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The one-pot solution phase preparation of fused tetrazole-ketopiperazines†

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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 tetrazole-ketopiperazine libraries. The reaction of an aldehyde, primary amine, methyl isocyanoacetate and trimethylsilylazide in methanol at reflux affords bicyclic tetrazole-ketopiperazines in good yield. This efficient one step protocol, producing products with three potential diversity points, may 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 in fact powerful tools for producing diverse arrays of compounds, often in one step and high yield. Despite this synthetic potential, the Ugi reaction is limited by producing products that are flexible and peptidic-like, often being classified as 'non-drug-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 after initial formation of the classical Ugi product, often by unmasking a protected amino internal nucleophile.[5,6]

This letter discloses a novel solution phase, post-condensation, application of $TMSN_3$ and substituted methylisocyanoacetates, **1**, affording fused ketopiperazine-tetrazoles, **2**, in good yield (Scheme 1).[7] Such rigid, hydrophobic molecules are clearly of interest in lead discovery applications, where the biological utility of both ketopiperazine[7] and tetrazole[8] cores have been

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† This article is dedicated to Professor Ivar Ugi on the occasion of his 70th birthday.

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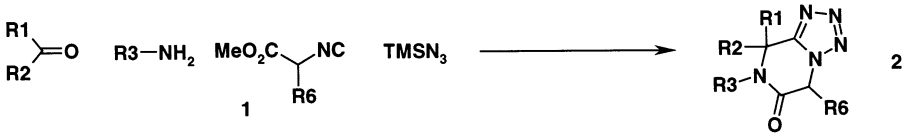
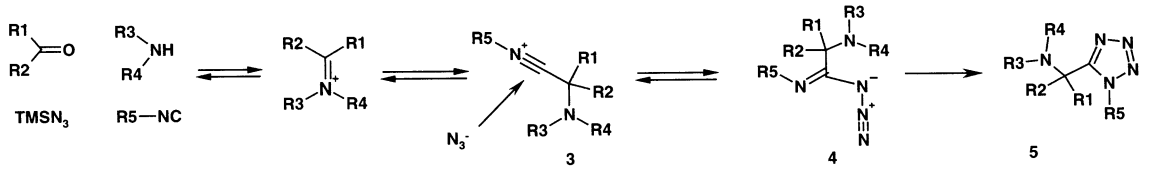


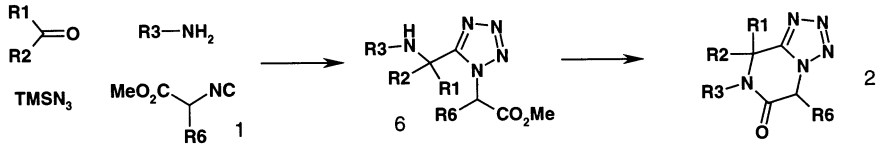
Scheme 1.

widely reported to occur in a variety of bio-active substances. The formation of monocyclic tetrazoles was originally reported in 1961[2] using a variation of the classical Ugi reaction and only a few reports exploiting this reaction have appeared since that date.[9] Condensation of an appropriately substituted aldehyde or ketone with a primary or secondary amine and subsequent reaction with an isonitrile produces the intermediate nitrilium ion, **3**, as a key intermediate. Reaction with azide, followed by sigmatropic rearrangement affords the desired tetrazole, **5** (Scheme 2).



Scheme 2.

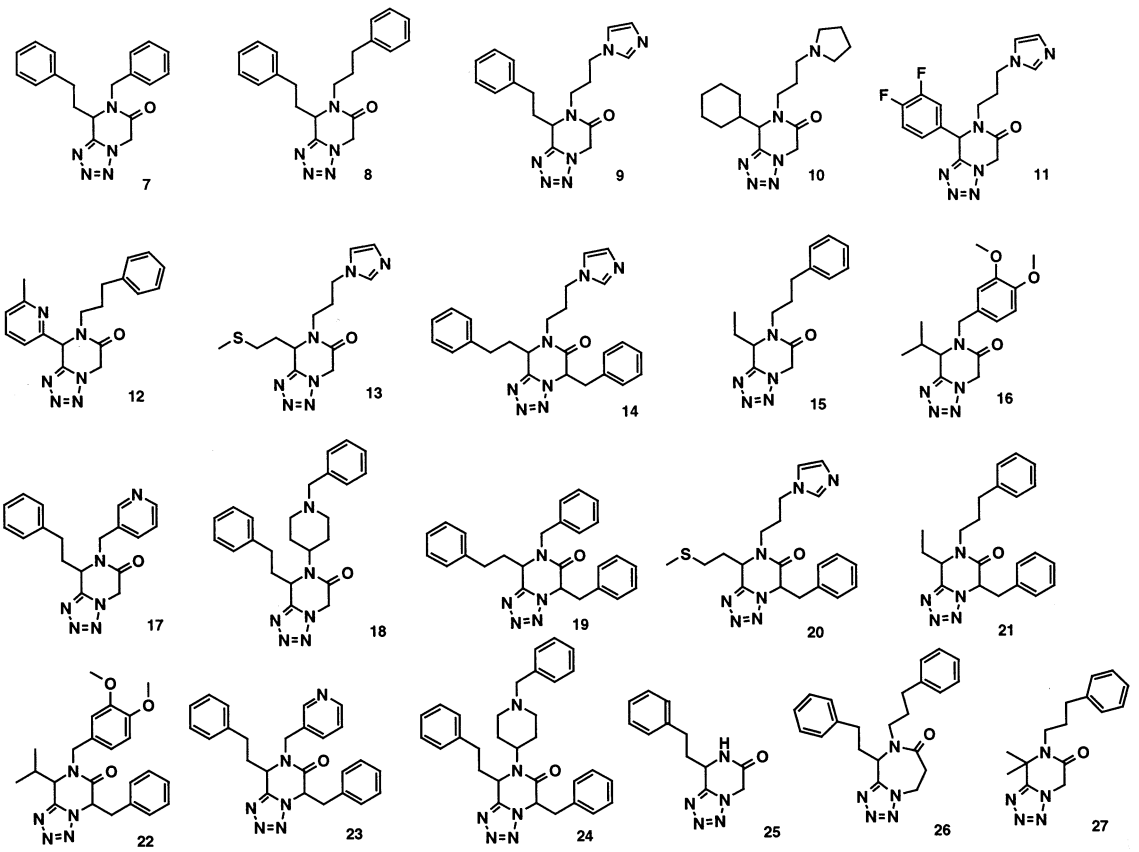
The initial tetrazole forming reaction is particularly well-suited for the solution phase preparation of monocyclic tetrazoles and efficient enough to generate libraries with three points of diversity in the 10 000 member range. We were especially interested in continuing to exploit post-condensation reactions in an attempt to access 6,5- or 7,5-fused tetrazole systems, and the feasibility of utilizing appropriately substituted cyanoacetate derivatives was thus investigated (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) $R_1R_2C{=}O$ (2 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, then 24 h at reflux

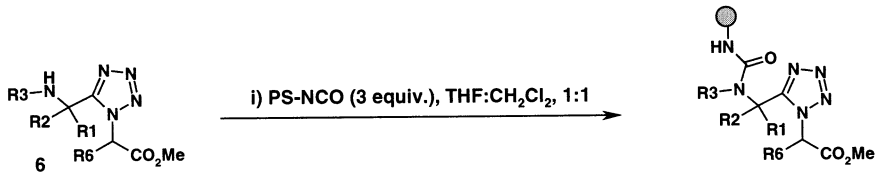
The condensation reaction with methylisocyanoacetate was found to proceed in high yield (in most cases >70% A % as judged by LC/MS at UV220 nm[10]). A simplified experimental procedure was developed in which each reagent was added in order of its participation in the Ugi reaction. Thus, equal amounts (0.2 ml of 0.1 M solutions in methanol) of the four components were employed, followed by agitation at room temperature for 6 hours, and reflux for 24 hours. The solvent was evaporated at 65°C[11] to give the desired products, as shown in Table 1.[12] Final compound purities were improved substantially by removal of the acyclic amine, **6**, via dissolution in THF:CH_2Cl_2 (1:1) and addition of PS-NCO (Scheme 4).[13]

Table 1



Cpd #	A%[a]	A%[b]	MH^{+}[c]	Cpd #	A%[a]	A%[b]	MH^{+}	Cpd #	A%[a]	A%[b]	MH^{+}
7	70	91	334	**14**	22	69	442	**21**	47	57	376
8	67	92	362	**15**	48	36	286	**22**	33	52	422
9	64	89	352	**16**	67	87	332	**23**	35	64	425
10	96	90	333	**17**	77	90	335	**24**	0	0	–
11	20	22	360	**18**	7	27	417	**25**	41	44	260
12	61	65	349	**19**	57	82	424	**26**	<5	<5	376
13	62	64	322	**20**	37	37	412	**27**	<5	<5	286

[a] Area % yields as judged by LC/MS UV220.
[b] Area % yields as judged by LC/MS UV220 after treatment with immobilized isocyanate.
[c] LC/MS-HP1100 LC with LCQ, YMC-AM 4.6 × 150 mm column, ESI source.



Scheme 4.

The reaction appears general for a range of commercially available aldehydes (e.g. with attached aryl, heteroaryl, alkyl, cycloalkyl, thioalkyl, functionality) and primary amines (e.g. with attached alkyl, aryl, heteroaryl, heterocycloalkyl and basic functionality), as judged by the results outlined in Table 1.

The role of the third diversity point on product cyclization rates was also investigated via the synthesis of the phenyl alanine-methyl ester derived isonitrile.[14] As expected, cyclization rates for analogous substituents at R_1, R_2 and R_3 were slower for the Phe derived isonitrile than unsubstituted derivative, **1** ($R_6 = H$), presumably reflecting an increased steric presence. This is exemplified by the pre-scavenging A% purities of **16** (67%) and **17** (77%) when compared to **22** (33%) and **23** (35%). Tetrazole-ketopiperazine formation also proceeds well on a larger scale with isolated yields corresponding closely with A% yields. For example, ketopiperazine-tetrazole, **8**, was synthesized with a yield of 60%.[15] Interestingly, ammonia and ketones also proved compatible with the methodology affording **25** (44%) and **27** (80%), respectively. A brief investigation into seven-membered ring formation via the use of methylisocyanopropionate showed a substantial decrease in the amount of cyclic material formed (**8** compared to **26**). The major product after reflux (2 days) proved to be acyclic material.

Encouraged by the results shown in Table 1, the protocol was advanced to 96-well production status. Production of an 80 member array of tetrazole-ketopiperazines 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 three 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. The purity distribution (A% as judged by UV220) of the 80 member library [8 (RCHO)×10 (RNH_2)×1 (RNC)] is shown below (Fig. 1).

Lc/ms Purity Distribution

A%	UV220
0 - 25%	17%
26 - 50%	10%
51 - 75%	19%
76 - 100%	54%

Figure 1.

In summary, a novel one-pot solution phase procedure for the preparation of the fused ketopiperazine-tetrazole class of molecule has been reported. With final products containing three points of potential 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.

Acknowledgements

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10. LC/MS analysis was performed using a C18 Hypersil BDS 32.1×50 mm column with a mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 15 min. HPLC was interfaced with APCI techniques.
11. Performed in a SAVANT® evaporator for 2 hours.
12. Note: Conversion to the condensation product may be increased by using excess aldehyde followed by scavenging with immobilized tosylhydrazine (Argonaut®).
13. Purchased from Argonaut® technologies.
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15. The following procedure was followed for the large scale preparation of **8**: A mixture of phenpropionaldehyde (0.1 M, 15 ml in MeOH), phenpropylamine (0.1 M, 15 ml in MeOH), methylisocyanoacetate (0.1 M, 15 ml in MeOH) and $TMSN_3$ (0.1 M, 15 ml in MeOH) was stirred at reflux for 48 hours. LC/MS analysis after 2 days revealed 72% (product at UV220 nm, 9% acyclic) and 30% (product at UV254 nm, 18% acyclic). The solvent was evaporated in vacuo and material dried under high vacuum for one hour. The crude material was re-dissolved in THF:DCM (1:1, 20 ml) and PS-NCO (300 mg) was added. The suspension was shaken for 15 hours at room temperature. The resin was filtered, the crude product was pre-absorbed onto flash silica and purified by column chromatography (EtOAc:hexane, 1:2) to yield, **8**, (321 mg, 60%) as an oil. ^1H (400 MHz, $CDCl_3$) 7.07–7.11, 7.17–7.20, 7.23–7.27 (10H, 3×m, 2×C_6H_5), 4.71–4.97 (2H, m, CH_2CO), 4.85–4.86 (1H, m, CH), 4.07–4.14, 2.99–3.03 (2H, 2×m, NCH_2), 2.60–2.65 (3H, m, CH_2CH_2), 2.36–2.41 (2H, m, CH_2), 1.89–2.02, 2.10–2.12 (3H, 2×m, CH_2CH_2); ^{13}C (100 MHz, $CDCl_3$) 161.37, 150.31, 140.88, 139.13, 129.14, 128.82, 128.68, 128.37, 127.11, 126.59, 53.92, 52.26, 48.12, 45.28, 35.20, 33.52, 30.19, 28.08. HMBC (heteronuclear multi-bond correlation) revealed connectivities between methine protons B and methide proton A confirming the cyclic structure. HRMS: Theoretical value 362.1981: Actual value 362.2000. dM/M = 5.24 ppm.