2. The mathematical model was used to show that the yield of the product may be raised by increasing the concentration of $CuCl_2$ and NaOAc with concurrent decrease in the relative amount of the palladium component of this catalyst.

LITERATURE CITED

1. O. G. Yashina and L. I. Vereshchagin, Usp. Khim., 47, 557 (1978).
2. R. Lespieau, Ann. Chim., 27, 178 (1982).
3. L. J. Haynes and E. R. H. Jones, J. Chem. Soc., 503 (1946).
4. E. R. H. Jones and M. C. Whiting, J. Chem. Soc., 1423 (1949).
5. B. A. Trofimov, Yu. M. Skvortsov, A. G. Mal'kina, and A. I. Gritsa, Zh. Org. Khim., 21, 2011 (1985).
6. I. G. Zedginidze, Experiment Planning for the Study of Multicomponent Systems [in Russian], Izd. Nauka, Moscow (1976).
7. N. Draper and H. Smith, Applied Regression Analysis, Wiley (1966).
8. B. I. Istomin, B. L. Finkel'shtein, Yu. I. Sukhorukov, and V. I. Donskikh, Reakts. Sposobn. Org. Soedin., 14, No. 4(52), 492-513 (1977).

A GENERAL METHOD FOR THE ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS BY THE ALKYLATION OF GLYCINE IN CHIRAL Ni(II) COMPLEXES

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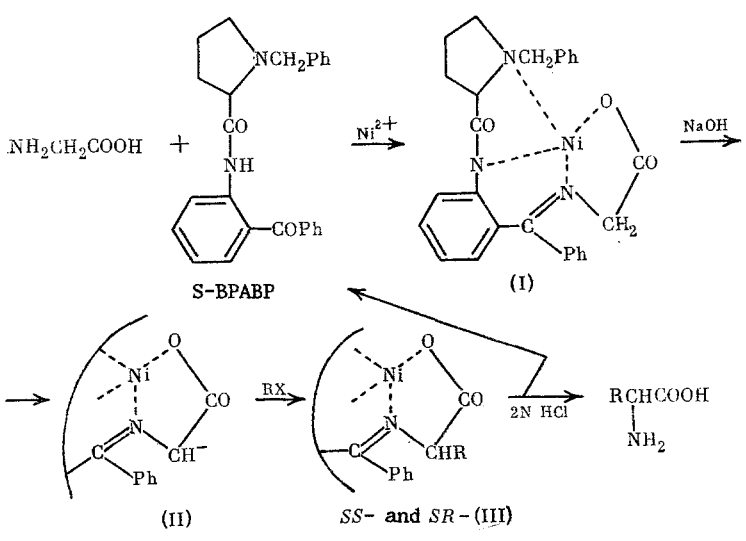
In our previous work [1], we showed that the alkylation of alanine in chiral Ni(II) complexes with subsequent chromatographic separation of the diastereomer mixture provides optically pure S- and R-α-methyl-α-amino acids. In the present work, we report the asymmetric synthesis of a series of natural α-amino acids by the alkylation of Ni(II) complexes of glycine Schiff bases with S-2-N-(N'-benzylpropyl)aminobenzophenone (S-BPABP) using alkyl halides (see Scheme below).

Scheme



Chiral complex (I) obtained by the reaction of glycine, $Ni(NO_3)_2$ and S-BPABP in methanol in the presence of MeONa is deprotonated by solid NaOH in DMF or acetonitrile to form carbanion (II), which reacts with the corresponding alkyl halide to form a mixture of diastereomeric alkylated complexes SS-(III) and SR-(III). Going from acetonitrile to DMF per-

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TABLE 1. Enantiomeric Purity and Chemical Yield of α-Amino Acids Obtained Upon the Alkylation of (I)

RX	Amino acid obtained as a result of alkylation	Enantiomeric purity,[a] %		Chemical yield,[b] %	
		alkylation method			
		1	2	1	2
MeI	Ala	70	84	82	75
$PhCH_2Br$	Phe	92	86 (>99)[c]	83	79
n-BuBr	Nle		>99		77
i-PrBr	Val	92	79	81	73
Ind–CH_2NMe_3I	Trp		95[d]		69
3,4-$(MeO)_2$–C_6H_3–CH_2Cl	3,4-Dimethoxy-Phe	94[d]		77	

[a]Determined by enantiomeric gas-liquid chromatographic analysis [3].
[b]Relative to starting (I).
[c]Value obtained after preliminary separation of the diastereomeric alkylated complexes (III) on silica gel using 5: $CHCl_3$–acetone as eluant.
[d]Determined polarimetrically.

mits a significant increase in the concentration of the reagents and decrease in the reaction time from 2-3 h to 15-30 min due to improved solubility.

Alkylation products (III) are diasteromeric complexes of α-amino acids with a labile α-hydrogen. Thus, the subsequent epimerization of these products proceeds under the reaction conditions to form an equilibrium mixture of diastereomeric complexes, which contains a significant excess of the diastereomer with S-α-amino acid [2-4].

Alkylated complexes (III) decompose readily upon the action of 2 N hydrochloric acid with the formation of α-amino acids and the chiral reagent S-BPABP, which is extracted from the reaction mixture in about 90% yield without loss of optical activity and may be reused.

The optical yield of most of the S-α-amino acids isolated directly after decomposition of the reaction mixture exceeds 90% (see Table 1). The enantiomeric purity may be additionally increased if some amount of the SR-diastereomer of (III) containing the R-α-amino acid is separated chromatographically on silica gel using 5:1 chloroform–acetone as eluant. After decomposition of the pure SS-diastereomer of (III), the S-α-amino acid with enantiomeric purity greater than 99% may be isolated.

EXPERIMENTAL

A sample of MeONa was prepared by the addition of metallic sodium to absolute methanol under argon with cooling. DMF and acetonitrile were purified according to Gordon and Ford [5]. The optical rotation was measured on a Perkin-Elmer 241 polarimeter. Samples of S-BPABP and complex (I) were prepared and described in our previous work [6].

Separation of S-BPABP and α-amino acids from complexes (III). The complexes were decomposed according to a general method. A solution of about 0.2 mmole complex in 5 ml methanol was added dropwise to 10 ml 2 N hydrochloric acid at reflux. The mixture was neutralized by 20% aq. NH_4OH to pH 8-9 and S-BPABP was extracted with chloroform. The reagent yield determined spectrophotometrically relative to absorption at 330 nm was about 90%. The amino acid was separated from the aqueous layer on Dowex-50 (H^+ form) resin. The enantiomeric purity of the amino acids was determined by gas–liquid chromatography [3] or polarimetrically.

Alkylation of (I) by alkyl halide. Two general methods were proposed for the alkylation of (I) by alkyl halides. Method 1. A sample of 10 g (20 mmoles) (I) was dissolved in 12 ml DMF and then, 20 mmoles alkyl halide and 2 g (50 mmoles) finely ground NaOH were added and stirred in an argon stream at about 20°C for 15-30 min. A sample of 200 ml 2% aqueous acetic acid was added to the reaction mixture. The precipitated complex was filtered off, washed on the filter with water and dried in vacuum.

Method 2. A sample of 0.5 g (1 mmole) (I) was dissolved in 20 ml acetonitrile and then 1.5 mmole alkyl halide and 0.1 g (2.5 mmoles) finely ground NaOH were added and stirred in an argon stream at about 20°C for 2-3 h. The alkylation was monitored by thin-layer chromatography on silica gel using 5:1 chloroform–acetone as eluant relative to the disappearance of starting complex (I). At the end of the reaction, the reaction mixture was neutralized by 0.1 N hydrochloric acid. Then, 25 ml water was added and (III) was extracted by chloroform. The extract was evaporated.

Complexes (III) obtained by these methods were decomposed and α-amino acids were isolated as described above. The optical and chemical yields of the α-amino acids are given in Table 1. The optical yield of S-BPABP was >99% according to polarimetric analysis.

CONCLUSION

The asymmetric synthesis of S-Ala, S-Val, S-Trp, S-Phe, S-Nle, and S-3,4-dimethoxy-Phe with optical yields of about 90% is carried out by the alkylation of glycine in Ni(II) complexes of its Schiff base with S-2-N-(N'-benzylpropyl)aminobenzophenone by the action of NaOH in DMF or acetonitrile.

LITERATURE CITED

1. Yu. N. Belokon', N. I. Chernoglazova, K. A. Kochetkov, N. S. Garbalinskaya, and V. M. Belikov, J. Chem. Soc., Chem. Commun., 171 (1985).
2. Yu. N. Belokon', I. E. Zeltser (Zeltzer), V. I. Bakhmutov (Bachmutov), M. B. Saporovskaya, M. G. Ryzhov, A. I. Yanovskii (Yanovsky), Yu. T. Struchkov, and B. M. Belikov, J. Am. Chem. Soc., 105, 2010 (1983).
3. Yu. N. Belokon', N. I. Chernoglazova, K. A. Kochetkov, N. S. Garbalinskaya, M. G. Ryzhov, V. I. Bakhmutov, M. B. Saporovskaya, E. A. Paskonova, V. I. Maleev, S. V. Vitt, and V. M. Belikov, Izv. Akad. Nauk SSSR, Ser. Khim., 803 (1984).
4. Yu. N. Belokon', V. I. Maleev, S. B. Vitt, M. G. Ryzhov, Yu. D. Kondrashov, S. N. Golubev, Yu. P. Vauchskii, A. I. Kazika, M. I. Novikova, P. A. Krasutskii, A. G. Yurchenko, I. L. Dubchak, V. E. Shklover, Yu. T. Struchkov, V. I. Bakhmutov (Bachmutov), and V. M. Belikov, J. Chem. Soc., Dalton Trans., 17 (1985).
5. A. Gordon and R. Ford, Chemist's Companion, Wiley (1973).
6. Yu. N. Belokon', A. G. Bulichev, V. I. Bakhmutov (Bachmutov), S. V. Vitt, Yu. T. Struchkov, A. G. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, and V. M. Belikov, J. Am. Chem. Soc., 107, 4252 (1985).