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Thomas Martzel, Julien Annibaleto, Pierre Millet, Etienne Pair, Morgane Sanselme, et al.. Organocatalytic Multicomponent Synthesis of α/β -Dipeptide Derivatives. *Chemistry - A European Journal*, 2020, 26, pp.8541. <10.1002/chem.202001214>. <hal-02523950>

HAL Id: hal-02523950

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Submitted on 21 Aug 2020

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Organocatalytic Multicomponent Synthesis of α/β -Dipeptide Derivatives

Thomas Martzel,^[a,c] Julien Annibaleto,^[a,c] Pierre Millet,^[a] Etienne Pair,^[a] Morgane Sanselme,^[b] Sylvain Oudeyer,^[a] Vincent Levacher^[a] and Jean-François Brière*^[a]

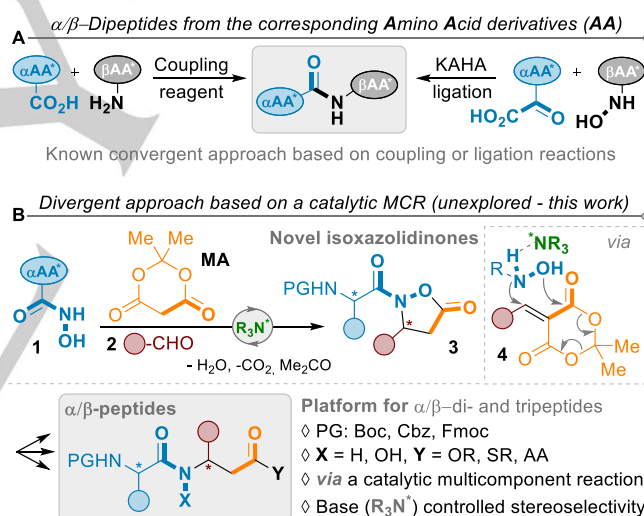
Dedication ((optional))

Abstract: A straightforward multicomponent Knoevenagel-aza-Michael-Cyclocondensation reaction involving readily available hydroxamic acid-derived from naturally occurring α -amino acids allows a diversity-oriented synthesis of novel isoxazolidin-5-ones possessing an *N*-protected α -amino acid pendant with good to high diastereoselectivities thanks to a match effect with a chiral organocatalyst. These diversely substituted heterocycles, easily isolated as a single diastereoisomer, proved to be versatile platforms for the formation of an array of α/β -dipeptide fragments.

Naturally occurring peptides currently hold a privileged place for the development of bio-inspired ingredients in pharmaceutical industry.^[1] In order to overcome the inherently sensitivity to proteolytic degradation of native peptides, while giving the opportunity to afford new properties and bio-tools to probe protein functions, synthetic chemists have tackled the elaboration of peptide analogues. In that peptidomimetic context, β -amino acids proved to be excellent building blocks for the elaboration of either β -peptides and hybrid α/β -polyamino acids having not only an improved stability towards peptidases but also displaying unique secondary structures and pharmacological activities.^[2] Furthermore, the α/β -dipeptide fragments are not only a key elements of naturally occurring products,^[3] but have met important successes in medicinal chemistry either in a linear form in case of cardiovascular diseases target for instance,^[2b] or to construct cyclic-peptide architectures in which the 1,4-diazepane-2,5-diones, and heterocycles derived thereof, proved to be privileged platforms in a large array of pharmaceutical applications.^[4] The attractiveness of these frameworks has fueled numerous research efforts dealing with the asymmetric synthesis of β -amino acids, and the elaboration of original derivatives is still of high added value.^{[3a],[5]}

The synthesis of the α/β -dipeptide motif essentially relies on the construction of the amide bond by means of coupling reagents, essentially stoichiometric, between suitably (orthogonal) protected and pre-elaborated α -amino acids (α AA) and β -amino

acids (β AA) derivatives (Scheme 1A).^[6] Bode and co-workers have made a major achievement in this field, by developing the α -ketoacid-hydroxylamine (KAHA) ligation between two pre-synthesized AA derivatives, one bearing a α -keto acid pendant and another possessing an hydroxylamine *N*-terminus functional group.^[7] Recently, Takemoto expended the portfolio of hydroxylamine-derived β AA to aspartic acid derivatives thanks to an organocatalytic aza-Michael addition to fumaric monoacid electrophiles.^[8] This elegant strategy, making use of hydroxylamine functions as key building blocks for the elaboration of β AA, was applied to the elaboration of α/β -dipeptides albeit with moderate diastereoselective ratio (dr).



Scheme 1. A new entry to β -amino acid derivatives.

Besides these convergent sequences, we tackled an alternative divergent approach in order to populate the chemical space within the biorelevant α/β -dipeptide series (Scheme 1B). We reasoned that the multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction would take place between readily available hydroxamic acids **1**,^[9] derived from naturally occurring and enantiopure α AA, various aldehydes **2** and Meldrum's acid (MA) as a C2-synthon (first point of diversity).^{[10],[11]} Then, this strategy would afford a straightforward elaboration of novel isoxazolidin-5-ones **3**,^[12] as masked β AA with an α AA side chain, providing eventually versatile platforms to elaborate a library of α/β -dipeptides (second point of diversity).^{[13],[14]} In order to be synthetically useful, this sequence should demonstrate a significant functional group compatibility and furnish one stereoisomer. Thanks to the marked electrophilic

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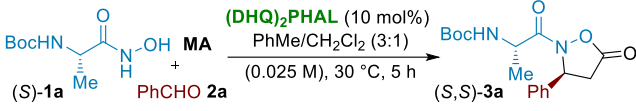
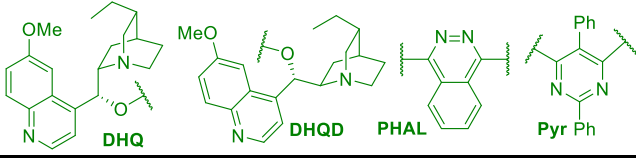
[c] These authors contributed equally to this work.

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reactivity of alkylidene **MA** intermediates **4**,^{[11],[15]} we postulated that (1) a facile domino addition process of hydroxamic acids **1** would occur and (2) the C-N bond formation between **1** and **4** would be under the influence of both a chiral nucleophile **1** and a Brønsted base organocatalysts to favor the formation one stereoisomer (Scheme 1B). We are delighted to report on the unprecedented diastereoselective multicomponent reaction (MCR) giving rise to versatile isoxazolidin-5-ones **3** thanks to the match influence of a suited organocatalyst, en route to the elaboration of various original α/β -dipeptide derivatives.

Table 1. Proof of principle and optimization.^[a]

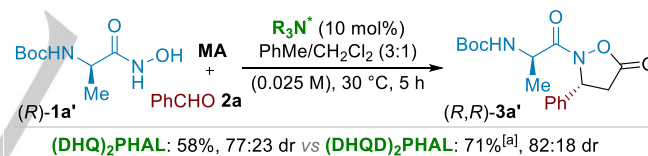



Entry	Deviation from the standard conditions	Yield [%]	dr ^[b]
1	Without catalyst	20 (55) ^[c]	57:43
2	Quinuclidine as catalyst	86	71:29
3	-	75	86:14
4	(DHQD) ₂ PHAL as catalyst	82	74:26
5	(DHQ) ₂ Pyr as catalyst	62	82:18
6	Quinine (QN) as catalyst	73	81:19
7	Quinidine (QD) as catalyst	66	48:52
8	MeCN (0.1 M) as solvent, 20 °C ^[d]	44	73:27
9	CH ₂ Cl ₂ (0.1 M) as solvent, 20 °C ^[d]	30	86:14
10	PhMe (0.1 M) as solvent, 20 °C ^[d]	traces	-
11	PhMe/CH ₂ Cl ₂ (3:1, 0.1 M) as solvent, 20 °C ^[d]	68	86:14

[a] Reaction conditions: **1a** (0.1 mmol), PhCHO **2a** (1 equiv), **MA** (1.5 equiv) in PhMe/CH₂Cl₂ (3:1, 0.025 M) at 30 °C for 5 h. Yields of both diastereoisomers determined by ¹H NMR with an internal standard. [b] dr determined by ¹H NMR on the crude product. [c] Bimolecular reaction from benzylidene Meldrum's acid **4a**. [d] **MA** (1 equiv), (DHQ)₂PHAL (20 mol%).

At the onset, it was shown that the model MCR involving the *N*-Boc alanine hydroxamic acid **1a** (Boc- α -AlaNH₂OH), **MA** and benzaldehyde **2a** furnished after 5 hours the corresponding isoxazolidinone **3a** in 20% yield (determined by ¹H NMR) as 57:43 mixture of diastereoisomers namely with virtually no stereoselection (entry 1, Table 1). By performing the di-component reaction with benzylidene Meldrum's acid **4a**, the putative intermediate involved into the formal domino aza-Michael-cyclocondensation process (see Scheme 1), similar poor dr was obtained with a better 55% yield (entry 1). The facility with which this MCR takes place is worthy of note, likely thanks to the high electrophilic reactivity of benzylidene MA,^[15] but the ability of a catalyst to accelerate this process and promote a stereoselective sequence remains an issue.^[10] To our delight the use of 10 mol% of a Brønsted base like the achiral quinuclidine allowed to improve significantly the yield to 86% and dr (71:29,

entry 2). A large screening of organocatalysts (see SI) showed that the commercially available and chiral amine (DHQ)₂PHAL turned out to be the more efficient catalyst leading to good 86:14 dr in 75% yield in 5 hours (entry 3 versus entries 4-7). Early optimization endeavors (see SI) showed that less polar solvents like CH₂Cl₂ (entries 8-9) benefited to the level of stereoselection, while a mixture of PhMe/CH₂Cl₂ was required for solubility issue (entries 10-11). Noteworthy, isoxazolidone **3a** proved to be somewhat unstable during the purification by silica-gel column chromatography but also in the presence of the Brønsted base in solution (*vide infra*). Then, some decomposition events occur during longer or forcing reaction conditions leading to erratic outcomes. However, the use of more diluted conditions and a slight excess of **MA** prevent the decomposition of product **3a** (thanks to its high acidity, pK_a = 4.8 in H₂O)^{[11],[16]} even at 30 °C, a temperature allowing both a faster process and a decrease of the amount of catalyst from 20 to 10 mol% while giving improved yield of 75% and the same dr in 5 hours (entries 3 vs 11, Table 1). This shows the key role of **MA** to secure soft reaction conditions. Interestingly, it was observed a match/mismatch effect between chiral Cinchona-derived organocatalysts and (S)-Boc- α -AlaNH₂OH **1a** (Table 1, entries 3-4 and 6-7) which demonstrated that quinine versus quinidine derivatives were more competent to give (S,S)-isoxazolidinone **3a** with a good dr. Accordingly, it was proven that quinidine derived (DHQD)₂PHAL catalyst was able to transform the (R)-Boc- α -AlaNH₂OH enantiomer **1a'** into isoxazolidinone (R,R)-**3a'** in 71% yield and 82:18 dr contrary to (DHQ)₂PHAL catalyst giving **3a'** only in 58% yield and 77:23 dr (Scheme 2). Eventually, it was validated that this MCR took place with no racemization and provided the major isoxazolidinones **3a** and **3a'** as a single enantiomer (>99:1 er, see SI).



Scheme 2. Molecular diversity towards a versatile synthesis of **3a'** - the other enantiomer of isoxazolidinone **3a**. Yields of both diastereoisomers determined by ¹H NMR with an internal standard. [a] 47% isolated yield after column chromatography.

The scope and limitation of this novel MC-strategy was next addressed (Table 2). Pleasingly, carrying out the reaction for 24 hours on a larger scale secured the complete transformation of Boc- α -AlaNH₂OH **1a** into isoxazolidinone **3a** in 88:12 dr (99% of NMR yield for both diastereoisomers). Importantly, the two diastereoisomers of isoxazolidinone **3a** could be separated by flash column chromatography, as a general behavior in this series, leading to the major (S,S)-**3a** in 71% isolated yield (slight drop of the theoretical yield of 88%).^[17] Starting from isovaleraldehyde **2b**, a facile synthesis of the corresponding isoxazolidinone **3b**, having β Leu backbone (homologated β^3 -Leucine), occurred in excellent dr > 95:5 and 96% yield for the pure major stereoisomer. As a rule of thumb, in comparison to the use of aromatic aldehydes such as **2a**, the isoxazolidinones **3** derived from aliphatic aldehydes **2** turned out to be more stable which allows (1) an easy purification by chromatography and (2) to carry out the reaction in higher

peptide-coupling reagents to give rise to the formation of either thioester **7** (94%), suited for further native ligation processes, or $\alpha/\beta/\alpha$ -tripeptide **8** in 91% yield. Interestingly, taking advantage of the reactivity of the N-EWG isoxazolidinone framework,^{[12], [17b], [7c]} the direct ring opening event of **3b** with *tert*-butyl-alanine furnished the $\alpha/\beta/\alpha$ -tripeptide **9**, similar to **8** but with a N-OH functionality known to be a valuable moiety to complex metal in bio-environment.^[21]

In summary, we have developed a multicomponent synthesis of novel isoxazolidin-5-ones possessing an N- α -amino acid. Thanks to the high reactivity of transient alkylidene Meldrum's acids, a smooth and diastereoselective domino addition reaction takes place upon the match influence of a commercially available quinine derived organocatalyst allowing to achieve good to excellent dr. The corresponding isoxazolidin-5-ones, easily obtained as single diastereoisomer after purification, proved to be versatile platforms for the diversity-oriented synthesis of an array of α/β -dipeptides, as useful fragment in medicinal chemistry.

Acknowledgements

This work has been partially supported by INSA Rouen Normandy, University of Rouen Normandy, the Centre National de la Recherche Scientifique (CNRS), EFRD, and Labex SynOrg (ANR-11-LABX-0029), and by Region Normandie (CRUNCH network). This research was also supported by the French National Research Agency (ANR) as part of the ANR-16-CE07-0011-01 project OMaChem.

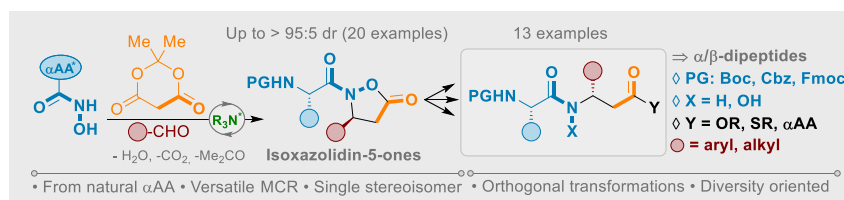
Keywords: amino acid • asymmetric synthesis • isoxazolidinone • Meldrum's acid • organocatalysis

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- [18] In case of aliphatic aldehydes such valeraldehyde **2b**, the catalyzed reaction (optimized conditions) could be performed with more concentrated conditions with only a moderate impact on dr (**3b**, 0.1 M, 99% NMR yield, 94:6 dr; 0.2 M, 99% NMR yield, 93:7 dr).
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**Organocatalytic Multicomponent
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The diversity: A straightforward organocatalyzed multicomponent reaction (MCR) involving readily available hydroxamic acids-derived from naturally occurring α -amino acids (α AA) allows a stereoselective and diversity-oriented synthesis of novel isoxazolidin-5-ones as versatile platforms for the elaboration of α/β -dipeptide fragments.