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Synthesis of 4-dialkylaminopyridine derivatives through ring-rearrangement of 3-nitro-2*H*-pyran-2-one acetamidines

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Abstract—A new synthesis of substituted 4-dialkylaminopyridines was developed, starting from 3-nitropyran-2-one *N*-functionalized amidines. Secondary amines were reacted with the amidines in a sealed tube and in ethanol as the solvent yielding exclusively 4-dialkylaminopyridine derivatives or a mixture with 4-methylpyridine derivative, depending on the C-α-linked substituents of the starting amidine. Structural elucidation of the 4-dialkylaminopyridines revealed their existence as two tautomeric forms, depending on the solvent.

1. Introduction

The pyridine ring, an integral part of several natural products of therapeutic importance, plays a key role in catalyzing both biological and chemical reactions. On the other hand, from a chemical perspective, many dialkylaminopyridines such as 4-dimethylaminopyridine (DMAP), 4-pyrrolidinopyridine (PPY), and their analogs have been extensively used as catalysts in acylation and alkylation reactions as well as catalysts for the esterification of unreactive alcohols and enantioselective acyl transfer.[1] A survey of the literature revealed that these molecules can usually be prepared by nucleophilic aromatic substitution of preformed 4-halopyridine derivatives or of their homologues with the appropriate amino compounds.[2] Other synthetic routes to 4-amino pyridines involve approaches based on either (i) the cyclization of the addition product derived from electrophilic attack of nitriles on to dianions of β-(monoalkylamino)-α,β-unsaturated ketones,[3] or (ii) the hydrolysis of the bicyclic iminium salt intermediates resulting from the reaction between 1,3-dialkoxy-2-azapropenylium salts and *N*-methyl-4-piperidone enamines.[4] On the other hand, the synthetic scheme herein reported is based on the use of substituted 2*H*-pyran-2-one acetamidines as a route to 4-dialkylaminopyridines.

Continuing our studies directed toward the synthesis of heterocyclic compounds, we have recently developed an unusual synthetic path to achieve 2-pyridinacetamides from amidines bearing pyran-2-one nucleus at N-1.[5] In this context, we obtained acetamidines bearing a 3-nitro-2*H*-pyran-2-one group on N-1, afterward used as starting materials for the synthesis of 4-dialkylaminopyridine derivatives.

It is well known that several kinds of nucleophiles can react with the pyran-2-one nucleus at C-2 and C-6 causing an initial ring opening, followed by a recyclization into a new heterocyclic ring.[6] As well, an electron-withdrawing substituent (NO_2) at the C-3 position of the pyran-2-one ring enhances the reactivity toward the nucleophiles at the C-6 site.[7] Additionally, the imino group of amidines reacts with nucleophilic reagents such as the carbanions resulting from 2-pyran-2-one ring opening.[8]

Thus, we proposed to take advantage of the enhanced electrophilic character of the C-6 atom in the pyran-2-one ring and of the nucleophilic features of the amidine imino group.

Herein, we present a new method for the synthesis of 4-dialkylaminopyridine derivatives starting from 3-nitro-2*H*-pyran-2-one acetamidines, which were transformed using secondary amines as a nucleophilic source.

2. Results and discussion

The acetamidines substituted at N-1 with an electron-withdrawing group are usually achieved in a chilled solution (−30 °C) by reaction of an isolated azide and enamine.[9]

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In our case, the 4-chloro-3-nitro-2*H*-pyran-2-one **1** was reacted with sodium azide in a DMF solution at −40 °C. In about 4 h, the chloro derivative **1** disappeared and most likely turned into the 4-azido-3-nitro-2*H*-pyran-2-one **A**. The known azide transformation through a nitrene intermediate into the 6-methyl-4*H*-pyrano[3,4-*c*][1,2,5]oxadiazol-4-one 3-oxide **3** was avoided by the low temperature adopted.[10]

Indeed, the furoxane[10] derivative **3** was the only obtained by performing the same reaction at −10 °C. The typical mass fragmentation[11] validated its structure and supported the azide **A** as the intermediate.

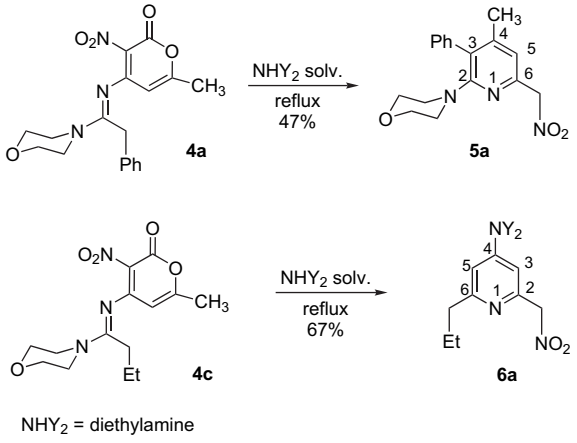
Maintaining the inner temperature at −50 °C the appropriate enamines **2a–e** were then added. These conditions allowed the isolation of the amidines **4a–e** (Scheme 1) in a short reaction time and with yields varying from 25 to 72% (see Section 4).

The unsuccessful isolation of the 4,5-dihydro-triazole **B** is not surprising, owing to its thermal instability as a result of the electron-withdrawing effect of the N-1 substituent,[12] which facilitates the cleavage of the N1–N2 bond and promotes the amidine rearrangement.

Spectroscopic data collected for the new amidines **4a–e** were consistent with the proposed structures and were concordant with the available literature data for similar substitution patterns in pyran-2-one derivatives.[13]

With the goal of synthesizing substituted 4-dialkylaminopyridines, we decided to screen the amidine behavior when the amidinic C-α-linked substituents R^1 were varied. Thus, we performed a preliminary experiment by refluxing compounds **4a** and **4c** in diethylamine as the solvent. In about 30 min, the starting materials turned into the pyridine derivatives **5a** and **6a**, respectively (Scheme 2), and the ^{1}H NMR spectra of the crude reaction mixtures did not reveal any signal referable to side products.

The structure of the pyridine **5a** was supported by the spectroscopic data.



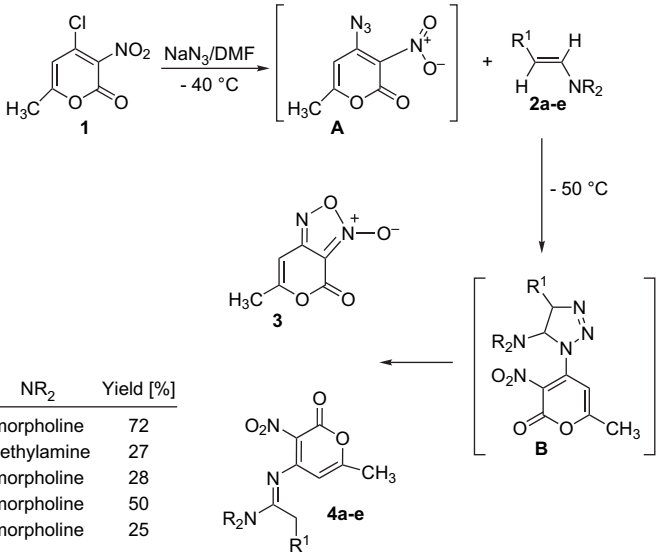
Scheme 2. Synthesis of pyridines **5a** and **6a**.

Besides the signals expected for the phenyl and morpholino substituents, the ^{1}H NMR spectrum of **5a** ($CDCl_3$) showed two singlets at δ 6.94 and δ 5.51, confirmed by the ^{13}C signals at δ 119.5 and δ 81.1 that are consistent with the pyridine CH-*meta* and the NO_2-linked CH_2, respectively.[14] A positive nuclear Overhauser effect supported the assigned structure by demonstrating the spatial proximity of these hydrogens.

The interpretation of the ^{1}H NMR spectrum of pyridine compound **6a** ($CDCl_3$) was more difficult due its complex signal pattern.

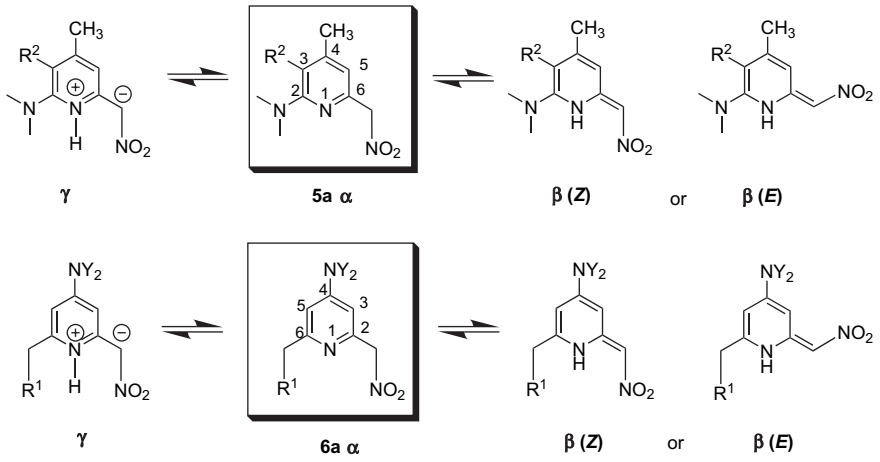
It is known that pyridine derivatives similar to **5a** and **6a** can exist in tautomeric[15] or zwitterionic[16] forms **α**, **β** (*E* or *Z*), **γ**, as depicted in Scheme 3.

Tautomeric equilibrium between aromatic and 1,2-dihydro structures has been widely studied in 2-methylene pyridines and in quinolines bearing an electron-withdrawing group on the pyridinic C-α-linked CH_2. The literature reports that the tautomeric ratio is dependent on solvent, temperature, and



2, 4	R^1	NR_2	Yield [%]
a	Ph	morpholine	72
b	Ph	diethylamine	27
c	Et	morpholine	28
d	*i*Pr	morpholine	50
e	CH_2Ph	morpholine	25

Scheme 1. Synthesis of the amidines **4a–e**.



Scheme 3. Tautomeric and zwitterionic forms in compounds **5a** and **6a**. Spectroscopic data of the pyridine derivatives **5a**,**b** and **6a–l** are discussed according to the carbon atom labeling showed in this Scheme.

substituents.[15] In our case, the acidic protons of the NO_2-linked CH_2 in the pyridine derivatives **5a** and **6a** might allow both tautomeric equilibria[17] and zwitterionic[16] forms.

The spectroscopic data (FTIR and ^{1}H NMR) recorded in different solvents (see Section 4) and collected for the 4-methylpyridine derivative **5a** ruled out both the tautomeric and dipolar forms showing in all cases the presence of the sole aromatic **α** structure.

In contrast, spectroscopic data collected for **6a** indicated the existence of different tautomeric forms depending on the selected solvents.

The ^{1}H NMR spectrum of 4-diethylaminopyridine **6a** (C_6D_6 at 500 MHz) displayed two doublets at δ 6.29 and δ 6.22, related to the H-3 and H-5 in accordance with a pyridine CH-*meta* having an amino group at the *ortho* position,[4] and one intense singlet at δ 5.16, which is related to the nitromethylene group. The ^{13}C NMR spectrum supported the above observations with the signals at δ 103.5 (CH-3), 104.1 (CH-5) and 81.1 (CH_2NO_2).[14d]

2D NMR experiments such as HSQC, HMBC, and NOESY performed in C_6D_6 further validated the **6a α** structure.

On the other hand, the ^{1}H NMR spectrum registered in $CDCl_3$ suggested the **6a β** structures. Indeed, pyridine derivative **6a** ($CDCl_3$ at 500 MHz) displayed two signals at δ 5.78 and δ 6.09 with the typical J_{meta}=2.4 Hz.[16] A singlet at δ 6.89 and another broad one-proton signal at δ 14.73, related to the NH, as confirmed by deuterium exchange with D_2O, were also observed.

Protons and carbons in ^{1}H and ^{13}C spectra were assigned according to two-dimensional experiments. HSQC experiment allowed the attribution of the CH-5 (δ 6.09, δ 100.7), the CH-3 (δ 5.78, δ 93.8) and the nitromethylene proton (C═C*H*–NO_2, δ 6.89, δ 104.5) signals,[16,18a,b] quaternary carbon being assigned from the results of an HMBC experiment.

Although the C═C*H*–NO_2 double bond of **6a** can in principle show two geometrical isomers (*E* or *Z*), only one isomer was detected by the ^{1}H NMR spectrum.

The high frequency shift referred to the NH proton (δ 14.73) shows that the NH is *cis*-oriented to the nitro group, and indicates that compound **6a** is the β tautomer in the shape of (*Z*) isomer. Indeed, such a steric arrangement allows an intramolecular hydrogen bond between the N–H and –NO_2 groups, [17–19] thus explaining the high frequency observed.

In order to further confirm the observed structure of the pyridine derivative **6a**, a NOESY experiment was carried out in $CDCl_3$ solution at 298 K.

This experiment displayed spatial proximity between the H-3 (δ 5.78) and both the vinylic-H (δ 6.89) and the C-4-linked diethylammino CH_2 (δ 3.43). The nuclear Overhauser effect was also observed between the H-5 proton (δ 6.09) and the signal at δ 3.43, as well as between the H-5 proton and the triplet at δ 2.66, related to the propyl CH_2. A weak interaction between the NH proton and the propyl CH_2 was also detected, and an exchange cross-peak between the NH signal at δ 14.73 and the vinylic-H signal at δ 6.89 was observed, thus proving that the tautomeric equilibrium takes place under the adopted analytical conditions.

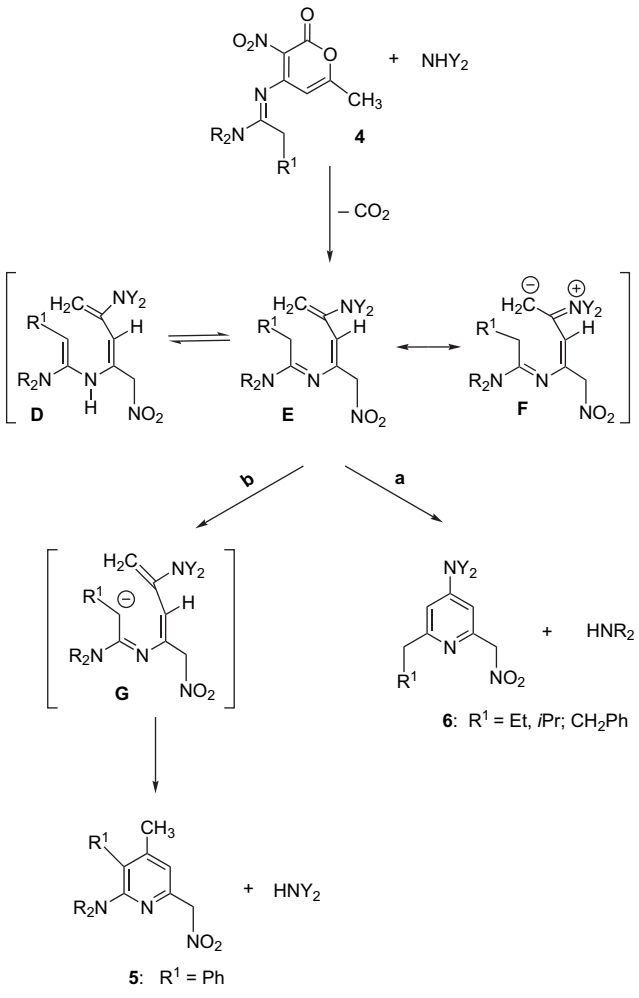
ROESY experiments performed at 213 K confirmed the structure assigned for compound **6a**.

Further structural elucidations were obtained by both the solid state and solution IR analyses, which ruled out the tautomeric β or zwitterionic γ forms of the compound **6a** depicted in Scheme 3. FTIR spectra of **6a**, both on the isolated crystal and in chloroform solution, were characterized by two absorption bands at 1621 (C═N) and 1582 (C═C) cm^{-1} and at 1622 (C═N) and 1596 (C═C) cm^{-1}, respectively, thus validating the aromatic pattern of the pyridine ring.

Analytical data led us to conclude that, unlike **5a**, the pyridine derivative **6a** can exist as the **6a α** tautomer in the solid state and in non-polar solvent (i.e., benzene), while the 1,2-dihydro **6a β** (*Z*) tautomer predominates in diluted $CHCl_3$ solution. Thus, the observed tautomeric equilibrium surely depends on the solvent,[15d] but an electronic effect of the substituents could also be hypothesized. Indeed, the 4-diethylamino substituent in **6a** is involved in a strong resonance interaction with the ring nitrogen atom, increasing

its basicity.[20] A proton transfer between the acidic $-CH_2NO_2$ hydrogen and the basic pyridine nitrogen can then be favored. Moreover, the resulting **6a** β (*Z*) tautomer, showing an exocyclic double bond, can be stabilized by the intramolecular six-term hydrogen bond between the N–H and the $-NO_2$ oxygen. In this context, the synergistic effect of the solvent is of importance: the chloroform proton, interacting with the NO_2 oxygen electron pair favors the equilibrium shift by stabilizing the previously mentioned intramolecular hydrogen bond. Thorough theoretical calculations are being performed in order to provide a better description of such an interesting tautomeric equilibrium.

The obtaining of the pyridine derivatives **5a** and **6a** can be rationalized by the reaction paths depicted in Scheme 4. Owing to the strong electron-withdrawing group at C-3 position, the expected nucleophilic attack occurred on the C-6 of the pyran-2-one ring,[7] followed by ring opening and decarboxylation to give enamine **E**. Starting from the enamine intermediate **E**, two different competing pathways were operating.



Scheme 4. Suggested mechanism for the formation of **5** and **6**.

According to *path a*, the 4-dialkylaminopyridine **6a** arose from enamine **E** (or from its corresponding zwitterion **F**) by way of subsequent nucleophilic addition to the amidine group and amine elimination providing the pyridine ring favored by aromatization.

According to *path b*, the 4-methylpyridine derivative **5a** was achieved from the ring closure of enamine **E** through the carbanion **G**, easily formed due to the electron-withdrawing effect of the phenyl group on the amidinic C-α.[5] Such results clearly show that the product ratio is strongly dependent on the substituent R^1 linked to the amidinic group. Under these reaction conditions, the large amount of amine and the peculiarity of the R^1 substituent could explain the two different transformations from the enamine intermediate **E** and the achievement of the 4-methylpyridine derivative **5a**.

To provide some insight into the mechanism of this rearrangement and to find an effective synthetic method to achieve 4-dialkylaminopyridines **6** from both the alkyl and phenyl substituted amidines **4a–e** we adopted new reaction conditions by employing ethanol as a solvent and avoiding the amine excess. Thus, to an ethanol solution of the C-α alkyl substituted amidines **4c–e** was added an equimolar amount of secondary amines by operating in a sealed tube put in an oil bath preheated at 70 °C (Table 1, method B).

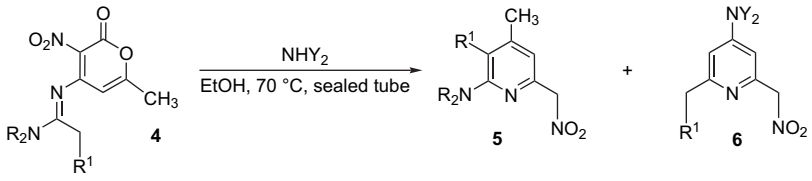
Moreover, C-α phenyl substituted amidines **4a**,**b** were reacted with an equimolar amount of secondary amines by adding a catalytic amount of *p*-toluenesulfonic acid (Table 1, method D) to the ethanol solution. It is well known that solvents can exert a considerable influence on both the position of chemical equilibria and reaction rates.[21] The ketone enamines exist predominantly as the least substituted double bond isomer, and the polar solvents,[22] for instance ethanol, affect the charge separation thus lowering the transition state energy. For the above reasons, it was expected that the polar solvent might enhance the achievement of the pyridine derivatives **6a**,**e–l** through their zwitterionic forms **F**, and that the acidic medium might afford the 4-dialkylamino derivatives **6b–d** also from the C-α phenyl substituted amidines **4a**,**b** by promoting the amine loss.

Reacted amines, methods, reaction times, and ratios of pyridine derivatives **6a–j** and **5a**,**b**, when obtained, are listed in Table 1.

The ratios between the 4-alkyl pyridine derivatives **5a**,**b** and 4-dialkylaminopyridine derivatives **6b–d** in the reaction mixture were determined by ^{1}H NMR spectroscopic analysis in C_6D_6. In fact the different hydrogen shift related to the CH_2NO_2 signal (at about δ 4.90 and δ 4.98 for **5a**,**b** and **6b–d**, respectively) allowed a clear distinction between the two obtained pyridines. Similarly, the ratios of the 4-dialkylaminopyridine derivatives **6a–l** were measured by ^{1}H NMR analysis of the crude mixtures in C_6D_6. The integral intensities of the three signals owing to the CH_2NO_2 (range δ 4.98–5.03), H-3 close to the CH_2NO_2 moiety (range δ 6.07–6.23), and H-5 (range δ 5.90–6.20) enabled to estimate the ratio of the obtained pyridines.

The reaction of morpholino substituted amidines **4c–e** in the ethanol solution containing an equimolar amount of amine afforded the expected pyridine derivatives **6e–g**,**i**,**j**,**l** bearing on C-4 either morpholine or piperidine in good yields. Performing the reaction with an equimolar amount of diethylamine, the amidines **4c–e** provided the 4-diethylaminopyridines **6a**, **6h**, and **6k**, respectively, as a minor product. The amine competition could explain the unsatisfactory yield of

Table 1. Synthesis of 4-methylpyridines **5** and 4-dialkylaminopyridines **6** from amidines **4**: effect of experimental conditions on **5** and **6** ratio



4, 5	R^1	NR_2
a	Ph	morpholine
b	Ph	diethylamine
c	Et	morpholine
d	*i*Pr	morpholine
e	CH_2Ph	morpholine

6	R^1	NY_2
a	Et	diethylamine
b	Ph	morpholine
c	Ph	diethylamine
d	Ph	piperidine
e	Et	morpholine
f	Et	piperidine
g	*i*Pr	morpholine
h	*i*Pr	diethylamine
i	*i*Pr	piperidine
j	CH_2Ph	morpholine
k	CH_2Ph	diethylamine
l	CH_2Ph	piperidine

Amidines **4**	NHY_2	Method	*t* (min)	Ratio[e] **5/6**	Yield of isolated products (%)
4a	Diethylamine	A[a]	30	**5a** (100)	**5a** (47)
4a	Morpholine	D[d]	60	**5a/6b** (10:90)	**5a** (5) **6b** (63)
4a	Diethylamine	D[d]	150	**5a/6c/6b** (22:25:53)	**5a** (8) **6c** (10) **6b** (40)
4b	Diethylamine	D[d]	300	**5b/6c** (25:75)	**5b** (15) **6c** (50)
4a	Piperidine	D[d]	40	**5a/6d/6b** (8:80:12)	**5a** (3) **6d** (67) **6b** (7)
4c	Diethylamine	A[a]	30	**6a** (100)	**6a** (67)
4c	Morpholine	B[b]	60	**6e** (100)	**6e** (80)
4c	Diethylamine	B[b]	90	**6a/6e** (38:62)	**6a** (20) **6e** (45)
4c	Piperidine	B[b]	60	**6e/6f** (13:87)	**6e** (8) **6f** (69)
4d	Morpholine	B[b]	60	**6g** (100)	**6g** (80)
4d	Diethylamine	B[b]	180	**6g/6h** (77:23)	**6g** (55) **6h** (12)
4d	Diethylamine	C[c]	60	**6g/6h** (10:90)	**6g** (4) **6h** (65)
4d	Piperidine	B[b]	60	**6g/6i** (15:85)	**6g** (9) **6i** (68)
4e	Morpholine	B[b]	60	**6j** (100)	**6j** (85)
4e	Diethylamine	B[b]	120	**6j/6k** (81:19)	**6j** (60) **6k** (8)
4e	Diethylamine	C[c]	60	**6j/6k** (13:87)	**6j** (7) **6k** (50)
4e	Piperidine	B[b]	60	**6j/6l** (8:92)	**6j** (3) **6l** (80)

[a] Amine as solvent at reflux: see Section 4.
[b] Amine 1 equiv/EtOH: see Section 4.
[c] Amine 5 equiv/EtOH: see Section 4.
[d] Amine 1 equiv/*p*-TSA cat pH ≅6.5/EtOH: see Section 4.
[e] Ratio of **5** and **6** estimated by ^{1}H NMR spectroscopy.

the 4-diethylamino derivatives **6a**, **6h**, and **6k**. Instead, the 4-diethylaminopyridines **6h** and **6k** were satisfactorily obtained by the reaction (Table 1, method C) of the amidines **4d** and **4e**, respectively, with 5 equiv of diethylamine. These experimental results confirm that the difficult formation of the C-α alkyl carbanion enables the alkyl amidines **4c–e** to react according to *path a*, also when a large amount of amine is used.

Significant yield improvements for the 4-dialkylaminopyridine derivatives **6b–d** were reached by reacting the R^1 phenyl substituted amidine **4a** under an acidic medium (Table 1, method D). The morpholino substituted amidine **4a**, when reacted with diethylamine, supplied an unsatisfactory amount of 4-diethylaminopyridine **6c**. The poor yield of the **6c** derivative was improved by mixing the corresponding amidine **4b** with diethylamine.

The results listed in Table 1 show that the behavior of amidines **4** depends on the C-α amidinic carbon substitution. The new selected reaction conditions enabled the synthesis of pyridine derivatives **6** from also C-α phenyl substituted amidines **4a**,**b**, thus supporting the formulated mechanistic hypothesis in which the pyridine derivatives **5** and **6** arise from the enamine intermediate **E**, and confirming that the polar solvent and the acidic medium can favor the *path a*.

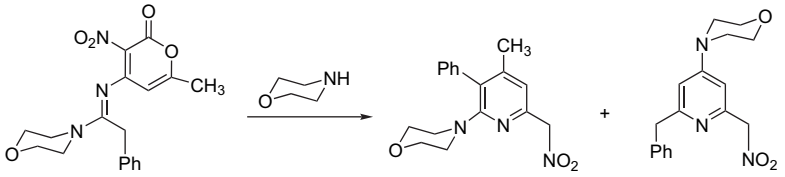
The ^{1}H and ^{13}C NMR spectra of the purified compounds **5b** and **6b–l** validated the proposed structure and were in accordance with similar substitution patterns observed for pyridines **5a** and **6a**, respectively.

The ^{1}H NMR spectra of the 4-dialkylaminopyridine derivatives **6b–l** recorded in benzene solution showed only the aromatic form **α**, as previously noticed for pyridine **6a**.

On the other hand, the proton spectra of compounds **6b–l**, recorded in chloroform solution, indicated that the pyridines **6b–l** exist as a tautomeric mixture of the **α** and **β** (*Z*) form, with a ratio that is likely influenced by the nature of the pyridine substituents.

To further confirm our methodological choices regarding the C-α phenyl substituted amidines **4a**,**b**, we reacted amidine **4a** with an equimolar amount of morpholine under the different reaction conditions presented in Table 2.

Table 2. Reaction of amidine **4a** with morpholine: effect of the experimental conditions on **5a** and **6b** ratio



4a **5a** **6b**

Amidine	Reaction medium	Ratio[a] **5a/6b**	*t* (min)
4a	EtOH, *p*-TSA	**5a/6b** (10:90)	60
4a	EtOH	**5a/6b** (28:72)	30
4a	C_6H_6, *p*-TSA	**5a/6b** (43:57)	60
4a	C_6H_6	**5a/6b** (37:63)	60
4a	CH_3NO_2, *p*-TSA	**5a/6b** (20:80)	90
4a	CH_3NO_2	**5a/6b** (20:80)	105

[a] Estimated by ^{1}H NMR spectroscopy in C_6D_6.

The reported ratios of **5a** and **6b** in the crude mixture were estimated by ^{1}H NMR spectroscopic analysis in C_6D_6.

The data in Table 2 highlight an effective yield improvement of pyridine **6b** when amidine **4a** is reacted in ethanol and *p*-TSA catalysis, thus confirming that the polar and protic solvent acts on the enamine intermediate **E** thus favoring *path a*, as well as that the acidic medium promotes the intramolecular condensation providing the pyridine derivatives **6b–d**.

3. Conclusions

Substituted 2*H*-pyran-2-one acetamidines proved to be useful building blocks in organic synthesis. We have developed a new method to synthesize substituted 4-dialkylaminopyridines through a one-pot reaction between amidines **4** and secondary amines, thus avoiding annoying multi-step reactions. Although two competitive routes were observed, the reaction pathways could be controlled with respect to prevailing 4-dialkylaminopyridine derivatives **6**. Not least, the use of ethanol as a reaction medium combines high polarity, useful to the condensation process, with environmental compatibility.

4. Experimental

4.1. General

Melting points were determined using a Buchi 510 (capillary) or an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured using a Perkin–Elmer FTIR 16 P.C. (Nujol) spectrometer, and a Perkin–Elmer FTIR 'Spectrum One' (KBr, $CHCl_3$ spectroscopic grade) spectrometer coupled with an FTIR microscope 'Multiscope' Perkin–Elmer (BaF_2 disc). ^{1}H and ^{13}C NMR spectra were recorded either on a Varian Mercury 200 MHz, or a Bruker Avance 500 spectrometers in C_6D_6 solution, unless otherwise stated. Chemical shifts are expressed in parts per million from internal standard tetramethylsilane (δ), coupling constants (J) are given in hertz. Mass spectroscopy data (MS) were obtained by electron impact ionization (EI) (70 eV) on ThermoQuest MD 800, or by electrospray ionization (ESI) on ThermoFinnigan 'LCQ Advantage'. Column chromatography was performed on Kieselgel 60 (Merck) 0.063–0.200 mm with eluants and ratios indicated in Section 4.

Materials. Enamines **2a**,[23] **2b**,[24] **2c**,[25] **2d**,[26] **2e**,[27] and 4-hydroxy-3-nitro-2*H*-pyran-2-one[28] have already been described. 4-Chloro-3-nitro-2*H*-pyran-2-one **1** is known compound,[29] but its analytical data have not been related.

4.1.1. 4-Chloro-3-nitro-2*H*-pyran-2-one 1. Phosphorus oxychloride (3.7 mL, 40 mmol) was mixed to absolute DMF (3.1 mL, 40 mmol) and chilled in an ice bath. With stirring, a solution of 4-hydroxy-3-nitro-2*H*-pyran-2-one (6.8 g, 40 mmol) in dry DMF (15 mL) was added dropwise. The mixture was stirred at 0 °C for 15 min and for 3 h at room temperature before being poured onto ice. The gold-yellow precipitate was filtered and recrystallized from AcOEt/cyclohexane (2:8) to give chloro derivative **1** (5.90 g, 78%) as yellow crystals, mp 111 °C; IR ν_{max} (Nujol) 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, d, J=0.9 Hz, CH_3), 6.23 (1H, q, J=0.9 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3), 106.2 (CH-5), 134.4 (*C*–NO_2), 145.3 (C-4), 153.7 (C-6), 165.2 (C=O); (EI) *m*/*z* (% relative intensity): 191 (20) (M^++2), 189 (51) (M^+), 145 (36), 130 (55), 87 (48), 72 (18), 63 (29). Anal. Calcd for $C_6H_4ClNO_4$: C, 38.02; H, 2.13; N, 7.39. Found: C, 37.93; H, 2.18; N, 7.46.

4.1.2. Synthesis of 6-methyl-4*H*-pyrano[3,4-*c*][1,2,5]oxadiazol-4-one 3-oxide 3. With careful monitoring of internal temperature (−40 °C) an equimolar amount of NaN_3 (0.39 g, 6 mmol) was added in one portion to a stirred solution of 4-chloro-3-nitro-2*H*-pyran-2-one **1** (1.13 g, 6 mmol) in dry DMF (5 mL). The mixture was kept at −40 °C until disappearance (EtOAc/cyclohexane, 7:3) of the chloro derivative **1**. The stirring was continued until room temperature was reached. The reaction mixture was poured onto ice, then the precipitate was filtered, dried, and recrystallized from EtOH to afford pure furoxane derivative **3** (0.62 g, 61%) as pale orange crystals, mp 146 °C (decomp.). IR ν_{max} (Nujol) 1765 (C=O), 1744, 1640, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, d, J=1.1 Hz, CH_3), 6.35 (1H, d, J=1.1 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 20.3 (CH_3), 89.1 (C-3), 94.2 (CH-5), 150.7 (C-4), 151.0 (C-6), 161.9 (C=O); (EI) *m*/*z* (%

relative intensity): 168 [M^+] (58), 138 [$M^+-N{=}O$] (23), 108 [$M^+-N{=}O$] (30), 66 (30), 52 (20), 43 (100). Anal. Calcd for $C_6H_4N_2O_4$: C, 42.87, H, 2.40; N, 16.66. Found: C, 42.76; H, 2.43; N, 16.54.

4.2. General procedure for the preparation of amidines 4a–e

To a solution of 4-chloro-3-nitro-2*H*-pyran-2-one **1** (1.89 g, 10 mmol) in dry DMF (10 mL) cooled at −40 °C an equimolar amount of NaN_3 (0.65 g, 10 mmol) was added in one portion. The resulting solution was stirred at −40 °C until disappearance of the chloro derivative **1** (about 4 h). After TLC monitoring (EtOAc/cyclohexane, 7:3), the suitable enamines **2a–e** (10 mmol) dissolved in dry DMF (20 mL) was dropped in at −50 °C, checking strictly the inner temperature. Then stirring was continued at the same temperature for the reaction times indicated close to the corresponding derivatives **4a–e**. The mixture was allowed to warm to −10 °C before being poured onto crushed ice. The brown precipitate was filtered, dried, and crystallized from AcOEt to give pure **4a**. In the case of the amidines **4b–e** the dark-brown oil was extracted with Et_2O (3×50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), then dried (Na_2SO_4), and concentrated in vacuo to give a crude product, purified by silica gel column (EtOAc/cyclohexane, 7:3 to 1:1). The resulting solid residue was crystallized as indicated below to give pure **4b–e**.

4.2.1. 6-Methyl-4-{[(1*E*)-1-morpholin-4-yl-2-phenylethylidene]amino}-3-nitro-2*H*-pyran-2-one 4a. Reaction time: 1 h. Yield 72%; oxide yellow crystals from AcOEt, mp 158–159 °C; IR ν_{max} (Nujol) 1739 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (3H, s, CH_3), 3.40–3.70 (8H, m, morpholine), 3.76 (2H, s, CH_2), 5.62 (1H, s, H-5), 7.11–7.18 and 7.29–7.38 (2+3H, 2m, ArH); ^{13}C NMR ($CDCl_3$) δ 20.2 (CH_3), 37.9 (CH_2), 46.6 (CH_2NCH_2), 66.5 (CH_2OCH_2), 104.9 (CH-5), 120.5 (C–NO_2), 127.8, 128.2, 129.5 (ArCH), 133.8 (ArCqu), 157.0 (N═C–N), 157.8 (C-6), 159.9 (C-4), 163.0 (C═O). ESI-MS *m/z* (% relative intensity): 380 [M+23] (100), 358 [M+1] (50), 314 [M+1−44, CO_2] (100). Anal. Calcd for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.37; H, 5.34; N, 11.95.

4.2.2. (1*E*)-*N*,*N*-Diethyl-*N*′-(6-methyl-3-nitro-2-oxo-2*H*-pyran-4-yl)-2-phenylethanimidamide 4b. Reaction time: 1 h. Yield 27%; deep yellow powder from AcOEt/*i*-Pr_2O, mp 140 °C; IR ν_{max} (Nujol) 1712 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (3H, t, J=6.9 Hz, CH_3), 1.21 (3H, t, J=6.9 Hz, CH_3), 2.11 (3H, s, CH_3), 3.31 (2H, q, J=6.9 Hz, CH_2NCH_2), 3.50 (2H, q, J=6.9 Hz, CH_2NCH_2), 3.73 (2H, s, CH_2), 5.57 (1H, s, H-5), 7.11–7.16 and 7.24–7.36 (2+3H, 2×m, ArH); ^{13}C NMR ($CDCl_3$) δ 11.9 (CH_3), 14.0 (CH_3), 20.0 (CH_3 on C-6), 38.2 (CH_2), 43.8 and 43.9 (CH_2NCH_2), 105.4 (CH-5), 119.8 (C–NO_2), 127.6, 128.4, 129.3 (ArCH), 134.3 (ArCqu), 157.1 (N═C–N), 157.3 (C-6), 160.6 (C-4), 162.1 (C═O); ESI-MS *m/z* (% relative intensity): 366 [M+23] (80), 344 [M+1] (100), 300 [M+1−44, CO_2] (100). Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.83; H, 6.10; N, 12.31.

4.2.3. 6-Methyl-4-{[(1*E*)-1-morpholin-4-ylbutylidene]amino}-3-nitro-2*H*-pyran-2-one 4c. Reaction time: 1 h. Yield 28%; yellow powder from AcOEt/*i*-Pr_2O, mp 118 °C; IR ν_{max} (Nujol) 1724 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, J=7.3 Hz, CH_3CH_2), 1.46–1.64 (2H, m, CH_3CH_2), 2.23 (3H, s, CH_3 on C-6), 2.33 (2H, q, J=7.7 Hz, CH_2C═), 3.57–3.69 (4H, m, CH_2NCH_2), 3.73–3.81 (4H, m, CH_2OCH_2), 5.69 (1H, s, H-5); ^{13}C NMR (500 MHz) δ 12.7 (CH_3), 18.4 (CH_3 on C-6), 19.5 (CH_2), 31.4 (CH_2), 45.9 (CH_2NCH_2), 66.1 (CH_2OCH_2), 102.9 (CH-5), 121.5 (C–NO_2), 155.9 (N═C–N), 156.8 (C-6), 161.3 (C-4), 162.3 (C═O); ESI-MS *m/z* (% relative intensity): 332 [M+23] (75), 310 [M+1] (100), 266 [M+1−44, CO_2] (100). Anal. Calcd for $C_{14}H_{19}N_3O_5$: C, 54.36; H, 6.19; N, 13.58. Found: C, 54.15; H, 6.15; N, 13.67.

4.2.4. 6-Methyl-4-{[(1*E*)-3-methyl-1-morpholin-4-ylbutylidene]amino}-3-nitro-2*H*-pyran-2-one 4d. Reaction time: 1 h. Yield 50%; yellow powder from AcOEt, mp 165 °C; IR ν_{max} (Nujol) 1710 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (6H, d, J=6.6, 2×CH_3), 1.81 (1H, sept, J=6.6 Hz, CH_3–C*H*–CH_3), 2.16 (3H, s, CH_3), 2.18–2.22 (2H, m, CH_2), 3.58–3.68 (4H, m, CH_2NCH_2), 3.70–3.79 (4H, m, CH_2OCH_2), 5.67 (1H, s, H-5); ^{13}C NMR ($CDCl_3$) δ 20.4 (CH_3 on C-6), 22.7 (2×CH_3), 27.6 (CH), 39.8 (CH_2), 46.9 (CH_2NCH_2), 66.9 (CH_2OCH_2), 105.5 (CH-5), 119.0 (C–NO_2), 157.3 (N═C–N), 157.4 (C-6), 162.5 (C-4), 163.0 (C═O); ESI-MS *m/z* (% relative intensity): 346 [M+23] (27), 324 [M+1] (100), 280 [M+1−44, CO_2] (100). Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.59; H, 6.44; N, 13.05.

4.2.5. 6-Methyl-4-{[(1*E*)-1-morpholin-4-yl-3-phenylpropylidene]amino}-3-nitro-2*H*-pyran-2-one 4e. Reaction time: 2 h. Yield 25%; yellow powder from AcOEt/*i*-Pr_2O, mp 141 °C; IR ν_{max} (Nujol) 1715 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (3H, s, CH_3), 2.40–3.00 (4 H, m, CH_2–CH_2), 3.45–3.60 (4H, m, CH_2NCH_2), 3.60–3.69 (4H, m, CH_2OCH_2), 5.12 (1H, s, H-5), 7.05–7.17 and 7.27–7.35 (2+3H, 2m, ArH); ^{13}C NMR ($CDCl_3$) δ 20.1 (CH_3), 33.0 (CH_2), 33.1 (CH_2), 46.6 (CH_2NCH_2), 66.5 (CH_2OCH_2), 104.6 (CH-5), 120.0 (C–NO_2), 127.1, 128.9, 129.0 (ArCH), 139.0 (ArCqu), 157.0 (N═C–N), 157.8 (C-6), 160.9 (C-4), 162.7 (C═O); ESI-MS *m/z* (% relative intensity): 394 [M+23] (48), 372 [M+1] (100), 328 [M+1−44, CO_2] (100). Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.28; H, 5.55; N, 11.40.

4.3. Reaction of the amidines 4a and 4c with *N*,*N*-diethylamine at reflux or *method A*: synthesis of compounds 5a and 6a

Amidine **4a** (3 mmol) or **4c** was suspended in *N*,*N*-diethylamine (15 mL). The reaction mixture was refluxed for 30 min. The amine excess was removed in vacuo and the crude residue chromatographed on a silica gel column, eluant EtOAc/cyclohexane (1:1). The thick oil obtained was crystallized from an appropriate solvent to give pure **5a** or **6a**, respectively.

4.3.1. 4-[4-Methyl-6-(nitromethyl)-3-phenylpyridin-2-yl]morpholine 5a. Yield 47%; yellow powder from AcOEt/petroleum ether, mp 92 °C; IR ν_{max} (KBr) 1592 (C═C), 1555 (NO_2) and ($CHCl_3$), 1591 (C═C), 1555 (NO_2) cm^{-1}; ^1H NMR δ 1.72 (3H, s, CH_3), 2.86–2.93 (4H,

m, CH_2NCH_2), 3.29–3.35 (4H, m, CH_2OCH_2), 4.91 (s, 2H, CH_2NO_2), 6.35 (1H, s, H-5), 6.93–7.09 (5H, m, ArH); ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s, CH_3), 2.97–3.03 (4H, m, CH_2NCH_2), 3.40–3.51 (4H, m, CH_2OCH_2), 5.51 (s, 2H, CH_2NO_2), 6.94 (1H, s, H-5), 7.20–7.49 (5H, m, ArH); ^{1}H NMR (DMSO-d_6) δ 2.05 (3H, s, CH_3), 2.80–2.85 (4H, m, CH_2NCH_2), 3.30–3.36 (4H, m, CH_2OCH_2), 5.70 (s, 2H, CH_2NO_2), 7.08 (1H, s, H-5), 7.29–7.52 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 20.6 (CH_3), 49.4 (CH_2NCH_2), 66.7 (CH_2OCH_2), 81.1 (CH_2NO_2), 119.5 (CH-5), 127.5, 128.8, 129.8 (ArCH), 137.4 (ArCqu), 145.7 (C-4), 148.1 (*Cqu*-CH_2NO_2), 160.1 (*Cqu*-morpholine); (EI) *m*/*z* (% relative intensity): 313 [M^+] (10), 267 [M^+-NO_2] (100), 223 (26), 209 (28), 181 (16). Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.10; H, 6.15; N, 13.49.

4.3.2. *N*,*N*-Diethyl-2-(nitromethyl)-6-propylpyridin-4-amine 6a. Yield 67%; yellow needles from *n*-pentane, mp 112 °C; IR ν_{max} (Neat crystal): 1621 (C═N), 1582 (C═C) and ($CHCl_3$), 1622 (C═N), 1596 (C═C) cm^{-1}; ^{1}H NMR (500 MHz) δ 0.84 (6H, t, *J*=7.1 Hz, $CH_3CH_2NCH_2CH_3$), 1.05 (3H, t, *J*=7.3 Hz, $CH_3CH_2CH_2$), 1.92 (2H, sex, *J*=7.3 Hz, $CH_3CH_2CH_2$), 2.76 (2H, t, *J*=7.3 Hz, $CH_3CH_2CH_2$), 2.83 (4H, q, *J*=7.1 Hz, $CH_3CH_2NCH_2CH_3$), 5.16 (2H, s, CH_2NO_2), 6.22 (1H, d, *J*=2.2 Hz, H-5), 6.28 (1H, d, *J*=2.2 Hz, H-3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (3H, t, *J*=7.4 Hz, $CH_3CH_2CH_2$), 1.24 (3H, t, *J*=7.2 Hz, $CH_3CH_2NCH_2CH_3$), 1.79 (2H, sex, *J*=7.4 Hz, $CH_3CH_2CH_2$), 2.66 (2H, t, *J*=7.4 Hz, $CH_3CH_2CH_2$), 3.43 (4H, q, *J*=7.2 Hz, $CH_3CH_2NCH_2CH_3$), 5.78 (1H, d, *J*=2.4 Hz, H-3), 6.09 (1H, d, *J*=2.4 Hz, H-5), 6.89 (1H, s, ═C*H*NO_2), 14.73 (1H, broad s, NH); ^{13}C NMR (125.7 MHz) δ 11.2 ($CH_3CH_2NCH_2CH_3$), 13.1 (CH_3 propyl), 22.3 (CH_2 propyl), 40.0 (CH_2Py), 42.7 (CH_2NCH_2), 81.1 (CH_2NO_2), 103.5 (CH-3), 104.1 (CH-5), 149.6 (*Cqu*-CH_2NO_2), 152.4 (C-4), 162.2 (C-6); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 11.6 (2×CH_3 amino group), 12.8 (CH_3 propyl), 20.8 (CH_2 propyl), 35.4 (CH_2Py), 44.1 (CH_2NCH_2), 93.8 (CH-3), 100.7 (CH-5), 104.5 (═*C*HNO_2), 146.7 (*C*═$CHNO_2$), 148.9 (C-6), 153.8 (C-4); (EI) *m*/*z* (% relative intensity): 251 [M^+] (11), 223 [M^+-28] (41), 205 [M^+-NO_2] (38), 190 (57), 177 (100), 162 (17). Anal. Calcd for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.00; H, 8.37; N, 16.58.

4.4. General procedure for the synthesis of pyridine derivatives 6a–l

Method B. Amidines **4c**–**e** (4 mmol) suspended in ethanol (10 mL) with an equimolar amount of the appropriate amine in a sealed tube were put in a preheated oil bath at 70 °C and heated for times indicated in Table 1. After disappearance (TLC monitoring) of the starting amidine the solvent was removed in vacuo and a small amount of the residue was dissolved in C_6D_6 and the ratio of pyridines **6a**,**e**–**l** was determined by ^{1}H NMR analysis (see Table 1). Amidines **4c**–**e** reacted with morpholine and gave a crude residue, which was crystallized from an appropriate solvent to afford pure pyrimidines **6e**, **6g**, and **6j**. The crude reaction mixtures arising from amidines **4c**–**e** reacted with diethylamine and piperidine were instead separated by column chromatography on a silica gel (EtOAc/cyclohexane, 1:9 to 9:1) giving the prevailing pyridines **6e**–**g**, **6i**,**j**, and **6l** in pure form and the minor pyridine derivatives **6a**, **6e**, **6g**,**h** and **6j**,**k**, respectively.

Method C. Amidines **4d**–**e** (4 mmol) suspended in ethanol (10 mL) with diethylamine (20 mmol) in a sealed tube were put in a preheated oil bath at 70 °C and heated for the time periods indicated in Table 1. After disappearance (TLC monitoring) of the starting amidine the solvent was removed in vacuo and a small amount of the residue was dissolved in C_6D_6 and the ratio of pyridines **6g**,**h** and **6j**,**k** was determined by ^{1}H NMR analysis (see Table 1). The crude reaction mixtures were then separated by column chromatography on a silica gel (EtOAc/cyclohexane, 1:9 to 9:1) giving the prevailing pyridines **6h** and **6k** in pure form and the minor pyridine derivatives **6g** and **6j**, respectively.

The reaction times and isolated yields of the products **6a**, and **6e**–**l** are listed in Table 1.

4.4.1. *N*,*N*-Diethyl-2-(nitromethyl)-6-propylpyridin-4-amine 6a. Analytical data were described earlier.

4.4.2. 4-[2-(Nitromethyl)-6-propylpyridin-4-yl]morpholine 6e. Yellow powder from *n*-pentane, mp 110 °C; IR ν_{max} (KBr) 1622 (C═N), 1596 (C═C) and ($CHCl_3$), 1622 (C═N), 1598 (C═C) cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (3H, t, *J*=7.4 Hz, $CH_3CH_2CH_2$), 1.91 (2H, sex, *J*=7.4 and 7.5 Hz, $CH_3CH_2CH_2$), 2.64–2.68 (4H, m, CH_2NCH_2), 2.76 (2H, t, *J*=7.5 Hz, $CH_3CH_2CH_2$), 3.42–3.47 (4H, m, CH_2OCH_2), 5.21 (2H, s, CH_2NO_2), 6.23 (1H, d, *J*=2.2 Hz, H-5), 6.31 (1H, d, *J*=2.2 Hz, H-3); ^{13}C NMR δ 13.8 (CH_3 propyl), 23.0 (CH_2 propyl), 40.6 (CH_2Py), 45.8 (CH_2NCH_2), 65.9 (CH_2OCH_2), 81.6 (CH_2NO_2), 106.2 (CH-3), 106.9 (CH-5), 150.3 (*Cqu*-CH_2NO_2), 156.4 (C-4), 163.1 (C-6); ESI-MS *m*/*z* (% relative intensity): 266 [M+1] (100), 220 [M+1−46, NO_2] (100). Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.77; H, 7.15; N, 15.90.

4.4.3. 2-(Nitromethyl)-4-piperidin-1-yl-6-proylpyridine 6f. Yellow crystals from AcOEt/*i*-Pr_2O, mp 125 °C; IR ν_{max} (KBr) 1622 (C═N), 1592 (C═C) cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (3H, t, *J*=7.3 Hz, $CH_3CH_2CH_2$), 1.27–1.34 (6H, m, $CH_2CH_2CH_2$), 1.90 (2H, sex, *J*=7.3 Hz, $CH_3CH_2CH_2$), 2.75 (2H, t, *J*=7.3 Hz, $CH_3CH_2CH_2$), 2.85–2.90 (4H, m, CH_2NCH_2), 5.17 (2H, s, CH_2NO_2), 6.35 (1H, d, *J*=2.2 Hz, H-5), 6.39 (1H, d, *J*=2.2 Hz, H-3); ^{13}C NMR (125.7 MHz) δ 13.8 (CH_3 propyl), 23.0 (CH_2 propyl), 24.1 and 24.9 ($CH_2CH_2CH_2$), 40.7 (CH_2Py), 46.9 (CH_2NCH_2), 81.7 (CH_2NO_2), 106.4 (CH-3), 107.0 (CH-5), 150.4 (*Cqu*-CH_2NO_2), 156.2 (C-4), 163.2 (C-6); ESI-MS *m*/*z* (% relative intensity): 264 [M+1] (100), 218 [M+1−46, NO_2] (100). Anal. Calcd for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.74; H, 8.00; N, 16.03.

4.4.4. 4-[2-Isobutyl-6-(nitromethyl)pyridin-4-yl]morpholine 6g. Yellow crystals from AcOEt/*i*-Pr_2O, mp 132 °C; IR ν_{max} (KBr) 1622 (C═N), 1595 (C═C) cm^{-1}; ^{1}H NMR δ 0.91 (6H, d, *J*=6.6 Hz, 2×CH_3), 2.22 (1H, sept, *J*=6.6 Hz, CH_3–C*H*–CH_3), 2.44–2.58 (4+2H, m, CH_2NCH_2 and CH_2), 3.20–3.30 (4H, m, CH_2OCH_2), 5.02 (2H, s, CH_2NO_2), 6.06 (1H, d, *J*=2.2 Hz, H-5), 6.11 (1H, d, *J*=2.2 Hz, H-3); ^{13}C NMR (125.7 MHz) δ 22.4 (2×CH_3),

28.9 (*CH*(CH_3)$_2$), 45.8 (CH_2NCH_2), 47.8 (CH_2Py), 65.9 (CH_2OCH_2), 81.6 (CH_2NO_2), 106.2 (CH-3), 107.6 (CH-5), 150.3 (*Cqu*-CH_2NO_2), 156.3 (C-4), 162.5 (C-6); ESI-MS *m/z* (% relative intensity): 280 [M+1] (100), 234 [M+1−46, NO_2] (100). Anal. Calcd for $C_{14}H_{21}N_3O_3$: C, 60.20; H, 7.58; N, 15.04. Found: C, 60.12; H, 7.65; N, 14.92.

4.4.5. *N*,*N*-Diethyl-2-isobutyl-6-(nitromethyl)pyridin-4-amine 6h. Pale yellow crystals from AcOEt/petroleum ether, mp 117 °C; IR ν_{max} (KBr) 1624 (C═N), 1594 (C═C) cm^{-1}; ^{1}H NMR (500 MHz) δ 0.83 (6H, t, *J*=7.1 Hz, *CH*$_3$CH$_2$NCH$_2$*CH*$_3$), 1.06 (6H, d, *J*=6.6 Hz, 2×CH_3), 2.39 (1H, sept, *J*=6.6 Hz, CH_3–C*H*–CH_3), 2.67 (2H, d, *J*=7.2 Hz, *CH*$_2$–CH(CH_3)$_2$), 2.83 (4H, q, *J*=7.1 Hz, *CH*$_2$N*CH*$_2$), 5.15 (2H, s, CH_2NO_2), 6.22 (1H, d, *J*=2.3 Hz, H-5), 6.28 (1H, d, *J*=2.3 Hz, H-3); ^{13}C NMR (125.7 MHz) δ 11.6 (*CH*$_3$CH$_2$NCH$_2$*CH*$_3$), 22.5 (2×CH_3), 28.8 (*CH* (CH_3)$_2$), 43.5 (CH_2 NCH_2), 47.5 (CH_2Py), 81.8 (CH_2NO_2), 104.2 (CH-3), 105.6 (CH-5), 150.3 (*Cqu*-CH_2NO_2), 153.0 (C-4), 162.2 (C-6); ESI-MS *m/z* (% relative intensity): 266 [M+1] (100), 220 [M+1−46, NO_2] (100). Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.20; H, 8.90; N, 15.98.

4.4.6. 2-Isobutyl-6-(nitromethyl)-4-piperidin-1-ylpyridine 6i. Pale orange crystals from AcOEt/cyclohexane, mp 133 °C; IR ν_{max} (Nujol) 1621 (C═N), 1590 (C═C) cm^{-1}; ^{1}H NMR (500 MHz) δ 1.06 (6H, d, *J*=6.7 Hz, 2×CH_3), 1.11–1.30 (6H, m, $CH_2CH_2CH_2$), 2.35 (1H, sept, *J*=6.7 Hz, CH_3–C*H*–CH_3), 2.58–2.70 (2H, m, CH_2), 2.80–2.95 (4H, m, CH_2NCH_2), 5.19 (2H, s, CH_2NO_2), 6.36 (1H, d, *J*=2.3 Hz, H-5), 6.40 (1H, d, *J*=2.3 Hz, H-3); ^{13}C NMR (125.7 MHz) δ 22.5 (2×CH_3), 24.1 and 25.0 ($CH_2CH_2CH_2$), 29.0 (*CH* (CH_3)$_2$), 47.0 (CH_2NCH_2), 47.9 (CH_2Py), 81.7 (CH_2NO_2), 106.5 (CH-3), 107.8 (CH-5), 150.4 (*Cqu*-CH_2NO_2), 156.2 (C-4), 162.5 (C-6); ESI-MS *m/z* (% relative intensity): 278 [M+1] (100), 232 [M+1−46, NO_2] (100). Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15. Found: C, 64.90; H, 8.27; N, 15.23.

4.4.7. 4-[2-(Nitromethyl)-6-(2-phenylethyl)pyridin-4-yl]-morpholine 6j. Yellow crystals from AcOEt/*i*-Pr_2O, mp 123 °C; IR ν_{max} (KBr) 1623 (C═N), 1595 (C═C) cm^{-1}; ^{1}H NMR (500 MHz) δ 2.55–2.60 (4H, m, CH_2NCH_2), 3.07 (2H, t, *J*=7.7 Hz, CH_2Py), 3.21 (2H, t, *J*=7.7 Hz, $CH_2C_6H_5$), 3.38–3.41 (4H, m, CH_2OCH_2), 5.20 (2H, s, CH_2NO_2), 6.08 (1H, d, *J*=2.2 Hz, H-5), 6.25 (1H, d, *J*=2.2 Hz, H-3), 7.22–7.28 (5H, m, ArH); ^{13}C NMR (125.7 MHz) δ 35.7 ($CH_2C_6H_5$), 40.5 (CH_2Py), 45.8 (CH_2NCH_2), 65.9 (CH_2OCH_2), 81.6 (CH_2NO_2), 106.3 (CH-3), 107.3 (CH-5), 126.0 (ArCH), 141.9 (ArCqu), 150.4 (*Cqu*-CH_2NO_2), 156.3 (C-4), 162.1 (C-6); ESI-MS *m/z* (% relative intensity): 328 [M+1] (100), 282 [M+1−46, NO_2] (100). Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.00; H, 6.37; N, 12.71.

4.4.8. *N*,*N*-Diethyl-2-(nitromethyl)-6-(2-phenylethyl)pyridin-4-amine 6k. Yellow amorphous powder from *i*-Pr_2O, mp 85 °C, dec; IR ν_{max} (KBr) 1625 (C═N), 1593 (C═C) cm^{-1}; ^{1}H NMR δ 0.62 (6H, t, *J*=7.0 Hz, *CH*$_3$CH$_2$ NCH$_2$*CH*$_3$), 2.60 (4H, q, *J*=7.0 Hz, *CH*$_2$N*CH*$_2$), 2.85–2.95 (2H, m, CH_2Py), 3.02–3.067 (2H, m, $CH_2C_6H_5$), 5.00 (2H, s, CH_2NO_2), 5.90 (1H, d, *J*=2.2 Hz, H-5), 6.09 (1H, d, *J*=2.2 Hz, H-3), 7.00–7.11 (5H, m, ArH); ^{13}C NMR (125.7 MHz) δ 12.0 (*CH*$_3$CH$_2$NCH$_2$*CH*$_3$), 35.8 (CH_2 C_6H_5), 40.5 (CH_2Py), 43.5 (CH_2NCH_2), 81.8 (CH_2NO_2), 104.5 (CH-3), 105.4 (CH-5), 125.9, 128.2, 128.8 (ArCH), 142.17 (ArCqu), 150.3 (*Cqu*-CH_2NO_2), 153.2 (C-4), 161.8 (C-6); ESI-MS *m/z* (% relative intensity): 314 [M+1] (100), 268 [M+1−46, NO_2] (100). Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 70.14; H, 7.48; N, 13.29.

4.4.9. 2-(Nitromethyl)-6-(2-phenylethyl)-4-piperidin-1-ylpyridine 6l. Yellow crystals from AcOEt/cyclohexane, mp 118 °C; IR ν_{max} (KBr) 1619 (C═N), 1591 (C═C) cm^{-1}; ^{1}H NMR δ 1.00–1.09 (6H, m, CH_2 CH_2CH_2), 2.59–2.73 (4H, m, CH_2NCH_2), 2.86–2.95 (2H, m, CH_2Py), 3.02–3.10 (2H, m, $CH_2C_6H_5$), 5.01 (2H, s, CH_2NO_2), 6.06 (1H, d, *J*=2.0 Hz, H-5), 6.21 (1H, d, *J*=2.0 Hz, H-3), 7.02–7.07 (5H, m, ArH); ^{13}C NMR (125.7 MHz) δ 23.4 and 24.2 ($CH_2CH_2CH_2$), 35.1 ($CH_2C_6H_5$), 39.8 (CH_2Py), 46.1 (CH_2NCH_2), 80.1 (CH_2NO_2), 105.8 (CH-3), 106.7 (CH-5), 125.1, 127.7, 128.0 (ArCH), 141.4 (ArCqu), 149.7 (*Cqu*-CH_2NO_2), 155.4 (C-4), 161.3 (C-6); ESI-MS *m/z* (% relative intensity): 326 [M+1] (100), 280 [M+1−46, NO_2] (100). Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.03; H, 7.16; N, 13.07.

Method D. A catalytic (0.03 g) amount of *p*-TSA was added to suspension of amidines **4a**,**b** (5 mmol) in ethanol solution (12 mL) with an equimolar amount of the appropriate amine. The mixture in a sealed tube was put in a preheated oil bath at 70 °C and heated for the time periods indicated in Table 1. After disappearance (TLC monitoring) of the starting amidine the solvent was removed in vacuo. The crude residue was quenched with water and extracted with dichloromethane (3×50 mL). The combined organic layers were washed with H_2O (100 mL), dried with Na_2SO_4, and then evaporated in vacuo. A small amount of the residue was dissolved in C_6D_6 and the ratio of pyridines **5a**,**b** and **6b–d** was determined by ^{1}H NMR analysis (see Table 1). The crude mixtures containing **5a**,**b** and **6b–d** were separated by column chromatography on silica gel (EtOAc/cyclohexane, 1:9 to 9:1) affording first 4-methylpyridines **5** and then 4-dialkylaminopyridines **6**. The reaction times and isolated yields of the compounds are presented in Table 1.

4.4.10. 4-[4-Methyl-6-(nitromethyl)-3-phenylpyridin-2-yl]morpholine 5a. Analytical data were described earlier.

4.4.11. *N*,*N*-Diethyl-4-methyl-6-(nitromethyl)-3-phenylpyridin-2-amine 5b. Thick yellow oil; IR ν_{max} (Nujol) 1585 (C═C), 1556 (NO_2) cm^{-1}; ^{1}H NMR δ 0.75 (3H, t, *J*=7.3 Hz, 2×CH_3), 1.68 (3H, s, CH_3), 2.93 (4H, q, *J*=7.3 Hz, 2×CH_2), 4.88 (s, 2H, CH_2NO_2), 6.25 (1H, s, H-5), 6.92–7.08 (5H, m, ArH); ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, t, *J*=6.9 Hz, 2×CH_3), 2.03 (3H, s, CH_3), 3.04 (4H, q, *J*=6.9 Hz, 2×CH_2), 5.49 (s, 2H, CH_2NO_2), 6.80 (1H, s, H-5), 7.20–7.48 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 13.2 (2×CH_3), 21.0 (CH_3 on C-4), 45.2 (CH_2NCH_2), 81.7 (CH_2NO_2), 117.8 (CH-5), 127.3, 128.9, 130.2 (ArCH), 138.9 (ArCqu), 145.7 (C-4), 148.1 (*Cqu*-CH_2NO_2), 160.2

(*Cqu*-diethylamine); ESI-MS *m/z* (% relative intensity): 300 [M+1] (100), 254 [M+1−46, NO_2] (100). Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.21; H, 7.07; N, 14.04. Found: C, 68.38; H, 7.16; N, 13.91.

4.4.12. 4-[2-Benzyl-6-(nitromethyl)pyridin-4-yl]morpholine 6b. Yellow crystals from AcOEt/*i*-Pr_2O, mp 120 °C; IR ν_{max} (KBr) 1629 (C═N), 1592 (C═C) and ($CHCl_3$), 1624 (C═N), 1600 (C═C) cm^{-1}; ^1H NMR δ 2.32–2.39 (4H, m, CH_2NCH_2), 3.12–3.19 (4H, m, CH_2OCH_2), 3.98 (s, 2H, $CH_2C_6H_5$), 4.98 (s, 2H, CH_2NO_2), 6.07 (2H, s, H-3 and H-5), 7.02–7.23 (5H, m, ArH); ^{13}C NMR (125.7 MHz) δ 44.9 (CH_2–C_6H_5), 45.6 (CH_2NCH_2), 65.8 (CH_2OCH_2), 81.4 (CH_2NO_2), 106.2 (CH-3), 107.1 (CH-5), 126.4, 129.6, 129.2 (Ar-CH), 139.9 (ArCqu), 150.3 (*Cqu*-CH_2NO_2), 156.6 (C-4), 162.1 (C-6); ESI-MS *m/z* (% relative intensity): 314 [M+1] (100), 268 [M+1−46, NO_2] (100). Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.07; H, 6.08; N, 13.46.

4.4.13. 2-Benzyl-*N*,*N*-diethyl-6-(nitromethyl)pyridin-4-amine 6c. Pale yellow crystals from AcOEt/*i*-Pr_2O, mp 123 °C; IR ν_{max} (Nujol) 1623 (C═N), 1590 (C═C) cm^{-1}; ^1H NMR δ 0.61 (3H, t, J=6.9 Hz, 2×CH_3), 2.58 (4H, q, J=6.9 Hz, 2×CH_2), 4.00 (s, 2H, $CH_2C_6H_5$), 4.98 (s, 2H, CH_2NO_2), 6.04 (1H, d, J=2.2 Hz, H-5), 6.10 (1H, d, J=2.2 Hz, H-3), 7.00–7.27 (5H, m, ArH); ^{13}C NMR δ 12.2 (2×CH_3), 43.8 (CH_2NCH_2), 45.3 ($CH_2C_6H_5$), 82.1 (CH_2NO_2), 104.8 (CH-3), 105.6 (CH-5), 126.6, 128.8, 129.6 (ArCH), 140.6 (ArCqu), 150.7 (*Cqu*-CH_2NO_2), 153.6 (C-4), 162.2 (C-6); (EI) *m/z* (% relative intensity): 299 [M^+] (26), 253 [M^+−NO_2] (100), 238 (53), 209 (25). Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.21; H, 7.07; N, 14.04. Found: C, 68.12; H, 7.00; N, 14.11.

4.4.14. 2-Benzyl-6-(nitromethyl)-4-piperidin-1-ylpyridine 6d. Pale orange crystals from AcOEt/*i*-Pr_2O, mp 120 °C; IR ν_{max} (KBr) 1623 (C═N), 1590 (C═C) cm^{-1}; ^1H NMR δ 0.90–1.10 (6H, m, $CH_2CH_2CH_2$), 2.53–2.62 (4H, m, CH_2NCH_2), 3.98 (s, 2H, $CH_2C_6H_5$), 4.99 (s, 2H, CH_2NO_2), 6.20 (2H, s, H-3 and H-5), 6.95–7.25 (5H, m, ArH); ^{13}C NMR δ 24.1 and 24.9 ($CH_2CH_2CH_2$), 44.9 ($CH_2C_6H_5$), 46.8 (CH_2NCH_2), 81.5 (CH_2NO_2), 106.8 (CH-3), 107.4 (CH-5), 126.4, 128.6, 129.3 (ArCH), 140.2 (ArCqu), 150.4 (*Cqu*-CH_2NO_2), 156.4 (C-4), 162.1 (C-6); ESI-MS *m/z* (% relative intensity): 312 [M+1] (100), 266 [M+1−46, NO_2] (100). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.36; H, 6.76; N, 13.38.

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