Synthesis of Spirocyclic Carbazole- and Acridine-Lactams

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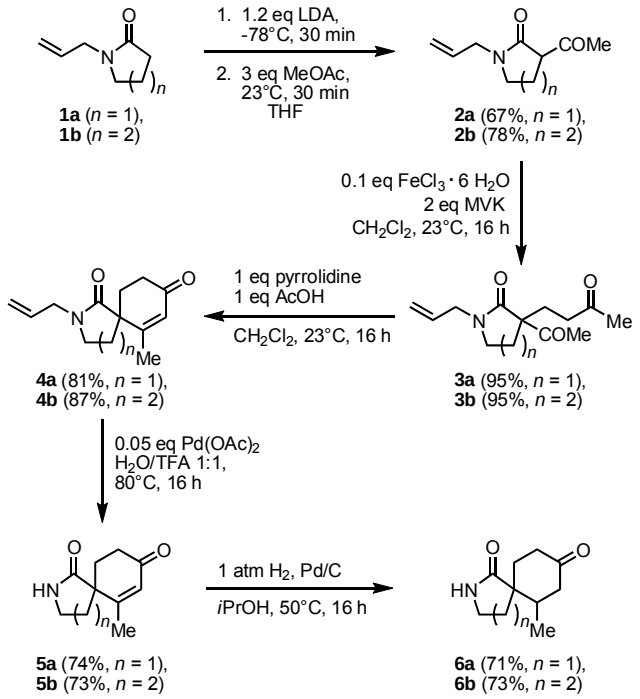
Spirocyclic structures are popular scaffolds in medicinal chemistry due to their conformational rigidity. A route to spirocyclic ketones with a five- or a six-membered lactam ring was developed starting from *N*-allyl-protected 2-pyrrolidone or 2-piperidone. These ketones were then converted to carbazole- and acridine-lactams by Fischer indole or Friedländer quinoline synthesis.

Synthesis of the Spirocyclic Core

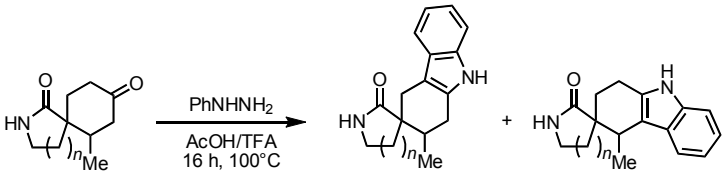
The spirocyclic keto-lactams **6** were prepared from *N*-allyl-protected 2-pyrrolidone **1a** or 2-piperidone **1b** in five steps with an overall yield of 27% and 34%, respectively. The sequence starts with the deprotonation and α-acetylation with MeOAc of the respective ketone **1**. The β-oxo esters **2** were then converted to the 1,5-diketones **3** with methyl vinyl ketone in an iron-catalyzed Michael reaction. The spirocyclic core was built up in an intramolecular Robinson annulation mediated by pyrrolidinium acetate. Deprotection of the *N*-allyl-lactams **4** took place with 5 mol% $Pd(OAc)_2$ in TFA/water and catalytic hydrogenation of the double bond proceeded with quantitative stereoselectivity to yield keto-lactams **6** as single diastereoisomers.[1]



1a (*n* = 1), **1b** (*n* = 2)
2a (67%, *n* = 1), **2b** (78%, *n* = 2)
3a (95%, *n* = 1), **3b** (95%, *n* = 2)
4a (81%, *n* = 1), **4b** (87%, *n* = 2)
5a (74%, *n* = 1), **5b** (73%, *n* = 2)
6a (71%, *n* = 1), **6b** (73%, *n* = 2)

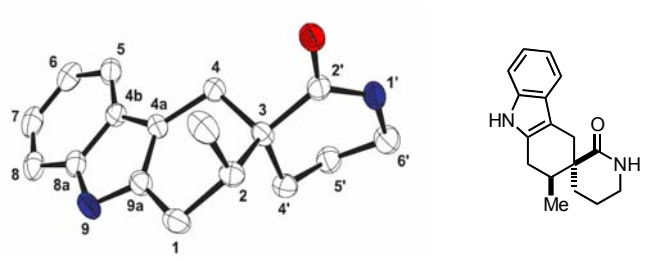
Fischer Indole Synthesis

The Fischer indolization of ketones **6** was accomplished using phenylhydrazine in a mixture of glacial acetic acid and TFA. The reaction yielded a mixture of two regioisomers which were separable by column chromatography.



6a (*n* = 1), **6b** (*n* = 2)
7a (45%, *n* = 1), **7b** (28%, *n* = 2)
8a (31%, *n* = 1), **8b** (50%, *n* = 2)

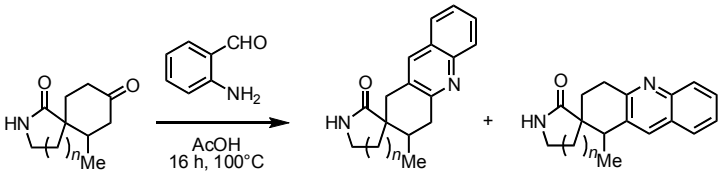
The overall yields were 76% for the five-membered lactam and 78% for the six-membered lactam. The constitution of the products was elucidated by 2D-NMR spectra and all the resonances were assigned. From compound **7b** single crystals could be obtained. The X-ray structure confirmed the constitution as assigned by NMR and established the relative configuration of the compounds to be *cis* (methyl and lactam carbonyl group).



X-ray structure of carbazole **7b**

Friedländer Quinoline Synthesis

The spiro-acridine-lactams **9** and **10** were obtained reacting ketones **6** with freshly prepared aminobenzaldehyde in glacial acetic acid. As before, a mixture of regioisomers was formed, which were separable by column chromatography and whose constitution was established by 2D-NMR spectra. The overall yields for this reaction were 77% and 71%, respectively.



6a (*n* = 1), **6b** (*n* = 2)
9a (56%, *n* = 1), **9b** (45%, *n* = 2)
10a (21%, *n* = 1), **10b** (26%, *n* = 2)

[1] M. Würdemann, J. Christoffers, *Org. Biomol. Chem.* **2010**, *8*, 1894-1898.