Investigating 3*N*-Alkylation Efficiency in 4-Quinazolinone: A Comparative Analysis of Different C2 Substituents

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Background

Quinazolinone: A Privileged Scaffold

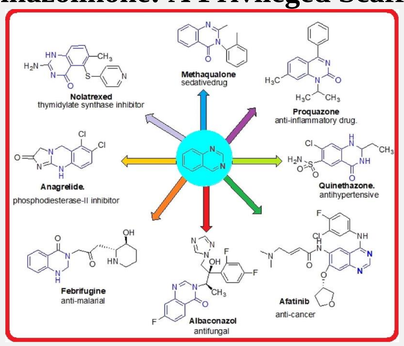


Figure 1. Quinazolinone is considered a 'privileged' scaffold due to its strong binding affinity for various biological targets, making it a promising candidate for therapeutic effects across diverse biological mechanisms **[1]**.

Our study focuses on exploring diverse approaches to modifying quinazolinone to assess the efficacy and practicality of various structural changes. By examining these modifications, we aim to establish foundational insights that will support future development of optimized derivatives. This work serves as a valuable resource for researchers by highlighting which structural changes are most effective, facilitating subsequent studies on therapeutic applications.

Antiparasitic Potential

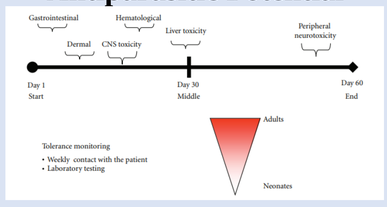


Figure 2. Side-effects of Current Treatments For Chagas Disease: Benznidazole and Nifurtimox **[3].**

One motivation for modifying quinazolinone, and developing new derivatives, is their potential as treatments for Chagas disease. Quinazolinone compounds have been identified as promising candidates for their ability to target and inhibit enzymes essential to the parasite's survival **[2]**. These findings suggest that quinazolinone derivatives could form the basis for novel therapies against Chagas, potentially offering improved efficacy and safety over existing treatments **[4][5]**.

Research Objectives

Objective 1: To determine the efficacy of *N*-alkylation in quinazolinone by varying the C2 substituents and assessing whether these changes lead to successful product formation.

Objective 2: To investigate the impact of different bases on proton abstraction at the *N*3 position, examining if this enables the formation of the alkylated product.

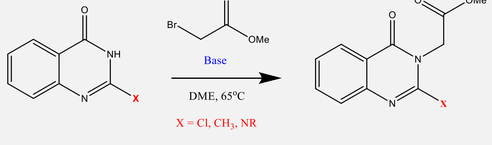
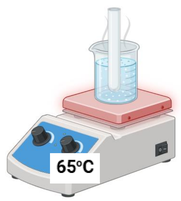


Figure 3. *N*-Alkylation of Quinazolinone: Evaluating the Impact of Various C2 Substituents and Bases.

Method

Chemical Synthesis



1.) Solvent
2.) Quinazolinone
3.) Base
4.) Methyl bromoacetate

Figure 4. Chemical Synthesis Process. Quinazolinone, solvent, and base are sequentially combined, followed by the addition of methyl bromoacetate. The reaction mixture is heated to 65 °C for 90 minutes. Conditions such as solvent and base identity were varied in different experiments.

Isolation and Purification

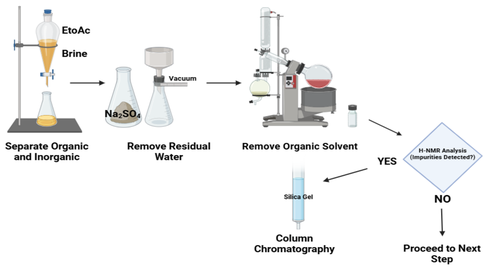


Figure 5. Isolation and Purification Process. The product undergoes liquid-liquid extraction using brine and ethyl acetate, followed by treatment with sodium sulfate to remove excess water. After filtering through vacuum to remove clumps, the organic solvents are evaporated via rotary evaporator. The TLC and the first ^{1}H NMR analysis checks product purity: if pure, no further purification is required; if impurities are present, the product is subjected to silica gel column chromatography, followed by a final ^{1}H NMR analysis to confirm purity.

Data Analysis

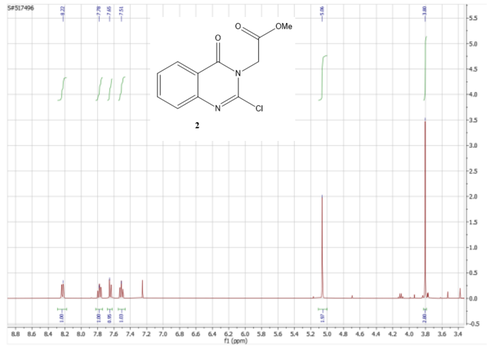
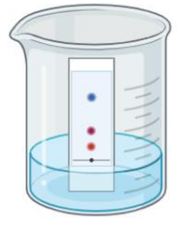


Figure 6: TLC analysis is crucial for tracking reaction progress and serves as an early indicator of product purity by detecting UV-active impurities in the crude product. In contrast, ^{1}H NMR provides a more detailed assessment of purity and structural integrity in the final stages. The ^{1}H NMR data shown above corresponds to product **2**.



Results

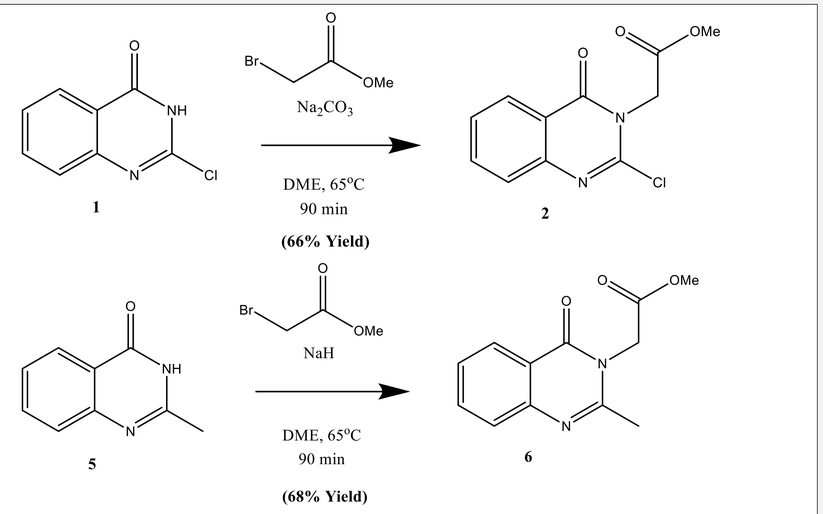


Figure 7. Synthesis of 4-Quinazolinone With Non-Bulky C2 Substituents. **Top:** *N*-Alkylation of 4(3H)-quinazolinone **1**, with a chlorine substituent at the C2 position, resulted in 66% yield of compound **2**. **Bottom:** *N*-Alkylation of 4(3H)-quinazolinone **5**, with a methyl substituent at C2 position and sodium hydride as base, resulted in 68% yield of compound **6**.

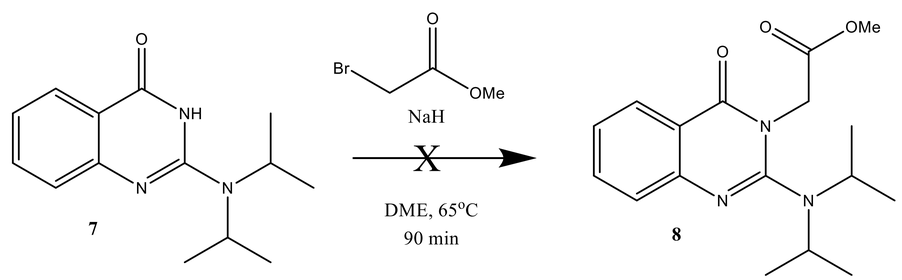


Figure 8. Synthesis Attempt with Bulky C2 Substituent. Successful synthesis of compound **7** from compound **1** was achieved with a bulky diisopropylamino C2 substituent. Efforts to alkylate compound **7** to form product **8** were unsuccessful.

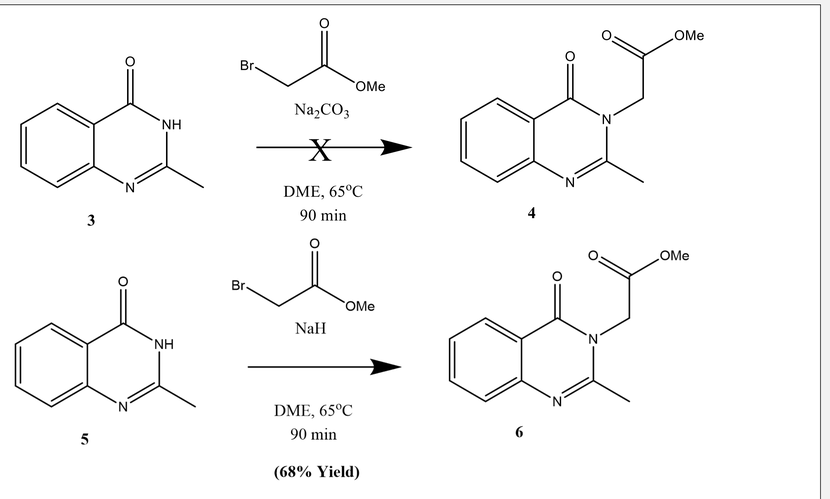


Figure 9. Base Selection Effects on N-Alkylation of 4-Quinazolinone. This figure compares two *N*-alkylation reactions with non-bulky C2 substituents. **Top:** Sodium carbonate (Na_2CO_3) was employed as the base. TLC and ^{1}H-NMR analysis suggest minimal conversion of compound **3** after 90 minutes. The ^{1}H-NMR analysis did not display the anticipated peaks for **4**. Instead, an unexpected peak suggesting the presence of the tautomerized **3** was observed rather than the expected product. **Bottom:** In the reaction from compound **5** to product **6**, using the stronger base sodium hydride (NaH) led to a successful outcome with a 68% yield.

Conclusions

- Less bulky substituents, such as methyl and chlorine, seem to facilitate successful *N*-alkylation, due to decreased steric hindrance.
- The bulkier substituent, diisopropylamine, might have hindered product formation due to steric hindrance around the reactive site.
- Using a stronger base, such as sodium hydride, improved alkylation efficacy. The weaker base, sodium carbonate, failed to yield the same product as reactions using sodium hydride within 90 minutes
- **Overall, the results suggest that reducing C2 substituent bulk enhances 3*N* alkylation, which is also facilitated by stronger bases for substrates lacking electron-withdrawing C2 substituents.**

Future Work

1. **Explore Base Strength and Steric Effects:** Investigate how different strong bases interact with both bulky and non-bulky C2 substituents to understand their combined impact on alkylation efficiency.
2. **Optimize Reaction Conditions:** Systematically vary parameters such as temperature, solvent choice, and reaction time to identify optimal conditions for N-alkylation of quinazolinone derivatives.
3. **Mechanistic Studies:** Conduct kinetic and computational analyses to elucidate the reaction mechanism, particularly the role of base strength in overcoming steric hindrance.

Acknowledgments

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References

[1] Alsibaee AM, Al-Yousef HM, Al-Salem HS. 2023. Quinazolinones, the winning horse in drug discovery. *Molecules.* 28(3):978. doi:10.3390/molecules28030978.
[2] Mercaldi GF, Ranzani AT, Cordeiro AT. 2014. Discovery of new uncompetitive inhibitors of glucose-6-phosphate dehydrogenase. *Journal of Biomolecular Screening.* 19(10):1362–1371. DOI: 10.1177/1087057114546896.
[3] Sosa-Estani S, Colantonio L, Segura E. 2012. Therapy of Chagas disease: implications for levels of prevention. *Journal of Tropical Medicine.* 2012:292138. doi:10.1155/2012/292138.
[4] Drugs for Neglected Diseases initiative (DNDi). 2020. UW series. *DNDi Research & Development Portfolio*. [accessed 2024 Nov 7]. https://dndi.org/research-development/portfolio/uw-series/
[5] Kim KE, Comber JR, Pursel AJ, Hobby GC, McCormick CJ, Fisher MF, Marasa K, Perry B. Modular and divergent synthesis of 2,N3-disubstituted 4-quinazolinones facilitated by regioselective N-alkylation. Org. Biomol Chem. 2024;22(24):4940-4949.