



Complications in the Castagnoli-Cushman reaction: An unusual course of reaction between cyclic anhydrides and sterically hindered indolenines



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ABSTRACT

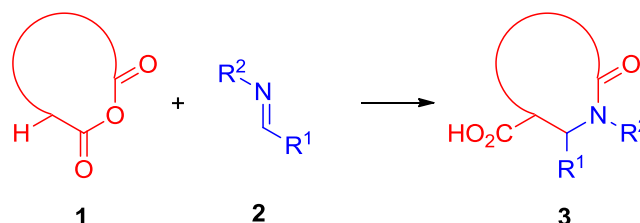
Attempted reaction of indolenines (which represent rather sterically hindered cyclic imines) with a series of dicarboxylic acid anhydrides yielded no expected product, the Castagnoli-Cushman lactam. Instead, products presumably formed via *N*-acyliminium species trapping by a carboxylate anion. Among them, hydrolytically labile 2:2 adducts of an indolenine and a cyclic anhydride, containing a 16-membered cyclic core, are particularly intriguing. This result contradicts the recently reported successful Castagnoli-Cushman reaction of indolenines with homophthalic anhydride suggesting a mechanistic switch in the course of the reaction.

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The formal cycloaddition of α -C–H cyclic anhydrides **1** with imines **2** (formed *in situ* or in a separate chemical step) offers a convenient entry into polysubstituted lactams **3** (Scheme 1). It was discovered by Castagnoli and Cushman over four decades ago¹ and has been referred to as the Castagnoli-Cushman reaction (CCR).

The diversity of cyclic anhydrides employed in this reaction was traditionally limited to homophthalic anhydride (HPA) as well as simple ones such succinic or glutaric; however, the range of structurally more complex anhydrides has been steadily expanding as was recently reviewed.²

Mechanistically, the reaction is thought to proceed via one of two possible mechanisms: (A) *N*-acylation of the imine component followed by intramolecular trapping of *N*-acyliminium species **4** in Mannich-type fashion and (B) Mannich-type addition of the anhydride's enol form to a protonated iminium species resulting in initial adduct **5** which then undergoes intramolecular *N*-acylation. Both of these pathways can lead to the formation of product lactams **3** and often there is no evidence but circumstantial which can allow selecting between them for a given reaction. It is likely that mechanism A dominates for many simple, poorly enolizable cyclic anhydrides. Indeed, it is almost impossible to obtain target lactams **3** using α -C–H imines: the initial formation of **4** immedi-



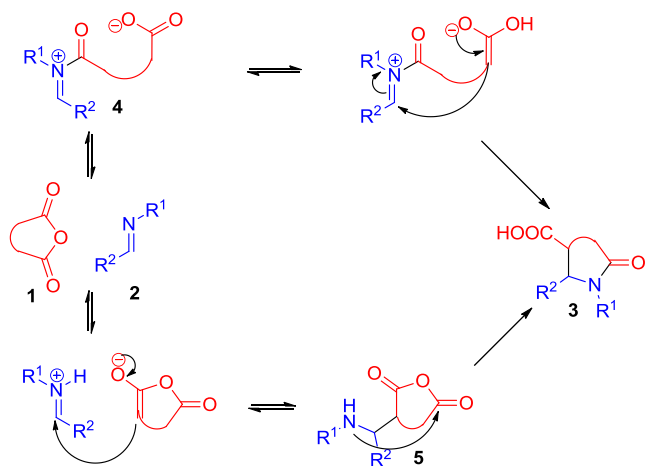
Scheme 1. The Castagnoli-Cushman reaction (CCR).

ately leads to the formation of enamides as was recently confirmed.^{3,4} At the same time, more enolizable HPA is likely to react via mechanism B based on the fact that several α -C–H imines have been previously condensed with this anhydride (Scheme 2).⁵ Moreover, we have recently isolated and characterized an adduct similar to **5** formed in the reaction of HPA with indolenines which spontaneously formed the respective CCR product on standing.⁶

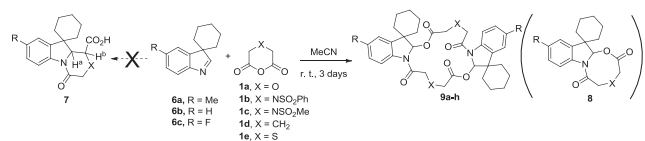
The latter reaction showcases the use of indolenines as a special case of cyclic imines for the CCR. Encouraged by its successful realization, we were keen to test other cyclic anhydrides – in particular, glutaric anhydride as well as the recently reported heteroatom-including analogs of it⁷ (**1a–e**) – in the reaction with indolenines (**6a–c**). The reaction was conducted in acetonitrile at ambient temperature (in analogy with the CCR of HPA⁶) and was markedly slow in each case, full consumption of the starting indolenines achieved

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Scheme 2. Mechanistic pathways for the CCR.



Scheme 3. The expected (left) and observed (right) outcome of the attempted CCR between **6a–c** and **1a–e**.

in 3 days.⁸ At the end of this period a precipitate formed which was collected by filtration. ¹H NMR analysis of the precipitate revealed a complete absence of the characteristic signals⁵ from protons H^a

and H^b which would be present in expected products **7**. However, the requisite signals from the indolenines as well as the former anhydride moiety were present in 1:1 ratio. Initially, we hypothesized that the products thus isolated could result from a known⁹ 1,2-addition of carboxylic acid anhydrides to imines and structure **8** was assigned. However, to our great astonishment, when we obtained single-crystal X-ray structures of these compounds, it showed the product to be a bis-lactam/bis-lactone 2:2 adduct of **6** and **1** possessing a 16-membered ring, i.e. **9** (Scheme 3).¹⁰

As it is shown in Table 1, the isolated yields of macrocyclic adducts **9a–h** are quite modest. Examination of the filtrate (obtained after isolation of **9**) by TLC, LC MS and ¹H NMR revealed the presence of a major product in addition to a number of minor components (minute quantities of **9** among them). Some of compounds **9a–h** were noted to be distinctly unstable to hydrolysis: indeed, their instability prevented compound **9g–h** from being isolated and fully characterized. Therefore, we hypothesized that the major product observed in the filtrate could be the product of hydrolytic degradation of **9** (and also of **8** if it formed initially) by adventitious water. In order to verify that, we conducted the reaction between **6a** and **1e** and then kept the crude product mixture at 5 °C in wet ethyl acetate from which, indeed, expected carboxylic acid **10**¹¹ slowly crystallized out in 57% yield (Scheme 4). The structure of **10** was additionally confirmed by single-crystal X-ray analysis (see ESI).

On initial viewing, the formation of products **9** containing a 16-membered cycle seems somewhat counterintuitive as such a process would be disfavored over the formation of product **8** incorporating an eight-membered ring (formation of the latter cannot be either confirmed or ruled out at the moment). However, the appreciable conversion of **1** and **6** into macrocycles **9** can be rationalized as follows. The reaction is likely to commence with *N*-acylation of indolenine **6** with cyclic anhydride **1** leading to the formation of

Table 1
16-Membered bis-lactams/bis-lactones **9a–h** obtained in this work.

Compound	Structure	Single-crystal X-ray structure	Isolated yield (%)
9a			17
9b		NA ^a	27
9c			18

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