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Titanium(IV) Chloride Promoted Condensation of *Ortho*-aminonitriles with δ-Valerolactone

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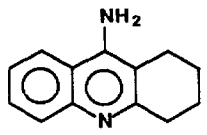
Abstract : The condensation of *vicinal* alicyclic or aromatic *ortho*-aminonitriles with δ-valerolactone is promoted by titanium(IV) chloride at room temperature in the presence of triethylamine to afford substituted 2,3-dihydropyrano[2,3-b]pyridines. These compounds are potentially useful as memory enhancing agents.

Tetrahydroaminoacridine (**1**, THA) has recently been shown to produce significant improvements in a variety of psychological tests in patients suffering from Alzheimer's Disease. More importantly, it is the first treatment which has had a significant effect on the quality of life of these patients.[1] As part of an ongoing effort to identify superior analogs of THA, we became interested in synthesizing compounds of the general structure **2**, characterized by the 2,3-dihydropyrano[2,3-b]pyridine ring system. Formation of **2** by a recently described route involving intramolecular Diels-Alder reaction of substituted 1,2,4-triazines was cumbersome.[2] We now report that these formerly unknown compounds can be readily prepared by the titanium(IV) chloride promoted condensation of appropriate *ortho*-aminonitriles with δ-valerolactone at room temperature in the presence of triethylamine.



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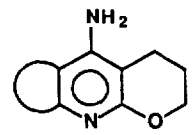

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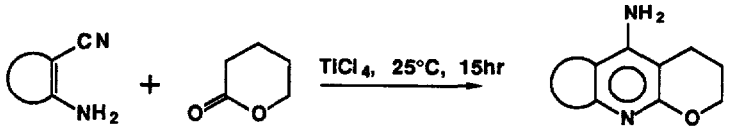
THA and its analogs have been prepared by the reaction of readily available *ortho*-aminonitriles or *ortho*-aminocarboxylic acid esters with ketones in the presence of zinc chloride,[3] cuprous chloride[4] or phosphorus pentoxide[5] under forcing conditions. Mechanistically, the first step in this reaction is the formation of an imine, followed by intramolecular addition to the nitrile group to afford **1**. Both steps are mediated by the Lewis acid.

Use of this method for the synthesis of **2** would require the condensation of appropriate *ortho*-aminonitriles with δ-valerolactone. However, this transformation fails because of the low electrophilicity of the carbonyl group of δ-valerolactone, which retards the required initial step of iminolactone formation .

Titanium(IV), when used in stoichiometric amounts, has been shown to facilitate the formation of enamines,[6] imines,[7] N-phosphinoyl imines and N-sulphonyl imines[8] from the reaction of aldehydes or ketones with amines. The success of these transformations can be attributed to the strong Lewis acidity of titanium(IV), which activates the carbonyl group toward attack by amines, and to its ability to remove water as it is formed. We

chose to investigate the titanium(IV) chloride promoted condensation of *ortho*-aminonitriles with δ-valerolactone we found that titanium(IV) chloride in the presence of triethylamine effects the following condensation:



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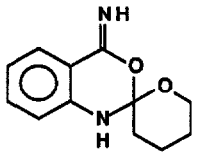
The condensation is best performed by stirring a mixture of δ-valerolactone (2.0 equiv), titanium(IV) chloride (2.0 equiv.) triethylamine (2.0 equiv.), and *ortho*-aminonitrile (1.0 equiv.) at room temperature for 15hr in methylene chloride. In the reaction of anthranilonitrile with δ-valerolactone, in addition to **2a** (58%), the spiro imino compound **3** (12%) was isolated. The formation of similar side products has been noted in the reaction of anthranilonitrile with cyclohexanone.[3]

Normally, lactones do not react with amines to form iminolactones. However, in the present case the high Lewis acidity of the titanium(IV) chloride and the irreversible conversion of the resultant iminolactone to **2** combine to make this a useful method. It is possible that the latter reaction is facilitated by titanium(IV) co-



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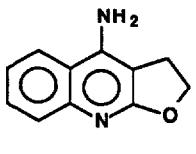

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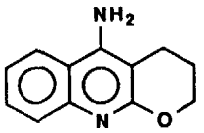
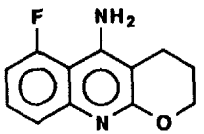
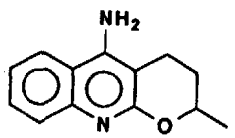
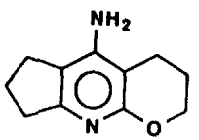
ordination with the nitrile group. As summarized in Table 1, the condensation is effective both for aromatic (**2a-2c**) and alicyclic (**2d**) aminonitriles. Attempts to extend this reaction to γ-butyrolactone afforded only a small amount (5%) of the desired condensation product **4** even under forcing conditions (1,2-dichloroethane/reflux).

This one pot procedure for the synthesis of substituted 2,3-dihydropyrano[2,3-b]pyridines **2** is very convenient and involves the unprecedented condensation of δ-lactones with *vicinal*- or *ortho*-aminonitriles. Specifically, the efficiency of titanium(IV) chloride in the present case is remarkable in view of the low reactivity of δ-valerolactone. In summary, we have found an attractive condensation for synthesis of 2,3-dihydropyrano[2,3-b]pyridines from readily available starting materials. Furthermore, the simplicity and the effectiveness of this one step process make it ideally suited for the development of structure activity relationships for these new biologically interesting compounds (**2,4**). This new methodology may broaden the scope of similar condensation reactions.

Table 1 : Condensation of aminonitriles with δ-lactones :

Product	Yield %	mp (°C) (ether)	HRMS	^{1}H-NMR ($CDCl_3$, 300MHz, δ)
 **2a**	58	195	200.0946	2H, m, 2.02-2.18; 2H, t, 2.63 (J = 6.0Hz); 2H, t, 4.36 (J = 6.0Hz); 2H, s, 4.64; 1H, t, 7.25 (J = 8.0Hz); 1H, t, 7.5 (J = 8.0Hz); 1H, d, 7.58 (J = 8.0Hz); 1H, d, 7.72 (J = 8.0Hz)
 **2b**	55[a]	202	218.0284	2H, m, 2.06-2.2; 2H, t, 2.6 (J = 6.0Hz); 2H, t, 4.37 (J = 6.0Hz); 2H, bs, 5.4; 1H, dd, 6.88 (J = 14.0,7.5Hz); 1H, m, 7.3-7.44 ; 1H, d, 7.56 (J = 8.6Hz)
 **2c**	50[b]	202-203	214.1138	3H, d, 1.45 (J = 6.5 Hz); 1H, m, 1.7-1.84; 1H, m, 2.04-2.18; 2H, m, 2.58-2.64; 1H, m, 4.22-4.36; 2H, bs, 4.69; 1H, t, 7.22 (J = 7.5Hz); 1H, t, 7.47 (J = 7.5Hz); 1H, d, 7.58 (J = 7.5 Hz); 1H, d, 7.71 (J = 7.5Hz)
 **2d**	62[c]	164	190.1107	4H, m, 2.0-2.2; 2H, t, 2.48 (J = 6.0Hz); 2H, t, 2.68 (J = 6.0Hz); 2H, t, 2.87 (J = 6.0Hz); 2H, bs, 4.06 (J = 6.0Hz); 2H, t, 4.24.

[a] Prepared by the condensation of 2-amino-6-fluorobenzonitrile and δ-valerolactone.

[b] Synthesized by the reaction of anthranilonitrile and 6-methyl-tetrahydropyran-2-one[9].

[c] Synthesized by the condensation of 2-amino-1-cyano-1-cyclopentene[10] and δ-valerolactone.

3,4-Dihydro-2H-pyrano[2,3-b]quinolin-5-amine (**2a**):

Typical Procedure:

To a stirred solution of δ-valerolactone (3.0 gms, 30.0 mmole) in methylene chloride (50 ml) at -20°C was added titanium(IV) chloride (11.4 gms, 60.0 mmole). The reaction mixture became dark yellow in color and then a mixture of triethylamine (6.1 gms, 60.0 mmole) and anthranilonitrile (3.5 gms, 30.0 mmole) in methylene chloride (10 ml) was added. The reaction mixture, which immediately darkened, was allowed to warm to room temperature and stirred for 8hr. Additional δ-valerolactone (3.0 gms, 30.0 mmole) was added and the stirring was continued for another 10hr. At the end of this period the reaction mixture was slowly poured into cold 15%aq. ammonium hydroxide (100 ml) and methylene chloride (100 ml). The mixture was stirred for 15 min. and filtered through a 2" celite pad which was washed with methylene chloride (50 ml) and water (100 ml). The organic layer was separated, washed with water(1 × 100 ml) and dried (anhydrous $MgSO_4$). The methylene chloride was removed under vacuum to afford oil which was triturated with ether to give **2a** as a yellowish solid contaminated with **3**. Crystallization from isopropyl alcohol afforded pure **2a** (3.5gms, 58%, m.p. 195-196°C). The mother liquor was evaporated to leave an oil (1.5 gms) which was loaded onto a silica column. Elution with 5% methanol : methylene chloride (1: 20) afforded pure **3** (800 mgs, 12%, m.p. 96°C). ^{1}H- NMR (300MHz, $CDCl_3$, δ) : 2H, m, 1.67; 2H, quin, 1.85 (J = 7Hz); 1H, bs, 2.17; 2H, t, 2.52 (J = 7Hz); 2H, bt, 3.7 (J = 5.8 Hz); 1H, t, 7.14 (J = 7.6); 2H, m, 7.5; 1H, bs, 8.07; 1H, d, 8.33 (J = 8.6Hz). ^{13}C-NMR ($CDCl_3$, δ) : 22.1, 31.4, 37.1, 62.4, 102.2, 116.6, 121.7, 124.1, 132.3, 134.2, 140.6 and 171.9.

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