naphthyl-1-amine, 4-fluoroaniline, 4-chloroaniline, 4-methoxyaniline, methyl anthranilate, *etc.*), we observed that the yield (85–96%) was somewhat better for anilines with electron-withdrawing groups. In all cases, a single isomer was observed, with *trans* geometry at the *A*/*B* ring junction.

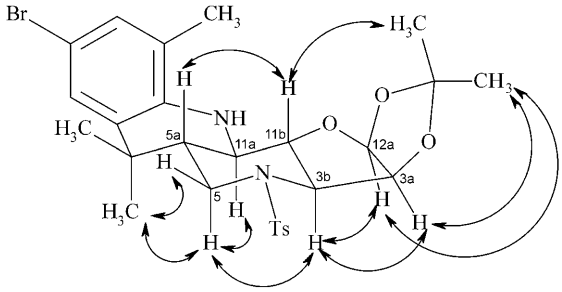


Figure. *Characteristic NOEs of compound* **3a**

In conclusion, we have found a novel synthetic protocol for the stereoselective and efficient preparation of a complex, carbohydrate-based heterocyclic system with several N- and O-functions based on the otherwise hardly accessible furo[3,2-*h*][1,6]naphthyridine skeleton. Currently, work is in progress aiming at the synthesis of the corresponding thia (S) analogs, as will be reported in due course.

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Experimental Part

All reactions were carried out under N_2 atmosphere and monitored by TLC on silica gel (60–120 mesh; *Merck*). Optical rotations were measured on a *Jasco DIP-370* polarimeter. IR Spectra were recorded on a *Thermo Nicolet Nexus-670* spectrometer; in *m*/*z*. ^{1}H- and ^{13}C-NMR Spectra were recorded on *Bruker* (300/75 MHz) and *Varian* (200/50 MHz, resp) spectrometers in $CDCl_3$; δ in ppm, *J* in Hz. ESI Mass spectra were recorded on an *Agilent LC-MSD-Trap-SL* apparatus; in *m*/*z*.

General Procedure for the Preparation of Compounds **3**. $BiCl_3$ (10 mol-%) was added to a mixture of the sugar derivative **1** (1.1 mmol) and the amine **2** (1 mmol) in MeCN (5 ml). The mixture was stirred at r.t. for 30 min (TLC control). On completion of the reaction, the mixture was filtered through *Celite*, the filtrate was concentrated, taken up in AcOEt, and washed with brine. The org. layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford the crude product, which was chromatographed (SiO_2; AcOEt/hexane 2 : 98) to afford pure **3**. All products are new compounds and were fully characterized. As an example, the anal. data of **3a** are given below.

*Data of (3a*R*,3b*R*,5a*R*,11a*S*,11b*R*,12a*R*)-8-Bromo-3a,3b,4,5,5a,6,11,11a,11b,12a-decahydro-2,2,6,6,10-pentamethyl-4-[(4-methylphenyl)sulfonyl]benzo[*b*][1,3]dioxolo[4,5]furo[3,2-*h*][1,6]naphthyridine* (**3a**). M.p. 226–227°. $[\alpha]_D^{25} = +61.6$ ($c = 0.5$, $CHCl_3$). IR (KBr): 3415, 2927, 1617, 1487, 1350, 1218, 1162, 1026, 864, 812, 605, 554, 475. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.06 (*s*, 3 H); 1.38 (*s*, 6 H); 1.55 (*s*, 3 H); 1.81 (*ddd*, *J* = 3.9, 11.3, 11.6, 1 H); 2.06 (*s*, 3 H); 2.39 (*dd*, *J* = 10.0, 11.3, 1 H); 2.40 (*s*, 3 H); 2.40 (*dd*, *J* = 3.9, 9.7, 1 H); 3.07 (*dd*, *J* = 11.6, 11.9, 1 H); 3.91 (*dd*, *J* = 3.9, 11.9, 1 H); 3.94 (*dd*, *J* = 9.7, 10.0, 1 H); 5.09 (*dd*, *J* = 3.3, 3.9, 1 H); 5.82 (*d*, *J* = 3.3, 1 H); 7.00 (*d*, *J* = 2.4, 1 H); 7.17 (*d*, *J* = 2.4, 1 H); 7.35 (*d*, *J* = 8.1, 2 H); 7.76 (*d*, *J* = 8.1, 2 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 144.4; 138.7; 132.7; 131.0; 130.7; 129.7; 128.2; 126.8; 123.4; 113.5; 109.0; 105.2; 80.3; 79.0; 62.6; 52.3; 48.9; 42.6; 34.4; 27.5; 27.3; 26.4; 26.3; 21.6; 17.5. LC-MS: 601 ($[M + Na]^+$).

REFERENCES

[1] 'Hetero *Diels–Alder* Methodology in Organic Synthesis', Eds. D. L. Boger, S. M. Weinreb, Academic Press, Orlando, 1987, Chapts. 2 and 9; S. M. Weinreb, in 'Comprehensive Organic Synthesis', Eds. B. M. Trost, I. Fleming, Pergamon Press, Oxford, 1991, Vol. 5, Chapt. 4.2, p. 401; L. F. Tietze, G. Kelt-schan, *Top. Curr. Chem.* **1997**, *189*, 1; I. A. Motorina, D. S. Grierson, *Tetrahedron Lett.* **1999**, 40, 7211; I. A. Motorina, D. S. Grierson, *Tetrahedron Lett.* **1999**, *40*, 7215.

[2] L. F. Tietze, J. Bachmann, J. Wichmann, Y. Zhou, T. Rasche, *Liebigs Ann.* **1997**, 881; D. A. Evans, J. S. Johnson, E. J. Othava, *J. Am. Chem. Soc.* **2000**, *122*, 1635; M. Toyota, C. Komori, M. Ihara, *J. Org. Chem* **2000**, *65*, 7110; B. R. Bear, K. J. Shea, *Org. Lett.* **2001**, *3*, 723.

[3] G. Sabitha, C. S. Reddy, C. Maruthi, E. V. Reddy, J. S. Yadav, *Synth. Commun.* **2003**, *33*, 3063; G. Sabitha, E. V. Reddy, J. S. Yadav, K. V. S. Rama Krishna, A. R. Sankar, *Tetrahedron Lett.* **2002**, *43*, 4029; G. Sabitha, C. Maruthi, E. V. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2002**, *43*, 1573; G. Sabitha, E. V. Reddy, J. S. Yadav, *Synthesis* **2002**, *3*, 409; G. Sabitha, E. V. Reddy, J. S. Yadav, *Synthesis* **2001**, *10*, 1979.

[4] K. Sasaki, A. S. S. Rouf, T. Hirota, *J. Heterocycl. Chem.* **1996**, *33*, 49; R. Kingford-Adaboh, S. Kashino, K. Sasaki, A. S. S. Rouf, T. Hirota, *Acta Cryst., Sect. C* **1996**, *52*, 372.

[5] S. A. W. Gruner, G. Kéri, R. Schwab, A. Venetianer, H. Kessler, *Org. Lett.* **2001**, *3*, 3723.

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