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Unusual rearrangement of spiro β-lactams to 1,4-diazabicyclo[4,4,0]decanes and 1,4-diazabicyclo[4,3,0]nonanes. Synthesis of conformationally restricted σ-receptor ligands

Alberto Macías, Eduardo Alonso, Carlos del Pozo* and Javier González*

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, Julián Clavería, 8, 33071 Oviedo, Spain

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Abstract—Synthesis of 1,4-diazabicyclo[4,4,0]decanes and 1,4-diazabicyclo[4,3,0]nonanes was achieved by using 4-formyl spiro β-lactams as easily available starting materials. Furthermore, the application of this protocol to the preparation of conformationally restricted σ-receptor ligands was also performed. Theoretical calculations were carried out on a model reaction, in order to give some understanding of the reaction mechanism.

Nitrogen-containing heterocycles such as 1,4-diazabicyclo[4,4,0]decanes and 1,4-diazabicyclo[4,3,0]nonanes are remarkable structural units encountered in several biologically active products (Fig. 1). Simple modifications in their skeletons impart intringuing biological activities to the parent molecule. In this respect, several different biological profiles were found in these pyrrolo and pyrido pyrazines just by changing the substituent placed at the nitrogen. Thus, compounds **1** were found to be potent and selective 5-hydroxy tryptamine (5-HT_6) receptor antagonist and therefore, promising candidates for the possible treatment of schizophrenia, depression and memory dysfunction.[1] Systems of type **2** that bear a diethylamido group attached to the heterocyclic moiety exhibited significant antifilarial activity.[2] Nonachlazine **3** ($n = 1$) is used in medical practice as an antianginal agent.[3] Finally, derivatives **4** constitute a series of conformationally restricted σ-receptor ligands, which play a significant role in mediating the behavioural and toxic effects of cocaine[4] (Fig. 1). Furthermore, compounds **4** were claimed for the treatment of central nervous system (CNS) disorders such as cerebral ischaemia, psychoses and convulsions.[4]

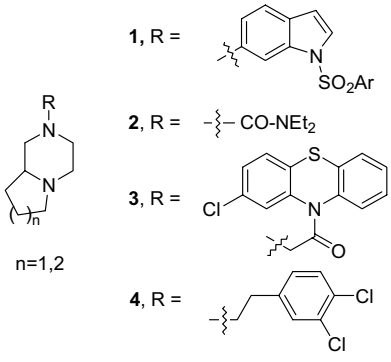

Figure 1.

Additionally, these types of chiral diamines were used as chiral ligands in the reduction of prochiral ketones by treatment of a mixture of stannous chloride and a diamine with diisobutylaluminium hydride.[5] Herein, we wish to report the preparation of these types of heterocyclic structures by means of an unusual rearrangement of readily available 4-formyl spiro β-lactams. The application of this protocol to the synthesis of the conformationally restricted σ-receptor ligand **4** ($n = 1$) will be presented as well.

According to previous results from our group,[6] β-lactam **8** (Scheme 1) was prepared by the [2+2]-cycloaddition of

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* Corresponding authors. Tel.: +34-985103456; fax: +34-985103446; e-mail: fjgf@uniovi.es

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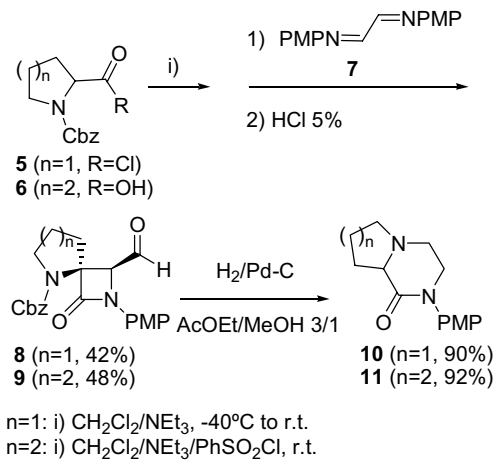


Scheme 1.

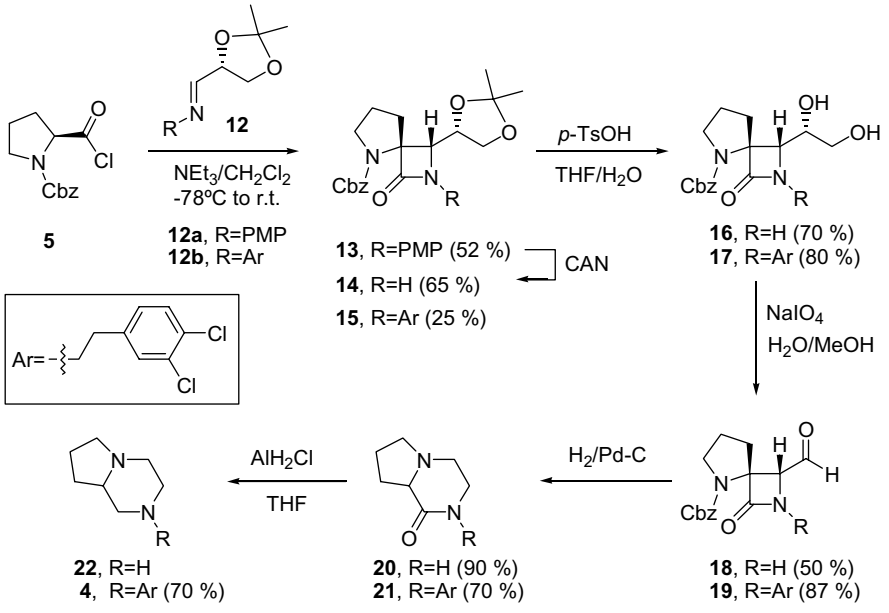
the unsymmetrical cyclic ketene derived from *N*-benzyloxycarbonyl L-proline acid chloride **5** ($n = 1$, R = Cl), with diimine **7**. The reaction was carried out at −40 °C to room temperature affording, after acidic work up, the 4-formyl spiro β-lactam **8** as a 9/1 mixture of diastereoisomers in 42% overall yield.[7] The major product showed a *cis* relative relationship between the pyrrolidine nitrogen and the formyl substituent at the carbon C4 of the azetidinone ring, as it was deduced from the NOESY spectra of β-lactam **8**.

The cycloaddition reaction of *N*-benzyloxycarbonyl D/L-pipecolinic acid **6** and diimine **7**, using the benzenesulfonyl chloride method,[8] afforded, after the acidic hydrolysis, the 4-formyl spiro β-lactam **9** as a single *cis* diastereoisomer (deduced from the NOESY spectra) in 48% overall yield. The starting spiro β-lactams **8**, and **9** were subjected to hydrogenolysis by treatment with hydrogen in the presence of palladium catalyst, and after the expected removal of Cbz protecting group,[9] the product rearranged under the reaction conditions to afford the bicyclic systems **10** and **11**, respectively, in excellent yields (Scheme 1).[10]

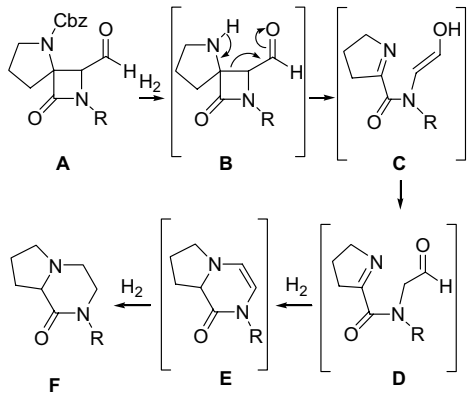
With these data in hand, the enantioselective version of the process was examined next. Recently, we have described the preparation of enantiomerically pure spiro β-lactam **13** by reaction of acid chloride **5** with chiral imine **12a** derived from glyceraldehyde acetonide (Scheme 2).[6b] Removal of the PMP protecting group by treatment with ammonium cerium(IV) nitrate (CAN), followed by the standard protocol for the transformation of the dioxolane ring into the corresponding aldehyde,[11] gave rise to the chiral starting aldehyde **18**. Hydrogenolysis of this spiro β-lactam led to the rearranged product **20** in good yield. Reduction of compound **20** to the bicyclic diamine **22** was previously described by treatment with lithium aluminium hydride[12] (Scheme 2).

Finally, we decided to apply this methodology to the preparation of pyrrolopyrazine **4** ($n = 1$) (Scheme 2), compound that, as we have mentioned before, was claimed for the treatment of CNS disorders.[4] With this purpose, we prepared imine **12b**, which contains attached to the nitrogen the aryl side chain present in the target compound.

Staudinger reaction with acid chloride **5** took place in a modest 25% yield with good diastereoselectivity affording the expected spiro β-lactam **15** as a 9/1 mixture of diastereoisomers. After chromatographic purification, aldehyde **19** was prepared using the methodology described before and then subjected to the rearrangement conditions. The process took place nicely to afford bicyclic system **21** that was reduced to the final diamine **4** by treatment with AlH_2Cl[13] (Scheme 2). In the process of characterization of all the intermediates described herein, we found out that optical rotation of compound



Scheme 2.

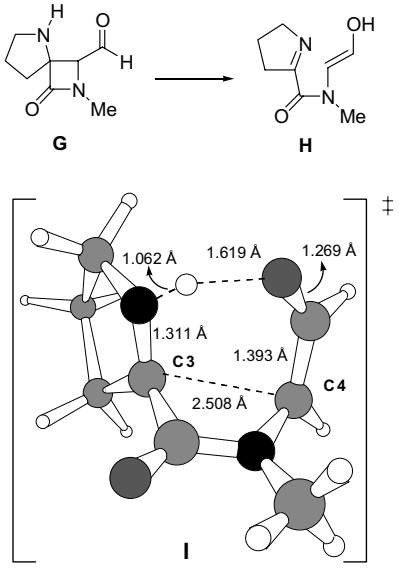


Scheme 3.

20 was zero. This fact means that a racemization event took place during the rearrangement, and therefore, that we have prepared compound **20** in its racemic form. With these considerations we proposed the mechanism outlined in Scheme 3 as a plausible explanation for this transformation.

After the initial removal of the Cbz group of **A**, a 'retro-Mannich' process that involves the ring-opening of the β-lactam in intermediate **B** took place. Hydrogenation of the iminic functional group and further nucleophilic addition of the secondary amine to the aldehyde group affords the bicyclic enamine **E**. Finally, hydrogenation of this enamine would lead to the bicyclic derivative **F**. Theoretical calculations carried out at the Becke3LYP/6-31G* level, support this assumption.[14]

The critical step of the mechanism outlined in Scheme 3, the retro-Mannich reaction, was studied using the model reaction showed in Scheme 4. The transition structure **I** was found for the ring-opening of the model β-lactam **G**. The hydrogen atom attached to the nitrogen of the pyrrolidine ring in the spiro β-lactam **G** is transferred to the oxygen of the carbonyl group, forming the enol intermediate **H**. In the transition structure **I**, the C3–C4 bond of the β-lactam is completely broken, while the CO double bond is slightly elongated as compared with the same bond in **G** (1.217 Å). The normal mode associated with the imaginary frequency of the transition structure corresponds basically to the stretching movement of the C3–C4 bond.[15] The barrier for the ring-opening of the β-lactam **G** is predicted to amount 8.7 kcal mol^{-1}; also, the enol intermediate **H** is 3.6 kcal mol^{-1} more stable than the reactant.[16] The reduced value of the activation energy is in good agreement with the experimental evidence indicating that the rearrangement of spiro β-lactams **A**, takes place under mild conditions.



Scheme 4.

In the rearrangement of **B** to **C**, the sp^3 C3 and C4 centres are transformed in sp^2 ones, which originates the lost of the stereochemical information. As the reduction of the imine intermediate **D** is not stereoselective, the final bicyclic compound **F** is obtained as a racemic mixture.

In conclusion, preparation of 1,4-diazabicyclo[4,3,0]-nonanes and 1,4-diazabicyclo[4,4,0]decanes by means of an unusual rearrangement of readily available spiro β-lactams was performed. The application of this protocol to the synthesis of the conformationally restricted σ-receptor ligand **4** ($n = 1$) was carried out, although in its racemic form since the process took place with racemization at the carbon C3 of the initial 2-azetidinone ring.

Acknowledgements

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7. The ratio of diastereoisomers was determined by ^{1}H NMR analysis of the reaction crude.
8. It was not possible to prepare *N*-benzyloxycarbonyl D/L-pipecolinic acid chloride, so the generation of β-lactam **9** was performed by using the benzene sulfonyl chloride method Sharma, S. D.; Kaur, V.; Saluja, A. *Indian J. Chem.* **1994**, 624.
9. For a description of the methods available for the removal the Cbz protecting group, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley and Sons: NY, 1999; pp 531–537.
10. *General procedure for the synthesis of bicyclic systems* (**10**, **11**, **20** and **21**). The corresponding *N*-Cbz 4-formyl β-lactam was dissolved in a 3/1 mixture of EtOAc/methanol and transferred via cannula to a flask under H_2 (1 atm) containing 20% weight of 10% Pd–C catalyst. The mixture was stirred overnight, the catalyst filtered off on Celite and the organic layer concentrated under vacuum to afford the diazabicyclic compounds.
Selected characterisation. Compound **10**: purified by acid–base extraction, to afford **10** as a colourless oil, (90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73–2.10 (m, 3H), 2.24 (m, 1H), 2.72 (m, 1H), 2.92–3.05 (m, 2H), 3.13 (dt, $J = 11.9$, $J = 4.3$, 1H), 3.40 (t, $J = 8.0$, 1H), 3.59 (dt, $J = 11.9$, $J = 4.3$, 1H), 3.79 (s, 3H), 3.85 (m, 1H), 6.89 (d, $J = 9.1$, 2H), 7.18 (d, $J = 9.1$, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 27.4, 47.3, 49.5, 53.0, 55.3, 64.3, 114.3, 127.0, 134.9, 158.0, 170.4; IR (CH_2Cl_2) 1656 cm^{-1}; MS (ESI$^+$) *m*/*z* (rel intensity): 269 [(M+Na), 20], 247 [(M+H), 100]. Compound **11**: purified by recrystallization from diethyl ether/hexane, to afford **11** as a white solid, (92% yield). Mp = 182–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.97 (m, 5H), 2.20 (dt, $J = 11.2$, $J = 3.9$, 1H), 2.42 (m, 1H), 2.97 (m, 2H), 3.42 (ddd, $J = 11.5$, $J = 4.0$, $J = 1.2$, 1H), 3.81 (s, 3H), 3.95 (dt, $J = 11.5$, $J = 4.8$, 1H), 6.91 (m, 2H), 7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 25.0, 27.6, 49.9, 51.8, 55.4, 56.2, 66.3, 114.3, 127.2, 135.2, 158.1, 168.8; IR (KBr) 1651 cm^{-1}; MS (EI) *m*/*z* (rel intensity): 260 [(M), 25]; HRMS calcd for $C_{15}H_{20}N_2O_2$ 260.1525. Found 260.1522.
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15. All stationary points were fully optimized and characterized by performing the corresponding frequency calculations. **G** and **H** were showed to present only real frequencies, while **I** had one imaginary frequency (−100.0 cm^{-1}).
16. The total energies (hartrees) of the stationary points located are as follows: **G** (−571.99028), **I** (−571.97635), **H** (−571.99604).