CYCLOCONDENSATION OF β-OXONITRILES WITH KETONES OR ALDEHYDES

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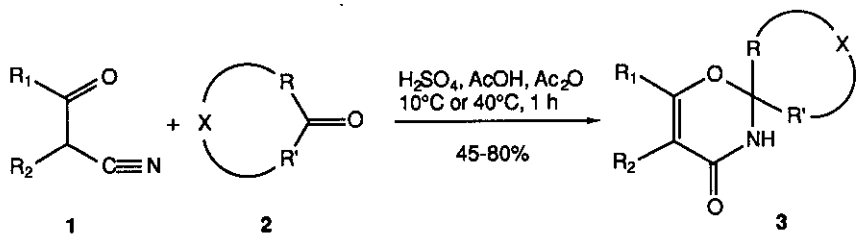
Abstract *- β-Oxonitriles (**1**) are easily condensed with cyclic ketones (**2a-e**) in anhydrous strong acidic conditions to give 1-oxa-5-azaspiro[5.5]undec-2-en-4-ones (**3a-e**). In the same manner acyclic ketones (**2f,g**) or aldehydes (**2h,i**) afford 2,3-dihydro-4H-1,3-oxazin-4-ones (**3f-i**). The mechanism of this cyclocondensation is discussed.*

In the course of our investigation on heterocyclic derivatives, we discovered that ethyl 3-cyano-3-phenylpyruvate reacts with cyclohexanone in the presence of concentrated sulfuric acid to give ethyl 4-oxo-3-phenyl-1-oxa-5-azaspiro[5.5]undec-2-ene-2-carboxylate in good yield.[1]
Encouraged by our first results, we attempted to extend this reaction to various β-oxonitriles (**1**) with cyclic as well as acyclic ketones and aldehydes (**2**) to obtain compounds (**3**).

In connection with other synthetic work,[2] it is well known that salicylamide could be condensed with aldehydes or ketones in acidic conditions.[3] Condensation of diketene with *S*-alkylthioureas or carbodiimides led to 2-imino analogues of this heterocycle.[4] Furthermore salicylamide was made to react with cyclohexanone in the presence of acid catalysis.[5]
We report here a new efficient synthesis of various substituted 2,3-dihydro-4*H*-1,3-oxazin-4-ones (**3f-i**) and ethyl 4-oxo-3-phenyl-1-oxa-5-azaspiro[5.5]undec-2-ene-2-carboxylates (**3a-e**) based on a cyclocondensation reaction and the possible mechanism of their formations.

At 10°C in glacial acetic acid and acetic anhydride, in the presence of concentrated sulfuric acid, β-oxonitriles (**1**) were condensed with the cyclic ketones (**2a,e**) to give the spiro compounds (**3a-e**). In the same manner the acyclic ketones (**2f,g**) and aldehydes (**2h,i**) led to 1,3-oxazin-4-ones (**3f-i**) in 45-80 % yield. (Scheme 1)



1 **2** **3**

3	**R_1**	**R_2**	**R**	**R'**	**X**	**Yield %**
a	Me	H		- $[CH_2]_5$ -		46
b	Et	Me		- $[CH_2]_5$ -		55
c	CO_2Et	C_6H_5		- $[CH_2]_5$ -		65
d	H	4-$CH_3OC_6H_4$		- $[CH_2]_5$ -		80
e	CO_2Et	4-$CH_3OC_6H_4$	- $[CH_2]_2$ -	- $[CH_2]_2$ -	N-Me	60
f	CO_2Et	C_6H_5	Me	Me		52
g	CO_2Et	C_6H_5	Me	Et		48
h	CO_2Et	C_6H_5	Me	H		45
i	CO_2Et	C_6H_5	C_6H_5	H		56

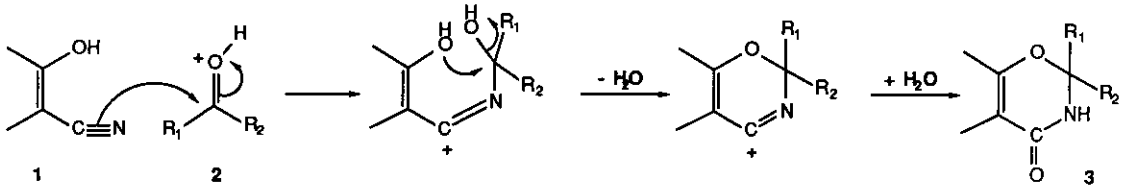
Scheme 1

In order to establish whether this method is generally applicable, we prepared a series of cyclic compounds (**3**) by using different β-keto nitriles (**1**), ketones or aldehydes (**2**). In the case of compounds (**1a,b**) and (**1d**) the absence of an ethoxycarbonyl group decreased the reactivity of the β-oxonitrile. Actually for R_1 = CO_2Et the reactivity is especially high, possibly due to a larger concentration of the enol forms. Thus, simple heating at 40° C for a few minutes allowed to achieve the cyclization. For compound (**1e**) the condensation with 1-methyl-4-piperidone (X =

NMe), proceeded in the same manner but the desired product (**3e**) was extracted in basic conditions.

All compounds (**3**) show ir absorptions at approximately ν_{NH} = 3420 cm^{-1}, ν_{CO} = 1665 cm^{-1}, $\nu_{C=C}$ = 1605 cm^{-1}, which are ascribed to the conjugated six membered lactam. Moreover sufficient structural informations were obtained from the ^{1}H-nmr spectra, detailed in the experimental part, to confirm the proposed structures of (**3a-i**).

Regarding the reaction path followed, we proposed a plausible mechanism. β-Oxonitriles (**1**) are known to be easily enolizable. These enolic forms exhibit two conjugated coplanar π bonds. In addition the strongly acidic conditions suggest a well known Ritter reaction of the nitrile group (**1**) with the activated carbonyl of compound (**2**) to give an iminium salt which cyclizes *via* the enol form. Then, addition of water to the residual carbocation affords the lactam (**3**). (Scheme 2)



Scheme 2

The starting aliphatic β-oxonitriles (**1**) were prepared by ring opening of isoxazoles with strong bases.[6,7] The aromatic β-oxonitriles were obtained by condensation of phenylacetonitriles with diethyl oxalate in usual methods.[8-10]

In conclusion β-oxonitriles react easily under enolic forms 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-oxazin-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 $CDCl_3$ or DMSO-d_6 as solvents. Infrared 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, 40:60)

Compounds 3; General procedure:

To a mixture of the β-oxo nitrile (**1**) (0.1 mol), glacial acetic acid (30 ml), acetic anhydride (10 ml) and a ketone or aldehyde (**2**) (0.12 mol) at 10°C, was added dropwise a solution of concentrated H_2SO_4 (15 ml) in glacial acetic acid (30 ml) kept at 0°C. The mixture was stirred at 10°C for 1 h. After 10 min at ambient temperature, Et_20 (100 ml) and water (250 ml) were successively added. The organic phase was separated and 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-Methyl-1-oxa-5-azaspiro[5.5]undec-2-en-4-one (**3a**)

Starting from 3-oxobutyronitrile[6] and cyclohexanone to give (**3a**) (46 %); mp 108°C. Ir ($CHCl_3$): ν = 3420 (NH), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.2-2.3 (m, 10H, H_{7-11}); 1.92 (d, J = 1.2, 3H, CH_3); 5.12 (q, J = 1.2, 1H, H_3); 7.80 (m, 1H, NH). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.33; N, 7.73. Found: C, 66.51; H, 8.29; N, 7.70.

2-Ethyl-3-methyl-1-oxa-5-azaspiro[5.5]undec-2-en-4-one (**3b**)

Following the general procedure described above using 2-methyl-3-oxovaleronitrile[7] and cyclohexanone to give (**3b**) (55 %); mp 100°C. Ir ($CHCl_3$): ν = 3420 (NH), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.04 (t, J = 7.6, 3H, CH_3CH_2); 1.3-2.1 (m, 10H, H_{7-11}); 1.73 (s, 3H,

CH_3 at C_3); 2.23 (q, J = 7.6, 3H, $CH_3C\underline{H_2}$); 7.60 (m, 1H, NH). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.88; H, 9.15; N, 6.69. Found: C, 68.49; H, 9.12; N, 6.66.

Ethyl 4-oxo-3-phenyl-1-oxa-5-azaspiro[5.5]undec-2-ene-2-carboxylate (**3c**)

Following the general procedure described above using ethyl 3-cyano-3-phenylpyruvate[8] and cyclohexanone to give (**3c**) (65 %); mp 150°C. Ir ($CHCl_3$): ν = 3420 (NH), 1725 (CO_2), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.12 (t, J = 7.8, 3H, CH_3); 1.3-2.5 (m, 10H, H_{7-11}); 4.00 (q, J = 7.8, 2H, CH_2O); 7.28 (s, 5H, Ar-H); 7.80 (s, 1H, NH). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N 4.44. Found: C, 67.99; H, 6.65; N, 4.42.

3-(4-Methoxyphenyl)-1-oxa-5-azaspiro[5.5]undec-2-en-4-one (**3d**)

In accordance with the general procedure presented above this compound was prepared from 2-cyano-2-(4-methoxyphenyl)acetaldehyde[9] and cyclohexanone. But after 10 min at ambient temperature the mixture was heated at 40°C for 5 min and cooled before continuing to give (**3d**) (80 %); mp 150°C. Ir ($CHCl_3$): ν = 3420 (NH), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.3-2.4 (m, 10H, H_{7-11}); 3.80 (s, 3H, CH_3O); 6.88 (d, J = 8.5, Ar-$H_{3,5}$); 7.06 (s, 1H, H_2); 7.41 (d, J = 8.5, Ar-$H_{2,6}$); 7.75 (m, 1H, NH). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.05; H, 6.98; N, 5.10.

Ethyl 3-(4-methoxyphenyl)-9-methyl-4-oxo-1-oxa-5,9-diazaspiro[5.5]undec-2-ene-2-carboxylate (**3e**)

In accordance with the general procedure presented above this compound was prepared from ethyl 3-cyano-3-(4-methoxyphenyl)pyruvate[10] and 1-methyl-4-piperidone. But after 10 min at ambient temperature, water (400 ml) and CH_2Cl_2 (200 ml) were added. The mixture was made alkaline with concentrated ammonia solution with continued cooling. The organic phase was decanted, washed with water, dried ($MgSO_4$), and evaporated. The solid residue was recrystallized from methanol to give (**3e**) (60 %); mp 144°C. Ir ($CHCl_3$): ν = 3420 (NH), 1725

(CO_2), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.02 (t, J = 7.8, 3H, C$\underline{H_3}$CH$_2$); 1.7-2.9 (m, 8H, $H_{7,8,10,11}$); 2.32 (s, 3H, CH_3N); 3.85 (s, 3H, CH_3O); 4.09 (q, J = 7.8, 2H, CH_2O); 6.89 (d, J = 6.8, Ar-$H_{3,5}$); 7.27 (d, J = 6.8, Ar-$H_{2,6}$); 7.80 (m,1H, NH). Anal. Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32;H, 6.71; N, 7.77. Found: C, 62.82; H, 6.67; N, 7.73.

Ethyl 2,2-*dimethyl*-4-*oxo*-5-*phenyl*-2,3-*dihydro*-4*H*-1,3-*oxazine*-6-carboxylate (**3f**)

Following the general procedure described above using ethyl 3-cyano-3-phenylpyruvate[8] and acetone to give (**3f**) (52 %); mp 186°C. Ir ($CHCl_3$): ν = 3420 (NH), 1725 (CO_2), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.10 (t, J = 7.6, 3H, C$\underline{H_3}$CH$_2$); 1.72 (s, 6H, 2xCH_3); 4.03 (q, J = 7.6, 2H, CH_2); 7.32 (s, 5H, Ar-H); 7.72 (m, 1H, NH). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 64.96; H, 6.20; N, 5.06.

Ethyl 2-ethyl-2-methyl-4-oxo-5-phenyl-2,3-dihydro-4*H*-1,3-oxazine-6-carboxylate (**3g**)

Following the general procedure described above using ethyl 3-cyano-3-phenylpyruvate[8] and butan-2-one to give (**3g**) (48 %); mp 130°C. Ir ($CHCl_3$): ν = 3420 (NH), 1725 (CO_2), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.92 (t,J = 7.5, 3H, C$\underline{H_3}$CH$_2$); 1.11(t,J = 7.8, 3H, C$\underline{H_3}$CH$_2$O); 1.63 (s, 1H, CH_3 at C_2); 1.98 (q, J = 7.5, 3H, $CH_3C\underline{H_2}$); 3.98 (q, J = 7.8, 2H, $CH_3C\underline{H_2}O$); 7.24 (s, 5H, Ar-H); 7.78 (m, 1H, NH). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.10; H, 6.56; N, 4.82.

Ethyl 2-methyl-4-oxo-5-phenyl-2,3-dihydro-4*H*-1,3-oxazine-6-carboxylate (**3h**)

Following the procedure described above for (**3d**) using ethyl 3-cyano-3-phenylpyruvate[8] and acetaldehyde to give (**3h**) (45 %); mp 135°C. Ir ($CHCl_3$): ν = 3420 (NH), 1725 (CO_2), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.05 (t,J = 7.8, 3H, C$\underline{H_3}$CH$_2$); 1.61 (d, J = 6.2, 3H, C$\underline{H_3}$CH); 4.03 (q, J = 7.8, 2H, CH_2); 5.50 (dd, J = 6.2 and J = 2.3, 1H, H_2); 7.32 (s, 5H, Ar-H); 7.70 (m, 1H, NH). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 63.98; H, 5.74; N, 5.32.

Ethyl 4-oxo-2,5-diphenyl-2,3-dihydro-4*H*-1,3-oxazine-6-carboxylate (**3l**)

Following the procedure described above for (**3d**) using ethyl 3-cyano-3-phenylpyruvate[8] and benzaldehyde to give (**3l**) (56 %); mp 146°C. Ir ($CHCl_3$): ν = 3420 (NH), 1725 (CO_2), 1665 (CO), 1605 (C=C) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.08 (t, *J* = 7.8, 3H, CH_3); 4.00 (q, *J* = 7.8, 2H, CH_2); 6.30 (d, *J* = 2.4, 1H, H_2); 7.20-7.50 (m, 10H, Ar-H); 7.72 (m, 1H, NH). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 69.97; H, 5.24; N, 4.30.

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