SYNTHESIS OF 3-SUBSTITUTED-3-HYDROXY-2-OXINDOLES

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Резюме: *Был разработан эффективный и простой метод синтеза 3-индолил-3-гидрокси-2-оксиндола на основе изатина. Полученное соединение далее может быть использовано для проведения реакций О-алкилирования, С-алкилирования, реакций циклоРис.оединения с альдегидами и аминокислотами и т.д., с целью синтеза биологически активных производных индола.*

Resume: *An efficient and simple synthetic procedure for the synthesis of 3-indolyl-3-hydroxy-2-oxindole, starting from isatin, was successfully developed. Obtained derivative can be subsequently used in different kinds of reactions: O-alkylation, C-alkylation, cycloaddition reactions with aldehydes and aminoacids etc. in order to create heterocyclic compounds, that are expected to possess different types of biological activity.*

Relevance. 3-Substituted-3-hydroxy-2-oxindoles are heterocyclic organic compounds that possess a carbonyl group at the 2-position of the 5-membered ring and a quaternary carbon centre at the 3-position of this ring [7]. Such structural frameworks were found in many natural products and are known for their broad variety of significant types of biological activity. For example, convolutamydines A-E inhibit differentiation of promyelocytic leukemia cells HL-60 [3], paratunamides A-D and maremycins A-D also reveal cytotoxicity against particular cell lines of carcinoma and leukemia [2, 6]. The list of bioactive 3-hydroxyindoline-2-ones is growing rapidly. Basically they display diverse biological and pharmacological activities such as potent antioxidant, anticancer, anti-HIV, and neuroprotective properties [7]. Therefore both chemists and pharmacists are interested in drug discovery programs connected with the synthesis of 3-substituted-3-hydroxy-2-oxindoles.

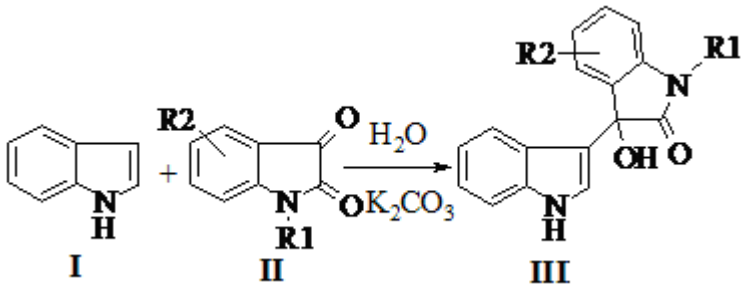
The most direct approach to 3-substituted-3-hydroxyoxindoles is a nucleophilic addition to isatins [5]. The isatin scaffold and its derivatives have received much attention for their potential biological applications such as antioxidant, antibacterial, antifungal, anticonvulsant, anti-inflammatory and antiangiogenic properties [4]. Furthermore isatin is nowadays one of the lead molecules for such synthesis, because of its' reactive keto-carbonyl group. Different condensation reactions are available for isatin and its' derivatives under mild conditions.

That's why safe and economical green chemistry methods of synthesis of 3-substituted-3-hydroxy-2-oxindoles based on isatin represent useful route for the preparation of new biologically active compounds.

Aim: The main goal of our research was to synthesize 3-indolyl-3-hydroxy-2-oxindole from isatin, to study possible conditions for this reaction and to investigate chemical properties of the obtained compound.

Objectives: 1. To synthesize 3-indolyl-3-hydroxy-2-oxindole and to confirm its' chemical structure. 2. To determine the optimal reaction mode for the interaction of isatin and indole. 3. To study the possibility of alkylation of the target compound by epichlorohydrin.

Materials and methods. To synthesize target 3-indolyl-3-hydroxy-2-oxindole (III) the reaction of isatin (I) and indole (II) (in the molar ratio 1:1) was used. As a solvent we used purified water. Potassium carbonate was added to the reaction mixture in a molar equivalent. The reaction proceeded under reflux (50 – 60°C) and with stirring for 4 hours (Pic. 1).



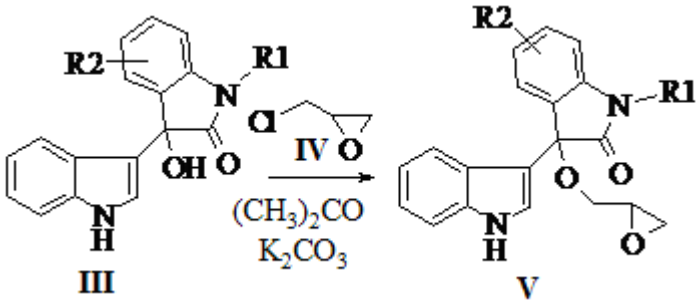
Picture 1

The reaction product (III) – a light yellow amorphous precipitate – was recrystallized from the minimal amount of purified water. On the average 80% yield was obtained.

The completion of the reaction was determined using TLC.

The structure of synthesized compound was confirmed using ^{1}H NMR spectroscopy.

The alkylation of the obtained product by epichlorohydrin (IV) was carried out under reflux (50 – 60°C), using acetone as a solvent, in the presence of molar equivalent of potassium carbonate (Picture2).



Picture 2

The expected product (V) wasn't obtained.

Throughout the research next methods were used: organic synthesis, spectral methods (^{1}H NMR spectroscopy), thin layer chromatography (TLC).

Results and discussion. In order to improve the yield of the target 3-indolyl-3-hydroxy-2-oxindole we made efforts to optimize such reaction parameters as solvents and reaction time. However using polar solvents (ethanol, isopropanol) or their mixture with

water (1:1) had no significant effect. Prolongation of the reaction time did not increase the yield of the target compound too.

After testing different reaction temperatures and catalyst loading we determined next optimal conditions: molar equivalent of potassium carbonate, solvent – minimal amount of purified water at 50 – 60°C for 4 hours.

At the next stage we tested different recrystallization modes. Recrystallization from water gave 80% yield, either ethanol and isopropanol gave much poorer results.

Obtained compound, 3-indolyl-3-hydroxy-2-oxindole, can be subsequently used in different kinds of reactions: O-alkylation, C-alkylation, cycloaddition reactions with aldehydes and aminoacids etc.

However the attempt to alkylate 3-indolyl-3-hydroxy-2-oxindole (III) with epichlorohydrin (IV) in order to obtain product V wasn't successful. The reaction was carried out under reflux (50 – 60°C), using acetone as a solvent, in the presence of potassium carbonate. Changing of the reaction mode (using polar solvents, prolongation of the reaction time, testing other reaction temperatures) didn't give the supposed product of the O-alkylation reaction.

Such difficulties may occur due to the possible competitive N-alkylation reaction in the oxindole core. For example, authors [1] prepared 3-substituted-3-hydroxy-2-oxindoles from N-substituted isatins, conveniently prepared in turn from commercial isatin.

That's why we are interested in additional research involving N-substituted isatins.

Moreover, according to the last researches in oxindoles area, condensation cycloaddition reactions of 3-hydroxyindoline-2-one give great synthetic opportunities to create spirocyclic compounds, which are expected to possess different types of biological activity.

Conclusions: We have developed a synthetic route to 3-substituted-3-hydroxy-2-oxindoles, namely 3-indolyl-3-hydroxy-2-oxindole. This efficient and simple method opens the way to a general synthesis of wide variety of such derivatives, including spirocyclic compounds.

Consequently, synthesis of 3-hydroxyindoline-2-one derivatives remains the key purpose of our future researches. Further studies and investigation of the properties of these compounds are currently in progress in our laboratory.

References

1. Abderrahman El Bouakher, Stéphane Massip, Christian Jarry, Yves Troin, Isabelle Abrunhosa-Thomas, Gérald Guillaumet A General and Efficient Method to Access Tetracyclic Spirooxindole Derivatives // Eur. J. Org. Chem.. - 2015. - №3. - C. 556-569.

2. Kagata, T., Saito, S., Shigemori, H., Ohsaki, A., Ishiyama, H., Kubota, T., Kobayashi, J. Paratunamides a-d, oxindole alkaloids from Cinnamodendron axillare // J. Nat. Prod.. - 2006. - №69. - C. 1517-1521.

3. Kamano, Y., Zhang, H. -P., Ichihara, Y., Kizu, H., Komiyama, K., Pettit, G. R. Convolutamydines A, a novel bioactive hydroxyoxindole alkaloid from marine bryozoan Amathia convoluta // Tetrahedron Lett.. - 1995. - №36. - C. 2783-2784.

4. Parvathaneni Sai Prathima, Keesara Srinivas, Kodicherla Balaswamy, Racha Arundhathi, Gajjaia Narsimha Reddy, Balasubramanian Sridhar, Mandapati Mohan Rao, Pravin R. Likhar

Biscinchona alkaloid catalysed Henry reaction of isatins: Enantioselective synthesis of 3-hydroxy-3-(nitromethyl)indolin-2-ones // Tetrahedron. - 2011. - №22. - С. 2099-2103.

5. Satyamaheshwar Peddibhotla 3-Substituted-3-hydroxy-2-oxindole, an Emerging New Scaffold for Drug Discovery with Potential Anti-Cancer and other Biological Activities // Current Bioactive Compounds. - 2009. - №5. - С. 20 - 38.

6. Tang, Y. -Q., Sattler, I., Thiericke, R., Grabley, S., Feng, X.-Z. Maremycins c and d, new diketopiperazines, and maremycins e and f, novel polycyclic spiro-indole metabolites isolated from Streptomyces sp. // Eur. J. Org. Chem.. - 2001. - №2. - С. 261-267.

7. Tingting Yan, Xiaoyan Wang, Hongbao Sun, Jie Liu,Yongmei Xie Facile Creation of 3-Substituted-3-Hydroxy-2-Oxindoles by Arginine-Catalyzed Aldol Reactions of α,β-Unsaturated Ketones with Isatins // Molecules. - 2013. - №18. - С. 14505-14518.