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Remarkable three-step-one-pot solution phase preparation of novel imidazolines utilizing a UDC (Ugi/de-Boc/cyclize) strategy †

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Abstract

This communication reveals the novel solution phase synthesis of an array of biologically relevant imidazolines in a remarkable 'three-step-one-pot' procedure, utilizing a Ugi/de-Boc/cyclization (UDC) strategy. Transformations are carried out in excellent yield by condensation of *N*-Boc-α-amino-aldehydes and supporting Ugi reagents. The described protocol represents a highly attractive solution phase procedure for the rapid generation of this class of molecule.

Solution phase synthesis[1] for the rapid generation of large, diverse and highly pure combinatorial arrays is currently under-exploited in the field of combinatorial chemistry and new lead generation when compared to solid phase procedures.[2] Multi-component reactions (MCRs) are now receiving increased scrutiny as solution protocols for efficient ways of introducing several points of diversity (>3) in one synthetic step.[3] The widely used Ugi reaction[4] is one such condensation, however products are classically non-drug-like, being flexible and peptidic in nature. This communication reports an interesting and novel 'three-step-one-pot' procedure for producing rigid and basic imidazolines[5] containing four points of potential diversity, employing *N*-Boc-α-amino aldehydes, **1**, in the Ugi reaction with subsequent acid mediated cyclization to **2**. Imidazolines have been shown to have biological utility as anti-depressants and additionally imidazoline receptors are widely distributed in both the peripheral and central nervous system playing potential roles in the regulation of several physiological effects.[6] The imidazoline moiety has also been extensively studied as an amide bond replacement in biologically active peptides.[7] Clearly rapid access to large numbers of this class of molecule is of major significance for new lead generation in both the industrial and academic pharmaceutical sectors. The general reaction for solution phase imidazoline formation is shown in Scheme 1. The Ugi reaction with *N*-Boc-α-amino aldehydes proceeds in high yield (in most cases >80% area % yield as judged by lc/ms UV 220 nm[8]). This is a key feature of the methodology as yields from Ugi reactions are often limited by the poor reactivity of the aldehyde

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† This article is dedicated to Professor Ivar Ugi on the occasion of his 69th birthday.

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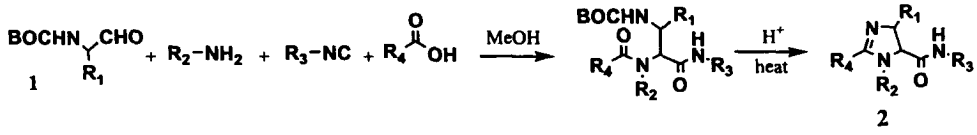
being employed. Boc removal and cyclization with loss of water proceeds via acid and heat treatment affording imidazolines with the general structure, **2**. This transformation was adapted to high throughput



Scheme 1. General reaction to dihydroimidazoles

synthesis in a 96 well plate format and lc/ms results of six examples, **3–8**, taken at random are shown in Fig. 1.[9] The 96 compounds produced were prepared as a $1(R_1CHO)\times2(R_2NH_2)\times6(R_4CO_2H)\times8(R_3NC)$ array. The reaction is general for a range of commercially available carboxylic acids [e.g., with attached alkyl, thioalkyl, aryl, cycloalkyl, heterocycloalkyl functionality], isonitriles [e.g., with attached alkyl, aryl, cycloalkyl and heteroalkyl functionality], and primary amines [e.g., with attached alkyl, thioalkyl, aryl, cycloalkyl, heterocycloalkyl, acid and basic functionality]. A limiting factor in production of these

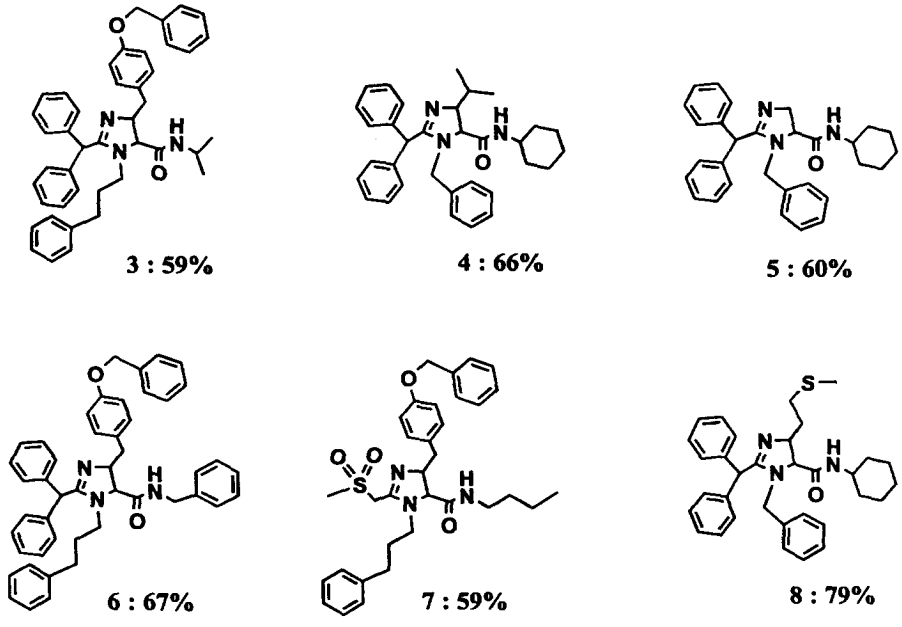
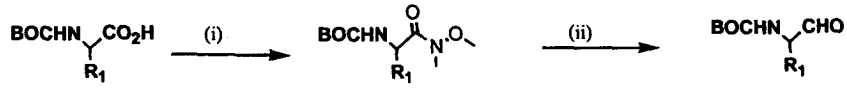


Figure 1.

libraries is the shortage of commercially available *N*-Boc-α-amino aldehydes.[10] Multi-gram quantities were available via the synthetic route shown in Scheme 2, utilising the Weinreb amide[11] and subsequent reduction with LAH. Imidazolines, **4**, **5** and **8** in Fig. 1 are all derived from aldehydes prepared via this route.



Scheme 2. Reagents and conditions: (i) EDC, CH_3NHOCH_3, pyridine, CH_2Cl_2; (ii) $LiAlH_4$, THF

The general procedure for production of the 96 well plate of imidazolines is as follows. Equal amounts (0.1 ml) of 0.1 M solutions of the four Ugi components were used to generate a theoretical 10 μmol of final imidazoline product in a 96 well plate format. Reagents were transferred into a 96 well plate using either a Quadra 96® (Tom-tech) or Rapid Plate 96® (Zymark). The four component condensation step was performed in MeOH at room temperature and the solvent evaporated in vacuo at 65°C.[12] The

deprotection/cyclization step was achieved using a 10% solution of TFA in dichloroethane (400 µl/well) at room temperature. The solvent and excess acid were removed via evaporation in vacuo at 65°C for 6 h. TFA (10%) in DCE was shown to be optimal as either increasing or reducing acid concentrations lead to decreases in product formation as shown in Table 1 for example **9**. Acetonitrile and nitromethane are also compatible as solvents for the cyclization protocol, as is the dioxan/HCl reagent combination. Increasing the time spent during solvent removal forces the reaction near to completion as can be seen in Table 2 for **9**, at time intervals of 0, 2, and 6 hours. The reported A% yields (UV 220 nm) represent the combined yields of the two diastereomers of the imidazoline product.

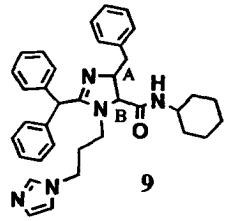


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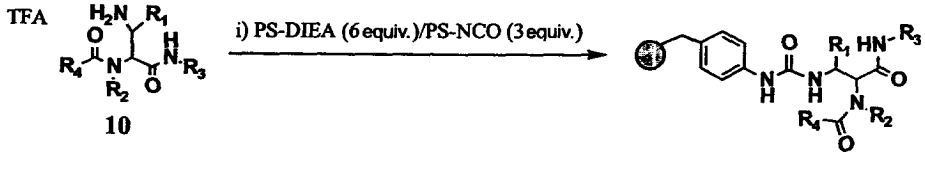
Table 1

TFA/DCE	A% Yield
1%	26%
2.5%	42%
5%	67%
10%	**71%**
30%	61%
50%	57%
70%	53%
100%	49%

Table 2

EVAPN at 65°C	0 h	2 h	6 h
TFA/CH_3NO_2	41%	53%	78%
TFA/CH_3CN	40%	66%	**80%**
TFA/DCE	36%	54%	68%

The process may be scaled up (0.15 mmol scale) and performs well in a solution of refluxing 10% TFA/toluene (24 hours). Isolation and characterization of the two imidazoline diastereomers of **9** (approx. 3:1 ratio by lc/ms UV 220 nm) indicated the minor diastereomer possessed the *cis* orientation of protons H_A and H_B.[13] In the majority of examples, the remaining mass balance of material is accounted for by the non-cyclized amine, **10**. These amines can be subsequently removed via a solution phase scavenging step,[14] utilizing the simultaneous addition of PS–DIEA (6 equiv.) and PS–NCO (3 equiv.) in dichloromethane:THF, 1:1.[15] Purities of the imidazolines revealed in this letter were thus improved to >90%.[16] Scheme 3 demonstrates the removal of the primary amine, **10**, by a resin bound isocyanate.



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Scheme 3. Solution phase scavenging

In summary, a novel three-step-one-pot solution phase procedure for the preparation of the imidazoline class of molecule has been reported. With final products containing four points of potential diversity and a facile and rapid production protocol, access to thousands of diverse analogues of this important peptidomimetic derived from the Ugi reaction is now feasible. In fact, a 10000 member library was recently successfully generated in this laboratory. Current efforts are now focusing on the development of mild and general oxidative procedures for conversion of imidazolines to imidazoles.

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8. Lc/ms analysis was performed using a C18 Hypersil BDS 3μ 2.1×50 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.
9. Note: evaporation was performed over only 2 hours at 65°C in vacuo with a SAVANT evaporator for compounds **3** to **8**.
10. The *N*-Boc-α-amino aldehydes may be purchased from Peninsula laboratories.
11. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
12. Performed in a SAVANT® evaporator for 2 hours.
13. For imidazoline **9**, the major diastereomer: ^1H (CD_3OD) 0.9–1.05 (1H, m), 1.05–1.2 (2H, m), 1.25 (2H, m), 1.5–1.58 (1H, m), 1.6–1.63 (1H, m), 1.64–1.7 (2H, m), 1.72–1.81 (2H, m), 1.95–2.05 (1H, m), 3.1–3.2 (3H, 2×m), 3.5–3.58 (1H, m), 3.6–3.7 (1H, m), 3.98–4.00 (1H, m), 5.00–5.01 (2H, H_A, H_B multiplets overlap), 5.8 (1H, s), 7.2–7.6 (18H, Ar region), 8.75 (1H, br s). Retention time 7.74 min for mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 15 min. MS (APCI) 560 (MH^+). For the minor diastereomer: ^1H (CD_3OD) 1.15–1.25 (3H, m), 1.25–1.4 (4H, m), 1.6–1.7 (1H, m), 1.7–1.85 (4H, m), 3.0–3.03 (1H, m), 3.05–3.1 (1H, m), 3.5–3.7 (2H, m), 3.75–3.8 (1H, m), 3.8–3.85 (1H, m), 4.5 (1H, m, H_A), 4.6 (1H, d, *J* 5.5 Hz, H_B), 5.5 (1H, s), 7.01–7.5 (18H, Ar region), 8.4 (1H, br s). Retention time 7.05 min for mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 15 min. MS (APCI) 560 (MH^+).
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15. Purchased from Argonaut® technologies (PS–DIEA — polystyrene bound disopropylethylamine).
16. Note the following limitation: imidazoline products containing hydroxyl groups are removed during the scavenging step.