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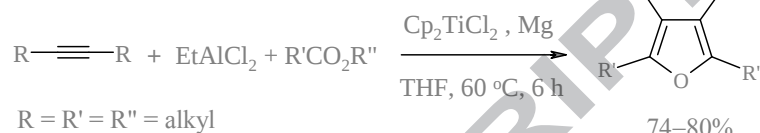
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Graphical Abstract

The efficient one-pot synthesis of tetraalkyl substituted furans from symmetrical acetylenes, EtAlCl₂ and carboxylic esters catalyzed by Cp₂TiCl₂

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Abstract

A new one-pot method for the synthesis of tetraalkyl substituted furans in 74–80% yields has been implemented via the reaction between symmetrical acetylenes, ethylaluminum dichloride, and carboxylic esters in the presence of metallic Mg as an acceptor of halide ions, catalyzed by bis(cyclopentadienyl)titanium dichloride. A mechanism for the reaction is proposed and discussed.

Keywords: Furans; Symmetrical acetylenes; Carboxylic esters; Titanium catalyst; Ethylaluminum dichloride.

The synthetic chemistry of heterocyclic compounds, in particular, the chemistry of furans represents an important section of organic chemistry, which is closely related to the problem of producing biologically active compounds. The furan moiety is present in many natural products and

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important pharmaceuticals.¹⁻⁴ Substituted furans are the key structural units in many biologically active compounds, and they are widely used as intermediates in organic synthesis.^{5,6}

Most synthetic methods for preparing substituted furans described in the literature are multi-step or require expensive reagents.⁷⁻¹² Therefore, the search for convenient and promising methods to synthesize furans is of practical interest for chemists.

We have previously shown that the reaction between α -olefins, alkylalanes, and carboxylic esters in the presence of metallic Mg as an acceptor of halide ions and Cp_2ZrCl_2 as the catalyst affords alkoxy(hydroxy)cyclopropanes.^{13,14} In continuation of our ongoing investigations, we have studied the reaction between symmetrical acetylenes, ethylaluminum dichloride and different carboxylic esters under the action of bis(cyclopentadienyl)zirconium and bis(cyclopentadienyl)titanium catalysts. Hex-3-yne, oct-4-yne, and dec-5-yne as well as carboxylic esters, namely, ethyl acetate, ethyl propionate, and isoamyl butyrate were selected as the substrates for this study.

Our experiments revealed that the model reaction of oct-4-yne with EtAlCl_2 and ethyl acetate mediated by metallic Mg and 10 mol% Cp_2ZrCl_2 (oct-4-yne:[Al]:ester:Mg:[Zr] = 1:4:2:4:0.1, THF, 20 °C, 48 h), after hydrolysis of the reaction mixture, gave 2,5-dimethyl-3,4-dipropylfuran (**1**) (40% yield) together with two by-products, namely, 1,2,3,4-tetrapropylbuta-1,3-diene (**2**) and hexapropylbenzene (**3**) (3:3:1 ratio) in 95% total yield (Scheme 1).¹⁵ Product **2** can be derived from 1-ethyl-2,3,4,5-tetrapropylaluminacyclopentadiene resulting from the catalytic cycloalumination of the starting oct-4-yne.¹⁶

Scheme 1

Using this approach, we have optimized the reaction parameters by varying the catalyst and solvent, temperature and duration of the reaction as well as the ratio of reactants.

Thus, we found that the solvent plays a significant role in this reaction, which occurs only in tetrahydrofuran. The use of other solvents such as hexane, benzene, toluene, diethyl ether, and also methylene dichloride suppressed furan formation. The use of an elevated temperature (60 °C) greatly reduced the reaction time from 48 to 6 hours and the highest yield of furan **1** (48%) was achieved at a molar ratio of [Zr]/oct-4-yne/[Al]/ethyl acetate/Mg = 0.1:1:4:2:4.

However, the most surprising effect was observed, when Cp_2ZrCl_2 was replaced by Cp_2TiCl_2 . With this catalyst, the highest yield of 2,5-dimethyl-3,4-dipropylfuran (**1**) was achieved (78%) under optimum reaction conditions (THF, 60 °C, 6 h, [Ti]/oct-4-yne/[Al]/ester/Mg = 0.1:1:4:2:4).

The developed reaction is of a general nature allowing the formation of furans **4a** and **4b**,¹⁷ from ethyl propionate and isoamyl butyrate.

In an analogous fashion, hex-3-yne and dec-5-yne, reacted with EtAlCl_2 and carboxylic esters in the presence of the Cp_2TiCl_2 as the catalyst giving rise to the corresponding tetraalkyl substituted furans **4c** and **4d**,¹⁸ under similar reaction conditions with good yields (Scheme 2).

Scheme 2

The structures of the prepared furans **1** and **4** were proved by means of spectroscopic methods including one-dimensional (^1H , ^{13}C) and two-dimensional (HSQC, HMBC) NMR, IR, and also by using mass spectrometry.

The published literature data and also our own experimental findings allow us to propose a mechanism for the formation of tetraalkyl substituted furans via the reaction of acetylenes with EtAlCl_2 and carboxylates catalyzed by Cp_2TiCl_2 as follows.

The first stage of the reaction under the optimized reaction conditions involves generation of the metallocene " Cp_2Ti ", which then undergoes a reaction with the initial acetylene yielding the titanacyclopropene **5** (Scheme 3).^{19–24} The reaction between **5** involving both the active Ti–C bonds and two molecules of the appropriate ester leads to ring expansion and formation of dioxatitanacycloheptene **6**.²⁵ Transmetalation of the latter mediated by EtAlCl_2 leads to oxadialuminum species **7** with simultaneous regeneration of Cp_2TiCl_2 .

Scheme 3

Migration of the alkoxide group to the aluminum atom in **7** followed by elimination of aluminum alkoxide $\text{EtAlCl}(\text{OR}'')$ leads to 1,4-diketone **8**, which under the reaction conditions forms furan **1** or **4**. Similar examples of furan formation have been reported.^{26–28}

In conclusion, we have developed a new and efficient procedure for the synthesis of tetraalkyl substituted furans in 74–80% yields through the reaction between symmetrical acetylenes (hex-3-yne, oct-4-yne, dec-5-yne), EtAlCl_2 and carboxylic esters (ethyl acetate, ethyl propionate, isoamyl butyrate) under the action of bis(cyclopentadienyl)titanium dichloride as the catalyst. Currently, systematic investigations on the formation of substituted furans in order to apply this method to other acetylenes and carboxylates are being carried out.

Acknowledgments

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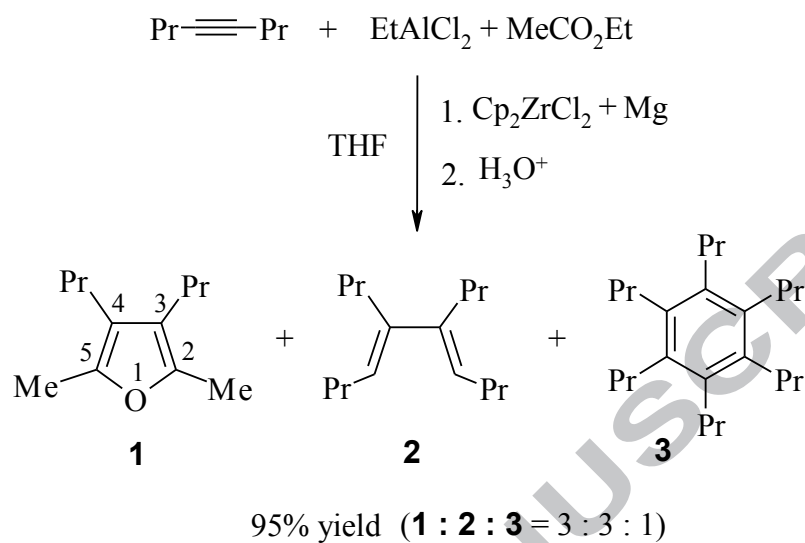
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15. *The reaction of acetylenes with EtAlCl₂ and R'CO₂R'' catalyzed by Cp₂MCl₂ (where M is Zr or Ti).* A 50 mL glass reactor equipped with a magnetic stirrer under a dry argon atmosphere at 0 °C, was charged under stirring with THF (15 mL), EtAlCl₂ (20 mmol), Mg (20 mg, powdered), and catalyst (1.0 mmol). After an 1 h, acetylene (hex-3-yne, oct-4-yne, dec-5-yne) (10 mmol) and the ester (ethyl acetate, *n*-butyl acetate, allyl acetate, isoamyl propionate, or methyl caproate) (20 mmol) were added. The temperature was raised to 60 °C and the mixture was stirred for an additional 6 h. The mixture was cooled under an argon stream to 0 °C. After addition of Et₂O (10–15 mL) the mixture was quenched with a 5% aqueous solution of HCl. The organic layer was separated. The aqueous layer was extracted with Et₂O (2 x 30 mL). The combined organics were washed with NaHCO₃ (until neutral) and dried over MgSO₄. The final products were isolated by vacuum distillation.
2,5-Dimethyl-3,4-dipropylfuran (**1**): Yield 78%. B.p. 73 °C (3 mm Hg). IR (ν, cm⁻¹): 3445, 2959, 2930, 2871, 1714, 1459, 1384, 1252, 1223, 1096, 1071. UV (CHCl₃), λ_{max}, nm (lg ε): 359 and 304. ¹H NMR (400 MHz, CDCl₃): δ 0.93 (t, *J* = 7.2 Hz, 6H, CH₃), 1.47 (sextet, *J* = 7.6 Hz, 4H, CH₂), 2.17 (s, 6H, CH₃), 2.24 (t, *J* = 7.6 Hz, 4H, CH₂). ¹³C NMR (100 MHz, CHCl₃): δ 11.6, 14.0, 23.9, 25.8, 119.2, 144.5. MS, *m/z* 180 (M⁺). Anal. Calcd for C₁₂H₂₀O: C 79.94; H 11.18. Found: C 79.66; H 10.87.
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17. 2,5-Diethyl-3,4-dipropylfuran (**4a**). Yield 74%. B.p. 81 °C (1 mm Hg). ¹H NMR (400 MHz, CDCl₃): δ 0.96 (t, *J* = 7.2 Hz, 6H, CH₃), 1.19 (t, *J* = 7.2 Hz, 6H, CH₃), 1.46 (sextet, *J* = 7.6 Hz, 4H, CH₂), 2.25 (t, *J* = 7.6 Hz, 4H, CH₂), 2.54 (q, *J* = 7.6 Hz, 4H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 13.4, 14.2, 19.6, 24.2, 25.8, 28.3, 118.2, 149.8. MS, *m/z*: 208 (M⁺). Anal. Calcd for C₁₄H₂₄O: C 80.71; H 11.61. Found: C 80.46; H 11.33. Tetrapropylfuran (**4b**). Yield 79%. B.p. 98 °C (1 mm Hg). ¹H NMR (400 MHz, CDCl₃): δ 0.90–0.97 (m, 12H, CH₃), 1.46 (sextet, *J* = 7.6 Hz, 4H, CH₂), 1.62 (sextet, *J* = 7.6 Hz, 4H, CH₂, CH₂), 2.25 (t, *J* = 7.2 Hz, 4H, CH₂), 2.48 (t, *J* = 7.2 Hz, 4H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 14.2, 22.2, 24.2, 25.9, 28.3, 118.9, 148.7. MS, *m/z*: 236 (M⁺). Anal. Calcd for C₁₆H₂₈O: C 81.29; H 11.94. Found: C 81.13; H 11.66.
18. 2,5-Dimethyl-3,4-diethylfuran (**4c**). Yield 74%. B.p. 54 °C (10 mm Hg). ¹H NMR (400 MHz, CDCl₃): δ 1.09 (t, *J* = 7.6 Hz, 6H, CH₃), 2.18 (s, 6H, CH₃), 2.32 (q, *J* = 7.6 Hz, 4H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 11.4, 15.5, 16.8, 120.8, 144.0. MS, *m/z*: 152 (M⁺). Anal. Calcd for C₁₀H₁₆O: C 78.90; H 10.59. Found: C 78.61; H 10.27. 2,5-Dimethyl-3,4-dibutylfuran (**4d**). Yield 80%. B.p. 77 °C (1 mm Hg). ¹H NMR (400 MHz, CDCl₃): δ 0.93 (t, *J* = 7.2 Hz, 6H,

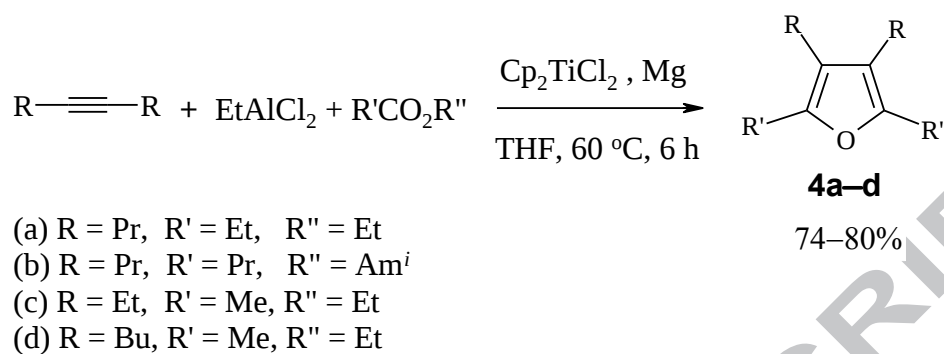
- CH₃), 1.45–1.50 (m, 8H, CH₂), 2.18 (s, 6H, CH₃), 2.26 (t, $J = 7.6$ Hz, 4H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 11.6, 14.0, 22.6, 23.4, 32.9, 119.4, 144.3. MS, m/z : 208 (M⁺). Anal. Calcd for C₁₄H₂₄O: C 80.71; H 11.61. Found: C 80.40; H 11.45.
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Highlights

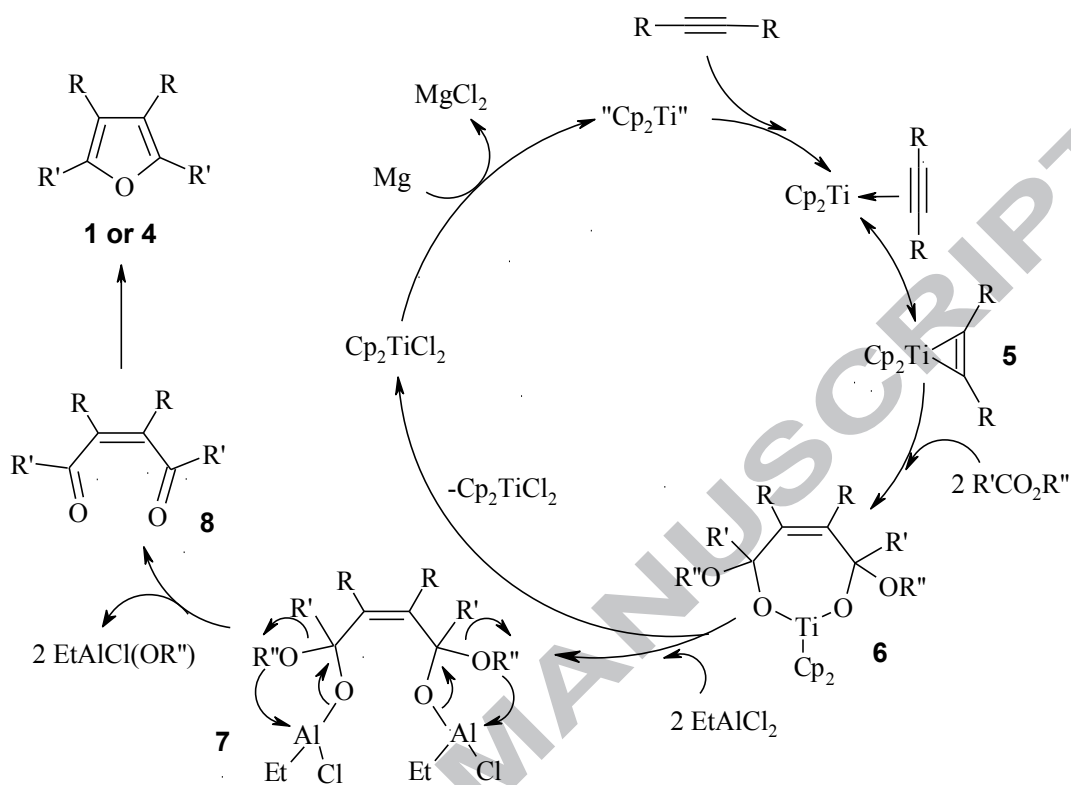
- Cp_2TiCl_2 catalyzes the reaction of symmetrical alkynes with EtAlCl_2 and $\text{R}'\text{CO}_2\text{R}''$.
- Tetraalkyl substituted furans are the final products.
- Good product yields (74–80%) are obtained at 60 °C in tetrahydrofuran.
- Titanacyclopropenes are proposed as key intermediates.



Scheme 1



Scheme 2.



Scheme 3.