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Novel applications of ethyl glyoxalate with the Ugi MCR

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Abstract

This letter describes novel high-yielding solution phase preparations of 1,4-benzodiazepine-2,5-dione, diketopiperazine, ketopiperazine and dihydroquinoxalinone libraries via a UDC (Ugi/de-Boc/cyclization) strategy in combination with ethylglyoxalate. The methodology represents a 'three step, one-pot procedure', employing the Ugi multi-component reaction (MCR), followed by Boc deprotection and cyclization.

Pressures on the pharmaceutical industry have increased significantly to meet the economic challenges of the 1990s. As a consequence, with the recent development of combinatorial chemistry and high speed parallel synthesis within the Lead Discovery arena, the multi-component reaction (MCR) has witnessed a resurgence of interest. From a practical consideration one-pot reactions, such as the Ugi[1] and Passerini[2] reactions, are easily automated and production of diverse or directed libraries of small organic molecules is thus both facile and high-throughput.[3] Despite this tremendous synthetic potential, the Ugi reaction is limited by producing products that are flexible and peptidic-like, often being classified as 'non-drug-like' and suffering from bioavailability problems. 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.[4] An alternative approach is to constrain the Ugi product via a post-condensation modification after initial formation of the classical Ugi product.[5,6]

This communication reveals a versatile solution phase 'three step, one-pot' procedure using UDC (Ugi/de-Boc/cyclization) methodology to access, in high yield and purity, diverse arrays of 1,4-benzodiazepine-2,5-diones, **2**, diketopiperazines, **3**, ketopiperazines, **4**, and dihydroquinoxalinones, **5** (Scheme 1). Reports of the biological utility of compounds containing these core templates are widespread.[7] Reaction of commercially available ethyl glyoxalate, **1**, in the Ugi MCR with the *N*-Boc amines, **6**,[8] **7**, **8**,[8] or **9** affords classical Ugi products, **10**, **11**, **12** or **13**, respectively, as shown in Schemes 2–5. Subsequent acid treatment of these products mediates cyclization of the deprotected internal amino nucleophile onto the glyoxal ester functionality. Desired cyclic material is obtained

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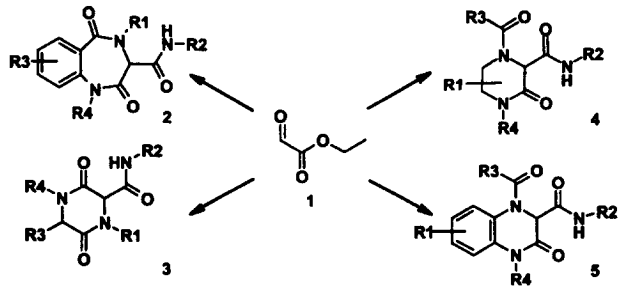
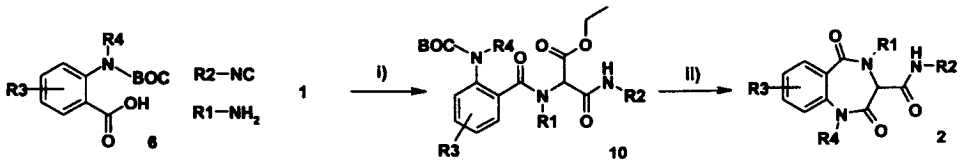
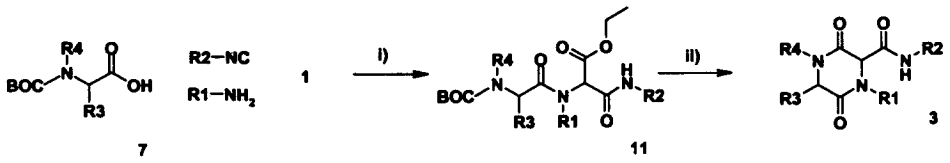
in good yield for the benzodiazepines, **2** (Scheme 2), diketopiperazines series, **3** (Scheme 3), and ketopiperazines,[9] **4** (Scheme 4).



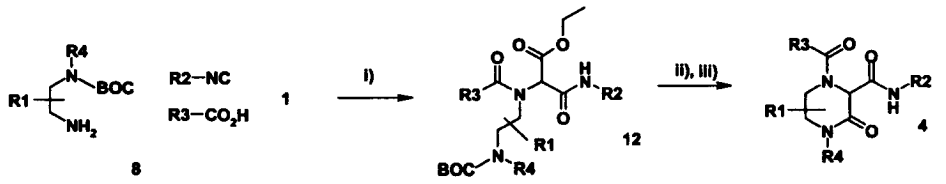
Scheme 1.



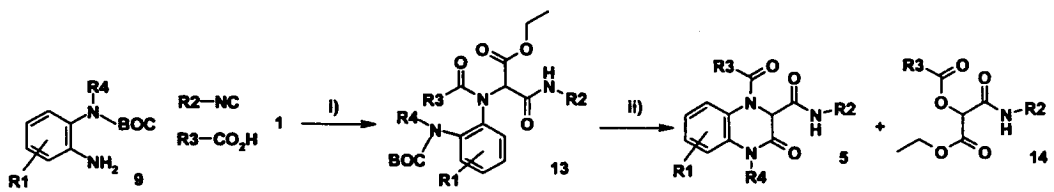
Scheme 2. Reagents and conditions: (i) **1** (1.25 equiv.), 24 h, rt, MeOH. (ii) 10% TFA in dichloroethane, 24 h, rt, evaporation at 65°C in SAVANT™ evaporator for 3 h



Scheme 3. Reagents and conditions: (i) **1** (1.25 equiv.), 24 h, rt, MeOH. (ii) 10% TFA in dichloroethane, 24 h, rt, evaporation at 65°C in SAVANT™ evaporator for 3 h



Scheme 4. Reagents and conditions: (i) **1** (1.25 equiv.), 24 h, rt, MeOH. (ii) 10% TFA in dichloroethane, 24 h, rt, evaporation at 65°C in SAVANT™ evaporator for 3 h (iii) MP-carbonate (3 equiv.), dichloroethane



Scheme 5. Reagents and conditions: (i) **1** (1.25 equiv.), 24 h, rt, MeOH. (ii) 10% TFA in dichloroethane, 24 h, rt, evaporation at 65°C in SAVANT™ evaporator for 3 h

Area (A%) yields of 22 examples as judged by both Evaporative Light Scattering (ELS) and UV (220 nm)[10] are presented in Table 1. Highest A% yields (ELS and UV 220) are observed in the diketopiperazine series, **20**, **21** and **22**. Dramatically lower yields were seen in the dihydroquinoxalinone

series, **31**, **32**, and **33**, where the reduced nucleophilicity of the aniline-like diamine results in preferential formation of the Passerini[2] product, **14**, over the Ugi product, **5**. Ketopiperazines, **23**, **24**, **25** and **26**, represent products prepared via the UDC strategy described in Scheme 4. However, ketopiperazines **27**, **28**, **29** and **30**, were all derived from symmetrical diamines in an efficient one-pot procedure as shown in Scheme 6.[11] In this case the symmetric nature of the diamine obviates the need for a Boc protecting strategy. It is noticeable, however, that yields (as seen by UV 220 nm) are higher with the UDC approach.

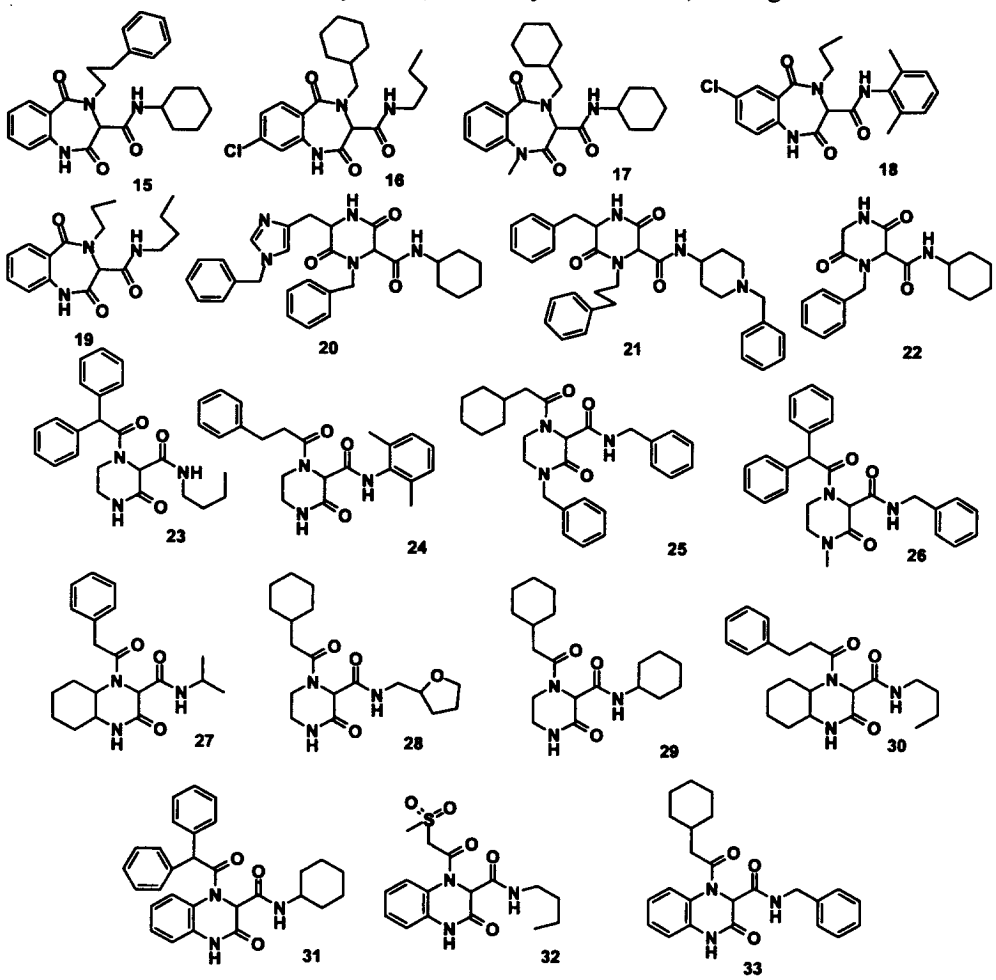
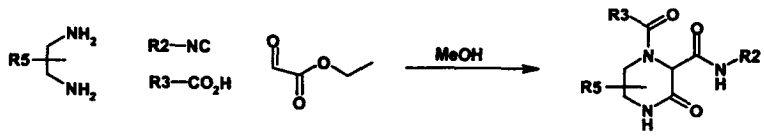


Table 1

N°	Ret. Time	Mr	ELS (A%)	UV220 (A%)	N°	Ret. Time	Mr	ELS (A%)	UV220 (A%)
15	4.26	419	82%	78%	25	4.84	447	31%	52%
16	4.30	455	60%	40%	26	4.37	441	79%	62%
17	4.47	411	63%	40%	27[a]	3.36/3.46	357	96%	35%
18	3.97	399	84%	60%	27[b]	3.63	357	100%	34%
19	3.16	317	39%	30%	28	3.29	351	100%	75%
20	3.89/3.96	499	70%	95%	29	3.97	349	94%	32%
21	3.50/3.63	538	84%	63%	30[a]	4.09	385	100%	47%
22	3.53	329	100%	72%	31	5.17	467	30%	28%
23	4.05	379	100%	85%	32	3.03	367	43%	40%
24	3.82	329	77%	50%	33	4.04	405	20%	30%

Elution conditions :- 0 to 0.1% TFA H_2O/CH_3CN 10% to 100%, 5 min run. Ret. time = retention time. a = product derived from *cis*-cyclohexyl diamine. b = product derived from *trans*-cyclohexyl diamine.



Scheme 6.

The methodology is also amenable to scale up, with isolated yields of the diketopiperazine, **22**, (71%) and the benzodiazepine, **15**, (70%) closely paralleling yields observed via UV detection.[12] The procedure has additionally been successfully advanced to 96-well production status and a 13 000 member diketopiperazine library recently completed.[13]

In summary, reaction of ethyl glyoxalate in the Ugi MCR, with a supporting reagent containing an internal amino nucleophile, allows rapid access to a collection of cyclic, biologically important core templates. Each of the four series described has ≥3 potential points of diversity, making 10 000 member libraries easily accessible. The methodology is high in atom economy and easily automatable[13] and compares favorably to several multi-step solid phase syntheses reported recently.[14]

Acknowledgements

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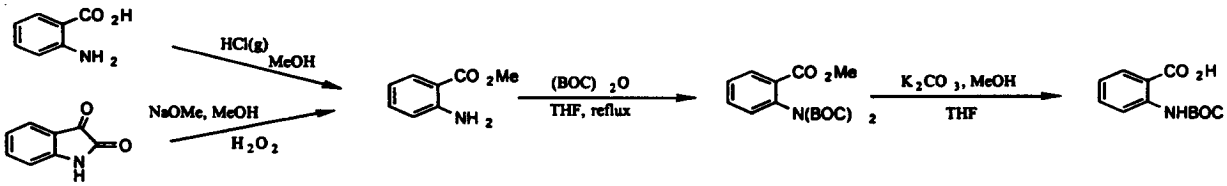
8. *N*-Boc anthranilic acids are readily accessible in multi-gram quantities via the synthetic route shown below from the corresponding anthranilic acid or isatin. *N*-Boc diamines are readily available as described in: Krapcho, A. P.; Maresh, M. J.; Lunn, J. *Synth. Commun.* **1993**, *23*, 2443.



9. MP-carbonate (Argonaut™ Technologies) was used to facilitate cyclization in the ketopiperazine series.
10. LC/MS analysis was performed using a C18 Hypersil BDS 3u 2.1×50 mm column (UV 220 nm) 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.
11. Note: during the preparation of this manuscript a similar one-pot procedure to this class of molecule was reported: Ugi, I.; Zychlinski, A. V. *Heterocycles* **1998**, *49*, 29.
12. Stoichiometric amounts (6.2 ml) of 0.1 M methanolic solutions of the three supporting Ugi components and ethyl glyoxalate (7.75 ml) were combined and stirred at reflux overnight. The solvent was evaporated in vacuo and crude Ugi product dried under high vacuum. A 10% solution of AcCl in MeOH (25 ml) or a 10% solution of TFA (trifluoroacetic acid) in dichloroethane (25 ml) was added to the crude material and stirred at room temperature overnight. The solvent was evaporated in vacuo. The crude material was pre-adsorbed onto flash silica and purified by flash column chromatography (EtOAc:hexane, 1:4) to yield the desired product, **11**, (192 mg, 71%) as a white solid.
13. In a typical procedure, equal amounts (0.1 ml) of 0.1 M solutions in methanol of the 4 components are employed generating a theoretical 10 μmol of final product. Reagents were dispensed into a 96-well plate using either a Tom-tech™ or Rapid Plate™ 96-well dispenser. The deprotection/cyclization steps were performed using either a 10% solution of acetyl chloride in methanol or a 10% solution of TFA in dichloroethane. Evaporations were performed at 65°C in a SAVANT™ evaporator.
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