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Synthesis of substituted 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine as new scaffolds for potential bioactive compounds

N. Henry,[a] I. Sánchez,[a] A. Sabatié,[b] V. Bénéteau,[b] G. Guillaumet[b,*] and M. D. Pujol[a,*]

[a]*Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, Universitat de Barcelona, 08028 Barcelona, Spain*
[b]*Institut de Chimie Organique et Analytique (UMR-6005), Université d'Orléans, 45067 Orléans, France*

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Abstract—The title compounds having different substituents on the heterocyclic framework were prepared by several methods from 2-acetamido-3-hydroxypyridine. The condensation of 2-protected-amino-3-hydroxypyridine with 2-chloroacrylonitrile or ethyl 2,3-dibromopropionate provided in several cases two isomeric pyrido-oxazines. Whereas the reaction of 2-acetamido-3-hydroxypyridine with methyl 2,3-dibromopropionate or with α-halocarbonyl compounds gave exclusively the 2-substituted pyrido-oxazine, in a one-step operation.

1. Introduction

3,4-Dihydro-2*H*-1,4-benzoxazine derivatives (**I**) have attracted considerable interest due to their presence in a number of biologically active compounds.[1] Bioisosteric replacement of the benzene by pyridine leads to pyrido-oxazines (**II**), which have rarely been described (Fig. 1).[2]

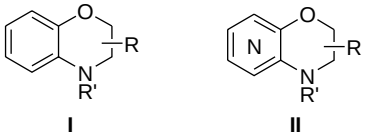

Figure 1.

The synthetic methods for obtaining 1,4-benzoxazines are not suitable for the pyridine derivatives. Whereas the pyrido[4,3-*b*][1,4]oxazine nucleus is well known,[3] the position isomer pyrido[3,2-*b*][1,4]oxazine is practically unknown. The first synthesis of the practically unknown 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine was carried out by reduction of 3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazin-3-one.[4] Our investigation of this system forms part of an ongoing study of pyrido derivatives, initiated by the preparation of hydroxymethylpyrido[3,2-*b*]oxazines from chiral glycidyl tosylates.[5] In this communication, we report the synthesis of pyrido[3,2-*b*][1,4]oxazines-2- and 3-substituted.

2. Chemistry

In our first attempt to access to pyrido-oxazines, when the 2-amino-3-hydroxypyridine was condensed with 2-chloro-acrylonitrile in refluxing acetone, neither DMF nor acetonitrile gave the desired pyrido-oxazine and both yielded only the starting material or degradation products (Table 1, entries 1 and 2).

In the same way, the condensation of 2-amino-3-hydroxypyridine with 1,3-dichloropropanon-2-one yielded the 2-chloromethyl-8-hydroxyimidazo[1,2-*a*]pyridine **2** (Scheme 1). When toluene was used as solvent and PTSA (*p*-toluenesulfonic acid) as catalyst only the imidazopyridine **2** was obtained in 62% yield, whereas treatment with K_2CO_3 in acetonitrile led to the imidazopyridine in only 24% yield together with starting material. Under these acidic or basic conditions the pyrido-oxazine ring was not detected. The results can be explained if the nucleophilic attack of the *N*-pyridinic occurs more rapidly than the attack of the hydroxyl group placed at the C-3. The most common method for preparing imidazo[1,2-*a*]pyridines is that reported by Tschitschibabin, which involves the reaction of 2-aminopyridines with aldehydes or ketones in acidic media.[6]

Keywords: Pyrido-oxazines; α-Halocarbonyl compounds; Protected 2-aminopyridine.
* Corresponding authors. Tel.: +34 93 4024534; fax: +34 93 4035941 (M.D.P.); e-mail addresses: gerald.guillaumet@univ-orleans.fr; mdpujol@ub.edu

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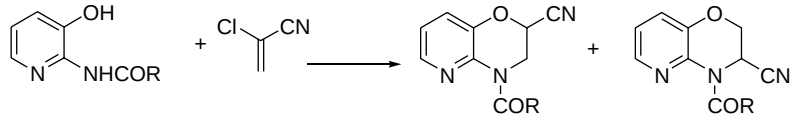
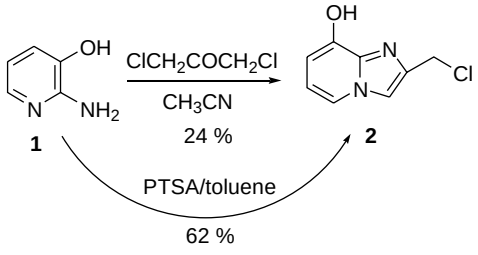
Table 1. Reagents and conditions for the preparation of pyrido-oxazines



1, 3-5 **6a-c** **7a,b**

Entry	R	Solvent	Base	*t* (h)	Compound (%)	Compound (%)
1	H (**1**)	Acetone	K_2CO_3	24	—	—
2	H (**1**)	Acetonitrile	K_2CO_3	2	—	—
3	–$COCH_3$ (**3**)	Acetone	K_2CO_3	24	**6a** (36)	**7a** (36)
4	–$COCH_3$ (**3**)	DMF	K_2CO_3	20	**6a** (26)	**7a** (24)
5	–$COCH_3$ (**3**)	Acetonitrile	K_2CO_3	2	**6a** (70)	—
6	–$COCH_3$ (**3**)	Acetonitrile	Cs_2CO_3	2	**6a** (68)	—
7	–$COCH_3$ (**3**)	Acetonitrile	DBU	2	**6a** (42)	—
8	–$COCH_3$ (**3**)	Acetonitrile	Et_3N	5	**6a** (23)	—
9	–$COOCH_2CH_3$ (**4**)	Acetonitrile	K_2CO_3	2	**6b** (40)	**7b** (40)
10	–$COOCH_2CH_3$ (**4**)	Acetone	K_2CO_3	2	**6b** (30)	**7b** (28)
11	–$COOCH_2CH_3$ (**4**)	Acetonitrile	Cs_2CO_3	2	**6b** (38)	**7b** (36)
12	–$COC(CH_3)_3$ (**5**)	Acetonitrile	K_2CO_3	2	**6c** (50)	—



Scheme 1.

The protection of the amino group at C-2 by conversion to acetylamino, ethoxycarbonylamino or *t*-butylcarbonylamino facilitates the condensation with alkylating reagents. The 2-acetamido-3-hydroxypyridine (**3**) was the best starting compound for the preparation of 2-substituted pyrido-oxazines, whereas the carbamate derivative (**4**) leads to a mixture 1:1 of 2-, and 3-substituted compounds (**6b**, **7b**). Both regioisomers were separated by SiO_2 column chromatography. The *t*-butyl carbonyl group hindered the condensation reaction, and the 2-substituted compound (**6c**) was isolated as the only regioisomeric product in 50% yield, when *t*-butyl amide (**5**) was condensed with 2-chloroacrylonitrile (Table 1, entry 12). This last protecting group was unstable and easily hydrolysed.

In order to find appropriate conditions for the pyrido-oxazine structure formation we carried out the reaction of protected 2-amino-3-hydroxypyridine with 2-chloroacrylonitrile varying: (a) solvent, (b) reaction time, and (c) base.

The condensation of **3** with 2-chloroacetonitrile (entry 5, Table 1) proceeded with acceptable yield, and so we considered this method as an effective procedure for pyrido-oxazine formation; moreover, the obtained compounds were easily purified. With this condensation, it is possible, in principle, to obtain two regioisomeric pyrido-oxazine compounds. These isomeric compounds can be easily distinguished on the basis of their ^{13}C NMR spectral data, and in this respect the signal of the methylene group of the oxazine moiety is the most indicative one with differences in chemical shifts of 40.9 and 61.2 ppm (CH_2–N, and CH_2–O, compounds **6a** and **7a**, respectively). In order to confirm the main isomer formed, we performed 2D NMR-experiments (HETCOR, HMQC, HMBC), and the results prove the proposed structure for **6a**. The signal (CH) at 63.5 ppm is assignable as the C-2 and this carbon shows a cross peak with H-2 (see HETCOR spectrum). The ^{13}C signal (CH_2) at 40.9 ppm shows two cross peaks. These results suggest that C-3 is bonded to two protons (CH_2), which are non-equivalent, having different chemical shifts. It is seen that the protons on C-3 appear at 3.95 ppm (H-3) and 4.93 ppm (H-3′) (Fig. 2).

Although it is difficult to correlate the regioselectivity of the oxazine ring formation from the same starting material with a particular solvent parameter, acetonitrile appears to be an appropriate solvent for this process when the amino at C-2 was protected with acetyl group (Table 1, entries 5 and 6). Whereas, the same reaction in acetone give a mixture of **6a** (36%) and **7a** (36%) (Table 1, entry 3), DMF also afforded mixture in a ratio 1:1 of **6a** and **7a** in a 26 and 24% yield, respectively (entry 4). The reaction in DMF required more time to completely react (20 h) and provided lower yields.

It should be noted that the *N*-substituent of the 2-amino-3-hydroxypyridine has a substantial effect on the regioselectivity of the reaction with 2-chloroacrilonitrile. Thus, while acetyl group of **3** in acetonitrile facilitates the 2-substituted isomer formation (Table 1, entries 5–8), when the carbamate (**4**) was used as starting material under reflux in acetone or acetonitrile it gave a mixture of isomers **6b** and **7b** without regioselectivity (Table 1, entries 9–11). As pointed at the beginning of this work, under the same conditions, the condensation of *t*-butylamide **5** and 2-chloroacrylonitrile gave only the 2-substituted isomer (Table 1, entry 12).

The experimental results demonstrate that K_2CO_3 (Table 1, entries 5 and 9) and Cs_2CO_3 (Table 1, entries 6 and 11) behaved similarly, whereas DBU and Et_3N afforded the same products in lower yields (Table 1, entries 7 and 8, respectively).

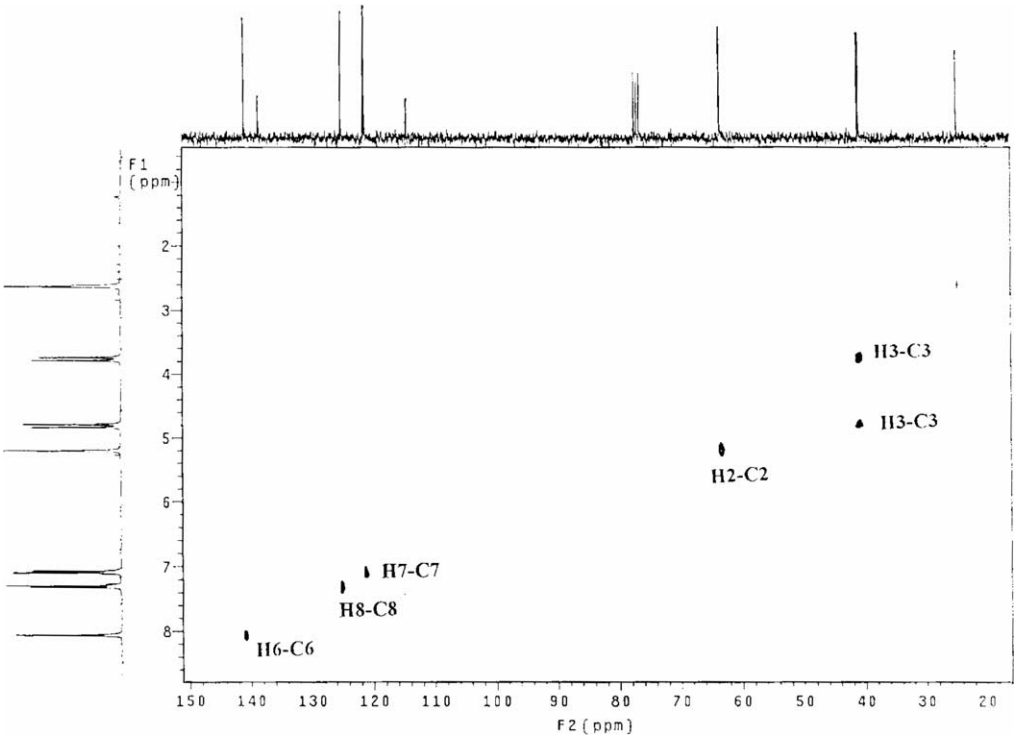
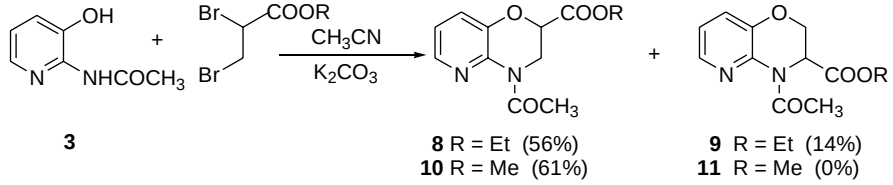


Figure 2. HETCOR spectrum of **6a** (300 MHz, $CDCl_3$). The horizontal axis of the spectrum corresponds to the ^{13}C spectrum and the vertical axis refers to the ^{1}H spectrum.

Having established a one pot two-component condensation method that operates under mild conditions, we next decided to investigate the scope of the reaction with respect to the nature and structure of the alkylating agent; thus, this methodology was applied to the synthesis of other pyrido-oxazines as **8**–**10**. The mixture of **8** and **9** was prepared by condensation of the acetamido **3** with ethyl 2,3-dibromo-propionate in the presence of K_2CO_3 and CH_3CN in 56% (**8**) and 14% (**9**) yield (Scheme 2). It seemed likely that under these conditions (K_2CO_3/CH_3CN/82 °C/24 h) elimination of hydrogen bromide from ethyl 2,3-dibromopropionate to give the α-bromoolefinic ester would occur more rapidly than nucleophilic displacement of bromide ion by the formed anion.[7] The same conditions of reaction, using methyl 2,3-dibromopropionate gave regioselectively the 2-substituted ester **10** in 61% yield, whereas the reaction of **3** with methyl 2,3-dichloropropionate gave the same ester **10** in only 35% yield (Scheme 2). The diminished yield can probably be attributed to the reduced reactivity of the chloro alkylating reagent in comparison with the bromo analogue. At this point, it is interesting to mark that the regioisomer in 2-position is nearly always predominant and it is in accord with other works related with 1,4-oxazines reported before.[8]

More recently, we investigated the formation of substituted ketones and aldehydes by the same condensation strategy, employing a reagent with a preformed α-halocarbonyl unit. The bromoderivative had been shown to be a suitable reagent for this purpose, whereas the chloroderivative was found to be less reactive (to see Table 2, entry 2 vs entry 1; entry 4 vs entry 3; entry 6 vs entry 5). When the acetamide **3** was reacted with a chloroketones tipus **B** only decomposition compounds were obtained (Table 2, entry 2), starting material was recovered (entry 6) or the expected product was obtained in poor yield (entry 4). Conjugated aldehydes did not react (entries 7 and 8, Table 2), and we believe that aldehydes are unstable under the tested conditions. The most efficient conditions were the treatment of **3** with the α-bromocarbonyl compound under reflux in acetonitrile in the presence of K_2CO_3 for 5 h (Table 2, entry 1). These conditions applied to the condensation of **3** with several α-halocarbonyl compounds provided only the 2-substituted isomer in respect of the chemical shift of N–CH_2 at 39.6/40.5 ppm (^{13}C NMR) (**12a**–**c**, Table 2). The quantity of alkylating reagent added is significant. Reactions of **3** with 5 equiv of haloalkenyl compounds did increase the yields of **12a** (Table 2, entry 1), and **12b** (Table 2, entry 4). Heating in



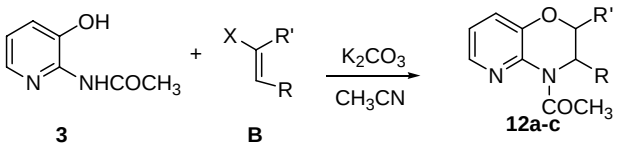
3

8 R = Et (56%)
10 R = Me (61%)

9 R = Et (14%)
11 R = Me (0%)

Scheme 2.

Table 2. Condensation of **3** with haloalkenyl compounds (**B**)



3 **B** **12a-c**

Entry	Compound **B**	Conditions	Product (% yield)
1	X=Br R=H R′=–CO–CH_3 (**13**)	Reflux, 24 h (1.5 equiv) Reflux, 24 h (2 equiv) Reflux, 5 h (5 equiv) Sealed tube, 60 °C, 2 h 30 (5 equiv)	**12a** (5) **12a** (24) **12a** (52) **12a** (26)
2	X=Cl R=H R′=–CO–CH_3 (**14**)	Reflux, 2 h (5 equiv) Sealed tube, 60 °C, 4 h	Decomposition Decomposition
3	X=Br R=H R′=–COC_6H_5 (**15**)	Reflux, 2 h 30 (5 equiv)	**12b** (48)
4	X=Cl R=H R′=–COC_6H_5 (**16**)	Reflux, 2 h 10 (5 equiv) Reflux, 2 h 10 (2 equiv)	**12b** (34) **12b** (16)
5	X=Br R′–R=$CO(CH_2)_3$– (**17**)	Reflux, 4 h (5 equiv)	**12c** (53)
6	X=Cl R′–R=$CO(CH_2)_3$– (**18**)	Reflux, 60 h (5 equiv)	—
7	X=Br R=–C_6H_5 R′=–COH (**19**)	Reflux, 5 h (5 equiv)	—
8	X=Cl R=–C_6H_5 R′=–COH (**20**)	Reflux, 5 h (5 equiv)	—

acetonitrile at reflux during 2–5 h was an appropriate detail. Stronger reaction conditions (<24 h, <5 equiv, reflux) were tested but only decomposed compounds were generated.

It is notable that the intermediate compounds types **B** are not commercially available, and were prepared previously from readily accessible starting materials in a one pot procedure. These compounds were isolated directly from the crude reaction mixture in high purity and in poor to moderate yields according to described methods for bromoketones **13** and **15**,[9] chloroketones **14** and **16**,[10] the bromocyclohexenone **17**,[11] chlorocyclohexenone **18**,[12] and the bromo- and chloroaldehydes **19** and **20**.[13]

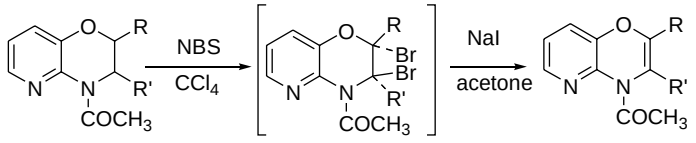
A possible mechanism for the formation of pyrido-oxazines 2-substituted involves Michael addition of the amide to the double bond, followed by ring-closure involving elimination of bromide.

The condensation of the acetamido **3** with 1,3-dichloropropanon-2-one, in the same conditions (K_2CO_3, CH_3CN, reflux) was unfruitful and gave degradation compounds or only starting material was recovered.

Antecedents of the reactivity of 1,4-benzodioxine were considered for the insaturation of the pyrido-oxazines **6a** and **7a**. First the dibromination of the saturated pyrido-oxazine with NBS (*N*-bromosuccinimide) in CCl_4 was performed. This unstable intermediate could be isolated and purified; however it could be easily transformed into a stable product by dehalogenation with NaI in acetone affording the unsaturated nitriles **21** and **22** in an acceptable yield in a single flask (Scheme 3). Using the same conditions the ester **10** and the ketone **12a** were transformed into the corresponding unsaturated analogues **23a**,**b** in isolated yields of 81 and 91%, respectively. Under these conditions, the acetamido protecting group was not affected.

3. Conclusion

Effective methods for the preparation of new pyrido-oxazines have been developed using commercially



6a R = CN, R' = H
7a R = H, R' = CN
10 R = $COOCH_3$, R' = H
12a R = $COCH_3$, R' = H

21 R = CN, R' = H (55%)
22 R = H, R' = CN (60%)
23a R = $COOCH_3$, R' = H (81%)
23b R= $COCH_3$, R' = H (91%)

Scheme 3.

available 2-amino-3-hydroxypyridine as starting compound. The procedure makes it possible to obtain pyridooxazines-2 or 3-substituted in one pot. Conversion of the 2-acetamido-3-hydroxypyridine to the corresponding pyrido-oxazine-2-nitrile was readily accomplished using 2-chloroacrylonitrile in acetonitrile at reflux. Protection of the amino group at C-2 as amide or carbamate is completely required. The steric nature of the *N*-substituent affected both the reaction rate and the yield. Our future investigations will aim to functionalize the pyrido-oxazine substructure in order to synthesize a new series of compounds.

4. Experimental

4.1. General

Melting points were determined on an MFB 595010 M Gallenkamp melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or Varian Gemini 300 spectrometer or on a Varian VXR-500 spectrometer or on a Brucker 250 MHz with tetramethylsilane as internal standard and using $CDCl_3$ as solvent or CD_3OD. Chemical shifts were expressed in ppm downfield from internal TMS or residual signal of deuterated solvent (δ). IR spectra were recorded on a FTIR Perkin Elmer 1600 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard spectrometer 5988-A (70 eV). The chromatography was carried out on SiO_2 (silica gel 60, SDS, 60–200 (μm). Microanalyses were determined on a Carlo Erba 1106 Analyzer by Serveis Científico-Tècnics, Universitat de Barcelona, and analytical values obtained were within $\pm 0.4\%$ of the calculated values. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures.

4.1.1. 2-Chloromethyl-8-hydroxyimidazo [1,2-*a*]pyridine (2). To a solution of 2-amino-3-hydroxypyridine (200 mg, 1.82 mmol) in toluene (20 mL) was added dropwise 1,3-dichloropropan-2-one (350 mg, 2.73 mmol) and a catalyst amount of PTSA (*p*-toluenesulfonic acid monohydrate). The resulting mixture was refluxed for 3 h. The solvent was removed under vacuum and a solution of NaOH 2 N was added dropwise until pH basic, followed by extraction with ethyl acetate (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered off and the solvent removed, the resulting residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 6:4) giving 210 mg of this compound as a colorless solid (62% yield). Mp 248–250 °C. IR (KBr) υ (cm^{-1}), 1567 (CN); 1210 (Ar–O); 723 (C–Cl). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 3.39 (s, 2H, CH_2–Cl); 6.70–6.75 (m, 2H, H-6, H-7); 7.59 (s, 1H, H-3); 7.64–7.70 (m, 1H, H-5). Anal. Calcd for $C_8H_7ClN_2O$: C, 52.62%; H, 3.86%; N, 15.34%. Found: C, 52.38%; H, 3.98%; N, 15.01%.

4.1.2. 2-Acetamido-3-hydroxypyridine (3). To a solution of 2-amino-3-hydroxypyridine (400 mg, 3.64 mmol) in dry dichoromethane (20 mL), triethylamine (1 mL, 7.28 mmol) was added. Then the mixture was cooled to 0 °C and acetyl chloride (314 mg, 4 mmol) was added. Finally, the mixture was stirred at room temperature for 12 h (TLC: ethyl acetate/MeOH, 9:1), dichloromethane was evaporated and the residue was purified on a silica gel chromatography column, using ethyl acetate as eluent, to give 490 mg (89%) of a yellow solid. Mp 98–100 °C (hexane/ethyl acetate). IR (KBr) υ (cm^{-1}), 3214 (OH), 3014 (NH), 1661 (CO), 1228 (Ar–O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.30 (s, 3H, CH_3); 7.15 (dd, $J=3.0$, 5.0 Hz, 1H, H-5); 7.40 (dd, $J=1.0$, 5.0 Hz, 1H, H-4); 7.87 (dd, $J=1.0$, 3.0 Hz, 1H, H-6); 10.98 (s, 2H, OH, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 23.3 (CH_3); 122.7 (CH, C-5); 128.5 (CH, C-4); 138.0 (CH, C-6); 140.6 (C, C-3); 145.3 (C, C-2); 172.0 (C, CO). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26%; H, 5.30%; N, 18.41%. Found: C, 55.58%; H, 5.74%; N, 18.12%. MS (*m*/*z*; IS) calcd for: $[C_7H_8N_2O_2]^+$: 152.15; found: 153 $[M+H]^+$.

4.1.3. 2-(Ethoxycarbonylamino)-3-hydroxypyridine (4). To a solution of 2-amino-3-hydroxypyridine (200 mg, 1.82 mmol) in dichloromethane (30 mL) was added triethylamine (0.5 mL, 3.64 mmol). Then the mixture was cooled to 0 °C and ethyl chloroformate (217 mg, 2 mmol) was added dropwise. The mixture was stirred at room temperature for 4 h (TLC: ethyl acetate). Finally, the solution was diluted with dichloromethane (20 mL) and water (20 mL), the organic phase was washed sequentially with $NaHCO_3$ (5% in water) and brine (20 mL), dried over $MgSO_4$ and evaporated to yield a residue, which was purified on silica gel chromatography column using ethyl acetate as eluent. The compound **3** (129 mg, 39%) was obtained as a white solid. Mp 102–104 °C. IR (NaCl) υ (cm^{-1}), 3310 (OH); 2980 (NH); 1686 (CO); 1262 (Ar–O); 1092 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.36 (t, $J=7.2$ Hz, 3H, –CH_3); 4.30 (q, $J=7.0$ Hz, 2H, –CH_2); 7.06 (dd, $J=4.8$, 8.2 Hz, 1H, H-5); 7.29 (dd, $J=1.8$, 8.2 Hz, 1H, H-4); 7.97 (dd, $J=1.8$, 4.8 Hz, 1H, H-6); 8.97 (br s, 1H; OH, NH). ^{13}C NMR ($CDCl_3$, $J=50.3$ Hz) δ (ppm), 14.5 (CH_3); 62.9 (CH_2); 121.3 (CH, C-5); 128.0 (CH, C-4); 138.6 (C, C-3); 140.2 (CH, C-6); 143.9 (C, C-2); 156.7 (C, CO). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74%; H, 5.53%; N, 15.38%. Found: C, 52.43%; H, 5.67%; N, 15.01%.

4.1.4. 2-(*tert*Butylcarbonyl)-3-hydroxypyridine (5). In a similar way to that described for 2-acetylamino-3-hydroxypyridine, starting from 2-amino-3-hydroxypyridine (150 mg, 1.36 mmol) and *tert*butyl acide chloride (327 mg, 1.27 mmol) was obtained the amide *tert*butyl in a 90% yield as a white solid. Mp 82–84 °C. IR (NaCl) ν (cm^{-1}), 3485 (OH); 3164 (NH); 1768 (CO); 1231 (Ar–O); 1100 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.54 (s, 9H, –CH_3); 4.54 (br s, 2H, -OH, NH); 6.69 (dd, $J=4.8$, 7.8 Hz, 1H, H-5); 7.39 (dd, $J=1.0$, 4.8 Hz, 1H, H-4); 7.97 (dd, $J=1.0$, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 27.9 (CH_3); 42.8 (C, $C(CH_3)_3$); 122.0 (CH, C-5); 129.1 (CH, C-4); 138.2 (CH, C-6); 138.2 (C, C-3); 141.8 (C, C-2); 171.5 (C, CO). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84%; H, 7.27%; N, 16.47%. Found: C, 62.03%; H, 7.65%; N, 16.23%.

4.2. Formation of [1,4]oxazine ring. General procedure

To a suspension of K_2CO_3 (454 mg, 3.29 mmol) in acetonitrile (20 mL) was added 3-protected-2-hydroxypyridine (0.66 mmol). The resulting mixture was stirred at room temperature for 15 min, then chloroacrilonitrile or

2,3-dibromopropionate ethyl ester (0.72 mmol) was added dropwise in a twice separated by 1 h. The mixture was stirred at reflux for 2–24 h. The solvent was evaporated, the residue was suspended in cold water (20 mL), and the aqueous solution was further extracted with CH_2Cl_2 (3× 15 mL). The combined organic phases were washed with 0.5% $NaHCO_3$, dried (Na_2SO_4), and concentrated to providing crude nitrile or ester. The residue was purified by column chromatography on silica gel eluting with mixtures of hexane/ethyl acetate. The yields reported correspond to analytically pure isolated compounds.

4.2.1. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile (6a). Following the general procedure described above starting from 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) and 2-chloroacrylonitrile (63 mg, 0.72 mmol) a mixture of two isomeres was obtained. The 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile was obtained as a white solid in 70% yield. Mp 113–115 °C. IR (KBr) υ (cm^{-1}), 2230 (CN); 1671 (CO); 1580 (CN); 1268 (Ar–O); 1081 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.66 (s, 3H, CH_3); 3.95 (dd, J=4.4, 14.2 Hz, 1H, CH_2N); 4.93 (dd, J=4.4, 14.2 Hz, 1H, CH_2N); 5.21 (dd, J=1.0, 6.8 Hz, 1H, H-2); 7.13 (dd, J=4.6, 7.9 Hz, 1H, H-7); 7.38 (dd, J=1.0, 7.9 Hz, 1H, H-8); 8.18 (dd, J=1.0, 4.6 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 24.8 (CH_3); 40.9 (CH_2); 63.5 (CH–O); 114.6 (C, CN); 121.5 (CH, C-7); 125.3 (CH, C-8); 138.8 (C, C-8a); 141.2 (C, C-8); 151.2 (C, C-4a); 170.1 (CO, amide). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11%; H, 4.46%; N, 20.68%. Found: C, 59.34%; H, 4.63%; N, 20.54%. The 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-3-nitrile (**7a**) was obtained as a white solid in 36% yield when acetone was used as a solvent (see Table 1). Mp 110–112 °C. IR (KBr) υ (cm^{-1}), 2236 (CN); 1675 (CO); 1567 (CN); 1243 (Ar–O); 1032 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 3.67–3.78 (m, 1H, CHN); 3.80 (s, 3H, CH_3); 4.80–4.90 (m, 2H, H-2); 6.61 (dd, J=4.5, 8.0 Hz, 1H, H-7); 7.18 (dd, J=1.0, 8.0 Hz, 1H, H-8); 7.72 (dd, J=1.0, 8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 27.2 (CH_3); 42.5 (CH_2); 61.2 (CH_2–O); 115.9 (C, CN); 122.3 (CH, C-7); 126.2 (CH, C-8); 137.5 (C, C-8a); 141.8 (C, CH-6); 150.8 (C, C-4a); 168.2 (CO, amide). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11%; H, 4.46%; N, 20.68%. Found: C, 59.02%; H, 4.72%; N, 20.72%.

4.2.2. 4-Ethoxycarbonyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-[1,4]oxazine-2-nitrile (6b). From 2-ethoxycarbonyl-3-hydroxypyridine (100 mg, 0.55 mmol) and 2-chloroacrylonitrile (53 mg, 0.60 mmol) a mixture of two isomers was obtained. The majority isomer 4-ethoxycarbonyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile was obtained as a yellow pale solid in 40% yield. Mp 103–104 °C. IR (KBr) υ (cm^{-1}), 2251 (CN); 1784 (CO); 1576 (CN); 1151 (Ar–O); 1080 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.26 (s, 3H, CH_3); 2.20 (dd, J=1.0, 8.4 Hz, 1H, CHN); 2.73 (dd, J=1.0, 8.5 Hz, 1H, CHN); 4.07–4.19 (m, 2H, CH_2–O); 4.81 (dd, J=1.0, 9.1 Hz, 1H, H-2); 7.20 (dd, J=4.5, 8.0 Hz, 1H, H-7); 7.41 (dd, J=1.0, 8.0 Hz, 1H, H-8); 8.21 (dd, J=1.0, 8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 14.4 (CH_3); 43.4 (CH_2); 62.8 (CH_2–O); 72.9 (CH, C-2); 119.2 (C, CN); 121.2 (CH, C-7); 124.6 (CH, C-8); 138.5 (C, C-8a); 140.6 (CH, C-6); 153.2 (C, C-4a); 168.4 (CO, amide). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65%; H, 4.75%; N, 18.02%. Found: C, 56.34%; H, 4.43%; N, 17.69%. The minor isomer 4-ethoxycarbonyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-3-nitrile (**7b**) was obtained as a white solid in 40% yield. Mp 199–201 °C. IR (KBr) υ (cm^{-1}), 2280 (CN); 1784 (CO); 1556 (CN); 1210 (Ar–O); 1046 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.26 (t, J=7 Hz, 3H, CH_3); 4.12 (m, 3H, CHN and CH_2–O); 4.72 (d, J=14.2 Hz, 1H, CH_2O); 7.08–7.12 (m, 1H, H-7); 7.41 (dd, J=1.0, 8.0 Hz, 1H, H-8); 8.18 (dd, J=1.0, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 14.8 (CH_3); 40.8 (CH, CH–N); 62.8 (CH_2, CH_2–O); 63.5 (CH_2–O); 115.9 (C, CN); 121.8 (CH, C-7); 126.7 (CH, C-8); 138.5 (C, C-8a); 141.5 (C, C-8a); 153.2 (C, C-4a); 168.2 (CO, amide). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65%; H, 4.75%; N, 18.02%. Found: C, 56.87%; H, 5.02%; N, 17.71%.

4.2.3. 4-*tert*Butylcarbonyl-2,3-dihydro-4*H*-pyrido[3,2-*b*]-[1,4]oxazine-2-nitrile (6c). From 2-*tert*butylcarbonyl-amino-3-hydroxypyridine (100 mg, 0.52 mmol) and 2-chloroacrylonitrile (50 mg, 0.57 mmol) the 2-substituted pyrido-oxazine was obtained with 50% yield as a yellow pale instable solid. IR (KBr) υ (cm^{-1}), 2242 (CN); 1717 (CO); 1568 (CN); 1254 (Ar–O); 1097 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.55 (s, 9H, CH_3); 3.81–3.85 (m, 1H, H-3); 4.50–4.61 (m, 1H, H-3); 5.10–5.19 (m, 1H, H-2); 7.05–7.09 (m, 1H, H-7); 7.24–7.28 (m, 1H, H-8); 8.21 (dd, J=1.8, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 28.1 (CH_3); 43.9 (CH_2, CH_2–N); 63.2 (CH, CH–O); 83.2 (C); 116.8 (C, CN); 121.2 (CH, C-7); 124.9 (CH, C-8); 138.9 (C, C-8a); 141.9 (CH, C-6); 150.0 (C, C-4a); 168.1 (C, CO). Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66%; H, 6.16%; N, 17.13%. Found: C, 63.99%; H, 6.54%; N, 16.08%.

4.2.4. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid ethyl ester (8). Following the general procedure described above starting from 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) and 2,3-dibromo-propionate ethyl ester (188 mg, 0.72 mmol) the 4-acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid ethyl ester was obtained in 56% yield. Colorless oil. IR (KBr) υ (cm^{-1}), 1745 (CO); 1653 (CO), 1228 (Ar–O); 1059 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.28 (t, J=7.0 Hz, 3H, CH_3); 2.54 (s, 3H, CH_3); 3.98 (dd, J=4.0, 7.0 Hz, 2H, CH–N); 4.24 (q, J=7.0 Hz, 2H, CH_2–O); 4.94–4.99 (m, 1H, CH–O), 7.09 (dd, J=1.4, 4.7 Hz, 1H, H-7); 7.18 (dd, J=1.3, 8.0 Hz, 1H, H-8); 8.01 (dd, J=1.4, 4 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 14.1 (CH_3); 24.5 (CH_3); 40.3 (CH_2–N); 62.0 (CH_2–O); 73.1 (CH–O); 121.4 (CH, C-7); 124.6 (CH, C-8); 139.7 (CH, C-6); 141.1 (C, C-8a); 141.3 (C, C-4a); 168.1 (CO, ester); 170.1 (CO, amide). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59%; H, 5.64%; N, 11.19%. Found: C, 57.78%; H, 5.89%; N, 11.40%. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-[1,4]oxazine-3-carboxylic acid ethyl ester (**9**) the 4-acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-3-carboxylic acid ethyl ester was obtained in 14% yield. Colorless oil. IR (KBr) υ (cm^{-1}), 1756 (CO); 1667 (CO), 1232 (Ar–O); 1045 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.30 (t, J=7.0 Hz, 3H, CH_3); 2.53 (s, 3H, CH_3); 3.97 (m, 1H, CH–N); 4.24 (q, J=7.0 Hz, 2H, CH_2–O); 4.87–4.95 (m, 2H, CH_2–O), 6.83 (m, 1H, H-7); 7.21 (dd, J=1.3, 8.0 Hz, 1H,

H-8); 7.87 (dd, J=1.5, 4.0 Hz, 1H, H-6). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59%; H, 5.64%; N, 11.19%. Found: C, 57.82%; H, 5.43%; N, 11.45%.

4.2.5. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid methyl ester (10). Following the general procedure described above starting from 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) the title compound was obtained in 61% yield. Colorless oil. IR (NaCl) ν (cm^{-1}), 1755 (CO); 1673 (CO). ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm), 2.54 (s, 3H, CH_3); 3.76 (s, 3H, OCH_3); 3.82 (dd, J= 3.4, 13.8 Hz, 1H, CHN); 4.69 (dd, J=3.8, 13.8 Hz, 1H, CHN); 4.92 (t, J=3.8 Hz, 1H, H-2); 7.09 (dd, J=4.7, 8.1 Hz, 1H, H-7); 7.35 (dd, J=1.4, 8.1 Hz, 1H, H-8); 8.01 (dd, J=1.4, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 24.6 (CH_3); 40.6 (CH_2); 52.9 (OCH_3); 73.3 (CH, C-2); 121.7 (CH, C-7); 124.9 (CH, C-8); 139.9 (C, C-8a); 140.1 (CH, C-6); 141.3 (C, C-4a); 168.9 (CO); 170.4 (CO). MS (IS) (m/z) calcd for: $[C_{11}H_{12}N_2O_4]^+$: 236.23; found: 237 $[M+H]^+$, 259.5 $[M+Na]^+$.

4.3. General procedure for the condensation of α-halo-vinylcarbonyl compounds

A solution of 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) and K_2CO_3 (454 mg, 3.29 mmol) in acetonitrile (5 mL) was stirred at room temperature for about 30 min. After addition of the α-haloene (3.29 mmol) the mixture was refluxed for 2 to 24 h (see in detail Table 2). After cooling to room temperature, the solution was filtered through a pad of Celite and the filtrate concentrated in vacuum. The residue was then purified by column chromatography on silica gel.

4.3.1. 2,4-Diacetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]-oxazine (12a). Purification on silica gel (ethyl acetate/petrol ether, 6:4) yielded 75 mg (52%) of **12a** as a yellow solid. IR (NaCl) υ (cm^{-1}), 1729 (CO); 1669 (CO); 1456. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 2.29 (s, 3H, CH_3); 2.54 (s, 3H, CH_3); 4.03 (dd, J=3.5, 13.8 Hz, 1H, N–CH_2); 4.46 (dd, J=5.0, 13.8 Hz, 1H, N–CH_2); 4.81 (dd, J=3.5, 5.0 Hz, 1H, O–CH); 7.08 (dd, J=4.7, 8.2 Hz, 1H, H-7); 7.35 (dd, J=1.6, 8.2 Hz, 1H, H-8); 7.99 (dd, J=1.6, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 24.7 (CH_3); 26.5 (CH_3); 39.6 (CH_2, CH_2–N); 79.4 (CH, CH–O); 121.6 (CH, C-7); 124.7 (CH, C-8); 139.7 (C, C-8a); 139.9 (CH, C-6); 141.3 (C, C-4a); 170.3 (CO, amide); 203.4 (CO, ketone). HRMS (m/z; IS) calcd for $[C_{11}H_{12}N_2O_3]^+$: 220.08479; found: 220.0849.

4.3.2. 4-Acetyl-2-benzoyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-[1,4]oxazine (12b). Purification on silica gel (ethyl acetate/petrol ether, 6:4) yielded 89 mg (48%) of **12b** from B, X= Br or 63 mg (34%) from B, X=Cl as a yellow solid. IR (NaCl) υ (cm^{-1}), 3064 (Ar–H); 3015 (Ar–H); 1694 (CO); 1578; 1456. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 2.54 (s, 3H, CH_3); 4.24 (dd, J=3.5, 13.8 Hz, 1H, N–CH_2); 4.42 (dd, J=5.3, 13.8 Hz, 1H, N–CH_2); 5.72 (dd, J=3.5, 5.0 Hz, 1H, O–CH); 7.09 (dd, J=4.7, 8.2 Hz, 1H, H-7); 7.36 (dd, J= 1.6, 8.2 Hz, 1H, H-8); 7.48 7.54 (m, 2H, Ar); 7.60–7.70 (m, 1H, Ar); 7.94–7.98 (m, 2H, Ar); 8.02 (dd, J=1.6, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 24.5 (CH_3); 40.5 (CH_2, CH_2–N); 75.6 (CH, CH–O); 121.6 (CH, C-7); 124.8 (CH, C-8); 128.6 (CH, C-3′, C-5′); 129.2 (CH, C-2′, C-6′); 131.8 (C, C-8a); 134.2 (C, C-1′); 134.3 (CH, C-4′); 139.8 (CH, C-6); 141.9 (C, C-4a); 170.5 (CO, amide); 194.0 (CO, ketone). HRMS (m/z; IS) calcd for $[C_{16}H_{14}N_2O_3]^+$: 282.10044; found: 282.1007.

4.3.3. 10-Acetyl-8,9,9a,10-tetrahydro-7*H*-pyrido[3,2-*b*]-benzo[1,4]oxazin-6-one (12c). Purification on silica gel (ethyl acetate/petrol ether, 6:4) yielded 85 mg (53%) of **12c** as a colorless oil. IR (NaCl) υ (cm^{-1}), 1726 (CO); 1668 (CO); 1577, 1451. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 1.57 (ddd, J=3.84, 12.63, 25.56 Hz, 1H, H-9); 1.70 (dddd, J=3.84, 3.84, 13.68, 27.39 Hz, 1H, H-8); 1.87–1.92 (m, 1H, H-9); 2.02–2.08 (m, 1H, H-8); 2.38–2.41 (m, 1H, H-7); 2.63 (s, 3H, CH_3); 2.76 (ddd, J=6.2, 13.7, 13.7 Hz, 1H, H-7); 4.29–4.30 (m, 1H, H-5a); 5.14 (ddd, J=2.7, 5.0, 12.7 Hz, 1H, H-9); 7.06 (dd, J=4.7, 8.2 Hz, 1H, H-3); 7.28 (dd, J= 1.6, 8.2 Hz, 1H, H-4); 8.03 (dd, J=1.6, 4.7 Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 22.2 (CH_2, C-8); 24.0 (CH_2, C-9); 25.9 (CH_3) 36.8 (CH_2, C-7); 50.3 (CH, C-9a); 79.6 (CH, C-5a); 120.9 (CH, C-3); 124.5 (CH, C-4); 138.6 (C, C-4a); 139.8 (C, C-10a); 140.5 (CH, C-2); 141.3 (C, C-4a); 169.9 (CO, amide); 204.0 (CO, ketone). HRMS (m/z; IS) calcd for $[C_{13}H_{14}N_2O_3]^+$: 246.10044; found: 246.1007.

4.4. Unsatured compounds. General procedure

To a stirred solution of the pyrido-oxazine (0.50 mmol) in dry CCl_4 (15 mL) *N*-bromosuccinimide (3 equiv) and a catalytic amount of AIBN were added. The reaction mixture was stirred and heated with a bulb lamp (100 W) for 60 min and then allowed to cool to room temperature. Upon cooling to room temperature the NBS was filtered off, and the solvent was removed on vacuum. The oil obtained sufficiently pure was used directly in the next step. The crude of reaction was dissolved in acetone (20 mL). Then sodium iodide (1.23 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. Finally, the solvent was evaporated to dryness in vacuum followed by addition of ethyl acetate (20 mL) and washed with water and after with 1 M solution of sodium thiosulfate. The organic phase was dried over $MgSO_4$. Evaporation of the solvent gave the desired compound, which was subjected to column chromatography of silica gel eluting with hexane/ethyl acetate.

4.4.1. 4-Acetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile (21). Following the general procedure the title compound was obtained with a 55% yield as a white solid. Mp 126–128 °C. IR (KBr) υ (cm^{-1}), 2227 (CN); 1724 (C=O); 1580 (C=N); 1230 (Ar–O); 1102 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.67 (s, 3H, CH_3); 7.05–7.12 (m, 2H, H-7 and H-8); 7.54 (s, 1H, H-3); 7.99 (dd, J=1.8, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 26.4 (CH_3); 112.4 (C, C-2); 116.4 (C, CN); 121.5 (CH, C-3); 122.8 (CH, C-7); 124.6 (CH, C-8); 139.9 (C, C-8a); 140.6 (CH, C-6); 153.2 (C, C-4a); 168.4 (CO, amide). Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70%; H, 3.51%; N, 20.89%. Found: C, 59.92%; H, 3.81%; N, 20.58%.

4.4.2. 4-Acetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine-3-nitrile (22). Following the general procedure the title compound

was obtained with a 60% yield as a colorless oil. IR (KBr) υ (cm^{-1}), 2229 (CN); 1735 (C=O); 1565 (C=N); 1260 (Ar–O); 1100 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.69 (s, 3H, CH_3); 7.02–7.18 (m, 2H, H-7 and H-8); 7.42 (s, 1H, H-3); 8.18 (dd, $J=1.8$, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 25.2 (CH_3); 116.6 (C, CN); 126.7 (CH, C-3); 122.8 (CH, C-7); 124.8 (CH, C-8); 140.3 (C, C-8a); 141.7 (CH, C-2); 142.8 (CH, C-6); 152.5 (C, C-4a); 166.9 (CO, amide). Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70%; H, 3.51%; N, 20.89%. Found: C, 59.83%; H, 3.76%; N, 20.77%.

4.4.3. 4-Acetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid methyl ester (23a). Following the general procedure described above starting from the corresponding saturated ester the title compound was obtained. After purification on silica gel (hexane/ethyl acetate) were obtained 48 mg (81%) as a yellow solid (mp=83–84 °C). IR (NaCl) υ (cm^{-1}), 1732 (CO), 1687 (CO). ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 2.68 (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 7.02 (dd, $J=4.7$, 7.9 Hz, 1H, H-7); 7.21 (dd, $J=1.6$, 7.9 Hz, 1H, H-8); 7.88 (s, 1H, H-3); 7.94 (dd, $J=1.6$, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 26.6 (CH_3); 52.5 (OCH_3); 118.4 (CH, C-3); 119.2 (C, C-2); 122.6 (CH, C-7); 124.7 (CH, C-8); 131.3 (C, C-8a); 141 (C, C-4a); 142.2 (CH, C-6); 161.3 (CO, ester), 167.7 (CO, amide). MS (IS) (*m*/*z*) calcd for: $[C_{11}H_{10}N_2O_4]^+$: 234.21; found: 235.5 $[M+H]^+$, 257.5 $[M+Na]^+$.

4.4.4. 2,4-Diacetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine (23b). After purification on silica gel (ethyl acetate/petrol ether, 1:1) were obtained 54 mg (91%) of **23b** as a yellow solid (mp 139–141 °C). IR (NaCl) ν (cm^{-1}), 1690 (CO); 1682 (CO). ^1H NMR ($CDCl_3$, 250 Hz): δ (ppm), 2.34 (s, 3H; CH_3); 2.70 (s, 3H; CH_3); 7.02 (dd, $J=5$, 8.2 Hz, 1H; H-7); 7.22 (dd, $J=1.6$, 8.2 Hz, H-8); 7.88 (s, 1H; H-3); 7.93 (dd, $J=1.6$, 5 Hz, 1H; H-6). ^{13}C NMR ($CDCl_3$, $J=62.9$ Hz): δ (ppm), 25.2 (*C*H_3); 26.7 (CH_3); 119.2 (*C*H); 122.7 (*C*H); 124.7 (*C*H); 138.2 (C); 140.8 (*C*); 142.1 (*C*H); 142.2 (*C*); 168 (*C*O, amide); 189.5 (*C*O, ketone). HRMS (*m*/*z*; IS) calcd for: $[C_{11}H_{10}N_2O_3]^+$: 218.06914; found: 218.0697.

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