

Extended Abstract (mini-review)

Ti-Catalyzed Cross-Cyclomagnesiation in the Synthesis of Natural and Synthetic Dienoic and Trienoic Fatty Acids Exhibiting a Wide Range of Biological Activities [†]

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Abstract: The mini-review summarizes the latest achievements of the authors in the field of Ti-catalyzed cross-cyclomagnesiation in the synthesis of natural dienoic and trienoic fatty acids exhibiting a wide range of biological activities.

Keywords: unsaturated fatty acids; 1Z,5Z-dienes; cross-cyclomagnesiation; anti-cancer activity.

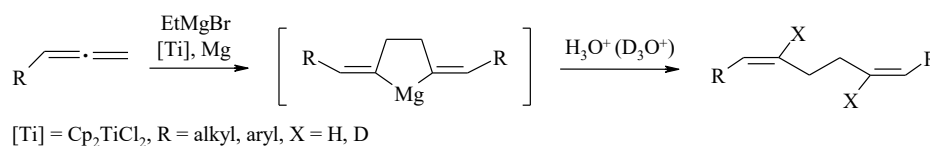
1. Introduction

The development of new, promising for practical application methods for the synthesis of functionally substituted hydrocarbons containing in their structure 1Z,5Z-diene group, is stimulated by their wide distribution in the composition of a large number of insect pheromones, a number of biologically active compounds of natural structure and precursors of acetogenins and indolizidines with antiviral, antibacterial and antitumor properties [1-7].

In the world literature, there are no general, universal methods for the synthesis of 1Z,5Z-diene compounds of high stereochemical purity, in addition, the known methods for the synthesis of 1Z,5Z-dienes are multistage and the total yields of the final compounds vary within 5-15% [8, 9].

The previously developed reaction of intermolecular homo-cyclomagnesiation of aliphatic 1,2-dienes leads to the formation of hard-to-reach 1Z,5Z-dienes in high yields and, as we suggested, can serve as an effective tool in the synthesis of 1Z,5Z-dienes of a given structure [10-12].

Scheme 1



The main disadvantages of this approach were two circumstances: the production of only symmetric hydrocarbons containing the 1Z,5Z-diene moiety and the absence of any information on the possibility of joint cyclomagnesiation of functionally

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substituted 1,2-dienes with alkyl(aryl)allenes, which significantly reduced the value of approach for its application in the directed synthesis of unsymmetrical 1,5-diene compounds of a given structure.

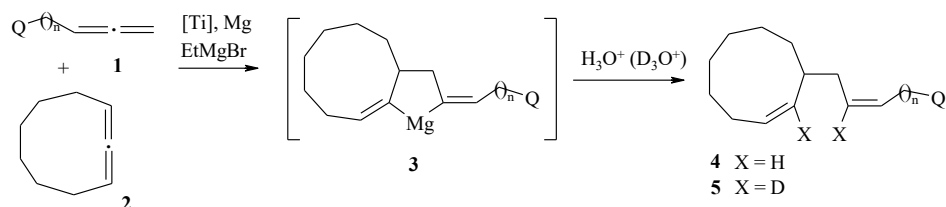
This work makes a significant contribution to the development of research on the design of 1Z,5Z-dienes of a given structure, filling the gaps indicated above and demonstrates the possibilities of the catalytic cross-cyclomagnesiation reaction of 1,2-dienes in the synthesis of O-, N-, and Si-containing 1Z,5Z-dienes, including in relation to the synthesis of biologically active compounds of natural origin.

2. Synthesis of unsymmetrical functional-substituted compounds containing 1Z,5Z-diene group

The previously obtained results on the homo-cyclomagnesiation of functionally substituted allenes allowed us to suggest the possibility of synthesizing non-symmetric functionally substituted magnesacyclopentanes by cross-cyclomagnesiation of 1,2-dienes different structures.

To implement the proposed idea, we studied the reaction of cyclonona-1,2-diene with O-, N- and Si-containing allenes using EtMgBr in the presence of Mg and a Cp₂TiCl₂ catalyst (1:2:EtMgBr:Mg:[Ti] = 10:15:30:32:1, Et₂O, 6 h, 20–22 °C), leading mainly to the formation of bicyclic organomagnesium compounds (OMC) **3**, which, after hydrolysis and deuteration, are converted into the corresponding cyclononene derivatives **4**, **5** in 81–86% yield (Scheme 2) [13–15].

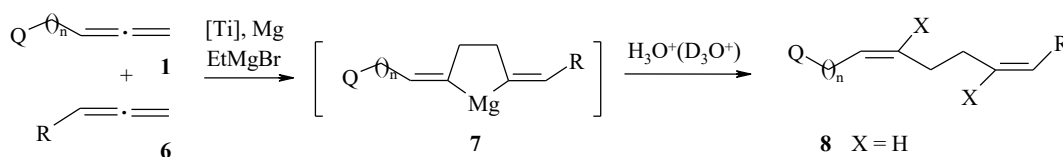
Scheme 2



[Ti] = Cp₂TiCl₂; Q = OTHP, n = 2 (a); Q = OBn, n = 2 (b); Q = Morpholyl; n = 1 (c), 2 (d); Q = TMS, n = 1 (e).

Having obtained encouraging results on the intermolecular cyclomagnesiation of cyclonona-1,2-diene with functionally substituted allenes, we subsequently developed optimal conditions for the cross-cyclomagnesiation of O-, N-, Si-containing 1,2-dienes with terminal alkyl- and aryl-substituted allenes **6** in presence of EtMgBr and Cp₂TiCl₂ as a catalyst (1:6:EtMgBr:Mg:[Ti] = 10:12:40:32:0.5; Et₂O, 6 h, 20–22 °C) to obtain extremely unsymmetrical OMC **7** of high stereochemical purity (>99%) in yields >80% (Scheme 3) [17–19].

Scheme 3



[Ti] = Cp₂TiCl₂; n = 1, Q = TMS: R = Bn (**k**), Hex (**l**); n = 2: Q = OBn, R = Hex (**a**); Q = OTHP, R = Hex (**b**); Q = OTHP, R = Bn (**e**); Q = Morph, R = Bn (**h**); Q = Morph, R = Hex (**i**) n = 3: Q = THP, R = C₁₂H₂₅ (**d**); n = 4: Q = THP, R = Bu (**e**); Q = THP, R = Hex (**f**); n = 6: Q = THP, R = Bu (**g**).

Under the conditions we have chosen, the absence of by-products of homo-cyclomagnesiation of aliphatic 1,2-dienes **6** is due to the reaction in diethyl ether, in which, as previously shown, 2,5-dialkylidenemagnesacyclopentanes are not formed.

A small excess of aliphatic 1,2-diene **6** almost completely blocks the formation of symmetric OMC, the yield of which under the reaction conditions is ~5–8%.

As a result of the studies carried out, a large number of MOC **7** have been obtained, which are of interest as starting reagents for the targeted synthesis of hard-to-reach asymmetric functionally substituted 1Z,5Z-dienes.

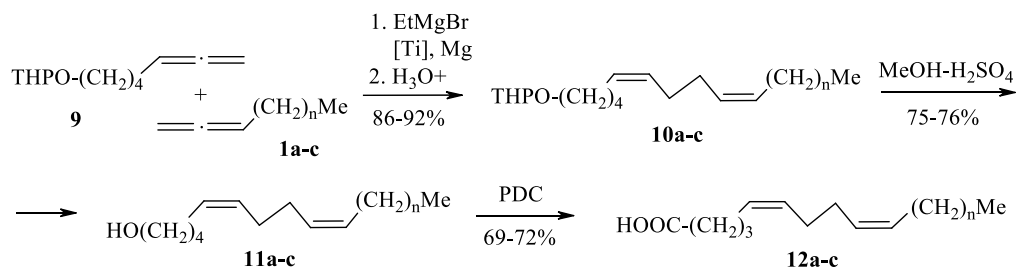
3. Synthesis of natural and synthetic di- and trienoic acids containing bis-methylene separated Z-double bonds

The developed reaction is the basis for the development of a new effective method for the synthesis of 5Z,9Z-dienoic acids, based on the literature data, exhibiting a wide spectrum of biological action, possessing antimalarial, antimicrobial, antitumor and antiviral activity, which, along with the low toxicity of C20–C30 acids, makes this class compounds are very attractive as a basis for the development of modern drugs [1].

We hypothesized that the developed approach to the synthesis of O-containing dienes using the cross-cyclomagnesiation reaction can serve as a basis for the development of a new approach to the synthesis of 5Z,9Z-dienoic acids.

So, in accordance with our proposed scheme, at the first stage, the cross-cyclomagnesiation of terminal aliphatic alleles **1** with tetrahydropyran ether of hepta-5,6-diene-1-ol **9** using EtMgBr catalyzed by Cp₂TiCl₂ is carried out under the conditions developed above, followed by hydrolysis of the reaction mixture leads to O-containing dienes **10**. Removal of the pyranyl protective group and oxidation of the resulting 5Z,9Z-diene alcohols **11** leads to the target 5Z,9Z-diene acids **12** with a yield of 69–72% and a stereoselectivity of 98% (Scheme 4).

Scheme 4



[Ti] = Cp₂TiCl₂; n = 5 (**a**); 8 (**b**); 13 (**c**).

It should be noted that the methods described in the literature for the synthesis of 5Z,9Z-dienoic acids, in particular, 5Z,9Z-hexadecadienoic acid, have multistep (5–20 steps) yields of the target compounds (0.5–15)%.

Using the developed ideology, we have implemented original approaches to the synthesis of natural and synthetic di- and triene acids, as well as studied their antitumor activity using modern methods of flow cytometry and multiplex analysis [20–23].

4. Conclusions

Thus, for the first time, cross-cyclomagnesiation of O-, N-, Si-containing allenes with aliphatic 1,2-dienes of cyclic and acyclic structures was carried out using Grignard reagents under the action of a Cp₂TiCl₂ catalyst to obtain functionally substituted mono- and bicyclic organomagnesium compounds with a wide potential in the synthesis of practically important natural and synthetic functionally substituted 1Z,5Z-dienes of a given structure. An efficient approach to the synthesis of natural and synthetic di- and trienoic acids in high yields with antiviral, antitumor and antifungal activity has been developed.

Experimental section, ¹H and ¹³C NMR spectra and general procedure for all synthesized compounds are presented in previously published articles [10–19].

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Conflicts of Interest: The authors declare no conflict of interest.

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