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Ugi-Based Approaches to Quinoxaline Libraries

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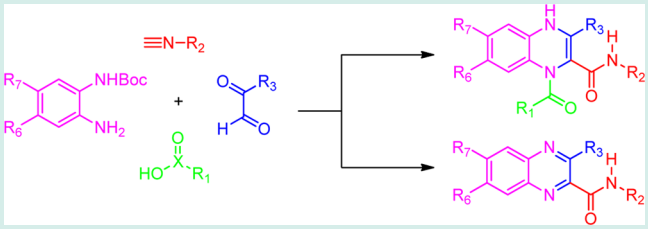
Supporting Information

ABSTRACT: An expedient and concise Ugi-based unified approach for the rapid assembly of quinoxaline frameworks has been developed. This convergent and versatile method uses readily available commercial reagents, does not require advanced intermediates, and exhibits excellent bond-forming efficiency, thus exemplifying the operationally simple synthesis of quinoxaline libraries.



KEYWORDS: *Ugi-based approach, quinoxaline libraries, operationally simple synthesis*

INTRODUCTION

Quinoxalines have long attracted significant attention due to their prolific bioactivity profiles (Figure 1). The quinoxaline unit is featured in therapeutic agents,[1] pharmacologically active derivatives,[2] agrochemicals[3] and natural occurring compounds[4] [e.g., vitamins (such as riboflavin), alkaloids, or antibiotics (such as echinomycin, actinomycin and leromycin)]. Accordingly, quinoxaline chemotypes are recognized as privileged scaffolds[5] and frequently employed as bioisosters of other heterocyclic cores (e.g., quinoline, quinazoline or pteridine). In addition to its bioactivity profile, molecular architectures that incorporate the quinoxaline framework have demonstrated the potential of this unit in diverse areas of materials science[6] (e.g., electroluminescent materials, dyes, organic semiconductors and chemical switches). The different applications notwithstanding, synthetic methodologies that target this chemotype remain somewhat scarce,[7] a situation that is evident on considering the limited skeletal and functional diversity of the available quinoxaline libraries.[8]

The classical synthesis of quinoxaline derivatives is carried out using strategies based on Körner[9] and Hinsberg[10] methods (Figure 2); both of these approaches rely on the condensation of 1,2-arylenediamines with synthons that contain reactive 1,2-dicarbonyl moieties (e.g., 1,2-diketones, 1,2-ketoesters, or oxalic acid derivatives).[7,11] A useful modification of these synthetic methods employs 1,2-dicarbonyl compound surrogates (e.g., α-haloketones, α-hydroxyketones, epoxides, or alkynes).[7,11] The discovery of the Beirut reaction[12] (Figure 2), that is, the cycloaddition between benzofurazan *N*-oxide and diverse two-carbon reactive partners (e.g., dienes, enones, enamines, or enolates derived from ketones, β-diketones, β-ketoesters, etc.), unveiled an elegant preparative entry to quinoxaline-1,4-dioxides, which can subsequently be reduced to afford quinoxaline derivatives (Figure 2). Although existing methods usually provide satisfactory yields, they do suffer from intrinsic limitations; for example, narrow substrate scope, the need for elevated temperatures, expensive and detrimental catalysts, and reaction outcomes that are influenced by the electronic and steric effects of substituents. Moreover, the use of unsymmetrically substituted precursors (e.g., *o*-phenylenediamines or benzofurazan *N*-oxides) leads to regioisomeric mixtures of quinoxalines.

The recent emergence of multicomponent reactions (MCR)[13] has provided novel approaches that expand the compendium of methods to assemble libraries of heterocyclic compounds.[13] A few MCR-based methods targeting quinoxalines (Figure 3) have been described,[14−17] with relevant examples exploiting the reactivity of isocyanides in the Ugi,[14,17] Ugi-Smiles,[15] or Van Leusen[16] reactions. As the demand of privileged heterocyclic collections for drug discovery programs remains a priority, particularly libraries of underrepresented chemotypes (e.g., quinoxalines), novel contributions in this area are highly desirable. As part of our program aimed at the design of succinct and operationally simple MCR-based routes to libraries of privileged scaffolds, we report here an integrated strategy to synthesize novel skeletal and functionally diverse quinoxaline libraries in a time-efficient and cost-effective manner.

RESULTS AND DISCUSSION

The Ugi four-component reaction (U-4CR),[18] that is, the condensation of an amine, a carboxylic acid, a carbonyl component (aldehyde or ketone) and an isocyanide, constitutes an exceptional preparative tool that has well documented versatility and robustness for the assembly of heterocyclic frameworks.[19] Among the Ugi-based approaches to target heterocycles, those that involve the Ugi/deprotect/cyclize (UDC)[20] sequence encompass a highly attractive strategy that exemplifies the reconciliation of molecular complexity and experimental simplicity. In the context of a hit optimization

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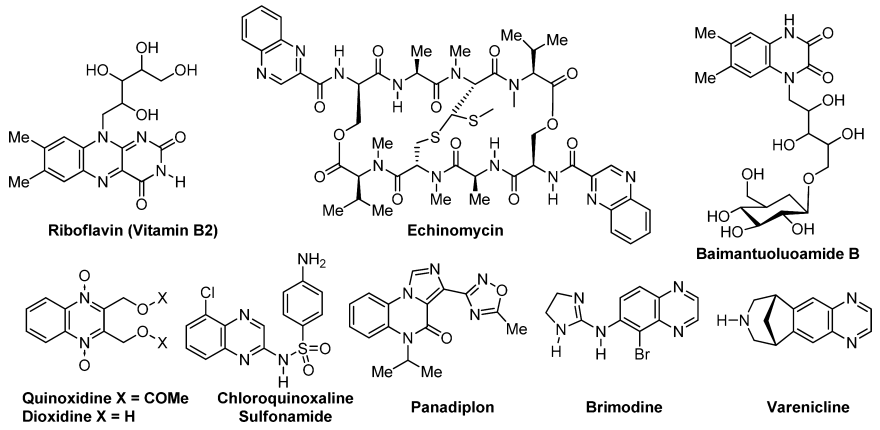

Figure 1. Representative drug, bioactive, and naturally occurring compounds that feature a quinoxaline scaffold.

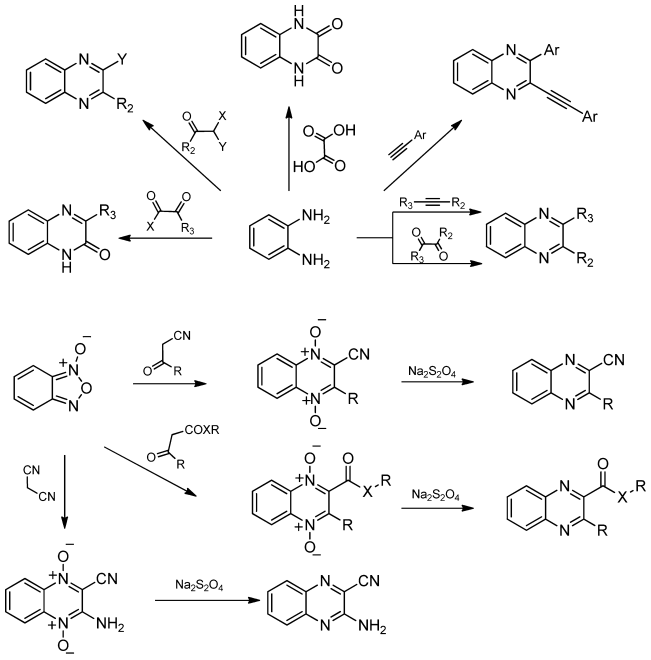

Figure 2. Classical methods for the synthesis of quinoxaline scaffolds.

program we needed to validate experimentally the in silico bioactivities predicted for virtual libraries of quinoxaline frameworks that incorporate amide groups at position 2 of the heterocyclic core. Given the limitations of established methods to access the target structures we decided to assess the feasibility of an unprecedented Ugi-based approach to quinoxalines (Figure 4). It was envisioned that the Ugi reaction with glyoxal derivatives (**1**) and mono-Boc protected phenylenediamines (**3**) as key precursors would enable the rapid assembly of adducts **5**, which could subsequently be cyclized and, after removal of the Boc group, afford 1,4-dihydroquinoxalines **6** (Figure 4).

The viability of the proposed pathway was evaluated by employing phenylglyoxal (**1**{*1*}), *tert*-butyl(2-amino-phenyl)-carbamate (**3**{*1*}), three isocyanides (**2**{*1*−*3*}), and either propanoic or benzoic acids ((**4**{*1*}) and **4**{*2*}) as model substrates (Figure 5). Equimolar amounts of these precursors were submitted to the standard U-4CR conditions[18] in methanol at room temperature for 48 h. Analysis of these reactions confirmed the chemoselectivity of the transformations, with the Ugi adducts **5** obtained with satisfactory yields (56−80%). It should be noted that the increasing steric hindrance present in the varied components [carboxylic acids (**4**) or isocyanides (**2**)] did not affect the reaction behavior or yield. The resulting Ugi adducts (**5**) were submitted to a brief screening to identify the optimal conditions to remove the Boc group (30% TFA/DCE, 1 M HCl/Ether, 85% H_3PO_4/H_2O). These experiments demonstrated the superiority of TFA (30% TFA/DCE at 80 °C, 1 h), which efficiently and rapidly

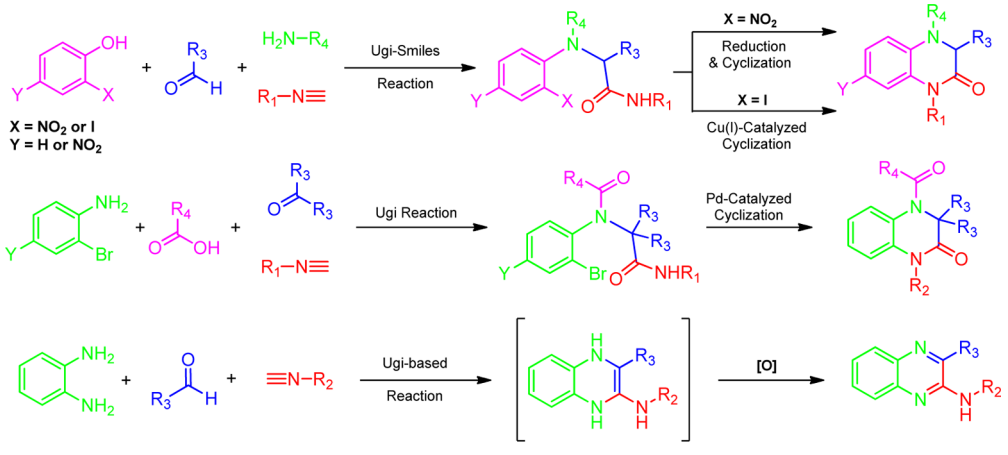

Figure 3. Ugi-based multicomponent synthesis of quinoxaline derivatives.[14−17]

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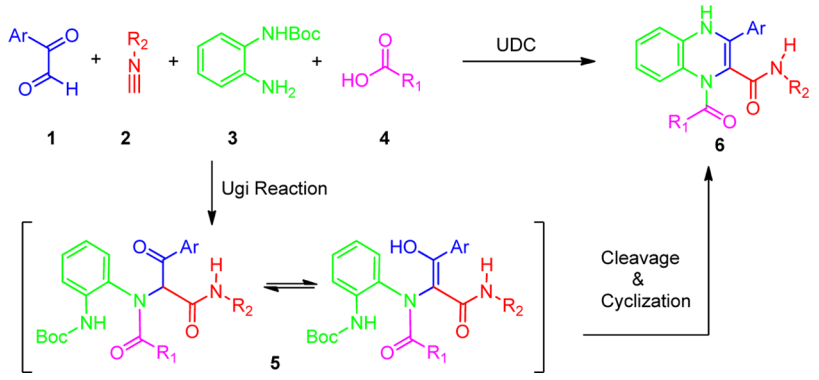

Figure 4. Proposed synthetic route to quinoxaline derivatives **6**.

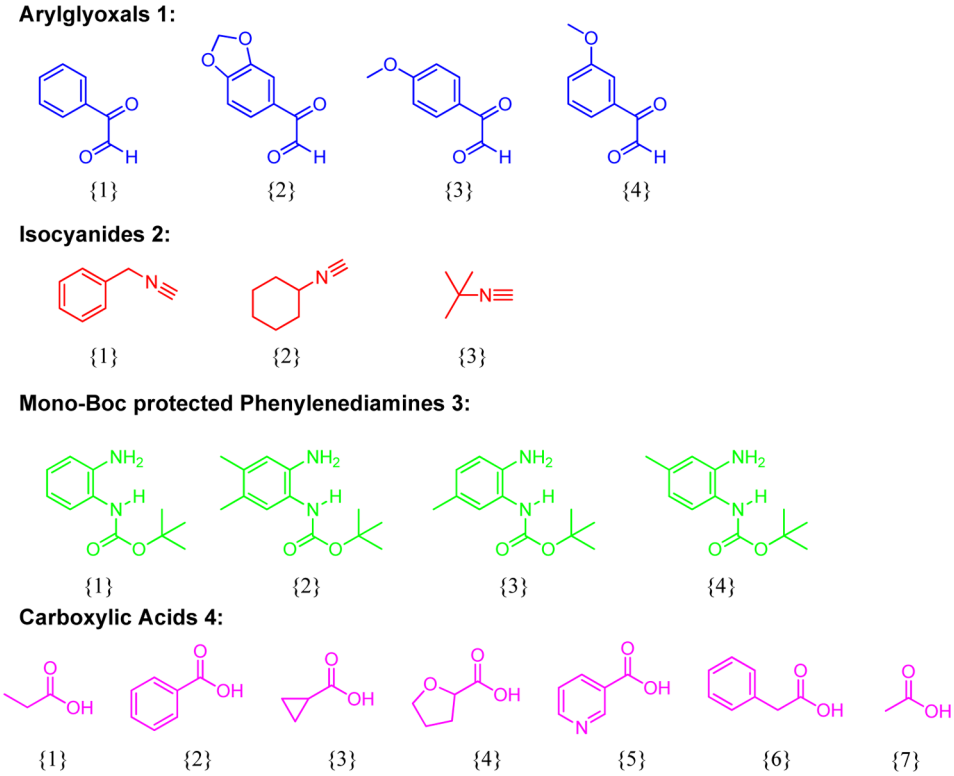

Figure 5. Diversity elements employed for library synthesis. Arylglyoxals **1**{*1*–*4*}, isocyanides **2** {*1*–*3*}, mono-Boc protected phenylenediamines **3**{*1*–*4*}, and carboxylic acids **4**{*1*–*6*}.

promoted the cleavage-cyclization sequence to provide quinoxalines **6** in yields in the range of 70–86%. Having established the feasibility of the proposed approach in a sequential fashion, we focused on the development of a one-pot assembly of quinoxalines **6**. It was gratifying to verify that a simple work up (see Experimental Procedures) once the Ugi reaction had finished (TLC monitoring) and subsequent treatment of the crude Ugi adduct (**5**) with 30% TFA in DCE at 80 °C for 1 h delivered targeted quinoxalines (**6**) with satisfactory overall yields (Scheme 1). A set of assorted precursors [Figure 5, carboxylic acids (**4**), isocyanides (**2**), arylglyoxals (**1**) and mono-Boc protected phenylenediamines (**3**)] expecting to modify the electronic, steric and lipo-/hydrophilic features of the scaffold itself, were submitted to the previously optimized conditions to evaluate the scope and robustness of the Ugi-based assembly of 1,4-dihydroquinoxalines documented here (Figure 5). According to the requirements of the medicinal chemistry program that inspired the method development, we focused on the exploration of structurally diverse carboxylic acids (including alkyl, cycloalkyl, aryl, and heterocyclic residues at R_1).

It can be observed from Scheme 1 that the method proved to be broadly successful, providing the target structures with yields ranging from 57% to 77%. It should be pointed out that the reported values (Scheme 1) refer to the overall yield of the synthetic steps involved (U-4CR, deprotection and cyclization), thus indicating excellent yields for each simple step. The information contained in Scheme 1 also supports the excellent reactivity and chemoselectivity profile obtained for all components (Figure 5, compounds **1**–**4**) in a process that allowed the incorporation of diverse residues at variable positions (R_1, R_2, Ar, R_6, R_7) of the heterocyclic core (Scheme 1). A remarkable feature of the de novo 1,4-dihydroquinoxaline assembly documented here concern its bond-forming efficiency, which allows compounds **6** to be obtained in an experimentally

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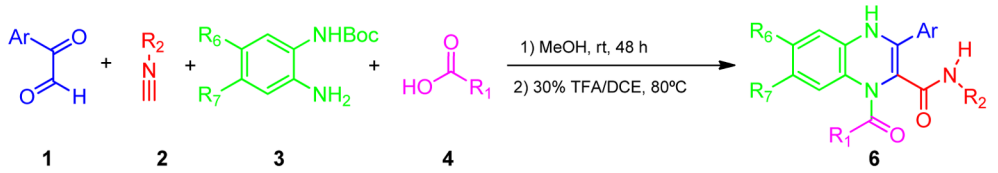
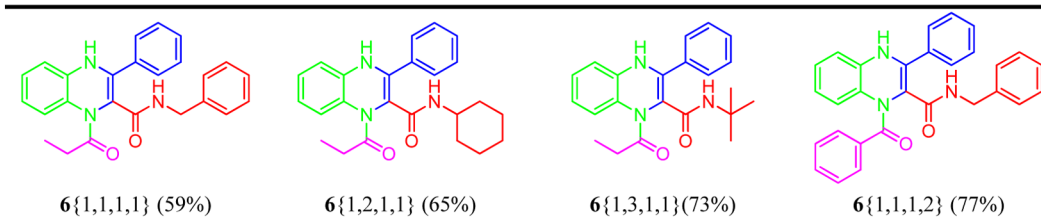
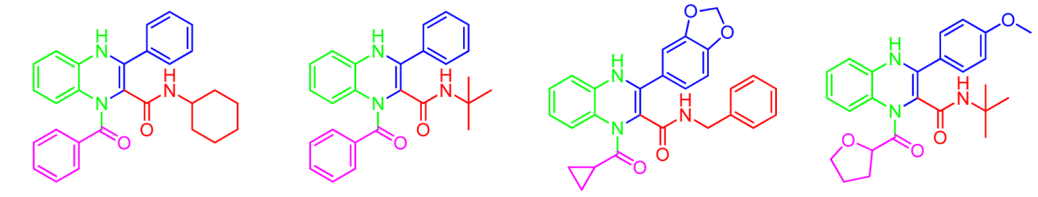
Scheme 1. Ugi-Based Assembly of 1,4-Dihydroquinoxalines 6

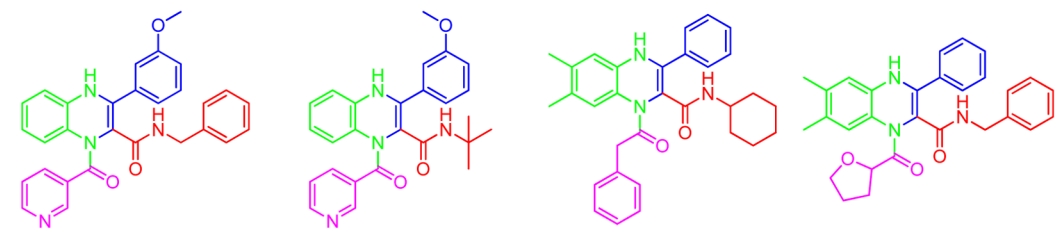




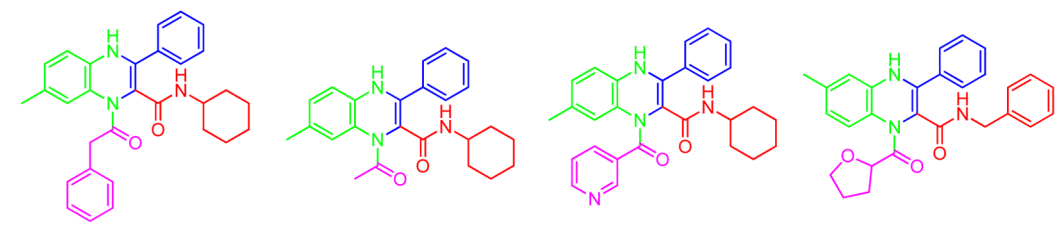
6{1,1,1,1} (59%) **6**{1,2,1,1} (65%) **6**{1,3,1,1}(73%) **6**{1,1,1,2} (77%)



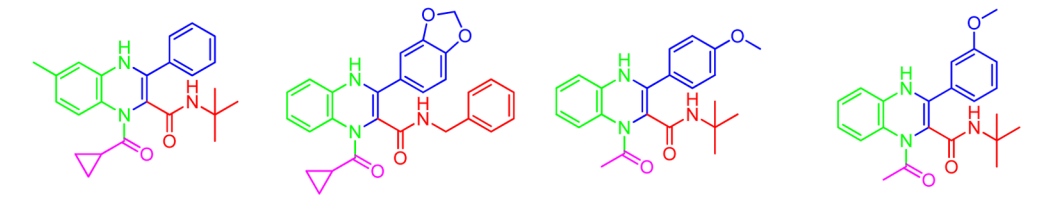
6{1,2,1,2} (73%) **6**{1,3,1,2} (69%) **6**{2,1,1,3} (57%) **6**{3,3,1,4} (62%)



6{4,1,1,5} (63%) **6**{4,3,1,5} (59%) **6**{1,2,2,6} (63%) **6**{1,1,2,4}(58%)



6{1,2,3,6} (71%) **6**{1,2,3,7} (67%) **6**{1,2,3,5} (70%) **6**{1,1,4,4} (65%)



6{1,3,4,3} (64%) **6**{2,1,1,3} (58%) **6**{3,3,1,7} (76%) **6**{4,3,1,7} (72%)

simple and covergent one-pot process that involves the formation of four new bonds.

In an effort to broaden the versatility of the approach outlined in Scheme 1, we decided to assess its applicability for the assembly of other quinoxaline chemotypes (Scheme 2). The recently developed acid-catalyzed Ugi three-component synthesis (U-3CR)[17] of 2-aminoquinoxalines (**7**), which involves the reaction of aldehydes, *o*-phenylenediamines (**8**) and isocyanides (Scheme 2a), led us to evaluate the viability of a similar approach with phenylglyoxal derivatives (**1**) used as the carbonyl partner (Scheme 2b). The feasibility of the proposed pathway, which should afford 2-carboxamidoquinoxalines **9**, would be heavily dependent on the availability of the isocyanide to rapidly attack (α-addition) the initially formed iminium ion (**10**) (Scheme 2b). The U-3CR process would generate an Ugi adduct (**11**) that should render **9** following the

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Scheme 2. Proposed Direct Ugi-Based Assembly of 2-Carboxamidoquinoxalines 9

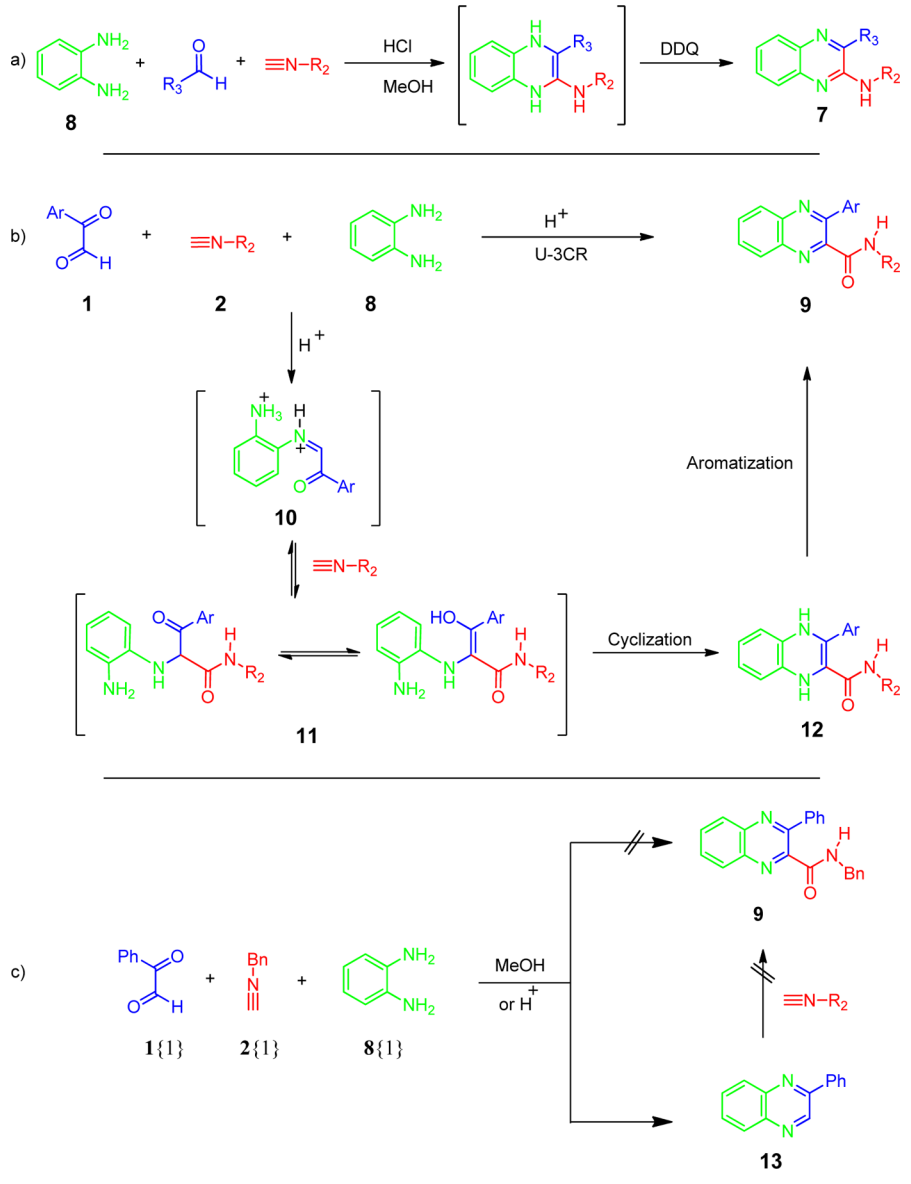

Figure 6. Proposed Ugi-based route to quinoxalines **9**.

cyclization-aromatization sequence (Scheme 2b). Phenylglyoxal (**1**{*1*}), benzyl isocyanide (**2**{*1*}) and *o*-phenylenediamine (**8**{*1*}) were employed as model substrates to assess the practicality of the transformation (Scheme 2c). The reactions were tested under the acidic conditions (HCl) described by Krasavin[17a] and also on neutral media. These experiments

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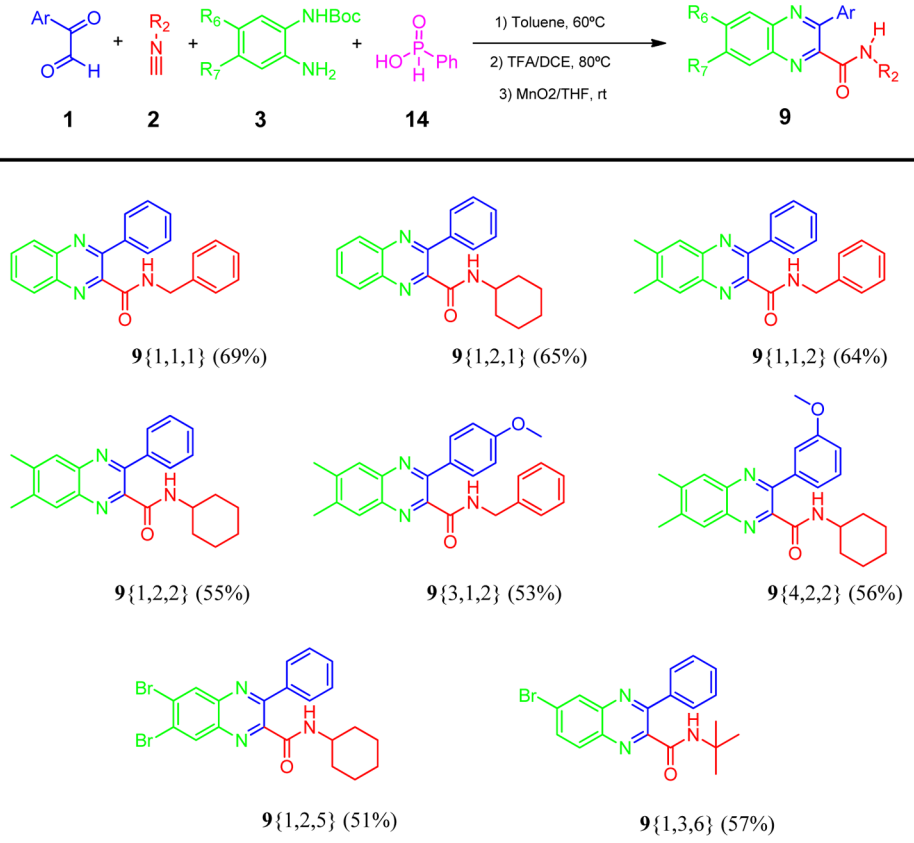
Scheme 3. U-3CR-Based Assembly of Quinoxalines 9



revealed that, irrespective of the experimental conditions, the isolated product was not the desired 2-carboxamidoquinoxaline **9** (or its 1,4-dihydroderivative **12**), but rather the 2-phenylquinoxaline **13**. The experimental behavior outlined above was observed consistently irrespective of the experimental parameters modified (e.g., isocyanide equivalents, acid employed, solvent or temperature). The reaction outcome, which reflects the inability of the isocyanide to intercept the iminiun ion intermediate (**10**), confirms that monoprotonation of the phenylenediamine does not effectively prevent the cyclocondensation pathway to afford **13**. Alternative efforts to access 2-carboxamidoquinoxaline **9** by the direct reaction of benzyl isocyanide (**2a**) and **13**, or its *N*-benzoylquinoxalinium salt,[21] also failed (Scheme 2c).

The results described in Scheme 2 highlight the convenience of using mono-Boc protected phenylenediamines (**3**) as key precursors during the projected pathways. In an effort to overcome the aforementioned failures, and inspired by a recent paper[22] describing an Ugi three-component reaction (U-3CR) that employs catalytic amounts (10 mol %) of phenylphosphinic acid (**14**) to transform an amine, an aldehyde, and an isocyanide into a α-amino amide, it was envisioned that a conceptually simple U-3CR-based assembly of quinoxalines **9** could be developed. The designed pathway (Figure 6), which follows the UDC strategy,[20] utilizes three of the reactive partners previously employed for the synthesis of the 1,4-dihydroquinoxalines **6** (Figure 5, precursors **1**−**3**), with phenylphosphinic acid being critical to protonate the in situ generated imine and, in particular, to enable a water molecule to intercept the electrophilic nitrilium ion. Such a sequence (Figure 6) would afford α-aroyl aminoacetamides **15** and subsequent acid-mediated cleavage and cyclization would afford the 1,4-dihydroquinoxalines **12**. Finally, aromatization of **12** would generate 2-carboxamidoquinoxalines **9**.

Phenylglyoxal (**1**{*1*}), benzylisocyanide (**2**{*1*}), and *tert*-butyl(2-amino-phenyl)carbamate (**3**{*1*}) were selected to explore the viability of the transformation under the conditions described by Pan and List[22] [10 mol % of phenylphosphinic acid (**14**), toluene at 80 °C, 12−24 h]. Nevertheless, these experiments were unsuccessful and the targeted Ugi adduct (**15**) was not detected. Attempts to modify the reaction behavior by changing the experimental conditions [e.g., solvent (dioxane, chloroform or DMF), temperature (50, 70 °C) or reaction times (3−48 h)] proved fruitless. The only parameter that was able to modify the reaction performance was the amount of phenylphosphinic acid (**14**) employed in the transformation, with the best results obtained on changing from a catalytic to a stoichiometric procedure. The use of 1 equiv of phenylphosphinic acid (**14**) during the projected U-3CR (toluene, 80 °C, 24 h) directly afforded the *N*-benzyl-3-phenyl-1,4-dihydroquinoxaline-2-carboxamide (**9**{*1,1,1*}) (41%), together with 2-phenylquinoxaline **13** (26%). This result provides evidence that, under stoichiometric conditions, **14** is able to cleave the Boc group within the Ugi adduct (**15**) and also in the starting *tert*-butyl(2-amino-phenyl)carbamate (**1**{*1*}) or the corresponding iminium ion intermediate. Slight modifications of the experimental conditions [e.g., lowering the temperature (80 to 60 °C) and reaction times (24 to 8 h)] negated the side pathways to **13**. These changes allowed the Ugi adduct (**15**{*1,1,1*}) to be isolated as the main product

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(58%) together with small amounts (5−7%) of cyclized quinoxaline derivative (**12**{*1,1,1*}). Hydrolytic cleavage (30% TFA/DCE) of the crude reaction mixture promoted a deprotection-cyclization sequence that led to *N*-benzyl-3-phenyl-1,4-dihydroquinoxaline-2-carboxamide **12**{*1,1,1*} (52%). It should be noted that 1,4-dihydroquinoxalines **12** are unstable compounds that easily aromatize (either spontaneously or during chromatographic purification). Accordingly, it was decided to treat the crude reaction mixture after Boc cleavage with a mild oxidant to exclusively obtain quinoxalines **9**. Brief exposure (0.5−1 h) of the reaction mixture with MnO_2 (3 equiv) provided the target 2-carboxamidoquinoxalines **9** in satisfactory yields. Once the feasibility of the proposed method had been established for a model system, and having identified a set of experimental conditions that afforded quinoxaline **9**{*1,1,1*}, the scope of the method was briefly assessed by employing representative compounds of precursors **1**−**3** (Figure 5) as well as two novel mono-Boc protected phenylenediamines [**3**{*5*} and **3**{*6*}]. All reactions were performed in a one-pot fashion. After monitoring the multicomponent reaction and judging it complete, the solvent was evaporated and the crude adduct (**15**) was submitted to the cleavage-cyclization-aromatization sequence (Scheme 3). A preliminary assessment of the efficiency and scope of the convergent and experimentally simple three-component quinoxaline synthesis documented here is provided in Scheme 3. It can be observed that the yields obtained range from 51 to 69%, with the reported values referred to the overall yield of the three synthetic steps involved (U-3CR, deprotection, cyclization and aromatization). It can also be seen from Scheme 3 that the reaction proved to be successful with all variable components (**1**−**3**), thus enabling the heterocyclic core to be decorated with different residues.

In summary, we report here two novel Ugi-based approaches that provide an integrated and straightforward entry to novel quinoxaline-based libraries encompassing skeletal and functional diversity. This convergent and versatile method, which uses readily available commercial reagents and does not require advanced intermediates or anhydrous solvents, exhibits high bond-forming efficiency; thus exemplifying the operationally simple synthesis of quinoxaline libraries in a time-efficient and cost-effective manner.

EXPERIMENTAL PROCEDURES

Commercially available starting materials and reagents were purchased and used without further purification from freshly opened containers. Monoprotected phenylenediamines (**3**) were acquired from commercial sources or obtained following previously described procedures.[23] All solvents were purified and dried by standard methods. Organic extracts were dried with anhydrous Na_2SO_4. The reactions were monitored by TLC and purified compounds each showed a single spot. Unless stated otherwise, UV light and iodine vapor were used for the detection of compounds. The synthesis and purification of all compounds were accomplished using the equipment routinely available in organic chemistry laboratories. Most of the preparative experiments were performed in coated vials on an organic synthesizer with orbital stirring. Purification of isolated products was carried out by column chromatography. Compounds were routinely characterized by spectroscopic and analytical methods. Melting points were determined on a melting point apparatus and are uncorrected. The chemical structures of the obtained compounds were determined by nuclear magnetic resonance spectroscopy (^1H and ^{13}C) and high-resolution mass spectroscopy (HRMS). Unless otherwise stated NMR spectra were recorded in $CDCl_3$. Chemical shifts are given as δ values against tetramethylsilane as internal standard and J values are given in Hz.

General Procedure for the One-Pot Synthesis of 1,4-Dihydroquinoxalines 6. A mixture of the glyoxal derivative (0.5 mmol), the monoprotected phenylenediamine (0.5 mmol), the isocyanide (0.5 mmol) and the carboxylic acid (0.5 mmol) in MeOH (2 mL) was submitted to orbital stirring at room temperature for 48 h. After completion of the reaction, CH_2Cl_2 (3 mL) and PS-*p*-TsOH (1.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature until the unreacted isocyanide had been consumed (0.5 h). The polystyrene-supported reagent was filtered off and successively washed [3 × 5 mL] with MeOH, EtOAc, and CH_2Cl_2. The solvents were evaporated from the filtrate to afford an oily residue, which was dissolved in DCE (10 mL) and then treated with 30% TFA and stirred at 80 °C for 1−3 h. The solution was then treated with saturated $NaHCO_3$. The product was extracted with ethyl acetate and the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue, which was purified by chromatography on silica gel using hexane/EtOAc mixtures.

N-Benzyl-3-phenyl-1-propionyl-1,4-dihydroquinoxaline-2-carboxamide ***6****{1,1,1,1}*. Yield: 59%, 116 mg (EtOH, mp 175−176 °C). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19−8.07 (m, 2H), 7.62 (dt, J = 7.9, 1.0 Hz, 1H), 7.54−7.46 (m, 3H), 7.39−7.29 (m, 1H), 7.28−7.14 (m, 5H), 6.96−6.80 (m, 2H), 6.69 (s, 1H), 6.36 (t, J = 6.4 Hz, 1H), 4.41 (dd, J = 15.1, 6.7 Hz, 1H), 4.18 (dd, J = 15.1, 5.2 Hz, 1H), 2.75 (dq, J = 16.2, 7.4 Hz, 1H), 2.59 (dq, J = 16.2, 7.3 Hz, 1H), 1.16 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.6, 166.3, 162.2, 138.7, 137.5, 136.4, 131.4, 128.8, 128.5, 128.0, 127.6, 127.5, 127.3, 127.1, 127.1, 126.6, 122.8, 43.3, 27.3, 9.6. HRMS (CI) m/z calcd. for $C_{25}H_{24}N_3O_2$ $[M + H]^+$: 398.1869; found 398.1871.

General Procedure for the One-Pot Synthesis of Quinoxalines 9. A mixture of the glyoxal derivative (0.5 mmol), the monoprotected phenylenediamine (0.5 mmol), the isocyanide (0.5 mmol), and phenylphosphinic acid (0.5 mmol) in dry toluene (3 mL) was submitted to orbital stirring at 60 °C for 8−10h. After completion of the reaction, CH_2Cl_2 (3 mL) and PS-*p*-TsOH (1.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature until the unreacted isocyanide had been consumed (0.5 h). The polystyrene-supported reagent was filtered off and successively washed [3 × 5 mL] with MeOH, EtOAc and CH_2Cl_2. The solvents were evaporated from the filtrate to afford an oily residue, which was dissolved in DCE (10 mL) and then treated with 30% TFA and stirred at 80 °C for 1−3 h. The solution was then treated with saturated $NaHCO_3$. The product was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue, which was dissolved in THF, treated with MnO_2 (3 equiv) and stirred at room temperature for 1 h. The oxidizing agent was filtered off and successively washed with DCM, THF and MeOH. The solvents were evaporated to afford an oily residue, which was purified by chromatography on silica gel using hexane/EtOAc mixtures.

*N-Benzyl-3-phenylquinoxaline-2-carboxamide (****9****{1,1,1}).* Yield: 69%, 119 mg (EtOH, mp 188−189 °C). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.32−8.00 (m, 2H), 7.98−7.62

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(m, 5H), 7.59−7.42 (m, 3H), 7.43−7.18 (m, 5H), 4.66 (d, J = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 153.7, 144.9, 142.5, 139.2, 138.5, 137.9, 131.6, 130.4, 129.3, 129.1, 129.1, 128.8, 128.7, 128.1, 127.9, 127.6, 43.7. HRMS (CI) m/z calcd. for $C_{22}H_{18}N_3O$ $[M + H]^+$: 340.1450; found 340.1449.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, complete description of the spectroscopic and analytical data of all compounds described, including copies of ^{1}H NMR, ^{13}C NMR, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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