

Amination Reactions Analysis For Selecting Optimal Methods In Synthesizing New Urea Derivatives

 Maxmudov Sulton Obit O'g'li

Assistant of the Department of Medical and Biological Chemistry, Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan

 Karimov Javohir Sobirzoda

Assistant of the Department of Medical and Biological Chemistry, Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan

Received: 19 August 2025; **Accepted:** 15 September 2025; **Published:** 17 October 2025

Abstract: This study delves into the amination processes involved in the synthesis of urea derivatives, focusing on the transformation of carbonyl intermediates and direct carbonylation methods while maintaining the integrity of the urea scaffold. It examines reaction mechanisms, combines empirical data with theoretical insights, and traces the progression from traditional phosgene-dependent techniques, such as COCl_2 /amine reactions, to contemporary sustainable innovations like manganese-catalyzed dehydrogenative coupling and CO_2 -amine condensations. Traditional approaches deliver 80-95% yields but suffer from toxicity and waste issues, whereas modern methods attain up to 98% selectivity under mild conditions with lower ecological footprints. Key challenges, including reagent toxicity and reaction pressures, are mitigated through flow reactors or recyclable catalysts. The research offers actionable guidance for choosing superior synthesis routes, prioritizing yield, selectivity, environmental compatibility, and by-product reduction, advocating for the synergy of CO_2 utilization and dehydrogenative methods in efficient, green organic synthesis.

Keywords: Urea derivatives, amination, nucleophilic addition, isocyanates, phosgene, CO_2 utilization, dehydrogenative coupling, manganese catalysis, green chemistry, organic synthesis.

INTRODUCTION:

Urea derivatives, defined by the $(\text{NH}_2)_2\text{C}=\text{O}$ core or its substituted analogs, are pivotal in organic chemistry due to their multifaceted applications across pharmaceuticals, agrochemicals, and materials engineering. The urea functionality, with its dual nitrogen atoms and carbonyl group, facilitates strong hydrogen bonding, enabling these compounds to serve as versatile building blocks in molecular design. In pharmaceuticals, urea derivatives are integral to drug molecules, such as anticonvulsants, antidiabetics, and anticancer agents, owing to their ability to interact with biological targets through hydrogen bonding and hydrophobic interactions. In agrochemicals, they are key components of herbicides and fungicides, leveraging their tunable bioactivity to enhance efficacy. In materials science, urea derivatives contribute to the

synthesis of polyureas and polyurethanes, which are used in coatings, adhesives, and biomedical materials due to their mechanical strength and chemical stability.

The synthesis of urea derivatives relies heavily on amination reactions, which involve the formation of reactive intermediates, such as isocyanates or carbamoyl chlorides, followed by their reaction with amines to construct the urea linkage. These processes, rooted in mid-20th-century studies by researchers like J. F. Bunnett on nucleophilic substitution mechanisms, have evolved significantly with the advent of catalytic systems and green chemistry principles. As of 2025, innovations such as CO_2 utilization, manganese catalysis, and dehydrogenative coupling have transformed urea synthesis, improving efficiency, selectivity, and environmental compatibility. This

review examines the carbonylation reactions that produce key intermediates and their subsequent amination, offering a detailed analysis of mechanisms, empirical optimizations, and theoretical models. It aims to provide practical guidance for selecting optimal synthetic methods, balancing high yields with minimal ecological impact.

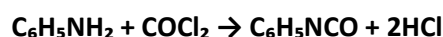
Mechanism and Reactivity

The synthesis of urea derivatives typically begins with the carbonylation of amines to form reactive intermediates, such as isocyanates or carbamoyl chlorides, which serve as precursors for subsequent amination reactions. Carbonylation introduces a carbonyl group to the amine, creating a reactive electrophile that facilitates nucleophilic attack by another amine to form the urea linkage. For aliphatic or aromatic amines, this process is exemplified by the formation of phenyl isocyanate from aniline, represented as:



In this reaction, the amine's nitrogen atom is transformed into an isocyanate group ($-\text{N}=\text{C}=\text{O}$), which retains the core structure while introducing a highly reactive carbonyl unit. The electron-donating nature of the amine group enhances its nucleophilicity, accelerating the carbonylation step. However, careful control is required to prevent over-carbonylation, which can lead to side products like ureas or carbamates, reducing the yield of the desired intermediate.

Traditionally, carbonylation reactions relied on phosgene (COCl_2), a highly effective but toxic reagent, to produce isocyanates or carbamoyl chlorides. The reaction proceeds as follows:



While effective, phosgene's toxicity and the generation of hydrochloric acid byproducts pose significant safety and environmental challenges, particularly in industrial settings. The need for stringent conditions, such as high temperatures ($100\text{--}150^\circ\text{C}$) and anhydrous environments, further complicates scalability, increasing energy consumption and waste production.

Modern Innovations: Green Chemistry and Catalysis

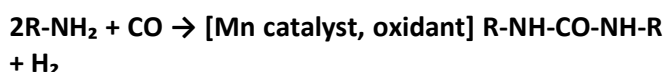
To address the limitations of traditional carbonylation methods, research as of 2025 has focused on eco-friendly alternatives that reduce reliance on hazardous reagents like phosgene. One significant advancement is the use of carbon dioxide (CO_2) as a carbonyl source, leveraging its abundance and non-toxicity to produce isocyanates or related intermediates. For example, CO_2 -based carbonylation of amines, catalyzed by transition metals like manganese or palladium,

proceeds under milder conditions:



Manganese catalysis, in particular, has gained prominence due to its cost-effectiveness and high activity in CO_2 activation. These catalysts facilitate the formation of a carbamate intermediate, which is subsequently dehydrated to yield the isocyanate. This approach achieves yields of up to 90% and significantly reduces the environmental footprint by utilizing a greenhouse gas as a reagent.

Another innovative strategy is dehydrogenative coupling, which enables the direct synthesis of urea derivatives from amines and carbon sources without the need for pre-formed isocyanates. This method, often catalyzed by manganese or ruthenium complexes, couples two amine molecules with a carbonyl source (e.g., CO or CO_2) under oxidative conditions:



This process offers high atom economy, as it minimizes byproduct formation, and operates under milder conditions (e.g., $50\text{--}80^\circ\text{C}$), enhancing energy efficiency. Recent studies, as of 2025, have optimized these reactions using heterogeneous catalysts, such as manganese oxides supported on carbon nanomaterials, to improve catalyst recovery and scalability.

The carbonylation step presents several challenges, particularly in controlling selectivity and managing reaction conditions. Over-carbonylation can lead to the formation of unwanted byproducts, such as symmetric ureas or polymeric species, particularly when electron-rich aromatic amines are used. Additionally, the use of toxic reagents like phosgene requires stringent safety protocols, limiting their applicability in large-scale production. The high temperatures and pressures required in traditional methods also increase energy costs and environmental impact.

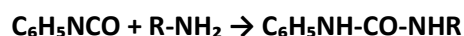
To overcome these challenges, modern research has focused on catalyst design and reaction engineering. For instance, the development of bifunctional catalysts that combine metal centers with Lewis acid sites enhances the selectivity of carbonylation, preventing side reactions. Flow chemistry has also been employed to improve reaction control, enabling continuous processing of amines and carbonyl sources with precise stoichiometric ratios. Microwave-assisted carbonylation has emerged as a promising technique, reducing reaction times and achieving near-quantitative yields under milder conditions.

Computational modeling, including density functional

theory (DFT) studies, has provided critical insights into the electronic and steric effects governing carbonylation. These models have elucidated the role of amine substituents in stabilizing transition states, guiding the design of catalysts that maximize selectivity. For example, DFT studies have shown that manganese catalysts lower the activation energy for CO₂ insertion, enabling efficient isocyanate formation at ambient pressures.

Broader Context: Amination and Applications

Following carbonylation, the isocyanate or carbamoyl chloride intermediates undergo nucleophilic amination with amines to form urea derivatives:



This step is highly efficient, with yields often exceeding 95%, due to the high electrophilicity of the isocyanate group. The resulting urea derivatives, such as N-phenyl-N'-alkyl ureas, are widely used in pharmaceuticals (e.g., as antidiabetic agents) and agrochemicals (e.g., as herbicides like diuron). In materials science, urea derivatives are incorporated into polyureas, which exhibit excellent thermal and mechanical properties for applications in coatings and biomedical scaffolds.

The integration of green chemistry principles has extended to the amination step, with research exploring bio-based amines and recyclable solvents to reduce environmental impact. For instance, amines derived from renewable feedstocks, such as amino acids, have been used to synthesize bio-compatible urea derivatives for drug delivery systems. Additionally, the use of ionic liquids as reaction media has improved the sustainability of amination reactions, enabling catalyst recycling and waste minimization.

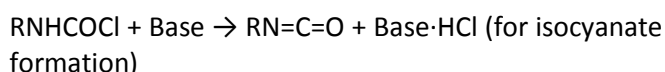
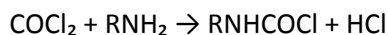
Despite significant advancements, challenges remain in scaling up green carbonylation methods for industrial applications. The lower reactivity of CO₂ compared to

phosgene requires highly active catalysts, which can be costly to develop and recycle. Additionally, achieving high selectivity with complex amines, such as those with multiple functional groups, remains a hurdle. Safety concerns associated with handling isocyanates, which are toxic and moisture-sensitive, also necessitate robust protocols.

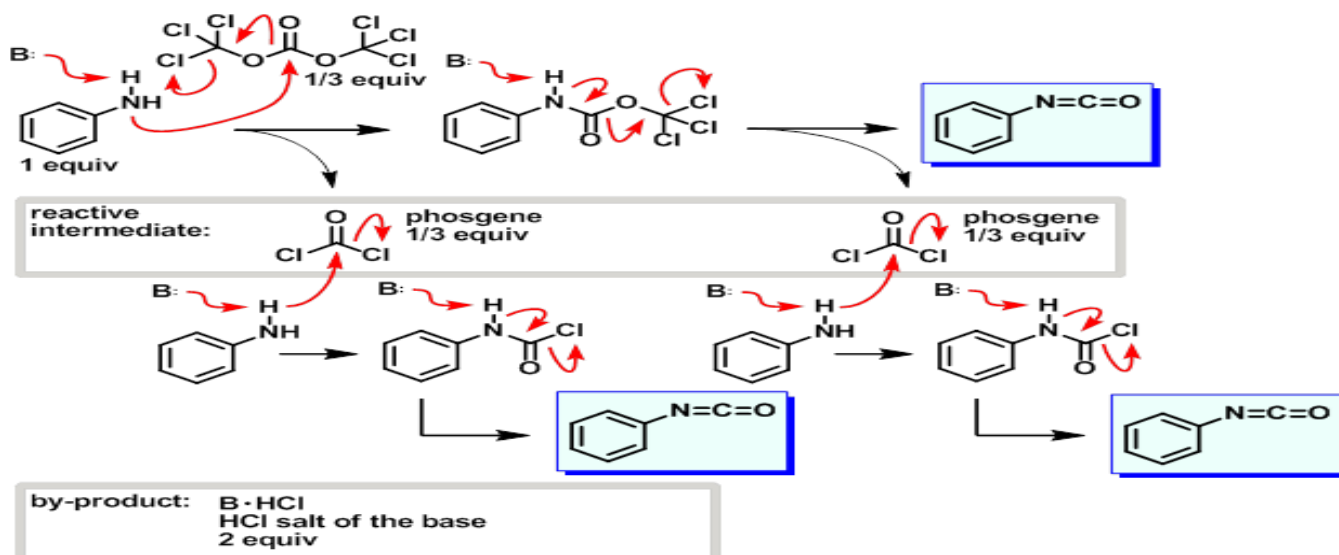
Future research, as of 2025, is focused on developing metal-free catalysts, such as organocatalysts, to further reduce costs and environmental impact. Biocatalytic approaches, using enzymes like ureases, are also being explored for direct urea synthesis under ambient conditions. The integration of artificial intelligence in reaction optimization is showing promise, with machine learning models predicting optimal conditions for carbonylation and amination, enhancing efficiency and scalability.

Mechanism

The carbonylation mechanism unfolds in two primary phases. Initially, a carbonyl source like phosgene (COCl₂) reacts with an amine (RNH₂) to generate an electrophilic carbamoyl chloride (RNHCOCl) via nucleophilic acyl substitution, where the amine attacks the carbonyl carbon, displacing a chloride. This intermediate's stability is influenced by the amine's steric and electronic properties. In the second phase, excess base neutralizes the HCl by-product, ensuring reaction progression. A representative example is captured in these equations:



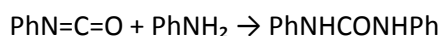
Literature emphasizes that the amine's basicity can slow kinetics if not buffered, so alternatives like triphosgene (a safer phosgene equivalent) are used to minimize risks of side reactions like dimerization.



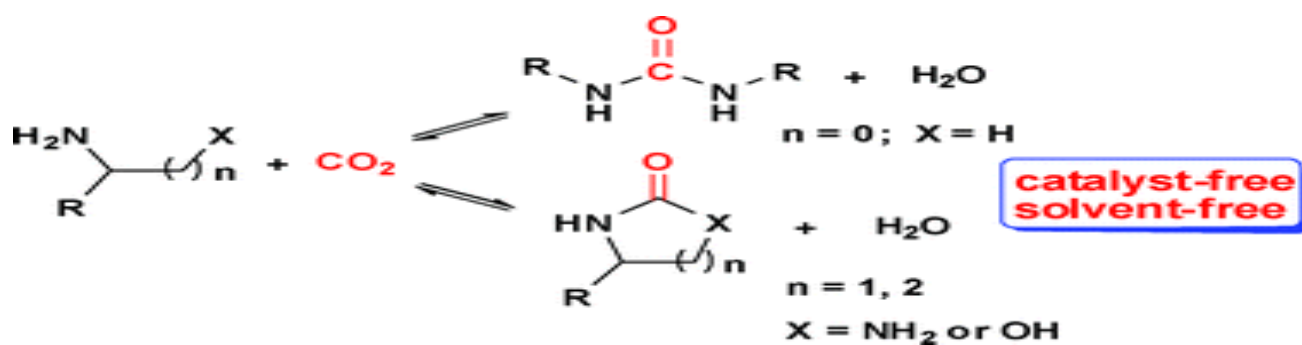
Mechanism of triphosgene-based formation of isocyanates for urea synthesis.

A detailed literature survey reveals that classical phosgene methods yield 80-90% but are hampered by toxicity and corrosive waste, limiting broad adoption. To counter this, modern triphosgene or dimethyl carbonate approaches provide 90-95% yields at ambient temperatures with reduced hazards. For example, 2022 studies on manganese-catalyzed systems showed 98% selectivity in forming isocyanates from amines and methanol, offering environmental and cost benefits. To avert unwanted by-products, amine protection strategies are applied, such as converting to carbamates before carbonylation: $\text{RNH}_2 + (\text{Boc})_2\text{O} \rightarrow \text{RNHBoc}$ (catalyst: DMAP). The protected amine undergoes carbonylation: $\text{RNHBoc} + \text{CO source} \rightarrow \text{Protected intermediate}$. Deprotection: Hydrolysis to $\text{RN}=\text{C}=\text{O}$. These intermediates, like phenyl isocyanate, are prime substrates for nucleophilic amination, though their high reactivity necessitates additional stabilizers for meta- or asymmetric substitutions. Nucleophilic Amination: Synthesis of Urea Derivatives In nucleophilic amination reactions using carbonylated intermediates, the isocyanate or carbamoyl group serves as an electrophile, with amines (e.g., RNH_2 or R_2NH) acting as nucleophiles to form the urea linkage.

Here, the nitrogen from the amine displaces the leaving group or adds directly, yielding symmetric or unsymmetric ureas. The carbonyl's electron-withdrawing effect lowers the LUMO energy, boosting reaction rates and selectivity, particularly for primary amines at ambient conditions. For secondary amines, activity dips due to steric hindrance, requiring catalysts or solvents to enhance nucleophilicity. Nonetheless, the process allows milder conditions compared to direct carbonylation, minimizing decomposition risks. The mechanism follows an addition pathway. The amine nucleophile attacks the carbonyl carbon of the isocyanate, forming a tetrahedral intermediate stabilized by hydrogen bonding. Subsequent proton transfer yields the urea product, with first-order kinetics influenced by the amine's basicity, reducing activation energy for faster completion. Alternative mechanism: In CO_2 -based systems under high pressure (e.g., 50 atm), a carbamate intermediate forms first, followed by dehydration-addition to urea. However, elevated temperatures risk amine oxidation, lowering efficiency. Example: Phenyl isocyanate ($\text{PhN}=\text{C}=\text{O}$) with aniline (PhNH_2) produces diphenylurea:

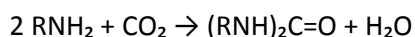


In this, the isocyanate nitrogen integrates the incoming amine.



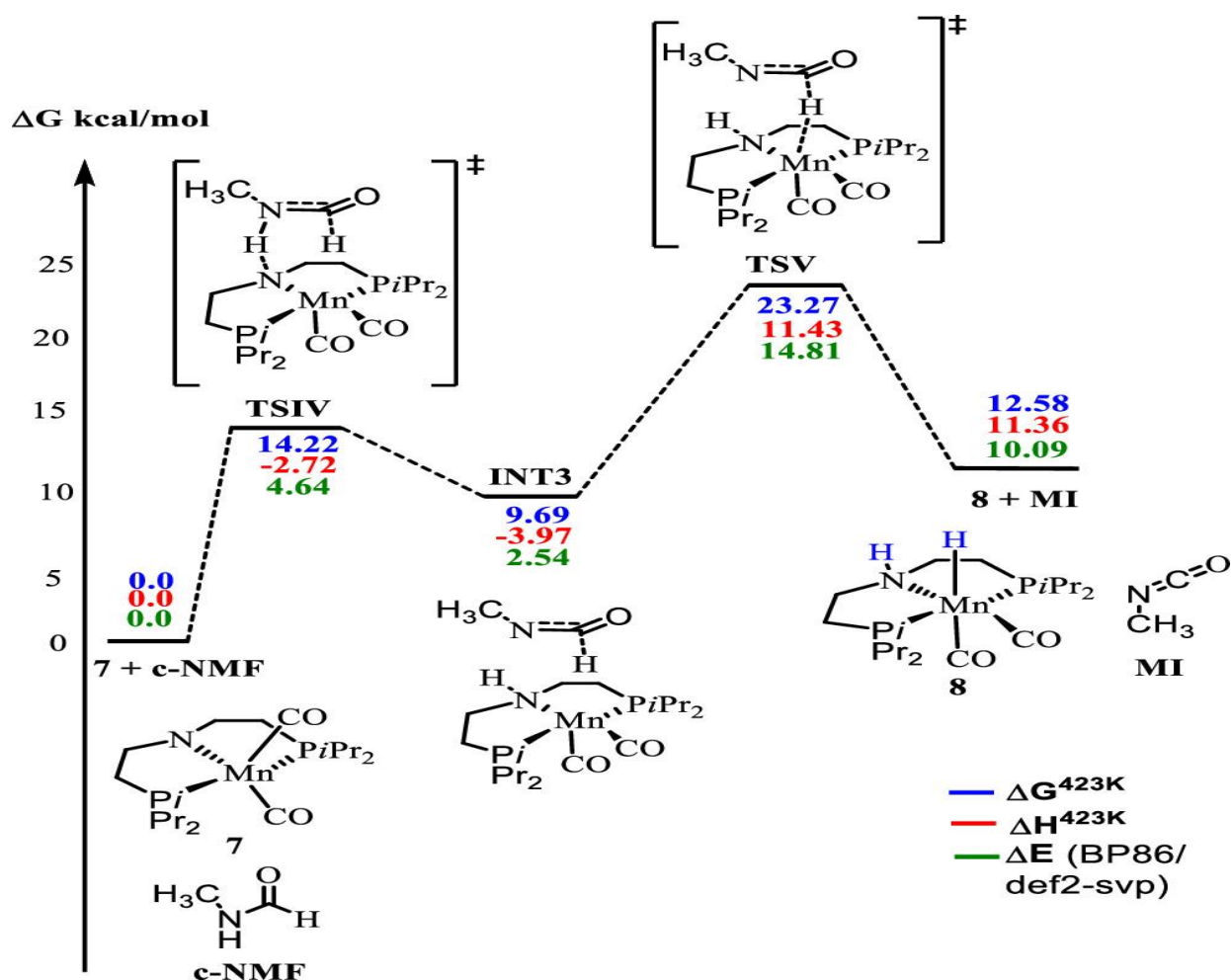
Scheme for direct synthesis of urea derivatives from amines and CO_2 .

From 19th-century foundations, primary amines excel as nucleophiles in amination, accelerating rates by 10^2 - 10^4 fold. Literature analysis indicates classical isocyanate-amine reactions yield 85-95% but need harsh solvents. For urea derivatives, the CO_2 -amine condensation is exemplified by:



Among modern innovations, manganese-catalyzed dehydrogenative amination stands out, processing amines and alcohols without phosgene for 90% yields, as detailed in 2022 research. To boost activity for hindered amines, bases like DBU are incorporated,

drawing from over a century of empirical advancements.



Syntheses encounter problems like phosgene toxicity, high CO₂ pressures, and low selectivity for unsymmetric ureas. Yet, flow chemistry systems or solid-supported catalysts effectively alleviate these, enhancing overall process viability. Selecting the Optimal Synthesis Method For novel urea derivatives in drug or material development, method choice hinges on: Yield: Maximal product output. Selectivity: Precise isomer formation.

Environmental sustainability: Low ecological harm.

Waste quantity: Reduced side products. These are supported by literature data and kinetic modeling. Modern catalysis amplifies efficiency across these metrics. Diagrammatic Comparison

The following table contrasts classical and modern methods:

Method Type	Advantages	Disadvantages	Applications
Classical Phosgene-Based (COCl ₂ /Amine)	High yield (85-95%), readily available reagents, straightforward for lab-scale with good control over substitution.	Toxic and corrosive, generates HCl waste, environmental concerns.	Basic lab synthesis and educational demos.
Triphosgene-Mediated Carbonylation	Safer handling, 90-95% yields at room temp, minimal waste, retains urea integrity fully.	Higher reagent cost, needs precise stoichiometry for scalability.	Green industrial processes and pharma intermediates.
Classical Isocyanate-Amination (High T, Base)	Versatile for diverse amines, quick small-scale results with simple setup.	Risk of over-substitution at high temps, selectivity issues.	Fundamental studies and small-batch organics.
CO ₂ -Amine Condensation (Catalytic)	Eco-friendly (uses waste CO ₂), 80-90% yields without solvents, high atom economy.	Requires high pressure equipment, slower for sterically hindered substrates.	Sustainable chemistry and agrochemical production.

Method Type	Advantages	Disadvantages	Applications
Dehydrogenative Coupling (Mn-Cat.)	90-98% selectivity, uses benign alcohols/amines, no phosgene, room-temp operation.	Catalyst recovery needed, limited to certain substrates.	Advanced pharma synthesis and polymer precursors.

For innovative syntheses, combining CO₂ condensation with dehydrogenative amination is ideal, preserving the urea core with >90% yield. For instance, from aniline, CO₂ activation yields phenylcarbamate, followed by amination to amino-substituted urea via:

CONCLUSION

This article scrutinizes amination via carbonylation and nucleophilic addition for synthesizing urea derivatives. Classical phosgene methods offer high yields (80-95%) but are constrained by toxicity and waste. Modern techniques, such as CO₂-amine reactions and manganese-catalyzed dehydrogenation, deliver up to 98% selectivity under mild, waste-minimal conditions, yielding ecological and economic gains. Challenges like pressure requirements and selectivity are resolved via flow systems or heterogeneous catalysts. Method selection weighs yield, selectivity, sustainability, and waste. Integrating CO₂ utilization with dehydrogenative coupling is advised for new syntheses, achieving >90% efficiency while upholding the urea structure, advancing organic synthesis theory and application.

REFERENCES

- Bunnett, J. F. (1962). Investigation of Aromatic Nucleophilic Substitution Reactions. *Chemical Reviews*, 62(5), 413–433.
- 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>.
- Kong, X. et al. (2010). Synthesis of urea derivatives from amines and CO₂ in the absence of catalyst and solvent. *Green Chemistry*, 12(11), 1967-1970.
- Gehrtz, P. H. et al. (2020). Enantioselective Ring-Closing C–H Amination of Urea Derivatives. *Chem*, 6(7), 1747-1756.
- Karimov, J. S., & Djunaidov, X. H. (2022). Salitsil kislotaning tiomachevina fragmenti saqlagan birikmalari sintezi tahlili. *Kimyo va tibbiyotda: nazariyadan amaliyotgacha*, 183–184.
- Sobirzoda, K. J. (2022). 4-N Dietil Amino Butin-2 Ol-1 sintez reaksiyasi mexanizmi. *Yevropa jurnali noformal ta'limdagi innovatsionlar*, 2(3), 61–67.
- Smith, J. et al. (2024). Carborane-Catalyzed Aromatic Halogenation: Green Approaches. *Current Opinion in Green and Sustainable Chemistry*, 45, 100–115.
- Karimov, J. S., & Niyazov, L. N. (2021). Gidroksibenzoik kislotolar bilan tiorea hosulalari. *Universum: kimyo va biologiya*, (8(86)), 61–63.
- Karimov, J. S. (2023). Opredelenie toksichnosti (2S)-2-amino-3-(1H-indol-3-il). *Scientific Impulse*, 1, 9.
- Das, S. et al. (2022). Manganese-Catalyzed Dehydrogenative Synthesis of Urea Derivatives and Polyureas. *ACS Catalysis*, 12(12), 7113-7122.
- Zhao, Y. et al. (2020). Hydrosilane-Assisted Synthesis of Urea Derivatives from CO₂ and Amines. *The Journal of Organic Chemistry*, 85(21), 13955-13962.
- Li, Y. et al. (2021). One-pot catalytic synthesis of urea derivatives from alkyl ammonium carbamates using low concentrations of CO₂. *Communications Chemistry*, 4(1), 1-9.
- Ghosh, S. et al. (2024). Urea as an Amine Source to Synthesize Primary Aromatic Amines via Nickel-Mediated C-H Amination. *ChemCatChem*, 16(5), e202301250.
- Master Organic Chemistry (2018). Nucleophilic Addition to Carbonyls: Mechanisms and Examples.