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Access to novel amino trifluoromethyl cyclopropane carboxylic acid derivatives

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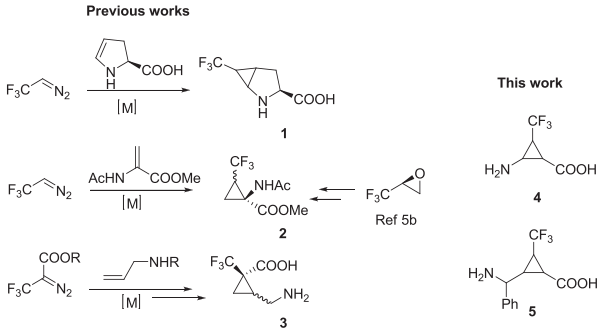
ABSTRACT

Novel regioisomers of trifluoromethylated cyclopropanes have been synthesized by Michael addition and nucleophilic cyclization process. The reaction was carried out with the trifluoromethylcrotonate **6** and nucleophilic reagents. Fluorinated cyclopropanes were obtained with good to excellent diastereoselectivities. Furthermore, interesting constrained building blocks have emerged from this methodology.

1. Introduction

Structures containing the cyclopropane motif have been of great interest within the organic chemistry community. They are widely distributed in a range of naturally occurring products and in particular biologically active compounds such as peptidomimetics due to their small, rigid structure.[1,2] The introduction of a fluoroalkyl group into organic compounds is accompanied by a profound change in physical properties, chemical reactivity, and biological activity.[3] On the other hand, due to the high electronegativity of fluorine, the presence of a trifluoromethyl group in a molecule increases its lipophilicity and metabolic stability and enhances the capacity of neighboring labile hydrogen to make a hydrogen bond that could enhance the interaction with an enzyme or receptor.[3] In medicinal chemistry trifluoromethyl-substituted cyclopropanes have been used as building blocks in the design of many target compounds.[2] The synthesis of trifluoromethylated cyclopropanes is still challenging, especially for fluorinated cyclopropane amino acids. There are mostly three regioisomers of trifluoromethyl substituted cyclopropane amino acids described in the literature (Scheme 1): trifluoromethyl-substituted proline analogs **1** used as a fluorine label for studies of a proline-rich cell-penetrating peptide,[4] *trans* or *cis*-trifluoronorcoronamic acid[5] **2**, and a GABA analog **3**.[6] These scaffolds are generally synthesized from trifluoromethyl diazo compounds and alkenes using a metal catalyst (Scheme 1). With the aim of exploiting new peptidomimetics that incorporate cyclopropane motifs, it may be important and innovative to develop new stereoisomers of trifluoromethyl substituted cyclopropane amino acids. We report herein a straightforward method of synthesis of new stereoisomers **4** and **5**, where the CF_3, ester, and amine groups are attached to different positions of the cyclopropane (Scheme 1).



Scheme 1. 3-Trifluoromethyl 2-aminocyclopropanecarboxylic acid scaffolds.

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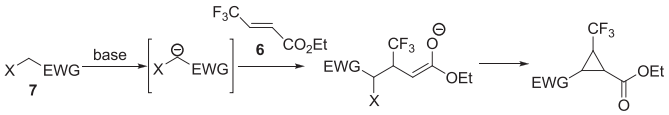
2. Results and discussion

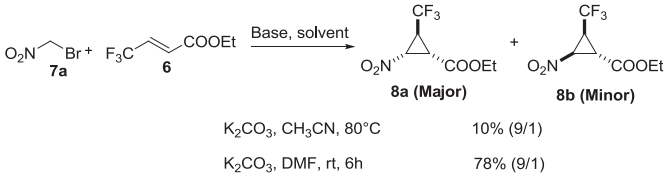
2.1. Cyclopropane formation

The synthesis of cyclopropanes **4** and **5** could be investigated by the addition of trifluoromethyl diazo compounds on olefins with electron withdrawing groups. While a number of catalytic systems worked exceptionally well with styrene derivatives and some electron-rich olefins, cyclopropanation of electron-deficient olefins such as α,β-unsaturated carbonyl compounds and nitriles has proven to be a challenging problem.[1a,7] Interestingly a milder route to compounds **4** and **5** could involve the cyclopropanation of Michael acceptors (tandem Michael Addition–Nucleophilic Cyclization (MA–NC)) (Scheme 2). Surprisingly, only a few cases of synthesis of trifluoromethyl cyclopropanes from trifluorocrotonate via ylides (sulfur ylides[8] and arsenic ylides[9]) and lithium enolates[10] have been reported but not for the synthesis of trifluoromethylated cyclopropane amino acids. In order to prepare the corresponding trifluoromethylated cyclopropanes **4** and **5**, we focused our studies on in situ formation of the nucleophile without prior preparation. We performed the MA–NC reaction on the trifluorocrotonate **6** as electrophile with α halogeno derivatives **7** as nucleophiles under basic conditions (Scheme 2).[1a,7a]



Scheme 2. Cyclopropanation sequence.

In this context, nitrocyclopropane can be a very important starting building block for the synthesis of **4** and different CF_3 cyclopropane peptidomimetics. We applied conditions reported in the literature[11] for the preparation of nitrocyclopropanes with bromonitromethane **7a** and electrophilic alkene **6** in the presence of carbonate as base. The reaction was first conducted in acetonitrile with K_2CO_3 and only 10% of the desired product was obtained (Scheme 3). In order to improve the conversion, we screened a range of solvents and bases. Low conversion (5–12%) was observed after 48 h in DCM, THF, or toluene with Na_2CO_3 or $CsCO_3$, and the best conditions were DMF with K_2CO_3 (2.5 equiv). The conversion was complete after 6 h at room temperature with 2 equiv of bromonitromethane **7a** and 1 equiv of ethyl trifluorocrotonate **6**. The cyclopropanes **8** were obtained in very good yield (78%) (Scheme 3).



Scheme 3. Cyclopropanation reaction with bromonitromethane **7a** and CF_3-acrylate **6**.

Interestingly in the crude product, we observed the formation of only two diastereomers in a 9:1 ratio out of four possible isomers, with the major compound having the CF_3 group in trans position with respect to the nitro and ester groups (Scheme 3). The relative stereochemistry of diastereoisomers **8a** and **8b** was established by NMR. The analysis of vicinal coupling constants could not provide unambiguous stereospecific assignments due to close values (^3J ~7–9 Hz). However 1D HOESY difference spectra clearly showed distinct sets of NOEs for the two diastereomers. In the major form (90%), NOEs are observed between the trifluoromethyl group and both H_1 and H_3 protons (Fig. 1), indicating that these protons and the CF_3 group lie on the same face of the cyclopropyl ring. In contrast, in the minor form (10%), a NOE is observed between the CF_3 group and H_3 proton only, indicating that H_1 proton lies on the face opposite to H_3 proton and CF_3 group (Fig. 1 and see Supplementary data).

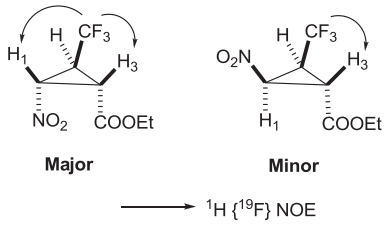
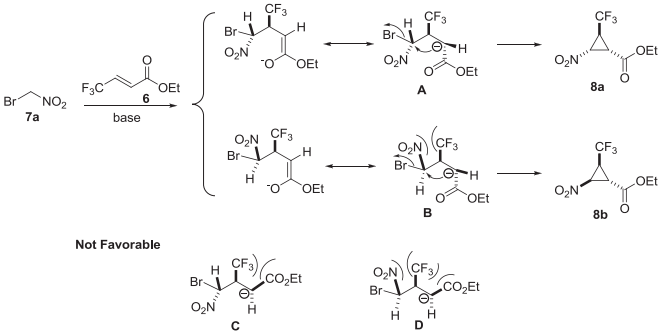


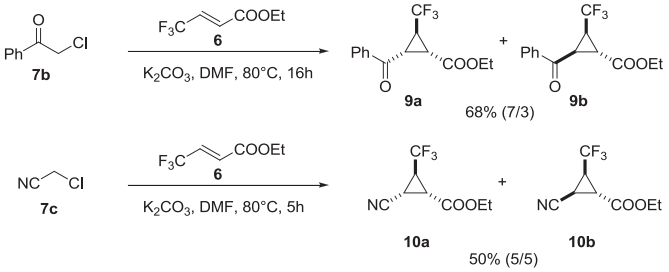
Fig. 1. Determination of the stereochemistry of **8a**/**8b** by HOESY.

Based on the configuration of the trifluoromethyl nitrocyclopropanes **8a** and **8b**, we propose the following mechanism (Scheme 4). The Michael addition between the generated anion after deprotonation in α of bromonitromethane and the ethyl trifluorocrotonate afforded conformer intermediates **A**–**D**. The formations of the enolate diastereoisomers **A** and **B** presented are reversible and under thermodynamic control. More they have less steric hindrance in comparison with the others, and their transition states should be lower than conformers **C** and **D**. The intermediate **A** conducted to **8a**. The minor intermediate **B** afforded **8b** after cyclization.



Scheme 4. Mechanism of the tandem reaction.

Encouraged by this result, and in order to obtain additional products that present a central cyclopropane unit with a CF_3 group, we tested other nucleophilic reagents. We report here only the best results over a wide range of nucleophiles (Scheme 5).



Scheme 5. Cyclopropanation Michael addition on trifluorocrotonate **6**.

The best conditions for the various reagents are DMF as solvent and K_2CO_3 as base at 80 °C. From the phenacyl chloride, the corresponding trifluoromethyl cyclopropanes **9** are obtained in good yield (68%). The next functional group investigated was the