Pergamon

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Tetrahedron Letters 44 (2003) 8445–8448

TETRAHEDRON LETTERS

A practical approach to the fused β-carboline system. Asymmetric synthesis of indolo[2,3-*a*]indolizidinones via a diastereoselective intramolecular α-amidoalkylation reaction

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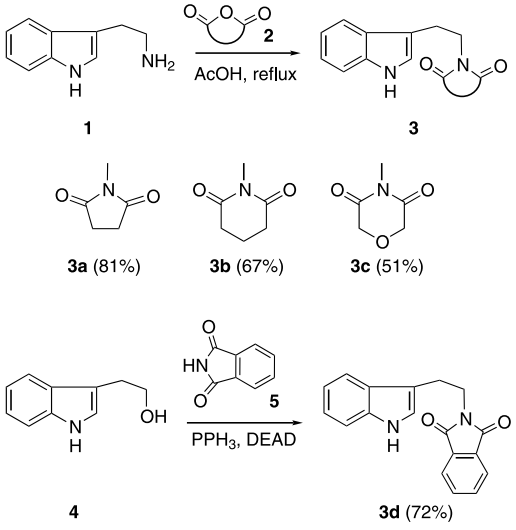
Received 29 July 2003; revised 1 September 2003; accepted 12 September 2003

Abstract—Fused β-carboline systems, as indolo[2,3-*a*]indolizidinones, indolo[2,3-*a*]quinolizidinones, their 2-oxa analogues, and benzo[*a*]indolo[2,3-*a*]indolizidinones are prepared efficiently via an RLi addition-*N*-acyliminium ion cyclisation sequence on readily available imides. In an enantioselective variant of these α-amidoalkylation reactions, the addition of MeLi to a chiral non-racemic imide derived from tryptophan yielded an oxo amide, which was cyclised diastereoselectively upon treatment with $BF_3{\cdot}OEt_2$, to afford 5,11b-*trans*-indoloindolizidinone in moderate yield and high ee (99%).

N-Acyliminium ions have historically occupied an important position as versatile intermediates in organic synthesis. Of particular importance are the reactions of the cyclic *N*-acyliminium ions with π-nucleophiles in carbon–carbon bond forming processes, with a great deal of attention given to cyclisations leading to alkaloids and other nitrogen-containing biologically active compounds.[1] These intramolecular α-amidoalkylations proceed stereoselectively[2] due to steric control by the substituents already present in the ring[3] or along the chain connecting the π-nucleophiles and the nitrogen atom.[4] In this context, we have described an efficient procedure for the synthesis of several types of isoquinoline alkaloid, based on an organolithium addition-*N*-acyliminium ion cyclisation sequence with *N*-phenethylimides.[5] We have also investigated the stereoselectivity of intramolecular reactions of cyclic *N*-acyliminium ions with a substituent adjacent to the iminium carbon, which has led to the diastereoselective synthesis of 1,10b-*cis* thiazoloisoquinolines.[6] This methodology has recently been directed towards the enantioselective synthesis of pyrrolo[2,1-*a*]-isoquinolones via a stereocontrolled *N*-acyliminium ion cyclisation of an enantiopure *N*-phenethylsuccinimide derived from L-DOPA[7] or a *N*-phenethylnorborn-5-en-2,3-dicarboximide with a 2-*exo*-hydroxy-10-bornylsulfinyl group as chiral auxiliary.[8] Allin[9] has reported a related stereoselective approach to the pyrroloisoquinoline ring system based on the intramolecular α-amidoalkylation reaction of a bicyclic lactam derived from (*S*)-phenylalaninol.



Scheme 1.

Keywords: stereoselective α-amidoalkylation; *N*-acyliminium ions; β-carbolines; enantioselective synthesis.

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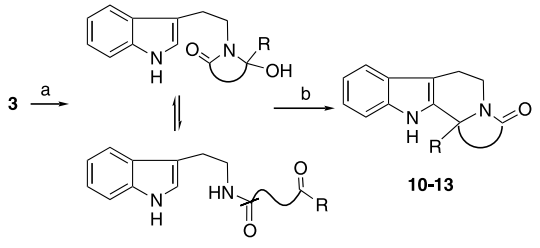
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.097

We now wish to report our investigations into the extension of this methodology to the construction of the fused β-carboline structural framework of the Corynanthe-type alkaloids. This approach has also allowed us to develop an enantioselective variant in order to control the absolute stereochemistry at the newly formed stereogenic centre α to the nitrogen atom.[10] While this manuscript was being prepared, Allin reported a related stereoselective approach to the indoloindolizine ring system.[11]

For the initial investigations it was decided to employ *N*-[2-(3-indolyl)ethyl]imides **3**. Imides **3a–c** were prepared by acylation of tryptamine **1** with cyclic anhydrides **2** under classical conditions, while **3d** was synthesised by Mitsunobu reaction of tryptophol **4** and phthalimide **5**, as depicted in Scheme 1.

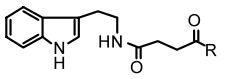
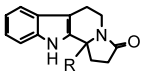
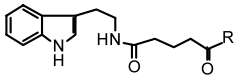
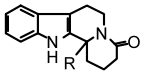
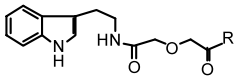
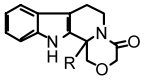
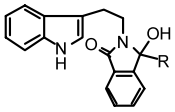
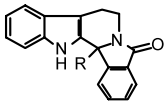
When these imides **3a–d** were subjected to reaction with MeLi or *n*-BuLi (4 equiv.), smooth nucleophilic addition of the organolithium was observed affording the oxo amides **6–8** or their cyclic tautomeic hydroxylactams **9**. (Scheme 2, Table 1). Subsequent treatment with TFA in dichloromethane at room temperature resulted in the formation of the corresponding *N*-acyliminium ions, which cyclised to the fused β-carboline systems: indolo[2,3-*a*]indolizidones **10a**,**b**, indolo[2,3-*a*]quinolizidinones **11a**,**b**, 2-oxa analogues **12a**,**b**, and benzo[*a*]-indolo[2,3-*a*]indolizidinones **13a**,**b**. However, when the organolithium addition-*N*-acyliminium ion cyclisation sequence was applied to imides **3a–d** using *t*-BuLi, the adducts were obtained in low yields and no cyclisation took place. These facts could be explained by the basicity of *t*-BuLi and the steric bulk of the *t*-butyl group.

Therefore, this procedure constitutes an effective route to several Corynanthe-type alkaloids, with the ability to introduce a variety of R substituents at the new quaternary position of the β-carboline unit by changing the organolithium reagent used in the first step. In related strategies, indoloindolizidinones have been accessed in good yields by Pictet–Spengler condensation of tryptamine with carbonyl compounds, although the procedure is less flexible for introducing substituents to C-11b.[12] Similarly, Padwa[13] and Heaney[14] have used *N*-acyliminium cyclisations to obtain excellent yields of indoloindolizidines, although with no substitution on C-11b.

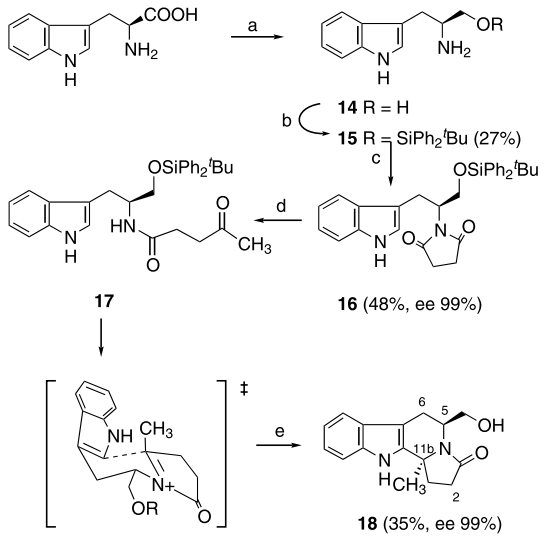


Scheme 2. *Reagents*: (a) RLi (4 equiv.), THF, −78°C, 6 h; (b) TFA, CH_2Cl_2; rt.

Table 1. RLi Addition–*N*-acyliminium cyclisation of imides **3**

Subs.	Addition products, (Yield, %)	Cyclisation products (Yield, %)
3a		
	6a R = Bu (58%) **6b** R = Me (17%) **6c** R = *t*-Bu (27%)	**10a** R = Bu (90%) **10b** R = Me (90%)
3b		
	7a R = Bu (66%) **7b** R = Me (76%) **7c** R = *t*-Bu (16%)	**11a** R = Bu (92%) **11b** R = Me (99%)
3c		
	8a R = Bu (59%) **8b** R = Me (45%) **8c** R = *t*-Bu (18%)	**12a** R = Bu (45%) **12b** R = Me (55%)
3d		
	9a R = Bu (77%) **9b** R = Me (90%) **9c** R = *t*-Bu (48%)	**13a** R = Bu (90%) **13b** R = Me (89%)

Our next challenge was to achieve the asymmetric synthesis of the fused β-carbolines. We chose, therefore, to apply the tandem organolithium addition-*N*-acyliminium ion cyclisation to an imide derived from L-tryptophan. Thus, a diastereoselective intramolecular α-amidoalkylation could be carried out by steric control of the stereogenic centre α to the nitrogen atom. Imide **16** was prepared by reduction of the carboxyl group of L-tryptophan, followed by protection of the hydroxyl group by treatment of the alcohol with *t*-butyldiphenylsilyl chloride, and subsequent condensation with succinic anhydride. Succinimide **16** was treated with MeLi to afford the corresponding oxoamide **17**, which was cyclised with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to afford enantiomerically pure indoloindolizidinone **18**, in which hydrolysis of the TBDPS group had also occurred, in moderate overall yields. Cyclisation with $TiCl_4$ in CH_2Cl_2 at −78°C, afforded **18**, but with a significantly lower yield (8%). The best results were obtained when the addition–cyclisation sequence was carried out without purification of the oxoamide **17**, affording **18** in an overall yield of 35%.[15] Thus, the intramolecular α-amidoalkylation reaction was stereoselective and **18** was obtained as the single 5,11b-*trans* diastereomer; the presence of the corresponding *cis* diastereomer was not detected.[16] The stereochemical outcome is consistent with a late chair-like transition state, in which the substituent on C-5 is placed in a *pseudo*-equatorial disposition. Attack of the aromatic ring onto the *Re* face of the *N*-acyliminium ion leads to the observed stereochemistry, in which the methyl substituent on C-11b assumes a *pseudo*-axial



Scheme 3. *Reagents*: (a) $LiBH_4$, TMSCl, THF; (b) TBDPSCl, imidazole; (*c*) succinic anhydride, Et_2O, reflux; then NaOAc, Ac_2O; (d) MeLi (4 equiv.), THF, −78°C; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, reflux.

position. This result is consistent with our previous results in the synthesis of pyrroloisoquinolines,[7] and with the results reported by Allin,[11] and could be explained by a balance between $A^{(1,3)}$ strain and *syn*-axial 1,3-interactions, favouring the *pseudo*-equatorial disposition of the C-5 substituent in the transition state (Scheme 3).

In conclusion, the stereoselective synthesis of enantiomerically pure indolo[2,3-*a*]indolizidinones is feasible via a diastereoselective α-amidoalkylation reaction that leads to the 5*S*,11b*S*-*trans* diastereomer. This result illustrates the influence of the nature of the substituent on C-11b. Thus, in the synthesis of related β-carboline derivatives with no substitution on C-11b, *cis* diastereomers in which the substituent α to nitrogen is in an axial orientation are preferentially formed.[17]

Acknowledgements

Financial support from Gobierno Vasco (PI-1999-165), MCYT (BQU2000-0223), and Universidad del País Vasco is gratefully acknowledged. We also thank the Gobierno Vasco for grants (A.A., E.G.).

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15. All compounds gave satisfactory spectroscopic data. Typical procedure for **18**: To a solution of imide **16** (193 mg, 0.4 mmol) in dry THF (20 mL), MeLi (1.5 mL of a 1.0 M solution in diethyl ether, 1.5 mmol) was added at −78°C, and the resulting solution was stirred at this temperature for 6 h. The reaction was quenched by the addition of H_2O (5 mL), and allowed to warm to 20°C. Standard work-up afforded the corresponding oxoamide **17** as a colourless oil. **17**: ^{1}H NMR ($CDCl_3$, 250 MHz) (δ, ppm): 1.14 (s, 9H), 2.13 (s, 3H), 2.31 (q, $J=6.3$ Hz, 2H), 2.70 (t, $J=6.3$ Hz, 2H), 3.07 (d, $J=6.7$ Hz, 2H), 3.61–3.73 (m, 2H), 4.32 (broad s, 1H), 5.91 (d, $J=8.3$ Hz, 1H), 6.85 (s, 1H), 7.07–7.20 (m, 2H), 7.31–7.44 (m, 7H), 7.62–7.68 (m, 4H), 7.73 (d, $J=7.9$ Hz, 1H), 8.18 (s, 1H)]. Without further purification, **17** was dissolved in dry CH_2Cl_2 (10 mL) and $BF_3{\cdot}Et_2O$ (0.76 mL, 6.2 mmol) was added. The reaction mixture was heated under reflux for 4 days. After addition of aqueous saturated $NaHCO_3$ (5 mL), standard work-up followed by flash column chromatography (silica gel, 80% hexane:AcOEt) afforded (5*S*,11b*S*)-5-hydroxymethyl-10b-methylindolo[2,3-*a*]indolizidin-3-one (**18**) (38 mg, 35%): ee 99% (Chiralcel OD, 15% hexane:2-propanol, 0.7 mL/min, $t_R=34.5$ min) ; $[\alpha]_D^{20}$ −0.18 (*c* 0.31, CH_2Cl_2); IR (KBr): 3392, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) (δ, ppm): 1.64 (s, 3H), 2.22–2.34 (m, 2H), 2.48 (ddd, $J=17.0$, 8.7, 3.6 Hz, 1H), 2.67–2.81 (m, 2H), 3.03 (dd, $J=1$ 5.5, 11.5 Hz, 1H), 3.64–3.70 (m, 1H), 4.14–4.19 (m, 2H), 5.07 (t, $J=7.1$ Hz, 1H), 7.10–7.23 (m, 2H), 7.34 (d, $J=7.5$ Hz, 1H), 7.47 (d, $J=7.5$ Hz, 1H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) (δ, ppm): 25.4, 24.2, 31.3, 32.7, 55.5, 62.3, 107.3, 111.0, 118.5, 120.0, 122.3, 126.5, 127.7, 136.2, 137.0, 174.5. MS (EI) *m*/*z* (%): 271 (M^++1, 11), 270 (M^+, 29), 256 (19), 255 (100), 252 (16), 239 (15), 237 (21), 223 (15), 183 (13), 182 (12), 150 (11), 149 (83), 168 (14), 167 (44), 130 (10), 113 (13), 112 (10), 83 (13), 71 (34), 70 (22), 69 (13), 57 (51), 56 (11), 55 (30).
16. The stereochemistry was deduced by ^{1}H NMR. The *J* values of the ABX system formed by H-5 and H-6 protons indicate that H-5 is in a *pseudo*-axial position. Besides, NOE difference spectroscopy showed an enhancement between H-5 and the methyl protons on C-11b.
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