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The Castagnoli-Cushman reaction in a three-component format

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ABSTRACT

The first example of the Castagnoli-Cushman reaction of homophthalic acid with an amine and an aldehyde conducted in a three-component format is reported. This new protocol employs no dehydrating agents and, unlike the traditional Castagnoli-Cushman reaction of homophthalic anhydride, allows simultaneous mixing of all three reagents and provides good to excellent yields of *trans*-configured tetrahydroisoquinolonic acids.

The formal cycloaddition of imines **1** and α-C—H anhydrides of dicarboxylic acids **2**[1] was recently dubbed the Castagnoli-Cushman reaction (CCR)[2] in honour of the researchers who were the first to describe[3] this powerful entry into polysubstituted lactams **3**. Initially thought to be applicable only to the preparation of γ- and δ-lactams, the reaction has been recently shown to give ε-lactams from suitable seven-membered cyclic anhydrides.[4] Perhaps the most developed variant of the CCR is that involving the use of homophthalic anhydride **4**. The resulting tetrahydroisoquinolonic acids **5**, often obtained as pure *trans*-diastereomers (Fig. 1),[5] have found utility as medicinal chemistry leads (or key precursors thereof) in diverse disease areas including cancer,[6] malaria,[7] and diabetes.[8]

In many literature reports the CCR is regarded as multicomponent,[9] likely due to the fact that imines **1** can be considered as intermediates formed *in situ* from the respective amine and aldehyde. However, a true three-component format (i. e. when all three components –an aldehyde, an amine and a dicarboxylic acid anhydride such as **4** - are simultaneously combined in the reaction vessel) – cannot be realized. We observed that such a combination of reagents results in rapid acylation of the amine by **4** (at the more reactive 'phenylacetyl' rather than more inert 'benzoyl' center[10,11]), prior to the formation of **1**, which produces monoamide **6** and

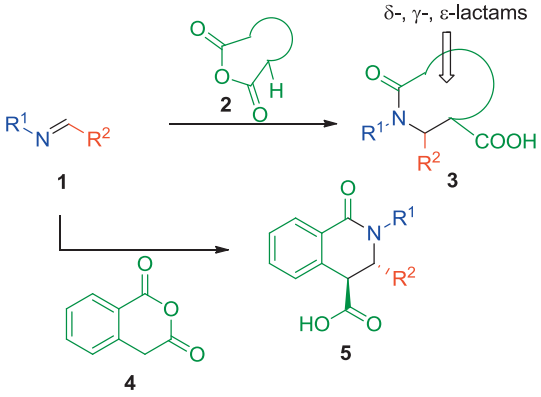

Fig. 1. The Castagnoli-Cushman reaction (CCR).

shuts off any further possibility for the aldehyde component to be incorporated in the product structure (Scheme 1). This observation is in contrast to an earlier report by Azizian and co-workers[12] who described an alum-catalyzed CCR conducted in a multicomponent format. The authors stated that in presence of alum (KAl $(SO_4)_2 \cdot 12H_2O$), anhydride **4** acylates the amine at its 'benzoyl' center to give monoamide **7**, and the latter is transformed into *cis*-configured tetrahydroisoquinolonic acid **9** *via* the formation of an *N*-acyliminium intermediate **8** (Scheme 1).

We reasoned that we should be able to conduct said three-component CCR and avoid the unwanted, terminal transformation of

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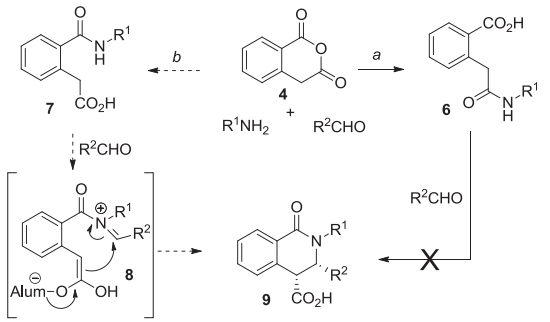


Scheme 1. Results of the three-component CCR: (*a*) observed in this work[a] and (b) reported by Azizian and co-workers..12 [a]Reaction was conducted in presence of alum (0.5 equiv.); R^1 = 4-ClC_6H_4, R^2 = Ph.

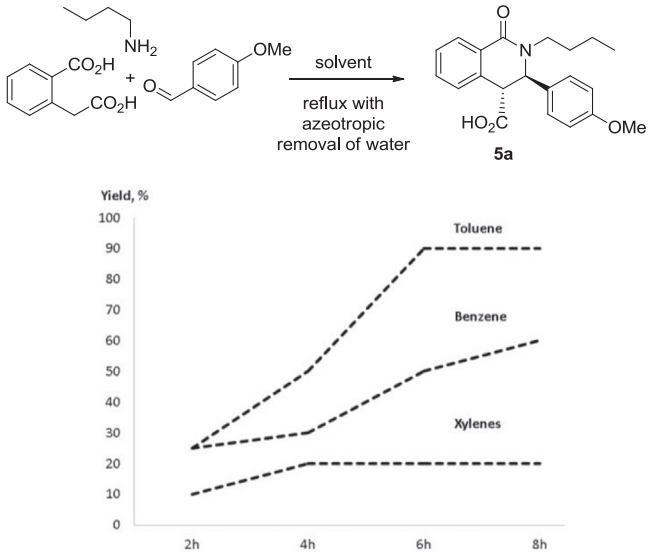


Fig. 2. Results of the CCR conducted under azeotropic distillation conditions.[a]. [a]Yield was determined by HPLC analysis of the reaction mixtures.

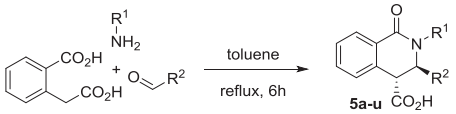
anhydride **4** into monoamide **6** if anhydride **4** is generated, *via* the cyclodehydration of homophthalic acid, in presence of a mixture of a primary amine and an aldehyde which, in turn, would produce the imine partner for the CCR (**1**) under dehydrative conditions. Recently, we demonstrated that the cyclodehydration of dicarboxylic acids for the CCR can be efficiently promoted by acetic anhydride in the presence of imine **1**.[13] However, this method would not be applicable for the desired three-component CCR format since acetic anhydride (as any other reactive dehydrating agent such as oxalyl chloride[14] or Boc_2O[15]) would likely acylate the amine component thereby excluding it from participation in the CCR. As an alternative, we decided to investigate the dehydration of a mixture of homophthalic acid with an amine and an aldehyde by azeotropic removal of water. Herein, we describe the first multicomponent format for the CCR of homophthalic acid[16] which was realized using such an approach.

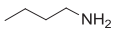
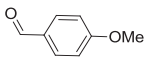
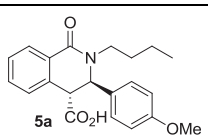
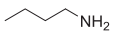
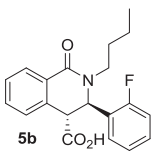
To the best of our knowledge, the cyclodehydration of homophthalic acid under azeotropic distillation conditions has not been described in the literature. Therefore, we investigated the model reaction of homophthalic acid with *n*-butylamine and *p*-anisaldehyde in aromatic hydrocarbon solvents capable of forming azeotropes with water (xylenes, toluene and benzene). The reaction progress was monitored by HPLC analysis of the reaction mixtures. To our delight, the desired CCR product **5a** was detected in all cases, however, the best result was obtained in toluene (Fig. 2).

The maximum HPLC yield was observed under these conditions after reflux with azeotropic removal of water for 6 h; prolonged heating (8h) did not alter the yield. The HPLC yield of 90% translated quite well to the 83% isolated yield of compound **5a**. These conditions[17] were adopted to the preparation of other *trans*-configured tetrahydroisoquinolonic acids **5b-u** (Table 1).[18]

The scope of the reaction was studied for aliphatic and aromatic amines in combination with aromatic and heteroaromatic aldehydes, i. e. within the reagent space that usually provides the best results when employed in the CCR.[1,13] The reaction generally resulted in good to excellent isolated product yields. In all cases, *trans*-configuration was assigned to the CCR products based on the appearance of signals corresponding to the vicinal methine protons as singlets (or unresolved doublets) as opposed to the larger coupling constants usually obtained for *cis*-diastereomers.[1] Particularly notable is the reaction where a chiral, racemic amine was employed (Table 1, entry 17). This reaction provided a good yield of a single diastereomer of the respective CCR adduct (**5q**)

Table 1
trans-Tetrahydroquinolonic (THIQ) acids **5a-u** prepared by the three-component CCR.



Entry	R^1NH_2	R^2CHO	THIQ acid	Isolated yield (%)
1				83
2				92