Multicomponent Reactions

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The Synthesis of Stable, Complex Organocesium Tetramic Acids through the Ugi Reaction and Cesium-Carbonate-Promoted Cascades

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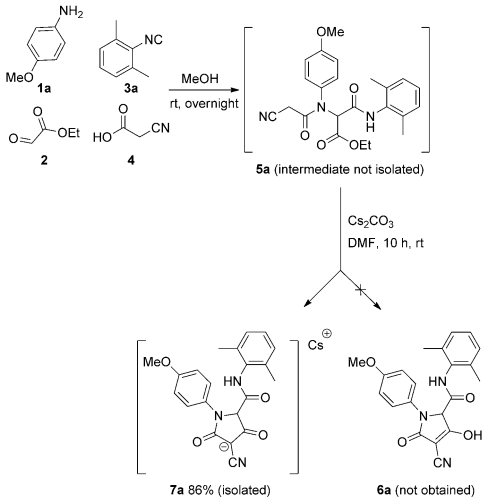
Abstract: *Two structurally unique organocesium carbanionic tetramic acids have been synthesized through expeditious and novel cascade reactions of strategically functionalized Ugi skeletons delivering products with two points of potential diversification. This is the first report of the use of multicomponent reactions and subsequent cascades to access complex, unprecedented organocesium architectures. Moreover, this article also highlights the first use of mild cesium carbonate as a cesium source for the construction of cesium organometallic scaffolds. Relativistic DFT calculations provide an insight into the electronic structure of the reported compounds.*

The synthesis of cesium organometallics is a challenging task for the chemist, because their preparation often involves the use of pyrophoric cesium metal which is highly sensitive to air and moisture. As such, preparations are often carried out at low temperature in combination with either vacuum/air-free or glove-box/inert atmosphere protocols. Similarly, purification of cesium organometallics using everyday laboratory techniques can be very challenging[1–3] and, moreover, the resulting metal complexes often lack stability which limits their use. However, some cesium-containing complexes (i.e., salts) have been found to be air-stable with applications in material sciences, for example, luminescence,[4] catalysis, and polymer synthesis.[5] Thus, the development of concise synthetic protocols that afford novel and stable organocesium complexes in a parallel expedited fashion may open up new avenues of study in material sciences.[6,7] Herein, we reveal unique 2-step one-pot and 3-step one-pot reaction sequences, in which the initial assembly of two diversity elements and two complementary electrophilic and nucleophilic sites is achieved by the four-component Ugi isocyanide-based multicomponent reaction (IMCR).[8] Subsequent treatment of the designer Ugi adduct with a mild underexploited cesium source in organometallic chemistry—cesium carbonate—triggers completion of the two cascade sequences[9] to access structurally complex and stable cesium organometallic tetramic acids in exquisite non-obvious ways.

Post-condensation strategies to manipulate IMCRs for molecular diversity generation are highly productive for the construction of a variety of heterocyclic scaffolds, particularly in a library compatible manner.[10] Surprisingly, MCRs in general have been rarely used to synthesize libraries of organometallics,[11–13] and to the best of our knowledge there are no reported examples of MCRs affording cesium-based organometallics. With an on-going interest in MCRs and molecular diversity generation,[14–16] our original intent was to use the Dieckmann condensation[17] on an Ugi adduct to access tetramic acids (pyrrolidine-2,4-diones; Scheme 1).



Scheme 1. Ugi/Dieckmann sequence toward organocesium tetramic acids.

Tetramic acids display a spectrum of biological activity that includes cytotoxic, fungicidal, and anti-ulcerative properties. Moreover, nootropic activity is exemplified by the drug oxiracetam (**I**; Figure 1).[18,19] This chemotype is likewise known for its presence in a variety of biologically relevant natural products such as: sintokamide A (**II**) with anticancer properties; cryptocin (**III**), with antifungal activity; and reutericyclin (**IV**) with antibacterial action (Figure 1).[20,21]

Initial studies started with optimization of the model sequence shown in Scheme 1, with the four Ugi reagents, *p*-methoxyaniline (**1a**), ethyl glyoxalate (**2**), 2,6-dimethylphe-

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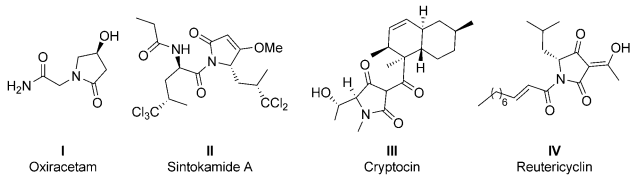


Figure 1. Bioactive drugs and natural products containing tetramic acids and analogues.

nylisonitrile (**3a**), and cyanoacetic acid (**4**), yielding the expected product **5a**. After solvent evaporation, the crude unpurified Ugi adduct **5a** was subjected to a variety of bases to initiate an intramolecular Dieckmann condensation. Cesium carbonate in DMF at room temperature proved optimal (entry 6, Table S1 in the Supporting Information, SI) delivering what was expected to be **6a** (89% purity as judged by Area% under the curve, UV 254 nm, eluent: 90% H_2O, 10% acetonitrile, LC/MS). However, reaction work-up was solvent evaporation, followed by column chromatography (note: no base quenching step was performed). Interestingly NMR analysis revealed a missing proton in the tetramic acid (Figure 2) and subsequent X-ray crystallography[22] confirmed

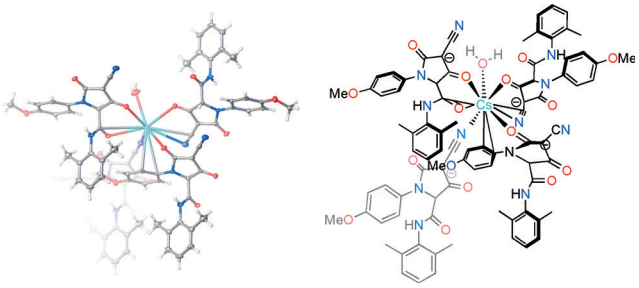
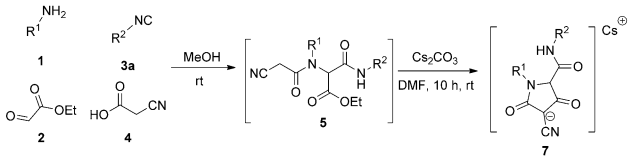


Figure 2. X-ray structure of **7a** showing the Cs coordination sphere.

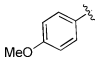
the presence of an unprecedented organocesium complex **7a** (see Figure 2 as well as Figures S1 and S2). Interestingly, by changing the LC/MS eluent (to H_2O/CH_3CN, 1:9), the mass of the expected tetramic acid plus the cesium atom was found to be consistent with the observed X-ray data. Crystallographic bond lengths and angles (Tables S3 and S4) show that the negative charge is centered at the carbon α to the nitrile functionality as expected. It was gratifying that the two step one-pot Ugi/Dieckman sequence had gone as planned and even more pleasing that a simple failure to quench cesium carbonate during work-up had afforded an unprecedented, complex and stable cesium-based species with organometallic character. Close inspection of the X-ray crystallographic data shows that the cesium coordination sphere of **7a** contains one nitrile nitrogen atom, one η^2-nitrile, one water molecule (proposed source: non-anhydrous crystallization solvents), four carbonyl oxygen atoms, and a η^2-phenyl. Cesium atoms are connected into an extended array in the crystallographic *ab* plane through bridging nitrile nitrogen atoms and carbonyl oxygen atoms (shown in Figure S2). Note that there is apparently a water molecule in the cesium coordination sphere. The hydrogen atoms were not visible in the electron density map, however, the environment is appropriate with putative hydrogen bonds to the carbonyl oxygen atoms O2 (X,Y−1,Z) and O1 (1+X,Y,Z). The coordination sphere is predominantly inorganic, binding primarily oxygen and nitrogen atoms. Inspection of the web-based Cambridge Structure Database [(Web CSD v1.1.1); search performed 2/6/2015] indicates that this is the first reported structure of an organocesium species that simultaneously binds a water molecule, a carbonyl, a nitrile, and a phenyl group.

To demonstrate the feasibility to make libraries of these complexes, a small collection of congeners was quickly assembled using the aforementioned conditions (Scheme 2 and Table 1). As expected, all analogues **7a**–**7d** lacked the proton α to the cyano moiety, which was confirmed by NMR spectroscopy, LC/MS, and HRMS. This data was also consistent with the presence of one cesium atom per molecule of tetramic acid.



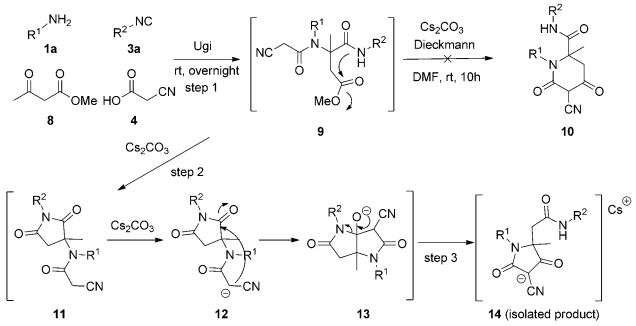
Scheme 2. Ugi/Dieckmann sequence toward organocesium tetramic acids.

Table 1: Ugi/Dieckmann-derived cesium-containing pyrrolidine-2,4-diones.

Entry	Compound	R^1	R^2	Yield [%][a]
1	**7a**			86
2	**7b**		*n*Bu	64
3	**7c**			37
4	**7d**			47

[a] Yield of isolated product.

At this stage of the project, interest in preparing alternate succinct routes to tetramic acids was still high, albeit by using a slightly different methodology. Concise stereoselective routes to fused 5,5-heterocyclic ring systems proceeding through an Ugi condensation, imide formation, and subsequent ring closure through imide enolate generation were described by this laboratory in a sequential MCR/three-step domino process and provided the impetus for these new studies.[23a] Aiming to exploit the susceptibility of cyclic imides **11** to nucleophilic attack and imide ring opening, ethyl glyoxylate (**2**) was thus replaced with methylacetoacetate (**8**) as the carbonyl input of the Ugi reaction. Treatment of the Ugi adduct **9** with cesium carbonate enabled formation of the cyclic imide **11** and, in the same pot, the base-promoted formation of the tetramic acid **14** through nucleophilic ring closure onto the imide carbonyl originally derived from



Scheme 3. Sequential Ugi/cesium-carbonate-promoted cascades toward highly substituted cesium organometallic tetramic acids.

methylacetoacetate (**8**; Scheme 3). Dieckmann cyclization of **9** to **10** was, as expected, not observed. Intriguingly, following a similar work-up procedure to that employed in Scheme 1, structures of two products were unambiguously established using X-ray crystallography (**14a** and **14b**, Figures 3 and 4, respectively). Both were found to have similar cesium coordination spheres which included η^2- and η^6-phenyl rings, and Cs dimers bridged by nitrile nitrogen and carbonyl oxygen atoms, distinctly different from **7a**.

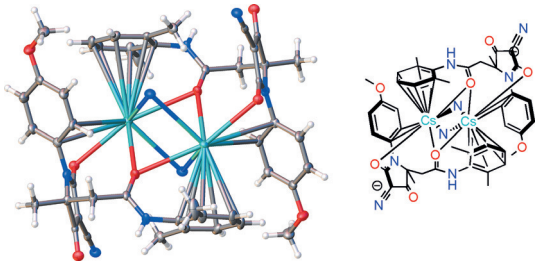


Figure 3. X-ray crystal structure of **14a** showing the Cs coordination sphere. (Note that the two nitrogen atoms bridging the Cs atoms are coming from the nitrile of additional tetramic acids that were removed for simplicity.)

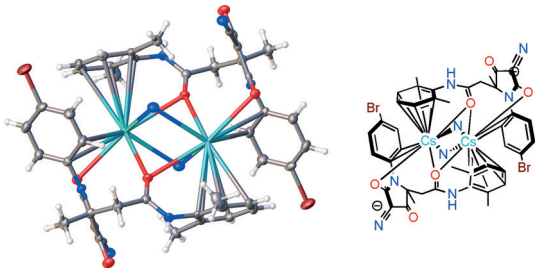
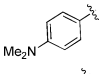
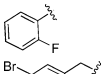
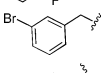
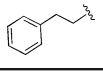


Figure 4. X-ray crystal structure of **14b** showing the Cs coordination sphere. (Note: that the two nitrogens bridging the Cs atoms are coming from the nitrile of additional tetramic acids that were removed for simplicity.)

Both **14a** and **14b** are the first examples of organocesium species with unique coordination spheres that involve binding phenyl rings in two different modes, and simultaneously picking up interactions with carbonyl and nitrile groups. Interestingly, the coordination sphere of **14a** and **14b** has more organometallic character than that of **7a** which is probably best exemplified by the η^6 coordination of aromatic rings. Moreover, the cesium coordination spheres spanning all three crystal structures detailed herein contain a startling mix of ligands, ranging from η^6-phenyl rings to solvent molecules. Note that cesium organometallics are generally acknowledged to be highly ionic,[1] and their coordination sphere contents and geometry are largely controlled by steric constraints of the scaffold rather than metal–ligand coordinate bond formation, suggestive of the high novelty and complexity in these new examples. In particular, the distance from the cesium cation to the centroid of the η^6-phenyl rings is as expected for organocesium complexes (3.305 Å in **14b** and 3.375 Å in **14a**). A search of the Cambridge Data Base V. 5.36 (7/10/15) found 38 structures containing Cs–η^6 phenyl ring bonds. A few longer ones, those above 3.7 Å and belonging to benzene solvates, were eliminated from consideration. For the other 61 instances (some structures contained multiple instances of such bonds), the mean Cs–centroid distance was 3.34 Å, with a standard deviation of 0.1 Å. Thus, the Cs–η^6 ring bond lengths observed in **14a** and **14b** are in the range expected for such bonds. The distribution of Cs–centroid distances is bifurcated, with bond distances of wholly organometallic complexes peaking near 3.26 Å and those containing both organometallic and more inorganic ligands peaking near 3.37 A, but there is overlap between the distances observed in these two groups of compounds.[24] With regard to the overall covalency, Morokuma–Ziegler energy decomposition analysis (EDA) for **14a** and **14b** at the scalar relativistic level (Table S11) indicates 21.1 % and 23.5 % covalent character, respectively.

A small library of analogous organocesium tetramic acids was thus prepared in rapid fashion to demonstrate scope and amenability to library creation (**14a**–**14i**, Table 2; Scheme 3).

Table 2: Highly substituted tetramic acids generated through a sequential Ugi/three-step one-pot cascade.

Entry	Compound	R^1	R^2	Yield [%][a]
1	**14a**			52
2	**14b**			41
3	**14c**			40
4	**14d**			36
5	**14e**			41
6	**14f**			46
7	**14g**		*n*Bu	31
8	**14h**		*n*Bu	40
9	**14i**			49

[a] Yield of isolated product.

The observed yields are moderate yet impressive, representing yields from a three-step, one-pot process with no intermediary purification. Indeed, if one considers the formation of the organocesium species as an additional step, Schemes 2 and 3 actually represent three- and four-step, one-pot processes. Note that all products lack the α-proton to the cyano group, confirmed by NMR spectroscopy, LC/MS, HRMS, and the two X-ray crystal structures (**14a** and **14b**).

All compounds (**14a**–**14i**, Table 2) were found to be air- and moisture-stable, which is relatively rare for cesium organometallics,[1–3] and the organometallic architecture was fully intact after flash column chromatography. Specifically, no significant decomposition of **7a**, **14a**, or **14b** was observed over a period of six months (as judged by LC/MS). Indeed, **14b** was crystallized for X-ray analysis 6 months after the initial synthesis. With regard to moisture stability, the crystallization was conducted in non-anhydrous solvents (THF/acetone and/or dioxane/THF; see SI) with no apparent detrimental effects on stability. Moreover, a water molecule was also observed in **14a**, albeit not bound to cesium (see Figure S3). Several factors presumably play a role for this stability. The carbanions of the tetramic acids are strongly stabilized by the three adjacent electron-withdrawing groups (one ketone carbonyl, one amide carbonyl, and one cyano group) and the cesium cation. Secondly, enhanced stability may also be attributed to the large size of the Cs^+ cation enabling the formation of polymeric architectures enjoying multiple bonding interactions (Figures S2, S4, and S6). Taken together, both factors contribute to the noteworthy stability of these unique cesium-based organometallics.[25] [Note: treatment with HCl breaks up the organometallic structures to give the originally desired tetramic acid.][26]

In summary, reported herein is the discovery of two succinct one-pot, two- and three-step synthetic routes that enable the preparation of libraries of tetramic acids and intriguingly two highly unique Cs^+-based organometallics with complex molecular architectures. Ugi/Dieckmann methodology enables access to products of generic structure **7** and, by taking advantage of the susceptibility of Ugi-derived cyclic imides to nucleophilic ring opening, affords a new avenue to further cesium-containing tetramic acids with organometallic character **14**. Noteworthy is the use of mild cesium carbonate to promote organometallic formation and the stability of the final products to air, moisture, and silica gel. Moreover, they are amenable to high-throughput production containing two potential points of diversification derived from the amine and isonitrile inputs of the Ugi reaction. As such, this should allow for fine tuning of molecular properties in a search for applications of these structures in material sciences. Relativistic DFT calculations on **14a** and **14b** revealed that the HOMO is largely centered on the carbanionic group, whereas the LUMO is localized on the phenyl acetamide group of the organic ligand for both systems; moreover, these systems present large HOMO–LUMO gaps of 2.40 eV and 2.41 eV, respectively. Energy decomposition analysis provides evidence of the strong ionic character for both compounds that increases with the electron–donor character of the tetramic acid substituent, which favors dipole formation (charge separation) and hence the ionic interaction. As perspective, computational results related to the substitution of the Cs^+ centers with isoelectronic La^{3+} and Th^{4+} suggest that the optimal covalent character of the ligand–metal interaction will be observed with Th^{4+} (further details can be found in SI, that is, Figure S7 and Tables S11–S13). As such, this user-friendly multicomponent reaction may thus be extendable to other isoelectronic metals (La^{3+} and Th^{4+}); noteworthy La^{3+} shows a far greater structural diversity of lanthanide-based organometallics than the Cs^+ cation.[27]

Hence, future studies in our laboratories will be aimed at MCR-based syntheses of organometallic compounds containing alternate cations and heterocycles, coupled with more extensive computational studies on alternate alkali metal substitutions. Examination of optical properties will also be conducted.

Acknowledgements

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Keywords: cascade reactions · Dieckmann condensation · multicomponent reactions · tetramic acids · Ugi reaction

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