Brief Communications

Intramolecular alkene—alkyne metathesis and 1,4-*cis*-hydrogenation as a stereocontrolled route to compounds with exocyclic double bonds

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Intramolecular alkene—alkyne metathesis of diethyl (but-3-en-1-yl)(propargyl)malonate affords diethyl 3-vinylcyclohex-3-ene-1,1-dicarboxylate whose conjugated diene system was 1,4-*cis*-hydrogenated in the presence of η^6-(naphthalene)chromium tricarbonyl. The exocyclic double bond of thus formed diethyl 3-ethylidenecyclohexane-1,1-dicarboxylate is strictly (*E*)-configured.

Key words: enynes, dienes, metathesis, 1,4-cis-hydrogenation, stereocontrolled synthesis.

Stereospecific 1,4-*cis*-hydrogenation of conjugated dienes performed over chromium carbonyl complexes (see priority reports[1,2] and reviews[3,4]) and more rarely over special ruthenium catalysts[5—7] is a convenient strategy for formation of olefins with specified configuration of the double bond. The expedience of its employment in target synthesis of complex compounds is largely determined by the availability of the corresponding diene precursors (see review[8]). Since the late 1990s promising procedures for performing alkene—alkyne (enyne) metathesis affording conjugated dienes were developed (see review[9]). Therefore, the sequence of such metathesis and 1,4-*cis*-hydrogenation seems to be a good protocol for stereocontrolled synthesis of olefins restricted only by the accessibility of the required precursors. In the late 1990s, the preparation of 2,3-disubstituted butadienes by intermolecular metathesis of alkynes and ethylene[10,11] in the presence of Grubbs I catalyst was proposed. Using this procedure, we converted 1-acetoxy-5-benzyloxypent-2-yne into the corresponding 2-acetoxymethyl-3-(2-benzyloxyethyl)buta-1,3-diene, which was further 1,4-*cis*-hydrogenated into a *Z*-configured tetrasubstituted olefin,[12] a potent precursor for the pheromones faranal and lasiol. It is noteworthy that only in 2018 other scientists[13] turned their attention to the possibility of employing the enyne metathesis—*cis*-hydrogenation sequence for the alkene stereosynthesis.

At the same time, 1,4-*cis*-hydrogenation of dienes of the 1-(alk-1-en-1-yl)cycloalk-1-ene type can serve as

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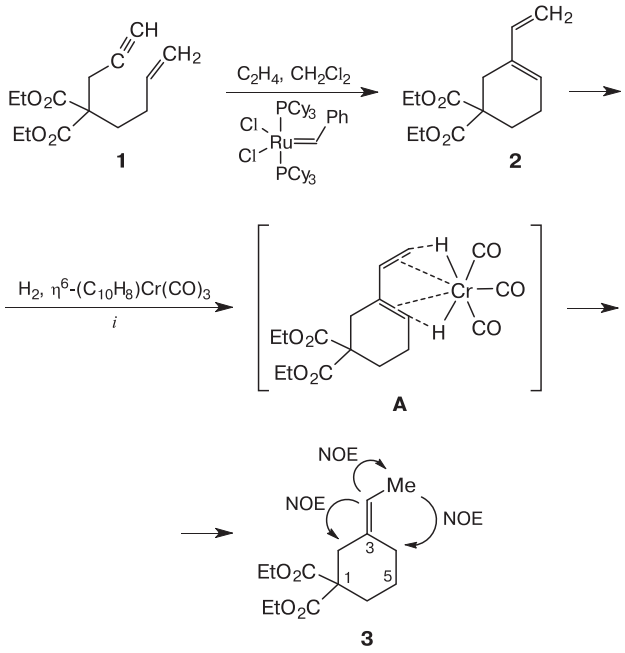
a practically non-competitive strategy to obtain compounds with exocyclic double bonds of required configuration (see review[3] and original works[14,15]). The necessary alkenylcycloalkenes were prepared by complicated multistep synthesis. In 1998, an interesting access to such dienes by intramolecular alkene—alkyne metathesis was reported,[16] the model enyne precursors being rather available. Hence, extension of the enyne metathesis—*cis*-hydrogenation protocol onto compounds bearing both multiple bonds in one molecule seems to be an expedient route to alkylidenecycloalkanes with specified configuration of the double bond.

Herein, with model enyne **1** the possibility of accomplishing such a protocol is demonstrated (Scheme 1). Enyne **1** was subjected to intramolecular metathesis in the presence of Grubbs I catalyst under an ethylene atmosphere following the earlier described procedure[16] (the positive effect of ethylene to promote the reaction was reported[16]). In our hands, the reaction proceeded rather slowly (within 1—4 days); however, the yield of vinylcyclohexene **2** was essentially quantitative. Apparently, the full conversion was due to a higher thermodynamic stability of the cyclization product.

Scheme 1



i. H_2 (40 atm), THF, 45—50 °C, 3 h.

Subsequent 1,4-*cis*-hydrogenation of diene **2** employing η^6-(naphthalene)chromium tricarbonyl at 40 atm and 45-50 °C within 3 h afforded alkene **3** with the exocyclic double bond in quantitative yield (^{1}H NMR data). Its configuration was established based on NOE experiments (see Scheme 1). In particular, irradiation of an olefin proton at δ 5.24 caused response on the singlet of $C(2)H_2$ group at δ 2.59 (7%) and on the doublet of the CH_3 group at δ 1.54 (13%). Irradiation of this methyl group produced no effect on the $C(2)H_2$ group but had a weak (~1%) correlation with the other 4-positioned methylene group of the cycle at δ 2.10 along with that of the olefin proton (~3%). This result is in agreement with a mechanism comprising formation of intermediate **A** (see Scheme 1 and works[1,2]).

Concerning the positive effect of ethylene to promote metathesis,[16] we anticipated to obtain some other more complex dienes from the starting enynes by replacing ethylene for other alkenes. In particular, it seemed intriguing to access dienes with chlorine atoms at the double bonds. In our experiments, metathesis of enyne **1** in the presence of *trans*-1,2-dichloroethylene (10 mmoles) gave quantitatively the same diene **2**. According to the balance, transformation **1**→**2** is an isomerization and there is no demand to incorporate or release any species. Therefore, the role of dichloroethylene in the course of **1**→**2** metathesis and its promotion in view of full conversion of reactant **1** remains unclear.

In conclusion, the sequence of intramolecular alkene—alkyne metathesis and 1,4-*cis*-hydrogenation can serve as a convenient protocol for the stereocontrolled preparation of olefins with exocyclic double bond. We believe that extension of this approach to more complex compounds can simplify schemes for the total synthesis of physiologically valuable compounds (see, *e.g.*, review[3]).

Experimental

NMR spectra were recorded on a Varian Unity-400 spectrometer (working frequencies of 399.95 (^{1}H) and 100.57 MHz (^{13}C)) in $CDCl_3$. High resolution electrospray ionization mass spectrometry was performed with a Bruker micrOTOF II instrument operating on a positive ion mode (capillary voltage was 4500 V), the mass scanning range (*m*/*z*) was 50—3000 Da with internal calibration using Electrospray Calibrant Solution (Fluka). Acetonitrile solutions of the samples were injected *via* a syringe at a flow rate of 3 L min^{-1}. Nitrogen was used as the nebulizer gas (4 L min^{-1}), the interface temperature was 180 °C. High resolution mass spectra were recorded in the Department of Structural Studies of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (Moscow, Russia).[17] η^6-(Naphthalene)chromium tricarbonyl was synthesized as earlier reported.[18] Hydrogenation was carried out in a 250 mL stainless steel Parr autoclave equipped with a mechanical stirrer. Benzylidenebis(tricyclohexylphosphine)dichlororuthenium (Grubbs I catalyst) was purchased from Fluka. Silica gel MATREX LC 60/A/35-70 MY 80/25 85040 (GRACE Davison) was used for column chromatography in amounts of 30—40 mL in volume per 1 g of the material to be separated, the column diameter was selected to provide silica layer height of 15—20 cm.

Diethyl (but-3-en-1-yl)(propargyl)malonate (1). To a solution of diethyl malonate (4.01 g, 25 mmol) and 4-bromobut-1-ene

(3.38 g, 25 mmol) in DMSO (35 mL), freshly powdered K_2CO_3 (13.8 g, 100 mmol) was added and the mixture was stirred at 55 °C for 5 h. An aliquot was treated with water, extracted with ether, dried with $CaCl_2$, evaporated, and dissolved in $CDCl_3$. The ^1H NMR spectrum of thus prepared sample contained signals of diethyl (but-3-en-1-yl)malonate (*cf.* Ref. 19), *ca* 5% of the starting diethyl malonate, and no dialkylated product. Then propargyl bromide (3.27 g, 27.5 mmol) was added. After 4 h stirring at 50 °C, another portion of propargyl bromide (0.5 g, 4.2 mmol) was added and the reaction was continued for 2 h. The mixture was treated with water (100 mL), extracted with diethyl ether (3×20 mL), dried with $CaCl_2$, concentrated, and the residue was co-evaporated with toluene. The residue was subjected to silica gel column chromatography (gradient elution with 3.5→5% EtOAc in pentane) to afford along with mixed fractions (the major impurity was diethyl dipropargylmalonate) 2.5 g (39%) of pure title compound **1**. ^1H NMR (400 MHz, $CDCl_3$), δ: 1.24 (t, 6 H, J = 7.1 Hz); 1.96 (m, 2 H); 1.99 (t, 1 H, J = 2.7 Hz); 2.14 (m, 2 H); 2.82 (d, 2 H, J = 2.7 Hz); 4.19 (q, 4 H, J = 7.1 Hz); 4.96 (d, 1 H, J = 10.1 Hz); 5.04 (d, 1 H, J = 17.2 Hz); 5.78 (m, 1 H). The ^1H NMR spectrum is in accord with that reported previously.[20]

Diethyl 3-vinylcyclohex-3-ene-1,1-dicarboxylate (2). A solution of enyne **1** (0.65 g, 2.6 mmol) in CH_2Cl_2 (12 mL) was stirred with $Cl_2Ru{=}CHPh(PCy_3)_2$ catalyst (50 mg) under an ethylene atmosphere at room temperature for 18 h. An aliquot was evaporated, the residue was dissolved in $CDCl_3$ (0.5 mL), passed through silica (*ca*. 0.1 mL), the silica pad was rinsed with $CDCl_3$ (0.2 mL), and the filtrate was analyzed by ^1H NMR, which revealed 91% conversion. The reaction mixture was left for 3 days, which provided full conversion. In another experiment with 2.5 g of enyne **1**, 46 mL of CH_2Cl_2, and 70 mg of the catalyst, the conversion in 18 h was 14%. Additional 50 mg portion of the catalyst was added, the conversion reached 87% in 1 day and 100% in 4 days in total. The combined reaction mixtures were concentrated, co-evaporated with toluene, and the residue was purified by silica gel column chromatography (gradient elution with 1→3.5% EtOAc in pentane). Overall yield 2.9 g (92%). ^1H NMR (400 MHz, $CDCl_3$), δ: 1.24 (t, 6 H, J = 7.1 Hz); 2.13 (m, 2 H); 2.22 (m, 2 H); 2.68 (br.q, 2 H, J = 1.7 Hz); 4.19 (q, 4 H, J = 7.1 Hz); 4.96 (d, 1 H, J = 11.0 Hz); 5.15 (d, 1 H, J = 17.7 Hz); 5.70 (br.t, 1 H, J = 1.7 Hz); 6.35 (dd, 1 H, J = 11.0 Hz, J = 17.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.0 (CH_3), 22.8 (CH_2), 27.3 (CH_2), 29.3 (CH_2), 53.1 (C), 61.3 (OCH_2), 110.7 ($=CH_2$), 127.7 (=CH of the cycle), 133.1 (=C), 138.8 (=CH vinyl), 171.5 (C=O). The spectrum is in accord with that reported previously.[16]

Diethyl (*E*)-3-ethylidenecyclohexane-1,1-dicarboxylate (3). Diene **2** (2.9 g, 11.5 mmol) was hydrogenated in the presence of η^6-(naphthalene)chromium tricarbonyl (0.2 mg) in THF at 45—50 °C for 3 h under an initial hydrogen pressure of 40 atm, which provided a complete conversion of the starting compound (^1H NMR data). The product was purified by silica gel column chromatography (gradient eluton with 2→3.5% EtOAc in pentane) to afford 2.7 g (93%) of the title compound as a thick colorless oil. ^1H NMR (400 MHz, $CDCl_3$), δ: 1.21 (t, 6 H, $CH_2C\underline{H}_3$, J = 7.1 Hz); 1.54 (d, 3 H, $=CCH_3$, J = 6.7 Hz); 1.62 (m, 2 H, $C(5)H_2$); 2.03 (t, 2 H, $C(6)H_2$, J = 6.1 Hz); 2.10 (t, 2 H, $C(4)H_2$, J = 6.4 Hz); 2.59 (s, 2 H, $C(2)H_2$); 4.08—4.21 (m, 4 H, OCH_2); 5.24 (br.q, =CH, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 12.8 ($=C\underline{C}H_3$), 14.0 (CH_3), 23.5 (CH_2), 26.9 (CH_2), 31.6 (CH_2), 41.0 (CH_2), 56.6 (C), 61.0 (OCH_2), 119.2 (=CH), 134.2 (=C), 171.4 (C=O). HRMS (ESI), *m/z*: found 255.1591 $[M + H]^+$, 277.1410 $[M + Na]^+$; $C_{14}H_{22}O_4$; calculated: [M + H] = = 255.1596, [M + Na] = 277.1416.

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