Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dual use of propargylamine building blocks in the construction of polyheterocyclic scaffolds

Anna Bakholdina [a], Alexei Lukin [a], Olga Bakulina [b], Natalia Guranova [b], Mikhail Krasavin [b,c,*]

[a] Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University, Moscow 119571, Russian Federation
[b] Saint Petersburg State University, Saint Petersburg 199034, Russian Federation
[c] Immanuel Kant Baltic Federal University, Kaliningrad 236016, Russian Federation

ARTICLE INFO

Article history:
Received 29 March 2020
Revised 17 April 2020
Accepted 21 April 2020
Available online xxxx

Keywords:
Hydroamination-cyclization
Zinc triflate
Cesium carbonate
Propargyl group cyclization
Polyheterocycles
Blue emitters

ABSTRACT

The cyclization reactions of 2-(*N*-propargyl)imidazole-2-yl)indoles (synthesized *via* the hydroamination reaction between *N*-propargyl indole-2-carboxamides and propargylamine) have been investigated under Lewis acid- and base-promoted conditions. The polyheterocyclic compounds thus obtained were shown to possess promising photophysical properties.

Ring-forming reactions involving positions 1 and 3 of the indole nucleus and a propargylamino motif attached at position 2 *via* various linkers is a common method of building polycyclic heteroaromatic scaffolds. Recent noteworthy examples of utilizing this strategy include the Au(III)- and Pt(II)-catalyzed cyclizations of propargylic indole-2-carboxamides reported by Padwa [1] and Beller [2], respectively. Interestingly, a similar cyclization was achieved by Watkins and co-workers upon heating in the presence of weakly basic sodium bicarbonate [3]. Cyclizations onto N-1 of an indole core are also typically achieved under base-promoted conditions. The use of a rather strong base is considered necessary as the propargylamide moiety needs initially to be converted into the respective C-reactive allene amide. This approach is illustrated by the DBU-promoted cyclization reported by Llauger [4] and post-condensational modification of indole- and propargyl-containing products of the Ugi reaction achieved by Shafiee and co-workers upon brief treatment with *t*-BuOK [5]. We became interested in exploring the possibility of employing 2-(imidazol-2-yl)indoles **1** as a template for complexity-generating cyclizations at either position N-1 or C-3, depending on the reaction conditions. We reasoned that compounds **1** could be obtained *via* the $Zn(OTf)_2$-catalyzed hydroamination-cyclization sequence described by Beller and co-workers [6] as well as Krasavin and co-workers [7]. If applied to readily available *N*-propargyl indole-2-carboxamides **2** and propargylamine, this approach would deliver the expected starting materials **1** for further cyclizations. The possibility of cyclization at position C-3 was preliminarily indicated by the recent report by Nagarajan and co-workers [8] of cyclizations involving position 3 of *N*-substituted indole and a propargyl group attached to position 2 *via* various heterocycles. However, similar cyclization at position N-1 has not been investigated. Both of these divergent cyclizations would deliver tetracyclic aromatic imidazo[1′,2′:1,2]pyrido[3,4-*b*]indole (**3**) and imidazo[2′,1′:3,4]pyrazino[1,2-*a*]indole (**4**) scaffolds (Fig. 1) which are known for their analogy to anticancer kinase inhibitors [9] as well as their valuable photophysical properties [10], respectively.

Unfortunately, the yields of *N*-propargyl imidazoles **1a**–**d** from the respective *N*-propargyl indole-2-carboxamides **2a**–**d** proved disappointingly low, under modified literature conditions employing 20 mol% $Zn(OTf)_2$ [7b]. Lowering the amount of the catalyst to 5 mol% (as described by Beller and co-workers [6]) led to no product formation while raising it to 50 mol% [7a] did not improve the yield (Scheme 1). Notably, attempts to carry out the same transformations with N^1-methylated versions of **2** did not result

* Corresponding author at: Laboratory of Chemical Pharmacology, Institute of Chemistry, Saint Petersburg State University, 26 Universitetskii Prospect, Peterhof 198504, Russian Federation.
E-mail address: m.krasavin@spbu.ru (M. Krasavin).
URL: http://krasavin-group.org (M. Krasavin).

https://doi.org/10.1016/j.tetlet.2020.151970
0040-4039/

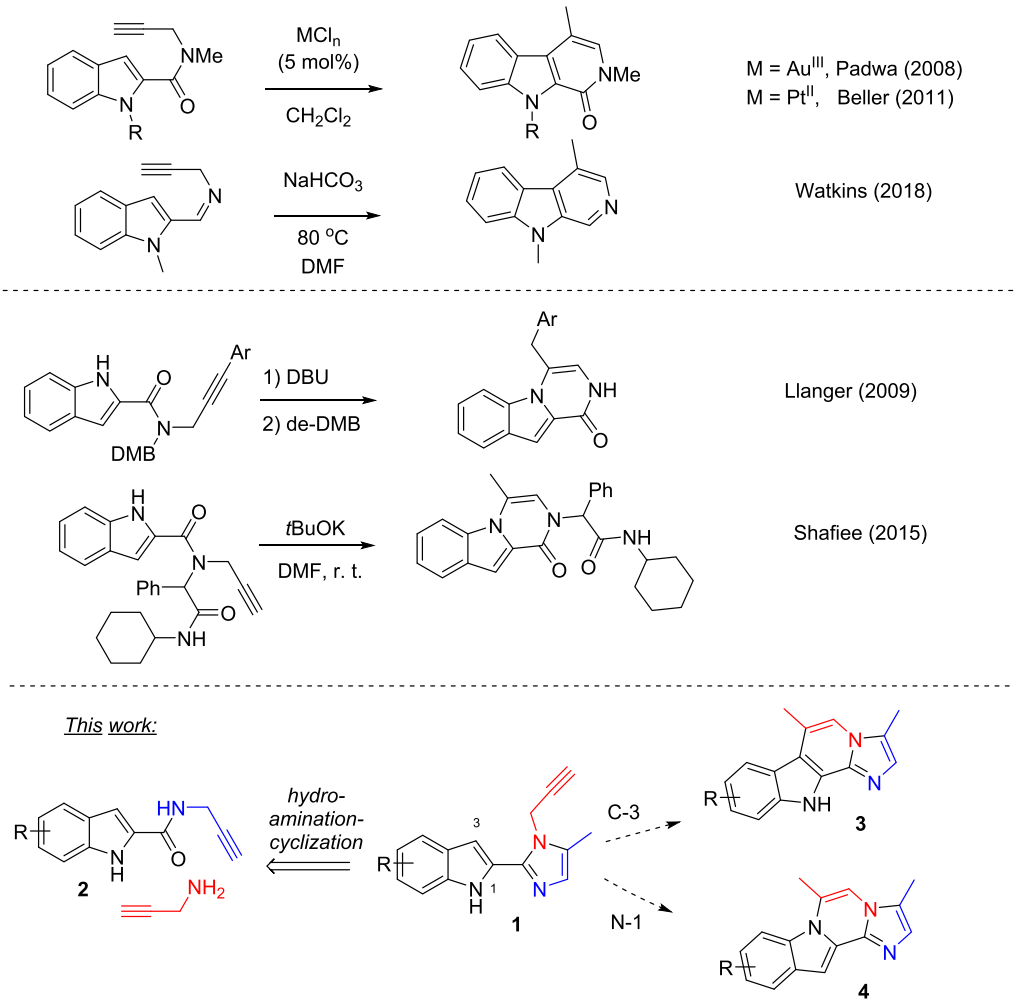
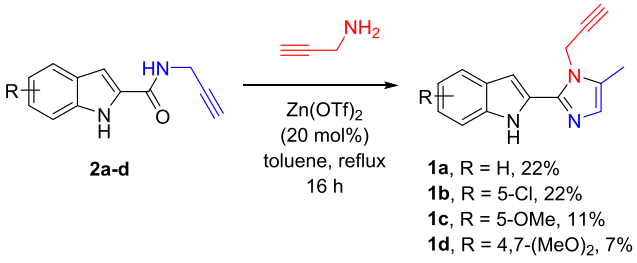
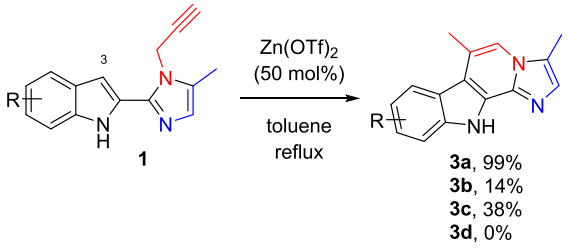


Fig. 1. Examples of cyclization of a propargylamino moiety onto C-3 or N-1 of the indole core and the chemodivergent strategy investigated in this work.



Scheme 1. Synthesis of *N*-propargyl imidazoles **1a–d**.



Scheme 2. Zn(OTf)$_2$-catalyzed cyclizations of substrates **1a–d**.

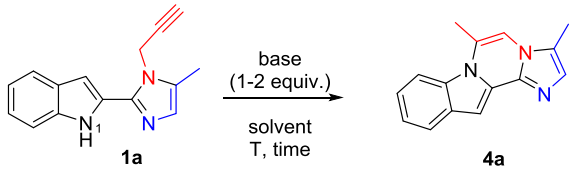
in the formation of the imidazole product. Nonetheless, this approach provided a rapid entry into *NH*-indoles **1a–d** which we intended to engage in regiodivergent cyclizations involving the propargyl moiety and either C-3 or N-1 of the indole core.

Screening of Lewis acid catalysts for the cyclization at C-3 using **1a** as a model substrate, identified Zn(OTf)$_2$ (50 mol%) as the optimum catalyst which gave 99% yield of the respective cyclized product (**3a**). Among the examined catalysts (including Gd(OTf)$_3$, Cu(OTf)$_2$, AuPPh$_3$Cl, AuPPh$_3$Cl/AgOTf, AgOTf, PtCl$_2$, PtCl$_2$/AgOTf, K$_2$PtCl$_6$, Pd(OAc)$_2$, TfOH, CuI, CuBr, Ce$_2$(SO$_4$)$_3$, Yb(OTf)$_3$, Zn(OAc)$_2$, Sc(OTf)$_2$) screened at 10 mol% in compatible solvents and at temperatures varying from ambient to reflux, only Cu(OTf)$_2$ and Gd(OTf)$_3$ also gave the desired product **3a** in 10% and 70% yield, respectively. With Zn(OTf)$_2$ as a catalyst, the cyclizations were extended to substrates **1b–d**; however, the reaction was rather sensitive to the substitution pattern with the most electron-rich substrate **1d** affording no product (Scheme 2).

For the cyclization involving the propargyl substituent and the N-1 atom of the indole nucleus, presumably proceeding *via* the corresponding allene, various base promoters (employed in equimolar amount or two-fold excess) were screened against substrate **1a**. As is evident from the data provided in Table 1, the range of inorganic as well as organic bases capable of driving the reaction forward is rather wide. While the reaction was faster at elevated temperature, the product purity was better for reactions conducted over 7 h at ambient temperature. Overall, the use of Cs$_2$CO$_3$ (2 equiv.) at room temperature (Table 1, Entry 1) was deemed optimal. These conditions were then applied to substrates **1a–d** (Scheme 3). To our delight, the desired cyclization products **4** formed in each case;

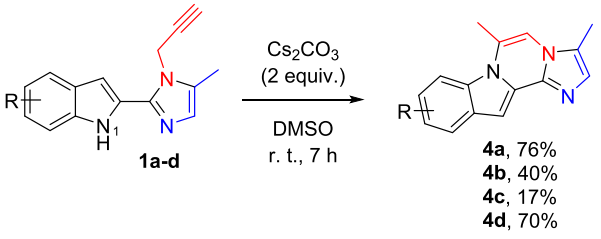
Please cite this article as: A. Bakholdina, A. Lukin, O. Bakulina et al., Dual use of propargylamine building blocks in the construction of polyheterocyclic scaffolds, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2020.151970

Table 1
Optimization of the base-promoted cyclization of **1a**.



Entry	Base (equiv.)	Solvent	T (°C)	Yield **4a** (%)
1	Cs_2CO_3 (2.0)	DMSO	22[a]	76
2	Cs_2CO_3 (1.0)	DMSO	22[a]	66
3	Cs_2CO_3 (2.0)	DMSO	120[b]	74[c]
4	KOH (2.0)	DMSO	22[a]	70
5	KOH (2.0)	DMSO	120[b]	68
6	*t*-BuOK (1.0)	THF	22[a]	70
7	TBAF (1.0)	THF	22[a]	70
8	K_2CO_3 (2.0)	DMSO	22[a]	63
9	NaHCO3 (2.0)	DMSO	22[a]	30
10	DBU (1.0)	CH_2Cl_2	22[a]	10
11	TEA (1.0)	$CHCl_3$	22[a]	0
12	None	DMF	120[a]	0

[a] Reaction time – 7 h.
[b] Reaction time – 1 h.
[c] The product was contaminated with an unknown impurity.



Scheme 3. $CsCO_3$-promoted cyclizations of substrates **1a**–**d**.

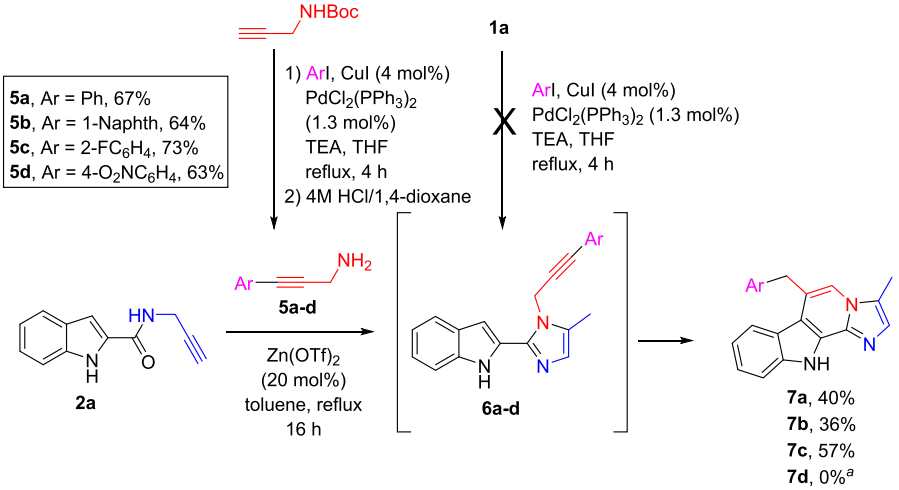
however, for substrates bearing substituents at position 5 the yield was markedly lower.

Finally, capitalizing on the prior work of Nagaraja and co-workers [8] who described similar cyclizations of *N*-(3-aryl) propargyl 2,2′-bis-indolyl derivatives, we became interested in introducing aryl substituents at the terminus of the propargyl group in **1a**. Surprisingly, the standard Sonogashira coupling protocol failed to give the expected derivatives **6**. Therefore, we resorted to preparing 3-arylprop-2-yn-1-ylamines **5a**–**d** from Boc-protected propargylamine as described in the literature [11]. The use of these 3-arylpropargylamines in the Beller imidazole synthesis under catalysis by $Zn(OTf)_2$ (20 mol%) led directly to the double cyclization products **7a**–**c**. In the case of propargylamine bearing the electron-poor 4-nitrophenyl group (**5d**), the second cyclization did not proceed, even under forcing conditions, and the respective imidazole product **6d** was isolated in low yield (Scheme 4).

It should be noted that positioning the (*N*-propargyl)imidazole-2-yl moiety at C-2 of the indole appears crucial for the success of subsequent $Zn(OTf)_2$-catalyzed cyclization. Indeed, imidazoles **9a**–**b** prepared from propargylic indole-3- (**8a**) and indole-4-carboxmides (**8b**), respectively, did not undergo subsequent cyclization (Scheme 5).

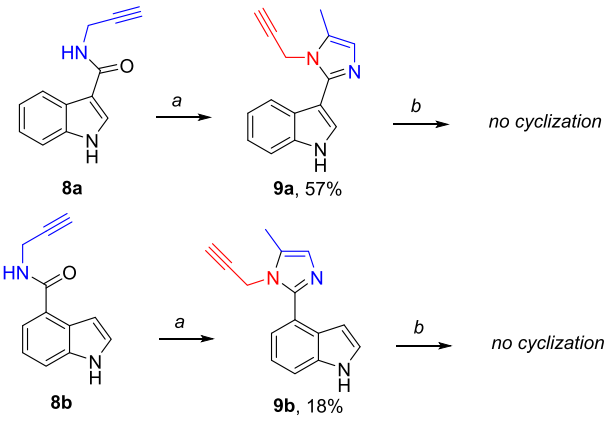
Considering the propensity of polycyclic heteroaromatic systems such as imidazo[2′,1′:3,4]pyrazino[1,2-*a*]indole (**4**) to display useful photophysical properties, we recorded emission and absorption spectra for selected compounds in the **3**, **4** and **7** series. All of the compounds were found to be phosphors and showed blue emission with maxima at 350–400 nm under excitation at 305–355 nm in DMSO solutions at concentrations of 50 μM (Fig. 2a). All compounds exhibited complex absorption spectra with maxima in the UV region at 270–320 nm (Fig. 2b). Each series of compounds (**3**, **4** or **7**) showed its own characteristic absorption and emission pattern (Figs. S1 and S2). More detailed information on the absorption and emission characteristics of compounds investigated is provided in the Supplementary data.

In summary, we have investigated the cyclization reactions of 2-(*N*-propargyl)imidazole-2-yl)indoles (synthesized *via* a previously described hydroamination-cyclization protocol from readily available indole-2-(propargyl)carboxamides) at the C-3 and N-1 atom of the indole nucleus under the influence of a Lewis acid ($Zn(OTf)_2$) and base (Cs_2CO_3) promoter, respectively. Although the reaction was found to be rather sensitive to the indole substitution pattern, it provided a rapid access to two distinct polyheterocyclic cores. Interestingly, the attempted preparation of terminally arylated propargyl derivatives from *N*-propargyl indole-2-carboxamide led directly to the corresponding tetracyclic products.



Scheme 4. Preparation of 1-arylproparylamines **5a**–**d** and their use in the hydroamination-cyclization sequence with **2a** ([a]compound **6d** was isolated in 11% yield).

Please cite this article as: A. Bakholdina, A. Lukin, O. Bakulina et al., Dual use of propargylamine building blocks in the construction of polyheterocyclic scaffolds, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2020.151970



Reagents and conditions: (a) propargylamine, $Zn(OTf)_2$ (20 mol%), toluene, reflux,16 h;
(b) $Zn(OTf)_2$ (50 mol%), toluene, reflux, 7 h

Scheme 5. Attempted positioning of the (*N*-propargyl)imidazole-2-yl moiety at positions 3 and 4 of the indole nucleus.

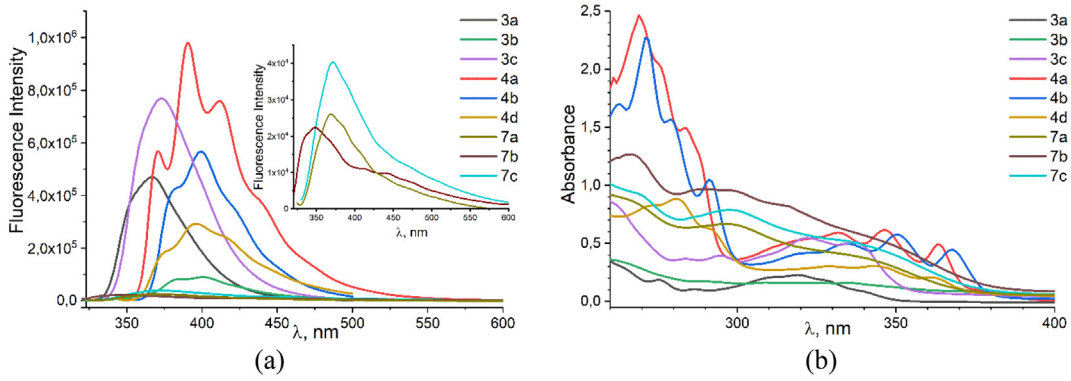


Fig. 2. Emission (a) and absorption (b) spectra of selected compounds in the **3**, **4** and **7** series measured in DMSO (50 μM).

Acknowledgement

This research was supported by the Russian Foundation for Basic Research (project grant 19-33-90169).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151970.

References

[1] D.B. England, A. Padwa, Org. Lett. 10 (2008) 3631–3634.
[2] M. Gruit, A. Pews-Davtyan, M. Beller, Org. Biomol. Chem. 9 (2011) 1148–1159.
[3] D. Uredi, D.R. Motati, E.B. Watkins, Org. Lett. 20 (2018) 6336–6339.
[4] L. Llauger, C. Bergami, O.D. Kinzel, S. Lillini, G. Pescatore, C. Torrisi, P. Jones, Tetrahedron Lett. 50 (2009) 172–177.
[5] M. Mahdavi, R. Hasanzadeh-Soureshjan, M. Saeedi, A. Ariafard, R. BabaAhmadi, P.R. Ranjbar, A. Shafiee, RSC Adv. 5 (2015) 101353–101361.
[6] (a) A. Pews-Davtyan, A. Tillack, A.-C. Schmöle, S. Ortinau, M.J. Frech, A. Rolfs, M. Beller, Org. Biomol. Chem. 8 (2010) 1149–1153;
(b) A. Pews-Davtyan, M. Beller, Org. Biomol. Chem. 9 (2011) 6331–6334.
[7] (a) A. Lukin, A. Bakholdina, A. Kryukova, A. Sapegin, M. Krasavin, Beilstein J. Org. Chem. 15 (2019) 1061–1064;
(b) A. Safrygin, E. Krivosheyeva, D. Dar'in, M. Krasavin, Synthesis 50 (2018) 3048–3058.
[8] S. Ramesh, R. Nagarajan, Synthesis 47 (2015) 3573–3582.
[9] (a) R. J. Andersen, M. Roberge, J. Sanghera, D. Leung, PCT Int. Appl. WO 9947522A1, Chem. Abstr. 131 (1999) 243451.;
(b) E. Piers, R. Britton, R.J. Andersen, J. Org. Chem. 65 (2000) 530–535;
(c) J.B. Jaquith, A. Fallis, J. Gillard, PCT Int. Appl. WO 2001087887A2, Chem. Abstr. 136 (2001) 6198.;
(d) G. Tremblay, A. Kalbakji, M. Filion, PCT Int. Appl. WO 2009127059A1, Chem. Abstr. 151 (2009) 478570.
[10] (a) S. Matsumoto, K. Sakamoto, M. Akazome, Heterocycles 91 (2015) 795–814;
(b) G.H. Bae, S. Kim, N.K. Lee, A. Dagar, J.H. Lee, J. Lee, I. Kim, RSC Adv. 10 (2020) 7265–7288.
[11] T. Ishida, R. Kobayashi, T. Yamada, Org. Lett. 16 (2014) 2430–2433.