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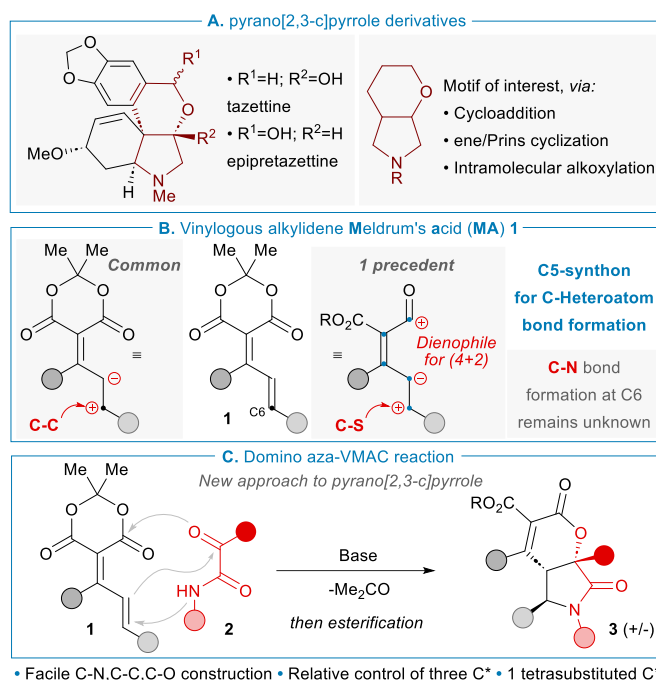
# Vinylogous and Stereoselective Domino Synthesis of Pyrano[2,3-c]pyrroles from Alkylidene Meldrum's acids

Mariia Savchuk,<sup>a</sup> Giang Vo-Thanh,<sup>b</sup> Sylvain Oudeyer,<sup>a</sup> H  l  ne Beucher<sup>a</sup> and Jean-Fran  ois Bri  re\*<sup>a</sup>

A domino Vinylogous aza-Michael-Aldol-Cyclocondensation (aza-VMAC) reaction was achieved with a series of alkylidene Meldrum's acid derivatives under simple operational conditions paving the way to novel pyrano[2,3-c]pyrroles in an excellent diastereoselectivity (> 96:4), encompassing the relative control of three contiguous stereocenters.

Pyrrolidine is a privileged heterocycle, which is the core-structure of several biologically active molecules.<sup>1</sup> The hydroxy-pyrrolidine motif, particularly embedded into a fused bicyclic architecture (e.g. pyrano[2,3-c]pyrrole derivatives), has spurred some interest in synthetic methodology to explore the chemical diversity in this series of azaarenes,<sup>2</sup> but also to adopt the "conformation restriction" approach appreciated in medicinal chemistry, as a better target binding is thereby expected (Scheme 1A).<sup>2b</sup> The development of strategies leading efficiently to original pyrano[2,3-c]pyrrole derivatives is therefore a valuable endeavor in organic synthesis, addressing the "escape from the flatland" principle, which increases Fsp<sup>3</sup> towards better druggable molecules.<sup>3</sup>

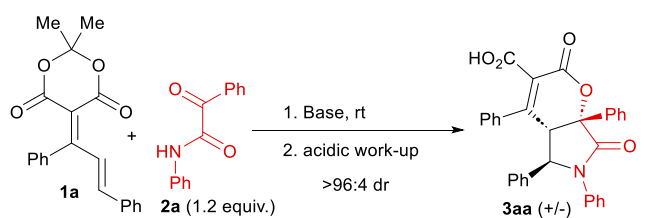
The vinylogous alkylidene Meldrum's acids **1** (MA, Scheme 1B) proved to be versatile platform molecules involved in various 1,6-conjugate additions or annulation sequences taking place at the terminal alkene moiety through C-C bond forming processes.<sup>4,5</sup> We recently challenged the C-heteroatom bond forming event through a 1,6-sulfa-Michael addition to vinylogous alkylidene MA **1**.<sup>6</sup> In order to prevent the expected equilibrated C-S bond formation, we took advantage of a subsequent domino aldol-cyclocondensation reaction, as a formal (4+2) annulation, highlighting an emerging vinylogous reactivity of ketone-derived alkylidene MA architectures.<sup>7,8</sup>



Scheme 1 Vinylogous alkylidene MA towards pyrrolidine derivatives.

This strategy opens a new avenue to the synthesis of original chiral heterocycles triggered by a C-heteroatom bond formation at C6 of vinylogous alkylidene MA, a platform molecule behaving thereby as a C5 synthon. Subject to the use of suited bifunctional nucleophiles like **2**<sup>8a,9,10</sup> we questioned whether a domino Vinylogous aza-Michael-Aldol-Cyclocondensation (aza-VMAC) reaction could be achieved with the aim of opening a new and expeditious route to original pyrrolidinones **3** embedded into a fused-bicyclic backbone (Scheme 1C). We are delighted to report on our endeavours towards the development of an original domino aza-VMAC reaction, encompassing a C-N/C-C/C-O bond forming process to build a three-dimensional shape architecture of type pyrano[2,3-c]pyrrole and having three contiguous stereogenic centers among which a valuable tetrasubstituted carbon atom.

Table 1 Optimization of the domino aza-VMAC reaction<sup>a</sup>



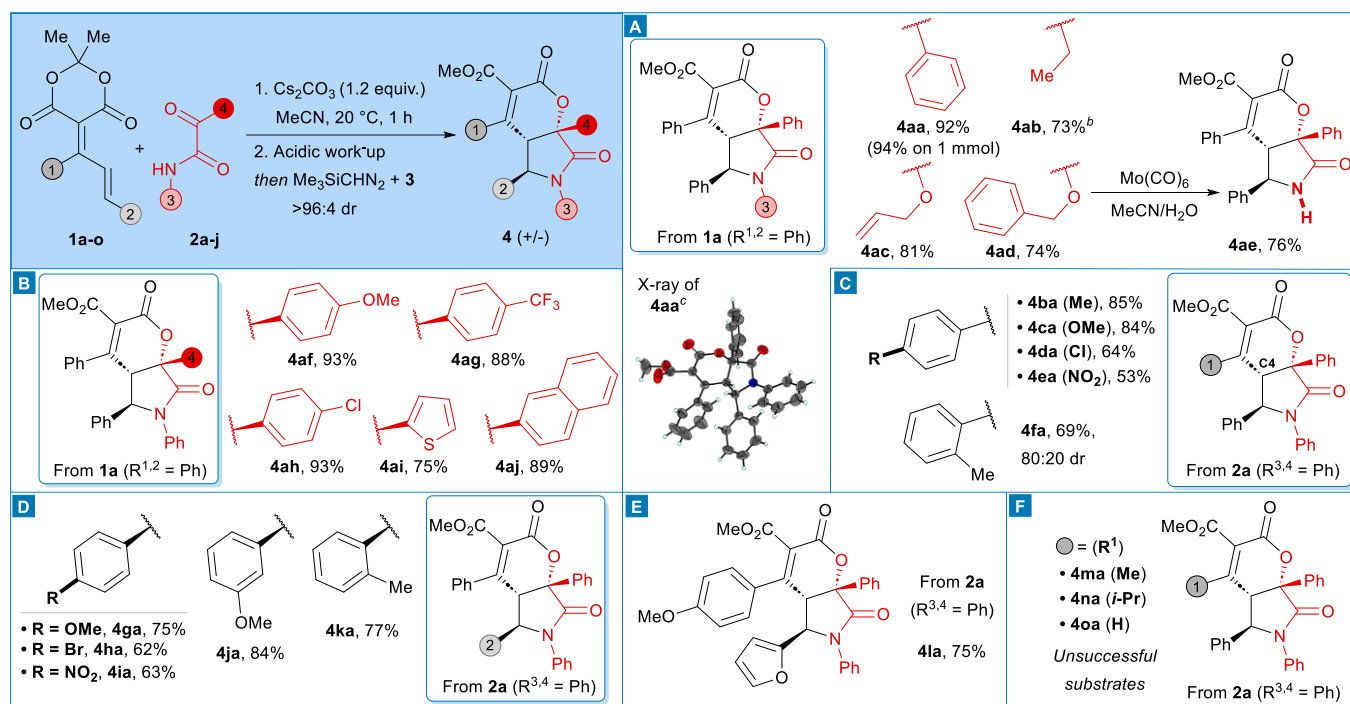
Entry	Base and additive (equiv.)	Solvent	Time (h)	Conversion (%) <sup>b</sup>
1	Na <sub>2</sub> CO <sub>3</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	16	0
2	K <sub>2</sub> CO <sub>3</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	16	0
3	K <sub>3</sub> PO <sub>4</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	16	0
4	K <sub>3</sub> PO <sub>4</sub> (2) + PPh <sub>3</sub> (0.2)	CH <sub>2</sub> Cl <sub>2</sub>	16	0
5	K <sub>3</sub> PO <sub>4</sub> (2) + Et <sub>3</sub> N (0.2)	CH <sub>2</sub> Cl <sub>2</sub>	16	0
6	K <sub>3</sub> PO <sub>4</sub> (2) + BnEt <sub>3</sub> NCl (0.2)	CH <sub>2</sub> Cl <sub>2</sub>	16	67
7	Cs <sub>2</sub> CO <sub>3</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	5	>99
8	Cs <sub>2</sub> CO <sub>3</sub> (1)	CH <sub>2</sub> Cl <sub>2</sub>	5	36
9	Cs <sub>2</sub> CO <sub>3</sub> (0.2)	CH <sub>2</sub> Cl <sub>2</sub>	5	traces
10	Cs <sub>2</sub> CO <sub>3</sub> (1)	toluene	5	30
11	Cs <sub>2</sub> CO <sub>3</sub> (1)	THF	5	45
12	Cs <sub>2</sub> CO <sub>3</sub> (1)	AcOEt	5	54
13	Cs <sub>2</sub> CO <sub>3</sub> (1)	MeCN	5	89
14	Cs <sub>2</sub> CO <sub>3</sub> (1.2)	MeCN	4	>99
15	Cs <sub>2</sub> CO <sub>3</sub> (1.2)	MeCN	1	>99

<sup>a</sup>Reaction performed at 0.04 M on 0.07 mmol scale (versus **1**) with 1.2 equiv. of acetamide **2** and a base, followed by an acidic work-up before extraction and analysis of the crude reaction mixture. <sup>b</sup>Conversion (**1** versus **3**) determined on the crude product by an <sup>1</sup>H NMR after an acidic work-up.

We first investigated the possibility of performing a domino aza-VMAC reaction by means of the model vinylogous alkylidene MA **1a** in the presence of various bifunctional aza-nucleophiles like **2** (Table 1, see Supplementary Information -SI- for details). Nevertheless, only the  $\alpha$ -ketoamide **2a** afforded promising results, providing that the suited basic conditions were used.<sup>8a, 9b, 10</sup> At first, the addition of 2 equivalents of sodium or potassium carbonate (entries 1-2), as well as potassium phosphate (entry 3) in dichloromethane as solvent led to the recovery of starting materials. Then, we wondered whether an organocatalytic process could occur using a phosphorus Lewis base (0.2 equiv. of PPh<sub>3</sub>, entry 4) or an amino Lewis or Brønsted base (0.2 equiv. of Et<sub>3</sub>N, entry 5) in the presence of K<sub>3</sub>PO<sub>4</sub>, as an “innocent” co-base. We did not get any reactivity in these cases. However, the Phase-Transfer Catalysis (PTC) conditions (0.2 equiv. of BnEt<sub>3</sub>NCl, entry 6), allowed 67% of conversion of **1a** into **3aa** after 16 hours. The product was isolated after an acidic work-up in order to restore the carboxylic acid functional group from the *in situ* formed carboxylate under basic conditions and the loss of acetone. This outcome shows that the nature of the lipophilic cation, and the ion pairs derived thereof, is an important parameter for getting a successful reactivity for this domino sequence. Eventually, it was found that the simple addition of cesium carbonate as a base promoted a complete transformation of **1a** into the corresponding pyrano[2,3-*c*]pyrrole derivative **3aa** (entry 7). Worthy of note, a single diastereoisomer was observed on the <sup>1</sup>H NMR of the crude reaction mixture (> 96:4 dr), showing an excellent stereocontrol throughout the domino sequence. A screening of reaction conditions was carried out by decreasing the amount of the mineral base Cs<sub>2</sub>CO<sub>3</sub> to 1 equivalent (entry 8, 36% of conversion in CH<sub>2</sub>Cl<sub>2</sub>). While the transformation was slowed down in a less polar solvent like toluene (30%, entry 10), better conversions were observed in THF and AcOEt (45% and 54%, entries 11-12). Eventually, the use of acetonitrile as solvent displayed a much faster reaction rate (entry 13), and a complete conversion was measured in only 1 hour using 1.2 equivalent of Cs<sub>2</sub>CO<sub>3</sub> (entries 13-14). This constitutes an expeditious construction of a novel pyrano[2,3-*c*]pyrrole **3aa**,

through a highly diastereoselective domino aza-VMAC reaction performed under very simple operational conditions (only a slight excess of Cs<sub>2</sub>CO<sub>3</sub> was used). Then, the investigation of the scope of this original sequence was undertaken.

Thanks to the readily accessibility of  $\alpha$ -ketoamides **2**, we were able to probe the influence of its nature on the reaction in the presence of alkylidene MA **1a** and Cs<sub>2</sub>CO<sub>3</sub> (1.2 equivalent) in MeCN as solvent for 1 hour (Scheme 2A). The esterification of the crude acid **3** was carried out using Me<sub>3</sub>SiCHN<sub>2</sub> to facilitate the purification by column chromatography and thus giving the corresponding methyl ester compound **4**. The model  $\alpha$ -ketoamide **2a** furnished the corresponding pyrrolidinone methyl ester **4aa** in an excellent 92% isolated yield, validating thereby the previously measured conversion into **3aa** (see Table 1). Uneventfully, the reaction could be scaled up to 1 mmol while maintaining a high yield of 94%. The structure of compound **4aa** and its relative configuration was unequivocally proven by X-ray analyses. The reaction rate was much slower with the  $\alpha$ -ketoamide **2b** having an *N*-Et group, and hence a less acidic N-H bond, albeit a descent 73% yield was obtained for product **4ab** in 16 hours of reaction and an excess of base (2 equiv. of Cs<sub>2</sub>CO<sub>3</sub>). The precursors **2c-d** with a *N*-alkoxyamide moiety proved to be competent nucleophiles for the domino aza-VMAC reaction, affording the corresponding products **4ac** (R<sup>3</sup> = OCH<sub>2</sub>CH=CH<sub>2</sub>) and **4ad** (R<sup>3</sup> = OBn) in 81% and 74% yields, respectively. However, the starting material **2e** with a primary amide functional group showed no reactivity towards the Michael acceptor **1a**. Nonetheless, a facile and chemoselective molybdenum N-O bond cleavage was carried out to transform compound **4ad** into the *N*-H product **4ae** in 76% yield. Interestingly, the ketone part of the  $\alpha$ -ketoamides **2f-h** could also be varied and we were delighted to observe that an aryl moiety with an electron-donating (**4af**, R = OMe, 93%) or electron-withdrawing group (**4ag-4ah**, R = CF<sub>3</sub>, Cl, 88-93%) at the *para*-position did not impact the reactivity. Moreover, other nucleophiles **2i-j**, with a thiophene or a 2-naphthyl pendant, also furnished the corresponding products **4ai-4aj** in excellent yields (75 and 89%, respectively, Scheme 2B).



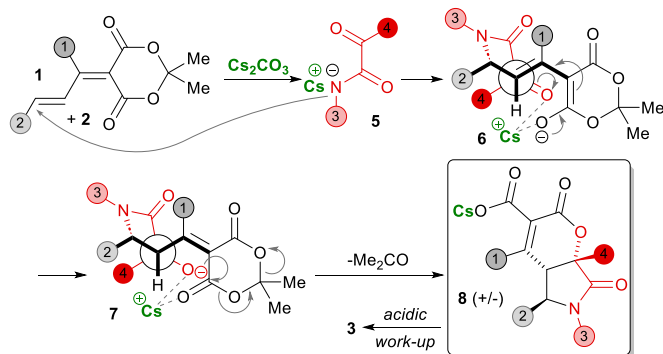
**Scheme 2** Scope and limitations. <sup>a</sup>Reaction conditions: reaction performed at 0.04–0.09 M on 0.06–0.08 mmol scale (*versus* **1**) with 1.2 equiv. of  $\alpha$ -ketoamides **2** and 1.2 equiv. of  $\text{Cs}_2\text{CO}_3$ , followed by an acidic work-up; the isolated product after extraction was treated with  $\text{Me}_3\text{SiCHN}_2$  in PhMe/MeOH mixture. Isolated yield after purification by column chromatography. *Note:* the first letter of compounds **4** corresponds to the letter of alkylidene Meldrum's acids **1** and the second letter corresponds to the letter of  $\alpha$ -ketoamides **2**. <sup>b</sup>Outcome with  $\text{Cs}_2\text{CO}_3$  (1.2 equiv.) gave respectively 14% conversion in 1 hour and 60% conversion in 16 hours, but an improved 73% yield was obtained using  $\text{Cs}_2\text{CO}_3$  (2 equiv.) in 16 hours. <sup>c</sup>Structure **4aa** (CCDC2328277) was ascertained by X-ray analyses.

Then, we studied the substitution pattern of the alkylidene MA **1** using the *N*-Ph  $\alpha$ -ketoamide **2a** as the model nucleophile (Scheme 2C,  $\text{R}^{3,4} = \text{Ph}$ ). Various *para*-substituted aryl groups were tolerated as a  $\text{R}^1$  substituent, affording the corresponding products **4ba–4ea** with yields ranging from 53 to 85%. The strong electron-withdrawing  $\text{NO}_2$  group might have a slight impact on the reactivity considering the partial conversion of 82% into intermediate **3ea** after one hour of reaction (*vide infra*), although the lower yield of 53% after esterification to **4ea** is essentially explained by purification issues. Interestingly, the more hindered *ortho*-substituted tolyl moiety afforded product **4fa** in a lower 69% yield. Worth to point out that all the reactions thus far gave products **4** in high diastereoselectivities (>96:4), with respect to the  $^1\text{H}$  NMR of the crude product. Only compound **4fa** appeared with two sets of signals in a ratio of 80:20 after esterification (50:50 before esterification). We believe that the rotation around the C4– $\text{R}^1$  bond of **4fa** is hindered enough to reveal a chiral axis, which gave a diastereoisomeric ratio at room temperature. As long as  $\text{R}^2$  pendants on the alkylidene MA **1g–k** are concerned, *para*-substituted aryl moieties with electron-donating or electron-withdrawing functional groups led to the corresponding pyrrazolidiones **4ga–4ia** with 62–75% yields (Scheme 2D). *Meta*- (from **1j**) and *ortho*-substituted aryl (from **1k**) groups were also nicely tolerated, affording products **4ja** and **4ka** in 84 and 77% yields, respectively. Interestingly, no clear stereoisomers were observed in the latter case with an *ortho*-substituted aryl group at this position but broad signal might account for the existence of rotamers with a rather rapid interconversion. Eventually, a product mixing an electron-rich aryl group like  $\text{R}^1$  and a furan

heterocycle like  $\text{R}^2$  was easily synthesized in 75% yield (**4la**, Scheme 2E). At that stage, under these  $\text{CS}_2\text{CO}_3$  promoted conditions, alkylidenes MA **1m** and **1n**, having an alkyl group like  $\text{R}^1$  (Me, *iso*-propyl), led to extensive decompositions in our hands (Scheme 2F). Although we cannot rule out a competitive deprotonation of the methyl group by the carbonate base,<sup>7</sup> this outcome tends to show the required stabilization by an aromatic group at this position ( $\text{R}^1$ ). This was reinforced by a similar decomposition event observed by means of the unsubstituted derivative **4oa** ( $\text{R}^1 = \text{H}$ ), which might lead also to a competitive 1,4-addition event.

Taking into account the stereoselective outcome of the domino aza-VMAC reaction, we propose the mechanistic pathway depicted in Scheme 3. After deprotonation of  $\alpha$ -ketoamide **2** by  $\text{Cs}_2\text{CO}_3$ , the corresponding cesium amide ions pair **5** would add, in a vinylogous fashion, to the presumed more stable *s-trans* to alkylidene MA **1**. The resulting aza-Michael adduct **6** would undergo a vinylogous aldol reaction giving rise to the formation of alkoxide **7** and triggering a cyclocondensation to the proximal carbonyl group to furnish the cesium carboxylate **8** after releasing a molecule of acetone. The corresponding acid product **3** is then isolated after a simple acidic work-up. Two important features were noteworthy during the achievement of the domino aza-VMAC reaction. First of all, the key role of cesium carbonate, which might generate a more soluble and nucleophilic amide ion pair **5**, facilitating the initial C–N bond forming process. This enhanced reactivity could also favour the subsequent C–C and C–O bonds formation (**6** to **7** to **8**) through less tight ion pairing events. Next, the excellent diastereoselective outcome obtained throughout the scope of

this domino sequence is remarkable. One can imagine that the R<sup>1</sup> substituent of the ketone moiety of **6** is located at the less hindered position, a conformation favored by a chelation with cesium cation and which prevents a clash with R<sup>2</sup>. But we assume that, after the vinylogous aldol reaction, this conformation ideally orientates the alkoxide group of intermediate **7** in order to allow the addition to the proximal carbonyl function. Then, the loss of acetone (fragmentation) prevents the potential equilibration of compound **7** back to starting materials **1** and **2**.



**Scheme 3** Proposed mechanism of the domino aza-VMAC reaction.

In summary, we reported a novel exploitation of vinylogous alkylidene Meldrum's acids **1** as platform molecules to be engaged into a domino aza-VMAC reaction affording a new entry to pyrano[2,3-*c*]pyrrole derivatives, encompassing the control of three contiguous stereocenters in an excellent diastereoselectivity. The extension of this expeditious domino strategy with two vinylogous steps to the construction of other medicinally important heterocycles, especially in an asymmetric version, is currently under investigation in our laboratory.<sup>11,12</sup>

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## Conflicts of interest

There are no conflicts to declare.

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