Atti Accademia Nazionale dei Lincei

Classe Scienze Fisiche Matematiche Naturali

Rendiconti

Giambattista Consiglio, Paul Hälg, Piero Pino

On the Hydrocarbalkoxylation of N-Vinylsuccinimide

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Serie 8, Vol. **68** (1980), n.6, p. 533–538.

Accademia Nazionale dei Lincei

<http://www.bdim.eu/item?id=RLINA_1980_8_68_6_533_0>

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Accademia Nazionale dei Lincei, 1980.

SEZIONE II

(Fisica, chimica, geologia, paleontologia e mineralogia)

Chimica. — *On the Hydrocarbalkoxylation of N-Vinylsuccinimide.* Nota di GIAMBATTISTA CONSIGLIO, PAUL HÄLG e PIERO PINO (*), presentata (**) dal Corrisp. P. PINO.

RIASSUNTO. — Per idrocarbalcossilazione asimmetrica della N-vinilsuccinimmide è stato possibile preparare con buone rese l'alanina. Sebbene l'eccesso enantiomerico raggiunto finora sia basso (~ 16%), la possibilità di un controllo praticamente totale della regioselettività della reazione ed i miglioramenti recentemente ottenuti nelle rese ottiche in altre idrocarbonilazioni rendono promettente lo studio di tali reazioni.

Optically active amino acids are in general obtained via enzymatic reactions or by resolution of racemic mixtures [1]. Recently, asymmetric hydrogenation of dehydro α-aminoacids has been used to prepare optically active aminoacids, particularly (L)-Dopa [2].

As the use of asymmetric catalysis makes it possible to synthesize large amounts of optically active compounds using catalytic amounts of optically active ligands [3], we have investigated the possibility of synthesizing optically active α-amino acids starting with readily available substrates. An interesting possibility is offered by the hydrocarboxylation of enamides or enimides which can be readily prepared from the corresponding amides or imides [4, 5]. There have been very few reports concerning the hydrocarbonylation of similar substrates [6, 7, 8].

We present here some preliminary results on the hydrocarbolkoxylation of N–vinylsuccinimide (Scheme I) catalyzed by palladium complexes.

In the reaction two isomers ((**1**) and (**2**)) are formed, only one of which is chiral. The results we have obtained are summarized in Table I.

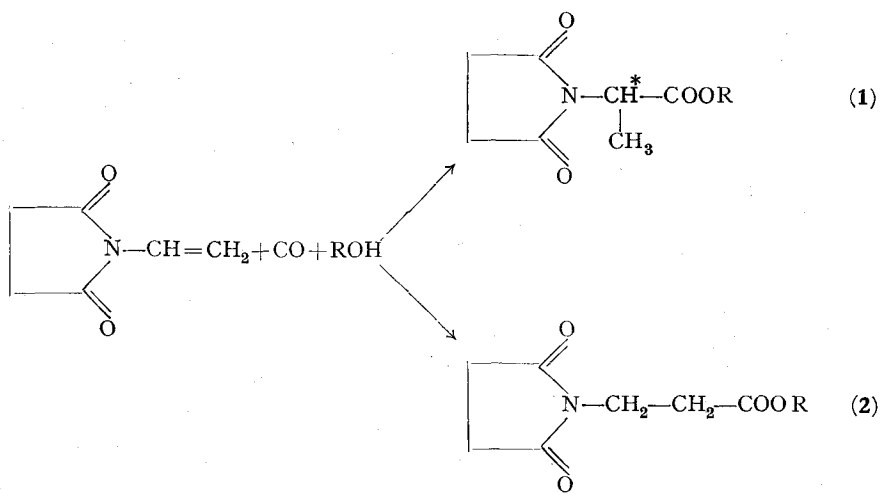
Chemical yields in all experiments are fair to good with the exception of the one hydrocarbalkoxylation where *t*-butanol was used as the hydrogen donor.

The regioselectivity of the reaction can be regulated to a large extent as in the use of olefinic substrates containing aromatic rings such as styrene or α-substituted styrenes [9, 10]. When either triphenylphosphine or neomenthyldiphenylphosphine is used as the ligand (runs 1 and 3 in Table I), preferential carboxylation (up to 97 %) in the α position with respect to the imidic nitrogen takes place, leading to the branched isomer (**1**). On the contrary, the diphosphine DIOP (2,2-dimethyl–4,5–bis (diphenylphosphinomethyl)-1,

(*) Swiss Federal Institute of Technology, Department of Industrial and Engineering Chemistry, 8092 Zurich, Universitätstrasse 6, Switzerland.

(**) Nella seduta del 26 giugno 1980.

SCHEME I



3-dioxolane) induces preferential formation of the straight chain isomer (run 4). The presence of an excess of DIOP shifts regioselectivity further towards the formation of the straight chain isomer (compare runs 4 and 7). The same effect is brought about by a decrease of the carbon monoxide pressure; under 50 atm p_{CO} only small amounts of the branched isomer (2 %) of the product were obtained (run 5). The type of hydrogen donor (methanol vs. ethanol) has practically no effect on regioselectivity when $(Ph_3P)_2PdCl_2$ is used as the catalyst precursor (runs 1 and 2); on the contrary, in the presence of DIOP as the ligand, a small variation of the isomeric composition is observed.

The fact that a practically complete control of the regioselectivity can be achieved in the hydrocarbalkoxylation of N-vinyl-succinimide strongly suggests that regioselectivity mostly depends on the steric factors.

In the presence of chiral ligands, optical active (**1**) is formed. The value of the maximum rotatory power and the relationship between the sign of the optical rotation and the absolute configuration have been determined, as illustrated in Scheme II. The value for the rotation of optically pure N-succinyl-L-alanine ethyl ester must be between + 29.2° and + 32.3°.

When either NMDPP or (R , R)–DIOP is used, products having opposite prevailing absolute configurations of (**2**) are obtained. The latter chiral ligand produces higher optical yields; furthermore the optical yield is increased by increasing the (R , R)–DIOP/$PdCl_2$ molar ratio. This effect is opposite to that found in asymmetric hydrocarbalkoxylation of 2-phenyl-1-propene [11].

Another effect in opposition to the case of 2-phenyl-1-propene hydrocarbalkoxylation is the decrease in optical yield found when a 1 : 2 mixture of

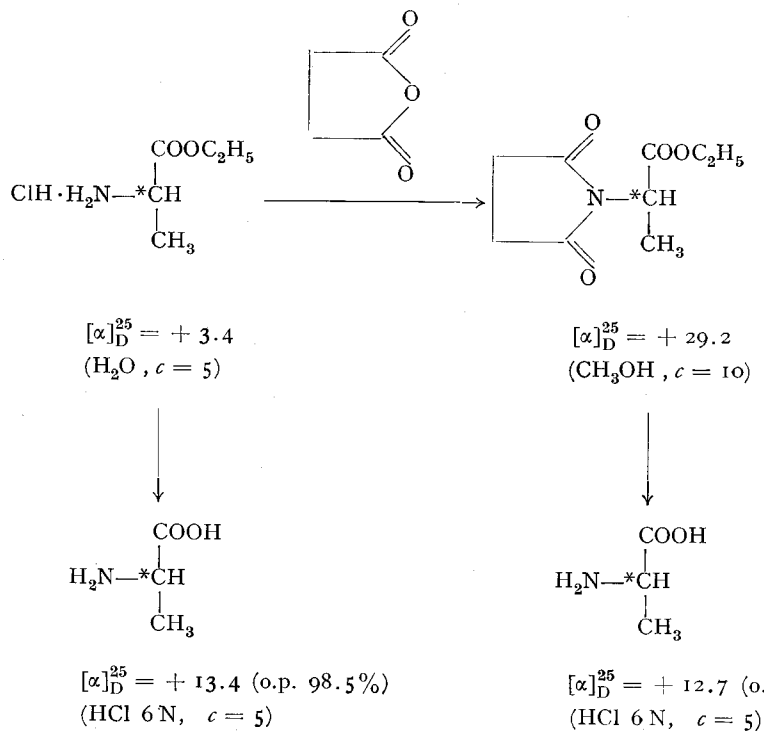
TABLE I.

Hydrocarbalkoxylation of N-Vinylsuccinimide [a]

Run	CATALYST PRECURSOR	$PdCl_2$ to phosphorus molar ratio	ROH R =	Reaction time (hrs)	Yield [b] (%)	(**1**)/(**2**) Molar ratio [c]	CHIRAL ESTER (**1**)	
							$[\alpha]_D^{25}$	Minimum optical purity (%) and absolute configuration
1	$(Ph_3P)_2PdCl_2$	1/2	CH_3	16	83	97/3	—	—
2	$(Ph_3P)_2PdCl_2$	1/2	C_2H_5	9	90	96/4	—	—
3	NMDPP [e]/$PdCl_2$	1/2	C_2H_5	39	84	97/3	—1.07	3.3 (R)
4	[(R , R)–DIOP]$PdCl_2$	1/2	C_2H_5	38	89	22/78	+2.21	6.8 (S)
5 [d]	[(R , R)–DIOP]$PdCl_2$	1/2	C_2H_5	60	72	2/98	n.d.	n.d.
6	[(R , R)–DIOP]$PdCl_2$	1/2	CH_3	9	89	15/85	n.d.	n.d.
7	[(R , R)–DIOP]$PdCl_2$	1/6	C_2H_5	65	87	9/91	+5.00	15.5 (S)
8	[(R , R)–DIOP]$PdCl_2$+ $(Ph_3P)_2PdCl_2$ [f]	1/2	C_2H_5	4.6	95	73/27	+0.19	0.6 (S)

(*a*) Reaction conditions: solvent C_6H_6, 100 °C, p_{CO} (100 °C) 400 at, [Olefin] = 1 mol l^{-1}, [Alcohol] = 2 mol l^{-1} [Catalyst] = 0.01 mol l^{-1}.
(*b*) In moles with respect to the moles of the substrate. (*c*) Determined by gas/chromatography.
(*d*) p_{CO} (100 °C) 50 at. (*e*) NMDPP = (+) neomenthyldiphenylphosphine. (*f*) Molar ratio between both complexes = 1.

SCHEME II.



(R , R)–DIOP and PPh_3 is added to $PdCl_2$ [12]. Both facts might be connected with a strong interaction of the imido group of the substrate with the catalyst.

The prevailing absolute configuration observed using (R , R)–DIOP as the chiral ligand corresponds to the prediction obtained by model for the catalytically active species disclosed in preceding papers [13, 14].

Even though optical yields are low, the results presented here show that asymmetric hydrocarbalkoxylation of imides as a route to α-aminoacids is indeed possible. Therefore we shall continue our investigation on this reaction using different chiral ligands.

Taking into account the difficulties met in synthesizing substituted α-acyl-amino–acrylic acids, which are the necessary precursors to obtain optically active α-amino acids by asymmetric hydrogenation [2], the asymmetric hydrocarboxylation of enamides and enimides, if asymmetric induction can be substantially improved, might represent an interesting alternative synthetic route to the above compounds.

Experimental Part.

G. C. analyses were performed on a Perkin–Elmer F 11 gas chromatograph using a Silicon SF 96 packed column at 210 °C.

Optical rotations were measured at 589 nm and 25 °C on a Perkin–Elmer 141 Polarimeter.

[(R , R)–DIOP] $PdCl_2$ [15], $(Ph_3P)_2PdCl_2$ [16] and N-vinylsuccinimide [4] were prepared according to the methods in the literature.

Hydrocarbalkoxylation of N-Vinylsuccinimide.

Run 7 is described as an example. In a 150 ml stainless steel autoclave containing 1.0 g (R , R)–DIOP (2 mmol) and 119 mg $PdCl_2$ (0.67 mmol), 10.0 g of N-vinylsuccinimide (0.08 mmol) in 30 ml of benzene and 9.5 ml of ethanol (0.16 mmol) was introduced by suction. Carbon monoxide was then introduced up to a pressure of 315 atm and the autoclave was heated to 100 °C, until gas uptake ceased. After cooling, the purple reaction mixture was filtered and analysed by gas chromatography. The products were purified by rectification. The optical rotation of the ester (**2**) measured neat at 589 nm and 25 °C was $\alpha_D^{25} = +6.2°$ ($l = 1$).

N-succinyl-L-alanine ethylester.

8.0 g (0.052 mol) L-alanine ethylester hydrochloride having $[\alpha]_D^{25} = +3.4°$ (H_2O , $c = 5$) and 6.0 g (0.058 mol) triethylamine was dissolved in 120 ml of ethanol. The solution was concentrated to 50 ml and 10.4 g (0.104 mol) of succinic anhydride in 100 ml of ethanol was added. The reaction mixture was stirred at room temperature for 30 minutes. After refluxing for 16 hours the solution was concentrated and the residue was extracted three times with 100 ml of ether. Evaporation of the ether left a yellow oil. High vacuum distillation yielded 2.15 g (21 %) of pure product. $[\alpha]_D^{25} = +29.2°$ ($c = 10$, methanol).

Hydrolysis of N-succinyl-L-alanine ethylester [16].

1.0 g of the above ester was refluxed for 24 hours in 30 ml of 12 N hydrochloric acid. The solution was cooled to room temperature and extracted with ether. The water layer was concentrated and aniline was added until pH 6. By addition of ethanol 400 mg of L-alanine was precipitated. Sublimation (140 °C, 10^{-2} Torr) produced 343 mg (77 %) of pure L-alanine. $[\alpha]_D^{25} = +12.7°$ ($c = 10$, 6 N HCl).

Hydrolysis of L-alanine ethylester hydrochloride [16].

1.0 g of L-alanine ethylester hydrochloride having $[\alpha]_D^{25} = +3.4°$ (H_2O , $c = 5$) was refluxed for 20 hours in 30 ml of 6 N hydrochloric acid. The solution was concentrated and the residue dissolved in 5 ml of water. Aniline was added until pH 6 was reached. By addition of ethanol L-alanine was obtained (520 mg). Sublimation (140 °C, 10^{-2} Torr) produced 478 mg (75 %) of pure L-alanine. $[\alpha]_D^{25} = +13.4$ ($c = 5$, 6 N HCl).

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