

Condensation of oxazolidines with 2-hydroxybenzaldehydes

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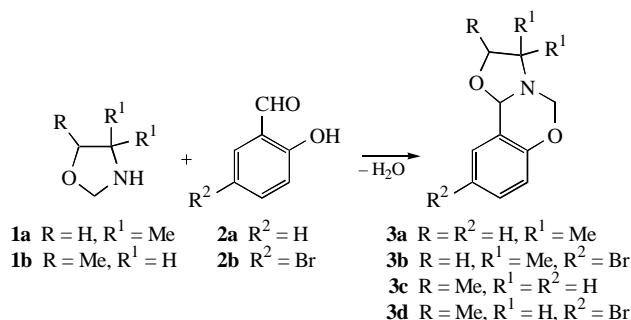
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10.1070/MC2001v011n04ABEH001467

The reaction of N-unsubstituted oxazolidines with 2-hydroxybenzaldehydes resulted in 2,3,5,10*b*-tetrahydrooxazole[3,2-*c*][1,3]-benzoxazines.

It is known that cyclic O,N-acetal derivatives, oxazolidines, can be involved in the exchange reaction with aldehydes to give new oxazolidines and aldehydes.¹ Reactions of oxazolidines with phenols result in *N*-(2-hydroxyethyl)aminomethylphenols.² Reactions of *N*-unsubstituted oxazolidines with aldehydes containing phenyl hydroxyl groups have not been investigated.

We found that salicylic and 5-bromosalicylic aldehydes react with 4,4-dimethyl- and 5-methyloxazolidines to give 2,3,5,10b-tetrahydrooxazole[3,2-c][1,3]benzoxazine derivatives **3a–d**.



Scheme 1

The reaction took place under reflux of an equimolecular mixture of an oxazolidine and a corresponding aldehyde in benzene followed by the azeotropic distillation of water.[†]

An attempt to involve the simplest oxazolidine in the reaction

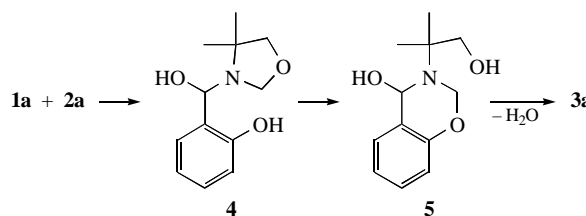
† A mixture of oxazolidine **1a,b** (0.1 mol), aldehyde **2a,b** (0.1 mol) and benzene (100 ml) was refluxed with a Dean-Stark condenser trap until water isolation was ceased. The mixture was distilled in a vacuum to give 2,3,5,10*b*-tetrahydrooxazole[3,2-*c*][1,3]benzoxazines **3a-d**.

¹H NMR spectra were measured at 400.13 MHz in CDCl₃ solution, standard TMS.

3a: yield 59%, bp 129–131 °C (6 torr), n_D^{20} 1.5466, d_4^{20} 1.1132. ^1H NMR, δ : 1.24 (s, 3H, Me), 1.31 (s, 3H, Me), 3.67 (d, 1H, $\text{OCH}_2\text{A}_\text{H}_\text{B}$, $^2J_{\text{AB}}$ 7.8 Hz), 3.71 (d, 1H, $\text{OCH}_2\text{H}_\text{B}$, $^2J_{\text{AB}}$ 7.8 Hz), 4.85 (d, 1H, $\text{NCH}_2\text{A}_\text{H}_\text{B}$, $^2J_{\text{AB}}$ 11.0 Hz), 4.93 (d, 1H, $\text{NCH}_2\text{H}_\text{B}$, $^2J_{\text{AB}}$ 11.0 Hz), 5.87 (s, 1H, OCHN), 6.78 (dd, 1H, 7-HC, $^3J_{7-8}$ 8.2 Hz, $^4J_{7-9}$ 1.1 Hz), 6.94 (ddd, 1H, 9-HC, $^3J_{8-9}$ 7.4 Hz, $^3J_{9-10}$ 7.6 Hz, $^4J_{7-9}$ 1.1 Hz), 7.17 (ddd, 1H, 8-HC, $^3J_{7-8}$ 8.2 Hz, $^3J_{8-9}$ 7.4 Hz, $^4J_{8-10}$ 1.7 Hz), 7.26 (dd, 1H, 10-HC, $^3J_{9-10}$ 7.6 Hz, $^4J_{8-10}$ 1.7 Hz). Found (%): C, 70.03; H, 7.51; N, 6.53. Calc. for $\text{C}_{17}\text{H}_{15}\text{NO}_7$ (%): C, 70.22; H, 7.37; N, 6.82.

3b: yield 65%, bp 170–172 °C (3 torr), mp 43–44 °C. ¹H NMR, δ: 1.22 (s, 3H, Me), 1.27 (s, 3H, Me), 3.66 (d, 1H, OCH_AH_B, ²J_{AB} 7.9 Hz), 3.71 (d, 1H, OCH_AH_B, ²J_{AB} 7.9 Hz), 4.87 (d, 1H, NCH_AH_B, ²J_{AB} 11.3 Hz), 4.91 (d, 1H, NCH_AH_B, ²J_{AB} 11.3 Hz), 5.83 (s, 1H, OCHN), 6.64 (d, 1H, 7-HC, ³J₇₋₈ 8.8 Hz), 7.25 (dd, 1H, 8-HC, ⁴J₈₋₁₀ 2.4 Hz, ³J₇₋₈ 8.8 Hz), 7.37 (d, 1H, 10-HC, ⁴J₈₋₁₀ 2.4 Hz). Found (%): C, 50.94; H, 5.06; Br, 28.03; N, 4.77. Calc. for C₁₀H₈BrNO₂ (%): C, 50.72; H, 4.97; Br, 28.12; N, 4.93.

3c: yield 67%, bp 120–123 °C (4 torr), η_D^{20} 1.5465, d_4^{20} 1.1335. $^1\text{H NMR}$, δ : (major) 1.28 (d, 3H, Me, 3J 6.1 Hz), 2.88 (dd, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 9.6 Hz, $^3J_{AX}$ 6.8 Hz), 3.40 (dd, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 9.6 Hz, $^3J_{BX}$ 7.0 Hz), 4.11 (m, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X\text{Me}$), 4.74 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 9.7 Hz), 4.82 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 9.7 Hz), 5.75 (s, 1H, OCHN), 6.82 (m, 1H, 7-HC), 6.95 (m, 1H, 9-HC), 7.18 (m, 1H, 8-HC), 7.27 (m, 1H, 10-HC); (minor): 1.22 (d, 3H, Me, 3J 6.1 Hz), 2.80 (t, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 8.9 Hz, $^3J_{AX}$ 8.9 Hz), 3.32 (dd, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 8.9 Hz, $^3J_{BX}$ 5.9 Hz), 4.28 (m, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X\text{Me}$), 4.71 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 9.6 Hz), 4.76 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 9.6 Hz), 5.61 (s, 1H, OCHN), 6.82 (m, 1H, 7-HC), 6.95 (m, 1H, 9-HC), 7.18 (m, 1H, 8-HC), 7.27 (m, 1H, 10-HC). Found (%) C, 69.17; H, 6.97; N, 7.11. Calc. for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ (%): C, 69.09; H, 6.85; N, 7.32.



Scheme 2

was unsuccessful. Probably, this was due to the high rate of oxazolidine trimerization to stable *N,N',N''*-tris(2-hydroxyethyl)-perhydro-1,3,5-triazine.³

It is likely that oxazolidine, which is a typical secondary amine, forms semi-acetal **4** at the first stage; then, the oxazolidine ring is decomposed with a phenyl hydroxyl group to give benzoxazine **5**, which transforms to oxazolobenzoxazine **3** (Scheme 2).

The structure of the compounds obtained was confirmed by ^1H NMR spectroscopy and elemental analysis.

Compounds **3c** and **3d** (mixtures of diastereomers) were obtained when oxazolidine **1b** having an asymmetric carbon atom was involved in the reaction. In ^1H NMR spectra, the proton signals of both the methyl groups and the OCNH fragment of the oxazolidine ring of a minor isomer were upfield shifted in comparison with those in the major isomer. The ratio between diastereomers calculated from the integral intensity of the proton signals was approximately 1:1.1 for compounds **3c** and **3d**.

References

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Received: 27th April 2001; Com. 01/1793

3d: yield 57%, bp 158–160 °C (3 torr), mp 61–62 °C. ^1H NMR, δ : (major): 1.27 (d, 3H, Me, 3J 6.2 Hz), 2.85 (dd, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 9.5 Hz, $^3J_{AX}$ 6.5 Hz), 3.36 (dd, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 9.5 Hz, $^3J_{BX}$ 7.0 Hz), 4.09 (m, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X\text{Me}$), 4.76 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 10.2 Hz), 4.81 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 10.2 Hz), 5.72 (s, 1H, OCHN), 6.67 (d, 1H, 7- HC , $^3J_{7-8}$ 8.9 Hz), 7.24 (dd, 1H, 8- HC , $^4J_{8-10}$ 1.8 Hz, $^3J_{7-8}$ 8.9 Hz), 7.37 (d, 1H, 10- HC , $^4J_{8-10}$ 1.8 Hz); (minor): 1.20 (d, 3H, Me, 3J 6.2 Hz), 2.79 (dd, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 8.9 Hz, $^3J_{AX}$ 8.5 Hz), 3.29 (dd, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X$, $^2J_{AB}$ 8.9 Hz, $^3J_{BX}$ 5.6 Hz), 4.29 (m, 1H, $\text{NCH}_A\text{H}_B\text{CH}_X\text{Me}$), 4.73 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 9.9 Hz), 4.75 (d, 1H, $\text{NCH}_A\text{H}_B\text{O}$, $^2J_{AB}$ 9.9 Hz), 5.61 (s, 1H, OCHN), 6.70 (d, 1H, 7- HC , $^3J_{7-8}$ 8.9 Hz), 7.24 (dd, 1H, 8- HC , $^4J_{8-10}$ 1.8 Hz, $^3J_{7-8}$ 8.9 Hz), 7.38 (d, 1H, 10- HC , $^4J_{8-10}$ 1.8 Hz). Found (%): C, 48.74; H, 4.59; Br, 29.17; N, 5.02. Calc. for $\text{C}_{11}\text{H}_{11}\text{BrNO}$: (C, 48.91; H, 4.48; Br, 29.58; N, 5.19).