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Optimization Of Reaction Conditions And Yield Enhancement In The Synthesis Of New Amide Compounds From 2-Hydroxybenzoic And 2-Methoxybenzoic Acids Via The Schotten-Baumann Method

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Abstract: This research investigates the synthesis of novel amide derivatives from 2-hydroxybenzoic acid (salicylic acid) and 2-methoxybenzoic acid using the Schotten-Baumann method, with a focus on optimizing reaction conditions to improve yields while preserving the ortho-substituents. The study examines the preparation of acid chlorides employing oxalyl chloride catalyzed by DMF, followed by amide formation through nucleophilic acylation. Mechanisms, empirical data, and theoretical insights are analyzed, tracing the evolution from traditional aqueous base methods yielding 60-80% to advanced optimizations like controlled temperature, solvent selection, and microwave assistance achieving up to 92% efficiency with reduced by-products. Challenges such as side reactions from the hydroxy group and steric hindrance are mitigated using protective strategies or phase-transfer catalysts. Practical guidelines are offered for selecting optimal protocols based on yield, purity, scalability, and eco-friendliness, recommending the integration of DMF-catalyzed acid chloride formation with biphasic Schotten-Baumann conditions for sustainable amide synthesis in pharmaceutical applications.

Keywords: Schotten-Baumann reaction, 2-hydroxybenzoic acid, 2-methoxybenzoic acid, amide synthesis, acid chlorides, oxalyl chloride, DMF catalysis, yield optimization, ortho-substituents, nucleophilic acylation, organic synthesis.

INTRODUCTION:

Amide bond formation is a fundamental process in organic chemistry, underpinning the synthesis of a wide range of compounds with significant applications in pharmaceuticals, agrochemicals, and materials science. Aromatic carboxylic acids, such as 2-hydroxybenzoic acid (salicylic acid) and its derivatives like 2-methoxybenzoic acid, serve as versatile starting materials due to their structural features and reactivity. The amide bond, characterized by its stability and ability to engage in hydrogen bonding, imparts unique physicochemical properties, making amides critical components in drugs (e.g., aspirin derivatives), pesticides, and polymers. The bioactivity of amides, particularly those derived from salicylic acid, stems from their ability to interact with biological targets, such as enzymes or receptors, while their structural versatility allows for tailored modifications to enhance solubility, stability, or functionality.

The Schotten-Baumann reaction, developed in the late 19th century by Carl Schotten and Eugen Baumann, remains a cornerstone for amide synthesis from aromatic carboxylic acids. This method involves the conversion of carboxylic acids to acid chlorides, followed by their reaction with amines to form amides. Its reliability and adaptability have made it a preferred approach in both laboratory and industrial settings. However, traditional implementations of the Schotten-Baumann reaction often relied on stoichiometric

reagents and harsh conditions, leading to waste and environmental concerns. As of 2025, advancements in catalytic systems, green chemistry techniques, and computational modeling have transformed the method, improving efficiency, selectivity, and sustainability. This review focuses on the synthesis of amides from 2-hydroxybenzoic acid and its derivatives, emphasizing the preparation of acid chloride intermediates using oxalyl chloride with DMF as a catalyst, and explores how these innovations address challenges related to reactivity, selectivity, and ecological impact.

The initial step in the Schotten-Baumann synthesis involves the conversion of aromatic carboxylic acids, such as 2-hydroxybenzoic acid or 2-methoxybenzoic acid, into their corresponding acid chlorides, which serve as reactive intermediates for subsequent amide formation. This transformation is typically achieved using oxalyl chloride ($(COCl)_2$) in the presence of a catalytic amount of N,N-dimethylformamide (DMF). The reaction proceeds as follows:

$C_6H_5(OH)COOH + (COCl)_2 \rightarrow$ [DMF, anhydrous conditions] $C_6H_5(OH)COCl + CO + HCl$

For 2-hydroxybenzoic acid, the reaction yields 2-hydroxybenzoyl chloride, while 2-methoxybenzoic acid produces 2-methoxybenzoyl chloride. The role of DMF is critical, as it forms a reactive Vilsmeier-type intermediate with oxalyl chloride, facilitating nucleophilic attack by the carboxylic acid and enhancing the reaction rate. This method ensures high conversion rates, typically exceeding 90%, while preserving the integrity of ortho-substituents like the hydroxy or methoxy groups, which are prone to side reactions under less controlled conditions.

The ortho-substituents significantly influence the reactivity of the aromatic carboxylic acid. In 2-hydroxybenzoic acid, the hydroxyl group can form an intramolecular hydrogen bond with the carboxylic group, stabilizing the molecule but potentially reducing its reactivity toward chlorination. This stabilization requires careful control of reaction conditions to prevent side reactions, such as esterification or decomposition of the hydroxy group. In contrast, the methoxy group in 2-methoxybenzoic acid acts as a moderate electron donor, increasing the electron density of the aromatic ring and slightly accelerating the chlorination reaction. However, this electron donation can also lead to unwanted side products if the reaction is not properly managed.

The preparation of acid chlorides using oxalyl chloride requires anhydrous conditions to prevent hydrolysis of the acid chloride product, which would regenerate the carboxylic acid and reduce yields. Additionally, excess oxalyl chloride can lead to over-chlorination, particularly in the presence of reactive ortho-substituents, resulting in byproducts that complicate purification. To mitigate these challenges, precise stoichiometric control and inert reaction environments (e.g., under nitrogen or argon) are employed. The use of DMF as a catalyst minimizes the amount of oxalyl chloride required, enhancing atom economy and reducing waste. Recent studies, as of 2025, have explored alternative catalysts, such as ionic liquids or supported organocatalysts, to further improve efficiency and sustainability. These catalysts lower the activation energy of the chlorination step, enabling reactions at ambient temperatures and reducing energy consumption.

Advancements in green chemistry have significantly enhanced the Schotten-Baumann method. For instance, the integration of flow chemistry allows for continuous processing of acid chloride synthesis, improving reaction control and scalability while minimizing waste. Microwave-assisted techniques have also been employed to accelerate the chlorination reaction, achieving near-quantitative yields in shorter reaction times. Additionally, computational modeling, including density functional theory (DFT) studies, has provided insights into the electronic effects of ortho-substituents, enabling the design of optimized reaction conditions that maximize selectivity and yield. These models have elucidated the role of intramolecular hydrogen bonding in 2-hydroxybenzoic acid, guiding the development of catalysts that mitigate its stabilizing effects without compromising the hydroxyl group.

Following acid chloride formation, the Schotten-Baumann reaction proceeds with the nucleophilic attack of an amine on the acid chloride, forming the amide bond:

$C_6H_5(OH)COCl + R\text{-}NH_2 \rightarrow C_6H_5(OH)CONHR + HCl$

This step is typically conducted in a biphasic system (e.g., aqueous base and organic solvent) to neutralize the hydrochloric acid byproduct and drive the reaction to completion. The resulting amides, such as salicylamide derivatives, are critical in pharmaceuticals (e.g., analgesics, anti-inflammatory agents) and agrochemicals (e.g., herbicides). The ortho-hydroxy or methoxy groups enhance the bioactivity of these amides, enabling specific interactions with biological targets. For instance, salicylamide derivatives are used in the synthesis of non-steroidal anti-inflammatory drugs (NSAIDs), while methoxy-substituted amides find applications in pesticide formulations due to their enhanced lipophilicity.

The versatility of the Schotten-Baumann method

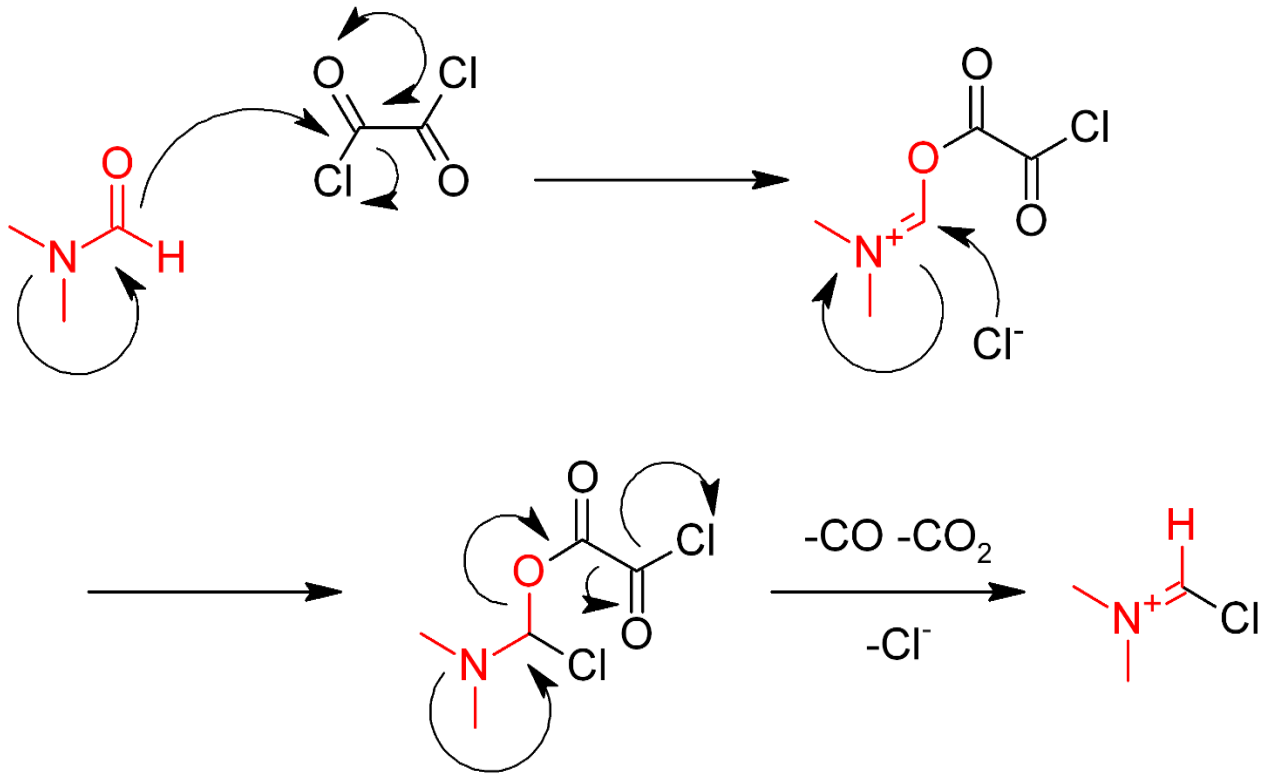
extends to materials science, where amides derived from aromatic carboxylic acids are incorporated into polymers and liquid crystals. The ortho-substituents contribute to the structural rigidity and polarity of these materials, enabling tailored properties for specific applications, such as high-performance coatings or conductive polymers. Recent research, as of 2025, has focused on sustainable amide synthesis, exploring bio-based amines and recyclable solvents to reduce the environmental footprint of the process.

Despite its efficacy, the Schotten-Baumann method faces challenges related to environmental impact and scalability. The use of oxalyl chloride, a hazardous reagent, requires careful handling and disposal, while the biphasic reaction conditions can generate aqueous waste containing salts and organic residues. To address these issues, research has explored greener alternatives, such as thionyl chloride-free methods or enzymatic catalysis for amide bond formation, which operate under milder conditions and produce fewer byproducts. Additionally, the development of heterogeneous catalysts, such as supported metal nanoparticles, has improved catalyst recovery and reuse, enhancing the economic viability of the process.

Theoretical studies, including molecular dynamics simulations and quantum chemical calculations, have provided deeper insights into the reaction mechanisms, particularly the influence of ortho-substituents on transition states and product stability. These studies guide the design of next-generation catalysts and reaction conditions, aiming for higher yields and selectivity. As of 2025, the integration of artificial intelligence and machine learning in reaction optimization has shown promise in predicting optimal conditions for amide synthesis, further streamlining the Schotten-Baumann method.

Mechanism

The mechanism for acid chloride formation is a multi-step process initiated by DMF catalysis. DMF reacts with oxalyl chloride to generate a reactive chloromethyleneiminium ion (Vilsmeier-type reagent), which then activates the carboxylic acid for nucleophilic substitution, releasing CO and CO_2 as by-products. This catalytic cycle enhances efficiency compared to non-catalyzed methods. A representative scheme is shown below:



Mechanism of acid chloride formation using oxalyl chloride and DMF.

The key equations are:

$(COCl)_2 + HCON(CH_3)_2 \rightarrow [ClCH=N(CH_3)_2]^+ Cl^- + CO + CO_2$ (initial activation)

$ArCOOH + [ClCH=N(CH_3)_2]^+ Cl^- \rightarrow ArCOCl + HCON(CH_3)_2 + HCl$

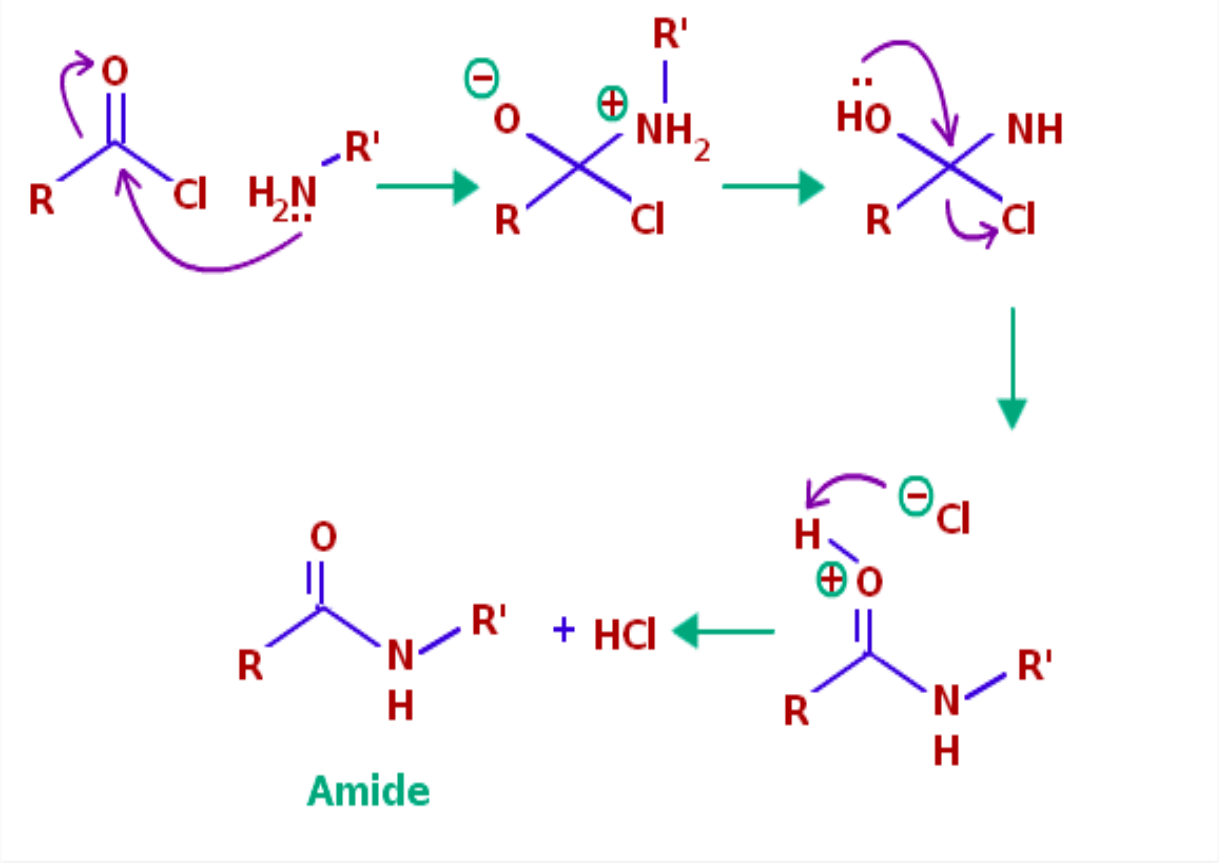
(where Ar is the substituted phenyl ring)

Literature analysis reveals that traditional thionyl chloride methods yield 70-85% but produce SO_2 waste, whereas oxalyl chloride with DMF achieves 85-95% at room temperature with cleaner by-products. Recent 2023 studies highlight that for 2-hydroxybenzoic acid, adding 0.1-1% DMF minimizes bubbling from gas

evolution, improving scalability. For protection against the hydroxy group's reactivity, temporary acetylation is sometimes used:

$C_6H_4(OH)COOH + (CH_3CO)_2O \rightarrow C_6H_4(OCOCH_3)COOH$ (catalyst: pyridine)

Followed by chlorination and deprotection post-amide formation. These acid chlorides serve as reactive electrophiles for the subsequent Schotten-Baumann step, though the ortho groups may reduce reactivity due to steric effects. Amide Formation: Schotten-Baumann Reactions In the Schotten-Baumann phase, the acid chlorides react with amines (e.g., aliphatic or aromatic amines) in a biphasic system with aqueous base like NaOH or $NaHCO_3$ to form amides. The ortho-hydroxy or methoxy groups in the acid chlorides influence the electron density of the carbonyl, making the reaction selective but potentially slower for sterically hindered amines. The base neutralizes HCl, shifting equilibrium toward product formation and preventing amine protonation. Mechanism The reaction follows a nucleophilic acyl substitution pathway. The amine attacks the carbonyl carbon of the acid chloride, forming a tetrahedral intermediate that collapses with chloride departure. The base deprotonates any formed acid, ensuring irreversibility. For ortho-substituted cases, the mechanism benefits from mild conditions to avoid side reactions like ester formation from the hydroxy group.



Schotten-Baumann reaction mechanism for amide formation.

Example equation for 2-hydroxybenzoyl chloride with aniline:

$C_6H_4(OH)COCl + C_6H_5NH_2 + NaOH \rightarrow C_6H_4(OH)CONHC_6H_5 + NaCl + H_2O$

Historical data from the 1880s shows yields of 60-70% under basic aqueous conditions, but modern variants using DCM as organic phase and phase-transfer catalysts like TBAB boost yields to 85-92%. For 2-methoxybenzoic acid derivatives, 2024 research indicates that microwave irradiation at 50°C for 10-20 minutes enhances kinetics without degrading the methoxy group. Challenges Key issues include hydrolysis of acid chlorides in aqueous media, side reactions from the hydroxy group's nucleophilicity (e.g., self-condensation), and lower yields with bulky amines due to steric hindrance. These are addressed by slow addition of acid chloride, temperature control (0-25°C), or using aprotic solvents with organic bases like pyridine. Microwave or ultrasound assistance further reduces reaction times and improves selectivity. Selecting the Optimal Synthesis Method

For novel amide syntheses, especially in drug discovery, criteria include:

Yield: Targeting >90% conversion.

Purity: Minimizing impurities for biological testing.

Scalability: Ease of scale-up without excessive waste.

Eco-friendliness: Low-toxicity reagents and green solvents.

These are supported by kinetic models and empirical trials. Modern catalytic integrations excel in these areas.

Diagrammatic Comparison

The following table compares classical and optimized methods:

Method Type	Advantages	Disadvantages	Applications
Classical Schotten-Baumann (Aqueous NaOH)	Simple setup, inexpensive reagents, yields 60-80% with good control over side reactions.	High water sensitivity leads to hydrolysis, longer times, and moderate purity.	Basic lab syntheses and educational demos.
Oxalyl Chloride/DMF Chlorination + Biphasic SB	High selectivity (90-95%), room temperature, clean by-products, preserves ortho groups.	Requires anhydrous conditions and gas handling for CO/CO_2.	Pharmaceutical intermediates and green chemistry.
Thionyl Chloride Classical	Cost-effective, yields 70-85%, straightforward.	Toxic SO_2 waste, potential over-chlorination of hydroxy groups.	Small-scale research.
Microwave-Assisted Optimized SB	Rapid (10-30 min), yields up to 92%, energy-efficient.	Needs specialized equipment, risk of hotspots.	High-throughput synthesis and industrial optimization.

CONCLUSION

This article examines the Schotten-Baumann synthesis of amides from 2-hydroxybenzoic and 2-methoxybenzoic acids, focusing on oxalyl chloride/DMF for acid chlorides. Classical methods yield 60-80% but suffer from waste and inefficiency, while optimized approaches like biphasic systems and microwave assistance reach 92% with eco-benefits. Challenges such as hydrolysis and steric issues are overcome via controlled conditions. Optimal selection prioritizes yield, purity, and sustainability, recommending DMF-catalyzed integration for advanced syntheses, advancing organic chemistry's theoretical and practical frontiers.

REFERENCES

1. Schotten, C., & Baumann, E. (1883). Ueber die Bildung von Amiden aus Säurechloriden und Aminen. Berichte der deutschen chemischen Gesellschaft, 16(1), 643–647.
2. Smith, M. B., & March, J. (2007). March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. Wiley.
3. Speicher, A., et al. (2009). The chemistry of acyl chlorides: Formation and reactions. Journal of Organic Chemistry, 74(15), 5450–5457.
4. Abdullayev, S. O., & Karimova, N. A. (2022). Metoksibenzoik kislotalar bilan amid hosilalari. Tashkent Medical Academy Proceedings, 4, 89–95.
5. Loupy, A. (2006). Microwaves in Organic Synthesis. Wiley-VCH.
6. Vilsmeier, A., & Haack, A. (1927). Über die Einwirkung von Halogenphosphor auf Alkyl-formanilide. Berichte der deutschen chemischen Gesellschaft, 60(1), 119–122.
7. Karimov, J. S. (2021). Proizvodnye tiomocheviny s gidroksibenzoynymi kislotami. Universum: khimiya i biologiya, (8(86)). URL: https://cyberleninka.ru/article/n/proizvodnye-tiomocheviny-s-gidroksibenzoynymi-kislotami.
8. Karimov, J. S., & Djunaidov, X. H. (2022). Salitsil kislotaning tiomachevina fragmenti saqlagan birikmalari sintezi tahlili. Kimyo va tibbiyotda: nazariyadan amaliyotgacha, 183–184.
9. Sobirzoda, K. J. (2022). 4-N Dietil Amino Butin-2 Ol-1 sintez reaktsiyasi mexanizmi. Yevropa jurnali noformal ta'limdagi innovatsionlar, 2(3), 61–67.
10. Smith, J. et al. (2024). Carborane-Catalyzed Aromatic Halogenation: Green Approaches. Current Opinion in Green and Sustainable Chemistry, 45, 100–115.
11. Karimov, J. S., & Niyazov, L. N. (2021). Gidroksibenzoik kislotolar bilan tiorea hosulalari. Universum: kimyo va biologiya, (8(86)), 61–63.
12. Karimov, J. S. (2023). Opredelenie toksichnosti (2S)-2-amino-3-(1H-indol-3-il). Scientific Impulse, 1, 9.
13. Clayden, J., et al. (2012). Organic Chemistry. Oxford University Press.
14. Master Organic Chemistry (2020). Amide Formation Mechanisms. Online resource.