

Condensation of oxazolidines with 2-hydroxybenzaldehydes

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

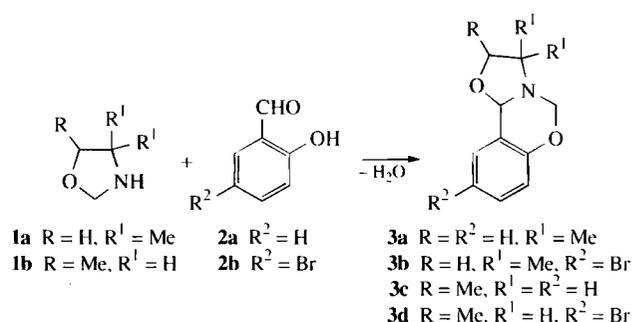
It is known that cyclic O,N-acetal derivatives, oxazolidines, can be involved in the exchange reaction with aldehydes to give new oxazolidines and aldehydes.¹ Reactions of oxazolidines with phenols result in *N*-(2-hydroxyethyl)aminomethylphenols.² Reactions of N-unsubstituted oxazolidines with aldehydes 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 2,3,5,10*b*-tetrahydrooxazole[3,2-*c*][1,3]benzoxazine derivatives **3a–d**.

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 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

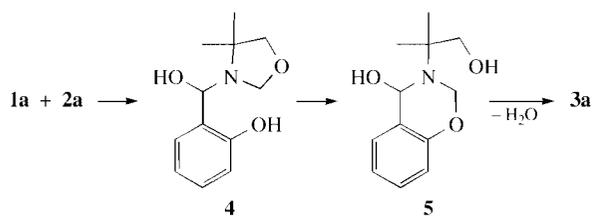
It is likely that oxazolidine, which is a typical secondary amine, forms semi-acetal **4** at the first stage; then, the oxazolidine ring



Scheme 1

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.



Scheme 2

* 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, OCH_AH_B, ²*J*_{AB} 7.8 Hz), 3.71 (d, 1H, OCH_AH_B, ²*J*_{AB} 7.8 Hz), 4.85 (d, 1H, NCH_AH_B, ²*J*_{AB} 11.0 Hz), 4.93 (d, 1H, NCH_AH_B, ²*J*_{AB} 11.0 Hz), 5.87 (s, 1H, OCHN), 6.78 (dd, 1H, 7-HC, ³*J*₇₋₈ 8.2 Hz, ⁴*J*₇₋₉ 1.1 Hz), 6.94 (ddd, 1H, 9-HC, ³*J*₈₋₉ 7.4 Hz, ³*J*₉₋₁₀ 7.6 Hz, ⁴*J*₇₋₉ 1.1 Hz), 7.17 (ddd, 1H, 8-HC, ³*J*₇₋₈ 8.2 Hz, ³*J*₈₋₉ 7.4 Hz, ⁴*J*₈₋₁₀ 1.7 Hz), 7.26 (dd, 1H, 10-HC, ³*J*₉₋₁₀ 7.6 Hz, ⁴*J*₈₋₁₀ 1.7 Hz). Found (%): C, 70.03; H, 7.51; N, 6.53. Calc. for C₁₂H₁₅NO₂ (%): 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, ²*J*_{AB} 7.9 Hz), 3.71 (d, 1H, OCH_AH_B, ²*J*_{AB} 7.9 Hz), 4.87 (d, 1H, NCH_AH_B, ²*J*_{AB} 11.3 Hz), 4.91 (d, 1H, NCH_AH_B, ²*J*_{AB} 11.3 Hz), 5.83 (s, 1H, OCHN), 6.64 (d, 1H, 7-HC, ³*J*₇₋₈ 8.8 Hz), 7.25 (dd, 1H, 8-HC, ⁴*J*₈₋₁₀ 2.4 Hz, ³*J*₇₋₈ 8.8 Hz), 7.37 (d, 1H, 10-HC, ⁴*J*₈₋₁₀ 2.4 Hz). Found (%): C, 50.94; H, 5.06; Br, 28.03; N, 4.77. Calc. for C₁₅H₁₄BrNO₂ (%): C, 50.72; H, 4.97; Br, 28.12; N, 4.93.

3c: yield 67%, bp 120–123 °C (4 torr), n_D^{20} 1.5465, d_4^{20} 1.1335. ¹H NMR, δ : (major) 1.28 (d, 3H, Me, ³*J* 6.1 Hz), 2.88 (dd, 1H, NCH_AH_BCH_X, ²*J*_{AB} 9.6 Hz, ³*J*_{AX} 6.8 Hz), 3.40 (dd, 1H, NCH_AH_BCH_X, ²*J*_{AB} 9.6 Hz, ³*J*_{BX} 7.0 Hz), 4.11 (m, 1H, NCH_AH_BCH_XMe), 4.74 (d, 1H, NCH_AH_BO, ²*J*_{AB} 9.7 Hz), 4.82 (d, 1H, NCH_AH_BO, ²*J*_{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, ³*J* 6.1 Hz), 2.80 (t, 1H, NCH_AH_BCH_X, ²*J*_{AB} 8.9 Hz, ³*J*_{AX} 8.9 Hz), 3.32 (dd, 1H, NCH_AH_BCH_X, ²*J*_{AB} 8.9 Hz, ³*J*_{BX} 5.9 Hz), 4.28 (m, 1H, NCH_AH_BCH_XMe), 4.71 (d, 1H, NCH_AH_BO, ²*J*_{AB} 9.6 Hz), 4.76 (d, 1H, NCH_AH_BO, ²*J*_{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 C₁₁H₁₃NO₂ (%): C, 69.09; H, 6.85; N, 7.32.

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**.

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3d: yield 57%, bp 158–160 °C (3 torr), mp 61–62 °C. ¹H NMR, δ : (major) 1.27 (d, 3H, Me, ³*J* 6.2 Hz), 2.85 (dd, 1H, NCH_AH_BCH_X, ²*J*_{AB} 9.5 Hz, ³*J*_{AX} 6.5 Hz), 3.36 (dd, 1H, NCH_AH_BCH_X, ²*J*_{AB} 9.5 Hz, ³*J*_{BX} 7.0 Hz), 4.09 (m, 1H, NCH_AH_BCH_XMe), 4.76 (d, 1H, NCH_AH_BO, ²*J*_{AB} 10.2 Hz), 4.81 (d, 1H, NCH_AH_BO, ²*J*_{AB} 10.2 Hz), 5.72 (s, 1H, OCHN), 6.67 (d, 1H, 7-HC, ³*J*₇₋₈ 8.9 Hz), 7.24 (dd, 1H, 8-HC, ⁴*J*₈₋₁₀ 1.8 Hz, ³*J*₇₋₈ 8.9 Hz), 7.37 (d, 1H, 10-HC, ⁴*J*₈₋₁₀ 1.8 Hz); (minor): 1.20 (d, 3H, Me, ³*J* 6.2 Hz), 2.79 (dd, 1H, NCH_AH_BCH_X, ²*J*_{AB} 8.9 Hz, ³*J*_{AX} 8.5 Hz), 3.29 (dd, 1H, NCH_AH_BCH_X, ²*J*_{AB} 8.9 Hz, ³*J*_{BX} 5.6 Hz), 4.29 (m, 1H, NCH_AH_BCH_XMe), 4.73 (d, 1H, NCH_AH_BO, ²*J*_{AB} 9.9 Hz), 4.75 (d, 1H, NCH_AH_BO, ²*J*_{AB} 9.9 Hz), 5.61 (s, 1H, OCHN), 6.70 (d, 1H, 7-HC, ³*J*₇₋₈ 8.9 Hz), 7.24 (dd, 1H, 8-HC, ⁴*J*₈₋₁₀ 1.8 Hz, ³*J*₇₋₈ 8.9 Hz), 7.38 (d, 1H, 10-HC, ⁴*J*₈₋₁₀ 1.8 Hz). Found (%): C, 48.74; H, 4.59; Br, 29.17; N, 5.02. Calc. for C₁₁H₁₂BrNO₂ (%): C, 48.91; H, 4.48; Br, 29.58; N, 5.19.