2-(1-ALKENYL)- AND 2-ARYL-SUBSTITUTED FOUR-MEMBERED CYCLIC NITRONES

AS PRECURSORS FOR 2,3,4-SUBSTITUTED PYRIDINES AND QUINOLINES

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Abstract - Reaction of the 2-(1-alkenyl)-substituted four-membered cyclic nitrones 3 with KOtBu gave the corresponding α,β-γ,δ-unsaturated oximes 6 which were converted into the substituted pyridines 9, either by azeotropic removal of water in refluxing benzene or by reaction in a 1:1 mixture of acetic anhydride and acetic acid at room temperature. Treatment of pyridine 9c with boron tribromide afforded the benzopyrano[4,3-c]pyridine derivative 10. Reaction of the 2-aryl-substituted four-membered cyclic nitrones 4 with acetyl chloride yielded the O-acetylated oximes 12 which cyclized upon irradiation to the 2,3,4-substituted quinolines 14.

We have shown previously that four-membered cyclic nitrones (2,3-dihydroazete 1-oxides) are very useful synthetic intermediates in the preparation of heterocyclic compounds. We have reported the synthesis of e.g. β-lactams[1], 6H-1,2-oxazin-6-ones[2,3], aziridines[1], isoxazolidines[4], and other interesting heterocycles[5,6] starting from four-membered cyclic nitrones.

Treatment of four-membered cyclic nitrones with a non-nucleophilic base produces substituted α,β-unsaturated oximes which can subsequently be converted into 6H-1,2-oxazin-6-ones[2] and isoxazoles[4] upon reaction in acid. Providing this 4π-system of the α,β-unsaturated oximes could be further extended with a vinylic (2π) or an aromatic (6π) substituent at the 4-position of the 1-aza-1,3-diene system, these compounds would be interesting starting materials for the preparation of pyridines and quinolines via electrocyclization of the 6π or 10π-system.

In the literature only a few papers have been published on the synthesis of pyridines[7-9] and quinolines[10,11] starting from 1-hydroxy-1-aza-1,3,5-hexatrienes or the corresponding O-derivatives. In most cases the yields are low. The stereochemistry of the central bond of the hexatriene system appears to be very important since only oximes with the correct stereochemistry of this bond can cyclize to the desired reaction products.

In the present paper we describe the facile and selective preparation of α,β-γ,δ-unsaturated oximes starting from the corresponding four-membered cyclic nitrones and the subsequent conversion into specifically substituted pyridines and quinolines in acceptable yields.

RESULTS AND DISCUSSION

The four-membered cyclic nitrones 3,4 were easily prepared in variable yields (Table 1) by reaction of nitroalkenes 1 and ynamines 2 in acetonitrile as a solvent[12]. As reported previously these nitrones are formed by a ring contraction of the initially formed (4+2) cycloadducts[13,14]. As by-products N,N-dialkylnitrocyclobutenamines[16] (e.g. 5) are formed as the result of a competing (2+2) cycloaddition of the nitroalkenes and the ynamines.
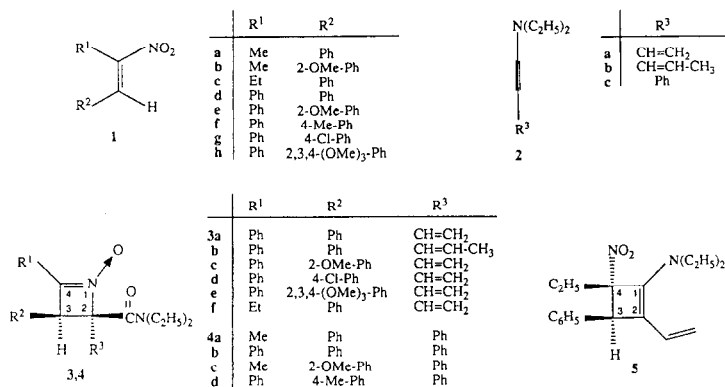
		R^1	R^2
	a	Me	Ph
	b	Me	2-OMe-Ph
	c	Et	Ph
	d	Ph	Ph
	e	Ph	2-OMe-Ph
	f	Ph	4-Me-Ph
	g	Ph	4-Cl-Ph
	h	Ph	2,3,4-(OMe)$_3$-Ph

	R^3
a	CH=CH$_2$
b	CH=CH-CH$_3$
c	Ph

		R^1	R^2	R^3
	3a	Ph	Ph	CH=CH$_2$
	b	Ph	Ph	CH=CH-CH$_3$
	c	Ph	2-OMe-Ph	CH=CH$_2$
	d	Ph	4-Cl-Ph	CH=CH$_2$
	e	Ph	2,3,4-(OMe)$_3$-Ph	CH=CH$_2$
	f	Et	Ph	CH=CH$_2$
	4a	Me	Ph	Ph
	b	Ph	Ph	Ph
	c	Me	2-OMe-Ph	Ph
	d	Ph	4-Me-Ph	Ph

Chart 1

The compounds $\underline{3},\underline{4}$ exhibit the characteristic spectroscopic features of four-membered cyclic nitrones with the cis-stereochemistry at C-2 and C-3[14]. The hydrogen atoms of the methyl groups of the diethylamino functions (NCCH$_3$) are present as two triplets in the ^{1}H-NMR spectra and in the ^{13}C-NMR spectra the C=O of the carbamoyl moiety absorbs at δ 164.5 ± 1.0 (Table 1). Electron-rich ortho-substituents in the aryl group at C-3 (e.g. $\underline{3c},\underline{e}$) cause a downfield shift of about 0.5 ppm of the H-3 absorptions in the ^{1}H-NMR spectra and an upfield shift of about 9 ppm for C-3 in the ^{13}C-NMR spectra.
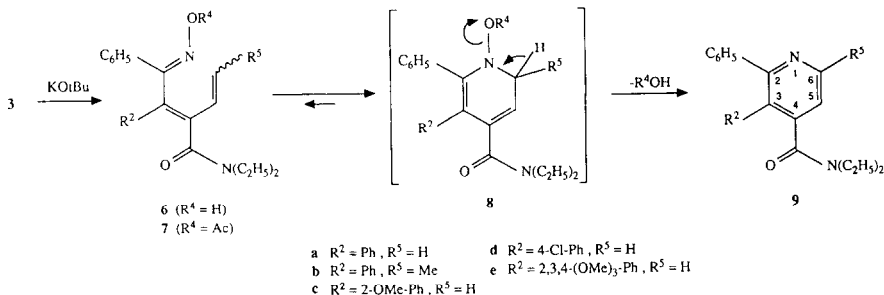
In our previous work i.e. the reaction of four-membered cyclic nitrones ($\underline{3}$ with R^3 = aryl, methyl) with potassium tert-butoxide (KOtBu)[2,3] we had obtained oxime derivatives, which had the appropriate stereochemistry to serve as the starting materials in the preparation of pyridines and quinolines. Upon reaction of these nitrones with e.g. KOtBu the proton at C-3 is abstracted, resulting in the formation of 2-azetine derivatives. Subsequent concerted thermal ring opening of these 2-azetines gives rise to α,β-unsaturated oximes (like $\underline{6}$), the stereochemistry of which was proven with NOE difference spectroscopy and X-ray analysis.

Reaction of the nitrones $\underline{3a}$-$\underline{e}$ with KOtBu in diethyl ether gave the corresponding oximes $\underline{6a}$-$\underline{e}$ which could not be purified by silica gel chromatography on account of a slow cyclization to the corresponding pyridines $\underline{9}$ under these conditions. Therefore the oximes were not further purified and not characterized but immediately used. Reaction of nitrone $\underline{3f}$ with KOtBu gave a mixture of products which could not be separated and characterized. These products are probably formed by abstraction of an α-methylene proton from the ethyl group at C-4 instead of abstraction of H-3.

The oximes $\underline{6}$ can be converted into the pyridine $\underline{9}$ in two different ways. Heating of a solution of the oximes $\underline{6a},\underline{e}$ in benzene for 4 hr in a Dean Stark apparatus gave under azeotropic removal of water the pyridines $\underline{9a},\underline{e}$ in 60% yield (method A). In order to perform the synthesis of pyridines at room temperature it appeared to be necessary to convert the oxime hydroxyl group into a better leaving acetate moiety. The crude oximes $\underline{6a}$-$\underline{d}$ were stirred overnight in a 1:1 mixture of acetic anhydride and glacial acetic acid at room temperature to afford upon in situ acylation of the oxime moiety ($\underline{7}$) the pyridines $\underline{9a}$-$\underline{d}$ in yields of 60-84% (method B). This reaction could also be accomplished with 2 equiv. of acetic anhydride in dichloromethane as a solvent in the presence of ethyldiisopropylamine and 4-(dimethylamino)pyridine (DMAP). Starting from the oximes $\underline{6a},\underline{e}$ the pyridines $\underline{9a},\underline{e}$ were obtained both in 60% yield, but only after a reaction time of 48 hr. In the case of cyclization of oxime $\underline{6b}$ to pyridine $\underline{9b}$ the stereochemistry of the 1-propenyl moiety appeared to be important, because only oxime $\underline{6b}$ in which this group has the trans-configuration underwent the cyclization; the cis-isomer was isolated from the reaction mixture in 25% yield.

For both pathways the mechanism involves an electrocyclization of the 6π system of $\underline{6}$ and $\underline{7}$, respectively. Subsequent elimination of either water or acetic acid from the resulting intermediate $\underline{8}$ affords the pyridines $\underline{9}$.

The structures of the pyridines $\underline{9}$ are in full agreement with their spectral data. Mass spectrometry revealed the correct molecular composition. In the ^{1}H-NMR spectra of the starting nitrones $\underline{3}$

$$3 \xrightarrow{KOtBu} \quad \longleftrightarrow \quad \xrightarrow{-R^4OH}$$

6 (R⁴ = H)
7 (R⁴ = Ac)

8

9

a R^2 = Ph , R^5 = H   d R^2 = 4-Cl-Ph , R^5 = H
b R^2 = Ph , R^5 = Me   e R^2 = 2,3,4-(OMe)$_3$-Ph , R^5 = H
c R^2 = 2-OMe-Ph , R^5 = H

Scheme 1

vinylic absorptions (δ 5.5-6.5) and a benzylic ring proton absorption (H-3, δ 4.5 ± 0.5) are present. However, in the ^{1}H-NMR spectra of the pyridines these signals have disappeared. In addition to the diethylamino and ArH absorptions the spectra exhibit a doublet at δ 8.7 which is characteristic for pyridine H-α protons[17]. Substantial evidence for the presence of H-α in the pyridines 9a,c-e is the absence of a signal at this chemical shift in the case of 9b (R^5 = CH$_3$).

By selecting the appropriate substituents it is possible to synthesize polyaromatic compounds. Previous work[2,3] has demonstrated that a diethylamino moiety as in 6 can serve as a leaving group under acidic conditions. Moreover, intramolecular acid catalyzed hydrolysis of amides has been reported in the literature[18]. Reaction of pyridine 9c with boron tribromide (BBr$_3$) in dichloromethane afforded phenyl-5H-[1]benzopyrano[4,3-c]pyridin-5-one (10) in 45% yield. In the ^{1}H-NMR

9c $\xrightarrow{BBr_3}$

10

Scheme 2

spectrum the original absorptions of the methoxy and diethylamino groups are absent; the only characteristic signals are those of the pyridine hydrogen atoms at δ 8.85 and 8.18 (d, J = 4.9 Hz).
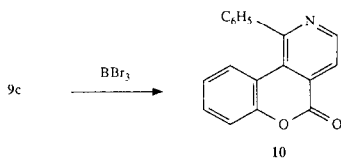
This example demonstrates the synthetic viability of this route to a variety of substituted pyridines, the substitution pattern of which is determined by the substitution pattern of the original starting materials, viz. nitroalkenes 1 and ynamines 2. Moreover, reactive groups R^1 and R^2 can serve as tools for the modification of the pyridine formed. The carbamoyl moiety at the 4-position might be modified e.g. by selective reduction[19,20].

A second way to obtain α,β-unsaturated oximes is the reaction of four-membered cyclic nitrones with acetyl chloride. Reaction of the nitrones 4a-d with acetyl chloride in dichloromethane gave the corresponding acetylated oximes 12a-d with the appropriate stereochemistry in 62-70% yield. The stereochemistry was proven by saponification of 12a. The spectroscopic data of the hydrolysis product were identical with those of oxime 11a obtained upon reaction of nitrone 4a with KOtBu the stereochemistry of which has been unequivocally established[2]. Due to the aromatic 6π-system the (O-acetylated) α,β-unsaturated oximes 11,12 are potential starting materials for the preparation of quinolines. Under the conditions employed for the synthesis of pyridines (vide supra) both the oximes 11a,b[2] and the acetylated oximes 12a-d could not be converted into the quinolines 14a-d. However, irradiation of 12a-d in benzene afforded the desired quinolines 14a-d in yields of 59-96%. In this case the aromaticity of the phenyl moiety is lost in the electrocyclization reaction. Rearomatization by elimination of acetic acid in the intermediate 13 will be the driving force for the reaction.

The spectral data of the quinolines 14a-d are in accordance with their structures. The molecular composition of the quinolines 14 was revealed by mass spectrometry. In the ^{1}H-NMR spectra among others a doublet is present at δ 8.07-8.23 which is the characteristic absorption of H-5 in [(C=O)R]quinolines[21]. The low field shift of H-5 is caused by the deshielding effect of the carbonyl moiety.
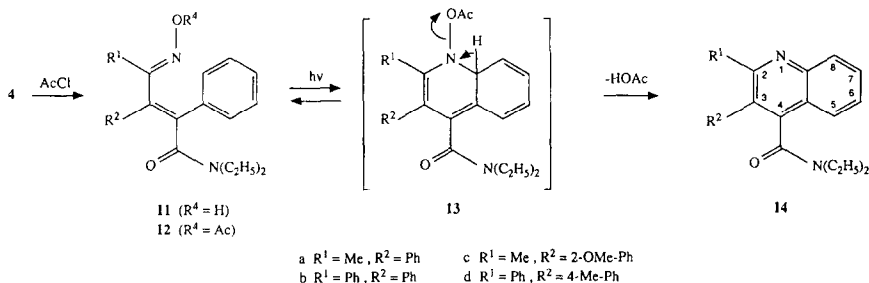
Scheme 3

From these results it can be concluded that specifically substituted pyridines 9 and quinolines 14 can easily be prepared starting from four-membered cyclic nitrones 3 and 4, respectively. Upon reaction of 3 and 4 with base (KOtBu) or with an electrophile (acetyl chloride) the α,β-γ,δ-un-saturated oximes formed have the appropriate stereochemistry to give the heteroaromatics 9 and 14, respectively, upon electrocyclization.

EXPERIMENTAL

M.ps were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker WP-80 spectrometer and ^{13}C-NMR spectra were recorded with a Nicolet MT 200 spectrometer, using $CDCl_3$ as a solvent with Me_4Si as an internal standard, unless otherwise stated. Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 or a Nicolet 5SXC FT-IR spectrophotometer. Elemental analyses were carried out by A. Montanara-Christenhusz of the Laboratory of Chemical Analysis of our institute.

The nitroalkenes 1a-g were prepared as described in ref. 14 according to a general literature method[22,23]. The ynamines 2a,b[24] and 2c[25], and the four-membered cyclic nitrones 4a-c were pre-pared as described. Petroleum ether refers to the fraction boiling at 60-80°. All the reactions were performed in a nitrogen atmosphere.

(E)-2,3,4-Trimethoxy-1-(2-nitro-2-phenylethenyl)benzene (1h) was prepared at 0.125 mol scale from 2,3,4-trimethoxybenzaldehyde and (nitromethyl)benzene according to the method described in ref. 23.
Yield 80%, m.p. 121-122° dec (methanol). ^{1}H-NMR δ: 8.55 (s, 1H, =CH), 7.5-7.2 (m, 5H, Ph), 6.37 (s, 2H, ArH), 4.00, 3.86, and 3.79 (s, 3H, OCH_3). ^{13}C-NMR δ: 156.1, 154.4, and 148.2 (s, ArC-2, ArC-3, and ArC-4), 141.9 (s, $=CNO_2$), 125.4 (d, =CH), 118.0 (s, ArC-1), 107.2 (d, ArH), 61.9, 60.9, and 56.0 (q, OCH_3). IR (KBr) cm^{-1}: 1640 (C=C), 1590 and 1460 (NO_2). MS: m/e 315.103 (M$^+$, calc. 315.111). (Found: C, 64.74; H, 5.66; N, 4.29. Calc. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44%).

General procedure for the preparation of the cis-2-(1-alkenyl)- and 2-aryl-N,N-diethyl-2,3-dihydro-2-azetecarboxamide 1-oxides 3,4. A soln of ynamine 2 (5.5 mmol) in dry acetonitrile (10 ml) was added dropwise at 0° to a soln of nitroalkene 1 (5.0 mmol) in dry acetonitrile (10 ml). After the mixture was stirred for 3 hr at 15-20°, the solvent was removed under reduced pressure (bath temperature < 25°). Trituration of the resulting residue with diisopropyl ether afforded the nitrones 3,4 as white solids. The nitrones could not be recrystallized on account of thermal in-stability and consequently no satisfactory elemental analyses could be obtained. The yields, melt-ing points, and selected spectroscopic data are summarized in Table 1.

(trans)-2-Ethenyl-N,N,4-triethyl-4-nitro-3-phenyl-1-cyclobuten-1-amine (5) was obtained as an orange oil after purification of the concentrated filtrate of the reaction of 1c and 2a by column

Table 1.   Yields, Melting Points, and Selected Spectroscopic Data of the Nitrones <u><u>3a</u>-<u>f</u></u> and <u><u>4d</u></u>.

Compd.	Yield (%)	m.p. (°C)	^{1}H-NMR, δ		^{13}C-NMR, δ					MS (M$^+$)
			H-3 (s)	NCCH$_3$ (t)	C=O (s)	C-4 (s)	C-3 (d)	C-2 (s)	NC$\underline{C}$H$_3$ (q)	found (calc.)
<u><u>3a</u></u>	64	157-158	4.46	0.82 0.60	163.9	147.5	51.1	91.6	12.0 11.5	348.188 (348.184)
<u><u>3b</u></u>[a]	30	140-140.5	4.40[b]	0.80 0.61	165.3	146.9	51.9	91.8	d	362.201 (362.199)
			4.33[c]	0.87 0.56	164.5	146.5	52.7	90.0	d	
<u><u>3c</u></u>	43	100-101	5.13	0.83 0.59	164.2	147.0	42.5	92.0	12.5 11.5	378.193 (378.194)
<u><u>3d</u></u>	34	156-159	4.45	0.87 0.67	163.9	146.9	50.6	91.8	12.3 11.6	382.146 (382.145)
<u><u>3e</u></u>	34	132-135	4.91	0.89 0.65	164.2	e	42.9	92.2	12.5 11.5	438.213 (438.216)
<u><u>3f</u></u>	25	115-120	4.05 (t)	0.76 0.66	164.1	153.1	52.6	91.7	12.2 11.7	300.181 (300.184)
<u><u>4d</u></u>	58	256.5-257.5	5.15	0.59 0.14	164.7	146.3	46.6	93.6	11.4 11.2	412.215 (412.215)

a) <u>Cis-trans</u> mixture (1:2). b) <u>Trans</u> isomer. c) <u>Cis</u> isomer. d) For the 2 isomers together 3 absorptions were observed at δ 12.4, 11.8, and 11.6. e) δ 153.9, 152.0, 146.7, and 141.7 (s, C-4, ArC-2, ArC-3, and ArC-4).

chromatography [Al$_2$O$_3$ (neutral) IV, diethyl ether/petroleum ether 2:1] in a yield of 22%. ^{1}H-NMR (toluene-d$_8$) δ: 7.26 (s, 5H, PhH), 6.78 (dd, 1H, <u>J</u> = 16.9 and 11.0 Hz, =CH), 4.80 (dd, 1H, <u>J</u> = 11.0 and 1.5 Hz, =CH$_2$), 4.48 (dd, 1H, <u>J</u> = 16.9 and 1.5 Hz, =CH$_2$), 4.27 (s, 1H, H-3), 3.19 (q, 4H, <u>J</u> = 7.1 Hz, NCH$_2$), 2.74 (q, 2H, <u>J</u> = 7.1 Hz, CH$_2$), 1.16 (t, 6H, <u>J</u> = 7.3 Hz, NCCH$_3$), 0.54 (t, 3H, <u>J</u> = 7.1 Hz, CH$_3$). ^{13}C-NMR (toluene-d$_8$) δ: 139.6 (s, C-1), 112.2 (t, =CH$_2$), 108.8 (s, C-2), 95.7 (s, C-4), 52.6 (d, C-3), 43.3 (t, NCH$_2$), 25.2 (t, CH$_2$), 12.8 (q, NC$\underline{C}$H$_3$), 8.8 (q, CH$_3$). IR (KBr) cm^{-1}: 1635 (C=C), 1530 and 1440 (NO$_2$). MS: <u>m/e</u> 300.185 (M$^+$, calc. for C$_{18}$H$_{24}$N$_2$O$_2$ 300.184).

General procedure for the preparation of the pyridines <u><u>9</u></u>. The nitrone <u><u>3</u></u> (2.0 mmol) was added in one portion to a suspension of KO<u>t</u>Bu (0.24 g, 2.1 mmol) in dry diethyl ether (20 ml), whereupon the soln turned brown. After stirring for 1 hr at room temperature the reaction was quenched by the addition of sat NH$_4$Cl aq (100 ml). The partly solidified oximes <u><u>6</u></u> were dissolved in chloroform (25 ml) and subsequently the resulting aqueous soln was extracted with chloroform (3 x 20 ml). Drying with MgSO$_4$ and subsequent evaporation of the combined organic layers gave the crude oximes <u><u>6</u></u> which were used without purification on account of partly cyclization on silica gel. Method A: A soln of the crude oxime <u><u>6</u></u> (1.0 mmol) in benzene (200 ml) was heated in a Dean Stark apparatus for 4 hr. Removal of the benzene under reduced pressure afforded the crude pyridines. Method B: A soln of the crude oxime <u><u>6</u></u> (2.0 mmol) in a 1:1 mixture of acetic anhydride and acetic acid (20 ml) was stirred overnight at room temperature. The reaction was quenched by the addition of ice water (150 ml) and then the remaining soln was extracted with chloroform (3 × 20 ml). The combined organic layers were washed with sat NaHCO$_3$ aq (3 × 20 ml) and water (20 ml), dried with MgSO$_4$, whereupon the solvent was removed under reduced pressure.

In the cases of <u><u>9a</u></u> and <u><u>9e</u></u> the residue was purified by column chromatography (silica gel, ethyl acetate). In the cases of <u><u>9c</u></u> and <u><u>9d</u></u> the crude pyridine solidified which could be purified by trituration with diisopropyl ether while pyridine <u><u>9b</u></u> was isolated in a pure state as the hydrochloric acid salt.

N,N-Diethyl-2,3-diphenyl-4-pyridinecarboxamide (9a). Yield 60% (method A and B), m.p. 96.5-98° (diisopropyl ether/ethyl acetate/petroleum ether). ^{1}H-NMR δ: 8.73 (d, 1H, J = 4.9 Hz, H-6), 7.5-7.1 (m, 11H, PhH), 4.0-2.5 (m, 4H, NCH$_2$), 0.86 and 0.73 (t, 3H, J = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 167.8 (s, C=O), 158.0 (s, C-2), 148.5 (d, C-6), 119.2 (d, C-5), 42.1 and 38.0 (t, NCH$_2$), 13.4 and 11.7 (q, NCCH$_3$). IR (KBr) cm^{-1}: 1635 (C=O). MS: m/e 330.167 (M$^+$, calc. for C$_{22}$H$_{22}$N$_2$O 330.173)[26].

N,N-Diethyl-6-methyl-2,3-diphenyl-4-pyridinecarboxamide hydrochloric acid salt (9b). Yield 57% (method B), m.p. 112.5-113.5° (ethyl acetate/petroleum ether). ^{1}H-NMR (CD$_3$OD) δ: 7.95 (s, 1H, H-5), 7.5-7.1 (m, 10H, PhH), 3.8-2.7 (m, 4H, NCH$_2$), 2.91 (s, 3H, CH$_3$), 0.98 and 0.72 (t, 3H, J = 7.0 Hz, NCCH$_3$). ^{13}C-NMR (CD$_3$OD) δ: 166.5 (s, C=O), 155.6, 155.0, and 154.3 (s, C-2, C-4, and C-6), 124.6 (d, C-5), 43.8 and 39.5 (t, NCH$_2$), 19.5 (q, CH$_3$), 13.6 and 11.8 (q, NCCH$_3$). IR (KBr) cm^{-1}: 1630 (C=O). MS: m/e 344.188 (M$^+$, calc. for C$_{23}$H$_{24}$N$_2$O 344.188).

After the crystals of 9b.HCl had been removed the filtrate was concentrated and submitted to preparative TLC (silica gel, diethyl ether/petroleum ether 3:2) to afford (Z)-N,N-diethyl-2-[2-oxo-1,2-diphenylethylidene]-3-pentenamide O-acetyl oxime (7b) as an oil in 25% yield. ^{1}H-NMR δ: 7.9-7.6 (m, 2H, PhH), 7.5-7.0 (m, 8H, PhH), 6.43 (b dq, 1H, J = 15.9 and 1.5 Hz, =CH), 6.00 (dq, 1H, J = 15.9 and 6.5 Hz, =CHCH$_3$), 3.5-3.0 (m, 4H, NCH$_2$), 2.12 (s, 3H, CH$_3$), 1.81 (dd, 3H, J = 6.5 and 1.5 Hz, =CCH$_3$), 1.03 and 0.92 (t, 3H, J = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 168.9, 167.6, and 163.7 (s, OC=O, NC=O, and C=N), 42.8 and 38.0 (t, NCH$_2$), 19.8 and 18.6 (q, CH$_3$ and =CCH$_3$), 13.5 and 12.2 (q, NCCH$_3$). IR (KBr) cm^{-1}: 1775 and 1630 (C=O). MS: m/e 404.210 (M$^+$, calc. for C$_{25}$H$_{28}$N$_2$O$_3$ 404.210).

N,N-Diethyl-3-(2-methoxyphenyl)-2-phenyl-4-pyridinecarboxamide (9c). Yield 84% (method B), m.p. 107-108° (ethyl acetate/petroleum ether). ^{1}H-NMR δ: 8.70 (d, 1H, J = 4.9 Hz, H-6), 7.6-6.5 (m, 10H, PhH), 4.0-2.5 (m, 4H, NCH$_2$), 3.21 (s, 3H, OCH$_3$), 0.86 and 0.70 (t, 3H, J = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 168.0 (s, C=O), 159.2 (s, C-2), 155.7 (s, ArC-2), 148.4 (d, C-6), 119.2 (d, C-5), 54.7 (q, OCH$_3$), 41.7 and 38.2 (t, NCH$_2$), 13.6 and 11.8 (q, NCCH$_3$). IR (KBr) cm^{-1}: 1630 (C=O). MS: m/e 360.181 (M$^+$, calc. 360.184). (Found: C, 76.56; H, 6.87; N, 7.23. Calc. for C$_{23}$H$_{24}$N$_2$O$_2$: C, 76.70; H, 6.72; N, 7.78%).

3-(4-Chlorophenyl)-N,N-diethyl-2-phenyl-4-pyridinecarboxamide (9d). Yield 75% (method B), m.p. 107-112° (toluene/petroleum ether). ^{1}H-NMR δ: 8.73 (d, 1H, J = 4.9 Hz, H-6), 7.4-7.0 (m, 10H, PhH), 4.0-2.5 (m, 4H, NCH$_2$), 0.89 and 0.81 (t, 3H, J = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 167.6 (s, C=O), 158.2 (s, C-2), 148.9 (d, C-6), 119.2 (d, C-5), 42.2 and 38.2 (t, NCH$_2$), 13.6 and 11.8 (q, NCCH$_3$). IR (KBr) cm^{-1}: 1620 (C=O). MS: m/e 364.133 (M$^+$, calc. 364.134). (Found: C, 72.43; H, 5.86; N, 7.63. Calc. for C$_{22}$H$_{21}$ClN$_2$O: C, 72.42; H, 5.80; N, 7.68%).

N,N-Diethyl-2-phenyl-3-(2,3,4-trimethoxyphenyl)-4-pyridinecarboxamide (9e). Yield 60% (method A), m.p. 91.5-93° (diisopropyl ether/ethyl acetate/petroleum ether). ^{1}H-NMR δ: 8.71 (d, 1H, J = 4.9 Hz, H-6), 7.5-7.1 (m, 7H, PhH), 6.69 (d, 1H, J = 8.0 Hz, PhH), 3.85 and 3.61 (s, 3H, OCH$_3$), 3.13 (bs, 3H, OCH$_3$), 0.92 and 0.71 (t, 3H, J = 7.0 Hz, NCCH$_3$). ^{13}C-NMR δ: 168.0 (s, C=O), 158.4 (s, C-2), 148.5 (d, C-6), 119.0 (d, C-5), 60.3, 59.8, and 56.0 (q, OCH$_3$), 41.8 and 37.7 (t, NCH$_2$), 13.7 and 11.9 (q, NCCH$_3$). IR (KBr) cm^{-1}: 1631 (C=O). MS: m/e 420.205 (M$^+$, calc. for C$_{25}$H$_{28}$N$_2$O$_4$ 420.209)[26].

1-Phenyl-5H-[1]benzopyrano[4,3-c]pyridin-5-one (10). Pyridine 9c (0.36 g, 1.0 mmol) was added in one portion to a soln of BBr$_3$ (0.75 g, 3.0 mmol) in dry dichloromethane (20 ml) at -70°. The temperature was gradually raised to room temperature whereupon the reaction mixture was stirred an additional hr at that temperature. The reaction was quenched by addition of ice water (100 ml). After separation of the layers, the aqueous layer was extracted with dichloromethane (3 × 20 ml). The combined organic layers were washed with sat NaHCO$_3$ aq (20 ml) and water (20 ml), and dried with MgSO$_4$. After removal of the solvent under reduced pressure the resulting residue was triturated with diethyl ether to give pure 10. Yield 46%, m.p. 150-158° dec (chloroform/petroleum

ether). ^{1}H-NMR δ: 8.85 (d, 1H, $\underline{J}$ = 4.9 Hz, H-3), 8.18 (d, 1H, $\underline{J}$ = 4.9 Hz, H-4), 7.7-6.7 (m, 9H, ArH). ^{13}C-NMR δ: 157.9 (s, C=O), 151.5 (s, C-6a), 147.9 (d, C-3), 141.1 (s, C-1), 139.8 (d, C-4). IR (KBr) cm^{-1}: 1740 (C=O) and 1600 (C=C). MS: $\underline{m/e}$ 273.077 (M$^+$, calc. for $C_{18}H_{11}NO_2$ 273.079)[26].

General procedure for the preparation of the $\underline{N}$,$\underline{N}$-diethyl-α-alkylidenebenzeneacetamide $\underline{O}$-acetyl oximes $\underline{12}$. A mixture of freshly distilled acetyl chloride (1 ml) and dichloromethane (2 ml) was added dropwise to nitrone $\underline{4}$ (1 mmol) at -20°. The temperature was gradually raised to room tempe-rature in 1.5 hr. After stirring for 3 hr at that temperature the reaction was quenched by the addition of ice water (50 ml). After separation of the layers the water layer was extracted with chloroform (4 × 25 ml). The combined organic layers were washed with sat NaHCO$_3$ aq (25 ml), and dried with MgSO$_4$. After evaporation of the solvent the resulting residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 1:1) in the cases of $\underline{12b-d}$ or by trituration with diisopropyl ether in the case of $\underline{12a}$.

$\underline{N}$,$\underline{N}$-Diethyl-α-(2-oxo-1-phenylpropylidene)benzeneacetamide $\underline{O}$-acetyl oxime ($\underline{\underline{12a}}$). Yield 65%, m.p. 124-126° (diisopropyl ether). ^{1}H-NMR δ: 7.6-7.3 (m, 10H, ArH), 2.07 and 1.84 (s, 3H, CH$_3$), 0.82 and 0.66 (t, 3H, $\underline{J}$ = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 169.1, 168.0, and 164.5 (s, C=O and C=N), 42.2 and 37.9 (t, NCH$_2$), 19.8 and 17.4 (q, CH$_3$), 13.2 and 11.7 (q, NCC̲H$_3$). IR (KBr) cm^{-1}: 1769 (C=N) and 1627 (C=O). MS: $\underline{m/e}$ 378.194 (M$^+$, calc. 378.194). (Found: C, 72.97; H, 7.14; N, 7.26. Calc. for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40%).

$\underline{N}$,$\underline{N}$-Diethyl-α-(2-oxo-1,2-diphenylethylidene)benzeneacetamide $\underline{O}$-acetyl oxime ($\underline{\underline{12b}}$). Yield 63%, m.p. 66-68° (diisopropyl ether/ethyl acetate/petroleum ether). ^{1}H-NMR δ: 7.8-7.2 (m, 15H, ArH), 2.01 (s, 3H, CH$_3$), 0.82 and 0.70 (t, 3H, $\underline{J}$ = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 168.6, 168.1, and 162.7 (s, C=O and C=N), 42.3 and 38.0 (t, NCH$_2$), 19.6 [q, C(O)C̲H$_3$], 13.3 and 11.7 (q, NCC̲H$_3$). IR (KBr) cm^{-1}: 1769 (C=N) and 1625 (C=O). MS: $\underline{m/e}$ 440.212 (M$^+$, calc. for $C_{28}H_{28}N_2O_3$ 440.210)[26].

$\underline{N}$,$\underline{N}$-Diethyl-α-[1-(2-methoxyphenyl)-2-oxopropylidene]benzeneacetamide $\underline{O}$-acetyl oxime ($\underline{\underline{12c}}$). Yield 62%, m.p. 150-151.5° (ethyl acetate). ^{1}H-NMR δ: 7.5-7.15 (m, 7H, ArH), 7.05-6.8 (m, 2H, ArH), 3.77 (s, 3H, OCH$_3$), 2.03 and 1.82 (s, 3H, CH$_3$), 0.83 and 0.65 (t, 3H, $\underline{J}$ = 7.0 Hz, NCCH$_3$). ^{13}C-NMR δ: 169.5, 168.2, and 166.8 (s, C=O and C=N), 156.6 [s, ArC̲(OCH$_3$)], 55.5 (q, OCH$_3$), 42.2 and 37.8 (t, NCH$_2$), 19.8 and 17.7 (q, CH$_3$), 13.0 and 11.7 (q, NCC̲H$_3$). IR (KBr) cm^{-1}: 1774 (C=N) and 1637 (C=O). MS: $\underline{m/e}$ 408.197 (M$^+$, calc. 408.205). (Found: C, 70.25; H, 7.01; N, 6.67. Calc. for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86%).

$\underline{N}$,$\underline{N}$-Diethyl-α-[1-(4-methylphenyl)-2-oxo-2-phenylethylidene]benzeneacetamide $\underline{O}$-acetyl oxime ($\underline{\underline{12d}}$). Yield 70%, m.p. 137-137.5° (ethyl acetate/petroleum ether). ^{1}H-NMR δ: 7.6-7.0 (m, 14H, ArH), 2.29 (s, 3H, ArCH$_3$), 1.99 [s, 3H, C(O)CH$_3$], 0.87 and 0.67 (t, 3H, $\underline{J}$ = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 168.9, 168.3, and 162.7 (s, C=O and C=N), 42.3 and 38.1 (t, NCH$_2$), 21.2 (q, ArCH$_3$), 19.6 [q, C(O)C̲H$_3$], 13.3 and 11.8 (q, NCC̲H$_3$). IR (KBr) cm^{-1}: 1770 (C=N) and 1625 (C=O). MS: $\underline{m/e}$ 454.226 (M$^+$, calc. 454.226). (Found: C, 77.15; H, 6.67; N, 6.17. Calc. for $C_{29}H_{30}N_2O_3$: C, 76.73; H, 6.65; N, 6.16%).

General procedure for the preparation of the $\underline{N}$,$\underline{N}$-diethyl-4-quinolinecarboxamides $\underline{14}$. A soln of the acetylated oximes $\underline{12}$ (1.0 mmol) in freshly distilled benzene (300 ml) was irradiated for 17 hr using a high-pressure Hanau lamp (400 W) after which the reaction mixture was washed with sat NaHCO$_3$ aq (2 × 50 ml) and water (50 ml) and dried with MgSO$_4$. After evaporation of the solvent the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 1:1) to give the pure $\underline{14}$[26]. The solid compounds were recrystallized from diisopropyl ether/ethyl acetate-/petroleum ether.

$\underline{N}$,$\underline{N}$-Diethyl-2-methyl-3-phenyl-4-quinolinecarboxamide ($\underline{\underline{14a}}$). Yield 59%, m.p. 96.5-98°. ^{1}H-NMR δ: 8.07 (bd, 1H, $\underline{J}$ = 7.3 Hz, H-5), 7.9-7.1 (m, 8H, ArH), 4.1-2.5 (m, 4H, NCH$_2$), 2.55 (s, 3H, CH$_3$), 0.81 and 0.72 (t, 3H, $\underline{J}$ = 7.3 Hz, NCCH$_3$). ^{13}C-NMR δ: 166.7 (s, C=O), 157.7 (s, C-2), 147.1 (s, C-8a), 42.4 and 38.4 (t, NCH$_2$), 24.8 (q, CH$_3$), 13.8 and 11.7 (q, NCC̲H$_3$). IR (KBr) cm^{-1}: 1775 and 1750 (C=N), and 1630 (C=O). MS: $\underline{m/e}$ 318.172 (M$^+$, calc. for $C_{21}H_{22}N_2O$ 318.173).

$\underline{N},\underline{N}$-Diethyl-2,3-diphenyl-4-quinolinecarboxamide ($\underline{\underline{14b}}$).   Yield 60%, m.p. 145-147°. ^{1}H-NMR δ:
8.23 (dd, 1H, $\underline{J}$ = 8.5 and 1.3 Hz, H-5), 7.9-7.1 (m, 13H, ArH), 4.1-2.5 (m, 4H, NCH$_2$), 0.81 and
0.73 (t, 3H, $\underline{J}$ = 7.3 Hz, NCCH$_3$). ^{13}C-NMR δ: 166.9 (s, C=O), 158.7 (s, C-2), 42.3 and 37.9 (t,
NCH$_2$), 13.6 and 11.9 (q, NCC$\underline{H}_3$). IR (KBr) cm^{-1}: 1765 (C=N) and 1630 (C=O). MS: $\underline{m/e}$ 380.186 (M$^+$,
calc. for $C_{26}H_{24}N_2O$ 380.189).

$\underline{N},\underline{N}$-Diethyl-3-(2-methoxyphenyl)-2-methyl-4-quinolinecarboxamide ($\underline{\underline{14c}}$).   Yield 78%, oil.
^{1}H-NMR δ: 8.08 (d, 1H, $\underline{J}$ = 8.3 Hz, H-5), 7.7-6.85 (m, 7H, ArH), 4.0-2.6 (m, 4H, NCH$_2$), 3.74 (s,
3H, OCH$_3$), 2.50 (s, 3H, CH$_3$), 0.78 and 0.70 (t, 3H, $\underline{J}$ = 7.1 Hz, NCCH$_3$). ^{13}C-NMR δ: 166.8 (s, C=O),
159.0 (s, C-2), 156.4 (s, PhC-2), 147.0 (s, C-8a), 111.5 (s, PhC-1), 109.7 (d, PhC-3), 54.9 (q,
OCH$_3$), 41.8 and 37.7 (t, NCH$_2$), 23.6 (q, CH$_3$), 13.9 and 11.8 (q, NCC$\underline{H}_3$). IR (KBr) cm^{-1}: 1765 (C=N)
and 1631 (C=O). MS: $\underline{m/e}$ 348.180 (M$^+$, calc. for $C_{22}H_{24}N_2O_2$ 348.184).

$\underline{N},\underline{N}$-Diethyl-3-(4-methylphenyl)-2-phenyl-4-quinolinecarboxamide ($\underline{\underline{14d}}$). Yield 96%, m.p. 148.5-
149.5°. ^{1}H-NMR δ: 8.20 (d, 1H, $\underline{J}$ = 8.0 Hz, H-5), 7.9-7.1 (m, 7H, ArH), 4.0-2.5 (m, 4H, NCH$_2$), 2.29
(s, 3H, CH$_3$), 0.84 and 0.71 (t, 3H, $\underline{J}$ = 7.2 Hz, NCCH$_3$). ^{13}C-NMR δ: 167.1 (s, C=O), 159.2 (s, C-2),
147.2 (s, C-8a), 42.3 and 37.9 (t, NCH$_2$), 21.2 (q, CH$_3$), 13.6 and 11.9 (q, NCC$\underline{H}_3$). IR (KBr) cm^{-1}:
1762 (C=N) and 1631 (C=O). MS: $\underline{m/e}$ 394.198 (M$^+$, calc. for $C_{27}H_{26}N_2O_3$ 394.205).

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