

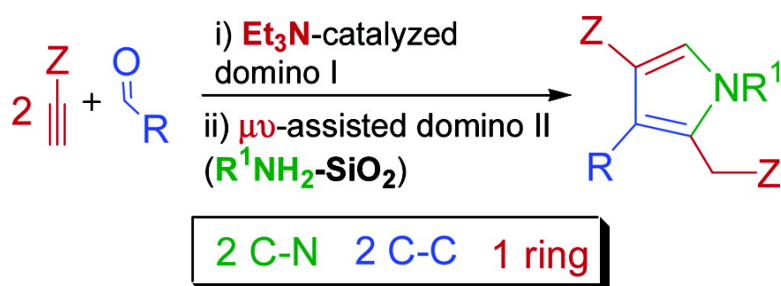
Communication

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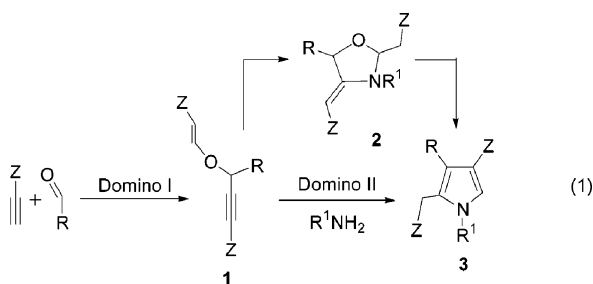
## A Diversity-Oriented Strategy for the Construction of Tetrasubstituted Pyrroles via Coupled Domino Processes

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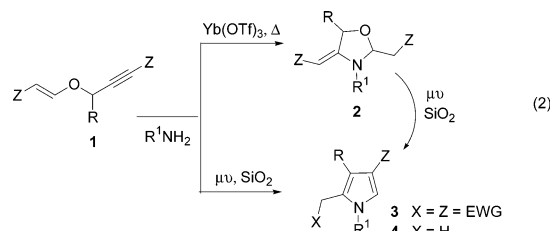
Domino processes have received great attention from the chemical community because they address fundamental principles of synthetic efficiency and reaction processing.<sup>1</sup> Over the last four years, we have been involved in a research program aimed at developing metal-free and diversity-oriented domino-based syntheses of biologically relevant heterocyclic scaffolds.<sup>2</sup> Our design principle is based on the expected multiplicative effect on molecular complexity achieved by a chain of two or more coupled domino processes in the same reaction vessel. This approach requires a careful design of each of the participant domino processes. To be coupled in a chain manner, each domino process must generate a suitably functionalized molecule able to be simultaneously engaged in the subsequent complexity-generating domino process and so on. Additionally, the whole process would be performed in a format amenable for application in combinatorial chemistry. Experimentally, the transformation of this concept in a one synthetic step strategy is not a simple task because of the unattainable kinetic tuning of each of the numerous chemical reactions involved. A more feasible approach should consist in the transformation of this concept in a one-pot synthetic strategy. In this new scenario, the consecutive coupled domino processes should be performed one at a time and linked in a one-pot operation. In a first experimental approach, we chose the simple model shown in eq 1, addressing the synthesis of polysubstituted pyrroles. The protocol combines two coupled domino processes: the trialkylamine-catalyzed synthesis of enol-protected propargylic alcohols **1**<sup>2</sup> (domino I) and their sequential transformation into pyrroles **3** (domino II). The key for this transformation came from a serendipitously discovered spontaneous rearrangement of 1,3-oxazolidines **2** to pyrroles **3**.



Polysubstituted pyrroles are common pharmacophores of numerous natural antibiotics and alkaloids,<sup>3</sup> and they have also found applications in the field of material chemistry.<sup>4</sup> These properties are of considerable interest in the development of new efficient

syntheses of these heterocycles. Among the plethora of methods available for pyrrole construction,<sup>3</sup> metal-based strategies<sup>5</sup> and 1,3-dipolar cycloadditions<sup>6</sup> have received the most attention. In contrast, the number of examples reported in the literature dealing with metal-free, modular, and direct syntheses of these heterocycles is scarce.<sup>7</sup> Therefore, there is a clear demand for new metal-free, modular, and direct synthetic protocols with atom economy, easy reaction processing, general applicability, and environmental care performance.

1,3-Oxazolidines **2** are readily obtained in a one-pot manner by the ytterbium-catalyzed reaction<sup>8</sup> of the conjugated alkynoates **1** and primary amines (eq 2). Pure 1,3-oxazolidines **2** rearrange to



pyrroles **3** when they are stored on the bench without solvent (eq 2). This rearrangement is very slow at room temperature and needs months to be completed.<sup>9</sup> While heating speeds up this process from months to hours (see Supporting Information for full details), microwave ( $\mu\nu$ )-irradiation assists this rearrangement, reducing the reaction time from hours to minutes. As an example,  $\mu\nu$ -irradiation (900 W) of a sample of **2i** absorbed on silica gel (1 g silica gel/mmol) (neat **2** is transparent to  $\mu\nu$ -irradiation) for 5 min in a domestic  $\mu\nu$ -oven cleanly afforded the 1,2,3,4-tetrasubstituted pyrrole **3i** in 78% yield with traces of the decarboxylated derivative **4**. This result proved to be general for all of the oxazolidines assayed. After some experimentation, we found that tetrasubstituted pyrroles **3** could be directly synthesized from scaffolds **1** and the primary amines by  $\mu\nu$ -irradiation of a silica gel absorbed mixture of both components (eq 2; Table 1). Overall, this transformation constitutes a solvent-free domino process involving a 1,3-oxazolidine synthesis and its subsequent skeletal rearrangement. The process is general for the amine (entries 1–7) and tolerates a range of functionalities in the aldehyde (entries 8–16). Even aniline, a bad nucleophile, transforms alkynoate **1a** into oxazolidine **3b** (entry 2).  $\alpha$ -Oxygenated aldehydes afford conjugated alkynoates **1p** and pyrroles **3p** with moderate efficiency (entry 16).

The complete synthetic protocol was performed by linking the two coupled domino processes involved (domino I and domino II) in a one-pot manner (Figure 1; Table 1). Overall, these two linked and coupled domino processes build up two carbon–carbon bonds,

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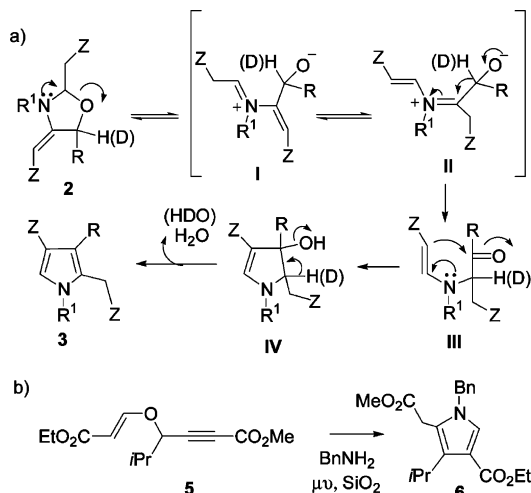
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**Table 1.** Synthesis of Pyrroles **3** from Conjugated Alkynoates **1** (Domino)<sup>a</sup> and from Alkyl Propiolate and Aldehydes (One-Pot)<sup>b</sup>

entry	Z	R	R <sup>1</sup>	<b>1</b> (%)	domino <sup>c</sup>	one-pot <sup>e</sup>
1	CO <sub>2</sub> Me	Et	Bn	<b>1a</b> (87)	<b>3a</b> (74)	(44)
2	CO <sub>2</sub> Me	Et	Ph		<b>3b</b> (38) <sup>d</sup>	
3	CO <sub>2</sub> Me	Et	pOMe-Ph		<b>3c</b> (56) <sup>d</sup>	
4	CO <sub>2</sub> Et	Et	pOMe-Ph		<b>3d</b> <sup>d</sup>	(53)
5	CO <sub>2</sub> Et	Et	Bn	<b>1e</b> (88)	<b>3e</b> (77)	(51)
6	CO <sub>2</sub> Me	Et	(S)PhCHMe		<b>3f</b> (72)	(47)
7	CO <sub>2</sub> Me	Et	amino acid <sup>e</sup>		<b>3g</b> (69)	(42)
8	CO <sub>2</sub> Et	Me	Bn	<b>1h</b> (73)	<b>3h</b> (76)	
9	CO <sub>2</sub> Me	Hex	Bn	<b>1i</b> (76)	<b>3i</b> (61)	
10	CO <sub>2</sub> Et	Hex	Bn		<b>3j</b>	(47)
11	CO <sub>2</sub> Et	3-butenyl	Bn	<b>1k</b> (79)	<b>3k</b> (60)	(41)
12	CO <sub>2</sub> Et	cit. <sup>f</sup>	Bn	<b>1l</b> (68)	<b>3l</b> (65)	(49)
13	CO <sub>2</sub> Et	iPr	Bn	<b>1m</b> (85)	<b>3m</b> (63)	(46)
14	CO <sub>2</sub> Me	iPr	Bn	<b>1n</b> (81)	<b>3n</b> (58)	
15	CO <sub>2</sub> Et	cPr	Bn	<b>1o</b> (72)	<b>3o</b> (70)	(46)
16	CO <sub>2</sub> Et	BnOCH <sub>2</sub>	Bn	<b>1p</b> (41)	<b>3p</b> (55)	

<sup>a</sup> Conjugated alkynoate **1** (1 mmol) and the amine (1.3 mmol) were absorbed on 1 g of silica gel and irradiated at 900 W for 8 min; <sup>b</sup> (1) Aldehyde (1 mmol), alkyl propiolate (2 mmol), Et<sub>3</sub>N (0.5 mmol), 0 °C, 30 min. (2) silica gel (1 g), amine (1.3 mmol). (3)  $\mu\nu$ -irradiation (900 W), 8 min. <sup>c</sup> Yields of isolated pyrroles, in percent. <sup>d</sup> Silica gel (2g) was used. <sup>e</sup> Amino acid is ethyl 3-aminobutyrate. <sup>f</sup> Cit. from (S)-(-)-citronellal.

**Scheme 1.** Proposed Mechanism for the  $\mu\nu$ -Assisted Rearrangement of 1,3-Oxazolidines **2** to Pyrroles **3**.



two carbon–nitrogen bonds, and an aromatic ring in a regioselective and efficient manner. The overall yields range from 40 to 55%, reflecting the high chemical efficiency of each of the reactions involved (at least nine reactions, >90% average yield). In addition, the reaction times are very short (less than 1 h), and the processing is extremely bench- and environment-friendly (see Supporting Information).

A plausible mechanism for this new  $\mu\nu$ -assisted rearrangement of 1,3-oxazolidines **2** is outlined in Scheme 1a. Two experimental features support this mechanism: (1) acetaldehyde-*d*<sub>4</sub> produces the pyrrole **3e** with deuterium at the methyl position but not in the ring and (2) conjugated alkynoate **5**, with two different ester groups, produces pyrrole **6** as the only isomer (Scheme 1b).

Finally, selective hydrolysis of the aliphatic ester generates an additional point for functional diversity on the pyrrole molecule (see Supporting Information for full details).

In summary, we have developed a metal-free, modular, and direct synthesis of 1,2,3,4-tetrasubstituted pyrroles from simple and commercially available components. The synthetic protocol embodies two coupled domino processes and is neatly accomplished in a one-pot manner according to the new chemical efficiency paradigm.<sup>10</sup> We believe that this method will have a significant application in the fields of combinatorial chemistry, diversity-oriented synthesis, and drug research.

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**Supporting Information Available:** Crystallographic data of **3n** (CIF) and experimental preparations for **1a–p**, **3a–p**, **5**, and **6** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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