APPLICATION OF $TiCl_4$ INDUCED IMINIUM ION CYCLIZATIONS TO THE PREPARATIONS OF PIPERIDINE ALKALOIDS : TOTAL SYNTHESES OF (±)-CONIINE

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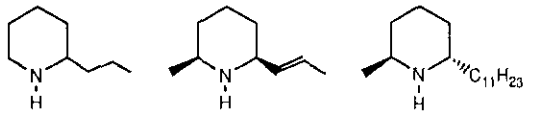
Abstract - Syntheses of (±)-coniine via $TiCl_4$ induced iminium ion cyclizations of α-cyanoamines are described. Moreover, (α-cyanoalkyl)amine could lead to the cyclic piperidine system in good yields.

The nitrogeneous six-membered ring containing compounds play an important role in the naturally occurring alkaloids. Of them the piperidine rings are the most commom basic skeletons in their structures.[1] According to the literatures, most of the piperidine alkaloids have substituents on carbon 2 and/or 6 positions, i.e. coniine, pinidine, and solenopsin A (Figure I).[2] During the study of $TiCl_4$ induced iminium ion cyclizations of α-cyanoamines, we found with appropriate modifications of the α-cyanoamines that the reaction could lead to the piperidine alkaloids family.[3] Herein we report our initial results on the total syntheses of (±)-coniine via two different routes.

Figure I :



1 (±)-Coniine Pinidine Solenopsin A

Cyanoamine 5, the key intermediate for $TiCl_4$ induced cyclization, was prepared in three steps. Mesylation of Z-4-trimethylsilyl-3-buten-1-ol 2 with mesyl chloride and triethylamine in dichloromethane(yield 98%), followed by condensation of mesylate 3 with benzylamine produced 55% of secondary amine 4. The preparation of cyanoamine 5 was carried out under the conditions analogous to Strecker's amino acid synthesis only without hydrolysis of the nitrile functionality.[4] The desired cyanoamine 5 was quickly submitted to the $TiCl_4$ induced cyclization.[5] Unfortunately, a complex mixture was obtained which consisted of hydrolyzed secondary amine 6,[6] desilylated amine 7, and small amount of desired cylic amine 8. Lowering the reaction temprature from ambient temperature to -20°C and shortening the reaction time only resulted more starting cyanoamine 5 recovery and produced another hydrolyzed secondary amine 9.[7,8] The yield of desired cyclization product 8 was even diminished. After quite a bit experimentations, we found that reversing the procedure of our traditional addition sequence improved the results dramatically. Slow addition of cyanoamine 5 to a solution of 1.0 M solution $TiCl_4$ in dichloromathane gave 73% of 8 with only trace amount of amine 9 (Scheme I and

Table I).[5] Having cyclic amine 8 in hand, the synthesis was accomplished by hydrogenolysis of the protected benzyl group to give (±)-coniine in 90% yield (Scheme II).

Scheme I:

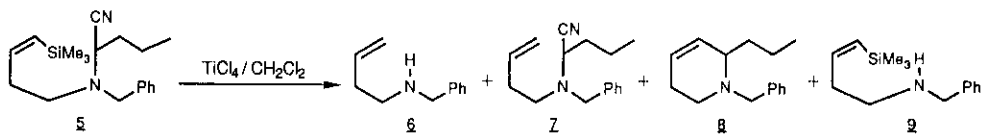
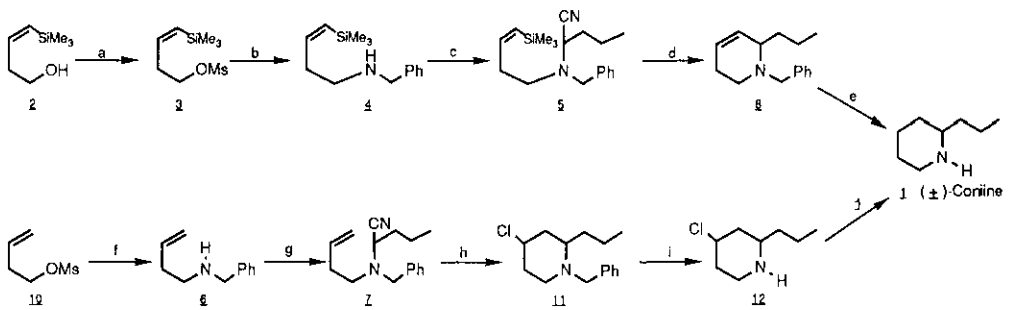


Table I:

Entry	Reaction Conditions				Yields	Products distributions(%)				
	Temperature	Time	$TiCl_4$	Procedure[a]	(%)	6	7	8	9	5 (Starting Material)
1	Ambient	24 h	4 eq.	A	76	50	32	18	0	0
2	-20°C	1 h	4 eq.	A	89	0	22	0	34	34
3	Ambient	1 h	4 eq.	B	74	0	8	8	84	0
4	Ambient	60 h	4 eq.	B	56	0	8	92	0	0
5	Ambient	60 h	2 eq.	B	74	0	0	99	1	0

a. Procedure A: To a solution of α-cyanoamine in CH_2Cl_2 was added 1.0 M of $TiCl_4$ in CH_2Cl_2 over a period 30 seconds.
Procedure B: A solution of α-cyanoamine was added to 1.0 M of $TiCl_4$ solution of CH_2Cl_2 over a period of 15 min.

Scheme II :



(a) MsCl, NEt_3, CH_2Cl_2, 3 h, 98%; (b) $PhCH_2NH_2$, NEt_3, CH_2Cl_2, 2 days, 55%; (c) Butyraldehyde, KCN, 6N HCl, H_2O, 3 days, 65%; (d) 1.0 M $TiCl_4$ in CH_2Cl_2 , ambient temperature , 73%; (e) H_2, MeOH, 5% Pd/C, ambient temperature, 2 h, 90%; (f) $PhCH_2NH_2$, NEt_3, CH_2Cl_2, refulx, 7 days, 77%; (g) Butyraldehyde, KCN, 6N HCl, H_2O, ambient temperature, 2.5 days, 75 %; (h) 1.0 M $TiCl_4$ in CH_2Cl_2, ambient temperature, 24%; (i) H_2, MeOH, 5% Pd/C, 24 h, 97%; (j) n-Bu_3SnH, AIBN, Toluene, 80°C, 30 min, 51%.

In the other approach, mesylate 10 of 3-buten-1-ol was treated with 2 eq. of benzylamine and triethylamine for 7 days in refluxing dichloromethane to produce 77% of secondary amine 6, which was then subjected to Strecker's conditions[4] for the preparation of cyanoamine 7(75%). The cyclization was carried out as mentioned above to give 24% of cyclic amine 11[8] which was then debenzylated (50 psi H_2, 5% Pd/C, MeOH; yield 97%) and reduced with tri-n-butyltin hydride to yield 51% (±)-coniine (Scheme II). The final product, (±)-coniine, produced from two different pathways, has the same properties in all aspects.

In brief, (α-cyanoalkyl)amines 5 and 7 have been successfully cyclized, and the sequence of addition was found to be crucial for this tpye of reactions. Meanwhile, $TiCl_4$ induced iminium ion cyclizations could be used in the syntheses of piperidine alkaloids.

ACKNOWNLEDGEMENT

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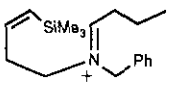
4. (a) A. Strecker, Ann.,1850, 75, 27. For recent similar examples see (b) C. Flann, T. C. Malone, and L. E. Overman, J. Am. Chem. Soc., 1987, 109, 6097. (c) H. Ahlbrecht, W. Raab, and C. Vonderheid, Synthesis, 1979, 127. (d) A. R. Katritzky, M. Latif, and L Urogdi J.Chem. Soc. Perkin Trans. I, 1990, 667.
5. A typical cyclization procedure is described as follow : To 1.4 ml of 1.0 M dichloromethane solution of $TiCl_4$ (1.40 mmol) was added 220 mg(0.7 mmol) of α-cyanoamine 5 in 2.0 ml dichloromethane of at ambient temperature. The reaction mixture was stirred for 60 h, then diluted with 5 ml of dichloromethane and 6 ml of 5% aqueous Na_2CO_3. The aqueous layer was seperated and extracted with with three 25 ml portions of dichloromethane. The combined organic layers were dried(Na_2SO_4), filtered, and concentrated in vacuo to give 120 mg of yellowish oil, which was chromatographed over 20 g of silica gel (eluted with ethyl acetate : hexane= 1 : 100) to give 110 mg (73%) of amine 8 as a colorless liquid and 2 mg(1.4%) of amine 9 as a pale yellow oil.
6. Both secondary amines 6 and 9 might resulted from the hydrolysis of uncyclized iminium ion 13 during the aqueous workup.



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7. Compound 5: ^1H Nmr(300 MHz, $CDCl_3$) δ 0.11(s, 9H, $SiCH_3$), 0.87(t, J=7.5 Hz, 3H, CH_3), 1.34-1.52(m, 2H, CH_2), 1.68-1.78(m, 2H, CH_2), 2.26-2.42(m, 2H, $=CCH_2$), 2.48-2.57(m, 1H, NCH_2), 2.67-2.76(m, 1H, NCH_2), 3.39(d, J=14 Hz, 1H, $PhCH_2$), 3.55(t, J=7.5 Hz, 1H, NCH), 3.99(d, J=14 Hz, 1H, $PhCH_2$), 5.59(dt,

J=14, and 1.5 Hz, 1H, =CH), 6.28(dt, J=14, and 7 Hz, 1H, =CH), 7.25-7.38(m, 5H, PhH). ^{13}C Nmr(300MHz, $CDCl_3$) δ 0.07, 13.26, 19.09, 31.77, 33.57, 50.86, 53.34, 56.04, 118.05, 127.51, 128.53, 128.76, 131.06, 138.08, 145.41. *Exact mass* calcd for $C_{19}H_{30}N_2Si$: 314.2178, found: 314.2192.

Compound 6: ^{1}H Nmr(300 MHz, $CDCl_3$) δ 1.58(br.s, 1H, NH), 3.80(s, 2H, $PhCH_2$), 5.02-5.13(m, 2H, $=CH_2$), 5.79(tdd, J=17, 10, and 7 Hz, 1H,=CH),7.22-7.36(m, 5H, PhH).^{13}C Nmr (300MHz, $CDCl_3$) δ 34.21, 48.23, 53.83, 116.38, 126.93, 128.15, 128.41, 136.47, 140.37.

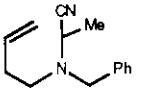
Compound 7: ^{1}H Nmr(300 MHz, $CDCl_3$) δ 0.86(t, J=7.5 Hz, 3H, CH_3), 1.32-1.55(m, 2H, CH_2),1.64-1,82(m, 2H, CH_2), 2.24-2.35(m, 2H, $=CCH_2$), 2.54(ddd, J=13, 7.5, and 4.8 Hz, 1H, NCH_2), (td, J=13 and 8 Hz,1H, NCH_2), 3.39(d, J=14 Hz, 1H, $PhCH_2$), 3.56(t, J=8 Hz, 1H, NCHCN), 3.99(d, J=14 Hz, 1H, $PhCH_2$), 5.02-5.13(m, 2H, $=CH_2$), 5.72-5.86(m, 1H, =CH) 7.22-7.36(m, 5H, PhH).^{13}C Nmr(300MHz, $CDCl_3$) δ 13.20, 18.98, 50.40, 53.22, 55.92, 116.10, 118.00, 127.41, 128.43, 128.68, 136.03,138.11.

Anal. Calcd for $C_{16}H_{22}N_2$: C, 79.28; H, 9.15; N, 11.57. Found: C, 79.18; H, 9.11; N, 11.51.

Compound 8: ^{1}H Nmr(300 MHz, $CDCl_3$) δ 0.89(t, J=10.5 Hz, 3H, CH_3), 1.22-1.62(m, 4H, CH_2), 1.96-2.07(m, 2H, $=CCH_2$), 2.37(dt, J=18 and 9 Hz, 1H, NCH_2), 2.81-2.96(m, 2H, NCH_2 and NCH), 3.38(d, J=20 Hz, 1H, $PhCH_2$), 3.93(d, J=20 Hz, 1H, $PhCH_2$), 5.56-5.66(m, 1H, =CH), 5.73-5.84(m, 1H, =CH), 7.15-7.40(m, 5H, PhH). ^{13}C Nmr(300MHz, $CDCl_3$) δ14.35, 18.58, 23.91, 29.66, 35.63, 46.12, 55.06, 58.81, 125.04, 126.75, 128.15, 128.86, 130.21. *Exact mass* calcd for $C_{15}H_{21}N$: 215.1674, found: 215.1665.

Compound 9: ^{1}H Nmr(300MHz, $CDCl_3$) δ 0.12(s, 9H, CH_3Si), 1.42(br.s, 1H, NH), 2.33(ddd, J=7.2, 6.9, and 1.5 Hz, 2H, CH_2), 2.68(t, J=7.2 Hz, 2H, CH_2), 3.78(s, 2H, $PhCH_2$), 5.62(td, J=14 and 1.5 Hz, 1H, =CH),6.26(td, J=14 and 6.9 Hz, 1H, =CH), 7.18-7.32(m, 5H, PhH). ^{13}C Nmr(300MHz, $CDCl_3$) δ 0.14, 33.94, 49.02, 53.91, 126.91, 128.06, 128.40, 131.20, 140.46, 146.16. *Exact mass* calcd for $C_{14}H_{23}NSi$: 233.1600, found: 233.1603.

8. The yield was only 3% if the $TiCl_4$ solution was added to the solution of α-cyanoamine 11 at ambient temperature. We also found α-cyanoamines 14 with methyl substitution at the α-cyano-α-amino carbon gave 4% of the cyclization product. However, up to 45% yield could be obtained if the α-cyanoamines was added to the $TiCl_4$ solution.



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