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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7335–7338

Highly diastereoselective synthesis of new indolopyrroloquinolines through intramolecular imino Diels–Alder reactions

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Received 22 June 2007; revised 30 July 2007; accepted 7 August 2007
Available online 10 August 2007

Abstract—A new, efficient and highly diastereoselective one-pot synthesis of cis-fused indolopyrroloquinoline derivatives is described through imino Diels–Alder reaction of substituted anilines or naphthylamines with *N*-prenylated-2-formyl-3-chloroindoles catalyzed by $La(OTf)_3$.

Pyrroloquinoline systems have been found in Nature and their syntheses have been reviewed.[1] The unusual pyrroloquinoline nucleus of the martinellines has attracted attention due to their antibacterial activity as well as affinity for adrenergic, muscarinic and bradykinin receptors.[2] Pyrroloquinoline quinone (PQQ) is an important redox-active co-factor used by a number of bacterial dehydrogenases.[3]

Interest in the pyrrolo[1,2-*a*]indole skeleton is connected with its structural relationship with mitomycins,[4] an important class of antibiotics characterized by noteworthy antitumour activity.[5] In particular, mitomycin C is used in clinical cancer chemotherapy. Following the discovery and total synthesis of mitomycin C, a number of compounds have been synthesized by molecular modifications at the pyrrolo[1,2-*a*]indole without significant loss of biological activity.[6] Therefore, large efforts have been directed towards the synthesis of functionalized pyrrolo[1,2-*a*]indole derivatives as mitomycin analogues and as a result, numerous heterocycle-annulated pyrrolo[1,2-*a*]indole derivatives have been reported.[7]

The imino Diels–Alder reaction provides a rapid means for the construction of functionalized rings containing nitrogen with control of regio-, diastereo- and enantioselectivity.[8] The reaction of imines with electron rich dienophiles have been reported to be catalyzed by Lewis acids,[9] however, most of the Lewis acids are either decomposed or deactivated due to the formation of water during imine formation. Lanthanum(III) triflate has been used to catalyze a variety of reactions.[10] It is stable under aqueous conditions, and catalyzes aldol and allylation reactions in aqueous media.[11]

We are interested in annulation reactions at the 1,2-position of the indole ring in light of the fact that pyrrolo[1,2-*a*]indole units are present in mitosenes and mitomycins. These compounds show antibiotic and antitumour activity and inhibit bacterial cell division through a mechanism involving DNA alkylation.[12] Herein, we report the syntheses of biologically important pyrroloquinolines and pyrroloindoles[5] in a single step reaction (Fig. 1).

The imine derived from the reaction of *N*-prenylated-2-formyl-3-chloroindole **1** with aniline in 1,4-dioxane at reflux temperature underwent intramolecular [4+2] cycloaddition in the presence of a Lewis acid to yield indolopyrroloquinolines **3a** and **4a** as a mixture of

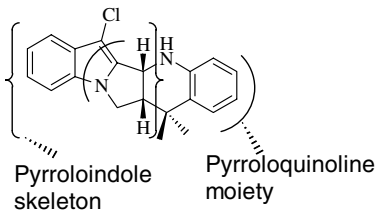

Figure 1.

Keywords: Pyrroloindole; Pyrroloquinoline; Indolopyrroloquinoline; Imino Diels–Alder reactions; Lanthanum triflate.
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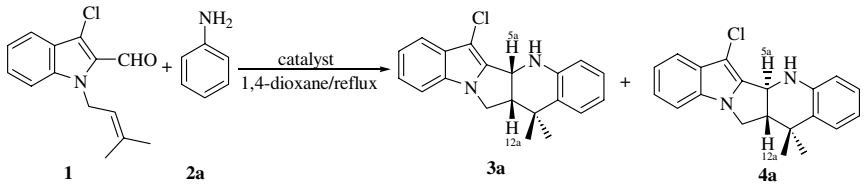
doi:10.1016/j.tetlet.2007.08.016



Scheme 1.

diastereomers where the cis-isomer was the major product (Scheme 1). The diastereoselectivity varied with respect to the nature of the catalyst (Table, see Supplementary data), however, in all the cases, the cis diastereomer was the major product. Several catalysts were screened and amongst them, $Sc(OTf)_3$, $Yb(OTf)_3$ and $La(OTf)_3$ provided excellent diastereoselectivity and also had similar reactivity in terms of reaction yield, diastereomer ratio and reaction time. The diastereoselectivity was further improved by maintaining the reaction at 130–140 °C and only the cis diastereomer was obtained with $La(OTf)_3$ (10 mol %). An increase in temperature did not improve the diastereomer ratio with the other catalysts listed (Table, see Supplementary data), except for $Sc(OTf)_3$ and $Yb(OTf)_3$. The reaction was faster in 1,4-dioxane than CH_3CN and THF. Moderate yields were obtained with DMSO or toluene as the solvent.

The diastereomers were readily separated by column chromatography on silica gel, and their stereochemistry was assigned based on ^1H NMR and NOE studies. The five-membered pyrrolidine and six-membered piperidine rings were cis-fused, as indicated by the coupling constant $J_{5a–12a} = 7.2$ Hz between H_{5a} (δ 5.05) and H_{12a} (δ 3.22) in product **3a** and also the strong NOE (8.0%) enhancement of H_{12a} upon irradiation of H_{5a}. The N–H peak was not observed in the ^1H NMR spectra of compounds **3a**–**g** since it undergoes deuterium exchange with $CDCl_3$, however, a broad singlet at δ 5.79 due to N–H was observed for **3a** in DMSO-d_6. The stereochemistry of the cis-isomer was also confirmed by single crystal X-ray diffraction of **3a** (Fig. 2).[13] The high coupling constant, $J_{5a–12a} = 10.4$ Hz between H_{5a} (δ 4.77) and H_{12a} (δ 3.02) supported the trans configuration of product **4a** and there was no considerable NOE between these two protons.

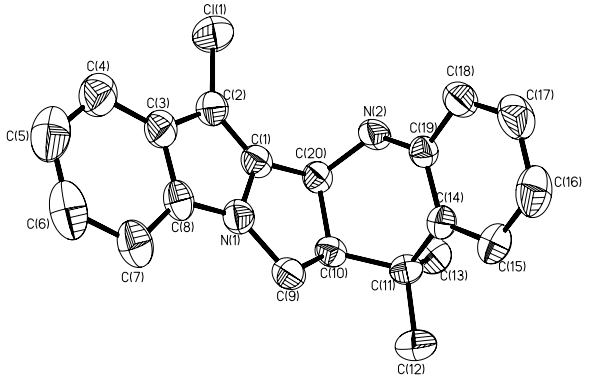
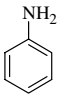
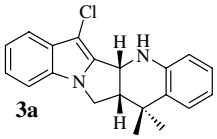
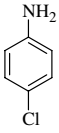
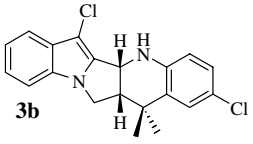
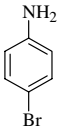
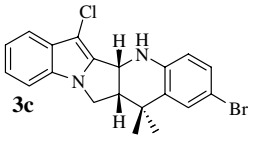
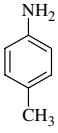
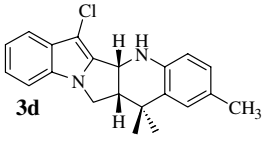
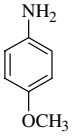
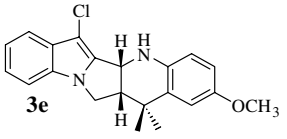
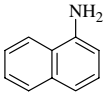
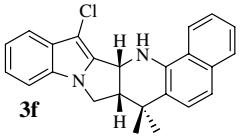
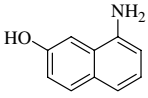
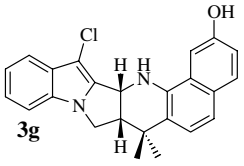
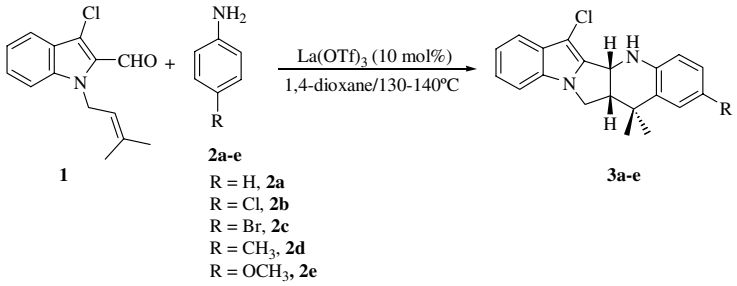


Figure 2. ORTEP diagram of **3a**.

The preparation of indolopyrroloquinoline derivatives with other *p*-substituted anilines under the optimized conditions was carried out and the results are summarized in Table 1. In all cases, the one-pot cycloaddition reaction proceeded smoothly and yielded the corre-

Table 1. Synthesis of new indolopyrroloquinoline derivatives

Entry	Substrate	Product	Yield (%)
1		 **3a**	80
2		 **3b**	92
3		 **3c**	88
4		 **3d**	65
5		 **3e**	52
6		 **3f**	85
7		 **3g**	80



1

2a-e
R = H, **2a**
R = Cl, **2b**
R = Br, **2c**
R = CH_3, **2d**
R = OCH_3, **2e**

3a-e

Scheme 2.

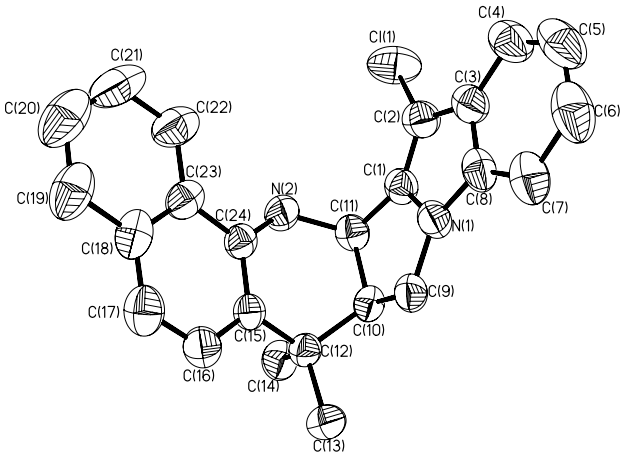


Figure 3. ORTEP diagram of **3f**.

sponding product as a single diastereomer having the cis-configuration. Extending the methodology further, we examined the reactivity of naphthylamines with **1** in 1,4-dioxane at 130–140 °C. The reaction was clean and highly diastereoselective and afforded the corresponding cis-fused indolopyrroloquinolines **3f** and **3g** in good yields (Scheme 2 and Table 1). The structure of **3f** was confirmed by single crystal X-ray analysis (Fig. 3).[14]

In summary, we have successfully synthesized indolopyrroloquinolines[15] via intramolecular imino Diels–Alder [4+2] cycloadditions. This method provides synthetically useful indole-annulated pyrroloquinolines in good yields.

Acknowledgements

We are grateful for the funds provided by the DST and also for the single crystal X-ray diffractometer facility in our school. G.V. thanks the CSIR for a senior research fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.016.

References and notes

1. Black, D. StC.; Kumar, N. *Org. Prep. Proced. Int.* **1990**, *23*, 67–92.
2. 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.
3. (a) Anthony, C. *Antioxid. Redox Signaling* **2001**, *3*, 757–774; (b) Goodwin, P. M.; Anthony, C. *Adv. Microb. Physiol.* **1998**, *40*, 1–80.
4. (a) Hata, T.; Sano, Y.; Sugawara, A.; Matsune, A.; Kanamori, K.; Shima, T.; Hoshi, T. *J. Antibiot., Ser. A* **1956**, *9*, 141 (mitomycins A and B); (b) Wakaki, S.; Marumo, H.; Tomioka, K.; Shimizu, G.; Kato, E.; Kamada, H.; Kudo, S.; Fujimoto, Y. *Antibiot. Chemother.* **1958**, *8*, 288 (mitomycin C).
5. (a) Takahashi, K.; Kametani, T. *Heterocycles* **1979**, *13*, 411–467; (b) Carter, S. K.; Crooke, S. T. In *Current Status and New Development*; Mitomycin, C., Ed.; Academic: New York, 1979.
6. Kinoshita, S.; Uzu, K.; Nakano, K.; Takahashi, T. *J. Med. Chem.* **1971**, *14*, 103–109, and references cited therein.
7. (a) Padwa, A.; Gascaska, J. R. *J. Am. Chem. Soc.* **1986**, *108*, 1104–1106; (b) Rebek, J.; Shaber, S. H., Jr.; Shue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164–5174; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (d) Prajapati, D.; Gadhwal, S. *Tetrahedron* **2004**, *60*, 4909–4913; (e) Beccalli, E. M.; Broggini, G.; La Rosa, C.; Passarella, D.; Pilati, T.; Terraneo, A.; Zecchi, G. *J. Org. Chem.* **2000**, *65*, 8924–8932; (f) Borah, H. N.; Deb, M. L.; Boruah, R. C.; Bhuyan, P. J. *Tetrahedron Lett.* **2005**, *46*, 3391–3393; (g) González-Pérez, P.; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2002**, *43*, 4765–4767; (h) Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413–5418; (i) Yavari, I.; Adib, M.; Sayahi, M. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1517–1519.
8. (a) Waldmann, H. *Synlett* **1995**, 133–141; (b) Barluenga, J.; Joglar, J.; Gonzalez, F. J.; Fustero, S. *Synlett* **1990**, 129–138; (c) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27; (d) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Chem. Commun.* **2002**, 444–445; (e) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16–22; (f) Waldmann, H. *Synthesis* **1994**, 535–551; (g) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259–5288; (h) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939; (i) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1–120; (j) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348.
9. (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939; (b) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579–582; (c) Fadel, F.; Titouani, S. L.; Soufiaoui, M.; Ajamay, H.; Mazzah, A. *Tetrahedron Lett.* **2004**, *45*, 5905–5908; (d)

Yadav, J. S.; Reddy, B. V. S.; Venkateswara Rao, C.; Srinivas, R. *Synlett* **2002**, 993–995.
10. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.
11. (a) Kobayashi, S. *Chem. Lett.* **1991**, 2087–2090; (b) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625–1628; (c) Wang, R.; Lim, C.-M.; Tan, C.-H.; Lim, B.-K.; Sim, K.-Y.; Lob, T.-P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825–1828.
12. (a) Verboom, W.; Reinhoudt, D. N.; Lammerink, B. H. M.; Orlemans, E. O. M.; Van Veggel, F. C. J. M.; Lelieveld, P. *Anti-Cancer Drug Des.* **1987**, *2*, 271; (b) Verboom, W.; Orlemans, E. O. M.; Scheltinga, M. W.; Reinhoudt, D. N.; Lelieveld, P.; Fiebig, H. H.; Winterhalter, B. R.; Double, J. A.; Bibby, M. C. *J. Med. Chem.* **1989**, *32*, 1612–1620; (c) Maliepaard, M.; de Mol, N. J.; Janssen, L. H. M.; Hoogvliet, J. C.; van der Neut, W.; Verboom, W.; Reinhoudt, D. N. *J. Med. Chem.* **1993**, *36*, 2091–2097.
13. The CCDC deposition number for **3a** is 648978; molecular formula: $C_{20}H_{19}ClN_2$, chemical formula weight 322.82, Orthorhombic, unit cell parameters: *a* 14.8375(10), *b* 10.6479(8), *c* 20.4659(15) and space group *Pbca*.
14. The CCDC deposition number for **3f** is 648977; molecular formula: $C_{24}H_{21}ClN_2$, chemical formula weight 372.88, monoclinic, unit cell parameters: *a* 8.6556(10), *b* 21.084(2), *c* 10.6112(12), β 96.368(2) and space group *P*2(1)/*c*.
15. *General experimental procedure*: La(OTf)$_3$ (10 mol %) was added to a mixture of aniline (1 mmol) and 3-chloro-1-(3-methylbut-2-ene)-1*H*-indole-2-carboxaldehyde (1 mmol) in 1,4-dioxane (5 mL). The reaction mixture was heated at 130–140 °C and stirred for the appropriate time. After completion of the reaction, as indicated by TLC, excess 1,4-dioxane was distilled off and the residue was poured into water (20 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 silica gel (100–200 mesh size) and eluted with hexane–ethyl acetate to afford pure cis-fused pyrroloquinoline derivatives as solids. Spectral data for *cis*-6-chloro-13,13-dimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6]pyrrolizino[1,2-*b*]quinoline **3a**: Yield: 80%; mp: 170–171 °C; IR (KBr): 3337, 3061, 2926, 2854, 1711, 1668, 1614, 1510, 1460, 877, 742 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ 7.56 (1H, d, $J = 7.2$ Hz); 7.09–7.17 (4H, m); 6.94 (1H, t, $J = 7.2$ Hz); 6.67 (1H, t, $J = 7.2$ Hz); 6.38 (1H, d, $J = 8.0$ Hz); 5.05 (1H, d, $J = 7.2$ Hz); 4.12 (1H, t, $J = 9.2$ Hz); 3.55 (1H, t, $J = 9.6$ Hz); 3.22 (1H, q, $J = 8.4$ Hz); 1.46 (3H, s); 1.43 (3H, s); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ 142.3, 141.5, 131.6, 129.1, 127.3, 126.6, 125.1, 122.3, 120.0, 118.5, 117.8, 113.8, 110.0 (aromatic C), 54.1, 49.3, 47.1, 34.3, 28.6, 25.6 (aliphatic C); LC–MS: $m/z = 323$ (M+H$^+$), positive mode. Anal. Calcd for $C_{20}H_{19}ClN_2$: C, 74.41; H, 5.93; N, 8.68. Found: C, 74.44; H, 5.93; N, 9.04. *trans*-6-chloro-13,13-dimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6]pyrrolizino[1,2-*b*]-quinoline **4a**: mp: 129–130 °C; IR (KBr): 3337, 3059, 2962, 2856, 1709, 1668, 1614, 1510, 1460, 877, 742 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ 7.63 (1H, d, $J = 7.6$ Hz); 7.34 (1H, d, $J = 8.0$ Hz); 7.21–7.27 (2H, m); 7.18 (1H, d, $J = 6.4$ Hz); 7.12 (1H, t, $J = 7.2$ Hz); 6.88 (1H, t, $J = 7.6$ Hz); 6.80 (1H, d, $J = 7.6$ Hz); 4.77 (1H, d, $J = 10.4$ Hz); 4.37 (1H, t, $J = 8.0$ Hz); 3.94 (1H, t, $J = 10.0$ Hz); 3.02 (1H, q, $J = 7.6$ Hz); 1.52 (3H, s); 1.46 (3H, s); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ 143.7, 137.7, 132.1, 132.0, 128.9, 127.2, 127.3, 122.3, 119.9, 119.6, 118.4, 116.9, 109.7 (aromatic C), 57.7, 51.7, 43.8, 35.5, 29.3, 28.1 (aliphatic C); LC–MS: $m/z = 323$ (M+H$^+$), positive mode. Anal. Calcd for $C_{20}H_{19}ClN_2$: C, 74.41; H, 5.93; N, 8.68. Found: C, 74.61; H, 5.92; N, 8.59. 14-chloro-7,7-dimethyl-7a,8,14b,15-tetrahydro-7*H*-benzo[*h*]-benzo[5,6]pyrrolizino[1,2-*b*] quinoline **3f**: Yield: 85%; mp: 240–241 °C; IR (KBr): 3431, 3053, 2961, 1666, 1521, 1261, 1111, 989, 875 cm^{-1}; ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ 7.42 (1H, d, $J = 8.8$ Hz); 7.37–7.40 (2H, m); 7.25–7.28 (3H, m); 7.10–7.19 (4H, m); 5.28 (1H, d, $J = 6.8$ Hz); 4.17 (1H, t, $J = 8.0$ Hz); 3.63 (1H, t, $J = 9.6$ Hz); 3.30 (1H, q, $J = 9.2$ Hz); 1.59 (3H, s); 1.53 (3H, s); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ 141.5, 136.7, 133.1, 131.7, 129.1, 128.5, 125.3, 124.9, 123.7, 122.4, 121.8, 120.0, 119.8, 119.5, 118.6, 117.2, 110.1 (aromatic C), 54.2, 49.4, 47.2, 34.5, 29.3, 26.0 (aliphatic C); LC–MS: $m/z = 373$ (M+H$^+$), positive mode. Anal. Calcd for $C_{24}H_{21}ClN_2$: C, 77.30; H, 5.68; N, 7.51. Found: C, 77.40; H, 5.63; N, 7.59.