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Novel applications of resin bound α-amino acids for the synthesis of benzodiazepines (via Wang resin) and ketopiperazines (via hydroxymethyl resin)

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Abstract

This communication reveals a novel application of resin bound α-amino acids coupled with the UDC (Ugi/DeBOC/cyclize) strategy. Reaction with either *N*-BOC-α-amino aldehydes or *N*-BOC anthranilic acids and subsequent acid treatment allows the preparation of highly pure and diverse arrays (approx. 10 000 in size) of 1,4-benzodiazepines (Wang resin) and ketopiperazines (hydroxymethyl resin), respectively. Notable for the benzodiazepine series of compounds are the five potential points of diversity available from this two-step protocol.

Interest in polymer-supported reagents has blossomed in recent years with the emergence of combinatorial chemistry and automated parallel synthesis. Multi-component reactions (MCRs) are especially attractive for automated parallel synthesis and are proving to be powerful tools for producing diverse arrays of compounds, often in one step and high yield.[1] Several groups have used polymer-supported reagents in combination with the Ugi multi-component reaction[2] giving a resin bound flexible Ugi product. Subsequent synthetic manipulation has allowed generation of a wide range of constrained derivatives, such as diketopiperazines,[3] imidazoles[4] and pyrroles.[5] Interestingly, several novel intramolecular derivatives of this versatile reaction have recently been reported where constrained products result from interception of the intermediate nitrilium ion using a bifunctional input.[6] An alternative approach is to constrain the Ugi product via a post-condensation modification after initial formation of the classical Ugi product.[7]

This letter reveals two novel applications of resin bound α-amino acids for the synthesis of 1,4-benzodiazepine-2,5-diones **1** (via Wang resin) and ketopiperazines **2** (via hydroxymethyl resin) shown in Scheme 1.[8] From a medicinal chemistry viewpoint, these templates constitute an important class of bioactive compounds and have shown promise as fibrinogen receptor antagonists, anticonvulsant agents and hypocholesteremic agents.[9] Access to these classes of molecules is possible in only two

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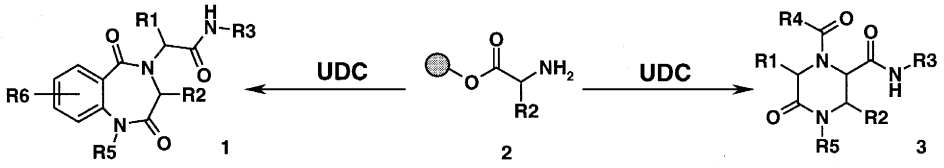
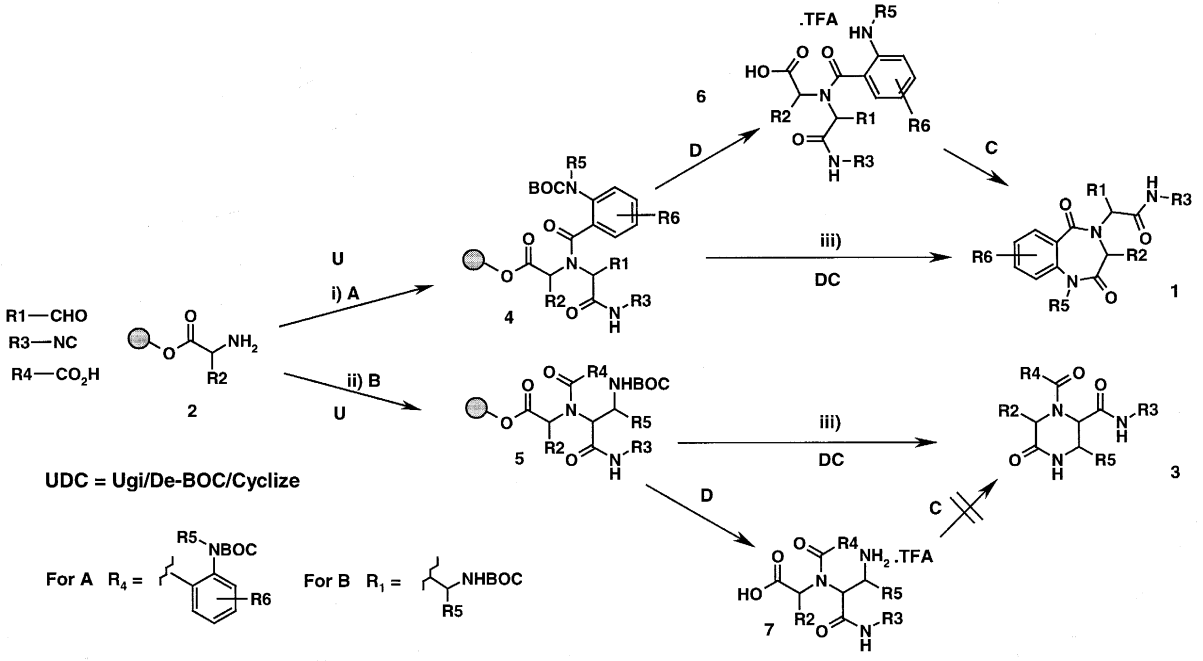


Scheme 1.

steps and represents a novel solid phase extension of the UDC (Ugi/DeBOC/cyclize) strategy previously reported from this laboratory.[10] Fmoc-protected amino acids on Wang or hydroxymethyl resins are readily available[11] and is easily deprotected with piperidine to give the desired amine **2**. Reaction in the Ugi condensation with an excess of supporting reagents proceeds well in the majority of cases giving resin bound Ugi products **4** and **5**. Treatment of the Wang bound product **4** (R_4CO_2H=*N*-BOC anthranilic acid[12]) with a 10% TFA solution in dichloromethane removes the BOC group, and evaporation (Note: SAVANT™ evaporator used at room temperature setting[13]) gives the desired benzodiazepine (BDP) **1** in good to excellent yield. Interestingly, the resin cleaved acyclic carboxylic acid **6** was not detected upon product analysis. It is suspected that intermediate **6** undergoes rapid cyclization to BDP **1**. A similar observation was reported by Armstrong for an analogous BDP synthesis.[7] A direct cyclocleavage mechanism may also be in operation for this series and is not ruled out (Scheme 2). However, the Wang support was not suitable for the preparation of ketopiperazines **3**. Thus, reaction of *N*-BOC-α-amino aldehydes[14] with Wang bound amino acids affords the Ugi product **5**. Subsequent TFA treatment gave ketopiperazines **3** in only low yield, with significant amounts of acyclic resin cleaved carboxylic acid **7** being detected — a direct result of TFA salt formation deactivating the aliphatic amine towards cyclization. Such deactivation towards cyclization is not observed in the BDP series, presumably due to the lower pKa of aniline-like amines. Improved yields of **3** were observed using acid stable hydroxymethyl bound amino acids, mechanistically resulting from direct cyclocleavage.



Scheme 2. Reagents and conditions: (i) R_1CHO (3 equiv.), **A** (3 equiv.), R_3NC (3 equiv.), all 0.5 M solutions ($MeOH:CH_2Cl_2$, 1:1), **2**=Wang resin, room temperature, 24 h. Wash resin CH_2Cl_2 (×3), MeOH (×3); (ii) **B** (3 equiv.), R_3NC (3 equiv.), R_4CO_2H (3 equiv.), all 0.5 M solutions ($MeOH:CH_2Cl_2$, 1:1), **2**=hydroxymethyl resin. Wash resin CH_2Cl_2 (×3), MeOH (×3); (iii) 10% TFA in CH_2Cl_2, wash resin CH_2Cl_2 (×2)

Area% (A%) LC/MS purities as judged by both evaporative light scattering (ELS) and UV 220 nm detection for 14 examples, Fig. 1, are presented in Table 1.[15] Results for the benzodiazepine series are good to excellent ranging from 67 to 100% (ELS) with the recovered mass of BDP product in a similar range.[16] LC/MS data support the structures shown and detailed NMR studies confirm the structure of compound **6**.[16] Cyclization of 2° internal amino nucleophiles is also possible as exemplified by the *N*-methyl derivative **10** (92% [ELS]). Another noteworthy feature is the ease with which acid and basic functionality may be introduced into the final product. TFA treatment releases such functionality by simple *t*-butyl ester hydrolysis (for CO_2H, **12** and **17**) or BOC removal (for 2°, amines **14** and **15**). This is an important feature with respect to the ability of these compounds to potentially pick up charge re-enforced hydrogen bonds with biologically relevant receptors or enzymes and dramatically increases the importance of this methodology in the drug discovery arena. The ketopiperazines **19** to **21** were formed with moderate A% purity with a similar mass recovery. Interestingly, the benzodiazepine methodology is also amenable to solution phase as shown in Scheme 3. Reaction of the 0.1 M MeOH solutions of the four components and acid treatment gives the desired BDP **24** (65% [ELS], 60% [UV220]). The solid phase approach is preferable, however, due to the better stability of the resin bound amino acid when compared to methyl esters which are prone to diketopiperazine formation.

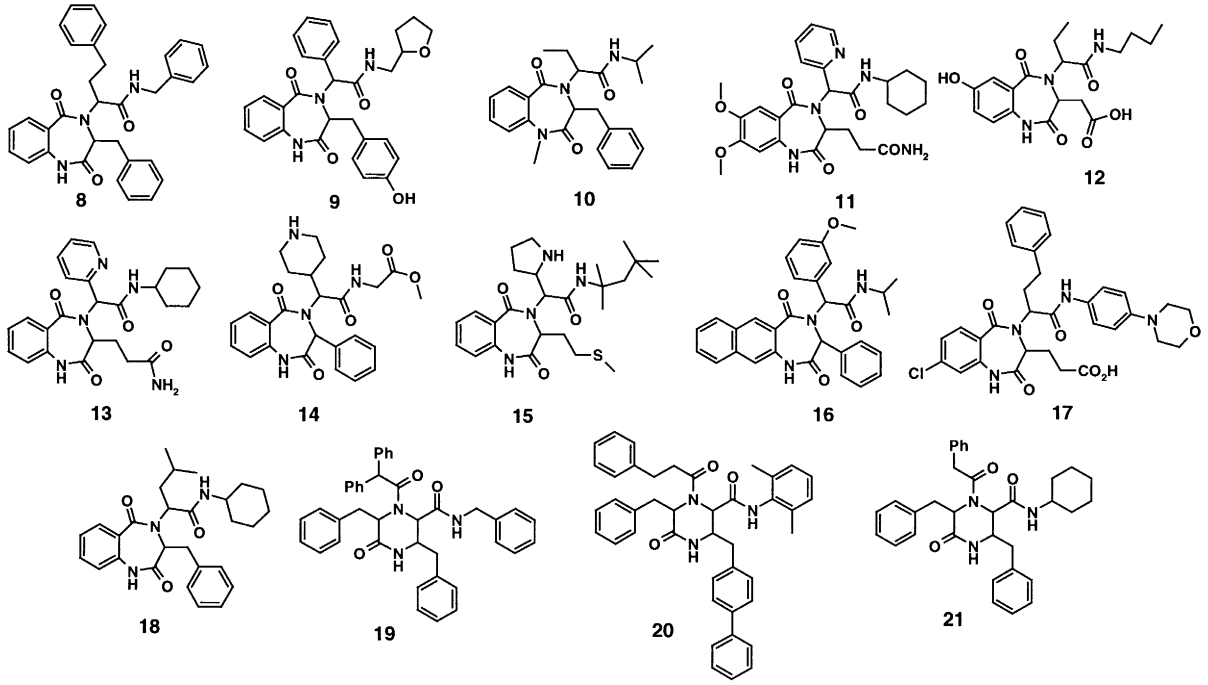
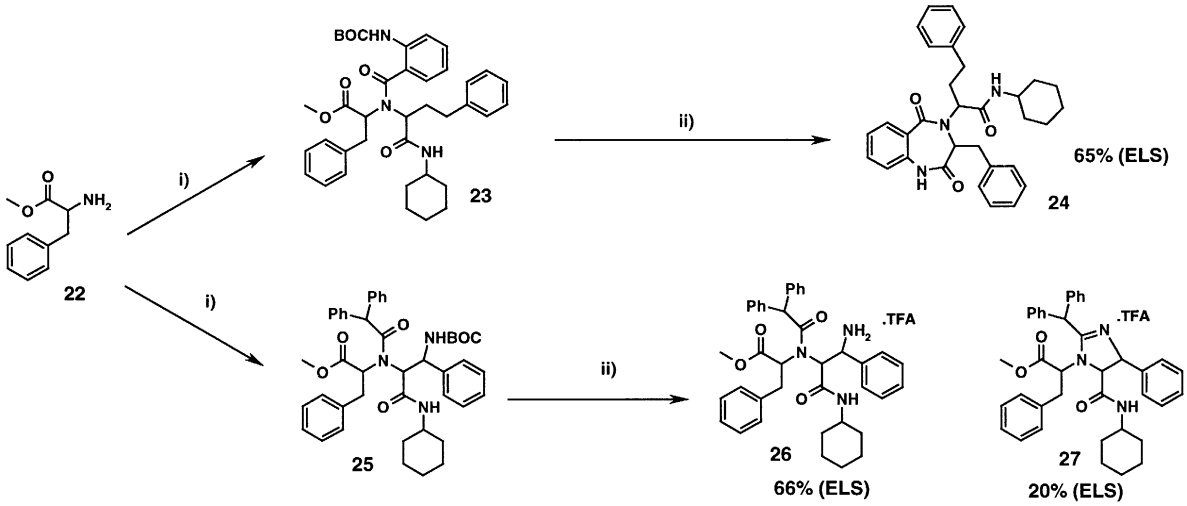


Fig. 1.

Table 1

N°	ELS (A%)	UV 220 (A%)	N°	ELS (A%)	UV 220 (A%)
8	100%	100%	15	100%	78%
9	91%	78%	16	100%	65%
10	92%	81%	17	100%	90%
11	80%	47%	18	100%	100%
12	90%	80%	19	67%	57%
13	83%	48%	20	39%	37%
14	100%	92%	21	72%	59%

Elution conditions :- 0 to 0.1% TFA H_2O/CH_3CN 10% to 100%, 5 min run. Ret. time = retention time.



Scheme 3. Reagents and conditions: (i) **22**, phenpropionaldehyde, cyclohexylisonitrile, *N*-BOC anthranilic acid (all 0.1 M solutions in methanol, 1:1:1:1); (ii) 10% TFA in dichloroethane

Unlike the BDP series, the ketopiperazine **21** was barely detectable after acid treatment (<5%) via the solution phase procedure. The major product was, as expected, the deactivated uncyclized amine **26** (66% [ELS]). Closer inspection of side products revealed a novel product **27** formed via addition of the internal nucleophile to the carbonyl group derived from the original carboxylic acid input. Imidazolines of this class are important amide bond replacements[17] in bioactive peptides and have shown biological utility as anti-depressants.[18] Further investigation of this side reaction will be reported in the near future.[19]

Encouraged with the results shown in Table 1 for the BDP series, the chemistry was advanced to production in a 96-well format. The resins were loaded into a 96-well Polyfiltronic™ filter plate (20 mg per well) using a Millipore™ column loader. The reagents in an 8 (amino acids)×8 (*N*-BOC anthranilic acids)×10 (RNC)×15 (RCHO) array were transferred into 96-well Polyfiltronic™ filter plates encapsulated within a Calypso™ frame assembly using a specially modified Zymark™ rapid plate. Ten plates per hour can be processed using this automation procedure. After shaking o/n, excess reagents were removed by filtration and resins washed (squirt bottle). TFA solutions (10%) were then added with a Robbins™ jet pipette and products subsequently collected in a Beckman 2 ml deep well plate. The LC/MS purity distribution (four wells per plate) of a 9750 member library shown in Fig. 2 along with the eight resin bound amino acids used in this library (Fig. 3).

Lc/ms Purity Distribution

A%	ELS	UV220
0 - 25%	19%	17%
26 - 50%	7%	10%
51 - 75%	10%	19%
76 - 100%	64%	54%

Fig. 2.

In summary, the reaction of resin bound α-amino acids in the Ugi MCR, with a supporting reagent containing an internal amino nucleophile, allows rapid access to the benzodiazepines **1** and ketopiperazines **3** described in this letter. More specifically, Wang resin is a suitable support for production of the BDPs, their formation proceeding via either a cleavage/cyclization or direct cyclative cleavage mechanism. Hydroxymethyl resin is the support of choice in the ketopiperazine series, formation presumably proceeding via a direct cyclocleavage mechanism. Each of the two series described has ≥4 potential points of diversity, making 10 000 member libraries easily accessible. The methodology is also high in atom economy and is easily automatable.

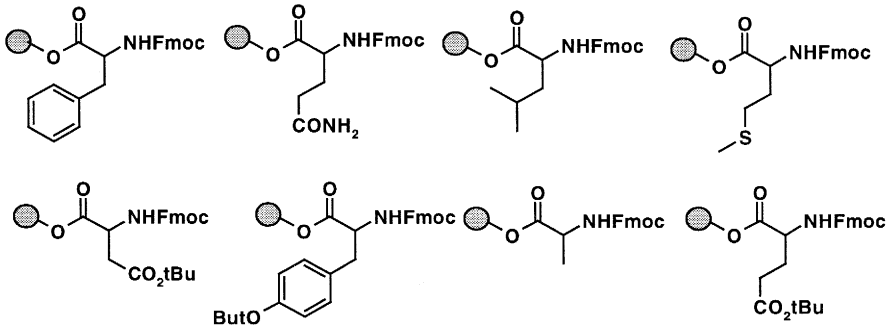


Fig. 3.

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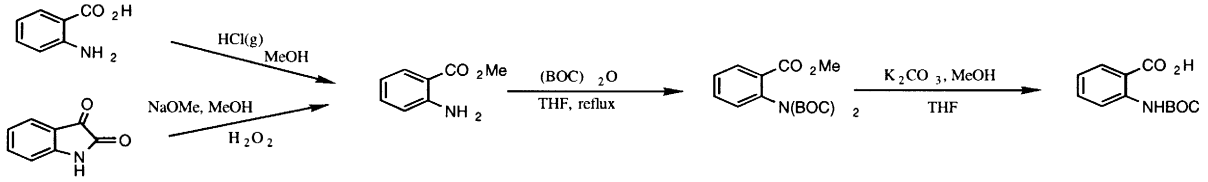
11. Wang bound Fmoc-α-amino acids were purchased from Advanced Chem-tech™.
12. *N*-BOC anthranilic acids are readily accessible in multi-gram quantities via the synthetic route shown below from the corresponding anthranilic acid or isatin. *N*-BOC diamines are readily available as described in: Krapcho, A. P.; Maresh, M. J.; Lunn, J. *Synth. Comm*. **1993**, *23*, 2443. A series of functionalized *N*-BOC anthranilic acids were prepared by Medichem Research, Inc for this project.



13. Note: Evaporation at elevated temperatures (or the use of higher percentage TFA solutions) leads to hydrolysis of the isonitrile-derived amide bond giving the corresponding carboxylic acid.
14. A series of *N*-BOC-α-amino-aldehydes are commercially available from BACHEM™.
15. LC/MS analysis was performed using a C18 Hypersil BDS 3u 2.1×50 mm column (UV 220 nm and ELSD — evaporative light scattering detection) with a mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 5 min. HPLC was interfaced with APCI techniques.
16. For a typical procedure: 350 μl of 1.0 M MeOH solutions of phenpropionaldehyde, benzyl isocyanide, and *N*-BOC anthranilic acid were added to 100 mg of Wang bound *L*-phenyl alanine (0.7 mmol/g loading). CH_2Cl_2 (0.8 ml) was added to help swell the resin and the reaction was shaken overnight in a Jones tube at room temperature. The excess reagents were removed by filtration and resin washed (CH_2Cl_2×3, THF×3, MeOH×3, CH_2Cl_2×3). A 10% TFA solution in CH_2Cl_2 (1.5 ml) was added to the resin and the reaction stirred at room temperature overnight. The solution was collected and the resin washed with CH_2Cl_2 (1 ml). The solvent was then evaporated in a SAVANT™ evaporator at room temperature to give the desired benzodiazepine **8** (20 mg, 56%) as a mixture of diastereomers. BDP **8** was characterized in detail using 2D NMR (^{1}H frequency of 500 MHz in $CDCl_3$). The sample consisted of two diastereomers in approximately 3:1 ratio and most of the critical resonances were well resolved under the present experimental conditions. DQFCOSY spectra of both the diastereomers showed three independent spin systems (-CH-CH2, -NH-CH2 and -CH-CH2-CH2 fragments) in addition to the aromatic spin systems. HMBC spectra showed numerous three-bond connectivities supporting the structure shown for the compound **8**.
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