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Synthesis and Characterization Spectroscopic of the Chiral 1, 3-Oxazolidines

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Abstract: The condensation of para-substituted aromatic aldehydes with 1, 2-aminoalcohols such as (L)-prolinol, gives 1, 3- oxazolidines (potential proinsecticides). Starting of (S) amino alcohol, thanks to asymmetric carbone C_2, we can obtain (S, S) and (S, R) diastereoisomers. The substituent situated on para position to aldehyde function in aromatic ring, affects the obtained proportion on diastereoisomers. If it is an electro-donor, the (S, S) diastereoisomer is clearly dominent; if it is an electro-attractor, the proportion of (S, S) and (S, R) diastereoisomers is practically the same.

Key words: 1, 2-secondary chiral amino alcohol, aromatic aldehyde, 1, 3- oxazolidine, asymmetric carbone

INTRODUCTION

Within the framework of a program devoted in search of heterocyclic biologically active, we put to profile oxazolidine structures as a possibility of pro insecticidal (Ladjama, 1992; Oumeddour, 1988) it presents some beneficial applications in the domain of agrochemical such as pesticide or herbicide. In this study, the synthesis of this compound was attempted using a route that has been widely applied for other oxazolidine derivatives, that is the condensation of the appropriate β-amino alcohols with an aromatic aldehyde. Generally the reaction of condensation that uses secondary β-ethanol amines (Hoppe *et al*., 1991; Yamauchi *et al*., 1998) only generates some heterocyclic compounds (Pararov *et al*., 2002) under shape of a diastereoisomers mixture due to the formation of new stereocenter C-2 on the oxazolidine ring. The object of our research is to evaluate the influence of the electronic factors of the substituents placed on para position to the aldehyde function. However, while using the non substituted benzaldehyde we observed the formation of an equimolar mixture with 2 diastereoisomers, this allows us to think about a possible impact of the electronic factor (Paukstelis and Lambing, 1970) on such or such diastereoisomers.

MATERIALS AND METHODS

All solvents and liquids used in hydrogenations distilled and kept under Ar. Other commercial reagents were used without additional purification. The IR spectra were taken on PYE-UNICAM SP3-200 instrument, in KBr pellets. ^{1}H NMR spectra were recorded with BRUKER AC 200 a 250 MHz. Chemical shifts are reported in ppm on δ-scale are given for ^{1}H relative to TMS as internal standard $CDCl_3$ Spin-spin coupling constants (*j*) values are given in Hz. Mass spectra was obtained on JEOL SX DX-102 with high-resolution spectrometer using the chemical ionisation on micro mass water (ZQ) in positive or negative mode (EI) and the electronic ionisation methods at (30 eV).

General procedure for the condensation of the 1, 2-aminoalcohols with the aromatic aldehydes: A mixture of an aromatic aldehyde (5mmoles), (L)-prolinol, (5mmoles) and p-toluenesulfonic acid (*p* -TsOH) (20 mg, 0.1mmoles) in toluene (30 mL) was refluxed, using a Dean-Stark water separation and by vigorous stirring on oil bath. After 4 h, the collection of water was stopped, the cooled reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL), the organic layer was separated and the aqueous layer was extracted with benzene (2×10mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was subjected to column chromatography on silica gel with CH_2Cl_2-hexane to give the corresponding oxazolidine as yellow viscous liquid.

2-Phenyl-1-aza-3-oxabicyclo [3.3.0] octane, ($C_{12}H_{15}NO$), Diastereoismeric mixture of (1) (58:42 mixture) as yellow viscous oil. Yield: 68 %. RMN ^{1}H: ($CDCl_3$/ δ in ppm): δ = 1.75 (m, 4H, CH_2-CH_2); 2.90 (t, 2H, -CH_2-N); 3.20 (m, 1H, *CH), 3.76-3.80 (d, 2H, CH_2-OH) for the majority and the minority, 5.30 (s, 1H', OH-CH-N, majority isomer), 5.49 (s, 1H', OH-CH-N, minority isomer), 7.40 (m, 5H arom, majority), 7.50 (m, 5H arom, minority) .IR: (ί in cm $^{-1}$): 2900 valence vibration of aliphatic (C-H); 1600 - 1400 (C = C) of

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core benzenic; 1080 - 1200 (N-C-OH), 700 vibration out of the plan of the (C-H) of the benzene (benzene monosubstituted). S.M: 30V (ESI+) m/z (%): 101.02 (18), 112.20 (33), 190.10 (88).

2-(4-nitro-phenyl)-1-aza-3-oxabicyclo [3.3.0] octane, ($C_{12}H_{14}N_2O_3$), diastereoismeric mixture of (2) (52: 48 mixture) as yellow viscous oil.

Yield: 69 %. RMN ^{1}H: ($CDCl_3$/ δ in ppm): δ = 1.90 (m, 4H, CH_2-CH_2); 2.90 (t, 2H, CH_2-N); 3.25 (m,1H,*CH); 3.50-3.87 (d, 2H, CH_2-OH) for the majority and minority; 5.30 (s,1H'', OH-CH-N, majority isomer); 5.60 (s, 1H'', OH-CH-N, minority isomer); 7.12 (d, 2H'$_2$ majority arom, j = 7.95 Hz); 7.5 (d, 2H'$_2$ minority arom j = 8.74 Hz); 8.12 (d, 2H'$_1$ majority arom, j = 12.9 Hz); 8.42 (d, 2H'$_1$ minority arom, j = 7.64 Hz). IR: (í in cm $^{-1}$): 2900 valence vibration of aliphatic (C-H); 1600-1400 (C = C) of benzenic core; 1080-1200 (N-C-OH), 750-830 vibration out of the plan of the (C-H) of the benzene (bi-substituted benzene). S.M: 30V (ESI+) M/Z (%): 101.97 (68), 235.07 (100), 257.25 (45). 20V (ESI -) M/Z (%): 233.02 (100).

2-(4-methoxyphenyl)-1-aza-3-oxabicyclo [3.3.0] octane, ($C_{13}H_{17}NO_2$), diastereoismeric mixture of (3) (90:10 mixture) as yellow viscous oil. Yield:72 %. RMN ^{1}H: ($CDCl_3$/ δ en ppm): δ =1.90 (m, 4H, CH_2-CH_2); 2.50 (t, 2H, CH_2-N); 3.30 (m, 1H, *CH); 3.75 (d, 2H, CH_2-OH); 3.75 (s, 3H, CH3-OH, minority isomer), 3.90 (s, 3H, CH3-OH, majority isomer); 5.30 (s, 1H'', OH-CH-N, majority isomer), 4.66 (s, 1H'', OH-CH-N, minority isomer); 7.00 (d, 2H'$_1$ majority arom, j = 11.48 Hz); 7.20 (d, 2H'$_1$ minority arom, j = 8.16 Hz); 7.75 (d, 2H'$_2$ minority arom, j = 7.90 Hz); 7.90 (d, 2H'$_2$ arom majority, j = 11.37 Hz). IR: (í in cm $^{-1}$): 2900: valence vibration of aliphatic (C-H); 1600 - 1400 (C = C) of benzenic core; 1080-1200 (N-C-OH), 750-830 vibration out of the plan of the (C-H) of the benzene (bi-substituted benzene). S.M: 30V (ESI+) M/Z (%): 112.20 (32), 123.02 (43), 220.05 (89). 20V (ESI -) M/Z (%): 218.10 (98).

RESULTS AND DISCUSSION

The reduction of various amino acids with sodium borohydride ($NaBH_4$) can be achieved in acidic environment (H_2SO_4) (Kennon and Meyers, 1993) or with the iodine in THF (Abiko and Masamune, 1992). For the formation of these oxazolidines, we opted for the reaction between secondary amino alcohols prepared from (L)-proline, amino acid which already possesses a secondary amino function and an aromatic aldehyde (Fig. 1). We used the no substituted benzaldehyde, then the para-nitrobenzaldehyde and finally the para methoxybenzaldehyde, or anisaldehyde.

We adopted as an operative protocol, the azeotropic removal of water formed during the reaction of an equimolar mixture of para-substituted aromatic aldehyde and the (L)-prolinol in the presence of catalyst p-toluenesulfonic acid and in toluene.

The reactional mechanism is made in 2 stages, the first consists the formation of an iminium ion, after attack the doublet of the nitrogen atom on the carbon of the carbonyl and elimination of a water molecule. The second stage which concerns the cyclization, the hydroxyl group attacks the iminium bond (C = N). The attack should occur from the upper and lower side of the plan (Fig. 2).

We obtain 2 diastereoisomers. The proposed structures are based on Infrared, ^{1}H NMR and mass spectral.

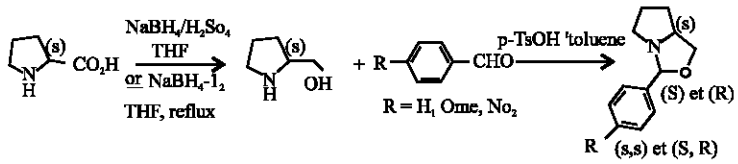


Fig. 1: A secondary amino function and an aromatic aldehyde

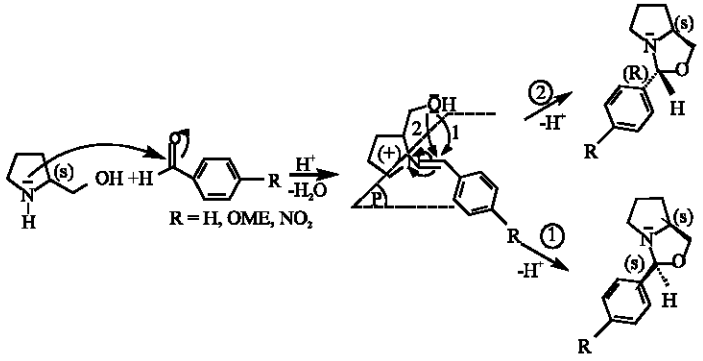


Fig. 2: The hydroxyl group attacks the iminium bond (C = N)

PROPORTION OF EPIMERS AND ASSIGNMENT OF PROTON SIGNALS OF THE OXAZOLIDINE CYCLE

Oxazolidine resulting from the benzaldehyde condensation: In all the observed synthesis, a new chiral center at C-2 of the heterocyclic ring is formed. The infrared spectrum of the product permitted to note the disappearance of the characteristic bands of initial products (hydroxyl and carbonyl function) and the appearance of a new band at 1080-1200 cm^{-1} assigned to N-C-O bond, further more the wide absorption at 2900 cm^{-1} which was found, assigned to aliphatic C-H. The absorption at 1400-1600 cm^{-1} corresponds to double bonds of aromatic ring.

Analysis of the ^{1}HNMR spectra shows the formation of the 2 diastereoisomers, thanks to signals of the proton carried by the asymmetric carbon generated at the time of the asymmetric induction and that we will name H'. The existence ratio was calculated from the peak height at the 2 position proton of the 1,3-Oxazolidine ring. These 2 peaks appear at 5.30 ppm and 5.49 ppm because of the immediate neighborhood of hetero-atoms (nitrogen and oxygen). The relative proportions of the 2 epimers are 58% for one and 42% for the other. The aromatic protons occur at 7.40 ppm for the majority and 7.50 ppm for the minority. In mass spectrometry, this product is characterized by the apparition of a molecular peak with a high abundance of m/z (%) = 190.10 (88).

Oxazolidine resulting from the condensation with para-nitrobenzaldehyde: In this case the condensation takes place with para-nitrobenzaldehyde that possesses a substituent electro-attractor at 4 position. We could identify the structure of products of the reaction by spectroscopic methods. In analysis by infrared spectrum, the cyclization results in the apparition of an absorption band at 1080-1200 cm^{-1} characteristic of N-C-O bond and the disappearance of hydroxyl and carbonyl bonds. The absorption at 1400-1600 cm^{-1} assigned to double bonds of the aromatic ring, as well as distinct to absorption due to C-H aliphatic at 2900 cm^{-1}. According to ^{1}H NMR 2 singulars of proton H' occurs at 5.30 and 5.60 ppm, correspond to the 2 epimers, that are the result of the condensation of the L-prolinol with para-nitrobenzaldehyde.The relative proportions of the 2 diastereoisomers majoritar and minoritar of oxazolidine contained in the mixture are respectively 52 and 48%. The phenyl hydrogen's are not equivalent; their signals appear under shape of doublet. The peaks of the 2 protons H'_2 appear at 7.12 and 7.50 ppm, whereas the H'_1 appear at 8.12 and 8.42 ppm and they are for this case shifts at downfield because of electro-attractor effect of the NO_2 group. As are the mass spectral data, this product is characterized by the apparition of 2 molecular peaks with a high abundance of m z^{-1} (%) = 233.02 (100) and 235.07 (100).

Oxazolidine resulting from the condensation with the anisaldehyde: We take the same type of reaction as for the condensation of the L-prolinol with the benzaldehyde, but for this case we have a substituent methoxy on para position to aldehyde function in benzenic ring.

The reactional mechanism is therefore the same, the product of the reaction possesses the following spectral features:

The IR spectrum indicates the presence of a new absorption band at 1080-1200 cm^{-1} assigned to N-C-O bond; it proves that the reaction of cyclization take place. The absorption band at 2900 cm^{-1} with weak intensity assigned to the aromatic ring, we note that double bond of benzenic ring appear effectively between 1400 and 1600 cm^{-1}. According to ^{1}H NMR spectrum, we note that we have a mixture of diastereoisomers, 2 singulars of the protons H' appears at 4.66 ppm and 5.30 ppm. The methoxy group (OCH_3) appears under the shape of 2 singulars at 3.75 ppm for the minority and at 3.90 ppm for the majority. The phenyl hydrogen's are not equivalent, indeed the 2 H'_2 protons of the benzenic ring appear toward 7.75 and 7.90 ppm, whereas the 2 H'_1 protons shifts at high fields, because of electro-donor effect of the methoxy group and appear at 7.00 and 7.20 ppm.The yield of the reaction is 72%. The integration of the 2 signals H', that is well distinct, permits to establish that the proportion for the majority epimer is 90% and 10% for the minority. In mass spectrometry, this product is characterized by the apparition of 2 molecular peaks with a high abundance of m z^{-1} (%) = 218.10 (98) and 220.04 (89).

It appears that the relative proportions of the 2 diastereoisomers contained in the mixture are appreciably equal with the benzaldehyde and para-nitrobenzaldehyde, whereas with para-methoxybenzaldehyde proportions are 90 and 10%. This result is interesting in this sense that the asymmetric induction signalled in the literature doesn't go beyond 55% for the majority product. Furthermore, it is importance to note that the degree of diastereoselectivity is influenced by the kind of substituent at 2 position on the 1.3-oxazolidine ring.

Absolute configuration of the C_2: All the absolute configuration of newly formed chiral centres was determined. It is considered that the reaction proceeds via an iminium intermediate by cleavage of the 1, 3-oxazolidine rings as proposed by Takahashi *et al.* (1986). ^{1}H NMR studies show that the condensation of (S)-2-(Hydroxydiphenyl methyl) pyrrolidine 1 with an

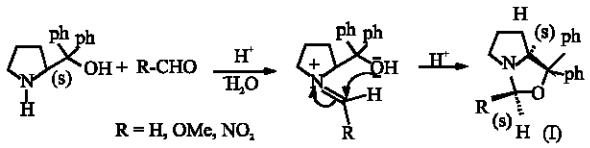


Fig. 3: Cis-(S,S)-2-substitues 4,4-diphenyl, 3,1-oxazabicyclo[3.3.0] octane

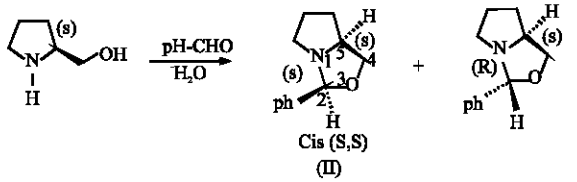
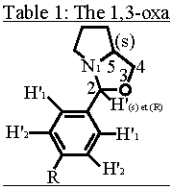


Fig. 4: 2-Phenyl-1aza-3-oxabicyclo [3.3.0]. Octane

Table 1: The 1,3-oxazolidine ring are the cis configuration



	Cis ou (S,S) (%)	Trans ou (R,S) (%)
(1) R = H	58	42
(2) R = NO_2	52	48
(3) R = OMe	90	10

aromatic aldehydes (Kanth, 1993) takes place in highly stereo selective, a single diastereoisomer was obtained (Zuo *et al*., 2003) whose stereochemistry is «cis» configuration (Bailey *et al*., 1991) (Fig. 3).

This stereo selectivity is absent in á-o non-substituted of oxazolidines and we obtain 2 epimers in different proportions (Fig. 4).

Recent ^{1}H NMR studies suggest that a «cis» relationship between C-2 and C-4 residues predominates. Agami and Rizk (1985) Arseniyadis *et al*. (1990) and Takahashi *et al*. (1990) demonstrated that a fast epimerisation takes place between cis and trans, via an iminium ion that generates the «cis» isomer favored thermodynamically. By comparing the ^{1}H NMR spectrum with literature data, the absolute configuration of the majors products of the chiral 1,3-oxazolidines (Ð) were estimated to be (2S, 5S), which means that functionalities of 2 and 5 positions of the 1, 3-oxazolidine ring are the cis configuration (Table 1).

CONCLUSION

The condensation of para substituted aromatic aldehydes with the secondary 1, 2-amino alcohols, such as (L)-prolinol, gives 1, 3-oxazolidines ring. Starting from the (S) amino alcohol, we get 2 diastereoisomers (S, S) and (S, R) because of asymmetric induction of the C-2. Indeed, concerning the synthesis, we confirmed the bibliographic results; the secondary amino function exclusively deals the cyclic derivatives, whereas with the primary amino we get the basic form, the so-called basis of Schiff and the cyclized shape.

The attribution of the chemical shifts of the different protons of oxazolidines has been achieved thanks to the IR analysis, ^{1}H NMR and mass spectral. The relative proportions of every diastereoisomers have been calculated from the spectrum of ^{1}H NMR of the proton. The substituent situated on para position to aldehyde function in aromatic ring, affects the obtained proportion on diastereoisomers. If it is an electro-donor, the (S, S) diastereoisomer is clearly dominent, if it is an electro-attractor, the proportion of (S, S) and (S, R) diastereoisomers is practically the same.

The absence of stereoselectivity during the cyclization has been confirmed, the proposition concerning the stereochemistry of the 2 epimers majority and minority has been showed.

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