ChemComm

# A three-component coupling protocol for the synthesis of substituted hexahydropyrrolo[3,2-*c*]quinolines

**Robert A. Batey,* Paul D. Simoncic, Denny Lin, Robert P. Smyj and Alan J. Lough†**

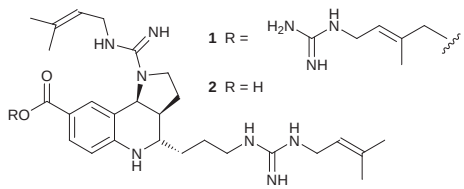
*Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 3H6.*
*E-mail: rbatey@alchemy.chem.utoronto.ca*

***Received (in Corvallis, OR, USA) 7th December 1998, Accepted 10th February 1999***

**One pot reaction of anilines, benzaldehydes and 2-pyrrolines under lanthanide triflate catalysis affords substituted hexahydropyrrolo[3,2-*c*]quinolines in good to excellent yields.**

Multi-component coupling reactions are of growing interest in synthetic organic chemistry, because of their applications in combinatorial chemistry.[1] Those reactions that provide access to novel heterocyclic structures are particularly useful, because of the importance of heterocycles as scaffolds in pharmaceutical development. However, there are relatively few examples of such reactions, and a need exists to expand the repertoire of multi-component coupling methods leading to heterocycles. Accordingly, we now report a versatile one-pot synthesis of substituted hexahydropyrrolo[3,2-*c*]quinolines utilizing a Lewis acid promoted three component coupling reaction.[2]

We have become interested in hexahydropyrrolo[3,2-*c*]quinolines because of the recent isolation of the alkaloids martinelline **1** and martinellic acid **2** from the roots of the



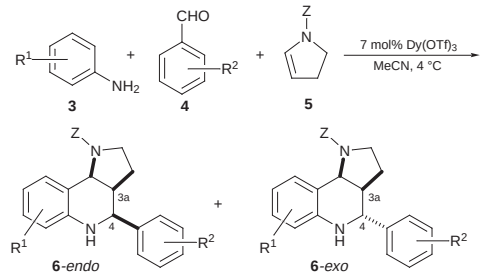

Amazonian plant *Martinella iquitosensis*.[3] These compounds are the first natural products containing a hexahydropyrrolo[3,2-*c*]quinoline core structure. Tetrahydroquinolines and 4-aminoquinolines, of which **1** is an example, are found in a number of pharmaceutically active compounds.[4] Indeed, martinelline has antibiotic activity, affinity for several G-protein coupled receptors, and was the first example of a naturally occurring non-peptidic bradykinin receptor antagonist.[3,5] The core structure is thus of pharmaceutical interest, with the potential for functionalization of the rigid heterocyclic scaffold and/or the two differentiated amine groups.

Although there are several reports of the synthesis of pyrrolo[3,2-*c*]quinolines, these usually require a number of steps, proceed in modest yields, and do not give compounds at the same oxidation state as **1**.[6] We envisaged a highly convergent route, involving a three-component coupling reaction of anilines **3**, benzaldehydes **4**, and the *N*-substituted 2-pyrroline **5**, for the synthesis of differentially substituted analogs **6** (Scheme 1). The *in situ* formed imine generated upon condensation of **3** and **4** can act as a diene, in a formal hetero-Diels–Alder reaction with the electron-rich dienophile **5**.[7] This approach is analogous to the formation of 4-alkoxytetrahydroquinolines, such as the $BF_3{\cdot}OEt_2$ and $EtAlCl_2$ promoted reaction of 2,3-dihydrofuran and the imine formed between aniline and benzaldehyde.[8] Recent findings by Kobayashi have shown that lanthanide triflates[9] will similarly catalyze the reaction of cyclopentadiene or dihydrofuran with *in situ* formed imines derived from anilines and aldehydes.[10]

Endocyclic enamine derivatives such as **5**[11] have not previously been employed in these reactions, and we were delighted to find that lanthanide triflates catalyze their addition (Table 1). Treatment of PhCHO (1.4 equiv.), $PhNH_2$ (1.4 equiv.) and **5** with $Dy(OTf)_3$ (0.07 equiv.) afforded **6a**‡ in 91% yield as an approximately 1 : 1 mixture of readily separable *endo* and *exo* diastereomers, where H3a and H4 have a *cis* and *trans* relationship respectively.[12] The reaction is remarkably facile, and because of the air and water stability of the catalyst, the reaction requires no special precautions. There is little effect on the choice of lanthanide triflate catalyst on the outcome of the reaction, although $Dy(OTf)_3$ gives marginally better yields. Deprotection of the $BnO_2C$ group in the adducts is readily achieved by hydrogenolysis with Pearlman's catalyst. For example, deprotection of the *endo* and *exo* diastereomers of **6a** occurs in 87 and 98% yield, respectively.

The mechanism for the three component coupling reaction presumably involves complexation of the *in situ* formed imine by the lanthanide triflate catalyst, promoting stepwise nucleophilic addition of the electron-rich 2-pyrroline **5** (*i.e.* formation of the C3a–C4 bond), followed by electrophilic aromatic substitution of the aniline ring by the incipient *N*-acyl iminium ion intermediate (*i.e.* formation of the C9a–C9b bond). The initial addition step thus controls the diastereoselectivity of the reaction. The diastereoselectivity is strongly solvent dependent (Table 2). Although there is relatively little effect using dry solvents, a significant change in diastereoselectivity in favor of the *endo* product was observed using water as a co-solvent (entries 6–8, Table 2). The use of THF–water (4 : 1) as solvent results in an enhancement of the de to 92%, but occurs in lower yields (entry 8, Table 2). The origin of the enhanced diastereoselectivity is unclear, but the hydrophobic effect[13] would presumably favor the more compact transition state leading to the *endo* products.

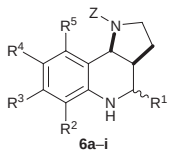
Interestingly, we have found that in the absence of an aldehyde, anilines **3** will couple with *two equivalents* of endocyclic enamines such as **5**. For example, treatment of methyl 4-aminobenzoate with **5** gave **7** in excellent yield as mainly the *endo* diastereomer (Scheme 2).[14] Deprotection of **7** proceeded smoothly with Pearlman's catalyst to yield the free amine **8** in 88% yield as an 85 : 15 mixture of diastereomers in favour of the *endo* product (Scheme 2). The formation of **7** is the first example of a coupling of this type, and presumably occurs *via* the imine formed on condensation of the aniline with the *in situ* hydrolysis product of **5**. This imine may also form directly




**Scheme 1**

† To whom correspondence concerning crystal data should be addressed.

**Table 1** Synthesis of substituted hexahydropyrrolo[3,2-*c*]quinolines **6**[a,b]

| | Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%) | *endo* : *exo* |
|---|---|---|---|---|---|---|---|---|
|  | **6a** | Ph | H | H | H | H | 91 | 51 : 49 |
| | **6b** | 3,4-$Cl_2C_6H_3$ | H | H | H | H | 93 | 57 : 43 |
| | **6c** | 4-$MeOC_6H_4$ | H | H | H | H | 84 | 50 : 50 |
| | **6d** | 2-$MeC_6H_4$ | H | H | H | H | 96 | 42 : 58 |
| | **6e** | 4-$O_2NC_6H_4$ | H | H | H | H | 96 | 53 : 47 |
| | **6f** | Ph | H | H | $MeO_2C$ | H | 61 | 50 : 50 |
| | **6g** | 3,4-$Cl_2C_6H_3$ | Cl | H | Cl | Cl | 47 | 40 : 60 |
| | **6h** | 3,4-$Cl_2C_6H_3$ | H | $O_2N$ | H | H | 65 | 55 : 45 |
| | **6i** | 3,4-$Cl_2C_6H_3$ | –N=CHCH=CH– | | H | H | 78 | 63 : 37 |

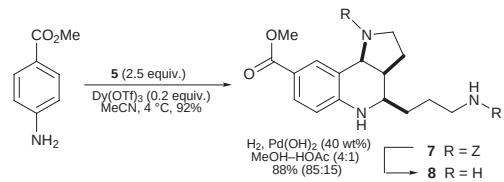
**6a–i**

[a] *Conditions*: **5** (1.0 equiv.), **3** (1.4 equiv.), **4** (1.4 equiv.), $Dy(OTf)_3$ (7 mol%), MeCN, 4 °C, 16 h. [b] Yields are for chromatographically pure material, and diastereomeric ratios are based upon NMR analysis of the crude products.

**Table 2** Solvent effects on the diastereoselectivity of the formation of **6a**

| Entry | Solvent[a] | Dr (*endo* : *exo*)[b] | Yield (%)[c] |
|---|---|---|---|
| 1 | MeCN | 51 : 49 | 91 |
| 2 | $CH_2Cl_2$ | 54 : 46 | 72 |
| 3 | $MeNO_2$ | 45 : 55 | 86 |
| 4 | DMF | 70 : 30 | 35[d] |
| 5 | $CF_3CH_2OH$ | 45 : 55 | 73 |
| 6 | MeCN–$H_2O$ (9 : 1) | 65 : 35 | 55 |
| 7 | DMF/$H_2O$ (4 : 1) | 97 : 3 | 26 |
| 8 | THF–$H_2O$ (4 : 1) | 96 : 4 | 47 |

[a] *Conditions*: [**5**] = 0.14 M, **3a** (1.4 equiv.), **4a** (1.4 equiv.), $Dy(OTf)_3$ (7 mol%), 4 °C, 16 h. [b] Diastereomeric ratios are based upon NMR analysis of the crude products. [c] Yields are for chromatographically purified material. [d] Material isolated was 95% pure by $^1$H NMR analysis.




**Scheme 2**

*via* addition of aniline to protonated **5**, followed by ring-opening. The structural similarities of **7** with **1** may indicate an analogous process occurs in the biosynthesis of martinelline.

In summary, a convergent method for the synthesis of hexahydropyrrolo[3,2-*c*]quinolines has been established, using a lanthanide triflate catalysed three-component coupling reaction. Further studies towards control of the diastereoselectivity of this process for the synthesis of **1**, and other multi-component coupling reactions of endocyclic enamine derivatives, will be reported in due course.

We thank Astra Pharma Inc. and the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support of this work. P. D. S. thanks the NSERC for a Postgraduate Scholarship. We thank Dr A. B. Young for mass spectroscopic assistance.

## Notes and references

‡ The synthesis of **6a** is representative. To a solution of $Dy(OTf)_3$ (32 mg, 0.05 mmol) in MeCN (2.0 ml) at 4 °C was added PhCHO (100 µl, 0.98 mmol) and $PhNH_2$ (89 µl, 0.98 mmol) in MeCN (1.0 ml) *via* cannula. After stirring for 5 min, a solution of **5** (108 mg, 0.705 mmol) in MeCN (1.0 ml) was added *via* cannula. The reaction was stirred under $N_2$ for 16 h at 4 °C. The reaction was quenched with $H_2O$ and extracted with $CH_2Cl_2$ (3 × 30 ml). The combined organic extracts were washed with brine, dried, concentrated *in vacuo* and filtered through a plug of silica gel. The crude products were purified *via* flash chromatography (silica gel, EtOAc–hexanes, $CH_2Cl_2$ or $CH_2Cl_2$–MeOH) to yield the two separable diastereomers. Ratios of diastereomers were determied *via* $^1$H NMR analysis of the crude mixtures.

1 R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123; A. Nefzi, J. M. Ostresh and R. A. Houghten, *Chem. Rev.*, 1997, **97**, 449.
2 Presented in part at the 15th International Symposium on Synthesis in Organic Chemistry of the Royal Society of Chemistry, Oxford, UK, July 1997; paper P47, and at the 79th Canadian Society for Chemistry Conference, St. John's, Newfoundland, June 1996.
3 K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger and S. L.Varga, *J. Am. Chem. Soc.*, 1995, **117**, 6682.
4 A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15 031.
5 Bradykinin (BK) is an endogenous nonapeptide, and BK antagonists have potential for the treatment of chronic inflammatory conditions, shock, pain, rhinitis and asthma: J. M. Hall, *Gen. Pharmacol.*, 1997, **28**, 1.
6 S. S. Kim, H. G. Cheon, S. K. Kang, E. K. Yum and J. K. Choi, *Heterocycles*, 1998, **48**, 221; T. C. T. Ho and K. Jones, *Tetrahedron*, 1997, **53**, 8287; M. K. Gurjar, S. Pal and A. V. R. Rao, *Heterocycles*, 1997, **45**, 231; K. K. Park and H. Rapoport, *J. Heterocycl. Chem.*, 1992, **29**, 1031; T. H. Brown, R. J. Ife, D. J. Keeling, S. M. Laing, C. A. Leech, M. E. Parsons, C. A. Price, D. R. Reavill and K. J. Wiggall, *J. Med. Chem.*, 1990, **33**, 527.
7 For reviews on hetero-Diels–Alder reactions: D. L. Boger, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 451; S. M. Weinreb, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 401.
8 For the first examples of this type of cycloaddition reaction, see: L. S. Povarov, *Russ. Chem. Rev.*, 1967, **36**, 656. See also: T. Kametani, H. Furuyama, Y. Fukuoka, H. Takeda, Y. Suzuki and T. Honda, *J. Heterocycl. Chem.*, 1986, **23**, 185; T. Kametani, H. Takeda, Y. Suzuki and T. Honda, *Synth.Commun.*, 1985, **15**, 499. For a detailed mechanistic discussion: V. Lucchini, M. Prato, G. Scorrano, M. Stivanello and G. Valle, *J. Chem. Soc., Perkin Trans. 2*, 1992, 259.
9 T. Imamoto, *Lanthanides in Organic Synthesis*, Academic Press, London, 1994; G. A. Molander, *Chem. Rev.*, 1992, **92**, 29.
10 S. Kobayashi, H. Ishitani and S. Nagayama, *Chem. Lett.*, 1995, 423; *Synthesis*, 1995, 1195; Y. Makioka, T. Shindo, Y. Taniguchi, K. Takaki and Y. Fujiwara, *Synthesis*, 1995, 801; S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.*, 1996, **118**, 8977.
11 G. A. Kraus and K. Neuenschwander, *J. Org. Chem.*, 1981, **46**, 4791; Y. Nomura, K. Ogawa, Y. Takeuchi and S. Tomoda, *Chem. Lett.*, 1977, 693.
12 The $^1$H NMR spectra of the *endo* and *exo* products are easily distinguished, and correlate well along the series **6a-i**. The *endo* and *exo* stereochemistry was determined unambiguously by crystal structure determinations of **6f**-*endo* and **6g**-*exo*. *Crystal data* for **6f**-*endo*: $C_{27}H_{26}N_2O_4$, $M$ = 442.50, orthorhombic, $P2_12_12$, $a$ = 11.0687(14), $b$ = 25.113(3), $c$ = 7.8901(8) Å, $V$ = 2193.2(5) Å$^3$, $Z$ = 4, $T$ = 173(2) K, $D_c$ = 1.340 Mg m$^{-3}$, $\mu$ = 0.090 mm$^{-1}$, 3622 reflections collected, 3622 independent reflections, $R1$ = 0.0426, $R2$ = 0.1042. For **6g**-*exo*: $C_{25}H_{19}Cl_5N_2O_2$, $M$ = 556.67, monoclinic, $P2_1/c$, $a$ = 12.4852(8), $b$ = 20.673(2), $c$ + 19.5393(14) Å, $\beta$ = 105.48(2)°, $V$ = 4860.4(6) Å$^3$, $Z$ = 8, $T$ = 293(2) K, $D_c$ = 1.521 Mg m$^{-3}$, $\mu$ = 0.624 mm$^{-1}$, 21842 reflections collected, 6312 independent reflections, $R1$ = 0.0528, $wR2$ = 0.1333. CCDC 182/1171.
13 C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997.
14 Attempted three-component coupling of simple aliphatic aldehydes such as pentanal with **5** and an aniline does not result in the formation of aldehyde derived adducts, but instead leads to the formation of **7**.

*Communication 8/09614G*