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Enantioselective synthesis of pyrrolo[2,1-*a*]isoquinolones via stereocontrolled *N*-acyliminium ion cyclisations

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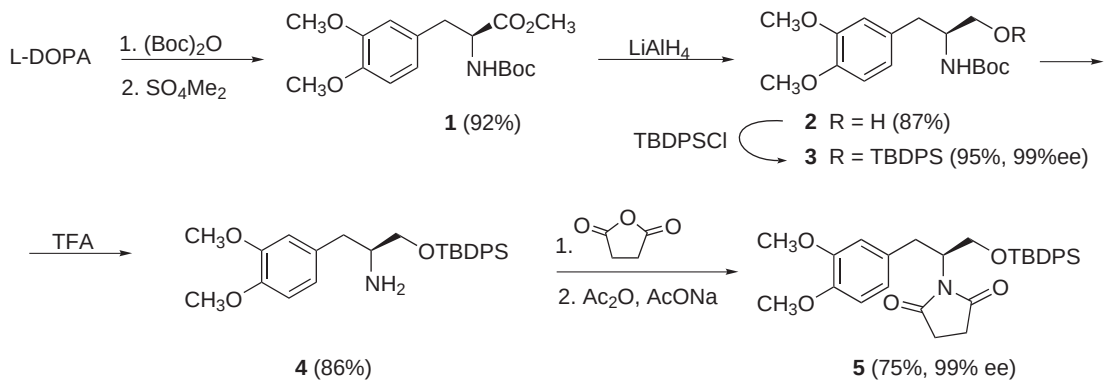
Abstract—Stereocontrolled *N*-acyliminium ion cyclisation of L-DOPA derived succinimide **5** has been investigated. Addition of organolithiums to chiral non-racemic **5** yields oxoamides, which are cyclised diastereoselectively upon treatment with $BF_3{\cdot}OEt_2$, to afford 5,10b-*trans* pyrroloisoquinolones in moderate yields and high ee (99%).

N-Acyliminium ion cyclisation[1] is a valuable carbon–carbon bond formation method for the stereocontrolled synthesis of nitrogen heterocycles which has been applied to the preparation of enantiomerically enriched compounds.[2] It has been shown that intramolecular reactions of cyclic *N*-acyliminium ions with π-nucleophiles proceeds stereoselectively 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]

We have described an efficient procedure for the synthesis of several types of isoquinoline alkaloids based on *N*-acyliminium ion chemistry.[5] Recently, we have 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] In this paper, we wish to report the enantioselective synthesis of 5,10b-*trans* pyrroloisoquinolones from an enantiomerically pure *N*-phenethylimide **5**. The key step would be the stereocontrolled cyclisation of an *N*-acyliminium ion, which bears a stereogenic centre α to the nitrogen atom.

Imide **5** was prepared from L-DOPA by standard functional group manipulation, as outlined in Scheme 1. Thus, protection of the amino group of L-DOPA, followed by methylation yielded ester **1**, which was submitted to successive steps of $LiAlH_4$ reduction, protection of the resulting primary alcohol and hydrolysis of Boc amide to afford amine **4**. Sequential treatment of this amine with succinic anhydride followed by Ac_2O and NaOAc yielded succinimide **5**. Thus, this imide was prepared in high overall yield from L-DOPA (50%), and without epimerisation of the stereogenic



Scheme 1.

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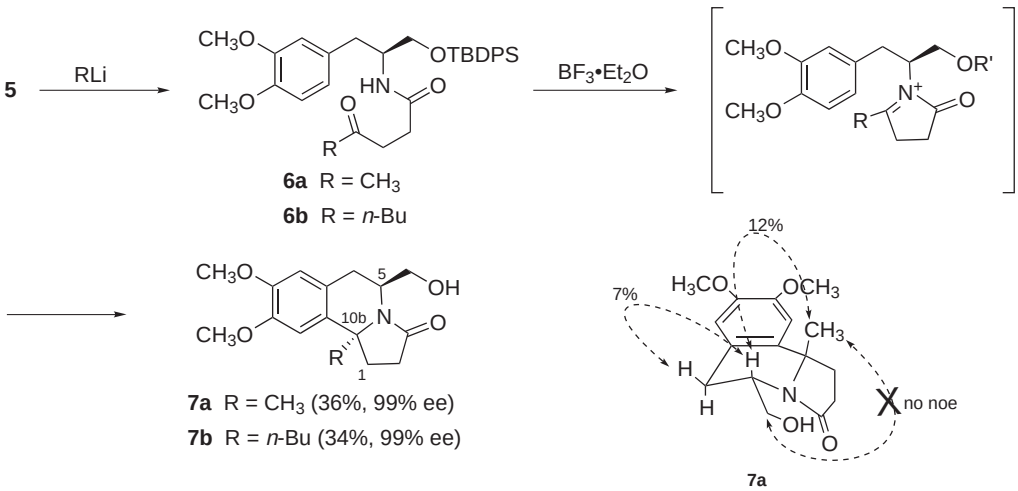

Scheme 2.

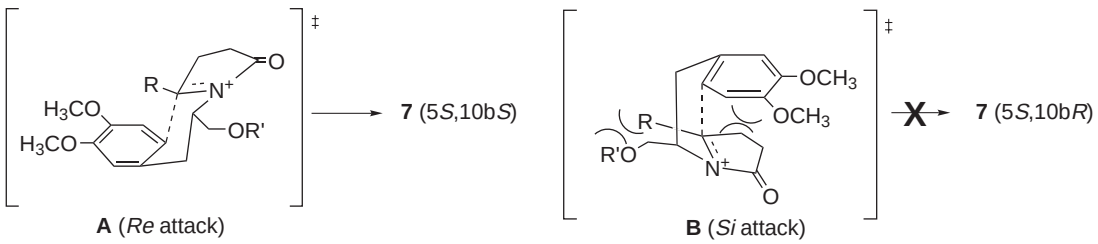

Figure 1.

centre, as imide **5** showed an enantiomeric excess equal to the starting amino acid (99% ee), determined by chiral phase HPLC.[7]

Succinimide **5** was treated with organolithiums (MeLi or BuLi) to afford the corresponding oxoamides **6a**,**b**. Cyclisation of these oxoamides was accomplished with $BF_3{\cdot}Et_2O$ in CH_2Cl_2[8] to afford pyrroloisoquinolones **7a**,**b**, in which hydrolysis of the TBDPS group had also occurred, in moderate overall yields. Cyclisation was stereoselective, and the resulting pyrroloisoquinolones were isolated as single 5,10b-*trans* diastereomers, not detecting the presence of the corresponding *cis* diastereomers. The stereochemistry was deduced by ^1H 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 substituent in 10b (Me or Bu), as shown in Scheme 2 for **7a**. These data are consistent with a preferred half-chair conformation in which the substituents in C-10b and in C-5 are in *pseudo*-axial and *pseudo*-equatorial positions, respectively. Thus, the configuration was assigned as 5*S*,10b*S* and both pyrroloisoquinolones were isolated with high enantiomeric purity (99%).[9]

The stereochemical outcome of the cyclisation may be explained as a result of conformational factors in the transition state, being the rate determining step of the attack of the aromatic onto the *N*-acyliminium ion. The stereochemical results are consistent with a late chair-like transition state, in which the substituent in 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 substituent in 10b (Me or Bu) assumes a *pseudo*-axial position (**A**, Fig. 1). This stereochemical result is in sharp contrast with related examples described in the literature. According to Hart's model, the most favoured transition state would minimise $A^{(1,3)}$ strain.[10] Thus, for intramolecular cyclisations of π nucleophiles on the *N*-acyliminium ion with substituents adjacent to the nitrogen atom, an axial orientation is preferred to avoid $A^{(1,3)}$ strain between the substituent and the carbonyl of the *N*-acyl group.[2] This results in the preferred formation of *cis* diastereomers of, for instance, 5-phenyltetrahydro[2,1-*a*]isoquinolones,[4b] 5-aryl-10b-butyltetrahydro[2,1-*a*]isoquinolones,[11] indolizidines,[12] β-carboline derivatives[13] or polycyclic isoindolinone derivatives.[14] However, in our case, a balance between $A^{(1,3)}$ strain and severe *syn*-axial 1,3 interactions in transition state **B**, that would lead to a *cis* diastereomer, favours the *pseudo*-equatorial disposition for the C-5 substituent in the transition state **A**, leading to **7a**,**b** (Fig. 1). Similar effects have been described for related structures that led to reversal of diastereoselectivity as a result of competing steric interactions.[4d]

In conclusion, a stereoselective synthesis of enantiomerically pure pyrrolo[2,1-*a*]isoquinolones via tandem organolithium addition–*N*-acyliminium ion cyclisation has been achieved. Of particular interest is the stereocontrol in the cyclisation step that leads to the 5,10b-*trans* diastereomers.

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8. All compounds gave satisfactory spectroscopic and analytical data. Typical procedure for **7a**: To a solution of succinimide **5** (270 mg, 0.51 mmol) in dry THF (10 mL), MeLi (2 mL of a 1.0 M solution in diethyl ether, 2 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 **6a** as a yellowish oil. [**6a**: ^{1}H NMR (δ, ppm): 1.11 (s, 9H), 2.14 (s, 3H), 2.22–2.38 (m, 2H), 2.67–2.74 (m, 2H), 2.86 (d, $J=7.1$ Hz, 2H), 3.60–3.62 (m, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 4.10–4.21 (m, 1H), 5.87 (d, $J=8.7$ Hz, 1H), 6.67–6.75 (m, 3H), 7.37–7.45 (m, 6H), 7.60–7.65 (m, 4H)]. Without further purification, **6a** was dissolved in dry CH_2Cl_2 (10 mL), $BF_3{\cdot}Et_2O$ (0.76 mL, 6.2 mmol) and 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, AcOEt) afforded (5*S*,10b*S*)-5-hydroxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3[*2H*]-one (**7a**) (54 mg, 36%): ee 99%; $[\alpha]_D^{20}$ −203 ($c=0.046$, CH_2Cl_2); mp 124–126°C (*n*-pentane). IR (KBr): 3392, 1654 cm^{-1}; ^{1}H NMR (δ, ppm): 1.55 (s, 3H), 2.05–2.19 (m, 1H), 2.31–2.47 (m, 2H), 2.59 (dd, $J=16.2$, 3.6 Hz, 1H), 2.59–2.73 (m, 1H), 3.02 (dd, $J=16.2$, 11.2 Hz, 1H), 3.55–3.67 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.98–4.03 (m, 2H), 4.92 (t, $J=7.1$ Hz), 6.52 (s, 1H), 6.69 (s, 1H); ^{13}C NMR (δ, ppm): 27.3, 31.1, 31.3, 34.9, 53.9, 55.8, 56.1, 62.4, 64.4, 107.4, 112.2, 124.3, 133.9, 147.8, 148.0, 174.0. EM (IE) m/z (%): 291 (M^+, 8), 277 (17), 276 (100), 260 (40), 244 (11), 143 (9), 130 (10), 71 (10), 57 (15). Anal. calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.77; H, 7.53; N, 4.67.
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