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Three-Component Castagnoli-Cushman Reaction of 3-Arylglutaconic Acid Anhydrides, Carbonyl Compounds, and Ammonium Acetate: a Quick and Flexible Way to Assemble Polysubstituted *NH*-δ-lactams

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A practical straightforward synthesis of medicinally important *NH*-δ-lactams through the three-component Castagnoli-Cushman reaction of 3-arylglutaconic anhydrides with carbonyl compound and ammonium acetate has been developed. The scope of the protocol has been thoroughly explored paying particular attention to the carbonyl component using wide array of aliphatic and aromatic aldehydes as well as rarely involved cyclic and acyclic ketones. Synthetic potential of prepared compounds was demonstrated by a series of post-modifications, including unexpected isomerization.

Introduction

2-Piperidone (δ-lactam) moiety undoubtedly belongs to privileged cores for medicinal chemistry design.[1–2] Likewise, natural-likeness of 2-piperidone derivatives is apparent considering the presence of this scaffold (in various degrees of saturation) in numerous natural products including anticancer piperlongumine (**1**),[3] chymotrypsin inhibitory depsipeptide streptopeptolin B (**2**),[4] antimicrobial alkaloid myrionine (**3**),[5] GABA antagonist alantrypinone (**4**)[6] and antinociceptic alkaloid allomatrin (**5**)[7] (Figure 1). α-Amino γ- and δ-lactams (the so-called Freidinger lactams) have been widely employed as a bridging moiety in the design of conformationally constrained peptidomimetics.[8] The relevance of the 2-piperidone scaffold to the bioactive and natural product chemical space makes the development of new 2-piperidone compound libraries for drug discovery highly worthwhile.[9] Lead generation libraries should be based on robust, streamlined and flexible synthetic approaches which would entail short (preferably, one-step) synthetic routes and allow for independent variation of substituents around the core in question simply by drawing from relevant pools of reagents. Multicomponent reactions (MCRs) are unrivaled in terms of providing all of the above.[10]

As far as the 2-piperidone scaffold is concerned, its MCR-based assembly was traditionally achieved *via* the use of four-center, three-component Ugi reaction of bifunctional reagents **6** comprising δ-oxopentanoic acid motif.[11] Recently, we developed an approach to 1,4,6-trisubstituted 1,6-dihydropyridine-2(3*H*)-ones **7** *via* the three-component Castagnoli-Cushman reaction (CCR)[12] of aldehydes and amines (pre-condensed to form the respective imine) and 3-arylglutaconic acid anhydrides **8**.[13] High yields, generality of scope and mild reaction conditions prove these substrates to be among most reactive anhydrides known up to date. Unlike most previous reported studies this CCR was accompanied by decarboxylation. Compounds **7**, formed in just one step from readily available reagents could be oxidized to the respective pyridin-2-ones **9** or hydrogenated to give *cis*-configured 2-piperidones **10**.[14] This method, however, did not allow obtaining 1,6-dihydropyridine-2(3*H*)-ones unsubstituted at the nitrogen atom. *NH*-δ-Lactam is an important pharmacophoric moiety[15] capable of forming a dual hydrogen bond donor/acceptor interaction with the protein target.[16] Moreover, the hydrogen bonding of *NH*-lactams in general was recently emphasized as an important control element in transition metal-catalyzed and photochemical reactions.[17] Considering these aspects, having a method at hand to access *NH*-δ-lactams **11** directly (and not *via* the use of removable protecting groups such as allyl[18] or benzyl[19] as deprotection may not always be compatible with periphery groups and the scaffold itself) was deemed highly desirable.

Recently, we successfully employed ammonium acetate as a source of ammonia for the preparation of NH-tetrahydroisoquinolonic (NH-THIQ) acids *via* the three-component Castagnoli-Cushman reaction of homophtalic anhydride (HPA) with carbonyl compounds. The reaction gave high yields of the desired products on simple stirring of the reaction components in acetonitrile at 80 °C overnight.[20] Inspired by this example, we set off to investigate the applicability of the same three-component approach to the synthesis of *NH*-δ-lactams **11** from 3-arylglutaconic acid anhydrides **8** (Scheme 1). Herein we report on the result of this investigation.

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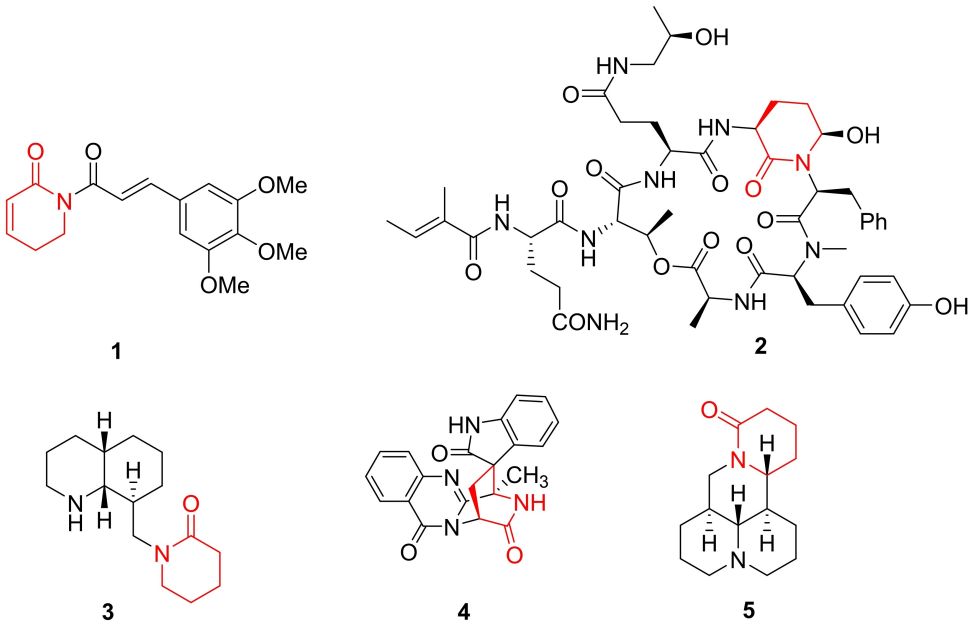
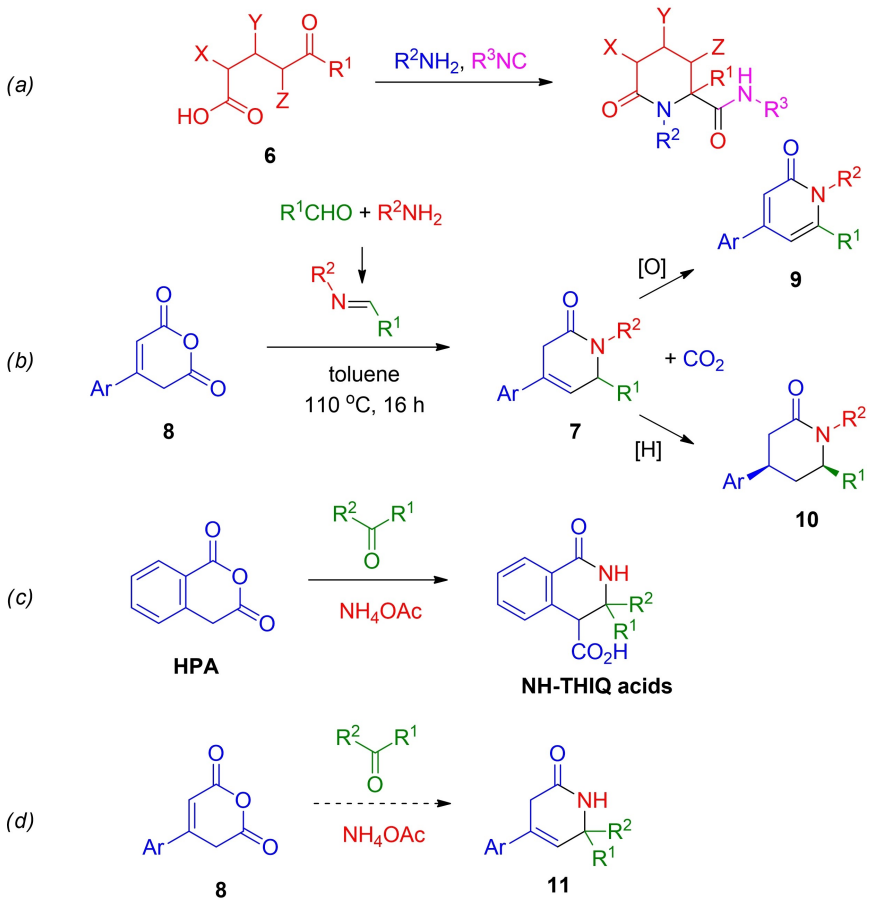


Figure 1. Examples of biologically active natural products incorporating 2-piperidone moiety.



Scheme 1. Known MCR-based approaches to the construction of 2-piperidone scaffolds (*via* (a) the Ugi reaction and (b) the Castagnoli-Cushman reaction), (c) previously reported multicomponent CCR-type synthesis of NH-THIQ acids and (d) the approach to *NH*-δ-lactams **11** investigated in this work.

Results and discussion

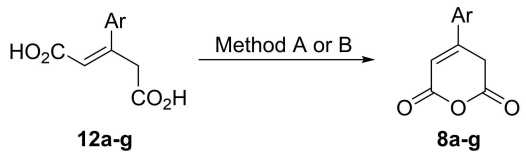
Cyclic anhydrides **8a**–**g** were synthesized from 3-arylgluraconic acids **12a**–**g**[21] using one of the two methods (Scheme 2): diacids **12** with electron-neutral and electron-rich aryl groups were efficiently cyclodehydrated on simple reflux in toluene with azeotropic removal of water (Method A); those with electron-deficient aryl groups required being reacted for 2 days at room temperature with trifluoroacetic anhydride in acetonitrile in order to cyclize (Method B).[14]

Mostly relying on the set of conditions developed for the three-component synthesis of NH-tetrahydroisoquinolonic acids from homophthalic anhydride,[20] we experimented briefly with reaction times using equimolar amounts of anhydride **8a**, *p*-tolualdehyde and two-fold excess of NH_4OAc. In contrast to the syntheses with homophthalic anhydrides which required 16 h for the reaction to complete, 91% yield of 1,6-dihydropyridine-2(3*H*)-one **11a** was obtained after reaction proceeded for only 2 hours. These conditions were applied to the other 30 combinations of cyclic anhydrides **8a**–**g** and various aldehydes and ketones. The results of these experiments are summarized in Scheme 3.

The scope of the reaction appears rather wide with respect to the carbonyl compounds although the yields vary between 21% and 91%. Reactions with aromatic electron poor and heteroaromatic aldehydes (except for thiophene-2-carboxaldehyde, *cf.* **11ae**) generally gave lower yields. Likewise, using volatile aldehydes (*cf.* **11n**, **11p**, **11r**) diminished the yields despite the doubling of the amount of the carbonyl compound. The reaction worked generally well for ketones, including cyclic ones: spirocyclic products **11i**–**m** are quite appealing from the structural point of view, considering the general value of spirocycles for drug discovery.[22] Analogously to our previous studies[13–14] the substitution pattern in anhydride aryl moiety has no significant influence on the reaction yield. The structure of the compound **11c** was confirmed by single-crystal X-ray analysis matching reported data.[13]

As had been proposed earlier[13] and subsequently corroborated by deuterium labeling experiments,[14] the formation of 1,6-dihydropyridine-2(3*H*)-ones **11** likely proceeds as the typical Castagnoli-Cushman reaction. It commences with the Mannich-type reaction of the enol form of cyclic anhydride **8′** and the imine formed *in situ* from the carbonyl compound and ammonium acetate. The resulting Mannich adduct **12** then undergoes an intramolecular acylation (cyclic anhydride aminolysis) to give α,β-unsaturated lactam carboxylic acid **13**. Transformation of the latter intermediate (postulated in this case and observed at lower temperature in the mechanistic investigation reported on earlier[14]) in the final product **11** is accompanied by decarboxylation (Scheme 4). Based on the previous observations,[14] it can also be suggested that **13** exists in a tautomeric equilibrium with **13′** but the latter should not be prone to the direct decarboxylation into **11**.

In analogy to N-substituted Castagnoli-Cushman adducts **7**,[13] partially unsaturated *NH*-δ-lactam **11a** (taken as an example) can be fully reduced to 2-piperidone **14** or aromatized to 2-hydroxypyridine **15**. Interestingly, treatment of **11a** with DBU in toluene at 100 °C did lead to isomerization of the double bond. However, contrary to the expectations and prior observations,[13] the major product was cyclic *N*-acyl enamide **16** (isolated in 70% yield) and not α,β-unsaturated lactam **16′** which was isolated in 20% yield and 90% purity (Scheme 5).



12a-g **8a-g**

8a, Ar = Ph, quant.[a]
8b, Ar = 4-$MeOC_6H_4$, 90%[a]
8c, Ar = 4-$NH_2SO_2C_6H_4$, 79%[b]
8d, Ar = 3-$CF_3C_6H_4$, 62%[b]
8e, Ar = 4-FC_6H_4, 89%[a]
8f, Ar = 3-FC_6H_4, 97%[a]
8g, Ar = 2-FC_6H_4, 57%[b]

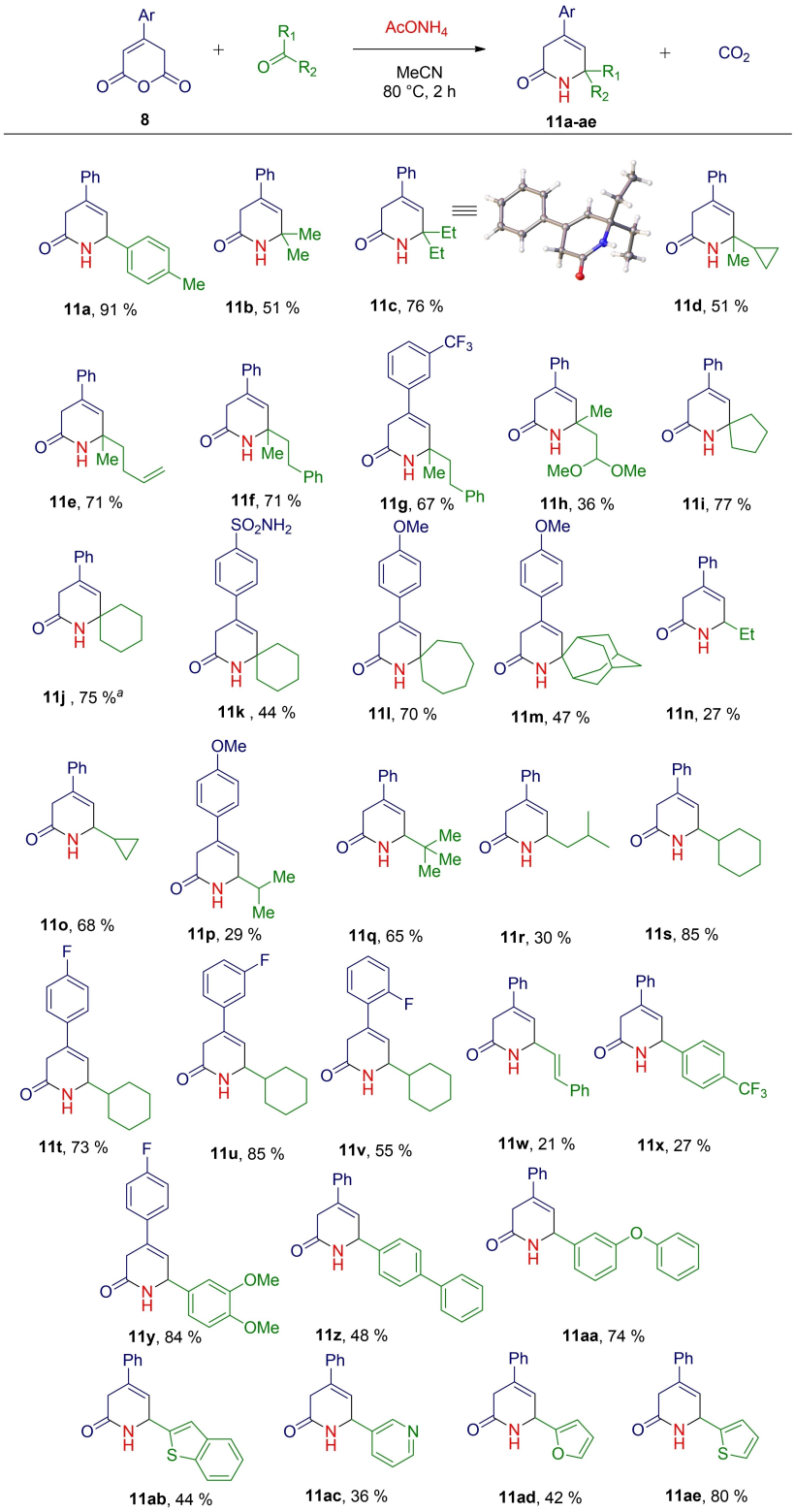
Scheme 2. Preparation of 3-arylglutaconic anhydrides **8a**–**g**: [a]Method A: toluene, reflux, Dean-Stark trap, 24 h; [b]Method B: EtOAc, TFAA, r. t., 2 days.

Conclusion

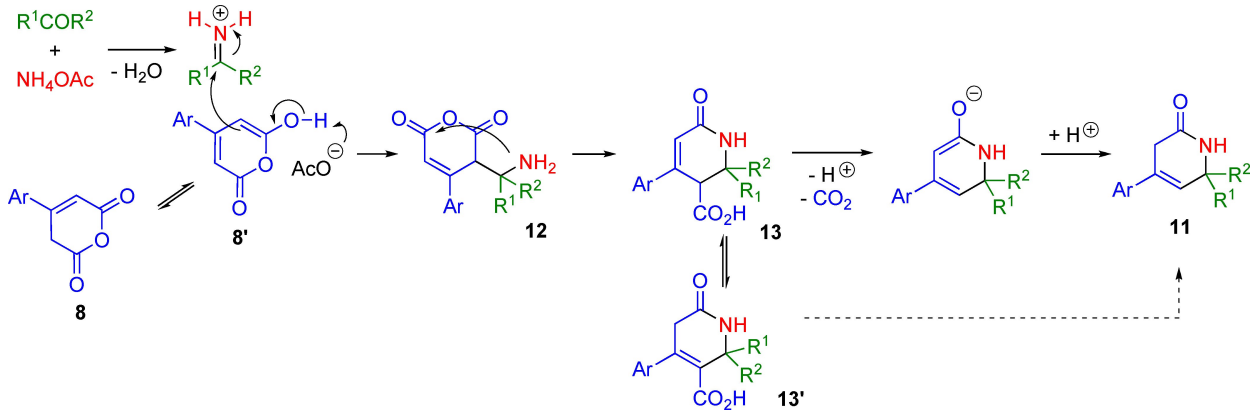
In summary, we have described a practically convenient synthesis of medicinally important *NH*-δ-lactams *via* the three-component Castagnoli-Cushman reaction of 3-arylglutaconic anhydrides with carbonyl compound and ammonium acetate. The reaction is applicable to a wide range of aldehydes and ketones (including cyclic ones) and is amenable to parallel synthesis. The product structure featuring an unconjugated double bond (as confirmed by single-crystal X-ray analysis) is in accordance with prior observations and proposed mechanistic reasoning. The partially unsaturated adducts can be oxidized or reduced to give 2-piperidones and 2-hydroxypyridine, respectively. Isomerization of the double bond on treatment with base (DBU) delivered the expected α,β-unsaturated lactam as minor product while the major product was the unexpected cyclic *N*-acyl enamide. These findings will be of utility for the array synthesis of druglike compound libraries for lead generation. Should the biological activity associated with these 4,6-disubstituted *NH*-δ-lactams be discovered, the method is also conducive to subsequent SAR exploration and lead optimization due to its simplicity and multicomponent character.

Deposition Number 2034845 (for **11c**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

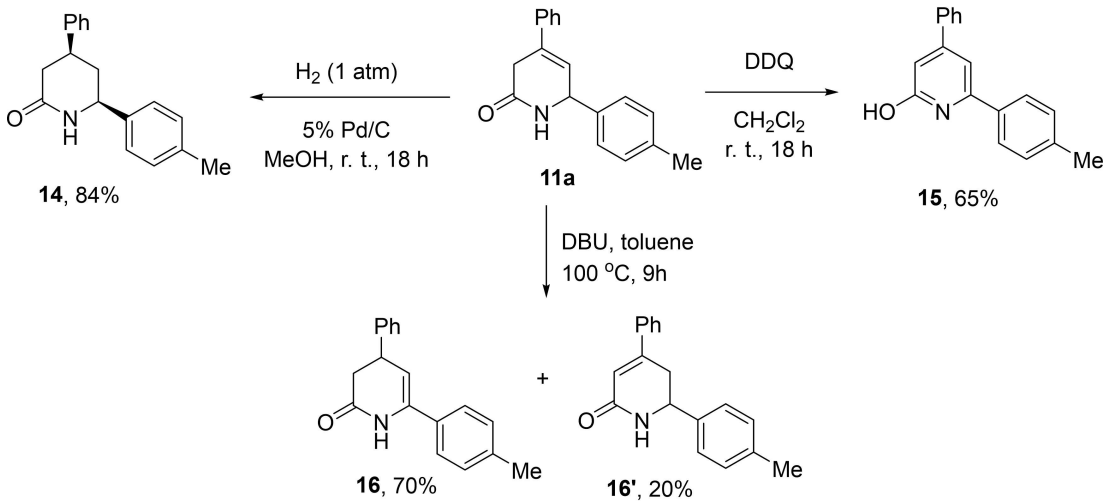
Supporting Information (see footnote on the first page of this article): Experimental procedures, analytical data, copies of the NMR spectra.



Scheme 3. Three-component synthesis of 1,6-dihydropyridine-2(3*H*)-ones **11a**–**ae** *via* the three-component reaction of 3-arylglutaconic anhydrides **8**, carbonyl compounds and ammonium acetate ([a]reaction was performed on 7.0 mmol scale).



Scheme 4. Plausible mechanism for the formation of *NH*-δ-lactams **11**.



Scheme 5. Scaffold transformations of compound **11 a**.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Ammonium acetate · Aromatization · Castagnoli-Cushman reaction · Decarboxylation · Double bond isomerization

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