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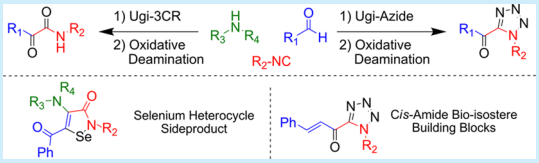
Oxidative Deaminations and Deisatinylations of Ugi-Azide and Ugi-3CR Products: A Two-Step MCR-Oxidation Protocol toward Functionalized α-Ketoamides and α-Ketotetrazoles

Christopher Foley,[†] Arthur Shaw,[‡] and Christopher Hulme*[,†,‡]

[†]Department of Chemistry and Biochemistry, College of Science, and [‡]Department of Pharmacology and Toxicology, College of Pharmacy, The University of Arizona, Tucson, Arizona 85721, United States

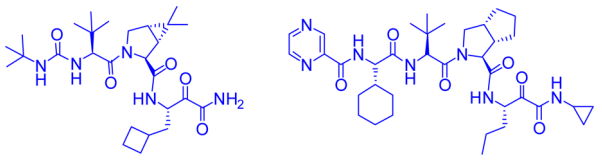
Supporting Information

ABSTRACT: A new postcondensation multicomponent reaction (MCR) methodology, comprising oxidative deaminations enabling access to multiple privileged carbonyl-containing scaffolds in two steps, is described. These protocols allow facile access to functionalized α-ketoamide and α-ketotetrazole small-molecule peptidomimetic-like building blocks from prototypical synthons with two points of diversity. Incorporation of chalcone and alkynyl moieties with further ring-forming reactions enables access to additional novel heterocyclic ring systems, including a unique and potentially highly pharmacologically relevant scaffold, a 1,2-selenazol-3(2*H*)-one.



α-Ketoamides are quintessential privileged motifs found in many natural products and pharmaceuticals. Reminiscent of endogenous peptide bonds, the α-ketoamide motif has demonstrated significant utility as a peptidomimetic transition state inhibitor, as exemplified by Boceprevir and Telaprevir, agents effective against hepatitis C virus-NS3-4A serine protease[1] (Scheme 1). α-Ketoamide constructs have been extensively developed as histone deacetylase,[2] peptidase,[3] protease,[4] peptidyl proline isomerase,[5] lipase,[6] and hydrolase inhibitors.[7] Additionally, α-ketoamides are embedded in many building blocks, notably the versatile isatins.

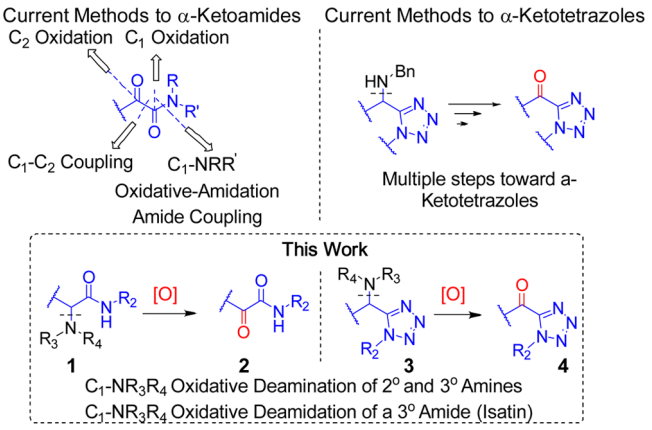
Scheme 1. Pharmaceutically Important α-Ketoamides



Diverse synthetic methods developed toward α-ketoamides (Scheme 2) include examples of C_1 oxidation, C_2 oxidation, C_1−NHRR formation by oxidative amidation, amide coupling, and C_1−C_2 coupling.[8] Although many routes to α-ketoamides are currently available, each suffers from innate methodological limitations, such as poor general substrate diversity, lack of commercially available starting materials, and the need for main group and precious metals. Moreover, current synthetic protocols that access bioisosteres of α-ketoamides, namely, α-ketotetrazoles, are arduous with limited scope, being incompatible with the demands of production scale high-throughput library generation.[9]

In previous studies toward N-functionalized peptidomimetic-like isatins,[10] we serendipitously discovered a sequence-ending oxidative deisatinylation reaction, effectively an oxidative deamidation reaction of a tertiary amide (isatin).

Scheme 2. Generic Routes to α-Ketoamides and α-Ketotetrazoles



We rationalized that if an oxidative deisatinylation (deamidation) reaction could occur with isatinic tertiary amides, then an analogous transformation was likely feasible with secondary and tertiary amines through a similar iminium ion intermediate in an oxidative deamination. Initially, we focused our studies on using aniline as the primary amine input in both the Ugi-azide and Ugi-3CR,[11,12] where MCR products **1** and **3** act as oxidizable surrogates to generate ketones **2** and **4**.

The methodology described herein is compatible for the conversions of secondary and tertiary amine MCR products to ketones. Interestingly, despite transamination methodology being a crucial part of biological processes in the conversion

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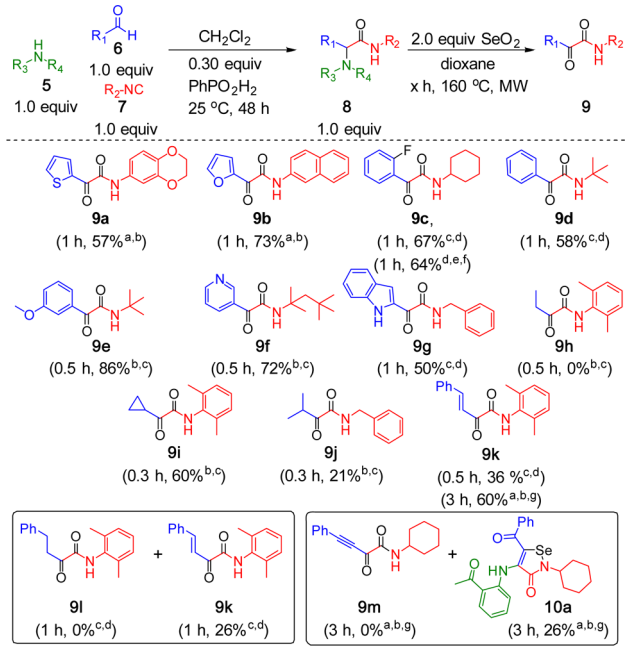
of amino acids to keto acids, few laboratory methods exist for the high-throughput conversion of amines to ketones. Furthermore, numerous C−N bond cleavage/insertion strategies have been developed.[13] However, general methodology for the oxidative deamination of *sec*-secondary amines, *sec*-tertiary amines, and *sec*-tertiary amides to ketones is seemingly nonexistent in the literature. Examples of organo-catalyst-mediated oxidative deamination reactions have been reported with primary amines.[14] Some related reactions of free amines and SeO_2 include nitrone formation from reaction of piperidine and selenium dioxide[15] as well as nitrosoarenes and diazo compounds from reaction of aniline and SeO_2/H_2O_2.[16]

Our preliminary investigations began with the oxidative deisatinylation reaction, which afforded the general structures, α-ketoamides **2** and α-ketotetrazoles **4**, when aromatic aldehydes were employed. Thiophene and furan aldehydes (Scheme 3) were run in conjunction with *o*-aminoacetophenone

Scheme 3. Multicomponent U-3CR of Amines, Aldehydes, and Isonitriles Proceeded by Oxidative Deamination



[a]*o*-Amino acetophenone used in the MCR. [b]Dry dioxane. [c]Aniline used in the MCR. [d]Dioxane, H_2O 9:1. [e]Piperidine used in the MCR. [f]Percent yield based on recovery of starting material. [g]3 h, 100 °C (sandbath).

in the phenylphosphinic acid catalyzed Ugi-3CR to afford condensation products **8a** and **8b**, which were then oxidatively cyclized to an isatin and in the same pot deisatinylated, all by treatment with selenium dioxide, to give **9a** (57%) and **9b** (73%) in good yield. These yields compared favorably to our previously reported example **9c** (46% yield)[10] and established that this may indeed be a general transformation.

We replaced *o*-aminoacetophenone **5** through an analogous oxidative deamination with cheaper and more atom-economical amines, thus avoiding an intermediary isatin-forming step (Scheme 3).[16] In a head-to-head comparison, **9c** was prepared in 67% yield (aniline = amine input in 3CR) and 64% yield (piperidine = amine input in 3CR), an improvement of 20% over the previously nominally reported deisatinylation process.[10] The scope of methodology was further explored with aniline proving compatible with benzaldehydes to give **9d** (58%) and **9e** (86%). Heteroaromatic aldehydes (3-pyridylaldehyde and 2-indole aldehyde) afforded corresponding α-ketoamides **9f** and **9g** in 72 and 50% yields, respectively. Aliphatic aldehydes, specifically propionaldehyde, proved more temperamental, with **9h** not detected in a complex mixture. However, cyclopropylaldehyde and isobutyraldehyde afforded **9i** and **9j**, albeit in moderate to poor yields (60 and 21%, respectively).

Moreover, when aniline was replaced by *o*-aminoacetophenone coupled with heating in a sandbath (3 h, 100 °C), **8k** was oxidatively deisatinylated to **9k** with cleaner conversion and in higher yield (60%). We found this result very promising as it demonstrated the process could clearly be optimized on an individual reaction basis for more challenging and highly decorated Ugi-3CR reagents.

Employing phenylpropionaldehyde-derived **8l** in the Ugi-3CR/oxidative deamination sequence afforded further oxidized conjugated product **9k** (26%), as opposed to **9l**, derived from an oxidative deamination/oxidative dehydrogenation sequence.[17]

Conversion of **8m** to ynamide derivative **9m** proved stubborn, despite changes in reaction temperature and the amine. Only upon heating **8m** prepared from *o*-aminoacetophenone (3 h, sandbath, 100 °C) was a main product fraction obtained. X-ray crystallography of the product (Figure 1) led to the discovery of

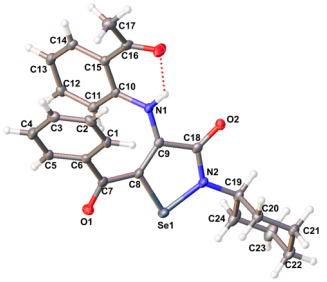
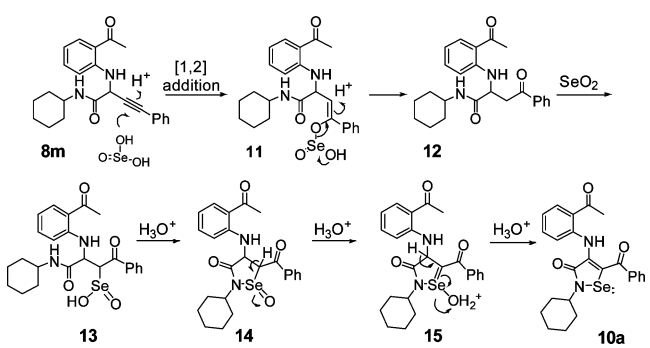


Figure 1. ORTEP diagram of **10a** with displacement ellipsoids at 50% probability.[18]

the peculiar monocyclic selenium heterocycle **10a**, a 1,2-selenazol-3(2*H*)-one, whose unsaturated isomer has not yet been reported. In regard to pharmacological relevance, it must be noted that the related bicyclic benzo[*d*][1,2]selenazol-3(2*H*)-one system is observed in Ebselen, a potent scavenger of H_2O_2, which is being investigated for a variety of indications, including stroke and bipolar disorder.[19]

Mechanistically, we propose an unusual intermolecular [1,2] addition of selenious acid (H_2SeO_3) to the alkyne **8m** to afford the selenite ester **11** (Scheme 4), which is followed by

Scheme 4. Proposed N−Se Selenocyclization Mechanism



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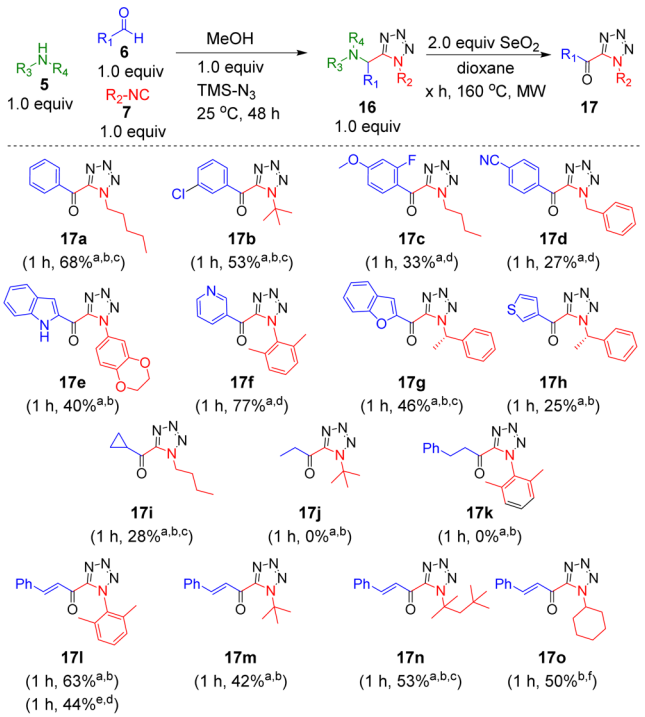
decomposition to ketone **12**. The enol tautomer of **12** further reacts with SeO_2 to give **13**, which undergoes an intramolecular N−Se bond-forming cyclization to **14**. [1,3]-Hydride shift to **15** and subsequent loss of water delivers **10a**, a 1,2-selenazol-3(2*H*)-one.

Analogously, we also obtained dual functionalized *α*-ketotetrazole compounds in two steps using our MCR-oxidative deamination approach with the Ugi-azide reaction (Scheme 5).

Scheme 5. Ugi-Azide Reaction of Amines, Aldehydes, and Isonitriles Proceeded by Oxidative Deamination



[a]Aniline used in the MCR. [b]Dioxane, H_2O 9:1. [c]Percent yield based on recovery of starting material. [d]Dry dioxane. [e]*o*-Aminoacetophenone used in the MCR. [f]Benzylamine used in the MCR.

As 1,5-disubstituted tetrazole products are *cis*-amide isosteres,[20] acyl tetrazoles have been utilized in many discovery campaigns as building blocks for small-molecule library generation.[21]

From the aniline-derived MCR products **16a**−**16d** that utilized aromatic aldehydes in the Ugi-azide reaction, **17a**−**17d** were produced in moderate yields (27−68%). Other heterocyclic variants, indole **17e**, pyridine **17f**, benzofuran **17g**, and thiophene **17h**, performed moderately well (25−77% yield). Cyclopropyl variant **17i** was accessible in only moderate yield (28%), and propionaldehyde and phenylpropionaldehyde congeners (**17j**,**k**) proved inaccessible.

Fortunately, *trans*-cinnamaldehyde-derived tetrazole chalcones **17l**−**17o** were readily produced through the use of either aniline, *o*-aminoacetophenone, or benzylamine in moderate yields (42−63%). The latter work showcases the first synthesis of the tetrazole chalcone moiety (definitively confirmed by X-ray crystallography, Figure 2), which proves to be an extremely valuable building block for further elaboration (Scheme 6).

Tetrazole building blocks **17l** and **17m** were employed in various chalcone reactions[23] (Scheme 6). Compounds **19**, **21**, and **23** were produced through 1,4-conjugate addition cyclizations of chalcones **17l** and **17m**. 1*H*-Pyrazolo[3,4-*b*]pyridine **19** (52% yield) proceeded through a 1,4-addition/

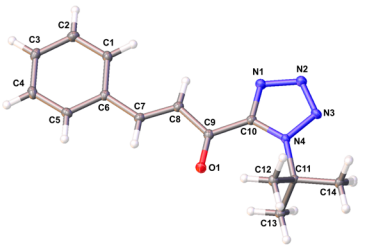
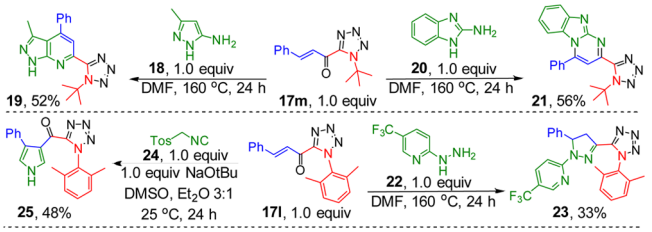


Figure 2. ORTEP diagram of **17m** with displacement ellipsoids at 50% probability.[22]

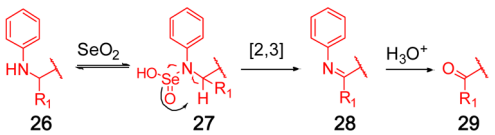
Scheme 6. Applications of Tetrazole Chalcones To Produce Diverse C_5 Arylated Tetrazole Chemotypes



electrophilic aromatic substitution cascade[24] of **17m** and **18**. Benzimidazolopyridine **21** (56% yield) was produced via 1,4-addition/imine condensation of **20** and **17m**.[25] 4,5-Dihydropyrazole **23** (33% yield) was also accessible by condensing pyridinyl hydrazine **22** with **17l**.[26] In addition, an analogous 3-acyl pyrrole, **25**, was prepared through a Tosmic [3 + 2] cycloaddition[27] (48% yield) through reaction of **17l** and 4-toluenesulfonylmethylisocyanide **24**, which may be viewed as a disconnected "union" of both the Ugi-azide reaction and Van Leusen's pyrrole synthesis. Chemical manipulation of these tetrazole chalcone synthons represents a path toward multiple privileged nitrogen-containing heterocyclic compounds with an embedded *cis*-amide isostere.

Mechanistically, oxidative deamination seems to occur when R_1 is aryl, arylallyl, or dialkyl (Scheme 7). Conversion of **26** to

Scheme 7. Proposed Mechanistic Pathway



27 proceeds through N-selenyation followed by a [2,3]-sigmatropic rearrangement of **27** to form imine **28**, which hydrolyzes to form carbonyl **29**. However, when the R_1 substituent of tetrazole congener **26** is a linear alkane, lack of electron density favors other pathways over C−N oxidation to the imine.

In summary, routes to *α*-ketoamides and *α*-ketotetrazoles are completed in two steps from MCR-oxidation methodology, the latter driven by selenium dioxide. In exploring the scope of these succinct chemistries, green shoots have been unearthed delivering undocumented access to 1,2-selenazol-3(2H)-ones, the subject matter of ongoing studies. Furthermore, the utility of undocumented chalcone tetrazoles and their affiliated chemistry reveals rich new veins of accessible molecular diversity.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00710.

Experimental procedures, characterization data, ^{1}H, ^{13}C NMR spectra for new α-ketoamide and α-ketotetrazole compounds (PDF)
X-ray data for **10a** (CIF)
X-ray data for **17m** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hulme@pharmacy.arizona.edu.

ORCID

Christopher Foley: 0000-0002-9028-5841
Christopher Hulme: 0000-0001-6602-9613

Notes

The authors declare no competing financial interest.

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