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Cyanoethylation of Aromatic Aldehyde Imines Containing a Hydroxy Group in the β- or γ-Position. Synthesis of 3-Cyanoethyl-1,3-oxazacycloalkanes

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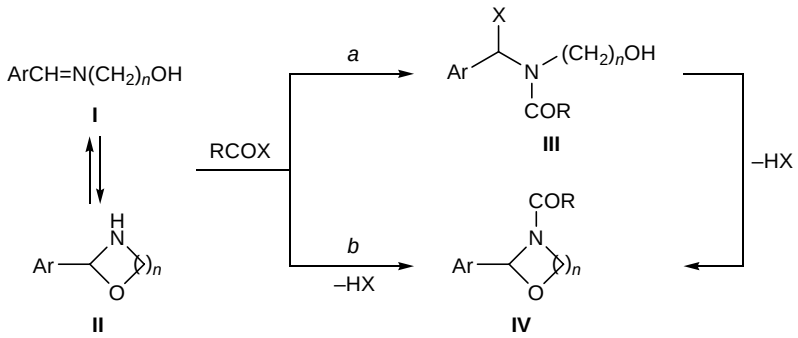
Abstract—Acrylonitrile reacts with aromatic aldehyde imines containing a hydroxy group in the β- or γ-position to give 70–85% of the corresponding 2-aryl-3-cyanoethyltetrahydro-1,3-oxazines or 2-aryl-3-cyanoethyl-1,3-oxazolidines, respectively. The results of these reactions are rationalized in terms of ring–chain isomerism of the initial imines.

We previously reported [1] on the formation of 2-aryl-3-cyanoethyltetrahydro-1,3-oxazines and 2-aryl-3-cyanoethyl-1,3-oxazolidines in reactions of acrylonitrile with Schiff bases **I** derived from aromatic aldehydes and containing a hydroxy group in the β- or γ-position of the alkyl chain on the nitrogen atom. In continuation of these studies, in the present work we examined in more detail the reaction of compounds **I** with acrylonitrile in order to elucidate general relations holding therein and reveal tautomerism of the initial hydroxy-containing Schiff bases.

The formation of O,N-heterocycles may be interpreted on the assumption that initial hydroxy imines give rise to ring–chain tautomerism [2, 3]. However, the NMR data indicated the absence of cyclic tautomer of compounds **Ia**–**Id** in various organic solvents. The existence of ring–chain tautomerism in these systems follows from the results of their reactions with carboxylic acid chlorides and anhydrides. Depending on the conditions and/or substrate structure, the products are either cyclic or open-chain compounds [4, 5] (Scheme 1). Taking into account that all acylating agents used are capable of reacting at the double C=N bond of initial Schiff base to give intermediates which can undergo cyclization to the corresponding O,N-heteroring (**IV**, path *a*), it is impossible to assert unequivocally whether compound **IV** is formed along pathway *a* or *b*.

We have found that acrylonitrile reacts with Schiff bases **Ia**–**Id** in anhydrous ethanol at 75–80°C to give the corresponding *N*-(2-cyanoethyl)-1,3-oxazacycloalkanes **Va**–**Vd** in 70–85% yield (Scheme 2). Insofar

Scheme 1.



n = 2, 3.

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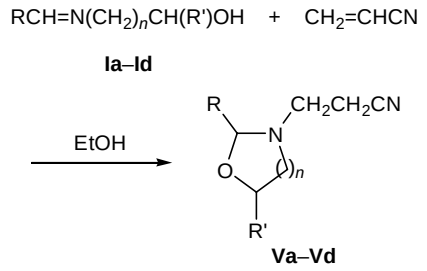
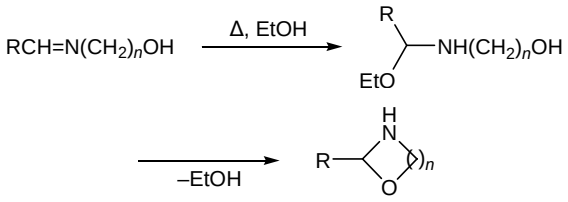
Scheme 2.



R = Ph, R' = H (**a**, **b**); R = $NO_2C_6H_4$, R' = H (**c**); R = Ph, R' = Me; *n* = 1 (**a**, **c**, **d**), 2 (**b**).

as the reaction of acrylonitrile with imines was not reported previously, we concluded that the cyclic tautomer is present in solution. Theoretically, two other ways of formation of cyclic products are possible. The first of these includes addition of alcohol (solvent) at the double C=N bond on heating, followed by intramolecular cyclization to give 1,3-oxazacycloalkane **II** (Scheme 3) which then reacts with acrylonitrile. This pathway seems to be especially probable for *N*-(β-hydroxyethyl) derivatives, for which 5-*endo*-trigonal cyclization is hindered for steric reasons (according to the Baldwin rule [6]). However, an analogous scheme of formation of cyclic compounds **V** is ruled out, for cyanoethylation occurs in benzene as well, but with a lower yield. The second pathway implies intramolecular cyclization of hydroxy imines at elevated temperature with formation of intermediates **II**. However, no compounds **II** were isolated when hydroxy imines were heated to 75–80°C and then cooled.

Scheme 3.

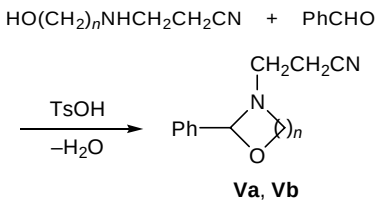


The structure of the products was confirmed by the ^{1}H and ^{13}C NMR spectra. Signals in the ^{13}C NMR spectra were assigned using NMQC 2D-correlation technique.

There are published data that 1,3-oxazacycloalkanes are characterized by generalized anomeric effect [7] and that unbranched alkyl groups on the nitrogen atom in tetrahydro-1,3-oxazines occupy the axial position [8]. Therefore, we presume that the 2-cyanoethyl group in compounds **V** is oriented pseudoaxially. This follows from the large difference ($\Delta\delta$ = 0.62 ppm) in the chemical shifts of 5-H_A and 5-H_B in the ^{1}H NMR spectrum of compound **Vb** and from the difference in the geminal coupling constants.

The structure of compounds **V** was also proved by independent synthesis according to Scheme 4.

Scheme 4.



n = 2 (**a**), 3 (**b**).

EXPERIMENTAL

The NMR spectra were recorded at 303 K on a Varian Mercury-300 spectrometer (300 MHz for ^{1}H and 75.46 MHz for ^{13}C) from solutions in DMSO-d_6–CCl_4 (1:3); tetramethylsilane was used as reference. The IR spectra were obtained on a Specord 75IR instrument from samples dispersed in mineral oil.

3-(2-Phenyl-1,3-oxazolidin-3-yl)propanenitrile (Va). *a*. A solution of 3 g (0.02 mol) of *N*-benzylidene-2-hydroxyethylalmine (**Ia**) and 2.12 g (0.04 mol) of acrylonitrile (stabilized with hydroquinone) in 10 ml of anhydrous ethanol was heated for 8 h. The solvent was distilled off, and the residue was distilled under reduced pressure. Yield 3.1 g (76%), bp 152–153°C (3 mm), n_D^{20} = 1.5330. IR spectrum, ν, cm^{-1}: 2260 (C≡N); 1130, 1180 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 2.54 t (2H, CH_2CN, *J* = 6.5 Hz), 2.67 d.d.d (1H, NC**H**$_2$CH$_2$CN, *J* = 12.6, 6.7, 5.5 Hz), 2.76–2.84 m (1H, NC**H**$_2$CH$_2$O, and 1H, NC**H**$_2$CH$_2$CN), 3.30 d.t (1H, NC**H**$_2$CH$_2$O, *J* = 9.9, 5.8 Hz), 3.94 d.d (2H, OCH_2, *J* = 7.4, 5.8 Hz), 4.99 s (1H, CH), 7.30–7.50 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 17.26 (C**H**$_2$CN), 47.44 (N**C**H$_2$CH$_2$CN), 50.86 (N**C**H$_2$CH$_2$O), 63.94 (OCH_2), 95.64 (CH), 117.93 (CN), 126.99 and 127.43 (C^o , C^m), 127.85 (C^p), 138.97 (C^i). Found, %: C 71.79; H 7.11; N 14.15. $C_{12}H_{14}N_2O$. Calculated, %: C 71.28; H 6.93; N 13.86.

b. A solution of 3 g (0.02 mol) of *N*-benzylidene-2-hydroxyethylalmine (**Ia**) and 2.12 g (0.04 mol) of acrylonitrile (stabilized with hydroquinone) in 10 ml of dry benzene was heated for 8 h. The solvent was distilled off, and the residue was distilled under reduced pressure to isolate 1.9 g of initial Schiff base **Ia**, bp 104–106°C (2 mm), n_D^{20} = 1.5690 [9], and 1.1 g (27%) of **Va**, bp 145°C (2 mm), n_D^{20} = 1.5350.

3-(2-Phenyltetrahydro-1,3-oxazin-3-yl)propanenitrile (Vb) was synthesized in a similar way from 3.26 g (0.02 mol) of *N*-benzylidene-3-hydroxypropylamine (**Ib**) and 2.12 g (0.04 mol) of acrylonitrile in 10 ml of anhydrous ethanol. Yield 3.5 g (81%), bp 160–161°C (3 mm), n_D^{20} = 1.5344. IR spectrum, ν, cm^{-1}: 2240 (C=N); 1120, 1160 (C–O–C). ^1H NMR spectrum, δ, ppm: 1.40 d.q (1H, $CH_2CH_2CH_2$, *J* = 13.5, 3.2 Hz), 2.02 m (1H, $CH_2CH_2CH_2$), 2.23 t.d (2H, CH_2CN, *J* = 6.7, 3.2 Hz), 2.60 d.t (1H, NCH_2CH_2CN, *J* = 13.5, 6.7 Hz), 2.73 d.t (1H, NCH_2CH_2CN, *J* = 13.5, 6.7 Hz), 3.04 d.d.d (1H, $NCH_2CH_2CH_2$, *J* = 13.5, 11.5, 3.2 Hz), 3.24 m (1H, $NCH_2CH_2CH_2$, *J* = 13.5, 11.5, 3.2 Hz), 3.80 t.d (1H, CH_2O, *J* = 11.1, 2.8 Hz), 4.13 d.q (1H, OCH_2, *J* = 11.1, 2.4 Hz), 5.13 s (1H, CH), 7.24–7.44 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 16.68 (CH_2), 20.85 (CH_2), 42.79 (NCH_2), 48.67 (NCH_2CH_2O), 66.62 (OCH_2), 91.98 (CH), 118.01 (CN), 126.46 and 127.52 (C^o, C^m), 127.34 (C^p), 138.58 (C^i). Found, %: C 71.93; H 7.18; N 13.05. $C_{13}H_{16}N_2O$. Calculated, %: C 72.22; H 7.40; N 12.96.

3-[2-(4-Nitrophenyl)-1,3-oxazolidin-3-yl]propanenitrile (Vc) was synthesized in a similar way from 2 g (0.01 mol) of Schiff base **Ic** and 1.06 g (0.02 mol) of acrylonitrile in 6 ml of anhydrous ethanol. Yield 1.77 g (71.6%), bp 220–224°C (2 mm), n_D^{20} = 1.5564. IR spectrum, ν, cm^{-1}: 2245 (C=N); 1110, 1170 (C–O–C). ^1H NMR spectrum, δ, ppm: 2.61 t (2H, CH_2CN, *J* = 6.5 Hz), 2.78 d.t (1H, CH_2CH_2CN, *J* = 12.3, 6.3 Hz), 2.88 m (1H, NCH_2CH_2CN), 2.99 m (1H, NCH_2CH_2O), 3.20 d.d.d (1H, NCH_2CH_2O, *J* = 10.3, 7.1, 6.0 Hz), 3.94 m (2H, OCH_2), 5.26 s (1H, CH), 7.70 d (2H, *o*-H, *J* = 8.7 Hz), 8.17 d (2H, *m*-H, *J* = 8.7 Hz). Found, %: C 58.01; H 4.99; N 16.86. $C_{12}H_{13}N_3O_3$. Calculated, %: C 58.29; H 5.26; N 17.00.

3-(5-Methyl-2-phenyl-1,3-oxazolidin-3-yl)propanenitrile (Vd) was synthesized in a similar way from 1.63 g (0.01 mol) of Schiff base **Id** and 1.06 g (0.02 mol) of acrylonitrile in 10 ml of anhydrous ethanol. Yield 1.83 g (85%), bp 147–148°C (2 mm), n_D^{20} = 1.5170. IR spectrum, ν, cm^{-1}: 2245 (C=N); 1120, 1160 (C–O–C). ^1H NMR spectrum, δ, ppm: 1.73 d.d (3H, CH_3), 2.45 d.t (2H, CH_2CN), 2.55–2.75 m (2H, NCH_2CH_2CN), 2.95 d.d and 3.47 d.d (2H, NCH_2CH_2O), 4.28 d.q (1H, $CHCH_3$), 4.86 d (1H, NCHO), 7.28–7.50 m (5H, C_6H_5). Found, %: C 71.79; H 7.20; N 12.55. $C_{13}H_{16}N_2O$. Calculated, %: C 72.22; H 7.40; N 12.96.

Reaction of *N*-(2-cyanoethyl)-2-hydroxyethylamine with benzaldehyde. A mixture of 2.3 g (0.02 mol) of *N*-(2-cyanoethyl)-2-hydroxyethylamine, 2.12 g (0.02 mol) of benzaldehyde, and 0.1 g (0.00058 mol) of *p*-tolenesulfonic acid in 25 ml of benzene was heated in a flask equipped with a Dean–Stark trap until 0.36 g of water separated. The solvent was removed, and the residue was distilled under reduced pressure to obtain 3.3 g (81.6%) of compound **Va** with bp 165°C (4–5 mm), n_D^{20} = 1.5305.

Following an analogous procedure, from 2.56 g (0.02 mol) of *N*-(2-cyanoethyl)-3-hydroxypropylamine, 0.02 mol of benzaldehyde, and 0.1 g (0.00058 mol) of *p*-toluenesulfonic acid we obtained 3.65 g (84.4%) of compound **Vb** with bp 162°C (3 mm), n_D^{20} = 1.5334.

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