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New alkaloid-like heterocycles via formal aza-[3+2] cycloaddition reaction of cyclic enaminones with cyclopropenones

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Abstract—The formal aza-[3+2] cycloaddition reactions of cyclopropenones and cyclic enaminones, including a chiral one, were employed for the first time in the direct formation of new pyrrolidine and indolizidine derivatives. The regiochemistry of cyclization is dependent of both ring size and steric factors of enaminones.

1. Introduction

The synthesis of 1-azabicyclo[3.3.0]octanes and 1-azabicyclo[4.3.0]nonanes is a theme of ongoing interest because these heterocycles are present in a diverse number of biologically active natural occurring alkaloids and unnatural analogues.[1] Motivated by these characteristics several synthetic methodologies have been developed to access pyrrolizidines and indolizidines.[2] Among them, the enaminone's approach to the construction of these heterocycles caught our attention because enaminones are easily prepared in good yield and have been used in the synthesis of a broad spectrum of heterocycle compounds.[3]

In this context, Kascheres and co-workers described that the reaction of diphenylcyclopropenone[4] **1** with primary and secondary acyclic enaminones **2** provides a convenient route to 5-functionalized 1,5-di-hydro-2*H*-pyrrol-2-ones **3**, Figure 1.[5] Formation of **3** can be envisioned as a formal aza-[3+2] cycloaddition where the cyclopropenone nucleus and enaminone correspond to the 3C and NC units of **3**, respectively. The regiochemistry of this stepwise process can be classified according to the orientation of carbonyl moieties of enaminone and cyclopropenone. The head-to-tail regiochemistry (Kascheres's aza-annulation) results from carbonyl carbons orientated to opposite side, whereas the head-to-head

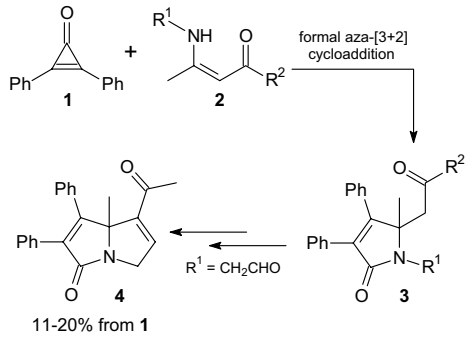

Figure 1.

regiochemistry arises from the orientation of both carbonyl carbons at the same side, Figure 2.[5–7]

Despite two monocyclic five-membered regioisomeric heterocycles can be formed, only the Kascheres's regioselectivity was observed for acyclic enaminones, and only two examples of spiro compounds with regiochemistry opposite to **3** has been reported for cyclic enaminones.[5] Additionally, the presence of an activated methylene group in C5 of heterocycle **3** was pivotal to the extension of this approach to the multistep synthesis of pyrrolizidine **4** via reaction of a carbonyl group in the N-substituent of **3**, Figure 1. This is the sole example of a 1-azabicyclo[3.3.0]octane compound synthesized by the reaction of enaminone and cyclopropenone.[8]

The synthesis of N-heterocycles having two aryl groups on adjacent positions has attracted the attention of diverse research groups, because of the potential

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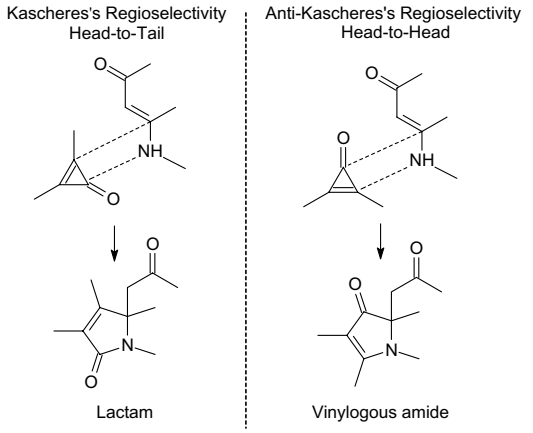
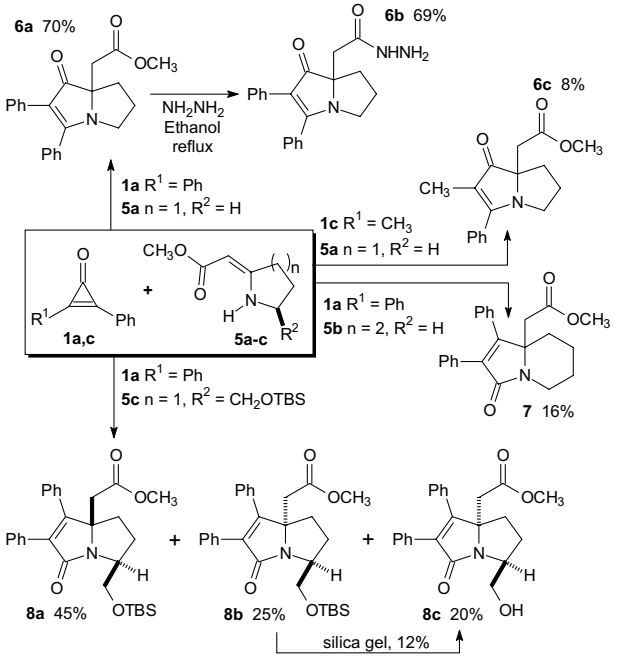


Figure 2. Regiochemistry of the formal aza-[3+2] cycloaddition of enaminones and cyclopropenones.

biological activity of such compounds.[9] We disclose herein our results concerning the direct route towards 1-azabicycles with the structural features of two aryl groups on adjacent positions, using the formal aza-[3+2] cycloaddition reaction of cyclic enaminones, including a chiral one, with cyclopropenones in search of new polyfunctionalized pyrrolizidine and indolizidine derivatives.

2. Results and discussion

To test the possibility of a direct route towards pyrrolizidines and indolizidines, five and six-membered cyclic enaminones **5a–c** were reacted with **1a** in toluene under reflux, Scheme 1. A slow reaction occurred with **5a**, which afforded pyrrolizidine **6a** in good yield, Scheme 1. The regiochemistry assignment was investi-



Scheme 1.

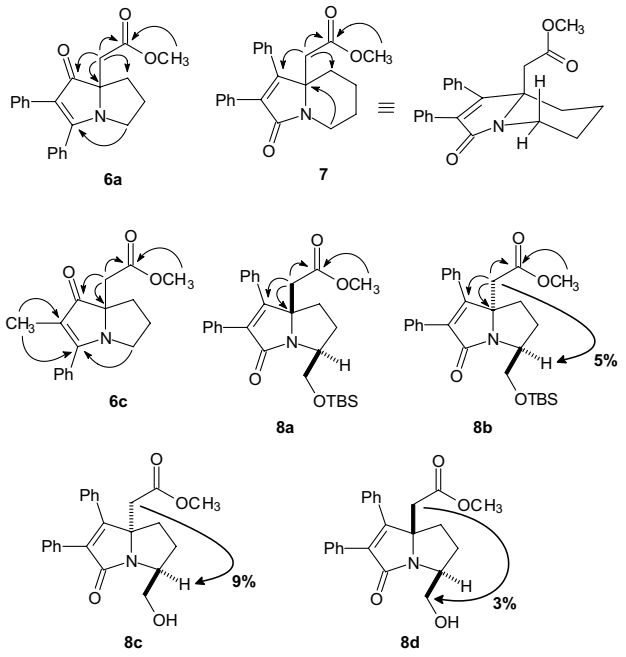


Figure 3. ^{1}H, ^{13}C long range correlations for **6a**, **6c**, **7**, **8a** and **8b**, and NOE difference experiment performed on **8b–8d** (bold curve arrows).

gated by ^{1}H, ^{13}C long range correlation experiment performed on **6a**, which showed a correlation (^{3}J) involving the α methylene $CH_2CO_2CH_3$ and the carbonyl carbon of the C=C–C=O moiety, as indicated in Figure 3. No such correlation would be observed for the opposite regiochemistry. The additional observed long range ^{1}H, ^{13}C correlations indicated in Figure 3 corroborated the assigned regiochemistry for **6a**, which corresponds to the head-to-head orientation (see Fig. 2). Thus, the formation of heterocycle **6a** from **1a** and cyclic enaminone **5a** occurred with opposite regiochemistry in the formal aza-[3+2] cycloaddition, as compared to the formation of **3**, from acyclic enaminones.[5–7] For the purpose of obtaining a more crystalline derivative for X-ray investigation, **6a** was treated with hydrazine affording **6b** in good yield, Scheme 1, but no monocrystal could be obtained.

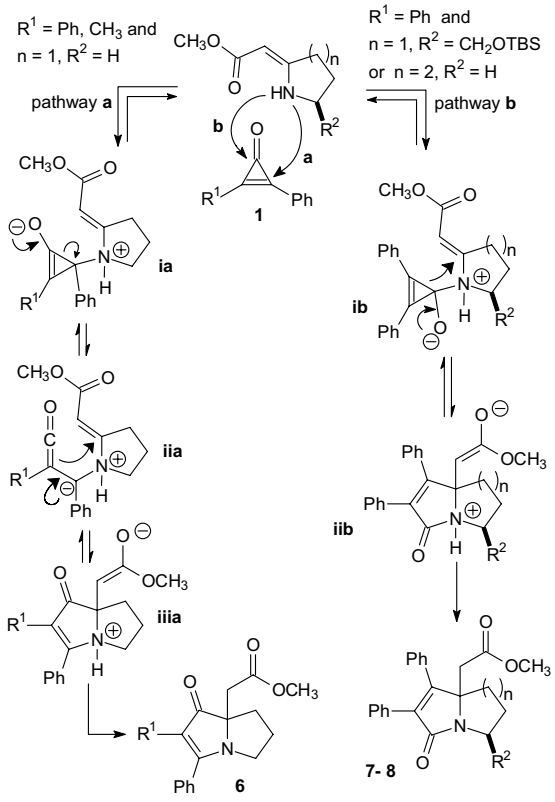
Extension of the aza-annulation to the six-membered enaminone **5b** formed a complex mixture (analyzed by spectroscopic and chromatographic techniques), from which indolizidine **7** could be isolated in yield comparable to the route previously developed to pyrrolizidine **4**.[8] However, the regiochemistry of **7** was opposite to **6a**, as deduced from ^{1}H, ^{13}C long range correlation experiment performed on **7**, which showed a ^{3}J correlation involving the α methylene $CH_2CO_2CH_3$ and the β vinyl carbon of the C=C–C=O moiety, among others correlations indicated in Figure 3 corroborating the assigned structure. Besides, the ^{1}H NMR spectrum of **7** reveals a strong anisotropic deshielding effect on one diastereotopic hydrogen of methylene adjacent to the bridgehead nitrogen, which suggests the parallelism between this equatorial hydrogen and the carbonyl group of the adjacent ring, in the frozen conformation indicated in Figure 3, required to produce such effect.

To gain insight into the steric induction of the formal aza-[3+2] cycloaddition, the reaction of chiral enaminones **5c** with **1a** was investigated, Scheme 1. Two diastereoisomeric pyrrolizidines **8a** and **8b** were isolated, together with the unprotected alcohol **8c**, formed from **8b** probably during the purification on silica gel column because it was also isolated during the obtaining of an analytical sample of **8b**. This fact indicated that no diastereomeric excess was achieved in the aza-annulation from chiral enaminone **5c**. Analogously, the free alcohol **8d** (Fig. 3) was also isolated in 16% yield from the $CDCl_3$ solution of **8a**, after three days in the NMR tube.

Contrary to our expectation, the regiochemistry of isomers **8a**,**b** was opposite to **6a**. Here again, the regiochemistry was deduced from ^{1}H, ^{13}C long range correlation experiment performed on **8a**,**b**, which showed a ^{3}J correlation involving the α methylene $CH_2CO_2CH_3$ and the β vinyl carbon of the C=C–C=O moiety, among others correlations indicated in Figure 3 corroborating the assigned structures. Isomer **8b** showed to be the trans on the basis of NOE difference experiment, which showed a significant increment in methine hydrogen adjacent to nitrogen upon irradiation of the α methylene $CH_2CO_2CH_3$, showing that they are at the same face. In this same way, additional NOE difference experiments of alcohols *cis* **8c** and *trans* **8d** corroborated the assigned stereochemistries for all obtained chiral pyrrolizidines, according to increments indicated in Figure 3. It is noteworthy that the azabicyclo[3.3.0]-oct-2-en-3-one nucleus of **6a**,**b** and the regioisomeric azabicyclo[3.3.0]oct-3-en-2-one nucleus of **8a**–**d** are scaffolds present in some bioactive natural products such as the alkaloids jenamidines A_1/A_2[10] and pyrrolams A–D,[11] respectively, as well as in a recently reported new class of lymphocyte function-associated antigen-1 (LFA-1) antagonists.[12]

We extended the formal aza-[3+2] cycloaddition of cyclic enaminones to alkylphenylcyclopropenones. Thus, isopropylphenylcyclopropenone **1b** was reacted with **5a**, but no product was detected in the ^{1}H NMR spectrum of the crude reaction mixture after 20 days of reflux in toluene. Reaction of **5a** with methylphenylcyclopropenone **1c** furnished a complex mixture, but a small amount of pyrrolizidine **6c** could be isolated, Scheme 1, together with its dimer (7% yield).[13] The regiochemistry of the bicycle derivative was assigned though analyses of ^{1}H, ^{13}C long range correlation experiment performed on **6c**, which showed the similar correlations observed for **6a**, Figure 3.

Mechanistically, the formation of bicycle **6a,c** from enaminone **5a** can be rationalized as an ionic stepwise process initiated by attachment of nitrogen of enaminone to the electrophilic vinyl carbon of **1**, yielding adduct **ia**, pathway a in Scheme 2. In sequence, **iia** suffers a 5-*exo*-*trig* cyclization via a Michael reaction forming enolate **iiia**, which gives **6a**. The regioselectivity of this formal aza-[3+2] cycloaddition corresponds to the head-to-head orientation (see Fig. 2). Meanwhile, the presence of a more flexible six-membered ring in **5b** and a C5-substitution in **5c**, as compared to **5a**, should



Scheme 2. Mechanistic proposal for **6**–**8**.

be responsible for a sterically hindered environment surrounding the nucleophilic nitrogen of the cyclic enaminones, and thus driving the attack to the carbonyl carbon of **1**, pathway b in Scheme 2. Here again, cyclization of **ib** via a Michael reaction forming the enolate **iib**, which gives bicycles **7**–**8**, corresponds to the head-to-tail Kascheres's regiochemistry (see Fig. 2).

In conclusion, this study shows for the first time that the one-step formal aza-[3+2] cycloaddition reaction of cyclopropenones (mainly diphenylcyclopropenone) and cyclic enaminones can be conveniently employed as a direct synthetic route to new alkaloid-like pyrrolidine and indolizidine derivatives.

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Supplementary data

Experimental procedures, spectral data for **6a**–**6c**, **7**, **8a**–**8d**. ^{1}H NMR, ^{13}C NMR spectra for compounds HMBC

and HMQC spectra for compounds **6a**, **6c**, **7**, **8a**–**8d**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.087.

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