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Sequential Ugi four-component/nucleophilic substitution/Staudinger–aza-Wittig/hydrolysis strategy for the efficient construction of 1-benzyl-6-(tetrazolo[1,5-*a*]quinolin-4-yl)piperazine-2,5-dione

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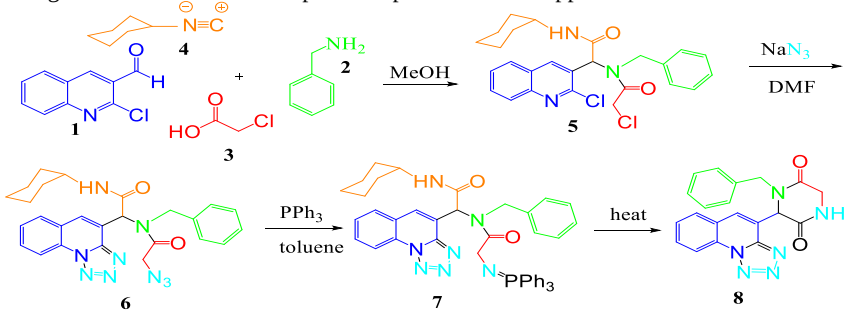
ABSTRACT

A sequential synthetic strategy integrating multiple transformations has been established for the efficient construction of 1-benzyl-6-(tetrazolo[1,5-a]quinolin-4-yl)piperazine-2,5-dione, a complex heterocyclic scaffold of potential medicinal relevance. The synthetic route commenced with a Ugi four-component reaction (Ugi-4CR) involving 2-chloro-3-formylquinoline (**1**), an amine (**2**), 2-chloroacetic acid (**3**), and an isocyanide (**4**), furnishing the corresponding Ugi adduct **5** in excellent yield. This intermediate was subsequently subjected to nucleophilic substitution with sodium azide to afford the azide derivative **6**. Conversion of **6** through a Staudinger reduction with triphenylphosphine generated the iminophosphorane intermediate **7**, which underwent an intramolecular aza-Wittig transformation followed by hydrolysis to provide the desired product **8** in good yield (Scheme 1).

This convergent and modular approach highlights the synthetic versatility of combining multicomponent reactions with post-condensation modifications. The use of readily available starting materials, mild reaction conditions, and the absence of transition-metal catalysts underscore the practicality and cost-effectiveness of the method. Furthermore, the integration of Ugi condensation, azide substitution, Staudinger reduction, and aza-Wittig cyclization demonstrates an efficient bond-forming sequence that rapidly assembles architecturally complex frameworks. Importantly, the developed strategy enables access to heterocycles containing a tetrazole ring, a quinoline core, and a piperazine-2,5-dione motif, structural features frequently encountered in bioactive molecules. Collectively, this work provides not only a valuable synthetic route to a novel heterocyclic system but also a broadly applicable methodology for the construction of nitrogen-rich frameworks with potential pharmaceutical applications.



Scheme 1. *Schematic representation of the synthetic pathway: the Ugi four-component reaction of 2-chloro-3-formylquinoline, amine, carboxylic acid, and isocyanide affords the Ugi adduct **5**. Subsequent nucleophilic substitution with sodium azide in DMF generates azide derivative **6**, which undergoes a Staudinger reduction with triphenylphosphine (PPh_3) to give intermediate **7**. The aza-Wittig reaction of **7**, followed by hydrolysis, furnishes the final product **8**.*

Keywords:
Quinoline derivatives; Ugi four-component reaction; Staudinger reaction; Aza-Wittig transformation; Intramolecular cyclization.

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1. Introduction

The Ugi reaction is a four-component condensation involving carbonyl compounds, carboxylic acids, isocyanides, and amines, which provides a one-step access to structurally diverse products. Because of its efficiency in generating molecular diversity, the Ugi-4CR has become an important tool in diversity-oriented synthesis and is widely applied in drug discovery [1–2]. Isocyanide-mediated multicomponent reactions (IMCRs) in general represent powerful one-pot strategies for the rapid assembly of complex molecules from simple starting materials. These reactions have become indispensable in modern medicinal and combinatorial chemistry [3]. In recent years, the integration of IMCRs with subsequent transformations has emerged as a particularly effective approach for the synthesis of heterocyclic scaffolds with broad structural diversity [4–8].

In the classical Ugi-4CR, an isocyanide, an amine, an aldehyde (or ketone), and a carboxylic acid combine to yield α-acylamino amide intermediates, which serve as versatile precursors for further modifications [9]. Post-condensation transformations of Ugi adducts have therefore been recognized as valuable synthetic strategies for constructing structurally diverse heterocycles [10]. Among these, the aza-Wittig reaction has attracted considerable attention due to its versatility in the preparation of nitrogen-containing heterocycles [11]. The strategic merger of Ugi condensation with aza-Wittig transformations thus provides an efficient route for generating libraries of biologically relevant heterocyclic frameworks [12].

Likewise, the Staudinger reaction, which enables the conversion of azides into amines, has recently regained attention as a robust method for accessing nitrogen-containing heterocycles [13–15]. Consequently, the combination of IMCRs with post-condensation Staudinger transformations offers a convergent and efficient pathway to a wide range of biologically significant heterocycles [16–17].

To the best of our knowledge, no precedent exists in the literature for a sequential Ugi four-component reaction combined with nucleophilic substitution, Staudinger–aza-Wittig transformation, and subsequent hydrolysis for the synthesis of piperazine-2,5-dione derivatives. Building upon our ongoing studies on heterocyclic synthesis [18] and the development of biologically relevant quinoline-based scaffolds [19], we now describe an efficient synthetic route to 1-benzyl-6-(tetrazolo[1,5-a]quinolin-4-yl)piperazine-2,5-dione (Scheme 1).

2. Experimental

Materials:

^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were obtained using a Bruker Avance 400 spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard at room temperature. Melting points were measured on a Büchi apparatus and are reported uncorrected. Analytical thin-layer chromatography (TLC) was conducted on silica gel 60 Å plates (0.20 mm thickness). Column chromatography was carried out using silica gel 60 Å (60–200 mesh). All commercially available reagents and solvents were used as received without further purification.

General procedure for the synthesis of Ugi adduct (5):

A solution of 2-chloro-3-formylquinoline (**1**, 1 mmol) in MeOH (2 mL) was treated sequentially with benzylamine (**2**, 1 mmol), chloroacetic acid (**3**, 1 mmol), and cyclohexyl isocyanide (**4**, 1 mmol). The resulting mixture was stirred at room temperature for 24 h, and the reaction progress was monitored by TLC. Upon completion, the colorless solid that precipitated was collected and dried for use in the subsequent step.

General procedure for the synthesis of compound (6):

Ugi adduct (**5**, 1 mmol) was dissolved in DMF (5 mL), followed by the addition of sodium azide (162.5 mg, 2.5 mmol). The mixture was heated at 90 °C for 24 h under stirring, and the progress was monitored by TLC. After completion, the reaction was cooled to room temperature, diluted with H_2O (10 mL), and the precipitated solid was filtered and washed with water to afford compound **6** as a colorless solid.

General procedure for the synthesis of compound (8):

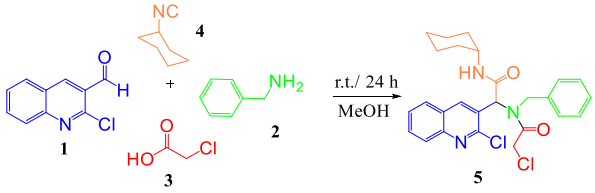
Triphenylphosphine (262 mg, 1 mmol) was added to a solution of compound **6** (0.9 mmol) in toluene (3 mL) under nitrogen atmosphere and stirring condition. After 2 h, the formation of iminophosphorane (**7**) was confirmed by TLC. The mixture was then heated to 90 °C for 6 h. Following completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified by column chromatography to yield the desired product.

1-Benzyl-6-(tetrazolo[1,5-*a*]quinolin-4-yl)piperazine-2,5-dione (**8**): White solid; Mp 200–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.98 (1H, d, J = 15 Hz, CH_2), 4.27

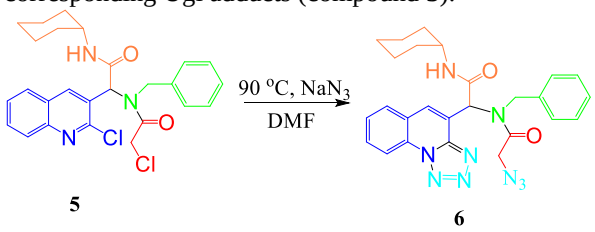
(1H, dd, J = 17.4, 2.9 Hz, CH_2), 5.07 (1H, d, J = 17.4 Hz, CH_2), 5.14 (1H, d, J = 15 Hz, CH_2), 5.26 (1H, s, CH), 7.12–7.18 (5H, m, Ar-H), 7.30 (1H, s, NH), 7.75 (1H, t, J = 7.6 Hz, Ar-H), 7.86 (1H, s, Ar-H), 7.92 (1H, t, J = 7.5 Hz, Ar-H), 7.98 (1H, d, J = 7.9 Hz, Ar-H), 8.63 (1H, d, J = 8.3 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 45.9, 47.6, 61.5, 116.7, 121.2, 123.2, 127.9, 128.3, 128.4, 128.6, 129.2, 130.6, 131.9, 134.7, 134.9, 145.4, 164.1 (CON), 164.6 (CON).

3. Results and Discussion

Initially, a mixture of 2-chloro-3-formylquinoline (**1**), benzylamine (**2**), 2-chloroacetic acid (**3**), and cyclohexyl isocyanide (**4**) was stirred in methanol at room temperature for 24 h, affording the corresponding Ugi adduct **5** (Scheme 2). Upon removal of methanol, the obtained white precipitate of compound **5** was dissolved in DMF, followed by the addition of sodium azide (2.5 equiv). The reaction was heated at 90 °C, and after 24 h, compound **6** was isolated in 90% yield (Scheme 3).

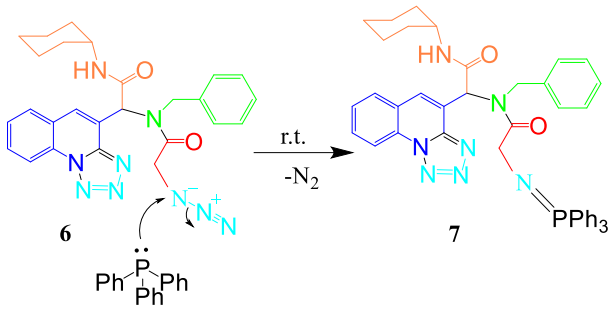


Scheme 2. Ugi four-component reaction of 2-chloro-3-formylquinoline, amine, carboxylic acid, and isocyanide leading to the formation of the corresponding Ugi adducts (compound **5**).

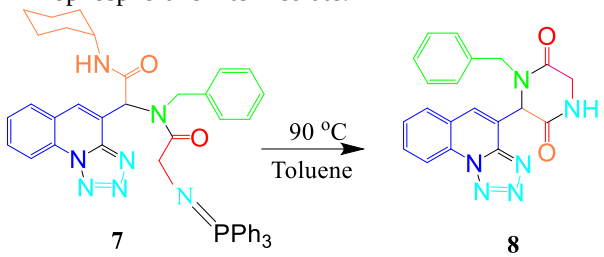


Scheme 3. Synthesis of azide derivative **6** through nucleophilic substitution of 2-chloro-3-formylquinoline-based Ugi adduct **5** with sodium azide in DMF.

To access the target compound **8**, different reaction conditions were evaluated. Treatment of compound **6** with triphenylphosphine in toluene furnished the iminophosphorane intermediate **7** within 2 h (Scheme 4). Subsequent heating of the reaction mixture at 90 °C for 6 h led to the formation of compound **8** in 75% yield (Scheme 5).

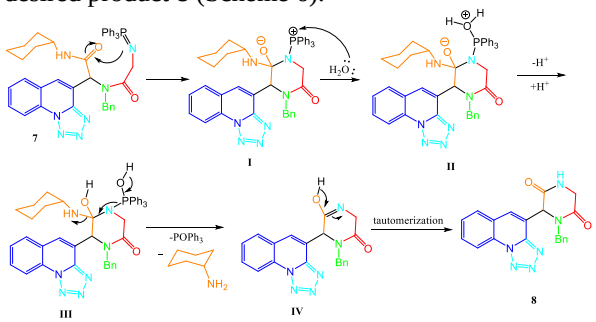


Scheme 4. Staudinger reduction of azide derivative **6** with triphenylphosphine (PPh_3) in toluene at room temperature, affording the corresponding iminophosphorane intermediate.



Scheme 5. Aza-Wittig reaction of compound **7** in toluene at 90 °C, followed by hydrolysis to afford the corresponding product.

A plausible mechanism for the formation of compound **8** is illustrated in Scheme 6. The reaction initiates with the intramolecular cyclization of iminophosphorane **7** through an aza-Wittig type process, leading to the six-membered intermediate **I**. Trace amounts of water present in the toluene medium then participate, generating intermediate **II**. Subsequent proton transfer affords intermediate **III**, accompanied by the elimination of triphenylphosphine oxide and cyclohexylamine, to yield intermediate **IV**. Finally, tautomerization of intermediate **IV** furnishes the desired product **8** (Scheme 6).



Scheme 6. Proposed mechanism of the aza-Wittig reaction in toluene, followed by hydrolysis in the presence of moisture, leading to the corresponding hydrolyzed products.

Under the optimized conditions, a series of 2-chloro-3-formylquinoline derivatives, amines, and isocyanides were successfully utilized to afford the corresponding Ugi adducts **5**. However, the subsequent azide derivatives **6** displayed significant instability during the drying process, decomposing into unidentified products.

Several drying methods were examined, including storage in the dark, placement in a desiccator, and treatment in a vacuum oven. In all cases, compound **6** transformed into a black, greasy residue with an increased volume and the appearance of internal bubbles, indicating decomposition of the azide moiety into nitrogen and nitrene species.

4. Conclusion

In conclusion, we have demonstrated a concise and efficient route to 1-benzyl-6-(tetrazolo[1,5-a]quinolin-4-yl)piperazine-2,5-dione through a multistep sequence integrating Ugi-4CR, azide substitution, Staudinger/aza-Wittig transformations, and hydrolysis. The method proceeds under catalyst-free conditions, provides high bond-forming efficiency, and enables straightforward isolation of the final product. The incorporation of a tetrazole ring, quinoline scaffold, and piperazine-2,5-dione core underscores the potential medicinal significance of this compound and highlights the synthetic value of the developed protocol.

Conflicts of Interest

The authors declare no conflict of interest.

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Authors' Contributions

Mostafa Kiamehr: Supervision, Investigation, Methodology, Visualization, Conceptualization, Data curation, Writing-Reviewing and Editing. Mohadeseh Fathizadeh: Methodology, Writing-Original draft preparation, Visualization, Data curation, Writing.

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