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Short solution phase preparation of fused azepine-tetrazoles via a UDC (Ugi/de-Boc/cyclize) strategy†

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Abstract—A novel application of the $TMSN_3$ modified Ugi 4-component reaction is disclosed for the solution phase synthesis of fused azepine-tetrazole libraries. The reaction of a *N*-Boc-α-amino aldehyde, secondary amine, methyl isocyanoacetate and trimethylsilylazide in methanol, followed by acid treatment, proton scavenging and reflux affords bicyclic azepine-tetrazoles. This efficient protocol, producing products with three diversity points, can be used to generate arrays of biologically relevant small molecules for general and targeted screening.

With the recent emergence of combinatorial chemistry and high speed parallel synthesis in the lead discovery arena, the multi-component reaction (MCR) has witnessed a resurgence of interest.[1] Easily automated one-pot reactions, such as the Ugi[2] and Passerini[3] reactions, are powerful tools for producing diverse arrays of compounds, often in one step and high yield. Despite this synthetic potential, the Ugi reaction is limited to producing products that are flexible and peptide-like. Interestingly, several novel intramolecular variations on the Ugi reaction have recently been reported, where constrained more biologically relevant products result from interception of the intermediate nitrilium ion using a bi-functional input.[4] An alternative approach is to constrain the Ugi product via a post-condensation modification, often by unmasking a protected amino internal nucleophile.[5,6]

This letter discloses a novel solution phase methodology, utilizing $TMSN_3$, secondary amines, *N*-Boc-α-amino-aldehydes, **1**, and substituted methylisocyanoacetates, **2**, for the preparation of fused azepine-tetrazoles, **3**. Compounds produced are of high purity and suitable for high-throughput evaluation in primary assays, without the need for extensive purification (Scheme 1).

As such, the above transformation represents the first example of the UDC approach[7] (Ugi/de-Boc/cyclize) applied to the $TMSN_3$ modified Ugi reaction.[8] These, rigid, hydrophobic molecules with generic structure, **3**, are of interest in lead discovery applications, where the biological utility of both azepines and tetrazoles has been widely reported in a variety of bio-active substances.[9]

Originally reported in 1961,[2] the $TMSN_3$ modified Ugi involves condensation of an appropriately substituted aldehyde or ketone with a primary or secondary amine. Reaction of the Schiff base with an isonitrile and intermediate nitrilium ion trapping with azide, affords monocyclic tetrazoles in good overall yield.

The initial tetrazole forming reaction is particularly well-suited for the solution phase preparation of monocyclic tetrazoles and efficient enough to generate libraries with three points of diversity in the 10,000 member range. We were especially interested in contin-

Scheme 1.

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† This article is dedicated to Professor Ivar Ugi on the occasion of his 72nd birthday.

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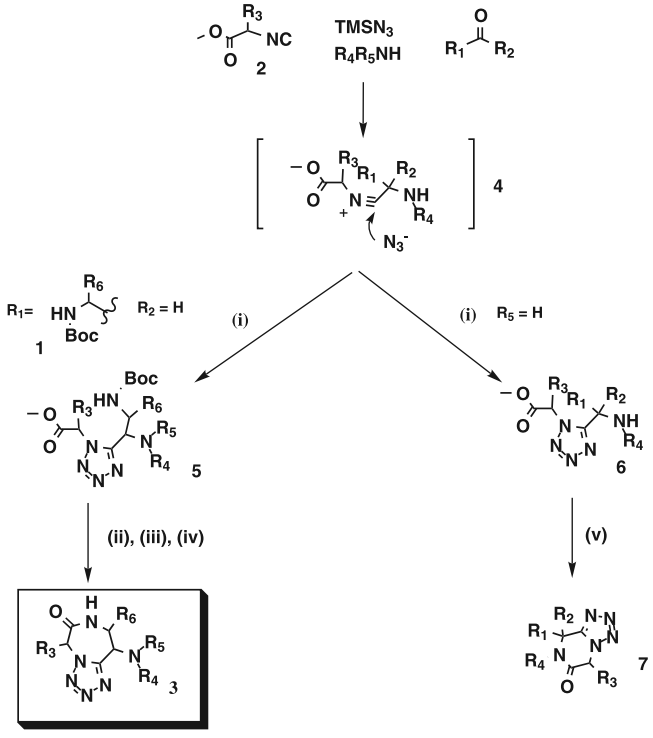
uing to exploit post-condensation reactions in an attempt to access 7,5-fused azepine-tetrazole systems (Scheme 2). Thus, reaction of methyl-isocyano acetate, *N*-BOC-α-aminoaldehydes, $TMSN_3$ and secondary amines was found to proceed with high yield and final product purity (in most cases >70% area%, as judged by LC/MS at UV215 nm[10]), giving products with generic structure, **5**. The reaction proceeds via the so-called nitrilium ion, **4**. Subsequent acid treatment with 10% trifluoroacetic acid in dichloromethane liberates the masked internal amino nucleophile, enabling partial cyclization to azepine-tetrazole, **3** (<30%), with mass balance being accounted for by the acyclic amine TFA salt. Further cyclization was promoted by proton scavenging with PS-diisopropylethylamine and reflux for 24 h. Final compound purities were substantially improved by removal of the acyclic amine and excess aldehyde, via dissolution in THF:CH_2Cl_2 (1:1) and addition of PS-NCO and PS-$TsNHNH_2$, producing the desired 7,5-fused product, **3**.[11] Interestingly, use of a primary amine with aldehydes or ketones delivers a potentially competing secondary amino internal nucleophile, **6**, which upon reflux in methanol produces fused tetrazole-ketopiperazines of generic structure, **7**.[12] Application of a secondary amine circumvents this reaction pathway allowing formation of the desired azepine, **3**, containing three points of potential diversity. The reaction proved general for a range of commercially available *N*-Boc-α-amino-aldehydes [e.g. with attached aryl, heteroaryl, alkyl, cycloalkyl, thioalkyl, functionality] and secondary amines [e.g. with attached alkyl, aryl, heteroaryl, heterocycloalkyl and basic functionality], as judged by the results outlined in Table 1.



Scheme 2. *Reagents and conditions*: (i) $R_1R_2C{=}O$ (1.5 equiv., 0.1 M in MeOH), $TMSN_3$ (1 equiv., 0.1 M in MeOH), R_3NH_2 (1 equiv., 0.1 M in MeOH), methylisocyanoacetate (1 equiv., 0.1 M in MeOH), 24 h, rt. (ii) 10% TFA in CH_2Cl_2. (iii) PS-DIEA, DMF/dioxane, 1:1, reflux. (iv) PS-NCO, PS-$TsNHNH_2$ THF/DCE, 1:1. (v) Reflux, MeOH.

Final A% purities for the 13 scavenged examples range from 53 to 100% (av. = 86%). The high average area% purity was not unexpected as the superior reactivity of *N*-Boc-α-amino aldehydes in Ugi condensations was previously reported in a two-step preparation of dihydroimidazoles.[13] The scope of the methodology was demonstrated as a variety of substituted methylisocyanoacetates proved compatible with the protocol, as exemplified by **9** (100%), **12** (48% isolated yield), **20** (90%) and **23** (45% isolated yield). The final cyclization was possible with both primary and secondary amines, the latter exemplified by **11** (80%) and **24** (83%). Azepine-tetrazole formation also proceeded well on a large scale with isolated yields corresponding closely to A% yields. For example, tricyclic azepine-tetrazole, **24**, was synthesized with an isolated yield of 75% (0.7 mmol scale).[14] Subsequent recrystallization of the major diastereomeric product and X-ray analysis[15] confirmed the fused 7,5 structure, possessing an *anti*-relationship for H_A and H_B. Interestingly, the other diastereomeric product was not observed.

Encouraged by the results shown in Table 1, the protocol was advanced to 96-well production status, and production of an 80 member array was successfully completed using a Charybdis® 96 well Teflon block, encapsulated in a Calypso® reaction frame assembly.[16] The purity distribution (A% as judged by UV215) of the 80 member library [4 (RCHO)×10 (R_1R_2NH)×2 (RNC)] is shown below (Fig. 1).

In summary, a novel solution phase procedure for the preparation of the fused azepine-tetrazole class of molecule has been reported. With final products containing three points of diversity and a facile and rapid production protocol, access to thousands of diverse analogues with the aforementioned core structure is now feasible. Current efforts are now focusing on the development of potentially higher yielding solid phase approaches to this methodology.

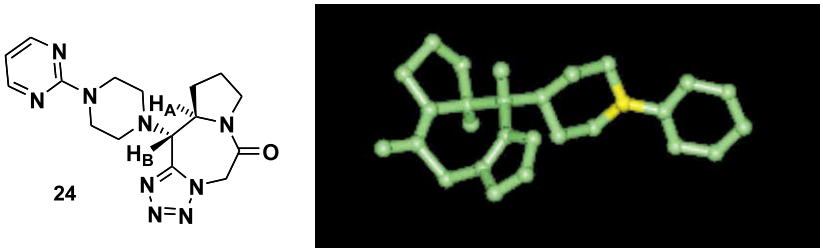
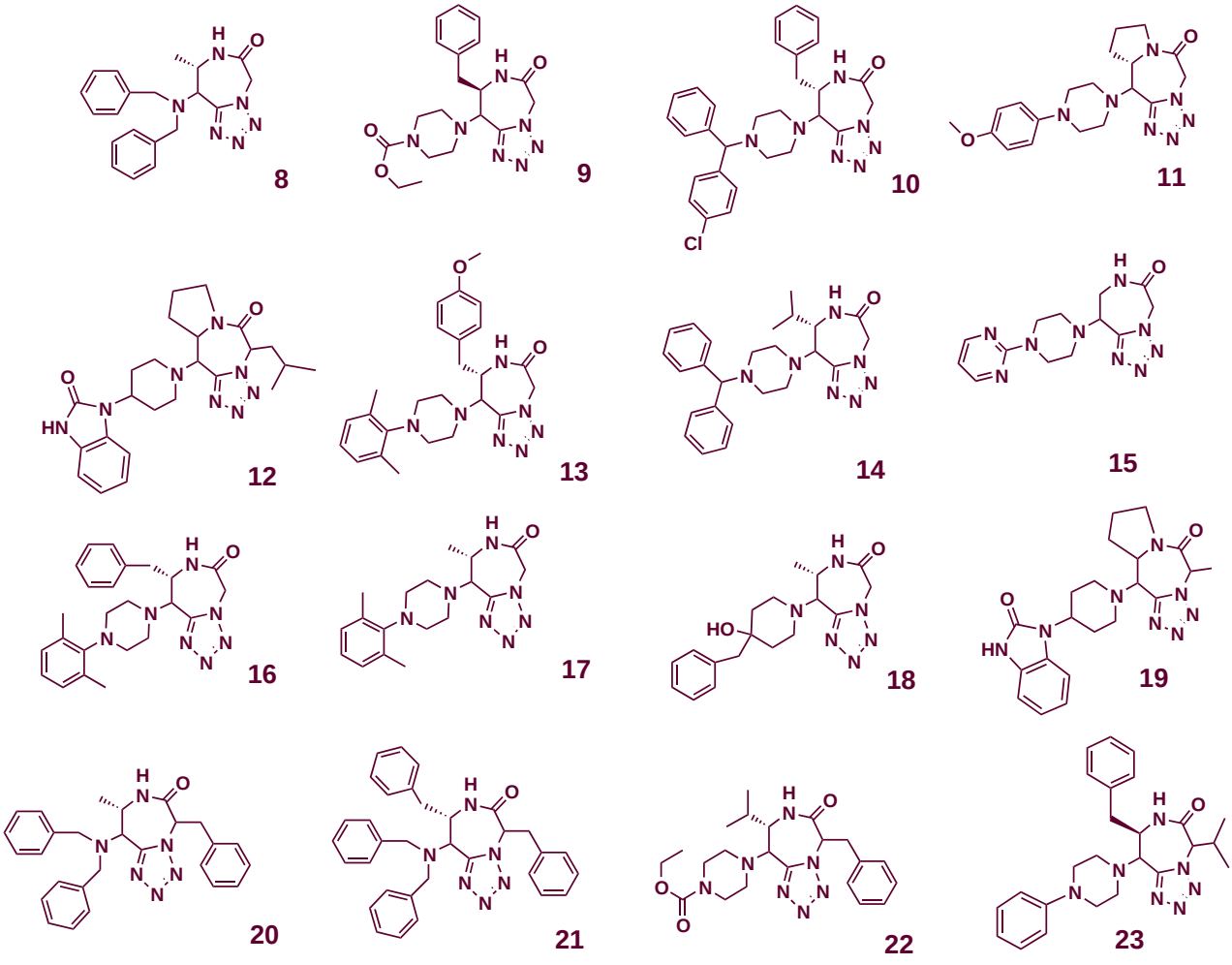


Table 1.



Cpd #	A%[a]	A%[b]	MH$^+$	Cpd #	A%[a]	A%[a]	MH$^+$	Cpd #	A%[a]	A%[b]	MH$^+$
8	76	84	363	**14**	76	90	446	**20**	n/a	90	453
9	66	100	400	**15**	66	80	316	**21**	n/a	82	529
10	70	84	528	**16**	n/a	100	432	**22**	n/a	79	442
11	28	80	384	**17**	n/a	100	356	**23**	52	45[c]	445
12	53	48[c]	465	**18**	n/a	100	357	**24**	83	75[c]	356
13	60	53	462	**19**	64	58[c]	423				

[a] A% purities as judged by 1 c/ms UV215 after step (iii) PS-DIEA/reflux.
[b] A% purities as judged by 1 c/ms UV215 after step (iv) PS-NCO and PS-TsNHNH$_2$.
[c] Isolated yield after column chromatography (no scavenging).

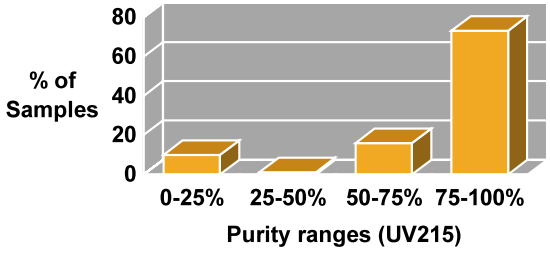


Figure 1. Purity distribution for an 80 member library.

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14. The following procedure was followed for the large scale preparation of **24**: The following procedure was followed for the large scale preparation of **A**. Solutions of *N*-(*tert*-butoxycarbonyl)-D-prolinal (0.1 M, 10 ml in MeOH), 1-(2-pyrimidyl)piperazine (0.1 M, 10 ml in MeOH), methylisocyanoacetate (0.1 M, 10 ml in MeOH) and $TMSN_3$ (0.1 M, 10 ml in MeOH) were added to a RBF and stirred at rt for 18 h. The solution was concentrated and the resulting oil was re-dissolved in 10% TFA/DCM. After an additional 18 h the solution was concentrated and PS-DIEA (3.54 mmol/g, 0.85 g, 3 mmol) was added to the oil followed by a solution of DMF/dioxane (50%, 60 mL). The slurry was heated in a shaker-oven at 80°C for 96 h, followed by filtration and evaporation of the solvent. The oil was fractionated by flash column chromatography (2% MeOH/chloroform) to yield an off-white solid (267 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.28 (2H, d, $J=4.5$ Hz), 6.50 (1H, dd, $J=4.5$, 4.5 Hz), 5.41 (1H, d, $J=15.5$ Hz), 5.13 (1H, d, $J=15.5$ Hz), 4.37 (1H, m), 4.01 (1H, d, $J=11.5$ Hz), 3.85 (4H, m), 3.64 (1H, m), 3.52 (1H, m), 2.99 (2H, m), 2.56 (1H, m), 2.41 (3H, m), 2.05 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 163.9, 161.3, 157.7, 151.5, 110.1, 63.0, 56.9, 52.5, 50.0, 47.2, 43.8, 30.7, 22.3. FTIR: 3272, 1633, 1150, 636 cm^{-1}. HRMS: MH^+ theoretical value 356.1947: actual value 356.1952. dM/M = 1.4 ppm.
15. X-Ray single crystal structure determination of **24** (crystallized from chloroform). Crystal data: $C_{16}H_{27}N_9O$. Cell constants and an orientation matrix for data collection, obtained from a least squares refinement using the setting angles of 25 carefully centered reflections in the range 51.98<2∅<54.98o corresponded to a primitive orthorhombic cell with dimensions $a=8.026(1)$, $b=32.417(1)$, $c=6.575(1)$ Å, $V=1710.6(3)$ Å^3. For $Z=4$ and FW = 361.45, calculated density was 1.40 g/cm^3. The systematic absences of $h00$: $h\pm2n$, $0k0$: $k\pm2n$, $00l$: $l\pm2n$ uniquely determined the space group to be $P2_12_12_1$ (#19).
16. Production of an 80 member array was successfully completed using a Charybdis® 96 well Teflon block, encapsulated in a Calypso® reaction frame assembly. Reagents were transferred into the 96 well plate using either a Quadra 96® (Tom-tech) or Rapid Plate 96® (Zymark). The blocks were then heated at 65°C for 3 days and the solvent evaporated in vacuo at 65°C.[12] Scavenging with PS-$TsNHNH_2$ (6 equiv.) and PS-NCO (1 equiv.) was performed at the plate level and the resins were added using a Millipore® column loader. Evaporation was performed in a SAVANT® evaporator for 2 h.