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Efficient Synthesis of the Indoloazocine Framework via Intramolecular Alkyne Carbocyclization

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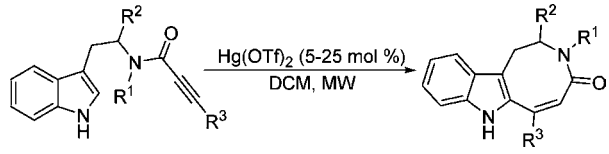
ABSTRACT



A microwave-assisted protocol based on an $Hg(OTf)_2$ catalyzed intramolecular alkyne carbocyclization reaction was developed for selective construction of the indoloazocine core.

The eight-membered N-containing azocine ring fused with the indole nucleus represents an interesting but scarcely investigated synthetic target. This ring system is present in some indole alkaloids such as deoxyisoaustamide,[1] okaramine N,[2] balasubramide,[3] and the lundurines[4] (Figure 1). Most of the existing preparative pathways[5] toward indoloazocines lack generality and involve poorly available starting material or require multistep synthetic transformations. Recently reported solutions to this problem include the approach via tandem cleavage of hydrogenated β- and γ-carbolines[6] and an Au-catalyzed intramolecular reaction of indoles with alkynes.[7] The latter approach, however, suffers in many cases from competition between 7-exo-dig and 8-endo-dig pro-

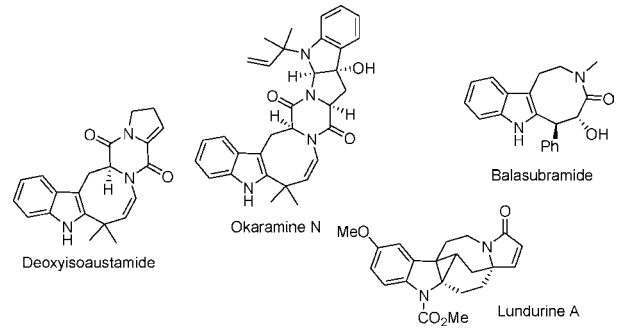


Figure 1. Alkaloids containing the indoloazocine core.

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[‡] Biomolecular Architecture.

(1) (a) Steyn, P. S. *Tetrahedron Lett.* **1971**, *12*, 3331. (b) Steyn, P. S. *Tetrahedron* **1973**, *29*, 107. (c) Sames, P. G. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51. (d) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.

(2) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.

(3) (a) Johansen, M. B.; Leduc, A. B.; Kerr, M. A. *Synlett* **2007**, 2593. (b) Yang, L.; Deng, G.; Wang, De. X.; Huang, Z. T.; Zhu, J. P.; Wang, M. X. *Org. Lett.* **2007**, *9*, 1387.

(4) (a) Kam, T. S.; Lim, K. H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739. (b) Kuehne, M. E.; Cowen, S. D.; Xu, F.; Borman, L. S. *J. Org. Chem.* **2001**, *66*, 5303.

(5) (a) Yoneda, R.; Kimura, T.; Kinomota, J.; Harusawa, S.; Kurihara, T. *J. Heterocycl. Chem.* **1996**, *33*, 1909. (b) Bonjoch, J.; Casamitjana, N.; Gracia, J.; Ubeda Carmen, M.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 2449. (c) Blechert, S.; Knier, R.; Schroers, H.; Wirth, T. *Synthesis* **1995**, 592. (d) Diker, K.; Döe de Maindreville, M.; Levy, J. *Tetrahedron Lett.* **1995**, *36*, 3511.

(6) Voskressensky, L. G.; Borisova, T. N.; Kulikova, L. N.; Varlamov, A. V.; Catto, M.; Altomare, C.; Carotti, A. *Eur. J. Org. Chem.* **2004**, 3128.

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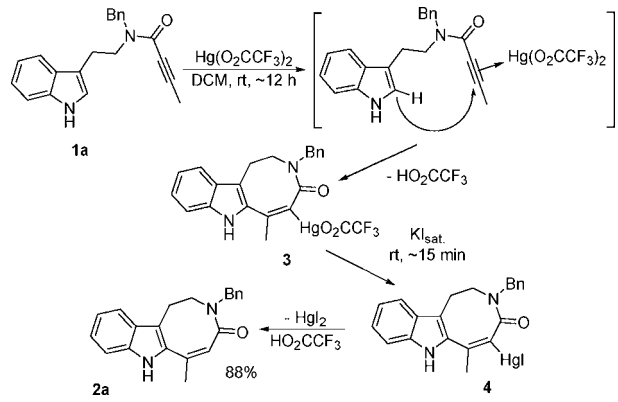
cesses, thus producing mixtures of 7- and 8-membered rings, and may also be complicated by allenylation.

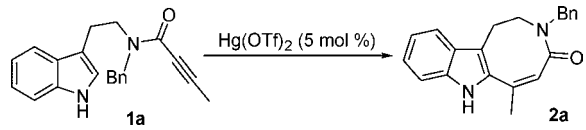
On the other hand, we found out that amide **1a** selectively and efficiently undergoes cyclization into indoloazocinone **2a** upon treatment with a stochiometric amount of $Hg(O_2CCF_3)_2$ followed by workup with saturated aqueous KI solution (Scheme 1). Apparently, this carbocyclization proceeds[8] via intermediates **3** and **4**, the latter resulting from **3** after ion exchange. Nevertheless, we failed to isolate the iodomercurate **4** or the analogous chloromercurate because of rapid protodemercuration in aqueous media. The selective formation of the 8-membered ring is undoubtedly the result of electronic control during nucleophilic addition to the conjugated triple bond.

Scheme 1



Unfortunately, the cyclization failed to proceed under catalytic conditions applying up to 15 mol % of $Hg(O_2CCF_3)_2$. The reaction also did not occur in the presence of Brönsted acids like CF_3CO_2H and TfOH. Thus, we tested several Lewis acids (5 mol %) which are often successfully used as catalysts for alkyne carbocyclizations:[9] AuCl, $AuCl_3$, AgOTf, AgO_2CCF_3, $PdCl_2$, $PtCl_2$, $Hg(OTf)_2$. However, the product was formed (Table 1) only in the case of $Hg(OTf)_2$.[10] Initially the reaction was performed at rt in MeCN and required almost 2 days for completion. Switching to DCM resulted in a shortened reaction time and slightly higher yield. Moderate heating at 80 °C greatly accelerated the reaction but led to a decrease in yield. Microwave irradiation produced further shortening of the reaction time and gave a comparable yield. As a compromise between reaction rate and yield the microwave-assisted protocol was chosen for further elaboration. Experiments were carried out in a monomode CEM Discover microwave reactor in sealed vials.

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	T (°C)	time (h)	yield (%)
1	MeCN	rt	40	91
2	DCM	rt	24	95
3	DCM	80	0.5	84
4	DCM	80 (MW)[b]	0.25	85

[a] Run on a 0.3 mmol scale in dry solvent (1.2 mL) in a sealed vial; [b] Run in a monomode CEM Discover microwave reactor at a maximum power of 60 W.

A number of amides **1a**−**m** were synthesized[11] starting from the corresponding tryptamines and 3-substituted 2-propynoic acids. In most cases conditions initially applied for the synthesis of **2a** with minor variation of the reaction time were suitable for fast and efficient conversion of the starting amides (Table 2, entries 1−3 and 5−7). However, several limitations on the structure of the starting material were discovered. Thus, secondary amide **1d** (Table 2, entry 4) was found to be an unsuitable substrate for the cyclization providing an ill-defined mixture of products. A higher temperature and an increased amount of catalyst (15 mol %) were required to drive to completion the cyclization of **1h** bearing a bulky *i*-Pr group (Table 2, entry 8). Nevertheless, the corresponding product **2g** was obtained in a high yield (79%). The more bulky *t*-Bu group (Table 2, entry 9) completely inhibited the reaction preserving the starting amide **1i** unchanged. The phenylpropiolic acid amide **1j** (Table 2, entry 10) had a reactivity comparable with that of amide **1h** and afforded the indoloazocinone **2h** in 61% yield. Amide **1k** containing a highly electron-donating 3,4,5-trimethoxyphenyl moiety (Table 2, entry 11) required particularly harsh conditions for complete conversion. With 30 mol % of $Hg(OTf)_2$ at a ceiling temperature of 120 °C, the corresponding indoloazocinone **2i** was obtained in only 40% yield after 50 min of irradiation.

Surprisingly, **1l** and **1m** containing the terminal triple bond, which is more susceptible toward an intramolecular nucleophilic attack, turned out to be very sluggish substrates in the cyclization. The reaction mixtures had to be irradiated for a long time (>60 min) even with up to 15 mol % of the catalyst to reach complete conversion of the starting material. The yields of the indoloazocinones **2j** and **2k** were, however, extremely low.

Finally, we obtained some improvement applying conventional heating at 50 °C (Table 2, entries 12 and 13); thus, **2h** and **2i** were isolated with respective yields of 25 and 21%. *N*-Tosylated and *N*-acylated amides **1n** and **1o** (Table 2, entries 14 and 15) were left unchanged, presumably, due to the reduced nucleophilicity of the indole core.

(7) (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358.

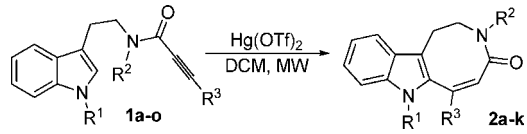
(8) (a) Bates, D. K.; Jones, M. C. *J. Org. Chem.* **1978**, *43*, 3856. (b) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218.

(9) For reviews on metal-catalyzed carbocyclization, see: (a) Ojima, I.; Tzamarioudaki, M. L. Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (c) Trost, B. M. *Chem.—Eur. J.* **1998**, *4*, 2405.

(10) (a) Nishizawa, M.; Takenaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581. (b) Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett* **1995**, 169.

(11) See the Supporting Information for the exact experimental procedures.

Table 2. Cyclization of Amides **1a**−**o**[a]



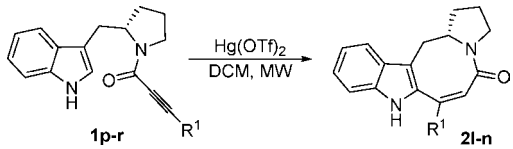
entry	1	R^1	R^2	R^3	$Hg(OTf)_2$ (mol %)	MW	2	yield (%)
1	**a**	H	Bn	Me	5	60 W, 80 °C, 15 min	**a**	85
2	**b**	H	Bn	*n*-Pr	5	60 W, 80 °C, 15 min	**b**	82
3	**c**	H	PMB	Me	5	60 W, 80 °C, 15 min	**c**	59
4[b]	**d**	H	H	Me				0
5	**e**	H	Me	Me	5	60 W, 80 °C, 20 min	**d**	86
6	**f**	H	Me	Et	5	60 W, 80 °C, 20 min	**e**	67
7	**g**	H	Me	*n*-Pr	5	60 W, 80 °C, 20 min	**f**	75
8	**h**	H	Me	*i*-Pr	15	90 W, 100 °C, 20 min	**g**	79
9	**i**	H	Me	*t*-Bu				0
10	**j**	H	Me	Ph	20	90 W, 100 °C, 20 min	**h**	61
11	**k**	H	Me	3,4,5-trimethoxyphenyl	30	120 W, 120 °C, 50 min	**i**	40
12[c]	**l**	H	Bn	H	5	50 °C, 48 h	**j**	25
13[c]	**m**	H	Me	H	5	50 °C, 48 h	**k**	21
14[b]	**n**	Ts	Bn	Me				0
15[b]	**o**	Ac	Bn	Me				0

[a] Run on a 0.6 mmol scale in dry DCM (2.4 mL) in sealed microwave reactor vials. [b] Several MW conditions were tried with varying temperature (80−100 °C) and $Hg(OTf)_2$ loading (5−15 mol %); [c] Conventional heating.

Having investigated the basic limitations of the $Hg(OTf)_2$-catalyzed cyclization we decided to expand the scope of the employed substrates varying the tryptamine part. Thus, amides **1p**−**r** (Table 3) were synthesized[11] starting from the corresponding tryptamine containing the pyrrolidine ring.[12] As with previous cases, amides of alkylpropiolic acids **1p** and **1q** (Table 3, entries 1 and 2) proved to be excellent substrates for the cyclization affording the indoloazocinones **2l** and **2m**, respectively, with good yields under relatively mild conditions. Phenylpropiolic acid amide **1r**, however, required a somewhat more rigorous approach, than the similar amide **1j**. The yield of the resulting indoloazocinone **2n** was again lower than in the cases of aliphatic propiolic acids.

Another group of substrates **1s**−**v** was synthesized[11] from derivatives of L-tryptophan (Table 4). Interestingly, amide **1s** (Table 4, entry 1) containing a carboxymethyl group did not undergo the expected cyclization and instead gave rise to a complex mixture of products. A similar result was obtained in the case of **1t** (Table 4, entry 2) bearing a hydroxymethyl group. On the other hand, TIPS-*O*-protected amides **1u** and **1v** were cleanly cyclized to indoloazocinones **2o** and **2p**, albeit the substrate **1v**, encumbered with a bulky

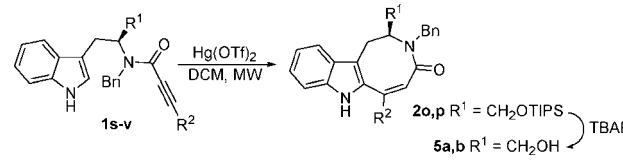
Table 3. Cyclization of Amides **1p**−**r**[a]



entry	1	R^1	$Hg(OTf)_2$ (mol %)	MW	2	yield (%)
1	**p**	Me	5	90 W, 100 °C, 15 min	**l**	75
2	**q**	Et	5	90 W, 100 °C, 15 min	**m**	71
3	**r**	Ph	25	90 W, 110 °C, 20 min	**n**	58

[a] Reactions were run on a 0.3−0.4 mmol scale under H_2 atmosphere (1 atm) in 6−10 mL of THF/MeOH (1:1) with 10% Pd/C (5 mol %) at rt for 24 h.

Table 4. Cyclization of L-Tryptophan Derivatives **1s**−**v**[a]



entry	1	R^1	R^2	$Hg(OTf)_2$ (mol %)	MW	2	yield (%)
1[b]	**s**	CO_2Me	Me				0
2[b]	**t**	CH_2OH	Me				0
3[c]	**u**	CH_2OTIPS	Me	10	90 W, 100 °C, 25 min	**o**	78
4[c]	**v**	CH_2OTIPS	*n*-Am	20	90 W, 100 °C, 45 min	**p**	71

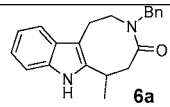
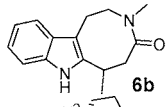
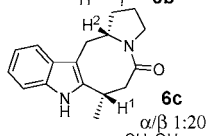
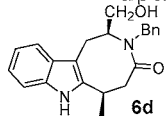
[a] Run on a 0.6 mmol scale in dry DCM (2.4 mL) in sealed microwave reactor vials. [b] Several MW conditions were tried with varying temperatures (80−100 °C) and $Hg(OTf)_2$ loadings (5−15 mol %). [c] TIPS group was removed with TBAF yielding the alcohols **5a** (86%) and **5b** (84%).

(12) (a) Abatea, C.; Kolanosa, R.; Dukat, M.; Setola, V.; Roth, B. L.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3510. (b) Macor, J. E.; Blake, J.; Fox, C. B.; Jonhson, C.; Koe, B. K.; Lebel, L. A.; Morrone, J. M.; Ryan, K.; Schmidt, A. W.; Schulz, D. W.; Zorn, S. H. *J. Med. Chem.* **1992**, *35*, 4503.

n-amyl group, required prolonged reaction time and a high catalyst loading. Subsequently, indoloazocinones **2o** and **2p** were deprotected with TBAF yielding the corresponding alcohols **5a** and **5b** (84 and 86%).

To the best of our knowledge, the scaffold of indoloazocinones **2a**−**p** containing an amide conjugated with a double bond has not yet been described in the literature. Thus, we decided to explore the hydrogenation of the double bond as well as the amide reduction on several compounds. Indoloazocinones **2a**,**d**,**j** and **5a** were smoothly hydrogenated over 10% Pd/C under atmospheric pressure of H_2 affording the reduced compounds **6a**−**d**, respectively, with excellent yields (Table 5). Compound **6c** was obtained as a 1:20 mixture of

Table 5. Hydrogenation of the Indoloazocinones **2a**,**d**,**j** and **5a**[a]

entry	substrate	product	solvent	yield (%)
1	**2a**	 **6a**	EtOH/ THF (5:2)	95
2	**2d**	 **6b**	EtOH/ THF (5:2)	98
3	**2j**	 **6c** α/β 1:20	EtOH	94
4	**5a**	 **6d**	EtOH	96

[a] Run on a 0.2 mmol scale with 10% Pd/C (15 mol %) under H_2 atmosphere (1 atm) at rt for 24 h

inseparable α/*β* epimers. The structure of the major *β*-Me epimer was established by the NOE effect between protons H1 and H2 (Table 5, entry 3). Variation of solvent did not result in any improvement in the diastereomeric ratio. However, **6d** was produced as a single diastereomer[13] as a result of hydrogen addition from the less hindered surface of the starting **5a**. A single-crystal X-ray structure[14] of **6d** was obtained for unambiguous assignment of configuration at C13 (*R*) (Figure 2).

Finally, indoloazocinones **2a**,**e**,**g** were treated with excess LAH in THF at 60 °C overnight (Table 6). Reduction proceeded smoothly affording the indoloazocines **7a**−**c** in essentially quantitative yields.

(13) We failed to assign the configuration of **6d** by NMR since no significant NOE effects were observed.

(14) CCDC 735454 contains the structure and supplementary crystallographic data for the structure of **6d**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif.

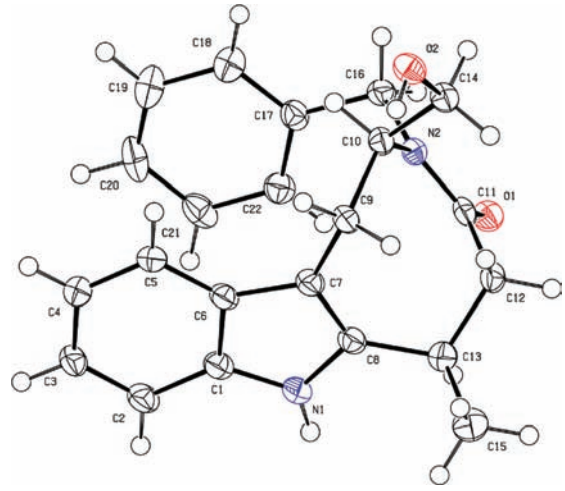
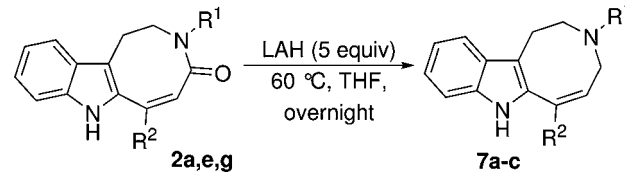


Figure 2. Single-crystal X-ray molecular structure of **6d** with atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Table 6. LAH Reduction of the Indoloazocinones



2a,e,g **7a-c**

entry	**2**	R^1	R^2	**7**	yield (%)
1	**a**	Bn	Me	**a**	95
2	**e**	Me	Et	**b**	97
3	**g**	Me	*i*-Pr	**c**	95

In summary, we have developed a short and selective approach toward the system of indoloazocinones. The 8-membered ring is constructed by applying a microwave-assisted $Hg(OTf)_2$-catalyzed intramolecular alkyne carbocyclization reaction. The applicability of this strategy for the synthesis of some indoloazocine alkaloids and analogues is under current investigation.

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Supporting Information Available: Spectroscopic data for all new compounds prepared as well as detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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