ORGANIC LETTERS

2011
Vol. 13, No. 24
6331–6333

One-Step Construction of Tetrahydro-5*H*-indolo[3,2-*c*]quinolines from Benzyl Azides and Indoles via a Cascade Reaction Sequence

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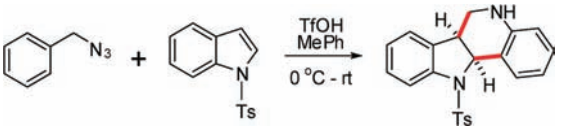
Received October 3, 2011

ABSTRACT

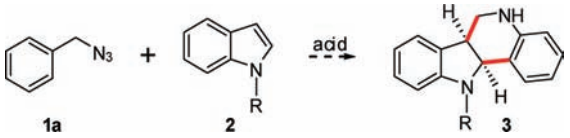


A novel one-step assembly of tetrahydro-5*H*-indolo[3,2-*c*]quinolines from benzyl azides and indoles via a formal [4 + 2] cycloaddition is described. A cascade reaction sequence, which involves benzyl azide-to-iminium rearrangement followed by two sequential Pictet–Spengler reactions, generates the tetracycles in moderate to excellent yields. The current method is applicable to a broad substrate scope and holds significant potential in constructing polycyclic indolines with tertiary and/or quaternary carbon centers.

Development of efficient, practical, and environmentally benign synthetic methods for constructing structurally complex scaffolds continues to attract the attention of synthetic chemists. Thus, cascade reactions,[1] which involve multistep transformations in a *one-pot* fashion to convert readily available reactants into complex molecular architectures, have become particularly powerful and attractive in modern synthetic chemistry.

Aubé and co-workers demonstrated that, in the presence of an acid, azides, especially benzyl azides, underwent rearrangement to generate the corresponding iminium species, which could be trapped by carbonyl compounds via a Mannich-type reaction.[2] Inspired by this observation, we envisioned that treatment of indoles with benzyl azides in the presence of certain acids would form tetrahydro-5*H*-indolo[3,2-*c*]quinolines[3] via a formal [4 + 2] cycloaddition[4] (Scheme 1). It is well-known that both quinolines[5] and indolines[6] are important heterocycles in organic synthesis. Herein, we wish to report our findings in constructing the structurally appealing tetrahydro-5*H*-indolo[3,2-*c*]quinoline scaffolds in a one-pot fashion.

Scheme 1. Proposed Synthesis of Tetrahydro-5*H*-indolo[3,2-*c*]quinoline via a Formal [4 + 2] Cycloaddition



(1) For recent reviews, see: (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581.

(2) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232.

(3) Desimoni and co-workers first reported the synthesis of this type of skeletons via a multicomponent reaction of indole, *ethyl glyoxylate*, and *3,4-dimethoxy-* or *3,4-methylenedioxyanilines*. The method suffers from a limited substrate scope. See: Desimoni, G.; Faita, G.; Mella, M.; Toscanini, M.; Boiocchi, M. *Eur. J. Org. Chem.* **2009**, 2627–2634.

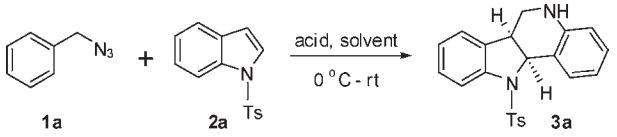
(4) For selected papers, see: (a) Moustafa, M. M. A. R.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4732–4735. (b) Teng, T.-M.; Das, A.; Huple, D. B.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 12565–12567. (c) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202–14203. (d) Yu, S. H.; Zhu, W.; Ma, D. W. *J. Org. Chem.* **2005**, *70*, 7364–7370. (e) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Org. Lett.* **2004**, *6*, 4829–4831.

(5) For selected papers, see: (a) Hughes, C.; Fenical, W. *J. Am. Chem. Soc.* **2010**, *132*, 2528–2529. (b) Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603–1606.

10.1021/ol202656u
Published on Web 11/10/2011

An initial attempt (Scheme 1) was made by employment of benzyl azide (**1a**, 1.1 equiv), which was treated with triflic acid (1.2 equiv) in dichloromethane. After the iminium species formation was complete as monitored by TLC (within 15 min at 0 °C), indole (**2**, R = H, 1.0 equiv) was added to the reaction mixture at room temperature, which, however, failed to yield the desired tetrahydro-5*H*-indolo[3,2-*c*]quinoline **3** (R = H). After extensive experiments, we found that tetracycle **3a** could be isolated in 65% yield under the same conditions when *N*-Ts protected indole **2a** was used (Table 1, entry 1). The *cis* relationship of the two newly generated tertiery carbon centers was confirmed by relevant NOE experiments.[7] The acid here seemed to play a pivotal role in the formation of **3a**, and triflic acid performed the best among all the Brönsted and Lewis acids screened (entries 1–4). Next, we investigated the solvent effects for this particular transformation (entries 5–11), and toluene was found to be superior to any other solvents screened (entry 10).

Table 1. Screening of the Acids and Solvents

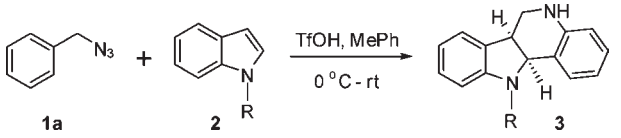


entry[a]	acid	solvent	time[b] (h)	yield[c] (%)
1	TfOH	DCM	1	65
2	TFA	DCM	24	0
3	$BF_3 \cdot OEt_2$	DCM	24	0
4	$AlCl_3$	DCM	2	47
5	TfOH	DCE	2	82
6	TfOH	THF	24	0
7	TfOH	MeCN	17	18
8	TfOH	MeOH	24	0
9	TfOH	benzene	2	73
10	TfOH	toluene	1.5	88
11	TfOH	xylene	2	82

[a] Reaction conditions: **1a** (1.1 mmol), **2a** (1.0 mmol), and the acid (1.2 mmol) in the solvent specified (10 mL). [b] Reaction time after the addition of the acid. [c] Isolated yield.

We then investigated the effects of *N*-protecting groups on the indoles (Table 2). Surprisingly, much lower yields were obtained for the tetracyclic products in the case of *N*-nosyl (**2b**, entry 2) and *N*-mesyl indoles (**2c**, entry 3). Even worse was the fact that no desired product could be isolated when *N*-acetyl indole (**2d**, entry 4) or *N*-methyl indole (**2e**, entry 5) was employed. Hence, the presence of a tosyl group on the indolic nitrogen proved to be crucial for the reaction.

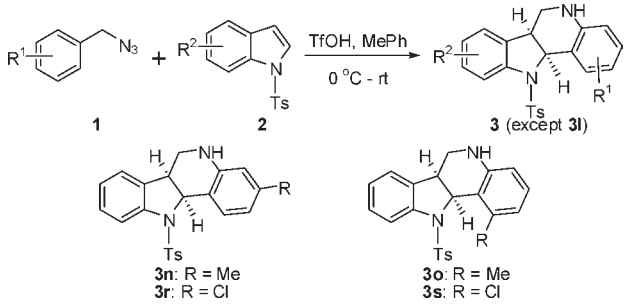
Table 2. Screening of the *N*-Protecting Groups on the Indole



entry	R (indole)	time[a] (h)	product	yield[b] (%)
1	Ts (**2a**)	1.5	**3a**	88
2	Ns (**2b**)	1.0	**3b**	73
3	Ms (**2c**)	1.0	**3c**	63
4	Ac (**2d**)	12	**3d**	0
5	Me (**2e**)	12	**3e**	0

[a] Reaction time after the addition of TfOH. [b] Isolated yield.

Table 3. Exploration of the Substrate Scope



entry	R^1	R^2	time[a] (h)	product	yield[b] (%)
1	H (**1a**)	H (**2a**)	1.5	**3a**	88
2	H (**1a**)	6-F (**2f**)	1.5	**3f**	79
3	H (**1a**)	6-Cl (**2g**)	1.5	**3g**	93
4	H (**1a**)	5-Br (**2h**)	1.5	**3h**	95
5	H (**1a**)	5-CHO (**2i**)	1.5	**3i**	68
6	H (**1a**)	5-OMe (**2j**)	1.5	**3j**	72
7	H (**1a**)	7-Me (**2k**)	12	**3k**	54
8	H (**1a**)	3-Me (**2l**)	12	**3l**[c]	60
9	2-Me (**1b**)	H (**2a**)	0.5	**3m**	77
10	3-Me (**1c**)	H (**2a**)	0.5	**3n**, **3o** (1.4:1)	86[d]
11	4-Me (**1d**)	H (**2a**)	0.5	**3p**	91
12	2-Br (**1e**)	H (**2a**)	0.5	**3q**	92
13	3-Cl (**1f**)	H (**2a**)	0.5	**3r**, **3s** (7:1)	75[d]
14	4-F (**1g**)	H (**2a**)	0.5	**3t**	87
15	2-Br (**1e**)	5-OMe (**2j**)	0.5	**3u**	81
16	2-Br (**1e**)	5-Br (**2h**)	0.5	**3v**	96
17	2-Br (**1e**)	5-CHO (**2i**)	0.5	**3w**	67

[a] Reaction time after the addition of TfOH. [b] Isolated yield. [c] See Scheme 2b for the structure of **3l**. [d] The ratio was obtained from the ^{1}H NMR spectral integrals.

Under the optimized conditions, the scope of the current method was tested (Table 3). A series of substituted indoles (bearing electron-donating or -withdrawing groups

(6) For selected papers, see: (a) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317–4320. (b) Espejo, V. R.; Rainier, J. D. *Org. Lett.* **2010**, *12*, 2154–2157.

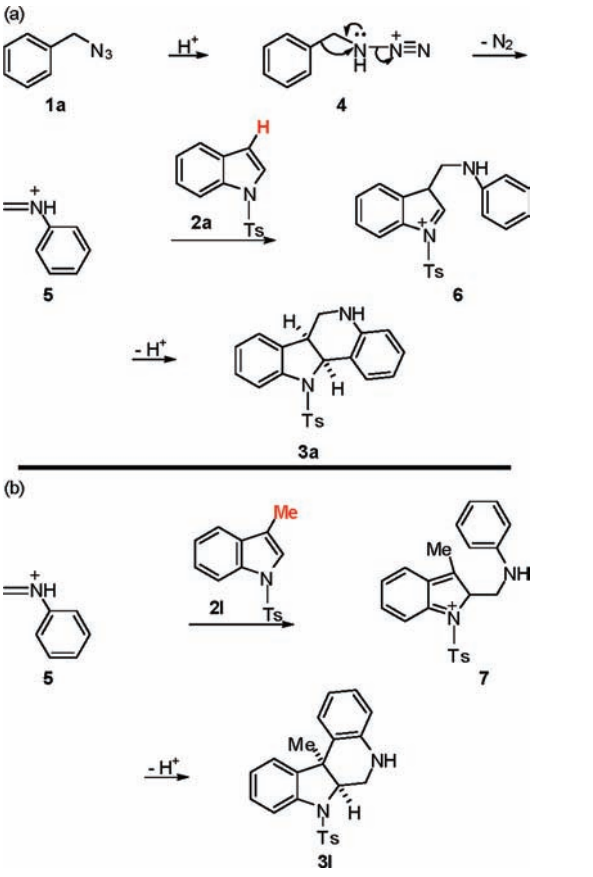
(7) See the Supporting Information.

at various positions) reacted with **1a** to generate the corresponding tetracycles in moderate to excellent yields (entries 2–6). However, much lower yields were obtained in the cases of the methylated indoles **2k** and **2l** (entries 7 and 8). Clearly, positional substituents on indole had an effect on the yields of the tetracycles (entries 2–8). The scope of benzyl azides was examined by fixing **2a** as the indole partner. Good to excellent yields of the products were obtained for the reaction of **2a** with benzyl azides with a methyl or halo substituent at various positions on the phenyl ring (entries 9–14). For those with a *meta*-substituent, two possible regioisomeric products were formed with ratios of 1.4:1 and 7:1 (entries 10 and 13). Better regioselectivity was observed for the azide with a weakly deactivating chloro group at the *meta*-position on the phenyl ring due to the relatively low reactivity of **1f** (entry 13) compared to **1c** (entry 10). Finally, the reactions of **1e** with substituted indoles **2h**–**2j** proceeded smoothly (entries 15–17).

A general mechanism[8] was proposed by taking 3-unsubstituted indole **2a** as an example (Scheme 2a). Upon protonation, azide **1a** presumably produced species **4**, which underwent rearrangement to form iminium ion **5** with concomitant loss of molecular nitrogen.[2] Trapping of **5** by **2a** to generate **6** through a carbon–carbon bond formation preferably at C-3 of **2a**, followed by cyclization at C-2 of **2a**, afforded **3a** via two consecutive Pictet–Spengler reactions. In contrast, reaction of 3-methylated indole **2l** with **1a** led exclusively to **3l** through a formal [4 + 2] cycloaddition featuring a different regioselectivity (see Table 3, entry 8; Scheme 2b). Because C-3 of indole **2l** was blocked by a methyl group, the intermolecular Pictet–Spengler reaction occurred at C-2 of **2l** to give **7**, which further cyclized to furnish **3l** via an intramolecular Fridel–Crafts reaction. A similar regioselectivity reversal was observed by Davies[9] in the rhodium-catalyzed [3 + 2] annulation of indoles. It is noteworthy that **3l** possesses a newly generated quaternary carbon center that would otherwise be difficult to construct.[10]

In conclusion, we have developed a direct synthetic route to tetrahydro-5*H*-indolo[3,2-*c*]quinolines from benzyl azides and indoles via a formal [4 + 2] cycloaddition involving an *in situ* generated iminium ion. Due to the mild conditions and broad substrate scope, this method holds great potential in constructing polycyclic indolines with tertiary and/or quaternary carbon centers that are widely present in complex indoline alkaloids.

Scheme 2. Proposed Mechanism for the Formation of **3a** and **3l**



Acknowledgment. We are grateful for the financial support from the National Basic Research Program of China (973 Program: 2010CB833200), NSFC (21172100), and '111' Program of MOE.

Supporting Information Available. Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) Desimoni and co-workers postulated that, in their case, the tetracyclic framework was possibly produced via an aza-Diels–Alder reaction mechanism.[3] Further mechanistic studies are necessary in this regard.

(9) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440–441.

(10) (a) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716–9719. (b) Lin, S. H.; Lu, X. Y. *Org. Lett.* **2010**, *12*, 2536–2539.