

# Synthetic Studies on the MARDi Cascade: Stereoselective Synthesis of Heterocyclic Seven-Membered Rings

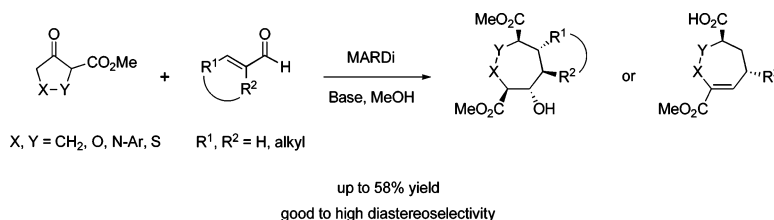
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## ABSTRACT



A versatile stereoselective synthesis of substituted and functionalized heterocyclic seven-membered rings is described. The approach involves a formal two-carbon ring expansion of heterocyclic cyclopentanones through a base-induced anionic domino three-component transformation named the MARDi cascade leading either to oxa-, aza-, or thiacycloheptanes bearing up to five contiguous stereogenic centers.

Heterocyclic seven-membered rings constitute the core or a key fragment of a number of bioactive compounds, isolated from natural sources or not.<sup>1</sup> The known biological properties of these compounds and the huge potential in drug discovery of this nuclei still render desirable the development of simple and general methodologies for their regio- and stereoselective synthesis. Although the preparation of thiepanes is less documented,<sup>2</sup> the number of methodologies made available for the preparation of azepanes<sup>3,4a</sup> and oxepanes<sup>4</sup> has steadily

increased in the past decades.<sup>5</sup> Among the approaches recently developed, one-carbon ring expansion taking advantage of the strain associated with cyclopropanes largely leads the way. In the oxepane series, representative examples are the rearrangement of fused cyclopropapyranes<sup>4c,6</sup> and the cleavage of hydroxy dithianes,<sup>7</sup> hydroxy epoxides,<sup>8</sup> and

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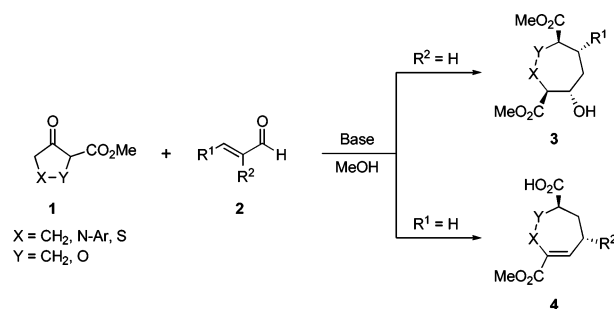
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hydroxy methoxyallenyl pyranes.<sup>9</sup> The azacycloheptane unit can be prepared by nitrogen insertion using a Beckmann or Schmidt reaction,<sup>10</sup> by ring enlargement of fused aziridines,<sup>5b,11</sup> and from the reaction of piperidones with diazoacetates,<sup>12</sup> and to a lesser extent, some free-radical transpositions are documented, which can also be used in the sulfur series.<sup>13</sup> The two-carbon ring enlargement approach is much more limited and essentially rests upon the reactivity of four-membered rings<sup>5b</sup> or involves very specific intermediates.<sup>14</sup> Oxepines and azepines can be prepared by palladium-catalyzed cyclization of bromoallenes bearing a nucleophilic heteroatom,<sup>15</sup> and [5 + 2] rhodium-catalyzed cycloaddition of cyclopropyl imines with electron-poor alkynes provides an entry to dihydroazepines.<sup>16</sup> Ring-closing methathesis has also proven popular for the synthesis of these unsaturated heterocycles in recent years.<sup>17</sup>

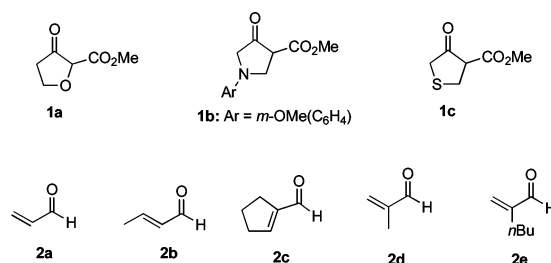
In this paper, we wish to report on a new approach for the selective preparation of aza-, oxa-, and thiacycloheptanes using the MARDi cascade, a domino reaction discovered in our group.<sup>18</sup> The overall process is an indirect two-carbon ring expansion of the easily accessible heterocyclic five-membered  $\beta$ -ketoesters **1** which, in the presence of base and methanol, combine with an  $\alpha,\beta$ -unsaturated aldehyde **2** to give stereoselectively either the cycloheptanols **3** or the cycloheptenic acids **4** as a function of the substitution pattern of the aldehyde (Scheme 1). This cascade reaction involving MeOH as a third component proceeds in substantial yields under thermodynamic control via an heterocyclic bicyclo-[3.2.1]-bridged intermediate.<sup>19</sup>

The MARDi cascade in the different heterocyclic series was first tested with furanone **1a**,<sup>20</sup> pyrrolidone **1b**,<sup>21</sup> and

**Scheme 1.** MARDi Cascade



thiafuranone **1c**<sup>22</sup> depicted in Figure 1 using acrolein (**2a**)



**Figure 1.** Substrates and aldehydes used for the study.

as the aldehyde partner (Table 1). The reactions were conducted in dry MeOH at various concentrations, and a substoichiometric amount of  $K_2CO_3$  proved to be the most efficient base for the transformation. The best yields of the expected seven-membered rings were obtained in relatively diluted medium. Actually, these cycloheptanols are relatively unstable in the reaction mixture, particularly in concentrated basic media. For example, at concentrations higher than 0.2 M, the furanone **1a** gave the corresponding hydroxyoxepane **3a** ( $R = H$ ) in very low yield as a 1.5:1 mixture of epimers (entry 1). Lowering the concentration to 0.1 and 0.04 M (entries 2 and 3) had no effect on diastereoselectivity but allowed the formation of **3a** in 24% and 46% yield, respectively. Unfortunately, this compound suffered degradation upon silica gel chromatography and only a small quantity of **3a** could be isolated. Thus, the crude product **3a** ( $R = H$ ) was silylated prior purification, allowing the isolation of the corresponding silyl ether **3a** ( $R = TMS$ ) in 42% yield from **1a** (entry 4). The reaction between the pyrrolidone **1b** and acrolein under the optimized conditions for **1a** provided a 1:1 mixture of the expected hydroxyazepane **3b** ( $dr = 3.5$ :1) and the corresponding azepine **3c** ( $R = Me$ ) in 36% yield (entry 5). Increasing the quantity of  $K_2CO_3$  to 1 and 1.5 equiv

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**Table 1.** MARDi Cascade in Heterocyclic Series with Acrolein<sup>a</sup>

entry	subst.	conc.	product <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>1a</b>	0.25 M		14 <sup>e</sup>
2	<b>1a</b>	0.1 M		24 <sup>e</sup>
3	<b>1a</b>	0.04 M		46 <sup>e</sup>
4 <sup>f</sup>	<b>1a</b>	0.04 M		42
5	<b>1b</b>	0.04 M		<b>3b</b> : 19 <b>3c</b> (R = Me): 17
6 <sup>g</sup>	<b>1b</b>	0.04 M		<b>3b</b> : 8 <b>3c</b> (R = Me): 25
7 <sup>h</sup>	<b>1b</b>	0.04 M		<b>3b</b> : 0 <b>3c</b> (R = Me): 31 <b>3c</b> (R = H): 51
8	<b>1c</b>	0.04 M		55

<sup>a</sup> All reactions were performed in dry MeOH at room temperature using K<sub>2</sub>CO<sub>3</sub> (0.5 equiv unless stated otherwise) for 16–30 h. <sup>b</sup> For **3a** and **3b**, the major isomer is the thermodynamically favored isomer (α-OH). <sup>c</sup> Isolated. <sup>d</sup> dr = 1.5:1. <sup>e</sup> Estimated from crude <sup>1</sup>H and <sup>13</sup>C NMR. <sup>f</sup> Crude **3a** (R = H) is treated with Me<sub>2</sub>NTMS in CH<sub>2</sub>Cl<sub>2</sub>. <sup>g</sup> 1 equiv of K<sub>2</sub>CO<sub>3</sub> was used. <sup>h</sup> 1.5 equiv of K<sub>2</sub>CO<sub>3</sub> was used. <sup>i</sup> dr = 3.5:1.

avored the formation of the dehydrated product **3c** (R = Me) without significant alteration of the global yield (entries 6 and 7). However, in the latter case the crude product was very clean and contained only the dehydrated product **3c** (R = Me), so the aqueous layer was acidified and extracted again to provide pleasingly 51% of the acid **3c** (R = H). The structure of **3c** (R = H) was confirmed by conversion to its methyl ester **3c** (R = Me). Finally, starting from thiafuranone **1c** (entry 8) the MARDi cascade was also successful and led exclusively to the thiepine **3d** in 55% yield, following dehydration of the intermediate hydroxy-thiepane.

Stimulated by these encouraging results, we next studied the evolution and the diastereoselectivity of the reaction with substituted aldehydes. The results are reported in Tables 2 and 3. In that case, DBU gave the best results under the optimized concentration conditions. The reaction of furanone **1a** with crotonaldehyde (**2b**) gave the expected substituted hydroxyoxepane **3e** (dr = 6:1, Table 2, entry 1). Also, the reaction of **1a** with cyclopentene carboxaldehyde (**2c**) gave stereoselectively the corresponding bicyclic compound **3f** (dr = 4:1, entry 2) showing an all-trans relationship of five contiguous asymmetric carbon atoms. Not surprisingly, the reaction of pyrrolidone **1b** with aldehyde **2c** provided the hydroxyazepane **3g** and the azepine **3h** (dr = 1.6:1) with a yield and a ratio hydroxyazepane/azepine similar to those obtained in the reaction with acrolein (compare entry 6 of Table 1 and entry 3 of Table 2). Similarly, the reaction of thiofuranone **1c** with aldehydes **2b,c** gave the expected substituted and bicyclic thiepines **3i** and **3j**, respectively (entries 4 and 5). The relative configurations of compounds **3a**, **3b**, **3e–h**, and **3j** have been established by 2D NMR techniques, and the structure of **3g** has been secured by X-ray diffraction analysis. It should be stressed here that the

**Table 2.** MARDi Cascade in Heterocyclic Series with β- or α,β-Substituted Acroleins<sup>a</sup>

entry	subst.	ald.	product <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>1a</b>	<b>2b</b>		28
2	<b>1a</b>	<b>2c</b>		21
3	<b>1b</b>	<b>2c</b>		<b>3g</b> : 10 <b>3h</b> : 22
4	<b>1c</b>	<b>2b</b>		58
5	<b>1c</b>	<b>2c</b>		28

<sup>a</sup> All reactions were performed in dry MeOH (0.04 M) at room temperature using DBU (1 equiv) for 20 h. <sup>b</sup> For **3e,f** and **3h–j** the major isomer is the thermodynamically favored isomer (α-OH or β-CO<sub>2</sub>Me). <sup>c</sup> Isolated. <sup>d</sup> dr = 6:1. <sup>e</sup> dr = 4:1. <sup>f</sup> dr = 1.6:1. <sup>g</sup> dr = 5:1. <sup>h</sup> dr = 1.3:1.

**Table 3.** MARDi Cascade in Heterocyclic Series with α-Substituted Acroleins<sup>a</sup>

entry	subst.	ald.	product <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>1a</b>	<b>2d</b>		42
2	<b>1b</b>	<b>2d</b>		7
3	<b>1c</b>	<b>2d</b>		51
4	<b>1c</b>	<b>2e</b>		42

<sup>a</sup> All reactions were performed in dry MeOH (0.04 M) at room temperature using DBU (0.5 equiv) for 20 h. <sup>b</sup> dr ≥ 10:1, except for **4b** (dr = 5:1). <sup>c</sup> Isolated.

reactions with the cyclopentene carboxaldehyde (**2c**) always furnish the trans-fused bicyclic product with total diastereoselectivity. Furthermore, the uncontrolled carboxylate stereogenic center can potentially be epimerized. With α-substituted acroleins the issue of the reaction is somewhat different, and the heterocycloheptenic carboxylic acids **4a–d**

are the only MARDi products (Table 3). These compounds are obtained with high diastereoselectivity ( $dr \geq 10:1$  except for **4b**) and show a trans relationship between the alkyl and the carboxyl group, as determined by 2D NMR techniques. Despite considerable efforts we were not able to obtain a crystalline derivative suitable for X-ray analysis in this series. The acids **4a–d** result from a stereoselective five-step domino transformation: the three steps of the MARDi cascade followed by a formal dehydration/saponification sequence.

When the MARDi cascade is performed with pyrrolidone **1b** or thiofuranone **1c**, the presence of the heteroatom  $\beta$  to the hydroxyl group in the cycloheptanol clearly favors the dehydration. In almost every case, the best yield of MARDi product was obtained with thiofuranone **1c**. This can be rationalized by the relative higher acidity of the proton  $\alpha$  to the sulfur atom compared to nitrogen, which might accelerate the dehydration process, thus avoiding unwanted over reaction of the cycloheptanol.

In conclusion, a variety of diversely functionalized and substituted heterocyclic seven-membered rings have been prepared from the easily available products **1a–c**, using the

MARDi cascade with up to five steps in the domino process. The reaction proceeds with good to high stereocontrol of up to five contiguous stereocenters and substantial yields of product are obtained under extremely simple and clean experimental conditions. The application of this reaction to the synthesis of biologically relevant compounds is currently under investigation in our laboratory.

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**Supporting Information Available:** Experimental procedures, spectroscopic data, copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds, and X-ray data for **3g** and the carbocyclic derivative of **4** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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