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NEW 2-SUBSTITUTED ISOQUINOLINE DERIVATIVES

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ABSTRACT

A series of new 2-substituted isoquinoline derivatives were obtained from tetrahydroisoquinolines and N-protected amino acids in the presence of ethylchloroformate. The newly synthesized amides are with expected biological activity.

Keywords: isoquinoline alkaloids, amino acids, synthesis, biological activity

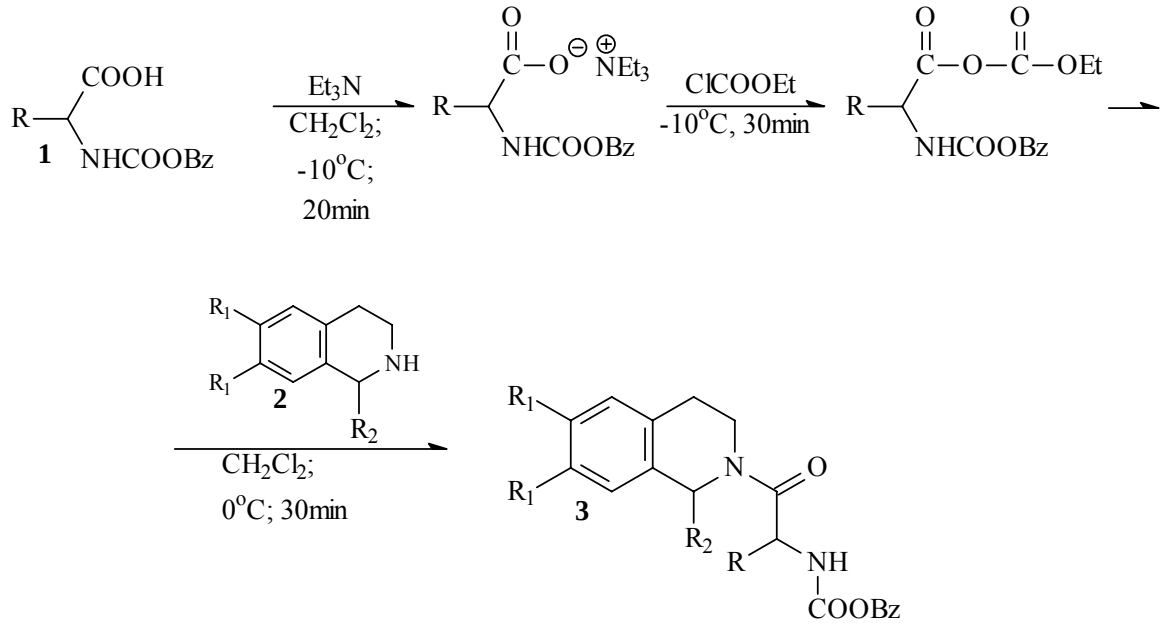
INTRODUCTION

The biological activity attached to the isoquinoline nucleus has provided a great deal of interest in the synthesis of isoquinolines [1-3]. Also the natural amino acids derivatives, as benzyloxycarbonyl-L-tryptophan showed generally moderate antagonist activity on tachykinin NK-receptors [4]. Different derivatives of tetrahydroisoquinoline were prepared from fluorous benzyloxycarbonyl amino acids [5]. Other derivatives were obtained from 2-phenylethylamides of benzyloxycarbonyl glycine with following cyclization with $POCl_3$ by reaction of Bischler-Napieralski [6]. Different amides with 2-phenylethylamines were obtained by reaction of Pictet-Spengler with arylpiruvic acid [7].

RESULTS AND DISCUSSION

Interesting applications of amino acids and their derivatives in the synthesis of tetrahydroisoquinoline and β-carboline alkaloids and related systems have recently appeared in the literature. In a search of a new approach for similar synthesis of derivatives with expected biological activity in this paper we investigated into reaction of tetrahydroisoquinolines and different amino acids. We investigated the synthesis of tetrahydroisoquinoline derivatives with different N-protected natural amino acids. It is known that 2-phenylethylamines easily formed amides with benzyloxycarbonyl glycine in the presence of derivatives of carbonic acid, as ethylchloroformate or isopropylchloroformate. We applied this reaction for the synthesis of amide of tetrahydroisoquinolines and benzyloxycarbonyl glycine. We

assumed that when to the stirred and cooled dichloromethane solution of equimolar amount of N-benzyloxycarbonyl-amino acid 1 and Et_3N in was added ethylchlorophormate (or resp. isopropylchloroformate) dropwise, an anhydride was formed. Then following addition of equimolar amount of tetrahydroisoquinoline 2 led to carbon dioxide separation out of reaction mixture and obtained product 3 (Scheme 1) with high yield (70 %) and purity. By analogy we synthesized amides of tetrahydroisoquinolines with of NH-protected with benzyloxycarbonyl L-alanine and L-valine 3 and same derivatives of 3,4-dimethoxy tetrahydroisoquinoline.



Scheme 1

Table 1

Entry	R	R_1	R_2	Yield [%]
3a	H	H	H	70
3b	CH_3	H	H	72
3c	$CH(CH_3)_2$	H	H	75
3d	H	OCH_3	H	69
3e	CH_3	OCH_3	H	70
3f	$CH(CH_3)_2$	OCH_3	H	74

In conclusion we synthesized new derivatives of tetrahydroisoquinoline with protected amino acids. The successful application of this method to synthesis indicated to enlarge applications. These derivatives are with expected biological activity and suggested method showed to application possibilities for the preparation of unusual amides of alkaloids, as salsolidin, norcriptostilin, etc. The hydrolysis of amide bond in the living organism led to separation of tetrahydroisoquinoline and eliminated the amino acid residue, which doesn't damage the organism.

EXPERIMENTAL

Melting points were determined on a Boetius hostage apparatus and are uncorrected. Unless otherwise noted, NMR spectra were recorded on a Bruker 250 MHz devise by using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) are downfield from TMS as an internal standard and coupling constants are in Hz.

Amides of tetrahydroisoqionolines with amino acids 3a-f; Typical procesure: To a stirred and cooled (ice-salt bath) solution of equimolar amount of N-benzyloxycarbonyl-amino acid and Et_3N in dichloromethane was added ethylchlorophormate dropwise at a rate low enough to keep the internal temperature below –10 °C. After 5 min, a solution of equimolar amount of corresponding tetrahydroisoquinoline in dry dichloromethane was added dropwise to the mixture, the internal temperature being kept below 0 °C. When the addition was complete, the reaction mixture was slowly heated to reflux and refluxed 5 min. The mixture was allowed to cool to room temperature and washed with saturated aqueous $NaHCO_3$ solution (2x50 ml) and water (2x50 ml) after the addition of CH_2Cl_2 (100 ml).The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo to give cristaline product, which was filtrated off, washed with Et_2O, dried and recrystallized from EtOAc or CH_2Cl_2 (yield 70 %).

Supporting Information Available: Chemical characterization data is available free of charge via the Department of Organic Chemistry.

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