chemistry proceedings

Proceedings Paper

Ti(O-*i*Pr)$_4$-EtMgBr-Catalyzed Reaction of Dialkyl-Substituted Alkynes with Et$_2$Zn †

Azat M. Gabdullin, Oleg S. Mozgovoj, Rita N. Kadikova *, Ilfir R. Ramazanov and Usein M. Dzhemilev

Institute of Petrochemistry and Catalysis of Russian Academy of Sciences, 141 Prospekt Oktyabrya, 450075 Ufa, Russia; e-mail1 (A.B.); e-mail2 (C.D.); e-mail3 (E.F.); e-mail4 (H.I.)
* Correspondence: kadikritan@gmail.com; Tel.: +07-917-481-8647

† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: For the first time Ti(O-*i*Pr)$_4$-EtMgBr carbozincation of dialkyl-substituted alkynes with Et$_2$Zn was carried out. It was found that the reaction of 1,2-disubstituted alkynes (5-decyne, 4-octyne, 3-hexyne) with Et$_2$Zn is accompanied by the regioselective formation of stereoisomeric tetra-alkyl-substituted hexa-1,3-diene derivatives in high yield. It was found that 2-zincoethylzincation of dialkyl-substituted alkynes in the presence of catalytic amounts of Ti(O-*i*Pr)$_4$ and EtMgBr does not stop at the stage of ethylzincation of the triple bond, but is accompanied by the involvement of a second alkyne molecule with the formation of two stereoisomeric hexa-1,3-diene derivatives. The effect of the solvent on the carbozincation of dilkyl-substituted alkynes under the conditions of titanium-magnesium catalysis was studied.

Keywords: alkynes; diethylzinc; tetraisopropoxytitanium; ethylmagnesium bromide; carbozincation

Citation: Gabdullin, A.M.; Mozgovoj, O.S.; Kadikova, R.N.; Ramazanov, I.R.; Dzhemilev, U.M. Ti(O-*i*Pr)$_4$-EtMgBr-Catalyzed Reaction of Dialkyl-Substituted Alkynes with Et$_2$Zn. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Julio A. Seijas

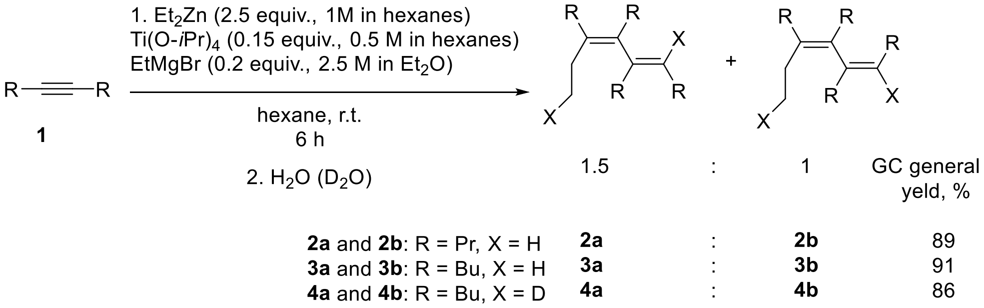
Published: 15 November 2021

1. Introduction

The catalytic reaction of carbozincation of alkynes is an effective tool for the synthesis of multi-substituted olefins of various structures. The high tolerance of organozinc reagents to the presence of functional groups in the structure of the acetylene molecule allowed us for the first time to perform Ti(O-*i*Pr)$_4$-EtMgBr-catalyzed 2-zincoethylzincation of such heterofunctional alkynes as 1-alkynylphosphines, 2-alkynylamines [1] and ethylzincination of 1-alkynyl phosphine sulfides [2]. Negishi was the first to use a catalytic system based on Ti(O-*i*Pr)$_4$ and EtMgBr for carbocyclization of non-functionalized and oxygen-containing enynes [3]. Despite the wide range of currently known catalytic systems for carbozincation of functionally substituted alkynes using dialkyl and halogen-containing zinc derivatives, carbozincation of non-activated alkynes is poorly developed. The literature [3] describes the only example of Cp$_2$ZrCl$_2$-EtMgBr-catalyzed regio- and stereoselective 2-zincoethylzincation of 5-decyne with Et$_2$Zn. In this work we studied for the first time the Ti(O-*i*Pr)$_4$-EtMgBr-catalyzed reaction of dialkyl-substituted alkynes with Et$_2$Zn.

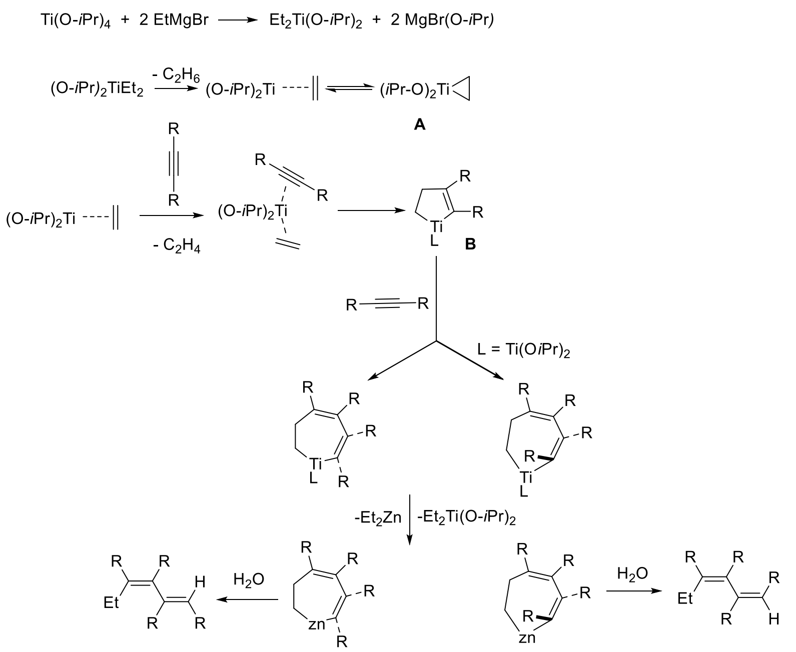
2. Results and Discussion

We found that the reaction of dialkyl-substituted alkynes 1 (5-decyne, 4-octyne, 3-hexyne) with 2.5 equivalents of Et$_2$Zn (1 M in hexanes) in the presence of 15 mol.% Ti(O-*i*Pr)$_4$, (0.3 M in hexanes) and 20 mol.% EtMgBr (2.5 M in Et$_2$O) in hexane solution at room temperature for 6 h after deuterolysis or hydrolysis gives stereoisomeric hexa-1,3-diene derivatives 2,3,4 in a ratio of ~1.5:1 (Scheme 1). The structure of the resulting compounds was established using 1D- and 2D-NMR spectroscopy of the products of their deuterolysis 4 and hydrolysis 2,3. It should be emphasized that hexane—diethyl ether (in an approximate volume ratio of ~30:1) solvent system was used, since the Grignard reagent used in the reaction is a 2.5 M solution in Et_2O. It was found that the reaction proceeds equally effectively in a solution of a mixture of methylene chloride with diethyl ether (hexane is replaced by methylene chloride). According to [4], the reaction of 5-decyne with Et_2Zn in diethyl ether—hexane solvent system in the presence of catalytic amounts of Ti(O-*i*Pr)$_4$, and EtMgBr follows the classical route of the carbozincation reaction and leads to the formation of the product of 2-zincoethylzincation. However, the reaction of 5-decyne with a reaction system consisting of 2.5 equiv. of Et_2Zn, 10 mol.% Ti (O-*i*Pr)$_4$, and 20 mol.% EtMgBr in a solution of a mixture of diethyl ether—hexane (approximate volume ratio 1:1) at 23 °C proceeds slowly. The formation of (Z)-5-ethyl-5-decene with a yield of 64% is observed only after 4 days, provided that an additional portion of Ti(O-*i*Pr)$_4$ in the amount of 10 mol% is added to the reaction system after 24 h.



Scheme 1. Ti (O-*i*Pr)$_4$-EtMgBr-catalyzed reaction of dialkyl-substituted alkynes with Et_2Zn.

We believe that the formation of tetra-alkylhexa-1,3-diene derivatives in the studied reaction occurs as follows. According to Scheme 2, a rapid ligand exchange between titanium (IV) isopropoxide and ethylmagnesium bromide gives an unstable diethyltitanium compound, which is further converted into a titanacyclopropane intermediate (titanium (II)-ethylene complex). Kulinkovich was the first to suggest the generation of titanacyclopropane intermediate upon the interaction of Grignard reagents with titanium (IV) alkoxides [5]. According to Scheme 2, further insertion of the triple bond of alkyne at the Ti-C bond of titanacyclopropane intermediate **A** leads to the formation of titanium-cyclopentene intermediate **B**. As a result of deuterolysis of the carbometallation reaction of 5-decyne, we obtained a mixture of two dideuterated compounds—(5*E*, 7*E*)-6,7-dibutyl-5-(ethyl-2-*d*)dodeca-5,7-diene-8-*d* **4a** and (5*E*, 7*Z*)-6,7-dibutyl-5-ethyldodeca-5,7-diene **4b**. Based on the observed regiochemistry of the reaction, we assumed that the formation of the diene occurs as a result of the insertion of the triple bond of the second acetylene molecule at the Ti-C(sp^2) bond of the titanium cyclopentene intermediate **B**. We believe that the metal-carbon bond of intermediate **B**, where the titanium atom is bonded to the more nucleophilic sp^2-hybridized carbon atom, is more reactive towards the second alkyne molecule. The process of insertion of the second molecule of the acetylene substrate can proceed non-stereoselectively, which leads to the formation of the second stereoisomer—(5*E*, 7*Z*)-6,7-dibutyl-5-ethyldodeca-5,7-diene. Further *trans*-metalation of tetralkyltitanacyclohepta-2,4-diene and subsequent hydrolysis leads to the formation of a mixture of stereoisomers—(5*E*, 7*E*)-6,7-dibutyl-5-ethyldodeca-5,7-diene and (5*E*, 7*Z*)-6,7-dibutyl-5-ethyldodeca-5,7-diene in a 1.5:1 ratio.



Scheme 2. The proposed mechanism of the carbozincation reaction of dialkyl-substituted alkynes.

3. Conclusions

It was found that the Ti(O-*i*Pr)$_4$-EtMgBr-catalyzed reaction of dialkyl-substituted alkynes (5-decyne, 4-octyne, 3-hexyne) with Et$_2$Zn in hexane-diethyl ether or methylene chloride-diethyl ether solution system is accompanied by the quantitative formation of stereoisomeric tetraalkyl-substituted-1,3-diene derivatives in a ratio of ~1.5:1. A mechanism is proposed for the conversion of dialkyl-substituted alkynes into hexa-1,3-dienes under conditions of Ti-Mg-catalyzed organozinc synthesis.

4. Experimental Part

The reagents were obtained from Sigma-Aldrich or Acros. Hexane and dichloromethane were distilled over P_2O_5. Diethyl ether were dried over sodium. Nuclear magnetic resonance spectroscopy was performed on a Brucker Avance 500. The ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C-{^{1}H} NMR spectra at 100 MHz in CDCl$_3$. The chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. Elemental analysis was performed using a Carlo-Erba CHN 1106 elemental analyser. Mass spectra were obtained on a Finnigan 4021 instrument.

(5*E*,7*E*)-6,7-dibutyl-5-ethyldodeca-5,7-diene (**3a**) and (5*E*,7*Z*)-6,7-dibutyl-5-ethyldodeca-5,7-diene (**3b**); Typical Procedure. To a solution of 276 mg of dec-5-yne (2 mmol) and Et$_2$Zn (1 M in hexanes, 5 mL, 5 mmol) in hexane (6 mL) was added Ti(O-*i*Pr)$_4$ (0.5 M in hexanes, 0.6 mL, 0.3 mmol). Ethylmagnesiurn bromide (2.5 M in Et$_2$O, 0.16 mL, 0.4 mmol) was then added and the reaction mixture rapidly turned black. After 18 h at 23 °C, the reaction mixture was diluted with Et$_2$O (5 mL), and 25 wt% KOH solution (3 mL) was added dropwise while the reaction flask was cooled in an ice bath. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous CaCl$_2$. The reaction mixture was filtered through a filter paper and concentrated in vacuo to give crude product as a yellow oil. The residue was distilled through a micro column at 1 mmHg to afford **3a** and **3b** (559 mg, 91%) as a colourless oil. b.p. 159–161 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.86–0.99 (m, 15H), 1.28–1.43 (m, 8H), 1.99–2.08 (m, 18H), 4.99–5.03 (q, *J* = 14 Hz, *J* =7.05 Hz, 18H). ^{13}C NMR (500 MHz, CDCl$_3$): δ = 13.58 (1C), 13.92, 13.89* (1C), 14.04 (1C), 14.54, 14.34* (1C), 14.65, 14,63* (1C), 21.38 (1C), 21.83, 21.77* (1C), 22.08 (1C), 22.68 (1C), 23.26, 23.24* (C(1)), 25.64 (1C), 29.85 (1C), 29.89 (1C), 31.89 (1C), 32.04 (C1), 32.13 (1C), 32.26, 32.22* (1C), 34.89 (1C), 127.44, 127.27* (1C), 136.05, 135.75* (1C), 137.71, 137,48* (1C), 140.06, 139.94 (1C). MS (EI): *m*/*z*, % = 204 (15) [M+], 161 (11), 147 (13), 117 (18), 105 (100). Anal. calcd for $C_{22}H_{42}$, (%): C, 86.19; H, 13.81; Found, %: C, 86.25; H, 13.77. (5*E*,7*E*)-6,7-dibutyl-5-(ethyl-2-d)dodeca-5,7-diene-8-d (**4a**) and (5*E*,7*Z*)-6,7-dibutyl-5-(ethyl-2-d)dodeca-5,7-diene-8-d (**4b**). Using the procedure described above 276 mg of dec-5-yne (2 mmol) and D_2O (instead of H_2O) gave crude product that was distilled through a micro column at 1,2 mmHg to afford **4a** and **4b** (531 mg, 86%) as a colourless oil. b.p. 160–162 °C (1,2 mmHg). ^1H NMR (500MHz, $CDCl_3$): δ = 0.89–0.94 (m, 6H), 0.97–1.02 (m, 2H), 1.31–1.36 (m, 8H), 1.99–2.04 (m, 6H). ^{13}C NMR (500MHz, $CDCl_3$): δ = 12.49–12.95 (1C), 14.06 (2C), 22.44 (1C), 22.87 (1C), 27.26, 27,37* (1C), 29.42, 29.49* (1C), 29.91 (1C), 30.79 (1C), 32.42 (1C), 122.89–123.44 (t, *J* = 22Hz, 1C), 140.96, 141.05* (1C) (GAM-155-2). Anal. calcd for $C_{22}H_{40}D_2$, (%): C, 85.63; Found, %: C, 85.71.

Author Contributions: Conceptualization, R.N.K.; methodology, U.M.D.; software, O.S.M.; validation, A.M.G.; formal analysis, A.M.G.; investigation, A.M.G.; resources, I.R.R.; data curation, R.N.K.; writing—original draft preparation, R.N.K.; writing—review and editing, I.R.; visualization, R.N.K.; supervision, U.M.D.; project administration, R.N.K.; funding acquisition, R.N.K. All authors have read and agreed to the published version of the manuscript.

Funding: The study was supported by a grant from the Russian Foundation for Basic Research (Project no.20-33-90274).

Acknowledgments: The structural studies of all compounds were performed with the use of Collective Usage Centre “Agidel” of Ufa Research of Russian Academy of Science at the Institute Petrochemistry and Catalysis (AAAA-A19-119022290004-8).

References

1. Kadikova, R.N.; Ramazanov, I.R.; Mozgovoi, O.S.; Gabdullin, A.M.; Dzhemilev, U.M. 2-Zincoethylzincation of 2-alkynylamines and 1-alkynylphosphines catalyzed by titanium(IV) isopropoxide and ethylmagnesium bromide. *Synlett* **2019**, *30*, 311–314. https://doi.org/10.1055/s-0037-1612009.
2. Kadikova, R.N.; Gabdullin, A.M.; Mozgovoi, O.S.; Dzhemilev, U.M. $NbCl_5$-Mg reagent system in regio- and stereoselective synthesis of (2*Z*)-alkenylamines and (3*Z*)-alkenylols from substituted 2-alkynylamines and 3-alkynylols. *Molecules* **2021**, *26*, 3722. https://doi.org/10.3390/molecules26123722.
3. Negishi, E.I.; Takahashi, T. *Science of Synthesis. Product Class 11: Organometallic Complexes of Zirconium and Hafnium;* 2003; pp. 681–848.
4. Montchamp, J.-L.; Negishi, E.-I. Carbozincation of enynes catalyzed by titanium(IV) alkoxides and alkylmagnesium derivatives. *J. Am. Chem. Soc*. **1998**, *120*, 5345–5346. https://doi.org/10.1021/ja973841n.
5. Kulinkovich, O.G.; Sviridov, S.V.; Vasilevskii, D.A. Titanium(IV) isopropoxide-catalyzed formation of 1-substituted cyclopropanols in the reaction of ethylmagnesium bromide with methyl alkanecarboxylates. *Synthesis* **1991**, *3*, 234. https://doi.org/10.1055/s-1991-26431.