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Construction of 5,6-Ring Fused 2-Pyridones: An Effective Annulation Tactic Achieved in Water

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Abstract

An efficient protocol for elaboration of the 5,6-fused 2-pyridone ring system, exploiting the tandem condensation of propiolamide and cyclic β -ketomethyl esters in water, followed by acid or base promoted intramolecular ring closure and decarboxylation, has been developed.

Keywords

Heterocycles; condensation; fused-ring systems; Tandem reactions; Michael additions

The 2-pyridone ring system comprises the central structural element in numerous important bioactive natural products and related congeners, including the camptothecins,¹ drug candidates active against leukemia,^{1b} Huperzine A,² a potent acetylcholine esterase inhibitor,^{2b} and Merck's L-697,661,³ an HIV-1 reverse transcriptase inhibitor. In addition, the similarity of 2-pyridone ring system to nucleoside bases, in conjunction with the aromatic nature permitting π - π stacking interactions, as well as the availability of two tautomeric forms capable of participating in multidirectional hydrogen bonds raises the 2-pyridone ring systems to that of a "privileged structure"⁴ in the context of drug discovery and development.

To date most protocols for the construction and/or annulation of the 2-pyridone ring by enlarge are limited to the conversion of 2-pyrones employing ammonia,⁵ the oxidation of pyridines⁶ and the Guareschi-Thorpe⁷ condensation of acyclic precursors such as cyanoacetamide with 1,3-diketones. There is thus a need for alternative, efficient synthetic tactics to construct the pyridone ring systems.

In conjunction with our recently achieved enantiospecific syntheses of (+)-lyconadin A and (–)-lyconadin B⁸ (Scheme 1), we envisioned late stage installation of the requisite 2-pyridone ring employing advanced amino ketone **1**. We initially selected a one-pot tactic, employed to great advantage by Kozkowski and coworkers in their syntheses of huperzine A and analogs,⁹ which entails the condensation of methyl propiolate and ammonia with a ketone or β -ketoester. The poor Michael acceptor ability of the unsaturated amide in our case however precluded addition, resulting in the recovery of starting materials. Increasing the reactivity of the ketone by conversion to the β -ketoester **2**, employing acrylonitrile, a tactic similar to that used in the Mulzer synthesis of huperzine A,¹⁰ followed by somewhat

modified conditions for cyclization and decarboxylation (*cf.* Me₄NOAc, MeCN) permitted completion of the total synthesis of (+)-lyconadin A (**4**).⁸

In this letter we report the culmination of a study to explore the scope and utility of this tactic as a general protocol for the construction of 5,6-fused 2-pyridones. We first examined the Michael addition of α -carbomethoxy-cyclopentanone with propiolamide (Table 1). When the lyconadins' conditions⁸ (Cs₂CO₃ in DMSO) were employed, no reaction was observed at room temperature (entry 1); elevated temperatures were also not profitable leading to extensive polymerization (entry 2). Given the low electrophilicity as well as their inability to stabilize effectively the resulting carbanion acetylenic amides are poor Michael acceptors.¹¹ Indeed, to the best of our knowledge, there is only one report where in a propiolamide has proven to be a competent Michael acceptor.¹² Notwithstanding this lack of literature precedent, screening a variety of conditions quickly revealed that Na₂CO₃ in water at room temperature proved optimal.¹³ Use of, K₂CO₃ in acetone at 50 °C also provided the requisite addition product, albeit in somewhat lower yield.

Having achieved an effective Michael addition process, we turned to the development of a one-pot protocol to generate the 2-pyridone ring. Here we called upon a tandem reaction sequence, involving cyclization, ester hydrolysis and decarboxylation (Scheme 2).

In our total synthesis of (+)-lyconadin A, tetrabutylammoniumacetate proved to be the optimal reagent since stronger nucleophilic reagents such as sodium cyanide or thiophenol resulted in the conjugate addition to the initially derived Michael adduct to furnish 4-substituted 2-pyridones.⁸ However, when this reagent was applied to **5** (Table 2) only polymerization was observed. Examination of other Krapcho decarboxylation conditions¹⁴ exploring a variety of substrates, including 6- and 7-membered rings possessing ethyl esters revealed the sensitivity of these substrates to nucleophilic attack. Of particular note, at elevated temperatures complex mixtures consisting of hydrolyzed and decarboxylated substrates, spirobicyclic and 3-substituted glutarimides and polymers in conjugation with decomposition products were observed. We reasoned that use of the acidic conditions might suppress these alternative pathways, in particular intramolecular attack of amide nitrogen with the ester to yield the spiro glutarimides¹⁵ as well as aldol reactions leading to polymeric byproducts. Weakly acidic conditions proved somewhat promising, albeit providing the desired 2-pyridone **7** in low yield (18 %) along with the recovered starting material and enamide **6**. Strong acidic conditions (*cf.* conc. HCl) on the other hand not only accelerated the reaction but pleasingly led to the desired pyridone **7** in nearly quantitative yield (Table 2).¹⁶

Having optimized the tandem cyclization/decarboxylation reaction sequence with **5**, we next applied the conditions to substrates possessing different ring sizes (Table 3). Substrates possessing 5 and 6 membered rings furnished good yields upon addition of pro-piolamide, whereas increasing the ring size reduced the yields with accompanying polymerization. Best results were obtained with 5,6 and 7 membered ring ketones while 8 membered ring did not lead to the desired product. Strong base¹¹ was however was effective in furnishing 2-pyridone **16**.

We next explored the effect of α -substitution on the 6-membered ring. Both electron withdrawing and donating substituents not surprisingly led to lower yields in the Michael addition step, possibly due to steric hinderance. In particularly noticable is the drop in the yield of **20** most likely due a Favorskii reaction leading to polymerization (Table 4). Ring closure, hydrolysis and decarboxylation leading to the 5,6-substituted 2-pyridones than proceeded in good to excellent yield, similar to the un-substituted system.

We also examined systems having different distal ring fusions (Table 5). Substrates leading to structure with higher ring strains not surprisingly provided somewhat lower yields in both Michael addition and subsequent annulation and decarboxylation processes. Basic and neutral (NH₄OAc) conditions were also tested with **32**, a substrate lacking ability to enolize (Table 6). Although the acidic protocol provided **34** in 69% yield, basic and neutral conditions also delivered the product in modest yield, thus providing alternative protocols for substrates with base or acid sensitive functionalities.

In summary, an effective, versatile protocol comprising the tandem condensation of propiolamide with cyclic β -ketomethylesters followed by cyclization, dehydration and decarboxylation to furnish 5,6-fused 2-pyridones has been developed. To demonstrate the utility of the protocol, a small library of fused 2-pyridones was prepared and submitted to the NIH Molecular Libraries Small Molecule Repository (MLSMR).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. xx
13. Representative procedure for Michael addition: To a solution of propiolamide (325 mg, 4.70 mmol) and sodiumcarbonate (270 mg, 2.75 mmol) in water (5 mL) at 0 °C methyl-2-oxocyclopentanecarboxylate (**3**) (390 mg, 2.75 mmol) was added dropwise. The reaction mixture was warmed to room temperature over a 2 h. and than extracted with CH₂Cl₂ (3×20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (eluent 1:1 ethyl acetate/hexanes r.f. 0.2) afforded **13** as a white solid (511 mg, 88% yield).
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16. Representative procedure for annulation: A thick walled tube containing a stirbar and methyl 1-(3-amino-3 oxoprop-1-enyl)2-oxocyclopentanecarboxylate (154.1 mg, 0.730 mmol) (**13**) was dissolved in concentrated HCl (2 mL). The tube was sealed tightly and heated to 130 °C in an oil bath. After 6h the reaction mixture was allowed to cool to room temperature, the tube carefully opened and the reaction mixture poured onto ice (5g). The pH was adjusted to 7 by dropwise addition of saturated aqueous NaHCO₃ and then the mixture extracted with ethylacetate. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to furnish a white solid. Purification through a short pad of silica gel (eluent 100% ethyl acetate) afforded **23** as a white amorphous solid (97.4 mg, 99% yield).

Scheme 1.

Installation of the 2-pyridone ring in the total synthesis of (+)-lyconadin A.

Scheme 2.
Proposed formation of fused 2-pyridones

Table 1

Conditions examined to effect Michael addition

	Base	Solvent	Time (h)	T (°C)	Result
1	Cs ₂ CO ₃	DMSO	12	rt	No reaction
2	Cs ₂ CO ₃	DMSO	2	80	Polymerization
3	NaH	DMF	12	rt	No reaction
4	NaH	DMF	2	60	Polymerization
5	NaOH	MeOH	12	rt	Polymerization
6	K ₂ CO ₃	Acetone	1	50	76 %
7	Na ₂ CO ₃	H ₂ O	1	rt	88 %

Table 2

Optimization of the cyclization conditions

Reagent	Solvent	t	T °C	Result
Me ₄ NOAc	MeCN	3 h	130	no desired product
Me ₄ NOAc	MeCN	12 h	130	polymerization
NaOH	H ₂ O/DMSO	12 h	130	polymerization
LiI	DMF	12 h	120	no desired product
TBAI, LiI	DMF/H ₂ O	12 h	130	Polymerization
HCl(1M)	H ₂ O	24 h	130	24% 6 , 18% 7
HCl (conc)	H ₂ O	6 h	130	99% 7

Table 3

Effect of ring size

Starting Material

Starting Material

Starting Material

Table 4 Effect of α -substitution 6-membered rings

Starting Material

9

Starting Material

Starting Material

Starting Material

24

Table 5

Substrates having different ring fusions

Starting Material	
 27	 30

Starting Material

33

Table 6

34				35
Reagent	Solvent	Time	T °C	Result
Me ₄ NOAc	MeCN	40 h	150	42 %
NaOH	H ₂ O/DMSO	18 h	150	50 %
HCl (conc)	H ₂ O	6 h	130	69%