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ENVIRONMENTALLY BENIGN SYNTHESIS OF NEW 1,3-OXAZOLIDINES AND AZOMETHYNES ON THE BASE OF ARYLAMINOPROPANOLS

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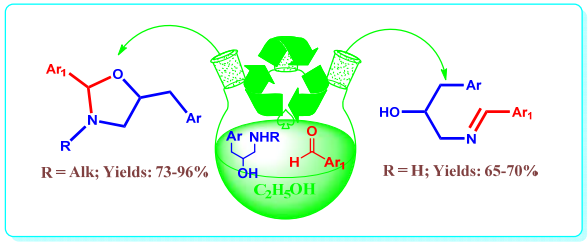
A series of condensation products were synthesized by treatment of some aryl-substituted 1,2-amino alcohols with various aromatic aldehydes in the catalyst-free medium in ethanol. The amino alcohols bearing NH group give rise to the 1,3-oxazolidines, while their NH_2 group holding analogs lead to the formation of Schiff bases. Some advantages of this protocol are a simple work-up procedure, short reaction time, mild conditions, and good to high yields.



INTRODUCTION

β-Amino alcohol unity is a common structural component in a range of biologically active natural and synthetic compounds such as antibiotics, alkaloids, enzyme inhibitors, and β-blockers.[1-5] Also, various chiral reagents utilize amino alcohols as ligands or chiral auxiliaries.[6,7] Therefore amino alcohols are one of the most essential molecules in medicinal and synthetic chemistry, a number of synthesis methods have been reviewed in the literature.[7-11] Functionalization of β-amino alcohol derivatives with various carbonyl compounds gives rise to the broad class of organic compounds such as amides, esters, enaminones, ureas, carbamates, aziridines, oxazolidines, oxazolines, oxazolidinones, oxazines, pyrroles, pyridones, morpholines, acridinones, and etc (Figure 1).[12-16]

1,3-Oxazolidine and Schiff bases, obtained by the condensation of β-amino alcohols with oxo compounds are a well-investigated topic in organic synthesis. Although to our best knowledge there are very rare reports about the short-time facile synthesis of these compounds in a catalyst-free environmentally benign medium.[17] In this context, herein we disclose our results in condensation of our previously obtained aryl-substituted β-amino alcohols with aromatic aldehydes.

EXPERIMENTAL

Materials and methods

General: All chemicals were of reagent grade and used without further purification. Melting points (mp's) were recorded on a Stuart SMP30 melting point apparatus using open capillaries and were uncorrected. NMR spectra were recorded at room temperature on a Bruker Avance II+ 300 (UltraShield^{TM} Magnet) spectrometer operating at 300.130 and 75.468 MHz for proton and carbon-13, respectively. All NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (Me_4Si) for ^1H and ^{13}C NMR spectra, with the residual solvent proton and carbon resonances used as internal standards. The following abbreviations are used to describe peak patterns: s = singlet, d = doublet, t = triplet, m = multiplet, d-d = doublet of doublets. Elemental analyses were performed using a Carlo Erba 1108 analyzer.

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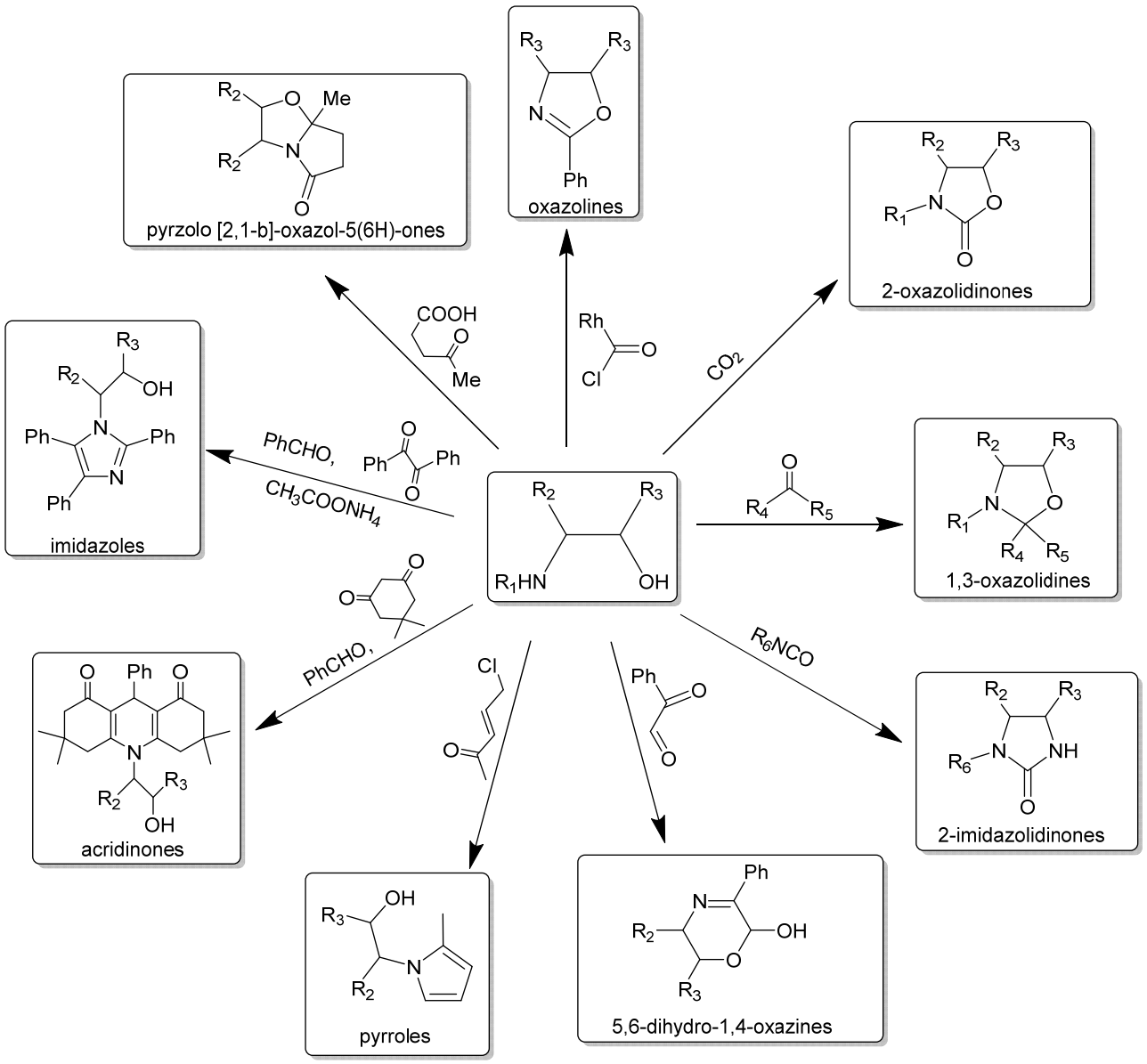


Fig. 1 – Functionalization of β-amino alcohols with carbonyl compounds.

Chemistry

General synthesis procedure of the 1,3-oxazolidines and Schiff bases: To the solution of 3 mmol of amino alcohol in 5 mL ethanol was added 3 mmol of aromatic aldehyde and vigorously stirred at 60-70^{0}C for 15 min. Only in the case of **6**, the reaction mixture was refluxed for 2 hours. Then the reaction mixture was cooled down. Reaction products were precipitated from reaction mixture, collected by filtration and was recrystallized in ethanol. The yellow oiliest product **4** was purified by column chromatography over silica gel and eluted with hexane: 2-propanol (60:40, v/v).

1-Mesityl-3-((4-nitrobenzylidene)amino)propan-2-ol **(1)***:* Yield 65%; Mp 117-119^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.26 (s, 3H, CH_3), 2.34 (s, 6H, $2CH_3$), 2.95 (m, 2H, CH_2Ar), 3.75-3.85 (d-d, 2H, CH_2N), 4.21 (m, 1H, CH-O), 6.89-8.30 (6H, Ar), 8.45 (s, 1H, CH-=N); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.09 ($2CH_3$-Ar), 22.17 (CH_3-Ar), 35.33 (CH_2-Ar), 66.19 (CH_2-N), 72.34 (CH_2-O), 118.16($2CH_{arom}$), 128.18 ($2CH_{arom}$), 129.16 ($2CH_{arom}$), 132.07 (C_{arom}), 136.25 (C_{arom}), 138.44 ($2C_{arom}$), 142.27(C_{arom}), 148.95 (C_{arom}), 161.07 (CH-=N); Anal. Calcd for: $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58; Found: C, 69.77; H, 6.65, N, 8.71.

4-Bromo-2-(((2-hydroxy-3-mesitylpropyl)imino)methyl)phenol **(2)***:* Yield 70%; Mp 122-124^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.25 (s, 3H, CH_3), 2.39 (s, 6H, $2CH_3$), 2.95 (m, 2H, CH_2Ar), 3.65-3.85 (d-d, 2H, CH_2N), 4.15 (m, 1H, CH-O), 6.83-7.45 (5H, Ar), 8.35 (s, 1H, CH-=N), 13.35 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.08 ($2CH_3$-Ar), 22.19 (CH_3-Ar), 35.30 (CH_2-Ar), 65.21 (CH_2-N), 72.40 (CH-O), 110.09 (C_{arom}) 118.19(CH_{arom}), 120.06 (C_{arom}), 129.22($2CH_{arom}$), 132.13 (C_{arom}), 134.15(CH_{arom}), 136.22 (CH_{arom}), 136.27 (C_{arom}), 137.09 (C_{arom}), 160.11 (C_{arom}), 166.09(CH=N); Anal. Calcd for: $C_{19}H_{22}BrNO_2$: C, 60.65; H, 5.89; N, 3.72; Found: C, 60.52; H, 5.68, N, 3.84.

4-Bromo-2-(3-methyl-5-(2,4,6-trimethylbenzyl)oxazolidin-2-yl)phenol **(3)***:* Yield 86%; Mp 115-116^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.22 (s, 3H, CH_3), 2.27 (s, 3H, CH_3),

2.31 (s, 6H, $2CH_3$), 2.34 (s, 6H, $2CH_3$), 2.43 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.52 (t, 1H, CH_2N), 2.75 (t, 1H, CH_2N), 2.95 (m, 2H, CH_2Ar), 3.10 (m, 2H, CH_2Ar), 3.23 (d-d, 1H, CH_2N), 3.51 (d-d, 1H, CH_2N), 4.45 (m, 2H, 2CH-O), 4.75 (s, 1H, CH), 4.82 (s, 1H, CH), 6.70-7.41 (10H, Ar), 11.4 (s, 2H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.85 ($2CH_3$), 26.89 ($2CH_3$), 26.90 (CH_3), 26.91 (CH_3), 39.91 (CH_2-Ar), 41.76 (CH_2-Ar), 44.71 (CH_3-N), 44.72 (CH_3-N), 64.03 (CH_2-N), 66.11 (CH_2-N), 82.07 (CH-O), 83.12 (CH-O), 104.03 (O-CH-N), 105.09 (O-CH-N), 117.52 (C_{arom}), 124.31 (CH_{arom}), 124.50 (CH_{arom}), 127.33 (C_{arom}), 128.01 (C_{arom}), 136.98 (CH_{arom}), 137.07 (CH_{arom}), 137.45 (C_{arom}), 139.05 (CH_{arom}), 139.09 (CH_{arom}), 142.82 (C_{arom}), 143.05 (C_{arom}), 163.19 (C_{arom}); Anal. Calcd for: $C_{20}H_{24}BrNO_2$: C, 61.54; H, 6.20; N, 3.59; Found: C, 61.39; H, 6.03, N, 3.71.

***3-Methyl-2-(4-nitrophenyl)-5-(2,4,6-trimethylbenzyl)oxazolidine* (4)**: Yield 74%; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.23 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.43 (s, 6H, $2CH_3$), 2.44 (s, 6H, $2CH_3$), 2.49 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.60 (t, 1H, CH_2N), 2.75 (t, 1H, CH_2N), 3.00 (d-d, 1H, CH_2N), 3.50 (d-d, 1H, CH_2N), 3.1 (m, 4H, $2CH_2Ar$), 4.45 (m, 1H, 1CH-O), 4.62 (m, 1H, 1CH-O), 4.75 (s, 1H, CH), 4.87 (s, 1H, CH), 6.70-8.40 (12H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.10 ($4CH_3$), 20.3 ($2CH_3$), 20.6 ($2CH_3$-N), 34.07 (CH_2-Ar), 35.11 (CH_2-Ar), 37.09 (CH_3-N), 38.23 (CH_3-N), 58.25 (CH_2-N), 62.19 (CH_2-N), 77.65 (CH-O) , 78.49 (CH-O), 97.36 (O-CH-N), 98.27 (O-CH-N), 124.41 (CH_{arom}), 125.01 (C_{arom}), 127.75 (C_{arom}), 129.86 (CH_{arom}), 129.95 (CH_{arom}), 130.09 (C_{arom}), 132.56 (C_{arom}), 136.45 (C_{arom}), 137.22 (C_{arom}), 147.39 (C_{arom}), 148.45(C_{arom}); Anal. Calcd for: $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23; Found: C, 70.40; H, 7.25, N, 8.37.

***2-(3-Benzyl-2-(2,4,6-trimethylbenzyl)oxazolidin-5-yl)-4-bromophenol* (5):** Yield 96%; Mp 133-134^{0}C; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.15 (s, 2H, CH_3), 2.25 (s, 6H, $2CH_3$), 2.45-3.30 (m, 4H, CH_2N, CH_2Ar), 3.95 (s, 2H, NCH_2Ar), 4.45 (m, 1H, CHO), 5.10 (s, 1H, CH), 6.70-7.40 (10H, Ar), 11.20 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.09 ($2CH_3$), 22.06 (CH_3), 34.29 (CH_3-Ar), 56.75 (CH_2-N), 57.22 ($2CH_2$-Ar), 78.35 (CH-O), 97.42 (O-CH-N), 115.3 (C_{arom}), 118.77 (CH_{arom}), 122.56 (C_{arom}), 127.65 (CH_{arom}), 128.24 (CH_{arom}), 127.31 (CH_{arom}), 127.40 (CH_{arom}), 131.55 (C_{arom}), 132.05 (C_{arom}), 133.24 (CH_{arom}), 134.01 (CH_{arom}), 135.99 (C_{arom}), 137.25 (C_{arom}), 157.35 (C_{arom}); Anal. Calcd for: $C_{26}H_{28}BrNO_2$: C, 66.95; H, 6.05; N, 3.00; Found: C, 66.72; H, 5.89, N, 3.21.

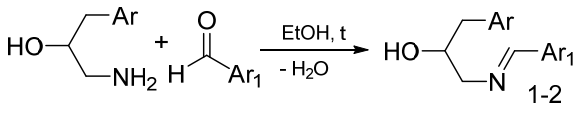
***4-Bromo-2-(3-(tert-butyl)-5-(2,4,6-trimethylbenzyl)oxazolidin-2-yl)phenol* (6):** Yield 73%; Mp 167-169^{0}C; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15 (s, 9H, $3CH_3$), 2.21 (s, 3H, CH_3), 2.23 (s, 6H, $2CH_3$), 2.72-3.23 (m, 4H, CH_2N, CH_2Ar), 4.30 (m, 1H, CHO), 5.60 (s, 1H, CH), 6.60-7.30 (5H, Ar), 13.00 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.88 (CH_3), 21.21(CH_3), 28.09 (CH_3), 33.14 (CH_2-Ar), 52.43 (CH_2-N), 54.65 (C_{arom}), 78.33 (CH-O), 91.15 (O-CH-N), 111.13 (C_{arom}), 118.86 (CH_{arom}), 125.94 (C_{arom}), 128.75 (CH_{arom}), 132.86 (C_{arom}), 133.14 (CH_{arom}), 134.42 (CH_{arom}), 136.51 (C_{arom}), 137.05 (C_{arom}), 158.36 (C_{arom}); Anal. Calcd for: $C_{23}H_{30}BrNO_2$: C, 63.89; H, 6.99; N, 3.24; Found: C, 63.68; H, 6.71, N, 3.38.

***4-Bromo-2-(5-(2,5-dimethylbenzyl)-3-methyloxazolidin-2-yl)phenol* (7):** Yield 80%; Mp 68-70^{0}C; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.15 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3N), 2.41 (s, 3H, CH_3N), 2.48 (t, 1H, CH_2N), 2.75 (t, 1H, CH_2N), 2.76-3.10 (m, 4H, $2CH_2Ar$), 3.22 (d-d, 1H, CH_2N), 3.45 (d-d, 1H, CH_2N), 4.45 (m, 1H, CH-O), 4.56 (m, 1H, CH-O), 4.85 (s, 2H, 2CH), 6.74-7.40 (m, 12H, Ar), 11.3 (s, 2H, 2OH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 17.25 (CH_3), 18.33 (CH_3), 18.34 (CH_3), 22.05 (CH_3), 37.45 (CH_2-Ar), 37.49 (CH_2-Ar), 38.57 (CH_3-N), 38.58 (CH_3-N), 57.33 (CH_2-N), 59.07 (CH_2-N), 77.22 (CH-O), 78.31 (CH-O), 98.22 (O-CH-N), 99.01 (O-CH-N), 111.09 (C_{arom}), 118.42 (CH_{arom}), 122.34 (C_{arom}), 127.75 (CH_{arom}), 127.78 (CH_{arom}), 130.04 (CH_{arom}), 132.34 (CH_{arom}), 133.16 (CH_{arom}), 135.22 (C_{arom}), 136.34 (C_{arom}), 156.87 (C_{arom}), 156.89 (C_{arom}); Anal. Calcd for: $C_{19}H_{22}BrNO_2$: C, 60.65; H, 5.89; N, 3.72; Found: C, 60.43; H, 5.64, N, 3.87.

RESULTS AND DISCUSSION

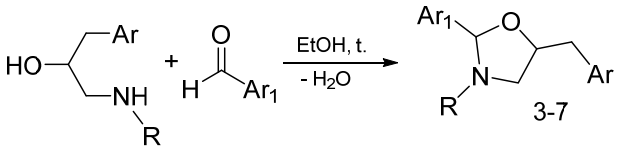
Our previous studies on the synthesis of amino alcohols and exploring their utility in two-component, as well as multi-component synthesis, have been reported earlier.[16,18] In the context of our studies, herein, we have described the green synthesis of novel Schiff bases and 1,3-oxazolidines on the base of racemic 1,2-amino alcohols. There are plenty of works in this field using hazardous solvents, strong acids, hypervalent iodine reagents under conventional heating or microwave irradiation conditions.[19-22] Therefore, environmentally benign chemical methods have received considerable growing attention in recent years.[23-25] The employment of green chemistry techniques efficiently minimizes the generation of hazardous substances. Consequently, we tried to employ an eco-friendly, facile, cost- and time-effective synthetic procedure that allowed us a quick synthesis of new Schiff bases from 1-amino-3-mesitylpropan-2-ol (Scheme 1).

Under a similar reaction condition, β-amino alcohols containing a secondary amine group lead to the formation of 1,3-oxazolidines with good yields. In the case of **6** (R= *tert*-butyl), reaction time took 2 hours under reflux condition, probably due to steric hindrance of the bulky alkyl group (Scheme 2).



Ar = 1,3,5-trimethylphenyl; Ar1= 4-nitrophenyl (1), 5-bromo-2-hydroxyphenyl (2).

Scheme 1 – Synthesis of Schiff bases.



R = Methyl; Ar = 1,3,5-trimethylphenyl ; Ar_1 = 5-bromo-2-hydroxyphenyl (3);
R = Methyl; Ar = 1,3,5-trimethylphenyl ; Ar_1 = 4-nitrophenyl (4);
R = Benzyl; Ar = 1,3,5-trimethylphenyl ; Ar_1 = 5-bromo-2-hydroxyphenyl (5);
R = tert-Butyl; Ar = 1,3,5-trimethylphenyl ; Ar_1 = 5-bromo-2-hydroxyphenyl (6);
R = Methyl; Ar = 2,5-dimethylphenyl ; Ar_1 = 5-bromo-2-hydroxyphenyl (7);

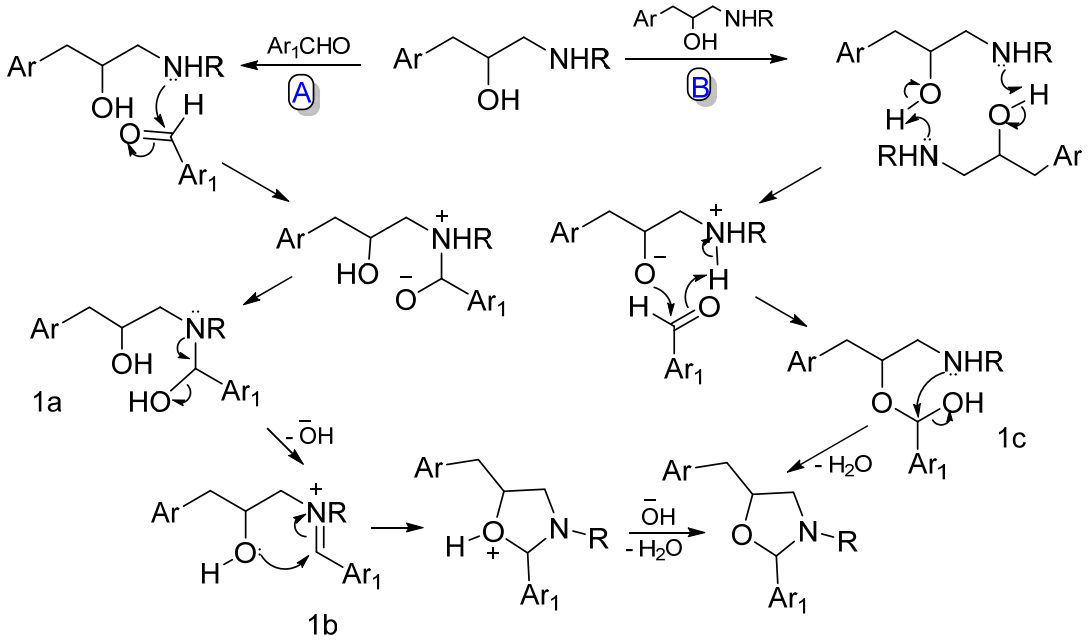
Scheme 2 – Synthesis of 1,3-oxazolidines.

Only in the case of aromatic substituents (R = phenyl, 4-bromophenyl) at the secondary amine group, all efforts to reach corresponding 1,3-oxazolidines, unfortunately, were unsuccessful, obviously due to poor nucleophilicity of secondary amine. On the other hand, in the case of bulky groups at the amine group (R=tert-butyl, benzyl) the reaction occurred stereoselectively, wherein in the case of small substituents (R=CH_3) have been formed mixture of 1,3-oxazolidine diastereoisomers in a 1:1 ratio.

The structures of N-unsubstituted 1,3-oxazolidines can be characterized by three-component tautomeric equilibria (ring^{cis}-open-ring^{trans}) of the cyclic and the corresponding Schiff base open-chain forms.[17] But in this case, we did not observe the appearance of characteristic chemical shifts of cationic Schiff base imine proton **1b** and ring-opened intermediate **1a** (Scheme 3), well-reported in the literature.[17,26] Also, some signals (mainly aromatic signals) were overlapped for the diastereomeric mixtures in the NMR spectra, like in a similar precedent reported in the literature.[27,28]

Finally, a plausible mechanism for the formation of 1,3-oxazolidines from β-amino alcohols has been proposed and illustrated in **Scheme 3**. It has been proposed that nucleophilic addition of a primary amine to the carbonyl group of an aromatic aldehyde generates an intermediate **1a**, which in turn undergoes dehydration to deliver oxazolidine ring (Path A).

As well, an attraction of the alcoholic proton from amino alcohol molecule by the nitrogen atom of another counterpart could also allow the oxygen to attack in a nucleophilic manner to lead to another intermediate **1c**, which also undergoes dehydration to deliver the desired product (Path B). Our further efforts are focused on optimizing and studying the influence of the nature of substituents on the stereochemistry of these reactions.



Scheme 3 – Proposed mechanism for the formation of 1,3-oxazolidines.

CONCLUSION

In conclusion we have performed an efficient and simple green synthesis of Schiff bases and oxazolidine derivatives in catalyst free medium. This approach has several advantages such as simplified workup procedures, mild conditions, and good yields of reaction products.

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