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Two-Step Route to Diverse *N*-Functionalized Peptidomimetic-like Isatins through an Oxidation/Intramolecular Oxidative-Amidation Cascade of Ugi Azide and Ugi Three-Component Reaction Products

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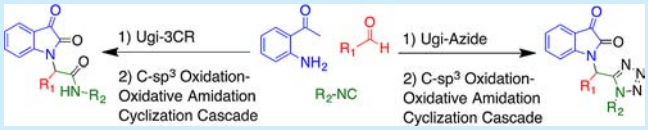
Supporting Information

ABSTRACT: Two-step methodology described herein showcases the first example of an oxidation/oxidative amidation cyclization cascade of MCR products toward diverse *N*-functionalized isatins. Products of both the Ugi 3CR and the Ugi azide reactions are oxidatively cyclized through a postcondensation process utilizing selenium dioxide. This methodology was found to be applicable for the generation of bis-peptidomimetic-like isatins containing multiple points of diversification.

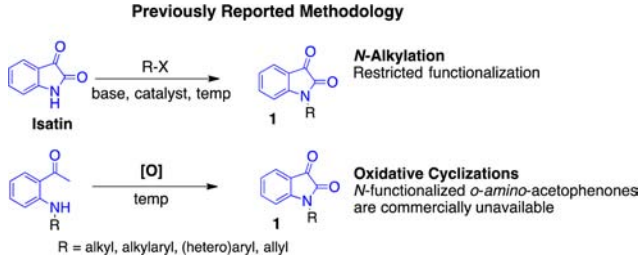


The colorful isatins are ubiquitous fundamental building blocks with diverse utility in material sciences, in synthetic chemistry, and recently, as biologically active small molecules. Examples of *N*-functionalized isatin-containing medicinally active compounds include CB2 inverse agonists,[1] the Src homology-2 domain containing protein tyrosine phosphatase (Shyp2) inhibitors,[2] noncovalent SARS corona virus 3C-like protease inhibitors,[3] caspase-3/7 inhibitors,[4] cytotoxic tubulin destabilizers,[5] and pan-antiangiogenic receptor tyrosine kinase inhibitors,[6] mostly reported in the academic arena. Moreover, there have been multiple successful efforts toward the syntheses of natural products containing isatins and structurally related oxindoles, notably the welwitindolinone series.[7]

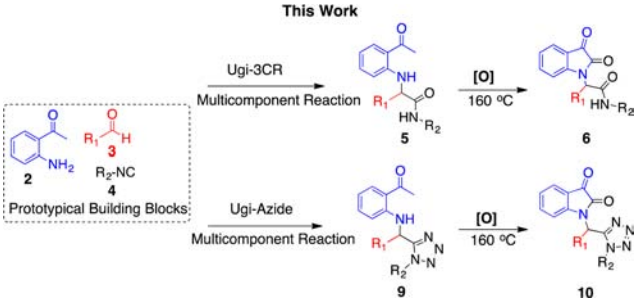
Interestingly, isatins are also absent motifs from currently approved small molecule therapeutics despite being highly utilized building blocks.[8] Reasons for this include lengthy synthetic procedures and limited access to diverse, commercially available *N*-substituted isatins with appropriate handles for diversification. These factors combined have rendered current isatin-forming methodology unsuitable for high-throughput synthetic efforts and library generation,[9] and therefore, concise routes to such species **1** (Scheme 1) are of high value. Existing protocols include alkylation of the ring nitrogen directly from isatin or modification of substituted *o*-aminoacetophenones.[10] The latter species require preparation in several steps and reported oxidants often result in undesired reaction with the aryl ring.[11]

This paper thus details a facile synthesis of isatins through a two-step process utilizing the Ugi-azide multicomponent reaction (MCR) or the Ugi three-component reaction (Ugi 3CR),[12,13] followed by an oxidation/intramolecular oxidative amidation process utilizing selenium dioxide (Scheme 2).

Scheme 1. Current Synthetic Methodology toward *N*-Functionalized Isatins



Scheme 2. Two-Step MCR/Oxidation−Intramolecular Oxidative Amidation Protocol



MCRs are inherently efficient, defined as reactions that afford products in one step derived from three or more starting materials. The work detailed herein exemplifies the increasing value and exploratory power[14] often witnessed through study of postcondensation modifications,[15] in this case, toward isatins that contain three points of diversification.

The journey toward this MCR oxidation/intramolecular oxidative amidation protocol was influenced by previous work

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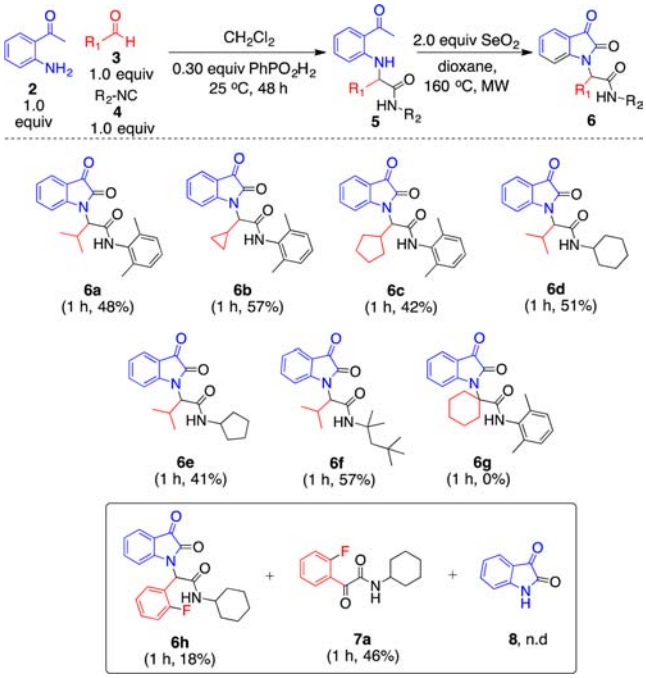
by our group on the oxidative amidation of glyoxals with secondary amines mediated by SeO_2 to afford α-ketoamides.[16]

Interestingly, successful conversion of the glyoxaldehyde to the desired α-keto amide during these studies was limited to secondary amines, and no conversion was observed with primary amines.[16] This phenomenon was subsequently observed by others with different oxidizing agents.[17]

As such, realizing that both the Ugi 3CR and the Ugi azide reactions afford secondary amines (**5** and **9**, respectively, Scheme 2), it was envisioned that a tandem MCR−oxidation−intramolecular oxidative amidation sequence to highly decorated isatins would be feasible.

Thus, initially employing *o*-amino acetophenone **2** in the Ugi-3CR with supporting reagents to afford **5** (Scheme 3),

Scheme 3. Ugi Three-Component Reactions of *o*-Aminoacetophenone, Aldehydes, And Isonitriles Followed by an Oxidation/Intramolecular Oxidative Amidation



followed by a SeO_2 driven one step oxidation to glyoxal and oxidative 5-*exo*-*trig* intramolecular amidation, enticingly proved fruitful, yielding the *N*-functionalized isatin **6a** (48% yield). The structure of **6a** was definitively confirmed by X-ray crystallography (Figure 1). Attempted optimization of this process through use of aqueous co-oxidants (H_2O_2 or TBHP) and catalytic SeO_2 yielded complex product mixtures. The scope of this MCR cascade sequence was thus examined for congeners of secondary amines, **5** and **9**, derived from the Ugi 3CR (Scheme 3) and Ugi azide MCRs (Scheme 4), respectively. (Note: this protocol effectively allows the synthesis of a variety of ring-locked tertiary amides from the secondary amine MCR product.)

The classical Ugi 3CR products (Scheme 3), derived from simple mixing of **2**, **3**, and **4**, with reaction driven by List's catalyst[13b] (phenylphosphinic acid), were obtained in good yields (**5**, 73−87% after purification through a silica plug). These highly decorated products generally underwent the subsequent SeO_2-mediated cascade in dioxane in good yield to afford **6a**−**f** (41−57%), proving compatible with functionality

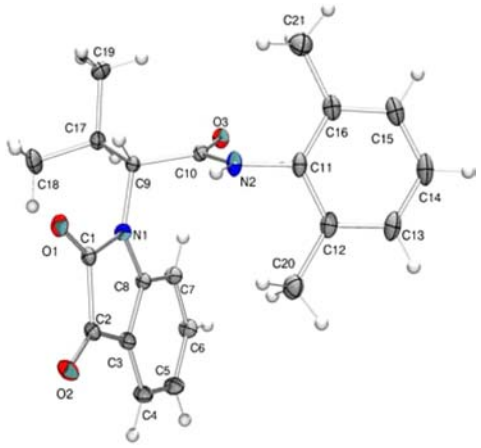
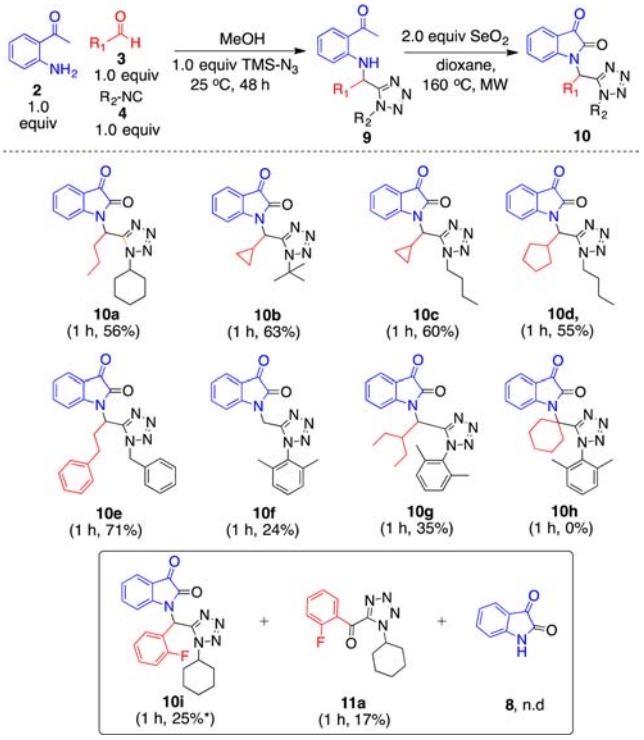


Figure 1. X-ray ORTEP diagram of **6a** with displacement ellipsoids at 50% probability.[18]

Scheme 4. Ugi Azide Reaction of *o*-Aminoacetophenone 1, Aldehydes 2, Isonitriles 3, and $TMSN_3$ Followed by an Oxidation/Intramolecular Oxidative Amidation



from a variety of aliphatic aldehydes and isonitriles. However, attempted isatin formation after utilizing a ketone (cyclohexanone) in the Ugi 3CR resulted in a complex mixture of products where **6g** was not detected by LC/MS. Although not confirmed, we believe the isatin **6g** may feasibly be formed as an unstable intermediate that then decomposes via an acid-catalyzed elimination of isatin **8** to afford unstable *N*-(2,6-dimethylphenyl)cyclohex-1-ene-1-carboxamide. The analogous aldehyde-derived congeners of **6g** have a less optimal spatial alignment of H atoms and isatin for elimination and hence do not deviate through this reaction path.

Intriguingly, use of an aromatic aldehyde afforded three products after the MCR and oxidation sequence was completed, the expected isatin **6h** (18% yield), the α-keto

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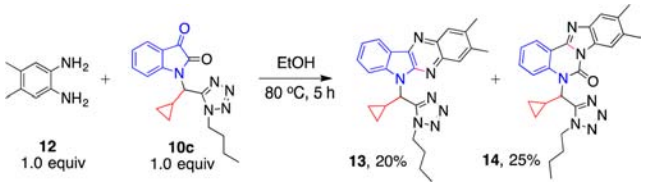
amide **7a** (46% yield), and isatin **8** (yield not determined). The formation of **7a** was unexpected and provides a new route to α-ketoamides, which is complementary to our previously published work where these key pharmacologically relevant motifs were produced through an oxidative amidation with only secondary amines.[16] This observation represents a very succinct and nonobvious route, through an additional oxidative deisatinylation step, to α-ketoamides, which at first glance may appear to be derived from primary amines. However, in reality, the sole nitrogen atom of **7a** is derived from the initial isonitrile reagent **3** in the MCR. It must be noted that this observation is not confined to *o*-fluoroaryls, and studies of this extension to the cascade reaction will be reported in due course.

The feasibility and scope of the same sequence was also evaluated with the Ugi-azide MCR, where reagents **2**, **3**, and **4** react with TMS-N_3, generating a secondary amine containing a 1,5-disubstituted tetrazole **10** (Scheme 4). The peptidomimetic nature of these tetrazoles as *cis*-amide bond surrogates[19] was thought to be intriguing as the completed two-step methodology affords congeners of **10**, which represent unique conformationally locked chemotypes, containing both a constrained *cis*- and *trans*-amide bond isostere.

Reactivity profiles tracked closely to those observed in the Ugi 3CR sequence (Scheme 3). Aliphatic aldehydes and a variety of isonitriles performed well in the MCR with a subsequent robust isatin-forming sequence to afford the desired isatins **10a**−**e**,**g** (Scheme 4) in good yield (35−71%). Encouragingly, for those looking to use these building blocks in medicinal chemistry campaigns, formaldehyde was also compatible with the two-step sequence, **10f** (24%). In analogous fashion to the Ugi 3CR/oxidative sequence (Scheme 3), cyclohexanone failed to afford the desired isatin. Moreover, previous findings with 2-fluorobenzaldehyde were replicated to afford the desired isatin **10i** in low yield (25%). Interestingly, the acyltetrazole bioisosteric side product **11a** (17%) of the α-ketoamide **7a** was also observed, resulting from an additional oxidative deisatinylation step. Indeed, acyltetrazoles are of high utility as building blocks for small molecule library generation.[20] (Note: multiple attempts to chromatographically separate **10i** from the precursor Ugi azide product failed, and the represented yield was determined by NMR.)

To demonstrate initial utility of these new chemotypes, the *N*-functionalized isatin **10c** was condensed with 4,5-dimethylphenylenediamine **12** in a similar fashion to work very recently reported by Mironov (Scheme 5).[21a] Two major products were

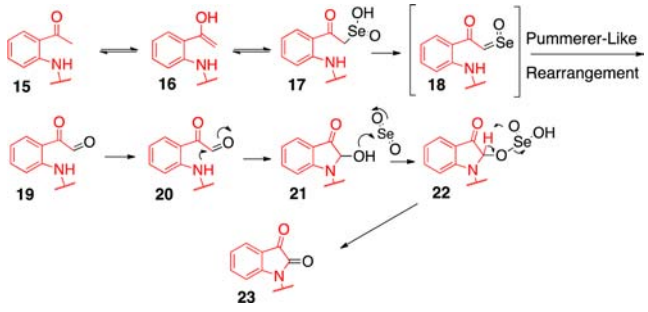
Scheme 5. Condensation of 10c toward Tetracyclic Chemotypes of *N*-Functionalized Isatin Scaffolds



obtained, the quinoxaline **13** (20% yield) and fused benzimidazole **14** (25% yield), where the remaining mass balance was accounted for by unreacted starting material **10c**. Mechanistically, formation of the latter product **14** is proposed to proceed through rearrangement of a spiro-indoline intermediate.[21b] The three-step route to these currently unknown *N*-functionalized tetracyclic chemotypes, composed of an MCR/oxidation/intramolecular oxidative amidation/condensation process, may find utility in DOS strategies.[22]

A proposed mechanism for the key step in the tandem MCR/cascades leading to isatins (Scheme 6) is in accordance

Scheme 6. Proposed Mechanism of the Oxidation/Intramolecular Oxidative Amidation



with Riley's seminal work[23] where selenium dioxide or selenious acid (H_2SeO_3) in aqueous media was reported to act as a stoichiometric oxidant to form intermediate glyoxal **19**. Subsequent mechanistic studies[24] on the conversion of methyl ketones to glyoxals solidified a now widely accepted mechanism that is proposed herein for the conversion of **15** to **19**. Thus, the in situ generated glyoxal is trapped by the secondary amine **20** to afford hemiaminal **21**, which is oxidized through a selenious acid intermediate **22**, leading to isatin **23.**

In conclusion, this work presents novel routes to highly functionalized isatins containing significant functionality amenable to rapid diversification, initially exemplified by the preparation of **13** and **14**. Both routes are highly concise, involving MCRs (the Ugi 3CR and $TMSN_3$ modified Ugi reactions, respectively) and subsequent SeO_2-mediated oxidation/intramolecular oxidative amidation methodologies affording products in a mere two functional operations. Intriguingly, transformations to side products **7a** and **11a** are being investigated further and represent "switchable reactions" where α-ketoamides and α-ketotetrazoles may be formed in only two steps through introduction of a sequence-ending oxidative deisatinylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02383.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new isatin compounds (PDF)
X-ray data for **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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