Published in final edited form as:

Tetrahedron Lett. 2012 March 28; 53(13): 1664–1667. doi:10.1016/j.tetlet.2012.01.080.

Concise route to a series of novel 3-(tetrazol-5-yl)quinoxalin-2(1*H*)-ones

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Abstract

This report presents a novel three step solution phase protocol to synthesize 3-(tetrazol-5-yl)quinoxalin-2(1*H*)-ones. The strategy utilizes ethyl glyoxalate and *mono-N*-Boc-protected-*o*-phenylenediamine derivatives in the Ugi-Azide multi-component reaction (MCR) to generate a unique 1,5-disubstituted tetrazole. Subsequent acid treatment stimulates a simultaneous Boc deprotection and intramolecular cyclization leading to bis-3,4-dihydroquinoxalinone tetrazoles. Direct oxidation using a stable solid-phase radical catalyst (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) with ceric ammonium nitrate (CAN) in catalytic fashion initiating aerobic oxidation, completes the entire procedure to generate a series of original unique bis-quinoxalinone tetrazoles. The method was also expanded to produce a bis-benzodiazepine tetrazole.

The emerging need to enrich the national US compound collection has inspired the development of methodology that enables concise access to diverse pharmacologically relevant compounds. The Ugi reaction, probably the premiere example of an isocyanide based MCR, contains 4 reagents namely an amine, aldehyde, isocyanide and carboxylic acid. In addition to the development of new MCRs, tremendous efforts have been made by several groups with strategies entailing intramolecular variants of the Ugi and post condensation modifications of the Ugi product.¹ Indeed, such chemistry allows rapid access to new molecular diversity and there are examples of hits being discovered, optimized and entering the clinic without a need to scaffold hop.² One interesting facet of the classical Ugi reaction is the interchangeability of the carboxylic acid, exemplified by replacement with hydrazoic acid, cyanates, thiocyanates, carbonic acid monoesters, salts of secondary amines, hydrogen sulfide as Na₂S₂O₃, hydrogen sulfide, thiocarboxylic acid, phenol or water.³ All these Ugi variants afford enticing structures for further diversification and possibly the most versatile is the Ugi MCR with azidotrimethylsilane (TMSN₃). This reaction affords 1,5-disubstituted tetrazoles **3** (Scheme 1), reported effective bioisosteres for the *cis*-amide bond conformation.⁴

Indeed, rigidification of the core scaffold from the Ugi-Azide MCR has led to the generation of unique cyclic scaffolds such as ketopiperazine-tetrazoles, azepine-tetrazoles, benzodiazepine-tetrazoles, and quinoxaline-tetrazoles.⁵ However, there is no report of

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utilization of the Ugi-Azide MCR to produce a quinoxalinone framework which represents an important biological motif found in antithrombotic agents,⁶ several inhibitors for metalloproteinase,⁷ hepatitis C virus,⁸ glycogen phosphorylase,⁹ poly(ADP-ribose)polymerase-1,¹⁰ cyclin-dependent kinases¹¹ and α -amino-3-hydroxy-5-methylisoxazole propionate receptor (AMPA-R) antagonists.¹² A common route to access the quinoxalinone template employs *o*-phenylenediamine derivatives and glyoxylic acids or glyoxylates.^{11,13} As part of our on-going venture to generate unique small molecules via the Ugi-Azide MCR, we herein report a concise three-step method utilizing *mono-N*-Boc-protected-*o*-phenylenediamine derivatives **4** together with ethyl glyoxalate **5** and isocyanides to synthesize arrays of bis-quinoxalinone tetrazoles **6** (Scheme 2).

Initial pilot efforts were focused on the synthesis of 3-(1-butyl-1*H*-tetrazol-5-yl)quinoxalin-2(1*H*)-one **12** (Scheme 3) from *N*-Boc-1,2-phenylenediamine **7**, *n*-butyl isocyanide **8** and ethyl glyoxalate **5**. Using MeOH as solvent proved unfruitful, affording **9**, presumably arising from Schiff-base **1** solvent addition. Previous Ugi MCR-related articles suggest trifluoroethanol (CF₃CH₂OH), a non-nucleophilic protic solvent, as a viable alternative for MeOH.¹⁴ Thus, precondensation of ethyl glyoxalate **5** and *N*-Boc-1,2-phenylenediamine **7** in DCE followed by addition of trifluoroethanol, *n*-butyl isocyanide **8** and TMSN₃ afforded Ugi-tetrazole **10** in moderate yield of 45%. Subsequent acid treatment removed the Boc group and the unmasked amine immediately cyclized to form dihydroquinoxalinone **11** in 67% yield. A number of synthetic operations have been reported for quinoxalinone oxidation from dihydroquinoxalinones that include DDQ^{6b}, H₂O₂-NaOH,¹⁵ MnO₂,¹⁶ *p*-chloroanil¹⁷ and air oxidation.¹⁸ Fortuitously, the bis-quinoxalinone tetrazole **12** was attained using a stable solid-phase radical catalyst TEMPO and catalytic CAN under aerobic conditions. This method simplified the work-up to filtration of catalyst and solvent extraction of the oxidized product. To the best of the author's knowledge, this is the first example of dihydroquinoxalinone oxidation by means of TEMPO, typically employed for the oxidization of primary and secondary alcohol.¹⁹ Encouragingly, compound **11** did not require purification and was moved forward in crude form to provide **12** in 63% yield in two steps (**10** to **12**).

With compound **12** in hand, a series of eleven bis-quinoxalinone tetrazoles **15** were prepared to establish the generality of the reaction sequence. The procedure represents an example of a post-condensation Ugi-Azide modification that utilizes one internal nucleophile with two points of diversity arising from *mono-N*-Boc-protected-*o*-phenylenediamine derivatives **13** and isocyanides **14**, generating a novel structure in a concise three-step process. Various *mono-N*-Boc-protected-*o*-phenylenediamine derivatives **13a–d** were employed in library production and synthesized via Boc protection from the diamine. Table 1 summarizes the isolated yields with corresponding diversity inputs. Definitive structural confirmation for this chemotype was provided by X-ray crystallography **15d**²⁰ (Figure 1).

For further extension, application of this methodology to *N*-Boc-2-aminobenzylamine²¹ **16** offered an opportunity to access benzodiazepine scaffolds. When **16** was mixed with TMSN₃, ethyl glyoxalate **5** and *n*-butyl isocyanide **8** in MeOH, the MCR-derived tetrazole **17** was isolated in 48% yield (Scheme 4). Unexpectedly, acid treatment of **17** only afforded **18**. Attempts to cyclize **18** to **19** through aminolysis of the ester by either activating the ester²² or the amine²³ were also unsuccessful. Ultimately, hydrolysis of **18** was performed under basic conditions followed by an EDC-promoted intramolecular amide coupling to provide **19** in 35% (three steps).

In conclusion, a succinct three-step synthesis of a collection of 3-(tetrazol-5-yl)quinoxalin-2(1*H*)-ones **6** that employs the Ugi-Azide MCR followed by cyclization under acidic condition and immediate oxidation with TEMPO/CAN under aerobic conditions has

been reported. The method was expanded to afford bis-benzodiazepine tetrazole **19** using *N*-Boc-2-aminobenzylamine **16** in the Ugi-Azide MCR followed by sequential acid-base treatment and EDC-mediated benzodiazepine formation. Due to the uniqueness of these chemotypes, the promising pharmacological properties, and the ease of synthesis, these procedures offer new feasible strategies for file enhancement by the medicinal chemist.

Acknowledgments

The authors thanked the Office of the Director, NIH and the National Institute of Mental Health for funding (1RC2MH090878-01), Kristen Keck for compound purification, Alex Laetsch for compound management and Nicole Schechter for proof-reading.

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20. 3-(1-benzyl-1*H*-tetrazol-5-yl)-6,7-dimethylquinoxalin-2(1*H*)-one (**15d**): Light yellow solid (m.p. 235–236 °C); ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.91 (s, 1H), 7.62 (s, 1H), 7.39 – 7.22 (m, 5H), 7.17 (s, 1H), 5.82 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm 154.2, 151.2, 144.1, 143.8, 135.5, 133.9, 132.0, 131.2, 129.9, 129.5, 129.2, 129.1, 116.5, 52.4, 20.9, 19.7; [M+H]⁺ = 333.0; HRMS (ESI): m/z calcd for (C₁₈H₁₇N₆O): 333.1458; found: 333.1455.
21. The procedure for the synthesis of *N*-Boc-2-aminobenzylamine **7** can be found in Nichol GS, Chappeta S, Dietrich J, Hulme C. *Tetrahedron Lett.* 2010; 51:4689–4692. [PubMed: 20802841]
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Figure 1.
X-Ray crystal structure of **15d**

Scheme 1.
General Ugi-Azide reaction

Scheme 2.
Overall synthesis protocol

Scheme 3.
Synthesis of 3-(1-butyl-1*H*-tetrazol-5-yl)quinoxalin-2(1*H*)-one **12**

Scheme 4.

Synthesis of 3-(1-butyl-1*H*-tetrazol-5-yl)-4,5-dihydro-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one **19**

Table 1

Arrays of bis-quinoxalinone tetrazoles **15**

13	14	Product	Final Yield* (%)
		15a	58
		15b	66
		15c	47
		15d	49
		15e	47
		15f	59
		15g	62
		15h	41
		15i	47
		15j	43

*Two steps for deprotection-cyclization with TFA and oxidation using CAN-TEMPO from Ugi product