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Synthesis of Oxazolidin-4-ones: Domino *O*-Alkylation/Aza-Michael/Intramolecular Retro-Claisen Condensation

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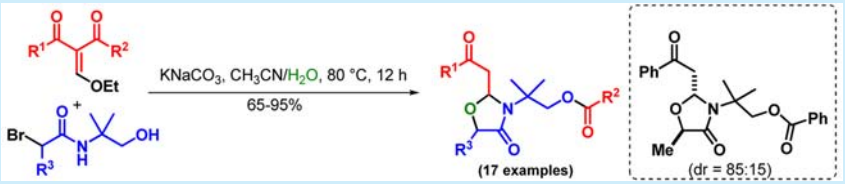
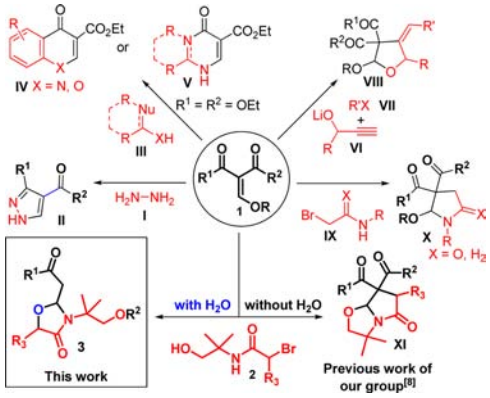
Supporting Information



ABSTRACT: An original and rapid domino reaction for access to oxazolidin-4-ones is presented. Simply by heating α-bromoamido alcohol in the presence of $KNaCO_3$ and water with readily prepared Michael acceptors, an unprecedented molecular rearrangement is generated. This new methodology enables the hitherto unreported synthesis of functionalized oxazolidin-4-ones. The process was proved to be compatible with a wide variety of substrates, and high regioselectivities were achieved.

Enol ethers **1** bearing *gem* bis-electrophiles on the double bond are versatile Michael acceptors allowing the use of a wide variety of nucleophiles (Scheme 1).[1] They are either commercially available or easily synthesized.[2] When engaged with polyfunctional nucleophiles, they lead to cyclic or heterocyclic products, usually via a tandem/domino process. For example, in the case of hydrazine **I** acting as a 1,2-bis-nucleophile, pyrazoles **II** are isolated in good yields.[3] When reacted with 1,3-bis-nucleophiles **III** (X = N, O), various heterocyclic products can be obtained such as chromone derivatives **IV**[4] or pyrimidin-4-one derivatives **V**.[5] A three-component reaction was also reported for the efficient access to tetrahydrofuran derivatives **VIII**.[6] We also contributed in this field with the synthesis of pyrrolidines (X = H_2) or pyrrolidin-2-ones (X = O) **X** by an aza-Michael/intramolecular nucleophilic substitution tandem sequence.[7] More recently, we reported an efficient one-pot synthesis of polysubstituted oxazolo-pyrrolidinones **XI** by a domino process between hydroxyl α-bromoamides **2** and Michael acceptors **1** in water-free conditions.[8] Nonetheless, opportunities to extend the scope of enol ethers **1** remain. Herein, we report an innovative single-step strategy for the synthesis of original oxazolidin-4-one derivatives **3** starting from the same two reactants with only a simple change in the reaction conditions (Scheme 1). More precisely, in the presence of water, the behavior of **1** is totally altered, implying a complete switch from Michael acceptors to nucleophilic species in the first step of the domino process. In addition, the sequence is ended by an unexpected retro-Claisen rearrangement. The oxazolidin-4-ones obtained by our pathway bearing a reactive ketone and a protected alcohol could become interesting targets for further modifications aimed at preparing various polysubstituted *N*-heterocyclic scaffolds with high potentials.

Scheme 1. Work Outline



Oxazolidinones are a class of compounds with a wide range of biological activities, including antidepressant, antihistaminic, antifungal, antihypertensive, anticancer, antiviral, and antibacterial.[9] Because of their presence in nature and biological activities, the synthesis of oxazolidin-4-ones remains a source of inspiration for organic chemists. For example, lipoxazolidinones A−C and synoxazolidinones A and B, which were, respectively, isolated from a Guam marine sediment and the subarctic ascidian *Synoicum pulmonaria*, exhibit excellent antibacterial and antifungal activities (Figure 1).[10]

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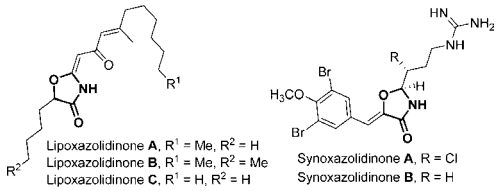
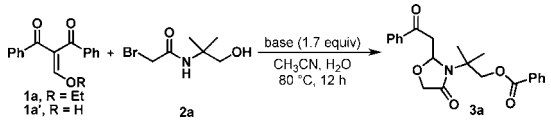


Figure 1. Structures of the natural products lipoxazolidinones A–C and synoxazolidinones A and B.

Compared to oxazolidin-2-ones, for which several synthetic strategies have been published, only a few syntheses have been reported to yield oxazolidin-4-ones.[11] This clearly underlines the need to develop efficient methods for access to original oxazolidin-4-one derivatives. Hence, the synthesis of oxazolidin-4-one derivatives provides an interesting challenge both for organic and medicinal chemists.

We first investigated the general reaction conditions with the symmetric diketone Michael acceptor **1a** (R = Et) and the amido alcohol **2a** as the model substrates (Table 1). Contrary to our previous work,[8] in the presence of water traces, we observed the formation of oxazolidin-4-one **3a** instead of the previously observed bicyclic lactam **XI** (Table 1, entry 1, and Scheme 1). In fact, 10 equiv of water was found to lead to the desired product **3a** in optimal yield (Table 1, entry 2). The presence of an excess of water in the medium allows the formation of the mandatory enolate **A**, which initiates the domino sequence (Scheme 2). The reaction was then found to be dependent on both basicity and solubility of the carbonated bases (Table 1, entries 2–5). The most basic ones, K_2CO_3 or Cs_2CO_3, lead to lower yields due to the formation of byproducts (Table 1, entries 2 and 3). However, employing the less soluble Na_2CO_3 improved the yield up to 60% (Table 1, entry 4). In order to overcome these problems, the less common potassium sodium carbonate ($KNaCO_3$) was used as base instead. We anticipated that this base should display both higher solubility than Na_2CO_3 and lower basicity than K_2CO_3. As expected, in the presence of $KNaCO_3$, the desired oxazolidin-4-one **3a** was isolated in 70% yield (Table 1, entry 5). The structure of compound **3a** was confirmed by X-ray structural analysis (see the Supporting Information).

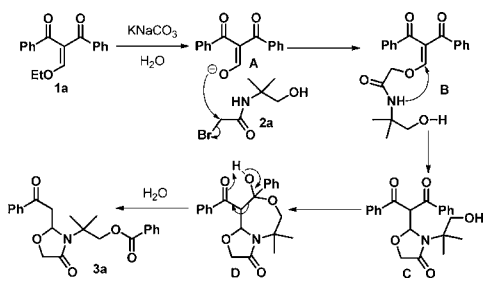
Table 1. Optimization of Reaction Conditions[a]



entry	R	base	water (equiv)	yield[b] (%)
1	Et	K_2CO_3	traces	traces
2	Et	K_2CO_3	10	40
3	Et	Cs_2CO_3	10	39
4	Et	Na_2CO_3	10	60
5	Et	$KNaCO_3$	10	70
6	H	$KNaCO_3$	10	71

[a]Typical conditions: Michael acceptor **1a** or **1a**′ (0.25 mmol, 1 equiv), amido alcohol **2a** (0.3 mmol, 1.2 equiv), $KNaCO_3$ (0.425 mmol, 1.7 equiv), and water (2.5 mmol, 10 equiv) in 2 mL of acetonitrile at 80 °C for 12 h. [b]Isolated yield.

Scheme 2. Proposed Mechanism for Access to the Oxazolidin-4-one 3a



We then turned our attention to the mechanism of this new domino process. In fact, a reverse reactivity of substrate **1**, converted in situ to nucleophilic reactivity, is the basis of this original sequence. Treatment of the Michael acceptor **1a** with $KNaCO_3$ in the presence of water affords enolate **A** resulting from the hydrolysis of **1** (Scheme 2). This compound then reacts with α-bromoacetamide **2a** to give enol ether **B**, which cyclizes via an aza-Michael addition leading to the intermediate *gem*-diketone oxazolidin-4-one **C**. The latter is finally converted into 2,3-disubstituted oxazolidin-4-one **3a** via a seldom described intramolecular retro-Claisen fragmentation.[12] Implication of enolate **A** in the sequence was confirmed by running the reaction with enol **1a**′ obtained by hydrolysis of the diphenyl ketone **1a** with LiOH in THF.[8a] As expected, the oxazolidin-4-one **3a** was obtained in almost the same yield (Table 1, compare entries 5 and 6).

The retro-Claisen rearrangement was studied by DFT (density functional theory) at the M06-2X/6-311+G(d,p) level using the SMD (universal solvation model based on density) model (acetonitrile). A diagram displaying the energy profile from **D** to **3a** via enol **E** is given in Figure 2. In the quest for the transition state, it appeared necessary to introduce up to three molecules of water to reach an energy profile consistent with the reaction conditions.[13] In the absence of water, the prototropy necessary for the reaction becomes more complicated, leading to a very high energy barrier for the transition state (see the Supporting Information) and confirming the key role of water in the reaction and not only for the first step of the domino process. In addition, the energy profile shows a clear tendency in favor of the formation of **3a** via the retro-Claisen rearrangement.

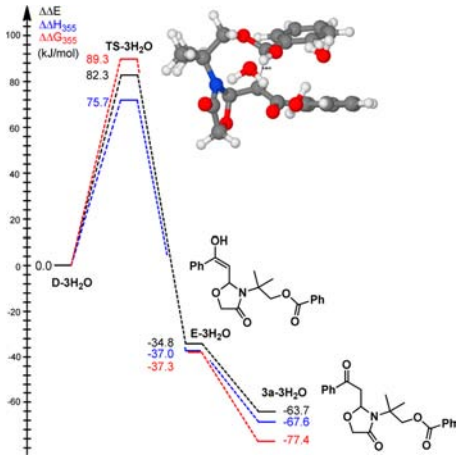


Figure 2. Energy profile of the rearrangement.

In order to demonstrate the importance of the intramolecular retro-Claisen fragmentation, the reaction was performed under the same conditions with *N*-benzyl-α-bromoacetamide **4** (Scheme 3). As expected, the oxazolidin-4-one **5** bearing a β-

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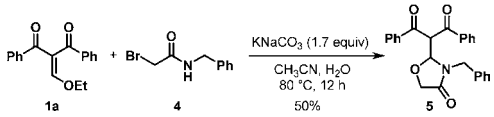
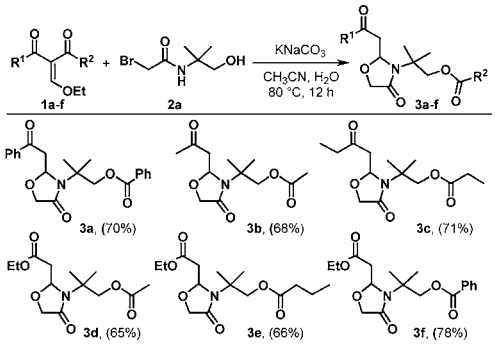
Scheme 3. Comparison of the Reaction Starting from α-Bromoacetamide 8



diketone was obtained in only 50% yield. Compared to the yield achieved with **2a**, this lower yield is probably due to the deprotonation of the resulting β-diketone leading to the formation of byproducts. The structure of compound **5** was confirmed by X-ray structural analysis (see the Supporting Information).

The scope of the reaction was then explored with various substituted Michael acceptors **1a−f** and α-bromoamido alcohol **2a** (Scheme 4). The domino process was carried out using

Scheme 4. Domino Reaction Using Both Symmetrical and Unsymmetrical Michael Acceptors

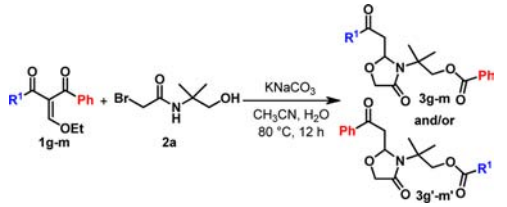


Michael acceptors bearing symmetrical dialkyl ketone **1b**,**c**, and the corresponding oxazolidin-4-ones **3b**,**c** were obtained in 68% and 71% yields, respectively. Three unsymmetrical β-keto ester derived Michael acceptors **1d−f** were then engaged and gave, after transfer of the ketone moiety, the related oxazolidin-4-ones **3d−f** with 65−78% yield. Thus, the process is compatible with aryl and alkyl ketones and ester functions onto Michael acceptors.

The Michael acceptors **1g−m** holding unsymmetrical 1,3-diketones were then considered in order to study the regioselectivity of the domino process resulting from the intramolecular retro-Claisen fragmentation step (Table 2 and Scheme 2). First, the Michael acceptors **1g−j** bearing substituted aromatic or heteroaromatic ketones were investigated. Competition between electronically enriched aromatic or heteroaromatic and a phenyl moiety led to poor selectivity, and only *N*-methylpyrrole gave high regiocontrol (Table 2, compare entries 1−4). In fact, the more sterically hindered systems were found to reach high regiocontrols (Table 2, compare entries 5−7). In the case of the methyl ketone derived Michael acceptor **1k**, an almost equimolar amount of both regioisomers was formed (Table 2, entry 5).[14] Bulkier isopropyl and cyclopentyl substituents gave rise to excellent regioselectivities with only the phenyl ketone transfer observed for the latter with no impact on the yields (Table 2, entries 6 and 7). Structures of compounds **3g′**, **3h**, and **3k′** were confirmed by X-ray structural analyses (see the Supporting Information).

Remarkably, only the products **6n−p** displaying a free alcohol function were obtained in good yields when the Michael acceptors **1n−p** bearing a trifluoromethyl ketone were tested

Table 2. Domino Reaction Using Unsymmetrical 1,3-Diketone-Derived Michael Acceptors[a]

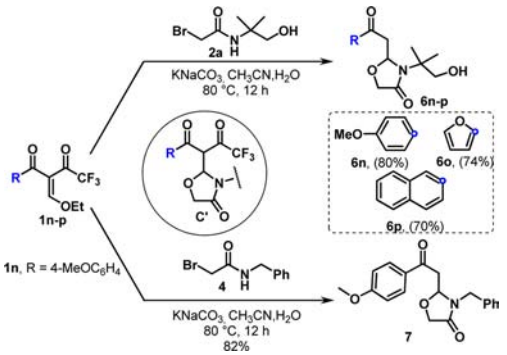


entry	R^1	product	global yield[b] (%)	3/3'[c]
1		**3g/3g'**	75	65:35[d]
2		**3h/3h'**	92	73:27[d]
3		**3i/3i'**	90	67:33[e]
4		**3j/3j'**	80	100:0
5	Me	**3k/3k'**	90	45:55[d]
6	i-Pr	**3l/3l'**	85	91:9[e]
7		**3m/3m'**	95	100:0

[a]Typical conditions: Michael acceptor **1g−m** (0.25 mmol, 1 equiv), amido alcohol **2a** (0.3 mmol, 1.2 equiv), $KNaCO_3$ (0.425 mmol, 1.7 equiv), and water (2.5 mmol, 10 equiv) in 2 mL of acetonitrile at 80 °C for 12 h. [b]Isolated yield. [c]The ratios were determined from ^1H NMR of the crude mixture. [d]Separable products. [e]Inseparable products.

(Scheme 5). The fact that only a free alcohol was isolated could result either from the saponification of a possible trifluoromethyl

Scheme 5. Selective Access to Oxazolidin-4-ones 6n−p and 7



ester formed during the domino process or from a highly competitive and regioselective intermolecular retro-Claisen condensation promoted by the water on **C′**.

In order to decide between these two hypotheses, *N*-benzyl-α-bromoacetamide **4** was engaged with the 1,3-diketone derivative **1n**. Compound **7**, resulting from the loss of the trifluoromethyl ketone moiety, was obtained as the sole product in a similar 82% yield (Scheme 5, compare **6n** and **7**). Thus, formation of oxazolidin-4-ones **6n−p** is probably the result of a competitive intermolecular retro-Claisen C−C bond cleavage of intermediate **C′** promoted by H_2O.[15]

Stereoselective synthesis of oxazolidin-4-one **8** was considered starting from the model substrate **1a** and the racemic amido

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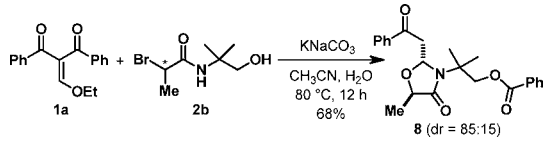
alcohol **2b** bearing a stereogenic center. Gratifyingly, when the standard conditions determined above were employed, the desired *trans*-oxazolidin-4-one **8** was obtained in 85:15 diastereomeric ratio (dr) in 68% yield (Scheme 6, see the Supporting Information).[16] This first result proves that our methodology is compatible with α-methylated α-bromoacetamides with almost no impact on the yield (compare Table 1 entry 5 and Scheme 6). Moreover, access to more challenging compounds such as lipoxazolidinones A–C could be considered employing this strategy (see Figure 1).

Scheme 6. Stereoselective Synthesis of Oxazolidin-4-one 8



In summary, we have reported an unprecedented domino *O*-alkylation/aza-Michael/retro-Claisen condensation reaction starting from Michael acceptors and α-bromoamido alcohols. This sequence provides novel access to functionalized oxazolidin-4-one derivatives via a unique transfer of the (hetero)aroyl or alkanoyl group promoted by an intramolecular retro-Claisen reaction. This new strategy opens access to a wide variety of substitutions onto oxazolidin-4-one backbones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00851.

General procedures, X-ray crystal structure determination, NMR spectra, and DFT calculations (PDF)
X-ray crystallographic data for **3a** (CIF)
X-ray crystallographic data for **3g′** (CIF)
X-ray crystallographic data for **3h** (CIF)
X-ray crystallographic data for **3k′** (CIF)
X-ray crystallographic data for **5** (CIF)

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Notes

The authors declare no competing financial interest.

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