



Cite this: *Org. Biomol. Chem.*, 2017, **15**, 2906

Received 10th February 2017,
Accepted 12th March 2017

DOI: 10.1039/c7ob00535k

rsc.li/obc

Structurally diverse arene-fused ten-membered lactams accessed *via* hydrolytic imidazoline ring expansion†

Alexander Sapegin, Angelina Osipyan and Mikhail Krasavin*

Imidazoline-fused [1,4]oxazepines (prepared in two simple steps from methyl 2-hydroxyaroates, ethylene diamine and bis-electrophilic aromatics) undergo a facile, good-yielding hydrolytic imidazoline ring expansion (HIRE) upon *N*-alkylation and treatment with aqueous K₂CO₃. The resulting arene-fused ten-membered lactams significantly add to the contemporary arsenal of small-molecule scaffolds where medium-sized ring systems are severely underrepresented.

Small molecule libraries containing medium-sized (8- to 11-membered) rings are currently recognized as a drug discovery platform with many advantages compared to linear scaffolds or those based on flat heteroaromatic rings.¹ The introduction of a cycle drastically reduces the rotatable bond count (compared to a linear molecule), which improves permeability through cell membranes and intestinal absorption.² Yet medium-sized rings are more flexible compared to their smaller-size counterparts and thus can adopt a greater number of conformations, amongst which the one with an optimum presentation of the molecular periphery toward the biotarget has a higher chance to be found.³ This particular consideration has made medium-sized cyclic scaffolds popular, among other areas, in drug discovery against poorly 'druggable' targets such as protein-protein interactions.⁴

The ring closure approaches to medium-sized ring construction are encumbered by entropy constraints,⁵ hence ring expansion has manifested itself as a complementary and a lot more prolific strategy.⁶ The latter usually involves the construction of a polycyclic system with some degree of instability where breaking one of the central bonds leads to stabilization (*e.g.*, *via* aromatization or strain relief) and thus provides the driving force for ring expansion. Such an approach is elo-

quently illustrated, among many others, by the recent reports from the Tan group describing oxidative ring expansion of cyclic enol ethers (or enamines) **1** to give macrocyclic lactones (or lactams) **2**,⁷ or re-aromatization of tricyclic quinone precursors **3** generating ring-expanded products **4**.⁸

Our recent interest in *N*-(hetero)aryl 2-imidazolines for drug discovery⁹ and scaffold-oriented synthesis¹⁰ alarmed us due to the fact that polycyclic 2-imidazolines **5** have not been explored in the context of ring expansion (though such a possibility is indicated by the expansion of related polycyclic systems¹¹ and benzimidazoles¹² on treatment with aluminium hydride agents reported in the literature). When activated by protonation¹³ or alkylation¹⁴ to form **6**, 2-imidazolines can undergo hydrolysis *via* tetrahedral intermediate **7**. We reasoned that the latter can potentially evolve in two alternative directions one of which could lead to 2-aminoethyl side chain expulsion (to give **8**) and the other to the formation of ring-expanded product **9**. For monocyclic 2-imidazolines, forms **8** and **9** were shown to be interconvertible depending on the pH.¹⁵ Bicyclic 2-imidazoline-containing compounds such as **5** (*i.e.* with *N*¹ and *C*² at the bridgehead) are relatively scarce, which may explain why ring-expansion methodologies involving hydrolytic disruption of a 2-imidazoline moiety are lacking in the literature (though such a possibility was indicated by an isolated example related to this study).¹⁶ Recently, we gained a practically simple access to tetracyclic [1,4]oxazepines **10**,¹⁷ which, in our view, represent suitable objects for enabling the hydrolytic imidazoline ring expansion (HIRE) (Fig. 1). Herein, we report on a successful realization of this potential in compounds **10**.

In order to verify, in principle, the possibility of engaging compounds **10** in a ring expansion sequence **5** → **6** → **8**, we identified a suitable 2-imidazoline quaternization protocol by exposing previously reported tetracyclic compound **10a**¹⁷ (prepared as detailed below) to various *N*-methylation conditions (Table 1). The employment of dimethyl sulfate in acetonitrile at ambient temperature (entry 7) gave the best isolated yield of respective imidazolium salt **11a**. Surprisingly, all attempts to bring about the same transformation using either MeI or MeOTf left the starting material unchanged.

Institute of Chemistry, Saint Petersburg State University, 26 Universitetskii prospekt, Peterhof 198504, Russia. E-mail: m.krasavin@spbu.ru

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data, copies of the NMR spectra. CCDC 1520950. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob00535k



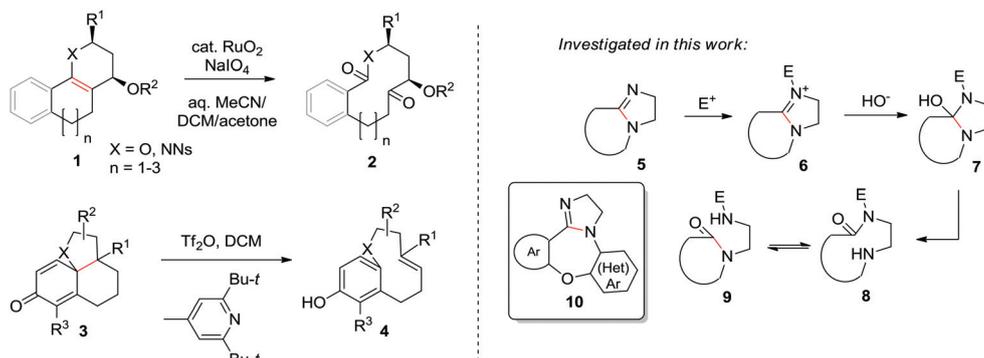


Fig. 1 Recent examples of ring expansion toward medium-sized rings and the goal of the present study.

Table 1 Screening of conditions for quaternization of **10a**

Entry	MeX	Solvent	T, °C	Time, h	Isolated yield (%)
1	MeI	MeCN	25	24	—
2	MeI	MeCN	Reflux	24	—
3	MeI	Toluene	Reflux	24	—
4	MeOTs	MeCN	25	24	—
5	MeOTs	MeCN	Reflux	24	—
6	MeOTs	Toluene	Reflux	24	—
7	(MeO) ₂ SO ₂	MeCN	25	12	73
8	(MeO) ₂ SO ₂	DMF	25	8	49
9	(MeO) ₂ SO ₂	Toluene	25	24	61

Table 2 Conditions for hydrolytic ring expansion **11a** → **12a**

Entry	Base	Solvent	Time, h	Isolated yield (%)
1	NaOH (5%)	H ₂ O	5	34
2	K ₂ CO ₃ (5%)	H ₂ O	8	51
3	NH ₄ OH (5%)	H ₂ O	8	48
4	K ₂ CO ₃ (1%)	H ₂ O	8	63
5	K ₂ CO ₃ (0.1%)	H ₂ O	8	74
6	K ₂ CO ₃ (0.1%)	H ₂ O/MeCN (1 : 1)	6	79
7	K ₂ CO ₃ (0.1%)	H ₂ O/MeOH (1 : 1)	6	71
8	K ₂ CO ₃ (0.1%)	H ₂ O/THF (1 : 1)	6	75
9	K ₂ CO ₃ (0.1%)	H ₂ O/MeCN (1 : 1)	5 ^a	77
10	None	H ₂ O/MeCN (1 : 1)	24	0

^a Reaction was performed at 40 °C.

For the hydrolytic ring expansion (such as **6** → **8**) envisioned as the likely fate for compound **10a** we tested various conditions employing diluted base solutions in pure water or aqueous organic solvents (Table 2). To our utmost delight, the ring expansion did take place in all cases tested while the best isolated yield of ten-membered lactam **12a** was obtained on exposing **11a** to 0.1% w/v K₂CO₃ solution in 1 : 1 MeCN–water over 6 hours at ambient temperature (entry 6). Employing no base (entry 10) resulted in no conversion.

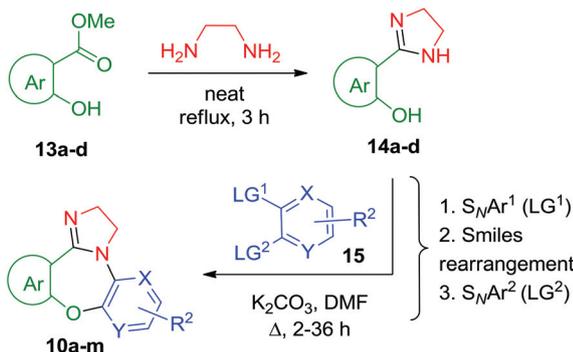
Besides the ¹H and ¹³C NMR and high-resolution mass spectrometry data, the structure of **12a** was confirmed by single-crystal X-ray analysis (ESI⁺). We also performed the transformation of **10a** to **12a** without the interim isolation of **11a** (by adding an equal volume of 0.2% aqueous K₂CO₃ solution to the reaction mixture after quaternization of **10a** was complete) and found the resulting yield (73%) to be significantly higher than the combined yield (58%) over separate quaternization/ring expansion steps (*vide supra*). Therefore, the one-pot protocol was adopted for all ring expansion examples discussed below.

Tetracyclic imidazoline-fused [1,4]oxazepines **10a–m** were prepared in two practically simple steps from 2-hydroxyaroate

esters **13** and ethylene diamine followed by coupling of resulting 2-hydroxyarylimidazolines **14** with bis-electrophilic (hetero)aromatic substrates **15** as described previously (specific structures of cyclocondensation partners **14–15** can be found in the ESI⁺).¹⁷ As was also demonstrated earlier,^{17,18} the regiochemistry of compounds **10a–m** is defined by two S_NAr events leading to the [1,4]oxazepine cycle formation being intermitted by a Smiles rearrangement (Scheme 1).

Gratifyingly, the *N*-alkylation/HIRE protocol developed for **10a** (*vide supra*) was found to be fully transferrable (Scheme 2) onto the other twelve substrates (**10b–m**). Surprisingly, *N*-alkylation with diethyl sulfate required refluxing temperatures, which resulted in generally lower yields of [1,4,7]oxadiazecin-9(*6H*)-ones (**16n–q**). Notably, compounds **16a–q** (Fig. 2) represent three distinctly novel¹⁹ scaffolds: 7,8-dihydro-5*H*-benzo[*z*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9(*6H*)-one (**16a–c**, **16g**, **16j–o**, **16q**), 7,8-dihydro-5*H*-dibenzo[*b*,*i*][1,4,7]oxadiazecin-9(*6H*)-one (**16e–f**, **16h**, **16p**), and 7,8-dihydro-5*H*-benzo[*z*]pyrazino[2,3-*b*][1,4,7]oxadiazecin-9(*6H*)-one (**16d** and **16i**). The





Scheme 1 Synthesis of tetracyclic 2-imidazoline-fused [1,4]oxazepines **10a–m**.



Scheme 2 Synthesis of [1,4,7]oxadiazecin-9(6H)-ones **12a–q**.

medium to good isolated yields of compounds **16a–q** shown in Fig. 2 were obtained using the same general procedure (ESI⁺) and have not been optimized for specific compounds. The nature of substituents in the salicylate portion of the compounds (shown in green color) does not appear to have any influence on the product yields. The electron-poor character of the other aromatic portion of the molecule (shown in blue

color) is mandated by the method used to prepare precursors **10a–m** (*vide infra*). However, it does not appear to have a significant impact on the outcome of the reaction.

In conclusion, we have reported the first example where hydrolytic instability of the 2-imidazoline moiety (activated by *N*-alkylation) is exploited to achieve ring expansion of a smaller cycle into a medium-ring system. The starting materials are distinctly easy to prepare and the ring expansion is brought about by two chemical operations performed in a one-pot format. Considering the scarcity of medium-sized scaffolds in the contemporary arsenal of small molecules for biological screening, the approach described is expected to significantly aid in filling this void. Research aimed at expanding the diversity of polycyclic systems as substrates for HIRE is underway in our laboratories; we will report the results in due course.

This research was supported by the Russian Scientific Fund (project grant 14-50-00069). We thank the Research Centre for Magnetic Resonance, the Centers for Chemical Analysis and Materials Research and the Centre for X-ray Diffraction Methods of Saint Petersburg State University Research Park for the analytical data.

Notes and references

- 1 L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens and W. P. Unsworth, *Chem. – Eur. J.*, 2017, **23**, 2225.
- 2 D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615.

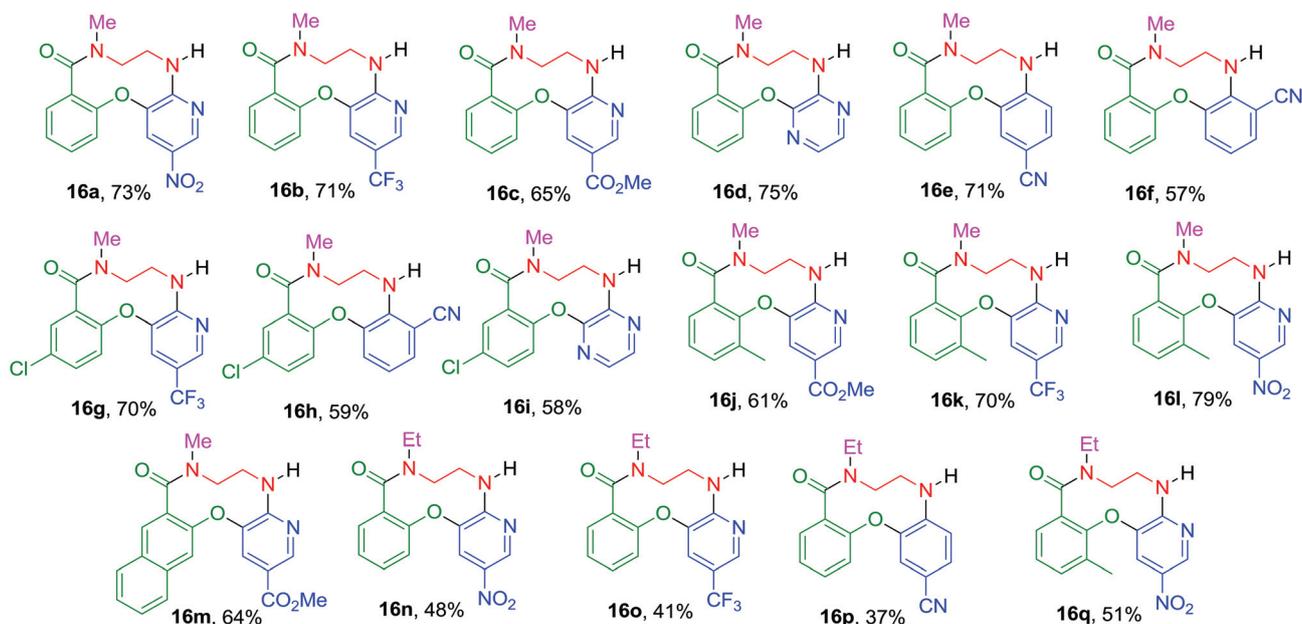


Fig. 2 [1,4,7]Oxadiazecin-9(6H)-ones **16a–q** synthesized in this work.



- 3 L. A. Marcaurelle, E. Comer, S. Dandapani, J. R. Duvall, B. Gerard, S. Kesavan, M. D. Lee, H. Liu, J. T. Lowe, J.-C. Marie, C. A. Mulrooney, B. A. Pandya, A. Rowley, T. D. Ryba, B.-C. Suh, J. Wei, D. W. Young, L. B. Akella, N. T. Ross, Y. L. Zhang, D. M. Fass, S. A. Reis, W.-N. Zhao, S. J. Haggarty, M. Palmer and M. A. Foley, *J. Am. Chem. Soc.*, 2010, **132**, 16962.
- 4 J. Kim, J. Jung, J. Koo, W. Cho, W. S. Lee, C. Kim, W. Park and S. B. Park, *Nat. Commun.*, 2016, **7**, 13196.
- 5 I. Shiina, *Chem. Rev.*, 2007, **107**, 239.
- 6 (a) L. Huang, L. X. Dai and S. L. You, *J. Am. Chem. Soc.*, 2016, **138**, 5793; (b) J. E. Hall, J. V. Matlock, J. W. Ward and J. Clayden, *Angew. Chem., Int. Ed.*, 2016, **55**, 11153.
- 7 F. Kopp, C. F. Stratton, L. B. Akella and D. S. Tan, *Nat. Chem. Biol.*, 2012, **8**, 358.
- 8 R. A. Bauer, T. A. Wenderski and D. S. Tan, *Nat. Chem. Biol.*, 2013, **9**, 21.
- 9 (a) P. Sarnpitak, P. Mujumdar, C. Morisseau, S. H. Hwang, B. Hammock, V. Iurchenko, S. Zozulya, A. Gavalas, A. Geronikaki, Y. Ivanenkov and M. Krasavin, *Eur. J. Med. Chem.*, 2014, **84**, 160; (b) M. Krasavin, P. Mujumdar, V. Parchinsky, T. Vinogradova, O. Manicheva and M. Dogonadze, *J. Enzyme Inhib. Med. Chem.*, 2016, **31**, 1146; (c) C. T. Supuran, S. Kalinin, M. Tanç, P. Sarnpitak, P. Mujumdar, S.-A. Poulsen and M. Krasavin, *J. Enzyme Inhib. Med. Chem.*, 2016, **31**(Suppl. 1), 197; (d) P. Sarnpitak, P. Mujumdar, A. Shetnev, M. Dorogov and M. Krasavin, *Tetrahedron Lett.*, 2015, **56**, 2827; (e) P. Sarnpitak, P. Mujumdar, P. Taylor, M. Cross, M. J. Coster, A.-D. Gorse, M. Krasavin and A. Hofmann, *Biotechnol. Adv.*, 2015, **33**, 941.
- 10 (a) M. Krasavin, *Tetrahedron Lett.*, 2012, **53**, 2876; (b) P. Mujumdar, M. Korsakov, M. Dorogov and M. Krasavin, *Synlett*, 2014, 2323; (c) D. Dar'in and M. Krasavin, *J. Org. Chem.*, 2016, **81**, 12514.
- 11 H. Yamamoto and K. Maruoka, *J. Am. Chem. Soc.*, 1981, **103**, 4186.
- 12 T. Shvidenko, K. Nazarenko, K. Shvidenko and A. Kostyuk, *Tetrahedron Lett.*, 2014, **55**, 279.
- 13 P. Mujumdar, T. Grkovic and M. Krasavin, *Tetrahedron Lett.*, 2013, **54**, 3336.
- 14 C. Xia, J. Hao, Y. Tang, Y. Ni and P. Zhou, *Synth. Commun.*, 2002, **32**, 1457.
- 15 B. M. Fernandez, A. M. Reverdito, G. A. Paolucci and I. A. Perillo, *J. Heterocycl. Chem.*, 1987, **24**, 1717.
- 16 J. M. Villalgordo and H. Heimgartner, *Helv. Chim. Acta*, 1997, **80**, 748.
- 17 K. Karamysheva, E. Reutskaya, A. Sapegin, M. Dorogov and M. Krasavin, *Tetrahedron Lett.*, 2015, **56**, 5632.
- 18 (a) A. V. Sapegin, S. A. Kalinin, A. V. Smirnov, M. V. Dorogov and M. Krasavin, *Synthesis*, 2012, 2401; (b) A. V. Sapegin, S. A. Kalinin, A. V. Smirnov, M. V. Dorogov and M. Krasavin, *Tetrahedron*, 2014, **70**, 1077; (c) A. V. Sapegin, S. A. Kalinin, A. V. Smirnov, M. V. Dorogov and M. Krasavin, *Eur. J. Org. Chem.*, 2015, 1333; (d) A. Sapegin, E. Reutskaya, A. V. Smirnov, M. Korsakov and M. Krasavin, *Tetrahedron Lett.*, 2016, **57**, 5877; (e) A. Sapegin, V. Panova, E. Reutskaya, A. V. Smirnov and M. Krasavin, *Tetrahedron*, 2016, **72**, 7570.
- 19 According to SciFinder® search performed on February 10th, 2017.

