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ADVANCES IN THE SYNTHESIS OF QUINAZOLINONES VIA THE CONDENSATION OF 2-AMINOBENZAMIDE AND ALDEHYDES: A JOURNEY FROM CLASSICAL TO SUSTAINABLE PROTOCOLS

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ABSTRACT

The condensation of 2-Aminobenzamide with aldehydes represents a cornerstone strategy for constructing Quinazolin-4(3*H*)-one and 2,3-Dihydroquinazolin-4(1*H*)-one scaffolds, privileged structures in medicinal chemistry due to their diverse pharmacological profiles. This review chronicles the significant evolution of this transformation, tracing its progression from early classical methods reliant on strong acids and high temperatures to contemporary green and sustainable synthetic paradigms. We highlight key advancements including the adoption of Lewis acid catalysts, microwave irradiation, and innovative oxidative systems. A particular focus is placed on modern breakthroughs such as metal-free organocatalysis, solvent-free mechanochemical approaches, and the application of nanocatalysts and reusable heterogeneous systems. These developments have collectively enhanced the environmental compatibility, efficiency, and stereoselectivity of this reaction, solidifying its status as a versatile and indispensable tool in synthetic and medicinal chemistry.

KEYWORDS: 2-Aminobenzamide; Aldehydes; Quinazolinone; Green Chemistry; Heterogeneous Catalysis; Organocatalysis; Mechanochemistry; Sustainable Synthesis.

1. INTRODUCTION

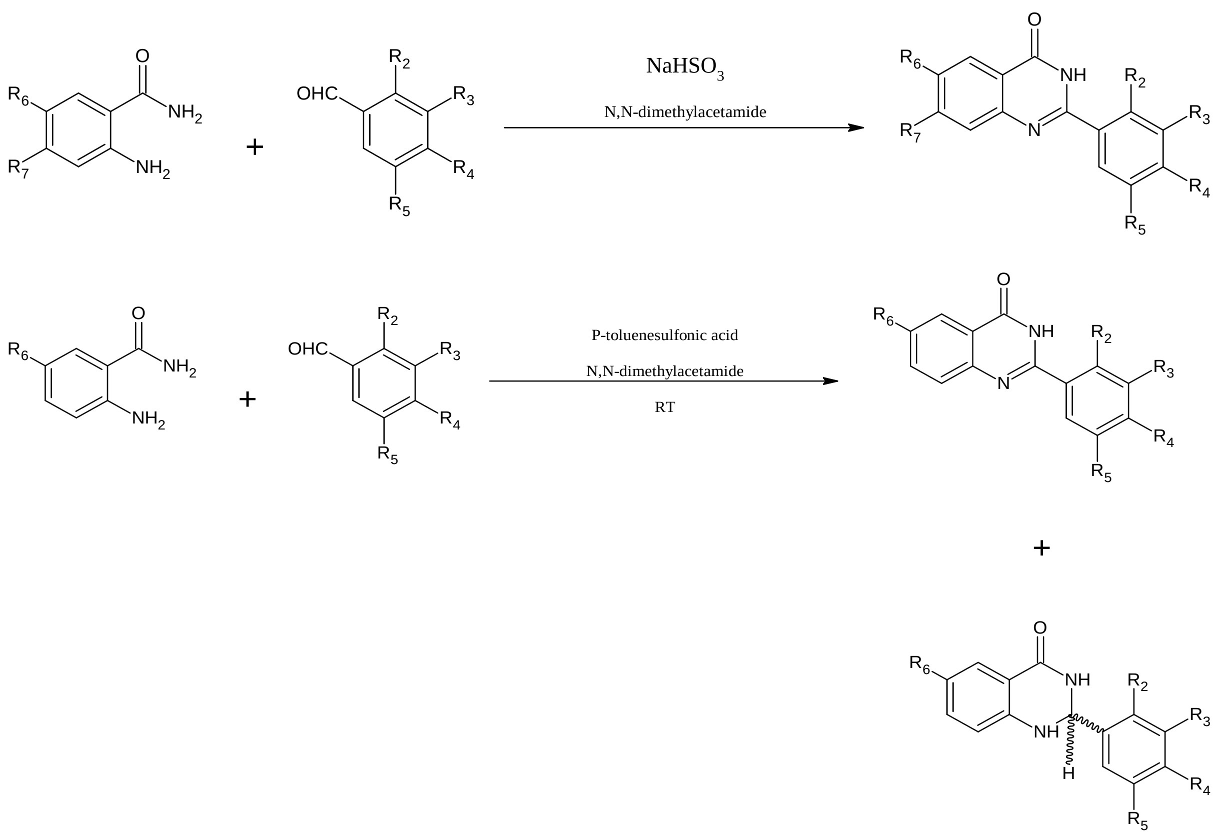
Quinazolinones are nitrogen-containing heterocycles that constitute a core structural motif in numerous bioactive molecules and pharmaceuticals. Their broad spectrum of biological activities encompassing anticancer, antimicrobial, anti-inflammatory, and anticonvulsant properties has sustained significant interest in their synthesis.[1,2] Among the various synthetic routes, the condensation of 2-Aminobenzamide (anthranilamide) with aldehydes stands out as a highly efficient and atom-economical one-pot method for accessing 2-substituted quinazolinones.[2] The reaction typically proceeds via the initial formation of a Schiff base, followed by intramolecular cyclization. Depending on the reaction conditions, the product can be isolated as the 2,3-Dihydroquinazolinone or undergo subsequent oxidation to yield the fully aromatic Quinazolin-4(3*H*)-one.

Despite its conceptual simplicity, achieving high yields under mild conditions often necessitates catalytic promotion. This review systematically explores the catalytic landscape and strategic innovations that have shaped this fundamental transformation, emphasizing the shift towards sustainability and operational simplicity.

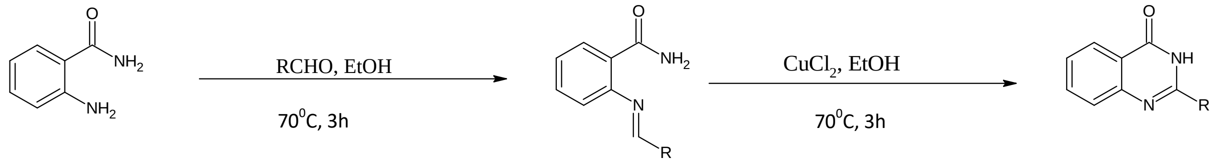
2. Classical and Early Catalytic Methods

Initial protocols for this condensation were often characterized by harsh conditions. Early work by Hour *et al.* demonstrated the reaction's sensitivity to temperature and additives.[3] Using *N*,*N*-dimethylacetamide (DMAc) as a solvent with sodium bisulfite at 150 °C afforded the fully aromatic 2-Phenylquinazolin-4(3*H*)-one. In contrast, employing a catalytic amount of p-toluenesulfonic acid (p-TSA) at a lower temperature (80 °C) selectively yielded the 2,3-dihydroquinazolinone derivative (scheme 1).

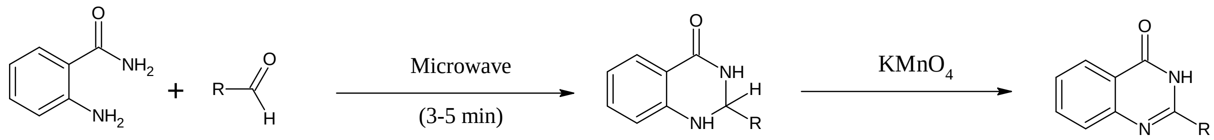
The introduction of Lewis acids and stoichiometric oxidants marked a significant improvement. Abdel-Jalil *et al.* reported a one-pot synthesis using $CuCl_2$ in refluxing ethanol (scheme 2), where the metal salt served a dual role as a Lewis acid catalyst and an oxidant, directly providing Quinazolin-4(3*H*)-ones in good yields.[4] Similarly, Bakavoli *et al.* leveraged microwave irradiation witrth $KMnO_4$ as an oxidant in DMAc (scheme 3), drastically reducing reaction times from hours to minutes while maintaining high yields.[5] Mulakayala *et al.* further advanced Lewis acid catalysis by identifying $InCl_3$ as a highly efficient and moisture-tolerant catalyst (scheme 4), enabling the synthesis of 2-arylquinazolinones at room temperature with excellent yields and broad functional group tolerance.[6]



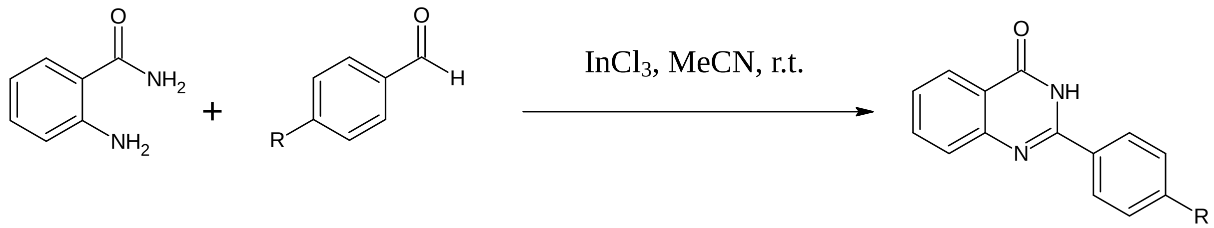
Scheme 1: $NaHSO_4$- and p-TsOH-catalyzed cyclocondensation of 2-Aminobenzamide with aldehydes.



Scheme 2: $CuCl_2$-catalyzed oxidative cyclocondensation.



Scheme 3: Microwave-assisted synthesis of Quinazolin-4(3*H*)-ones followed by $KMnO_4$-mediated oxidation.



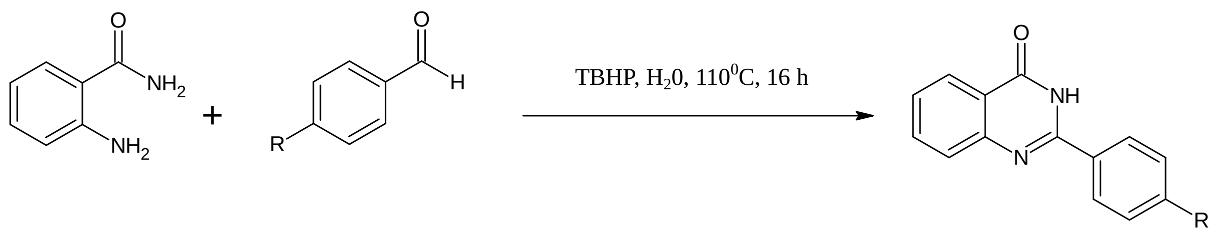
Scheme 4: $InCl_3$-catalyzed synthesis of 2-arylquinazolin-4(3*H*)-ones from 2-Aminobenzamide and aromatic aldehydes.

3. Emergence of Green and Sustainable Protocols

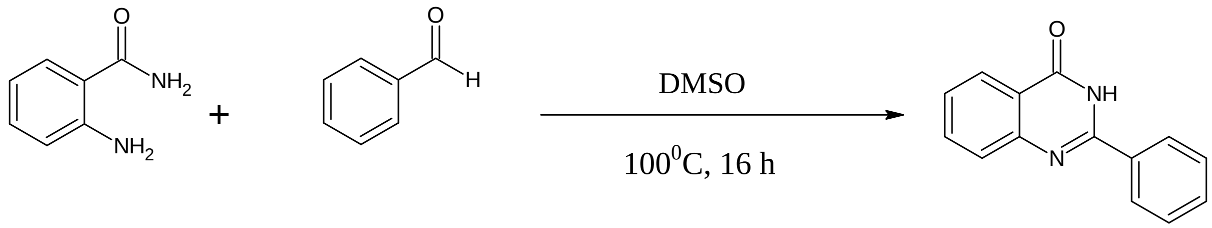
The 21st century has witnessed a paradigm shift towards environmentally benign synthesis, profoundly influencing this reaction.

3.1. Green Solvents and Oxidants

A major thrust has been the replacement of hazardous solvents. Sharif *et al.* demonstrated a catalyst-free oxidative cyclization in water using *tert*-butyl hydroperoxide (TBHP) (scheme 5), accommodating a wide range of aldehydes, including challenging aliphatic substrates.[9] Kim and Cheon developed an exceptionally green protocol using molecular oxygen as the terminal oxidant in wet DMSO, providing a metal and stoichiometric oxidant-free route to quinazolinones (scheme 6).[10] Kausar *et al.* utilized graphene oxide (GO) nanosheets as a metal-free carbocatalyst (scheme 7) for the synthesis of dihydroquinazolinones in water at room temperature, with the catalyst being recyclable over multiple runs.[11]

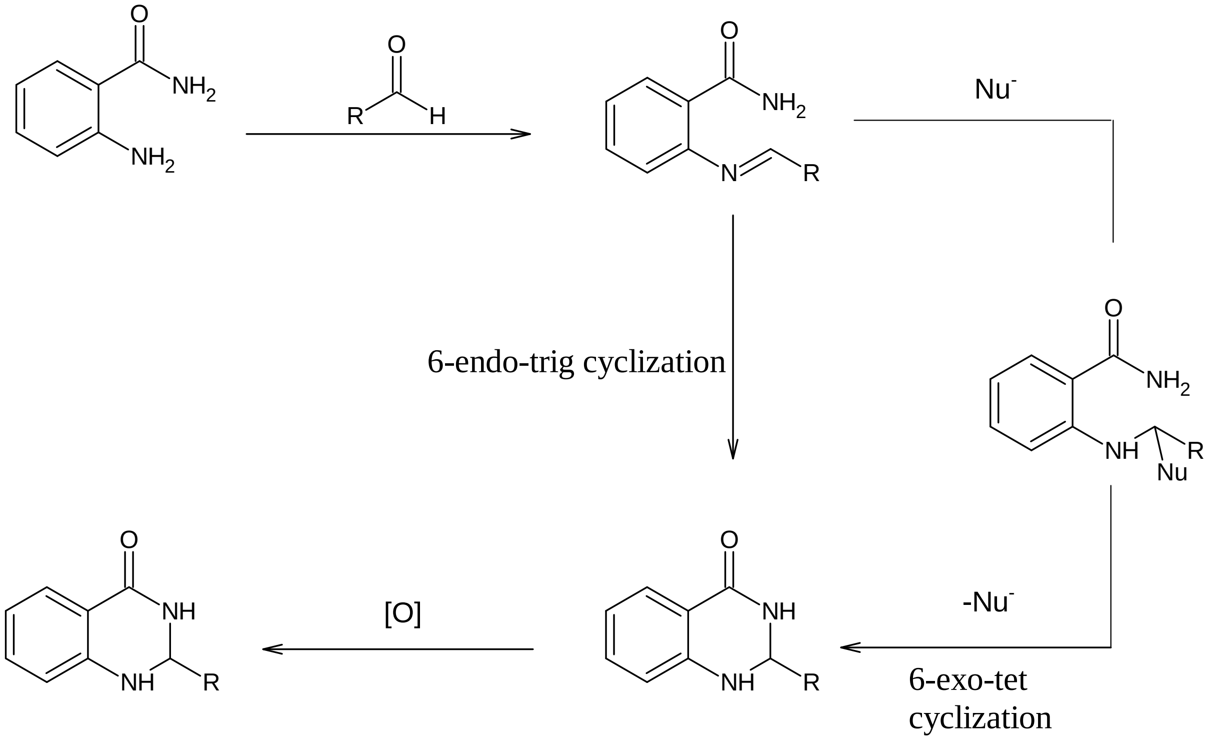


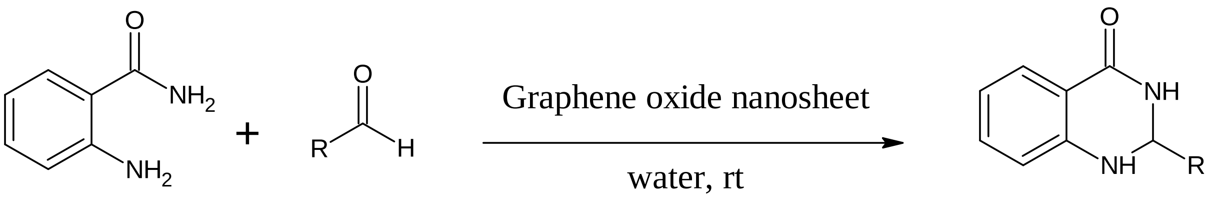
Scheme 5: TBHP-Mediated Oxidative Cyclocondensation.



Scheme 6: DMSO-Mediated Oxidative Cyclocondensation.

Mechanism

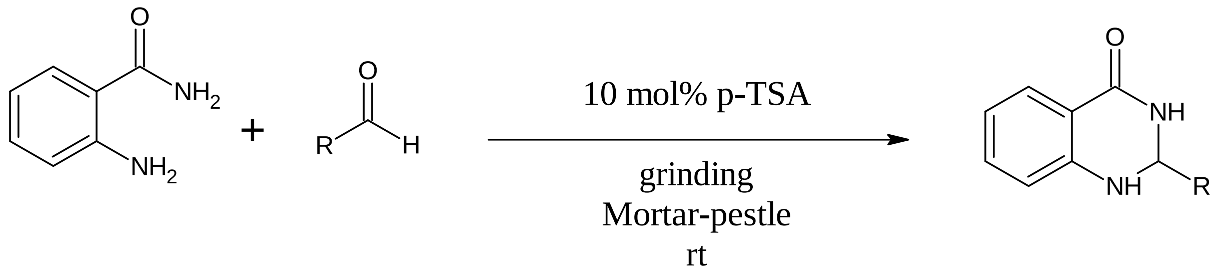




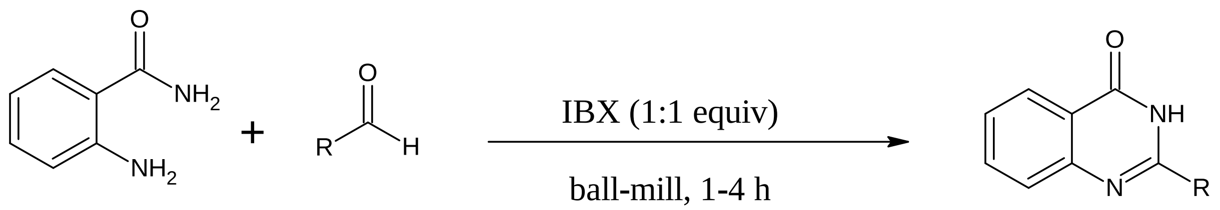
Scheme 7: Graphene Oxide Nanosheet-Catalyzed Green Synthesis of Quinazolinone.

3.2. Solvent-Free and Mechanochemical Approaches

Eliminating solvents entirely represents the pinnacle of green synthesis. Yashwantrao *et al.* reported a highly efficient mechanochemical synthesis of dihydroquinazolinones using p-TSA, achieving excellent yields within minutes through manual grinding or ball milling (scheme 8).[14] In a remarkable study, Alam *et al.* safely harnessed the powerful oxidant o-iodoxybenzoic acid (IBX) under solvent-free ball-milling conditions (scheme 9), a feat made possible by the unique moderating effect of the *ortho*-amide group in 2-Aminobenzamide, which prevents the explosive decomposition typically associated with such reagents.[13]



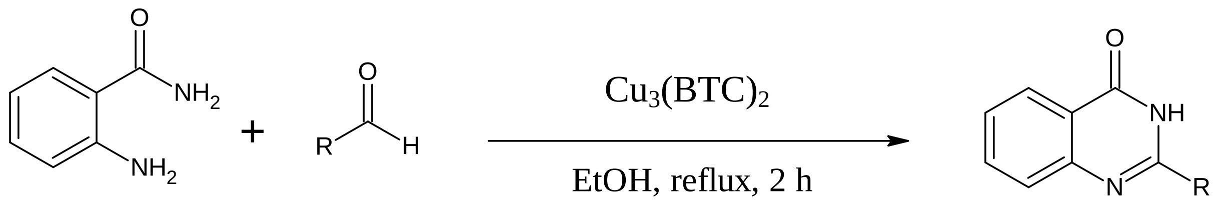
Scheme 8: p-TSA Catalyzed Solvent-Free Grinding Method for Quinazolinone.



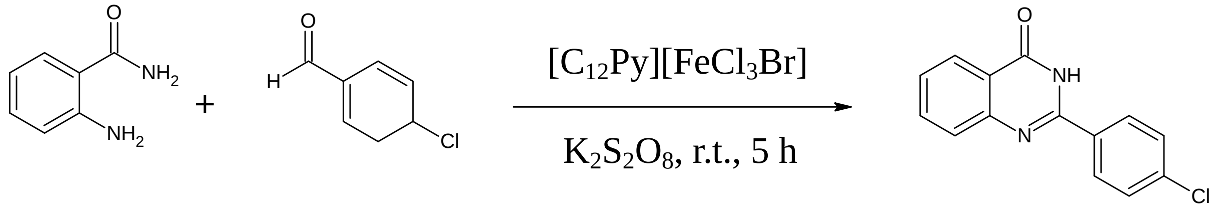
Scheme 9: IBX-Promoted Solvent-Free Synthesis of Quinazolinones under Ball-Milling Conditions.

3.3. Advanced and Reusable Catalytic Systems

The development of sophisticated, recyclable catalysts has been a key advancement. Latha *et al.* employed a copper-based metal-organic framework ($Cu_3(BTC)_2$) as a robust and reusable heterogeneous catalyst in ethanol (scheme 10), achieving high yields with easy catalyst recovery.[15] Dutta *et al.* designed an iron-containing ionic liquid that acted as both catalyst and reaction medium in water (Scheme 11), showcasing remarkable versatility by allowing selective synthesis of either dihydroquinazolinones or their oxidized analogues simply by adjusting the reaction parameters.[16]



Scheme 10: $Cu_3(BTC)_2$-Catalyzed One-Pot Synthesis of Quinazolinones.

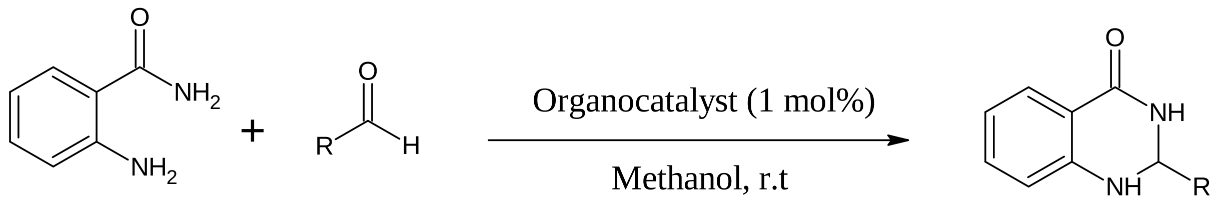


Scheme 11: Ionic Liquid $[C_{12}Py][FeCl_3Br]$-Catalyzed Oxidative Cyclization for Quinazolinone Synthesis Using $K_2S_2O_8$ as Oxidant.

3.4. Asymmetric Organocatalysis

A landmark in the field was achieved by Siva *et al.*, who introduced enantioselectivity to this transformation.[12] Using a novel chiral organocatalyst derived from Cinchona alkaloids, they accomplished an asymmetric condensation/amine addition cascade at room temperature (scheme 12). This protocol provided access to enantioenriched 2,3-

dihydroquinazolinones with exceptional yields (up to 99%) and enantioselectivities (up to 97% ee), highlighting the potential for creating stereochemically complex targets.



Scheme 12: Organocatalyst-Mediated Synthesis of Quinazolinones.

4. CONCLUSION

The journey of the 2-Aminobenzamide-aldehyde condensation reflects the broader evolution of organic synthesis from traditional, resource-intensive practices to modern, sustainable methodologies. The transition to green solvents, the adoption of energy-efficient techniques like microwave and mechanochemistry, the design of versatile and reusable catalysts, and the introduction of sophisticated strategies like enantioselective organocatalysis have collectively transformed this classical reaction.

These advancements have not only minimized environmental impact but also expanded the synthetic utility and accessibility of quinazolinone scaffolds. Future research will likely focus on further refining catalytic efficiency, exploring new modes of activation (e.g., photoredox catalysis), and integrating these methods with continuous flow processes for industrial-scale applications. The continued innovation in this area ensures that this fundamental reaction will remain a vital and evolving tool for drug discovery and the synthesis of complex heterocyclic systems.

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