Novel Synthesis of Cyclic α-Amino Acid Esters via Ene Reaction and Ruthenium-catalyzed Ring Rearrangement

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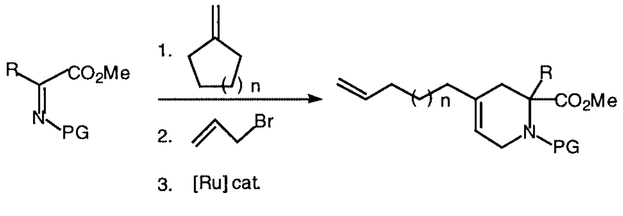
Received 24 January 2001

Abstract: New fluorinated unsaturated cyclic α-amino acid esters were obtained by ene reaction of methylenecycloalkanes with electrophilic imines $(CF_3)(MeO_2C)C{=}N\text{-}PG$, followed by ruthenium-catalyzed ring rearrangement involving mixed ROM-RCM metathesis.

Key words: fluorinated amino acids, cyclic amino esters, ene reaction, ROM-RCM metathesis

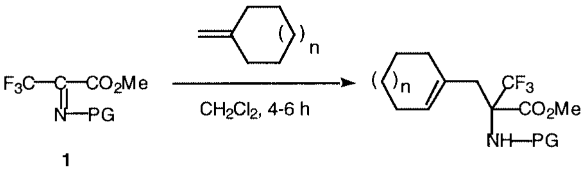
The ring closing metathesis reaction (RCM) has become an important synthetic tool, due to the development of the well-defined Schrock's molybdenum[1] and Grubbs' ruthenium[2] catalysts, which are able to tolerate most functional groups and are very efficient for the selective synthesis of a variety of carbo- and heterocycles.[3] These compounds were shown to catalyze ring opening metathesis (ROM),[4] which can be combined with cross metathesis.[4-6] To our knowledge, no application of combined ROM-RCM reactions has been described for the preparation of fluorine containing cyclic α-amino acid derivatives, despite the special interest of β-fluorinated α-amino acids, which can function as highly selective and potent inhibitors of pyridoxal phosphate-dependent enzymes.[7,8] The development of straightforward methods for the synthesis of β-fluorinated α-amino acid derivatives thus remains of current interest especially via simple catalytic processes.

We now report a novel synthesis of 2-CF_3-4-alkenyl cyclic amino esters based on two successive reactions: the uncatalyzed ene reaction of methylenecycloalkanes with electrophilic trifluoromethylated imines, followed by ruthenium-catalyzed mixed ROM-RCM reactions leading to ring rearrangement of the resulting cyclopentene or cyclohexene groups, which can potentially be applied to most ene reaction products (Scheme 1).



Scheme 1

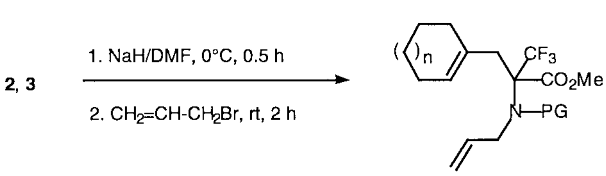
The ene reaction with imines has been performed in the presence of Lewis acid and metal catalysts[9] in order to increase the electrophilicity of the imine carbon atom. The highly electrophilic α-CF_3-substituted imines of type **1**,[10] by contrast, readily react in the absence of catalysts with methylenecyclopentane and methylenecyclohexane to selectively give the ene reaction product, the fluorinated unsaturated α-amino esters **2a-c** and **3a-c** in 68-98% yields (Scheme 2). The reaction takes place at room temperature for *N*-protecting groups of the type PG = SO_2R, whereas the use of the Boc protecting group requires heating at 90-100 °C.



n = 0: **2a** (98%), **2b** (85%), **2c** (83%)
n = 1: **3a** (68%), **3b** (79%), **3c** (71%)

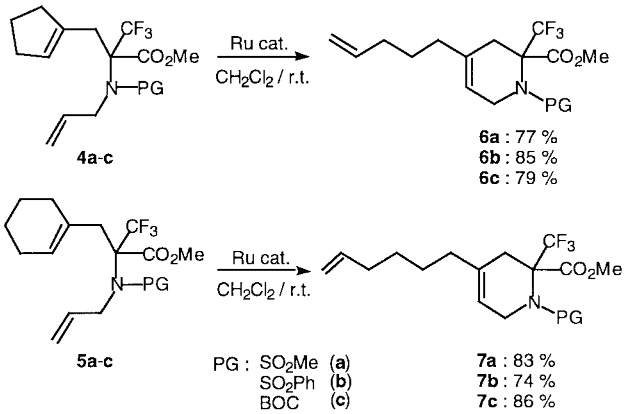
Scheme 2 PG = SO_2Me (**a**); SO_2Ph (**b**); Boc (**c**)

In order to perform the alkene metathesis reaction, an allyl group was attached to the nitrogen atom of the amino esters. The *N*-allylated derivatives **4**, **5** were obtained in 49-68% yields on deprotonation of **2**, **3** with NaH in DMF and subsequent alkylation with allyl bromide (Scheme 3).[11]



Scheme 3 **4a-c** (n = 0); **5a-c** (n = 1)

Alkene metathesis of the 5-membered ring containing derivatives **4a-c** was attempted with 10 mol% of the Grubbs' catalyst $Ru{=}CHPh(Cl)_2(PCy_3)_2$[2] in dichloromethane. After 6-8 hours of stirring at room temperature the reaction yielded the ROM-RCM rearranged products, the cyclic amino esters **6a-c** in 77-85% yields[11] (Scheme 4). Analogously, the cyclohexene derivatives **5a-c** with the catalytic ROM-RCM action of 10 mol% of Ru=CHPh(Cl)$_2$(PCy$_3$)$_2$ led to the derivatives **7a-c** in 74-86% yield[11]. Thus, this reaction allows the straightforward formation of fluorinated, unsaturated 6-membered cyclic α-amino esters with a terminal alkene chain of variable length. It demonstrates that the formation of the 6-membered amino ester cycle is the driving force of the ROM-RCM reaction.



Scheme 4 Ru cat.: Ru=CHPh(Cl)$_2$(PCy$_3$)$_2$

α-CF$_3$ Cyclic amino esters can be obtained via classical ring closing metathesis of dienes.[12] However, the present method opens new possibilities of structural modifications of the amino esters: (i) the ring size is controlled by the length of the alkene chain introduced on the nitrogen atom and (ii) the resulting pendent chain length in **6-7** is controlled by the ring size of the methylenecycloalkane initially involved in the ene reaction.

In summary, we have found a novel pathway to 6-membered heterocycles with endocyclic double bond and pendent terminal alkene chain. This method allowed us to develop an effective access to novel α-CF$_3$-containing amino esters based on ruthenium-catalyzed ROM-RCM reaction. The presence of the pendent chain, whose length can be modulated, offers potential for functionalization and copolymerisation.

Acknowledgement

The authors thank the European Union INTAS programm 97-1874 and the COST programm D12/0025/99 for support.

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(11) Selected data for **4c**: 1.40 (s, 9H, *t*-Bu), 1.79 (pent, J_{HH} 7.2 Hz, 2H, CH$_2$), 2.17 (m, 4H, 2 CH$_2$), 2.92 (s, 2H, CH$_2$), 3.71 (s, 3H, OMe), 3.76 and 4.12 (m, 2H, NCH$_2$), 5.15 (d, J_{HH} 10.4, 1H, =CH$_2$), 5.29 (d, J_{HH} 17.2, 1H, =CH$_2$), 5.52 (s, 1H, =CH), 5.86 (m, 1H, =CH); δ_F(CDCl$_3$) -70.53 (s, 3F, CF$_3$). For **5b**: 1.43 (m, 4H, 2 CH$_2$), 1.88 (m, 4H, 2 CH$_2$), 2.62 (d, J_{AB} 13.2 Hz, 1H, CH$_2$), 2.83 (d, J_{AB} 13.2 Hz, 1H, CH$_2$), 3.82 (s, 3H, OMe), 3.90 (d, J_{AB} 18.2 Hz, 1H, NCH$_2$), 4.02 (d, J_{AB} 18.2 Hz, 1H, NCH$_2$), 4.79 (d, J_{HH} 10.4, 1H, =CH$_2$), 4.90 (d, J_{HH} 17.2, 1H, =CH$_2$), 5.36 (m, 1H, =CH), 5.48 (s, 1H, =CH), 7.45-7.91 (m, Ph); δ_F(CDCl$_3$) -68.49 (s, 3F, CF$_3$); For **6a**: δ_H(CDCl$_3$) 1.55 (m, 2H, CH$_2$), 2.06 (m, 4H, 2 CH$_2$), 2.58 (d, J_{AB} 16.7 Hz, 1H, CH$_2$), 2.79 (d, J_{AB} 16.7 Hz, 1H, CH$_2$), 3.03 (s, 3H, SMe), 3.86 (s, 3H, OMe), 3.95 (m, 2H, NCH$_2$), 5.01 (m, 2H, =CH$_2$), 5.61 (m, 1H, =CH), 5.80 (m, 1H, =CH); δ_F(CDCl$_3$) -70.99 (s, 3F, CF$_3$); For **7c**: δ_H(CDCl$_3$) 1.18 (s, 9H, CMe$_3$), 1.47 (m, 4H, 2 CH$_2$), 2.01 (m, 4H, 2 CH$_2$), 2.50 (d, J_{AB} 18.0 Hz, 1H, CH$_2$), 2.69 (d, J_{AB} 18.0 Hz, 1H, CH$_2$), 3.79 (s, 3H, OMe), 3.89 (m, 2H, NCH$_2$), 4.91 (m, 2H, =CH$_2$), 5.08 (m, 1H, =CH), 5.73 (m, 1H, =CH); δ_F(CDCl$_3$) -69.49 (s, 3F, CF$_3$)

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Article Identifier:
1437-2096,E;2001,0,05,0621,0622,ftx,en;G01201ST.pdf