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Regio- and stereo-controlled copper organometallic addition to a piperidinyl aziridine: synthesis of *trans* 3-amino-4-alkyl-piperidines

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Abstract—3,4-Piperidinyl aziridine *N*-phosphonate underwent ring opening in Grignard addition catalyzed by a copper reagent to yield *trans* 3-amino-4-alkyl-piperidines. The nucleophilic addition occurred *trans* to the aziridine group and regioselectively at C-4 position of the piperidine ring. The high regioselectivity was rationalized by steric argument based on conformational analysis.

There have been numerous accounts in the literature on the synthesis of piperidines, due to their usefulness as very important synthetic intermediates to targets such as alkaloids[1] and amino sugars,[2] and also due to their frequent occurrence in biologically interesting molecules.[3] However, there have been only limited methods published in the literature for the synthesis of 3-amino piperidines.[2b,4] Especially rare are reports of the synthesis of 4-alkyl substituted 3-amino piperidines.[5] Nucleophilic addition to aziridines consists of one of the most useful tools for the synthesis of functionalized amines and their equivalents.[6] Organometallic additions to aziridines generally require activation of the aziridine nitrogen and a copper catalyst in order to achieve meaningful results.[7] To the best of our knowledge, there have been no reports on regioselective nucleophilic addition to piperidinyl aziridines. Due to our ongoing drug discovery research program in this field, we sought to develop an efficient method for stereo- and regioselective syntheses of 4-substituted 3-amino piperidines. In particular, we were prompted to communicate our results for the synthesis of *trans*-3-amino-4-alkyl-piperidines due to a recent publication on an asymmetric synthesis of 3-amino-4-alkyl-2-piperidinones.[8]

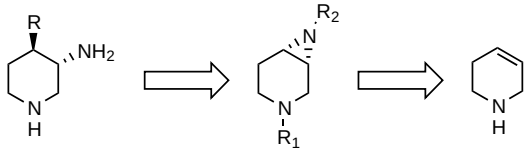

Figure 1.

Our interest in exploring substituted piperidines was focused specifically on variations at the C-4 position *trans* to the 3-amino group in the piperidine ring. We envisioned the most efficient approach to the 4-substituted 3-amino piperidines would be the nucleophilic addition to an aziridinyl piperidine intermediate, in which the simultaneous control of stereochemistry and regiochemistry was anticipated (Fig. 1). In addition, such a late step introduction of the alkyl variables to the piperidine ring would allow us to quickly examine such piperidine analogs of our interests.[9] Our retro-synthetic design strategy below suggested that an appropriately protected 3,4-aziridinyl piperidine would serve as a versatile intermediate for the synthesis of *trans* 3-amino-4-alkyl-piperidines.

We initiated our synthesis from 1,2,3,6-tetrahydropyridine **1** (Scheme 1). Our first attempts to directly convert Cbz-protected tetrahydropyridine **2** to a tolylsulfonated piperidinyl aziridine of **6**, based on literature aziridination with various nitrenes,[10] gave either no reaction or impractical yields; therefore, we turned our efforts to a stepwise approach to aziridination. The double bond was epoxidized to **3**, which underwent epoxide ring opening with azide to produce a mixture of **4a** and **4b** in a 1:4 ratio.[11] The regioiso-

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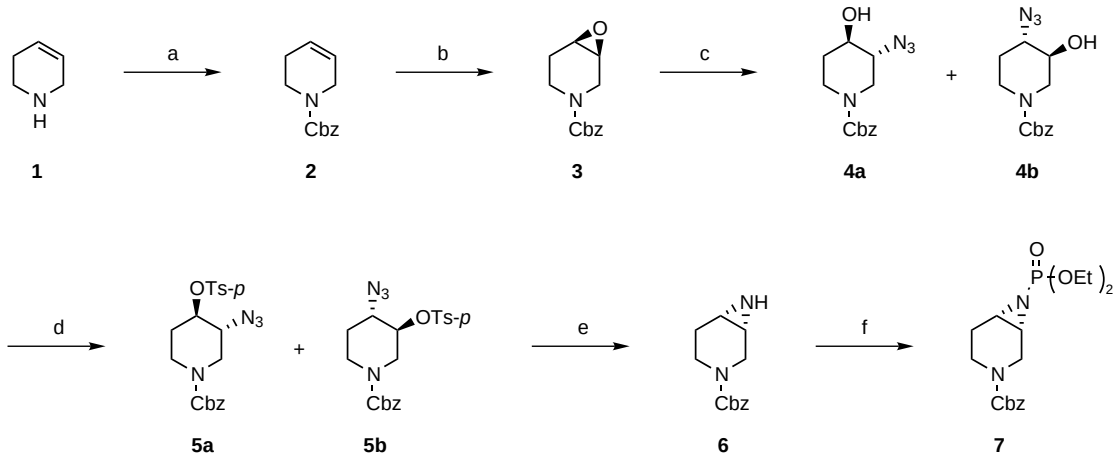
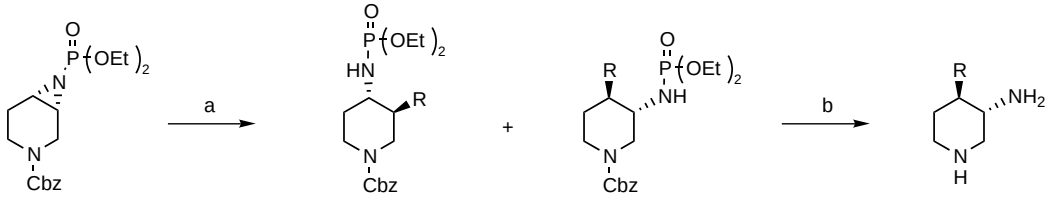


Scheme 1. *Reagents and conditions*: (a) CbzCl, Et_3N, CH_2Cl_2, rt, 16 h, 100%; (b) *m*-CPBA, CH_2Cl_2, rt, 1.5 h, 96%; (c) NaN_3 (2 equiv.), NH_4Cl (1 equiv.), MeOH, H_2O, 65°C, 18 h, 100%; (d) *p*-TsCl, pyridine, rt, 4 h, 84%; (e) PPh_3, toluene, at reflux, 45 min, 97%; (f) Cl-P(O)$(OEt)_2$, Et_3N, CH_2Cl_2, 0°C–rt, overnight, 80%.

mers were not separated, but carried to the next aziridination step. Tosylation (**5a** and **5b**) followed by ring closure[12] afforded piperidinyl aziridine **6**, which was converted to a key intermediate *N*-phosphonate **7**.[13] Although we utilized a stepwise sequence to generate the activated piperidinyl aziridine, we were able to achieve more rewarding high overall yield (63% for six steps, an average 92.5% yield for each step), which warranted the further investigation of regioselective addition of the piperidinyl aziridine. Moreover, we chose the phosphonate group not only for the proper aziridine ring activation for the addition reaction, but for the ease of deprotection in a later step.

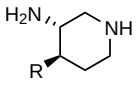
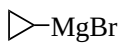
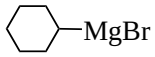
It was noted in one report[14] that nucleophilic addition to 3,4-epoxy piperidines resulted in a mixture of 3-azido-4-hydroxy piperidine and 4-azido-3-hydroxy piperidine, in which the C-3 addition product was assumed to be a major product in ~5:1 ratio. A contrary result was reported later by another group,[11] who assigned the C-4 addition product as the major regioisomer based on thorough structural analysis. By relying on the latter view of the regioselectivity in the 3,4-epoxy piperidine case, we expected it would be possible to develop an efficient method for the synthesis of 3-amino-4-alkyl-piperidines from the piperidinyl aziridine. Therefore, the regioselective nucleophilic addition to the aziridine was examined by organocuprate addition, a procedure developed by Zwierzak and co-workers.[13] As shown in Scheme 2, the addition reaction to aziridine **7** proceeded in THF at −30°C and then slowly warmed to 0°C. The crude ring opening products **8** and **9** were deprotected with HCl to afford 3-amino-4-alkyl piperidine dihydrochloride salts.[15]

The addition products **8** and **9** were characterized by HPLC and LC–MS analyses to determine relative ratio of the regioisomers. The yields were measured based on final product **10** after purification. As shown in Table 1, methyl (entry 1), ethyl (entry 2) and *n*-butyl (entry 5) Grignard additions resulted in 1:16, 1:15 and 1:13 ratio of 3-amino-4-methyl piperidine **9a**, **9b** and **9c** as the major isomers, respectively, while isopropyl (entry 8), cyclopropyl (entry 9) and cyclohexyl (entry 10) Grignard reagents afforded 1:22, 1:14 and 1:12 ratios of **9d**, **9e** and **9f** piperidines. Solvent effects were also examined and THF was found to be the most effective solvent for both good chemical yields and regioselectivity, whereas Et_2O and DME were less effective (entries



Scheme 2. *Reagents and conditions*: (a) RMgBr (4 equiv.), CuI (0.1 equiv.), THF, −30°C, 15 min, then **6** in THF, −30 to 0°C, 2 h; (b) 6N HCl, reflux, 1 h.

Table 1. Ring opening of aziridine with organometallic reagents

Entry	R-M	Solvent	Temperature	Time (h)		Yield (%)[a]	**8**/**9**[c]
1	MeMgBr	THF	−30°C to 0°C	3	Me	86	1/13
2	EtMgBr	THF	−30°C to 0°C	3	Et	78	1/15
3	EtMgBr	Et_2O	−30°C to rt	6	Et	30	1/5.8
4	EtMgBr	DME	−30°C to rt	14	Et	40	1/8
5	*n*-BuMgBr	THF	−30°C to 0°C	5	*n*-Bu	87	1/13
6	*n*-BuLi	THF	−30°C to 0°C	3	*n*-Bu	0	na
7	*n*-BuZnBr	THF	−30°C to rt	24	*n*-Bu	0	na
8	*i*-PrMgBr	THF	−30°C to 0°C	5	*i*-Pr	92	1/22
9		THF	−30°C to rt	3	Cyclopropyl	78	1/14
10		THF	−30°C to rt	5	Cyclohexyl	82	1/12
11	*t*-BuMgBr	THF	−30°C to rt	5	*t*-Bu	–	na
12	CH_2=CHMgBr	THF	−30°C to 0°C	24	CH_2=CH	–[b]	na
13	PhMgBr	THF	−30°C to rt	24	Ph	–[b]	na

[a] For two steps.
[b] Complex mixture.
[c] Determined by HPLC and LC–MS.

3 and 4). Other nucleophiles, such as organolithium or organozinc reagents (entries 6 and 7) were also studied, but only complex mixtures were obtained. Hindered nucleophiles such as *t*-butyl Grignard reagent (entry 11) provided no product. When organometallic reagents of vinyl and phenyl Grignard reagents were used (entries 12 and 13), essentially no ring opening products were observed under standard reaction conditions, but only the starting aziridine recovered. This is probably due to weaker nucleophilicity of sp^2 carbanions. Decomposition occurred with extended reaction time (24 h at rt).

The aziridine ring opening proceeds via 1,2-diaxial addition[16] of the nucleophiles to the piperidinyl aziridine in an *anti* attack fashion. To rationalize the selectivity, we first examined the nitrogen configuration in aziridine and piperidine. A search of the Cambridge Structural Database using Conquest[17] suggests that the aziridine amido nitrogen adopts an sp^3 configuration, while the piperidine amido nitrogen adopts an sp^2 configuration. Using this important structural information, random sampling of the conformational space of piperidine **7** was performed to locate the various energy minima using Sybyl 6.7 with the MMFF force field.[18] Two major conformers emerged from this search and are shown in Fig. 2. One has the Cbz group *cis* to the aziridine ring, and the other has it *trans*. Energy minimization of the two representative conformers using the MMFF force field indicates that the *trans* conformation is 0.8 kcal/mol more stable than its *cis* counterpart. A similar trend is observed upon energy minimization of the conformers at the 3-21G and 6-31G** levels (1 and 1.8 kcal/mol, respectively).

Two possible sites of addition (either at C-3 or at C-4) were examined in the favored *trans*-conformer to compare regiochemical outcome. Addition of a nucleophile (R^-) at the C-4 position gives an initial intermediate **A**, in which a twist boat conformation is assumed to satisfy maximum coplanar orbital interaction developed in the early transition state of the addition reaction. Then, the relaxation of the twist boat form leads to stable chair conformation to give the major regioisomer, the C-4 addition product. However, C-3 addition can also occur, but with 1,3-di-axial-like interaction between the nucleophile and the Cbz group, energetically disfavored relative to C-4 addition, resulting in the formation of the minor regioisomer. These regioselectivity results observed in the piperidinyl aziridine are consistent with those in piperidinyl epoxides[11] and pyranyl aziridine.[19] The more pronounced selectivity may presumably be attributed to the bulkier phosphonate group at the aziridine nitrogen, which may stereochemically favor the aziridine ring *trans* to the Cbz group.[20]

In conclusion, we have demonstrated a regio- and stereoselective organometallic additions to the activated piperidinyl aziridine catalyzed by a copper reagent, a robust method for the synthesis of *trans*-3-amino-4-alkyl piperidines. High regioselectivity was observed. The assignment of the major regioisomers in the cases of *trans*-4-methyl- and *trans*-4-ethyl-3-amino-piperidines was confirmed unambiguously by an independent asymmetric synthesis, the results of which will be reported in due course.[21]

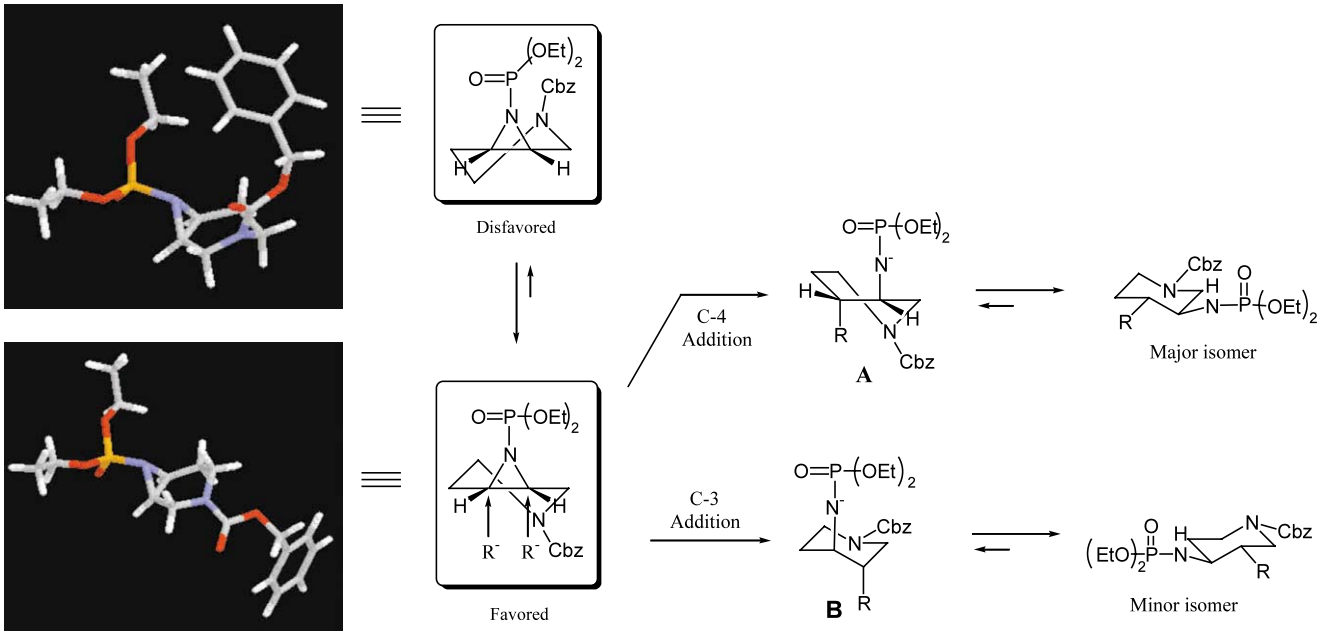


Figure 2.

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15. A typical procedure for the addition reaction: To a suspension of CuI (4.4 mg, 0.0231 mmol) in anhydrous THF (2.5 mL) was slowly added 1.0 M EtMgBr in THF (0.93 mL, 0.924 mmol) at −30°C. After stirring at that temperature for 15 min, a solution of the aziridine (**7**) (85 mg, 0.231 mmol) in THF (2.5 mL) was added at the same temperature and then the mixture was slowly warmed to 0°C in 2 h, at which time no starting aziridine was detected by TLC, HPLC and MS analyses. Water (2 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (2×10 mL), dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by flash chromatography using ethyl acetate:hexanes (1:1 and then 1:0) (R_f=0.10) to afford 75 mg (82%) of 4-ethyl-piperidine product (**9b**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, $J=7.2$, 3H), 1.48–1.12 (m, 8H), 1.94–1.78 (m, 2H), 2.58 (dd, $J=10.5$, 9.9, 1H), 2.76 (br, 2H), 3.17 (br, 1H), 4.19–3.93 (m, 5H), 4.28 (d, $J=10.5$, 1H), 5.12 (s, 2H), 7.42–7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 10.8, 16.3, 16.4, 24.3, 29.1, 43.7, 44.1, 44.2, 50.4, 52.3, 63.1, 67.5, 128.2, 128.3, 128.7, 136.8, 155.3; ^{31}P NMR (121 MHz, $CDCl_3$), 8.84 (s); EI-MS (m/z): 399 (M+H); HRMS 399.2058 (calcd for $C_{19}H_{32}N_2O_5P$: 399.2049).

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