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RESEARCH ARTICLE

One–Pot Synthesis of Quinazolin–4(3H) –ones Catalyzed by 2,4,6–Trichloro–1,3,5–triazine (TCT) Under Solvent–Free Conditions

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ABSTRACT: An efficient and environmentally benign one-pot synthesis of quinazolin-4(3H)-ones has been developed using 2,4,6-trichloro-1,3,5-triazine (TCT) as a cost-effective and commercially available catalyst under solvent-free conditions. This methodology involves a three-component reaction of anthranilic acid, diverse amines, and formic acid, proceeding smoothly in a single step without the need for intermediate isolation. The catalytic role of TCT significantly enhances reaction efficiency while maintaining mild conditions (room temperature), making the process both energy-efficient and operationally simple. Key advantages of this protocol include short reaction times (50–70 min), excellent product yields (88–95%), and broad substrate compatibility, accommodating both electron-donating and electron-withdrawing substituents on aromatic amines. The solvent-free approach aligns with green chemistry principles by eliminating hazardous organic solvents, reducing waste, and simplifying purification. Furthermore, the method avoids the use of expensive or moisture-sensitive reagents, addressing common limitations of traditional quinazolinone syntheses, such as harsh conditions, prolonged reaction times, and low yields. The synthesized quinazolin-4(3H)-ones are of significant pharmaceutical interest due to their diverse biological activities, including anticancer, antimalarial, and anti-inflammatory properties. This work not only provides a practical and scalable synthetic route but also highlights the potential of TCT as a versatile catalyst for multicomponent reactions. The combination of mild conditions, high atom economy, and environmental sustainability makes this protocol a valuable addition to the synthetic toolbox for medicinal and heterocyclic chemistry.

Keywords: Quinazolin-4(3H)-ones, 2,4,6-Trichloro-1,3,5-triazine (TCT), Solvent-free synthesis, Multicomponent reaction (MCR), Green chemistry, Heterocyclic compounds

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1. INTRODUCTION

Quinazolin-4(3H)-ones constitute a prominent class of nitrogen-containing heterocycles that have attracted substantial attention in pharmaceutical and medicinal chemistry due to their diverse biological activities. These compounds exhibit a broad spectrum of pharmacological properties, including antihypertensive [1], anticonvulsant [2], anticancer [3], diuretic, and anti-inflammatory effects. Their structural versatility allows them to interact with various biological targets, making them valuable scaffolds in drug discovery. Notably, the quinazolin-4(3H)-one core is found in several natural products with significant therapeutic potential. Among these, febrifugine [4-6] and isofebrifugine [7] stand out as potent antimalarial agents, demonstrating the clinical relevance of this heterocyclic system.

Beyond their occurrence in nature, quinazoline derivatives play a pivotal role in modern drug development,

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particularly as enzyme inhibitors. They serve as key pharmacophores in tyrosine kinase inhibitors [8-9], which are crucial for targeting cancer signaling pathways, as well as in dihydrofolate reductase inhibitors [10] for antibacterial and antiparasitic applications. Additionally, quinazolinones have been identified as effective tubulin polymerization inhibitors [11-12], further expanding their utility in anticancer therapy. The ability of these compounds to modulate multiple biological pathways underscores their importance in the design of novel therapeutic agents.

Traditional synthetic routes to quinazolin-4(3H)-ones often involve cycloaddition reactions between anthranilic acid derivatives and electrophilic reagents such as imidates and iminohalides [13-16]. Alternative strategies include multistep sequences, such as the condensation of benzoxazin-4-one carboxylic esters with amines [17] or other functionalized intermediates [18]. Anthranilic acid and its derivatives are particularly valuable starting materials, enabling access to a wide array of quinazolinone structures through various synthetic transformations [19-22]. Despite these advancements, many existing methods suffer from significant limitations, including low yields, extended reaction times, and the need for harsh conditions or expensive reagents. For example, intermediates like benzoxazin-4-ones are often hygroscopic and thermally unstable, complicating their isolation and handling [17].

Efforts to overcome these challenges have led to the development of more efficient and stereoselective synthetic approaches. One notable method involves the reaction of anthranilic acid derivatives with 1,3-oxazolidine-2-thiones, which provides homochiral quinazolinones in high optical purity [23]. Microwave-assisted synthesis has also emerged as a promising alternative, enabling rapid access to quinazolin-4(3H)-ones through the condensation of anthranilic acid with amines and formic acid or orthoesters under controlled conditions [24]. While these techniques offer improvements in reaction speed and yield, they often require specialized equipment or remain limited in substrate scope.

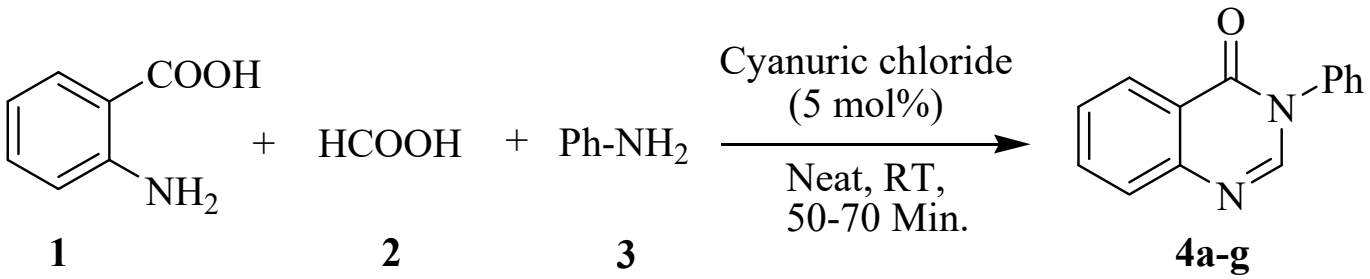
The persistent drawbacks of conventional methods—such as the use of toxic solvents, energy-intensive conditions, and complex purification steps—have driven the search for greener and more sustainable synthetic strategies. Surface-mediated reactions represent a promising avenue, as they can enhance reaction efficiency while minimizing waste and energy consumption. Solid-phase reactions often exhibit unique reactivity patterns that differ from solution-phase chemistry, leading to improved yields and selectivity. Furthermore, multicomponent reactions (MCRs) have gained prominence as a powerful tool for streamlining synthetic workflows. MCRs enable the construction of complex heterocycles in a single step, reducing the need for intermediate isolation and purification while maximizing atom economy [25-27].

In this context, 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, TCT) has emerged as a highly effective catalyst for organic transformations [28-30]. Its low cost, commercial availability, and ability to facilitate reactions under mild conditions make it an attractive choice for sustainable synthesis. Building on these advantages, we report a novel one-pot, three-component synthesis of quinazolin-4(3H)-ones using TCT as a catalyst under solvent-free conditions. This method leverages the synergistic benefits of MCRs and green chemistry, offering a straightforward, high-yielding, and environmentally benign route to these pharmacologically important heterocycles. By eliminating the need for solvents and reducing energy consumption, our approach aligns with the principles of sustainable chemistry while providing a practical and scalable alternative to traditional synthetic methods (Scheme 1). This study not only expands the synthetic toolkit for quinazolinone preparation but also highlights the potential of TCT as a versatile and eco-friendly catalyst. The combination of operational simplicity, broad substrate tolerance, and excellent yields positions this methodology as a valuable contribution to the field of heterocyclic and medicinal chemistry. Future investigations may explore further mechanistic insights and applications of this catalytic system in the synthesis of other biologically relevant scaffolds.

2. EXPERIMENTAL DETAILS

2.1. Experimental Procedure

The synthesis of quinazolin-4(3H)-one derivatives was carried out via a one-pot, three-component reaction under solvent-free conditions.



Scheme 1. Synthesis of quinazolin-4(3*H*)-ones.

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In a typical procedure, a mixture of anthranilic acid (1 mmol), aniline (1 mmol), formic acid (1.3 mmol), and cyanuric chloride (5 mol%) was stirred at room temperature. The reaction progress was monitored by thin-layer chromatography (TLC) using an appropriate solvent system until complete consumption of the starting materials was observed. Upon completion, the reaction mixture was quenched with water (10 mL), and the resulting solid product was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with 5% aqueous hydrochloric acid (3 × 5 mL) to remove any unreacted amines or acidic impurities, followed by drying over anhydrous sodium sulfate (Na_2SO_4). The solvent was then evaporated under reduced pressure to afford the crude product, which was further purified by recrystallization from ethanol when necessary. This procedure consistently provided the desired quinazolin-4(3H)-one derivatives in high yields (88–95%) with excellent purity, as confirmed by spectroscopic analysis.

2.2. Spectroscopic Data of Representative Compound

The structural characterization of the synthesized compounds was performed using FT-IR, ^{1}H NMR, and high-resolution mass spectrometry (HRMS). As a representative example, 3-bromo-4-(4-oxoquinazolin-3(4H)-yl)benzonitrile (4a) exhibited a melting point of 166–168°C. The FT-IR spectrum displayed characteristic absorption bands at 2210 cm^{-1} (C≡N stretch), 1700 cm^{-1} (C=O stretch), 1570 cm^{-1} (C=N stretch), and 1488 cm^{-1} (aromatic C=C vibrations). The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) revealed signals at δ 7.74 (d, J = 7.8 Hz, 1H), 7.69 (s, 1H), 7.55–7.61 (m, 3H), and 7.31–7.45 (m, 3H), corresponding to the aromatic protons of the quinazolinone and benzonitrile moieties. HRMS analysis confirmed the molecular formula $C_{15}H_8BrN_3O$, with an exact mass of 324.9851 and an observed $[M+H]^+$ peak at 325.1121, in full agreement with the proposed structure.

2.3. Substrate Scope and Reaction Optimization

The generality of this synthetic approach was demonstrated by employing various substituted anilines under the optimized reaction conditions, as summarized in Table 1. Electron-donating groups (e.g., methoxy) and electron-withdrawing substituents (e.g., bromo, nitro) were well-tolerated, affording the corresponding quinazolin-4(3H)-ones in excellent yields (90–95%) within 50–70 minutes. Notably, sterically hindered substrates such as 2,6-dibromoaniline (Entry 4e) and 2,4-dibromo-6-nitroaniline (Entry 4g) also participated efficiently, yielding the desired products in 93% and 92%, respectively. The consistency in reaction times and yields across diverse substrates underscores the robustness and versatility of this catalytic system. All synthesized compounds were fully characterized by IR, ^{1}H NMR, and HRMS, confirming their structural integrity and high purity.

This solvent-free, one-pot methodology not only simplifies the synthetic procedure but also enhances the sustainability of the process by eliminating the need for hazardous organic solvents and reducing energy consumption. The use of cyanuric chloride as a mild and efficient catalyst further contributes to the green chemistry aspects of this work, making it a practical and scalable approach for the synthesis of biologically relevant quinazolin-4(3H)-ones.

3. RESULTS AND DISCUSSION

The three-component coupling reaction between anthranilic acid, various amines, and formic acid was successfully achieved under solvent-free conditions at ambient temperature using 2,4,6-trichloro-1,3,5-triazine (TCT) as a catalyst (5 mol%) (Scheme 1). This synthetic strategy proved remarkably efficient, consistently delivering quinazolin-4(3H)-one derivatives in excellent yields (88–95%), as comprehensively documented in Table 1. The methodology demonstrates exceptional versatility, accommodating a wide range of structurally diverse amines while maintaining high reaction efficiency and product purity.

A key advantage of this catalytic system lies in its broad substrate compatibility. Both electron-rich and electron-deficient aromatic amines participated effectively in the transformation, with minimal influence on reaction kinetics or product yields. For instance, amines containing strongly electron-donating methoxy groups (Entries 4c, 4d, 4f) and those bearing electron-withdrawing substituents such as halogens (Entries 4a, 4b, 4e) or nitro groups (Entry 4g) all afforded the corresponding quinazolinones in uniformly high yields (90–95%). This remarkable insensitivity to electronic effects suggests that the reaction mechanism proceeds through a well-balanced pathway where neither nucleophilicity nor electrophilicity of the amine component becomes rate-limiting. Such robustness significantly enhances the synthetic utility of this method, as it eliminates the need for substrate-specific optimization.

The steric profile of the reaction was equally impressive, with ortho-substituted anilines (Entries 4b, 4e, 4g) reacting as efficiently as their para-substituted counterparts. This observation indicates that the catalytic system effectively overcomes steric hindrance, a common limitation in heterocyclic synthesis. Particularly noteworthy is the successful transformation of 2,6-dibromoaniline (Entry 4e), which produced the desired product in 93% yield despite the substantial steric encumbrance around the reactive amino group. Such tolerance to steric crowding is rare in conventional quinazolinone syntheses and underscores the unique advantages of this TCT-catalyzed approach.

The mild reaction conditions (room temperature, solvent-free) represent another significant improvement over existing methods. Traditional syntheses often require elevated temperatures, prolonged reaction times, or specialized equipment [13-16, 24], whereas this protocol completes within 50–70 minutes under ambient conditions.

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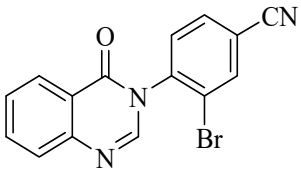
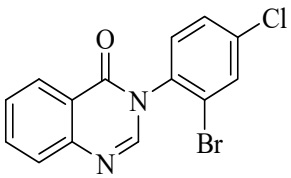
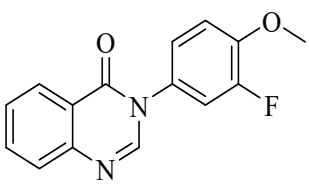
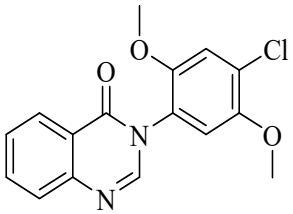
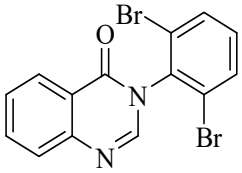
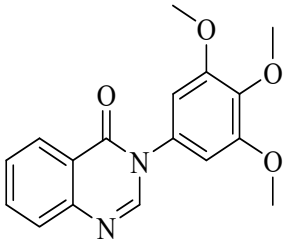
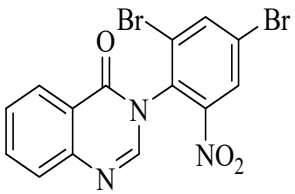
Table 1. Cyanuric chloride catalyzed synthesis of quinazolin-4(3*H*)-ones.

Entry	Anthranilic acid	Aniline	Formic acid	Product	Time (Min.)	Yield (%)
4a	Anthranilic acid	4-Amino-3-bromobenzonitrile	Formic acid	 **4a**	60	95
4b	Anthranilic acid	2-Bromo-4-chloroaniline	Formic acid	 **4b**	50	94
4c	Anthranilic acid	3-Fluoro-4-methoxyaniline	Formic acid	 **4c**	50	95
4d	Anthranilic acid	4-chloro-2,5-dimethoxyaniline	Formic acid	 **4d**	50	90
4e	Anthranilic acid	2,6-Dibromoaniline	Formic acid	 **4e**	50	93
4f	Anthranilic acid	3,4,5-Trimethoxyaniline	Formic acid	 **4f**	70	88
4g	Anthranilic acid	2,4-Dibromo-6-nitroaniline	Formic acid	 **4g**	60	92

[a]Yields refer to the pure isolated products. [b]All products are characterized by their IR ^{1}H NMR, and HRMS spectra.

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The energy efficiency of this process not only reduces operational costs but also minimizes the risk of thermal decomposition, particularly important for sensitive substrates. Furthermore, the solvent-free nature of the reaction aligns perfectly with green chemistry principles by eliminating volatile organic compounds (VOCs) from the synthetic workflow [25-27].

Mechanistically, TCT likely functions as a dual activator, simultaneously enhancing the electrophilicity of the formic acid carbonyl and facilitating the condensation between anthranilic acid and the amine component. This hypothesis is supported by the observation that reactions proceed to completion even with weakly nucleophilic amines, suggesting efficient activation of the carboxyl group. The catalyst's chloro substituents may serve as Lewis acidic sites, while the triazine core could participate in temporary covalent interactions with reaction intermediates, though detailed mechanistic studies would be required to confirm this proposal [28-31].

From a practical standpoint, the workup procedure is remarkably straightforward. The crude products precipitate upon aqueous workup and can be isolated through simple filtration or extraction, avoiding the need for column chromatography in most cases. When necessary, recrystallization from ethanol provides analytically pure compounds, as evidenced by the sharp melting points and unambiguous spectroscopic data (Section 2.2). This operational simplicity, combined with the high yields, makes the method particularly attractive for scale-up purposes.

The synthetic value of this methodology is further highlighted by comparison with existing literature. Conventional approaches often require multistep sequences [17-19], expensive catalysts, or generate stoichiometric amounts of waste [20-22]. In contrast, this one-pot protocol achieves comparable or superior yields while using a commercially available, inexpensive catalyst (TCT) and generating minimal byproducts. The atom economy is excellent, as all reactants are incorporated into the final product with only water as a byproduct.

The biological relevance of the obtained compounds adds another dimension to this work. The synthesized quinazolin-4(3H)-ones contain functional handles (halogens, nitriles, methoxy groups) at precisely the positions favored for medicinal chemistry applications [1-3,8-12]. For example, the bromo and nitro substituents in compounds 4a and 4g provide ideal sites for subsequent derivatization via cross-coupling reactions, potentially leading to libraries of bioactive molecules.

This TCT-catalyzed, three-component synthesis of quinazolin-4(3H)-ones represents a significant advancement in heterocyclic chemistry. The method combines broad substrate scope, exceptional functional group tolerance, mild reaction conditions, and operational simplicity with environmentally benign characteristics. Its efficiency, scalability, and alignment with green chemistry principles make it equally valuable for academic laboratories and industrial applications. Future studies could explore the extension of this catalytic system to other multicomponent reactions and investigate the biological activities of the synthesized quinazolinone derivatives.

4. CONCLUSION

In summary, this study presents a highly efficient, solvent-free, one-pot synthesis of quinazolin-4(3H)-ones catalyzed by TCT, demonstrating significant advancements over traditional methods. The three-component reaction of anthranilic acid, amines, and formic acid proceeds under mild conditions (room temperature) with excellent yields (up to 95%) and short reaction times (50–70 min), eliminating the need for energy-intensive heating or prolonged refluxing. The use of TCT as a low-cost, commercially available catalyst enhances reaction efficiency while avoiding the drawbacks of moisture-sensitive or expensive reagents. The solvent-free approach not only adheres to green chemistry principles but also simplifies workup procedures, as products can be isolated via simple extraction and recrystallization. The methodology exhibits broad substrate scope, tolerating a variety of functional groups (e.g., halogens, methoxy, nitro) on aromatic amines without compromising yield or reaction kinetics. This versatility is particularly valuable for medicinal chemistry, where structural diversity is crucial for bioactivity optimization. From a sustainability perspective, this protocol addresses key challenges in heterocyclic synthesis, including waste reduction, energy efficiency, and atom economy. The absence of solvents minimizes environmental impact, while the one-pot strategy reduces raw material consumption and synthetic steps. Furthermore, the operational simplicity and scalability of this method make it suitable for both academic research and industrial applications. Future directions could explore the catalytic mechanism of TCT in depth, as well as the application of this methodology to other heterocyclic systems. Additionally, the biological evaluation of the synthesized quinazolinones for pharmacological activity could further underscore the practical relevance of this work. By combining synthetic efficiency, environmental friendliness, and broad applicability, this study contributes to the growing field of sustainable organic synthesis and offers a robust platform for accessing biologically relevant quinazolinone derivatives.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

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Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally in the preparation of this manuscript.

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