A New and Direct Synthesis of 2-Substituted Pyrrolidines

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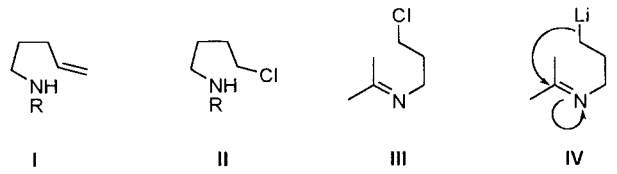
Introduction

Pyrrolidines are important structural units because they take part in many natural occurring alkaloids, such as hygrine, nicotine, tropine, or cocaine, which show strong biological activity.[1,2] Other compounds having this moiety belong to the amino acids kingdom, such as proline or kainic acid. In addition, prolinol derivatives, such as the couple (*S*)/(*R*)-1-amino-2-(methoxymethyl)-pyrrolidines (SAMP/RAMP) have found important applications as chiral auxiliaries, mainly in stereoselective deprotonation of hydrazones.[3]

Methodologies to construct the pyrrolidine ring include inter- or intramolecular reactions.[4−6] To the first group belong (a) radical, electrophilic, or metal-mediated metathesis of diallylamines; (b) 1,3-dipolar cycloaddition starting from aziridines; (c) samarium diiodide-promoted cyclization of bis(*β*-ketoalkyl)amine derivatives; and (e) aminomercuration of 1,5-hexadiene.[7] Among procedures involving intramolecular reactions, the most useful methods start from bishomoallylamines (**I**), or 4-chloroalkylamines (**II**) by radical (or electrophilic) cyclization, or an S_N reaction, respectively.[5] In this paper we propose a new approach to synthesize the pyrrolidine ring starting from chloroimines **III** (easily available from the corresponding carbonyl compounds and 3-chloropropylamine) and performing a chlorine−lithium exchange using a 4,4-di-*tert*-butylbiphenyl (DTBB) catalyzed lithiation,[8] so the corresponding functionalized intermediate[9] of type **IV** can undergo intramolecular addition to the imine group giving the expected cyclization reaction.



I II III IV

Results and Discussion

Starting chloroimines **1** were easily prepared by reaction of commercially available 3-chloropropylamine hydrochloride with the corresponding carbonyl compound (R^1R^2CO) and sodium carbonate in water (for $R^1 \neq H$, $R^2 = H$; compounds **1a**−**j**,**l**) or methanol (R^1,$R^2 \neq H$; compound **1k**) at room temperature (Table 1).[10]

The reaction of different *N*-(3-chloropropyl) imines **1a**−**l** with an excess of lithium powder (1:10 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio; 5% molar) in THF at −78 °C for 2 h led, after hydrolysis with water, to the expected pyrrolidines **2a**−**l** (Table 1). In the case of nornicotine (**2l**), and due to its high solubility in water and easy decomposition by column chromatography, it was not possible to isolate it in pure form. For these reasons, we transformed the initially formed nornicotine (**2l**) into its *N*-benzoyl derivative (**2′l**).

From a mechanistic point of view, we think that a chlorine−lithium exchange takes place (without changing the imine functionality) giving an intermediate of type **IV**, in which an intramolecular addition occurs via a *endo-trig* process, generating the corresponding cyclization to yield the expected *N*-lithium pyrrolidines. Final lithium−hydrogen exchange affords pyrrolidines **2**.

In summary, the methodology reported here represents a new route to prepare 2-substituted pyrrolidines, including nornicotine, starting from very simple materials, such as carbonyl compounds (mainly aromatic aldehydes) and 3-chloropropylamine, this being a new disconnection to generate this type of biologically interesting units (Scheme 1). In the case of imines derived from aliphatic ketones and aldehydes, this methodology gives significantly lower yields.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. All reagents were commercially available and were used as received. THF was distilled from sodium benzophenone ketyl. IR spectra were measured (neat) with a Nicolet Impact 400 D-FT Spectrometer. NMR spectra were recorded with a Bruker AC-300 using $CDCl_3$ as the solvent. LRMS and HRMS were measured with Shimadzu GC/HS QP-5000 and Finingan MAT95 S spectrometers, respectively. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett-Packard HP-5890 instrument equipped with a flame ionization detector and a 12 m capillary column (0.2 mm diameter, 0.33 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$ = 275 °C, $T_{detector}$ = 300 °C, T_{column} = 80 °C (3 min), and 80−270 °C (15 °C/min), P = 40 kPa; t_r values are given in min under these conditions.

(1) See, for instance: Dewick, P. M. *Medicinal Natural Products*; J. Wiley & Sons: Chichester, 1997; chapter 6.

(2) For biosynthesis studies, see: (a) Terssell, K. B. G. *Natural Product Chemistry*, 2nd ed.; Apotekarsocieteten: Stokholm, 1977; chapter 8. (b) Misra, N.; Luthra, R.; Singh, K. L.; Kumar, S. In *Comprehensive Natural Products Chemistry*; Barton, D.; Nakanishi, K.; Meth-Cohn, O.; Kelly, I. W., Eds.; Elsevier: Amsterdam, 1999; vol 4, chapter 4.03.

(3) Enders, D. In *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic Press: Orlando, 1984; vol 3, chapter 4, pp 275−339.

(4) For general information, see: Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862−2892 (Contemporary review) and former reviews on "Saturated nitrogen heterocycles" cited therein.

(5) For a review, see: Pichon, M.; Figadère, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964.

(6) Pyrrolidine is prepared industrially following two procedures: (a) Hydrogenation of pyrrole using a Rh−Al catalyst, and (b) reaction of 1,4-butanediol with ammonia at 350 °C in the presence of aluminum oxide. See, for instance Acheson, R. M. *An Introduction to the Chemistry of Heterocyclic Compounds*; John Wiley & Sons: New York, 1976; chapter III.

(7) (a) Gómez-Aranda, V.; Barluenga, J.; Yus, M. *An. Quim.* **1972**, *68*, 221−222. (b) Barluenga, J.; Nájera, C.; Yus, M. *J. Heterocycl. Chem.* **1981**, *18*, 1297−1299.

(8) Reviews: (a) Yus, M. *Chem. Soc. Rev.* **1996**, 155−161. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225−237 (Microreview).

(9) Reviews: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *1*, 155−181. (b) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67−96. (c) Yus, M.; Foubelo, F. *Rev. Heteroatom. Chem.* **1997**, *17*, 73−107.

(10) Grigg, R.; Nimal Gunaratne, H. Q.; Kemp, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 41−46.

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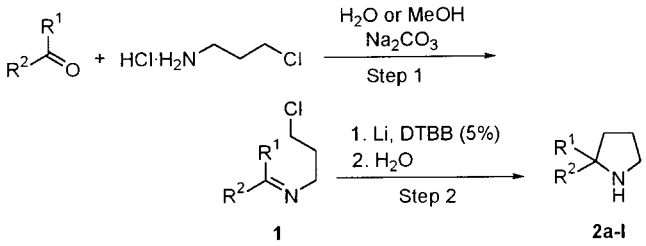
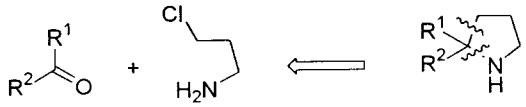
Table 1.



	step 1 (%)	step 2 (%)
a: $R^1 = Ph$, $R^2 = H$	84	>99[12]
b: $R^1 = 2\text{-}MeC_6H_4$, $R^2 = H$	88	>99
c: $R^1 = 2,5\text{-}Me_2C_6H_3$, $R^2 = H$	84	98
d: $R^1 = 2,4,6\text{-}Me_3C_6H_2$, $R^2 = H$	50	67
e: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = H$	70	>99[13]
f: $R^1 = 3,4\text{-}(MeO)_2C_6H_3$, $R^2 = H$	55	92
g: $R^1 = 3,5\text{-}(MeO)_2C_6H_3$, $R^2 = H$	75	84
h: $R^1 = 3,4\text{-}(CH_2O_2)C_6H_3$, $R^2 = H$	70	90
i: $R^1 = 4\text{-}Me_2NC_6H_4$, $R^2 = H$	48	>99[14]
j: $R^1 = Cy$, $R^2 = H$	89[11]	50
k: $R^1 = Ph$, $R^2 = Me$	90	41
l: $R^1 = 3\text{-pyridyl}$, $R^2 = H$	87	40 (as *N*-benzoyl derivative, **2′l**)[15]

Scheme 1



General Procedure for the Preparation of Chloroimines 1. A mixture of 3-chloropropylamine hydrochloride (0.29 g, 2.2 mmol), the corresponding aldehyde **1** (R^2 = H; 2.0 mmol), and sodium carbonate (0.32 g, 2.0 mmol) in water (10 mL) was stirred at room-temperature overnight. Then, the resulting solution was extracted with ethyl acetate (3 × 20 mL), and the organic layer was dried over Na_2SO_4) and evaporated (15 Torr) to give an essentially pure (>90% from GC and/or 300 MHz ^{1}H NMR) oily residue containing the title compounds **1**, which were used for the next reaction without further purification. In the case of the acetophenone derivative **1k**, the reaction was performed in methanol (1 mL) under the same reaction conditions as above. Yields are included in Table 1. Spectroscopic and analytical data are included as Supporting Information.

General Procedure for the Preparation of Substituted Pyrrolidines 2. To a blue suspension of lithium powder (75 mg, 10 mmol) and a catalytic amount of DTBB (30 mg, 0.10 mmol; 5% molar) in THF (5 mL) was added the corresponding imine **1** (1 mmol) at −78 °C, and the resulting mixture was stirred for 2 h at the same temperature. Then, it was hydrolyzed with water (20 mL) allowing the temperature to rise to 20 °C, and the resulting solution was purified by successively acid−base extraction with 2 M hydrochloric acid (3 × 15 mL) and 4 M sodium hydroxide (3 × 20 mL). The final solution was extracted with ethyl acetate (3 × 20 mL) and the organic layer dried over Na_2SO_4 and evaporated (15 Torr) to give pure title compounds **2** (≥95% for GLC and/or 300 MHz ^{1}H NMR). In the case of nornicotine (**2l**), after acidic extraction, the aqueous layer was basified with 4 M sodium hydroxide, and benzoyl chloride (0.35 mL, 3.0 mmol) was added dropwise at 0 °C to the resulting mixture. After 4 h stirring allowing the temperature to rise to 20 °C, the resulting solution was extracted with dichloromethane (3 × 20 mL) and evaporated (15 Torr) to give a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate/dichloromethane) to yield the expected compound **2′l**. Yields corresponding to compounds **2** are included in Table 1. Spectroscopic and analytical data are included as Supporting Information.

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Supporting Information Available: Spectral data of compounds **1** and **2** as well as copies of ^{1}H and ^{13}C NMR spectra for new compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838−5839.
(12) Chin, B.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 5650−5651.
(13) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083−1092.
(14) Mutel, V.; Vieira, E.; Wichmann, J. WO 2000058285; *Chem. Abstr.* **2000**, *133*, 266722.
(15) Seeman, J. I.; Secor, H. V.; Armstrong, D. W.; Timmons, K. E.; Ward, T. J. *Anal. Chem.* **1988**, *60*, 2120−2127.