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Remarkable switch of regioselectivity in epoxide ring opening of 3-benzyl-7-oxa-3-azabicyclo[4.1.0]heptane with amines: practical synthesis of *trans*-4-amino-3-hydroxypiperidines and *trans*-3-amino-4-hydroxypiperidines

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ABSTRACT

A simple and highly C3 selective ring-opening method for 3,4-epoxypiperidines has been developed. We also describe a practical improvement of the C4 selective ring-opening method using the same *N*-alkyl substituted 3,4-epoxypiperidines. This method provides access to pharmaceutically relevant *trans*-3-amino-4-hydroxypiperidines and *trans*-4-amino-3-hydroxypiperidines with simple procedures.

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Functionalized piperidines are important components of natural products and drug substances.[1,2] Among them, *trans*-4-amino-3-hydroxypiperidines **1** and *trans*-3-amino-4-hydroxypiperidines **2** have recently been receiving much attention from medicinal and process chemists as common building blocks of drug candidates (Fig. 1).[2–8] However, successful reports on the regioselective synthesis of these compounds are few.[3,4] As far as we know, there was no report on the synthesis of **1** and **2** via a regioselective ring opening by primary amines, although C4 selective ring opening of epoxide **3**[5] with cyclic secondary amines was recently reported by Beletskaya.[4]

We were, therefore, interested in the capability to use other amines as nucleophiles, such as $BnNH_2$ and allylamine, which could be deprotected and functionalized in a later step. Accordingly, we first tested the reaction using $BnNH_2$ instead of a cyclic secondary amine under Beletskaya's condition. As we expected, $BnNH_2$ was revealed to be a suitable nucleophile to provide *trans*-4-amino-3-hydroxypiperidine **4a** selectively (Table 1, entry 1). Furthermore, the additive could be replaced by LiCl, which is less Lewis acidic but cheaper and easy to handle on a large scale although the reactivity was slightly reduced (entry 2).[9,10] Even with a catalytic amount of LiCl, the reaction proceeded with good yield and regioselectivity (entry 4). A reduction of the amount of LiCl to 0.2 equiv unfortunately decreased both the reactivity and regioselectivity (entry 5).

Encouraged by these results, we next briefly investigated the substrate scope. Allylamine was also found to be a suitable nucleophile for this C4 selective ring opening of epoxide **3** (entry 6). In addition, aniline afforded the corresponding C4 aminated product with excellent regioselectivity albeit in a moderate yield (entry 7). The yield increased by the use of aniline substituted with an electron-donating group without changing the regioselectivity (entry 8). On the other hand, the presence of an electron-withdrawing group on the aromatic ring diminished the reactivity (entry 9). The employment of the pyrrolidine was applicable for this reaction (entry 10).

Besides amines, NaN_3 was also an available nucleophile to undergo the reaction with good yield and high regioselectivity (>99% yield, **4g**:**5g** = >20:1, see Scheme 1). As we expected, the absence of the Li salt sharply reduced the reactivity (<5% yield).

Interestingly, by just removing the Lewis acidic additive from the reaction condition in Table 1, the regioselectivity was drastically switched from C4 to C3 in spite of poor yield (Table 2, entry 1). Motivated by this result, we decided to develop C3 selective ring opening of epoxide **3**.[11] The result of solvent screening is summarized in Table 2. With toluene the reaction proceeded in good yield with moderate regioselectivity (entry 2). To our delight, the yield increased to be almost quantitative in EtOH with good regioselectivity (entry 3). The reduction of the amount of $BnNH_2$ further increased the desired regioselectivity (entry 4). Whilst 2-methoxyethanol also provided good regioselectivity (entries 5 and 6), based on yield and stereoselectivity, we decided that EtOH was the solvent of choice.

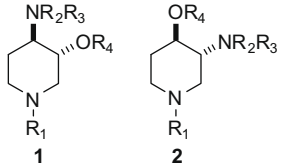

Figure 1.

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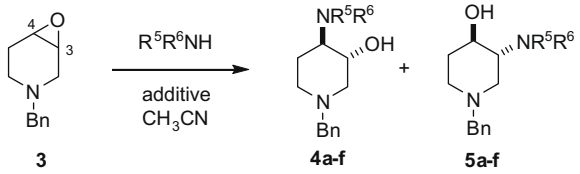
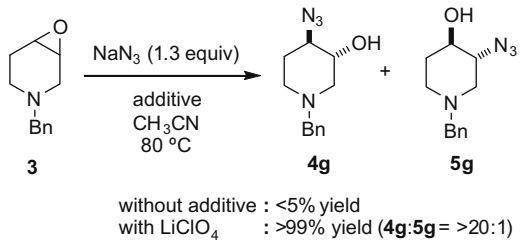
Table 1
C4 selective epoxide ring-opening reaction of **3** with various amines



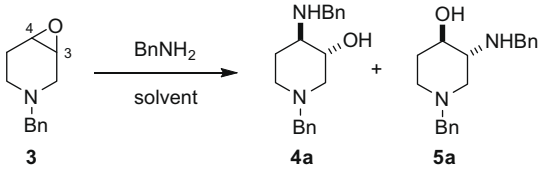
Entry	R^5	R^6	Amine (equiv)	Additive (equiv)	Temp (°c)	Time (h)	Yield[a] **4**+**5** (%)	Ratio[b] **4**:**5**
1	Bn	H	1.2	$LiClO_4$ (2.0)	rt	7	99	>20:1
2	Bn	H	1.2	LiCl (2.0)	rt	10	95	>20:1
3	Bn	H	1.2	LiCl (1.0)	rt	14	92	>20:1
4	Bn	H	1.2	LiCl (0.5)	rt	24	91	20:1
5	Bn	H	1.2	LiCl (0.2)	rt	42	64	10:1
6	Allyl	H	1.1	LiCl (1.0)	rt	5	75	>20:1
7	Ph	H	1.0	LiCl (2.0)	60	24	56	>20:1
8	2-$MeOC_6H_4$	H	1.0	LiCl (2.0)	60	18	64	>20:1
9	2-$O_2NC_6H_4$	H	1.2	LiCl (2.0)	60	20	—[c]	—[c]
10	–$(CH_2)_4$–		1.1	LiCl (0.7)	40	24	98	>20:1

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Desired product was not obtained.



Scheme 1. Epoxide ring opening of **3** with NaN_3.

Table 2
Initial screening of reaction condition for C3 selective epoxide ring-opening reaction of **3** with $BnNH_2$



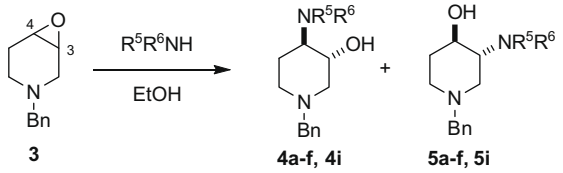
Entry	Solvent	Amine (equiv)	Temp (°C)	Time (h)	Yield[a] **4**+**5** (%)	Ratio[b] **4**:**5**
1	CH_3CN	1.5	70	18	<30[b]	1:2.7
2	Toluene	2.2	105	48	89[e]	1:4.4
3	EtOH	2.2	80	7	>99	1:6.8
4	EtOH	1.2	80	30	>99	1:10.2
5	2-Methoxyethanol	2.2	80	17	94	1:10.6
6	2-Methoxyethanol	1.2	80	36	82	1:9.7

[a] Isolated yield.
[b] Determined by ^{1}H NMR.

Having established the optimized condition for C3 selective ring opening of epoxide **3**, we investigated the scope and limitations (Table 3).[12,13]

Secondary amines as well as primary amines were proven to be good nucleophiles (entries 1, 2, 6, and 7). Similar to C4 selective ring opening of **3** mentioned above, aniline and aromatic

Table 3
C3 selective epoxide ring-opening reaction of **3** with various amines[a]



Entry	R^5	R^6	Temp (°C)	Time (h)	Yield[b] **4**+**5** (%)	Ratio[c] **4**:**5**
1	Bn	H	80	30	>99	1:10.2
2	Allyl	H	45	62	64[d]	1:>20
3	Ph	H	80	38	86	1:>20
4	2-$MeOC_6H_4$	H	80	38	81	1:>20
5	2-$O_2NC_6H_4$	H	80	20	—[e]	—[e]
6	–$(CH_2)_4$–		80	38	>99	1:>20
7	Bn	Bn	80	38	58[f]	1:>20

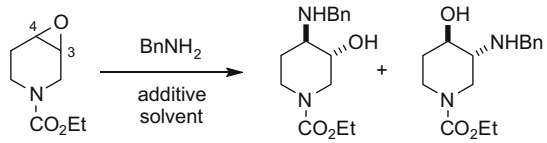
[a] 1.2 equiv of amine was used.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] 20% of **3** was recovered.
[e] SM was recovered.
[f] 38% of **3** was recovered.

amines possessing an electron-donating group on the aromatic ring gave good results in both yield and regioselectivity (entries 3 and 4) and utilizing aromatic amine with an electron-withdrawing group on the aromatic ring provided poor results (entry 5).

Because the results of the reaction using *N*-ethoxycarbonyl protected epoxide **6** with or without $LiClO_4$, in which the regioselectivity was sharply decreased in comparison with the reaction using epoxide **3** (Table 4), strongly suggested the importance of Lewis basicity on the nitrogen atom in the piperidine ring, we speculate the reason for the drastic switch in the regioselectivity on these reactions as discussed below.

The C4 selective ring opening of epoxide **3** would take place via the bidentate coordination of epoxide **3** with the lithium cation,

Table 4
Effect of N-protected group on epoxide ring-opening reaction



6 7 8

Entry	Additive (equiv)	Amine (equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] **7**+**8** (%)	Ratio[b] **7**:**8**
1	$LiClO_4$ (10)	1.5	CH_3CN	rt to 40	23	51	2:1
2	None	2.0	EtOH	70	25	84	1:<2

[a] Isolated yield.
[b] Determined by ^1H NMR.

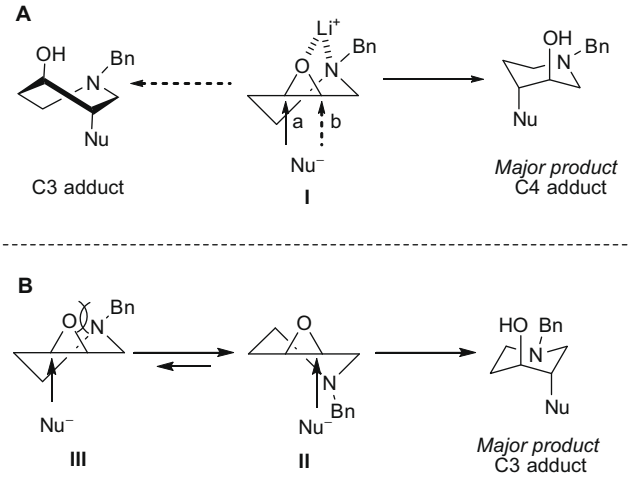


Figure 2. Explanation of high regioselectivity of ring opening of **3** with nucleophile.

which would enable a rigid conformer **I** to be formed because of high Lewis basicity of the nitrogen atom in the piperidine ring. In this circumstance, the axial attack of the nucleophile on C4 for conformer **I** is assumed to occur selectively depending upon the Fürst–Plattner rule and to afford C4 aminated product (**A**; Fig. 2).[14] Increasing the reactivity in comparison with the case without LiCl would also suggest the importance of the coordination of the Li cation.

Contrarily, for C3 selective ring opening of epoxide **3**, it would be considered that the conformational equilibrium was more shifted to conformer **II** than **III** because of electrostatic repulsion between the nitrogen atom in the piperidine ring and the oxygen atom in the epoxide. This conformational shift would dominantly lead to C3 aminated product through the axial attack of the nucleophile on C3 for **II** also in accordance with the Fürst–Plattner rule (**B**; Fig. 2).

In conclusion, a simple and highly C3 selective ring-opening method for 3,4-epoxypiperidines has been developed. A common starting material, 3-benzyl-7-oxa-3-azabicyclo[4.1.0]heptane **3**, was found to be an excellent substrate for both the C3 and C4 regioselective ring-opening reactions. This method provides access to pharmaceutically relevant piperidines **4** and **5** using simple procedures. Further study in order to develop the efficient synthesis of building blocks for drugs and drug candidates utilizing this methodology is currently ongoing in our laboratory.

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9. *General procedure for C4 selective ring opening of epoxide* **3** *with amines*: A mixture of epoxide **3** (2.0 mmol), LiCl (1.0 equiv), and $BnNH_2$ (1.2 equiv) in CH_3CN (2 mL) was stirred at room temperature. Water (5 mL) was poured into the reaction mixture and extracted with toluene (10 mL). The aqueous layer was extracted again with toluene (5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to provide desired adduct. The residue was purified by flash chromatography on silica gel to give the corresponding adduct.
10. *Analytical data for* **4a** (Table 1, entry 1):^1H NMR (400 MHz, CD_3OD): δ 7.20–7.36 (10H, m, Ph*H*), 3.85 (1H, d, *J* = 12.7 Hz, PhCH_2), 3.66 (1H, d, *J* = 12.7 Hz, PhCH_2), 3.44–3.56 (3H, m, PhCH_2 and OC*H*), 2.92–2.98 (1H, m, NC*H*), 2.80–2.86 (1H, m, NCH_2), 2.30–2.38 (1H, m, NCH_2), 1.93–2.03 (2H, m, NCH_2), 1.83 (1H, t, *J* = 10.3 Hz, CH_2), 1.34–1.48 (1H, m, CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 140.7, 138.6, 130.4, 129.5, 129.3, 129.2, 128.3, 128.1, 71.5, 63.5, 62.1, 60.2, 53.0, 51.6, 29.5 ppm.
11. The reaction of *tert*-butyl 3-aza-7-oxabicyclo[4.1.0]heptane-3-carboxylate with Me_2NH has been reported as only one example for highly C3 selective epoxide ring-opening reaction. However, the yield of product was low (27%) in their case: see Ref. 3.
12. *General procedure for C3 selective ring opening of epoxide* **3** *with amines*: A mixture of epoxide **3** (2.0 mmol) and $BnNH_2$ (1.2 equiv) in EtOH (2 mL) was stirred at 80 °C. Water (5 mL) was poured into the reaction mixture and extracted with AcOEt (10 mL). The aqueous layer was extracted again with AcOEt (5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to provide desired adduct. If necessary, the residue was purified by flash chromatography on silica gel to give the corresponding adduct.
13. *Analytical data for* **5a** (Table 2, entry 4): ^1H NMR (400 MHz, CD_3OD): δ 7.20–7.34 (10H, m, Ph*H*), 3.78 (1H, d, *J* = 13.2 Hz, PhCH_2), 3.61 (1H, d, *J* = 13.2 Hz, PhCH_2), 3.54 (1H, d, *J* = 12.4 Hz, PhCH_2), 3.50 (1H, d, *J* = 12.4 Hz, PhCH_2), 3.27–3.33 (1H, m, OC*H*), 3.06–3.08 (1H, m, NC*H*), 2.79–2.83 (1H, m, NCH_2), 2.53–2.58 (1H, m, NCH_2), 2.06–2.12 (1H, m, NCH_2), 1.79–1.88 (2H, m, NCH_2), 1.45–1.62 (1H, m, CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 140.5, 138.6, 130.5, 129.45, 129.35, 129.2, 128.3, 128.1, 72.9, 63.5, 61.0, 56.4, 52.8, 52.0, 33.8 ppm.
14. Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1994**, *50*, 1261. and references cited therein.