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# The first solvent-free synthesis of privileged $\gamma$ - and $\delta$ -lactams via the Castagnoli–Cushman reaction†

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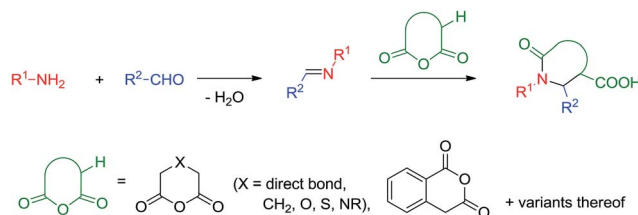
The first solvent-free protocol for the atom-economical Castagnoli–Cushman reaction is reported. It substantially broadens the reaction scope with respect to achievable substitution patterns around the privileged lactam cores compared to the traditional reaction format employing aromatic hydrocarbon solvents. The convenient product isolation protocol involves the use of aqueous base and acid solutions.

The formal cycloaddition reaction of imines (generated *in situ* or in a separate chemical step) with dicarboxylic acid anhydrides containing  $\alpha$ -protons, known as the Castagnoli–Cushman reaction (CCR),<sup>1</sup> provides a remarkably facile and, often, diastereoselective<sup>2</sup> access to polysubstituted  $\gamma$ - and  $\delta$ -lactams.<sup>3</sup> The latter are exceptionally useful, privileged<sup>4</sup> motifs in drug design considering the plethora of pharmacological effects reported for small molecules containing these heterocyclic cores.<sup>5</sup> In addition, the possibility of independently varying the reaction components offered by this reaction (and multicomponent reactions in general), allows pre-meditating further reactions within the product of the multicomponent step and thus quickly building up skeletal complexity.<sup>6</sup> One of the prominent features of this formally three-component process is its outstanding atom-economy:<sup>7</sup> indeed, all atoms originating from the aldehyde, primary amine and cyclic anhydride components<sup>8</sup> become incorporated into the product structure, except for the condensation water formed during the formation of the Schiff base (Scheme 1).

Considering that the crucial philosophical criterion of green chemistry, atom economy, is clearly fulfilled in the CCR, it is surprising that this important reaction has not been considered a tool for sustainable synthetic chemistry.<sup>9</sup> A possible reason for that could be that the CCR is most often

conducted in highly boiling aromatic hydrocarbon solvents (such as toluene or xylenes), while in many cases, chromatographic isolation of the reaction products is required.<sup>2</sup> This leads to a significant production of waste and certainly limits the environmental friendliness of the process. This consideration prompted us to investigate the opportunity to develop a new format for the CCR which would align it with the spirit of green chemistry.<sup>10</sup>

Another prominent multicomponent process, the Ugi reaction of an amine, a carbonyl compound (the two forming a Schiff base), a carboxylic acid and an isocyanide (leading to a diamide adduct in a simplest case<sup>11</sup>) is not only feasible but proceeds with higher rates and produces cleaner product mixtures when conducted in water.<sup>12</sup> This was a significant finding not only from the green chemistry<sup>13</sup> but also from the general chemical reactivity perspective. Indeed, the Ugi reaction involves two hydrolytically prone components – the Schiff base (which can be hydrolyzed back to the primary amine and the carbonyl components) and the isocyanide (which can be hydrated to form the respective formamide, especially in presence of a carboxylic acid<sup>13</sup>) and yet the rates of potential side-reactions with water turn out to be lower than the principal multicomponent reaction course. Initially, we became inspired by this example and attempted conducting the CCR in aqueous medium. However, it quickly became apparent that the hydrolysis of the cyclic anhydride component in this case proceeded faster than the desired formal cycloaddition and the target lactam product did not form. At the same time, we had



Scheme 1 The Castagnoli–Cushman reaction.

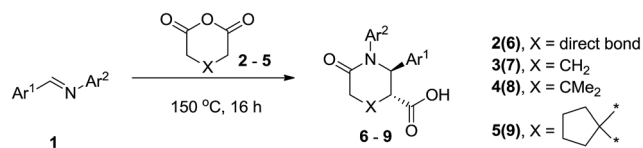
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† Electronic supplementary information (ESI) available. CCDC 1470615, 1470616 and 1470618. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra19196g



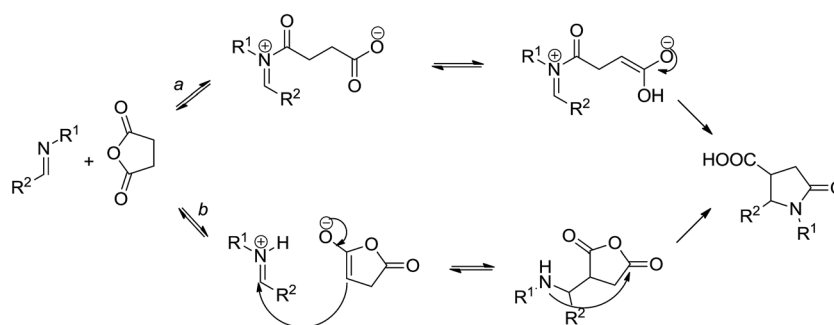
accidentally noted (in preliminary experiments that led to successful employment of thiodiglycolic anhydride in the CCR, X = S in Scheme 1(ref. 8)) that some reaction visibly occurred on neat mixing an imine and an anhydride components. This gave us an idea of conducting the CCR in the absence of any solvent which would not only eliminate the aromatic hydrocarbon solvent waste but also reduce the reaction volume and hence lower the energy requirements to achieve elevated reaction temperatures. In this communication, we report on a successful realization of this strategy using a set of *N*-arylidene anilines in combination with succinic and glutaric anhydrides (which are traditional inputs for the CCR<sup>1</sup>) as well as substituted versions of the latter.

The choice of the *N*-arylidene anilines as substrates (which were prepared in a separate step to improve product yield) was dictated primarily by the scarcity of the respective CCR products in the literature. Indeed, after the pioneering publication of Castagnoli,<sup>1a</sup> there has only been a handful of examples of 1,5-diaryl  $\gamma$ -lactams obtainable by the CCR of succinic anhydride<sup>15</sup> (in some cases, this chemotype was accessed using alternative strategies<sup>16</sup>). Similarly, 1,6-diaryl  $\delta$ -lactams amenable by the CCR are featured in only a few literature reports.<sup>17</sup>



Scheme 3 Solvent-free CCR of imines **1** with cyclic anhydrides **2–5** investigated in this work (the major, *trans*-isomer is shown for products **6–9**).

Consequently, medicinal chemistry potential of these lactams remains to be unraveled beyond the disclosed analgesic,<sup>15a</sup> aromatase inhibitory<sup>15b,17d</sup> and urokinase receptor targeting anticancer<sup>15d</sup> activities. The reason for such compounds' being underrepresented in the literature could lie in the reluctance of the respective *N*-aryl imines to undergo the CCR. Indeed, according to the current mechanistic understanding,<sup>18</sup> the CCR can proceed along two alternative mechanistic pathways (a: intermolecular *N*-acylation followed by intramolecular Mannich reaction or b: intermolecular Mannich reaction followed by intramolecular acylation) both of which include an acylation of the nitrogen atom in question (Scheme 2). Naturally, in aniline-derived imines, the nucleophilicity of that reactive center would



Scheme 2 Possible mechanistic pathways for the CCR (shown for succinic anhydride).

Table 1 Screening of temperature regimens for the solvent-free reaction *N*-benzylidene aniline with succinic or glutaric anhydrides

Temperature	<i>n</i> = 1		<i>n</i> = 2	
	Conversion of the imine (%)	<sup>1</sup> H NMR yield, % ( <i>trans</i> + <i>cis</i> )	Conversion of the imine (%)	<sup>1</sup> H NMR yield, % ( <i>trans</i> + <i>cis</i> )
90 °C	~50	<20	~40	<20
110 °C	~60	22	~50	24
130 °C	100	36	98	42
150 °C	100	48	100	65
170 °C	100	50	100	66



Table 2  $\gamma$ -Lactams **6a–l** synthesized in this work

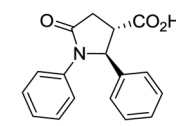
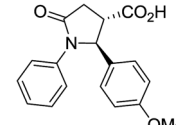
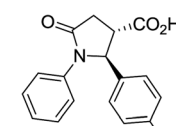
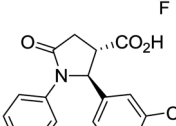
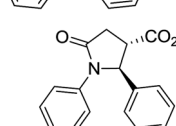
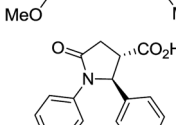
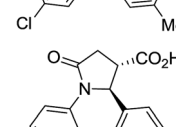
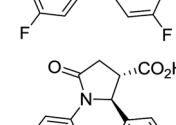
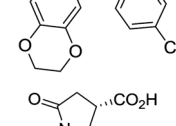
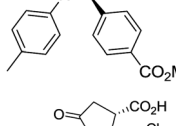
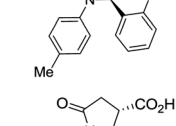
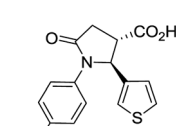
Compound	Product <b>6</b>	Isolated yield (%)	<i>Trans/cis</i> ratio
<b>6a</b>		50	7 : 1
<b>6b</b>		50	5 : 1
<b>6c</b>		40 <sup>a</sup>	7 : 1
<b>6d</b>		35	7 : 1 <sup>b</sup>
<b>6e</b>		35 <sup>a</sup>	9 : 1 <sup>a</sup>
<b>6f</b>		24 <sup>a</sup>	9 : 1 <sup>a</sup>
<b>6g</b>		36 <sup>a</sup>	7 : 1 <sup>a</sup>
<b>6h</b>		28 <sup>a</sup> 50 <sup>c</sup>	10 : 1 <sup>a</sup> 12 : 1 <sup>c</sup>
<b>6i</b>		37 <sup>a</sup> 54 <sup>c</sup>	10 : 1 <sup>a</sup> 11 : 1 <sup>c</sup>
<b>6j<sup>d</sup></b>		37 <sup>a</sup>	10 : 1 <sup>a</sup>
<b>6k</b>		37 <sup>a</sup>	10 : 1 <sup>a</sup>

Table 2 (Contd.)

Compound	Product <b>6</b>	Isolated yield (%)	<i>Trans/cis</i> ratio
<b>6l</b>		35 <sup>a</sup> 63 <sup>c</sup>	6 : 1 <sup>a</sup> 7 : 1 <sup>c</sup>

<sup>a</sup> The yield and *trans* : *cis* ratio obtained after crystallization of the crude product from aqueous ethanol after the basic/acidic workup. <sup>b</sup> Pure *trans*-isomer was obtained after additional crystallization from aqueous ethanol. <sup>c</sup> The yield and *trans* : *cis* ratio obtained after crystallization of the crude product from aqueous ethanol without the basic/acidic workup. <sup>d</sup> Reaction was run at 170 °C.

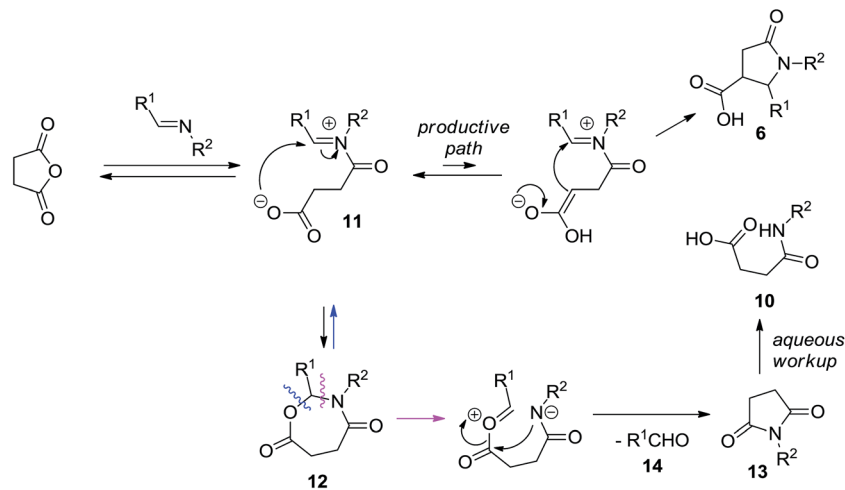
be reduced and the reactivity of such substrates in the CCR would be retarded.

In order to verify the viability of the solvent-free protocol and to determine the optimal temperature regimen for the CCR, neat equimolar mixtures of *N*-benzylidene aniline with succinic or glutaric anhydrides were heated at various temperatures ranging from 90 °C to 170 °C and the presence of the desired lactams as well as the yields were determined by the integration of the characteristic <sup>1</sup>H NMR signals corresponding to C<sup>2</sup>-H of *cis*- and *trans*-isomers of the lactam products (the *trans*-isomer always being in majority<sup>17a</sup>) relative to *n*-tetradecane internal standard (see ESI<sup>†</sup>).

As can be seen from the results presented in Table 1, full conversions of the imine **1** (obtainable, in turn, by several green protocols from the respective aniline and aldehyde<sup>19</sup>) were achieved at temperatures above 130 °C and, to our delight, the signals corresponding to the desired product were present in the spectrum of the reaction mixture. The optimum product yield was observed at 150 °C and no significant improvement was evident at 170 °C. Therefore, the temperature of 150 °C was used uniformly throughout this study as shown in Scheme 3 (heating to 170 °C was used occasionally as noted below, in order to drive up the conversion and product yield, which were lower if the reaction was run at 150 °C).

Reactions with succinic anhydride (**2**) all led to the formation of the desired products **6a–l** (Table 2). After the heating of the neat mixture of the imine and succinic anhydride finished and the reaction was cooled down to ambient temperature, a glassy solid mixture was obtained. To that mixture, 10% aqueous KHCO<sub>3</sub> (regarding the choice of the base – *vide infra*) was added and the solid mass gradually dissolved on overnight stirring, thus separating carboxylate-containing products from the insoluble by-products. The cloudy solution was filtered through a pad of Celite in order to further remove the latter and the filtrate was acidified causing the desired product of varying purity to precipitate. The isolated yield of **6a** corresponded very well to the yield determined in the initial <sup>1</sup>H NMR experiments (*vide supra*). Using





Scheme 4 Possible competing reaction pathways rationalizing the formation of the by-products observed after the basic reaction workup.

this simple environmentally friendly isolation protocol, compounds **6a**, **6b** and **6d** were obtained as analytically pure mixtures of *trans*- and *cis*-isomers with clear preference for the former (crystallization of **6d** from aqueous ethanol furnished pure *trans*-isomer), which is in line with the results usually obtained in the aromatic hydrocarbon solvents.<sup>2</sup> In the majority of cases, unfortunately, the product mixtures were contaminated with varying amounts of succinic monoanilide **10**.

The formation of **10** can be rationalized as follows. According to the current mechanistic understanding, acylation of the imine intermediate leads to zwitterionic species **11** that can productively cyclize to furnish the target compound **6**. Alternatively, the iminium moiety can undergo an intramolecular trapping with carboxylate anion to give rise to cyclic aminal **12**. The latter can, in principle, degrade back to **11** or it can eliminate aldehyde **14** and form succinimide **13** which can be hydrolyzed, on basic workup, to the contaminant **10** (Scheme 4). Some observations speak for the correctness of such mechanistic interpretation. Firstly, the use of more basic aqueous  $K_2CO_3$  solution for product isolation led to much higher content of **10** in the isolated product **6**. Secondly,  $^1H$  NMR analysis of the crude product prior to treatment with the aqueous base solution clearly displays characteristic signals corresponding to the aldehyde proton ( $\delta \sim 10.0$  ppm) and the succinimide bis-methylene bridge ( $\delta \sim 2.9$  ppm).

In all cases where the material precipitating on acidification of the basic solution of **6** was contaminated with **10**, additional crystallization from aqueous ethanol furnished pure products **6** in modest yields and pronounced *trans*-selectivity. In some cases (**6h**, **6i**, **6l**), basic/acidic workup step could be omitted and crystallization from aqueous ethanol gave analytically pure products with significant improvement of the yield.

Employment of glutaric anhydride (**3**) as well as its 3,3-disubstituted variant (**4–5**) in the solvent-free CCR followed by

the environmentally friendly basic/acidic aqueous isolation protocol described above, resulted in significantly improved product yields and purities while additional crystallization from aqueous ethanol was required in only one case, **7g** (Table 3). Such a satisfactory result was likely due to lower likelihood of the reaction proceeding along the non-productive path as the formation of an 8-membered analog of postulated cyclic adduct **12** would be much less favored (however, contamination with glutaric monoanilide akin to **10** was still quite noticeable for **7g** which mandated additional crystallization). Reactions involving **4** and **5** required higher temperature ( $170\text{ }^\circ\text{C}$ ) for better yields. This was likely due to much more sterically demanding situation around the  $\alpha$ -position in these anhydrides, which is involved in the cyclization, rather than to possible Thorpe–Ingold effect.<sup>20</sup> To the best of our knowledge, compounds **8a–d** and **9a–d** are the first examples of this type of highly sterically congested Castagnoli–Cushman-type  $\delta$ -lactams.

Notably, reactions summarized in Tables 2 and 3 appear to have a rather broad scope with respect to substituents in the aromatic groups originating from either the aldehyde or the aniline. In fact, the scarce examples of similarly diaryl-substituted CCR-derived lactams reported in the literature<sup>14–16</sup> only include electron-neutral and electron-rich aromatic groups. In this study, similar reaction yields were obtained for diverse substitution patterns, including electron-withdrawing substituents in either portion of the imine partner (or even both portions as in **7l**). We attempted to reproduce most striking examples of this sort (**7d**, **7h** and **7l**) in refluxing toluene and observed no formation of the respective products on prolonged (up to 72 h) reaction times. Therefore, the green, solvent-free protocol reported herein also enables the CCR reactions which are reluctant to proceed in solution.

In summary, we have reported the first solvent-free protocol for the synthesis of privileged  $\gamma$ - and  $\delta$ -lactams using the Castagnoli–Cushman reaction which is not only environmentally



Table 3  $\delta$ -Lactams 7a–o, 8a–d and 9a–d synthesized in this work

Compound	Product 7–9	Isolated yield (%)	<i>Trans/cis</i> ratio
7a		67	6 : 1 <sup>a</sup>
7b		65	7 : 1 <sup>a</sup>
7c		72	8 : 1
7d		66	6 : 1
7e		70	6.5 : 1
7f		64	7 : 1
7g		51 <sup>b</sup>	8 : 1 <sup>a,b</sup>
7h <sup>c</sup>		74	6 : 1 <sup>a</sup>
7i		80	7 : 1 <sup>a</sup>
7j		64	4 : 1
7k		72	6 : 1

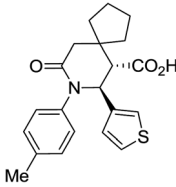
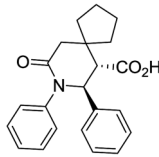
Table 3 (Contd.)

Compound	Product 7–9	Isolated yield (%)	<i>Trans/cis</i> ratio
7l		56	6 : 1 <sup>a</sup>
7m		59 <sup>d</sup>	Only <i>trans</i>
7n		89	5 : 1
7o		73	6 : 1
8a <sup>c</sup>		69	4 : 1 <sup>a</sup>
8b <sup>c</sup>		36	5 : 1
8c <sup>c</sup>		58	4 : 1
8d <sup>c</sup>		50	7 : 1 <sup>a</sup>
9a <sup>c</sup>		63	4 : 1 <sup>a</sup>
9b <sup>c</sup>		60	3 : 1





Table 3 (Contd.)

Compound	Product 7–9	Isolated yield (%)	Trans/cis ratio
9c <sup>c</sup>		30	2 : 1
9d <sup>d</sup>		82	5 : 1

<sup>a</sup> Pure *trans*-isomer was obtained after additional crystallization from aqueous ethanol. <sup>b</sup> The yield and *trans* : *cis* ratio obtained after crystallization of the crude product from aqueous ethanol after the basic/acidic workup. <sup>c</sup> Reaction was run at 170 °C. <sup>d</sup> The yield and *trans* : *cis* ratio obtained after crystallization of the crude product from aqueous ethanol without the basic/acidic workup.

friendly but also significantly broadens the scope of this important atom-economical reaction with respect to the accessible substitution patterns.

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