OXAZOLIDINES AND THIAZOLIDINES AS CARBON TRANSFER AGENTS SYNTHESIS OF TETRAHYDRO -β-CARBOLINE AND ISOQUINOLINE DERIVATIVES

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Abstract - Oxazolidines and thiazolidines transfer their C_2 units to appropriate nucleophiles and furnish the corresponding tetrahydro-β-carboline and isoquinoline derivatives.

The carbon transfer character of Δ^2-thiazolinium and oxazolinium cations[1] in a manner analogous to THF models, N-acetyl or tosyl-N'-methylimidazolinium cations[2], at the -COOH level, has been demonstrated. N-Acetyl or tosyl-N'-methylimidazolidines possessing differently basic nitrogen atoms perform carbon transfer at the -C=O level.[3,4] N-Methylpyrrolidine, tetrahydrothiophene and tetrahydrofuran exhibit pka values 10.4, -4.5 and -2.1, respectively.[5] We argued that when two of the heteroatoms such as N,O,S, are placed in identical environment in a perhydro five membered heterocycle, viz. thiazolidine and oxazolidine, a similar order of the difference in basicity of these heteroatoms would be available and such heterocycles could mimic the carbon transfer process of N^5,N^{10}-methylenetetrahydrofolate at carbonyl level.

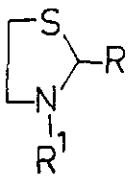
2-Phenylthiazolidine 1b with tryptamine 2a in acetonitrile in the presence of an anhydrous acid furnished 1-phenyl-1,2,3,4-tetrahydro-β-carboline 6a. The rate of the reaction is enhanced by the presence of an n-butyl group at nitrogen of 2-phenylthiazolidine 1a and the presence of an acetyl group 1c adversely affects the reaction. 2-Phenyl-4,4-dimethyloxazolidine 5a and tryptamine in acetonitrile in the presence of anhydrous HCl react exothermally at room temperature to give 5a, but in the presence of CH_3COOH or TFA, the reaction mixture has to be refluxed. On performing the reaction of 2a with 2-phenyl-3-methyloxazolidine 5b and 2,3-diphenyloxazolidine 5c, the N-substituent effect on reactivity has been found to be in the order N-CH_3 > N-H > N-C_6H_5. Similarly, 2-(p-methoxyphenyl)-4,4-dimethyloxazolidine 5d, 3-methyloxazolidine 5e and 3-phenyloxazolidine 5f react with tryptamine to furnish to corresponding tetrahydro -β-carboline derivatives. The harman alkaloid

eleagnine 6d has also been synthesised via transfer of $-\overset{+}{C}HCH_3$ from 2,3-dimethyl-oxazolidine 5g and 2-methyl-3-phenyloxazolidine 5h to tryptamine. The reactions of homoveratrylamine and phenethylamine with 2-aryl-4,4-dimethyloxazolidines yield Schiff's bases 7a-d and with anhydrous HCl, 7b could be cyclized to 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 3. However, homoveratrylamine and 5d in CH_3CN/HCl yield iminium chloride 7a.HCl. Besides lower reaction temperatures and better yields, the use of oxazolidines has the advantage that crystalline product could be isolated after neutralization of reaction mixtures as against the formation

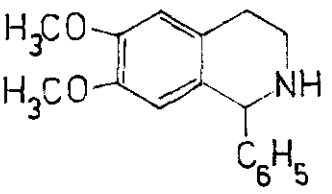
Tetrahydro -β-Carbolines and Schiff's Bases[i]

Amine	Reagent	Product	Time(h)			Yield(%)		
			a	b	c	a	b	c
2a	1a	6a	10	0.5	25	65	45	40
2a	1b	6a	12	200	30	70	50	50
2a	1c	6a	100	200	200	50	00	35
2a	5b	6a	4.5	0.2[d]	5	73	80	70
2a	5a	6a	5	0.2[d]	5'.5	85	85	65
2a	5c	6a	9	0.2[d]	10.5	66	26	60
2a	5d	6b	3	0.2[d]	3'.5	85	85	83
2a	5e	6c	2[e]	0.2[e]	0.5[e]	07	05	05
2a	5f	6c	3	0.2[e]	3.5	32	12	50
2a	5g	6d	2[d]	0.3[e]	10	53	04	00
2a	5h	6d	2[d]	0.3[e]	2	42	03	37
2b	5a	7b	2	0.2[d]	2.5	90	f	86
2c	5a	7d	4	0.2[d]	2	90	f	92
2b	5d	7a	10[d]	0.5[d]	12[d]	80	88[g]	78
2c	5d	7c	1.5	0.2[d]	2	89	f	90
2a	4a	6a	2	0.5[d]	3	70	65	65
2a	4a-d	6a		4[h]			80-88	
2a	4e-g	6b		4[h]			80-86	

a, b and c refer to reactions run in refluxing acetonitrile in the presence of TFA/HCl/CH_3COOH respectively. d - reactions run at rt e - reactions run at 0°C. f - unidentified products. g - yield of the corresponding iminium chloride. h - reactions run in refluxing acetic acid. i - for all the compounds satisfactory spectral data or comparison with authentic samples have been obtained.



	R	R^1
1a	C_6H_5	$CH_2CH_2CH_2CH_3$
1b	C_6H_5	H
1c	C_6H_5	$COCH_3$



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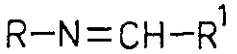
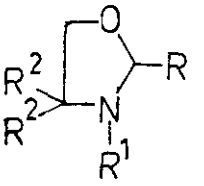
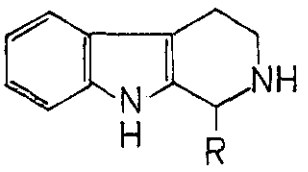


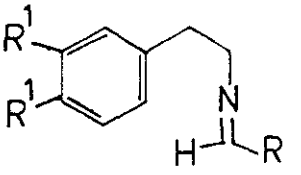
	R	R^1
4a	C_6H_5	C_6H_5
4b	C_6H_4Cl (p)	C_6H_5
4c	$CH(CH_2)_5$	C_6H_5
4d	$CH_2CH_2CH_2CH_3$	C_6H_5
4e	C_6H_5	$C_6H_4OCH_3$ (p)
4f	C_6H_4Cl (p)	$C_6H_4OCH_3$ (p)
4g	$CH(CH_2)_5$	$C_6H_4OCH_3$ (p)



	R	R^1	R^2
5a	C_6H_5	H	CH_3
5b	C_6H_5	CH_3	H
5c	C_6H_5	C_6H_5	H
5d	$C_6H_4OCH_3$ (p)	H	CH_3
5e	H	CH_3	H
5f	H	C_6H_5	H
5g	CH_3	CH_3	H
5h	CH_3	C_6H_5	H



	R
6a	C_6H_5
6b	$C_6H_4OCH_3$ (p)
6c	H
6d	CH_3



	R	R^1
7a	$C_6H_4OCH_3$ (p)	OCH_3
7b	C_6H_5	OCH_3
7c	$C_6H_4OCH_3$ (p)	H
7d	C_6H_5	H

of products as foams and in lower yields in the case of the reactions with imidazolidines.[3]

As oxazolidines exhibit tautomerism with imines and under acidic conditions provide iminium cations[6], the carbon transfer capability of simple imines has been studied. Acyclic imines 4a-g with tryptamine form β-carboline derivatives, irrespective of the nature of the amine being eliminated.

The overall reaction of azolidines with tryptamine represents the transfer of a -CHR fragment of the azolidines to a position between the nucleophilic centres, C-2 and the amino group of tryptamine. The reaction could be visualized to proceed through a mechanism similar to the one proposed for imidazolidines.[3] As 2-substituted oxazolidines and thiazolidines can be procured via addition of carbanions to appropriate azolines/azolinium cations, the process allows for the possibility of a wide variation in the nature of C-2 fragment in the masked aldehydes which may be either inaccessible or accessible with difficulty for Pictet-Spengler synthesis. The utility of these heterocycles in the synthesis of indole and isoquinoline alkaloids is being investigated.

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