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Conversion of γ-bicyclic lactams to 4,5-dihydro-2*H*-pyridazin-3-ones

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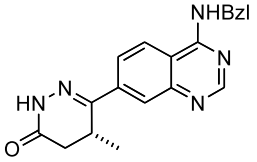
Abstract—Bicyclic lactams are uniquely suited as precursors for the synthesis of chiral substituted 4,5-dihydro-2*H*-pyridazinones. This paper describes the development of a method for the direct conversion of unsubstituted and 4-substituted γ-bicyclic lactams to 4,5-dihydro-2*H*-pyridazin-3-ones and 2-phenyl-4,5-dihydro-2*H*-pyridazin-3-ones.

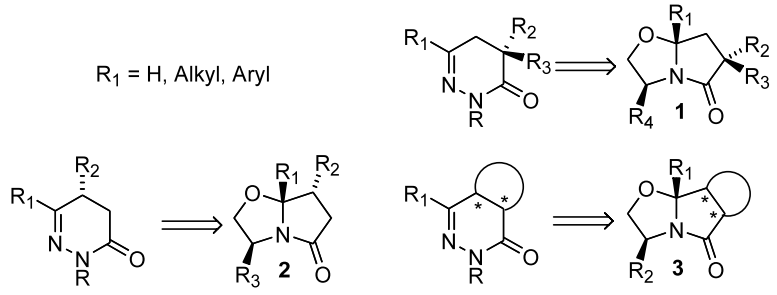
Pyridazines show a diverse range of agrochemical and pharmacological activities, including bronchodilatory, cardiotonic, anti-inflammatory and platelet aggregation activity, inspiring a variety of synthetic approaches.[1] Chiral substituted 4,5-dihydro-2*H*-pyridazinones, such as KF 15232, are of particular interest owing to the influence of chirality on general efficacy[2] and isozyme selectivity.[3] Synthetically, such chirality has been derived through the resolution of precursor racemic γ-ketoacids[4] or the lipase-catalyzed hydrolysis[5] of the racemic dihydro-2*H*-pyridazin-3-one.



(-) KF 15232

Pyridazin-3-ones are masked γ-dicarbonyl compounds. Any generally applicable synthetic scheme requires the ability to generate chiral centers, including cyclic systems, at the 4- and 5-positions of the pyridazin-3-one. Bicyclic lactams (Scheme 1), as amply demonstrated by Meyers et al., provide access to chiral γ-dicarbonyl frameworks needed.[6] The lacking component for the synthesis of chiral substituted 4,5-dihydro-2*H*-pyridazin-3-ones is the conversion of the γ-bicyclic lactams to the desired products.

Initially we considered the conversion of the 4-substituted γ-bicyclic lactams to the corresponding γ-ketoacids with subsequent conversion to the 4,5-dihydro-2*H*-pyridazin-3-one. The synthesis of chiral α,α-disubstituted-γ-ketoacids from bicyclic lactams has been demonstrated, but has not been widely utilized.[7] This may be due in part to the loss of stereochemistry on the conversion of monoalkylated bicyclic lactams,



Scheme 1.

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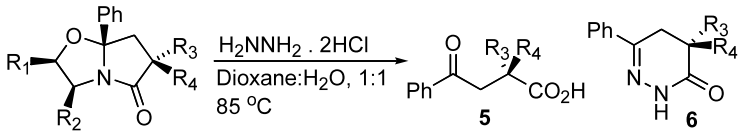
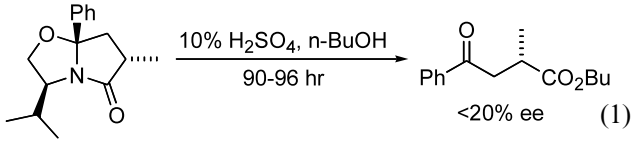
Table 1. Conversion of bicyclic lactam to 6-phenyl-4,5-dihydropyridazin-3-one



Entry	R_1	R_2	R_3	R_4	Time	**5**	**6**[a]
1	H	H	H	H	12	5	95
2	H	*i*-Pr	H	H	12	5	95
3	H	Ph	H	H	12	5	95
4	Ph	H	H	H	12	5	95
5	H	*i*-Pr	Me	H	24	0	99 (95)
6	H	Ph	Me	H	24	0	99 (94)
7	Ph	H	Me	H	24	0	92 (68)
8	H	*i*-Pr	Me	Me	96	0	34

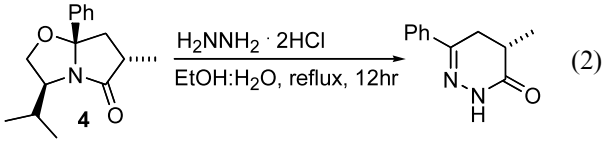
[a] Values in parentheses represent yields at 12 h based on gas chromatographic analysis.

owing to the strongly acidic conditions required for the transformation. Meyers et al. demonstrated that the racemization occurs on the bicyclic lactam prior to the solvolysis reaction (Eq. (1)).



(1)

Recognizing the inherent nucleophilicity of hydrazine, we reasoned that direct addition of hydrazine might allow direct conversion to the 4,5-dihydropyridazin-3-one under mild acid conditions. In our initial effort we utilized hydrazine dihydrochloride in a 1:1 ethanol:water mixture. Under these conditions the α-unsubstituted bicyclic lactams are converted to 6-phenyl-4,5-dihydro-2*H*-pyridazin-3-one in a 12 h reflux (Eq. (2)). Monoalkylated bicyclic lactams such as **4** showed lower reactivity and poor solubility in the ethanol:water solution. Bisalkylated bicyclic lactams show extremely poor solubility in this solvent system.



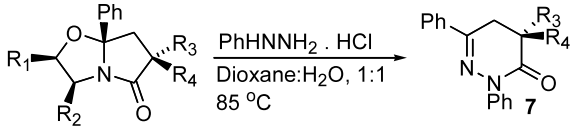
(2)

The use of a mixed dioxane:water solvent enabled us to solubilize both the hydrazine dihydrochloride and the bicyclic lactam. Under these conditions the reaction with 10 equiv. of hydrazine dihydrochloride and bicyclic lactam produced the desired 4,5-dihydro-pyridazin-3-ones (Table 1). In this solvent system low levels of 3-benzoylpropionic acid **5** were produced when α-unsubstituted bicyclic lactams (entries 1–4) were investigated. Analysis by GC of the reaction of methylated systems (entries 5–8) showed no acid formation at any point during the reactions. The bismethylated bicyclic lactam (entry 8) showed low reactivity requiring 4 days to reach 34% completion.

While the focus of this study is on the transformation of bicyclic lactam to pyridazinone, the retention of stereochemical configuration is critically important to the utility of the method. Our initial analysis by optical rotation shows that we have retained some level of enantiopurity in the conversion of **4** to the 4-methyl-4,5-dihydro-2*H*-pyridazin-3-one (Table 1: entry 5). Investigation of the extent of retention and the generality of this observation are underway and will be reported in the future.

Substitution at the amide nitrogen of the pyridazin-3-one is important to the efficacy of the target compounds. While substitution may be accomplished after synthesis of the pyridazin-3-one ring system, it would be useful to accomplish this substitution in the ring-forming step. We attempted the conversion to 2-phenyl substituted system by reaction with 10 equiv. of phenyl hydrazine hydrochloride (Table 2). The reactivity of this system is reduced, requiring 4 days to reach synthetically useful yields in the monomethylated case (entries 5–7).

Table 2. Conversion of bicyclic lactam to 2,6-diphenyl-4,5-dihydropyridazin-3-one



Entry	R_1	R_2	R_3	R_4	Time	**7**
1	H	H	H	H	12	82
2	H	*i*-Pr	H	H	12	89
3	H	Ph	H	H	12	85
4	Ph	H	H	H	12	75
5	H	*i*-Pr	Me	H	96	84
6	H	Ph	Me	H	96	65
7	Ph	H	Me	H	96	65
8	H	*i*-Pr	Me	Me	96	9

In both the hydrazine and phenyl hydrazine reactions little, if any, decomposition or byproduct formation is observed. Although steric issues may play a role, one rationale for the lower yields in the phenyl hydrazine case is that the concentration of acid is half that in the hydrazine dihydrochloride. We are currently investigating the influence of acid concentration on the reaction to determine if the addition of acid will improve the yields in these reactions.

The reactions described here demonstrate the feasibility of using γ-bicyclic lactams as precursors to substituted 4,5-dihydropyridazin-3-ones.[8] While this study has been limited to the 4-substituted-4,5-dihydro-2*H*-pyridazin-3-one, in bioactive pyridazin-3-ones, substitution at the 5-position is common. Our preliminary studies on these systems are promising and will be reported in the near future.

Acknowledgements

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8. **Experimental**: To a 25 mL flask was added 1 mmol of 5-isopropyl-2-methyl-7a-phenylhexahydropyrrolizin-3-one, 10 mmol of hydrazine dihydrochloride and 15 mL of 1:1 dioxane:water. The mixture was heated with stirring to 85°C for 12 h. The volatiles were removed in vacuo and the residue taken up in dichloromethane, and extracted with water. The organic phase was dried over magnesium sulfate and the solvent evaporated to yield the desired 4-methyl-4,5-dihydropyridazin-3-one as a white solid.