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Letter

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Concise One-Pot Preparation of Unique Bis-Pyrrolidinone Tetrazoles

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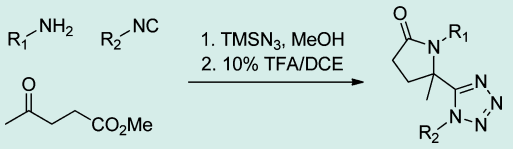
Supporting Information

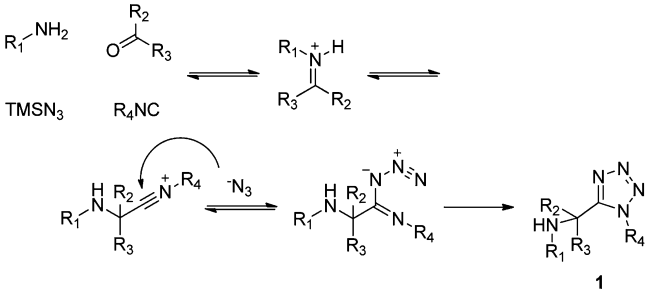
ABSTRACT: A one-pot, two-step synthesis of bis-pyrrolidinone tetrazoles has been established via the Ugi–Azide reaction using methyl levulinate, primary amines, isocyanides and azidotrimethylsilane with subsequent acid treatment to catalyze the lactam formation. The efficiency of the protocol was established followed by a successful transition to library production in four 24-well plates.



KEYWORDS: *1,5-disubstituted tetrazoles, Ugi reaction*

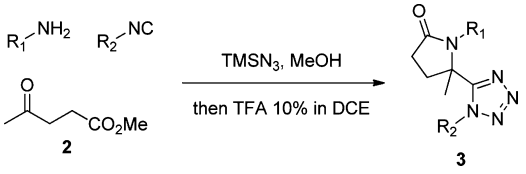
Derivatization of isocyanide based MCR products such as those from the Ugi reaction, followed by a postcondensation modification have received massive attention in medicinal chemistry for the pursuit of generating collections of small molecules with high molecular diversity.[1−6] Interestingly, substitution of the carboxylic acid in the generic Ugi MCR with azidotrimethylsilane ($TMSN_3$) makes it possible to afford 1,5-disubstituted tetrazoles, **1** (Scheme 1),[7,8] an effective conformational mimic for the *cis*-amide bond conformation.[9,10]

Scheme 1. General Ugi–Azide Reaction



Exploration of the Ugi–Azide MCR using a variety of diverse reagents have led to the creation of unique scaffolds as exemplified by ketopiperazine–tetrazoles,[8] azepine–tetrazoles,[11,12] benzodiazepine–tetrazoles,[13] and quinoxaline–tetrazoles.[14] This letter reports the establishment of unique methodology which utilizes keto-esters (methyl levulinate **2**), along with primary amines, isocyanides, and $TMSN_3$ to afford novel peptidomimetic-like bis-pyrrolidinone tetrazoles **3** (Scheme 2).

Scheme 2. General Synthetic Route to Access Bis-pyrrolidinone Tetrazole 3



The pilot reaction during optimization of the sequence utilized methyl levulinate **2**, 2-thiophenemethylamine **4**, 2,6-dimethylphenyl isocyanide **5** and $TMSN_3$ to generate 5-(1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)-5-methyl-1-(thiophen-2-ylmethyl)pyrrolidin-2-one **7** (Scheme 3). After allowing the mixture to stir overnight at room temperature, the Ugi condensation product **6** was typically observed in high yield (LC-MS > 90% A% purity as judged by UV214 and ELS) (Scheme 3). Subsequent microwave irradiation (100 °C, 5 min) failed to deliver the desired bis-heterocyclic product **7** (Table 1, entry 2). However, very encouragingly simple addition of a 10% solution of trifluoroacetic acid (TFA) in 1,2-dichloroethane (DCE) into the ongoing Ugi reaction afforded γ-lactam formation in good to moderate yield

Scheme 3. Synthesis of 5-(1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)-5-methyl-1-(thiophen-2-ylmethyl)pyrrolidin-2-one 7

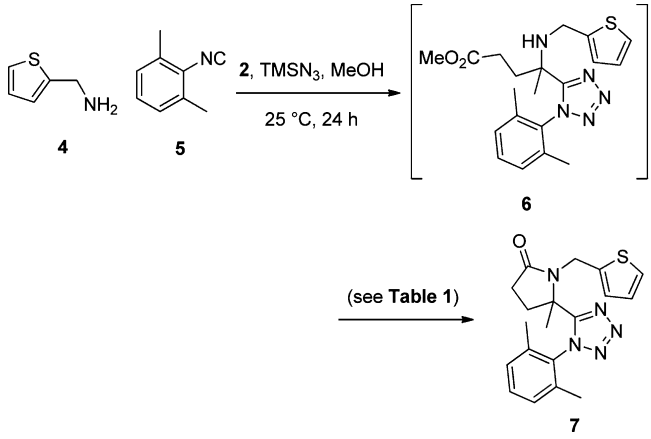


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Table 1. Optimization for the Pilot Synthesis of 7

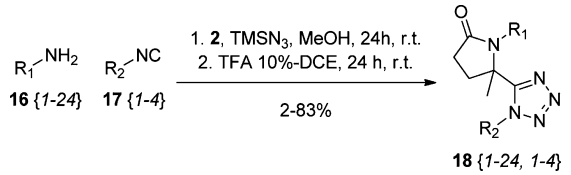
entry	conditions	**2** (equiv)	**4** (equiv)	**5** (equiv)	$TMSN_3$ (equiv)	yield of **7** (%)
1	25 °C, 24 h	1.0	1.0	1.0	1.0	
2	μwave 100 °C, 10 min	1.0	1.0	1.0	1.0	
3	10% TFA in DCE, μwave 100 °C, 10 min	1.0	1.0	1.0	1.0	40
4	10% TFA in DCE, μwave 100 °C, 10 min	1.5	1.0	2.0	1.0	56
5	10% TFA in DCE, 25 °C, 24 h	1.5	1.0	2.0	1.0	58
6	15% TFA in DCE, 25 °C, 24 h	1.5	1.0	2.0	1.0	59
7	20% TFA in DCE, 25 °C, 24 h	1.5	1.0	2.0	1.0	61
8	10% TFA in DCE, 25 °C, 24 h	1.0	1.0	1.0	2.0	39

(Table 1, entry 3). Indeed, to the best of the authors' knowledge, we believe this is the first example of TFA-mediated γ-lactam formation. The yield was also further improved with the use of excess keto-ester and isocyanide (Table 1, entry 4).

With these encouraging results from the pilot study in-hand, a small library comprised of eight compounds (Figure 1) was synthesized to further validate this one-pot, two-step synthetic protocol by varying the primary amine and isocyanide inputs. Predictably, given their poor nucleophilicity, use of anilines as the amine component resulted in lower yields (**14** and **15**).

Although microwave irradiation expedites the process, it is worth mentioning that each step can be performed at room temperature (Table 1, entry 5). Stoichiometry studies performed at room temperature (entries **6**, **7**, and **8**) failed to significantly increase yields of final product. The procedure was thus progressed to 4 24-well plate production (Scheme 4) with an assortment of primary amines **16**{*1*−*24*} and isocyanides **17**{*1*−*4*} where subsequently,

Scheme 4. Synthesis of Bis-pyrrolidinone Tetrazoles 18



final products were purified by in-house mass-triggered purification platforms, successfully yielding 84 products **18** from the 96 reactions.

The reaction seemed robust for a wide range of primary amines and isocyanides, Figure 2. Table 2 presents both isolated yields and purities of final target molecules demonstrating the generality of the protocol. Notably, 2,6-dichlorobenzylamine **16**{*2*}, which performed well in the Ugi reaction, did not undergo any cyclization upon addition of TFA, possibly due to strong steric and electronic effects. In addition, two amines, 4-morpholinoaniline **16**{*11*} and 1-benzylpiperidin-4-amine **16**{*22*} produced Ugi congeners which underwent ring formation in only low yield (8−23%, eight examples). Likewise, sterically hindered cyclohexylamine **16**{*23*} produced no final cyclized product. Taken as a whole, 84 compounds were obtained with overall yields ranging from 2 to 84% with 82 compounds having purity greater than 95% [as judged by UV absorbance at 214 nm, 254 nm, and evaporative light scattering (ELS)].

Virtual libraries derived from reagents used in both the initial pilot and plate based library (**7**, Figure 1 and 2) were also enumerated to establish their uniqueness relative to a collection of over 400 000 chemically diverse small molecules in the NIH molecular libraries small molecule repository (MLSMR).[15] As such, principle component analysis (PCA)[16] demonstrates the unique spatial occupancy of the bis-pyrrolidinone tetrazole scaffold when compared to 942 nearest MLSMR neighbors described herein Figure 3, with no substructure match in the MLSMR

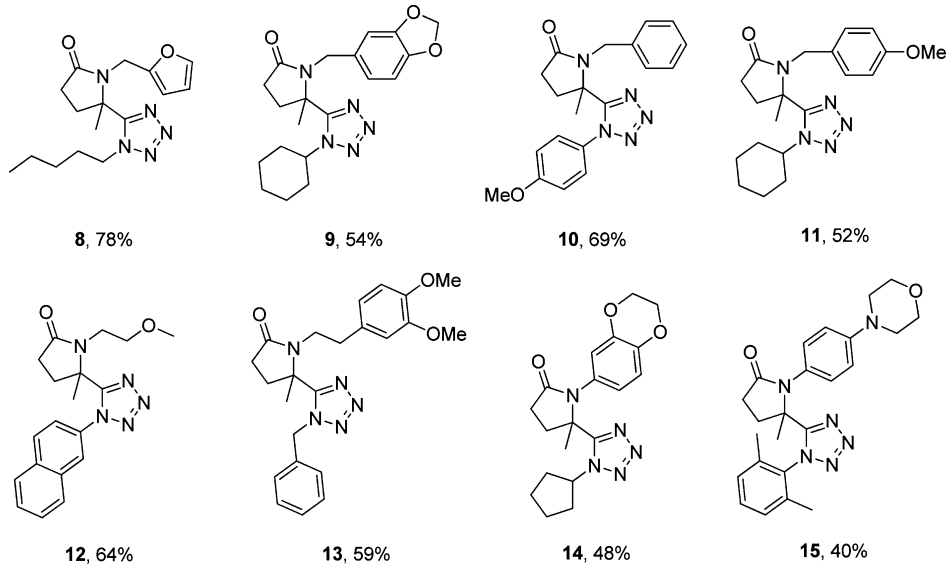


Figure 1. Example analogs (*x*% = overall yield).

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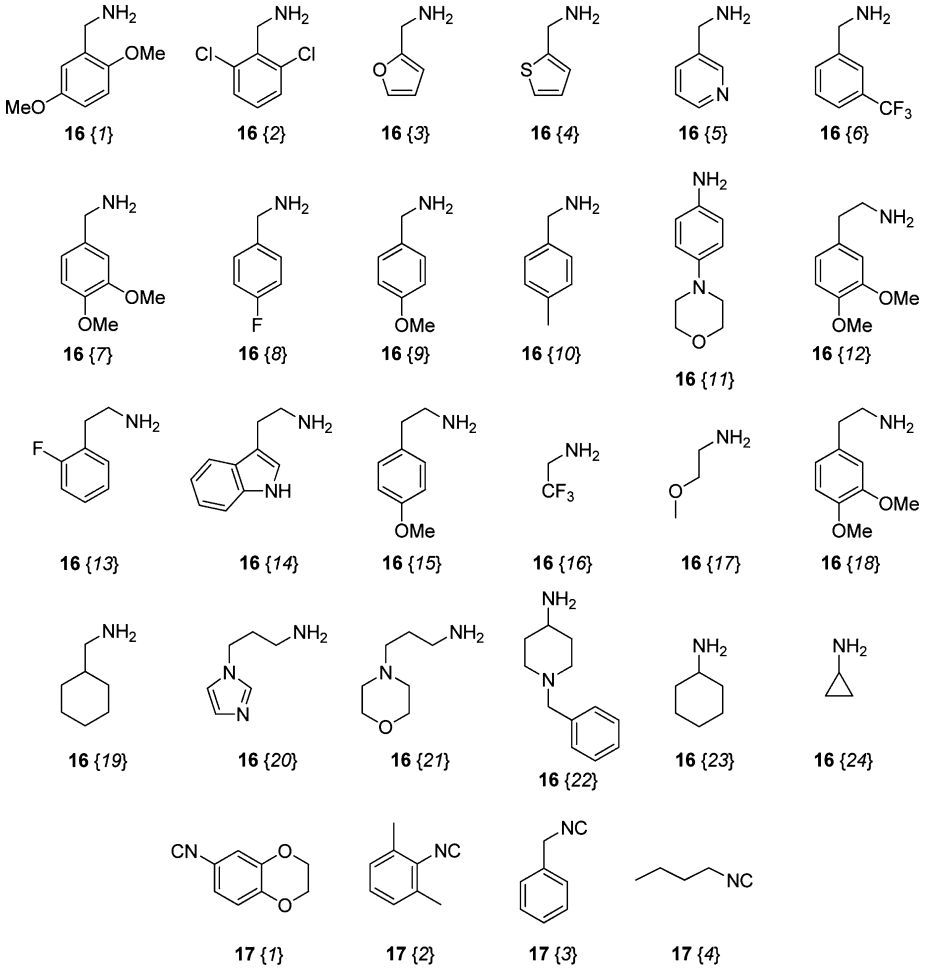

Figure 2. Diversity reagents **16**{*1*−*24*} and **17**{*1*−*4*}.

Table 2. Yield and Purity (%) of the 96-Well Plate Production of 18{*1*−*24,1*−*4*}[a]

	R$_2$NC (**17**)									R$_2$NC (**17**)							
	1		*2*		*3*		*4*			*1*		*2*		*3*		*4*	
R$_1$NH$_2$ (**16**)	*Y*	*P*	*Y*	*P*	*Y*	*P*	*Y*	*P*	R$_1$NH$_2$ (**16**)	*Y*	*P*	*Y*	*P*	*Y*	*P*	*Y*	*P*
1	nr		46	100	57	100	53	98	*13*	46	100	41	100	48	100	63	100
2	nr		un		un		un		*14*	49	100	nr		38	100	59	100
3	nr		45	100	45	100	66	100	*15*	38	100	27	100	43	100	47	100
4	nr		45	100	50	100	65	100	*16*	45	100*	47	100	27	100	8	100*
5	69	97	42	100	53	100	64	98	*17*	56	100	44	100	58	100	61	100
6	49	100	36	100	38	100	55	100	*18*	51	100	39	100	39	100	61	100
7	50	100	39	100	50	100	54	100	*19*	26	100	23	100	29	100	33	100
8	57	100	42	100	50	100	62	100	*20*	55	100	51	100	61	100	83	95
9	57	100	42	100	55	100	49	100	*21*	59	100	44	100	64	100	72	100
10	56	98	41	100	51	100	60	100	*22*	7	93*	22	100*	6	100*	2	100*
11	23	70	16	100	8	100	13	100	*23*	un		un		un		un	
12	47	100	34	100	50	100	53	100	*24*	28	96	24	100	18	100	55	100

[a] *Y* = Yield (%); *P* = Purity (%) based on UV 214 nm; nr = not recovered/lost during purification; un = no cyclization to **18** observed; * purity based on ELS

and only minor overlap in similarity space with its nearest neighbors.

In summary, a one-pot, two-step protocol for large scale production of libraries of bis-pyrrolidinone tetrazoles has been successfully developed using the tethered keto-ester methyl levulinate **2**, primary amines, isocyanides and azidotrimethylsilane through the use of the Ugi-Azide reaction followed by subsequent lactam formation under acidic conditions.

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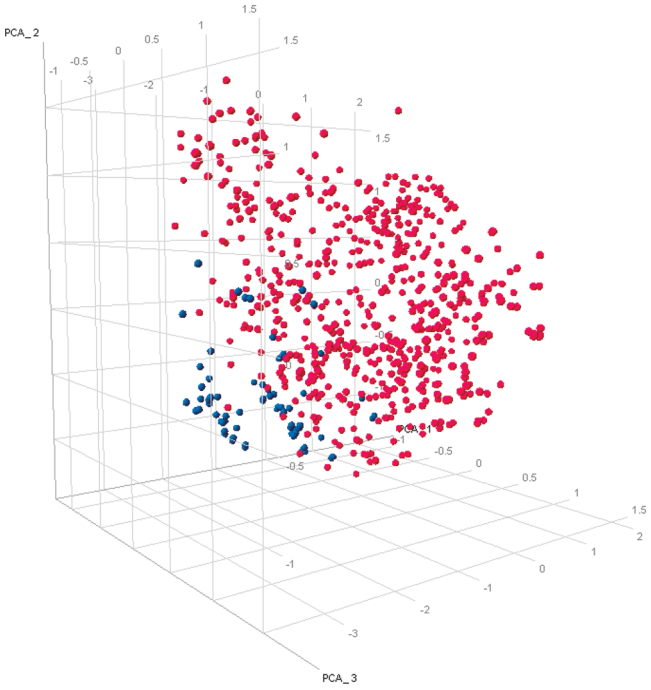

Figure 3. Similarity space occupied by the bis-pyrrolidinone tetrazoles library (blue dots) relative to the 942 nearest neighbors in MLSMR (red dots).

Because of the robustness of the described methodology, future studies will continue to expand readily available molecular diversity delivering scaffolds of interest, in particular to chemists involved in file enhancement programs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, ^{1}H and ^{13}C NMR, low and high resolution MS data for the nine analogs (**7**−**15**) from small library, and virtual library generation. 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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(15) Visit http://mli.nih.gov/mli/compound-repository/ for overview of molecular libraries program.

(16) Details of how PCA was conducted can be found in Supporting Information.