CREATING A SYNTHETIC ANALOGUE OF IL-4 ON THE BASIS OF DIPHENYLAMINE

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Abstract

This work is aimed at creating a synthetic analog of the human interleukin-4 (IL-4) which will be used for coating the surface of biomaterials based on biodegradable polymers (polylactic acid, polycaprolactone) in order to impart immunomodulatory properties and increase biocompatibility. Molecule-analogue is designed based on knowledge of the crystal structure of the ligand receptor complex (IL-4 / IL-4 R-1 / IL-4-R2). Our approach involves identifying specific sites of interaction between IL-4 and IL-4-R1 and, from the above, forecast the possible structure of the analogues of IL-4. The interaction between the proposed analogs and receptors of IL-4-R1 is estimated using computational methods such as molecular docking and molecular dynamics, which allow to determine the degree of structural complementarity synthetic analogue to a receptor Analysis has been performed and 4-[N-allyl-N-(4-formylphenyl)amino]benzaldehyde is a molecule, which most likely will lead to the assembly of the complex of IL-4 / IL-4-R1.

The molecule will be synthesized using the classical approach of organic synthesis.

Introduction

This work is aimed at creating a N-allyldiphenylamine with -CHO para-orienting formyl group.

Diphenylamine was selected as basic intermediate product.

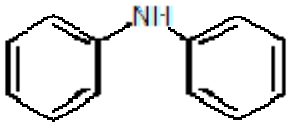


Fig. 1. Diphenylamine

The formylation is entering the group -CHO. To exclude side-reactions for NH, the amino group need to protect. [1], [2].

Most popular protecting groups are acyl and allyl.

Acetylization. The most known reagents for the introduction of the acyl protecting groups are acetyl chloride, benzoyl chloride, acetic anhydride and trivtoruksusny anhydride. Since HCl is escape during the acylation, with acid chlorides are not too comfortable to work. In addition то benzyl chloride is the inaccessible substance. Trifluoroacetic anhydride is an expensive compound. The most convenient and affordable is acetic anhydride. Acetyl protective is removed in one step by alkaline hydrolysis.

The allyl protective group [3]. Allyl radical is weak donor, thereby attaching the para-position is more active during formylation..

The acyl substitution is strong acceptor, dilatory electrons, which complicates the accession of the formyl group in the para position.

Thus, the allyl protection provides greater reactivity of para-positions which will host the formylation. Formylation proceeds more easily than in the presence of the acyl protection but deprotected in two steps.

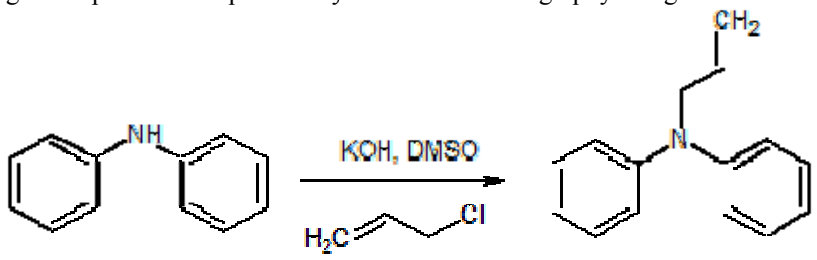
For formation of [4] are required DMF and phosphorus oxide chloride. DMFA- available reagent, which is used mainly as a solvent. $POCl_3$ is unstable, so we got it immediately before use. In this connection by-products are formed, which are removed by distillation.

Experimental

Synthesis of N-allyldiphenylamine (fig. 2)

The first step of the synthesis is the amino group protection by introducing an allyl protection, to exclude further secondary reaction.
For carrying out the reaction the following components were used: diphenylamine (5 g), potassium hydride (3,32 g), DMSO (15ml) chlorallylene (3,4 ml).
Diphenylamine was mixed with potassium hydride and then DMSO added to the reaction mixture. Chlorallylene was then added slowly drop-wise to the reaction mixture with continuous stirring at room temperature.

The resulting crude product was purified by column chromatography using hexane and ethyl acetate.



Diphenylamine *N-allyldiphenylamine*

Fig 2. Synthesis of N-allyldiphenylamine

Synthesis of phosphorous oxychloride.

The second stage of synthesis - is getting phosphorus oxychloride, required for the subsequent formation of N-allildifenilamina.

$$CH_3COOH + PCl_5 \rightarrow CH_3COCl + POCl_3 + HCl \quad (1)$$

After the reaction (1), phosphorus oxychloride is necessary distil to remove the by-products.

Synthesis of 4-[N-allyl-N-(4-formylphenyl)amino]benzaldehyde

The next stage of synthesis is to performed formylation of the allyl-diphenylamine.

The formylation being carried out in the following way.

Freshly distilled phosphorous oxychloride (12.6 ml, 82.6 mmol) was added drop-wise to 5.5 ml of anhydrous DMF at 0 ^{o}C. Later, N-allyldiphenylamine (5 g, 13.6 mmol in 20 ml of 1,2-dichloroethane) was added to the above solution and stirred at 90 ^{o}C for 48 h. Solution was cooled to room temperature, poured into ice water, and neutralized to pH 6–7 by the drop-wise addition of saturated sodium hydroxide solution. The dialdehyde was extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was subsequently removed. The crude product was purified by column chromatography.

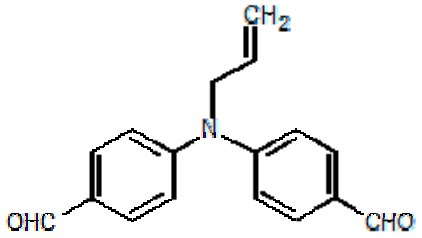


Fig 3. 4-[N-allyl-N-(4-formylphenyl)amino]benzaldehyde

Influence of the resulting product on the direction of differentiation of macrophages will be experimentally evaluated using human monocytes.

References

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