Ruthenium-Catalyzed Cyclotrimerization of 1,6- and 1,7-Azadiynes: New Access to Fluorinated Bicyclic Amino Acids

Grigorii T. Shchetnikov,[a] Sergey N. Osipov,*[a] Christian Bruneau,[b] Pierre H. Dixneuf*[b]

[a] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov str. 28, 119991 Moscow, Russian Federation
Fax +7(495)1355085; E-mail: osipov@ineos.ac.ru

[b] Institut Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France
E-mail: pierre.dixneuf@univ-rennes1.fr

Received 29 November 2007

Abstract: An efficient access to a variety of trifluoromethyl-substituted cyclic α-amino acid derivatives based on ruthenium-catalyzed cyclotrimerization of appropriate 1,6- and 1,7-diynes with terminal and internal alkynes has been developed.

Key words: fluorinated diynes, amino acids, ruthenium catalysis, cyclotrimerization, alkynes

Peptides modified by nonproteinogenic amino acids (AA) are useful building blocks for drug discovery. Therefore, the development of new synthetic pathways to non-natural amino acids containing various functionalities remains a constant challenge. On the other hand, α-amino acids containing the trifluoromethyl (CF_3) group[1] are of particular interest due to the unique characteristics of the trifluoromethyl group, such as high electronegativity, electron density, steric hindrance and hydrophobicity.[2] The advantages of peptides modified by CF_3-AA include enhanced proteolytic stability, affinity for lipid bilayer membranes, as well as stabilization of secondary supramolecular structures[3] owing to the ability of the fluorine atom to form hydrogen bonds.[4,5]

Previously we described the syntheses of α-CF_3-AA derivatives (e.g. such as CF_3-ornithine,[6a] CF_3-arginine,[6b] CF_3-thalidomide[6c]) based on addition of C-nucleophiles to acylimines of 3,3,3-trifluoropyruvates.[7] Unsaturated α-CF_3-AA derivatives obtained by this methodology were successfully further applied in ruthenium-mediated metathesis-type reactions to afford new families of the corresponding proline and pipecolic acid derivatives.[8] Now we disclose a new effective access to α-trifluoromethyl-substituted derivatives of tetrahydroisoquinoline-3-carboxylic acid (TIC) and benzoproline via ruthenium-catalyzed co-cyclotrimerization of α-CF_3-α-amino esters bearing two terminal alkyne chains with terminal and internal alkynes.

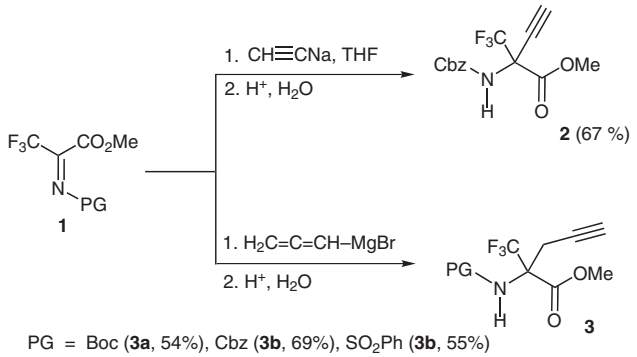
Inter- and intramolecular cyclotrimerization of acetylenes catalyzed by a variety of transition metal catalysts[9] has been recognized as a versatile synthetic approach for highly substituted benzene derivatives.[10] Cobalt-[11] and rhodium-based[12] catalysts have been successfully used to make this reaction the key step in a series of elegant syntheses of biologically relevant structures including natural products. To the best of our knowledge, this catalytic alkyne cyclotrimerization approach to produce cyclic amino acids has been applied only in rare examples. Thus, Kotha, starting from appropriate 1,7-diacetylenic precursors has applied Vollhardt's [$CoCp(CO)_2$] and Wilkinson's [$RhCl(PPh_3)_3$] catalysts for the synthesis of some TIC derivatives as constrained analogues of phenylalanine. However, the yields of the corresponding cyclic products were poor to moderate even upon increased amounts of catalyst (more then 10 mol%).[13]

Yamamoto and Itoh[14] have introduced RuCl(Cp*)(cod) as a catalyst for [2+2+2]-cycloaddition of diynes to different types of unsaturated compounds such as functionalized olefins, alkynes, nitriles, isocyanates and isothiocyanates to provide an efficient access to a variety of aromatic and heteroaromatic compounds. Generally, this catalyst precursor has proved to be effective in amounts from 1 mol% to 3 mol% to afford good yields of the desired cycloadducts. This efficiency is likely due to the ability of the $RuCl(C_5R_5)$ moiety to generate, after oxidative coupling of a diyne, a biscarbene intermediate rather than a classical ruthenacyclopentadiene.[15] Being inspired by these results we have investigated the catalytic activity of RuCl(Cp*)(cod) in cyclotrimerization of fluorinated diynes.

We have first developed an effective protocol for the preparation of new trifluoromethyl-containing 1,6- and 1,7-azadiynes starting from readily available imines of methyltrifluoropyruvate. The synthetic sequence includes two simple stages: (i) the addition of sodium acetylenide[16] or allenylmagnesium bromide[17] to electrophilic imines **1** takes place under mild conditions to give the corresponding α-alkynyl derivatives **2** and **3** (Scheme 1); (ii) the N-alkylation of alkynyl-substituted amino esters with propargyl bromide, after deprotonation with sodium hydride in DMF, affords azadiynes **4** and **5** with acceptable yields (Table 1).

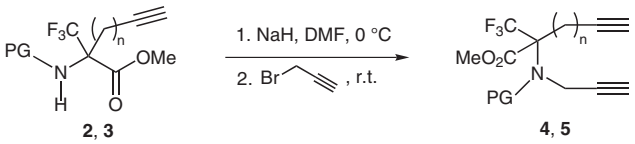
We found that cyclotrimerization of both 1,6- and 1,7-azadiynes with terminal alkynes proceeded at room temperature in DCE in the presence of 1 mol% of RuCl(Cp*)(cod) and led to completion of reaction after few minutes in the case of 1-hexyne and after one to two hours for acetylene (gas, normal pressure) to give CF_3-containing proline[18] and TIC derivatives[18] in high yields (Table 2, entries 1, 2,

SYNLETT 2008, No. 4, pp 0578–0582
Advanced online publication: 12.02.2008
DOI: 10.1055/s-2008-1032089; Art ID: G36707ST



Scheme 1 Synthesis of α-CF_3-α-amino acid derivatives with alkyne substituents in the α-position

Table 1 Synthesis of Fluorinated 1,6- and 1,7-Azadiynes



Entry	PG	n	Product	Yield (%)
1	Cbz	0	**4**	50
2	Boc	1	**5a**	55
3	Cbz	1	**5b**	75
4	SO_2Ph	1	**5c**	71

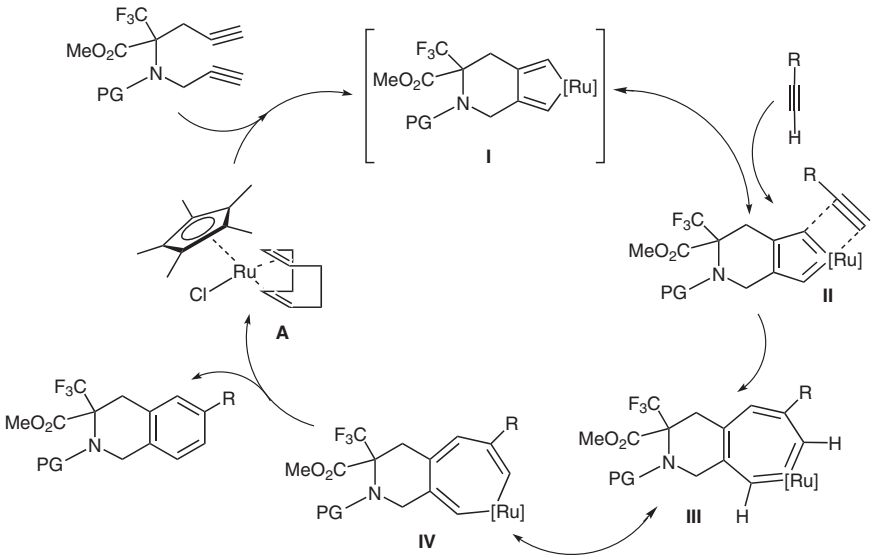
5–8). With 1-hexyne, the two regioisomers were formed in 1:1 ratio.

Internal alkynes such as diphenylacetylene and diethylacetylene reacted with diynes under the same conditions leading to the formation of the corresponding cycloadducts **6c**, **6d** and **7e** in poor to good yields (Table 2, entries 3, 4, 9). In these cases, dimers of starting diynes were detected as by-products according to NMR and MS spectroscopy. Electron-deficient alkynes (e.g. biscarboethoxyacetylene) did not form cyclotrimerization products even under more drastic conditions.

Blechert and his co-workers[19] have shown that triynes can undergo an intramolecular cascade of metathesis reactions to provide the corresponding arene derivatives using Grubbs' catalyst **B**. Later, Roy[20] and Witulski[21] have successfully demonstrated its application in an intermolecular version of alkyne co-cyclotrimerization. Based on these findings we have checked the catalytic activity of **B** in cyclotrimerization of fluorinated substrates. Thus, we found that **B** was also able to perform cyclotrimerization 1,6- and 1,7-azadiynes **4** and **5** in amount of 5 mol% at room temperature in DCE, although the yields of reaction products appeared slightly lower than those with **A** (Table 2, entries 5, 7, 8).

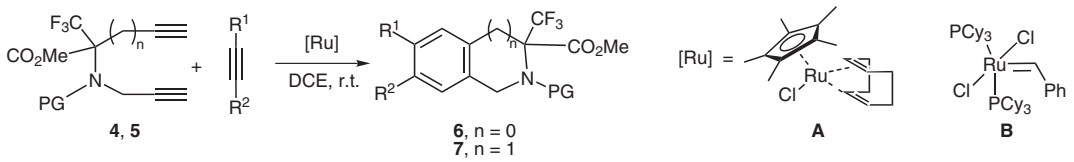
Whereas the action of the Grubbs catalyst is explained by successive alkyne/metal–carbene metathesis steps,[19] the most efficient co-cyclotrimerization by precatalyst **A** can be rationalized as described in Scheme 2. The first step corresponds to the oxidative coupling of the diyne to give the ruthenacyclopentadiene **I** close to the transition state affording the more stable biscarbene intermediate **II**.[15] A Ru–carbene bond of **II** can add regioselectively to alkyne bond, via a metathesis step, affording the new biscarbene ruthenium intermediate **III**, leading to the reductive elimination step via **IV** that is closed to the transition state. The identical reactivity of both Ru=C bonds of **II** is expected to give the two observed regioisomers (1:1).

To obtain free cyclic amino acids the methods for selective removal of protection groups from amino and carboxylic functions have been applied via standard protocols commonly used in peptide chemistry. Thus, Cbz-protective group could be easily removed by catalytic (10% Pd/C) hydrogenation in methanol at room temperature; subsequent basic hydrolysis of ester with KOH led to formation of the desired free amino acid[22] (Scheme 3).

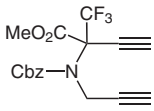
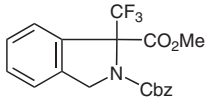
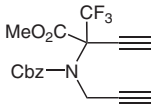
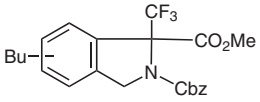
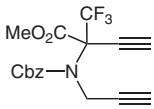
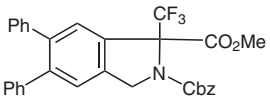
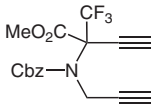
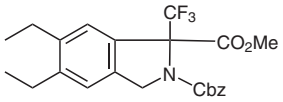
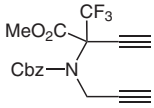
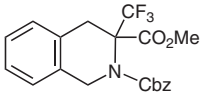
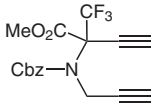
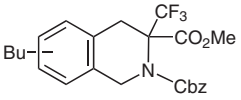
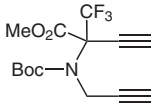
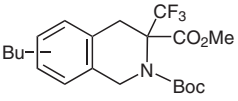
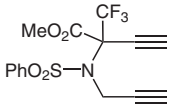
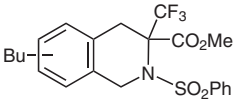
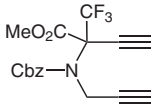
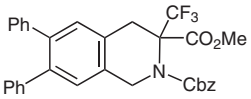


Scheme 2 Proposed mechanism for cyclotrimerization catalyzed by RuCl(Cp*)(cod)

Table 2 α-CF_3-Substituted Benzoproline and Tetrahydroisoquinoline Derivatives



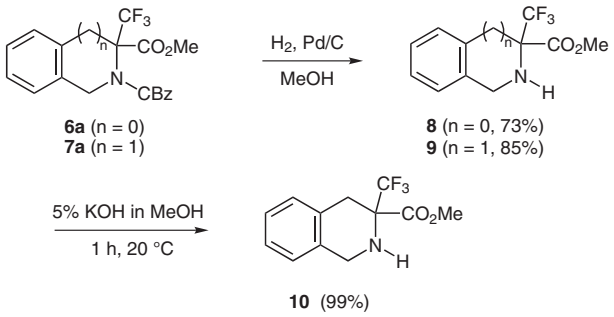
4, **5** **6**, n = 0 **7**, n = 1 **A** **B**

Entry	Diyne	Acetylene	Product	[Ru] catalyst **A/B**	Time (min)	Yield (%)
1		HC≡CH	 **6a**	**A**	120	82
2		BuC≡CH	 **6b**	**A**	10	76
3		PhC≡CPh	 **6c**	**A**	120	20
4		EtC≡CEt	 **6d**	**A**	240	40
5		HC≡CH	 **7a**	**A/B**	120	86/71
6		BuC≡CH	 **7b**	**A**	10	70
7		BuC≡CH	 **7c**	**A/B**	10	89/72
8		BuC≡CH	 **7d**	**A/B**	10	82/67
9		PhC≡CPh	 **7e**	**A**	120	25

In conclusion, we have developed an effective approach to CF_3-substituted benzoproline and tetrahydroisoquinoline-3-carboxylic acid derivatives based on ruthenium-catalyzed cyclotrimerization of 1,6- and 1,7-azadiynes with RuCl(Cp*)(cod) and the Grubbs catalyst. The new compounds obtained can be useful candidates for specific modification of biologically active peptides.

Acknowledgment

This work was supported by the Russian Foundation of Basic Research (grants NN 07-03-00593 and 07-03-92171-CNRS).



Scheme 3 The synthesis of free amino acids

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(18) **General Procedure for Ru-Catalyzed Cyclotrimerization**: The catalyst RuCl(Cp*)(cod) (2 mol%) was added to the solution of diyne (0.15 mmol) and alkyne (0.6 mmol) in degassed DCE under an argon atmosphere. The resulting mixture was stirred at r.t. until the reaction completion (TLC control). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: EtOAc–PE).
Data for Compound 6a: oil. ^{1}H NMR (400 MHz, DMSO-d_6, 80 ºC): δ = 3.61 (br s, 3 H, OMe), 4.84 (d, J_{AB} = 15.2 Hz, 1 H, NCH_2), 5.03 (d, J_{AB} = 15.2 Hz, 1 H, NCH_2), 5.23 (s, 2 H, OCH_2), 7.34–7.56 (m, 9 H, Ar). ^{19}F NMR (282 MHz, DMSO-d_6, TFA, 80 °C): δ = 5.3 (s, 3 F, CF_3). Anal. Calcd for $C_{19}H_{16}F_3NO_4$: C, 60.16; H, 4.25; N, 3.69. Found: C, 60.21; H, 4.35; N, 3.67.
Data for Compound 7a: oil. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ = 3.33 (d, J_{AB} = 15.4 Hz, 1 H, CH_2), 3.39 (d, J_{AB} = 15.4 Hz, 1 H, CH_2), 3.50 (s, 3 H, OMe), 4.49 (d, J_{AB} = 15.1 Hz, 1 H, NCH_2), 4.87 (d, J_{AB} = 15.1 Hz, 1 H, NCH_2), 5.15 (s, 2 H, OCH_2), 7.29 (m, 4 H, Ar), 7.33–7.43 (m, 5 H, Ph). ^{19}F NMR (282 MHz, $CDCl_3$, TFA, 80 °C): δ = 6.32 (s, 3 F, CF_3). ^{13}C NMR (150.9 MHz, DMSO-d_6, 80 ºC): δ = 32.51, 45.15, 56.21, 68.18, 70.10 (q, $^2J_{C-F}$ = 28.4 Hz), 122.23 (q, $^1J_{C-F}$ = 288.2 Hz), 127.88, 127.91, 128.04, 134.70, 136.51, 139.18, 156.32, 165.81. Anal. Calcd for $C_{20}H_{18}F_3NO_4$: C, 61.07; H, 4.61; N, 3.56. Found: C, 60.99; H, 4.55; N, 3.67.

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(22) **Data for Compound 10**: mp 234 °C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.35 (d, J_{AB} = 15.4 Hz, 1 H, CH_2), 3.39 (d, J_{AB} = 15.4 Hz, 1 H, CH_2), 3.86 (d, J_{AB} = 15.5 Hz, 1 H, NCH_2), 4.06 (d, J_{AB} = 15.5 Hz, 1 H, NCH_2), 7.23 (m, 4 H, Ar). ^{19}F NMR (282 MHz, DMSO-d_6): δ = 3.07 (s, 3 F, CF_3). ^{13}C NMR (150.9 MHz, DMSO-d_6): δ = 31.03, 45.12, 64.01 (q, $^2J_{C–F}$ = 29.9 Hz), 120.91 (q, $^1J_{C–F}$ = 281.3 Hz), 127.31, 128.01, 128.41, 129.21, 133.81, 138.14, 168.41. Anal. Calcd for $C_{12}H_{12}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.61; H, 4.32; N, 5.34.