Pergamon

Tetrahedron Letters 41 (2000) 1179–1182

TETRAHEDRON LETTERS

Diastereoselective synthesis of 2-aryl-3-aminoazepanes via a novel ring-enlargement process

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Received 15 October 1999; accepted 2 December 1999

Abstract

Syntheses of optically pure 2-aryl-3-aminoazepanes derived from 2-cyano 6-oxazolopiperidine are described. The key step involves a one-pot reduction and ring-enlargement process occurring in a highly regio- and stereoselective way.

Enantiomerically pure 1,2-diamines are of great interest, playing key roles in coordination chemistry, in asymmetric catalysis and as medicinal agents.[1] In these domains and more particularly in peptide research, constrained diamine systems have found application as biological active compounds. Among the seven-membered nitrogen containing rings, 3-aminocaprolactam is a particularly attractive scaffold which has been widely used during the past decade. More recently, original and significant biological activities were discovered in the 3-aminoazepane series. For instance, the arylether **1** is a dopamine reuptake inhibitor,[2] benzamides **2** are D_2 or $5HT_3$ receptor antagonists,[3] and the platinum complexes of **3** are employed as antitumor agents[4] (Fig. 1).

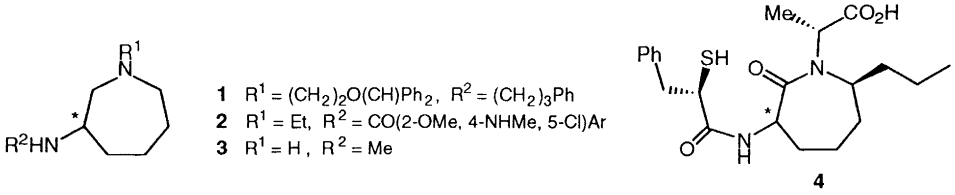

Fig. 1.

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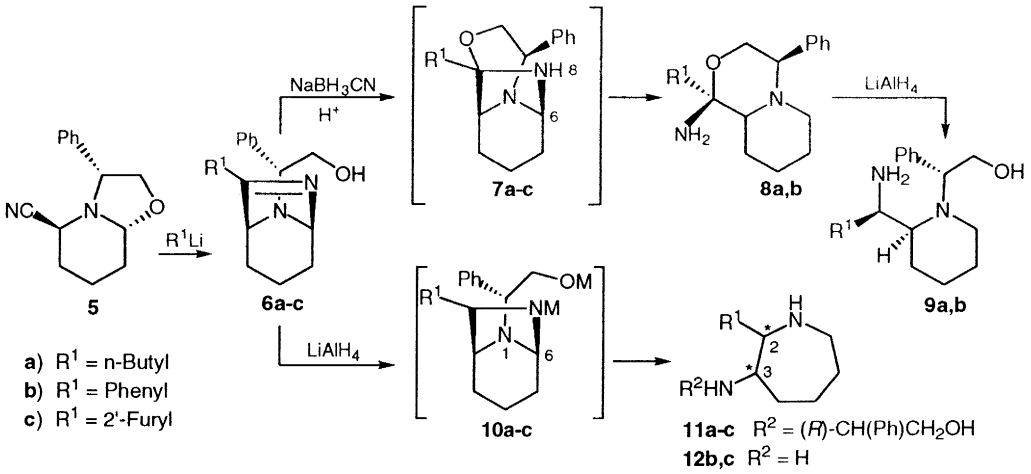
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02256-X

However, few asymmetric syntheses described the preparation of diversely C-substituted 3-aminoazepane compounds. Whereas 3-amino derivatives **1**–**3** were simply derived from 3-aminocaprolactam through $LiAlH_4$ reduction, di-substituted azepinones related to peptidomimetic compound **4** were prepared using various approaches, via Beckmann rearrangement, cyclization of aminoester or lysine derivatives.[5] Surprisingly, to our knowledge, no asymmetric syntheses have been yet reported in the 2-substituted 3-amino series, in contrast to the numerous methods developed for the preparation of corresponding piperidines.[6]

These observations prompted us to develop a novel and general synthetic route giving access to this type of constrained diamines. As part of our on-going programme on asymmetric synthesis we recently described a rapid and convenient route to optically pure 2-aminomethylpiperidines **8** or **9** starting with 2-cyano 6-oxazolopiperidine **5**[7] (Scheme 1).



Scheme 1.

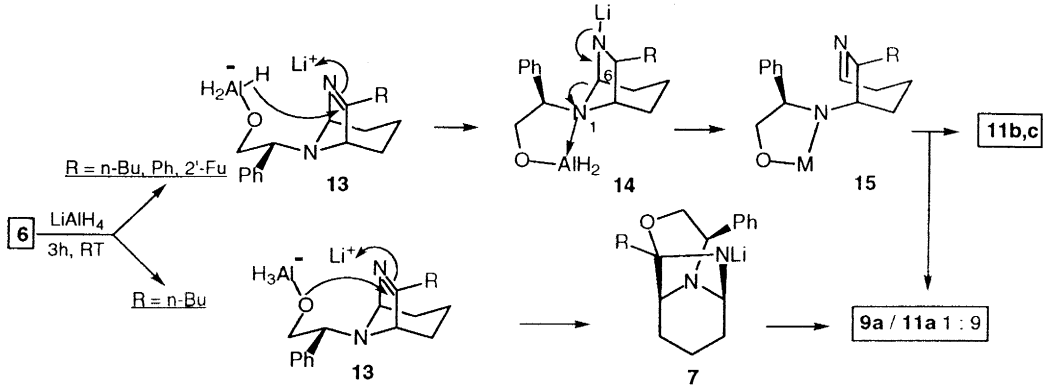
The excellent diastereoselectivities observed were explained by a preferential attack of the alcohol function on the *si* face of the protonated form of imines **6**, followed by regioselective cleavage of the C-6/N-8 bond of the resulting aminal intermediates **7**.

Considering the non-classical bridged-system of the bicyclic imines **6**, we were interested in testing other reduction methods allowing the C-6/N-1 bond cleavage giving a rapid access to the 3-aminoazepane ring system substituted in the C-2 position. We report herein our preliminary results in this novel diamine series with the synthesis of 2-substituted 3-aminoazepanes **12**.

Since previous protic conditions lead exclusively to the piperidine derivatives **8** or **9** via the tricyclic intermediates **7**, we were interested in testing mixed Lewis acid–hydride reagents in aprotic solvents. Indeed, we assumed that in such conditions a partial chelation of the tertiary amine (structures **10**) could enhance the cleaving ability of the C-6/N-1 aminal bond.

Initial experiments were conducted on the known *n*-butylimine **6a**.[7] Treatment of this compound with an excess of $LiAlH_4$ in Et_2O at 20°C afforded a 3/2 inseparable mixture of the desired azepane derivative **11a**[8] and piperidine **9a** (Scheme 2). Adding $AlCl_3$ as Lewis acid did not change the selectivity significantly giving a 1:1 mixture of the same products. Replacement of Et_2O by THF afforded the same results. Finally, the best conditions were found in adding LAH carefully to the imine etheral solution (20°C, 3 h; **11a**/**9a** 9:1). Interestingly, when LAH in Et_2O at −78°C (3 h) or $BH_3 \cdot THF$ (20°C, 3 h) were used, the morpholine **8a** was produced exclusively.

These results clearly show that morpholines **8** are always intermediates toward the formation of



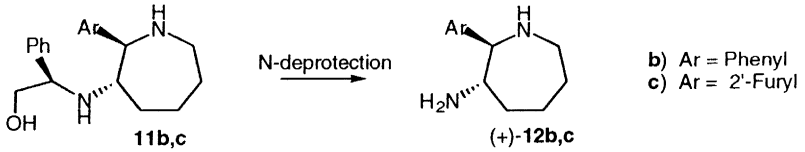
Scheme 2.

piperidines **9**. We therefore studied ring enlargements with aromatic imines, since these derivatives should be less proned to intramolecular attack by the alcoholate. Thus, for phenylimine **6b**,[7] as well as for furylimine **6c**, a total conversion to the derivatives **11b** and **11c** was achieved in good yield (91 and 65%, respectively).[9] Careful spectra analyses revealed that in each case, a single diastereomer was formed. A 2,3-*trans* configuration was proposed on the basis of the large 9 Hz coupling constant observed for the H-2 proton signals.

In order to explain the excellent regio and diastereoselectivities observed in these transformations, we propose a mechanism involving a chelated process (Scheme 2).

The formation of alcoxyaluminum derivative **13** could allow an intramolecular attack of the hydride nucleophile from the *si* face of the imine. Then a N,*O*-bimetallated species **14** can be considered, which could favor the cleavage of the C-6/N-1 bond. The second reduction can then occur on the resulting imine intermediate **15** leading to the 2,6-*trans* disubstituted azepanes **11b** and **11c**. For the butylimine **6a**, the lack of selectivity (**11a**/**9a** 9:1) is probably due to the more electrophilic character of imine carbon compared with the more stable arylimines. Thus piperidine **9a** can be formed via the second pathway in which imine carbon of **13** is preferentially attacked by the alcoholate rather than a hydride species.

To achieve our goal, we then had to cleave the chiral appendage of the secondary amine function. Thus, treatment of phenylderivative **11b** under classical hydrogenolysis conditions furnished the desired diamine **12b** in almost quantitative yield[10] (60% overall yield from cyanopiperidine **5**) (Scheme 3).



Scheme 3. *Reagents and conditions*: Ar=Phenyl: H_2, Pd/C, MeOH–HCl, rt, 48 h, 96%; Ar=2′-Furyl: (i) H_5IO_6 (2.6 equiv.), $MeNH_2$, H_2O, MeOH, rt, 3 h; (ii) MeOH–HCl, rt, 3 h, 80%

In contrast, applying the same reaction procedure to aminoalcohol **11c** provided a mixture of the diamine **12c** and its corresponding tetrahydrofuryl derivative.[11] In order to avoid such undesired reduction, we decided to apply oxidative conditions with periodic acid.[12] In two successive steps, oxidative cleavage and methanolysis of the imine intermediate gave 2′-furyldiamine **12c** in 74% yield (41% overall yield from **5**).[13]

In conclusion, we have developed an efficient diastereoselective synthesis of new 2-aryl-3-aminoazepanes, which also allows differentiation of amino group reactivity. As a key step, we have shown that LAH reduction can convert directly bicyclic piperidinylimines into 3-aminoazepane

derivatives in a totally regio- and diastereoselective way. Further application of this methodology to synthesize biological compounds is actually in progress in our laboratory.

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8. Satisfactory spectral and analytical data were obtained for all new compounds.
9. Typical procedure for imine reduction. Preparation of **11b**: To a cooled suspension of $LiAlH_4$ (0.8 g, 20.9 mmol) in ether (50 mL, −10°C) was carefully added a solution of phenylimine **6b** (0.81 g, 2.67 mmol) in ether (4 mL). After stirring the mixture for 3 h, NaOH (1N, 1.6 mL) was added dropwise, followed by H_2O (2.4 mL). After filtration and removal of the solvent under reduced pressure, the oily residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) to give aminoalcohol **11b** as a colorless oil in 91% yield (0.75 g, 2.42 mmol).
10. Diamine (+) **12b**. Colorless oil. $[\alpha]_D$= +14 (c=1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm; J, Hz): 2.1–1.5 (6H, m), 2.83 (2H, m, $2H_7$), 3.03 (1H, ddd, J=9.2, 7.8, 4.1, H_3), 3.21 (1H, d, J=9.2, H_2), 7.1–7.4 (5H, m, Ph); ^{13}C NMR (75.43 MHz, $CDCl_3$, δ, ppm): 21.8, 29.5, 35.6 (C_4, C_5, C_6 not assigned), 49.2 (C_7), 58.9 (C_3), 74.1 (C_2), 127.5, 128.3, 128.7, 144.3 (Ph). Anal. calcd for $C_{12}H_{18}N_2 \cdot 2HCl,0.5H_2O$: C 52.95, H 7.78, N 10.29; found C 52.65, H 7.49, N 10.11.
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13. Diamine (+) **12c**. Pale yellow oil. $[\alpha]_D$= +7 (c=0.45, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm; J, Hz): 1.80–1.28 (6H, m), 2.47 (1H, ddd, J=13.7, 8.4, 3.8, H_3), 3.64 (d, J=9, H_2), 6.06 (1H, J=3.1, 1.9, $H_{4'}$), 6.12 (1H, J=3.2, $H_{3'}$), 7.16 (d, J=1.3, $H_{5'}$); ^{13}C NMR (75.43 MHz, $CDCl_3$, δ, ppm): 21.6, 28.8, 30.7, (C_4, C_5, C_6 not assigned), 45.6 (C_7), 54.6 (C_3), 58.5 (C_2), 108.3, 110.3 ($C_{3'}$, $C_{4'}$), 142.5 ($C_{5'}$), 151.1 ($C_{2'}$); HRMS calcd for $C_{10}H_{16}N_20$: 180.1262, found: 180.1262.