Organic Chemistry

Ring-closing metathesis of 2,2-diallyl derivatives of pyrrolidine and piperidine: a route to azaspiroheterocyclic structures

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Transformations of 1-benzyl-2,2-di(2-propenyl)pyrrolidine and 1-benzyl-2,2-di(2-propenyl)piperidine into the corresponding 1-azaspiro[4.n]alkenes *via* ring-closing metathesis using accessible homogeneous catalytic systems $WCl_6—H_2SiPh_2$, $WOCl_4—H_2SiPh_2$, and $Ru(=CHPh)(PCy_3)_2Cl_2$ (Cy is cyclohexyl) were performed for the first time.

Key words: ring-closing metathesis of olefins, homogeneous tungsten catalysts, dihydrodiphenylsilane, 1-benzyl-2,2-di(2-propenyl)pyrrolidine, 1-benzyl-2,2-di(2-propenyl)piperidine, azaspirocyclic compounds.

Olefins metathesis that is essentially the redistribution of alkylidene fragments allows one to synthesize unsaturated compounds with a smaller number of stages and by-products compared to the traditional routes of organic chemistry.[1—2] The main types of catalytic metathesis reactions used in synthesis are the following (Scheme 1): (a) cross-metathesis of terminal olefins with ethylene elimination and the formation of new higher olefins or bifunctional compounds, (b) ring-closing metathesis of nonconjugated dienes to form the corresponding cycloolefins, (c) ring-opening metathesis polymerization of cycloolefins, and (d) cross-metathesis of cycloolefins with linear substrates.

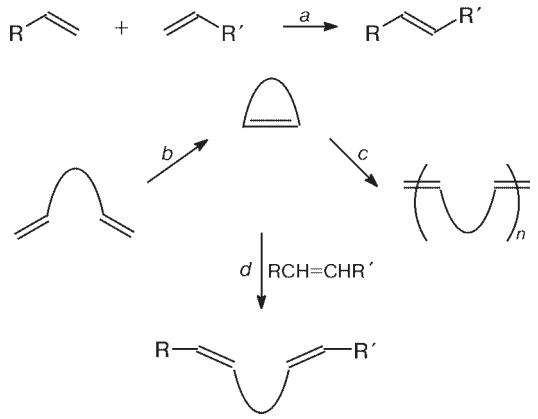
Metathesis was discovered more than 30 years ago but its wide use for preparative purposes became possible rather recently, which is due to a great extent to the creation of highly efficient catalysts, *viz.*, sufficiently stable carbene complexes of molybdenum[3] and ruthenium[4,5] tolerant to functional groups of the substrate. In recent years, the ruthenium carbene complexes have been prepared, which make it possible to perform metathesis in methanol or water[6] and obtain di-, tri-, and even tetrasubstituted carbo- and heterocycloolefins from the corresponding dienes.[7—9] Ring-closing metathesis was used for the preparation of nitrogen-containing heterocyclic compounds[10] and cyclic peptides,[11] diastereoselective synthesis of pyrrolidine derivatives[12] and N,O-containing heterocyclic spirocompounds.[13] In most

† Deceased.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 596—599, April, 2002.

1066-5285/02/5104-645 $27.00

Scheme 1



a. Cross metathesis of acyclic olefins.
b. Ring-closing olefin metathesis.
c. Ring-opening metathesis polymerization.
d. Cross-metathesis of cyclic olefins with acyclic olefins.

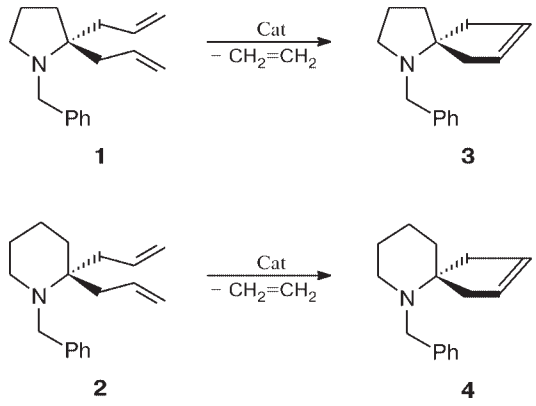
cases, Grabbs catalysts are used for these purposes, and the catalyst concentration usually does not exceed 10 mol.% but very often, especially for the preparation of five- and six-membered nitrogen-containing heterocycles, one has to use from 25 to 50% catalyst.[14] Therefore, the development of more accessible and cheaper catalytic systems in which active metal-carbene intermediates are generated *in situ* during the interaction of the components remains to be an urgent task.

The majority of the known catalytic systems are inactive for the metathesis of olefins containing functional groups. With these aims in view, researchers used only homogeneous and heterogeneous catalytic systems containing alkyl derivatives of tin or lead,[1] whose application is restricted by high toxicity of these compounds. Another type of catalysts for metathesis of functional olefin derivatives is represented by homogeneous systems based on tungsten chlorides in combination with organosilicon compounds (1,3-disilacyclobutane derivatives, dihydrodiarylsilanes). They have earlier been used for the preparation of the functional olefin derivatives in high yield and selectivity.[15–17] In this work, we present the results of application of the latter (catalytic systems) for the transformation of 2,2-diallyl derivatives of pyrrolidine and piperidine into the corresponding spiroheterocyclic compounds, *viz.*, synthetic analogs of natural compounds.

Results and Discussion

We studied the ring-closing metathesis reactions of 1-benzyl-2,2-di(2-propenyl)pyrrolidine (**1**) and 1-benzyl-2,2-di(2-propenyl)piperidine (**2**), which afford the azaspirocyclic compounds: 1-benzyl-1-azaspiro[4,4]non-7-ene (**3**) and 6-benzyl-6-azaspiro[4,5]-dec-2-ene (**4**), respectively.

Scheme 2



Cat is catalyst.

The following catalytic systems were tested:
(1) WCl_6—H_2SiPh_2,
(2) $WOCl_4$—H_2SiPh_2,
(3) WCl_6—$Me_2Si\langle\rangle SiMe_2$ (1,1,3,3-tetramethyl-1,3-disilacyclobutane),
(4) $WOCl_4$—$Me_2Si\langle\rangle SiMe_2$,
(5) $RuCl_3 \cdot (H_2O)_n$—H_2SiPh_2,
(6) $RuCl_2(PPh_3)_3$—H_2SiPh_2,
(7) $RuCl_2(PPh_3)_3$—$Me_2Si\langle\rangle SiMe_2$,
and (8) $Ru(=CHPh)(PCy_3)_2Cl_2$ (Grabbs catalyst).

We established that only compounds bearing benzyl substituents at the nitrogen atom entered into metathesis reactions and only under the effect of catalytic systems containing H_2SiPh_2 as a cocatalyst. The systems containing 1,1,3,3-tetramethyl-1,3-disilacyclobutane did not manifest catalytic activity. This was rather unexpected because these systems exhibited a high activity in the metathesis of nitrogen-containing linear compounds[16] and ring-closing metathesis of esters of unsaturated aliphatic acids.[17] The catalytic systems containing H_2SiPh_2 make it possible to perform the metathesis in moderate yields and with high selectivities, which is presented in Table 1. Under the chosen conditions at a low diene concentration in a solution (0.05 mol L^{-1}), intermolecular metathesis, which affords linear and cyclic oligo- and polymeric products, does not virtually occur (Scheme 3). The selectivity of the reaction decreases at higher concentrations of the substrate.

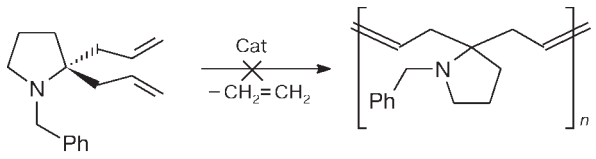
The replacement of the tungsten compounds by the $RuCl_2(PPh_3)_3$ ruthenium complex in the systems with H_2SiPh_2 slightly increased the selectivity of the reaction (see Table 1). The $RuCl_3 \cdot n\,H_2O$ systems in combina-

Table 1. Metathesis of 1-benzyl-2,2-di(2-propenyl)pyrrolidine (**1**) and 1-benzyl-2,2-di(2-propenyl)piperidine (**2**)

Catalytic system	[1]/[M]	[2]/[W]	Yield (%)		Selectivity (%)	
			3	**4**	**3**	**4**
WCl_6—H_2SiPh_2	10	10	17	18	67	69
	20	20	15	14	87	89
	40	40	9	8	85	89
$WOCl_4$—H_2SiPh_2	10	10	19	19	72	76
	20	20	16	15	89	89
	40	40	10	10	90	90
$RuCl_2(PPh_3)_3$—H_2SiPh_2	20		18		93	
$Ru(=CHPh)(PCy_3)_2(Cl)_2$	30		24		95	

Note. Reagents and conditions: toluene, 60 °C, 40 h, $[W]/[H_2SiPh_2] = 1/2$, $[I] = 0.05$ mol L^{-1}.

Scheme 3



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tion with H_2SiPh_2 and 1,1,3,3-tetramethyl-1,3-disilacyclobutane did not exhibit catalytic activity. When $[Ru(=CHPh)(PCy_3)_2(Cl)_2]$ (Grabbs catalyst) was used in amounts close to those applied for the tungsten-containing systems, we observed an increase in the yield of the target product by 5—7%. These reactions were carried out in open systems with ethylene removal. In addition, Cy_3P, $(PhCH_2)_2O$, and $PhCH=CH_2$ were found in the reaction mixture.

As it was revealed, 2,2-di(2-propenyl)pyrrolidine (**5**) without a protective group at the nitrogen atom did not give the metathesis products. In this case, the N-silylation of the pyrrolidine ring occurs (with H_2 evolution), and WCl_6, $WOCl_4$, and $RuCl_2(PPh_3)_3$ are, most likely, the catalysts of this reaction.[18]

Thus, the nitrogen-containing spiroheterocycles were obtained for the first time by the ring-closing metathesis of 2,2-diallyl-1-azacycloalkanes, and rather simple homogeneous systems based on tungsten chloride in combination with dihydrodiphenylsilane were used as the catalysts.

Experimental

Reaction mixtures were analyzed using a Finnigan MAT 95XL gas chromatograph/mass spectrometer (energy of ionizing electrons 70 eV, emission current 100 μA, temperature of the ionization of chamber 200 °C). A capillary column (SE-30; 30 m × 0.25 mm) was used in the chromatograph. The pressure of the carrier gas (helium) at the inlet of the column was 30 kPa, the flow division being 1 : 30. The temperature in the thermostat was risen from 30 to 120 °C with a velocity of 5 deg/min and from 120 to 270 °C with a velocity of 10 deg/min. NMR spectra were recorded in $CDCl_3$ on a Bruker WP-200 spectrometer using Me_4Si as the internal standard.

All procedures were conducted in dry argon or in a vacuum of $1 \cdot 10^{-3}$ Torr.

Toluene was boiled for 12 h above the Na/K melt, distilled, and stored in the Schlenk vessel. Chloroform was distilled, passed through a column packed with silica gel, and stored in the Schlenk vessel; WCl_6 was purified by distillation off *in vacuo* from hydroxychlorides ($WOCl_4$ and WO_2Cl_2); $WOCl_4$ was sublimed *in vacuo*. The tungsten compounds were used as solutions in toluene. The H_2SiPh_2 cocatalyst was prepared according to a known procedure,[19] and a solution of the compound was stored above $LiAlH_4$. 1,1,3,3-Tetramethyl-1,3-disilacyclobutane was prepared by a previously described procedure,[20] distilled above Na, and stored above molecular sieves 5 Å. 2,2-Di(2-propenyl)pyrrolidine (**5**) and 2,2-di(2-propenyl)piperidine were synthesized according to a known procedure[21] and stored in argon above sieves 5 Å.

1-Benzyl-2,2-di(2-propenyl)pyrrolidine (1). Benzyl bromide (5.34 mL, 44 mmol) and K_2CO_3 (12.5 g, 86 mmol) were added to a solution of compound **5** (6.5 g, 43 mmol) in MeOH (50 mL). The resulting mixture was boiled for 5 h, MeOH was evaporated, H_2O (40 mL) and benzene (20 mL) were added, the organic layer was separated, the aqueous layer was extracted with benzene, and the combined organic extract was dried with Na_2CO_3. The yield of product **1** was 9.5 g (92%), b.p. 119—121 °C (0.5 Torr). Found (%): C, 84.33; H, 9.51; N, 5.69. $C_{17}H_{23}N$. Calculated (%): C, 84.59; H, 9.60; N, 5.80. MS (EI, 70 eV), m/z (I_{rel} (%)): 241 (30) $[M^+]$, 226 (72) $[M - CH_3]^+$, 212 (10) $[M - C_2H_5]^+$, 198 (45) $[M - C_3H_7]^+$, 172 (68) $[M - C_3H_5 - C_2H_5]$, 91 (100) $[C_6H_5CH_2]^+$. ^1H NMR, δ: 1.70 (m, 4 H); 2.22 (m, 4 H); 2.60 (t, 2 H); 3.65 (s, 2 H); 5.02 (s, 2 H); 5.11 (s, 2 H). ^{13}C NMR, δ: 21.18 and 32.52 (C—$\underline{C}H_2$—$\underline{C}H_2$); 39.78 (2 $\underline{C}H_2$—CH=CH_2); 50.71 and 52.09 (N—$\underline{C}H_2$ and N—$\underline{C}H_2$Ph); 64.59 (N—C); 116.87 (CH_2—CH=$\underline{C}H_2$); 126.47, 128.08, 128.3 (CH phenylic); 135.75 (CH_2—$\underline{C}H$=CH_2); 140.83 ($C_{quarter}$ phenylic).

1-Benzyl-2,2-di(2-propenyl)piperidine (2) was synthesized using a similar procedure from 2,2-di(2-propenyl)piperidine. The yield of compound **2** was 6.81 g (89%), b.p. 130—132 °C (0.5 Torr). Found (%): C, 84.51; H, 9.83; N, 5.40. $C_{18}H_{25}N$. Calculated (%): C, 84.65; H, 9.87; N, 5.48. MS (EI, 70 eV), m/z (I_{rel} (%)): 255 $[M]^+$ (1), 240 $[M - CH_3]^+$ (2), 214 $[M - C_3H_5]^+$ (100), 91 $[C_6H_5CH_2]^+$ (60). ^1H NMR ($CDCl_3$), δ: 1.4 (m, 6 H); 2.1 (dd, 2 H, J = 14.7 Hz, J = 7.64 Hz); 2.38 (m, 2 H); 2.6 (dd, 2 H, J = 14.7 Hz, J = 6.92 Hz); 3.55 (s, 2 H); 5.05 (m, 4 H); 5.90 (m, 2 H); 7.25 (m, 5 H).

Metathesis of 1-benzyl-2,2-di(2-propenyl)pyrrolidine (1). ***A.*** Compound **1** (0.48 g, 2.0 mmol) was placed in a pre-evacuated and filled with argon 60-cm^3 ampule, and toluene solutions of WCl_6 or $WOCl_4$ (0.1 mmol) and of H_2SiPh_2 (0.2 mmol) were added in an Ar flow. The calculated amount of toluene was added in such a way that the concentration of **1** was 0.05 mol L^{-1}. The solution was frozen to the temperature of

liquid nitrogen and evacuated to 10^{-3} Torr, after which the ampule was sealed. The reactions were conducted for 40 h at 60 °C. The violet (for WCl_6) or dark-red (for $WOCl_4$) solution became dark-green, and a dark precipitate was formed. The ampule was open, toluene was distilled off, and the residue was distilled *in vacuo* and passed through a column packed with SiO_2 to separate the unreacted H_2SiPh_2 catalyst (eluent *n*-hexane, R_f = 0.93). The mixtures were analyzed by the GLC/MS method using toluene as the internal standard and qualitatively by TLC on the Kieselgel 60F plates (Merck). The composition of the mixture after the reaction was 74% compound **1**, 11% isomers **1**, and 15% 1-benzyl-10-azaspiro[4.4]non-7-ene (**3**). MS (EI, 70 eV), *m/z* (I_{rel} (%)): compound **1**, 241 $[M]^+$ (30), 226 $[M - CH_3]^+$ (72), 212 $[M - C_2H_5]^+$ (10), 198 $[M - C_3H_7]^+$ (45), 172 $[M - C_3H_5 - C_2H_5]^+$ (68), 91 $[C_6H_5CH_2]^+$ (100); compound **3**, 213 $[M]^+$ (52), 198 $[M - CH_3]^+$ (25), 184 $[M - C_2H_5]^+$ (50), 172 $[M - C_3H_5]^+$ (86), 91 $[C_6H_5CH_2]^+$ (100), 77 (10).

The metathesis reactions at other [substrate] : [catalyst] ratios and under the effect of the $Ru(Ph_3)_3Cl_2$ system were carried out using analogous procedures. The results are presented in Table 1.

B. Compound **1** (0.48 g, 2.0 mmol) in $CHCl_3$ (35 mL) was placed in a pre-evacuated and filled with argon reactor equipped with a reflux condenser. Then $Ru(=CHPh)(PCy_3)_2(Cl)_2$ (0.0543 g, 0.066 mmol) dissolved in $CHCl_3$ (5 mL) was added in an argon flow. The concentration of **1** was 0.05 mol L^{-1}. The reactions were conducted for 7 h at the temperature of chloroform boiling. Samples were taken each hour and analyzed by the GLC/MS method using toluene as the internal standard) and qualitatively using TLC on the Kieselgel 60F plates (Merck). The composition of the mixture after the reaction was 49% compound **1**, 24% compound **3**, 13% PCy_3, 10% $(PhCH_2)_2O$, and 4% $PhCH{=}CH_2$.

Metathesis of 1-benzyl-2,2-di(2-propenyl)piperidine (2) was carried out using a procedure described above. Compound **2** (0.51 g, 2.0 mmol) was placed in a 60-cm^3 ampule. A toluene solution of WCl_6 or $WOCl_4$ (0.1 mmol) and a solution of H_2SiPh_2 (0.2 mmol) were added. The calculated amount of toluene was added in such a way that the concentration of **2** was 0.05 mol L^{-1}. The mixture was frozen to the temperature of liquid nitrogen, and the ampule was evacuated to 10^{-3} Torr and sealed. The reactions were carried out for 40 h and at 60 °C. The violet (for WCl_6) or dark-red (for $WOCl_4$) solution became dark-gray, and then a dark precipitate was formed. The ampule was open, toluene was distilled off, and the residue was distilled *in vacuo*. The composition of the reaction mixture was 76% compound **2**, 10% isomers **2**, 14% 6-benzyl-6-azaspiro[4.5]dec-2-ene (**4**). MS (EI, 70 eV), *m/z* (I_{rel} (%)): compound **2**, 255 $[M]^+$ (2), 240 $[M - CH_3]^+$ (3), 214 $[M - C_3H_5]^+$(100), 91 $[C_6H_5CH_2]^+$ (60); compound **4**, 227 $[M]^+$ (20), 212 $[M - CH_3]^+$ (19), 198 $[M - C_2H_5]^+$ (38), 186 $[M - C_3H_5]^+$ (19), 172 $[M - C_4H_7]^+$ (10), 136 $[M - C_6H_5CH_2]^+$ (16), 122 $[M - C_6H_5CH_2CH_2]^+$ (37), 91 $[C_6H_5CH_2]^+$ (100), 82 (40).

The reactions in the presence of the WCl_6 (or $WOCl_4$)—1,1,3,3-tetramethyl-1,3-disilacyclobutane catalytic systems were carried out using the same procedure. The metathesis products were not observed.

The reactions of pyrrolidine **5** were carried out according to procedures described for compounds **1** and **2**, and no metathesis products were observed. Gas evolution was observed at the ratio [**5**] : $[H_2SiPPh_2]$: [W or Ru] = 2 : 2 : 1 and 20 °C.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32024) and the Program for State Support of Leading Scientific Schools (Grant 00-15-97378).

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Received August 8, 2001;
in revised form February 11, 2002