# JOC Notes

A Modular, One-Pot, Four-Component Synthesis of Polysubstituted 1,3-Oxazolidines

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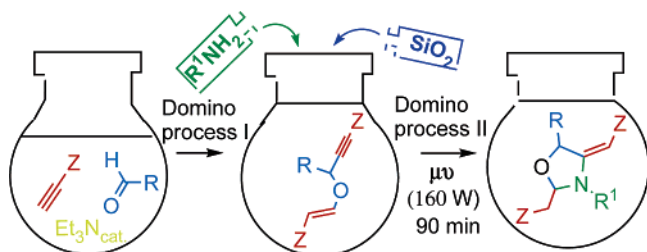
A modular, one-pot, two-step, four-component synthesis of polysubstituted 1,3-oxzolidines is described. The method comprises two linked domino processes: an organocatalyzed domino reaction of alkyl propiolate and an aliphatic aldehydes and a microwave-assisted amine addition cyclization domino process. An alternative modular, one-pot, three-step, four-component synthesis has also been developed by linking the organocatalyzed domino process to a sequential amine addition/Yb(OTf)$_3$-catalyzed enamine cyclization reaction.

The rapid and efficient generation of nitrogen-containing privileged structural motifs is a great challenge in biological, organic, and medicinal chemistry.[1] Domino processes[2] and multicomponent reactions (MCR)[3] offer excellent avenues to face these challenges. Notorious examples are the Biginelli,[3f] Mannich,[4] and Ügi,[3c–d]

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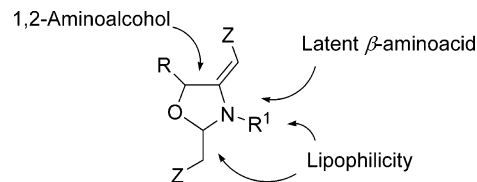
Z = chemically differentiated EWG

FIGURE 1. Fully substituted 1,3-oxazolidines combining an α,β-disubstituted 1,2-amino alcohol and a latent β-substituted β-amino acid.

reactions. As a part of a wide research program aimed at synthesizing nitrogen-containing druglike heterocyles by the combined use of domino and MCR,[5] we became interested in the 1,3-oxazolidine molecule shown in Figure 1. Our interest in these heterocyles lies in their particular chemical topology, which combines two biologically relevant structural motifs: an α,β-disubstituted 1,2-amino alcohol[6] and a latent β-substituted β-amino acid.[7,8] The masked form of this 1,2-amino alcohol functionality induces a lipophilicity enhancement and consequently, a facilitated drug delivery and a favorable use as prodrugs.[9] Additionally, the heterocyle is an excellent

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SCHEME 1. Two Modular, One-Pot, Four-Component Approaches to the Synthesis of Fully Substituted 1,3-Oxazolidines 3[a]
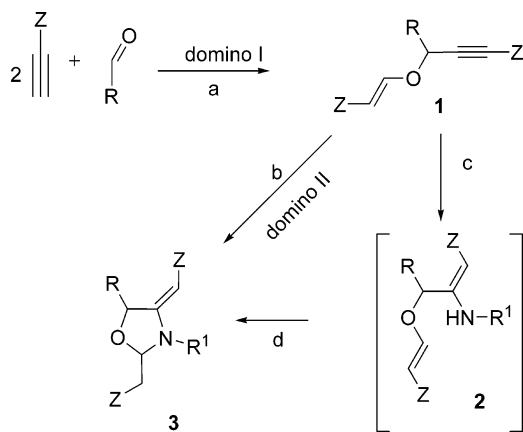
[a] Conditions: (a) Et$_3$N cat, CH$_2$Cl$_2$ (or ClCH$_2$CH$_2$Cl), 0 °C, 60 min; (b) R^{1}NH$_2$, SiO$_2$, μv-irradiation (160 W), 90 min; (c) R^{1}NH$_2$, ClCH$_2$CH$_2$Cl, reflux, overnight; (d) Yb(OTf)$_3$ (10 mol %), ClCH$_2$CH$_2$Cl, reflux, overnight.

TABLE 1. Modular, One-Pot, Four-Component Synthesis of 1,3-Oxazolidines 3a–j

entry	Z	R	R^1	prod	yields Yb^{3+} [b]	μv[a]
1	CO$_2$Me	Me	Bn	**3a**	71	60
2	CO$_2$Me	Et	Bn	**3b**	70	58
3	CO$_2$Me	Hex	Bn	**3c**	55	44
4	CO$_2$Me	^{i}Pr	Bn	**3d**	67	45
5	CO$_2$Me	4-penten-1-yl	Bn	**3e**	54	49
6	CO$_2$Me	^{i}Pr	all	**3f**	65	36[c,d]
7	CO$_2$Me	^{i}Pr	Bu	**3g**	68	30[c,e]
8	CO$_2$Me	Et	Ph	**3h**	NR	45[f]
9	CO$_2$Me	Et	pMeOPh	**3i**	NR	55
10	SO$_2$Tolyl[g]	^{i}Pr	Bn	**3j**	54	–

[a] (1) Aldehyde (1.1 mmol), alkyl propiolate (2 mmol), Et$_3$N (0.5 mmol), CH$_2$Cl$_2$, 0 °C, 60 min. (2) Silica gel (0.5 g), amine (1.3 mmol). (3) μv-Irradiation (160 W), 90 min. [b] (1) The same procedure as before but using 1,2-dichloroethane as solvent. (2) Amine (1.3 mmol), reflux, overnight. (3) Yb(OTf)$_3$ (0.10 mmol), reflux, overnight. [c] Amine (1.5 mmol). [d] Linear amide (10%). [e] Linear amide (20%). [f] Silica gel (1 g), amine (4 mmol). [g] No catalyst was needed to achieve the second domino process.

platform to place pending chemical functionalities in an ordered three-dimensional array. Herein we report on two complementary direct, modular, and diversity-oriented approaches to these 1,3-oxazolidines from single and commercially available components (Scheme 1). The first approach comprises a one-pot, three-step, four-component process and combines a trialkylamine-catalyzed synthesis of enol-protected propargylic alcohols[5b,d] (domino I) and a thermally driven amine addition/Yb-(OTf)$_3$-catalyzed enamine cyclization[10] (Scheme 1, steps a, c, and d). The second approach involves a metal-free, one-pot, two-step, four-component process and combines the same trialkylamine-catalyzed domino process (domino I) and a microwave-assisted amine addition/enamine cyclization domino process (domino II) (Scheme 1, steps a and b). The first approach was optimized for the synthesis of oxazolidine **3d** (R = ^{i}Pr, R^1 = Bn).

We pleasantly found that this heterocycle could be obtained in 76% yield by a sequential conjugated benzylamine addition on the enol-protected propargylic alcohol **1d** (R = ^{i}Pr) (CH$_2$Cl$_2$, reflux) followed by a Yb(OTf)$_3$ (10 mol %)-catalyzed enamine cyclization. While the amine is nucleophilic enough to give Michael addition on the triple bond,[11] the cyclization step requires a metallic activation of the β-oxygenated acrylate unit to proceed. This chemoselectivity is a very remarkable property of such linear scaffolds, and it can be productively used for the controlled generation of skeletal diversity. This tandem set of reactions was applied on other conjugated

alkynoates **1** with similar results. Once the heterocycle formation was standardized, we undertook the one-pot version of this 4-MCR (Scheme 1). After some experimentation, we found that the domino synthesis of linear scaffold **1** and its sequential transformation into 1,3-oxazolidine **3** could be coupled in a one-pot manner using 1,2-dichloroethane as solvent. Table 1 shows the data for this one-pot 4-MCR. Linear and branched aliphatic aldehydes afforded oxazolidines **3** in good yields (entries 1–4). The procedure is mild enough to allow an isolated double bond on the aldehyde (entry 5). This reactive isolated double bond is a well-suited anchor functionality for attachment to other biologically active structures.[12] In addition, it allows a ready increase in the molecular complexity. Aromatic aldehydes are not substrates for the first domino process, and they are not transformed into scaffolds **1**. Aromatic amines are not good nucleophiles, and they do not give Michael addition to the conjugated triple bond (entries 8–10). On the other hand, benzyl, allyl, or alkylamines launch the second domino reaction to afford oxazolidines **3** in good yields (entries 4, 6, and 7). Akynyl sulfones generate the corresponding oxazolidines in an efficient manner *without the aid of catalyst* (entry 11). With regard to diastereoselectivity, 1,3-oxazolidines **3** are obtained as mixtures of syn/anti isomers.[13] Under these experimental conditions, the kinetic syn isomer equilibrates with the thermodynamic anti isomer, affording irresolvable mixtures of both isomers (diastereomeric ratios are indicated for each product in the Supporting Information).

Although this first synthetic approach proved quite satisfactory in terms of chemical efficiency and easy processing, we were concerned with the imperative use of a transition-metal catalyst. Thus, we undertook the development of a fully organocatalytic 4-MCR approach. We have recently described that 1,3-oxazolidines **3** rear-

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(12) For an example, see: Brohm, D.; Metzger, S.; Bhargava, A.; Müller, O.; Lieb, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 307–311.

(13) For an interesting discussion on diastereoselectivity in the synthesis of 1,3-oxazolidines, see: Agami, C.; Couty, F. *Eur. J. Org. Chem.* **2004**, 677–685 and references therein.

range to pyrroles when they are heated or submitted to strong microwave irradiation (SiO$_2$, 900 W, 8 min).[5a] After some experimentation, we pleasantly found that mild microwave irradiation (90 min, 160 W) of silica gel absorbed mixtures of different scaffolds **1** and benzylamine cleanly afforded 1,3-oxazolidines **3** in good yields (Scheme 1). Under these mild conditions, 1,3-oxazolidines do not rearrange to pyrroles. With these experimental results at hand, we next moved to link this microwave-assisted domino process with the triethylamine-catalyzed synthesis of scaffolds **1** in a one-pot manner. Table 1 shows the data for this new one-pot protocol. In sharp contrast with the Yb^{3+}-catalyzed MCR, aromatic amines are efficient nucleophiles to launch the second domino process (entries 8 and 9). Even aniline, a bad nucleophile, is able to produce the corresponding 1,3-oxazolidine (entry 8), although with low atom efficiency: 4 equiv of the amine are required to complete the reaction. Volatile amines have to be used in excess to preclude material waste during the silica gel absorption process. In these cases, the direct 1,2-addition of the amine on the ester function competes with the 1,4-addition on the triple bond, reducing the overall yield of the 1,3-oxazolidines (entries 6 and 7). With regard to the aldehydes, both linear and branched ones are efficiently transformed into 1,3-oxazolidines (entries 1−5). A reactive isolated double bond on the aldehyde chain is tolerated (entry 5). Unlike the ytterbium-catalyzed MCR, alkynyl sulfones are not suitable substrates for this microwave-assisted domino process. As expected, the less reactive N-aromatic substituted oxazolidines are obtained mainly as the syn isomer (kinetic product) in contrast with the anti preference of the N-aliphatic derivatives.

Overall, this metal-free, one-pot, two-step, organocatalyzed 4-MCR builds up *one carbon−carbon bond, one carbon−oxygen bond, two carbon−nitrogen bonds, and a ring* in a selective and efficient manner. The protocol is modular and utilizes simple and commercially available reagents. In addition, the reaction times are short (less than 3 h), and the processing is extremely bench-friendly and environmental-considerate: the first domino process does not require special care with reagents nor solvents; the second one is a solvent-free process. Once the first domino process is completed, silica gel and the primary amine are added to the reaction flask, and the mixture is concentrated to dryness. The flask containing the solid mixture is placed in a domestic microwave oven and irradiated at 160 W for 90 min. Filtration and flash chromatography afford pure 1,3-oxazolidines **3**.

These fully substituted 1,3-oxazolidines are very well-suited molecular scaffolds for library synthesis of nitrogen-containing privileged structural motifs such as tetrasubstituted pyrroles,[10a] γ-hydroxy β-amino acids, 4-amino furanones, etc. These transformations are being developed in our lab, and they will be reported in due course.

In summary, we have described a novel modular, one-pot, two-step, four-component synthesis of fully substituted 1,3-oxazolidines **3** from simple and commercially available starting materials. The method comprises two linked domino processes: an organocatalyzed domino reaction of alkyl propiolate and an aliphatic aldehyde and a microwave-assisted amine addition cyclization domino process. An alternative modular, one-pot, three-step, four-

component synthesis has also been developed by linking the organocatalyzed domino process to a sequential amine addition/Yb(OTf)$_3$-catalyzed cyclization. Both methods complement each other, offering a wide scope of commercially available primary amines, aliphatic aldehydes, and alkynoates for the generation of diversity-oriented molecular collections. Bioactivity assays of these heterocyclic compounds are in progress and will be reported elsewhere in due course.

Experimental Section

One-Pot, Two-Step, 4-MCR Synthesis of 1,3-Oxazolidines 3a (Representative Example). Methyl propiolate (2.00 mmol) and ethanal (1.1 mmol) were dissolved in 10 mL of CH$_2$Cl$_2$. After the mixture was cooled to 0 °C, triethylamine (0.5 mmol) was added, and the reaction mixture was stirred for 60 min. The solvent and excess reagents were then removed under reduced pressure. The resulting mixture and benzylamine (1.3 mmol) were absorbed on silica gel (0.5 g), and it was subjected to microwave irradiation for 90 min at 160 W. Extraction of the products with ethyl acetate was followed by isolation of the 1,3-oxazolidine **3a** (syn/anti: 40/60) by flash column chromatography (silica gel, *n*-hexane/EtOAc 90/10) (60%). ^{1}H NMR (CDCl$_3$, 500 MHz): **syn** δ 1.47 (d, 3H, *J* = 6.4 Hz), 2.53 (dd, 1H, *J* = 15.5, 6.4 Hz), 2.66 (dd, 1H, *J* = 15.5, 3.7 Hz), 3.59 (s, 3H), 3.62 (s, 3H), 4.31 (d, 1H, *J* = 16.7 Hz), 4.44 (d, 1H, *J* = 16.7 Hz), 4.61 (d, 1H, *J* = 1.1 Hz), 5.48 (ddd, 1H, *J* = 6.4, 3.7, 1.3 Hz), 5.68 (qt, 1H, *J* = 6.4, 1.2 Hz), 7.09−7.18 (m, 2H), 7.27−7.34 (m, 3H). **anti** δ 1.60 (d, 3H, *J* = 6.4 Hz), 2.58 (dd, 1H, *J* = 15.4, 7.2 Hz), 2.67 (dd, 1H, *J* = 15.4, 4.0 Hz), 3.58 (s, 3H), 3.60 (s, 3H), 4.33 (d, 1H, *J* = 16.7 Hz), 4.41 (d, 1H, *J* = 16.7 Hz), 4.59 (d, 1H, *J* = 1.4 Hz), 5.43 (dd, 1H, *J* = 7.3, 4.0 Hz), 5.63 (qd, 1H, *J* = 6.4, 1.3 Hz), 7.09−7.18 (m, 2H), 7.27−7.34 (m, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz): **syn** δ 18.6, 39.5, 46.9, 50.3, 51.8, 78.4, 78.8, 88.7, 126.6, 127.7, 129.0, 135.0, 163.4, 168.3, 169.5. **anti** δ 22.1, 42.4, 47.6, 50.3, 51.8, 78.5, 79.6, 91.5, 126.4, 127.8, 128.9, 135.3, 163.4, 168.1, 169.7. IR (CHCl$_3$, cm^{-1}) 3019.4, 2953.3, 1732.0, 1690.4, 1611.8, 1147.9. Anal. Calcd for C$_{17}$H$_{21}$NO$_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.78; H, 6.61; N, 4.48. MS, *m/z* (relative intensities): 319 (M$^+$, 38), 246 (29), 217 (13), 186 (11), 158 (13), 129 (10), 91 (100).

One-Pot, Three-Step, 4-MCR Synthesis of 1,3-Oxazolidines 3b (Representative Example). Methyl propiolate (2.00 mmol) and propanal (1.1 mmol) were dissolved in 10 mL of ClCH$_2$CH$_2$Cl. After the mixture was cooled to 0 °C, triethylamine (0.5 mmol) was added, and the reaction mixture was stirred for 60 min. Benzylamine (1.3 mmol) was added, and the resulting mixture was refluxed overnight. Yb(OTf)$_3$ (10 mmol %) was added, and the reaction mixture was again refluxed overnight. After cooling, the mixture was poured on an aqueous saturated solution of sodium bicarbonate and decanted off. The aqueous layer further extracted with CH$_2$Cl$_2$ ($\times$2) and the organic phases were combined, washed with brine, dried over sodium sulfate, and filtered. Flash chromatography of the resulting residue afforded 1,3-oxazolidine **3b** (syn/anti: 40/60) (silica gel, *n*-hexane/EtOAc 90/10) (70%). ^{1}H NMR (CDCl$_3$, 400 MHz): **syn** δ 0.97 (d, 3H, *J* = 7.5 Hz), 1.62 (m, 1H), 1.89 (sextet of doublets, 1H, *J* = 7.5, 3.0 Hz), 2.50 (dd, 1H, *J* = 15.6, 6.1 Hz), 2.59 (dd, 1H, *J* = 15.6, 4.0 Hz), 3.53 (s, 3H), 3.56 (s, 3H), 4.25 (d, 1H, *J* = 16.4 Hz), 4.38 (d, 1H, *J* = 16.4 Hz), 4.57 (d, 1H, *J* = 1.0 Hz), 5.39 (m, 1H), 5.43 (m, 1H), 7.10 (td, 2H, *J* = 8.0, 1.2 Hz), 7.34 (m, 1H), 7.44 (m, 2H). **anti** 1.01 (t, 3H, *J* = 7.5 Hz), 1.62 (m, 1H), 2.12 (sextet of doublets, 1H, *J* = 7.5, 3 Hz), 2.52 (dd, 1H, *J* = 15.3, 7.4 Hz), 2.60 (dd, 1H, *J* = 15.3, 4.0 Hz), 3.52 (s, 3H), 3.55 (s, 3H), 4.27 (d, 1H, *J* = 16.4 Hz), 4.33 (d, 1H, *J* = 16.4 Hz), 4.54 (d, 1H, *J* = 1.3 Hz), 5.39 (m, 1H), 5.43 (m, 1H), 7.10 (td, 2H, *J* = 8.0, 1.2 Hz), 7.34 (m, 1H), 7.44 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): **syn** δ 10.2, 25.9, 39.6, 47.0, 51.8, 78.4, 83.8, 89.2, 126.4, 126.7, 127.7, 128.9, 135.3, 162.4, 168.4, 169.5. **anti** δ 10.0, 28.4, 42.1, 47.8, 50.3, 78.7, 84.5, 91.6, 126.4, 126.7, 127.7, 128.9, 135.0, 162.6, 168.2, 169.7. IR (CHCl$_3$, cm^{-1}):

3018.1, 2951.5, 1736.2, 1688.1, 1607.6, 1435.6, 1385.3, 1147.9. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.98; H, 6.82; N, 4.39. MS, *m/z* (relative intensities): 333 (M+, 5.9), 172 (5.3), 91 (100), 65 (7.9).

Supporting Information Available: Spectroscopic and analytical data for compounds **3c**−**j** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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