Tetrahedron Letters 61 (2020) 152405

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of heterocyclic enamine-zinc complexes as precursors of stereocontrolled substitution of nitrogen α-position

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ARTICLE INFO

Article history:
Received 24 June 2020
Revised 22 August 2020
Accepted 25 August 2020
Available online 21 September 2020

Keywords:
Alkaloids
Diastereoselective substitution
Enamine
Iminium
Zinc complexes

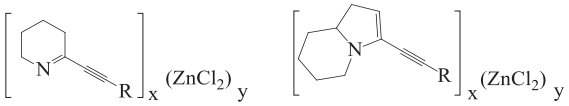
ABSTRACT

In the presence of $ZnCl_2$, chiral protected amino-ketones and amino-aldehydes gave zinc enamino-complexes. Both enamine and iminium structures of these complexes were observed in ^1H and ^{13}C NMR spectra depending on the solvent. Introduction of either an allyl or a hydrogen substituent was performed using allylmagnesium chloride or $NaBH_4$ in excess leading to various heterocycles. With the amino-ketones diastereoselectivity (*de* = 50) was observed respectively. Homoconiine and coniine precursors were prepared by this strategy.

Introduction

Stereocontrolled functionalization of the carbon in α-position of the nitrogen of heterocycles has been often a key-step in natural product synthesis [1]. Efficient strategies have been proposed for the monosubstitution of various heterocycles [2–4] but the quaternization of the carbon in nitrogen α-position remains poorly explored [2a,5] In some recent publications, we have shown that 1 M $ZnCl_2$ in solution in diethyl ether was a useful reactant to prepare iminocomplexes **I** [6] or enaminocomplexes **II** [7] which were very stable gums or solids (Fig. 1). The neutralization of the iminocomplexes **I** yielded to heterocyclic imines that revealed excellent ligands of Zn(II), Pd(II) and Au(III) [8] whereas the reduction of the enaminocomplexes **II** using $NaBH_4$ in EtOH allowed obtaining of 2-substituted indolizidine with low diastereomeric excess (*de* = 20) (Fig. 1) [7].

This latter result prompted us to design enamine-zinc complexes with α-methylbenzylamine acting as a chiral inductor in order to obtain heterocycles mono- or disubstituted in α-position of the heterocyclic nitrogen atom.



(**I**) (**II**)

Fig. 1. Structure of iminocomplexes (**I**) and enaminocomplexes (**II**).

Results and discussion

Access to the *N*-Boc protected aminoketones and aminoaldehydes was realized as follows (Scheme 1). The nucleophilic substitution of either the *(R, S)* α-methylbenzylamine **1** or the (*R*) 4-methoxy-α-benzylamine **2** with the ethyl 5-bromopentanoate **3** (n = 1) [9] led to the aminoesters **4** and **5** which were protected using $(Boc)_2O$ to give the compounds **6**–**7**. Then, the ester function was transformed into Weinreb amide **8**-**9** [10] in the presence of lithium phenylacetylide, lithium propylacetylide, allylmagnesium chloride or $LiAlH_4$ [6,11], which allowed the formation of the desired *N*-Boc protected aminoketones **10**–**13** and aminoaldehyde **14**. As indicated in the Scheme 2, yields were generally good. One can notice that the use of other bromoesters could allow introduction of diversity. Thus, with the ethyl 6-bromohexanoate **3′** (n = 2), the *N*-Boc protected aminoaldehyde **14′** was obtained.

Then, we carried out the formation of the zinc complexes (Scheme 2). The aminoketones **10**–**13** and the aminoaldehydes

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https://doi.org/10.1016/j.tetlet.2020.152405
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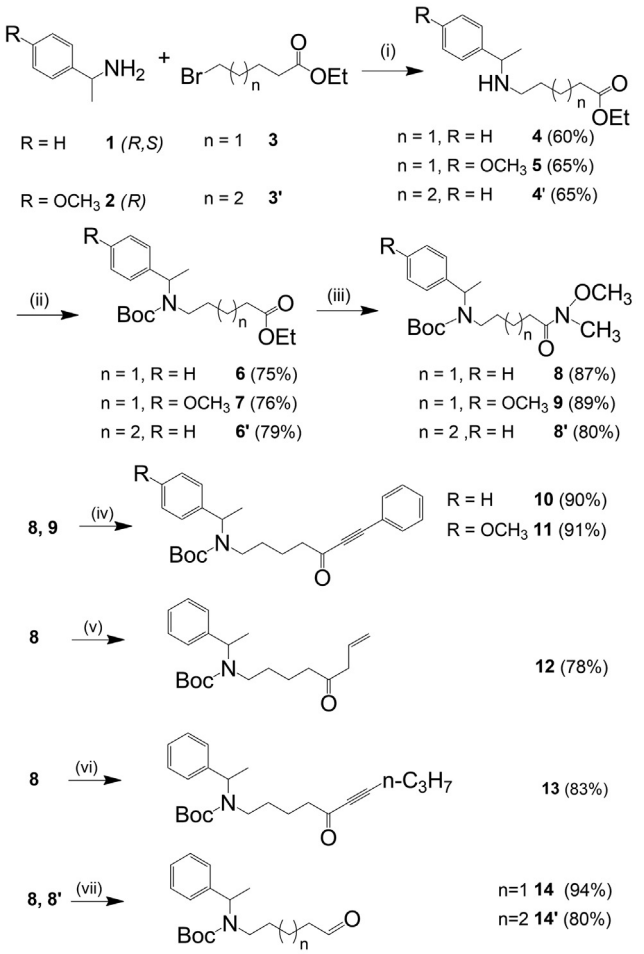
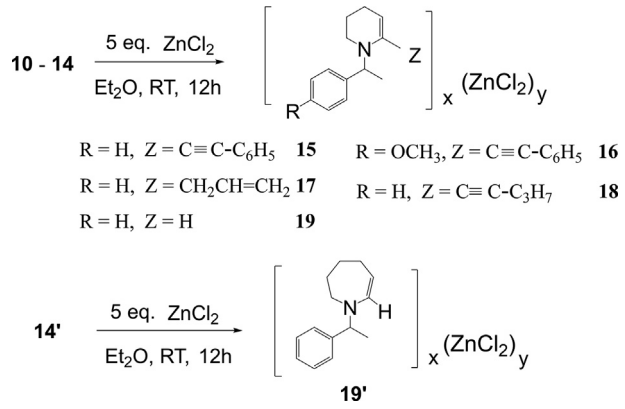
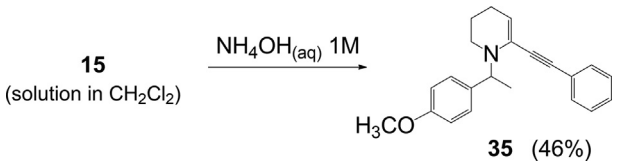


Scheme 1. Synthesis of the starting aldehydes and ketones. (i) K_2CO_3, KI/DMF, 100 °C, 4h (ii) Boc_2O (1.02 eq.)/CH_2Cl_2, RT, overnight; (iii) HN(OMe)Me.HCl (1.38 eq.), i-PrMgCl (2.78 eq.)/THF, –20 °C to 25 °C, 1h; (iv) C_6H_5 C≡Cli (3.0 eq.)/THF, –50 °C, 3h; (v) CH_2=CH CH_2MgCl (2.6 eq.)/THF; (vi) n-C_3H_7 C≡Cli (3.0 eq.)/THF, –50 °C, 3h; (vii) $LiAlH_4$ (50 mol%)/THF, 0 °C.



Scheme 2. Synthesis of enamine-zinc complexes.

14 and **14′** were allowed to react with 5 equivalents of a 1 M $ZnCl_2$ solution in diethyl ether, at room temperature for 12 h. Six zinc-complexes **15**–**19** and **19′** were obtained as gums or solids after work-up [6,7]. The neutralization of the zinc-complex **15** with 1 M NH_4OH (aq.) allowed obtaining the corresponding enamine **35** (Scheme 3). Degradation of the cyclic enamine **35** occurred during chromatography using silica gel.



Scheme 3. Synthesis of enamine 35.

The precise structure of these zinc-complexes could not be established. Some investigations showed the presence of several $ZnCl_2$, diethyl ether and H_2O, resulting in the imine or enamine formation (*see elemental analysis in the ESI*). On the ^1H and ^{13}C NMR, spectra recorded in CD_3CN or CD_3COCD_3, the observed signals did not correspond to an enamine but to an iminium intermediate (Fig. 2 bottom). Indeed, the only signal in the 5–7 ppm region was a quadruplet attributed to the α-methylbenzylamine and the imine carbon was observed near 160 ppm whereas; in the previously report of indolizidine, an enamine intermediate was observed [7].

The strains resulting from the indolizidine bicyclic structure disappeared in the piperidine six-membered ring leading to an iminium in CD_3CN. When the more polar d_6-DMSO is used, the enamine is observed (Fig. 2 top). The presence of H_2O in the zinc-complex should allow the enamine-iminium tautomerism [12]. In the case of **17**, the iminium formation resulted in an allylic transposition giving an aza-dienic iminium (Fig. 3) probably due to the medium acidity. The structure of **17** was clearly attested in ^1H NMR by the presence of an ABX system (J_{trans} = 17 Hz).

Then, we studied the reactivity of the zinc complexes **15**, **16**, **19** and **19′** with allylmagnesium chloride (Scheme 4) and $NaBH_4$ (Scheme 5). The allylmagnesium chloride was chosen as nucleophile because the allyl signals appear in a free area 4–7 ppm in ^1H NMR and the possibility of chemical transformations as used with allyl-boration [13]. Then, to the complexes **15**, **16**, **19** and **19′** were quickly added 10 equivalents of a 1 M allylmagnesium chloride solution in THF at 0 °C giving **20**, **21** and **23** in 30–50% yield, which were determined from the starting aminoketone or aminoaldehyde because the precise structure of the complexes was not established.

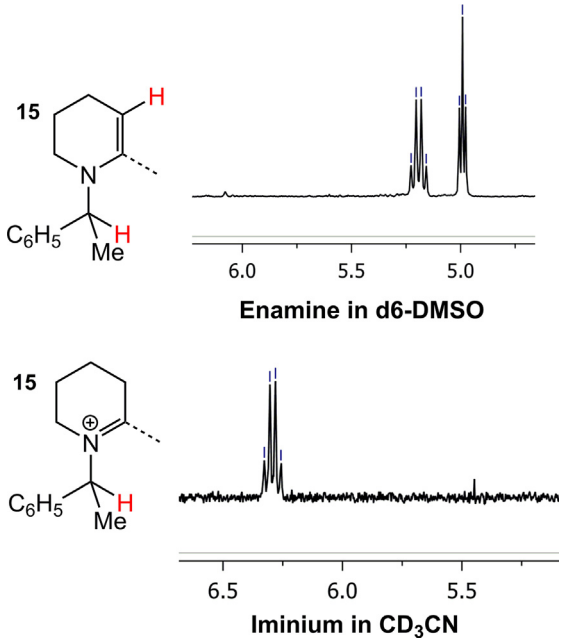


Fig. 2. ^1H NMR of **15**.

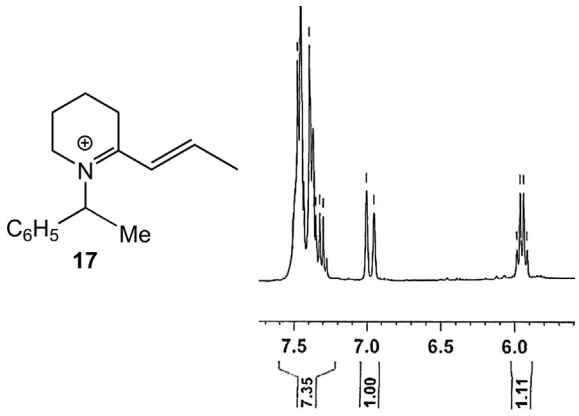
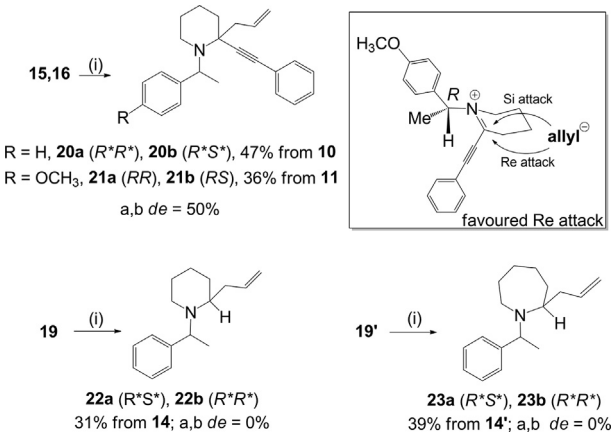
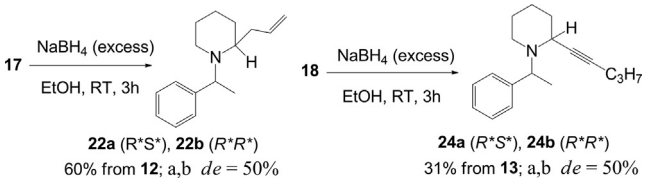


Fig. 3. ^{1}H NMR of **17** (CD_3CN).



Scheme 4. Reactivity of the zinc complexes with allyl magnesium chloride. (i) CH_2=CH CH_2MgCl 1M (10 eq.)/THF, 20 °C, 2h.

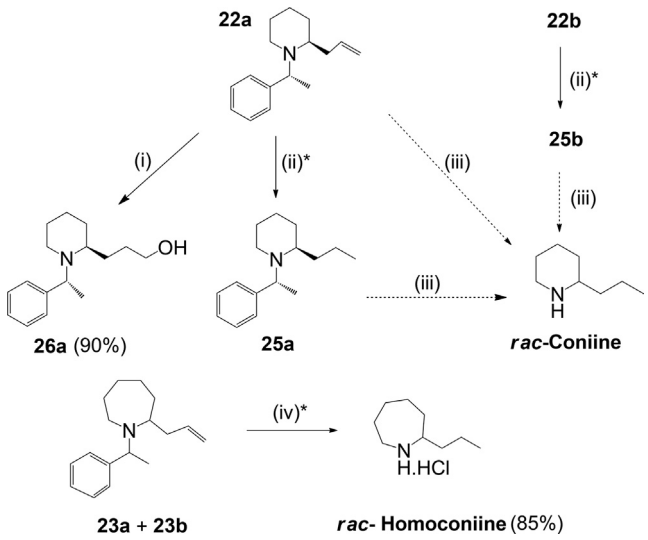


Scheme 5. Reactivity of **17**, **18** with $NaBH_4$.

All these piperidine derivatives were obtained as a mixture of **a** (major) and **b** (minor) diastereomers. A diastereoselectivity (*de* = 50) was only observed when the starting complex was substituted in position 2. The diastereomers were separated using column chromatography. The configurations of **21a** and **21b** (and then of **22**) have been determined by electronic circular dichroism. Thus, comparing the calculated (*see the ESI section for details*) and experimental ECD spectra of **21a** and **21b** (Fig. 4) led us to attribute the *RR* configuration to the major isomer **21a**.

The configurations of **22a** and **22b** (and then of **23** and **24**) were attributed using the literature data [4a]. These configurations were in accordance with a classical transition state postulated for nucleophilic attack involving piperidinium intermediates [14] and conformational analysis of **21** (*see the ESI*). Optical purity was checked with **21a** (*RR*) and **20** (*RR + SS*) by formation of salts with the (*R*)-(-)-*tert*-butylphenylphosphanylthioic acid [15,4a], because use of various chiral columns in HPLC has failed (*see the ESI*).

Some attempts of reduction/deprotection of **15** using H_2 (5 bar) in the presence of Pearlman's catalyst gave a mixture of compounds corresponding to both debenzylation and N-C_2 cleavage. Then, other strategies must be developed to obtain α, α- disubstituted heterocycles. The reactivity of **17** with $NaBH_4$ in EtOH [16] (Scheme 5) has been tested and interestingly, **22** was obtained with a 60% yield and *de* = 50. This result can be probably explained by the basicity of the medium which did not allow allylic transposition. As the hydride attack occurred by the same face as the allyl one the major diastereomer **20a** has the *R*S** absolute configura-



Scheme 6. Alkaloids synthesis. (i) 9-BBN (2.5 eq.)/THF, RT, overnight, then H_2O_2, NaOH, 3 min; (ii) H_2 (3 bar)/Wilkinson's catalyst (10%), EtOH, RT, 72h; (iii) H_2 (Pd/C); (iv) H_2 (3 bar)/$Pd(OH)_2$, EtOH, RT, 24h then HCl (excess)/dioxane. *The quantitative reduction was checked by TLC.

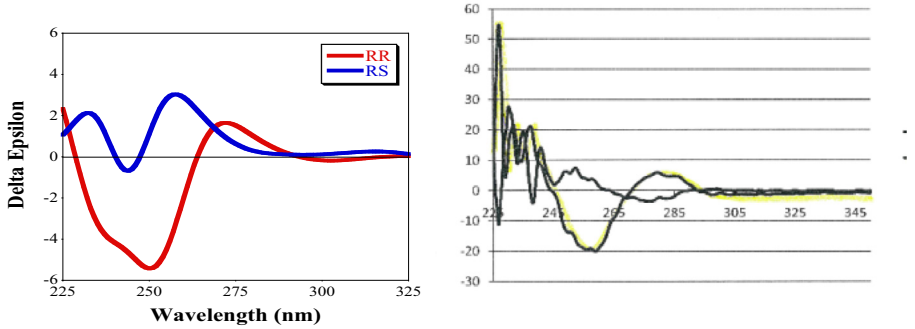


Fig. 4. TD-DFT-simulated (left) and experimental (right) electronic circular dichroism spectra of **19a-b**.

tion. The same behaviour was observed with **18** and **24a** has also the *R*S** absolute configuration.

We then carried out the synthesis to obtain natural alkaloids (Scheme 6). The *rac*-homoconiine has been quantitatively prepared from **23** in one step using H_2 in the presence of Pearlman's catalyst at 3 bar [5a]. Addition of 1 M HCl in dioxane furnished the hydrochloride. Starting from **22a** *(R*S*)* and **22b** (*R*R**) the coniine precursors **25a** *(R*R*)* and **25b** (*R*S**) [5a] were prepared using H_2 with Wilkinson's catalyst at 3 bar whereas the indolizidine precursor **26a** (*R*S*)* was obtained with 9-BBN/H_2O_2 [11]. The NMR spectra of **25** and **26** are consistent with the literature (*see the ESI*) [5a].

Conclusion

In conclusion, the proposed strategy for the 2-substituted heterocycles synthesis, involving formation and storage of iminium intermediates, is easy and can offer many possibilities. Then, diversity can be introduced by tuning the nature of the precursor (length, substitutions, cycle...) and/or changing the nature of the nucleophile. Finally, the use of enantiopure α-methylbenzylamine and the easy separation of the diastereomers by chromatography can allow obtaining enantiopure heterocycles. Deprotection strategies are in progress in order to obtain quaternary carbon in the nitrogen α-position.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are deeply grateful to P. Jéhan and F. Lambert for MS spectrometry (CRMPO, Scanmat, University of Rennes1) and to Prof J. P. Hurvois for providing NMR reference spectra.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152405.

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