Thermal [2+2] Cycloaddition of CF_3-Substituted Allenynes: Access to Novel Cyclobutene-Containing α-Amino Acids

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Abstract: An efficient approach for the preparation of novel CF_3-substituted cyclic α-amino acid derivatives fused with cyclobutene ring has been developed. The method is based on intramolecular thermal [2+2] cycloaddition of amino acid containing allenynes with internal triple bond obtained by successive [2,3]-sigmatropic rearrangement of propargyl-containing nitrogen CF_3-ylides and Sonogashira derivatization of the triple bond.

Key words: allenynes, Sonogashira coupling, [2+2] cycloaddition, cyclobutenes, amino acids

Transformation of acyclic functional molecules into bicyclic species is synthetically useful because bioactive compounds typically comprise polycyclic structural frameworks associated to the required functionality. In recent decade, carbo- and heterocyclic compounds fused with cyclobutene ring have attracted enhanced attention since they are the key structural units frequently observed in biologically relevant structures[1] (Figure 1).

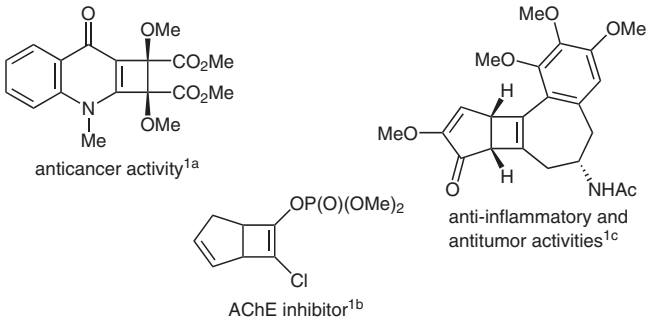
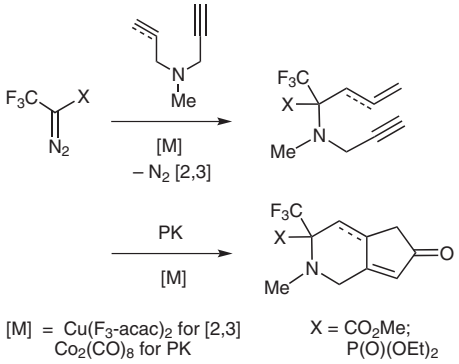


Figure 1 Selected biologically active cyclobutene-containing compounds

The combination of high strain and unsaturation renders cyclobutenes as versatile synthons for a number of useful synthetic transformations such as electrocyclic ring opening, metathesis-type reactions, epoxidation, or cyclopropanation.[2] The intramolecular [2+2] cycloaddition of allenynes represents the most prominent strategy for the construction of fused cyclobutene derivatives just in one step.[3] With respect to environmentally friendly chemical processes, the thermal version of this reaction occurring in the absence of any activation reagents or catalysts and without creating any waste products is an ideal carbon–carbon bond-forming process in terms of high atom economy and selectivity.

However, the synthesis of allenynes bearing different functionalities is not a trivial task requiring numerous synthetic stages.[4] Recently, we have developed an efficient one-step method for the preparation of fluorinated α-aminocarboxylic and α-aminophosphonic acid containing enynes and the unique allenynes based on [2,3]-sigmatropic rearrangement of allyl(propargyl) ylides. The synthetic potential of those doubly unsaturated systems has been further demonstrated in intermolecular cobalt-mediated Pauson–Khand reaction to afford the corresponding bicyclic amino acid derivatives and their phosphorous analogues (Scheme 1).[5]



Scheme 1 Synthesis of functionalized CF_3 heterocycles

Fluorine-containing amino acids, especially their constrained cyclic derivatives, attract a considerable interest as crucial targets in bioorganic and medicinal chemistry for the design of potent and highly selective bioactive compounds.[6] Along with our current investigations directed towards the development of new methodologies for the synthesis of trifluoromethylated cyclic α-amino acids,[7] we report now an efficient synthesis of α-CF_3-α-amino acid containing 1,6- and 1,7-allenynes with internal triple bond and their subsequent intramolecular termal [2+2] cycloaddition involving the terminal allene double bond to afford the corresponding fused cyclobutene derivatives, which are also potential bioactive compounds (Scheme 2).

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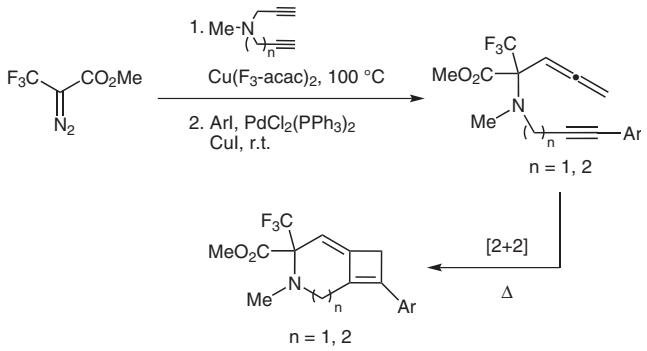
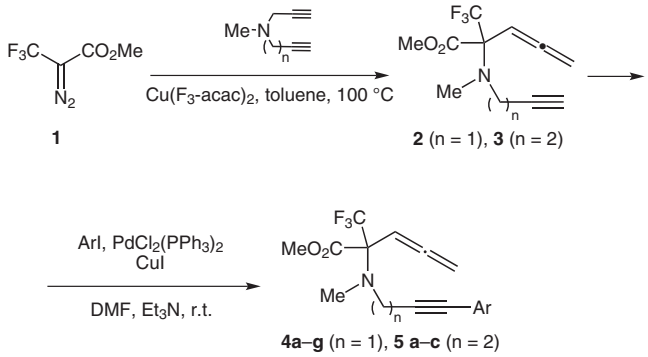


Scheme 2 Access to cyclobutene-containing α-CF_3-α-amino acid derivatives

Thus, we found that 1,6- and 1,7-allenynes **4** and **5** can be readily obtained in good yields by the two-step sequence involved [2,3]-sigmatropic rearrangement and Pd-catalyzed Sonogashira coupling reaction. For the rearrangement stage proceeding through the formation of propargyl-containing ylides,[5] methyl-2-diazocarboxylate (**1**) was heated with *N*,*N*-dipropargyl-*N*-methylamine or *N*-homopropargyl-*N*-propargyl-*N*-methylamine in the presence of 5–10 mol% of copper trifluoroacetylacetonate in toluene to give the corresponding 1,6- and 1,7-allenynes with terminal triple bond in 71% (**2**) and 60% (**3**) yields, respectively (Scheme 3).



Scheme 3 Synthesis of CF_3-allenynes with internal triple bond

To synthesize allenynes **4** and **5** with internal triple bond the palladium-catalyzed cross-coupling of **2** and **3** with different aryl iodides was successfully performed using 5 mol% $PdCl_2(PPh_3)_2$/CuI catalytic system in the mixture of *N*,*N*-dimethylformamide and triethylamine at room temperature. In each case the desired allenynes **4** and **5** were isolated in good yields (Table 1).

The investigation of intramolecular [2+2] cycloaddition of synthesized allenynes commenced with the reactions of 1,6- and 1,7-allenynes **2** and **3** bearing terminal alkyne unit. For this purpose they were heated in toluene or xylenes for 3–24 hours.

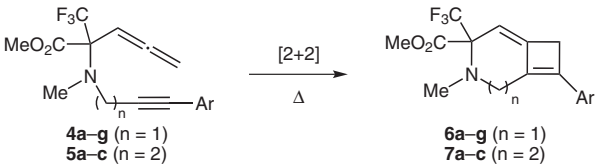
As a result, only decomposition of **2** has been detected under refluxing in toluene for 3 hours. In contrast, the compound **3** has proved to be completely inert even under heating in xylenes at 185 °C (plugged Schlenk tube) for 24 hours. The data obtained are in agreement with literature examples published for the related [2+2] thermal reactions of simple allenynes.[3] At the same time, it is known that the mechanism of this cycloaddition involves the formation of diradical intermediates[8] and any substituent on triple bond of allenyne, which can effectively stabilize these biradicals, is expected to be extremely essential for successful conversion.[3e]

Table 1 Synthesis of Allenynes **4** and **5** via Sonogashira Reaction

Entry	n	Ar	Product	Yield (%)[a]
1	1	Ph	**4a**	82
2	1	4-MeC_6H_4	**4b**	74
3	1	2-MeC_6H_4	**4c**	81
4	1	4-$MeOC_6H_4$	**4d**	77
5	1	2-$MeOC_6H_4$	**4e**	73
6	1	4-$O_2NC_6H_4$	**4f**	80
7	1	2-$O_2NC_6H_4$	**4g**	82
8	2	Ph	**5a**	84
9	2	4-$MeOC_6H_4$	**5b**	65
10	2	4-$O_2NC_6H_4$	**5c**	80

[a] After column chromatography on silica gel (hexanes–EtOAc).

Indeed, 1,6-allenynes **4a–g** comprising radical-stabilizing aryl groups on triple bond were successfully transformed into the corresponding bicyclo[4.2.0]octa-1,6-dienes **6** in excellent yields under refluxing in toluene for 2 hours (Scheme 4, Table 2, entries 1–7). It is significant that the formation of cyclobutene ring proceeds upon distal double bond of allene moiety exclusively. The nature of the substituents on the benzene ring did not significantly affect the outcome of the reaction.



Scheme 4 Thermal [2+2] cycloaddition of allenynes **4** and **5**

Thermal [2+2] cycloaddition of 1,7-allenynes **5a–c** requires more drastic conditions. Thus, in this case the full conversion was achieved only under heating in xylenes at 185 °C (plugged Schlenk tube) for 36 hours to afford the target CF_3-substituted azepine-2-carboxylates fused with cyclobutene ring **7a–c** in high yields (Scheme 4, Table 2, entries 8–10).

Table 2 Thermal [2+2] Cycloaddition of 1,6- and 1,7-Allenynes: Synthesis of Cyclobutenes **6** and **7**

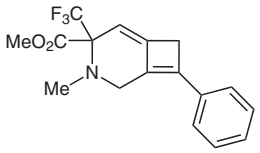
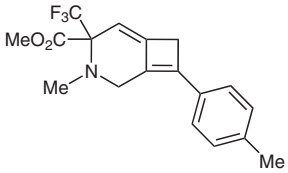
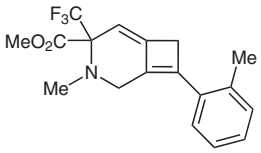
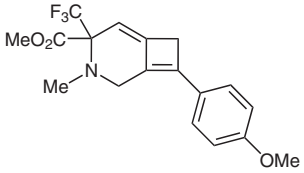
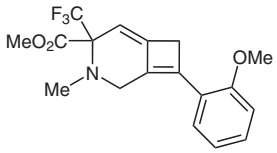
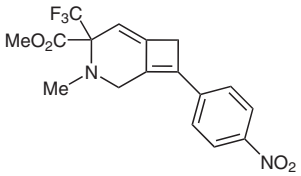
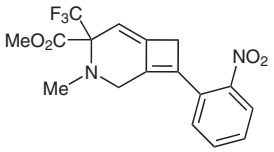
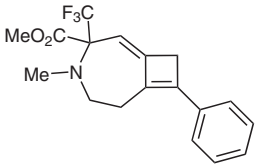
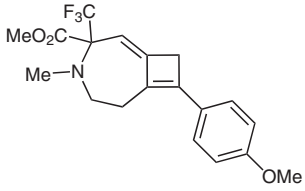
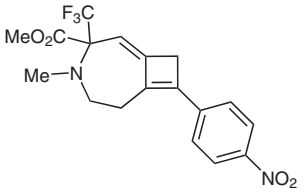
Entry	Product[a]	Structure	Yield (%)[b]
1	**6a**		80
2	**6b**		80
3	**6c**		90
4	**6d**		86
5	**6e**		74
6	**6f**		87
7	**6g**		93
8	**7a**		87
9	**7b**		88

Table 2 Thermal [2+2] Cycloaddition of 1,6- and 1,7-Allenynes: Synthesis of Cyclobutenes **6** and **7** (continued)

Entry	Product[a]	Structure	Yield (%)[b]
10	**7c**		91

[a] Conditions for **6**: refluxing in toluene for 2 h; conditions for **7**: heating in xylenes at 185 °C for 36 h (plugged Schlenk tube).
[b] Isolated yield after flash column chromatography on silica gel (hexanes–EtOAc).

In conclusion, the present study first demonstrated that allenynes possessing α-CF_3-α-amino acid skeleton can regioselectively undergo intramolecular [2+2] cycloaddition of the distal double bond of the allene moiety leading to a hitherto unknown class of CF_3-substituted cyclic α-amino acid fused with cyclobutene ring. This simple and environmentally benign process would extend the potential application of bicyclic amino acid derivatives in synthetic and medicinal chemistry. We are continuing our studies into the scope and limitations of this new method and also investigating the synthetic utility of these functional cyclobutenes.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental details and NMR spectra for all new compounds.

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