Tetrahedron Letters,Vol.30,No.37,pp 4973-4976,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

$TiCl_4$ INDUCED IMINIUM ION CYCLIZATIONS OF α-CYANOAMINES

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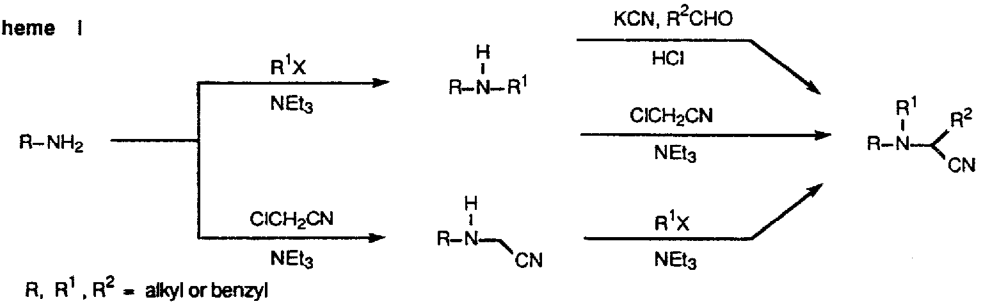
Abstract: Tertiary α-cyanoamines served as the precusors of iminium ions in the presence of titanium tetrachloride. Various intramolecular nucleophiles, olefinic and acetylenic, were found to produce cyclized products. The influences of ring sizes and substitutions on the double bonds were also investigated.

The construction of carbon-carbon bond adjacent to nitrogen plays an important role both in nature and in the laboratory synthesis of nitrogeneous compounds.[1] The most familiar member of this family of reactions is the Mannich reaction.[2] However, this traditional method always generates iminium ions in acidic and protic system which prevents the use of compounds having protic acid sensitive functionalities. Among the variants used in the generation of iminium ions, α-cyanoamines were recently recognized as excellent precusors due to their high stabilities and feasible preparations.[3] However, related applications were found only in a few cases in which either very strong bases, or acids in protic condition were used.[3] Here we report a very mild way to generate iminium ions under aportic condition. Meanwhile, the intramolecular alkenic and alkynic cyclizations were used as the tool to detect the existence of iminium ions.

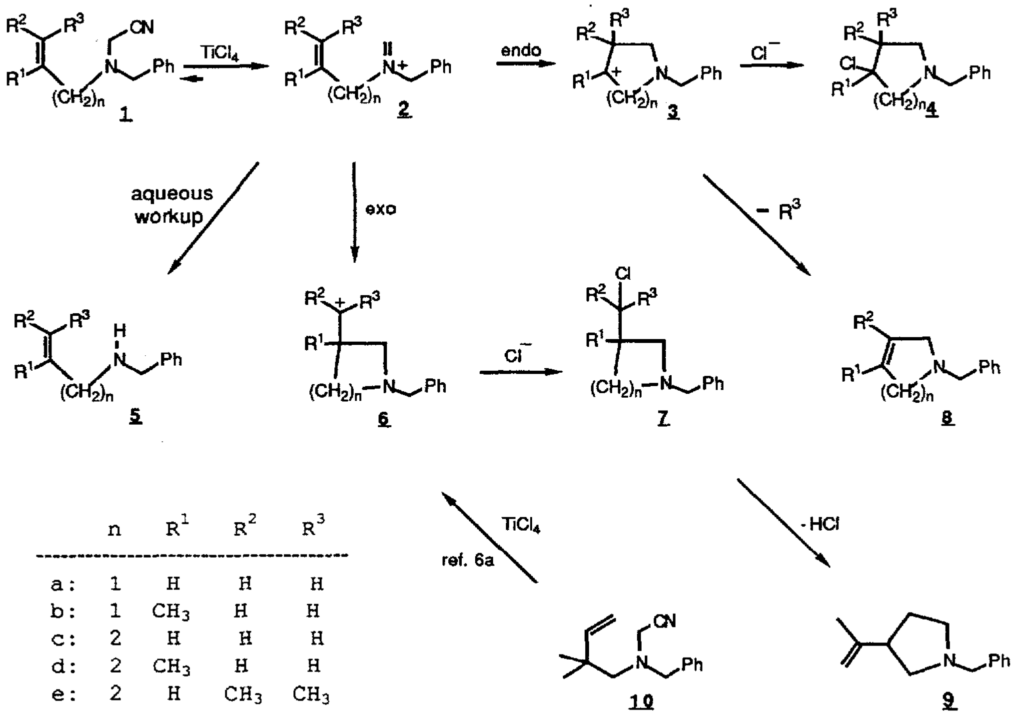
Scheme I



Most of the tertiary α-cyanoamines can be prepared very conveniently in one of the three ways as shown in scheme I. Nevertheless, we aquired all of our amines using the latter two methods.

The iminium ions were generated in CH_2Cl_2 with 3-4 equivalents of $TiCl_4$ at -78°C or higher temperatures.[4] Both alkenes and alkynes were found to give cyclized products which appeared to go through a general mechanism as shown in scheme II.

Scheme II



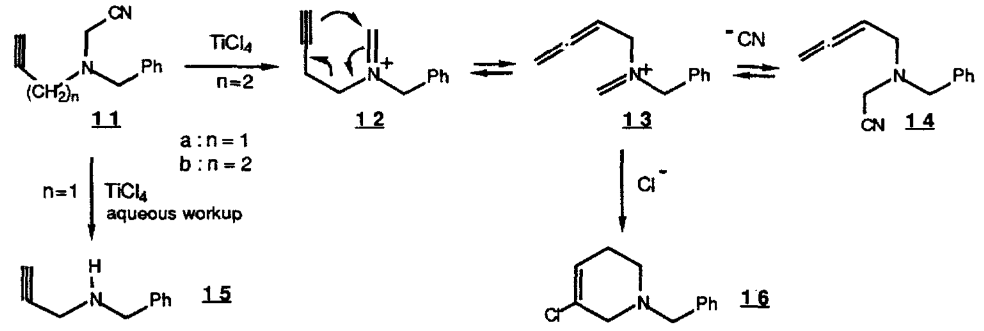
	n	R^1	R^2	R^3
a:	1	H	H	H
b:	1	CH_3	H	H
c:	2	H	H	H
d:	2	CH_3	H	H
e:	2	H	CH_3	CH_3

Table I

Entry	α-Cyanoamines	$TiCl_4$	Conditions		Recovered S.M.		Cyclized Products[5]
1	1a	4 eq.	-78°C - r.t.	(1.5h)	1a	(77%)	0
2	1a	4 eq.	reflux CH_2Cl_2	(160h)	0		5 a (15%)
3	1b	3 eq.	0°C	(5h)	1b	(18%)	8b (28%)
4	1b	3 eq.	r.t.	(22h)	1b	(2%)	8b (58%)
5	1c	3 eq.	-78°C - r.t.	(1.5h)	1c	(14%)	4 c (70%)
6	1d	3 eq.	0°C	(2h)	0		4d (35%) + 8d (50%)
7	1e	4 eq.	r.t.	(2h)	0		7e (50%) + 9 (10%)
8	10	4 eq.	r.t.	(2h)	0		7e (54%) + 9 (12%)
9	11a	4 eq.	r.t.	(24h)	11 a	(83%)	0
10	11a	4 eq.	reflux CH_2Cl_2	(120h)	11 a	(70%)	15 (14%)
11	11b	4 eq.	-78°c - r.t.	(3h)	11b	(12%)	14 (68%)
12	11b	4 eq.	reflux CH_2Cl_2	(39h)	0		14 (18%) + 16 (45%)

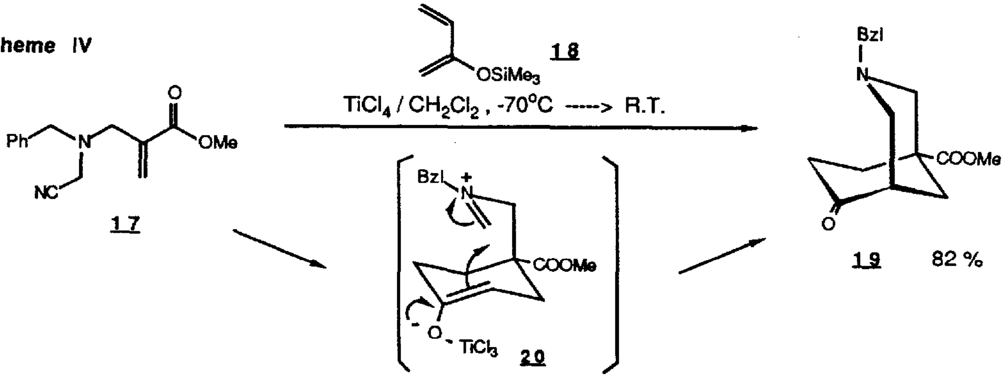
According to our results summarized in table I, the yields of the cyclized products depend on the ring size as well as the substituents on the olefins. The five membered ring compounds are much more difficult to obtained presumably due to the geometry of the two π-systems which prevents the orbitals to reach each other as in entry 1 and 2. On the contrary , in entry.5, 6, 7, and 8 the cyclization reaction went smoothly to produce six membered ring products. Meanwhile, in entry 11 and 12, the initially formed iminium ion 12 underwent 2-aza-Cope rearrangement^{6} to generate iminium ion 13 which would give allene 14 or furnish cyclic olefin 16 under forcing conditions as shown in scheme III.^{7}

Scheme III



On the other hand, we found that in more complicated system the α-cyanoamines can also couple with silyl enol type nucleophile as shown in scheme IV.^{8} The novel compound 19 is the key intermediate in our synthesis of potent enzyme inhibitor of chorismate mutase.^{9} It has been prepared from compound 17^{10} and 18 in one pot with 4 eq. of $TiCl_4$ under the condition described above.

Scheme IV



In brief, the iminium ions can now be prepared easily under mild aprotic condition from readily available α-cyanoamines. This method should be especially useful in the protic acid sensitive systems. And we are currently investigating the application of this reaction in the alkaloid synthesis.

Acknowledgement: We thank the National Science Council of R.O.C. for financial support under Grant NSC75-0201-005c-01.

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4. All of the reactions were carried out in dichloromethane at the concentration of 0.5M α-cyanoamines at the specified temperatures.
5. All reported yields are isolated yields, and all new compounds are characterized by IR, NMR, Mass, and elemental analysis.
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8. This reaction was carried out by T. K. Yang under the supervision of professor G.A. Berchtold at M.I.T. ,whom the author deeply appreciates.
9. (a) Chao, H. S. I.; Berchtold, G. A. *Biochemistry* **1982**, 21, 2778. (b) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, 109, 5008, 5013, and references cited therein.
10. Compound 17 was prepared in 92% yield from the coupling of benzylamine and chloroacetonitrile in $CHCl_3$ at ambident temperature followed by addition of methyl-2-bromomethylacrylate and 1.eq. of NEt_3 at reflux $CHCl_3$.

(Received in Japan 25 March 1989)