Possibility of a non-amino acid pathway in the biosynthesis of marine-derived oxazoles†

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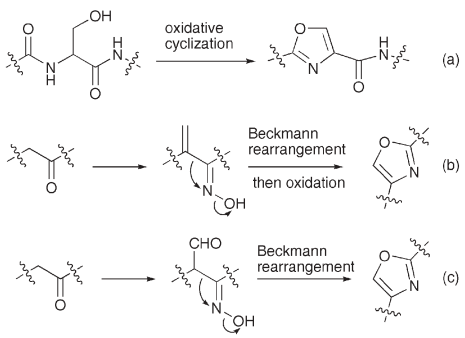
A novel avenue for oxazoles *via* Beckmann rearrangement of α-formyl ketoxime dimethyl acetals is described that indicates the possibility of a non-amino acid biosynthetic pathway in marine natural products.

Oxazoles are widely present in biologically important natural products.[1] These oxazole rings have been believed to be biosynthesized from amino acids (Scheme 1, eqn (a)).[2] Indeed, the oxazoles in natural products such as micronicin[3] and epothilone D[4] have been demonstrated to be of amino acid origin. Oxazole biosynthesis in marine natural products such as calyculins,[5] ulapualides,[6] mycalolide,[7] and phorboxazole[8] however, has remained elusive to date.

For example, the oxazole ring in calyculin is apparently located in the interior of a polyketide-derived carbon chain (Fig. 1). It would be difficult to argue that the oxazoles of this class were biosynthesized from amino acids.

Moore[9] and our group[10] independently suggested the possibility of non-amino acid biosynthetic pathways from polyketide chains to oxazoles, where Beckmann rearrangements of α,β-unsaturated oximes or α-formyl ketoximes (Scheme 1, eqn (b), (c)) are the key steps. Unfortunately, both of these proposals have been completely overlooked for more than a decade, and they have not yet been examined experimentally. Although these two proposals are similar, they differ significantly in terms of the oxidation stages of the rearrangement precursors. It remains unclear whether or not these transformations could be achieved in a flask. Here, we describe the novel transformation of α-formyl ketoxime dimethyl acetal to oxazole *via* Beckmann rearrangement, which is in accordance with the proposals regarding marine oxazole biogenesis.



Scheme 1 Proposed biosynthetic pathways to marine oxazoles; (a) oxidative cyclization of serine-containing poptides,[2] (b) Beckmann rearrangement of α,β-unsaturated oximes followed by oxidation,[9] (c) Beckmann rearrangement of α-formyl ketoxime.[10]

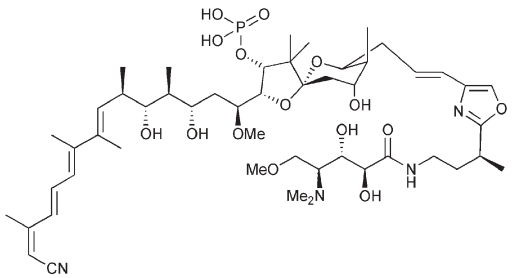
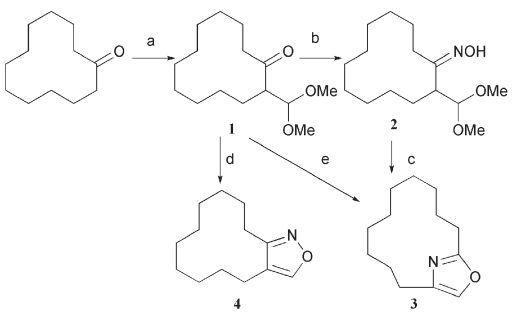


Fig. 1 Calyculin A; an oxazole-containing marine natural product.

Instead of utilizing α-formyl ketoximes as the rearrangement precursors, we chose the corresponding dimethyl acetals as stable substrates. Treatment of cyclododecanone with trimethyl orthoformate and $BF_3{\cdot}OEt_2$,[11] followed by oxime formation gave α-formyl ketoxime dimethyl acetal **2** as the single geometric isomer (Scheme 2).

After an extensive investigation (fuming H_2SO_4–toluene, $POCl_3$, $SOCl_2$, P_2O_5, MsCl–Et_3N *etc.*), we were delighted to find that the



Scheme 2 Reagents and conditions: (a) $HC(OMe)_3$ (2 equiv.), $BF_3{\cdot}OEt_2$ (2 equiv.), *i*-Pr_2NEt (3 equiv.), CH_2Cl_2, −78 °C, 2 h, quant.; (b) $HONH_2{\cdot}HCl$ (2 equiv.), pyridine, 50 °C, overnight, 81%; (c) polyphosphoric acid, toluene, reflux, overnight, quant.; (d) $HONH_2{\cdot}HCl$ (2 equiv.), toluene, reflux, 2 h, and then polyphosphoric acid, dioxane, reflux, overnight, 92%; (e) $HONH_2{\cdot}HCl$ (2 equiv.), toluene, reflux, 1 day, and then polyphosphoric acid, toluene, reflux, 4 h, 46%.

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† Electronic supplementary information (ESI) available: Typical experimental procedure for oxazoles, and NMR spectra of **1–4**. See DOI: 10.1039/b517149k

Beckmann rearrangement of oxime **2** indeed occurred by heating the sample with polyphosphoric acid in toluene, and the reaction intermediates subsequently cyclized to furnish oxazole **3**[12] as the sole product. A one-pot oxazole synthesis was also investigated without isolation of oxime intermediates. Thus, ketone **1** was heated with $HONH_2$·HCl in refluxing toluene for 1 day, and was subsequently treated with polyphosphoric acid to give oxazole **3** in 46% yield. The choice of solvents was shown to have a remarkable effect on this transformation and therefore the use of dioxane under otherwise similar conditions did not give oxazole **3**, but instead isoxazole **4**[12] in 92% yield. The high isoxazole selectivity might be attributed to the favorable geometry of intermediate oxime in dioxane solvent. However, we could not determine the geometric ratio, due to the rapid cyclization of transient oxime to isoxazole.

Similar Beckmann rearrangements worked for oximes with an 8-membered ring, as well as for those with larger membered rings (entries 3 and 4, Table 1). However, oximes with 6-membered or 7-membered rings gave isoxazoles. It is likely that in the latter cases, the ring strain in the course of Beckmann rearrangement prohibited oxazole formation (entries 1 and 2).

The scope of this reaction is not limited to cyclic compounds. Dialkyl-substituted oxime **8** (2.4 : 1 mixture of oxime diastereomers) also furnished the corresponding oxazole (entry 5).

In the Beckmann rearrangement, the group that migrates is the group trans to the OH moiety of the oxime. It is noteworthy that the geometric mixture of **8** gave oxazole **14** in 97% yield. The fact indicates an existence of *E*/*Z* isomerization of **8** before the rearrangement, and therefore the initial geometry of oxime would not be the determinant factor of oxazole/isoxazole selectivity.

The ketones (**9**,**10**) with aromatic substituents at the α or β position could also be converted to oxazoles (entries 7 and 8). These contiguous aromatic oxazole sequences are of interest with respect to naturally occurring polyoxazole compounds (*e.g.*, mycalolides).

The elucidation of biosynthetic pathways for marine oxazoles remains difficult to achieve. However, if actual producers of these compounds are symbiotic microalga or bacteria, the isolation and cultivation of these symbiotic microorganisms would enable the performance of labeling experiments.[13] We are currently screening the extracts of marine organisms that catalyze this type of Beckmann rearrangement. We expect that enzymes that phosphorylate or sulfate the oxime hydroxyl group are likely to be involved in non-amino acid oxazole biosynthesis.[14]

In summary, we have developed a novel and efficient process to synthesize oxazoles. These results provided the first experimental results in support of our previous proposal regarding the biogenesis of polyketide-derived oxazoles. Efforts toward the utilization of our protocol for natural product synthesis are also underway, and will be reported elsewhere.[15]

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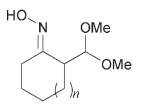
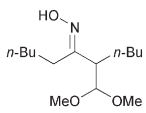
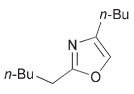
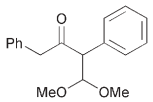
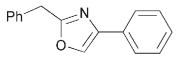
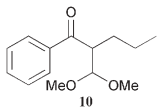
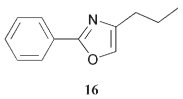
Table 1 Synthesis of substituted oxazoles *via* Beckmann rearrangement[a]

Entry	Substate	Method	Product	Yield (%)
				
1	**5**: $n = 1$	A	**11**: $n = 1$	0[b]
2	**6**: $n = 2$	A	**12**: $n = 2$	0[c]
3	**7**: $n = 3$	A	**13**: $n = 3$	74
4	**2**: $n = 7$	A	**3**: $n = 7$	100
5	 **8**	A	 **14**	97
6	**1**	B	**3**	46
7	 **9**	B	 **15**	42[d]
8	 **10**	B	 **16**	34[c]

[a] Method A: polyphosphoric acid–toluene, reflux, overnight; Method B: $HONH_2$·HCl (2 equiv.)–toluene, reflux, 1 day, then polyphosphoric acid–toluene, reflux, 4 h. [b] Unrearranged isoxazole was obtained in 57% yield. [c] Unrearranged isoxazole was obtained in 57% yield. [d] Unrearranged isoxazole was obtained in 18% yield. [e] Unrearranged isoxazole was obtained in 8% yield.

Notes and references

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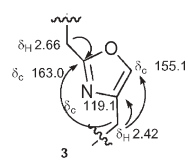
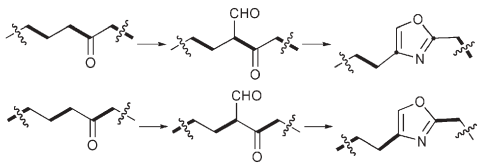
12 Selected HMBC correlations of oxazole **3** and isoxazole **4** ($CDCl_3$) are depicted below.



13 Labeling patterns of polyketide-derived marine oxazoles with ^{13}C-double-labeled acetates are expected, as shown below.



14 To the best of our knowledge, no report has yet described the enzyme that catalyzes Beckmann rearrangements in general. However, the mechanistically related dehydration of oxime to nitrile was achieved with a microbial enzyme. Y. Kato, R. Ooi and Y. Asano, *J. Mol. Catal. B: Enzym.*, 1999, **6**, 249.

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