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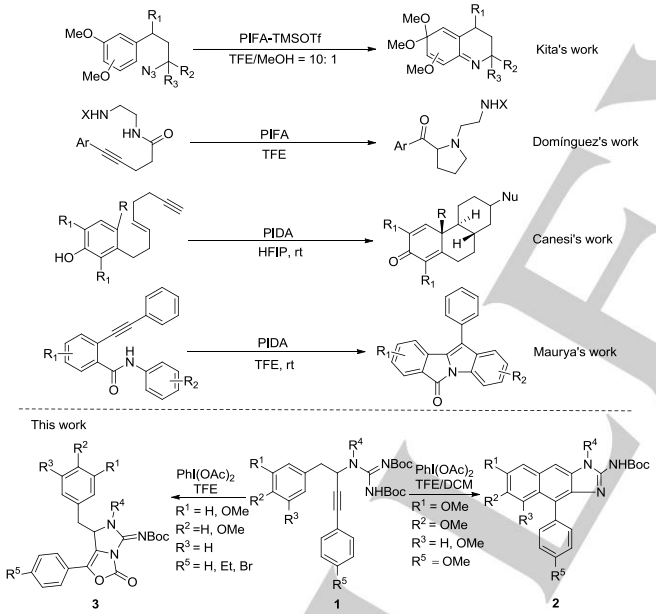
Hypervalent Iodine(III)-Mediated Cascade Cyclization of Propargylguanidines and Total Syntheses of Kealiinine B and C

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

Dedicated to Prof. 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.*

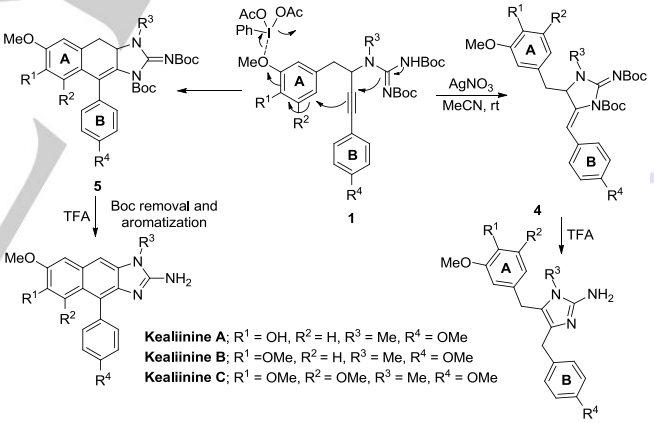
In the last years, hypervalent iodine reagents have attracted great attention due to their environmental friendliness and low cost, as well as their ease of handling. The synthetic efficiency in the construction of complex architectures via oxidative transformations proved its utility in many reports.[1]



Scheme 1. PIDA- or PIFA-promoted cyclizations.

Kita's [1a,c-f,j,l] and Domínguez's groups[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's group 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 there 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 2. Synthesis of protected 2-aminoimidazoles and Kealiinines; Boc = *tert*-butyloxycarbonyl. 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 formation of compound **5**. Obviously, this process should give access to the syntheses of Kealiinine 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

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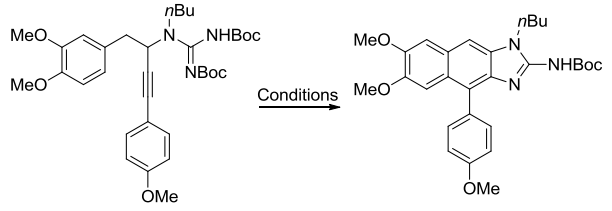
guanylation of the related *N*-butyl-propargylamine[6] which was accessed through A3 coupling[8].

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



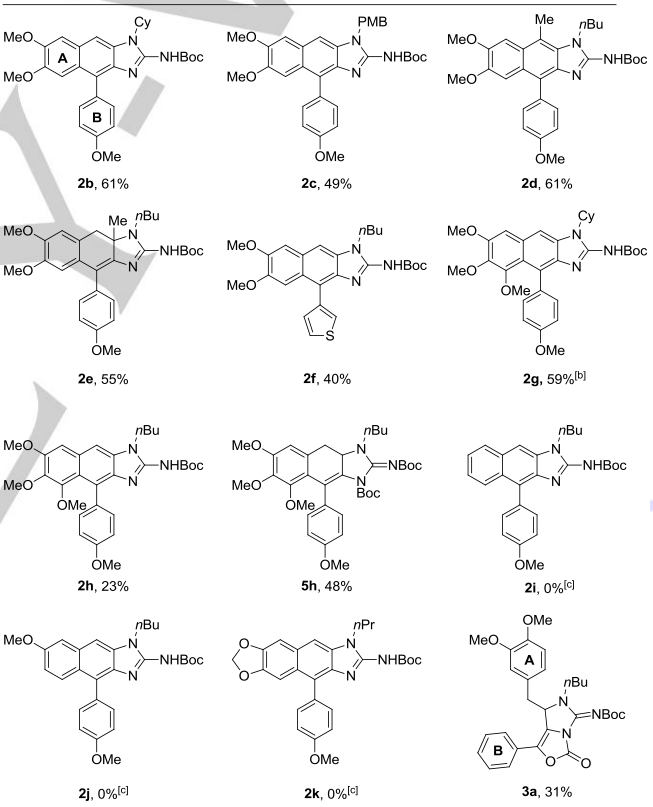
1a **2a**

Entry	Oxidizing agent (equiv)	Solvent	Additive[b]	*T* (°C)	Time (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	$PhI(O_2CF_3)_2$ (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_3CN	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/*m*CPBA[g]	TFE/DCM[f]	no	rt	24	0[d]

[a] The reaction was run on a 0.03 mmol scale; [b] 10mol% of additive was 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 2.1 equiv of PIDA as an oxidant in 2,2,2-trifluoroethanol (TFE) after 24 h with 44% yield (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 marterial 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 (entry 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.[g]

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



[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.

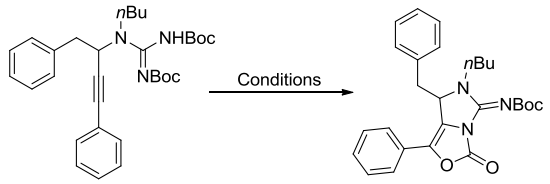
With the optimal conditions in hand, the scope and limitations of the process were evaluated (Table 2). The reaction does not seem to be sensitive to the nature of the N-substituent, as nBu, Cy and PMB are all performing well (**2a**, **b** and **c**). The methoxy groups on the phenyl-ring A play an important role for the cyclization. Two or three methoxy groups on the phenyl-ring A led to the formation of

10.1002/chem.201700934

the desired product (**2a**-**h**). However, the substrates with three methoxy groups were slow for aromatization. For the unstability 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 employing the standard conditions, even when 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).

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



1m **3b**

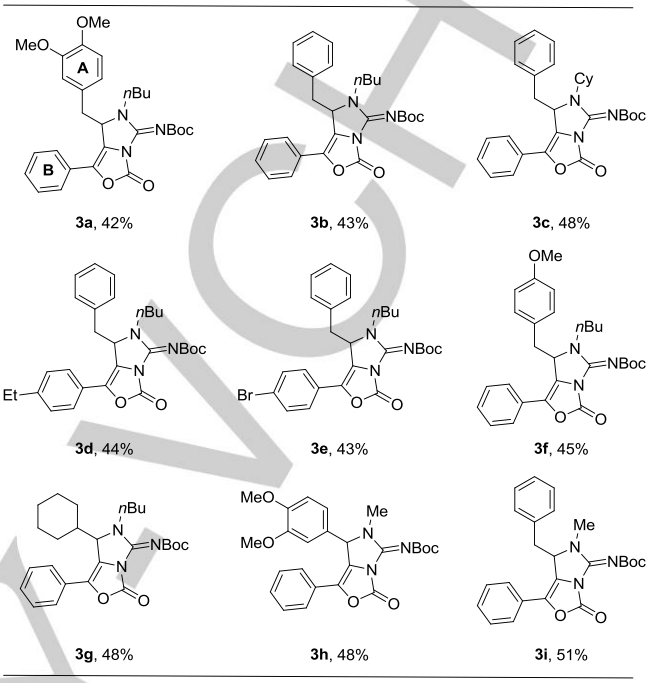
Entry	Oxidizing agent (equiv)	Solvent	*T* (°C)	Time (h)	Yield (%)[b]
1[c]	$PhI(OAc)_2$ (1.3)	TFE/DCM	rt	4	28
2	$PhI(OAc)_2$ (1.3)	TFE	rt	4	32
3	**$PhI(OAc)_2$ (2.1)**	**TFE**	**rt**	**4**	**43**
4	$PhI(OAc)_2$ (2.5)	TFE	rt	4	38

[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.

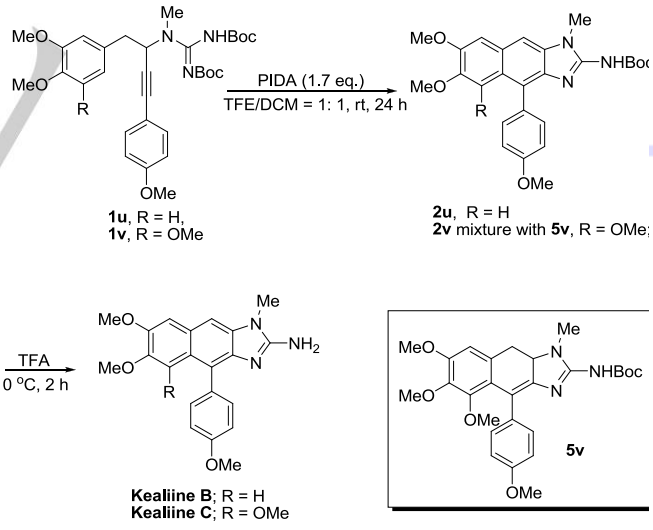
The N-substituent was found to not have a significant effect on the product yield (**3b**, **3c**, and **3i**). A bromine substituent on the aromatic ring B resulted in the formation of the desired compound in a little lower yield (**3e**). The reaction worked well when a cyclohexyl-substituent instead of a phenyl-ring A was used (**3g**).

Finally, propargylguanidines **1u**, **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**, the formation of a mixture of **2v** and the non-aromatized **5v** was obtained. Subsequent deprotection was performed without separarion of this mixture, resulting in the formation of **Kealiinine C** in 34% overall yield. To the best of our knowledge, so far only two total syntheses of the Kealiinine alkaloids were reported in the literature.[10-11]

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.

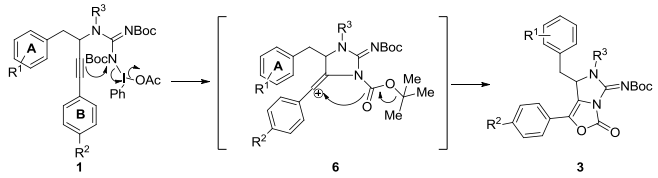


Scheme 3. Total syntheses of Kealiinine B and C.

Basing on our observations, we propose a plausible reaction mechanism. As PIDA can activate both the methoxy-group and the guanidine, there are two competing reaction pathways. Substrates bearing two or three methoxy-groups on the phenyl-ring A and an electron-rich

10.1002/chem.201700934

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 *via* PIDA-mediated activation of the guanidine[1m] (Scheme 4). The intermediate cation seems to prefer reaction with the carbamate moiety, rather than with ring A, resulting 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. A 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 ^{1}H, ^{13}C NMR spectra are available at the Supporting Information.

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Keywords: guanidines, cascade reaction, hypervalent iodine, 2-aminoimidazoles, Kealiinine alkaloids

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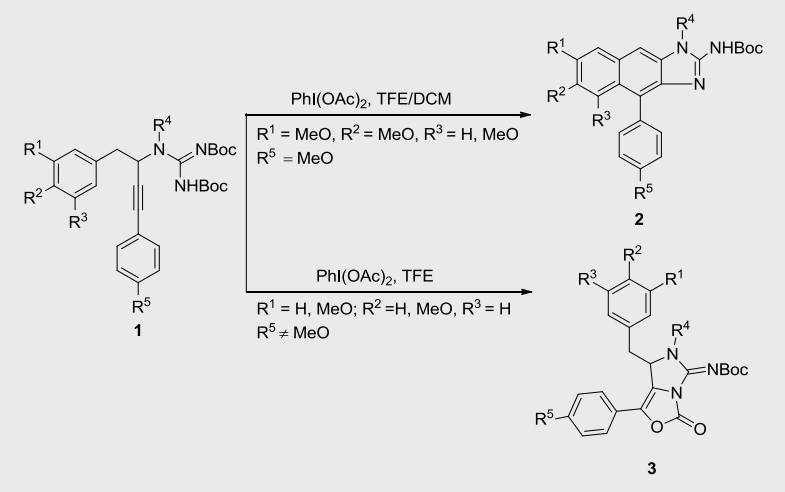

*Guilong Tian, Pavel Fedoseev, and Erik V. Van der Eycken**

Page No. – Page No.

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