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N-ACYLATED α-AMINONITRILES AND THEIR CONVERSION INTO 5-AMINOOXAZOLE, 5(4H)-OXAZOLONE AND 4(5H)-IMIDAZOLONE DERIVATIVES

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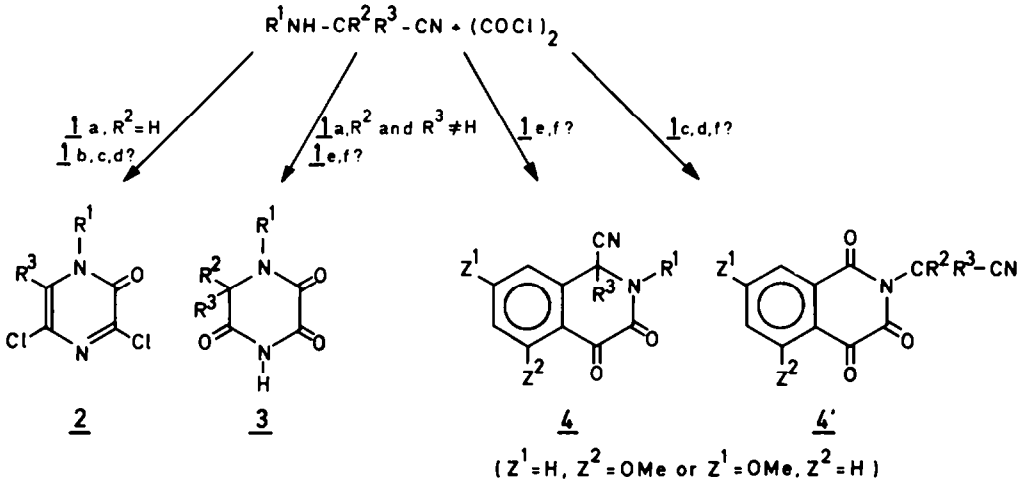
Abstract - In contrast with the reaction of α-aminonitriles 1a, the corresponding N-acylated α-aminonitriles 1b-f and oxalyl chloride do not yield pyrazinone derivatives, but 5-aminooxazoles 9-11 or 4(5H)-imidazolones 12, the latter being converted in some cases into imidazo [2,1-a]isoquinoline-2,5,6(3H)-triones. Reactions of compounds 1b-f and ethyl chlorooxoacetate provide evidence for a 5(4H)-iminooxazole intermediate 7, which aromatizes to yield 5-aminooxazoles 9-11; however, unaromatizable intermediates of type 7 - isolable as 5(4H)-oxazolones 13 after hydrolysis - undergo a catalyzed Dimroth-type rearrangement to give imidazolone derivatives 12.

N-Alkyl or N-aryl substituted α-aminonitriles of type 1a (R^2 and/or R^3= H) react with oxalyl chloride to form 2(1H)-pyrazinones 2a (Scheme 1). This cyclization has been proposed to occur through an attack of the nitrile function - transformed into an imidoyl chloride or the tautomeric α-chloroenamine - on the intermediate oxamoyl chloride.[1] The resulting 2,3-pyrazinedione is then converted into a compound of type 2a by chlorination of the CONH-group with excess of oxalyl chloride.

With compounds 1a (R^2 and $R^3 \neq$ H) cyclization only occurred in special conditions and piperazine-2,3,5-triones 3a could be isolated.[2] (Scheme 1)

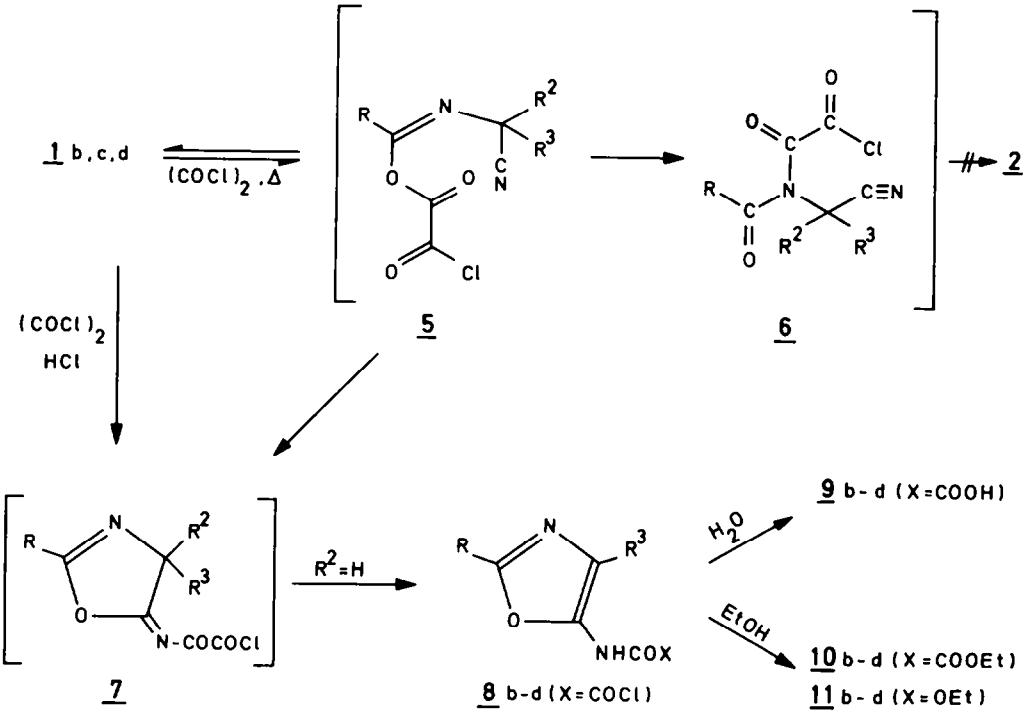
Continuing our work on this synthetic pathway towards pyrazine derivatives, we performed reactions with N-acylated α-aminonitriles 1b-f to see whether N-acylated compounds of type 2b-d or 3e-f could be formed. Taking into account the results[3] from the reaction of appropriate benzamides and oxalyl chloride one could also expect the formation of isoquinoline-diones or -triones of type 4 or 4'.

The spectral data of the products obtained on treatment of 1b-d with oxalyl chloride in o-dichlorobenzene (ODCB) at 65° and 120°, followed by work-up with water or ethanol, showed clearly that neither the pyrazine nor the isoquinoline skeleton was formed. According to the ^{13}C NMR and IR spectra of the isolated compounds 9-11 (Scheme 2), the nitrile function and the original amide group had disappeared. Their involvement in another heterocyclic skeleton - an oxazole - was presumed on the basis of a ^{13}C NMR absorption around δ = 158 ppm, as is found for C-2 of oxazoles.[4] The mass spectra of the reaction products 9-11c,d had a main fragment with m/z = 135 (100%), corresponding to [m-$MeOC_6H_4CO$]$^+$. This is in agreement with the mass spectral behaviour of 2-substituted oxazoles.[5] Final proof of the structure was obtained by treatment of 2-phenyl-5-aminooxazole[6a] with ethyl chlorooxoacetate, yielding compound 10b.



1 : $R^1NH-CR^2R^3-CN$							
suffix	R^1	R^2	R^3	suffix	R^1	R^2	R^3
a	alkyl, aryl	H,	alkyl or aryl	d	3-$MeOC_6H_4CO$	H	C_6H_5
b	C_6H_5CO	H	H	e	C_6H_5CO	Me	3-$MeOC_6H_4$
c	3-$MeOC_6H_4CO$	H	H	f	3-$MeOC_6H_4CO$	Me	3-$MeOC_6H_4$

Scheme 1.

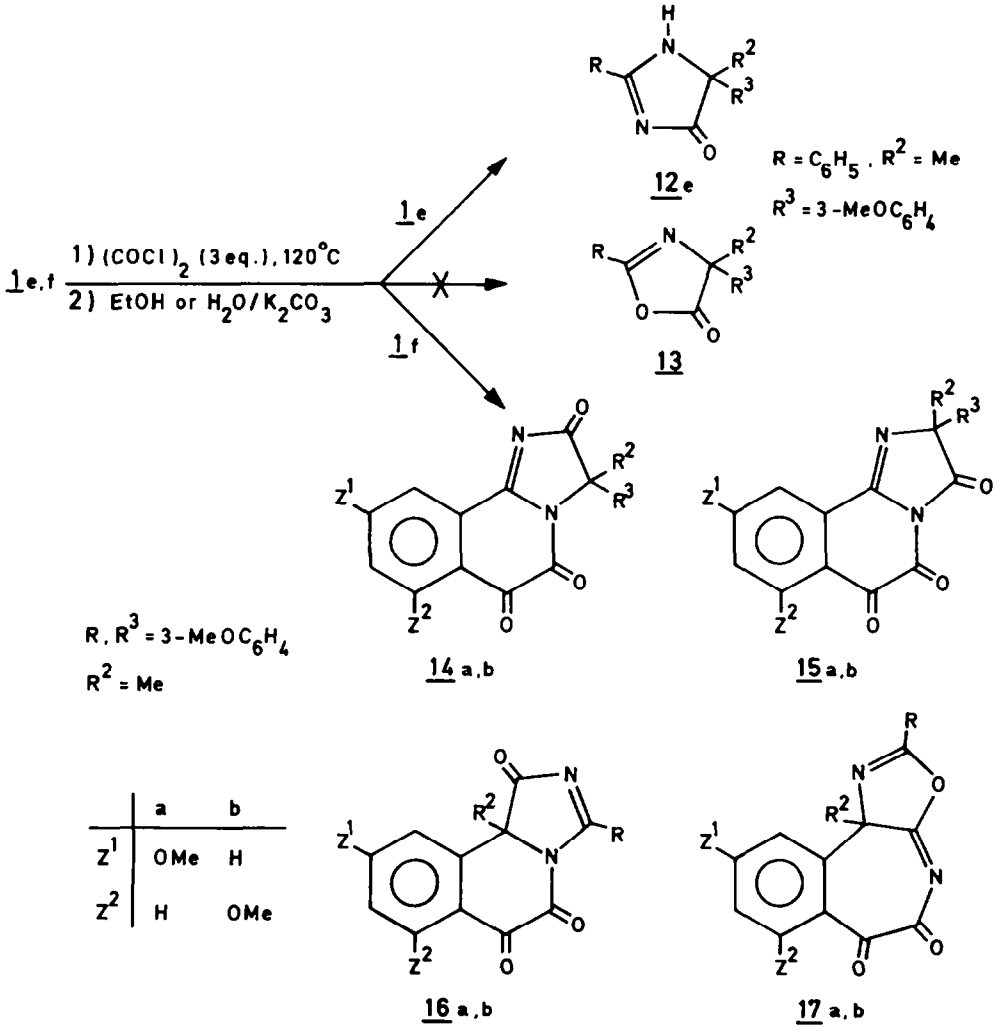


Scheme 2.

8-11	b	c	d
R	C_6H_5	3-$MeOC_6H_4$	3-$MeOC_6H_4$
R^3	H	H	C_6H_5

The formation of 2(1H)-pyrazinone skeleton 2 through an oxamoyl derivative 6, which is normally formed from the O-acylated intermediate 5,[7] obviously does not occur. This is probably due to an easy ring closure via the amide and the nitrile function. The reaction may proceed directly from compound 1b-d in a comparable way as proposed by Fleury[6b] for the proton catalysed conversion of N-acylated α-aminonitriles. However, HCl addition on the nitrile function of 5 followed by a rapid attack of the imino-group on the oxalate function and concomitant ring closure on the imidoyl carbon atom is an alternative pathway. The acylated 5(4H)-iminooxazole 7 then readily undergoes aromatization to yield compounds of type 8, which are isolated as 9 (after aqueous work-up) or 10 and 11 (after ethanolic work-up).

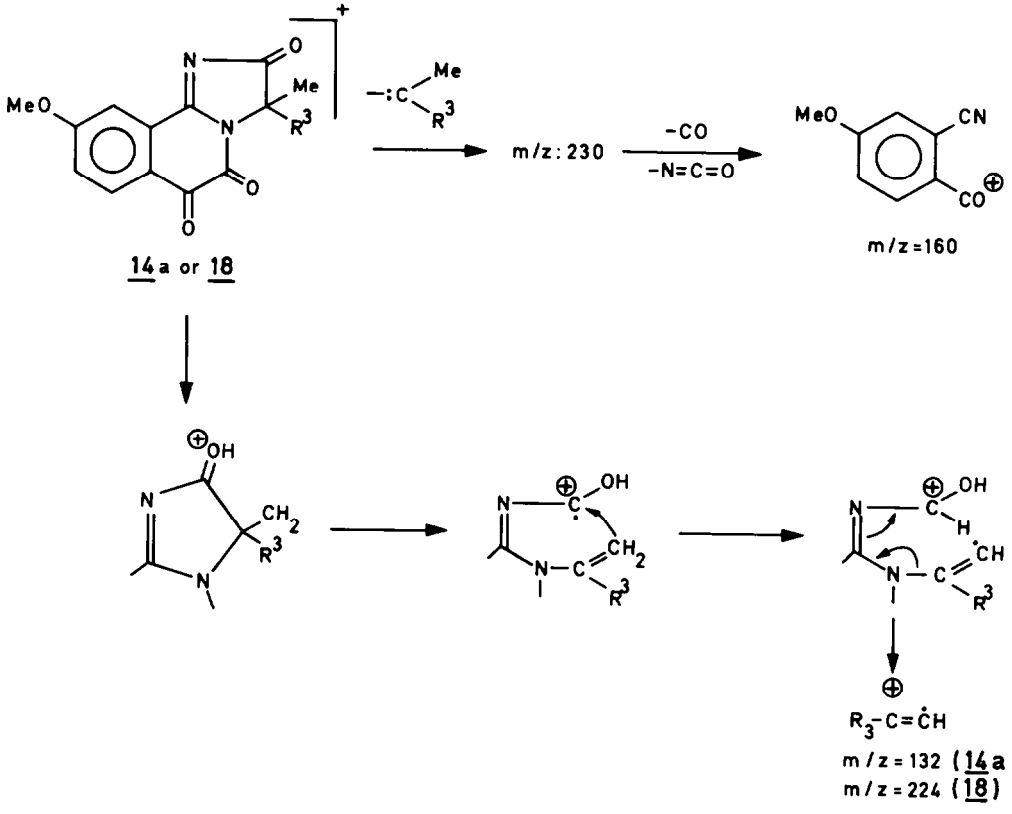
Although Poupaert[8] mentioned the formation of a 5(4H)-iminooxazole derivative, on treatment of a N-acylated α-aminonitrile of type 1e-f with hydrochloric acid at 0°, the reaction of 1e with oxalyl chloride at 120° yielded another cyclic product. Ethanolic or aqueous work-up of the reaction mixture yielded a product with a m/z-value of 280 for M^+, excluding the expected structure 13e. Main fragments in the mass spectrum had a m/z-value of 117 and 104, corresponding to $PhCN^+$ and $PhCNH^+$. The ^1H NMR spectrum with a broad D_2O-exchangeable NH absorption at δ = 10.9 ppm and the ^{13}C NMR absorptions at δ = 158.8 ppm and 188.3 ppm are in agreement with the 4(5H)-imidazolone structure 12e. A tautomeric structure containing the N=C-NHCO fragment is rejected on the basis of the ^{13}C NMR absorptions which are consistent[9] with a C=N-C=O fragment.



Scheme 3.

Treatment of compound 1f with oxalyl chloride gave two isomeric products, presumed to have structures 14a (main product) and 14b. Their ^{13}C NMR and IR spectra showed the absence of a nitrile function; the absorptions at δ = 170.9 ppm and 188.9 ppm in the ^{13}C NMR pointed to a C=N-C=O fragment[9] in an imidazole ring. The ^{1}H NMR spectra were in agreement with cyclization to an aromatic ring. Considering that appropriate benzamides and oxalyl chloride afforded isoquinoline derivatives,[3] other isomeric structures (15-17) were taken into account (scheme 3). They could be obtained by a ring closure of the acid chloride function of a 5(4H)-iminooxazole of type 7 (yielding 17) or of an acylated 4(5H)-imidazolone to yield one of the compounds 14-16.

Structures 16 and 17 were considered to be less probable as cyclized products of this type were not formed in the reaction with 1e. They were definitely eliminated due to the results obtained from treatment of 14a with HNO_3. This yielded a new compound 18, formed by dinitration of one aromatic ring. The molecular ion (m/z = 454) in the mass spectrum of the dinitrated product was unstable and split into two fragments : m/z = 230 (7%) and m/z = 224 (100%). The fragment m/z = 230 was also found for compound 14a, together with a fragment of m/z = 160 probably due to the loss of CO and NCO from 230.

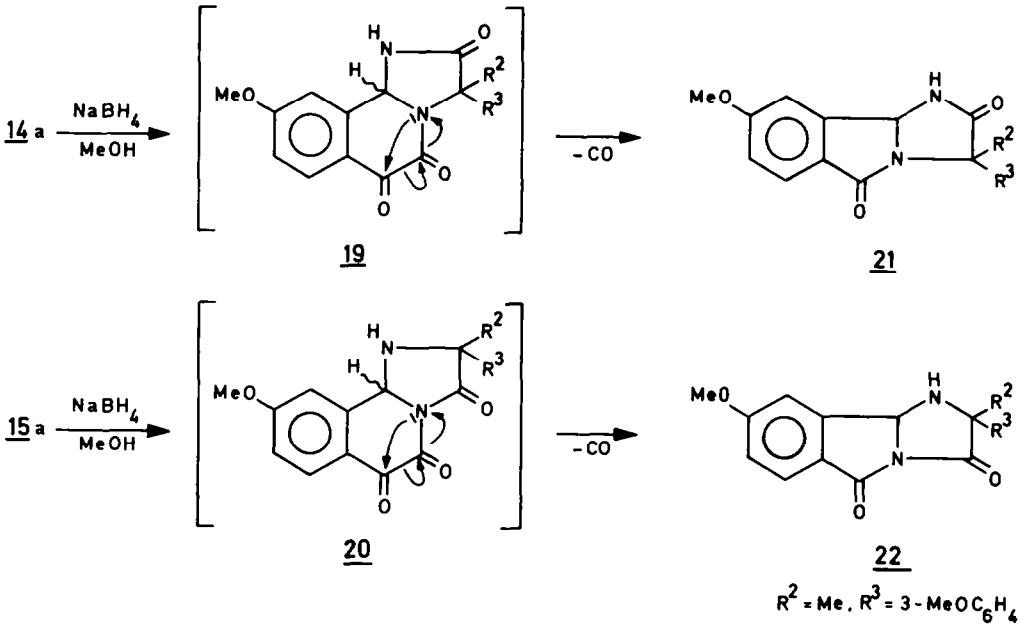


Scheme 4. Mass spectra, fragmentations from 14a (R^3 = 3-$MeOC_6H_4$) and its dinitrated analogue 18 (R^3 = 3-MeO-$C_6H_2(NO_2)_2$)

The ion with m/z = 224 (100%) is the dinitrated analogue of the fragment with m/z = 132, found in the mass spectrum of 14a and probably originating from fragmentations shown in scheme 4. These results pointed out that the aromatic ring, which is a part of the isoquinoline skeleton, was not attacked by nitric acid. This behaviour could be expected for structures of type 14 or 15, but not for structures as 16 or 17. In the latter both aromatic nuclei are similarly desactivated, but in the former structures the exocyclic aromatic ring R^3 is more activated than the isoquinoline nucleus. Further evidence on the structure of 14a was obtained by treatment with $NaBH_4$ in methanol[13] or Pd/C,H_2. Depending on the structure of the compound (14a or 15a) the reaction pro-

duct should have the structure 19 or 20 (Scheme 5), which could be differentiated by the presence or absence of a CONH-group. However, the mass spectrum of the reaction product indicated the uptake of one equivalent of hydrogen and the loss of CO.

The disappearance of ^{13}C NMR absorptions at δ = 170.9 ppm and at δ = 151.2 ppm pointed to reduction of the C=N-group and loss of a carbonyl function from the isoquinoline skeleton. An aromatic proton with a chemical shift of 7.85 ppm, acceptable for an isoindole skeleton, was observed in the ^1H NMR spectrum, which showed also a D_2O exchangeable proton at δ = 8.8 ppm.



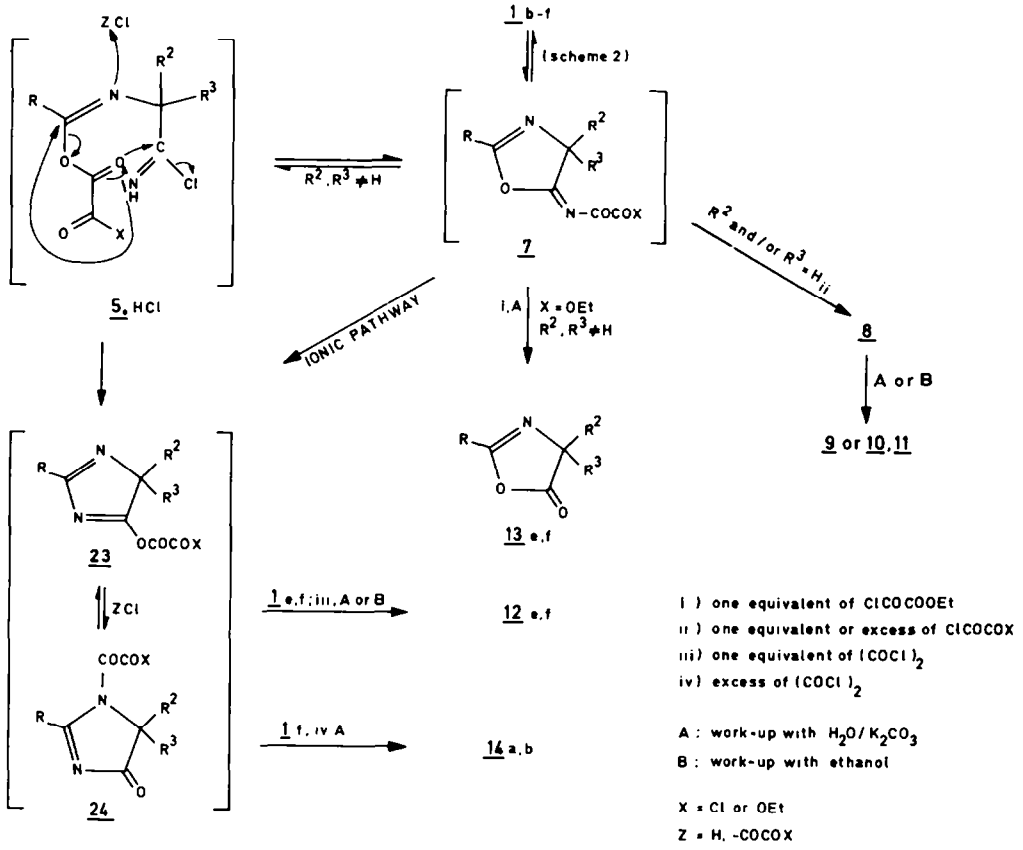
Scheme 5.

In the mass spectrum of the reduced product an important loss of NHCO from the molecular ion (M^+-NHCO : m/z = 295 (100%), metastable peak at m/z = 257.5) was found. These data are in agreement with structure 21, which was unequivocally established by its synthesis via an independent method.[12] The result of this reduction reaction shows clearly the formation of the structures 14a,b in the reaction of 1f and oxalyl chloride. The formation of 21 is assumed to occur through intermediate 19, which could lose CO by the path shown (Scheme 5).

Further experiments with 1e,f using various amounts of oxalyl chloride and ethyl chlorooxoacetate threw more light on the reaction paths followed on treatment of compounds 1 with oxalyl chloride:

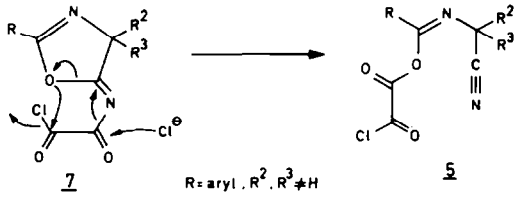
1. Using one equivalent of ethyl chlorooxoacetate, the reaction mixture contained only traces of the 4(5H)-imidazolone 12e,f. The main product was a 5(4H)-oxazolone 13e,f (ν_{CO} = 1810 cm^{-1}) obtained from hydrolysis of the 5(4H)-iminooxazole of type 7 (Scheme 6) during work-up. The mass spectrum of 13f showed a molecular ion at m/z = 311, with an important loss of CO_2 (m/z 267, 47%) and a [m-$MeOC_6H_4CNO$]$^+$ fragment (m/z = 149, 60%).
2. Reaction of one equivalent of ethyl chlorooxoacetate followed by addition of HCl gas or of two equivalents of ethyl chlorooxoacetate, led to the compounds 12e,f. Only traces of 13e,f were observed. The same results were obtained when three equivalents of ethyl chlorooxoacetate were used.
3. Using one equivalent of oxalyl chloride, instead of three equivalents (as usual), 12e,f and only traces of 14a and 14b (with 1f) were isolated. Further cyclization into 14 (with 1f) was only observed on subsequent addition of HCl gas or an excess (1 equivalent) of oxalyl chloride.

This behaviour is summarized in the reaction paths of scheme 6.



Scheme 6 .

Reaction of oxalyl chloride or ethyl chlorooxoacetate with 1 can lead to intermediate 7; the latter isomerizes into 8 when R^2 or R^3 = H, and the products 9-11 can be isolated (cf scheme 4). However, with an unaromatizable intermediate of type 7 - isolated as a 5(4H)-oxazolone on hydrolysis - a Dimroth-type rearrangement into an imidazole derivative 23 is assumed to occur. It is not obvious whether this process takes place via the O-acylated intermediate 5.HCl and ZCl (=HCl, $(COCl)_2$ or EtOOC-COCl)-catalyzed ring closure, or via an ionic pathway. Anyway, compound 12e was exclusively formed from 1e with oxalyl chloride as reagent; with one equivalent of ethyl chlorooxoacetate compound 13e was the main product. These results can be accounted for by the easy formation of compound 5 due to the ring opening of 7 and internal O-acylation as shown below. However, a competitive ionic pathway seems reasonable: indeed, when using the more polar solvent ni-



Scheme 7.

trobenzene instead of ODCB, a substantially higher amount of 12f was obtained in the reaction of 1f with one equivalent of ethyl chlorooxoacetate. A similar rearrangement of 5(4H)-iminooxazoles to 4(5H)-imidazolones was observed when 1e,f was treated with hydrogen chloride in ODCB. Treatment with one equivalent of hydrogen chloride, followed by aqueous work-up, yielded compound 13e,f; however, use of a continuous stream of hydrogen chloride led to compounds 12e,f.

With work-up method B the intermediates 23 or the isomer 24 (X = OEt) could be detected in the mass spectrum, but isolation of them could not be realized. Intermediate 24 (X = Cl) - obtained from 23 on isomerization with excess of oxalyl chloride or hydrochloric acid - is assumed to cyclize and to yield compounds 14a,b only with 1f, which contains an activated aromatic ring. Prior formation of the isoquinoline skeleton via direct cyclization of intermediate 6 does not occur probably due to the more easy pathway into the heterocyclic five membered ring.

We may conclude that N-acyl-α-aminonitriles and oxalyl derivatives do not produce 2(1H)-pyrazinones as do α-aminonitriles. The reaction proceeds via 5(4H)-iminooxazole intermediates, which can undergo aromatization to yield oxazolones or rearrange to give 4(5H)-imidazolones. On use of an excess of oxalyl chloride imidazo[2,1-a]isoquinoline-2,5,6(3H)-triones can be obtained in some cases.

EXPERIMENTAL

All m.ps. are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Mass spectra were taken on a AEI-MS-12 apparatus (ionization energy 70 eV) and NMR spectra on a Jeol JNM-MH-100 spectrometer at 100 MHz, on a Varian EM-390 at 90 MHz, and a Bruker WM-250 at 250 MHz. For the ^{13}C NMR spectra a Bruker WP80 spectrometer was used. The chromatographic purifications were performed with silica gel from Macherey & Nagel (70-230 mesh) and Merck (230-400 mesh). All $CHCl_3$ used was stabilised with amylene.

N-acyl-α-aminonitriles

The N-acyl-α-aminonitriles resulted from the reaction of an aroyl chloride on a cooled solution of a α-aminonitrile[10] according to known procedures.[11] The reactions were carried out in CH_2Cl_2, with pyridine (1b) or triethylamine (1c-f).

2-Benzamido-ethanenitrile (1b): yield 94%; m.p. 144°; IR (KBr) cm^{-1}: 3230 (NH), 2250 (CN), 1640 (amide); ^1H NMR δ (DMSO-d_6): 4.35 (2H, d, J=5Hz, CH_2), 7.30-7.65 (3H, m, H-aryl), 7.95 (2H, dxd, J=8x2Hz, o-H-aryl), 9.20 (1H, broad t, J=5Hz, NHCO).

2-(m-Methoxybenzamido)-ethanenitrile (1c): yield 91%; m.p. 107°; IR (KBr) cm^{-1}: 3260 (NH), 2250 (CN), 1650 (amide); ^1H NMR δ (DMSO-d_6): 3.82 (3H, s, OMe), 4.30 (2H, d, J=5Hz, CH_2), 7.05-7.20 (1H, m, 4'-H-aryl), 7.35-7.52 (3H, m, 2', 5', 6'-H-aryl), 9.18 (1H, broad t, J=5Hz, NHCO).

2-(m-Methoxybenzamido)-2-phenylethanenitrile (1d): yield 88%; m.p. 117°; IR (KBr) cm^{-1}: 3260 (NH), 2240 (CN), 1645 (amide); ^1H NMR δ ($CDCl_3$): 3.76 (3H, s, OMe), 6.24 (1H, d, J=8Hz, CHCN), 7.00-7.60 (10H, m, H-aryl and NHCO).

2-Benzamido-2-(m-methoxyphenyl)-propanenitrile (1e): yield 91%; m.p. 178°; IR (KBr) cm^{-1}: 3300 (NH), 2250 (CN), 1650 (amide); ^1H NMR δ (DMSO-d_6): 2.00 (3H, s, Me), 3.80 (3H, s, OMe), 6.90-7.65 (7H, m, H-aryl), 7.95 (2H, dxd, o-H of C_6H_5CO), 9.4 (1H, broad s, NHCO).

2-(m-Methoxybenzamido)-2-(m-methoxyphenyl)-propanenitrile (1f); yield 93%; m.p. 119°; IR (KBr) cm^{-1}: 3250 (NH), 2250 (CN), 1645 (amide); ^1H NMR δ ($CDCl_3$): 1.88 (3H, s, Me), 3.68 and 3.75 (2x3H, 2xs, 2xOMe), 6.75-7.30 (8H, m, H-aryl), 7.70 (1H, s, NHCO).

Reaction of N-acyl-α-aminonitriles with oxalyl chloride

General method. N-Acyl-α-aminonitrile 1b-f (5 mmole) in o-dichlorobenzene (ODCB) 50 ml was added to stirred oxalyl chloride (15 mmole) in 50 ml of ODCB at room temp. The temperature was gradually increased to 65° (1b-d) or 120° (1e-f). When the reaction was complete (± 3 hr), the solution was cooled in an ice bath. With compounds 1b-d and using work-up method A, compounds 9 were isolated; method B led to the products 10-11. The same products were obtained when the reaction was performed with one equiv. (5 mmole) of $(COCl)_2$ or at 120°.

Using 1e-f as starting material and three equiv. (15 mmole) $(COCl)_2$ (120°, work-up A or B) compounds 12e (1e) and 14a,b (1f) were isolated; traces of the N-acylated derivative 23-24 could be detected but not isolated (work-up B) due to easy deacylation. With 1f and one equivalent (5 mmole) of $(COCl)_2$, compound 12f and traces of 14a,b were obtained. Subsequent addition of excess $(COCl)_2$ or HCl gave 14a,b; addition of KCl and 18-crown-6 yielded 12f and traces of 14a,b.

Work-up method A : To the cooled and stirred reaction mixture, 100 ml of a 0.1M K_2CO_3 solution in water was gradually added. The mixture was then extracted with 200 ml of $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel.

Work-up method B : A solution of 50 ml of absolute ethanol in 50 ml of $CHCl_3$ was added to the cooled and stirred reaction mixture. After 15 min, 200 ml of $CHCl_3$ was added and the solution was washed consecutively with 100 ml of 0.1M K_2CO_3 and with 100 ml of saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel with solvent systems a(1b) and b (1c-f). Solvent system a is a gradient of $CHCl_3$-CH_3CN from 99:1 to 99:5. Solvent system b is a gradient of $CHCl_3$-CH_3CN from 99:1 to 9:1.

Ethyl N-(2-phenyloxazol-5-yl)-oxamate (10b): yellowish oil; yield 884 mg (68%); IR (KBr) cm^{-1}: 3290 (NH), 1735-1705 (CO); ^1H NMR, δ ($CDCl_3$): 1.40 (3H, t, Me), 4.44 (2H, q, OCH_2), 7.34-7.40 (4H,

m, H-aryl and 4-H), 7.89 (2H, dxd, J=2Hz, o-H-aryl), 9.90 (1H, broad s, NH); ^{13}C NMR, δ : 13.9 (Me), 63.9 $COCH_2$), 114.9 (4-C), 125.9 (o-C-aryl), 142.8 (5-C), 152.5 (NHCO), 156.7 (2-C), 159.3 (EtO-CO); m/z (%): 260 (M^+, 7), 232 (M^+ - CO, 3), 188 and 187 (5-oxazolyl-$NH_{(2)}CO^+$, 11 and 14), 186 (5-oxazolyl-NCO^+, 49), 160 and 159 (5-oxazolyl $NH_{(2)}^+$, 11 and 15), 158 (5-oxazolyl-N^+, 17), 105 ($PhCO^+$, 100), 104 ($PhCNH^+$, 26), 103 ($PhCN^+$, 17).

Ethyl N-(2-phenyloxazol-5-yl)-carbamate (11b): yellowish oil; yield 81 mg (7%); IR ($CHCl_3$) cm^{-1}: 3425 (NH), 1710 (CO); ^{1}H NMR, δ ($CDCl_3$): 1.40 (3H, t, Me), 4.40 (2H, q, OCH_2), 7.30-7.40 (4H, m, H-aryl and 4-H), 7.90 (2H, dxd, J=8x2Hz, o-H-aryl), 9.80 (1H, broad s, NH); m/z (%): 232 (M^+, 7), 214 (M^+ - CO, 1), 160 (M^+ - C_2H_4 - CO_2, 84), 105 ($PhCO^+$, 100).

Ethyl N-[2-(m-methoxyphenyl)-oxazol-5-yl]-oxamate (10c): yellowish oil; yield 943 mg (65%); IR ($CHCl_3$) cm^{-1}: 3320 (NH), 1745-1700 (CO); ^{1}H NMR, δ ($CDCl_3$): 1.40 (3H, t, Me), 3.80 (3H, s, OMe), 4.35 (2H, q, OCH_2), 6.80-7.50 (5H, m, H-aryl and 4-H), 9.85 (1H, broad s, NH); ^{13}C NMR δ : 13.8 (Me), 55.3 (OMe), 63.9 (OCH_2), 110.8-127.8 (4-C, C-aryl), 143.1 (5-C), 155.6 (NHCO), 159.4 (2-C), 159.9 and 160.3 (COMe , COOEt); m/z (%): 290 (M^+, 31), 262 (M^+ - CO, 1), 190 and 189 (5-oxazolyl-$NH_{(2)}^+$, 15 and 10), 188 (5-oxazolyl-N^+, 12), 135 (m-$MeOC_6H_4CO^+$, 100), 134 (m-$MeOC_6H_4CNH^+$, 17), 133 (m-$MeOC_6H_4CN^+$, 13).

Ethyl N-[2-(m-methoxyphenyl)-oxazol-5-yl]-carbamate (11c): yellowish oil; yield 131mg (9%); IR ($CHCl_3$) cm^{-1}: 3430 (NH), 1710 (CO); ^{1}H NMR, δ ($CDCl_3$): 1.40 (3H, t, Me), 3.90 (3H, s, OMe), 4.40 (2H, q, OCH_2), 6.80-7.50 (5H, m, H-aryl and 4-H), 9.70 (1H, broad s, NH); ^{13}C NMR, δ : 14.0 (Me), 55.5 (OMe), 64.2 (OCH_2), 110.9-130.2 (4-C and C-aryl), 143.2 (5-C), 152.8 (NHCOOEt), 159.6 (2-C), 160.2 (COMe); m/z (%): 262 (M^+, 5), 234 (M^+ - CO, 1, metastable peak at 209), 190 (M^+ - C_2H_4 - CO_2, 80), 135 (m-$MeOC_6H_4CO^+$, 100).

Ethyl N-[2-(m-methoxyphenyl)-4-phenyloxazo]-5-yl]-oxamate (10d): yellowish oil; yield 1.24 g (68%); IR ($CHCl_3$) cm^{-1}: 3300 (NH), 1735-1705 (CO); ^{1}H NMR, δ ($CDCl_3$): 1.35 (3H, t, Me), 3.85 (3H, s, OMe), 4.35 (2H, q, OCH_2), 6.90-7.80 (9H, m, H-aryl), 9.00 (1H, broad s, NH); ^{13}C NMR, δ : 14.3 (Me), 55.8 (OMe), 64.5 (OCH_2), 111.6-130.3 (4-C and CH-aryl), 128.6-133.6 (C-aryl), 135.2 (5-C), 156.1 (NHCO), 159.1 (2-C), 160.1 and 160.4 (COOEt, C-OMe); m/z (%): 366 (M^+, 63), 338 (M^+ - CO, 2), 266 and 265 (5-oxazolyl-$NH_{(2)}^+$, 29 and 21), 264 (5-oxazolyl-N^+, 33), 135 (m-$MeOC_6H_4CO^+$, 100), 134 (m-$MeOC_6H_4CNH^+$, 52), 133 (m-$MeOC_6H_4CN^+$, 17); exact mass: 366.121 ± 0.001, calc. for $C_{20}H_{18}N_2O_5$: 366.1216.

Ethyl N-[2-(m-methoxyphenyl)-4-phenyloxazol-5-yl]-carbamate (11d): yellowish oil; yield 152 mg (9%); IR ($CHCl_3$) cm^{-1}: 3420 (NH), 1715 (CO); ^{1}H NMR δ ($CDCl_3$): 1.25 (3H, t, Me), 3.80 (3H, s, OMe), 4.20 (2H, q, OCH_2), 6.90-7.80 (9H, m, H-aryl), 9.95 (1H, broad s, NH); ^{13}C NMR, δ : 14.3 (Me), 55.4 (OMe), 62.5 (OCH_2), 111.2-129.9 (4-C and CH-aryl), 128.5-132.9 (C-aryl), 137.1 (5-C), 154.9 (NHCO), 158.2 (2-C),159.9 (C-OMe); m/z (%): 338 (M^+, 3), 310 (M^+ - CO, 1), 266 (M^+ - C_2H_4 - CO_2, 83), 135 (m-$MeOC_6H_4CO^+$, 100); exact mass: 338.126 ± 0.001, calc. for $C_{19}H_{18}N_2O_4$: 338.1266.

N-[2-(m-Methoxyphenyl)-4-phenyloxazol-5-yl]-carbamic acid (9d): yellowish oil; yield 794 mg (47%); ^{1}H NMR, δ ($CDCl_3$): 3.85 (3H, s, OMe), 7.00-7.90 (9H, m, H-aryl), 11.50 (1H, broad s, NH), 14.4 (1H, broad s, COOH); ^{13}C NMR, δ :55.9 (OMe), 111.5-132.9 (4-C and C-aryl), 136.4 (5-C), 158.2 (2-C), 159.7 (C-OMe), 160.5 (NHCO), 161.4 (COOH); m/z (%): 338 (M^+, 55), 310 (M^+ - CO, 1), 294 (M^+ - CO_2, 8), 293 (M^+ - COOH, 6), 292 (5-oxazolyl-NCO^+, 17), 266 and 265 (5-oxazolyl-$NH_{(2)}^+$, 53 and 9), 264 (5-oxazolyl-N^+, 21), 177 (310 - m-$MeOC_6H_4CN$, 6), 135 (m-$MeOC_6H_4CO^+$, 100), 134 (m-$MeOC_6H_4CNH^+$, 100), 133 (m-$MeOC_6H_4CN^+$, 57).

5-(m-Methoxyphenyl)-5-methyl-2-phenyl-4(5H)-imidazolone (12e): yield 882 mg (63%); m.p. 158°; IR ($CHCl_3$) cm^{-1}: 3000 (NH), 1730 (CO); ^{1}H NMR, δ ($CDCl_3$): 1.85 (3H, s, Me), 3.80 (3H, s, OMe), 6.75-6.90 (1H, m, 4'-H of 5-aryl), 7.20-7.60 (6H, m, H-aryl), 8.05 (2H, dxd, o-H of 2-phenyl), 10.90 (1H, broad s, NH); ^{13}C NMR, δ : 25.7 (Me), 55.2 (OMe), 73.4 (5-C), 111.9-132.0 (CH-aryl), 128.4 (1-C of 2-phenyl), 141.3 (1-C of 5-aryl), 158.8 (2-C), 159.6 (3-C of 2-aryl), 188.3 (CO); m/z (%): 280 (M^+ 100), 265 (M^+ - Me, 24), 252 (M^+ - CO, 22), 251 (M^+ - CO - H, 83), 134 (m-$MeOC_6H_4$-C^+-Me, 25), 117 ($PhCN_2^+$, 11), 104 ($PhCNH^+$, 50).

2-(m-Methoxybenzamido)-2-(m-methoxyphenyl)-propanenitrile (1f) yielded 12f with one equiv. $(COCl)_2$; compounds 14a,b were obtained with three equiv. $(COCl)_2$: work-up A or B.

2,5-Di(m-methoxyphenyl)-5-methyl-4(5H)-imidazolone (12f): yield 978 mg (63%); IR ($CHCl_3$) cm^{-1}: 3005 (NH), 1730 (CO); ^{1}H NMR, δ ($CDCl_3$): 1.90 (3H, s, Me), 3.80 and 3.90 (2x3H, 2xs, 2xOMe), 7.00-7.70 (8H, m, H-aryl), 11 (1H, broad s, NH); ^{13}C NMR, δ : 25.8 (Me), 55.3 and 55.6 (2xOMe), 73.8 (5-C), 111.6-119.7 (C-aryl), 129.6 (1-C of 2-aryl), 141.2 (1-C of 5-aryl), 158.5 (2-C), 159.9 (3-C of 2-aryl), 160.2 (3-C of 5-aryl), 188.8 (CO); m/z (%): 310 (M^+, 100), 295 (M^+ - Me, 21), 282 (M^+ - CO, 20), 281 (M^+ - CO - H, 90), 148 (m-MeO-C_6H_4-CN_2H^+, 20), 134 (m-MeO-C_6H_4-C^+-CH_3 and m-$MeOC_6H_4CNH^+$, 93); exact mass: 310.131 ± 0.001, calc. for $C_{18}H_{18}N_2O_3$: 310.1317.

9-Methoxy-3-(m-methoxyphenyl)-3-methylimidazo[2,1-a]isoquinoline-2,5,6(3H)-trione, (14a): yield 1,2 g (66%), m.p. 146°; IR ($CHCl_3$) cm^{-1}: 1760, 1730, 1700 (CO); ^{1}H NMR, δ ($CDCl_3$): 2.10 (3H, s, Me), 3.80 (3H, s, 3' - OMe), 4.00 (3H, s, 9-OMe), 6.75-7.00 (3H, m, 2'-H, 4'-H, 6'-H), 7.30 (1H, m, 1'-H), 7.35 (1H, dxd, J=8x2Hz, 8-H), 8.00 (1H, d, J=2Hz, 10-H), 8.20 (1H, d, J=8Hz, 7-H); ^{13}C NMR, δ : 20.9 (Me), 55.4 and 56.6 (2xOMe), 68.8 (3-C), 126 and 128.6 (6a-C and 10a-C), 137.1 (1'-C), 151.2 (5-CO), 160.3 (3'-C), 166.3 (9-C), 170.9 (10b-C), 173.6 (6-CO), 188.9 (2-CO); m/z (%): 364 (M^+, 100), 336 (M^+ - CO, 77), 308 (M^+ - 2CO, 21), 307 (M^+ - 2CO - H, 76), 293 (M^+ - 2CO - Me, 57), 277 (M^+ - 2CO - OMe, 30), 232 (M^+ - m-$MeOC_6H_4C$=CH, 39), 160 ($CH_3O(CN)C_6H_3CO^+$, 36), 134 (m-$MeOC_6H_4CH$=CH_2^+, 14), 133 (m-$MeOC_6H_4C^+$=CH_2, 17), 132 (m-$MeOC_6H_4C^+$=CH, 8); exact mass: 364.107 ± 0.001, calc. for $C_{20}H_{16}N_2O_5$: 364.1059.

7-Methoxy-3-(m-methoxyphenyl)-3-methylimidazo[2,1-a]isoquinoline-2,5,6(3H)-trione (14b): yield 0.18 g (9%); m.p. 154°; ^{1}H NMR, δ ($CDCl_3$): 2.10 (3H, s, Me), 3.80 (3H, s, 3'-OMe), 4.05 (3H, s, 7-OMe), 6.75-7.35 (4H, m, 3-aryl-H), 7.45 (1H, dxd, J=7x2Hz, 8-H), 7.87 (1H, dxd, J=7Hz, 9-H), 8.30 (1H, dxd, J=7x2Hz, 10-H).

Nitration of 14a to the dinitrated analogue 18.

Compound 14a (3.64 g, 10 mmole) was dissolved in 100 ml of fuming HNO_3; this solution was heated at 80°C for 2 hr. After cooling, the solution was poured out on 300 g of ice and extracted three times with 200 ml of $CHCl_3$. The organic layer was separated, dried ($MgSO_4$) and evaporated. The

residue yielded 2.20 g (48%) of compound 18 after purification over silica gel (CH_3CN:$CHCl_3$ 1:9). m.p. 182°; IR ($CHCl_3$) cm^{-1}: 1770-1735-1705 (CO), 1560-1350 (NO_2); ^1H NMR, δ ($CDCl_3$): 2.15 (3H, s, Me), 4.05 (3H, s, 9-OMe), 4.25 (3H, s, 3'-OMe), 7.40-8.10 (2H, m, 3-aryl-H), 7.70 (1H, dxd, J=8x2 Hz, 8H), 8.25 (1H, d, J=8Hz, 7H), 8.40 (1H, d, J=2Hz, 10H); m/z (%): 454 (M^+, 0, the molecule is assumed to split up in two fragments (scheme 4), i.e. m/z = 230 and 224), 230 ($C_9H_8N_2O_5^+$, 7), 224 ($C_{11}H_6N_2O_4^+$, 100), 202 (230 - CO, 10), 160 (230 - CO - NCO, 25); exact mass of the two fragments of the molecular ion: 230.033 and 224.041 ± 0.001, calc. for $C_{11}H_6N_2O_4$ and $C_9H_8N_2O_5$: 230.0328 and 224.0433.

Reduction[13] of 14a :

Compound 14a (200 mg, 0.55 mmole) dissolved in 10 ml of abs. methanol was added to a stirred suspension of 21 mg $NaBH_4$ (0.55 mmole) in 10 ml of abs. methanol, at 0°. After 6 hr, the reaction mixture was poured out into 100 ml of 0.1 N HCl and extracted (3x) with 50 ml of $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified on preparative TLC-plates (SiO_2, CH_3CN-$CHCl_3$: 1-9) to yield 43% of compound 21; IR ($CHCl_3$) cm^{-1}: 3420-3200 (NH), 1720 (CO); ^1H NMR, δ ($CDCl_3$): 2.00 (3H, s, Me), 3.75 (3H, s, 3'-OMe), 3.85 (3H, s, 8-OMe), 5.80 (1H, broad s, 9b-H), 6.90-7.30 (6H, m, H-aryl), 7.85 (1H, d, J=11Hz, 6-H), 8.8 (1H, broad s, NH); ^{13}C NMR, δ : 2.40 (Me), 55.4 and 55.9 (2xOMe), 67.5 (3-C), 69.8 (9b-c), 125.9 (5a-C), 142.5 (1'-C), 145.4 (9a-C), 160.3 (3'-C), 164.4 (8-C), 170.7 (5-C), 177.6 (2-C); m/z (%): 338 (M^+, 86), 295 (M^+ - NHCO, 100, metastable peak at 257.5), 294 (295 - H, 58), 280 (M^+ - NHCO - Me, 11), 267 (M^+ - NHCO - CO, 10), 252 (M^+ - HNCO - Me - CO, 14), 162 (M^+ - NHCO - m-$MeOC_6H_4C{=}CH_2$, 26); exact mass: 338.126 ± 0.001 calc. for $C_{19}H_{18}N_2O_4$: 338.1266.

The reduction of 14a was also carried out with Pd(10%)/C and H_2 (10 PSI) in acetic acid - H_2O (8-2). However, the yield of 21 in this reaction was quite low (17%). The same compound 21, with identical spectroscopic characteristics was obtained following the method described by M. Los.[12]

Reaction of N-acyl-α-aminonitriles 1c-f with ethyl chlorooxoacetate

Reaction (120°, 2 hr) of 1 mmole of compounds 1e-f in 10 ml of ODCB and 1 mmole of ClCOCOOEt in 10 ml of ODCB followed by the usual aqueous work-up and chromatography led to the compounds 13e,f and traces of 12e-f. Use of nitrobenzene as solvent (1f) led to 12f (40%) as main product and 24% of compound 13f. On addition of 2 mmole of ClCOCOOEt or HCl-gas before work-up, compounds 12e-f were the main products in ODCB as solvent, only traces of compounds 13e-f were observed; addition of 2 mmole of $(COCl)_2$, when performing the reaction with 1f, led to compounds 14a,b.

4-(m-Methoxyphenyl)-4-methyl-2-phenyl-5(4H)-oxazolone (13e): yield 185 mg, 66%; m.p. 146°; IR ($CHCl_3$) cm^{-1}: 2830 (OMe), 1810 (CO); ^1H NMR, δ ($CDCl_3$): 1.90 (3H, s, Me), 3.80 (3H, s, OMe), 6.90-7.60 (9H, m, H-aryl); m/z (%): 281 (M^+, 100), 253 (M^+ - CO, 17), 237 (M^+ - CO_2, 50), 119 ($PhCON^+$, 50), 103 ($PhCN^+$, 58).

2,4-Di(m-methoxyphenyl)-4-methyl-5(4H)-oxazolone (13f): yield 201 mg, 64%; m.p. 134°; IR ($CHCl_3$) cm^{-1}: 2830 (OMe), 1810 (CO); ^1H NMR, δ ($CDCl_3$): 1.90 (3H, s, Me), 3.85 (3H, s, 4-aryl-OMe), 3.95 (3H, s, 2-aryl-OMe), 6.90-7.60 (8H, m, H-aryl); ^{13}C NMR, δ : 27.2 (Me), 55.4 and 55.6 (2xOMe), 70.9 (4-C), 127.5 (1'-C of 2-aryl), 140.7 (1'-C of 4-aryl), 160.2 (3'-C of 2- and 4-aryl), 160.5 (2-C), 179.2 (5-C); m/z (%) : 311 (M^+, 100), 283 (M^+ - CO, 23), 267 (M^+ - CO_2, 47), 149 (m-$MeOC_6H_4CON^+$, 60), 133 (m-$MeOC_6H_4CN^+$, 67); exact mass : 311.116 ± 0.001, calc. for $C_{18}H_{17}NO_4$: 311.1157.

Reaction of N-acylated-α-aminonitriles 1e-f with HCl :

On reaction of 1e-f (1 mmole) with HCl at 0° in 10 ml of o-dichlorobenzene, chloroform or an alcohol, the corresponding 5(4H)-iminooxazole hydrochlorides were isolated.[8] When 1e-f was heated in a HCl saturated solvent, the 4(5H)-imidazolones 12e (57% in ODCB) and 12f (61% in ODCB) were obtained.

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