Organic Synthesis

Hypervalent Iodine(III)-Mediated Cascade Cyclization of Propargylguanidines and Total Syntheses of Kealiinine B and C

Guilong Tian,^[a] Pavel Fedoseev,^[a] and Erik V. Van der Eycken^{*[a, b]}

Dedicated to Professor Qi-Lin Zhou on the occasion of his 60th birthday.

Abstract: An oxidative cascade cyclization of propargylguanidines promoted by phenyliodonium diacetate (PIDA) was developed. The protocol provides an efficient route for the synthesis of the alkaloids kealiinines B and C as well as homologues. The difference in the electronic nature of the acetylene substituent resulted in two ways of the cyclization. A plausible mechanism is proposed based on the experimental results.

In the last years, hypervalent iodine reagents have attracted great attention due to their environmental friendliness and low cost, as well as their ease of handling. The synthetic efficiency in the construction of complex architectures via oxidative transformations proved its utility in many reports.^[1]

The groups of Kita^[1a,c-f,j,l] and Domínguez^[1b,g,k] have performed a broad investigation of the utility of the hypervalent iodine reagents phenyliodonium diacetate (PIDA) and phenyliodonium ditrifluoroacetate (PIFA) with regards to their utility for oxidative cyclization reactions. In 2011, Canesi et al. designed a cascade cyclization mediated by PIDA for the synthesis of ring-fused skeletons.^[1i] Maurya's group reported in 2015 the utilization of PIDA in amide oxidations for cascade cyclizations^[1m] (Scheme 1).

A range of 2-aminoimidazole alkaloids displays a wide diversity of biological activities.^[2] Among them are potent modulators of the formation and dispersion of bacterial biofilms,^[3] human β -secretase (BACE-1) inhibitors,^[4] and tubulin-binding agents.^[5] In 2010, our group developed a Ag-mediated guanylation–cyclization procedure of propargylamines as a concise way towards the syntheses of polysubstituted 2-aminoimidazoles (Scheme 2).^[6]

Scheme 1. PIDA (phenyliodonium diacetate)- or PIFA (phenyliodonium ditrifluoroacetate)-promoted cyclizations.

Scheme 2. Synthesis of protected 2-aminoimidazoles and kealiinines; Boc = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid.

In continuation of this work, we designed a cascade reaction for the synthesis of the kealiinine alkaloids^[7] (Scheme 2). As the methoxy-group on the phenyl A ring of substrate 1 is sensitive to PIDA oxidation, attack by the alkyne on the *para* position of the anisole moiety and subsequent reaction of the guanidine moiety with the intermediate carbocation will result in the

[a] G. Tian, P. Fedoseev, E. V. Van der Eycken
Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC)
University of Leuven (KU Leuven)
Celestijnenlaan 200F, 3001 Leuven (Belgium)
E-mail: erik.vandereycken@chem.kuleuven.be
Homepage: <http://www.chem.kuleuven.be/research/organ/lomac/>

[b] E. V. Van der Eycken
Peoples Friendship University of Russia (RUDN University)
6 Miklukho-Maklaya street, Moscow, 117198, (Russia)

Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/chem.201700934>.

formation of compound **5**. Evidently, this process should give access to the syntheses of kealiin alkaloids and homologues after Boc removal and aromatization.

Inspired by our investigations of heterocyclization reactions, we used propargylguanidine **1a** as a model substrate (Table 1). This was readily prepared by guanylation of the related *N*-butyl-propargylamine,^[6] which was accessed through A3 coupling (aldehyde-alkyne-amine reaction).^[8]

Table 1. Optimization of the reaction conditions. ^[a]

Entry	Oxidizing agent (equiv)	Solvent	Additive ^[b]	T [°C]	t [h]	Yield ^[c] [%]
1	PhI(OAc) ₂ (2.1)	TFE	no	rt	3	0
2	PhI(OAc) ₂ (2.1)	TFE	no	rt	24	44
3	PhI(OAc) ₂ (2.5)	TFE	no	rt	24	25
4	PhI(OAc) ₂ (2.9)	TFE	no	rt	24	trace ^[d]
5	PhI(OAc) ₂ (1.7)	TFE	no	rt	24	51
6	PhI(OAc) ₂ (1.3)	TFE	no	rt	24	55
7	PhI(OAc) ₂ (1.0)	TFE	no	rt	24	48 ^[e]
8	PhI(Piv) ₂ (1.3)	TFE	no	rt	24	31 ^[e]
9	PhI(O ₂ CF ₃) ₂ (1.3)	TFE	no	rt	0.5	0 ^[d]
10	PhI(OAc) ₂ (1.3)	TFE	no	50	24	28 ^[d]
11	PhI(OAc) ₂ (1.3)	TFE	no	0	24	19 ^[d]
12	PhI(OAc) ₂ (1.3)	HFIP	no	rt	24	0 ^[d]
13	PhI(OAc) ₂ (1.3)	CH ₃ CN	no	rt	24	0 ^[e]
14	PhI(OAc) ₂ (1.3)	DCM	no	rt	24	0 ^[e]
15	PhI(OAc) ₂ (1.3)	TFE/DCM ^[f]	no	rt	24	56
16	PhI(OAc) ₂ (1.3)	TFE/DCM ^[f]	NaOAc	rt	24	51
17	PhI(OAc) ₂ (1.3)	TFE/DCM ^[f]	HOAc	rt	24	48
18	PhI/ <i>m</i> CPBA ^[g]	TFE/DCM ^[f]	no	rt	24	0 ^[d]

[a] The reaction was run on a 0.03 mmol scale. [b] 10 mol% of additive were used. [c] Isolated yield. [d] The starting material decomposed. [e] No full conversion. [f] TFE/DCM = 1:1, TFE = 2,2,2-trifluoroethanol, DCM = dichloromethane. [g] PhI (20 mol%), *m*CPBA (1.3 equiv); PhI = iodobenzene; *m*CPBA = *meta*-chloroperoxybenzoic acid.

To our delight, the fully aromatized mono-Boc-protected compound **2a** was directly formed using PIDA (2.1 equiv) as an oxidant in 2,2,2-trifluoroethanol (TFE) after 24 h with 44% yield (Table 1, Entry 2). Increasing the amount of PIDA resulted in decomposition of the substrate, while only 1 equiv of PIDA appeared to be insufficient (Entry 2–7). Application of 1.3 equiv led to the highest yield (Entry 6). When phenyliodonium dipivalate (PhI(piv)₂) was employed, incomplete conversion of the starting material was observed (Entry 8). Application of PIFA in the current protocol resulted in decomposition of the starting material (Entry 9). No improvement of the yield was observed at 0 °C or 50 °C (Entries 10 and 11). Switching to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent appeared to be deleterious for the reaction (Entry 12), while no reaction occurred in acetonitrile (ACN) or dichloromethane (DCM) (Entries 13 and 14). A small improvement of the yield was observed when choosing a mixture of dichloromethane (DCM) and TFE

(Entry 15), while other solvent mixtures led to low conversion. The addition of AcONa (Entry 16) or AcOH (Entry 17) was not beneficial for the reaction.^[9]

With the optimal conditions in hand, the scope and limitations of the process were evaluated (Table 2). The reaction

Table 2. Scope of the cascade cyclization.^[a]

<p>2b, 61%</p>	<p>2c, 49%</p>	<p>2d, 61%</p>
<p>2e, 55%</p>	<p>2f, 40%</p>	<p>2g, 59%^[c]</p>
<p>2h, 23%</p>	<p>2i, 48%</p>	<p>2j, 0%^[c]</p>
<p>2k, 0%^[c]</p>	<p>3a, 31%</p>	

[a] The reactions were run on a 0.1 mmol scale employing the conditions of Table 1, Entry 15. [b] 48 h. [c] The starting material decomposed.

does not seem to be sensitive to the nature of the *N*-substituent, as *n*Bu, Cy (cyclohexyl), and PMB (*p*-methoxybenzyl) are all performing well (**2a–c**). The methoxy groups on the phenyl ring A play an important role for the cyclization. Two or three methoxy groups on the phenyl ring A led to the formation of the desired products (**2a–h**). However, the substrates with three methoxy groups were slow for aromatization. Due to the instability of compound **5**, we only successfully isolated compound **5h**. When the phenyl ring A was bearing no or one methoxy- or a 1,3-dioxolane group, the starting material decomposed when employing standard conditions, even if the temperature was lowered to 0 °C (**2i**, **2j** and **2k**). For the aromatic ring B, with an unsubstituted phenyl, a 5-imino-6,7-dihydroimidazo[1,5-*c*]oxazol-3(5*H*)-one **3a** was obtained via Boc cyclization of the intermediate on the acetylene (vide infra for the mechanism). The reaction pathway was depending on the substitution pattern of the phenyl ring B.

Intrigued by this result, we optimized the conditions (Table 3) and evaluated the scope of this process (Table 4).

The *N* substituent did not significantly affect the product yield (**3b**, **3c**, and **3i**). A bromine substituent on the aromatic

Table 3. Optimization of the ring-fused guanidine formation.^[a]

Entry	Oxidizing agent (equiv)	Solvent	T [°C]	t [h]	Yield ^[b] [%]
1 ^[c]	PhI(OAc) ₂ (1.3)	TFE/DCM	rt	4	28
2	PhI(OAc) ₂ (1.3)	TFE	rt	4	32
3	PhI(OAc) ₂ (2.1)	TFE	rt	4	43
4	PhI(OAc) ₂ (2.5)	TFE	rt	4	38

[a] The reactions were run on a 0.03 mmol scale. [b] Isolated yield. [c] No full conversion; TFE/DCM = 1:1, TFE = 2,2,2-trifluoroethanol, DCM = dichloromethane.

Table 4. Scope of the process for ring-fused guanidines.^[a]

[a] The reactions were run on a 0.1 mmol scale employing the conditions of Table 3, Entry 3.

ring B resulted in the formation of the desired compound with a slightly lower yield (**3e**). The reaction worked well when a cyclohexyl substituent instead of a phenyl ring A was used (**3g**).

Finally, propargylguanidines **1u** and **1v** were used for the cascade cyclization (Scheme 3). Product **2u** was obtained in 53% yield (no full conversion when 1.3 equiv PIDA were used). After removing the Boc-group, kealiinine B was formed in 38% overall yield. In case of propargylguanidine **1w**, a mixture of **2v** and the nonaromatized **5v** was obtained. Subsequent deprotection was performed without separation of this mixture, resulting in the formation of kealiinine C in 34% overall yield. To the best of our knowledge, only two total syntheses of the kealiinine alkaloids were reported in the literature so far.^[10,11]

Bases on our observations, we propose a plausible reaction mechanism. As PIDA can activate both the methoxy and the guanidine group, there are two competing reaction pathways.

Scheme 3. Total syntheses of kealiinine B and C.

Substrates bearing two or three methoxy groups on the phenyl ring A and an electron-rich aromatic ring B, follow the pathway from our hypothesis (Scheme 2). On the contrary, substrates lacking a methoxy group on the aromatic ring B give rise to intermediate **6**, which is generated by PIDA-mediated activation of the guanidine^[1m] (Scheme 4). The intermediate cation seems to preferentially react with the carbamate moiety rather than with ring A, which results in the formation of the ring-fused guanidine **3**.

Scheme 4. Plausible mechanism (see also Scheme 2).

In summary, we have developed an oxidative PIDA-mediated cascade reaction resulting in two types of ring-fused skeletons depending on the substitution pattern of the aromatic rings. Thereby, total syntheses of kealiinines B and C in a concise way were realized.

Experimental Section

Full experimental details and spectroscopic data for all compounds along with the copies of ¹H, ¹³C NMR spectra are available in the Supporting Information.

Acknowledgements

The authors are thankful to the F.W.O. [Fund for Scientific Research–Flanders (Belgium)] and the Research Fund of the University of Leuven (KU Leuven) for financial support. The publication was financially supported by The Ministry of Education and Science of the Russian Federation (the Agreement number 02.a03.0008). We acknowledge the support by COST (European Cooperation in Science and Technology) Action (CA15106) CH-

Activation in Organic Synthesis. The authors thank Prof. Thomas Wirth from Cardiff University, United Kingdom (<http://blogs.cardiff.ac.uk/wirth/>) for the useful discussion. G.T. appreciates the CSC (China Scholarship Council) for providing a doctoral scholarship.

Conflict of interest

The authors declare no conflict of interest.

Keywords: 2-aminoimidazoles • cascade reactions • guanidines • hypervalent iodine • kealiinine alkaloids

- [1] a) Y. Kita, H. Watanabe, M. Egi, T. Saiki, Y. Fukuoka, H. Tohma, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1, 635; b) R. Olivera, R. SanMartin, S. Pascual, M. Herrero, E. Domínguez, *Tetrahedron Lett.* **1999**, 40, 3479; c) Y. Kita, M. Egi, H. Tohma, *Chem. Commun.* **1999**, 143; d) T. Dohi, A. Maruyama, Y. Minamitsuji, N. Takenaga, Y. Kita, *Chem. Commun.* **2007**, 1224; e) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, Y. Kita, *Tetrahedron* **2009**, 65, 10797; f) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073; g) L. M. Pardo, I. Tellitu, E. Domínguez, *Synthesis* **2010**, 6, 971; h) X. Du, H. Chen, Y. Chen, J. Chen, Y. Liu, *Synlett* **2011**, 7, 1010; i) S. Desjardins, J. C. Andrez, S. Canesi, *Org. Lett.* **2011**, 13, 3406; j) T. Dohi, T. Uchiyama, D. Yamashita, N. Washimi, Y. Kita, *Tetrahedron Lett.* **2011**, 52, 2212; k) I. Tellitu, E. Domínguez, *Synlett* **2012**, 2165; l) N. Yamaoka, K. Sumida, I. Itani, H. Kubo, Y. Ohnishi, S. Sekiguchi, T. Dohi, Y. Kita, *Chem. Eur. J.* **2013**, 19, 15004; m) K. Dev, R. Maurya, *RSC Adv.* **2015**, 5, 13102; n) P. Mizar, R. Niebuhr, M. Hutchings, U. Farooq, T. Wirth, *Chem. Eur. J.* **2016**, 22, 1614; o) X. Fang, Y. Z. Zhu, J. Y. Zheng, *J. Org. Chem.* **2014**, 79, 1184; p) S. Manna, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2016**, 55, 5290; *Angew. Chem.* **2016**, 128, 5376.
- [2] For reviews of the synthesis and activity of 2-aminoimidazole alkaloids, see: a) S. M. Weinreb, *Nat. Prod. Rep.* **2007**, 24, 931; b) H. Hoffmann, T. Lindel, *Synthesis* **2003**, 12, 1753; c) J. D. Sullivan, R. L. Giles, R. E. Looper, *Curr. Bioact. Compd.* **2009**, 5, 39.
- [3] For anti-biofilm activity of 2-aminoimidazoles, see: a) R. W. Huigens III, J. J. Richards, G. Parise, T. E. Ballard, W. Zeng, R. Deora, C. Melander, *J. Am. Chem. Soc.* **2007**, 129, 6966; b) T. E. Ballard, J. J. Richards, A. L. Wolf, C. Melander, *Chem. Eur. J.* **2008**, 14, 10745; c) H. P. L. Steenackers, D. S. Ermolat'ev, B. Savaliya, A. DeWeerd, D. De Coster, A. Shah, E. V. Van der Eycken, D. E. De Vos, J. Vanderleyden, S. C. J. De Keersmaecker, *J. Med. Chem.* **2011**, 54, 472; d) H. P. L. Steenackers, D. S. Ermolat'ev, B. Savaliya, A. De Weerd, D. De Coster, A. Shah, E. V. Van der Eycken, D. E. De Vos, J. Vanderleyden, S. C. J. De Keersmaecker, *Bioorg. Med. Chem.* **2011**, 19, 3462; e) H. P. L. Steenackers, K. Hermans, S. C. J. De Keersmaecker, J. Vanderleyden, *Food Res. Int.* **2012**, 45, 502.
- [4] a) M. S. Malamas, J. Erdei, I. Gunawan, K. Barnes, M. Johnson, Y. Hui, J. Turner, Y. Hu, E. Wagner, K. Fan, A. Olland, J. Bard, A. J. Robichaud, *J. Med. Chem.* **2009**, 52, 6314; b) P. Jain, H. R. Jadhav, *Med. Chem. Res.* **2013**, 22, 1740; c) K. Roos, J. Viklund, J. Meuller, K. Kaspersson, M. Svensson, *J. Chem. Inf. Model.* **2014**, 54, 818; d) D. Oehlrich, H. Prokop-cova, H. J. M. Gijzen, *Bioorg. Med. Chem. Lett.* **2014**, 24, 2033.
- [5] a) R. S. Coleman, E. L. Campbell, D. J. Carper, *Org. Lett.* **2009**, 11, 2133; b) M. Nodwell, A. Pereira, J. L. Riffell, C. Zimmermann, B. O. Patrick, M. Roberge, R. J. Andersen, *J. Org. Chem.* **2009**, 74, 995.
- [6] D. S. Ermolat'ev, J. B. Bariwal, H. P. L. Steenackers, S. C. J. De Keersmaecker, E. V. Van der Eycken, *Angew. Chem. Int. Ed.* **2010**, 49, 9465; *Angew. Chem.* **2010**, 122, 9655.
- [7] W. Hassan, R. Edrada, R. Ebel, V. Wray, A. Berg, R. Van Soest, S. Wiryowidagdo, P. Proksch, *J. Nat. Prod.* **2004**, 67, 817.
- [8] a) J. B. Bariwal, D. S. Ermolat'ev, E. V. Van der Eycken, *Chem. Eur. J.* **2010**, 16, 3281; b) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, 41, 3790.
- [9] More information about the optimal conditions can be found in the Supporting Information.
- [10] J. B. Gibbons, K. M. Gligorich, B. E. Welm, R. E. Looper, *Org. Lett.* **2012**, 14, 4734.
- [11] J. Das, P. B. Koswatta, J. D. Jones, M. Yousufuddin, C. J. Lovely, *Org. Lett.* **2012**, 14, 6210.

Manuscript received: February 28, 2017

Accepted Article published: March 6, 2017

Final Article published: ■ ■ ■ ■ 0000

COMMUNICATION

Hypervalent iodine cascade reaction:

An oxidative cascade cyclization of propargylguanidines promoted by phenyliodonium diacetate was developed, which resulted in two types of ring-fused skeletons depending on the substitution pattern of the aromatic rings. The protocol provides an efficient route for the total synthesis of the alkaloids kealiinine B and C.

Organic Synthesis

G. Tian, P. Fedoseev, E. V. Van der Eycken*

**Hypervalent Iodine(III)-Mediated
Cascade Cyclization of
Propargylguanidines and Total
Syntheses of Kealiinine B and C**