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SYNTHESIS OF OPTICALLY ACTIVE AMINO ACIDS DURING ASYMMETRIC PHASE-TRANSFER CATALYSIS

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UDC 541.63:542.941.7:541.65:547.466

Catalytic asymmetric synthesis is a promising and rapidly developing branch of organic chemistry. The greatest advances have been made in the catalytic hydrogenation of prochiral precursors of amino acids over chiral catalysts [1, 2]. There have recently been reports about high optical yields obtained in the Michael condensation [3] and C-alkylation [4] of prochiral analogs when treated with chiral phase-transfer catalysts. Considerable progress has also been made in the achiral catalytic C-alkylation of Schiff bases of amino acids [5, 6].

We previously developed a method for the synthesis of optically active amino acids using Cu^{2+} and Ni^{2+} complexes of their Schiff bases with a recoverable chiral reagent [7-11]. Despite the merits of this method it had all the disadvantages inherent in methods that employ a stoichiometric ratio of reagents.

In the present work we report on the preliminary results of the alkylation of Ni^{2+} complexes of the Schiff base of glycine with N-(2-pyridinecarbonyl)-o-aminobenzophenone (I) and the Schiff base of alanine with N-(2-pyridinecarbonyl)-o-aminobenzaldehyde (II) during asymmetric phase-transfer catalysis

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 631-635, March, 1989. Original article submitted November 16, 1987.

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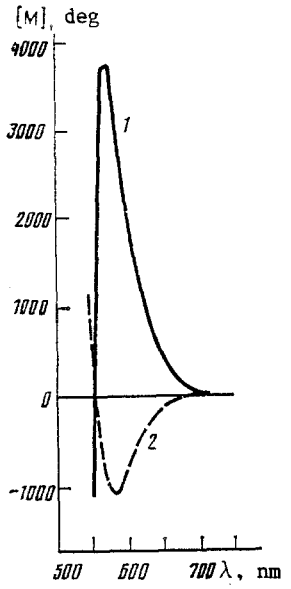
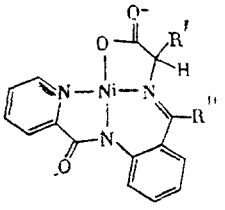


Fig. 1. Optical rotatory dispersion spectra of Ni^{2+} complexes of Schiff bases of N-(2-pyridinecarbonyl)-o-aminobenzophenone with (S)-α-methylphenylalanine (1) and with α-methylphenylalanine as obtained by alkylation (2).

TABLE 1. Data on Alkylation of Complexes

Initial complex	RX	Amino acid	Yield, %	Optical purity,* % (configuration)
(I)	$CH_2=CHCH_2Br$	Allyl-Gly	30	0
(I)	$2\text{-}C_{10}H_7CH_2Br$	2-Naphtyl-Ala	42	6(*S*)
(I)	$C_6H_5CH_2Br$	Phe	57–88	13±1,7(*S*) **
(II)	$C_6H_5CH_2Br$	α-Me-Phe	48	31(*R*) ***

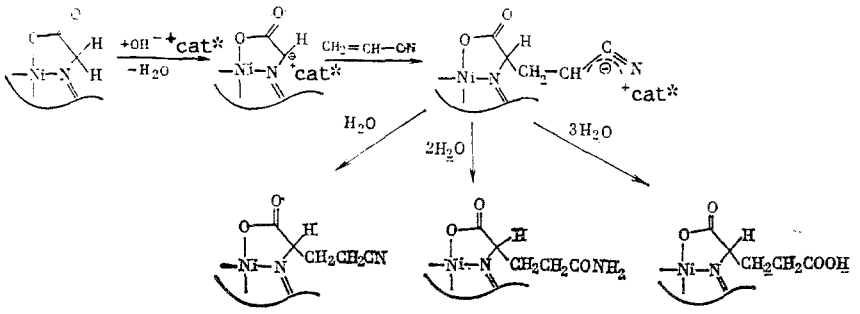
*After decomposition of the complexes the optical purities of the isolated amino acids were determined by GLC [10].
**Average result from 12 experiments.
***Optical purity of the complex determined by polarimetry.



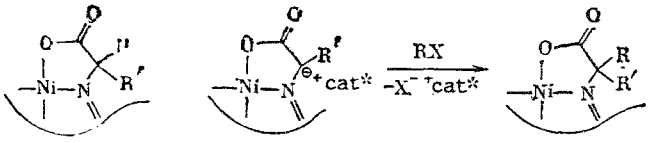
(I): R′ = H, R″ = Ph; (II): R′ = Me, R″ = H.

These complexes have quite a high C–H acidity in the amino acid fragment, they are readily formed and decomposed, and they are also diamagnetic, so that it is possible to use NMR spectroscopy.

We used N-benzylcinchonidinium chloride (NBCC), which was obtained according to the method in [12], as the chiral catalyst. The reaction does not take place in the absence of a catalyst. Under phase-transfer catalytic conditions, complex (I) undergoes a Michael condensation reaction with CH_2=CHCN in accordance with the following scheme:



The reaction gives a mixture of complexes of glutamine, glutamic and γ-CN-α-aminobutyric acids. All the complexes formed contain racemic amino acids. When complexes (I) and (II) were alkylated under phase-transfer catalytic conditions it transpired that this alkylation only occurred with active alkyl halides (allyl bromide, benzyl bromide, β-bromomethylnaphthalene) and did not take place with isobutyl bromide, isopropyl bromide, and n-butyl bromide. The alkylation of the complexes takes place in accordance with the following scheme:



On completion of the reaction the mixture of complexes (initial and alkylated) was separated chromatographically. No products derived by bis-alkylation were detected. For the reaction of (I) with $PhCH_2Br$, the specific rotation of the alkylated complex ($[\alpha]_{578}^{25}$ = +370°) isolated from the reaction mixture after 10, 40, 100, and 215 min (5, 41, 68, and 88% yield, respectively) remains constant. This indicates that there is no racemization of the amino acid fragment of the complexes (optical purity 13%) during reaction. After decomposition of the complexes, the amino acid and initial ligand were separated according to known methods [8-10]. The optical purity of the separated amino acids was determined by GLC. When complex (II) was alkylated with $PhCH_2Br$, a complex containing α-methylphenylalanine was obtained in 48% yield. The absolute configuration and optical purity of the amino acids in the alkylated complex were determined by comparing the optical rotatory dispersion curves (Fig. 1) of the complex obtained by reaction and a complex specially synthesized from optically pure (S)-α-methylphenylalanine obtained in [10]. The optical purity was determined in addition by PMR spectroscopy using the chiral shift reagent $Eu(TFC)_3$.

As the experimental results indicate (Table 1), the optical yield depends on the type of complex used and the nature of the alkyl halide. The reaction conditions also have an effect on the magnitude of the optical yield. The data on the alkylation of complex (I) with benzyl bromide under different conditions are summarized in Table 2.

EXPERIMENTAL

"REAKHIM" amino acids and Kiselgel PF_{254} silica gel (Merck) were used. Preparation of absolute CH_2Cl_2 was carried out according to [13]. PMR and ^{13}C NMR spectra were recorded on a Bruker WP-200 instrument (200 MHz), electronic spectra were recorded on a Specord M-40 instrument, optical rotatory dispersion spectra were recorded on a Jasco J-5 instrument, and GLC was carried out on a Carlo Erba Fractovap chromatograph with a glass capillary column with chiral polyamide phase.

N-(2-Pyridinecarbonyl)-o-aminobenzophenone (1). To a solution of 620 mg (5 mmoles) of picolinic acid in 1 ml of absolute Py with cooling to −70°C and agitation was added 0.35 ml (5 mmoles) of $SOCl_2$ and after 15 min a solution of 1 g (5 mmoles) of o-aminobenzophenone in 0.5 ml of absolute Py. The mixture was agitated for 30 min, poured into 10 ml of a 5% solution of Na_2CO_3, extracted with 3 × 10 ml of $CHCl_3$, and evaporated. The residue was chromatographed on a column of silica gel in $CHCl_3$. The product was recrystallized from ethanol. Yield 1.2 g (4 mmoles), 80%, mp 154-156°C. Found: C 75.27; H 4.42; N 9.56%. $C_{19}H_{14}N_2O_2$. Calculated: C 75.48; H 4.67; N 9.56%. ^{13}C NMR spectrum ($CDCl_3$, δ,

TABLE 2. Effect of Reaction Conditions on Optical Yield in the Alkylation of Complex (I) with Benzyl Bromide

Conditions	Optical yield, %*
KOH (solid); CH_2Cl_2	13
KOH (solid); CH_2Cl_2–C_6H_6 (1:1)	9
50% KOH (aqueous); CH_2Cl_2	13
50% KOH (aqueous); C_6H_6	2

*In all the experiments a complex containing (S)-phenylalanine is obtained. Optical purity determined by GLC [10].

TABLE 3. PMR Spectra of Alkylated Complexes (I) and (II) (relative to HMDS in $CDCl_3$)

Protons	δ, ppm (J, Hz)			
	(I) + allyl bromide	(I) + bromoethyl-naphthalene	(I) + benzyl bromide	(II) + benzyl bromide
α-H	4,8 m	4,25 (X) *	4,33 (X) **	1,55 s (α-CH_3)
$-CH_2-$	2,47 m	2,90; 3,15 (AB*)	2,85; 3,10 (AB**)	2,00; 3,33 (AB) AB system J_{AB} = 11.5
Ar		6,75–9,00		

*X and AB parts of ABX system: J_{AB} = 13; J_{AX} = 5; J_{BX} = 2 Hz.
**X and AB parts of ABX system: J_{AB} = 14; J_{AX} = 5.5; J_{BX} = 3 Hz.

ppm): 198.66 >C=O, 163.33 (–CONH–), 121.47-150.00 (Ar). UV spectrum [C 2.33×10^{-4}, $CHCl_3$, log ε, (λ, nm)]: 4.23 (248 min), 4.29 (265 max), 3.74 (310 min), 3.83 (340 max).

N-(2-Pyridinecarbonyl)-o-aminobenzaldehyde (2). This was obtained according to the method in [14]. Yield 68%, mp 134-135°C (cf. [14], mp 124-126°C).

Complexes (I) and (II). The Ni^{2+} complex of the Schiff base of glycine with (1) was obtained by a method similar to that described in [8, 10]. Yield of complex 95%, decomp. temp. >280°C (decomposes without melting). Found: C 60.27; H 3.61; N 10.19%. $C_{21}H_{15}N_3O_5Ni$. Calculated: C 60.62; H 3.63; N 10.10%.

The Ni^{2+} complex of the Schiff base of alanine with (2) was obtained by the same methods [8, 10], yield 80%, mp 286°C (with decomp.). Found: C 53.83; H 3.57; N 11.85%. $C_{16}H_{13}N_3O_3Ni$. Calculated: C 54.28; H 3.70; N 11.87%.

Alkylation of Complexes (I) and (II). To a mixture of 0.1 mmole of complex (I) or (II) and 4.2×10^{-3} g (0.01 mmole) of NBCC was added 2 ml of absolute CH_2Cl_2, the mixture was cooled to –78°C, 0.5 mmole of alkyl halide was poured in, and 11.2×10^{-3} g (0.2 mmole) of finely ground KOH was added. The apparatus was evacuated, then filled with Ar, the cooling was removed, and agitation was started. The reaction occurred at ~20°C for 1.5-2 h. The mixture was decomposed by addition of 0.5 ml of glacial AcOH and 5 ml of water. The organic layer was separated, the aqueous layer extracted with 3 × 5 ml of $CHCl_3$, and the organic extracts were combined and evaporated. The initial and final complex were separated by preparative TLC on silica gel in the system acetone–chloroform (1:7). The PMR spectral data of the complexes obtained are given in Table 3. Decomposition of the complexes and isolation of the amino acids were carried out according to the methods in [8-10].

Michael Condensation. To a mixture of 4.16×10^{-2} g (0.1 mmole) of complex (I) and 4.2×10^{-3} g (0.01 mmole) of NBCC was added 2 ml of absolute CH_2Cl_2, the mixture was cooled

to −78°C, and 0.01 ml (0.15 mmole) of CH_2=CHCN and 11.2×10^{-3} g (0.2 mmole) of finely ground KOH were added. The apparatus was evacuated, then filled with Ar, the cooling was removed, and agitation was applied for 2 h. Decomposition of the mixture, separation of the complexes, and isolation of the amino acids were carried out in a similar manner to that described above.

CONCLUSIONS

Asymmetric alkylation of the amino acid fragment of Ni^{2+} complexes of the Schiff bases of glycine with N-(2-pyridinecarbonyl)-o-aminobenzophenone and of alanine with N-(2-pyridinecarbonyl)-o-aminobenzaldehyde has been carried out under phase-transfer conditions using N-benzylcinchonidinium chloride as the chiral phase-transfer catalyst.

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