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Aza-Riley Oxidation of Ugi-Azide and Ugi-3CR Products toward Vicinal Tricarbonyl Amides: Two-Step MCR-Oxidation Methodology Accessing Functionalized α,β-Diketoamides and α,β-Diketotetrazoles

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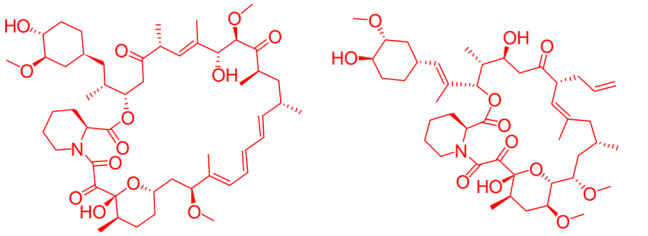
Supporting Information

ABSTRACT: Direct oxidative deamination of glyoxal-derived Ugi-azide and Ugi three-component reaction products readily affords vicinal tricarbonyls (α,β-diketoamides) and α,β-diketotetrazoles with two diversity elements. This significant extension of our previously described multicomponent reaction−oxidative deamination methodology is proposed to proceed through a mechanistically distinct SeO_2-mediated C−N oxidation derived from an active enol of α-amino-β-ketone systems, effectively an aza-Riley oxidation. This methodology accesses diverse VTC systems from prototypical amines, glyoxaldehydes, and isocyanide building blocks in a mere two steps.

Vicinal tricarbonyls (VTCs) are structures of paramount importance as building blocks and often behave as unusual turn-promoting structural elements in macrolide natural products.[1] Particularly noteworthy are vicinal tricarbonyl amides (VTAs, α,β-diketoamides) found in the biologically active natural product macrolides YM47141-2,[2] FK-506,[3] FR-900525,[4] and rapamycin.[5,6] Rapamycin and tacrolimus (FK-506) are venerable FDA-approved immunosuppressive agents that exist in a hemiketal form (Scheme 1). Additionally, the electrophilic polycarbonyl framework can be seen foundationally embedded in many heterocyclic structures, accessible through nucleophilic additions to the VTC system. Privileged heterocycles[7] accessible through such additions are exemplified by pyrroles, imidazoles, isoquinolines, quinoxalines, and furans.[8−11]

Scheme 1. Natural Product Macrolides Embedded with Vicinal Tricarbonyl Amides

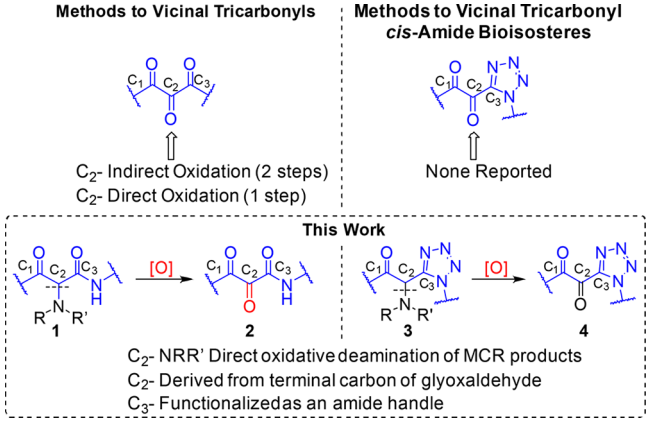


Rapamycin (*Rapamune*, Pfizer) **Tacrolimus** (*Protopic*, Astellas Pharma)

Notable examples of VTCs as building blocks in the total synthesis of natural products[12] include cladoniamide F/G,[13] papaveraldine, polstatin, prodigiosin,[14] and vasicine.[15] Perhaps even more interesting, cyclic VTC ninhydrin (indane-1,2,3-trione) and acyclic VTCs have been used as carbonyl sources in multicomponent reactions (MCRs).[16−18] Two approaches toward vicinal tricarbonyls predominate: direct or indirect oxidation of β-diketones. The most common is indirect oxidation of β-diketones by Regitz diazo transfer/oxidation with *t*-BuOCl or DMDO.[19] One step direct oxidation is more attractive, of which previous methods involving organoiodine-chemistry have recently been improved upon.[20,21]

Ultimately, these protocols rely on an oxidative reaction involving a (modified) central C_2 methylene of a β-diketone, typically in the form of β-ketoesters and β-ketoamides (Scheme 2). The former are readily prepared by the Claisen reaction.[22] However, diverse sets of β-ketoamides are difficult to prepare,

Scheme 2. Routes to Vicinal Tricarbonyls



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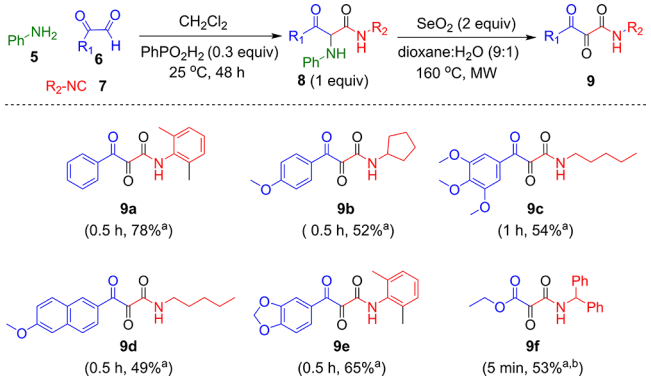
with recent methodology offering some improvement.[23] Unfortunately, in both cases β-diketone syntheses require catalysts or metal reagents and are restricted by a lack of diversity elements.

As such, we rationalized that our previous postcondensation oxidative deamination methodology,[24] which employed aldehydes, could be utilized analogously on glyoxal derived α-amino-β-ketoamides **1** and α-amino-β-ketotetrazoles **3**, affording α,β-diketoamides **2** and α,β-diketotetrazoles **4** (Scheme 2).

Fundamentally, the key C_2 center is derived from the terminal aldehydic carbon of the glyoxal, and the C_3 carbonyl is generated as a functionalized secondary amide, derived from the isocyanide diversity reagent. Interestingly, to the best of our knowledge, MCR products have never been rationally utilized as *pro*-VTC β-diketone synthons. As such, this work provides a substantial improvement on current direct oxidation methodology of β-keto-amides as the challenges associated with their syntheses and the restriction in diversity elements are negated due to the wide availability of diverse glyoxals and isocyanides; notably, the latter have high compatibility with MCR methodology.[25]

A collection of secondary-amide-containing α,β-diketoamide building blocks (**9**, Scheme 3) was produced by direct oxidative

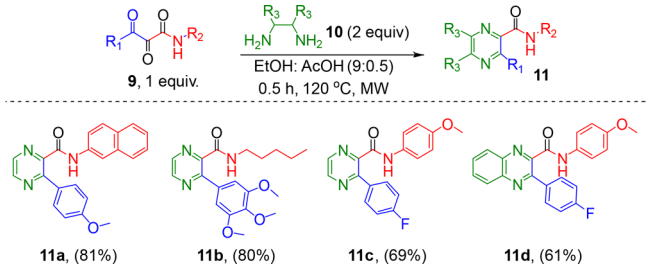
Scheme 3. Ugi-3CR of Amines, Glyoxals, and Isonitriles by Oxidative Deamination



[a]Aniline used in the initial MCR. [b]Anhydrous dioxane used.

deamination of α-amino-β-ketoamide products **8** of the Ugi-3CR[18] derived from the phenylphosphinic acid catalyzed condensation of aniline, **5**, glyoxals **6**, and isocyanides **7**. The oxidative deamination of the corresponding Ugi-3CR products **8a–f** [2 equiv of SeO_2, dioxane/H_2O (9:1), microwave 160 °C, 5 min to 1 h] ultimately afforded products with a variety of aryl groups **9a–c**, a naphthalene **9d**, and 3,4-(methylenedioxy)-benzene **9e**, coupled with examples of aromatic and aliphatic functionality at R_2 in good yield (49–78%). The related formation of oxomalonamide **9f** was also feasible (53%). Attempts to optimize yields by replacement of aniline **5** with piperidine, pyrrolidine, or *o*-aminoacetophenone in the MCR proved detrimental, and that process was not investigated further. Note that the purified α,β-diketoamides **9a–f** were characterized as a mixture of the tricarbonyl ketone and hydrate (i.e., a *gem*-diol), as is commonly observed with this functional group. To show utility as building blocks to access further diversity,[26] pyrazines **11a–c** and quinoxaline **11d** were produced by condensation of ethylenediamines **10** (2 equiv) with the corresponding α,β-diketoamides **9** by heating at 120 °C for 0.5 h in EtOH/AcOH (ratio 9:0.5 v/v) under microwave irradiation (Scheme 4) (61–81% yield).

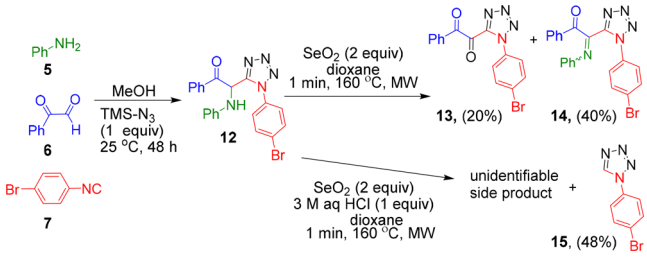
Scheme 4. Condensations of Vicinal Tricarbonyls



Satisfied with these results, further study of the oxidative deamination methodology was directed toward unreported α,β-diketotetrazoles. Containing a 1,5-disubstituted tetrazole, these VTC analogues were proposed to be potential *cis*-amide bioisosteres[27] of α,β-diketoamides and, thus, potentially valuable electrophilic tetrazole building blocks.[28]

The Ugi-azide reaction proceeded smoothly with the amine **5**, glyoxal **6**, and isocyanide **7** (stoichiometry 1:1:1) to afford the α-amino-β-ketotetrazole **12** (Scheme 5). Interestingly,

Scheme 5. Ugi-Azide Reaction of Amines, Glyoxals, and Isonitriles Proceded by Oxidative Deamination



initial oxidative deamination attempts on **12** under similar conditions to those employed to generate α,β-diketoamides **9** (60 min, 160 °C, MW) produced none of the desired α,β-diketotetrazole **13**. However, reducing the reaction time from 1 h to 1 min afforded the desired product **13** (20% yield) and its imine congener **14** (40% yield). Attempts to convert the imine **14** to **13** in situ with addition of 3 M aqueous HCl to the reaction mixture failed to garner **13** yet surprisingly afforded 1-(4-bromophenyl)tetrazole **15** (48%, yield) and an unidentifiable side product (Scheme 5).

To circumvent formation of the stable imine **14**, *N*-methylaniline and piperidine were used as 2° amine inputs **16** in the Ugi-azide MCR. Subsequently, optimization of the temperature and reaction time of the oxidative deamination step on the 3° amine **17** (140 or 150 °C, 5 min) afforded a collection of α,β-diketotetrazoles **18a–h** (Scheme 6) with good reaction scope and yields. Products were prepared from a variety of isocyanides and aryl glyoxals **18a–g** (30–74% yield) or ethyl glyoxylate **18h** (78% yield).

Encouragingly, the protocol was amenable to convertible isocyanides, which feasibly will allow access to free tetrazoles upon cleavage of the isocyanide substituent.[25] A noteworthy example is the α,β-diketotetrazole **18h**, which may be viewed as the tetrazole isologue of ethyl benzoyl formate and *cis*-amide bioisostere of oxomalonamide. Unfortunately, access to the pyruvaldehyde-derived **18i** proved incompatible with these

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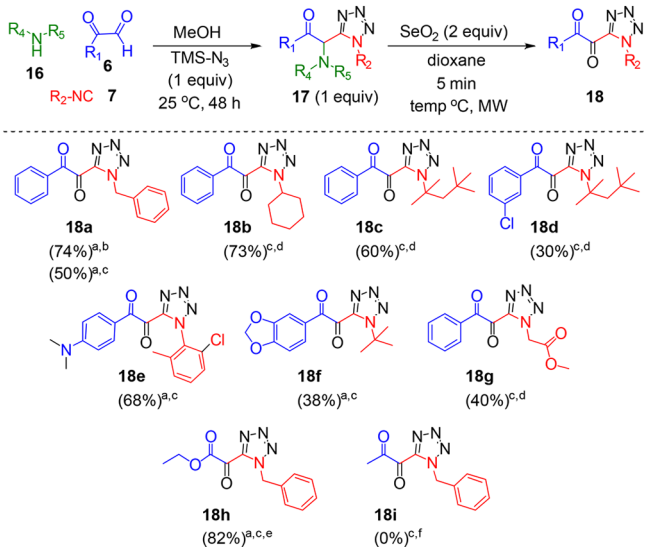
Scheme 6. Ugi-Azide Reaction of Amines, Glyoxals, and Isonitriles by Oxidative Deamination

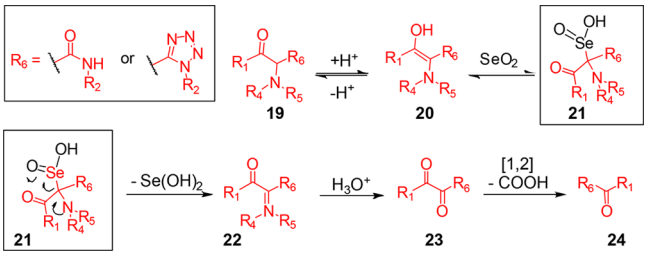


[a]5 min, 150 °C, [b]*N*-Methylaniline used in the initial MCR. [c]Piperidine used in the initial MCR. [d]5 min, 140 °C. [e]Percent yield based on recovery of starting material. [f]1 min, 140 °C.

reaction conditions. No starting material was recovered, and the only identified product was the N_1-benzyl tetrazole analogue of **15**.

Mechanistically, we propose the reactivity of these *α*-amino-*β*-ketoamide systems with SeO_2 at elevated temperatures follows what could be called an aza-Riley oxidation. In previous work, we described oxidative deamination of *α*-amino amides mediated by [2,3]-sigmatropic rearrangement of a penultimate *N*-selenamidate.[24] Indeed, early studies of SeO_2 mediated *α*-oxidations of carbonyls,[29] alongside a pK_a analysis of the *α*-hydrogens of these respective systems indicates that *α*-amino-*β*-ketoamides and *α*-amino-*β*-ketotetrazoles **19** can form enol **20** and then react which SeO_2, generating selenohemiaminal **21** (Scheme 7). Note that 2 equiv of SeO_2 are required as incomplete conversion and isolation of imines are observed when 1 equiv is used.

Scheme 7. Proposed Mechanism for Aza-Riley Oxidation of *α*-Amino *β*-Ketones



We believe that this enolization-mediated oxidation pathway does not seem to occur with *α*-amino amides as previously reported due to their lack of acidic *α*-hydrogens.

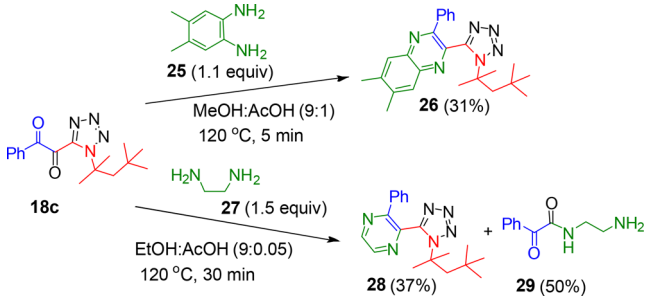
Selenohemiaminal **21** is then unable to undergo the traditional Riley oxidation pathway via a Pummerer-like rearrangement[30] to the corresponding ketone due to a lack of available *ipso* hydrogens. Instead, **21** is oxidized to iminium species **22** via elimination of selanediol, which is then hydrolyzed to *α*,*β*-diketoamide **23**. In the case of *α*,*β*-diketotetrazole congeners of **23** (**18a**–**18h**), upon prolonged heating we have also observed the benzilic acid rearrangement[31] with loss of formic acid to form *α*-ketotetrazoles **24**. The previous observation of 1-(4-bromophenyl)tetrazole **15**, likely originates from a nonspecific addition–elimination pathway due to the stability of the substituted tetrazole nucleus as a leaving group. These are observed as common major side products upon prolonged heating. X-ray crystallography of **18f** (see the Supporting Information) supports our claims regarding the unstable nature of the *α*,*β*-diketotetrazole systems under the conditions employed. The O_3–C_8–C_9–O_4 torsion angle is ~90° (92.09°), while the bond angles at C_8 and C_9 are close to those typical for sp_2 hybridization.

Hence, the *π*-system between C_8 and C_9 is broken, leading to an elongated C_8–C_9 bond (1.543 Å). Indeed, the torsion angles, bond lengths, and perpendicularity of both halves of each carbonyl system are nearly identical to that seen in the 1,2-diketone benzil.[32] Such 1,2-diketone character might further support our proposed mechanisms of rapid conversion to observed decomposition side-products.

Indeed, in comparison to X-ray structures of other *α*,*β*-diketoamides,[1,21] the *α*,*β*-diketotetrazoles do not appear to show exact structural bioisosterism. However, *α*,*β*-diketotetrazoles do appear to behave analogously to *α*,*β*-diketoamides in carbonyl addition reactions and ultimately produce bioisosteric products, although they are much more reactive than the corresponding *α*,*β*-diketoamides in both their synthetic procurement and synthetic utilization.

To demonstrate utility, we employed straightforward 1,2-dicarbonyl chemistry (Scheme 8). Thus, condensation of **18c**

Scheme 8. Condensations of *α*,*β*-Diketotetrazoles



with 4,5-dimethylphenylenediamine **25** in methanol/acetic acid promoted by microwave irradiation followed by direct crystallization from the reaction mixture produced 2-tetrazoylquinoxaline **26** (31% yield). However, condensation of **18c** with 1,2-ethylenediamine **27** afforded the 2-tetrazolylpyrazine **28** (37%) and the *α*-ketoamide **29** (50%), respectively, demonstrating that *α*,*β*-diketotetrazoles can function as acylating agents analogous to ethyl benzoyl formate in the synthesis of *α*-ketoamides. Although not directly competitive with many of the methods to synthesize *α*-ketoamides,[24,33] optimization of conditions will allow for the synthesis of other challenging *N*-bifunctional *α*-ketoamide analogues of **29**.

In summary, we have revealed an appealing and highly concise route to vicinal tricarbonyl amides containing two points of embedded diversity. The method improves upon existing routes in its simplicity while offering the ability to rapidly assemble collections of a fundamental key building

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block for further diversification. Moreover, we have reported the first route to unique VTA *pro*-bioisosteric building blocks, α,β-diketotetrazoles, which display interesting geometry and reactivity, worthy of further investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03977.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1554390 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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