Tetrahedron Letters 50 (2009) 1243–1248

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A one-pot synthetic approach to the functionalized isomeric ellipticine derivatives through an imino Diels–Alder reaction

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ARTICLE INFO

Article history:
Received 24 October 2008
Revised 31 December 2008
Accepted 9 January 2009
Available online 13 January 2009

Keywords:
Heterocycles
Isoellipticine
Cycloaddition
Ionic liquid
Indium trichloride

ABSTRACT

An efficient, three component, one-pot synthesis of new isomeric ellipticine derivatives prepared through an imino Diels–Alder reaction of 3-aminocarbazoles and substituted benzaldehydes with electron-rich alkenes such as 3,4-dihydro-2*H*-pyran, 2,3- dihydrofuran and ethyl vinyl ether catalyzed by $InCl_3$ (10 mol %) in ionic liquid is reported. In the case of substituted benzaldehydes, reductive amination is observed.

Nitrogen-containing heterocycles are widespread in nature and possess a broad spectrum of interesting biological properties. Ellipticine, an alkaloid isolated from Apocyanaceae plants, and several of its derivatives exhibit promising results in the treatment of osteolytic breast cancer metastases, brain tumors, kidney sarcoma, and myeloblastic leukemia.[1] More recent studies have also indicated activity against HIV.[2] The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects, and a complete lack of hematological toxicity.[3] Ellipticine is an antineoplastic agent, the mode of action of which was considered to be based mainly on DNA intercalation and/or inhibition of topoisomerase II.[1,3]

Ellipticine has proven to be a popular target for synthesis, and a wide variety of strategies have been reported.[4–6] Similarly, the structurally related aryl- and heteroaryl annulated carbazoles have also received considerable synthetic attention.[4–7] Despite the great interest that has given rise to much synthetic work on ellipticine and its derivatives, very little attention has been focused on the synthesis of its isomers or on fusion with other biologically important molecules.[8]

The imino Diels–Alder [4+2] cycloaddition reaction has been established as a powerful synthetic tool for the construction of a polycyclic ring system in a stereo- and regio-controlled manner and has been widely used in the preparation of a wide range of carbocyclic and heterocyclic compounds.[9] Moreover, cycloaddition reactions may offer wide scope in the generation of molecular diversity through the variation of the structures of both reactants, diene and dienophile. The reaction of imines with electron-rich dienophiles has been reported to be catalyzed by Lewis acids.[10] In this Letter, we present our recent results demonstrating that imines derived from substituted benzaldehydes and 3-aminocarbazoles are excellent substrates for an intermolecular imino Diels–Alder reaction with electron-rich dienophiles catalyzed by $InCl_3$ (10 mol %) in [Emim]-[BF_4] to provide highly functionalized isomeric ellipticine derivatives with high diastereoselectivity. Ionic liquids are increasingly used as reaction media in organic synthesis as they offer a wide range of advantages over classical organic solvents. [Emim]-[BF_4] has been exploited as an efficient Brønsted acid promoter in various organic transformations.[11]

Construction of the polycyclic isomeric ellipticine ring systems employing the cycloaddition of imine derived from 9-ethyl-3-aminocarbazole and benzaldehyde in [Emim]-[BF_4] at 100 °C underwent an intermolecular [4+2] cycloaddition reaction with 3,4-dihydro-2*H*-pyran in the presence of Lewis acid to yield 9-ethyl-5-phenyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2′,3′:4,5]pyrido[2,3-*c*] carbazole **4b** and **4ab** as a mixture of diastereomers, where the cis isomer **4b** is the major product along with regioisomer **4abc** (Scheme 1).

The reactions proceed smoothly in the presence of Lewis acids or Brønsted acids, but diastereoselectivity depends on the nature of the catalyst (Table 1). And in all cases cis diastereomer

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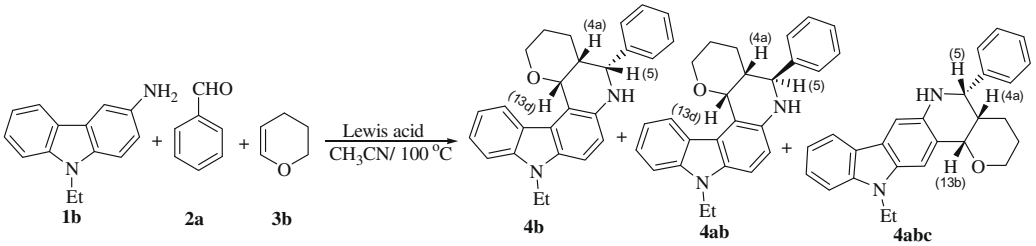
0040-4039/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.01.020



Scheme 1. Synthesis of isomeric ellipticine derivatives.

Table 1
Optimization of reaction conditions

Entry	Catalyst	Time (h)	Yield (%)	Product ratio[a] (**4b/4abc/4c**)
1	$BF_3{\cdot}OEt_2$ (20 mol %)	24	65	62:23:15
2	CF_3COOH (20 mol %)	24	70	67:17:16
3	CAN (20 mol %)	12	86	83:11:06
4	[Emim]-[BF_4]	24	41	61:29:10
5	[Emim]-[BF_4]/$InCl_3$/rt	24	76	77:20:03
6	[Emim]-[PF_6]/$InCl_3$/rt	24	72	74:22:04
7	[Emim]-[BF_4]/$InCl_3$/50 °C	12	81	70:25:05
8	[Emim]-[BF_4]/$InCl_3$/70 °C	05	85	77:19:04
9	**[Emim]-[BF_4]/$InCl_3$/100 °C**	**01**	**90**	**78:22:0**
10	[Emim]-[BF_4]/$La(OTf)_3$/100 °C	02	80	76:24:0

[a] Yields refer to purified product after column chromatography.

4b is the major product. Surprisingly, we have also observed a minor product **4abc**, which occurs through cyclization with the second position of aminocarbazole. Lower yields and longer reaction time are observed in [Emim]-[BF_4], without the catalyst. Among the catalysts screened, $InCl_3$ and $La(OTf)_3$ were found to be better in [Emim]-[BF_4]. However, compared to $InCl_3$, $La(OTf)_3$ gives a low yield (80%) and requires a longer reaction time (2 h). The positive role of indium chloride in the imino Diels–Alder reaction was reported earlier.[12] After the addition of $InCl_3$ (10 mol %), the reaction rate is faster and better diastereoselectivity is observed at 100 °C. Ionic liquids having the counter-ion [PF_6^-] have a lower yield as compared with [BF_4^-]. Further increase in the temperature did not improve the regioisomer ratio. The stereochemistry was assigned on the basis of the coupling constant values and also by NOE and 2D NOESY studies. The tetrahydropyran and the six-membered piperidine rings were cis fused, as indicated by the coupling constant $J_{13d\text{–}4a} = 5.7$ Hz between H_{13d} (δ 5.87) and H_{4a} (δ 2.45). Also, $J_{4a\text{–}5} = 2.3$ Hz, where H_5 (δ 4.64) in **4b** and the presence of NOEs between H_{13d}–H_{4a} and H_{4a}–H_5 confirm that these three protons are cis to each other.

In **4ab**, $J_{13d\text{-}4a} = 3.5$ Hz between H_{13d} (δ 5.21) and H_{4a} (δ 2.28) show cis coupling but $J_{4a\text{-}5} = 15.2$ Hz where H_5 (δ 4.82) are trans and NOE also confirms that H_{13d}–H_{4a} are cis to each other and H_{4a}–H_5 are in trans. In the case of **4abc**, H_{13b} (δ 5.56), H_{4a} (δ 2.29), and H_5 (δ 4.73) are cis with the coupling constants $J_{13d\text{-}4a} = 4.9$ Hz and $J_{4a\text{-}5} = 2.4$ Hz and NOE also confirms the same thing. 2D NOESY also supports this stereochemistry. Isomers **4b**, **4ab**, and **4abc** were also confirmed by single-crystal X-ray diffraction analysis. The crystal structures of **4b** and **4abc** are shown in Figure 1.[13]

Extending this methodology further, we have carried out the imino Diels–Alder reaction with various substituted amines in the presence of $InCl_3$ (10 mol %) under optimized conditions. The results are summarized in Table 2. In most cases, the corresponding imino Diels–Alder products **4a–c** were obtained in

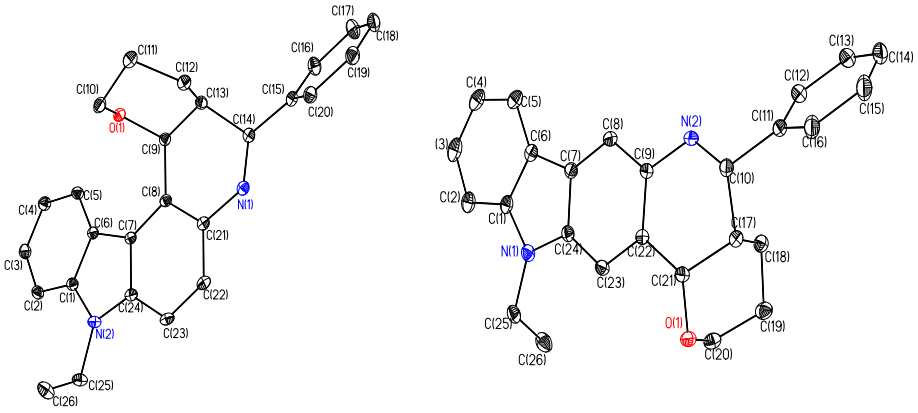
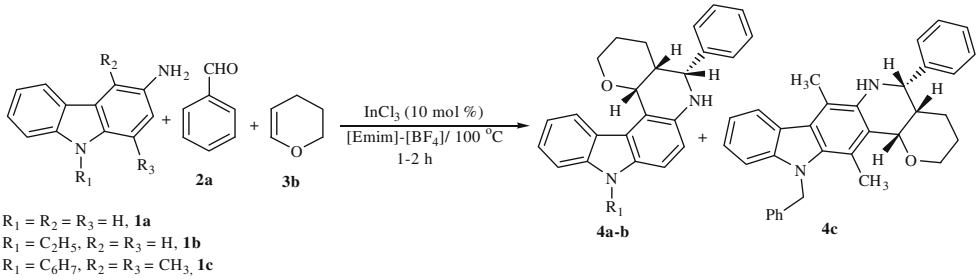
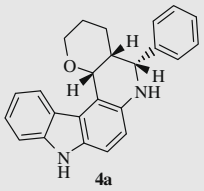
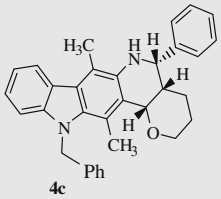


Figure 1. ORTEP diagrams of **4b** and **4abc**.

Table 2
The intermolecular imino Diels–Alder reaction of various substituted amines



$R_1 = R_2 = R_3 = H$, **1a**
$R_1 = C_2H_5$, $R_2 = R_3 = H$, **1b**
$R_1 = C_6H_7$, $R_2 = R_3 = CH_3$, **1c**

Entry	Reactant	Product	Yield (%)	Product ratio
1	**1a**	 **4a**	89	95:05
2	**1b**	**4a** and **4abc**	90	78:22
3	**1c**	 **4c**	71	93:07

good yields (Table 2). But in the case of **1c**, having substituents on the first and fourth positions ($R_3 = R_4 = CH_3$), the corresponding product (**4c**) was obtained in only 71% yield, and this may be due to the steric hindrance caused by the methyl groups. The X-ray crystal structure of (**4c**) is presented in Figure 2.[13]

2,3-Dihydrofuran undergoes a cycloaddition reaction with electron deficient dienes generated from 9-ethyl-3-aminocarbazole and benzaldehyde to give **4d** in 85% yield with 97:03 diastereoselectivity (Table 3). Similarly, ethyl vinyl ether reacts with the imine derived from benzaldehyde and aminocarbazole in the presence of

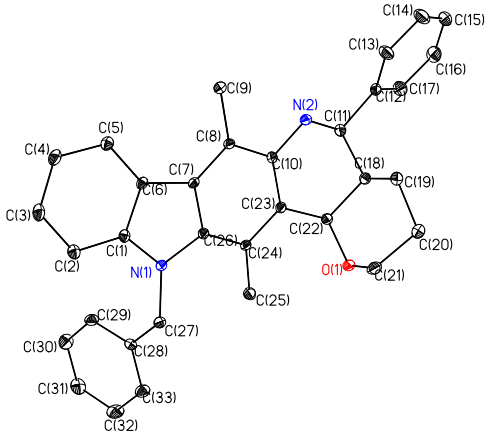


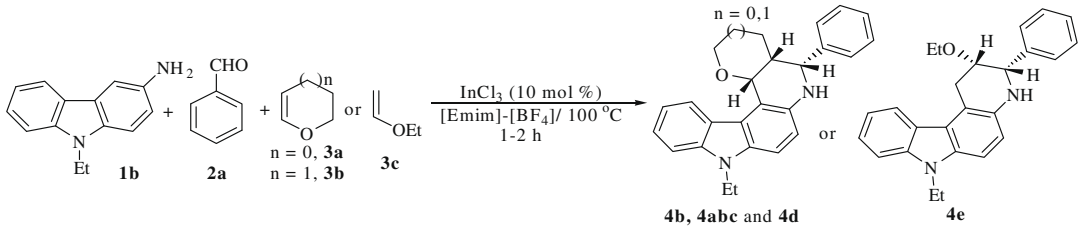
Figure 2. ORTEP diagram of **4c**.

$InCl_3$ (10 mol %) in ionic liquid to provide cycloadduct **4e** in a good yield. The reactions are performed at room temperature, but at 100 °C lower yields and side products were observed. Ethyl vinyl ether and dihydrofuran also exhibited behavior similar to dihydropyran with respect to the stereochemistry of the products. The coupling constants obtained from ^{1}H NMR and 2D NOESY support this stereochemistry.

To prove the generality of this reaction, we have also examined the reactions of substituted benzaldehydes under the same reaction conditions. The results are summarized in Table 4. The reaction proceeds smoothly to afford cycloadducts **4f–i**, and a surprisingly reductive amination is also observed as a side reaction (products **4fa–ia**). The same products were obtained when acetonitrile was used as the solvent without the use of ionic liquid and $InCl_3$ is used as a catalyst (with $La(OTf)_3$, a similar reactivity is observed). We assume this reduction may be due to the oxidation of 2,3-dihydro-2*H*-pyran, since without the use of pyran no reductive amination occurred. The X-ray crystal structure of **4ia** is shown in Figure 3.[13] By using a larger amount of dihydropyran (10 equiv), the yield of cycloadduct **4f** improved from 60% to 88%. Instead of substituted benzaldehydes, we have also checked with *N*-methylindole-2-carboxaldehyde, which gives only the single product **4j** under the same reaction conditions.

In summary, we have described a novel and practical method for the synthesis of new isomeric ellipticine derivatives through an intermolecular imino Diels–Alder reaction with high diastereoselectivity. This procedure has the advantage of high yields, easy availability, and flexibility of starting materials, short reaction times, and good diastereoselectivity.[14]

Table 3
The intermolecular imino Diels–Alder reaction of various electron-rich dienophiles



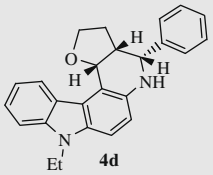
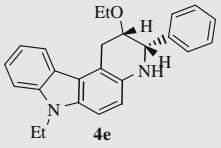
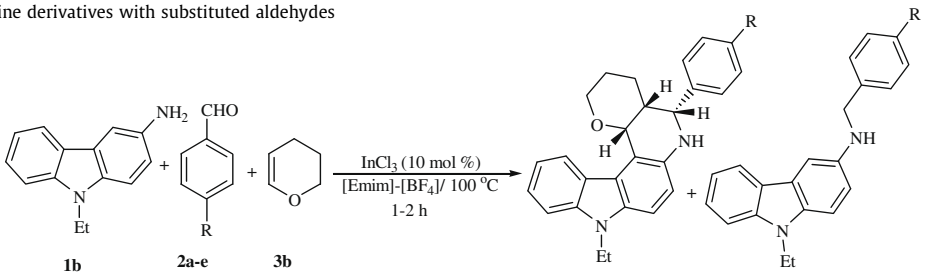
Entry	Reactant	Product	Yield (%)	dr ratio
1	**3a**	 **4d**	85	97:03
2	**3b**	**4a** and **4abc**	90	78:22
3	**3c**	 **4e**	92	96:04

Table 4
Synthesis of isomeric ellipticine derivatives with substituted aldehydes



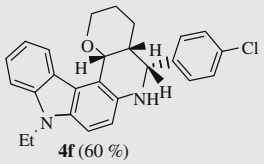
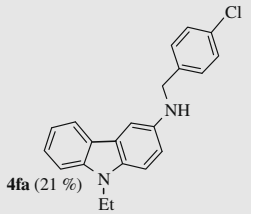
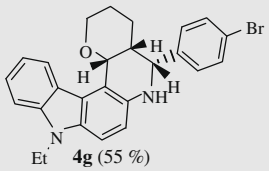
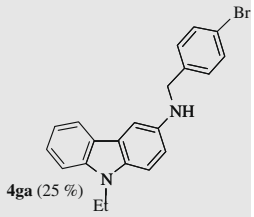
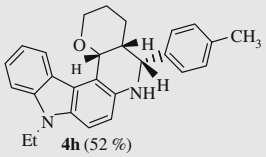
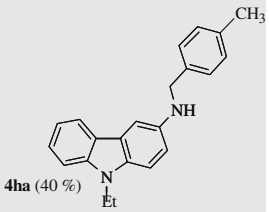
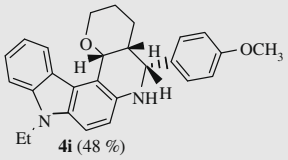
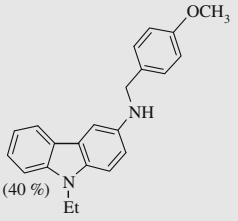
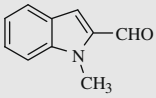
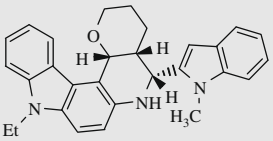
Entry	R	Products
1	H	**4a** and **4abc**
2	Cl	 **4f** (60 %)  **4fa** (21 %)
3	Br	 **4g** (55 %)  **4ga** (25 %)

Table 4 (*continued*)

Entry	R	Products
4	CH_3	 **4h** (52 %)  **4ha** (40 %)
5	OCH_3	 **4i** (48 %)  **4ia** (40 %)
6		 **4j** (67 %)

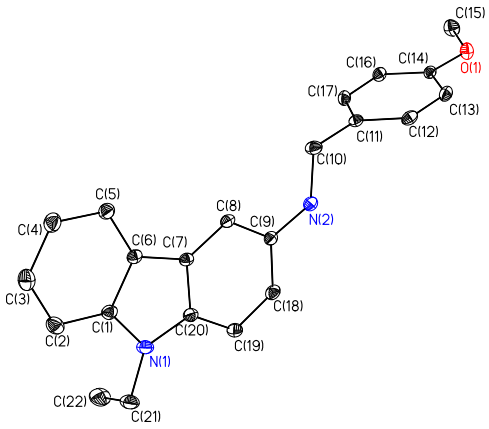


Figure 3. ORTEP diagrams of **4ia**.

Acknowledgments

We gratefully acknowledge DST for providing financial assistance and single crystal X-ray diffractometer facility in our school. G.V. thanks CSIR for a Senior Research Fellowship. We thank Dr. P. Raghavaiah for his help in solving the crystal structures and Mr. S. Satyanaryana for NMR experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.020.

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13. The CCDC deposition number for **4b** is 700692; molecular formula: $C_{26}H_{26}N_2O$, chemical formula weight 382.49, monoclinic, unit cell parameters: *a* 12.171(4), *b* 19.615(6), *c* 8.481(3), β 99.583(5) and space group $P2_1/c$. The CCDC deposition number for **4ab** is 700691; molecular formula: $C_{52}H_{54}N_4O_2$, chemical formula weight 766.99, monoclinic, unit cell parameters: *a* 17.345(6), *b* 9.953(3), *c* 28.955(7), β 124.743(14) and space group $P2_1/c$. The CCDC deposition number for **4abc** is 700693; molecular formula: $C_{26}H_{26}N_2O$, chemical formula weight 382.49, monoclinic, unit cell parameters: *a* 12.448(3), *b* 8.554(2), *c* 19.291(5), β 95.512(4) and space group $P2_1/n$. The CCDC deposition number for **4ia** is 700694; molecular formula: $C_{22}H_{22}N_2O$, chemical formula weight 330.42, monoclinic, unit cell parameters: *a* 21.435(4), *b* 10.400(2), *c* 8.2300(16), β 92.72(3) and space group $P2_1/c$. The CCDC deposition number for **4j** is 700695; molecular formula: $C_{29}H_{29}N_3O$, chemical formula weight 435.55, triclinic, unit cell parameters: *a* 8.694(3), *b* 10.223(4), *c* 14.049(5), α 91.585(5), β 107.682(5), γ 107.141(5) and space group $P\bar{1}$. The CCDC deposition number for **4c** is 700696; molecular formula: $C_{33}H_{32}N_2O$, chemical formula weight 472.61, monoclinic, unit cell parameters: *a* 12.009(2), *b* 23.983(5), *c* 8.8101(17), β 91.916(4) and space group $P2_1/c$.
14. *Typical procedure for the imino Diels–Alder reaction of* **4b**: To a solution of benzaldehyde (0.106 g, 1.0 mmol), 9-ethyl-3-aminocarbazole (0.210 g, 1.0 mmol), 3,4-dihydro-2*H*-pyran, (0.210 g, 2.5 mmol) in 0.5 g of ionic liquid was added $InCl_3$ (0.022 g, 10 mol %), and the reaction stirred at 100 °C for an appropriate time. After the completion of the reaction, as indicated by the TLC, the crude reaction mass was poured into water (50 mL) and extracted with DCM (3 × 20 mL). The organic layer was dried over Na_2SO_4 and distilled under reduced pressure. The residue was chromatographed over basic alumina and eluted with hexane–ethyl acetate to afford 0.268 g (70 %) of **4b**. Mp 158–159 °C; IR (KBr): 3369, 3026, 2941, 1585, 1153, 1086, 983, 929 cm^{-1}; ^1H NMR (400 MHz, TMS, $CDCl_3$) δ: 8.61 (1H, d, *J* = 8.1 Hz); 7.51 (2H, d, *J* = 7.4 Hz); 7.36–7.44 (4H, m); 7.25–7.33 (2H, m); 7.14–7.18 (1H, m); 6.87 (1H, d, *J* = 8.6 Hz); 5.87 (1H, d, *J* = 5.7 Hz); 4.64 (1H, d, *J* = 2.3 Hz); 4.35 (2H, q, *J* = 7.2 Hz); 3.55–3.58 (1H, m); 3.21–3.24 (1H, m); 2.42–2.45 (1H, m); 1.93–1.96 (1H, m); 1.49–1.57 (4H, m); 1.32–1.44 (3H, m); NMR (100 MHz, TMS, $CDCl_3$) δ: 142.1, 140.4, 139.4, 134.8, 128.3, 128.1, 127.3, 127.2, 126.2, 124.9, 122.6, 122.1, 118.1, 115.1, 114.9, 109.1, 107.8 (aromatic C); 72.7, 61.9, 59.9, 39.0, 37.3, 24.5, 19.3, 13.9 (aliphatic C); *m*/*z* = 383 (M+H), positive mode; Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.68; H, 6.89; N, 7.22.