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Decarboxylative Annulation of α-Amino Acids with β-Ketoaldehydes

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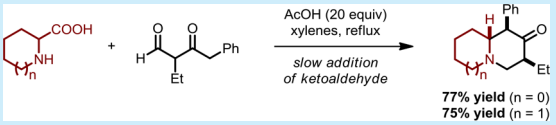
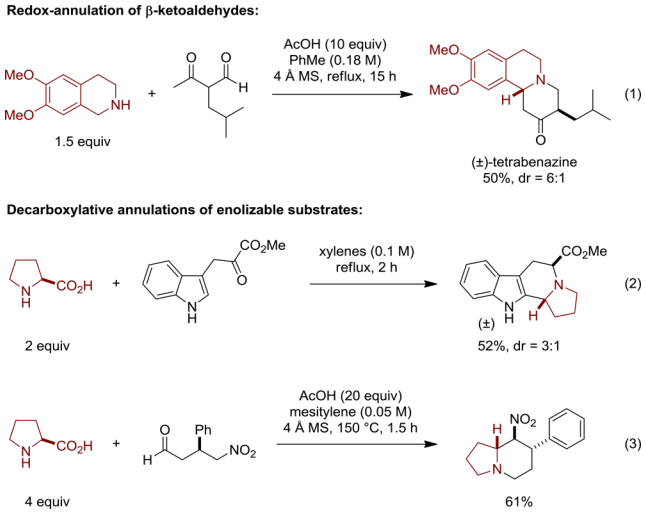
Supporting Information

ABSTRACT: Indolizidine and quinolizidine derivatives are readily assembled from L-proline or (±)-pipecolic acid and β-ketoaldehydes via a decarboxylative annulation process. These reactions are promoted by acetic acid and involve azomethine ylides as reactive intermediates.



In the course of our studies on the development of redox-neutral procedures for the C−H functionalization of amines,[1] we recently established a method for the synthesis of polycyclic amines via redox-neutral annulation of cyclic amines with β-ketoaldehydes.[1f] This method was applied to the synthesis of the commercial drug tetrabenazine (eq 1). A

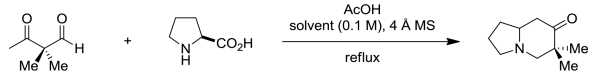


current limitation of this chemistry is the requirement for relatively activated amines such as 1,2,3,4-tetrahydroisoquinoline and tryptoline. Substrates such as pyrrolidine and piperidine, which would provide access to substituted indolizidines and quinolizidines, core structures of a significant number of natural products,[2] failed to undergo annulation with β-ketoaldehydes under a range of conditions. Here, we report a decarboxylative annulation approach to the synthesis of indolizidine and quinolizidine derivatives from L-proline/(±)-pipecolic acid and β-ketoaldehydes.

Amino acids formally derived from secondary amines, such as proline, sarcosine, and pipecolic acid, have long been known to undergo the formation of azomethine ylides upon decarboxylative condensation with an aldehyde.[3] The chemistry of these dipolar intermediates is dominated by pericyclic reactions.[4] We and others have shown that azomethine ylides, obtained via decarboxylative condensation, can undergo a range of non-pericyclic transformations.[5−8] Two main types of reactions have been identified, decarboxylative three-component coupling reactions and decarboxylative annulations.[5] The majority of these reactions are limited to nonenolizable aldehydes and ketones. An early example of a decarboxylative annulation with an enolizable species is the reaction of L-proline with an indole containing α-ketoester (eq 2).[5f] To our knowledge, decarboxylative annulations with enolizable aldehydes have thus far only been achieved with 4-nitrobutyraldehydes (eq 3).[5r]

The feasibility of a decarboxylative annulation of L-proline with β-ketoaldehydes was first evaluated with nonenolizable substrate **1a** (Table 1).[9] Only insignificant amounts of the desired product **2a** were obtained upon heating **1a** under reflux in xylenes in the presence of 4 equiv of L-proline (entry 1).

Table 1. Reaction Development[a]



entry	x	AcOH (equiv)	solvent	time[b] (h)	yield (%)
1	4		xylenes	0 + 2	6
2	4	5	xylenes	0 + 2	12
3	4	10	xylenes	0 + 2	21
4	4	20	xylenes	0 + 2	52
5	4	20	xylenes	0 + 15	51
6	4	20	PhMe	0 + 2	44
7	4	20	xylenes	15 + 2	75
8	8	20	xylenes	15 + 2	48
9	2	20	xylenes	15 + 2	26
10[c]	4	20	xylenes	15 + 2	40
11	4	neat	AcOH	15 + 2	18

[a]Reactions were performed with 0.5 mmol of ketoaldehyde **1**. Yields are isolated yields of chromatographically purified compounds. [b]Addition time for **1** + additional reaction time after completed addition. [c]Reaction was performed in the absence of 4 Å MS.

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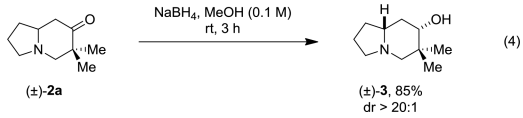
Upon addition of 5 equiv of acetic acid, **2a** was obtained in 12% yield (entry 2). The yield of **2a** increased to 21% with 10 equiv of acetic acid (entry 3) and to 52% with 20 equiv of acetic acid (entry 4). Prolonging the reaction time from 2 to 15 h had no discernible effect on reaction yield (entry 5). A change of solvent from xylenes to toluene resulted in a lower yield (entry 6). Slow addition of β-ketoaldehyde **1a** led to a marked increase in reaction efficiency and enabled the isolation of product **2a** in 75% yield (entry 7). An increase or decrease in the amount of L-proline had a detrimental effect on reaction yields (entries 8 and 9). Significant reduction in yield to 40% was noted in the absence of molecular sieves (entry 10). The utilization of acetic acid as the sole reaction medium provided unfavorable results (entry 11). It should be noted that, in all cases, complete consumption of β-ketoaldehyde **1a** was observed.

The scope of the decarboxylative annulation reaction of β-ketoaldehydes **1** was explored as summarized in Scheme 1, utilizing the optimized conditions (Table 1, entry 7). L-Proline and (±)-pipecolic acid readily underwent decarboxylative annulations with a range of nonenolizable β-ketoaldehydes **1**. The corresponding products were obtained in moderate to good yields. β-Ketoaldehydes **1** bearing a phenyl or methyl substituent in the 4-position provided the corresponding indolizidine and quinolizidine products as essentially single diastereomers. Gratifyingly, the standard reaction conditions were applicable to a number of enolizable β-ketoaldehydes **1**. Different substitution patterns were realized, and products were obtained with reasonable levels of diastereoselectivity.

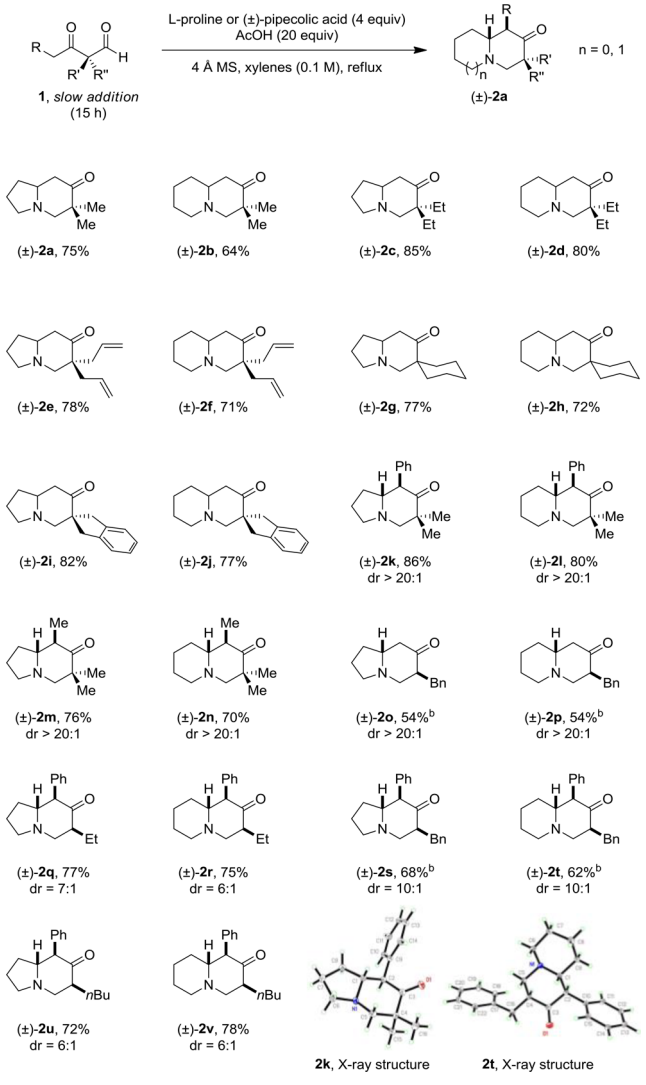
All annulation products contain a ketone moiety, offering numerous possibilities for further modification. For instance, reduction of indolizidine **2a** with sodium borohydride in methanol provided amino alcohol **3** in highly diastereoselective fashion and 85% yield (eq 4).



(4)

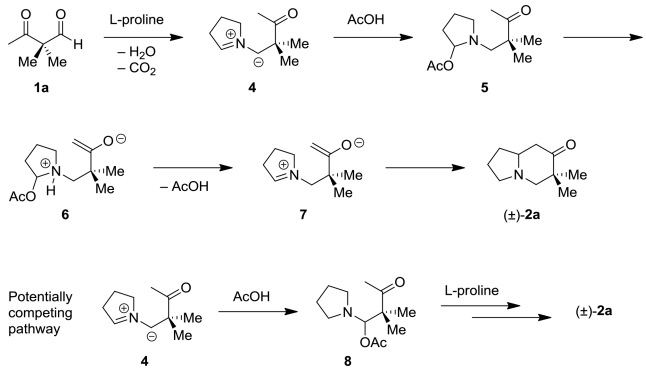
A proposed mechanism for the decarboxylative annulation reaction of β-ketoaldehyde **1a** with L-proline is shown in Scheme 2. Decarboxylative condensation of **1a** with L-proline gives rise to azomethine ylide **4**, which is thought to be a key intermediate.[4] In analogy to the established mechanism for the annulation of amines with 4-nitrobutyraldehydes,[1b] addition of acetic acid to **4** likely results in the formation of *N*,*O*-acetal **5**. Intramolecular proton transfer could then lead to the formation of zwitterion **6**, followed by elimination of acetic acid to provide zwitterion **7**. The latter undergoes a Mannich ring closure to give final product **2a**. A potential and unproductive albeit ultimately inconsequential side reaction involves addition of acetic acid to azomethine ylide **4** with formation of *N*,*O*-acetal **8**, a regioisomer of **5**. However, *N*,*O*-acetal **8** could reengage L-proline to ultimately form product **2a** while generating pyrrolidine as a byproduct. This ability of the system to correct for the "wrong" regiochemistry was recently demonstrated in the context of the decarboxylative Strecker reaction.[5i] Consistent with this notion, an excess of the amino acid reaction partner is typically beneficial in decarboxylative annulations. In regard to product diastereoselectivity, stereogenic centers in α-position of the ketone can likely undergo epimerization under the reaction conditions. In addition, the Mannich step has previously been shown to be reversible.[1f] Consequently, the diastereomeric ratios of the annulation products likely reflect their corresponding thermodynamic stabilities.

Scheme 1. Scope of the Decarboxylative Annulation[a]



[a]Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields of purified products. [b]Due to the limited solubility of the corresponding β-ketoaldehyde starting material in xylenes, both starting materials were mixed directly and allowed to react for 15 h.

Scheme 2. Proposed Mechanism



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In summary, we have achieved decarboxylative annulations of L-proline and (±)-pipecolic acid with enolizable and non-enolizable β-ketoaldehydes. This method provides rapid access to decorated indolizidines and quinolizidines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03721.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1557923−1557924 and 1581830 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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