

SHORT COMMUNICATIONS

Ketone *O*-(Tetrahydro-1,3-oxazin-3-ylmethyl)- and *O*-(Oxazolidin-3-ylmethyl)oximes

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Five- and six-membered cyclic N,O-acetals exhibit versatile biological activity; they are used in various fields of technics and as intermediate products in fine organic synthesis [1]. We recently reported that ketone oximes are capable of undergoing Mannich aminomethylation with formaldehyde and 4,5-dihydropyrazoles [2].

With a view to obtain potential biologically active compounds having both linear and cyclic N,O-acetal fragments, we examined aminomethylation of ketone oximes **Ia–Ic** with oxazolidine (**IIa**) and tetrahydro-1,3-oxazine (**IIb**).

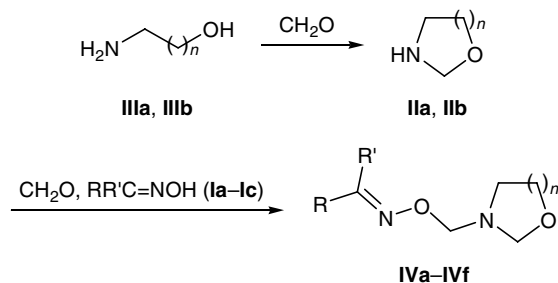
It is known that free oxazolidine (**IIa**) and tetrahydro-1,3-oxazine (**IIb**) are very unstable compounds and that they undergo trimerization to *N,N',N''*-tris-(hydroxyalkyl)triazines [3]. Therefore, the reaction was performed in a one-pot mode. Initially, amino alcohol **IIIa** and **IIIb** was reacted with paraformaldehyde, and an additional portion of paraformaldehyde and ketone oxime **Ia–Ic** were then added to the mixture. The amounts of the reactants were stoichiometric.

Both steps were carried out by heating in benzene with simultaneous removal of water as azeotrope. The yields of aminomethylation products **IVa–IVf** were 44–58%.

Compounds **IVa–IVf** showed in the IR spectra absorption bands in the region 1640–1665 cm^{−1} due to stretching vibrations of the oxime C=N bond, while neither amino nor hydroxy group absorption was observed at 3200–3500 cm^{−1}. The ¹H NMR spectra of **IVa–IVf** contained singlets at δ 4.25–4.52 and 4.33–4.98 ppm from protons of the NCH₂OC and NCH₂ON fragments, respectively. In addition, signals from the other protons in the acetal ring and oxime moiety were present. According to the ¹H NMR data, oximes **IVe** and **IVf** were isolated as a single isomer. Taking into account the chemical shift of the methyl protons (δ 2.23 ppm) in the acetophenone fragment and published NMR data for various acetophenone oxime derivatives [4], we can conclude that compounds **IVe** and **IVf** are *E* isomers.

Ketone *O*-(tetrahydro-1,3-oxazin-3-ylmethyl)- and *O*-(oxazolidin-3-ylmethyl)oximes **IVa–IVf (general procedure).** A mixture of 0.1 mol of amino alcohol **IIIa** or **IIIb**, 0.1 mol of paraformaldehyde, and 100 ml of benzene was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. The mixture was cooled, 0.1 mol of oxime **Ia–Ic** and 0.1 mol of paraformaldehyde was added, and the mixture was heated again under reflux until water no longer separated. Compounds **IVa–IVf** were isolated by vacuum distillation.

Acetone *O*-(oxazolidin-3-ylmethyl)oxime (IVa**).** Yield 48%, bp 73–76°C (6 mm), *d*₄²⁰ = 1.0507, *n*_D²⁰ = 1.4759. ¹H NMR spectrum, δ, ppm: 1.85 s (6H, Me),



I, R = R' = Me (**a**), RR' = (CH₂)₅ (**b**), R = Me, R' = Ph (**c**);
II, **III**, *n* = 1 (**a**), 2 (**b**); **IV**, R = R' = Me (**a**, **b**), RR' = (CH₂)₅ (**c**, **d**), R = Me, R' = Ph (**e**, **f**); *n* = 1 (**a**, **c**, **e**), 2 (**b**, **d**, **f**).

3.19 t (2H, NCH₂CH₂O, ³J = 6.8 Hz), 3.7 t (2H, NCH₂CH₂O, ³J = 6.8 Hz), 4.5 s (2H, OCH₂N), 4.89 s (2H, NCH₂ON). Found, %: C 53.02; H 9.03; N 17.59. C₇H₁₄N₂O₂. Calculated, %: C 53.15; H 8.92; N 17.71.

Acetone O-(tetrahydro-1,3-oxazin-3-ylmethyl)oxime (IVb). Yield 56%, bp 83–86°C (2 mm), $d_4^{20} = 1.0208$, $n_D^{20} = 1.4648$. ¹H NMR spectrum, δ, ppm: 1.67 m (2H, NCH₂CH₂CH₂O), 1.85 s (6H, Me), 3.07 t (2H, NCH₂CH₂CH₂O, ³J = 5.6 Hz), 3.78 t (2H, NCH₂CH₂CH₂O, ³J = 5.3 Hz), 4.45 s (2H, OCH₂N), 4.81 s (2H, NCH₂ON). Found, %: 55.98; H 9.27; N 16.08. C₈H₁₆N₂O₂. Calculated, %: C 55.79; H 9.36; N 16.27.

Cyclohexanone O-(oxazolidin-3-ylmethyl)oxime (IVc). Yield 52%, bp 106–109°C (3 mm), mp 35–36°C. ¹H NMR spectrum, δ, ppm: 1.58–2.50 m [10H, (CH₂)₅], 3.20 t (2H, NCH₂CH₂O, ³J = 6.78 Hz), 3.70 t (2H, NCH₂CH₂O, ³J = 6.78 Hz), 4.51 s (2H, OCH₂N), 4.74 s (2H, NCH₂ON). Found, %: 59.99; H 9.27; N 14.08. C₁₀H₁₈N₂O₂. Calculated, %: C 60.58; H 9.15; N 14.13.

Cyclohexanone O-(tetrahydro-1,3-oxazin-3-ylmethyl)oxime (IVd). Yield 54%, bp 128–131°C (1 mm), $d_4^{20} = 1.0844$, $n_D^{20} = 1.5080$. ¹H NMR spectrum, δ, ppm: 1.65–2.41 m [10H, (CH₂)₅], 2.89 m (2H, NCH₂CH₂CH₂O), 3.45 t (2H, NCH₂CH₂CH₂O, ³J = 6.8 Hz), 3.82 t (2H, NCH₂CH₂CH₂O, ³J = 5.3 Hz), 4.25 s (2H, OCH₂N), 4.33 s (2H, NCH₂ON). Found, %: C 62.19; H 9.56; N 13.31. C₁₁H₂₀N₂O₂. Calculated, %: C 62.23; H 9.50; N 13.20.

Acetophenone O-(oxazolidin-3-ylmethyl)oxime (IVe). Yield 44%, bp 155–158°C (3 mm), $d_4^{20} = 1.1431$, $n_D^{20} = 1.5635$. ¹H NMR spectrum, δ, ppm: 2.23 s (3H, Me), 3.27 t (2H, NCH₂CH₂O, ³J = 6.8 Hz), 3.71 t (2H, NCH₂CH₂O, ³J = 6.8 Hz), 4.59 s (2H, OCH₂N), 4.97 s (2H, NCH₂ON), 7.33–7.63 m (5H, C₆H₅). Found, %: C 65.38; H 7.45; N 12.78. C₁₂H₁₆N₂O₂. Calculated, %: C 65.43; H 7.32; N 12.72.

Acetophenone O-(tetrahydro-1,3-oxazin-3-ylmethyl)oxime (IVf). Yield 46%, bp 165–167°C (4 mm), $d_4^{20} = 1.0911$, $n_D^{20} = 1.5490$. ¹H NMR spectrum, δ, ppm: 1.70 m (2H, NCH₂CH₂CH₂O), 2.23 s (3H, Me), 3.12 t (2H, NCH₂CH₂CH₂O, ³J = 5.6 Hz), 3.77 t (2H, NCH₂CH₂CH₂O, ³J = 5.3 Hz), 4.52 s (2H, OCH₂N), 4.98 s (2H, NCH₂ON), 7.31–7.65 m (5H, C₆H₅). Found, %: C 66.54; H 7.79; N 11.82. C₁₃H₁₈N₂O₂. Calculated, %: C 66.64; H 7.74; N 11.96.

The ¹H NMR spectra were recorded at 26°C on a Bruker DPX-400 spectrometer (400 MHz) using CDCl₃ as solvent and hexamethyldisiloxane as internal reference. Commercial amino alcohols and ketone oximes were distilled just before use; they contained no less than 98.5% of the main substance (according to the GLC data); commercial paraformaldehyde had a purity of 95%.

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