Латвийский институт органического синтеза

Химия гетероциклических соединений **2016**, *52*(8), 524–526

ГЕТЕРОЦИКЛЫ В ФОКУСЕ

Химия гетероциклических соединений

Recent methods for the synthesis of indolizines (microreview)

Dmitrijs Čerņaks[1]*

[1] *Latvian Institute of Organic Synthesis, 21 Aizkraukles St., Riga, LV-1006, Latvia; e-mail: dmitrijs@osi.lv*

Submitted July 10, 2016
Accepted August 23, 2016

A summary of the most recent approaches toward indolizine derivatives is discussed. The microreview covers the latest selected examples on the synthesis of indolizines that might be gathered in four distinct categories: cyclocondensations, cycloadditions, cyclization/eliminations, and cycloisomerizations.

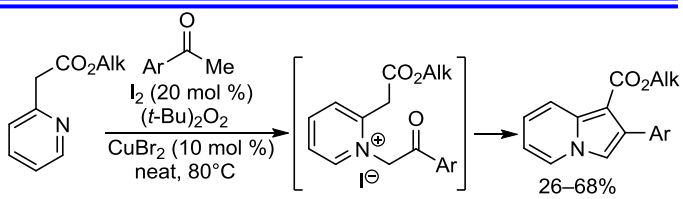
Introduction

Polycyclic nitrogen-containing heteroaromatics are pharmaceutically important scaffolds, widely present in naturally occurring and synthetic biologically active molecules.[1] Those containing an indolizine motif are particularly essential as they exhibit profound biological importance.[2]

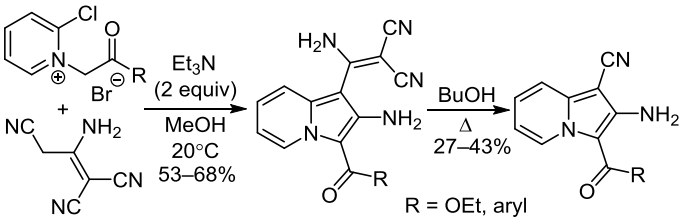
The discovery of camptothecin, a cytotoxic quinoline alkaloid, which inhibits the DNA topoisomerase I and is used to treat ovarian and lung cancer, lead to the major breakthrough and revealed the indolizine core as an important heterocyclic scaffold.[3]

Cyclocondensations

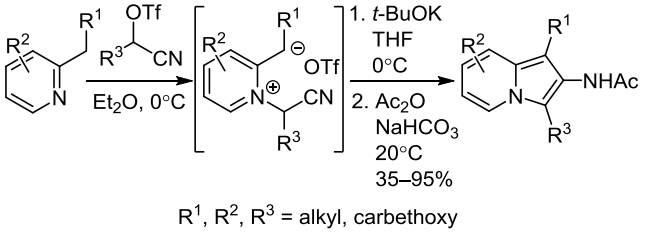
An efficient strategy for the synthesis of indolizine-1-carboxylates through the iodine-catalyzed Ortoleva–King reaction of 2-pyridylacetate with various benzophenones followed by the aldol condensation of pyridinium intermediate has been described by Chandra Mohan et al.[4] This protocol is compatible with a broad range of functional groups and affords 1,2-disubstituted indolizines in yields up to 68%.



Tverdokhleb et al. described the synthesis of highly functionalized 2-aminoindolizines *via* the reaction of substituted 2-chloropyridinium bromides with 2-amino-1,1,3-tricyanopropene in the presence of Et_3N. The reaction gives a dihydropyridin-1(2*H*)-yl anion, which upon Thorpe–Ziegler-type cyclization provides indolizines, followed by subsequent elimination of malononitrile in refluxing *n*-BuOH allows access to 1-cyanoindolizines.[5]



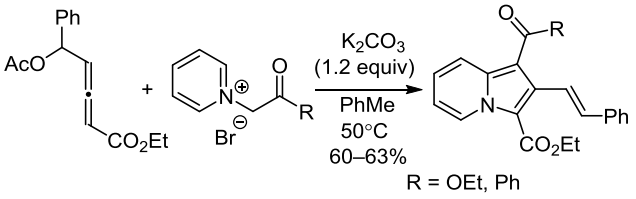
Opatz group recently developed an efficient method for the synthesis of 2-aminoindolizines by the *5-exo-dig* cyclization of 2-alkyl-1-(1-cyanoalkyl)pyridinium salts. These surrogates were obtained by *N*-alkylation of 2-alkylpyridines with easily accessible cyanohydrin triflates. This methodology allows the introduction of various substituents at 1, 3, 6, 7, and 8-positions of indolizine core and allows for absence of undesired acceptor groups in the indolizine product.[6]



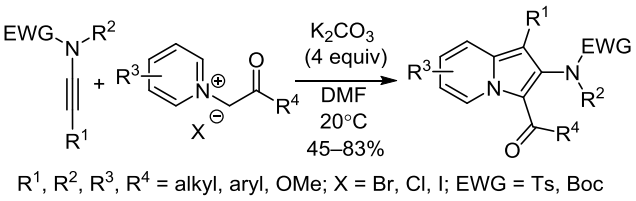
Dmitrijs Čerņaks was born in 1979 in Riga, Latvia. He received his PhD in chemistry in 2011 under supervision of Prof. V. Gevorgyan (University of Illinois at Chicago, USA). He then completed his postdoctoctoral studies at Northwestern University, Evanston, USA (Prof. K. Scheidt, 2013). At present he is research group leader at the Latvian Institute of Organic Synthesis, Latvia. His research interests are heterocyclic and heteroatom chemistry, reactive intermediates, and process chemistry.

Cycloadditions

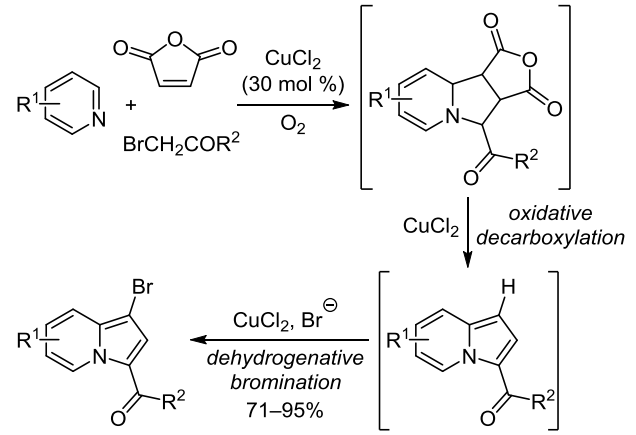
Li et al. demonstrated the base-promoted 1,3-dipolar cycloadditions of 4-acetoxyallenoates with various dipoles. Allenoates react with various pyridinium salts *via* a cycloaddition pathway followed by oxidative aromatization to give indolizines. It is proved that the reaction proceeds *via* a thermal 1,3-dipolar cycloaddition and the subsequent elimination of HOAc.[7]



Electron-deficient ynamides have been successfully elaborated in a 1,3-dipolar cycloaddition with stabilized pyridinium ylides for the first time. These reactions afford an efficient and general access toward a variety of substituted 2-aminoindolizines.[8]

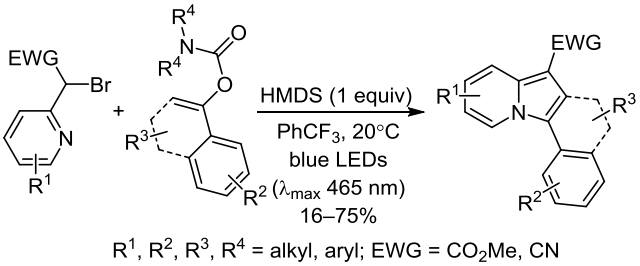


Recently, Wang et al. described one-pot, three-component cascade reaction between pyridines, α-acylmethyl bromides, and maleic anhydride leading to direct access of 1-bromoindolizines in high yields. This procedure is completed *via* a sequence of 1,3-dipolar cycloaddition of the pyridinium ylide with maleic anhydride, oxidative decarboxylation of the primary cycloadduct, and dehydrogenative bromination of the resulting 1-unsubstituted indolizine intermediate. Copper chloride was used as a catalyst and oxygen as the oxidant. This reaction represents the only example of transition metal-catalyzed direct dehydrogenative bromination of indolizine at C-1 position.[9]

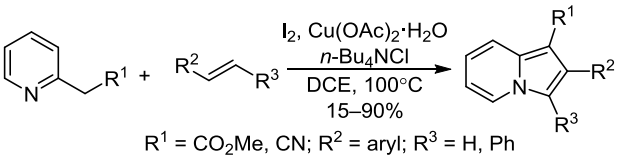


Cyclization/eliminations

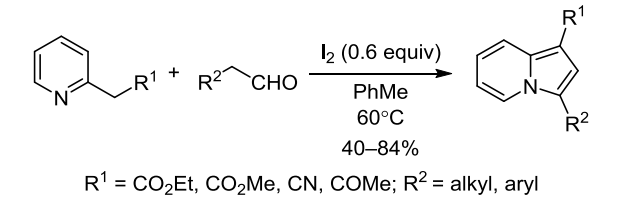
Sahoo et al. demonstrated a novel blue LED-mediated synthetic method that gives access to functionally diverse indolizines from various brominated pyridines and enol carbamates under mild conditions. The tetracyclic and pentacyclic structures obtained by using this approach represent a new class of heterocyclic scaffold.[10]



In 2015, a mild cupric acetate/I_2-mediated oxidative cross-coupling/cyclization of 2-(pyridin-2-yl)acetates and simple olefins was demonstrated, which provides a straightforward and efficient access to densely substituted indolizines. A series of 1,3-di- and 1,2,3-trisubstituted indolizines are easily obtained in modest to excellent yields.[11]

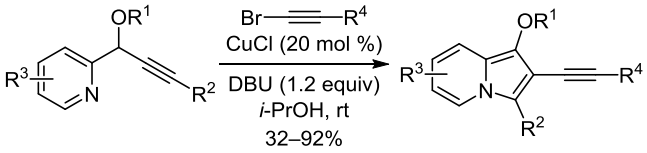


Xiang et al. showcased a direct method for the synthesis of substituted indolizines by means of I_2-mediated oxidative tandem cyclization *via* C–N/C–C bond formation. Number of substituted aromatic and aliphatic enolizable aldehydes underwent efficient reaction with 2-pyridylacetates and the desired 1,3-disubstituted indolizines were produced in moderate to good yields.[12]



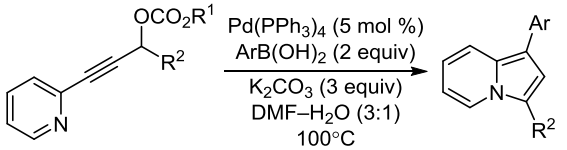
Cycloisomerizations

Oh et al. reported a base-mediated Cu-catalyzed tandem cyclization/alkylation of propargylic pyridines that provided an access to densely functionalized indolizines. The effective tandem reaction is ascribed to the inimitable property of DBU. The reaction first proceeded through a 5-*endo-dig* aminocupration, followed by a coupling between the copper intermediate and alkynyl bromide, to afford the products in good yields.[13]



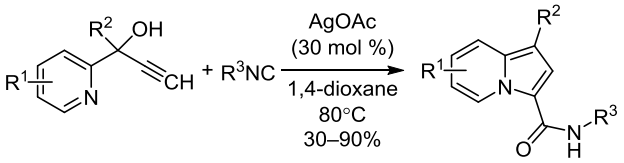
R^1 = Piv, TBDMS, Ph; R^2 = alkyl, vinyl, aryl;
R^3 = 2-Me, 3-Br, 4-F; R^4 = alkyl, (hetero)aryl

Very recently an efficient Pd-catalyzed cross-coupling/cycloisomerization of 3-(2-pyridyl)propargyl carbonates with arylboronic acids has been established,[14] which provides a straightforward route for the synthesis of 1,3-disubstituted indolizines with a wide variety of substituents.



R^1 = Me, Bn, *t*-Bu; R^2 = alkyl, aryl; Ar = aryl, (hetero)aryl

Lastly, the elegant synthesis of indolizines utilizing silver-catalyzed cyclization of 2-pyridyl alkynyl carbinols with isocyanides was described by Znang et al.[15] This method provide an effective route to highly functionalized indolizines in modest to excellent yields.



R^1 = 2-Me, 3-Me; R^2 = alkyl, aryl; R^3 = CH_2Ts, CH_2CO_2Et

Financial support by EC 7th Framework Program project (REGPOT-CT-2013-316149-InnovaBalt) is gratefully acknowledged.

References

1. (a) Igawa, H.; Takahashi, M.; Kakegawa, K.; Kina, A.; Ikoma, M.; Aida, J.; Yasuma, T.; Kawata, Y.; Ashina, S.; Yamamoto, S.; Kundu, M.; Khamrai, U.; Hirabayashi, H.; Nakayama, M.; Nagisa, Y.; Kasai, S.; Maekawa, T. *J. Med. Chem.* **2016**, *59*, 1116. (b) Sharma, V.; Kumar, V. *Med. Chem. Res.* **2014**, *23*, 3593. (c) Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237. (d) Michael, J. P. *Nat. Prod. Rep*. **2007**, *24*, 191.
2. Chen, P.; Chaikuad, A.; Bamborough, P.; Bantscheff, M.; Bountra, C.; Chung, C.; Fedorov, O.; Grandi, P.; Jung, D.; Lesniak, R.; Lindon, M.; Müller, S.; Philpott, M.; Prinjha, R.; Rogers, C.; Selenski, C.; Tallant, C.; Werner, T.; Willson, T. M.; Knapp, S.; Drewry, D. H. *J. Med. Chem.* **2016**, *59*, 1410.
3. (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc*. **1966**, *88*, 3888. (b) Sadowski, B.; Klajn, J.; Gryko, D. T. *Org. Biomol. Chem.* **2016**, *14*, 7804. (c) Elattar, K. M.; Youssef, I.; Fadda, A. A. *Synth. Commun.* **2016**, *46*, 719.
4. Chandra Mohan, D.; Ravi, C.; Pappula, V.; Adimurthy, S. *J. Org. Chem*. **2015**, *80*, 6846.
5. Tverdokhleb, N. M.; Khoroshilov, G. E.; Dotsenko, V. V. *Tetrahedron Lett.* **2014**, *55*, 6593.
6. Kucukdisli, M.; Opatz, T. *Eur. J. Org. Chem.* **2014**, *26*, 5836.
7. Li, F.; Chen, J.; Hou, Y.; Li, Y.; Wu, X.-Y.; Tong, X. *Org. Lett.* **2015**, *17*, 5376.
8. Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2015**, *17*, 2800.
9. Wang, F.; Shen, Y.; Hu, H.; Wang, X.; Wu, H.; Liu, Y. *J. Org. Chem.* **2014**, *79*, 9556.
10. Sahoo, B.; Hopkinson, M. N.; Glorius, F. *Angew. Chem.*, *Int. Ed.* **2015**, *54*, 15545.
11. Liu, R.-R.; Hong, J.-J.; Lu, C.-J.; Xu, M.; Gao, J.-R.; Jia, Y.-X. *Org. Lett*. **2015**, *17*, 3050.
12. Xiang, L.; Yang, Y.; Zhou, X.; Liu, X.; Li, X.; Kang, X.; Yan, R.; Huang, G. *J. Org. Chem.* **2014**, *79*, 10641.
13. Oh, K. H.; Kim, S. M.; Park, S. Y.; Park, J. K. *Org. Lett.* **2016**, *18*, 2204.
14. Meng, X.; Liao, P.; Liu, J.; Bi, X. *Chem. Commun*. **2014**, *50*, 11837.
15. Zhang, L.; Li, X.; Liu, Y.; Zhang, D. *Chem. Commun*. **2015**, *51*, 6633.