

Synthesis of 4-hydroxy and 6-hydroxyindoles: a renaissance of the Bischler reaction

A.D. Sharapov , R.F. Fatykhov, I.A. Khalymbadzha, O.N. Chupakhin

Institute of Chemical Engineering, Ural Federal University, Ekaterinburg 620002, Russia

* Corresponding author: a.d.sharapov@urfu.ru

This paper belongs to the MOSM2021 Special Issue.

© 2021, the Authors. This article is published in open access under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).



Abstract

In the present work, we have studied a modified Bischler-Möhlau reaction – synthesis of indoles from benzoin and aniline. Our proposed modification of this method differs from that described earlier in that the reaction is carried out at a lower temperature, which made it possible to improve yields and reduce formation of tarry side products. In addition, unlike previous contradictory works, which described the preparation of a single 4-hydroxy or 6-hydroxy isomer in condensation of m-aminophenol and benzoin, we have obtained both 4-hydroxy and 6-hydroxy isomers.

Keywords

4-hydroxyindoles
6-hydroxyindoles
Bischler-Möhlau reaction

Received: 02.11.21

Revised: 09.04.22

Accepted: 09.04.22

Available online: 13.04.22

Key findings

- This work reveals the possibilities for the synthesis of new 4-hydroxy and 6-hydroxyindoles under the conditions of the modified Bischler-Möhlau reaction.
- A distinctive feature of this work is the achievement regioselectivity in the synthesis of these hydroxyindoles.
- In addition, the one-step synthesis of two isomeric hydroxyindoles with good yields can be characterized as an undoubted advantage of this work.

1. Introduction

The creation of new potential medicinal agents based on hydroxyindoles fragments is one of the promising areas of medical and organic chemistry. For example, topsentin, first isolated from sponges of the genus *Spongosorites*, has pronounced antiviral, antitumor, adrenergic, and antibacterial properties [1–3]. Psilocin is an example of psychedelic tryptamines comprising 4-hydroxyindole moiety [4] (Scheme 1).

Several alkaloids, in particular harmine, harmalol and harmol contained in the plant *Peganum harmala* have a spectrum of antitumor activity on cancer cell lines [5, 6], exhibit antibacterial and neuroprotective properties and are also inhibitors of monoaminosidase A (MAO-A) [7, 8].

The modified Bischler reaction [9], a condensation reaction between aniline and benzoin, allows one to obtain indole with water as only by-product. This feature of the Bischler reaction, combined with solvent-free conditions, makes this reaction especially relevant to the aspect of green chemistry and atomic economy.

Hydroxyindoles are particularly convenient to prepare by the Bischler reaction, since in some cases it is not necessary to use protecting groups in order to block the phenolic hydroxyl.

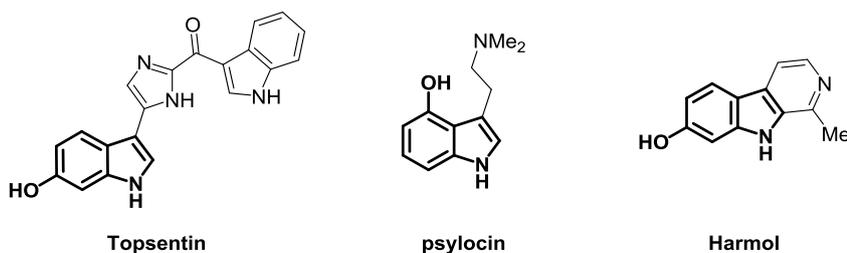
However, the reaction described in the literature is usually carried out at high temperatures (140–160 °C). This factor reduces the applicability of this process for the synthesis of complex compounds with labile groups.

In addition, some aspects of the regiochemistry of the formation of hydroxyindoles from meta-aminophenol and benzoin have remained unclear until now. So, in some works the structure of 2,3-diphenyl-6-hydroxyindole was attributed to the product of this reaction, in other works 2,3-diphenyl-4-hydroxyindole [10, 11].

In this work, we optimized the conditions for the Bischler reaction, and put an end to the issue of regiochemistry of this process.

2. Experimental section

Unless otherwise noted, all commercially available compounds were used without further purification.



Scheme 1 Biologically active examples of 4- and 6-hydroxyindole derivatives.

^1H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker Avance II 400 MHz spectrometer at 400 and 100 MHz, respectively, in DMSO- d_6 as a solvent.

Chemical shifts (δ) are given in ppm relative to the DMSO residual peak (2.50 ppm) as internal standard.

Aminophenol **1** was obtained from commercially available sources.

2.1. Typical procedure for synthesis of 3a-d and 4b, c.

Benzoin **2** (1 equiv.) was added to aminophenol **1** (3 equiv.) and then hydrochloric acid (1.5 ml of 10M per 0.082 mmol of aminophenol). Then the reaction mixture was heated for 30 minutes at 135 °C. During the reaction, water condensate was collected in a Dean-Stark apparatus attached to a weak vacuum. At the end of the reaction, the resulting mass was treated with 15% hydrochloric acid. Then the mixture was filtered off, washed with water and dried. The dry residue containing a mixture of 4 and 6-hydroxyindoles **3**, **4** was separated using column chromatography with a mixture of solvents $\text{CH}_2\text{Cl}_2:\text{C}_6\text{H}_{14} = 1:1$.

2.2. 2,3-Diphenyl-6-hydroxyindole 3a

^1H NMR (400 MHz, DMSO- d_6): $\delta = 10.99$ (*s*, 1H, OH), 8.81 (*s*, 1H, NH), 7.46–7.24 (*m*, 10H, 2Ph), 7.25 (*d*, $J = 8.6$ Hz, 1H, H-4), 6.80 (*d*, $J = 2.1$ Hz, 1H, H-7), 6.54 (*dd*, $J = 8.6, 2.1$ Hz, 1H, H-5).

2.3. 2,3-Diphenyl-4-hydroxyindole 4a

^1H NMR (400 MHz, DMSO- d_6): $\delta = 11.18$ (*s*, 1H, OH), 8.80 (*s*, 1H, NH), 7.39–7.15 (*m*, 10H, 2Ph), 6.93–6.83 (*m*, 2H, H-6, H-5), 6.34 (*dd*, $J = 6.4, 2.1$ Hz, 1H, H-7).

2.4. 2,3-bis(3,4-Dimethoxyphenyl)-6-hydroxyindole 3b

^1H NMR (400 MHz, DMSO- d_6): $\delta = 10.80$ (*s*, 1H, OH), 8.71 (*s*, 1H, NH), 7.22 (*d*, $J = 8.5$ Hz, 1H, H-4), 7.05–6.81 (*m*, 6H, Ph), 6.76 (*d*, $J = 2.0$ Hz, 1H, H-7), 6.51 (*dd*, $J = 8.5, 2.2$ Hz, 1H, H-5), 3.84–3.81 (*s*, 3H, 2OMe), 3.70 (*s*, 3H, OMe), 3.65 (*s*, 3H, OMe).

2.5. 2,3-bis(3,4-Dimethoxyphenyl)-4-hydroxyindole 4b

^1H NMR (400 MHz, DMSO- d_6): $\delta = 11.00$ (*s*, 1H, OH), 8.59 (*s*, 1H, NH), 7.07–6.76 (*m*, 9H, Ph), 3.80–3.75 (*s*, 3H, 2 OMe), 3.68 (*s*, 3H, OMe), 3.65 (*s*, 3H, OMe).

2.6. 2,3-bis(3,4,5-Trimethoxyphenyl)-6-hydroxyindole 3c

^1H NMR (400 MHz, DMSO- d_6): $\delta = 11.10$ (*s*, 1H, OH), 9.07 (*s*, 1H, NH), 7.29 (*d*, $J = 8.5$ Hz, 1H, H-4), 6.81 (*d*, $J = 2.1$ Hz, 1H, H-7), 6.76 (*s*, 2H, Ph), 6.63 (*s*, 2H, Ph), 6.58 (*dd*, $J = 8.5, 2.2$ Hz, 1H, H-5), 3.72–3.59 (*s*, 15H, OMe), 3.33 (*s*, 3H, OMe). ^{13}C NMR (101 MHz, DMSO- d_6): $\delta = 153.77, 152.90, 152.52, 152.42, 151.98, 136.85, 136.47, 136.08, 131.58, 131.31, 127.92, 121.76, 119.30, 113.56, 110.29, 107.32, 104.88, 96.09, 64.88, 60.07, 60.03, 55.80, 55.49, 55.42, 30.64, 15.13$.

2.7. 2,3-bis(3,4,5-Trimethoxyphenyl)-4-hydroxyindole 4c

^1H NMR (400 MHz, DMSO- d_6): $\delta = 11.10$ (*s*, 1H, OH), 9.03 (*s*, 1H, NH), 6.96–6.86 (*s*, 3H, Ph), 6.70 (*s*, 2H, Ph), 6.64 (*s*, 1H, Ph), 3.84 (*s*, 3H, OMe), 3.46–3.36 (*s*, 15H, OMe).

2.8. 2,3-bis(2-Chlorophenyl)-6-hydroxyindole 3d

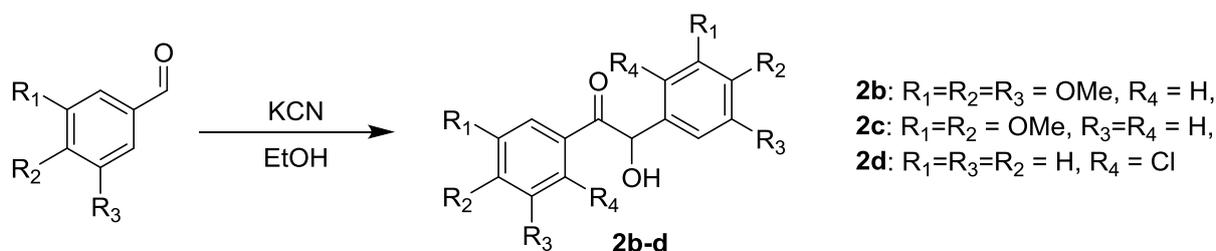
^1H NMR (400 MHz, DMSO- d_6): $\delta = 11.05$ (*s*, 1H, OH), 8.83 (*s*, 1H, NH), 7.52–7.36 (*m*, 3H, Ph), 7.36–7.26 (*m*, 3H, Ph), 7.20 (*m*, 2H, Ph), 7.09 (*d*, $J = 8.6$ Hz, H-4), 6.81 (*d*, $J = 2.2$ Hz, 1H, H-7), 6.56 (*dd*, $J = 8.6, 2.2$ Hz, 1H, H-5).

3. Results and discussion

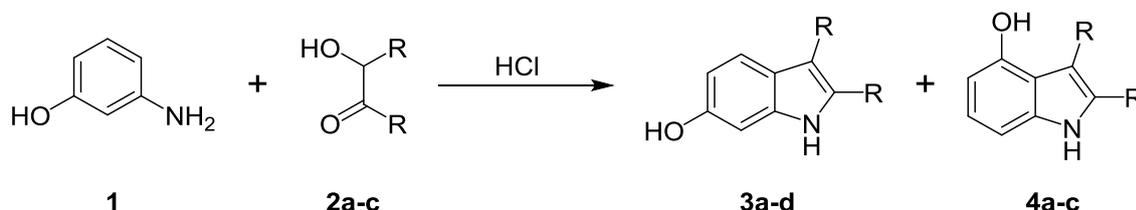
The use of a modified two-component reaction catalyzed by hydrochloric acid made it possible to isolate a mixture of new isomeric 4- and 6-hydroxyindoles from the reaction mixture in high yields.

For the synthesis of the starting benzoin **2b-d**, the procedure described in the literature [12–14] was used (Scheme 2).

It was found that fusion according to the modified procedure of 3-aminophenol **1** (3 equiv.) with benzoin **2a-d** (1 equiv.) at 135 °C under hydrochloric acid catalysis resulted in a mixture of isomeric 4 and 6-hydroxyindoles **3a-d**, **4a-c**. In this case, the formation of major 6-hydroxyindole was observed. 4-Hydroxyindole derivatives **4a-c** were separated using column chromatography ($\text{CH}_2\text{Cl}_2:\text{C}_6\text{H}_{14}$ 1:1). 6-Hydroxyindole derivatives were isolated by elution with a mixture of solvents $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 20:1 (Scheme 3). The course of condensation of benzoin with aminophenol can be observed by the distilled water removed using a weak vacuum (60–70 mm Hg) and a Dean-Stark apparatus.



Scheme 2 Synthesis of starting benzoin **2b-d**.



- a:** $R = \text{Ph}$, 80% (overall yield)
b: $R = 3,4\text{-dimethoxyphenyl}$, 72% (overall yield)
c: $R = 3,4,5\text{-trimethoxyphenyl}$, 61% (overall yield)
d: $R = 2\text{-chlorophenyl}$, 53%

Scheme 3 Interaction of aminophenol **1** with benzoin **2a-c**.

The structure of products **3** and **4** is confirmed by the data of ^1H and ^{13}C NMR spectroscopy. For example, in the ^1H NMR spectrum of compound **3c**, the signal of phenolic hydroxyl is recorded in the region of 11.1 ppm, the signal of the NH-proton is at 9.1 ppm, the signals of the proton H-5 are recorded as a doublet of doublets with $^1J_{(\text{H-5},\text{H-6})} = 8.5$ Hz and $^2J_{(\text{H-5},\text{H-7})} = 2.2$ Hz.

4. Conclusions

Thus, in the search for new potential medicinal agents, we have developed a convenient modified method for the synthesis of new 4- and 6-hydroxyindoles in good yields. The advantages of the modified procedure are characterized by a lower reaction temperature (which does not reduce the reaction yields), the convenience of isolating pure 4- and 6-hydroxyindoles, and a decrease in the formation of resinous by-products.

Supplementary materials

No supplementary materials are available.

Funding

The Russian Science Foundation (no. 21-13-00382) financially supported this research, <https://rscf.ru/en>.



Acknowledgment

None.

Author contributions

Conceptualization: A.D.S., I.A.K.
 Data curation: A.D.S.
 Formal Analysis: O.N.C., R.F.F., I.A.K.
 Funding acquisition: A.D.S., R.F.F.
 Investigation: A.D.S., I.A.K.
 Methodology: O.N.C., I.A.K., R.F.F.
 Project administration: A.D.S.
 Resources: R.F.F., I.A.K.
 Software: A.D.S., I.A.K.
 Supervision: A.D.S.
 Validation: I.A.K., R.F.F.
 Visualization: A.D.S.
 Writing – original draft: A.D.S., I.A.K.
 Writing – review & editing: O.N.C.

Conflict of interest

The authors declare no conflict of interest.

Additional information

Author ID's:

A.D. Sharapov, Scopus ID [57201740165](https://orcid.org/0000-0002-5720-1740);
 R.F. Fatykhov, Scopus ID [57190761230](https://orcid.org/0000-0002-5719-0761);
 I.A. Khalymbadzha, Scopus ID [18434200300](https://orcid.org/0000-0002-1843-4200);
 O.N. Chupakhin, Scopus ID [7006259116](https://orcid.org/0000-0002-7006-2591).

Institute's website:

<https://hti.urfu.ru/en>.

References

1. Gunasekera SP, Kashman Y, Cross SS, Lui MS, Pomponi SA, Diaz MC. Tospentin, Bromotospentin, and Dihydrodeoxybromotospentin: Antiviral and Antitumor Bis(indolyl)imidazoles from Caribbean Deep-sea Sponges of the Family Halichondriidae. Structural and Synthetic Studies. *J Org Chem.* 1988;53(23):5446–5453. doi:[10.1021/jo00258a009](https://doi.org/10.1021/jo00258a009)
2. Sakemi S, Sun HH. Nortospentins A, B, and C. Cytotoxic and antifungal imidazolediybis[indoles] from the sponge *Spongisorites ruetzleri*. *J Org Chem.* 1991;56(13):4304–4307. doi:[10.1021/jo00013a044](https://doi.org/10.1021/jo00013a044)
3. Phife DW, Ramos, RA, Feng M, King I, Gunasekera SP, Wright A, Patel M, Pachter, JA. Marine Sponge Bis(indole) Alkaloids that displace ligand Binding to α Adrenergic Receptors. *Bioorg Med Chem Lett.* 1996;6(17):2103–2106. doi:[10.1016/0960-894X\(96\)00376-9](https://doi.org/10.1016/0960-894X(96)00376-9)
4. Shulgin A, Shulgin A, Tihkal: A Continuation Paperback, U.S.: Transform Press; 1997. 804 p.
5. Yoshimitsu Y, Yasuhiro K. Inhibitory Effects of Herbal Alkaloids on the Tumor Necrosis Factor- α and Nitric Oxide Production in Lipopolysaccharide-Stimulated RAW264 Macrophages. *Chem Pharm Bull.* 2011;59(3):388–391. doi:[10.1248/cpb.59.388](https://doi.org/10.1248/cpb.59.388)
6. Khan SI, Abourashed EA, Khan IA, Walker LA. Transport of Harman Alkaloids across Caco-2 Cell Monolayers. *Chem Pharm Bull.* 2004;52(4):394–397. doi:[10.1248/cpb.52.394](https://doi.org/10.1248/cpb.52.394)
7. Li Y, Sattler R, Yang EJ, Nunes A, Ayukawa Y, Akhtar S, Rothstein JD. Harmine, a natural beta-carboline alkaloid, upregulates astroglial glutamate transporter expression. *Neuropharmacol.* 2010;60(7-8):1168–1175. doi:[10.1016/j.neuropharm.2010.10.016](https://doi.org/10.1016/j.neuropharm.2010.10.016)
8. Nenaah G. Antibacterial and antifungal activities of (beta)-carboline alkaloids of *Peganum harmala* (L) seeds and their combination effects. *Fitoterapia.* 2010;81(7):779–782. doi:[10.1016/j.fitote.2010.04.004](https://doi.org/10.1016/j.fitote.2010.04.004)
9. Gribble GW. Bischler Indole Synthesis. *Indole Ring Synthesis.* 2016;23:249–259. doi:10.1002/9781118695692.ch23
10. Orr H, Tomilson M. 4- and 6-Methoxy-2,3-diphenylindole. *J Chem Soc.* 1957:5097. doi:[10.1039/JR9570000004](https://doi.org/10.1039/JR9570000004)
11. Teuber HJ, Schnee K. Zur Frage des Ringschlusses bei der Indolsynthese nach Bischler mit m-Aminophenol. *Chem Ber.* 1958;91(10):2089–2094. doi:[10.1002/cber.19580911013](https://doi.org/10.1002/cber.19580911013)
12. Ohta K, Hasebe H, Ema H, Moriya M, Fujimoto T, Yamamoto I. Discotic Liquid Crystals of Transition Metal Complexes 111: The First π -Acceptor in Discotic Columnar Liquid Crystals Obtained from Octasubstituted Bis(diphenylethane-1,2-dithiolene)nickel Complexes. *Mol Cryst Liquid Cryst.* 1991;208(1):21–32. doi:[10.1080/00268949108233940](https://doi.org/10.1080/00268949108233940)
13. Richtzenhain H. Enzymatische Versuche zur Entstehung des Lignins, II. Mittel.: Die Dehydrierung des 5-Methylpyrogallol-1,3-dimethyläthers. *Ber Dtsch Chem Ges.* 1944;77(6-7):409–417. doi:[10.1002/cber.19440770608](https://doi.org/10.1002/cber.19440770608)
14. Singh P, Mittal A, Kaur S, Holzer W, Kumar S. 2,3-Diaryl-5-ethylsulfanylmethyltetrahydrofurans as a new class of COX-2 inhibitors and cytotoxic agents. *Org Biomol Chem.* 2008;6(15):2706. doi:[10.1039/b803608](https://doi.org/10.1039/b803608)