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Concise preparation of novel tricyclic chemotypes: fused hydantoin–benzodiazepines

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ABSTRACT

The following article describes a concise synthesis of a collection of 4,5-dihydro-1*H*-benzo[*e*][1,4]diazepines fused to a hydantoin ring. Molecular complexity and biological relevance are high and structures are generated in a mere three steps, employing the Ugi reaction to assemble diversity reagents. The protocol represents a novel UDC (Ugi-deprotect-cyclize) strategy employed in the Ugi-5-component CO_2-mediated condensation, followed by further cyclization under basic conditions, to afford the fused hydantoin. Mechanistic caveats, dependent on the aldehydes of choice will be revealed and a facile oxidation of the final products to imidazolidenetriones is briefly discussed.

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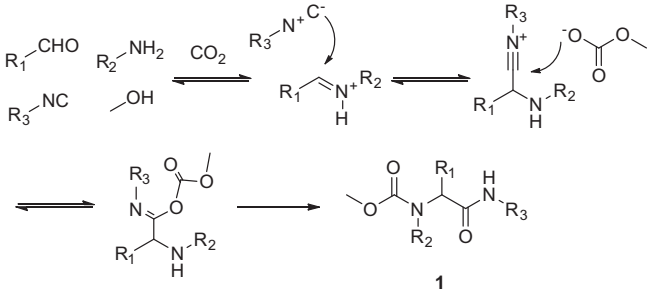
Operationally friendly protocols to produce libraries of novel small molecules of high molecular complexity are in huge demand for the interrogation of biological systems.[1] As such, development of new MCRs (multi-component reactions) and functional group modification of MCR products have proven fruitful tools in the quest for new molecular probes and their expedited progression along the drug discovery value chain.[2] Such products with high-iterative-efficiency potential[2] have found their way into numerous corporate compound collections and examples exist of hit to clinic campaigns were final drugs resided in the virtual diversity space of the original hit generation library.[3] This communication describes the development of a concise three step synthesis of novel tricyclic 4,5-dihydro-1*H*-benzo[*e*][1,4]diazepines fused to an hydantoin ring and employs the rarely used 5-component Ugi reaction (U-5-CR), Scheme 1. Essentially, CO_2 in MeOH produces carbonic acid and the reaction follows the widely accepted classical Ugi mechanism, even though the condensation product differs in that a urethane is now encapsulated within the final skeleton **1**. Prior reports on applications of this reaction are scarce[4], although our planned strategy builds on an early report from this laboratory which employed the amidic NH of U-5-CR as an internal nucleophile to afford fully functionalized libraries of hydantoins in a mere two steps.[4a]

A summary of the generic scaffolds **2** and **3** made accessible and introduced in this article is shown in Figure 1. Thus, construction of the desired Ugi precursor **6** is achieved via condensation of *ortho*-*N*-Boc benzylamines **4**, phenylglyoxaldehydes **5**, isonitriles and a saturated solution of CO_2 in methanol, Scheme 2. Note that **4** was prepared in three steps from the commercially available 2-aminobenzylamine as portrayed in Scheme 3 according to the referenced procedure.[5] The purified Ugi product is subsequently treated with trifluoroacetic acid promoting amine deprotection and



Scheme 1. 5-Component CO_2 modified Ugi reaction.

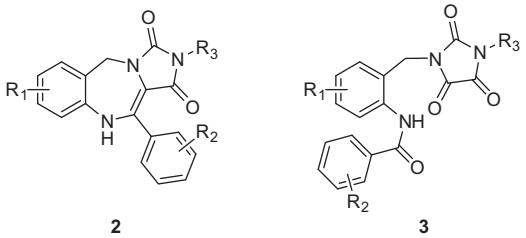


Figure 1. Generic scaffolds of 4,5-dihydro-1*H*-benzo[*e*][1,4]diazepines fused to a hydantoin ring **2** and imidazolidenetriones **3**.

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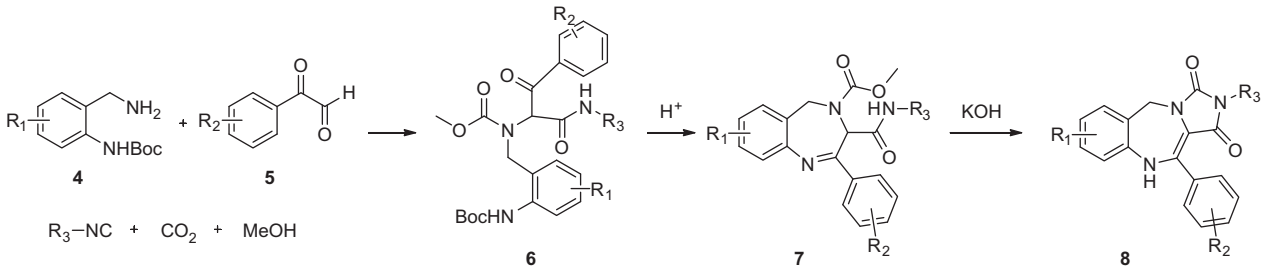
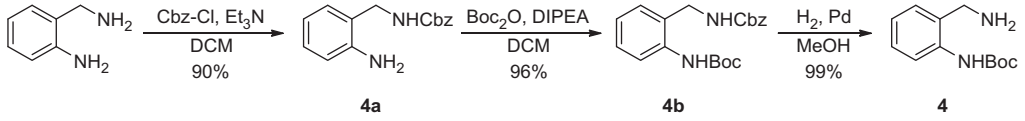


Scheme 2. Preparation of fused benzodiazepine–hydantoins.



Scheme 3. Synthesis of Boc-2-aminobenzylamine **4**.

cyclization to the 4,5-dihydro-1*H*-benzo[*e*][1,4]diazepine, **7** typically in good yield (>90%). Note that this transformation extends the repertoire of available chemotypes from UDC (Ugi/DeBoc/Cyclize) methodology and libraries of this benzodiazepine should now be readily accessible. Final ring construction was achieved by treatment of **7** with KOH, thus promoting cyclization and fusion of a hydantoin-like ring while simultaneously initiating a 1,3-H shift to give the tricyclic chemotype **8** in good yield. As such, the methodology represents an example of a post-condensation Ugi modification[4a] that employs two internal nucleophiles in distinct operations, generating a novel scaffold of high complexity in a succinct 3 functional operations.

With a satisfactory protocol to the generic structure 8 in place,[6] a small collection of these molecules were prepared to demonstrate the generality of the reaction sequence, Figure 2. Diversification was based on the commercial availability of different isonitriles and substituted phenylglyoxaldehydes. Reported percent yields represent conversions of the two combined steps from the Ugi product **6** to scaffold **8**. In essence, scaffold **7** did not require purification, thus simplifying the production protocol. Unequivocal evidence for the structure of this chemotype was provided by X-ray crystallography for **9**, Figure 3.[7]

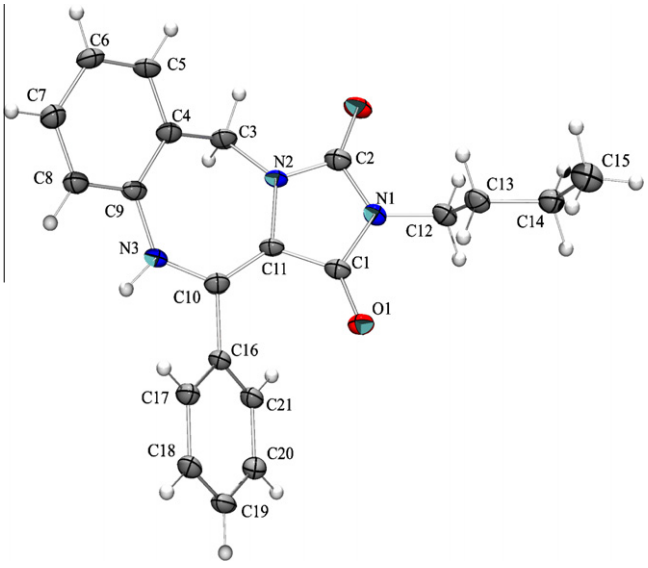


Figure 3. X-ray crystal structure of **9**.

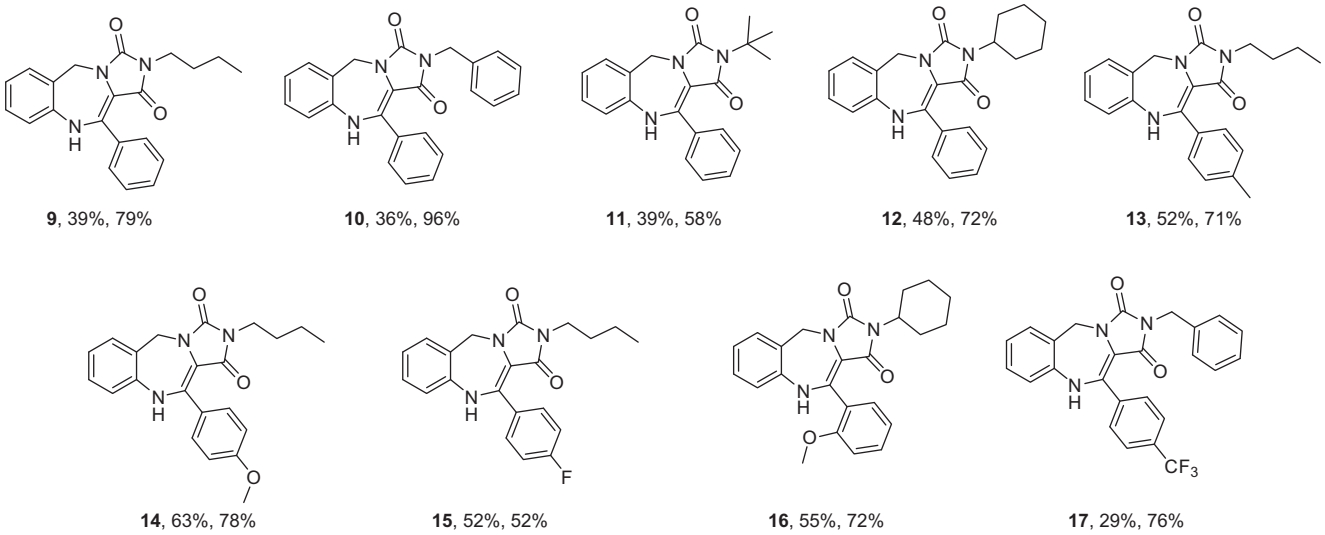
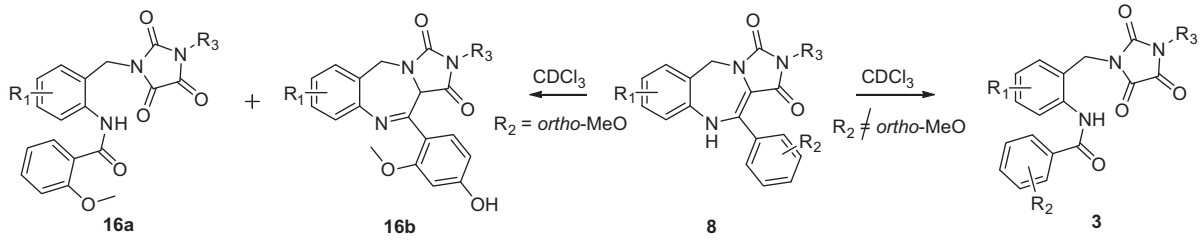
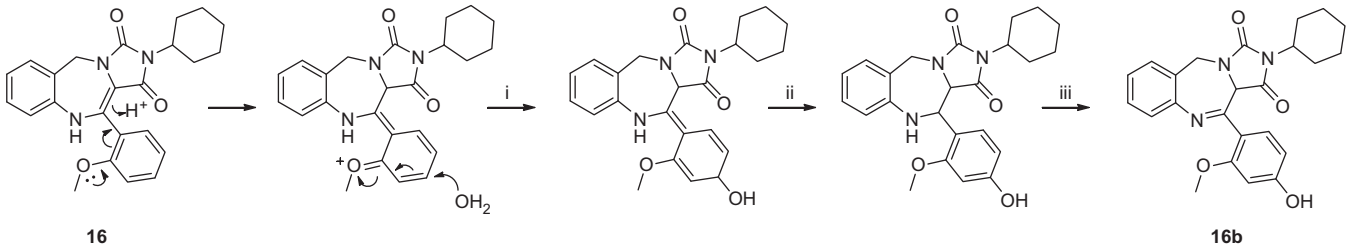


Figure 2. Example analogs (*x*% = Ugi yield, *x*% = yield of **8** from **6**).



Scheme 4. Aerobic chemical transformations of **8** on standing in $CDCl_3$.



Scheme 5. Proposed mechanism involving (i) aromatic substitution, (ii) tautomerization–rearomatization and (iii) oxidation to the imine.

Interestingly, the tri-cyclic scaffolds **8** underwent a chemical oxidative transformation to the pharmacologically relevant imidazolidinetriones[8] **3** (Scheme 4) on standing in $CDCl_3$. One particular example **9** showed 75% conversion to its imidazolidinetrione congener after 10 days in $CDCl_3$. Oxidative carbon–carbon double bond cleavage of similar hydantoin derivatives has been previously reported[9] and compound **9** was successfully proven to undergo such oxidation upon treatment with $KMnO_4$.[10] Encouragingly for future screening efforts the fused hydantoin compounds are stable in DMSO and other solvents, with no oxidation detected over prolonged periods in solution. As supported by a previous study,[11] this finding exemplifies the phenomenon of air oxidation in chloroform, suggested to be far more facile than in other regularly used solvents. Oxidative rate acceleration of **9** by light suggests a singlet oxygen mechanism may be involved in this process.

Note an exception was found with compound **16**, an analog derived from 2-methoxyphenylglyoxaldehyde. Interestingly, a second product was also observed during exposure to $CDCl_3$ (**16a**:**16b** = 1:4.5). Tentatively, the following mechanism, Scheme 5, is proposed that involves aromatic substitution with water, tautomerization/rearomatization, and oxidation to the imine, **16b**. Evidence for this structure was provided by detailed NMR studies.

In summary, a concise three-step synthesis of a collection of fused 4,5-dihydro-1*H*-benzo[*e*][1,4]diazepines-hydantoins has been successfully developed that utilizes the scarcely employed 5-component CO_2-modified Ugi reaction as the diversity generating event followed by two subsequent cyclization transformations. The first transformation occurs under acidic conditions to construct the benzodiazepine ring and is followed by a second cyclization under basic conditions to afford the fused hydantoin. Because of the uniqueness of these scaffolds, the desirable drug-like properties of the molecules generated, and the ease of synthesis, this methodology represents a viable strategy for future enrichment of small molecule compound libraries.

Acknowledgments

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5. For the preparation of **4**:
2-Aminobenzyl-Cbz-amine (**4a**): To a solution of 2-aminobenzylamine (5.70 g, 46.7 mmol) in anhydrous dichloromethane (150 ml) was added DIPEA (16.30 ml, 93.0 mmol). Next, benzyl chloroformate (6.66 ml, 46.7 mmol) in anhydrous dichloromethane (45 ml) was added drop-wise via syringe. The reaction proceeded for 2 h. Then, reaction mixture was poured into a separatory funnel and washed with brine solution (3 × 80 ml). Organic layer was dried over $MgSO_4$ and concentrated in vacuo to give yellowish white solid which was subsequently purified by Teledyne Isco CombiFlash R_f (hexane/EtOAc 5–50%) to afford **4a** (10.82 g, 42.2 mmol, 90%) of yellowish white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.30 (m, 5H), 7.13 (td, J = 7.7, 1.6 Hz, 1H), 7.06 (dd, J = 7.4, 1.3 Hz, 1H), 6.65–6.75 (m, 2H), 5.15 (s, 2H), 5.08 (s, 1H), 4.33 (d, J = 6.2 Hz, 2H), 4.05 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.34, 145.75, 136.74, 130.68, 129.63, 128.94, 128.59, 128.47, 122.53, 118.48, 116.33, 67.44, 42.92. $[M+H]^+$ = 257.
2-Boc-aminobenzyl-Cbz-amine (**4b**): To a solution of **4a** (10.74 g, 41.9 mmol) and DIPEA (14.64 ml, 84 mmol) in anhydrous dichloromethane (100 ml) was added Boc_2O (10.97 g, 50.3 mmol). The reaction was then refluxed for 3 days. The reaction was then concentrated *in vacuo* and toluene was added to pull out *t*-BuOH giving 19.76 g light yellowish white solid which was then purified by Teledyne Isco CombiFlash R_f (hexane/EtOAc 5–50%) to afford **4b** (14.30 g, 40.1 mmol, 96%) of yellowish white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.34–7.40 (d, J = 2.6 Hz, 5H), 7.31 (dd, J = 7.8, 1.7 Hz, 1H), 7.21 (dd, J = 7.5, 1.3 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 5.33 (s, 1H), 5.15 (s, 2H), 4.33 (d, J = 6.4 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.58, 154.23, 137.14, 136.58, 130.47, 129.20, 128.95, 128.65, 128.56, 124.40, 123.22, 80.66, 67.60, 42.35, 28.77. $[M+Na]^+$ = 379.
2-Boc-aminobenzylamine (**4**): To a solution of **4b** (14.2 g, 39.8 mmol) in methanol (50 ml) was added 0.5 g Pd/C (10%). H_2 (g) was flown into glass reactor at 40 psi. The reaction was then allowed to run at room temperature over night. Pd/C was removed using Celite then solution was collected using vacuum filtration to yield **4** (8.80 g, 39.6 mmol, 99%) of yellow sticky product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.27 (td, J = 7.7, 1.6 Hz, 1H), 7.11 (dd, J = 7.4, 1.4 Hz, 1H), 6.96 (td, J = 7.4, 1.1 Hz, 1H), 3.97 (s,

2H), 1.74 (s, 2H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.86, 139.46, 129.37, 129.00, 128.66, 122.73, 120.72, 80.17, 45.91, 28.83. $[M+H]^+$ = 223.

6. *For the standard preparation of generic structures* **8**: CO_2 gas was bubbled through a stirring solution of MeOH for 25 min to generate methyl carbonic acid. In a separate 25 ml flask, phenyl glyoxal **5** (226 mg, 1.687 mmol) was added to boc-2-aminobenyzlamine **4** (250 mg 1.125 mmol). Methyl carbonic acid (10 ml) and *N*-butyl isonitrile (0.237 ml, 2.252 mmol) were then added to the latter flask. The reaction was stirred at room temperature under an atmosphere of CO_2 for 16 h. The solvent was evaporated in vacuo and the crude product purified with a Biotage Isolera4™ system (hexane/EtOAc 10–30%) to afford the Ugi product (218 mg, 0.438 mmol, 39%) as a yellow oil. Ugi product (135 mg, 0.270 mmol) was treated with a 5 ml 10% TFA solution in 1,2-dichloroethane which was irradiated in a Biotage Initiator™ at 80 °C for 20 min. The resulting orange solution was washed with 1 M $NaHCO_3$ (4 × 2.5 ml) and the organic layer dried (Na_2SO_4), filtered, and evaporated in vacuo. MeOH (1.50 ml), THF (0.75 ml), H_2O (0.50 ml) were added to the crude product (102 mg, 0.269 mmol) followed by a 1 g/1 ml solution of KOH in H_2O (0.03 ml). The solution was irradiated at 100 °C for 20 min and the resultant orange solution partitioned between EtOAc (5 ml) and 1 M $NaHCO_3$ (5 ml). The organic layer was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The final crude product was purified with a Biotage Isolera4™ (hexane/EtOAc 30%) to afford the final product **9** (74 mg, 0.214 mmol, 79%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.44 (m, 5H), 7.35 (d, J = 7.5 Hz, 1H), 7.32–7.25 (td, J = 8.1, 1.3 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 5.95 (s, 1H), 4.98 (s, 2H), 3.49 (t, J = 7.4 Hz, 2H), 1.56 (m, 2H), 1.39–1.17 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.85, 153.72, 142.48, 135.43, 134.61, 130.66, 130.55, 129.71, 129.59, 129.11, 126.44, 123.92, 120.73, 109.36, 45.74, 39.01, 30.71, 20.47, 14.06. MS FT-ICR calcd for $C_{21}H_{22}N_3O_2$ $[M+H]^+$: 348.1707, found: 348.1707.
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10. A thirty mmol batch of the reagent was prepared by combining $KMnO_4$ (3 mmol, 0.474 g, finely ground) and alumina (Al_2O_3, neutral, 575 mg) in a mortar and pestle and grinding together until a free, homogeneous, purple powder is obtained (5–10 min). **9** (52 mg, 0.15 mmol) was dissolved in acetone and the $KMnO_4/Al_2O_3$ powder (66.50 mg supported reagent, 0.20 mmol $KMnO_4$) was added. After 15 min of vigorous stirring, the reaction mixture was filtered and the acetone filtrate condensed. The residue was taken up into hexane/EtOAc 30%, washed with 0.1 M HCl, dried over $MgSO_4$, and the solvent was evaporated in vacuo to give the crude material which was then purified by Biotage Isolera Four (hexane/EtOAc 10–30%) to afford the oxidized product (21 mg, 0.055 mmol, 27%) of white solid.
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