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Lewis acid promoted regio- and stereoselective hetero nucleophilic addition to a piperidinyl aziridine. Synthesis of *trans* 3-amino-4-substituted piperidines

X. Eric Hu

Procter & Gamble Pharmaceuticals, 8700 Mason-Montgomery Road, Mason, OH 45040, USA

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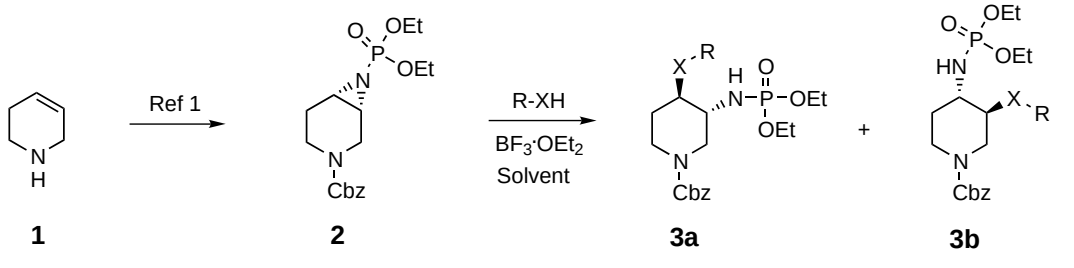
Abstract—A piperidinyl aziridine underwent alcoholic nucleophilic addition with alcohols to result in corresponding *trans* 3-amino-4-substituted piperidines. The addition reaction was catalyzed by $BF_3{\cdot}OEt_2$ in excellent regio- and stereoselectivity. The application of this method was extended to the addition of thiols, acids and halogens with sustained regio- and stereoselectivity.

Recently, we have been interested in nucleophilic addition to piperidinyl aziridines with controlled regio- and stereoselectivity, as part of our efforts toward synthesis of *trans* 3-amino-4-substituted piperidines. Since we have reported organometallic addition to piperidine aziridines[1] and demonstrated that the *anti* addition occurred at C-4 position of the piperidinyl aziridine in high regioselectivity, we sought to further apply this chemistry to various nucleophiles to broaden the scope of regio- and stereoselective addition to the piperidinyl aziridine. In this paper, we wish to report our results of nucleophilic addition of alkyl alcohols, thiols, acetic acid and halogens to a piperidyl aziridine under Lewis acid $BF_3{\cdot}OEt_2$ catalysis conditions.

In general, appropriately activated aziridines undergo Lewis acid catalyzed nucleophilic addition with alcohols[2] and thiols[3] to produce more functionalized aziridine ring opening products. The high stereoselectivity in the addition reaction is believed to be controlled by an *anti* attack of the nucleophiles, whereas the regiochemistry outcome may be a result of stereo and/or electronic effects dictating the site of the addition operating in a chelating or non-chelating fashion,[2b,4] similar to that seen in epoxide ring opening reaction by nucleophilic addition.[5,6] Although unsubstituted piperidinyl aziridines are such a simple structure, in which neither steric nor electronic effects are that obvious to predict the regioselectivity outcome, we were able to obtain a high ratio of the addition products favoring a C-4 attack in carbon anion addition reactions.[1] We anticipated that other nucleophiles such as oxygen and sulfur containing groups would add to the piperidinyl aziridine ring under a different set of reaction condi-



1 **2** **3a** **3b**

Scheme 1.

Keywords: aziridine; piperidine; *N*-phosphoramide; alcohols; thiols; acetic acid; halogens; ring opening and regioselectivity.

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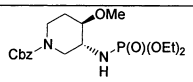
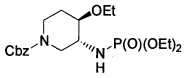
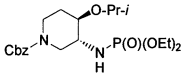
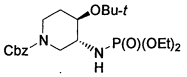
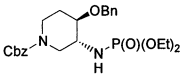
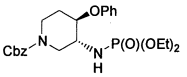
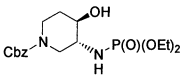
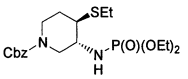
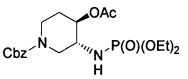
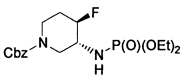
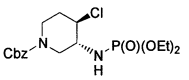
tions to afford similar regiochemical results to those observed in the organometallic addition. As shown in Scheme 1, the piperidinyl aziridine phosphonate (**2**), prepared from tetrahydropyridine (**1**),[1] was subjected to alcoholic addition conditions in the presence of $BF_3{\cdot}OEt_2$.[7] The addition produced the two possible regioisomers **3a** and **3b** as a result of C-4 and C-3 attacks of nucleophiles respectively. Once again, we observed the aziridine ring activated by the phosphonate group under Lewis acid conditions leading to the ring opening products in good chemical yields.

The reaction conditions and results are summarized in Table 1. The initial addition products **3a** and **3b** were characterized by HPLC and LC–MS analyses to determine relative ratio of the regioisomers. The yields were measured based on the products **3a** after chromatography purification. It should be noted that an alcohol having a low boiling point was used as a nucleophile and also as a solvent for the addition, otherwise, dry CH_2Cl_2 was used as the solvent. The addition reaction proceeded at 0°C in two hours in MeOH (entry 1) and EtOH (entry 2). The 4-methoxy and 4-ethoxy piperidines were obtained in 72 and 83% yields, respectively, and a high regioselectivity of C-4 adduct (**3a**) versus C-3 adduct (**3b**) in >20:1 was achieved. A consistently high level of regioselectivity was seen throughout of the addition to the aziridine, but accurate measurement of the relative ratio was difficult due to impurity interference in HPLC analysis. Hindered alcohols in the cases of *i*-PrOH (entry 3) and *t*-BuOH (entry 4), and slight excesses of alcohols in the cases of BnOH (entry 5) and PhOH (entry 6) resulted in longer reaction times, but in consistent good yields and high regioselectivities. Interestingly, a small quantity of 4-hydroxypiperidine by-product was observed in the addition reaction, which was believed to be the consequence of moisture present in the reaction system. Therefore, a simple experiment using water as a direct nucleophile source was carried out in wet CH_2Cl_2 (a few drops of water in CH_2Cl_2)

Table 1. Ring opening of aziridine with alcohols, thiols, acyl acid and halogens catalyzed by $BF_3{\cdot}OEt_2$

Entry	R-H	Solvent	Temperature	Time	Major Product (**3a**)	Yield (**3a**)[a]	**3a**/**3b**[b]
1	MeOH	MeOH	0 °C	2 hrs		72%	>20/1
2	EtOH	EtOH	0 °C	2 hrs		83%	>20/1
3	*i*-PrOH	*i*-PrOH	0 °C - RT	5 hrs		84%	>20/1
4	*t*-BuOH	*t*-BuOH	RT	16 hrs		87%	>20/1
5	BnOH[c]	CH_2Cl_2	RT	6 hrs		81%	>20/1
6	PhOH[c]	CH_2Cl_2	RT	6 hrs		78%	>20/1
7	H_2O	CH_2Cl_2	0 °C	3 hrs		79%	>20/1
8	EtSH	EtSH	0 °C	15 min		84%	>20/1
9	AcOH[c]	CH_2Cl_2	RT	30 min		88%	>20/1
10	BF_3[d]	CH_2Cl_2	RT	24 hrs		66%	>20/1
11	Et_3NHCl[d]	CH_2Cl_2	RT	16 hrs		70%	>20/1

[a] After chromatography purification.

[b] Determined by HPLC and LC-MS of crude products.

[c] 1.2 Equivalents used.

[d] 2.0 Equivalents used.

catalyzed by $BF_3{\cdot}OEt_2$. Unsurprisingly, the hydroxyl product was isolated in good yield and high selectivity (entry 7). This finding in fact provides a simple and complimentary method for introducing a hydroxyl group to aziridines.[8] We also found that the presence of activated 4 Å molecular sieves helped minimize the formation of the 4-hydroxypiperidine side-product in other addition reactions.

We further examined other nucleophiles such as ethanethiol (entry 8), and acetic acid (entry 9). In fact, they appeared to be stronger nucleophiles toward the aziridine and shorter reaction times were needed for the ring opening. Another interesting find in our experiment was the observation of about 5% of a fluoro adduct by MS-ESI analysis in most of the $BF_3{\cdot}OEt_2$ catalyzed nucleophilic additions to the aziridine as aforementioned. This finding triggered additional experiments to examine halogen addition reactions. When the aziridine was only treated with $BF_3{\cdot}OEt_2$ (2 equiv.) in dry CH_2Cl_2, 4-fluoropiperidine product was obtained in 66% yield and high regioselectivity, but a rather long reaction time was required (entry 10). This is probably one of the most convenient methods[10] to prepare α-fluoro amino compounds from aziridines.[9] In addition, we used $Et_3N{\cdot}HCl$ salt as a nucleophile source to synthesize 4-chloropiperidine in 70% yield and consistently high regioselectivity under the same reaction conditions (entry 11). The assignment of regio- and stereochemistry was initially assumed based on the results of other nucleophilic addition to pyranyl aziridines[11] and piperidinyl aziridine,[1,12] and later confirmed by comparison of spectroscopic data of the 1-Cbz-3-amino-4-hydroxypiperidine with those of our experimental results[1] and the literature data.[13]

The observed unusually high regioselectivity in such a simple piperidinyl aziridine system can be rationalized by conformational analysis as shown in Fig. 1. The structure highlighted in the box shows the preferred transition state conformation containing the phosphonate group *trans* to the Cbz group[1] and the catalyst $BF_3{\cdot}$ presumably coordinates with both the phosphonate group and the Cbz group. The former coordination is assumed to activate the aziridine ring for the addition reaction and the later may provide additional stereo hindrance to the bottom face shielding the C-3 attack of the nucleophiles so to minimize the formation of the C-3 addition by-products. It should be noted that our regiochemical rationalization may not be necessarily sufficient to explain the high level of regioselectivity.[14]

The choice of the diethyl phosphoramide group in the aziridine was not only for the proper activation of the aziridine addition, but also for the ease of deprotection in a later step. Scheme 2 shows the selective deprotection conditions: (a) conventional hydrogenation to remove the Cbz group of the piperidine ring nitrogen to afford **4** or (b) hydrolysis in 2N HCl to remove the phosphonate group[10] at the side chain nitrogen to form **5**, and complete deprotection conditions: (c) hydrolysis in conc. HCl on heating to give the free diamine **6**. These versatile and convenient deprotection methods serve as a useful synthetic procedure for further functionalization of the 3-amino-4-substituted piperidines of our interests.

In conclusion, we have synthesized *trans* 3-amino-4-substituted piperidines via hetero nucleophilic addition to the activated piperidinyl aziridine catalyzed by a Lewis acid, $BF_3{\cdot}OEt_2$. Excellent stereoselectivity and high regioselectivity were observed in this single step addition reaction. This convenient method has general utility for the synthesis of *trans* 4-hydroxyl, 4-alkoxy, 4-alkylthio, 4-acyl and 4-halo substituted 3-amino piperidines.

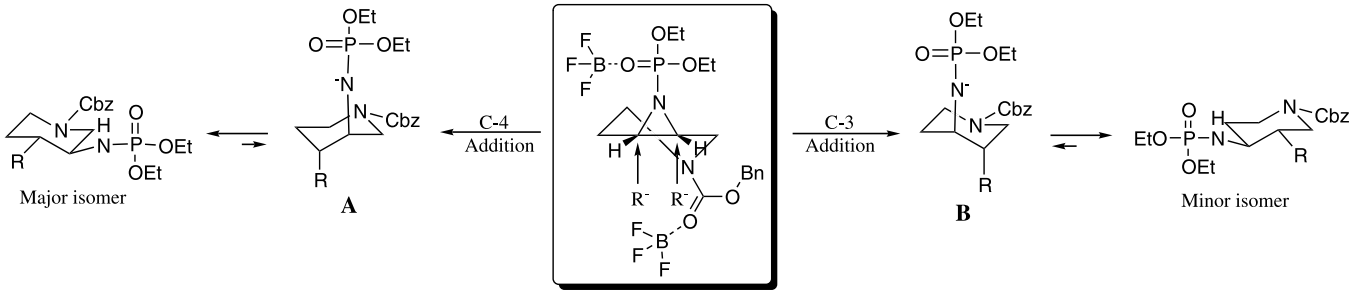
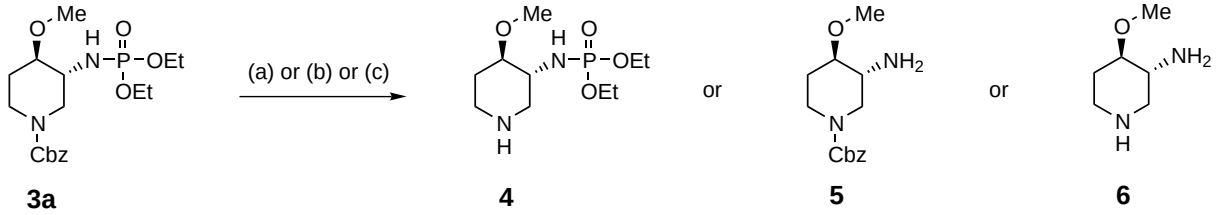


Figure 1.



Scheme 2. *Reagents and conditions*: (a) H_2, Pd/C, MeOH, 15 min, 95%; (b) 2N HCl, 1,4-dioxane, 25°C, 10 h, 84%; (c) conc. HCl, heating at 60°C, 0.5 h, 89%.

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7. A typical procedure for the synthesis of 1-Cbz-3-(diethoxyphosphorylamino)-4-ethoxypiperidine: To a solution of the piperidinyl aziridine (0.112 g, mmol) in absolute EtOH (3 mL) was added $BF_3{\cdot}OEt_2$ (0.077 mL, 2 equiv.) at 0°C under a nitrogen atmosphere. The resulting solution was stirred at that temperature for 2 h, at which time the reaction was complete by MS, TLC and HPLC. After evaporation, the crude product was purified by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, $J=6.9$, 3H), 1.46–1.23 (m, 6H), 1.47–1.68 (m, 1H), 2.07–1.93 (m, 1H), 3.40–2.98 (m, 4H), 3.52–3.42 (m, 1H), 3.68–3.57 (m, 1H), 3.70 (br, 1H), 420–3.85 (m, 5H), 5.12 (s, 2H), 7.42–7.32 (m, 5H), 9.38 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 16.0, 27.8, 39.8, 41.1, 47.2, 49.0, 52.2, 63.4, 64.6, 67.7, 78.8, 126.9, 127.5, 128.3, 136.6, 159.2; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.67 (s); EI-MS (m/z): 415 (M+H); HRMS 415.1995 (calcd for $C_{19}H_{32}N_2O_5P$: 415.1998).
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14. One other possible explanation may include an inductive effect as follows. Partially positive charge characters developed in both the aziridine nitrogen and the piperidine nitrogen in the transition state of the complexation with BF_3 should disfavor the ring opening at C-3 position, because the positively charged C-3 carbon atom is closer to the positively charged piperidine nitrogen than a positive charge at the more remote C-4 position.