Tetrahedron Letters, Vol. 34, No. 27, pp. 4343-4346, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

INTRAMOLECULAR CYCLIZATION WITH IMINIUM IONS SYNTHESIS OF 1,4-DIAZABICYCLO[4.3.1]DECENE DERIVATIVES

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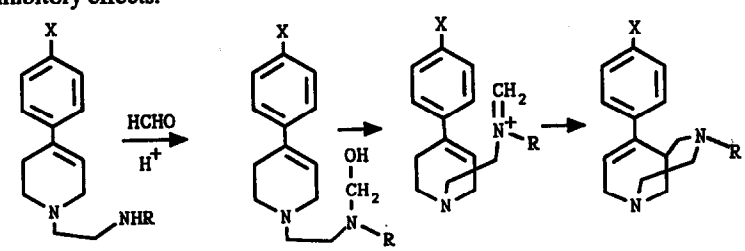
Abstract: Intramolecular cyclization reactions between iminium ion and conjugated double bond as a nucleophilic terminator producing 1.4-diazabicyclo[4.3.1]decene derivatives were observed.

Intramolecular cyclization between an iminium ion and an unsaturated carbon-carbon bond is a general method for the formation of nitrogen containing heterocyclic compounds in vitro as well as in vivo.[1-4] In organic synthesis the electrophilic iminium ions (cyclization initiators) usually are generated in situ from a condensation product of an amine, amide or carbamate with a reactive aldehyde i. e. formaldehyde,[5] alkyl glyoxalate[5,6] and alkyl mesoxalate.[6,7] The applied cyclization terminating groups (nucleophilic partners) are vinyl[8]- or allylsilanes,[9] isolated carbon-carbon double bonds[7,9] and aromatic π-systems[10,11] (see e.g. Pictet Spengler reaction). In this paper we wish to report on an intramolecular cyclization reaction between an iminium ion and a carbon-carbon double bond which is conjugated with a phenyl group (see scheme) To our knowledge, such a cyclization has not been known. In this work our aim was to synthesize compounds with a rigid tetrahydropyridine ring system to study their MAO enzyme and dopamine uptake inhibitory effects.



1-7 8 9,10,13-16

The cyclization reactions were carried out in a one pot reaction from the corresponding amine or amide using paraformaldehyde and different organic or mineral acids. The starting materials,[12] reaction conditions and products are shown in the table.

Reactions were performed with 3 equivalents of paraformaldehyde, in excess of an acid serving also as a solvent. After the reaction time indicated the mixture was diluted with water, made alkaline with potassium carbonate and extracted with ethyl acetate. After concentration in vacuo the residue was chromatographed on a silica gel[13] column.

To achieve the ring closure reaction with 1, the reaction mixture was heated, the only exception was the reaction with 70% sulfuric acid, where a short reaction time and room temperature was enough to carry out ring closure. At room temperature, with other acids, only the N-hydroxymethylated intermediate 8 was obtained together with some starting compound. With starting materials 2,4-6 the use of 70% sulfuric acid caused decomposition, therefore we applied trifluoroacetic acid.

Table

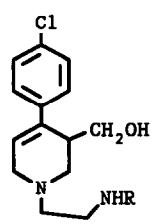
cyclization precursor no.	X	R	reaction conditions	products[a]	yield[b]	m.p °C
1	Cl	-COOEt	36%HCl,RT,40h	8	43%	oil
			HCOOH,RT,40h	8	40%	oil
			CF_3COOH,RT,40h	8	38%	oil
			70%H_2SO_4,RT,40min	9	69%	265-267[c]
			36%HCl,reflux,2,5h	9	57%	
			CF_3COOH,reflux,6h	9	59%	
2	Cl	$-CH_2COOEt$	CF_3COOH,reflux,8h	10	26%	oil
3	Cl	$-COCF_3$	CF_3COOH,reflux,6h	11	42%	oil
			70%H_2SO_4,RT,1h	12	61%	235-9[c]
4	Cl	$-CH_2C_6H_5$	CF_3COOH,reflux,6h	13	73%	229-30[d]
5	Cl	$-CH_2CH_2C_6H_5$	CF_3COOH,reflux,6h	14	20%	oil
				15	15%	120-1
6	H	$-CH_2C_6H_5$	CF_3COOH,reflux,8h	16	74%	235-6[d]

a) NMR data refer to the basic forms. See under ref 15

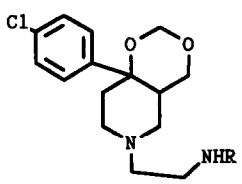
b) Isolated yield of purified product

c) HCl salt d) 2HCl salt

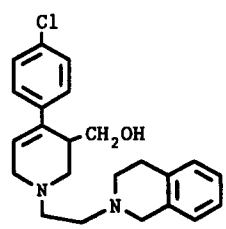
Interestingly, if the nitrogen atom serving for the iminium ion generation was integrated in an amide conjugation (see 3) no N-hydroxymethylated intermediate or ring closure reaction was observed. In this case product 11 results from a Prins reaction and 12 obviously arises from 11 through a reaction with an additional formaldehyde molecule. Such a reaction of tetrahydropyridines has been known[14]. Although earlier authors prepared 1,3-dioxane derivatives with at least a 10-fold excess of paraformaldehyde, we could reach product-selectivity merely through different reaction conditions using, in both cases, the same threefold paraformaldehyde excess. In the cyclization reaction of 5 the tetrahydroisoquinoline derivative 15 was also produced, as a byproduct, besides the expected 14. Compound 15 obviously resulted from a Pictet-Spengler reaction competing with the ring closure process. The formation of 15 is interesting because the phenyl group involved in the ring closure reaction had no electron-donating substituents. According to other observations[10] an alkoxy or hydroxy group were necessary for ring closure in meta or para position to the amine containing side chain.



11



12



15

None of the compounds synthesized showed a remarkable MAO-A or MAO-B inhibitory effect but some of them possessed weak dopamine uptake inhibitory characteristics.

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12. Starting materials 1,4-6 were prepared in the usual alkylation procedure from known unsubstituted tetrahydropyridines and the corresponding known 2-bromoethylamino derivatives in DMF using potassium carbonate as a base. Hydrolysis of 1 with Claisen alkali produced the N-(2- aminoethyl)tetrahydropyridine intermediate which in turn after alkylation with ethyl chloroacetate gave 2, and after acylation with trifluroacetic anhydride provided 3.
13. Column chromatography was performed on Kiselgel 60 (*MERCK*) using $CHCl_3$:MeOH (9:1) for 8,9; ratio (4:1) for 10,13,14,16 and (12:1) for 11,12.
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15. All the ^1H NMR data were determined at 250 MHz in $CDCl_3$ as solvent (TMS as standard), all the ^{13}C NMR data were determined at 63 MHz in $CDCl_3$ as solvent ($CDCl_3$ at 77.0 ppm), and temperature at T=298K

    8 ^1H NMR 7.25(4H,s) 6.04(1H,m) 4.75(2H,s) 4.18(2H,q, J=7.8 Hz) 3.54(2H,m) 3.25(2H,q, J=2.9 Hz) 2.82(2H,t, J=5.9 Hz) 2.6(4H,m) 1.28(3H,t, J=7.8 Hz)
    ^{13}C NMR 155.8(s) 138,5(s) 134.1(s) 133.0(s) 128.4(d) 126.1(d) 120.9(d) 72.6(t) 61.7(t) 56.7(t) 52.8(t) 49.8(t) 46.4(t) 27.1(t) 14.5(q)

    9 (two rotamers a/b 45:55) ^1H NMR 7.25(2H,d, J=8.0 Hz) 7.15(2H,d, J=8.0 Hz) 6.07(1H,m) 4.1-2.7(13H,m) 1.15(1.35H,t, J=7.0 Hz) 0.90(1.65H,t, J=7.0 Hz)
    ^{13}C NMR 156.0(s) 138.7(s) 138.6(s) 137.4(s) 133.1(s) 132.9(s) 128.6(d) 128.5(d) 127.4(d) 127.3(d) 126.9(d) 126.7(d) 61.2(d) 61.1(t) 56.9(t) 55.6(t) 52.9(t) 52.8(t) 50.9(t) 49.6(t) 48.3(t) 48.2(t) 46.6(t) 46.5(t) 34.5(d) 34.0(d)

    10 ^1H NMR 7.30(2H,d, J=7.8 Hz) 7.25(2H,d, J=7.8 Hz) 6.02(1H,s,br) 4.05(2H,q, J=7.2) 3.99(1H,d, partially overlap) 3.65(1H,d, J=14.7 Hz) 3.50(1H,m) 3.40-3.15(4H,m) 3.05-2.75(5H,m) 2.65(1H,d, J=11.8 Hz) 1.15(3H,t, J=7.2)
    ^{13}C NMR 170.9(s) 139.8(s) 138.2(s) 133.4(s) 128.7(d) 127.6(d) 123.0(d) 60.3(t) 59.8(t) 57.9(t) 56.4(t) 53.5(t) 52.5(t) 48.8(t) 34.1(d) 14.1(q)

11 ^{1}H NMR 7.75(1H,s,br NH) 7.22(4H,s,br) 6.01(1H,m) 4.10(1H,s,br, OH) 3.62(1H,dd, J_1=10.4 Hz J_2=2.8 Hz) 3.55-3.25(3H,m) 3.11(1H,d, J=11.1 Hz) 2.82(1H,d, J=17.1 Hz) 2.74(1H,s,br) 2.86-2.43(3H,m)
^{13}C NMR 157.6(q J_{CCF}=37 Hz) 137.8(s) 135.1(s) 133.1(s) 128.6(d) 127.1(d) 124.8(d) 115.8(q, J_{CF}=289 Hz) 64.4(t) 55.4(t) 53.7(t) 53.4(t) 38.5(d) 36.7(t)

12 ^{1}H NMR 7.35(4H,s,b) 5.0-4.1(1H, NH) 4.87(1H,d, J=7.0 Hz) 4.75(1H,d, J=7.0 Hz) 3.82(1H,d, J=11.8 Hz) 3.60(1H,d, J=11.8 Hz) 3.50(2H,m) 3.05(1H,t, J=11.0 Hz) 2.90(1H,dd, J_1=11.0 Hz J_2=5.0 Hz) 2.65(3H,m) 2.54(1H,td, $J_{1,2}$=11.8 Hz J_3=2.5 Hz) 2.44(1H,dd, J_1=10.8 Hz J_2=4.9 Hz) 1.8(1H,d, J=11.8 HzJ) 1.65(1H,td, $J_{1,2}$=11.8 Hz J_3=5.0 Hz)
^{13}C NMR 157.1(q, J_{CCF}=37 Hz) 141.8(s) 133.1(s) 129.1(d) 127.2(d) 115.8(q, J_{CF}=289 Hz) 89.4(t) 74.8(s) 65.9(t) 55.7(t) 52.7(t) 48.8(t) 41.8(t) 36.3(t) 35.4(d)

13 ^{1}H NMR 7.20(2H,d, J=8.8 Hz) 7.14(2H,d, J=8.8 Hz) 7.12(4H,s,br) 6.02(1H,m) 3.74(1H,dt, J_1=19.0 Hz J_2=3.0 Hz) 3.48(1H,d, J=13.5 Hz) 3.46(1H,d, J=14.0 Hz) 3.37(1H,d, J=13.5 Hz) 3.25-3.05 (3H,m) 2.77-2.58(3H,m) 2.53-2.32(3H,m)
^{13}C NMR 139.7(s) 139.4(s) 139.2(s) 132.6(s) 128.4(d) 128.3(d) 128.0(d) 127.5(d) 126.7(d) 126.2(d) 63.4(t) 58.3(t) 58.2(t) 54.4(t) 54.0(t) 49.0(t) 34.1(d)

14 ^{1}H NMR 7.40-6.90(9H,m) 5.99(1H,s,br) 3.75(1H,dt, J_1=19.0 Hz, J_2J_3=3.3 Hz) 3.41(1H,d, J=14.1 Hz) 3.25-3.05(3H,m) 2.85-2.65(3H,m) 2.65-2.40(7H,m)
^{13}C NMR 140.5(s) 139.6(s) 139.4(s) 132.7(s) 128.7(d) 128.5(d) 128.2(d) 127.5(d) 126.6(d) 125.8(d) 61.0(t) 58.4(t) 57.8(t) 54.5(t) 48.9(t) 34.3(d) 34.0(t) 29.6(t)

15 ^{1}H NMR 7.25-7.15(4H,m) 7.10-6.85(4H,m) 5.96(1H,m) 3.62(2H,s) 3.16(2H,q, J=2.8 Hz) 2.84(2H,t, J=5.9 Hz) 2.77-2.64(8H,m) 2.46(2H,m)
^{13}C NMR 139.2(s) 134.6(s) 134.2(s) 134.0(s) 132.6(s) 128.6(d) 128.3(d) 126.5(d) 126.2(d) 126.1(d) 125.6(d) 122.4(d) 56.5(t) 56.1(t) 55.9(t) 53.6(t) 51.4(t) 50.7(t) 29.0(t) 28.0(t)

16 ^{1}H NMR 7.40-7.10(9H,m) 6.10(1H,s,br) 3.85(1H,dt, J_1=19.0 Hz $J_{2,3}$=2.2 Hz) 3.57(1H,d, J=14.0 Hz) 3.55(1H,d, J=13.6 Hz) 3.45(1H,d, J=13.6 Hz) 3.30-3.05(3H,m) 2.9-2.65(3H,m) 2.57(2H,d, J=4.3 Hz) 2.55-2.35(1H,m)
^{13}C NMR 140.9(s) 140.7(s) 139.7(s) 128.4(d) 128.3(d) 128.0(d) 126.9(d) 126.6(d) 126.2(d) 125.7(d) 63.4(t) 58.4(t) 54.4(t) 53.9(t) 49.0(t) 34.1(d)

(Received in UK 7 May 1993)