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Research Article

An Unprecedented Straightforward Synthesis of Chiral Pyrrolo[3,4-*b*]quinolone and Pyrrolo[3,2-*b*]quinolone Backbones Starting from *trans*-4-Hydroxy-L-proline

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The straightforward synthesis of pyrrolo[3,4-*b*]quinolone and pyrrolo[3,2-*b*]quinolone backbones, which can be found in molecules exhibiting anticancer activities, is presented. The key step of the process is an efficient and unprecedented Friedländer condensation between an oxoproline carbamate, obtained in 3 steps and good yield starting from commercially available and relatively cheap *trans*-4-hydroxy-L-proline, and various 2-amino-substituted carbonyl derivatives. It was demonstrated that the formation of the two possible regioisomers was fully triggered by both the R substituent onto the 2-amino-substituted carbonyl compounds and the ester function onto the oxoproline carbamate. Thus, in some cases, a complete regiocontrol for the Friedländer reaction could be attained.

1. Introduction

Natural or synthetic *N*-heterocyclic compounds containing a condensed quinoline ring system continue to attract the interest of both organic and medicinal chemists mostly due to their antitumor activities [1, 2]. Among them, pyrrolo[3,4-*b*]quinolone **I** and pyrrolo[3,2-*b*]quinolone **II** are two backbones of important value which can be found in molecules of high biological interest (Figure 1). Indeed, pyrrolo[3,4-*b*]quinolone **I** is a key constituent of the alkaloid camptothecin (CPT, **1**), selective poison of DNA topoisomerase 1, and thus well known for its anticancer activities. Over the years, the synthesis or isolation of many analogues of CPT possessing a pyrrolo[3,4-*b*]quinolone backbone, together with their biological evaluation, has been published [3]. For example, the alkaloids luotonin A (**2a**) and rosettacin (**2b**), belonging to the aromathecin family, were proved to exhibit important cytotoxicity demonstrating once again the great interest of this skeleton [4]. Pyrrolo[3,2-*b*]quinolone moiety **II** is the central core of the alkaloid cryptolepine (**3**) traditionally used as an antimalarial drug [5, 6]. It was shown that this alkaloid was able to intercalate with DNA, prompting it as a potential chemotherapeutic agent [7]. Compounds **4** have been published recently and were tested successfully over different cancer types, highlighting their biological potential [8].

Interested for many years in the synthesis of aromathecins, we have devoted a lot of efforts for the development of short and efficient routes for the access to these skeletons [9, 10]. Recently, we have shown that the total synthesis of rosettacin (**2b**) could be achieved in few steps using an aryl radical cyclization onto an enamide [11].

In this paper, the unprecedented access to both pyrrolo[3,4-*b*]quinolone and pyrrolo[3,2-*b*]quinolone backbones **5** and **6** starting from oxoproline carbamate **8** using Friedländer reaction for the formation of the **C** ring is discussed (see lower part of Scheme 1). It is important to notice that very interesting works were published employing the Friedländer reaction for the synthesis of pyrrolo[3,4-*b*]quinolone and/or pyrrolo[3,2-*b*]quinolone backbones [12, 13]. Nevertheless, to the best of our knowledge, this is the first time that this reaction is used with oxoproline carbamate

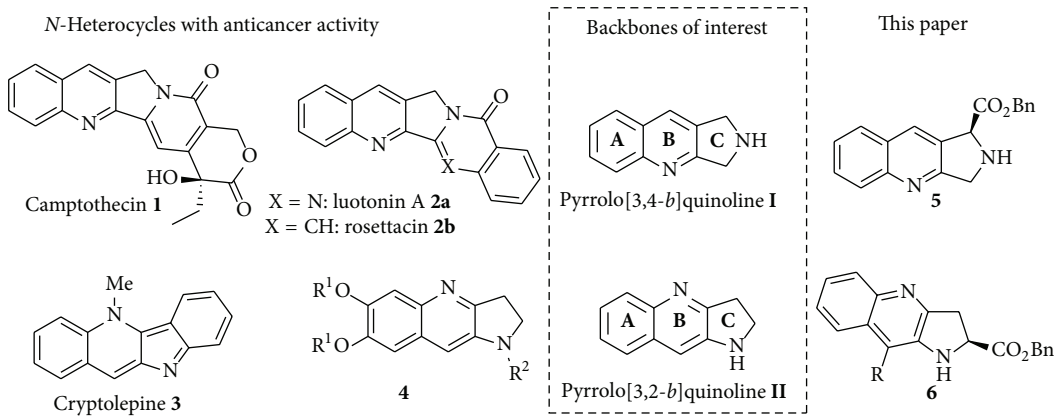
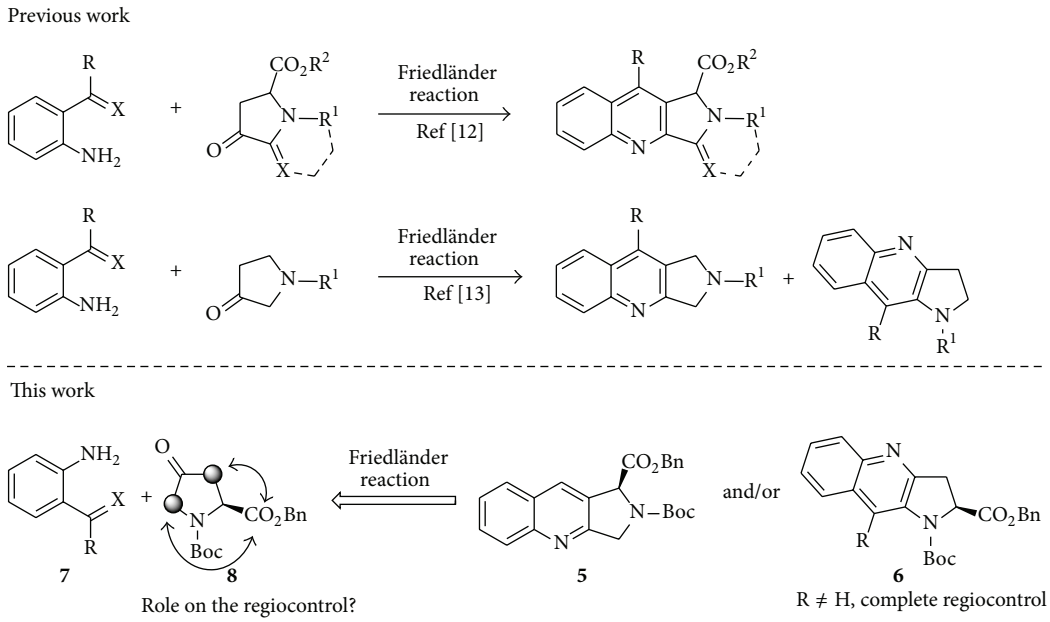


Figure 1: Interest of pyrrolo[3,4-*b*]quinolone and pyrrolo[3,2-*b*]quinolone backbones **I** and **II**.

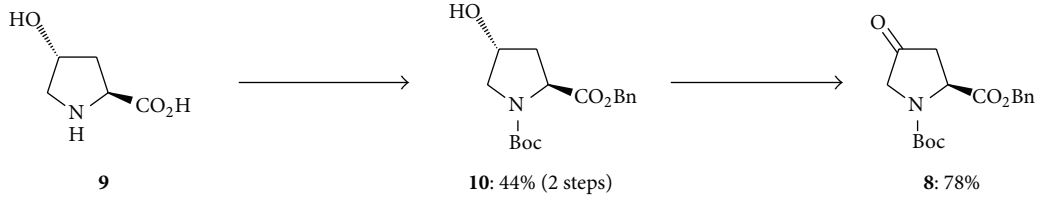


Scheme 1: Known strategies for the synthesis of pyrrolo[3,4-*b*]quinolone and pyrrolo[3,2-*b*]quinolone backbones and our retrosynthetic pathway to products **5** and **6**.

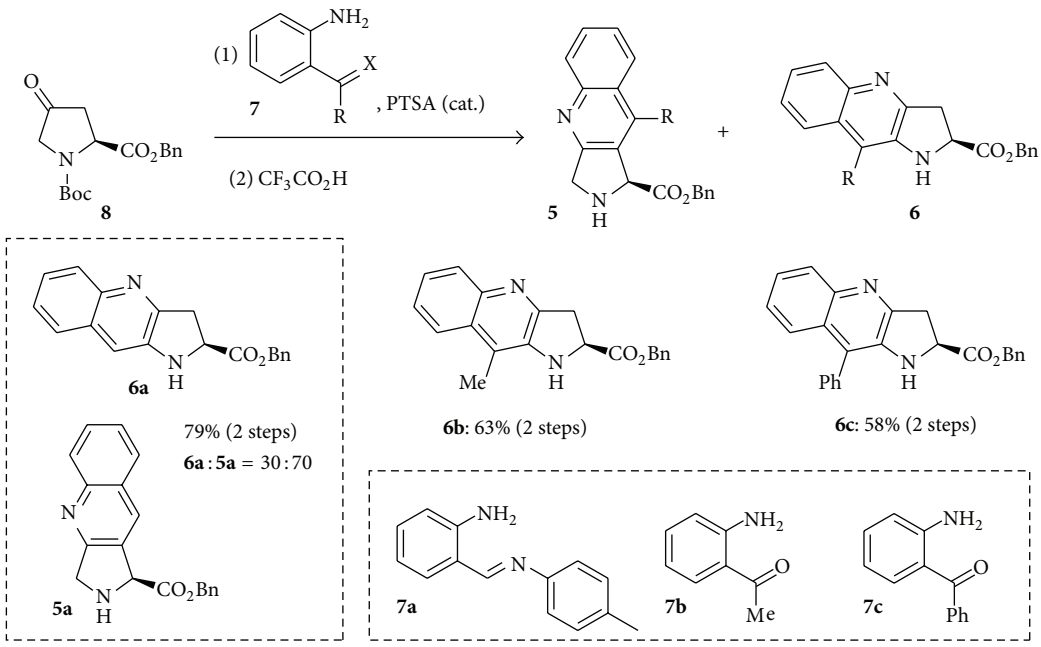
8 in order to study the influence of the ester function onto the regioselectivity of the process. In fact, we have shown that the formation of regioisomers **5** and/or **6** was triggered by both the R substituent onto **7** and the ester function onto **8**. Indeed, when R group is not a hydrogen atom, only regioisomers **6** were obtained in good yield, demonstrating the dramatic role of these two groups. Moreover, besides the biological interest of the scaffolds **5** and **6**, the access to these new proline derivatives could be of great importance in organocatalysis chemistry.

2. Materials and Methods

2.1. General Remarks. All commercially available starting materials were purchased from the Aldrich Chemical Co. or Acros Organics Co. and were used without further purification. Solvents were dried, when necessary, by standard methods. All reactions were carried out under argon. The progress of the reactions was monitored by thin layer chromatography (TLC). Thin layer chromatography (TLC) was performed using silica gel analytical plates (F254) of 0.25 mm thickness. The detection on TLC plates was performed by UV light at 254 or 365 nm or using a permanganate or p-anisaldehyde revelator. Compositions of stereoisomeric mixtures were determined by ^{1}H NMR analysis of the crude mixture before any purification. Melting points (Mp) were taken with a SMP10 capillary melting point apparatus (Stuart) and are uncorrected. The NMR spectra were recorded as solutions in $CDCl_3$ at 200 MHz (^{1}H) and 50 MHz (^{13}C), respectively, and chemical shifts (δ) are expressed in ppm.



Scheme 2: Synthesis of oxoproline carbamate **8**.



Scheme 3: Access to pyrrolo[3,4-*b*]- and pyrrolo[3,2-*b*]quinolone derivatives **5** and **6**.

The assignments for compounds **8** and **10** matched those previously published [14].

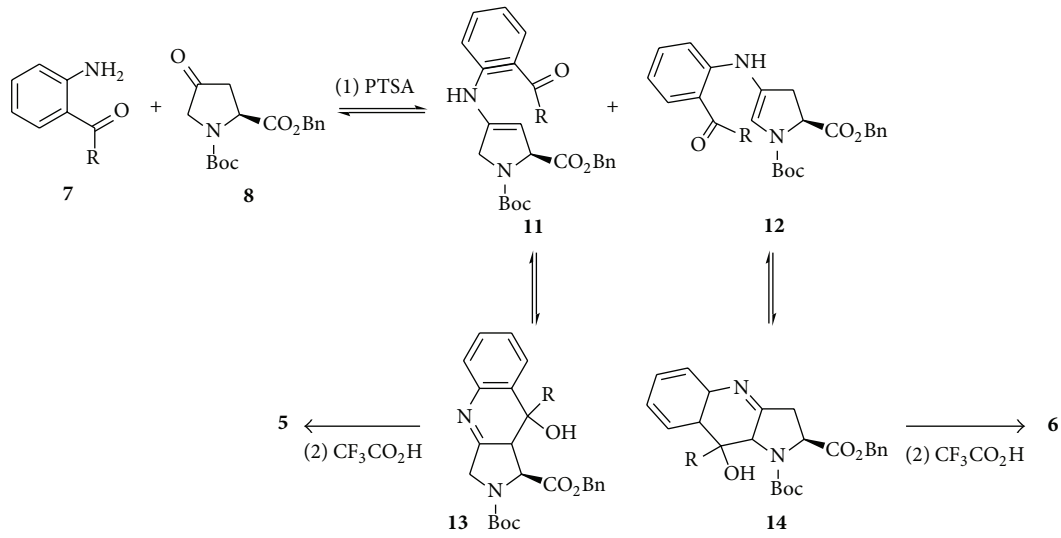
*2.2. General Procedure for the Synthesis of Compounds **5** and **6**.* The required aniline derivative **7** (0.55 mmol, 1.1 eq) and oxoproline carbamate **8** (160 mg, 0.5 mmol, 1 eq) were dissolved in freshly distilled toluene (5 mL). p-Toluenesulfonic acid (PTSA, 9.5 mg, 0.05 mmol, 0.1 eq) was then added. The mixture was stirred under reflux for 14 hours and the solvent was removed under vacuum. The crude mixture was dissolved in EtOAc (20 mL) and was then washed successively with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was directly used in the next step without further purification.

The crude of the previous step was dissolved in freshly distilled CH_2Cl_2 (5 mL) and trifluoroacetic acid (TFA, 0.37 mL, 10 eq) was then added. After one night of stirring at room temperature, the solvent was removed under vacuum. The crude mixture was dissolved in EtOAc (20 mL) and was then washed successively with a saturated aqueous solution of $NaHCO_3$ ($2 * 10$ mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was then chromatographed on silica gel to provide the desired compound (typically, AcOEt/cyclohexane, 20 : 80).

3. Results and Discussion

The key oxoproline carbamate **8** was synthesized starting from commercially available *trans*-4-hydroxy-L-proline (**9**) using a modified version of the route reported by Qiu and Qing (Scheme 2) [14]. Starting material (**9**) was first converted in two steps, that is, Boc protection of the nitrogen atom and benzylation of the acid function, into the corresponding *N*-Boc-benzyl ester **10** in 44% overall yield. Oxidation of the alcohol moiety was performed using PCC and led to the desired product **8** in a good 78% yield.

Friedländer condensations between oxoproline carbamate **8** and aniline derivatives **7** were carried out using classical procedure (Scheme 3) [15]. In order to facilitate the NMR spectra analysis, the Friedländer reaction was directly followed by Boc deprotection of the nitrogen atom of the pyrrolidine ring using trifluoroacetic acid. In the case of **7a** (see lower part of Scheme 3), the two regioisomers **5a** and **6a** were formed in a good 79% yield and in a 70 : 30 ratio. This regioselectivity is in accordance with the one observed by



Scheme 4: Proposed mechanism for the Friedländer reaction leading to **5** and **6**.

Akue-Gedu and coworkers for similar substrate [13]. Interestingly, when substrates **7b** and **7c** were employed, only regioisomers **6b** and **6c** were observed by ^{1}H NMR of the crude mixture prior to any purification. They were isolated after chromatographic purification in 63% and 58% yield, respectively.

The unprecedented high regioselectivity in favour of products **6** is not fully understood yet. Nevertheless, based on the mechanism commonly accepted for the Friedländer reaction [15], we propose the following mechanism (Scheme 4). In the presence of p-toluenesulfonic acid (PTSA), starting materials **7** and **8** led to the formation of the two possible enamines **11** and **12** in equilibrium with the corresponding tricyclic compounds **13** and **14**. The observed regioselectivity could result from the steric hindrance and interactions between the R group and the ester function in intermediate **13** *versus* the R group and the Boc function in intermediate **14**. This hypothesis will have to be confirmed by a computational analysis. Finally, when R ≠ H, intermediate **14** was favoured and led to **6** by loss of water and Boc deprotection.

The structure of product **5a** was deduced from its ^{1}H NMR and ^{13}C NMR spectral data and by comparison with similar structures [12, 13]. For example, the ^{1}H NMR spectrum of **5a** contained two doublets (δ = 4.64 and 4.40 ppm, J = 15.7 Hz) for the two CH_2 protons of the pyrrolidine ring confirming the presence of a stereogenic center.

*(S)-Benzyl 2,3-Dihydro-1H-pyrrolo[3,4-b]quinoline-1-carboxylate (**5a**)*. This product was obtained by reaction between **8** and **7a**. 54% over 2 steps (AcOEt/cyclohexane, 20 : 80). ^{1}H NMR (200 MHz, $CDCl_3$): 8.20–8.12 (m, 2H), 7.76–7.65 (m, 2H), 7.55–7.47 (m, 1H), 7.37 (bs, 5H), 5.32–5.19 (m, 3H), 4.64 (d, J = 15.7 Hz, 1H), 4.40 (d, J = 15.7 Hz, 1H), 2.36 (bs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 171.8, 163.6, 148.4, 135.1, 130.9, 129.7, 128.7, 128.4, 128.0, 127.0, 126.2, 67.6, 63.6, 52.4.

Moreover, **5a** ^{13}C DEPT-135 NMR spectrum showed both the presence of the carbonyl carbon at δ = 171.8 ppm and the CH and CH_2 carbons of the pyrrolidine ring at 63.6 and 52.4 ppm, respectively. In the case of the ^{1}H NMR spectrum for products **6**, they all displayed the same characteristic doublet of doublet for the two CH_2 and CH proton of the pyrrolidine ring. For example, compound **6b** exhibits a doublet of doublet (J = 9.4 and 5.5 Hz) for the CH at 4.58 ppm and two doublet of doublet (J = 18.0 and 9.4 Hz and J = 18.0 and 5.5 Hz) at 3.68 and 3.54 ppm, respectively.

*(S)-Benzyl 9-Methyl-2,3-dihydro-1H-pyrrolo[3,2-b]quinoline-2-carboxylate (**6b**)*. This product was obtained by reaction between **8** and **7b**. 63% over 2 steps (AcOEt/cyclohexane, 20 : 80). ^{1}H NMR (200 MHz, $CDCl_3$): 7.92–7.85 (m, 1H), 7.83–7.75 (m, 1H), 7.49–7.40 (m, 2H), 7.36 (bs, 5H), 5.20 (s, 2H), 4.59 (bs, 1H), 4.58 (dd, J = 9.4 and 5.5 Hz, 1H), 3.68 (dd, J = 18.0 and 9.4 Hz, 1H), 3.54 (dd, J = 18.0 and 5.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 173.3, 154.3, 143.8, 139.9, 135.2, 129.0, 128.8, 128.7, 128.4, 126.1, 125.4, 122.3, 117.6, 67.6, 57.8, 35.7, 12.1. $[\alpha]_D^{20}$ + 19.2 (c = 0.61, $CHCl_3$).

Finally, its ^{13}C DEPT-135 NMR spectrum also confirmed the presence of the carbonyl carbon at δ = 173.3 ppm when the CH and CH_2 carbons were observed at 57.8 and 35.7 ppm, respectively.

4. Conclusion

The regioselective access to both pyrrolo[3,4-*b*]quinolone and pyrrolo[3,2-*b*]quinolone backbones was achieved in 5 steps and good yield starting from commercially available *trans*-4-hydroxy-L-proline. The Friedländer condensation between 2-amino-substituted carbonyl compounds and an oxoproline carbamate was efficient and allowed the formation of the desired products in good yield. More importantly, and to the best of our knowledge, this is the first time that this reaction between these two partners was studied. We have shown that the access to the two possible regioisomers was controlled by both the R substituent onto

the 2-amino-substituted carbonyl derivatives and the ester function of the oxoproline carbamate. This synthetic strategy could be used in the future to regioselectively access either the pyrrolo[3,4-*b*]quinolone or pyrrolo[3,2-*b*]quinolone backbones by modulating substituents onto Friedländer reaction's partners. This reactivity is already under investigation and the results will be published in due course.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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