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Diasteroselective Synthesis of New Spiropiperidine Scaffolds from the CN(*R*,*S*) Building Block

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CN(*R*,*S*) building block n = 1, 2

A methodology allowing the construction of spiropiperidine scaffolds similar to those found in naturally occurring alkaloids has been developed. This approach begins with the well-established CN(*R*,*S*) strategy, the spiro-center being built by way of an intramolecular attack of a nitrile function by an organolithium species obtained by a halogen/lithium exchange reaction mediated by either *t*-BuLi or lithium naphthalenide.

Introduction

The unique structure of the spiropiperidine framework serves as an important constituent of simple or complex alkaloids (e.g., histrionicotoxins, nitraria, or pinnaic acid alkaloids) as well as non-natural biologically active compounds. As a consequence, many efforts have been directed toward the development of synthetic strategies for alkaloids in 2- and 3-spiropiperidine series. However, of the many methods available there have been very few solutions for polyfunctionalized systems[1] and more frustrating for enantiomerically pure products.[2] Some years ago, we initiated a project based upon the CN(*R*,*S*) strategy[3] to extend the pharmacological scope of this series. Indeed, efficient stereocontrolled formation of a quaternary aminonitrile center by alkylation of (−)-5-cyano-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]-pyridine **1** allowed different routes to the target molecules. In specific cases depending on experimental conditions, instead of behaving as an iminium equivalent, the nitrile group of the aminonitrile function can be engaged in the reaction as an electrophile rather than as a leaving group. In this event, our approach encompassed the ring closure of the functions borne at the quaternary stereogenic center (Figure 1).

Thus, preparation of 1,7-diazaspiro[5,5]undecane derivatives **3**[4] was based upon the facile generation of iminium salts by hydride reduction or organometallic attack at the CN group and subsequent easy intramolecular nucleophilic alkylation.

On the other hand, addition of a methyl Grignard to **4** led to a ketone precursor of spiro derivative **5**[5] through a subsequent aldol reaction.

Finally, we reported in a preliminary communication the spiroannulation of a piperidine ring via a facile alkyllithium intramolecular nucleophilic attack onto the nitrile group in derivative **2a**.[6] In this work, we wish to report the extension of this unique approach to the synthesis of chiral nonracemic substituted [5,6]- and [6,6]-spiropiperidines of type **A** or **B**, respectively (Figure 1). With respect to the noteworthy stereoselectivity[4] of the formation of the first chiral center at the C2 position of the piperidine ring, it appeared interesting to be able to perform further stereocontrolled functionalization at the C6 position.

(1) Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem*. **2004**, *69*, 5668−5675 and references herein cited.
(2) (a) Bahajaj, A. A.; Moore, M. H.; Vernon, J. M. *Tetrahedron* **2004**, *60*, 1235−1246. (b) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450−4452. (c) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 4453−4456 (d) Francois, D.; Lallemand, M.-C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H.-P. *Angew. Chem., Int. Ed*. **1998**, *37*, 104−105.
(3) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383−394.
(4) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem*. **1993**, *58*, 6451−6456.
(5) Zhu, J.; Royer, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1991**, *32*, 2485−2488.
(6) Ribeiro, C. M. R.; de Melo, S. J.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 7227−7230.

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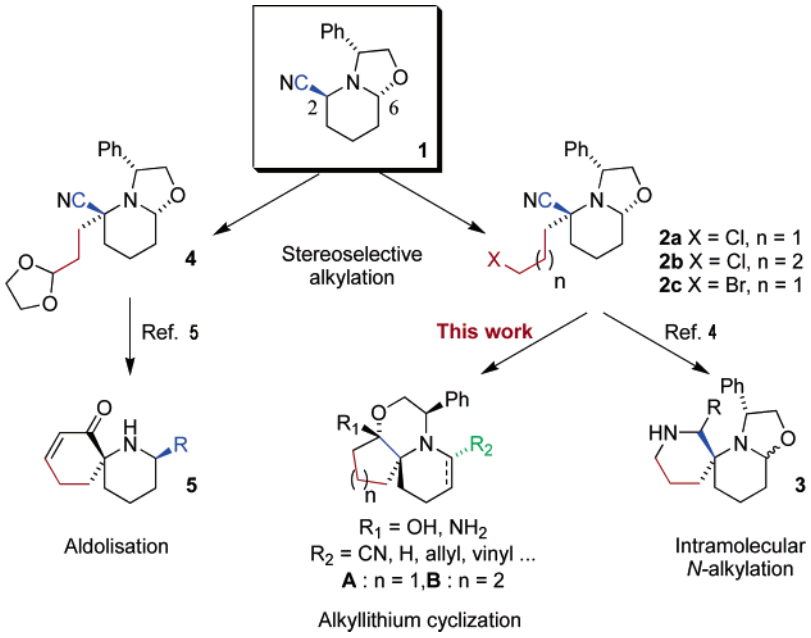
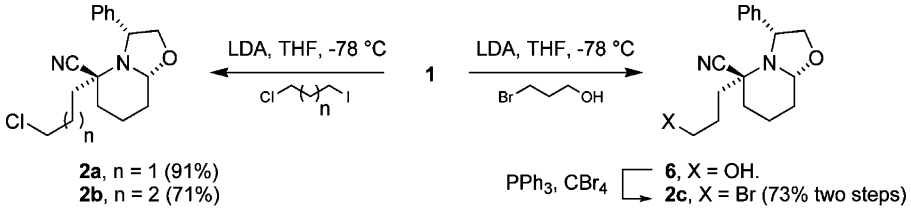
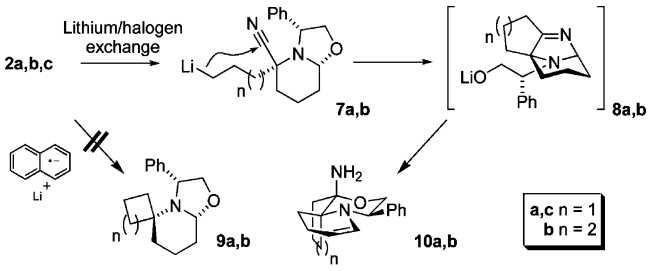


FIGURE 1. Spiropiperidine frameworks from the CN(*R*,*S*) building block **1**.

SCHEME 1. Diastereoselective Alkylation of the CN(*R*,S) Building Block 1



SCHEME 2. Halogen/Lithium Exchange and Spiroannulation Reaction



Results and Discussion

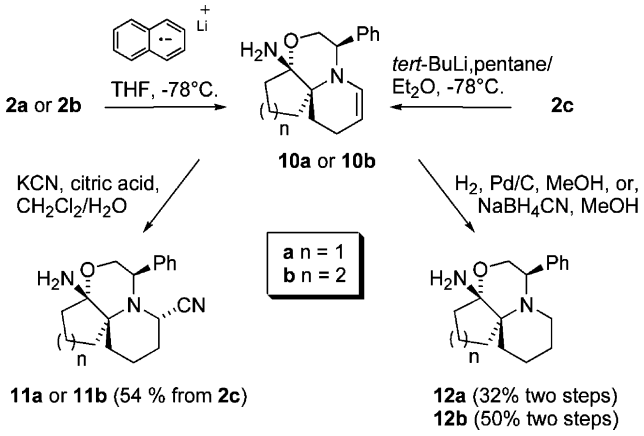
The chloro and bromo compounds **2a**−**c** were used as starting materials for the synthesis. Cyclization precursors **2a** and **2b** were obtained as single diastereomers by alkylation of **1** with 1-chloro-3-iodopropane and 1-chloro-4-iodobutane, respectively, while compound **2c** was obtained by alkylation of **1** with 3-bromopropanol yielding alcohol **6** which was subsequently brominated (Scheme 1).

The annulation reaction took place when the halogen was exchanged by a lithium atom leading to intermediates **7a** or **7b** (Scheme 2). The first type of metal/halogen exchange was attempted with chlorinated compounds **2a**[4] or **2b**. In these cases, the exchange was performed using 3 equiv of preformed lithium naphthalenide in THF at −78 °C under argon (Scheme 2). Lithiation of compound **2c** was cleanly performed by using *t*-BuLi in ether/pentane at low temperature.[7] A possible mechanism for the formation of the tricyclic system **10a**,**b** is presented in Scheme 2. The putative intermediate ketimine **8a**,**b** rearranged into enamines **10a** or **10b** along with opening of the oxazolidine ring. We postulate **8a**,**b** as plausible intermediates since similar nonspiranic but stable compounds are produced in high yield by nucleophilic attack of organolithium (^{n}BuLi or PhLi) on aminonitrile **1**.[8]

It is noteworthy that we obtained the cyclobutane derivative **9a**[6] using lithium di-*tert*-butylbiphenilide (LiDBB) instead of lithium naphthalenide. Compound **9a** resulted from a reductive cleavage of the tertiary nitrile function of **2a** followed by an intramolecular halogen substitution. This alternative spirocyclization example demonstrated that the reduction of the aminonitrile function was fast enough to compete with a halogen/lithium exchange reaction on the alkyl chloride chain. Those observations must be compared with the recent results published by Rychnovsky et al.[9] for 2-cyanotetrahydropyrans. In their case, they observed that chloronitrile derivatives (closely related to compound **2b**) exhibited similar selectivity when reacting with LiDBB; the nitrile function was the quicker to react, and no chloride/lithium exchange was seen. The selectivity

(7) Ashby, E. C.; Pham, T. N.; Park, B. *Tetrahedron Lett.* **1985**, *26*, 4691−4694.
(8) Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 6700−6705.
(9) (a) Rychnovsky, S. D.; Takaoka, L. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 818−820. (b) Wolckenhauer, S. A.; Rychnovsky S. D. *Tetrahedron* **2005**, *61*, 3371−3381.

SCHEME 3. Enamine Function Reactivity Studies



observed could be attributed to the difference of reduction potential between lithium di-*tert*-butylbiphenilide and lithium naphthalenide (−2.14 and −1.98 V, respectively).[10]

The enamines **10a**,**b** appeared to be too unstable to allow purification by column chromatography which led to polymerization products and low yields. Thus, crude enamines were directly used in the next step (Scheme 3). However, they were fully characterized as stable piperidines **12a** and **12b** obtained by reduction using palladium-catalyzed hydrogenation or using $NaBH_3CN$ in MeOH. Two possible isomers **12a-*cis*** and **12a-*trans*** can be envisioned in which the ring junction between the cyclopentane and the morpholine rings could be either *cis* or *trans*, but only one was observed. The same reasoning could be done for **12b**. The skeleton of these polycyclic compounds being quite rigid, the calculation of the conformation of lower energy is easy. Thus, the calculated difference of energy between isomers **12a-*cis*** and **12a-*trans*** (MM2 Chem3D) is around 16 kcal/mol, showing unambiguously that the *cis*-fused ring junction (**12a-*cis***) was the most likely to be formed (Figure 2).

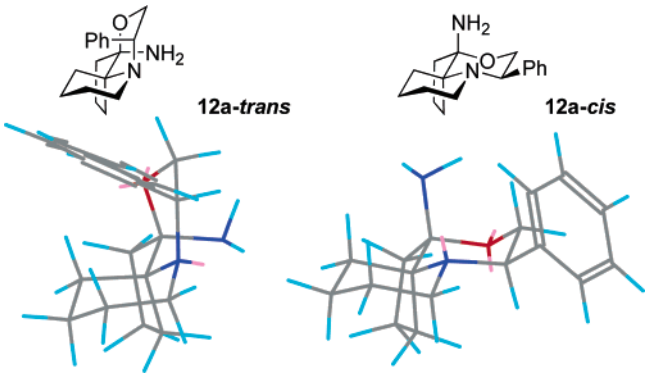
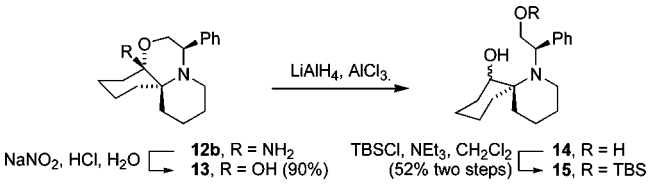


FIGURE 2. MM2 calculation of the minimum conformational energy for **12a-*trans*** and **12a-*cis***.

An attempt to perform a classical HCl hydrolysis of the hemiaminal function of **12b** failed to give the expected hemiketal **13**. Surprisingly, the reaction led to decomposition products. However, a nonclassical but facile nitrous deamination reaction of **12b** afforded the

(10) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930.

SCHEME 4. Reduction of Hemiketal System of Compound 13



expected hemiketal via an oxonium intermediate that was trapped by one molecule of water (Scheme 4).

The reduction of **13** with AlH_3 cleanly led to a mixture of diastereomeric and unseparable diols **14** followed by selective alcohol protection providing secondary alcohol **15** as a mixture of diastereomers.

As far as piperidine scaffolds are concerned it was necessary to obtain a multifunctional system allowing substitution at position C6, the C2 positions being already occupied by the functionalized spiro system. For this purpose, the enamine functions of **10a** and **10b** were protonated as iminium salts which were trapped as stable aminonitriles by reaction with CN^- giving **11a** and **11b** (Scheme 3). Only one diastereomer was detectable wherein the entering nitrile group was in axial disposition *anti* with respect to the developing nitrogen electron lone pair. This reaction occurred under stereoelectronic control that positioned the CN group axial by stabilization due to an anomeric effect ($n \rightarrow \sigma^*_{C-CN}$). The ^{13}C NMR shift of the C6 carbon atom is in accordance with the shift typically observed (δ_C 45−48 ppm) in other piperidine aminonitrile compounds with an axial nitrile function.[11] The ^1H NMR spectrum of the H6 proton is also typical for an axial position of the nitrile function since it shows only a small J_3 coupling constant with its neighbors H5a and H5b (J_3 = 1.6, 4.6 Hz for **11a**, 3.2 Hz for **11b**). A classical J_3 coupling constant for an axial H6 proton would have been typically around 12 Hz.[12]

The nitrous deamination reaction was also performed on **11a** leading to hemiketal **16**. Finally, the reactivity of the α-aminonitrile moiety was explored. A vinyl chain could be regio and stereoselectively introduced using vinylmagnesium bromide to give **17** having the same configuration as the nitrile group of **16** (Scheme 5).

This occurred after prior formation of an iminium species through the complexation of the nitrile function with one silver cation from $AgBF_4$ and subsequent precipitation of insoluble AgCN.[3] Similarly, an acetate chain could be introduced on **16** with total selectivity via a Mukaiyama-like[13] reaction with silyl-enol ether of ethyl acetate **18**.[14] The stereochemistry at C6 for both compounds **17** and **19** was unambiguously established by ^1H NMR NOESY experiments which showed a strong NOE confirming the axial position of the acetate and the vinyl side chains (Scheme 5).

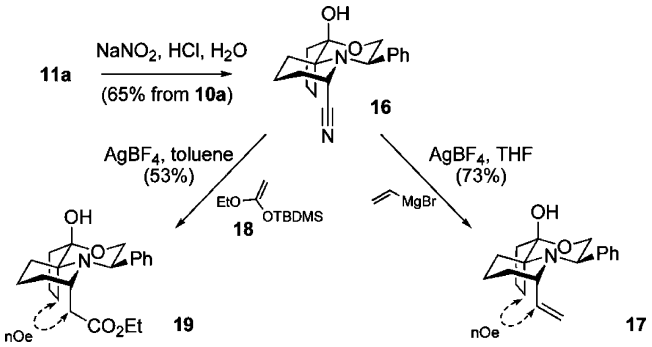
(11) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382−385. In this paper, the ^{13}C δ shift observed for compounds bearing an axial nitrile was 48.3 and 50.4 ppm for an equatorial nitrile. We observed δ = 47.6 ppm for compound **12a** and 46.0 ppm for **12b**.

(12) *Studies in Organic Chemistry 43, Piperidine*; Rubiralta, M., Giralt, E., Diez, A., Eds.; Elsevier: New York, 1991; p 297.

(13) Berrien, J.-F.; Billion, M.-A.; Husson, H.-P.; Royer, J.*J. Org. Chem.* **1995**, *60*, 2922−2924.

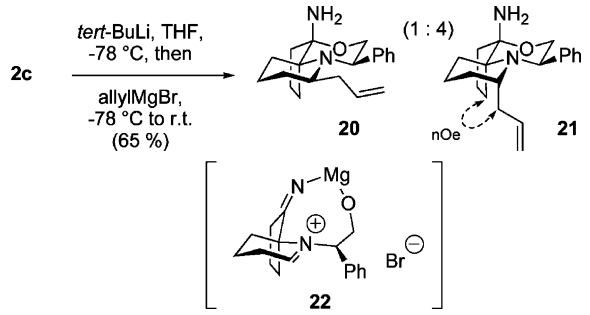
(14) Rathke M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67−72.

SCHEME 5. Reactivity Study of 16 Aminonitrile Function



We were also interested in trapping the intermediate that is formed during the spirocyclization step by reaction with a nucleophile. Thus, allyl derivatives **20** and **21** (1:4) were synthesized according to a one-pot procedure composed of two various steps (Scheme 6). The first step is the spirocyclization achieved by lithiation of **2c** using *t*-BuLi. The second step is addition of allylmagnesium bromide. The main diastereomer **21** exhibited an axial stereochemistry at position C6 attested by a strong NOE. Due to Schlenk equilibrium, $MgBr_2$ was obviously introduced in the reaction medium with the Grignard reagent. Since it behaves as a Lewis acid, the plausible iminium intermediate **22** (Scheme 6) might be formed. This iminium ion has very probably a different geometry compared with the one obtained from aminonitrile **16**.

SCHEME 6. One-Pot, Two-Step Annulation and Functionalization Process on 2c



As a result, a poor stereoselectivity is observed for the nucleophile addition step.

Conclusion

In summary, starting from the CN(*R,S*) building block **1**, a concise method for the preparation of enantiopure [5,6]- and [6,6]spiropiperidines has been developed. The usefulness of α-aminonitriles, generally considered as protected iminium functions, is thus significantly increased. The use of this strategy for the development of biologically active compounds having a spiropiperidine framework is presently being studied.

Supporting Information Available: Details of experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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