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Concise access to enantiopure (*S*)- and (*R*)-α-trifluoromethyl pyroglutamic acids from ethyl trifluoropyruvate-based chiral CF_3-oxazolidines (Fox)

Grégory Chaume [a], Marie-Céline Van Severen [a], Louis Ricard [b], Thierry Brigaud [a,*]

[a] *Laboratoire de Synthèse Organique Sélective et Chimie Organométallique (SOSCO), UMR CNRS 8123, Université de Cergy-Pontoise, 5, Mail Gay Lussac, Neuville sur Oise, 95031 Cergy-Pontoise Cedex, France*
[b] *Laboratoire Hétéroéléments et Coordination, UMR CNRS 7653, Ecole Polytechnique, 91128 Palaiseau, France*

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ABSTRACT

A straightforward synthesis of enantiopure (*S*)- and (*R*)-α-Tfm-pyroglutamic acid is reported. The strategy is based on the use of a chiral CF_3-hydroxymorpholinone intermediate conveniently obtained from ethyl trifluoropyruvate-based chiral CF_3-oxazolidines (Fox). The key step is an oxidative cyclization followed by a reductive cleavage of the (*R*)-phenylglycinol chiral auxiliary.

1. Introduction

Conformationally constrained cyclic amino acids have recently gained considerable interest because of their ability to control the conformation of peptides for structure–activity relationships investigations as well as for the design of peptidomimetics [1]. In particular, incorporation of a proline unit is known to restrict the amino acyl-proline *cis*/*trans* isomerization [2], to limit the protein folding and consequently to modulate the biological activity of peptides. Among the numerous proline derivatives reported in the literature, fluorinated proline-type amino acids have received increasing attention [3]. This is particularly due to the unique physical and biological properties induced by the introduction of fluorinated groups in peptides and peptidomimetics [4]. However, their use in peptide chemistry remains very limited due to the difficulty to prepare them efficiently, particularly in their enantiopure form. Pyroglutamic acid derivatives were also reported to be efficient tools for the control of the peptidyl bond geometry [5]. Although several examples of fluorine containing pyroglutamic derivatives are reported in the literature [6], the preparation of α-Tfm-pyroglutamic acids in enantiopure form has never been reported [7].

In the course of our studies, we recently reported several approaches for the stereoselective synthesis of α- and β-trifluoromethyl amino acids (Tfm AAs) starting from chiral CF_3-oxazolidines (Fox) or imines [8]. Among them, we developed an efficient route for the synthesis of (*S*)- and (*R*)-α-Tfm proline based on the use of the key chiral CF_3-hydroxymorpholinone **2** (Scheme 1) [9]. This compound was conveniently prepared in a few step from the oxazolidines **1** derived from ethyl trifluoropyruvate.

We present here another feature of the use of the CF_3-hydromorpholinone **2**. This versatile intermediate proved to be also highly valuable for the synthesis of α-Tfm-pyroglutamic acids in enantiopure form.

2. Results and discussion

The preparation of the starting CF_3-hydroxymorpholinone **2** was based on our reported procedure [9]. In addition, the first step involving the formation of oxazolidines **1** from ethyl trifluoropyruvate and (*R*)-phenylglycinol was significantly improved. We observed that the yield of the direct condensation was not entirely reproducible (65–90%) [10]. This was probably due to both bis-nucleophilic reactivity of (*R*)-phenylglycinol and bis-electrophilic reactivity of ethyl trifluoropyruvate. In order to increase the

* Corresponding author. Fax: +33 1 34 25 73 81.
E-mail address: thierry.brigaud@u-cergy.fr (T. Brigaud).

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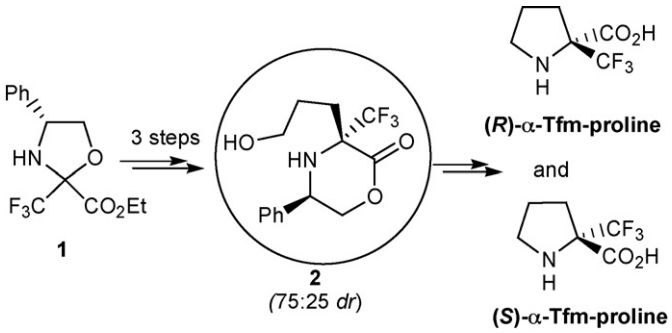
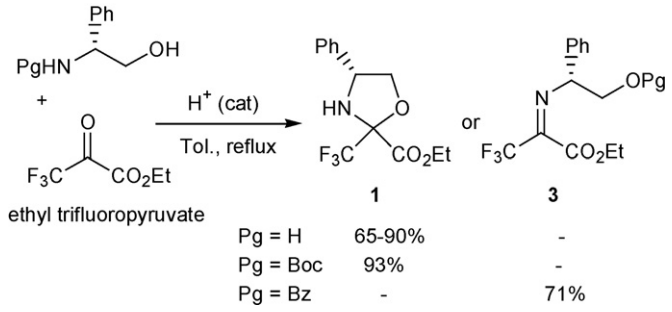


Scheme 1.

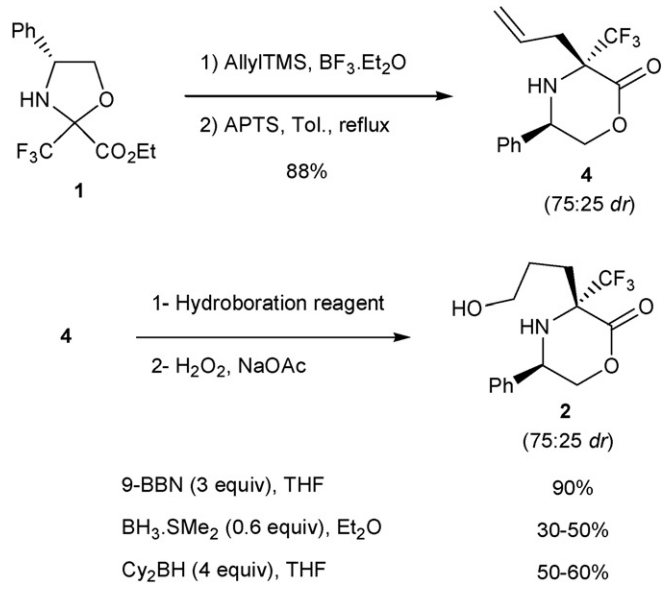


Scheme 2.

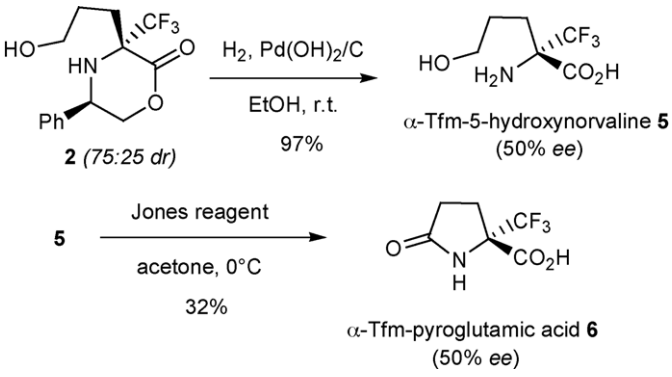
selectivity of the oxazolidine **1** formation, we designed to use a *N*-protected (*R*)-phenylglycinol which would give an intermediate ethyl trifluoropyruvate hemiacetal. After removal of the protecting group, the cyclization of the hemiacetals would lead to the expected oxazolidines. We were pleased to observe that the reaction of the *N*-Boc (*R*)-phenylglycinol under acidic catalysis (0.1 equiv. PPTS) gave directly the oxazolidines **1** (75:25 diastereomeric mixture) in a completely reproducible high yield (93%) (Scheme 2). Intriguingly, when reaction was performed starting from the *N*-Bz phenylglycinol, the only corresponding *O*-Bz imine **3** was isolated in 71% yield. We postulate that in both cases, there is a protecting group transfer from the amino to the hydroxyl group of the (*R*)-phenylglycinol in the acidic reaction conditions. The free amino group would then react selectively with the carbonyl group of the ethyl trifluoropyruvate to give an imine intermediate. The reaction stopped at the imine stage **3** when the stable benzoyle protecting group was used. However, with the Boc protecting group, the acidic mediated smooth removal of the Boc group should undergo a selective intramolecular cyclization of the resulting hydroxyimine into oxazolidines **1**.

The CF_3-hydroxymorpholinone **2** was then obtained as a non-separable 75:25 diastereomeric mixture following our previously reported three-step allylation/lactonisation/hydroboration sequence from oxazolidines **1** (Scheme 3) [9]. The hydroboration reaction of **4** was performed in high yield (90%) using 9-BBN. Lowest yield were achieved using $BH_3{\cdot}SMe_2$ or dicyclohexylborane (30–60%).

As an explorary study, the synthesis of the α-Tfm-pyroglutamic acid **6** from the 75:25 diastereomeric mixture of the hydroxymorpholinone **2** was investigated. The target compound was obtained by the following sequence involving the removal of the chiral auxiliary followed by the oxidation of the hydroxyl group into the corresponding acid and the ring closure by lactamization (Scheme 4). The hydrogenolysis of the hydroxymorpholinone **2** catalyzed by Pearlman's catalyst led to the new α-Tfm-5-hydroxynorvaline **5** in 97% yield. Finally, the expected α-Tfm-



Scheme 3.



Scheme 4.

pyroglutamic acid **6** (50% *ee*) was obtained by oxidative cyclization using Jones reagent in 32% non-optimized yield. The direct cyclization of the intermediate amino acid is in accordance with the observation of Burger et al. [7] since they reported in the racemic series that α-Tfm-glutamic acid gave rise to spontaneous cyclization into α-Tfm-pyroglutamic acid.

The main drawback of this synthetic pathway is that it supposes an efficient separation of both diastereomers of the CF_3-hydroxymorpholinone **2** in order to obtained enantiopure α-Tfm-pyroglutamic acids. As the chromatographic separation of both diastereomers of **2** is difficult, we anticipated that the separation of the bicyclic lactams resulting from oxidative cyclization of **2** would be more convenient [11]. Hence the diastereomeric mixture of **2** was subjected to oxidation using the convenient Jones reagent to give the corresponding bicyclic lactams **7** in high yield (Scheme 5) [12].

As expected, at this stage, both diastereomers of the bicyclic lactams **7** were very easily separated by silica gel chromatography to afford (*R*,*S*)-**7** in 61% isolated yield and (*R*,*R*)-**7** in 20% isolated yield (Scheme 5) [13]. Moreover, we were pleased to observe that both diastereomers could also be very conveniently separated by selective crystallization and filtration. Indeed, (*R*,*S*)-**7** is a white solid poorly soluble in diethyl ether, whereas (*R*,*R*)-**7** is an oil completely soluble in this solvent. This very efficient and convenient separation of both diastereomers will provide an easy