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Homogeneous isomerization of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine by ruthenium complexes *

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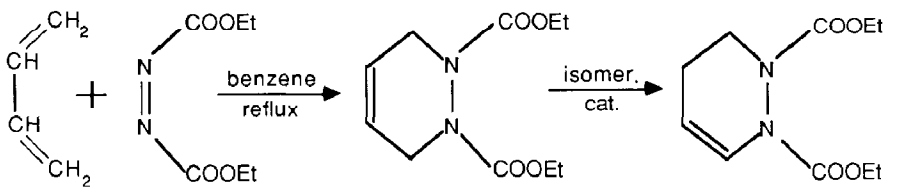
Abstract

N-protected 1,2,3,4-tetrahydropirydazines are readily obtained from the corresponding 1,2,3,6-tetrahydro-derivatives by double bond migration induced by ruthenium complexes. Almost quantitative conversions and complete chemioselectivities are achieved using $RuCl_2(PPh_3)_4$ as catalyst precursor at 100 °C in a pressure vessel. In the same conditions the cluster complex $H_4Ru_4(CO)_{12}$ shows lower activity, while $HRh(PPh_3)_4$ gives unsatisfactory results.

Introduction

As part of a synthesis project involving catalytic asymmetric hydroformylation of heterocyclic substrates containing two nitrogen atoms, we needed a substantial amount of *N*-protected 1,2,3,4-tetrahydropyridazines. Since compounds of this type had not yet been described in the literature, we thought that the isomerization of *N*-protected 1,2,3,6-tetrahydropyridazines would be the most convenient route for obtaining them. The Diels–Alder cycloaddition of 1,3-butadiene to diethyl azodicarboxylate [2] readily afforded in fact, under very mild conditions, quantitative yields of **1**:



1 **2**

* For preliminary results see ref. 1.

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On the other hand, double bond migration catalyzed by soluble transition metal compounds has found useful application in the preparation of various enamides in recent years [3,4]. At present a general catalyst is not available and therefore it is necessary to carefully investigate each reaction in order to find the most suitable catalyst, temperature, solvent and reaction time. Complexes of Fe^0, Rh^I or Ru^{II}, however, resulted to be the most efficient catalysts for effecting the isomerization of allylamide derivatives to enamide derivatives, but only few examples of isomerization of cyclic substrates of this type have been reported [3].

In this paper we wish to describe the results obtained in the conversion of **1** into **2** using some soluble ruthenium complexes as catalytic precursors.

Results and discussion

The double bond shift on **1** was best effected by heating the substrate in a pressure reactor with a catalytic amount ($\simeq 3.2\%$ mol) of the transition metal complex at 100 °C under nitrogen. The reaction product is readily recovered by extraction of the crude with n-hexane and successive fractional distillation (see Experimental). Neither isomerization nor secondary reactions occur in the absence of a catalyst precursor.

The first attempts to isomerize **1** to **2** were carried out using the Rh^I complex $HRh(PPh_3)_4$ that showed to be a powerful catalyst for the conversion of cyclic unsaturated amides to the corresponding enamides [3]. This complex, however, gave in the best case only 32.5% conversion at 100 °C after 72 h though with complete chemioselectivity (Table 1). Thus we turned to ruthenium derivatives which have been successfully employed in the isomerization of various olefins [5–7].

The most active and selective catalyst was the ruthenium complex $RuCl_2(PPh_3)_4$: the isomerization process afforded to 93% conversion after 8 h at 100 °C. Much longer reaction times (72 h) were required to achieve the same conversion with the cluster ruthenium hydride $H_4Ru_4(CO)_{12}$.

As a matter of fact, $RuCl_2(PPh_3)_4$ and $H_4Ru_4(CO)_{12}$ after 2 h gave 77.8 and 12.8% conversion, respectively. In the presence of $H_4Ru_4(CO)_{12}$ an enhancement of the temperature up to 120 °C improved the conversion (95.7% in 40 h), but at the

Table 1

Isomerization of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine to 1,2-dicarbethoxy-1,2,3,4-tetrahydropyridazine (Substrate 8.76 mmol; catalyst precursor 0.27 mmol of metal; T 100 °C; $p(N_2)$ 1 atm)

Catalyst precursor	Reaction time (h)	Conversion (%)
$HRh(PPh_3)_4$	72	32.5
$H_4Ru_4(CO)_{12}$	2	12.8
$H_4Ru_4(CO)_{12}$	72	90.0
$H_4Ru_4(CO)_8(PBu_3)_4$	72	5.4
$Ru(CO)_2(CH_3COO)_2(PBu_3)_2$	72	26.8 [a]
$Ru_2(CO)_4(CH_3COO)_2(PBu_3)_2$	72	3.0
$RuCl_2(PPh_3)_3$	2	70.2
$RuCl_2(PPh_3)_4$	2	77.8
$RuCl_2(PPh_3)_4$	8	93.2
$RuCl_2(PPh_3)_4$ [b]	2	3.1

[a] 0.7% of monocarbethoxylated compound is formed. [b] Ethyl alcohol (2.7 mmol) was added.

expence of the chemioselectivity. At the end of the reaction, in fact, a monocarbethoxylated product (11.6%), identified by GLC mass spectrometry, was recovered besides the expected olefin **2** (88.4%) in the liquid phase, while carbon dioxide and ethylene were detected in the reaction gases.

Substitution of four CO ligands of $H_4Ru_4(CO)_{12}$ with tri-n-butylphosphine caused an almost total loss of the catalytic activity (5.4% conv. in 72 h). Other ruthenium phosphine containing catalytic precursors such as carbonyl carboxylato complexes $Ru(CO)_2(CH_3COO)_2(PBu_3)_2$ and $Ru_2(CO)_4(CH_3COO)_2(PBu_3)_2$ showed a poor catalytic activity (26.8 and 3.0% conv. in 72 h, respectively). Using the mononuclear carboxylato complex, 0.7% of monocarbethoxylated compound was also found.

The results obtained in the isomerization experiments accomplished with $RuCl_2(PPh_3)_4$ and $RuCl_2(PPh_3)_3$ were very close (77.8 vs. 70.2% conversion in 2 h, respectively). These data could be reasonably explained assuming that both catalytic precursors give rise, after triphenylphosphine ligands dissociation, to a common catalytically active intermediate. As a matter of fact, the IR spectra (KBr pellets) of the ruthenium complexes recovered from the reaction mixtures were almost identical. These complexes exhibit an absorption at 1712 cm^{-1} (s) associated to the COOEt groups bound to the nitrogen atoms in addition to a band at 1092 cm^{-1} (s) characteristic of a coordinated triphenylphosphine [8]. Broad bands at 1972 (sh) and 1956 (m) cm^{-1} attributable to coordinated carbon monoxide are also present. Lyons [8] and James and co-workers [9] reported that the catalytically active species for the isomerization of hydrocarbon olefins carried out in the presence of $RuCl_2(PPh_3)_3$ was a carbonyl complex of the type $RuCl_2(CO)(PPh_3)_2$, able to coordinate easily a molecule of the substrate or the solvent. The CO ligand present in the complexes was reported to arise from traces of peroxides present as by-products in the starting olefin [8,9] or from hydroperoxides and other oxygenated promoters [10]. In our case the carbethoxy groups of the olefins could be the source of carbon monoxide.

Attempts to isolate the ruthenium complexes present at the end of the reaction in a pure form failed; however, it was found that at least two species, one of which greatly predominant, were present in the reaction crude.

The ^1H NMR spectrum of this mixture revealed the presence of COOEt and phenyls groups and excluded that of hydride hydrogen and of CH_2 and CH of the olefinic structure. The presence of triphenylphosphine ligands was confirmed by the room temperature ^{31}P NMR spectrum which showed a singlet at 29.74 ppm. The ^{13}C NMR spectrum confirmed the presence of COOEt, CO and PPh_3 groups and the absence of signals due to other carbon atoms. The presence of the chloro ligand was evidentiated by the prompt precipitation of AgCl when treating the recovered ruthenium containing species with $AgBF_4$. The above preliminary data and elemental analysis suggest a formulation of the type $RuCl_2(CO)(PPh_3)_2(NCOOEt)_2$ for the more abundant species. However further work is necessary to gain a deeper insight on the structure of these species and on the mechanistic aspects of their formation.

In our case it is conceivable that the catalytically active intermediate is not an hydride complex at variance of that postulated for other ruthenium catalyzed isomerization processes [9]. This hypothesis seems to be supported by the dramatic conversion drop (from 77.8 to 3.1% after 2 h) (Table 1) observed when the isomerization reaction is carried out in the presence of a hydrogen donor compound

like ethanol.

Probably the isomerization of olefin **1** involves a 1,3-hydrogen shift via a π-allyl hydride intermediate. Such a mechanism has been proposed for the double bond migration catalyzed by some ruthenium carbonyl complexes [7].

Both the catalytic residues deriving from the isomerization reactions carried out with $H_4Ru_4(CO)_{12}$ and $RuCl_2(PPh_3)_4$ may be reused for further isomerizations. Only a little decrease of activity was observed working in the presence of the second complex.

Conclusions

The results obtained in the preparation of the tetrahydropyridazine **2** through $RuCl_2(PPh_3)_4$ or $RuCl_2(PPh_3)_3$ catalyzed isomerization of **1** under homogeneous conditions show that this process is a valuable synthetic tool to produce substantial amounts of such heterocyclic compounds. In fact, it is possible to obtain olefin **2** with very high yields at 100 °C after 8 h (substrate/catalytic precursor molar ratio = 32); moreover, the reaction can be carried out up to 100% yield as the chemioselectivity is not affected by prolonged reaction times.

This catalytic process was performed in a pressure vessel under nitrogen atmosphere since attempts to carry out it in a flask gave unsatisfactory results (6.0 and 15.1% conversion in 2 and 48 h, respectively) indicating that the isomerization performed with $RuCl_2(PPh_3)_4$ is strongly light sensitive. In fact experiments carried out in the dark or in the light after 2 h gave 73.0 and 6.0% conversion, respectively. In the latter case extensive decomposition of the catalytic system was noticed.

Works are in progress to isolate the species present in the reaction crude in order to test their role in the catalytic cycle.

Experimental

GLC analyses were performed on a Perkin–Elmer Sigma 1 system; IR spectra were recorded on a Perkin–Elmer 580 B Data system; GLC mass spectra were recorded with a HP 5970 A spectrometer; NMR spectra were recorded with a Varian VXR 300 spectrometer operating at 299.9, 121.4 and 75.4 MHz for ^1H, ^{31}P and ^{13}C NMR, respectively. ^1H and ^{13}C were referred to internal TMS, whereas for ^{31}P NMR, external H_3PO_4 was used.

All boiling points are uncorrected.

Materials

1,2-Dicarbethoxy-1,2,3,6-tetrahydropyridazine (**1**) was prepared following a reported procedure [2] slightly modified by us. 1,3-Butadiene was bubbled in anhydrous benzene (300 ml) containing 25 g (1.45 mol) of diethyl azodicarboxylate until the yellow-orange solution decolorized (24 h). The excess of butadiene and the solvent were removed by distillation and the residue was distilled in vacuo. The expected olefin was quantitatively recovered at 120 °C/1 mm Hg.

^1H NMR and IR spectra were identical to those previously described [11].

$^{13}C\{^1H\}$ NMR (C_6D_6 solution): 14.40 (s, 2C, CH_3CH_2); 44.07 (s, 2C, CH_2CH=); 62.14 (s, 2C, CH_2CH_3); 124.04 (s, 2C, CH=CH) and 155.42 (s, 2C, $COOC_2H_5$) ppm.

GLC-mass spectrum showed peaks at *m/e*: 228 $(M)^+$, 183 $(M - OC_2H_5)^+$, 156 $(M - CO_2 - C_2H_4)^+$, 155 $(M - COOC_2H_5)^+$, 128 $(156 - C_2H_4)^+$, 111 $(128 - OH)^+$, 83 $(156 - COOC_2H_5)^+$, 56 $(C_2H_4N_2)^+$.

Catalyst precursors

$HRh(PPh_3)_4$ [12], $H_4Ru_4(CO)_{12}$ [13], $H_4Ru_4(CO)_8(PBu_3)_4$ [13], $Ru(CO)_2(CH_3COO)_2(PBu_3)_2$ [14], $Ru_2(CO)_4(CH_3COO)_2(PBu_3)_2$ [15], $RuCl_2(PPh_3)_3$ [16] and $RuCl_2(PPh_3)_4$ [16] were prepared as previously described.

Isomerization and analytical procedures

In the experiments reported in table 1, the catalyst precursor and olefin **1** were placed in a open glass ampoule inside a stainless steel rocking autoclave heated under nitrogen at 100 °C for the desired time. No solvent was used.

The amounts of reactants and reaction conditions are indicated in Table 1.

The conversion was determined by GLC [2 m column packed with Carbowax 20M (8%)/KOH (2%) on Chromosorb W (90%)].

Olefin **2** was identified by its GLC-mass spectrum which showed peaks at *m/e*: 228 $(M)^+$, 156 $(M - CO_2 - C_2H_4)^+$, 128 $(156 - C_2H_4)^+$, 111 $(128 - OH)^+$, 110 $(128 - H_2O)^+$, 97 $(C_4H_5N_2O)^+$, 83 $(156 - COOC_2H_5)^+$, 69 $(C_3H_5N_2)^+$, 56 $(C_2H_4N_2)^+$.

In the crudes of the experiments carried out in the presence of $Ru(CO)_2(CH_3COO)_2(PBu_3)_2$ (Table 1) and $H_4Ru_4(CO)_{12}$ at 120 °C a monocarbethoxylated compound was also identified through its GLC-mass spectrum which showed peaks at *m/e*: 156 $(M)^+$, 128 $(M - C_2H_4)^+$, 111 $(M - OC_2H_5)^+$, 97 $(C_4H_5N_2O)^+$, 84 $(M - CO_2 - C_2H_4)^+$, 83 $(M - COOC_2H_5)^+$, 69 $(C_3H_5N_2)^+$, 56 $(C_2H_4N_2)^+$. The residual gases from these experiments were monitored by IR spectroscopy and GLC analysis. Carbon dioxide (bands at 2349 and 667 cm^{-1} [17]) and ethylene (25 m column Al_2O_3 Plot) were detected.

The experiments performed in the light were carried out under nitrogen in a 10 ml flask containing olefin **1** (2.0 g, 8.76 mmol) and $RuCl_2(PPh_3)_4$ (0.33 g, 0.27 mmol of Ru) rapidly stirred at 100 °C: 6.0% of olefin **2** was formed after 2 h and 15.1% after 48 h.

A similar experiment performed in the dark gave in 2 h 73.0% conversion.

Recovery of olefin 2

Olefin **2** was recovered from an experiment brought to complete conversion (24 h) using $RuCl_2(PPh_3)_4$ as catalyst precursor. The title compound was readily separated from the catalyst by extraction with n-hexane which was then evaporated in vacuo. The residue, distilled under reduced pressure, gave olefin **2** (81 °C/0.02 mm Hg) in almost quantitative yield.

^1H NMR ($CDCl_3$ solution): 1.19 (t, 3H, CH_3), *J* 7.2 Hz; 1.23 (t, 3H, CH_3), *J* 7.2 Hz; 1.89 (dt, 1H, CH=CH-CH_2), *J* 13.8 and 4.3 Hz; 2.27 (m, 1H, CH=CH-CH_2); 3.04 (m, 1H, N-CH_2); 4.16 (q, 2H, COOC$H_2$$CH_3$); 4.19 (q, 2H, COOC$H_2$$CH_3$); 4.27 (m, 1H, N-$CH_2$); 5.00 (broad s, 1H, N-CH=C*H*) and 6.93 (broad s, 1H, N-C*H*=CH) ppm.

The proton assignments are supported by selective proton decoupling.

$^{13}C\{^1H\}$ NMR (C_6D_6 solution): 14.36 (s, 1C, CH_3); 14.44 (s, 1C, CH_3); 21.25 (s, 1C, CH=CH-CH_2); 43.91 (s, 1C, N-CH_2); 62.44 (s, 1C, COOCH_2); 62.49 (s, 1C,

$COOCH_2$); 105.90 (s, 1C, N-CH=*C*H); 125.49 (s, 1C, N-*C*H=CH); 152.28 (s, 1C, =CH-N-*C*OO) and 156.32 (s, 1C, CH_2-N-*C*OO) ppm.

IR (neat): 2983–2846m, 1749sh, 1717s, 1652m, 1410s, 1379s, 1337s, 1326m, 1286s, 1278s, 1246–1116m, 1080s and 1033m cm^{-1}.

n_D^{20}: 1.4804.

Recovery of the catalytic species from the isomerization with $RuCl_2(PPh_3)_4$

Treatments of the reaction mixture with n-hexane caused the separation of the metal containing species as hardly treatable oil. This oil, added of a very little amount of methylene chloride to decrease its viscosity, was repeatedly washed with hot n-hexane to eliminate the olefins. The residue, evaporated in vacuo, afforded a red-brown product.

Fractional crystallizations in order to separate the components of this residue product were not suitable; chromatographic methods caused an extensive decomposition.

The red-brown product was partially characterized by:

^1H NMR ($CDCl_3$ solution): 1.15 (broad t, 6H, $COOCH_2CH_3$); 4.07 (broad q, 4H, $COOCH_2CH_3$) and 7.2–7.7 (m, 30H, phenyls) ppm.

^{13}C {^1H} NMR ($CDCl_3$ solution): 14.5 (broad s, $COOCH_2CH_3$); 62.5 (broad s, $COOCH_2CH_3$); 127–136 (m, phenyls); 156.5 (broad s, $COOCH_2CH_3$) and 204.3 (broad s, CO) ppm.

^{31}P {^1H} NMR ($CDCl_3$ solution): 29.74 (s, PPh_3) ppm.

IR (KBr pellet): 3050m, 2980–2920m, 1972sh, 1956vs, 1712vs, 1548vs, 1480s, 1432vs, 1378m, 1340m, 1092s, 744s, 720m, 694vs, 540m, 520vs and 498sh cm^{-1}.

Elemental analysis: Found: C, 55.72; H, 5.00; N, 3.28. $C_{43}H_{40}Cl_2N_2O_5P_2Ru$ calc: C, 57.48; H, 4.49; N, 3.12%.

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