Synthesis of α-Trifluoromethylated Nitrogen Bicycles

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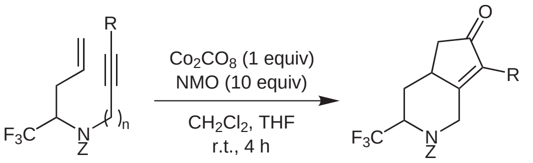
Abstract: The synthesis of α-trifluoromethylated nitrogen bicycles from trifluoromethylated homoallylamine or piperidine derivatives, through different cyclization reactions, is described.

Key words: bicyclic compounds, fluorine, metathesis, cyclizations, Diels–Alder reactions, Heck reaction

Nitrogen heterocyclic moieties are structural elements of many alkaloids, natural products, and drug candidates.[1] Among them, the bicyclic core constitutes a substructure common to many substrates. It is now well-known that the presence of the trifluoromethyl moiety generally increases the biological properties of such compounds, as recently demonstrated for the epothilone derivatives.[2]

In our program towards the synthesis of potential new drugs bearing a fluoroalkyl group, our attention was drawn to trifluoromethylated heterobicyclic structures. We recently described an easy and efficient synthesis of α-trifluoromethylated homoallylamine derivatives and fluorinated piperidines,[3] such substrates have been used as starting materials to access bicyclic structures. Our preliminary results are described in this communication.

A well known methodology to obtain easily functionalized bicyclic compounds is the Pauson–Khand (PK) reaction.[4] Thus, after N-alkylation by alkynyl moieties; trifluoromethylated homoallylamines underwent the PK reaction (Scheme 1).



1a (n = 1, R = H)
1b (n = 1, R = Me)
1c (n = 3, R = H)

2a: 54% (de >95%)
2b: 59% (de >95%)
2c: 0%

Scheme 1 Synthesis of trifluoromethylated bicyclic by the PK reaction.

Bicyclic compounds were obtained in satisfactory yield (**2a**,**b**), while the largest bicyclic derivative (**2c**) could not be obtained since the double and the triple bonds are too spatially distant from each other. An interesting feature is the high diastereoselectivity of the PK reaction since de >95% are observed for **2a** and **2b**. A NOE experiment was conducted to determine the relative configuration of the substituents. The absence of a correlation between H_1 and H_3 led us to suppose that H_1 and H_3 are in *anti* positions to each other. Such assertions have been confirmed by HOESY experiment, showing a correlation between CF_3 and H_3 (Figures 1, 2).

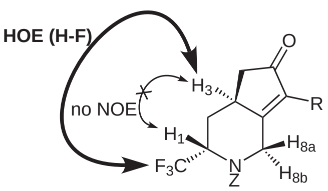


Figure 1 Relative configuration of the stereoisomers from the PK reaction.

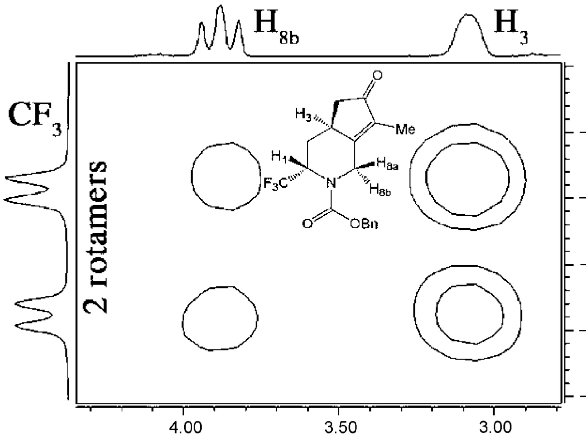


Figure 2 HOESY spectrum of **2b**.

To rationalize such excellent diastereoselectivity, transition states of the PK reaction were considered (Figure 3). Due to the planarity of the CH_2NZCH system, imposed by the amide moiety, the CF_3 group must occupy the axial position (**A$_{ax}$**), because of steric and electrostatic repulsions occurring in **A$_{eq}$**. Then, in the two possible transition states showing an axial CF_3 (**A$_{ax}$** and **B$_{ax}$**), if CF_3 occupies position **B$_{ax}$** steric hindrance between CF_3 and the ethylenic hydrogen occurs. Consequently, the most favorable transition state is **A$_{ax}$** which leads to the diastereomer observed (Figure 3).

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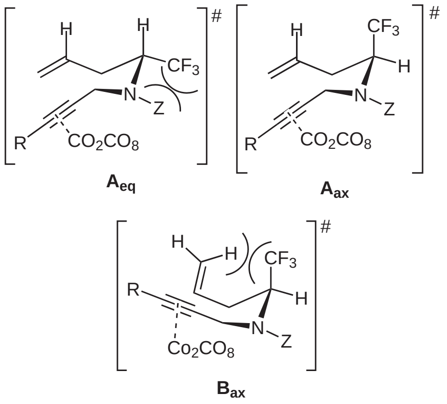
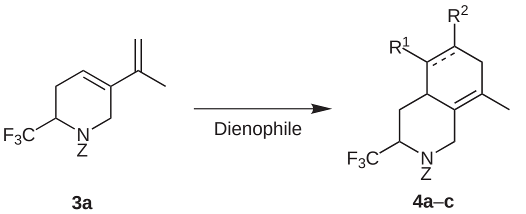


Figure 3 Transition states of the PK reaction.

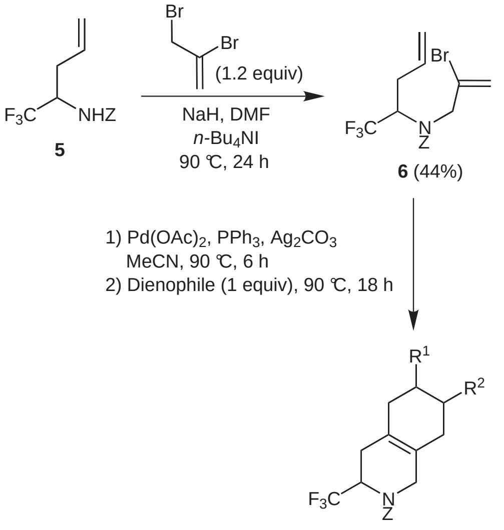
To synthesize other bicyclic structures, we turned our interest towards the Diels–Alder reaction, taking advantage of the fact that we had previously described the synthesis of dienic piperidines by RCM of **1a**,**b**.[3] Various dienophiles and conditions were tested to achieve such a cycloaddition from **3a** (Scheme 2 and Table 1).



Scheme 2 Diels–Alder cycloadditions of **3a**.

These Diels–Alder cycloadditions proved to be very difficult; indicating that diene **3** is quite unreactive. Attempts to realize these reactions under high pressure are currently underway. Nevertheless, neither regioselectivity (entry 1) nor diastereoselectivity (entries 1 and 3) have been observed.

Since diene **3a** appears to be too unreactive, we envisaged using a bis-exo diene derivative of piperidine that we expected to be more reactive. For this purpose, the domino Heck/Diels–Alder sequence developed by De Meijere[5] was carried out (Scheme 3).



7a (dienophile: methyl acrylate): 17%
7b (dienophile: dimethyl maleate): 27%

Scheme 3 Domino Heck/Diels–Alder reaction.

This domino sequence also gave disappointing results. A more accurate study of this process was carried out by ^{19}F NMR, which indicated that the Diels–Alder reaction is the limiting step. Therefore, it appears that dienic derivatives of trifluoromethylated piperidines are not reactive enough to undergo Diels–Alder cycloadditions. This can be rationalized by assuming that the geometrical strain of such compounds could disfavor the planarity of the π-σ-π system of dienes, lowering their reactivity. Theoretical modeling calculations of these compounds are presently being carried out in our laboratory.

To conclude, these preliminary results have shown that α-trifluoromethylated nitrogen bicyclic structures can be synthesized. The Pauson–Khand reaction turned out to be a very efficient, highly diastereoselective method for the synthesis of functionalized bicyclic compounds, which constitute interesting synthons for further synthesis. The Diels–Alder reaction seems to be more difficult, which most certainly is a result of the geometry of the starting substrates. Improvements to this reaction, by using well-known activation methods, such as high pressure or microwave irradiation, are in progress and will be published in due course. The domino sequence, has also allowed us to underline the possibility of synthesizing cyclic structures by organometallic processes, other than RCM; such methods are being further investigated to try to extend their range.

Table 1 Diels–Alder Cycloadditions of **3a**

Entry	Dienophile (1 equiv)	Conditions	Time (days)	Recovered **3a** (%)	**4** (%)
1	Methyl acrylate	Toluene/110 °C	6	56	**4a** (44)
2	Dimethyl maleate	Toluene/110 °C	6	100	**4b** (0)
3	Dimethyl maleate	Toluene/110 °C, $SnCl_4$ (0.1 equiv)	6	62	**4b** (38)
4	DMAD[a]	Toluene/110 °C	1	25	**4c** (75)

[a] DMAD: dimethyl acetylenedicarboxylate.

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