Synthesis of fluorine-containing cyclic amino acid derivatives *via* ring closing olefin metathesis

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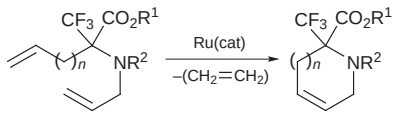
New N-protected α-CF_3 amino esters with two alkene chains (1,7-dienes 3 and 1,6-dienes 5) were reacted with the ring closing metathesis catalyst Ru=CHPh$(Cl)_2(PCy_3)_2$ to give the α-CF_3 dehydropipecolinate and prolinate derivatives 6 and 7.

Among various classes of fluorine-containing biologically active compounds, fluorinated amino acids attract considerable attention. They are especially useful candidates for peptide modification, and β-fluoro-containing amino acids offer potential as irreversible inhibitors of pyridoxal phosphate dependent enzymes.[1] A major drawback of peptide drugs is their rapid degradation by proteases, low lipophilicity and high conformational flexibility and the lack of transport systems to direct peptides into cells.[2] The incorporation of α,α-disubstituted amino acids into key positions in peptides is an efficient strategy to retard proteolytic degradation and to stabilize secondary structures.[3,4] Due to the unique properties of the CF_3 group (high electronegativity, lipophilicity and steric hindrance), α-trifluoromethyl amino acids are a special class of α,α-disubstituted amino acids that can profoundly improve the above mentioned characteristics of peptides.[5]

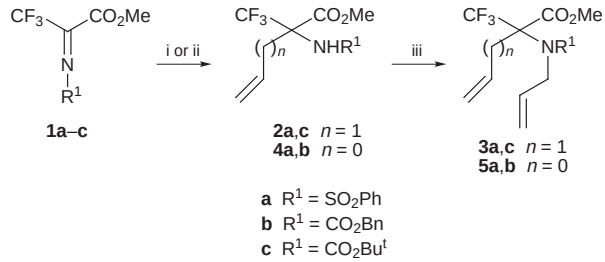
The preparation of rigidified α-amino acids to effect conformational constraints in peptides has played an important role in drug design and development.[6] An efficient access to α-difluoromethyl and α-trifluoromethyl substituted α-amino acids from electrophilic imines of type $XF_2CC(=NPG)CO_2R$ has recently been reported.[7,8] This reaction enabled the direct synthesis of α-fluoromethyl α-amino acids, but the restriction of their conformational flexibility by incorporation into an N-heterocycle was necessary. However, one possible approach is based on intramolecular Ring Closing Metathesis (RCM). The use of olefin metathesis has expanded tremendously in recent years, with applications including the construction of carbo- and hetero-cycles, macrocycles in peptides and other systems.[9] Especially useful are metathesis catalysts based on ruthenium, which have demonstrated remarkable tolerance towards oxygen, protic solvents, and a variety of functional groups.[10]

We now disclose a new effective synthesis of α-trifluoromethyl substituted derivatives of dehydropipecolinic acid and dehydroproline, from α-trifluoromethyl α-amino esters containing two terminal alkene chains, using ring closing olefin metathesis (RCM), according to Scheme 1.

Several imines with different protecting groups on nitrogen, including $PhSO_2$, Boc and Z groups, were successfully applied for the synthesis of α-CF_3 containing α-amino acid derivatives.[11,12] Thus, the preparation of α-CF_3 amino acid derivatives **3** and **5** with two alkene chains was achieved *via* a two-step



Scheme 1



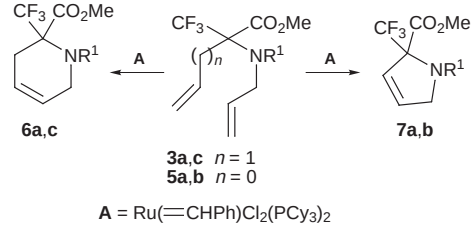
Scheme 2 *Reagents and conditions*: i, CH_2=$CHCH_2MgBr$, THF, −100 °C (1 h) to room temp. (2 h), then aq. HCl (1 M); ii, CH_2=$CHMgBr$, THF, −90 °C to room temp., then aq. HCl (1 M); iii, NaH, DMF, 0 °C, then allyl bromide, 10 h, room temp., then H_2O

procedure starting from the electrophilic imine **1**. The imine **1a** smoothly reacts with allylmagnesium bromide in THF to give the amino acid derivative **2a** in 75% yield. The latter is transformed on deprotonation with NaH and subsequent reaction with allyl bromide into the 1,7-diene derivative **3a** (72%). Similarly, imine **1a** reacts with vinylmagnesium bromide at −90 °C to give **4a** (69%). *N*-Allylation of **4a** *via* successive treatment with NaH and allyl bromide affords the 1,6-diene **5a** (81%) (Scheme 2).

Following the same procedure but starting from the Z and Boc N-protected imines **1b**,**c**, it was possible to isolate in two steps the 1,6-diene **5b** (65%) and the 1,7-diene **3c** (55%) *via* **4b** and **2c**, respectively.

The intramolecular ring closing metathesis reaction was attempted from the 1,7-diene **3a** in CH_2Cl_2 at room temperature in the presence of 10 mol% of the Grubbs catalyst Ru=CHPh$(Cl)_2(PCy_3)_2$ **A**.[9a] The cyclisation of **3a** took place and was completed within 10 h to give the dehydropipecolinate derivative **6a**[13] in high yield (93%) (Scheme 3). The RCM reaction with catalyst **A** (10 mol%) applied to **3c** led to the formation of the six-membered heterocycle **6c** which, after 10 h of reaction, was isolated in 98% yield.

Special interest in α-CF_3 proline derivatives is connected with the fact that proline is known to be unique among the natural amino acids in its abilities to induce β-turns and initiate the folding of an α-helix. Because of these structurally important properties, proline is often suggested as the primary contributor to the biological activity of several proteins, as well as having a key role in biological recognition phenomena.[14]



Scheme 3

Dehydroproline derivatives have also found use as starting materials for kanic acid derivatives.[15]

Recently, attempts to prepare dehydroproline derivatives *via* ring closing metathesis from a $BocN(CH_2CH{=}CH_2)CH(CO_2Me)CH{=}CH_2$ precursor have been made and failed. In the presence of $Ru{=}CHCH{=}CPh_2(Cl)_2(PCy_3)_2$ **B** as catalyst, the acyclic α,β-unsaturated ester $\{BocN[C(CO_2Me){=}CHMe]CH_2CH{=}\}_2$ has been obtained.[9a] This is likely due to the high lability of the vinylglycine α-proton of the precursor.

The absence of an acidic α-proton in the vinylglycine structure of compounds **5** was crucial to the suucessful first formation of the desired dehydroprolinates **7**. Under standard RCM conditions in the presence of 11 mol% of catalyst **A**, at room temperature, **5a** (0.23 mmol) was slowly cyclised into **7a**.[13] However, full conversion of **5a** could not be achieved even after 60 h (conversion ~55%) and derivative **7a** was separated from the starting product **5a** by chromatography over silica gel and isolated in 46% yield.

The benzyloxycarbonyl derivative **5b** (0.2 mmol) was also reacted with 10 mol% of catalyst **A** and after 50 h at room temperature the separation of the starting material **5b** by chromatography led to the isolation of 50% of **7b**.

To the best of our knowledge, the above results show the first use of ruthenium-based RCM catalysts for access to α-CF_3 containing heterocycles (the six- and five-membered cyclic α-CF_3 substituted α-amino acid derivatives). Based on known transformations of amino acid derivatives this direct access should open a route to a variety of fluorine-containing substrates.

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Notes and References

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13 Satisfactory spectroscopic data and elemental analyses were obtained for compounds **3–7**. *Selected data* for **6a**: $\delta_H(CDCl_3)$ 2.71 (m, 1 H, CH_2), 2.92 (m, 1 H, CH_2), 3.65 (m, 1 H, NCH_2), 3.83 (m, 1 H, NCH_2), 3.88 (s, 3 H, OCH_3), 5.72 (m, 2 H, HC=CH), 7.51(m, 3 H, Ph), 7.95 (m, 2 H, Ph); $\delta_F(CDCl_3)$ −71.1 (s, 3 F, CF_3). For **6c**: $\delta_H(CDCl_3)$ 1.52 [s, 9 H, $(CH_3)_3$], 2.77 (m, 2 H, CH_2), 3.82 (m, 1 H, NCH_2), 3.85 (s, 3 H, OCH_3), 4.25 (m, 1 H, NCH_2), 5.75–6.00 (br m, 2 H, HC=CH); $\delta_F(CDCl_3)$ −71.9 (s, 3 F, CF_3). For **7a**: $\delta_H(CDCl_3)$ 3.89 (s, 3 H, OCH_3), 4.07 (m, 1 H, CH_2), 4.62 (m, 1 H, CH_2), 5.63 (m, 1 H, HC=CH), 6.22 (m, 1 H, HC=CH), 7.51 (m, 3 H, Ph), 7.85 (m, 2 H, Ph); $\delta_F(CDCl_3)$ −72.1 (s, 3 F, CF_3). For **7b** (two conformers): $\delta_H(CDCl_3)$ 3.39 and 3.74 (2 s, 3 H, OMe), 4.27 (dm, 1 H, *J* 15.9, NCH_2), 4.41–4.61 (m, 1 H, NCH_2), 4.93–5.41 (m, 2 H, OCH_2), 5.59–5.76 and 5.83–6.00 (2 m, 1 H, =CH), 6.16–6.35 (m, 1 H, =CH), 7.24–7.40 (m, 5 H, Ph); $\delta_F(CDCl_3)$ −71.91, −71.89 (2 s, CF_3).
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