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

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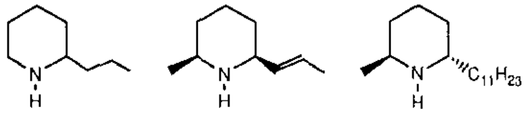
Abstract - Syntheses of (±)-coniine via $TiCl_4$ induced iminium ion cyclizations of α-cyanoamines are described. Moreover, (α-cyanoalkyl)amine could lead to the cyclic piperidine system in good yields.

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:

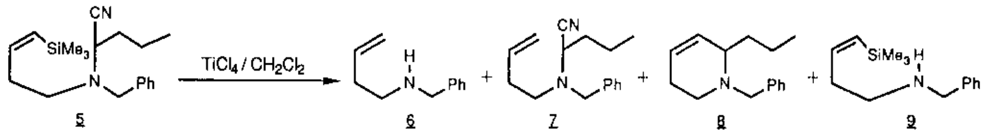
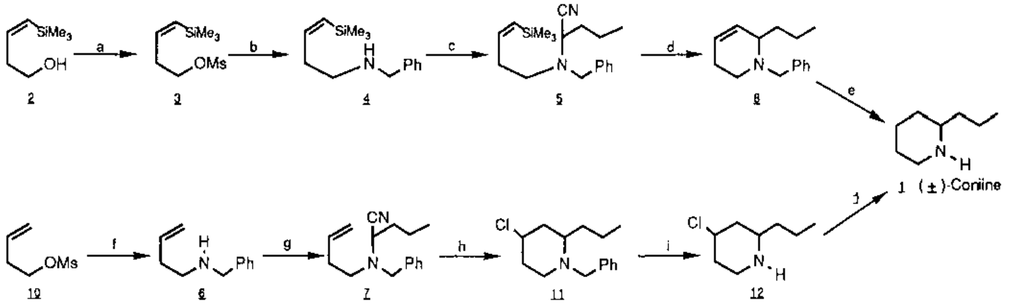


Table I:

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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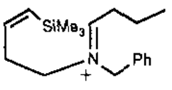
5. A typical cyclization procedure is described as follow : To 1.4 ml of 1.0 M dichloromethane solution of $TiCl_4$ (1.40 mmol) was added 220 mg(0.7 mmol) of α-cyanoamine 5 in 2.0 ml dichloromethane of at ambient temperature. The reaction mixture was stirred for 60 h, then diluted with 5 ml of dichloromethane 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.

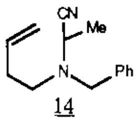
Compound 7: ^{1}H Nmr(300 MHz, $CDCl_3$) δ 0.86(t, J=7.5 Hz, 3H, CH_3), 1.32-1.55(m, 2H, CH_2),1.64-1,82(m, 2H, CH_2), 2.24-2.35(m, 2H, =CCH_2), 2.54(ddd, J=13, 7.5, and 4.8 Hz, 1H, NCH_2), (td, J=13 and 8 Hz,1H, NCH_2), 3.39(d, J=14 Hz, 1H, $PhCH_2$), 3.56(t, J=8 Hz, 1H, NCHCN), 3.99(d, J=14 Hz, 1H, $PhCH_2$), 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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