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Concise two-step solution phase syntheses of four novel dihydroquinazoline scaffolds

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ABSTRACT

Novel two-step solution phase protocols for the synthesis of dihydroquinazolines and fused dihydroquinazoline-benzodiazepine tetracycles are reported. The methodology employs the Ugi reaction to assemble the desired diversity and acid treatment enables ring-closing transformations. The protocols are further facilitated by the use of microwave irradiation and *n*-butyl isocyanide to control the rate of each ring-forming transformation.

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1. Introduction

The elucidation of the complete human genome in 2001[1] has resulted in a dramatic increase in the demand for the identification of small molecules to validate the pharmacological potential of new macromolecular targets.[2,3] In particular, isonitrile-based methodologies,[4–6] followed by a variety of secondary ring-forming transformations, have shown great utility in concisely producing highly functionalized and drug-like scaffolds with high iterative efficiency potential.[7–9] Methodologies developed in this laboratory have proven quite productive, delivering examples where initial hits have progressed into clinical trials for the treatment of both HIV infection[10,11] and pre-term labor,[12–15] importantly without the need to 'scaffold hop'. Recently, we have reported a contrite two-step synthesis of triazabenzulenones[16] that represents the first post-condensation Ugi modification employing two internal amino nucleophiles and a subsequent report that utilized microwave irradiation with *n*-butyl isonitrile in place of a traditional 'designer convertible isonitrile,[17] to form benzodiazepines and diketopiperazines. Herein, we report two-step syntheses that yield dihydroquinazolines **1** and **2** and fused dihydroquinazoline-benzodiazepine tetracycles **3** and **4**, Figure 1. The tetracyclic scaffolds represent a second example of a post-condensation Ugi modification employing two internal amino nucleophiles and all four syntheses rely on the reduced reactivity of an *n*-butyl amide carbonyl derived from *n*-butyl isonitrile relative to traditional convertible isonitriles to ensure the correct sequence of ring-forming events. It was envisioned that the dihydroquinazoline core could be produced in two steps: an Ugi reaction with *mono*-Boc protected 2-aminobenzylamines **5**, supporting aldehydes **8**, non-convertible isonitriles **7**, and carboxylic acids **6** to yield the condensation product **9** followed by acid-promoted deprotection and cyclization. Both the 1,4-dihydroquinazoline (Scheme 1a, (**10**) and 3,4-dihydroquinazoline (Scheme 1b, **12**) scaffolds can be produced from the corresponding *mono*-protected 2-aminobenzylamine input **5** or **11**. We have previously demonstrated a similar acid-promoted dehydration of an Ugi condensation product to generate an aromatic benzimidazole core[16,18] and this Letter expands the use of such methodology to obtain non-aromatic bicyclic rings such as the dihydroquinazolines **1** and **2** with significantly different physicochemical properties and spacial positioning of decorating functionality.

Optimal yields for the Ugi reaction were found to occur via pre-formation of the Schiff base in methanol for 30 min, followed by addition of the isonitrile and carboxylic acid inputs with subsequent microwave irradiation at 100 °C for 10 min (isolated yields 48–85%). The Ugi product was then treated with 10% TFA/DCE (irradiated at 120 °C) to form the desired quinazoline scaffolds **10** and **12** core in good yield (46–65% ~isolated overall yield for two steps).[19] With this protocol in hand, it was hypothesized that addition of a second protected amine, through the use of an *N*-Boc-protected anthranilic acid **13**, would enable the formation of novel fused dihydroquinazoline-benzodiazepines (Schemes 2a and 2b, **14** and **15**) after deprotection and two sequential cyclization steps. However, addition of the bulky Boc-protected amine group resulted in a dramatic decrease in the yield of the Ugi reaction (<5%).

This effect was also observed in the 1,4-quinazoline series with 2-chlorobenzoic acid (Fig. 3, **30**). Circumventing this problem,

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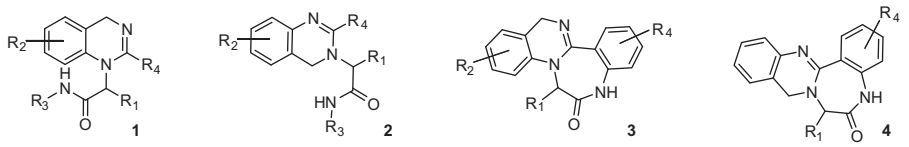
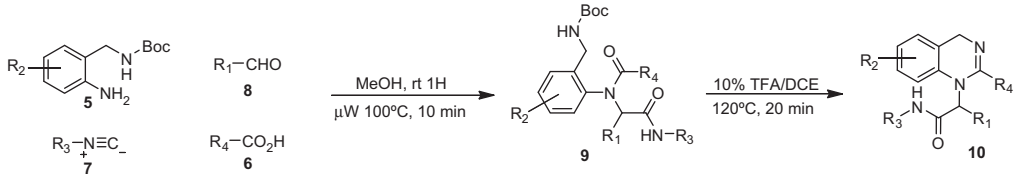
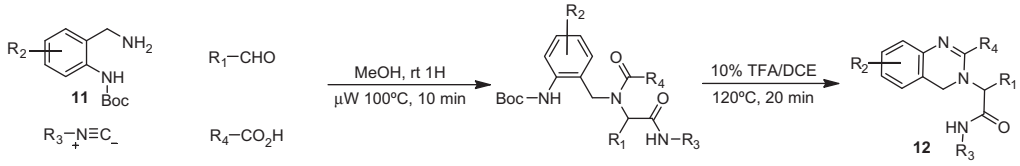


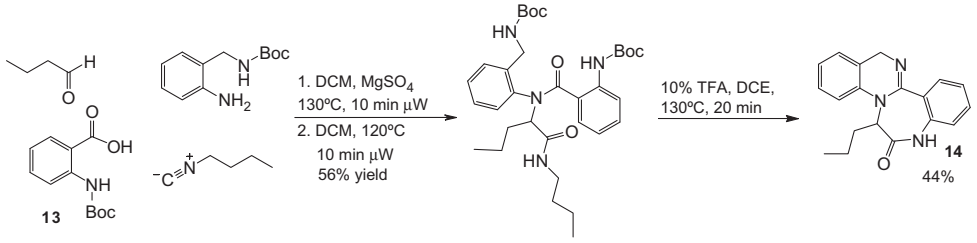
Figure 1. Representative dihydroquinazoline bicyclic and tetracyclic scaffolds.



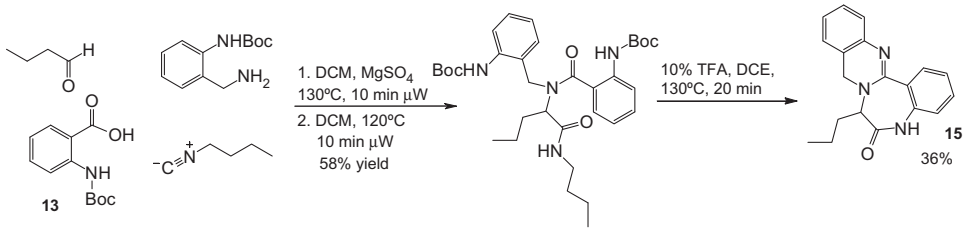
Scheme 1a.



Scheme 1b.



Scheme 2a.



Scheme 2b.

pre-formation of the Schiff base in toluene under microwave irradiation with removal of water ($MgSO_4$) provided the Schiff base in quantitative yields. Subsequent reaction in MeOH afforded the desired Ugi product in 44% yield [note: observed by-products arose from methanol addition to the Schiff base and the Passerini reaction]. Interestingly, reactions in trifluoroethanol yielded similar results—a strategy that is often successful in reducing solvent participation in the Ugi reaction. A modest improvement in yield was observed by pre-forming the Schiff base in dichloromethane in the presence of $MgSO_4$ (microwave, 120 °C). Following the

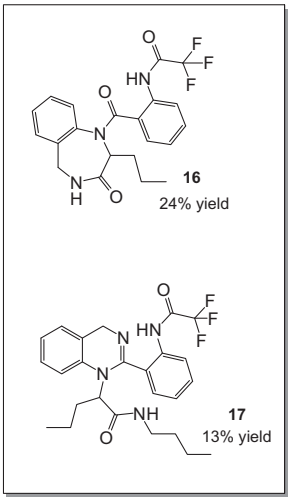
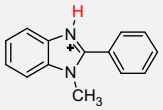
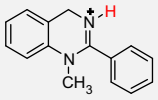
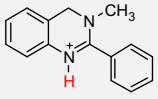


Figure 2.

Table 1

	$pK_a = 5.14$[a]
	$pK_a = 6.57$[a]
	$pK_a = 7.84$[a]

[a] pK_a values were estimated using ACD/pK_a.

addition of supporting reagents, the reaction was irradiated at 120 °C for 10 min with an acceptable improvement in yield (56%, Scheme 2a). Removal of the two Boc groups, cyclo-dehydration to the dihydroquinazoline core, and concomitant cyclization onto the *n*-butyl amide afforded the desired fused 1,4-dihydroquinazoline-benzodiazepines **14** and **15** in acceptable yields upon simple acid treatment and microwave irradiation.[20] Not surprisingly, the major side products of the cascade reaction were the benzodiazepine trifluoroacetamide **16** (24% yield) and the bicyclic trifluoroacetamide **17** (13% yield), Figure 2.

The scope of the methodology was evaluated with a selection of different reagents. Cyclization reactions of purified Ugi products were run in series on a Biotage Initiator 8 microwave and were purified in a sequential manner on a Biotage Isolera 4 system utilizing neutralized silica gel columns. The observed high polarity of dihydroquinazolines can be attributed to their relatively high pK_a values (Table 1). Thirteen examples are presented **18** through **30** containing all four dihydroquinazoline cores with isolated overall yields for the two-step procedure ranging from 21% to 64% Figure 3.

To demonstrate scaffold uniqueness, virtual libraries for **1** through **4** were enumerated (comprising scaffold **1**—168 compounds; **2**—168 compounds, **3**—144 compounds, **4**—48 compounds) and compared with the 375,000 compounds in the NIH molecular libraries small molecule repository (MLSMR). A total of 1043 nearest neighbors were indentified and a principle component analysis[21] clearly demonstrates the unique diversity space occupied by expanded libraries of the four scaffolds described herein Figure 4.

In summary, we have reported concise two-step solution phase syntheses that afford bicyclic dihydroquinazolines and fused tetracyclic dihydroquinazoline-benzodiazepines, which are under-represented in the literature and the MLSMR.[22] With amenability to high-throughput solution phase synthesis, it is expected that the methodology will be embraced by the lead generation community.

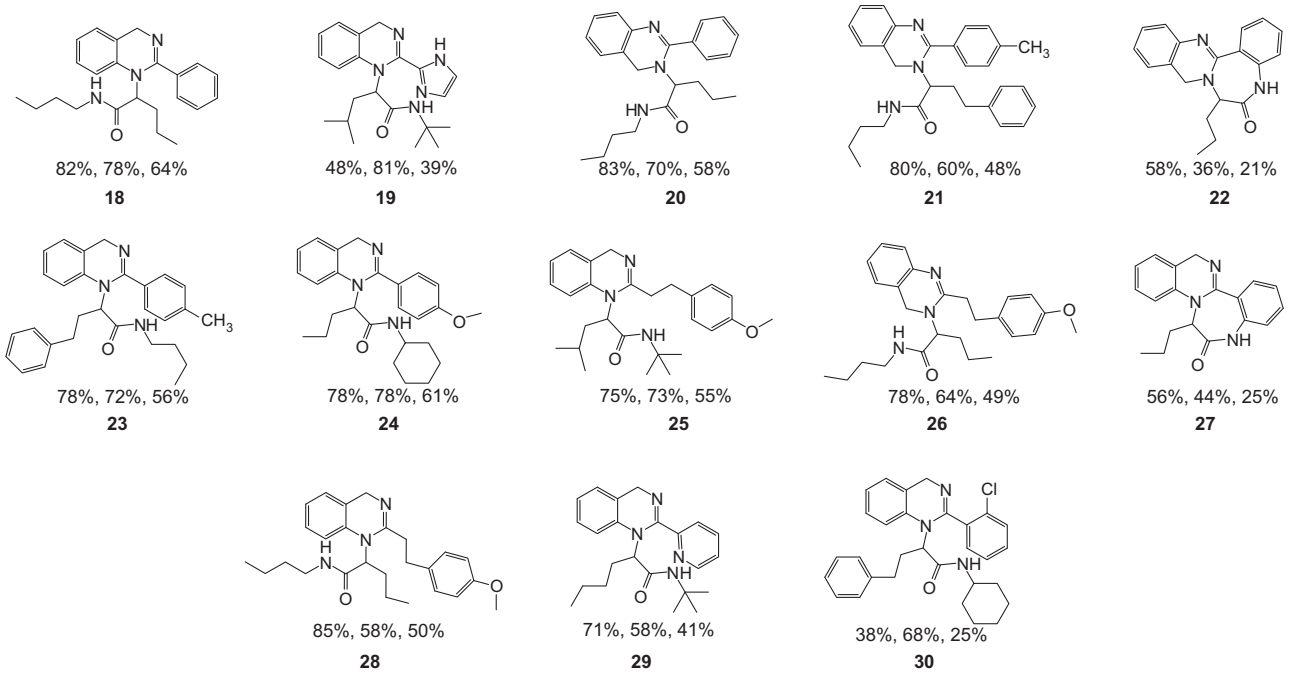


Figure 3. Reported % yields = Ugi yield, cyclization yield, overall yield.

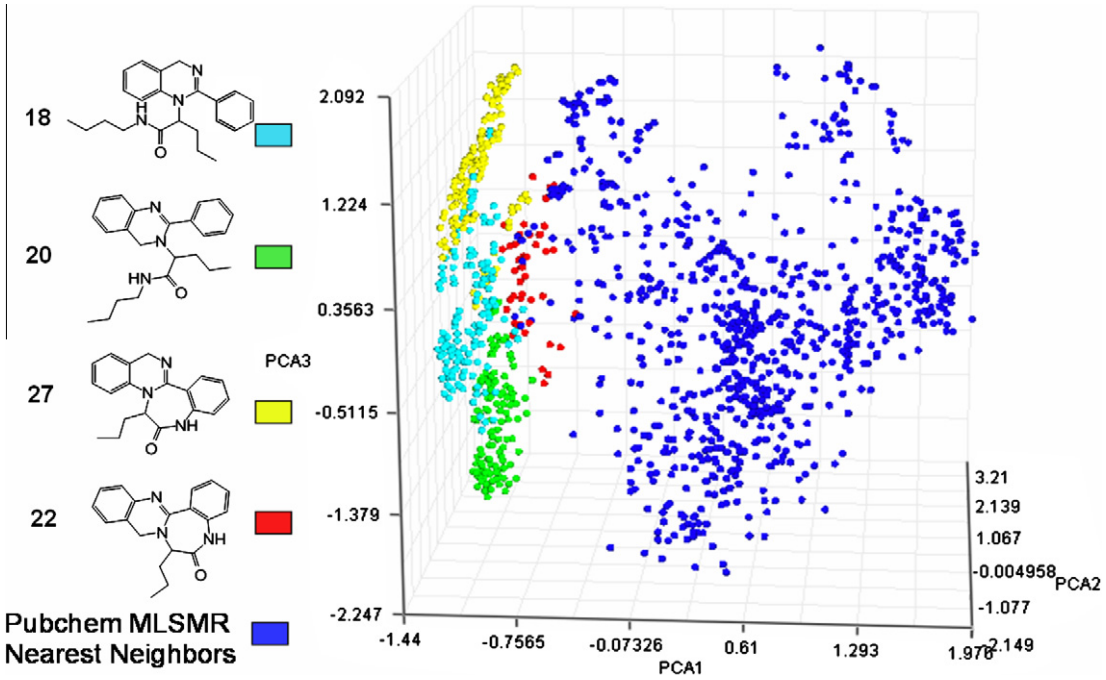


Figure 4.

Acknowledgments

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19. *General preparation of dihydroquinazolines*, **19**: To a solution of butyraldehyde (164 μl, 1.800 mmol) in methanol (3 mL) in a 2.0–5.0 ml microwave vial was added *tert*-butyl 2-aminobenzylcarbamate (200 mg, 0.900 mmol). The reaction was stirred at room temperature for 30 min followed by the addition of *n*-butyl isocyanide (95 μl, 0.900 mmol) and benzoic acid (110 mg, 0.900 mmol). The reaction was then irradiated for 10 min at 100 °C. The solvent was evaporated in vacuo, crude material taken up in 3 mL 10% EtOAc/Hexane and loaded onto a 12 g silica column with purification performed on a Biotage® Isolera 4 (gradient 10–20% EtOAc/hexane) to yield the desired Ugi product (344 mg, 0.738 mmol, 82% yield). The Ugi product was then taken up in 5 mL 10% TFA/DCE, transferred to a 2–5 mL microwave vial and irradiated at 120 °C for 20 min. The reaction was then poured into a separatory funnel that contained 50 mL saturated sodium carbonate and 50 mL DCM. The organic layer was collected and aqueous layer further extracted with DCM (50 ml). The combined organics were dried over $MgSO_4$, concentrated onto neutralized silica, and purified on a Biotage Isolera (25 g neutralized column, 20% EtOAc/1.5% TEA/hexane) to yield the desire 1,4-dihydroquinazoline product, *N*-butyl-2-(2-phenylquinazolin-1(4*H*)-yl)pentanamide **20** (209 mg, 0.576 mmol, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 7.50 (dd, 2H, *J* = 1.8 Hz, *J* = 14.7 Hz), 7.31–7.45 (m, 3H), 7.12 (dt, 1H, *J* = 7.5 Hz, *J* = 0.9 Hz), 7.05 (dt, 1H, *J* = 0.9 Hz, *J* = 7.5 Hz), 6.98 (d, 1H, *J* = 5.4 Hz), 6.78 (d, 1H, *J* = 7.5 Hz). 6.45 (t, 1H, *J* = 5.4 Hz), 4.83 (d, 1H, *J* = 18.6 Hz), 4.74 (d, 1H, *J* = 18.6 Hz), 4.25 (dd, 1H, *J* = 4.2 Hz, *J* = 10.2 Hz), 3.29 (m, 2H), 1.7–2.2 (m, 2H), 1.45–1.6 (m, 2H), 1.20–1.40 (m, 4H), 0.91 (t, 3H, *J* = 4.5 Hz), 0.79 (t, 3H, *J* = 4.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 171.05, 158.18, 137.03, 136.62, 130.05, 129.09 (2C), 128.40 (2C), 127.32, 126.78, 124.66, 123.92, 116.74, 62.99, 49.30, 39.90, 31.91, 29.89, 20.52, 20.18, 14.14, 14.03.
20. *General procedure for preparation of dihydroquinazoline-benzodiazepine tetracycle* **26**: To a 2.0–5.0 mL microwave vial was added a solution of butyraldehyde (246 μl, 1.350 mmol) in DCM (3 ml), *tert*-butyl (2-(aminomethyl)phenyl)carbamate (300 mg, 1.350 mmol), and $MgSO_4$. The reaction was sealed and irradiated for 10 min at 120 °C to yield the Schiff base in quantitative yields (R_f 0.82, 25% EtOAc/Hex). *n*-Butylisocyanide (143 μl, 1.350 mmol) and 2-((*tert*-butoxycarbonyl)amino)benzoic acid (320 mg, 1.350 mmol) were added and reacted at 120 °C under microwave irradiation. The crude mixture was poured into a separatory funnel containing saturated sodium bicarbonate and DCM. The organic layer was collected, dried, loaded onto 2 g silica gel and purified on a Biotage Isolera (40 g column, gradient 10–35% EtOAc/Hex) to yield the Ugi product (478 mg, 0.783 mmol, 58% yield). The Ugi product was then taken up in 10% TFA/DCE (5 ml), transferred to a 2–5 mL microwave vial and irradiated at 130 °C for 20 min. After heating, the reaction was poured into a separatory funnel that contained saturated sodium carbonate (50 mL) and DCM (50 mL). The organic layer was collected and then the aqueous layer was extracted twice more with DCM (2 × 50 mL). The combined organics were dried over $MgSO_4$, concentrated onto neutralized silica, and purified on a Biotage Isolera (25 g neutralized column, 50% EtOAc/2.0% TEA/hexane) to yield the desire 3,4-dihydroquinazoline-benzodiazepine tetracyclic product, 7-propyl-7,9-dihydrobenzo[5,6]-[1,4]diazepino[7,1-*b*]quinazolin-6(5*H*)-one **27** (87 mg, 0.283 mmol, 21% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 8.65 (s, 1H), 8.08 (d, 1H, *J* = 7.2 Hz), 7.45 (t, 1H, *J* = 7.2 Hz), 7.2–7.4 (m, 3H), 7.1–7.2 (m, 1H), 7.10 (t, 1H (dd, 2H, *J* = 1.8 Hz, *J* = 14.7 Hz), 6.95–7.10 (m, 3H), 4.41 (d, 1H, *J* = 13.2 Hz), 4.27 (d, 1H, *J* = 13.2 Hz), 4.12 (t, 1H,

7.5 Hz), 1.8–2.1 (m, 2H), 1.2–1.5 (m, 4H), 0.95 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 170.95, 143.533, 137.11, 132.12, 131.64, 129.16, 128.94, 126.07, 125.59, 125.46, 124.48, 122.63, 121.22, 56.41, 43.14, 27.79, 19.42, 14.32.

21. In an exercise to demonstrate uniqueness, virtual libraries for all four scaffolds were enumerated with Symyx Draw 3.2 (comprising scaffold **1**—168 compounds; **2**—168 compounds, **3**—144 compounds, **4**—48 compounds). The parent structure of each compound was then compared with the 375,000 compounds available in the NIH molecular libraries small molecule repository (MLSMR) described by pharmacophore fingerprints using PowerMV v0.61. A total of 1043 similar compounds were selected using a Tanimoto Similarity function as implemented in the nearest neighbor search tool in PowerMV (distance threshold for library 1 and 2 = 0.5; library 3 = 0.29; library 4 = 0.4). The libraries and the MLSMR subset (1571 compounds total) were imported into MOE (Molecular Operating Environment v2009.11, Chemical Computing Group) and represented by structural fingerprints (MACCS keys). Tanimoto similarities were computed based on the MACCS keys, which generated a 1571 by 1571 matrix. The columns of the matrix were used as input for a principle component analysis and the first three principle components were represented graphically using MOE (Fig. 4).
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