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Ti-Catalyzed Homo- and Cross-Cyclomagnesiation in the Synthesis of 1Z,5Z-Dienes Containing a Biologically Active 3,4-Dimethoxyphenyl Fragment in Their Structure †

Alexey A. Makarov [1,*], Elina Kh. Makarova [1], Lilya U. Dzhemileva [2] and Usein M. Dzhemilev [2]

[1] Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russia; makarovaelina87@gmail.com (E.K.M.)
[2] N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect 47, Moscow 119991, Russia; lilyadzhemileva@gmail.com (L.U.D.); dzhemilev@anrb.ru (U.M.D.)
* Correspondence: makarovalexin@gmail.com; Tel.: +7-9677468315

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Abstract: 1Z,5Z-diene compounds containing biologically active 3,4-dimethoxyphenyl fragments were synthesized. Molecules containing this moiety have attracted the attention of medicinal chemistry researchers due to their biological activities, including anti-inflammatory and antioxidant, anticancer, fungicidal and neuroprotective activities. The presence of methoxy groups in these structures enhances their biological activity as they participate in various interactions that are critical for their binding affinity and selectivity towards certain biological targets. The intermolecular homocyclomagnesiation reaction of 4-(buta-2,3-dien-1-yl)-1,2-dimethoxybenzene catalyzed by Cp_2TiCl_2 with the help of EtMgBr produced dialkylidenemagnesacyclopentane, the acid hydrolysis of which led to the production of (2Z,6Z)-1,8-bis(3,4-dimethoxyphenyl)octa-2,6-diene with a yield of 74%. Also, Ti-catalyzed cross-intermolecular cyclomagnesiation of 4-(buta-2,3-dien-1-yl)-1,2-dimethoxybenzene with octadeca-1,2-diene produces the corresponding dialkylidenemagnesacyclopentane, acid hydrolysis of which gives the target 1,2-dimethoxy-4-((2Z,6Z)-pentacose-2,6-dien-1-yl)benzene in 68% yield. Cyclomagnesiation reactions were carried out in an inert atmosphere of argon. The resulting products were isolated using column chromatography. The structures of the synthesized compounds were determined using elemental analysis, IR, 1H-NMR, 13C-NMR spectral data and mass spectroscopy. The resulting 1Z,5Z-dienes containing 3,4-dimethoxyphenyl fragments are of great interest as objects for studying their biological activity.

Keywords: 1Z,5Z-diene; biologically active 3,4-dimethoxyphenyl fragments; cyclomagnesiation

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1. Introduction

Cancer is one of the leading causes of death in the world, after cardiovascular diseases. According to the World Health Organization, in 2022, 20 million new cases of cancer and 9.7 million deaths from cancer were detected worldwide.

Treatment with chemotherapeutic drugs does not always lead to the desired result due to multidrug resistance (MDR). The drugs currently used to treat cancer act not only on tumor cells, but also on normal cells, which leads to undesirable side effects. The development of new targeted antitumor drugs is a critical task.

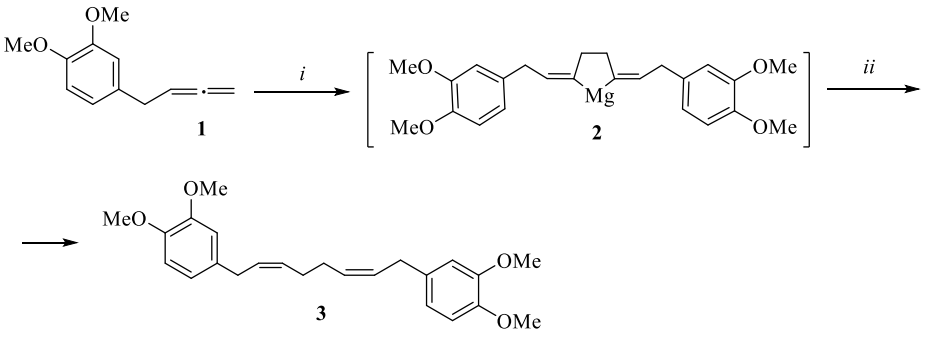
The 3,4-dimethoxyphenyl fragment is contained in the structure of many natural and synthetic biologically active compounds, such as lignans [1–3], tetramethyl derivative of nordihydroguaiaretic acid (NDGA), alkaloids [4], quinolizidines and indolizidines [5], exhibiting anti-HIV [6], antileishmanial activity [7], proangiogenic and proarteriogenic [8], anti-inflammatory [9] and antitumor [10] activities.

In our previous studies, we demonstrated the possibility of synthesizing symmetrical and asymmetrical 1Z,5Z-diene compounds with good yields and high stereoselectivity, on the basis of which natural dienoic acids, lembehynes and acetogenins were obtained [11–19].

2. Results and Discussion

We synthesized new, previously undescribed 1,5-diene compounds containing a biologically active 3,4-dimethoxyphenyl fragment in their structure.

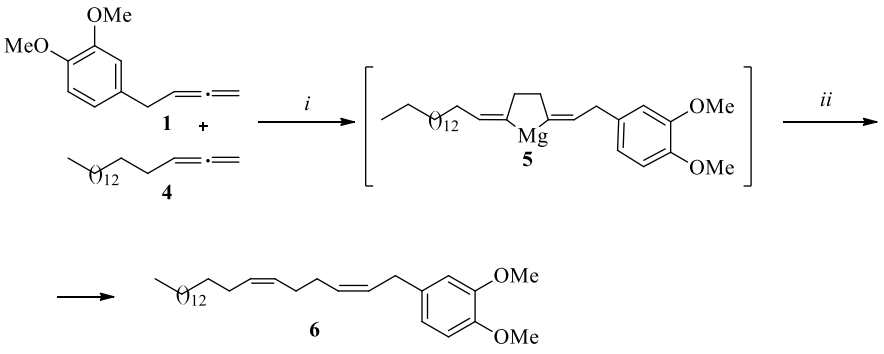
The intermolecular homocyclomagnesiation reaction of 4-(buta-2,3-dien-1-yl)-1,2-dimethoxybenzene **1** (**1**:EtMgBr:Mg:[Ti] = 10:20:24:0.5, Et_2O, 10 h, 20–22 °C) catalyzed by Cp_2TiCl_2 using EtMgBr afforded dialkylidenemagnesacyclopentane **2**, acidic hydrolysis of which led to the formation of (2Z,6Z)-1,8-bis(3,4-dimethoxyphenyl)octa-2,6-diene **3** in 74% yield (Scheme 1).



Reagents and reaction conditions: *i.* Cp_2TiCl_2 (5 mol.%), EtMgBr (2 eq.), Mg (2 eq.), Et_2O, 20-22 °C, 10 h; *ii.* HCl 5%, 74%.

Scheme 1. Synthesis of a (2Z,6Z)-1,8-bis(3,4-dimethoxyphenyl)octa-2,6-diene **3**.

Ti-catalyzed cross-intermolecular cyclomagnesiation of 4-(buta-2,3-dien-1-yl)-1,2-dimethoxybenzene **1** with octadeca-1,2-diene **4** (**1**:**4**: EtMgBr:Mg:[Ti] = 12:10:40:32:0.5, Et_2O, 10 h, 20–22 °C) yields the corresponding dialkylidenemagnesacyclopentane, acidic hydrolysis of which yields the target 1,2-dimethoxy-4-((2Z,6Z)-pentacosa-2,6-dien-1-yl)benzene **6** in 68% yield (Scheme 2).



Reagents and reaction conditions: *i.* Cp_2TiCl_2 (5 мол.%), EtMgBr (2 eq.), Mg (2 eq.), Et_2O, 20-22 °C, 10 h; *ii.* HCl 5%, 68%.

Scheme 2. Synthesis of a 1,2-dimethoxy-4-((2Z,6Z)-pentacosa-2,6-dien-1-yl)benzene.

3. Conclusions

Thus, we have obtained symmetrical and asymmetrical 1Z,5Z-dienes containing in their structure a biologically active 3,4-dimethoxyphenyl fragment, using at the key stage a Ti-catalyzed reaction of homo- and cross-cyclomagnesiation of terminal 1,2-dienes. The synthesized structures are of interest for subsequent study of their biological activity.

4. Experimental Part

Commercially available reagents (Sigma-Aldrich and Acros) were used. Reactions with organomagnesium compounds were carried out under dried argon atmosphere. 1,2-dienes was prepared according to the known procedure. Reaction products were analyzed on a Carlo Erba chromatograph (a Hewlett Packard Ultra-1 glass capillary column, 25 m×0.2 mm, flame ionization detector, operating temperature 50–170 °C, carrier gas helium). TLC was performed on Silufol UV-254 plates. Elemental composition of compounds was determined using a Carlo Erba-1106 instrument. Mass spectra were obtained using a Bruker MALDI-TOF/TOF Autoflex III instrument. 1H and 13C NMR spectra were recorded on a Bruker Avance 400 spectrometer (100.62 MHz for 13C and 400.13 MHz for 1H). Chemical shifts of 1H and 13C nuclei (δ) are given relative to the residual signals of the deuterated solvent (δ 7.28 for protons and 77.2 for carbon nuclei).

(2Z,6Z)-1,8-bis(3,4-dimethoxyphenyl)octa-2,6-diene (3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29–2.31 (m, 4H), 3.39 (d, 1H), 3.87 (s, 6H), 5.59–5.64 (m, 4H), 6.73–6.82 (m, 6H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 148.87, 147.22, 133.49, 129.81, 128.88, 120.03, 111.60, 111.25, 98.72, 55.77, 55.61, 31.89, 29.68. MS (MALDI-TOF), *m*/*z*: 382 $[M]^+$. $C_{24}H_{30}O_4$. Found (%): C 75.36; H 7.91**.** Calcd for $C_{24}H_{30}O_4$ (%): C 75.30; H 7.85.

4-((2Z,6Z)-docosa-2,6-dien-1-yl)-1,2-dimethoxybenzene (6). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, *J* = 6.6 Hz, 3H), 1.28–1.39 (m, 26H), 2.29–2.30 (m, 6H), 3.33–3.39 (m, 2H), 3.87 (s, 12H), 5.54–5.63 (m, 4H), 6.73–6.82 (m, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 148.91, 147.26, 133.61, 130.32, 129.97, 129.39, 128.94, 120.08, 111.64, 111.28, 55.95, 55.78, 33.07, 31.94, 30.73, 29.72, 29.68, 29.67, 29.56, 29.47, 29.38, 29.32, 27.36, 22.71, 14.14. MS (MALDI-TOF), *m*/*z*: 442 $[M]^+$. $C_{30}H_{50}O_2$. Found (%): C 81.29; H 11.29**.** Calcd for $C_{30}H_{50}O_2$ (%): C 81.36; H 11.38.

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