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Multicomponent Macrocyclization Reactions (MCMRs) Employing Highly Reactive Acyl Ketene and Nitrile Oxide Intermediates

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Abstract

An efficient synthesis of spiro-fused macrolactams by a multicomponent macrocyclization reaction (MCMR) is reported. The use of highly reactive, transient intermediates in this MCMR permits short reaction times, even at high dilution. The methods employed for this MCMR were first developed as a four component strategy for the synthesis of β -ketoamide isoxazolines.

Macrocycles occur widely in nature and have important applications in medicine, material science, and supramolecular chemistry.¹ Their intrinsic three-dimensional geometry is analogous to tertiary protein structure, lending to site-specific recognition, and macrocycles constitute a unique class of privileged scaffold.^{1a,2} Despite the promise of macrocycles, they are under-exploited in libraries for screening;³ one possible cause is the limited availability of macrocycle diversification chemistry. An area of study that begins to address this issue is macrocycle forming reactions involving the union of multiple reactive components, pioneered in the laboratories of Zhu,⁴ Wessjohann,⁵ Severin,⁶ and Luis.⁷ Herein, we demonstrate a unique multicomponent-macrocyclization reaction (MCMR), which derives from a new multicomponent reaction (MCR).

While acyl ketenes provide a powerful ring closing strategy in the synthesis of macrocycles (the Boeckman approach),⁸ we are unaware of any multicomponent reactions forming macrocycles with this methodology. As depicted in Scheme 1, we envisioned macrocyclization occurring by intramolecular condensation of a primary amine with an acyl ketenes. The resulting macrolactam, is poised to condense with a formaldehyde equivalent, yielding a methylene derivative that reacts as a dipolarophile in a KHCO_3 -initiated nitrile oxide (from a chlorooxime) 1,3-dipolar cycloaddition and would yield a spiro-fused macrolactam product. This MCMR strategy could potentially access a range of macrocycles that complement those made with previously reported strategies.^{4–7}

Spiro-heterocycles and isoxazolines are important biorelevant scaffolds that have been extensively used in the synthesis of natural products.⁹ However, there are few examples of MCRs leading to spirocyclic products¹⁰ and none, to our knowledge, including a

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Supporting Information. Full experimental details and characterization data (^1H -NMR, ^{13}C -NMR, IR, ESI-MS and m.p.) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

macrocyclization step. Our long-standing interest in 1,3-dipolar cycloadditions prompted development, and report herein, of the novel 4CR summarized in Scheme 2.

MCRs are attractive because they enable formation of complex structures while minimizing synthetic effort – reducing synthesis length and optimizing atom economy.^{3b,11} This 4CR strategy (Scheme 2) allows, in principle, for the incorporation of four independently variable components. Both aryl- (e-donating, e-withdrawing, and heterocyclic) and carboalkoxy functionalized nitrile oxides are tolerated. Aromatic and alky (1° or 2°) amines can be used in the amide bond-forming step. The keto R-group ($-R = -CH_3$ or $-C_6H_4OCH_3$) in the final product is easily modified by exploiting dioxinone **1** (Scheme 2a) or Meldrum's acid analog **11** (Scheme 2b; prepared by EDC coupling of a carboxylic acid with Meldrum's acid) as the acyl ketene precursor. Importantly, we have found that the acyl ketene's high reactivity toward the amine reactant effectively out-competes potential side reactions between the amine and chlorooxime reactants.

We also investigated a 3CR variant of this 4CR employing commercial β -ketoamide **18** (Scheme 3a). The yield of this 3CR was significantly improved over the 4CRs in Scheme 2 (85% compared to yields of 36–50%). Attempts at using benzaldehyde in place of Eschenmoser's salt in this 3CR gave condensation product **22** (19:1 undefined alkene selectivity) but no cycloaddition to **23** (Scheme 3b). Condensation with Eschenmoser's salt delivers effective MCR dipolarophiles (Scheme 2), whereas the dipolarophile derived from benzaldehyde (e.g., **22**) fails to yield the multicomponent product.

Having thus established these 3 and 4CR, we next investigated the corresponding MCMR. Intermediates **28a–c** (Scheme 4) were prepared by opening anhydride **25** with carbamate-protected amino-alcohol **24a** ($P = Cbz$) or diamines **24b/c** ($P = Boc$) to give **26a–c**. Meldrum's acid was next coupled to these carboxylic acids using EDC. Attempts at macrocyclization from **27a** gave hydrolyzed [e.g., $\sim C(=O)CH_2CO_2H$] then decarboxylated [e.g., $\sim C(=O)CH_3$] product – even with rigorous drying as analogously reported by Hoyer.^{8d} Removal of the nitrogen protecting group in **27a–c** delivers zwitterions **28a–c**, which we hoped would avoid hydrolysis/decarboxylation problems.

With **28a** in hand, we addressed the challenge of forming a large ring from a 5-acyl Meldrum's acid/amine-based precursor¹² with minimal conformational bias toward cyclization (Scheme 5). We were pleased to find that macrocyclization **28a** $\rightarrow$ **29a** proceeded in excellent yield (94%) portraying the MCMR potential of this ring closing strategy. We explored both Cbz and Boc protecting group strategies and found that Boc deprotection with $SnCl_4$ proceeds more cleanly than Cbz hydrogenolysis; that said, both strategies accommodate the Meldrum's acid moiety. As with **28a**, zwitterion **28b** cyclizes in excellent yield (**28b** $\rightarrow$ **29b** in 92%). We speculate that zwitterions **28a** and **b** form an internal ion pair taking on geometries that resemble the respective macrocyclic products. This preorganization perhaps aids ring closure, explaining in part these high macrocyclization yields. Additionally, deprotonated Meldrum's acids are reported to be thermally stable¹³ and decomposition of **28a** and **28b** occurs at $>180^\circ C$ and $>220^\circ C$, respectively. However, in solution, proton transfer presumably occurs allowing for effective cycloreversion. We are unaware of any examples of 5-acyl Meldrum's acid-based macrolactamizations.¹²

Our MCMR results are delineated in Scheme 6. Most macrocyclizations must be carried out under high dilution or with slow addition of a reactant/reagent to avoid bimolecular or oligomerization reactions.¹⁴ In contrast, MCRs are often carried out at high concentration to overcome entropic barriers.^{11c,11d,15} This portends a fundamental dichotomy when incorporating a macrocyclization within an MCR. In fact, our MCMR addresses this issue

by employing highly reactive intermediates – e.g., transient acyl ketene and nitrile oxide species – at concentrations of 0.0125 M. The reactive acyl ketene intermediate enables the MCMR to proceed effectively at this concentration, while still proceeding within a short reaction time. This methodology further benefits from microwave-assisted conditions.¹⁶ Collectively, the MCMRs depicted in Scheme 6 show the facile formation of spiro-fused macrolactam products with 12- and 14-membered ring macrocycles and considerable structural diversity. We also note that the yields are very good (70–74%) – indeed, much better than the yields of the 4CRs depicted in Scheme 2 (36–50%) and comparable to the 3CR yield reported in Scheme 3 (85%).

With the potential for two regioisomers in the 1,3-dipolar cycloaddition, the selectivity of these nitrile oxide cycloadditions were confirmed by X-ray crystallographic analysis (Figure 1). The products depicted in Schemes 2/3/6 are the only regioisomers observed.

The presumed MCMR sequence of events from Meldrum's acid analog **28a** (Scheme 7) begins with a proton transfer step to **28a'** as the literature suggests that deprotonated 5-acyl Meldrum's acids will not form an acyl ketene.¹³ Thermal cycloreversion of **28a'** forms the acyl ketene, which subsequently condenses with the ω -1° amine. The amide-enol form of the β -ketoamide then condenses with Eschenmoser's salt to give the unsaturated ketoamide allowing for a sequence-ending 1,3-dipolar cycloaddition.

These results constitute a new MCMR protocol resulting in a facile route to spiro-fused macrolactams wherein macrolactamization and a new multicomponent reaction have been successfully co-joined in a single transformation. Entropic barriers are overcome at dilutions of 0.0125M and reaction times are reduced by using highly reactive, transient intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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12. Macrolactamization reactions from dioxolinone-derived acylketenes have been well documented by Boeckman and others.⁸ In contrast, macrolactamization reactions of 5-acyl Meldrum's acids are, to our knowledge, absent in the literature and there are no examples of zwitterionic species like **28a/b** forming large rings
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Scheme 1.
Multicomponent macrocyclization plan

Scheme 3.
Beta-ketoamide 3CRs

24a: X = O, P = Cbz, $\text{R} = (\text{CH}_2)_3$; **24b:** X = NH, P = Boc, $\text{R} = (\text{CH}_2)_3$;
24c: X = NH, P = Boc, $\text{R} = \text{CH}_2\text{-}m\text{Ph-CH}_2$; **26a, 27a:** X = O,
 P = Cbz, $\text{R} = (\text{CH}_2)_3$; **26b, 27b, 28b:** X = NH, P = Boc,
 $\text{R} = (\text{CH}_2)_3$; **26c, 27c, 28c:** X = NH, P = Boc, $\text{R} = \text{CH}_2\text{-}m\text{Ph-CH}_2$

Scheme 4.
 Synthesis of macrocycle precursors 24a-c

Scheme 5.
12-Membered macrocycle-forming reactions

Scheme 6.
Four related MCMRs

Scheme 7.
Proposed MCMR sequence to a spiro-fused macrocycle.