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SYNTHESIS OF PERHYDRO-1,3-OXAZINE DERIVATIVES

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ABSTRACT. The results of the exhaustive literature investigations on the methods used in the synthesis of the perhydro-1,3-oxazine derivatives bearing different substituents are chritically presented.

INTRODUCTION

Despite the interest for the perhydro-1,3-oxazines (used in the synthesis of carbapenems - a new class of antibiotics) there are few papers about their synthesis.

The routes for the perhydro-1,3-oxazine derivatives synthesis are illustrated by the following scheme:

1.Direct reaction between γ-aminoalcohols and carbonyl compounds
- 1.1.Condensation of aldehydes
  - 1.1.1.Aliphatic aldehydes
  - 1.1.2.Aromatic aldehydes
- 1.2.Condensation of ketones

2. Reaction between carbonyl compounds and 1,3,2-oxazaborinanes
3. Reduction of dihydro-1,3-oxazine derivatives
4. Synthesis from isoxazolidines and isoxazolidinium salts
5. Other methods

DISCUSSION

1. Direct reaction between γ-aminoalcohols and carbonyl compounds

A likely mechanism for the formation of perhydro-1,3-oxazine derivatives is shown in Scheme 1 [1].

The condensation reaction of aminopropanol and carbonyl compound leads to the intermediate α,β-carbindiolamine ***I***, which can undergo cyclodehydration to the perhydro-1,3-oxazine ***III***, via the Schiff base ***II***.

The conditions used for the reaction of the carbonyl compounds with γ-aminoalcohols are quite different and correlated with the reactivity of the starting compounds and the stability of the reaction product.

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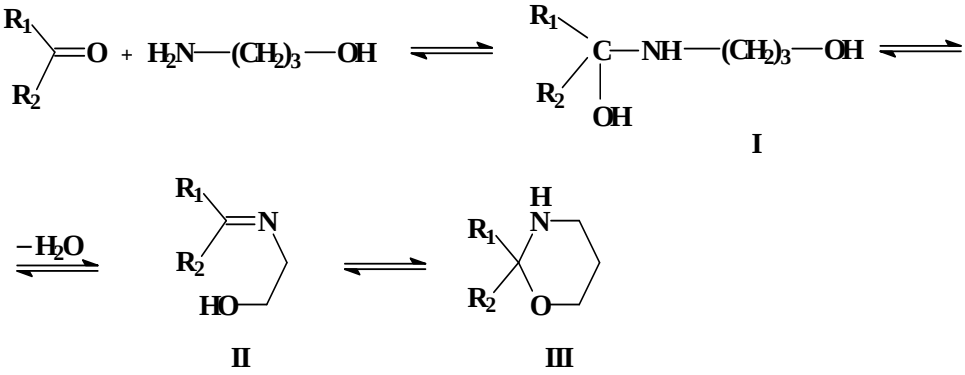
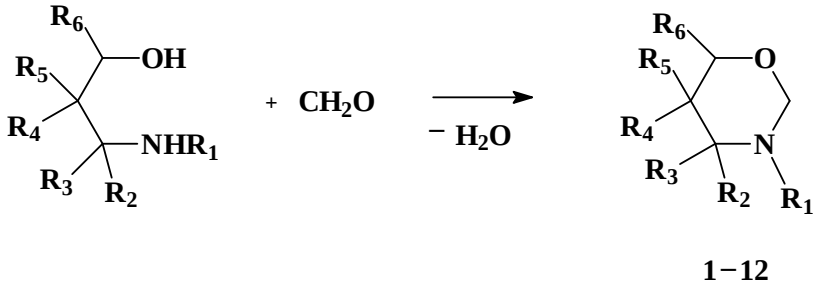


Scheme 1

1.1. Condensation of aldehydes

1.1.1. Aliphatic aldehydes

The condensation between CH_2O and γ-aminoalcohols was performed in different conditions depending on the structure of the used γ-aminoalcohol [Scheme 2;Tables 1 and 2]



Scheme 2

Table 1

Perhydro-1,3-oxazine derivatives obtained starting from formaldehyde

Compound	R_1	R_2	R_3	R_4	R_5	R_6
1	Me	H	H	H	H	H
2	Et	H	H	H	H	H
3	i-Pr	H	H	H	H	H
4	t-Bu	H	H	H	H	H
5	Me	Me	H	H	H	H
6	Et	Me	H	H	H	H
7	i-Pr	Me	H	H	H	H
8	Benzyl	H	H	H	H	H

Compound	R_1	R_2	R_3	R_4	R_5	R_6
9	Benzyl	Ph	H	H	H	H
10	Me	Me	H	Me	H	H
11	Benzyl	Me	H	Me	H	H
12	Me	Me	Me	H	H	Me

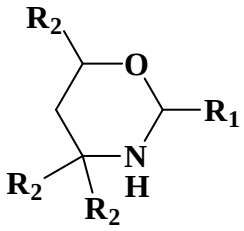
Table 2

Conditions used in the synthesis of compounds 1-12

Compounds	Solvent	Temp. ^{0}C	Yield %	Ref.
1-7	benzene	78	65-79	2, 3, 4
8-11	THF	20	45-92	5
12	water	20	35	6

The best results are obtained at room temperature, using tetrahydrofurane as solvent and N-phenyl- and N-cyclohexylamino propanols as starting materials.

The nature of the γ-aminoalcohol determines the choice of conditions used in reactions. Thus the compounds with unsubstituted nitrogen atom [Scheme 3] are obtained at room temperature, in anhydrous methanol [7] or CH_2Cl_2 [8] as solvent (in the last case, the water formed in the reaction is removed with anhydrous K_2CO_3).



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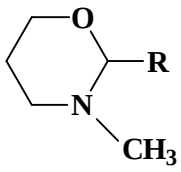
R_1 = CH_3 , CH_2CH_3 , CH_2Ph, CH_2OH

R_2 = H, CH_3

Scheme 3

The conditions used in the condensation reaction between N-substituted γ-aminoalcohols and aliphatic aldehydes are determinated by the volume of the N-alkyl substituent. The process for N-methyl substituted compounds [Scheme 4] can be performed without solvent, at room temperature (yields 36-59%) [2] or in water when higher yield (73% instead of 59%) [6] is obtained.



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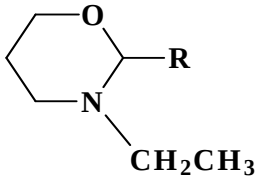
R = Me, Et, iPr, tBu

Scheme 4

The N-alkyl γ-aminoalcohols bearing ethyl or i-propyl groups react [Scheme 5] at room temperature, in diethyl ether under nitrogen atmosphere. The decreasing of the reactivity of carbonyl compound led to a decreasing of the yields.



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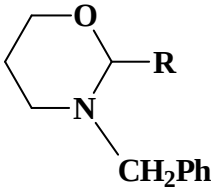
R = Me η = 89%
R = Et η = 46%
R = iPr η = 42%

Scheme 5

The steric effect of the alkylamino group determines the decreasing of the yield simultaneously with the increasing of the volume of the alkyl group [3].

The N-benzyl substituted compounds [Scheme 6] are obtained in toluene, at a temperature correlated with the reactivity of the carbonyl compound [9].



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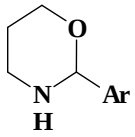
R = Me, Et, iPr, CH_2CH_2Ph, C_8H_{17}

Scheme 6

N-benzylaminopropanol and acetaldehyde (also propionaldehyde and butyraldehyde) react at room temperature. The water is remove using molecular sieves. The highest yield was obtained with the bulkyest aldehyde (the explanation being the better solvation in toluene). The carbonyl compounds with small reactivity react at the reflux of solvent in acidic conditions (para toluene sulphonic acid - PTSA; yields 91-94%).and the water resulted in the process is removed using a Dean-Stark trap.

1.1.2.Condensation of aromatic aldehydes

Aromatic aldehydes react with γ-aminoalcohols bearing a free amino group in anhydrous ethanol, at room temperature (yields 82-95%)[Scheme 7], [10-12].



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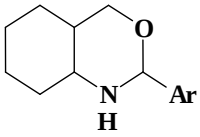

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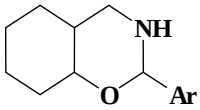

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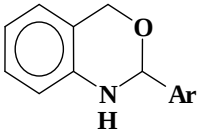

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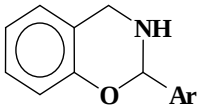

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Ar = C_6H_4X or 2 , 3, 4 – pyridyl

X = o, m, p – NO_2 , p – Cl, p – CH_3

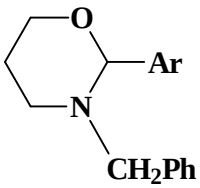
p– OCH_3 , p– NH_2 , p–$N(CH_3)_2$

Scheme 7

The reaction of nitrobenzaldehydes in anhydrous methanol revealed a decreasing of the yields in order o>m>p (93-86-60%) [7].

The N-alkyl aminopropanols (where the alkyl group can be methyl, ethyl, i-propyl) react with aromatic aldehydes in benzene or toluene, at the reflux of the solvent with the azeotropic removal of the water produced in the reaction. The yields (92-96%) are practically independent of the reactivity of the starting compounds [13].

For the series of N-benzyl derivatives **22** (obtained in toluene) yields of 91-98% are reported [9] [Scheme 8]



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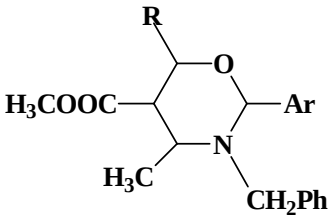
Ar = Ph, p–CH_3O–C_6H_4

Scheme 8

whereas the series of polysubstituted perhydro-3-benzyl-1,3-oxazines are obtained in benzene, in smaller yields (63%, chromatographic control) [14] [Scheme 9] using molecular sieves.



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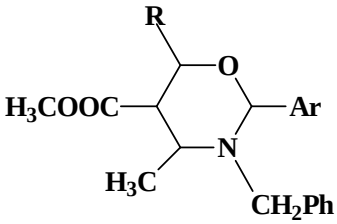
R = CH_3 , Ph

Ar = Ph, p– NO_2 – C_6H_4



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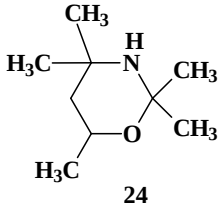
R = CH_3 , Ph

Ar = Ph, p– NO_2 – C_6H_4

Scheme 9

1.2.Condensation of ketones

Compound **24** derived from acetone was obtained at 65^{0}C, without solvent [15] [Scheme 10]



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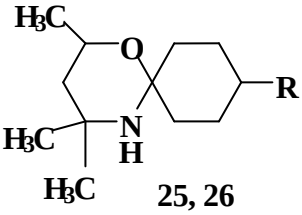
Scheme 10

The cyclic aliphatic ketones (cyclohexanone and derivatives) reacted with γ-aminoalcohols in benzene, at reflux [Scheme 11 and Table 3].

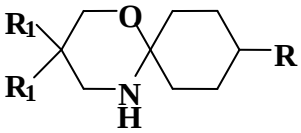
Table 3

Conditions used in the synthesis of spiro perhydro-1,3-oxazines

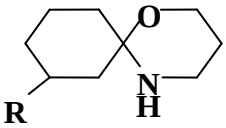
Compouns	Solvent	Temp ^{0}C	Yield %	Ref.
25, 26	-	65	-	15
27 - 34	Benzene	80		16
35 - 38	Benzene	80	-	15, 17, 18



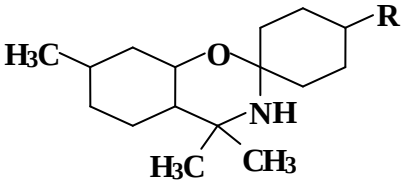
25, 26 R = H, tBu



27–34 R = H, Me, tBu, Ph; R_1 = H, Me



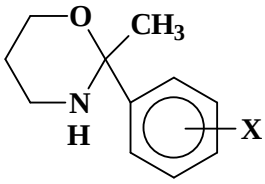
35, 36 R = H, Me



37, 38 R = H, tBu

Scheme 11

Acetophenone derivatives have been obtained in acidic conditions (PTSA), in toluene, at reflux [Scheme 12], [19, 20].



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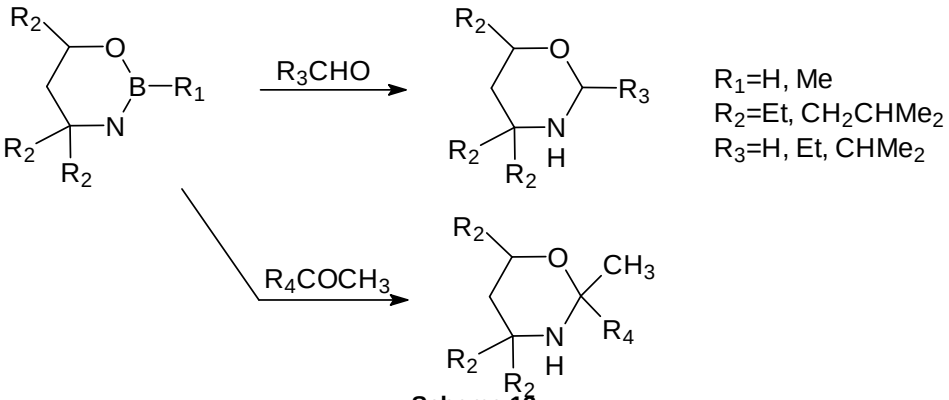
Scheme 12

2. Reaction between carbonyl compounds and 1,3,2-oxazaborinanes

The reaction of 1,3,2-oxazaborinanes with carbonyl compounds leads to perhydro-1,3-oxazine derivatives [Scheme 13], [21-23]



Scheme 13

The mechanism of the reaction involves transition structures obtained by the coordination of the carbonylic oxygen by boron or by the nucleophylic attack of the heterocyclic oxygen to the carbonylic carbon.

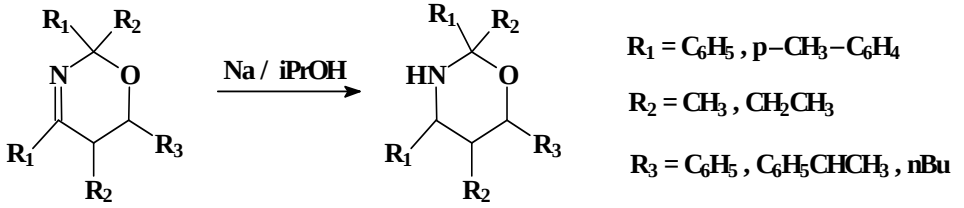
Different yield are reported for the reaction of ketones with 1,3,2-oxazaborinanes in different conditions: 83% in aqueous NaOH, 41% in the presence of $ZnCl_2$ and 30% without catalist.

1,3,2-Oxazaborinanes do not react with benzophenone and acetophenone.

3. Reduction of dihydro-1,3-oxazine derivatives

The reduction of dihydro-1,3-oxazine derivatives is performed in different conditions, depending on the position of the double bond.

5,6-Dihydro-2H-1,3-oxazine derivatives (obtained from 2-aza-1,3-dienes and aldehydes [24]) are reduced with Na/ i-PrOH, in tetrahydrofurane, at room temperature, in excelent yields (93-95%)[Scheme 14; 25]



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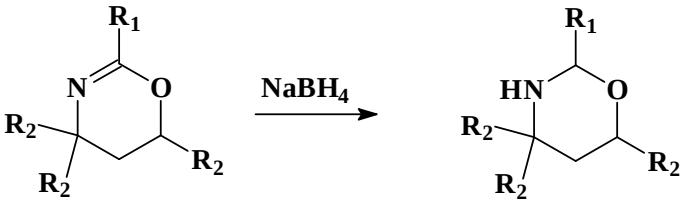
Scheme 14

The reduction with $LiAlH_4$ leads to γ-aminoalcohols by ring opening.

5,6-Dihydro-4H-1,3-oxazines (obtained from aldehydes and glycolonitril [26]) are reduced with $NaBH_4$ at low temperature (-45^0C)(yields 69-77%)[26-28; Scheme 15].



R_1 = H, Me , Ph

R_2 = H, Me

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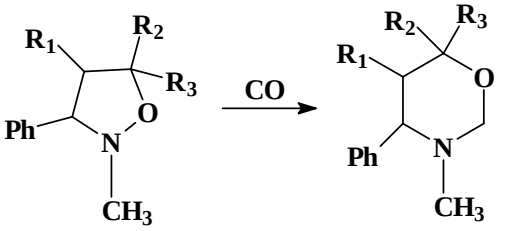
Scheme 15

4. Synthesis from isoxazolidines and isoxazolidinium salts

Isoxazolidines can react with CO, in catalitic conditions, to give perhydro-1,3-oxazines [Scheme 16; 29]



R_1 = $COOCH_3$, $COOC_2H_5$

R_2 , R_3 = alkyl, Ph

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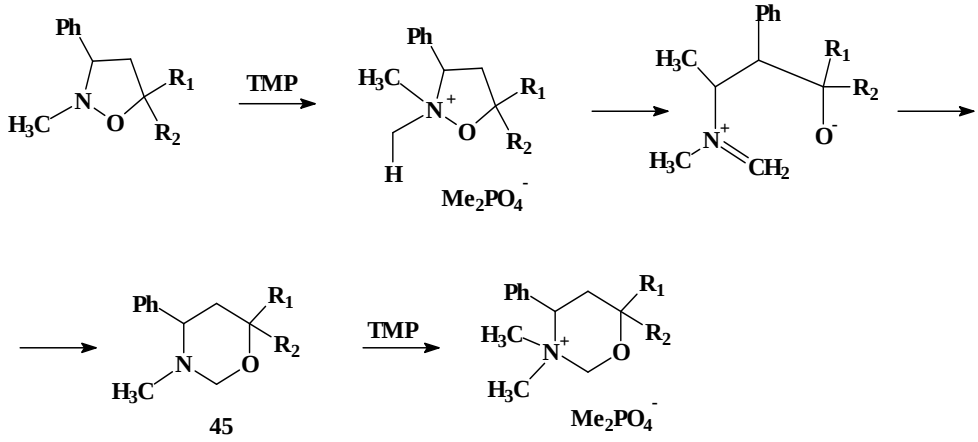
Scheme 16

The reaction is carried out in benzene, the catalists being Ir and Rh complexes.

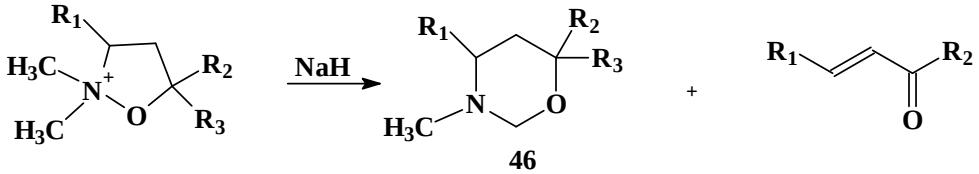
The reaction of isoxazolidines (available from nitrones and alkenes [30]) with trimethylphosphate arises into perhydro-1,3-oxazinium salts (yields 93-98%). The reaction proceeds under nitrogen, at 100^0C and follows a four steps mechanism [Scheme 17]:



Scheme 17

Perhydro-1,3-oxazinium salts are reduced with NaH in acceptable yields (44-56%).

Isoxazolidinium salts leads to perhydro-1,3-oxazines by reduction with NaH, in dimethoxyethane (yields 51-85%)[Scheme 18; 31].



$R_1 = C_6H_5$, $p-CH_3O-C_6H_4$

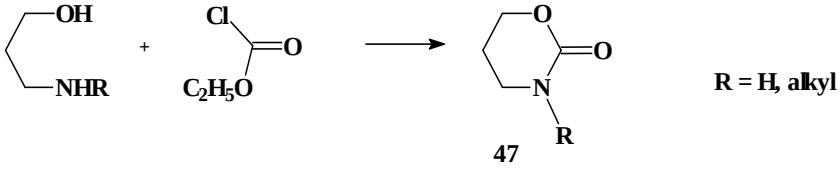
$R_2 = C_6H_5$, $p-CH_3-C_6H_4$, $p-CH_3O-C_6H_4$, $p-Cl-C_6H_4$

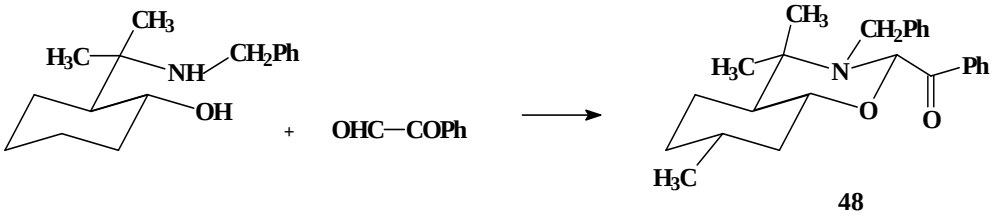
$R_3 = H, C_6H_5$

Scheme 18

The reaction proceeds probably by the attack of the base at the methyl connected to the nitrogen atom; the intermediate β-hydroxyiminic derivative can undergo cyclisation with ring expansion.
α,β-Enone has been obtained as minor product (formed by the extraction of the C(5) hydrogen followed by a Hofmann like reaction).
The reduction can proceed also in 10% aqueous NaOH (yield 52%) [31].

5. 2-Acyl perhydro-1,3-oxazine derivatives can be obtained from aminoalcohols and phenylglioxal (yield 85-91%) [26] or from aminopropanol and ethylchlorocarbonate (yield 77%) [32] [Scheme 19].





Scheme 19

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