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An efficient solution phase synthesis of triazadibenzoazulenones: 'designer isonitrile free' methodology enabled by microwaves

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ABSTRACT

A novel two-step solution phase protocol for the synthesis of arrays of triazadibenzoazulenones is reported. The methodology employs the Ugi reaction to assemble desired diversity and acid treatment enables two tandem ring closing transformations. The order of ring closure is shown to be key for optimal conversion to the desired tetra-cyclic product and initially proceeds through a benzimidazole intermediate, followed by second ring closure to give the desired fused benzodiazepine. The two-step protocol is further facilitated by microwave irradiation. Prudent selection of the isonitrile reagent enables the correct order of ring forming events. As such the methodology represents the first example of a post-condensation Ugi modification that employs two internal amino nucleophiles.

With the development of high speed parallel synthesis and dramatic need for new molecular probes, the multi-component reaction (MCR) has witnessed a resurgence of interest.[1] In particular, isonitrile-based MCRs have been at the forefront with highly significant advances in library methodology development utilizing both the Ugi[2] and Passerini[3] reactions as the initial diversity assembling methodology. The first report from this laboratory detailed a succinct two-step route to fully functionalized diketopiperazine libraries[4] and further routes to several widely employed scaffolds in the pharmaceutical sector were subsequently developed.[5] Moreover, the methodology (coined UDC—Ugi/de-protect/cyclize) has delivered several examples where initial hits have progressed along the drug discovery value chain into clinical trials for the treatment of both HIV infection[6] and pre-term labor,[7] importantly without the need to 'scaffold hop'. In many ways these vignettes are representative of the original 'Holy Grail' of combinatorial chemistry—clinical candidates residing in the virtual space of the initial hit generation library. Subsequently rigidifying the Ugi skeleton with the arsenal of available organic methodology via judicious placement of complementary reactive functionality, several groups have produced scaffolds of impressive molecular complexity.[8] Herein, we report a novel solution phase synthesis of tetra-cyclic triazadibenzoazulenones[9] **4** which represents the first example of a post-condensation Ugi modification employing two internal nucleophiles, Scheme 1.

It was envisioned that the scaffold would be accessible in two steps: an Ugi reaction utilizing mono-Boc protected phenylene diamines **1**, Boc-protected anthranilic acids **2**, a designer 'universal isonitrile' **3**[10] and supporting aldehydes, followed by acid treatment of **4** to unmask internal amino nucleophiles and to activate the isonitrile derived carbonyl to nucleophilic attack. A retrosynthetic analysis describes the two tandem ring forming reactions, Scheme 2. Note that precedents for both individual ring closures have been demonstrated in this laboratory.[11] Thus, for preliminary development work the solid odorless 4-phenyl-cyclohexyl isonitrile **8** was selected for the role of convertible isonitrile, and was prepared in two steps.[12] Condensation proceeded in good yield **9** (80%) and treatment with acid resulted in formation of three products. Encouragingly, the desired triazadibenzoazulenone **12** was observed albeit in low yield (~10%) along with the two monocyclic products **10** and **11**. The carboxamide **11** is presumably formed when water released after benzimidazole formation, hydrolyzes the activated *N*-acyliminium ion intermediate **13** (see Scheme 3).

In an attempt to elucidate the order of ring forming events that result in **12**, prolonged heating of **10** resulted in formation of its trifluoroacetamide congener **14** with no other products observed. This is consistent with earlier literature reporting extreme difficulty in performing amino-cyclodehydrations onto benzylic tertiary cyclic amides with a variety of acids.[13] Prolonged heating of **11** under acidic conditions showed substantial conversion (>70%) to the desired product **12**. The combined results suggest that the target molecule is derived from a sequential benzimidazole benzodiazepine ring forming sequence. Thus to avoid initial formation of **10**, experiments were performed to attenuate the reactivity of the isonitrile derived carbonyl, in such a way that would dramatically slow formation of **10** relative to the benzimidazole **11**. Moreover, this required a strategy devoid of a designer isonitrile, in favor of a cheap, sterically unencumbered readily available analog that

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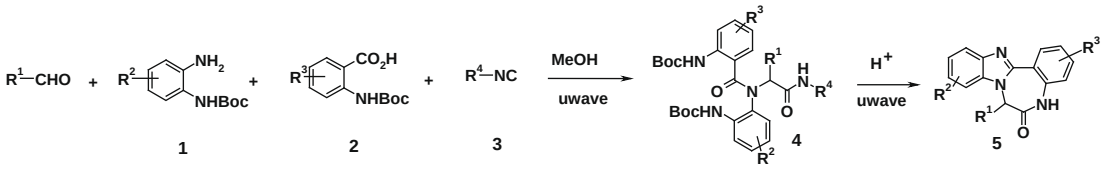
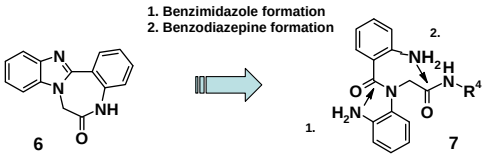


Scheme 1.



Scheme 2.

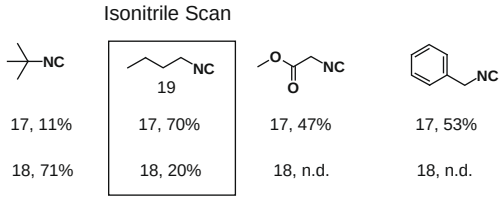
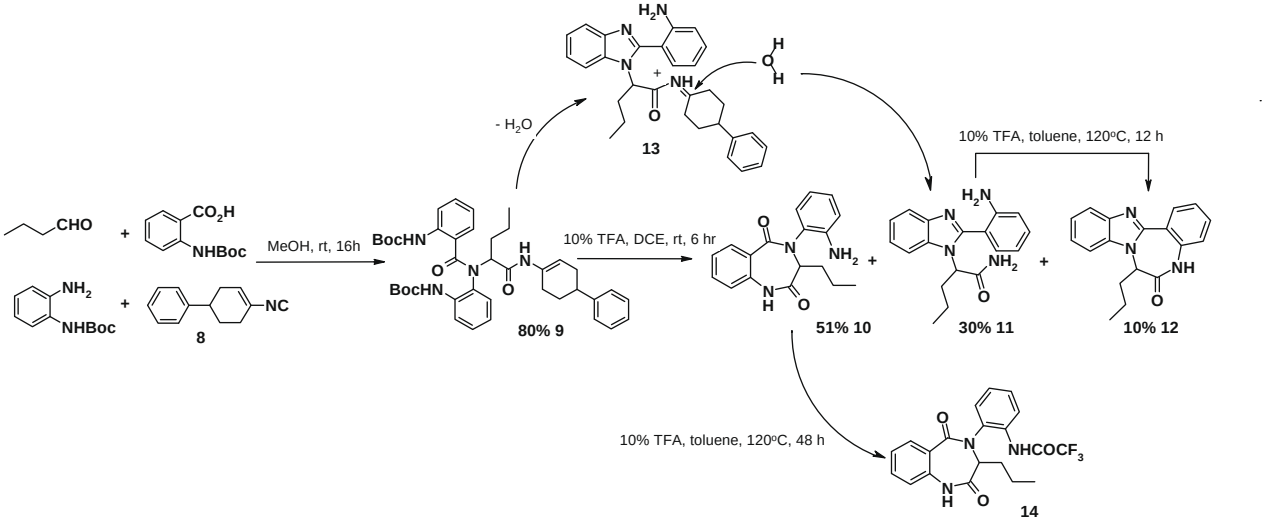


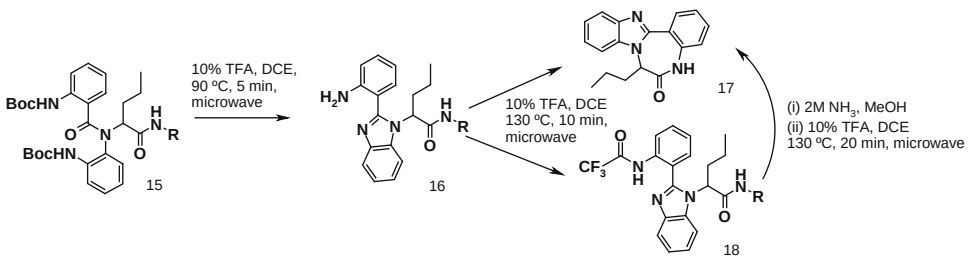
Figure 1. Isonitrile scan.

results in a condensation product containing a CONH moiety of reduced electrophilic character. Thus the microwave facilitated conditions,[14] Scheme 4, were deployed for four readily available isonitriles, Figure 1. Exposure of **15** to acid catalyzed dehydration conditions enabled clean transformation (as judged by thin layer chromatography) to benzimidazole **16** characterized by a typically clear to red color change associated with increased conjugation. The reaction mixtures were then subjected to further irradiation for 10 min at elevated temperatures (130 °C) to afford desired product **17** and the trifluoroacetylated benzimidazole **18**. Recycling the latter was straightforward with ammonia induced deacetylation and further TFA treatment improving yields of **17**. Noticeably, the ratio of **17** to **18** was dependent on the steric bulk of the isonitrile under investigation, Figure 1.

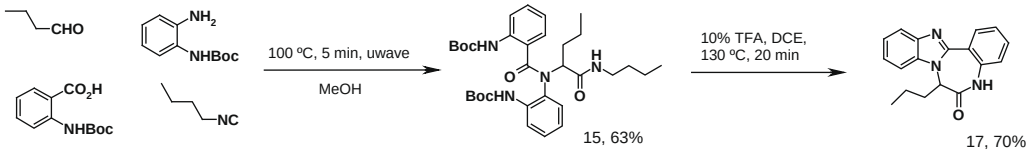
This is dramatically exemplified by the difference in isolated yields of triazadibenzoazulenone between use of *t*-butyl isonitrile (**17**, 11% yield) and *n*-butyl isonitrile **19** (**17**, 70% yield). The methyl ester and benzyl isocyanide were also evaluated. Interestingly, neither showed complete disappearance of the benzimidazole under these conditions and isolated yields of **17** were thus significantly lower. Yields of **18** were not determined for the latter two examples. Satisfied with the selection of inexpensive *n*-butyl isonitrile the double deprotection and tandem cyclization was



Scheme 3.



Scheme 4.



Scheme 5.

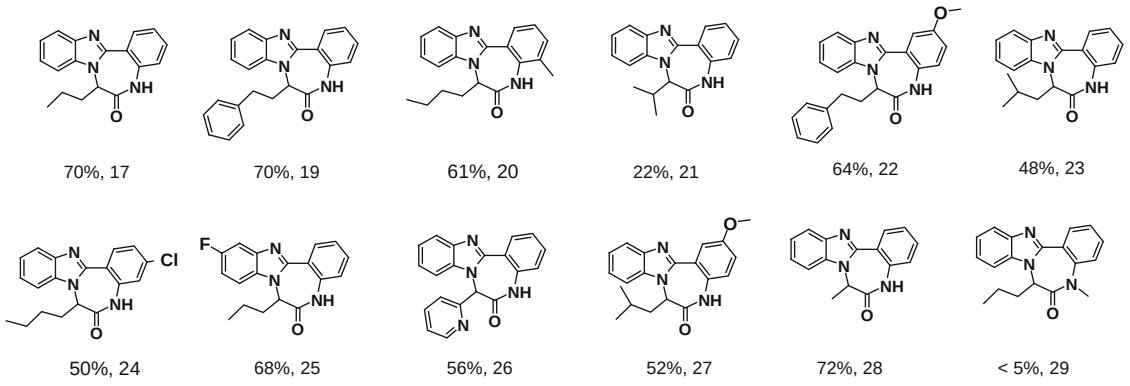


Figure 2.

evaluated in one step (130 °C, 20 min, microwave).[15] Product distribution and yield was found to be essentially the same as heating in two distinct operations, Scheme 5.

Representative scope of the protocol was then evaluated with a selection of different reagents. Reactions with purified Ugi products were assembled on a Biotage8 Initiator® and run in a sequential automated fashion. Products were then purified sequentially with a Biotage Isolera® system. Twelve examples (**17**, **19** to **29** are shown) with isolated yields ranging from <5% to 72%, Figure 2. The N-methylated anthranilic acid was noticeably a poor performer, **29**.

In summary, a concise two-step solution phase synthesis of triazadibenzoazulenones has been reported. The methodology has been shown to be amenable to high-throughput technologies, and is expected to be embraced by the lead generation community. The route also compares favorably to only one other reported six-step solid phase synthesis of this scaffold.[9] Significantly the methodology represents the first example of two amino internal nucleophiles being employed to constrain the Ugi product. The latter cyclization may be viewed as the first post-UDC modification. Control over the order of ring formation was required and in doing so it became evident that with the advent of microwave irradiation and 5 min reaction times, 'designer convertible isonitriles' are potentially rendered partially obsolete for UDC-like methodologies. Current efforts to improve the methodology are on-going by use of methyl isocyanide and investigations into alternate scaffolds derived from similar approaches, will be reported in due course.

Acknowledgement

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14. *For the preparation of* **17** *and general library protocol*: To a stirring solution of butyraldehyde (225 mg, 3.1 mmol) in methanol (4 ml) contained in a 5.0–10 ml microwave vial were added *tert*-butyl 2-aminophenylcarbamate (438 mg, 2.1 mmol), *n*-butylisonitrile dissolved in methanol (4 ml) (175 mg, 2.1 mmol), and 2-(*tert*-butoxycarbonylamino)benzoic acid (500 mg, 2.1 mmol). The reaction was irradiated for 5 min at 80 °C, solvent evaporated in vacuo and condensation product purified with a Biotage Isolera® to afford the Ugi condensation product (755 mg, 63%) as a white solid. This product (100 mg, 0.17 mmol) was dissolved in a solution of 10% TFA in dichloroethane (2 ml), and was irradiated in a 2.0–5.0 ml microwave vial for 20 min at 130 °C. The solvent was evaporated in vacuo and crude material partitioned between $NaHCO_3$ (20 ml) and ethyl acetate (20 ml). Organic layer was washed with brine (20 ml), dried ($MgSO_4$), and pre-absorbed onto flash silica. Automated purification afforded the desired triazadibenzoazulenone **17**, in 70% yield (41 mg, 1.41 mmol). Structural characterization: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.92 (m, 1H), 7.76 (m, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.29–7.36 (m, 4H), 5.46 (t, J = 7.6 Hz, 1H), 1.46–1.54 (m, 1H), 1.67–1.75 (m, 1H), 0.92–1.00 (m, 1H), 1.08–1.20 (m, 1H), 0.68 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 168.9, 148.6, 142.2, 135.4, 135.3, 131.7, 129.8, 124.4, 123.0 (2 peaks overlapped), 121.1, 120.0, 118.9, 110.3, 59.6, 31.1, 18.5, 13.1. Mass: MH^+ 292; HRMS calculated 292.1444, observed 292.1446. R_f = 0.34 (ethyl acetate/hexane = 1:1).
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