CYCLOCONDENSATION OF CYANOHYDRINS WITH ALDEHYDES OR KETONES

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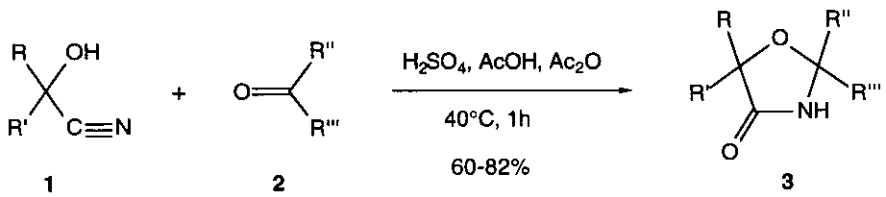
Abstract *- Cyanohydrins (**1**) are easily condensed with aldehydes or ketones (**2**) in anhydrous strong acidic conditions to give 1,3-oxazolidin-4-ones (**3a-i**) in good yields. The mechanism of this cyclocondensation is discussed.*

In previous paper we described the ability of β-oxonitriles to react with aldehydes or ketones to give six-membered heterocycles.[1] In the hope of extending our method to others substrates, we tried a condensation of cyanohydrins with aldehydes or ketones in the same way to obtain five-membered heterocycles.

As a further part of our chemical interest in this field, we wish to present here our approach of 1,3-oxazolidin-4-ones (**3**).

In connection with other synthetic routes,[2,3] it is well established that α-hydroxy amides condensed with ketones in acidic condition to give 1,3-oxazolidin-4-ones and analogues. This method was first developed by Fischer,[2] then generalized by various authors in the field of pharmaceutical interest.[3]

Using our standard experimental conditions,[1] cyanohydrins (**1**) reacted with acyclic ketones or aldehydes (**2**) to give substituted 1,3-oxazolidin-4-ones (**3**) in good to moderate yield. (Scheme 1)

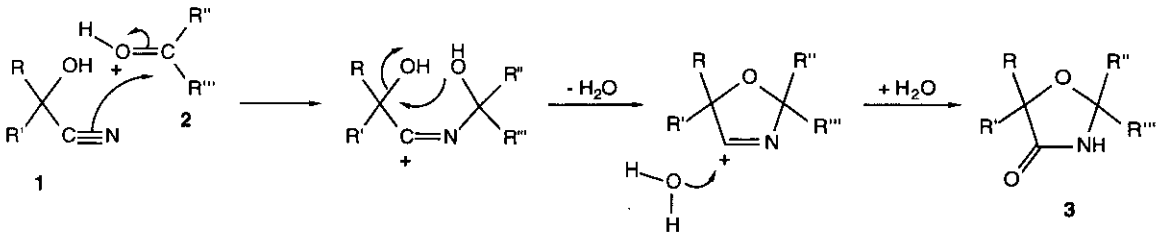


3	R	R'	R''	R'''	Yield %
a	CH_3	CH_3	CH_2-$(CH_2)_3$-CH_2		82
b	CH_2-$(CH_2)_3$-CH_2		CH_3	CH_3	76
c	CH_3	CH_3CH_2	CH_3	CH_3	68
d	CH_3	CH_3	CH_3	H	60
e	CH_2-$(CH_2)_3$-CH_2		CH_3	CH_2Cl	74
f	CH_3	CH_3	C_6H_5	H	65
g	CH_3CH_2	CH_3	4-$CH_3OC_6H_4$	H	70
h	CH_3	CH_3	C_6H_5	CH_3	80
i	C_6H_5	CH_3	CH_3CH_2	CH_3CH_2	78

Scheme 1

This finding of one-step access to heterocycles (**3**) prompted us to generalize the methodology to various cyanohydrins substrates (**1**) with several ketones or aldehydes (**2**). In the case of cyclic ketone (**2a**) or cyclic cyanohydrins (**1b,e**), heterocyclic spiro compounds were formed. Some representative structures are summerized in Scheme 1.

The reaction between cyanohydrins and carbonyl compounds most probably proceeds *via* the Ritter reaction.[4] In a first step the cyano group condensed with the activated carbonyl to give a carbonium intermediate. The latter cyclized by intramolecular dehydration followed by addition of water to form the heterocycle. (Scheme 2)



Scheme 2

Structure of 1,3-oxazolidinones and spiro compounds (**3a-i**) was ensured by spectroscopic methods. IR spectra showed the absence of any cyano band in the 2200 cm^{-1} region and the presence of lactam carbonyl band at 1700 cm^{-1}. IR absorption of δ-lactams at high wawenumbers for the carbonyl group (ν_{NH} = 3440 and ν_{CO} = 1700 cm^{-1}) agreed with five membered heterocycles due to the ring strain. The interpretation of the ^{1}H-NMR spectra which showed well separated signals of the cyanohydrins, ketones and aldehydes parts, allowed the assigment of the heterocyclic structures (**3**). In the experimental protocols spectral data on the most significant compounds have been reported.

In conclusion cyanohydrins react easily with acyclic and cyclic ketones or aldehydes catalyzed by sulfuric acid in anhydrous conditions. This simple methodology opens an easy access to a wide variety of 1,3-oxazolidin-4-ones and presents an effective synthesis of this heterocycle and further analogues.

EXPERIMENTAL

^{1}H-NMR spectra were recorded at 200 MHz with a Brucker AC 200 Spectrometer in $CDCl_3$ as solvent. IR spectra were recorded on a Beckman IR 4230 Spectrophotometer. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Combustion analyses were performed by the Service de Microanalyse de l'U.L.P., Strasbourg. All TLCs were performed on Merck silica gel F-254 plates (CH_2Cl_2/AcOEt, 50:50).

Compounds (**3**); General procedure:

To a mixture of the cyanohydrin (**1**) (0.10 mol) and the ketone or aldehyde (**2**) (0.12 mol) in glacial acetic acid (30 mL) at 10° C, was added dropwise acetic anhydride (5 mL, 49 mmol), then concentrated sulfuric acid (10 mL) in glacial acetic acid (10 mL) kept at 0° C. The mixture was stirred at 10° C for 40 min then 10 min at ambient temperature. The mixture was poured into cracked ice and extracted three times with ether. The organic phases were washed with 8% aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated *in vacuo*. The solid residue was collected and recrystallized from aqueous methanol to give **3**:

2,2-Dimethyl-1-oxa-4-azaspiro[4.5]decan-3-one (**3 a**)

Starting from 2-methyl-2-hydroxypropiononitrile and cyclohexanone to give **3 a** (82 %); mp 108°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20-2.30 (m, 10H, $H_{6\text{-}10}$); 1.43 and 1.47 (2s, 6H, CH_3); 7.60 (m, 1H, NH). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.53; H, 9.28; N, 7.65. Found: C, 65.49; H, 9.30; N, 7.69.

2,2-Dimethyl-1-oxa-3-azaspiro[4.5]decan-4-one (**3 b**)

Following the general procedure described above using 1-hydroxycyclohexanecarbonitrile and acetone to give **3 b** (76 %); mp 102°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30-2,50 (m, 10H, $H_{6\text{-}10}$); 1.68 and 1,72 (2s, 6H, CH_3); 7.70 (m, 1H, NH). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.53; H, 9.28; N, 7.65. Found: C, 68.49; H, 9.12; N, 6.66.

5-Ethyl-2,2,5-trimethyl-1,3-oxazolidin-4-one (**3 c**)

Following the general procedure described above using 2-methyl-2-hydroxybutanenitrile[5] and acetone to give **3 c** (68 %); mp 151°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (t, J = 6.8, 3H, CH_3-CH_2); 1.41 (s, 3H, CH_3 at C_5); 1,71 and 1,74 (2s, 6H, CH_3 at C_2); 1,96 (q, J = 6.8, 2H, CH_2); 7.80 (s, 1H, NH). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.10;

H, 9.55; N, 8.91. Found: C, 61.13; H, 9.51; N, 8.88.

2,5,5-Trimethyl-1,3-oxazolidin-4-one (**3 d**)

In accordance with the general procedure presented above this compound was prepared from 2-hydroxy-2-methylpropiononitrile and acetaldehyde to give **3 d** (60 %); mp 148°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 and 1,52 (2s, 6H, CH_3 at C_5); 1.62 (d, J = 7.1, 3H, CH_3 at C_2); 5.50 (m, 1H, H_2); 7.76 (m, 1H, NH). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.78; H, 8.52; N, 10.85. Found: C, 55.80; H, 8.49; N, 10.86.

2-Chloromethyl-2-methyl-1-oxa-3-azaspiro[4.5]decan-4-one (**3 e**)

In accordance with the general procedure presented above this compound was prepared from 1-hydroxycyclohexanecarbonitrile and 2-chloroacetone to give **3 e** (74 %); mp 144°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20-2.50 (m, 10H, $H_{6\text{-}10}$); 1.45 (s, 3H, CH_3); 3.85 (s, 2H, CH_2Cl); 7.80 (m,1H, NH). Anal. Calcd for $C_{10}H_{16}NO_2Cl$: C, 55.17; H, 7.36; N, 6.44. Found: C, 55.20; H, 7.34; N, 6.41.

5,5-Dimethyl-2-phenyl-1,3-oxazolidin-4-one (**3 f**)

Following the general procedure described above using 2-hydroxy-2-methylpropiononitrile and benzaldehyde to give **3 f** (65 %); mp 186°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO), 1600 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 and 1,45 (2s, 6H, CH_3); 6.32 (d, J = 7.6, 1H, H_2); 7.32 (s, 5H, Ar-H); 7.78 (m, 1H, NH). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.08; H, 6.80; N, 7.33. Found: C, 69.10; H, 6.82; N, 7.36.

5-Ethyl-2-(4-methoxyphenyl)-5-methyl-1,3-oxazolidin-4-one (**3 g**)

Following the general procedure described above using 2-hydroxy-2-methylbutanenitrile[5] and 4-methoxybenzaldehyde to give **3 g** (70 %); mp 163°C. IR ($CHCl_3$): ν = 3440 (NH), 1700

(CO), 1600 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (t,J = 7.6, 3H, CH_3CH_2); 1.40 (s, 3H, CH_3 at C_5); 1.96 (q, J = 7.6, 2H, CH_3CH_2); 3.83 (s, 3H, CH_3O); 6.27 (d, J = 6.8, 1H, H_2); 6.93 (d, J = 8.3, 2H, Ar-$H_{3,5}$); 7.55 (d, J = 8.3, 2H, Ar-$H_{2,6}$); 7.80 (m, 1H, NH). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.23; N, 5.95. Found: C, 66.32; H, 7.19; N, 5.98.

2,5,5-Trimethyl-2-phenyl-1,3-oxazolidin-4-one (**3 h**)

Following the procedure described above using 1-hydroxy-1-methylpropiononitrile and acetophenone to give **3 h** (80 %); mp 155°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO), 1600 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 and 1.49 (2s, 6H, CH_3 at C_5); 1.61 (s, 3H, CH_3 at C_2); 7.32 (s, 5H, Ar-H); 7.70 (m, 1H, NH). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.31; N, 6.83. Found: C, 70.18; H, 7.34; N, 6.80.

2,2-Diethyl-5-methyl-5-phenyl-1,3-oxazolidin-4-one (**3 i**)

Following the procedure described above using 2-hydroxy-2-phenylpropiononitrile[6] and pentan-3-one to give **3 i** (78 %); mp 146°C. IR ($CHCl_3$): ν = 3440 (NH), 1700 (CO), 1600 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, J = 7.8, 3H, CH_3CH_2); 1.01 (t, J = 7.5, 3H, CH_3CH_2); 1.40 (s, 3H, CH_3 at C_5); 1.98 (2q, J = 7.8, 4H, CH_2); 7.35 (m, 5H, Ar-H); 7.75 (m, 1H, NH). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.15; N, 6.00. Found: C, 72.10; H, 8.14; N, 5.97.

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