



## Synthesis of substituted gamma-lactams through petasis-type addition of boronic acids to N-acyliminium ions

Wu, Peng; Clausen, Mads Hartvig; Nielsen, Thomas Eiland

*Published in:*  
ChemMedChem

*Publication date:*  
2014

*Document Version*  
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

*Citation (APA):*  
Wu, P., Clausen, M. H., & Nielsen, T. E. (2014). Synthesis of substituted gamma-lactams through petasis-type addition of boronic acids to N-acyliminium ions. *ChemMedChem*.

---

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

### Acknowledgements:

This work was supported by Else Kröner-Fresenius-Stiftung, TRIP, LOEWE, OSF and Fonds der Chemischen Industrie.

### References:

- [1] H. Harizi, J.B. Corcuff, N. Gualde, *Trends. Mol. Med.* **2008**, *14*, 461–469.
- [2] M.W. Buczynski, D.S. Dumlao, E.A. Dennis, *J. Lipid. Res.* **2009**, *50*, 1015–1038.
- [3] G.A. FitzGerald, *N. Engl. J. Med.* **2004**, *351*, 1709–1711.
- [4] J. Suh, E.K. Yum, H.G. Cheon, Y.S. Cho, *Chem. Biol. Drug. Des.* **2012**, *80*, 89–98.
- [5] B. Smith, H.H. Chang, F. Medda, V. Gokhale, J. Dietrich, A. Davis, E.J. Meuillet, C. Hulme, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3567–3570.

## T074 | Synthesis of Substituted $\gamma$ -Lactams Through Pétasis-Type Addition of Boronic Acids to *N*-Acyliminium Ions

Peng Wu, Mads H. Clausen\*, Thomas E. Nielsen\*

Department of Chemistry, Technical University of Denmark, Kgs. Lyngby, 2800, Denmark

Substituted  $\gamma$ -lactams are important heterocyclic motifs found in various biologically active compounds and marketed drugs, such as glimepiride, doxapram, and levetiracetam. Among available methods for the synthesis of substituted  $\gamma$ -lactams, the addition of nucleophiles to *N*-acyliminium ions remains the most widely utilized approach. Even though hydroxylactams are important precursors of cyclic *N*-acyliminium ions, few approaches for their synthesis have been reported so far. By implementing a reductive cyclization reaction, linear *L*-malic acid derivatives were rapidly converted into cyclic *N*-acyliminium ions. Under the optimized conditions, entailing the use of HFIP as solvent, both electron-rich and electron-deficient boronic acids were successfully added to a range of cyclic *N*-acyliminium ions, thereby obtaining a collection of pharmaceutically relevant substituted  $\gamma$ -lactams.

## T075 | A Facile and Versatile Synthetic Route to Natural Product-Inspired N-Containing Heterocycles with Antitumor Properties

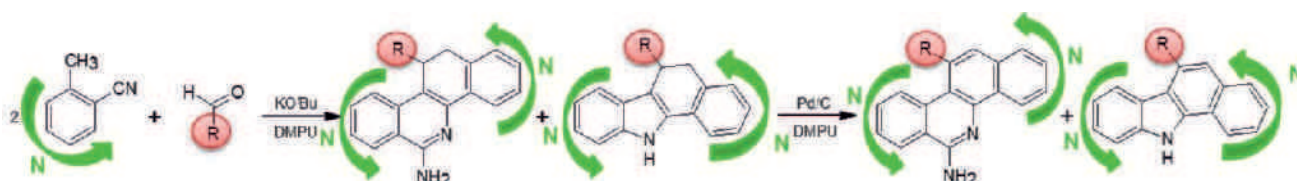
Tamara N. Steinhauer, Christopher Meier, Daniel S. Längle, Ilka Kock, Ulrich Girreser, Bernd Clement

Department of Pharmaceutical and Medicinal Chemistry, Christian-Albrechts-University of Kiel, Gutenbergstrasse 76, 24118 Kiel, Germany

In the year 2012, cancer was a leading cause of death with 14.1 million new cases and a mortality of 8.2 million people worldwide.<sup>[1]</sup> This fact and the currently limited therapeutic regimen shows up the necessity to find novel substances for cancer treatment.<sup>[2,3]</sup> Some naturally occurring benzo[*c*]phenanthridines were found to possess promising cytotoxic properties,<sup>[4]</sup> initiating the development of synthetic derivatives of this class. Since all common routes to gain these heterocycles were complex and multistep, it was necessary to establish a new efficient synthetic procedure.

We herein report a facile and efficient synthetic access to 11-substituted benzo[*c*]phenanthridines and structurally related substance classes.<sup>[5]</sup> The high variability of the reaction is not limited to the diversity of the substitution pattern in position 11, it is further possible to vary the quantity and position of nitrogen atoms by utilizing differently substituted *o*-methyl-heteroarylnitrile derivatives. With this simple base-catalyzed one-pot reaction followed by an optional dehydrogenation (Scheme 1) we were able to build up a large library of 11-substituted heterocyclic scaffolds, mainly unknown to literature.<sup>[5,6]</sup> Depending on the electronic structure of the used nitrile building block, either the 6-amino-dihydropyridophenanthrolines or the dihydro-11*H*-pyrido-azacarbazoles can be observed as main products. In the *NCI-60 DTP Human Tumor Cell Line Screen* (National Cancer Institute, Maryland, USA) various derivatives exhibited high antitumor activities.<sup>[7]</sup> Moreover studies regarding physicochemical properties revealed an improved water solubility at physiological pH value and a reduced lipophilicity in comparison to the closely related carbon-analogous benzo[*c*]phenanthridines.<sup>[6]</sup>

The great number of derivatives of these new substance classes and a facile possibility for functionalization in connection with strong cytotoxic properties emphasize the broad range of applicability and the importance of this synthetic procedure.



**Scheme 1.** Schematically illustrates synthetic route to 6-amino-pyridophenanthrolines and 11*H*-pyridoazacarbazoles with different quantity and position of nitrogen atoms.