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

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ABSTRACT

This Letter 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 $Na_2S_2O_3$, 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 ($TMSN_3$). 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 for the utilization of 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 kinases[11] 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 ongoing 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 (CF_3CH_2OH), 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 the addition of trifluoroethanol, *n*-butyl isocyanide **8,** and $TMSN_3$ 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 a 67% yield. A number of synthetic operations have been reported for quinoxalinone oxidation from dihydroquinoxalinones that include DDQ,[6b] H_2O_2-NaOH,[15] MnO_2,[16] *p*-chloroanil,[17] 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 the filtration of catalyst and solvent extraction of the

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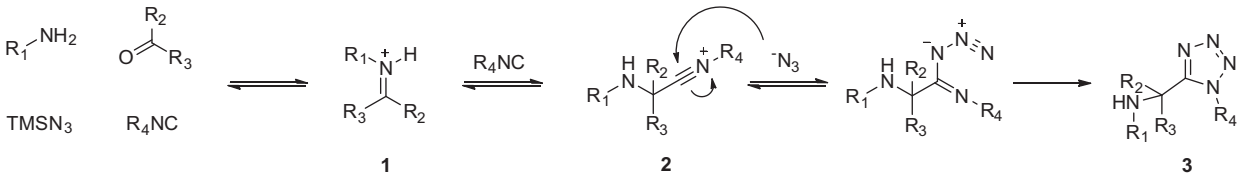
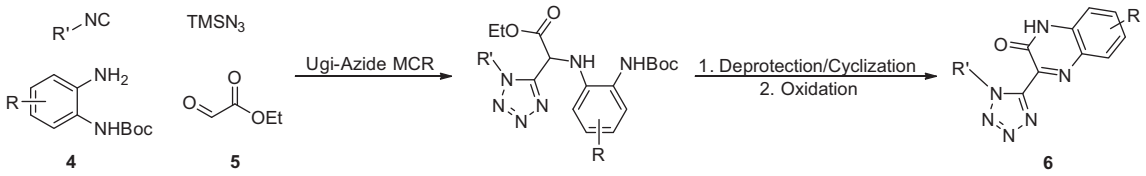
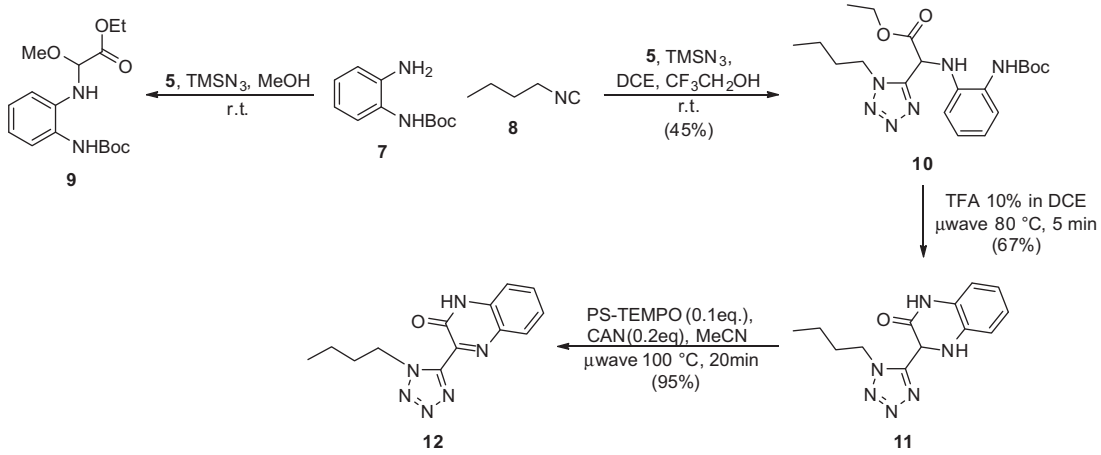


Scheme 1. General Ugi-Azide reaction.

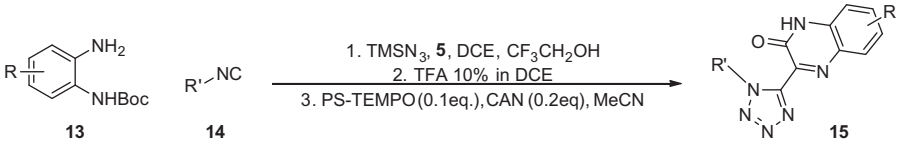


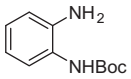
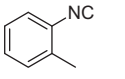
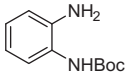
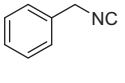
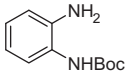
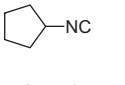
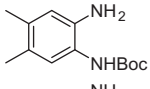
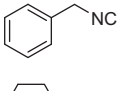
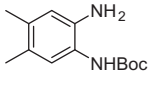
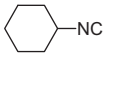
Scheme 2. Overall synthesis protocol.



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

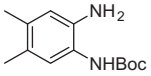
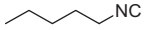
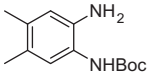
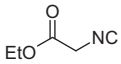
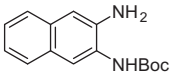
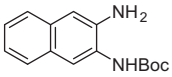
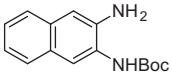
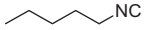
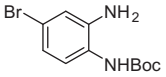
Table 1
Arrays of bis-quinoxalinone tetrazoles **15**



13		14	Product	Ugi (%)	Final yield* (%)
	**13a**		**15a**	73	58
	**13a**		**15b**	41	66
	**13a**		**15c**	41	47
	**13b**		**15d**	48	49
	**13b**		**15e**	47	47

(*continued on next page*)

Table 1 (*continued*)

13		14	Product	Ugi (%)	Final yield* (%)
	**13b**		**15f**	49	59
	**13b**		**15g**	31	62
	**13c**		**15h**	62	41
	**13c**		**15i**	47	47
	**13c**		**15j**	50	43
	**13d**		**15k**	60	27

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

oxidized product. To the best of author's knowledge, this is the first example of dihydroquinoxalinone oxidation by means of TEMPO, typically employed for the oxidization of primary and secondary alcohols.[19] Encouragingly, compound **11** did not require purification and was moved forward in crude form to provide **12** in a 63% yield in two steps (**10**–**12**).

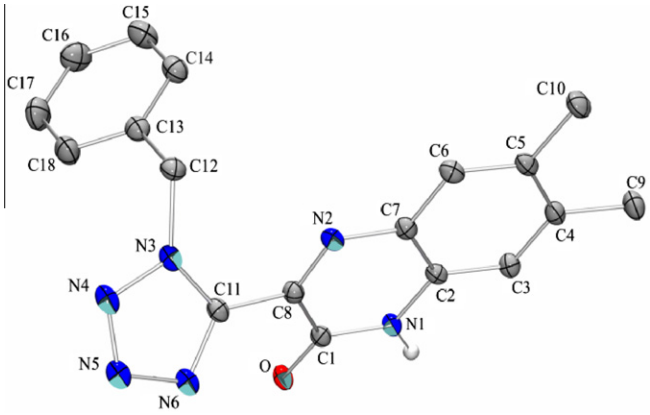
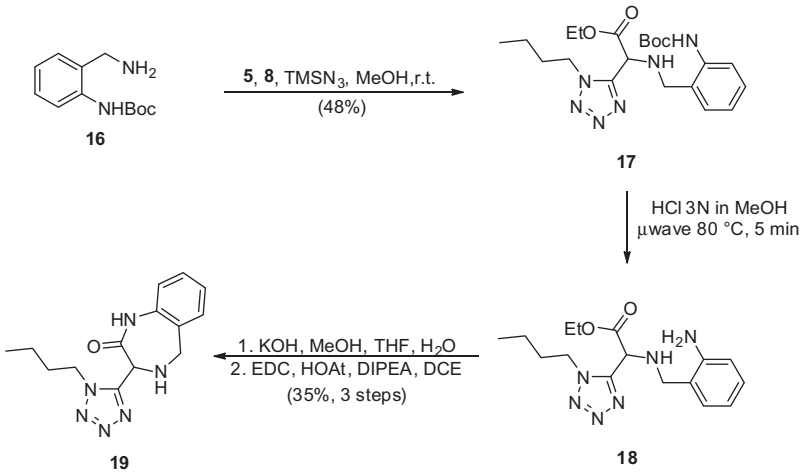


Figure 1. X-ray crystal structure of **15d**.

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] (Fig. 1).

For further extension, application of this methodology to *N*-Boc-2-aminobenzylamine[21] **16** offered an opportunity to access benzodiazepine scaffolds. When **16** was mixed with $TMSN_3$, ethyl glyoxalate **5,** and *n*-butyl isocyanide **8** in MeOH, the MCR-derived tetrazole **17** was isolated in a 48% yield (Scheme 4). Unexpectedly, acid treatment of **17** only afforded **18**. Attempts to cyclize



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**.

18 to **19** through aminolysis of the ester by either activating the ester[22] or the amine[23] 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.

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20. 3-(1-Benzyl-1*H*-tetrazol-5-yl)-6,7-dimethylquinoxalin-2(1*H*)-one (**15d**): Light yellow solid (mp 235–236 °C); ^{1}H NMR (300 MHz, $DMSO_{d6}$) 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); ^{13}C NMR (75 MHz, $DMSO_{d6}$) 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 ($C_{18}H_{17}N_6O$): 333.1458; found: 333.1455.
21. The procedure for the synthesis of *N*-Boc-2-aminobenzylamine **7** can be found in: Nichol, G. S.; Chappeta, S.; Dietrich, J.; Hulme, C. *Tetrahedron Lett.* **2010**, *51*, 4689–4692.
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