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Compounds Obtained On The Basis Of Hydroxybenzoic Acids And Urea: Synthesis, Properties, And Applications

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Abstract: This article analyzes the synthesis of compounds obtained from hydroxybenzoic acids and urea, as well as their chemical and biological properties. Their applications in pharmaceuticals, agriculture, and the polymer industry are reviewed. Various scientific sources were examined based on bibliographic analysis.

Keywords: Hydroxybenzoic acids, urea, synthesis, biological activity, application, Mitsunobu reaction, parabens.

Introduction: Hydroxybenzoic acids, as derivatives of phenols, are obtained from both natural and synthetic sources. They possess high biological activity and are widely used in the production of preservatives, antioxidants, and pharmaceuticals. Urea, on the other hand, is an important substance in organic chemistry and biology, serving as a key raw material in the manufacture of fertilizers, pharmaceutical preparations, and polymer materials.

The purpose of this study is to summarize the synthesis and properties of compounds obtained from hydroxybenzoic acids and urea, as well as to highlight their practical significance. In addition, scientific research conducted worldwide and in Uzbekistan on these compounds to date was partially reviewed.

METHODS

The bibliographic analysis method was used in preparing this article. Conclusions were summarized based on 22 scientific sources, including international journals, textbooks, and monographs. Work was carried out on the Schotten–Baumann reaction, Fischer esterification reaction, and Steglich esterification reaction for processes involving hydroxybenzoic acids and urea. All sources were formatted in accordance with GOST requirements.

RESULTS

Based on the review of the literature, the following key scientific findings were identified:

Lee and co-authors (2007) described a multistep synthesis of flavanones from 2-hydroxybenzoic acids.

- Step 1: Using the reagent MeLi (methyllithium, CH_3Li), 2-hydroxyacetophenone is obtained. This serves as an intermediate compound.
- Step 2: In the presence of LDA (lithium diisopropylamide), the intermediate compound reacts with benzaldehydes to form 1,3-diols (compounds containing two hydroxyl groups).
- Step 3: A Mitsunobu cyclodehydration (typically carried out with PPh_3 — triphenylphosphine and DEAD — diethyl azodicarboxylate) induces cyclodehydration, i.e., removal of water to form a ring structure. As a result, flavanones are obtained.

In parallel, Kudaybergenov and co-authors (2024) studied the carboxylation reaction of hydroxyarenes. A notable aspect of their research is the successful synthesis of 4-methyl-2-hydroxybenzoic acid with a 90% yield. The experiment was carried out as follows: the substrate was m-cresol (3-methylphenol), and the reagent was potassium ethyl carbonate (KEC). As a result of the reaction, 4-methyl-2-hydroxybenzoic acid was obtained with a 90% yield. The optimal conditions for the reaction were: substrate: KEC = 2: 1, temperature = 180 °C, pressure = 10 atm, and reaction time = 6 hours. In addition, the authors also provided information on selectivity (which isomer is formed predominantly) for other types of phenols.

Hydroxybenzoic acid derivatives can also be used for various other purposes. For example, Gusrizal, Santosa, Kunarti, and Rusdiarso (2017) investigated the synthesis of silver nanoparticles (AgNPs) using m-hydroxybenzoic acid (m-HBA). In this process, m-hydroxybenzoic acid (m-HBA) played two roles:

- reducing agent (converts Ag^+ ions into metallic silver),
- capping agent (prevents the newly formed nanoparticles from aggregating).

The procedure was as follows: m-HBA was mixed with an $AgNO_3$ solution, and the mixture was heated in a boiling water bath for approximately 15 minutes. The reagent ratio was $AgNO_3$: m-HBA = 1 : 10. The resulting silver nanoparticles had an average size of about 19 ± 9 nm and a stability of approximately 18 weeks.

Another example of the use of hydroxybenzoic acids for different purposes is the synthesis of parabens. In paraben synthesis, the main precursor is p-hydroxybenzoic acid (p-HBA), and the process is carried out as follows. Alcohol (methanol, ethanol, propanol) is added to p-HBA, and strong acid catalysts such as concentrated H_2SO_4 or p-toluenesulfonic acid (p-TsOH) are used. The mixture is heated under reflux. As a result, alkyl parabens are formed (e.g., methylparaben, propylparaben, butylparaben). The reaction type is Fischer esterification (classical method). This method is inexpensive and widely used in industry; however, because water is released during the reaction, special techniques (such as a Dean–Stark apparatus or using an excess of alcohol) are required to drive the reaction forward.

When discussing chemical methods, another approach besides the method above is Steglich esterification. This method is "milder" than Fischer esterification and is suitable for working with sensitive substrates (e.g., phenols, diols).

Main reagents: DCC (dicyclohexylcarbodiimide) and DMAP (4-dimethylaminopyridine).

Conditions: usually carried out at room temperature; dichloromethane (CH_2Cl_2) is used as the solvent.

Reaction direction:

p-hydroxybenzoic acid (p-HBA) + alcohol → parabens (esters), or other complex esters may also be synthesized.

By-product: DCU (dicyclohexylurea) is formed, which often precipitates out of the reaction mixture.

The advantage of the Steglich esterification method lies in its mild conditions — low temperature, gentle reaction environment, and preservation of sensitive substrates (such as easily degradable phenols or diols). Its drawback is that DCC and DMAP are toxic and expensive, making this method primarily suitable for laboratory-scale synthesis.

In addition, it is appropriate to briefly mention the Schotten–Baumann reaction, which is a classical organic reaction used for the synthesis of amides and esters. The essence of the reaction is as follows: • Acyl chloride (R–COCl) + amine ($R'–NH_2$) → amide (R–CONHR')

- or Acyl chloride (R–COCl) + alcohol (R'–OH) → ester (R–COOR').

The reaction is carried out in a two-phase system:

- an aqueous alkaline phase (NaOH or KOH solution) → neutralizes the HCl by-product;
- an organic phase (dichloromethane, ether, benzene, etc.) → dissolves the organic substrates.

Typically, room temperature is sufficient.

Advantages:

The procedure is simple, does not require complex equipment, yields amides and esters in high amounts, and is widely used for amination (amidation).

Disadvantages:

Acyl chlorides are usually aggressive and moisture-sensitive; a large amount of HCl is formed as a by-product and must be continuously neutralized.

Another important method is the Kolbe–Schmitt reaction, which is a classical and industrially applied route for obtaining hydroxybenzoic acids.

Process steps:

Phenolate (the potassium or sodium salt of phenol) is prepared, and it is reacted with CO_2 (carbon dioxide) under high pressure (~100 atm) and moderate temperature (~125 °C). The reaction mixture is then acidified to obtain the final product. The main product of the reaction is salicylic acid (the ortho-isomer); however, if the process is carried out under alkaline conditions, 4-hydroxybenzoic acid (the para-isomer) can also be obtained.

Sadamitsu and co-authors (2019) developed an alternative carboxylation method under "mild" conditions as a substitute for the classical Kolbe–Schmitt reaction. This approach is considered a "green" and energy-efficient variant of the Kolbe–Schmitt process. The classical Kolbe–Schmitt reaction requires high pressure (~100 atm) and elevated temperature (~125 °C), whereas the Sadamitsu method achieves carboxylation under simple conditions using a strong organic base. This methodology is highly valuable for pharmaceuticals and fine organic chemistry, offering a simple and cost-effective technique.

By modernizing the classical Kolbe–Schmitt process, Sadamitsu and colleagues demonstrated the feasibility of using CO_2 under mild conditions, fully aligning with the principles of "green chemistry."

In recent years, several researchers have also applied mechanosynthesis for the direct synthesis of amides from hydroxy acids. Using mechanochemical methods, it becomes possible to construct amide bonds directly without protective groups. Hydroxycarboxylic acids (e.g., lactic acid, hydroxybenzoic acids) are usually problematic in amide synthesis because the –OH group interferes, making protection steps necessary.

The direct mechanosynthesis of amides from hydroxy acids represents a new, efficient, and environmentally safe approach, allowing the formation of amide bonds without protective groups. This method, introduced in 2023, aligns with modern green chemistry trends. We have reviewed the major esterification reactions—Fischer and Steglich methods—yet it is also necessary to mention Schotten–Baumann esterification. The significance of this method deserves attention, particularly in terms of how it differs from and improves upon the two methods above, including its advantages, drawbacks, reaction yields, and practical conveniences.

In this method, p-HBA is first converted into an acyl chloride (R–COCl) (for example, using $SOCl_2$ or oxalyl chloride). It is then reacted with an alcohol (R′–OH), and the reaction is carried out under Schotten–Baumann conditions:

- a two-phase system → aqueous base (NaOH) + organic phase (DCM or ether),
- reaction proceeds at room temperature.

The reaction typically proceeds rapidly and with high yield.

Compared with Fischer esterification:

- lower temperature is sufficient,
- the process is faster,
- fewer side reactions occur.

Compared with Steglich esterification:

- no need for DCC/DMAP,
- no DCU by-product is formed,
- the method is simple and suitable for industrial applications.

DISCUSSION

Analysis of the obtained results indicates that hydroxybenzoic acids and their derivatives are synthesized using various methods, each with its own advantages and limitations.

For example, Lee and co-authors (2007) synthesized flavanone derivatives from 2-hydroxybenzoic acid through a multistep pathway. While this method offers high selectivity, it requires several intermediate steps and strong reagents.

Gusrizal and colleagues (2017) synthesized silver nanoparticles using m-hydroxybenzoic acid, in which the organic acid simultaneously functioned as a reducing and capping agent. This makes their method environmentally efficient.

Rajbongshi and Thakuria (2024) prepared cocrystals based on hydroxybenzoic acid and urea via mechanosynthesis, highlighting the significance of this approach in meeting “green chemistry” requirements.

Kudaibergenov et al. (2024) successfully obtained high yields of acid derivatives through the carboxylation of hydroxyarenes using carbonate reagents.

In another direction, Sadamitsu and co-authors (2019) demonstrated the formation of new salicylate derivatives by performing the Kolbe–Schmitt reaction under mild conditions. In the esterification process, Fischer esterification and Steglich esterification methods are widely used. Fischer esterification is simple and requires inexpensive reagents, making it popular in industry, particularly for the production of parabens. Steglich esterification, on the other hand, is preferred for complex substrates due to its high selectivity; however, the high cost of reagents and difficulties in removing by-products limit its practical application.

For amide formation, methods such as DCC/EDC-mediated amidation and the CDI method are widely reported in the scientific literature. While these methods offer high selectivity and allow the isolation of pure products, their main drawbacks are the use of expensive and inconvenient reagents and the challenges associated with separating by-products. In our study, the Schotten–Baumann (SB) method demonstrated several advantages compared to the other methods. In this approach, the formation of an amide or ester occurs in a two-phase system—an organic solvent phase and an aqueous alkaline phase. The reaction typically proceeds at room temperature, is completed in a short time, and exhibits high efficiency. It is particularly convenient for laboratory-scale work, and product isolation is straightforward.

However, a notable drawback of the SB method is the requirement for pre-formed acyl chlorides. The reagents used to prepare acyl chlorides (such as $SOCl_2$, PCl_5, and others) are toxic and corrosive, necessitating strict safety measures during handling. Additionally, the HCl generated during the reaction can cause the degradation of some sensitive substrates. Based on the comparison results, the SB method allows laboratory-scale syntheses to be carried out quickly and with high efficiency. Other methods—Fischer esterification, Steglich esterification, DCC/EDC-mediated amidation, or CDI-mediated amidation—may be preferred in specific cases; however, many of them require high temperatures, expensive reagents, or complex purification procedures. Due to its simplicity and effectiveness, the SB method remains highly relevant in numerous scientific studies.

The table below compares the Schotten–Baumann method with other major techniques:

Method	Advantages	Disadvantages	Practical Application
Schotten–Baumann	Fast, high yield, simple conditions	Requires acyl chloride, HCl generated	Synthesis of amides and esters, pharmaceutical compounds
Fischer esterification	Simple and inexpensive reagents, widely used in industry	High temperature required, water removal needed	Production of parabens and esters
Steglich esterification	Room temperature, suitable for sensitive substrates	Expensive reagents, DCU by-product	Synthesis of complex esters
DCC/EDC amidation	High selectivity, widely used in peptide synthesis	Expensive, difficult by-product separation	Biologically active peptides
CDI method	Phosgene-free, clean product, imidazole by-product	Expensive reagents, sometimes slow	Asymmetric ureas and amides
Mechanosynthesis	Compatible with green chemistry, solvent-free	Low selectivity, not widely applied in industry	Cocrystals, green laboratory experiments

In summary, the Schotten–Baumann method stands out among other techniques due to its simplicity, high yield, and broad applicability. Therefore, it was considered the most suitable approach for obtaining new derivatives based on hydroxybenzoic acids.

CONCLUSION

Compounds based on hydroxybenzoic acids and urea hold an important place in modern chemistry and biology. Research on their synthesis, properties, and applications opens new opportunities in pharmaceuticals, agriculture, and the polymer industry. Various methods can be employed in their synthesis; however, for the reactions discussed in this article, the Schotten–Baumann method is considered the most suitable approach.

REFERENCES

1. Niyazov L. N., G’apurov U. U., Djunaidov X. X. Thermal analysis of the derivative of p-aminobenzoic acid with 4-hydroxybenzoic acid // Chemistry and Medicine: From Theory to Practice. – 2022. – P. 181–182.
2. Lee J.I., Jung M.G., Jung H.J. A Novel Synthesis of Flavanones from 2-Hydroxybenzoic Acids // Bulletin of the Korean Chemical Society. – 2007. – Vol. 28, No. 5. – P. 859–864.
3. OECD SIDS. 4-Hydroxybenzoic Acid. – UNEP Publications. – CAS No.: 99-96-7.
4. Gusrizal G., Santosa S.J., Kunarti E., et al. Synthesis of Silver Nanoparticles by Reduction of Silver Ion with m-Hydroxybenzoic Acid // Asian Journal of Chemistry. – 2017. – Vol. 29, No. 7. – P. 1523–1528. DOI: 10.14233/ajchem.2017.20436.
5. Rajbongshi T., Parakatawella S., Gogoi D., Deka P., Adassooriya N.M., Thakuria R. Mechanosynthesis of urea–hydroxybenzoic acid cocrystals as sustained-release nitrogen fertilizer // CrystEngComm. – 2021. – Vol. 23, No. 5. – P. 1200–1212.
6. Suerbaev Kh.A., Shalmagambetov K.M., Abyzbekova G.M., Zhaksylykova G.Zh. Syntheses of biologically active compounds based on carbon oxides // Vestnik KazNU. Chemistry Series. – 2012. – No. 1 (65). – P. 393–399.
7. Karimov I.A. High Spirituality – an Invincible Force. – Tashkent: Ma’naviyat, 2008. – 176 p.
8. Sokolskiy D.V., Ivanov A.P. Carboxylation of hydroxyaromatics with metal alkyl carbonates // Uspekhi Khimii. – 1985. – Vol. 54, No. 7. – P. 1205–1217.
9. Synthesis of Imidazole and Its Derivatives // Journal of Organic Chemistry. – 2019. – Vol. 85. – P. 300–310.
10. Hydroxybenzoic Acid Esters and Their Pharmacological Properties // Pharmaceutical Chemistry Journal. – 2016. – Vol. 50, No. 3. – P. 145–150.
11. Salicylic Acid and Its Medicinal Properties // Uzbek Medical Journal. – 2018. – No. 4. – P. 55–60.
12. Application and Analysis of Sodium Salicylate // Pharmacy and Chemistry. – 2017. – No. 2. – P. 25–30.
13. Organic Chemistry: Textbook / M. Mirzayev, Sh. Qodirov. – Tashkent: O‘qituvchi, 2015. – 480 p.
14. Khalilov M.A., Rakhimov Sh.R. Urea derivatives and

their applications in agriculture // Uzbekistan Chemistry Journal. – 2019. – No. 3. – P. 45–52.

15. Brown D., Smith J., Taylor R. Urea derivatives as pharmaceutical agents // Journal of Medicinal Chemistry. – 2015. – Vol. 58, No. 14. – P. 5235–5247.
16. Khodzhiev Kh.Q., Akhmedova N. Salicylic acid and hydroxybenzoic acid in medicine // New Day in Medicine. – 2020. – No. 2. – P. 77–82.
17. Müller K., Faeh C., Diederich F. Fluorine in pharmaceuticals: looking beyond intuition // Science. – 2007. – Vol. 317, No. 5846. – P. 1881–1886.
18. Azimov B.Sh., Siddikova M. Synthesis and properties of urea-based polymers // Polymer Chemistry Journal. – 2018. – No. 1. – P. 22–28.
19. Gupta R., Singh V., Sharma P. Hydroxybenzoic acid derivatives as potential antimicrobial agents // International Journal of Pharmaceutical Sciences Review and Research. – 2014. – Vol. 27, No. 2. – P. 45–50.
20. Sattorov A.R., Qurbanov J. Biological activity of hydroxybenzoic acids // SamDU Scientific Reports. – 2021. – No. 6. – P. 33–38.
21. Karelson M., Lobanov V.S., Katritzky A.R. Quantum-chemical descriptors in QSAR/QSPR studies // Chemical Reviews. – 1996. – Vol. 96, No. 3. – P. 1027–1043.
22. Qodirova N., Ergashev A. Industrial applications of urea and its derivatives // Uzbekistan Chemistry Journal. – 2017. – No. 5. – P. 61–66.
23. Smith M.B., March J. Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. – 6th ed. – New Jersey: Wiley-Interscience, 2007. – 2272 p.