Stereoselective α-amidoalkylation reactions of phenylglycinol-derived bicyclic lactams

Mercedes Amat,* Carmen Escolano, Núria Llor, Marta Huguet, Maria Pérez, and Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

Abstract—The stereochemical outcome of α-amidoalkylation reactions from chiral non-racemic bicyclic lactams trans-1 and cis-1 using indole, allyltrimethylsilane, higher order organocuprates, TMSCN, and Grignard reagents is discussed. © 2003 Elsevier Science. All rights reserved

1. Introduction

Chiral bicyclic lactams derived from R- or S-phenylglycinol have emerged as powerful tools for the enantioselective synthesis of piperidine derivatives. In this context, in previous work we have reported the preparation of the phenylglycinol-derived lactams cis-1 and trans-1. Pure lactam cis-1 is easily accessible by cyclocondensation of (R)-phenylglycinol with methyl 5-oxopentanoate under neutral conditions, followed by column chromatography of the resulting 85:15 diastereomeric mixture of lactams, while lactam trans-1 is obtained by equilibration of the above mixture under acidic conditions followed by chromatographic purification (Scheme 1).

![Scheme 1](image)

Both lactams cis-1 and trans-1 have proven to be versatile chiral building blocks for the synthesis of diversely substituted enantiopure piperidines as they allow the stereocontrolled formation of C-C bonds at the different carbon positions of the piperidine ring. In particular, the enantioselective synthesis of 2-alkyl- and 2-arylpiperidines from these lactams requires the stereocontrolled introduction of the substituent at the piperidine α-position by asymmetric α-amidoalkylation, a process that has been reported to occur with moderate to high stereoselectivity from trans-1. Thus, reaction of trans-1 with indole in the presence of TiCl4 leads to a 3:1 mixture of 6-indolyl-2-piperidones 2a and 2b, whereas reaction of trans-1 with allyltrimethylsilane in the presence of TiCl4 gives a 9:1 mixture of the allylated products 3a and 3b (Table 1, entries 1 and 2).

Similarly, the addition of higher order alkyl and phenyl cyanocuprates in the presence of BF3:Et2O takes place in good yields and high stereoselectivities to give the corresponding 6-alkyl- and 6-aryl-2-piperidones (4-6; Table 1, entries 3-5). In all the above cases the major stereoisomer results from an inversion of the configuration at the C-8a stereocenter. This stereoselectivity can be accounted for by considering that the iminium ion generated by interaction of trans-1 with the Lewis acid undergoes nucleophilic attack upon the less hindered face as depicted in A (Figure 1).

![Figure 1](image)

* Corresponding author. Tel.: +34 93 4024538; fax: +34 93 4024539; e-mail: amat@farmacia.far.ub.es; jbosch@farmacia.far.ub.es
2. Results and discussion

In this article we report i) new α-amidoalkylation reactions from trans-1, which provide access to 2-piperidones bearing a functionalized substituent at C-6; ii) the dramatic change of stereoselectivity when Grignard reagents are used instead of higher order cyanocuprates, and iii) a comparative study of the behavior of cis-1 and trans-1 in α-amidoalkylation reactions.

As could be expected from previous results, treatment of lactam trans-1 with lithium 2-methyl-1-propenylcyanocuprate in the presence of BF₃.Et₂O gave the 6-substituted 2-piperidone 7a in 52% yield as the only isolable product (entry 6). Very minor amounts (<5%) of the C-6 diastereomer were detected from the crude reaction mixture. The interest of the above vinylation lies in the fact that lactam 7a could be converted to alcohol 8 in excellent yield by ozonolysis followed by NaBH₄ reduction (Scheme 3), thus opening a simple route for the stereoselective introduction of a hydroxymethyl substituent at the piperidine 2-position, an appendage present in many natural and synthetic azasugars. A similar stereoselectivity was observed in the addition of trimethylsilyl cyanide in the presence of TiCl₄: a 95:5 mixture of nitriles 9a and 9b, respectively, was obtained in 74% yield (Table 1, entry 7).

Table 1. Stereoselective α-amidoalkylation reactions from lactam trans-1

| Entry | Reagents and conditions | Product | R | Yield % | a:b ratio |
|-------|------------------------|---------|---|---------|-----------|
| 1     | Indole, TiCl₄          | 2a + 2b | R | 80%     | 3:1       |
| 2     | CH₂=CH-CH₂SiMe₃, TiCl₄ | 3a + 3b | R | 91b     | 9:1       |
| 3     | Me₂Cu(CN)Li, BF₃Et₂O   | 4a + 4b | CH₃| 70b     | >95:5     |
| 4     | n-Pr₂Cu(CN)Li, BF₃Et₂O | 5a + 5b | CH₂CH₂CH₃ | 65b      | 93:7      |
| 5     | (C₆H₅)₂Cu(CN)Li, BF₃Et₂O | 6a + 6b | C₆H₅| 75b     | 9:1       |
| 6     | (Me₂C=CH)₂Cu(CN)Li, BF₃Et₂O | 7a + 7b | CH=CMe₂ | 52      | >95:5     |
| 7     | TMSCN, TiCl₄           | 9a + 9b | CN | 74      | 95:5      |
| 8     | CH₃MgBr                | 4a + 4b | CH₃| 73      | 15:85     |
| 9     | n-PrMgBr               | 5a + 5b | CH₂CH₂CH₃ | 72      | 5:95      |
| 10    | C₆H₅MgBr               | 6a + 6b | C₆H₅| 72      | <5:95     |
| 11    | Me₂C=CHMgBr            | 7a + 7b | CH=CMe₂ | 56     | <5:95     |

References: 8. 4b.
The remarkable change of stereoselectivity in the above reactions with Grignard reagents can be explained by considering that, in the absence of an additional Lewis acid, the magnesium may coordinate with the oxygen of the oxazolidine ring. Subsequent delivery of the alkyl or aryl group from the same face of the C-O bond would account for the observed retention of configuration.

We then decided to study the stereochemical outcome of α-amidoalkylation reactions from the C-8α epimeric lactam cis-1. In fact, α, β-unsaturated lactams derived from cis-1 and trans-1 undergo conjugate addition reactions with opposite facial selectivity. Somewhat surprisingly, lactam cis-1 was recovered unchanged after treatment with indole (25 ºC, 30 min) or allyltrimethylsilane (25 ºC, 4 h) in the presence of TiCl₄, under the conditions previously employed in the reactions from trans-1. These α-amidoalkylations required longer reaction times (25 h) and took place in lower yields (trans-1, Scheme 4). In both cases, bicyclic lactams trans-1, formed by equilibration of the unreacted starting lactam cis-1, was also isolated to a considerable extent. The observed stereoselectivity in the reaction with indole is a consequence of an equilibration process after prolonged exposure of the resulting indolylpiperidines to TiCl₄. On the other hand, under the reaction conditions successfully used in the reaction with trans-1, cis-1 reacted with n-propylmagnesium bromide with very low yield and stereoselectivity to give a 4:3 diastereomeric mixture of products without remarkable change of stereoselectivity in the above α, β-unsaturated lactams derived from the cyanocuprate solution. The mixture was stirred for 45 min at this temperature until the metal was dissolved. This suspension was added via canula to a mixture of CuCN (495 mg, 5.52 mmol) in THF (24 mL) at −78 ºC, and the stirring was continued for 1.5 h.

A solution of lithium 2-propynyl-1-propynylcyanocuprate (30 mL, 3 equiv) was added via canula (the rest of the cyanocuprate solution was kept cool at −78 ºC) to a solution of trans-1 (200 mg, 0.92 mmol) and BF₃·Et₂O (0.22 mL, 1.84 mmol) in anhydrous THF (8 mL) at −78 ºC. The mixture was stirred at −78 ºC during 2.5 h. Then, additional BF₃·Et₂O (0.22 mL, 1.84 mmol) and lithium 2-propynyl-1-propynylcyanocuprate (30 mL, 3 equiv) were added, and the resulting suspension was stirred for 3 additional hours. The mixture was quenched with saturated aqueous NH₄Cl and saturated aqueous Na₂CO₃. The aqueous phase was extracted with AcOEt, and the combined organic extracts were dried and concentrated. The resulting residue was chromatographed (AcOEt) to give unreacted lactam trans-1 (30 mg) and pure 7a (130 mg, 52%) as a white solid: IR (NaCl) 1616 cm⁻¹, ¹H-NMR (CDCl₃, 300 MHz) δ 1.55 (s, 3H), 1.65-1.93 (m, 4H), 1.73 (s, 3H), 2.51-2.57 (m, 2H), 4.00 (dd, J = 12.3, 3.0 Hz, 1H), 4.02 (m, 1H), 4.18 (dd, J = 12.3, 6.6 Hz, 1H), 4.42 (dd, J = 6.6, 3.0 Hz, 1H), 5.22 (dd, J = 9.3 Hz, 1H), 7.24-7.33 (m, 5H), ¹³C-NMR (CDCl₃, 75.4 MHz) δ 17.5 (CH₃), 17.9 (CH₃), 25.8 (CH₃), 29.9 (CH₃), 33.1 (CH₃), 56.9.
(CH), 64.7 (CH₂), 66.2 (CH), 125.1 (C), 127.4 (CH), 127.5 (2 CH), 128.5 (2 CH), 135.7 (C), 137.6 (C), 172.0 (C); [α]D2O = 12.0, 7.5 Hz, 1H), 5.93 (t, J = 6.6 Hz, 1H), 7.32-7.40 (m, 5H); 13C NMR (CDCl₃, 75.4 MHz) δ = 17.9 (CH₃), 27.5 (CH₃), 31.3 (CH₃), 44.6 (CH), 58.4 (CH), 61.0 (CH₂), 118.9 (C), 128.1 (2 CH), 129.0 (CH), 128.5 (2 CH), 135.3 (C), 170.3 (CO).

3.5. General procedure for the reaction of lactam trans-I with Grignard reagents. A solution of trans-I (1 equiv) in anhydrous THF (2 mL) was added via canula to a solution of the Grignard reactant (3 equiv) in THF or Et₂O at 0 °C, and the mixture was stirred at this temperature for 8 h. The reaction was quenched by addition of saturated aqueous NaCl, and the mixture was extracted with AcOEt. The combined organic extracts were dried and concentrated.

3.5.1. With methylmagnesium bromide. Operating as described in the general procedure, from trans-I (300 mg, 1.38 mmol) and methylmagnesium bromide (3 M in Et₂O, 1.4 mL, 4.14 mmol) a residue was obtained. Purification by column chromatography (AcOEt) gave 4a (36 mg, 36%, [α]D2O = 11.6, 7.5 Hz, 1H), 5.22 (dd, J = 7.5, 4.5 Hz, 1H), 7.26-7.34 (m, 5H, ArH); 13C NMR (CDCl₃, 50.4 MHz) δ 16.6 (CH₃), 21.2 (CH₃), 30.3 (CH₂), 52.3 (CH), 63.4 (CH), 64.3 (CH₂), 127.4 (CH), 127.6 (2 CH), 128.5 (2 CH), 137.2 (C), 172.4 (CO); [α]D2O = 24.5 (c 1.0, EtOH); m/z 234 (1), 215 (26), 203 (31), 202 (100), 188 (7), 186 (6); HRMS calc. for C₁₆H₂₄NO₂ (M⁺) m/z 233.1416, found 233.1419.

3.5.2. With n-propylmagnesium chloride. Operating as described in the general procedure, from trans-I (500 mg, 2.30 mmol) and n-propylmagnesium chloride (2 M in Et₂O, 3.45 mL, 6.91 mmol) a residue was obtained. Purification by column chromatography (97:3 AcOEt-EtOH) gave 4b (36 mg, 6%) and 5b (397 mg, 66%) as colorless oils. 5b: [α]D2O = 64.5 (36 mg, 6%) and 5b (397 mg, 66%) as colorless oils. 5b: [α]D2O = 64.5 (36 mg, 6%) and 5b (397 mg, 66%) as colorless oils.
3.5.3. With phenylmagnesium bromide. Operating as described in the general procedure, from \textit{trans}-1 (200 mg, 1.38 mmol) and phenylmagnesium bromide (1 M in THF, 2.7 mL, 2.76 mmol) a residue was obtained. Purification by column chromatography (AcOEt) gave 6b (196 mg, 72%).

3.5.4. With 2-methyl-1-propenylmagnesium bromide. Operating as described in the general procedure, from \textit{trans}-1 (300 mg, 1.38 mmol) and 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 8.3 mL, 4.14 mmol) a residue was obtained. Purification by column chromatography (AcOEt) gave starting material \textit{trans}-1 (30 mg, 10%) and 6b (211 mg, 56%): \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 300 MHz) \(\delta\) 1.37 (s, 3H), 1.56 (m, 1H), 1.68-1.75 (m, 2H), 1.65 (s, 3H), 1.87 (m, 1H), 2.42-2.62 (m, 2H), 2.42-2.80 (m, 1H), 3.40 (br s, 1H), 3.94 (dt, \(J = 9.3\), 4.5 Hz, 1H), 4.08-4.21 (m, 2H), 5.26 (dm, \(J = 9.3\) Hz, 1H), 5.50 (dd, \(J = 8.0, 5.5\) Hz, 1H), 7.21-7.36 (m, 5H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 50.4 MHz) \(\delta\) 17.6 (CH\textsubscript{3}), 17.6 (CH\textsubscript{2}), 25.9 (CH\textsubscript{1}), 30.4 (CH\textsubscript{2}), 32.5 (CH\textsubscript{2}), 53.6 (CH), 60.7 (CH), 63.5 (CH\textsubscript{2}), 126.2 (CH\textsubscript{2}), 127.5 (CH), 128.1 (2 CH), 128.4 (2 CH), 133.7 (C), 137.1 (C), 172.3 (CO); \([\alpha]_{D}\)\textsubscript{b} = -63 (c 1.0, EtOH); m/z 274 (2), 255 (14), 242 (30), 212 (9); HRMS calc. for C\textsubscript{17}H\textsubscript{23}NO\textsubscript{2} (M\textsuperscript{+}) \([\alpha]_{D}\)\textsubscript{b} = 9.3 Hz, 1H), 5.50 (dd, \(J = 9.3, 4.5\) Hz, 1H), 4.08-4.21 (m, 2H), 5.26 (dm, \(J = 9.3\) Hz, 1H), 5.50 (dd, \(J = 8.0, 5.5\) Hz, 1H), 7.21-7.36 (m, 5H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 50.4 MHz) \(\delta\) 17.6 (CH\textsubscript{3}), 17.6 (CH\textsubscript{2}), 25.9 (CH\textsubscript{1}), 30.4 (CH\textsubscript{2}), 32.5 (CH\textsubscript{2}), 53.6 (CH), 60.7 (CH), 63.5 (CH\textsubscript{2}), 126.2 (CH\textsubscript{2}), 127.5 (CH), 128.1 (2 CH), 128.4 (2 CH), 133.7 (C), 137.1 (C), 172.3 (CO); \([\alpha]_{D}\)\textsubscript{b} = -63 (c 1.0, EtOH); m/z 274 (2), 255 (14), 242 (30), 212 (9); HRMS calc. for C\textsubscript{17}H\textsubscript{23}NO\textsubscript{2} (M\textsuperscript{+}) m/z 273.1729, found 273.1722.

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