CYCLOCONDENSATION OF β-OXONITRILES WITH KETONES OR ALDEHYDES

Jean-François Stambach*, Louis Jung, and Raymond Hug

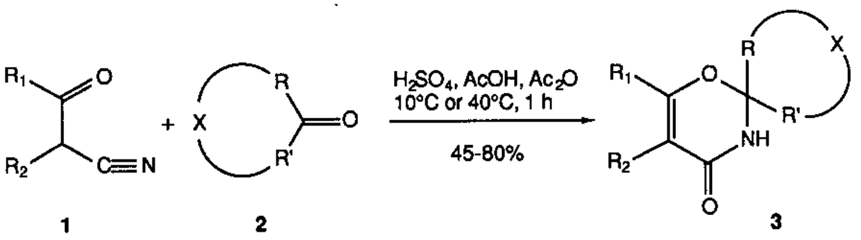
Laboratoire de Chimie Thérapeutique,
U.F.R. des Sciences Pharmaceutiques, Université Louis Pasteur,
74 route du Rhin, B.P. 24, F-67401 ILLKIRCH - France

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)



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	$4\text{-}CH_3OC_6H_4$		- $[CH_2]_5$ -		80
e	CO_2Et	$4\text{-}CH_3OC_6H_4$	- $[CH_2]_2$ -	- $[CH_2]_2$ -	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

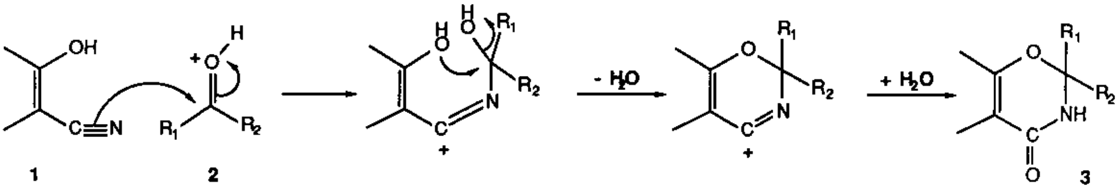
Scheme 1

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_2O (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, $C\underline{H}_3CH_2$); 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_3CH_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}. ^1H-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}. ^1H-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, $C\underline{H}_3CH_2$); 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, $C\underline{H}_3CH_2$); 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, $C\underline{H}_3CH_2$); 1.11(t,*J* = 7.8, 3H, $C\underline{H}_3CH_2O$); 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, $CH_3C\underline{H}_2O$); 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, $C\underline{H}_3CH_2$); 1.61 (d, *J* = 6.2, 3H, $C\underline{H}_3CH$); 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 ($CHCl_3$): $\nu = 3420$ (NH), 1725 (CO_2), 1665 (CO), 1605 (C=C) cm^{-1}. ^1H-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.

REFERENCES

1. P. Cordier, L. Jung, and R. Hug, Ger. Offen.,2,241,271 (Chem.Abstr.,1973, 78, 159632q). P. Cordier, L. Jung, and R. Hug, U.S 3,865,821 (Chem.Abstr.,1975, 83, 79256h).
2. R.R. Schmidt, Synthesis, 1972, 333-350.
3. C. A. Keane and W. W. S. Nicholls, J. Chem. Soc., 1907, 91, 264. H. Hicks, J. Chem. Soc., 1910, 97, 1032. H. Fischer, G. Dangschadt, and H. Stettiner, Ber., 1932, 65, 1032. G. Ohnacker and A. Kottler, Ger. Offen.,959 825 (Chem.Abstr., 1957, 53, 17154c).
4. R. Lacey, J. Chem. Soc., 1954, 845. R. Lacey and W. Ward, J. Chem. Soc., 1958, 2134.
5. J. L. Irvine and C. Piantadosi, Synthesis, 1972, 568.
6. L. Claisen, Ber., 1892, 25, 1776.
7. E. V. Meyer, J. Prakt. Chem., 1908, 78, 498.
8. G. S. Skinner, J. Am. Chem. Soc., 1966, 55, 2036.
9. I. C. Badhwar, W. Backer, B. K. Menon, and K. Venkataraman, J. Chem. Soc., 1931, 1541.
10. M. Asano and Y. Kameda, Ber. , 1934, 67, 1522.

Received, 4th August, 1993