HETEROCYCLES, Vol. 24, No. 8, 1986

STEREOSELECTIVITY IN THE SYNTHESIS OF 5′-ALKYLATED NICOTINES

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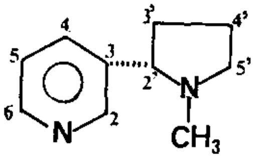
Abstract — In the hydride reduction of enamines formed by the alkylation of cotinine (2) with organolithium reagents, the effect of some reaction conditions on the stereochemistry of the resulting 5′-alkylnicotines was studied. The acidity of the reaction medium was the main factor determining the stereochemistry of the products.

In order to elucidate structure-activity relationships for nicotine analogues, many kinds of alkyl nicotine derivatives have been synthesized. There are two methods of obtaining these derivatives. One is the direct alkylation of nicotine (1) or its derivatives, and the other is the construction of a pyrrolidine and/or pyridine ring from appropriate starting materials. The former is prefferable when optically active derivatives are desired, and 2-, 4-, 6-, 4′-, and 5′-alkyl derivatives are known to result from that method.[1] In a previous paper,[2] we reported the synthesis of 5′-alkyl and aryl nicotines, which were obtained by the reaction of cotinine (2) with alkyl or aryl lithium, respectively, followed by reduction with sodium cyanoborohydride in acidic methanol. This method produces a large quantity of derivatives with which the biological activities can be examined. Because 1 is readily metabolised to 2 in men and animals,[3] the biological activities of 5′-alkylnicotines are of particular interest.



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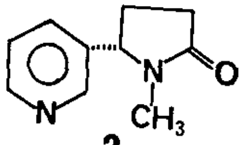

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The alkylation afforded in 50-70%

Table 1 The selectivity of the reduction[a)]

acid/base	Temp.	methyl		ethyl		n-butyl		isopropyl		phenyl	
mol. eq.	(°C)	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
4.0 HCl	25	97	3	98	2	97	3	97	3	98	2
1.0 HCl	25	78	22	82	18	86	14	89	11	90	10
0	25	62	38	77	23	82	18	84	16	80	20
1.5 KOH	25	56	44	65	35	70	30	72	28	55	45
3.0 KOH	25	-		-		65	35	-		40	60
2.0 HCl[b)]	25	-		-		65	35	-		-	
0[b)]	25	58	42	65	35	67	33	77	23	63	37
2.0 KOH[b)]	25	-		-		66	34	-		-	
4.0 HCl	-78	93	7	96	4	97	3	98	2	99	1
1.0 HCl	-78	64	36	80	20	79	21	89	11	81	19
0	-78	51	49	72	28	63	37	72	28	65	35
1.5 KOH	-78	49	51	64	36	60	40	71	29	50	50
3.0 KOH	-78	-		-		59	41	-		34	66
2.0 HCl[b)]	-78	-		-		61	39	-		-	
0[b)]	-78	49	51	61	39	60	40	74	26	49	51
2.0 KOH[b)]	-78	-		-		60	40	-		-	

a) Reduction with $NaBH_3CN$ (1.0eq.) in MeOH.

b) Reductant is $NaBH_4$(1.0eq.).

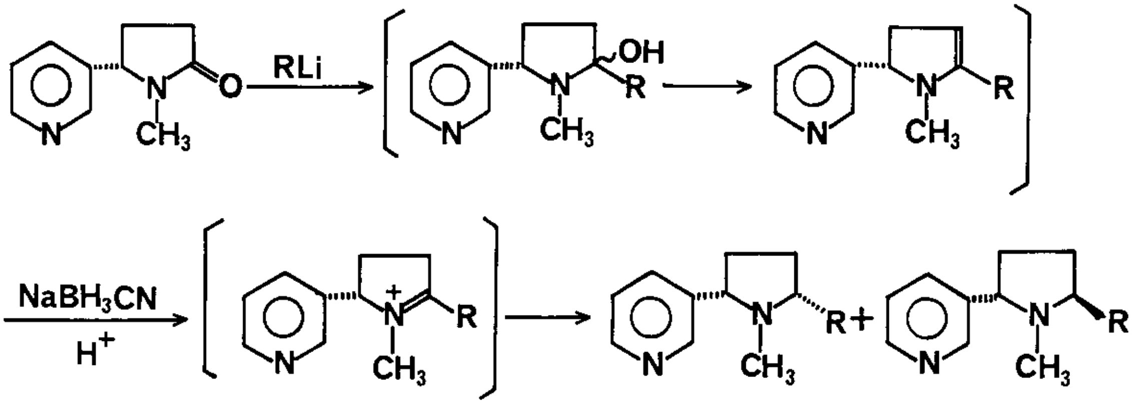

Table 2 Acid and temperature dependence[a)]

Temp. (°C)	acid	0		0.5 eq.		1.0 eq.		4.0 eq		0[b)]	
		cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
25	HCl	82	18	83	17	86	14	97	3	67	37
25	TsOH[c)]	-		83	17	87	13	96	4	-	
25	D-camp.[d)]	-		84	16	88	12	97	3	-	
25	DL-camp.[d)]	-		84	16	87	13	96	4	-	
-78	HCl	63	37	-		79	21	97	3	60	40
0	HCl	84	16	-		87	13	98	2	63	37
60	HCl	81	19	-		88	12	90	10	81	19

a) Reduction of 3 with $NaBH_3CN$(1.0eq.) in MeOH. b) Reductant is $NaBH_4$.
c) p-Toluenesulfonic acid d) Camphorsulfonic acid

yield a 4 : 1 mixture of diastereomers, which are separable chromatographically. In this work, we investigated the influence of the reaction conditions on stereoselectivity to improve the efficiency with which diastereomers can be obtained.

This reaction was assumed to proceed via an enamine which was formed by the 1,2-addition of alkyl lithium to the carbonyl group in 2 followed by dehydration.[4] Thus, reduction is a key step in determining the stereoselectivity. Some reaction conditions, such as reductants, temperature, solvent, and acidity of the solution, were examined.

The ratios of the diastereomers obtained from the reduction by sodium cyanoborohydride and by sodium borohydride under some acidic and basic conditions are listed in Table 1. The stereoselectivity was greatest in highly acidic solutions and virtually disappeared in basic solutions. And the ratio of cis-isomers to trans-ones increased as the acidity of the solution increased; and under highly acidic conditions, cis-isomers were obtained stereoselectively. The acidity had the most marked effect on the 5′-phenyl derivative. The dependence on the acidity was generally larger at low

Table 3 Reductant ratio and solvent dependence

reductant mol.eq.	Solvent	cis	trans
0.5	MeOH	85 :	15
1.0	MeOH	86 :	14
2.0	MeOH	84 :	16
5.0	MeOH	85 :	15
1.0	EtOH	87 :	13
1.0	i-PrOH	84 :	16
1.0	THF/MeOH[a)]	87 :	13

Reduction of 3 with $NaBH_3CN$ at 25°C 1.0 mol.eq. HCl was added.

a) THF : MeOH = 1 : 1.

temperatures. The yields of 5′-alkylnicotines remained largely unaffected by changing the reaction conditions examined. In order to investigate the effect of the bulkiness of the counter anion to the iminium salt, the reduction of enamine (3) derived from 2 and *n*-butyl lithium was carried out. As shown in Table 2, the product ratio did not seem to be affected by the bulkiness of the acids. Table 2 also shows that at lower temperatures, the effect of the acidity apparently increased.

This reduction was carried out in four kinds of solvents, and the ratio of the products was not greatly affected as shown in Table 3. In addition the ratio of sodium cyanoborohydride to the enamine did not change the product ratio.

Reduction by sodium borohydride was also carried out in both acidic or basic solutions. In contrast to sodium cyanoborohydride reduction, the ratio of the products was not changed by altering the acidity of the solution, and was similar to that from sodium cyanoborohydride reduction in basic media, as shown in Table 1. The attempted reduction by lithium aluminium hydride and lithium triethylborohydride was quite ineffective.

EXPERIMENTAL

To a solution of cotinine(2) (5mmol, 0.9g) in 20ml of ether was added dropwise 6mmol of alkyl lithium in 10ml of ether at 0°C. The reaction mixture was stirred at room temperature. After 1h, water was added to the mixture, and extracted with ether. The extract was dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was disolved in 20ml of solvent. After adding acid or base, a reductant was stirred into the reaction mixture. The molecular ratio of acid, base, or reductant to the enamine was calculated based on the amount of **2**. After 1 h, the solution was poured into 20ml of 0.1N NaOH, saturated with NaCl, and extracted with ether. The extract was dried over Na_2SO_4. The analysis of the product was performed by gas chromathography (capilary column OV-101 50m). The assigment of *cis*- and *tarns*-isomers was confirmed by Mass, ^1H NMR, and ^{13}C NMR after separation by reversed phase column chromathography.[2]

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Received, 12th May, 1986