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# Addition of carbon nucleophiles to substituted *N*-acyliminium ions. A stereoselective route to *trans*-fused decahydroquinoline systems

Adriano O. Maldaner and Ronaldo A. Pilli*

*Instituto de Química, UNICAMP, PO Box 6154, Campinas 13083-970, SP, Brazil*

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**Abstract**

A stereoselective route to *trans*-fused 2-substituted decahydroquinoline hydrochloride **11** featuring the addition of allyl tri-*n*-butyltin to a disubstituted *N*-acyliminium ion derived from glutarimide, followed by ring-closing metathesis is described (seven steps, 13% overall yield from lactam **4**). 

*Keywords:* *N*-acyliminium ions; metathesis; piperidinones; decahydroquinolines.

2,5-Disubstituted decahydroquinolines such as the *cis*-fused pumiliotoxin C (**1**), isolated from *Dendrobates pumilio* frogs,[1] and the *trans*-fused decahydroquinoline (+)-219A (**2**), isolated from skin extracts of Colombian frogs (*Dendrobates histrionicus*),[2] represent one of the major classes of alkaloids found in the skin extracts of amphibians. Recently, Jones and co-workers[3] reported on the isolation of *cis*-2-methyl-5-propyldecahydroquinoline (**3**) and another isomeric decahydroquinoline from a Brazilian myrmicine ant [*Solenopsis (Diplorhoptrum)* sp. *picea* group], which had its structure tentatively assigned based on mass and infrared spectra. As only minute amounts of several decahydroquinolines are available from natural sources, their structures have been proposed based mainly on GC/MS or GC/IR techniques.[4] The assignment of the relative and absolute configuration of many of them awaits further studies, particularly the development of stereoselective routes to this family of natural compounds (Fig. 1).

Among the synthetic approaches which lead to decahydroquinoline systems,[5,6] the addition reaction of carbon nucleophiles to *N*-acyliminium ions (α-amidoalkylation reaction)[7,8] emerges as a viable protocol for the preparation of substituted nitrogenated systems with two adjacent allylic groups, which should be amenable to ring-closing olefin metathesis en route to the bicyclic system.[9]

* Corresponding author. Tel: 55-19-7883083; fax: 55-19-7883023; e-mail: pilli@iqm.unicamp.br

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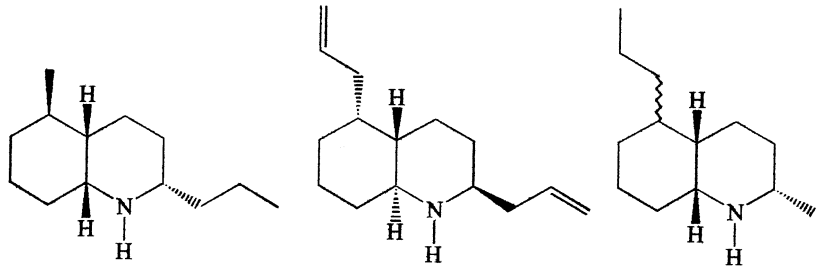


1 2 3

Figure 1.

Despite several reports of nucleophilic additions to cyclic *N*-acyliminium ions, only a few examples of stereoselective preparation of trisubstituted piperidine systems are found in the literature, such as the addition of silylenolethers to *N*-acyliminium ions derived from 3,6-*cis*-disubstituted piperidine derivatives which leads to *cis* addition of the nucleophile with modest diastereoselection.[10] The stereoelectronic preference for *cis*-2,6 relationship in the addition of nucleophiles to *N*-acyliminium ions derived from *N*-Boc-6-substituted piperidines is assigned to an allylic strain involving the nitrogen protecting group and the adjacent substituent attached to the piperidine ring leading to an axial approach of the nucleophile.[11]

## Results and discussion

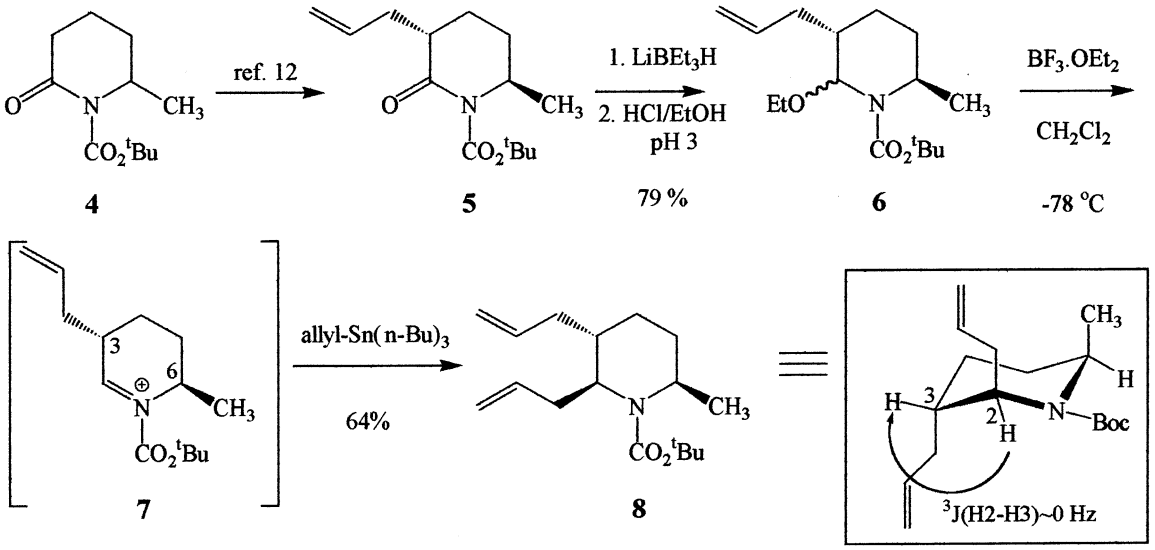
*N*-Boc-6-methyl-2-piperidinone (**4**) was prepared (three steps, 74% overall yield) from glutarimide through the addition of methylmagnesium iodide, followed by in situ $NaCNBH_3$ reduction in acidic media and nitrogen protection as the corresponding *tert*-butylcarbamate (Boc). The alkylation of the corresponding lithium enolate with allyl bromide proceeded stereoselectively to give *trans*-*N*-Boc-3-allyl-6-methyl-2-piperidinone (**5**) in 44% yield (60% yield based on recovered **4**).[12]

The conversion of piperidinone **5** to **6** was efficiently achieved in 79% yield with $LiEt_3BH$[13] in THF at −78°C, followed by treatment with ethanol at −78°C, acidification with 2 M ethanolic HCl at −78°C, and neutralization with 10% ethanolic KOH. The proclivity of 2-ethoxypiperidine **6** to undergo loss of ethanol giving rise to the corresponding tetrahydropyridine derivative dictated the need for strict control of temperature during the acidification and neutralization steps as well as in subsequent reactions.

Attempts to carry out allyltrimethylsilane addition to 2-ethoxycarbamate **6** at −78°C failed, while a significant amount of the corresponding tetrahydropyridine derivative was formed at −23°C. However, treatment of a $CH_2Cl_2$ solution of **6** with the more nucleophilic allyl tri-*n*-butyltin (2.0 equiv.) and $BF_3{\cdot}OEt_2$ (2.0 equiv.) at −78°C led to trisubstituted piperidine **8**, accompanied by two other diastereoisomers in 89:7:4 ratio as determined by GC–MS analysis (72% combined yield).[14] The loss of diastereoisomeric purity at this stage may be due to competitive addition of the nucleophile *cis* to the allyl substituent at C3 as well as to partial epimerization at this stereocenter at the stage of the intermediate *N*-acyliminium ion **7**.[15]

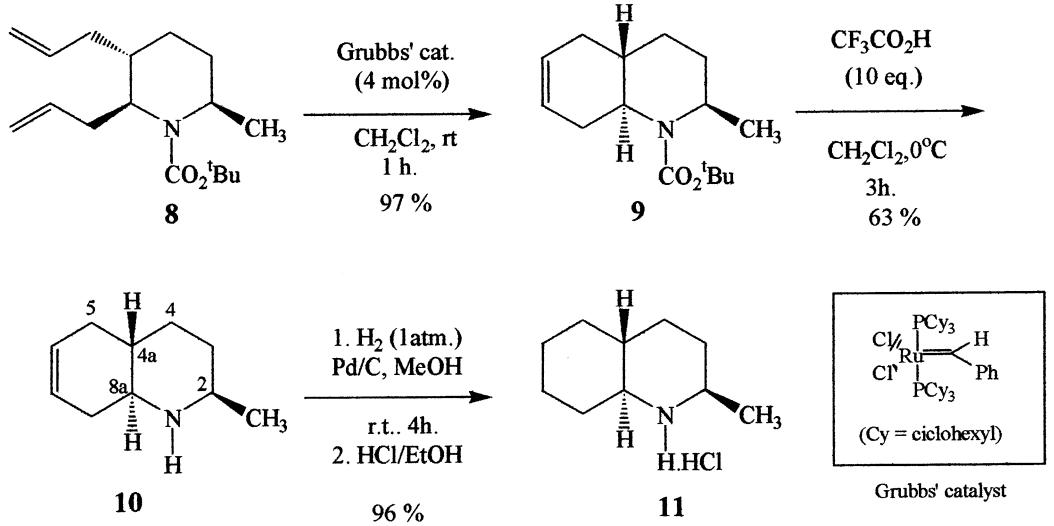
$^1$H NMR characterization of the major isomer **8** (64% yield) revealed a very small coupling constant ($\sim$0 Hz) between H-2 and H-3 suggesting a pseudoaxial orientation of the two allylic

groups as a result of allylic $A^{1,3}$ interaction between the *tert*-butyl carbamate group and the allyl substituent at C-2 thus supporting the *trans* orientation of the two allylic groups (Scheme 1).[16]




Scheme 1.

Ring closing metathesis[17] (RCM) carried out with **8** using Grubbs' catalyst (4 mol%) in $CH_2Cl_2$ at rt led to octahydroquinoline **9** in 97% yield (Scheme 2) and its *trans*-fused configuration was supported by two large coupling constants for H-8a signal ($J_{H8a-H4a} = J_{H8a-H8} = 11.0$ Hz) observed in the $^1H$ NMR spectrum. More conveniently, octahydroquinoline **9** was obtained in 62% overall yield (two steps) after column chromatography on silica gel when RCM was applied to the diastereoisomeric mixture formed in the addition of allyl tri-*n*-butyltin to 2-ethoxy carbamate **6**.




Scheme 2.

Nitrogen deprotection in acidic conditions and flash chromatography allowed the isolation of *trans*-fused octahydroquinoline **10** in 63% yield from **9** ($J_{H4a-H8a} = 10.7$ Hz). Finally, double bond hydrogenation ($H_2$, Pd/C, MeOH, 1 atm) and treatment with saturated methanolic HCl led to the isolation of decahydroquinoline **11** hydrochloride in 96% yield, fully characterized by NMR and FTIR spectroscopies and HRMS analysis.

In summary, decahydroquinoline hydrochloride **11** was efficiently prepared in seven steps and 13% overall yield from lactam **4** featuring a stereoselective allylation of a *N*-Boc *trans*-3,6-disubstituted *N*-acyliminium ion, followed by a ring-closing metathesis step using Grubb's catalyst. This approach to *trans*-fused 2-substituted octahydro- and decahydroquinolines is of potential use in the total synthesis of this class of natural products and is currently under investigation in our laboratory.

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