BIS(PENTALUOROPHENYL) SULFITE – A NEW REAGENT FOR THE SYNTHESIS OF ACTIVATED PENTAFLUOROPHENYL ESTERS OF N-PROTECTED AMINO ACIDS

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Lately pentafluorophenyl (PFP) esters of N-acyl amino acids [1-3] have become increasingly widely used for producing peptide bonds due to their high reactivity, considerably surpassing the reactivity of other activated esters. The principal method for the preparation of the PFP esters of N-protected amino acids involves the condensation of the carboxyl compound being activated with pentafluorophenol in the presence of dicyclohexylcarbodiimide (DCHC). Certain modifications of this method have also been described [4, 5]. It is known that besides its well-known positive qualities, DCHC has several drawbacks, restricting its utilization [6]. An alternative method for the preparation of the PFP esters, based on a transesterification reaction, includes the reaction of an N-protected amino acid with a transacylating (trans-esterifying) reagent. At the present time several reagents of this type are known [7-9], which, however, have not found wide application.

To produce an accessible and effective transesterifying reagent designed for the preparation of PFP esters of N-protected amino acids and peptides, we have carried out a synthesis of bis(pentafluorophenyl) sulfite (I) [9] according to the scheme

$$2C_6F_5OH + SOCl_2 \xrightarrow[-2HCl\cdot Py]{} (C_6F_5O)_2SO \qquad (I)$$

In the IR spectrum of (I) absorption bands characteristic for sulfites are observed. Its structure has also been confirmed by elemental analysis and ^{19}F NMR spectra. Sulfite (I) is well miscible with organic solvents, which are usually used in peptide synthesis; it is thus possible to obtain rapidly, under mild conditions and in good yield, the PFP esters of N-protected derivatives of amino acids

$$Z{-}NH{-}\underset{\displaystyle R}{\underset{|}{C}}HCOOH \xrightarrow{(I),\ B} Z{-}NH{-}\underset{\displaystyle R}{\underset{|}{C}}H{-}COOC_6F_5 + SO_2 + C_6F_5OH$$

(II) (III)

where Z is the N-protecting group of the amino acid or N-protected peptide residue; R is a side-substituent of the amino acid; B is a base (pyridine, N-methylmorpholine, triethylamine, dicyclohexyl amine).

The transesterification was carried out in the medium of an organic solvent (DMF, EtOAc, MeCN, CH_2Cl_2, etc.), the selection of which was determined mainly by the nature of the acid to be activated (II). The best results were obtained in the presence of an organic base; taking as an example the synthesis of the PFP esters of Boc-Ala and Boc-Phe, the possibility was shown of carrying out the transesterification reaction without using the base, but the yield is thereby decreased from 95-100% to 65-70%.

The synthesis of the PFP esters of amino acid derivatives usually does not cause any problems with respect to the occurrence of side-reactions and the isolation of the end product. Because of its good solubility in most organic solvents, pentafluorophenol formed in the course of the reaction is in general removed during the crystallization of the activated ester (III).

Sulfite (I) was also used for the synthesis of PFP esters of trifunctional derivatives of amino acids. It is known [10] that the preparation of activated esters of the Asn and Gln derivatives is usually accompanied by the formation of cyclic imides as byproducts, the yield of which increases with increase in the duration of the reaction or time of residence of the activated derivative in the solution. Using reagent (I), it was possible to obtain chromatographically homogeneous PFP esters of Asn and Gln in yields 76 and 87%, respectively (Table 1,

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Nos. 14, 15). The time of their preparation was 3-5 min.

To evaluate the optical purity of the PFP esters of N-protected amino acids obtained by using reagent (I), we synthesized protected model dipeptides of the Ala-Ala sequence. Enantiomeric analysis data for diastereomeric dipeptides, obtained by the aminolysis of the PFP ester of Boc-Ala and the tert-butyl ester of Ala (in the presence of an organic base: pyridine, N-methylmorpholine, triethylamine), carried out by ion-exchange chromatography, showed that there is no racemization at the stage of formation of the PFP esters. This result is further confirmed by those obtained on measuring values of specific rotation of the optically active amino acid derivatives in comparison with the data given in literature. The use of the Anderson test [11] also showed the absence of racemization.

EXPERIMENTAL

The Boc-, Z-, and Fmoc-amino acids were synthesized by the method in [12, 13], and commercially available derivatives were also used (Reanal, Scientific Industrial Association; Biokhimreactiv, Olaine). Thionyl chloride was purified as described in [14], and pentafluorophenol was obtained from the firm Fluka. The solvents were dehydrated as described in [14]. The UV spectra were run on a Specord UV-VIS spectrophotometer, the IR spectra in the form of a suspension in mineral oil on a Hitachi IRS 260-10 spectrophotometer, and the NMR spectra on a Bruker WR-200 spectrometer. The TLC was carried out on plates with a Silufol and Kieselgel-60 F-254 (Merck) silica gel in the systems benzene–acetone–acetic acid, 80:40:1, ethyl acetate–hexane, 7:3, chloroform–hexane–acetic acid, 8:1:1.

Bis(pentafluorophenyl)sulfite (I). A solution of 2.2 g (27.1 mmoles) of pyridine in 5 ml of ether was added dropwise with stirring to a cold (0°C) solution of 5 g (27.1 mmoles) of C_6F_5OH and 1.6 g (13.6 mmoles) of $SOCl_2$ in 10 ml of the same solvent. The reaction mixture was stirred for 30 min at 0-20°C, the pyridine hydrochloride precipitate was filtered, and washed with ether (3 × 10 ml). The combined filtrate was concentrated in vacuo at 25°C (70-80 mm). Compound (I) was purified by distillation in vacuo, bp 112-113°C (1 mm). Yield, 5 g (89%), n_D^{21} 1.4623. IR spectrum (ν, cm^{-1}): 1510 (arom), 1250-1130 (S=O), 1100 (C–F). UV spectrum (in MeCN), λ_{max} 215, 265 nm. ^{19}F NMR spectrum (CF_3COOH–external standard, δ, ppm): 76.1 d (o-2F), 81.5 t (p-1F), 87.2 t (m-2F). Found: C 34.93; F 45.27; S 7.62%. $C_{12}F_{10}O_3S$. Calculated: C 34.78; F 45.89; S 7.73%. Compound (I) is a yellowish liquid, whose properties do not change on storage in a refrigerator for several months.

Typical Method for the Synthesis of PFP Esters of N-Protected Amino Acids (III). A 10-mmoles portion of reagent (I) was added to a solution of 10 mmoles of the carboxylic component and 10 mmoles of pyridine in 10 ml of an organic solvent. The reaction mixture was stirred for 0.1-1 h at 20°C, the precipitate was filtered and washed with an organic solvent. The combined filtrate was concentrated in vacuo, the residue was diluted with ethyl acetate (50 ml), 3% solution of $NaHCO_3$ (3 × 10 ml) and a saturated solution of NaCl (1 × 10 ml). The organic extract was concentrated in vacuo and the residue was crystallized from a suitable solvent. The yields of the PFP esters are given in Table 1.

CONCLUSIONS

A method was proposed for the preparation of bis(perfluorophenyl) sulfite, an effective new reagent for the synthesis of pentafluorophenyl esters of N-protected amino acids without racemization.

TABLE 1. Yield of PFP Esters of N-Protected Amino Acids

Ord. No.	Carboxylic component	Yield, % on using reagent (I)	Ord. No.	Carboxylic component	Yield, % on using reagent (I)
1	Boc-Gly	96(70) * [15]	10	Boc_2-Tyr	87
2	Z-Gly	96	11	Boc-Thr(OBzl)	99
3	Boc-Ala	98(85) [15]	12	Boc-Ser(OBzl)	99
4	Boc-Pro	99(88) [15]	13	Boc-Ser	80(77) [15]
5	Fmoc-Leu	93(96) [1]	14	Boc-Asn	76(66) [15]
6	Boc-Phe	97(97) [15]	15	Boc-Gln	87(82) [15]
7	Z-Phe	100	16	Boc-Arg(NO_2)	85(91) [2]
8	Fmoc-Phe	93(93) [1]	17	Boc_2-His	73
9	Boc-Val	98(73) [15]	18	Boc_2-Lys	83

*The yield of PFP esters of N-protected amino acids obtained by using DCHC is shown in brackets.

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ASYMMETRIC SYNTHESIS OF S-5-BENZYLOXYTRYPTOPHAN, S-α-ALLYLGLYCINE AND S-β-(2-NAPHTHYL)ALANINE

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Many nonprotein α-amino acids in enatiomerically pure form have physiological activity and are used in medicinal preparations. Thus, for example, S-5-hydroxytryptophan is used for treating depressive states, insomnia, phenylketonuria and other conditions caused by serotonin deficiency in the organism [1-3]. Serotonin itself is formed by decarboxylation of S-5-hydroxytryptophan, which is a powerful neuromediator in nerve cells of the cerebral cortex [4]. S-β-(2-Naphthyl)alanine is used for the synthesis of peptide hormones [5].

Existing methods of chemical synthesis of these compounds inevitably include a stage of racemate separation, which is carried out by an enzymatic method. In the present work, we report a chemical asymmetric synthesis of S-5-benzyloxytryptophan, S-α-allylglycine and S-α-(2-naphthyl)alanine by alkylation of glycine in a Ni(II) complex of its Schiff base with S-2-N-(N-benzylprolyl)aminobenzophenone (S-BPABP). We have previously used a similar method for the synthesis of a series of protein α-amino acids [6].

The chiral complex (I), obtained by the reaction of glycine, $Ni(NO_3)_2$ and S-BPABP in MeOH in the presence of MeONa, by the action of solid NaOH in DMF or MeCN reacts with alkyl halides or 5-benzyloxygramine iodomethylate to form SS- and SR-isomeric alkylated complexes (II)-(IV) (see Scheme 1). The alkylation products (II)-(IV) are diastereomeric complexes of α-amino acids with a labile α-H atom. Under the reaction conditions, they epimerize with the formation of an equilibrium mixture of diastereomeric complexes, which, as we have previously shown [7], contains a considerable excess of a diastereomer with an S-α-amino acid. As a result, the alkylation reaction of glycine in the Ni(II) complex of its Schiff base with S-BPABP by the action of solid NaOH in DMF or MeCN proceeds with a high diastereoselectivity, and the amount of the SS-diastereomer (II)-(IV) in the mixture is >90% (Table 1).

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