Quaternization at the picolinic carbon. Application to the synthesis of pyridylalkanecarboxylic acids

Eric Pasquinet, Patrick Rocca,* Alain Godard, Francis Marsais and Guy Quéguiner

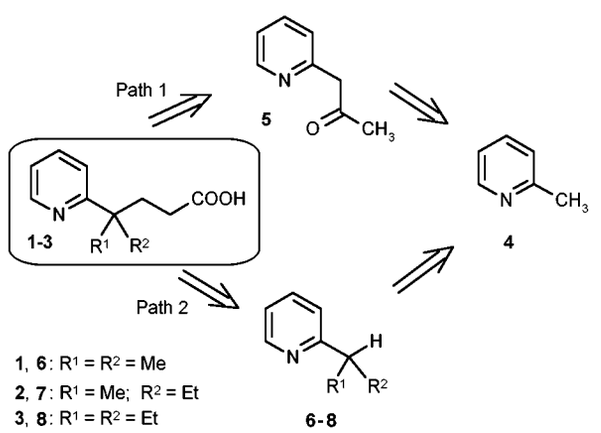
Institut de Recherche en Chimie Organique Fine, UPRESA 6014,
Institut National des Sciences Appliquées, BP 08, 76131 Mont Saint Aignan cedex, France

Received (in Cambridge) 23rd July 1998, Accepted 28th September 1998

The paper describes two different methodologies for the construction of a quaternary center at the picolinic site, and their application to the synthesis of pyridylalkanecarboxylic acids. The first one involves a one-pot acetylation–Michael addition procedure followed by an alkylative quaternization of the picolinic carbon. The second one is based on the deprotonation at the picolinic carbon of 2-(α,α-dialkyl)pyridines using the superbasic mixture BuLi–diisopropylamine–Bu′OK ("KDA"). Both routes give very good yields.

Introduction

Our group has long been interested in the metallation of π-deficient heterocycles (pyridine, quinoline and diazines),[1] which are present in numerous alkaloids with biological properties.[2] In the course of our studies, we have been looking for an efficient route to general structures **1**–**3** (Scheme 1) as building blocks for the synthesis of analogues of biologically active natural products. Metallation of the lateral chain of simple alkylpyridines (*e.g.* picoline) has been known for a long time,[3] however the synthesis of quaternary picolinic carbons has been less well studied. Most of the strategies rely on functionalization of the activated methylene by such groups as nitrile or ester[4] but these strategies are not applicable for our purpose. Thus, we designed two different and original routes to **1**–**3** using deprotonation reactions from 2-picoline† **4** (Scheme 1).



Scheme 1

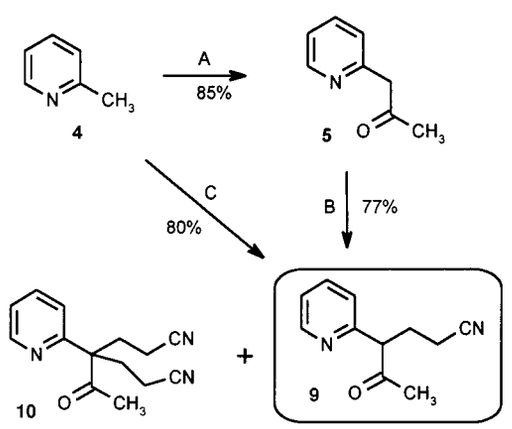
The first synthetic pathway (path 1) follows the classical activated methylene route using the acetyl group as the activating group. The acetyl group enables the introduction of the desired 3-carbon chain bearing an acid precursor by means of a Michael-type addition[5] and further easy transformation to the desired alkyl group by Wolff–Kishner reduction. The second pathway (path 2) is based on hydrogen abstraction at the picolinic carbon of compounds **6**–**8** by using the superbasic mixture BuLi–diisopropylamine–Bu′OK ("KDA") as recently described by our group.[4]

† IUPAC name: 2-methylpyridine.

Results and discussion

Path 1: synthesis of compounds 2 and 3 starting from 5

2-Pyridylacetone **5** was prepared according to the procedure described by Cassity and co-workers[6] by metallation of 2-picoline **4** with BuLi followed by action of dimethylacetamide (DMA). Then, **5** was cyanoethylated, adapting a Michael-type procedure in weakly basic conditions,[7] to afford ketonitrile **9** in 77% yield (Scheme 2). The bis-adduct **10** was produced in only a minor amount (5%).



Scheme 2 *Reagents and conditions*: A (a) 1 equiv. BuLi, THF, −20 °C, 1 h; (b) DMA, −70 °C, 30 min; B NEt_3, Bu′OH, H_2O, acrylonitrile, reflux, 4 days; C Metallation, then cyanoethylation; one-pot procedure using the conditions described in Table 1.

An improved one-pot procedure was designed, taking into account that the basicity of the medium after hydrolysis at the end of the metallation step could promote subsequent 1,4-addition without isolation of intermediate **5** (Scheme 2, C). Various conditions of metallation and hydrolysis were tried Table 1.

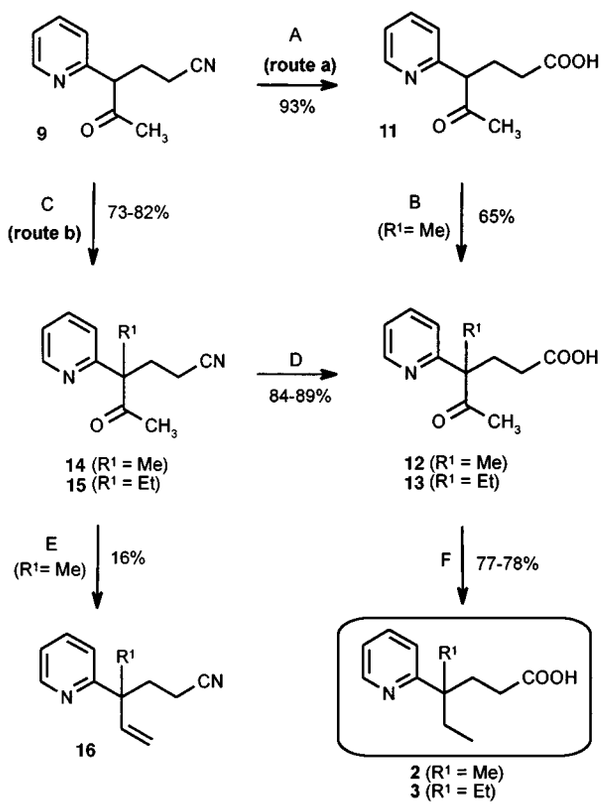
In the first experiment, one equivalent of sodium hydroxide (NaOH) was produced after hydrolysis. After Michael addition, equal amounts of mono- and bis-adducts (37% and 39% respectively) were obtained. In the second experiment, triethylamine was added after complete neutralization to recover the cyanoethylation conditions as described in Scheme 2 (B conditions) and very good results were obtained. Another one-pot synthesis of ketonitrile **9** was realised in the third experiment, where an incomplete neutralization was carried

Table 1

Exp.	Conditions of metallation[a]	Hydrolysis[a]	Yield (%)[b] 5	9	10
1	NDA[c] (1.1 equiv.)	H_2O	2	37	39
2	BuLi (1.1 equiv.)	HCl (1.1 equiv.)	3	78	3
3	BuLi (1.1 equiv.)	HCl (0.8 equiv.)	4	80	2

[a] See also Experimental section. [b] Isolated yield. [c] BuLi–diisopropylamine–Bu^{t}ONa.

out, leaving 0.3 equivalent of lithium hydroxide (LiOH) to smoothly achieve a clean 1,4-addition. At this stage, two options were available for the synthesis of ketoacids **12** and **13** with the desired quaternary carbon: either hydrolysis of the nitrile group followed by alkylation on the picolinic carbon (route a) or alkylation followed by hydrolysis (route b). Both routes were carried out (Scheme 3).



Scheme 3 *Reagents and conditions*: A (a) 30% H_2SO_4, 150 °C, 2 h; (b) 25% NH_4OH; B (a) 2 equiv. NaH, THF, 20 °C, 1 h; (b) MeI, 20 °C, 2 h (R^1 = Me); C (a) 1.1 equiv. NaH, THF, 20 °C, 1 h; (b) MeI or EtI, 20 °C, 2 h (R^1 = Me) or 12 h (R^1 = Et); D (a) 20% H_2SO_4, 100 °C, 40–60 min; (b) 25% NH_4OH; E (a) $TsNHNH_2$, EtOH, reflux, 4.5 h (90%); (b) LiH, toluene, reflux, 50 min (18%); F (a) $NH_2NH_2{\cdot}H_2O$, ethyleneglycol, 20 °C→160 °C, 1 h; (b) KOH, 170 °C, 3 h; (c) HCl.

Route a. Ketoacid **11** was obtained in good yield by action of hot dilute sulfuric acid. Unfortunately, quaternization of the picolinic site could not be cleanly achieved and this route was ruled out (Scheme 3).

Route b. Deprotonation by sodium hydride (NaH)[8] followed by alkylation with methyl or ethyl iodide proceeded cleanly, affording **14** and **15**. Hydrolysis of the nitrile group in acidic conditions gave ketoacids **12** and **13** in good yields (Scheme 3).

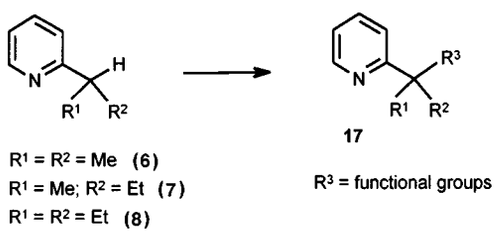
It should be noted that **14** could be directly obtained from commercial 2-ethylpyridine, using the tandem acetylation–Michael addition described above (1.1 equiv. of BuLi and water hydrolysis since no bis-adduct can be produced, 70% yield). However, low yields (*ca.* 35%) obtained in the acetylation of 2-propylpyridine prevented us from synthesizing **15** in the same way.

Reduction of the carbonyl moiety. First experiments on ketonitrile **14** were unsuccessful using the classical Wolff–Kishner procedure.[9] More selective conditions such as reduction of the corresponding tosylhydrazone appeared to be promising.[10] Unfortunately, all the attempted reductions on the latter failed. The only successful pathway was the conversion to alkene **16**, but in a very low yield, following the work of Caglioti and co-workers[11] (Scheme 3). Although this product (**16**) was of interest to us, we decided to reexamine the Wolff–Kishner reduction on ketoacids **12** and **13**. Thus, using a slightly modified Wolff–Kishner procedure[12] target acids **2** and **3** were obtained in good yields (Scheme 3).

To summarise this first synthetic reaction scheme, target molecules **2** and **3** were synthesized in satisfactory yields. In this series, to the best of our knowledge, the only reported example of α-quaternization using an acetyl group as an activating group arose from our team in the field of aza-steroids.[13]

Path 2: synthesis of compounds 1–3 starting from 6–8

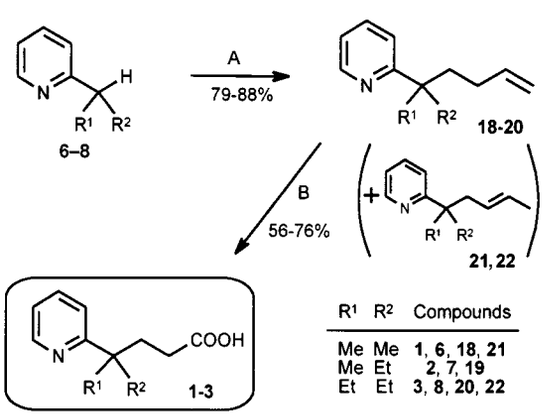
Having compounds **6–8** in our hands[14] (Scheme 4), we were



Scheme 4

interested in the quaternization of the picolinic site by metallation. Oxidative cleavage of an appropriate alkenyl chain could then lead to the desired acids. As lithiated bases proved to give poor yields in α-deprotonation of highly hindered alkylpyridines,[15] we studied stronger basic conditions.

We recently described[4] a general and efficient method using the superbasic mixture BuLi–diisopropylamine–Bu^{t}OK ("KDA") to afford complete deprotonation of the picolinic carbon on 2-isopropylpyridine. This method was successfully extended to even more hindered 2-(α,α-dialkyl)pyridines and allowed us to synthesize target acids **1–3**. Thus, alkylpyridines **6–8** were subjected to metallation by KDA, before rapid reaction with 4-bromobutene as electrophile, to give the corresponding alkenylpyridines **18–20** in very good yields (Scheme 5).



Scheme 5 *Reagents and conditions*: A (a) 1.3 or 1.8 equiv. [BuLi, diisopropylamine, Bu^{t}OK], THF, −50 °C or −30 °C, 1 h; (b) 4-bromobutene, −70 °C, 1.5–2 min; B $KMnO_4$, AcOH, H_2O, 20 °C, 30 min.

Table 2

R^1	R^2	Compounds	Yield (%)[a]	Ratio[b]
Me	Me	**18**, **21**	88	96:4
Me	Et	**19**	80	100:0
Et	Et	**20**, **22**	79	95:5

[a] Isolated yield. [b] ^{1}H NMR integration.

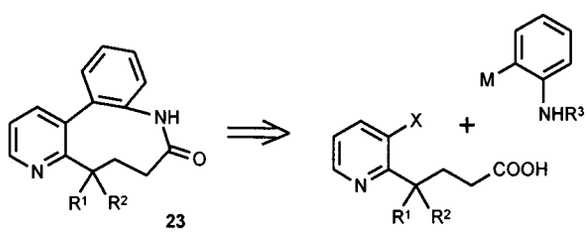
We also observed the formation of isomerized products **21** and **22**, surely arising from allylic metallation on the initially formed terminal alkenes **18** and **20**. As a matter of fact, both an increase in the quantity of base and reaction time resulted in lower selectivity. Consequently, we limited the reaction time with 4-bromobutene to 1.5–2 min, thus reducing the ratio of the undesired isomer to less than 5%, keeping very good chemical yields (Table 2).

Terminal alkenes **18**–**20** (containing their inseparable minor isomers **21** and **22**) were then subjected to an oxidative cleavage[16] by means of aqueous potassium permanganate ($KMnO_4$) in the presence of acetic acid. Flash chromatography on silica gel afforded pure acids **1**–**3** in good yields (Scheme 5).

Conclusion

Pyridylalkanecarboxylic acids have been prepared in good yields according to two routes. The first route (path 1), based on the introduction of a 3-carbon chain by means of a Michael-type addition, yielded 38 to 45% of the desired targets **2** and **3** in four steps from 2-picoline. The second route (path 2), based on hydrogen abstraction at the picolinic carbon using the superbasic mixture KDA, yielded 27 to 58% of the expected targets **1**–**3** in three or four steps from 2-ethylpyridine or 2-picoline, respectively.

The novelty and versatility of the second path should be emphasized and the successful application of this strategy in the field of natural products could lead to expedient routes for the total synthesis of alkaloids.[17] For instance, we are working on phenylpyridinic analogues **23** of the natural alkaloid rhazinilam[18] (Scheme 6). This type of compound could show interesting antitubulin activity.[19]



R¹, R² = alkyls; R³ = H, COBu^t, X= OR, halo; M= B(OH)$_2$, SnR$^1_3$

Scheme 6

Experimental

General data

The ^{1}H NMR spectra were obtained on a Brüker AM 200 spectrometer. They were recorded in ppm from an internal standard, Me_4Si in $CDCl_3$. Coupling constants (J) values are given in Hz. ^{1}H–^{1}H coupling constants of pyridine protons are in good agreement with the normal values for 2-alkyl substituted pyridines and are not given ($J_{3,4} = J_{4,5} \sim 8$ Hz, $J_{5,6} \sim 5$ Hz, $J_{4,6} \sim 2$ Hz). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer FTIR 1600 spectrometer. Elemental analyses were performed on a Carlo Erba 1110 CHNS-O apparatus. Refractive indices were recorded on an Abbe Refractometer at 20 °C. Mass Spectrometry was performed on a JEOL AX500 apparatus.

Solvents and reagents

Tetrahydrofuran (THF) was distilled from benzophenone–sodium and the water content was estimated to be lower than 45 ppm by the modified Karl–Fischer method.[20] Sodium and potassium *tert*-butoxides were commercially bought. Diisopropylamine was distilled over CaH_2. Commercial 2.5 M solutions of BuLi in hexanes were used as received.

1-(2-Pyridyl)propan-2-one (5)

The product was obtained as described[6] (85%, 100 mmol scale) as a yellow oil after distillation (102 °C/15 mmHg). As in analogous products,[21] the enol form is observable; using NMR integration in $CDCl_3$, we estimated the proportion keto form : enol form to be 92 : 8 (lit.,[6] 88 : 12), n_D^{20} 1.519 (Found: C, 70.9; H, 7.0; N, 10.55. Calc. for C_8H_9NO: C, 71.1; H, 6.7; N, 10.4%); ν_{max}(film)/cm^{-1} 3410 (OH, enol), 3009, 1716 (CO, ketone), 1654, 1592, 1570, 1475, 1436, 1358, 1160 and 756; δ_H(200 MHz; $CDCl_3$) keto form: 2.19 (3 H, s, $COCH_3$), 3.89 (2 H, s, CH_2), 7.15 (2 H, m, 3-H + 5-H), 7.62 (1 H, td, 4-H) and 8.52 (1 H, dd, 6-H); enol form: 1.99 (3 H, s, CH_3), 5.27 (1 H, s, C=CH), 6.84 (2 H, m, 3-H + 5-H), 7.50 (1 H, td, 4-H) and 8.15 (1 H, dd, 6-H), OH not observed.

Cyanoethylation of 1-(2-pyridyl)propan-2-one

5-Oxo-4-(2-pyridyl)hexanenitrile (9). We adapted the procedure described[7] for the cyanoethylation of 1,3-dicarbonyl compounds or malononitrile derivatives: 1-(2-pyridyl)-propan-2-one **5** was refluxed for 3 days with acrylonitrile in aqueous 2-methylpropan-2-ol containing triethylamine. After concentration, water was added and the mixture was extracted with dichloromethane, dried ($MgSO_4$) and evaporated. The residue was Kugelrohr distilled (140 °C/0.2 mmHg) to afford ketonitrile **9** (77%, 30 mmol scale) as a yellow oil, n_D^{20} 1.518 (Found: C, 69.9; H, 6.3; N, 14.9. Calc. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9%); ν_{max}(film)/cm^{-1} 2940, 2245 (CN), 1714 (CO), 1588, 1570, 1471, 1435, 1357, 1159, 782 and 753; δ_H(200 MHz; $CDCl_3$) 2.05 (3 H, s, $COCH_3$), 2.10–2.48 (4 H, m, CH_2 + CH_2CN), 3.97 (1 H, t, J 6.7, CH), 7.24 (2 H, m, 3-H + 5-H), 7.70 (1 H, td, 4-H) and 8.57 (1 H, dd, 6-H).

4-Acetyl-4-(2-pyridyl)heptanedinitrile (10). This compound could also be isolated (5%) along with **9** as a white solid, mp 103 °C (Found: C, 69.5; H, 6.2; N, 17.1. Calc. for $C_{14}H_{15}N_3O$: C, 69.7; H, 6.3; N, 17.4%); ν_{max}(KBr)/cm^{-1} 2953, 2250 (CN), 1707 (CO), 1587, 1567, 1469, 1430, 1358, 1168 and 752; δ_H(200 MHz; $CDCl_3$) 2.00 (3 H, s, $COCH_3$), 2.05–2.65 (8 H, m, 2 × CH_2 + 2 × CH_2CN), 7.24 (1 H, d, 3-H), 7.32 (1 H, dd, 5-H), 7.78 (1 H, td, 4-H) and 8.62 (1 H, dd, 6-H).

One-pot tandem acetylation–cyanoethylation

Experiment 1. In a dried, argon-flushed 100 cm^3 3-necked flask was placed sodium *tert*-butoxide (529 mg, 5.5 mmol), anhydrous THF (7 cm^3) and diisopropylamine (0.77 cm^3, 5.5 mmol). The mixture was cooled to −70 °C and BuLi (2.2 cm^3, 5.5 mmol) was slowly added. The reaction mixture was then warmed up to −50 °C over 15 min before adding 2-picoline (0.49 cm^3, 5 mmol). After 30 min of metallation at −50 °C, the solution was cooled to −75 °C and *N*,*N*-dimethylacetamide (0.51 cm^3, 5.5 mmol) was slowly added. The mixture was stirred at −75 °C for 30 min, after which 2 cm^3 of water were added. The solution was allowed to warm to 0 °C, 2-methylpropan-2-ol (6 cm^3) and acrylonitrile (0.66 cm^3, 10 mmol) were added before stirring at room temperature overnight. Further acrylonitrile was added (0.13 cm^3, 2 mmol) and stirring was continued for 1 more day to achieve almost complete conversion of intermediate ketone **5**. The mixture was neutralized with dilute acid, concentrated and extracted with dichloromethane (4 × 20 cm^3). After drying ($MgSO_4$), the solvent was removed and the residue

chromatographed over silica gel using CH_2Cl_2–acetonitrile, 9.5 : 0.5 as eluent.

Experiments 2 and 3. In a dried, argon-flushed 100 cm^3 3-necked flask was introduced a solution of 2-picoline **4** (3 cm^3, 30 mmol) in anhydrous THF (20 cm^3). The mixture was cooled to −30 °C and BuLi (13.2 cm^3, 33 mmol) was slowly added. After 1 h of metallation at −20 °C, the solution was cooled to −75 °C and *N*,*N*-dimethylacetamide (3.1 cm^3, 33 mmol) was slowly added. The mixture was stirred at −75 °C for 30 min, after which 4 M HCl (exp. 2: 8.2 cm^3, 33 mmol; exp. 3: 5.7 cm^3, 23 mmol) was added and the solution allowed to warm to room temperature. 2-Methylpropan-2-ol (18 cm^3), triethylamine (only in exp. 2, 4.2 cm^3, 30 mmol) and acrylonitrile (2.4 cm^3, 36 mmol) were added before refluxing for 5–7 days. During this time, it was necessary to add 2 or 3 further portions of acrylonitrile (0.59 cm^3, 9 mmol each portion) to achieve almost complete conversion of intermediate ketone **5**. The mixture was then worked up as in exp. 1 and the products separated by Kugelrohr distillation.

Alkylation of ketonitrile 9

Sodium hydride (60% dispersion in mineral oil, 660 mg, 16.5 mmol) was washed in a dried argon-flushed 100 cm^3 flask with petroleum ether (3 × 5 cm^3). Anhydrous THF was added (20 cm^3), before the dropwise addition of a solution of ketonitrile **9** (15 mmol) in THF (20 cm^3), the temperature being kept below 25 °C. The solution was stirred at 20 °C for 1 h, the alkyl iodide was added (20 mmol) and then allowed to react at room temperature for the time given below. After hydrolysis (20 cm^3 of water), extraction with dichloromethane (4 × 20 cm^3) and drying ($MgSO_4$), the solvent was removed and the residue chromatographed over silica gel using petroleum ether–ethyl acetate, 7 : 3 as eluent.

4-Methyl-5-oxo-4-(2-pyridyl)hexanenitrile (14). Alkyl iodide: MeI; reaction time: 2 h; yield: 2.48 g, 82% as a yellow viscous oil, n_D^{20} 1.520 (Found: C, 71.1; H, 6.9; N, 14.1. Calc. for $C_{12}H_{14}N_2O$: C, 71.3; H, 7.0; N, 13.85%); ν_{max}(film)/cm^{-1} 2978, 2245 (CN), 1710 (CO), 1587, 1571, 1468, 1433, 1354, 787 and 752; δ_H(200 MHz; $CDCl_3$) 1.46 (3 H, s, CH_3), 1.80 (3 H, s, $COCH_3$), 1.94–2.36 (4 H, m, CH_2 + CH_2CN), 7.14 (2 H, m, 3-H + 5-H), 7.63 (1 H, td, 4-H) and 8.43 (1 H, dd, 6-H).

This product could also be prepared by applying the tandem acetylation–cyanoethylation described above to 2-ethylpyridine (70% yield) but with formation of an undesirable and difficult to separate by-product.

4-Ethyl-5-oxo-4-(2-pyridyl)hexanenitrile (15). Alkyl iodide: EtI; reaction time: 18 h; yield: 2.37 g, 73% as a yellow viscous oil, n_D^{20} 1.518 (Found: C, 71.9; H, 7.55; N, 12.9. Calc. for $C_{13}H_{16}N_2O$: C, 72.2; H, 7.45; N, 12.95%); ν_{max}(film)/cm^{-1} 2970, 2246 (CN), 1709 (CO), 1586, 1571, 1468, 1433, 1354, 792 and 752; δ_H(200 MHz; $CDCl_3$) 0.70 (3 H, t, *J* 7.5, CH_3), 1.76 (3 H, s, CH_3), 1.80–2.43 (6 H, m, CH_2CH_3 + CH_2 + CH_2CN), 7.14 (2 H, m, 3-H + 5-H), 7.63 (1 H, td, 4-H) and 8.43 (1 H, dd, 6-H).

Acid hydrolysis of nitriles

A solution of nitrile (6 mmol) in dilute sulfuric acid (*x*%, 10 cm^3) was heated at the temperature and for the time given below. After cooling, toluene or ether (2 cm^3) was added and the mixture brought to pH 5 with 25% NH_4OH, whereupon most of the desired acid precipitated. The precipitate was washed with water and toluene. The filtrate was evaporated and chromatographed over silica gel using CH_2Cl_2–MeOH–AcOH, 97 : 3 : 0.5 as eluent to yield further product.

5-Oxo-4-(2-pyridyl)hexanoic acid (11). Acid concentration: *x* = 30%; temperature: 150 °C; reaction time: 120 min; yield: 1.16 g, 93% as a yellow solid, mp 125 °C (Found: C, 63.5; H, 6.25; N, 6.9. Calc. for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8%); ν_{max}(KBr)/cm^{-1} 2964, 2492, 1711 (CO), 1598, 1573, 1476, 1434, 1356, 1285, 1259, 1184, 789 and 753; δ_H(200 MHz; $CDCl_3$) 2.10 (3 H, s, $COCH_3$), 2.01–2.45 (4 H, m, CH_2 + CH_2CO_2H), 4.25 (1 H, t, *J* 7.2, CH), 7.26 (2 H, m, 3-H + 5-H), 7.73 (1 H, td, 4-H), 8.55 (1 H, dd, 6-H) and 10.11 (1 H, br s, CO_2H).

4-Methyl-5-oxo-4-(2-pyridyl)hexanoic acid (12). Acid concentration: *x* = 20%; temperature: 100 °C; reaction time: 60 min; yield: 1.18 g, 89% as a white solid, mp 90 °C (Found: C, 64.9; H, 6.75; N, 6.3. Calc. for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3%); ν_{max}(KBr)/cm^{-1} 2936, 1712 (CO), 1595, 1571, 1474, 1414, 1355, 1288, 1216, 1199, 1007 and 761; δ_H(200 MHz; $CDCl_3$) 1.52 (3 H, s, CH_3), 1.94 (3 H, s, $COCH_3$), 2.13–2.42 (4 H, m, CH_2 + CH_2CO_2H), 7.20 (2 H, m, 3-H + 5-H), 7.70 (1 H, td, 4-H), 8.58 (1 H, dd, 6-H) and 10.65 (1 H, br s, CO_2H).

This product could also be prepared by applying the NaH-promoted alkylation described above to ketoacid **11**, using 2.1 equivalents of base (65% yield). However, separation from unreacted starting material was tedious.

4-Ethyl-5-oxo-4-(2-pyridyl)hexanoic acid (13). Acid concentration: *x* = 20%; temperature: 100 °C; reaction time: 40 min; yield: 1.18 g, 84% as a white solid, mp 116 °C (Found: C, 66.6; H, 7.4; N, 6.1. Calc. for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 5.95%); ν_{max}(KBr)/cm^{-1} 2966, 1719 (CO), 1596, 1480, 1452, 1413, 1354, 1285, 1201, 1004, 795 and 762; δ_H(200 MHz; $CDCl_3$) 0.79 (3 H, t, *J* 7.5, CH_3), 1.94 (3 H, s, $COCH_3$), 2.05–2.50 (6 H, m, CH_2CH_3 + CH_2 + CH_2CO_2H), 7.23 (2 H, m, 3-H + 5-H), 7.71 (1 H, td, 4-H), 8.60 (1 H, dd, 6-H) and 9.75 (1 H, br s, CO_2H).

4-Methyl-4-(2-pyridyl)hex-5-enenitrile (16)

Compound **14** (607 mg, 3 mmol) was refluxed with tosylhydrazine (614 mg, 3.3 mmol) in ethanol (1 cm^3) for 4.5 h. After cooling, the solvent was removed and the crude solid was washed with cyclohexane–ethyl acetate, 1 : 1 to give the desired tosylhydrazone (1 g, 90%). To a solution of the previously prepared tosylhydrazone (593 mg, 1.6 mmol) in toluene (5 cm^3) was added lithium hydride (57 mg, 7.2 mmol). The mixture was refluxed for 50 min before cooling, 5 cm^3 of water were added and the reaction mixture brought to neutrality with dilute acid. After extraction with dichloromethane (3 × 10 cm^3) and drying ($MgSO_4$), the solvent was removed and the residue chromatographed over silica gel using petroleum ether–ethyl acetate (7 : 3) as eluent to yield the desired alkene **16** (54 mg, 18%) as a colourless oil, n_D^{20} 1.518 (Found: C, 77.1; H, 7.3; N, 15.3. Calc. for $C_{12}H_{14}N_2$: C, 77.4; H, 7.6; N, 15.0%); ν_{max}(film)/cm^{-1} 3084 (=CH_2), 2972, 2245, 1736, 1636 (C=C), 1587, 1470, 1430, 993 and 923 (=C–H), 791 and 750; δ_H(200 MHz; $CDCl_3$) 1.43 (3 H, s, CH_3), 2.28 (4 H, complex m, CH_2 + CH_2CN), 5.12 (1 H, d, H_{trans}), 5.24 (1 H, d, H_{cis}), 6.10 (1 H, dd, H_{vinyl}), 7.13 (1 H, dd, 5-H), 7.26 (1 H, d, 3-H), 7.62 (1 H, td, 4-H) and 8.56 (1 H, dd, 6-H).

Wolff–Kishner reduction of ketoacids 12 and 13

In a flask equipped with a short distillation path was placed the appropriate ketoacid (1 mmol) and ethylene glycol (1 cm^3). Hydrazine hydrate (0.73 cm^3, 15 mmol) was added and the mixture was heated to 160 °C over 1 h, allowing the distillation of the water formed and excess hydrazine. After cooling, molten, crushed potassium hydroxide (840 mg, 15 mmol) was added and the mixture heated with an oil bath at 170–175 °C for 3 h (nitrogen evolution). The mixture was allowed to cool to room temperature and then acidified to pH 5 with dilute hydrochloric acid and extracted with dichloromethane (4 × 10 cm^3). After drying ($MgSO_4$), the solvent was removed and the residue chromatographed over silica gel using CH_2Cl_2–MeOH–

AcOH, 97:3:0.5 as eluent to give the desired deoxygenated acids.

4-Methyl-4-(2-pyridyl)hexanoic acid (2). Yield: 160 mg, 77% as a white solid, mp 66 °C (Found: C, 69.2; H, 8.4; N, 6.5. Calc. for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8%); ν_{max}(KBr)/cm^{-1} 2966, 1707 (CO), 1596, 1570, 1478, 1432, 1310, 1218, 1186, 1007 and 756; δ_H(200 MHz; $CDCl_3$) 0.63 (3 H, t, *J* 7.4, CH_2CH_3), 1.29 (3 H, s, CH_3), 1.54–2.25 (6 H, m, CH_2CH_3 + CH_2 + CH_2CO_2H), 7.08 (1 H, dd, 5-H), 7.26 (1 H, d, 3-H), 7.63 (1 H, td, 4-H), 8.56 (1 H, dd, 6-H) and 11.52 (1 H, br s, CO_2H).

4-Ethyl-4-(2-pyridyl)hexanoic acid (3). Yield: 173 mg, 78% as a white solid, mp 100 °C (Found: C, 70.2; H, 8.7; N, 6.0. Calc. for $C_{13}H_{19}NO_2$: C, 70.5; H, 8.65; N, 6.3%); ν_{max}(KBr)/cm^{-1} 2967, 1704 (CO), 1592, 1568, 1470, 1433, 1307, 1221, 1008 and 753; δ_H(200 MHz; $CDCl_3$) 0.68 (6 H, t, *J* 7.4, 2 × CH_3), 1.77 (4 H, q, *J* 7.4, 2 × CH_2CH_3), 2.13 (4 H, m, CH_2 + CH_2CO_2H), 7.13 (1 H, dd, 5-H), 7.29 (1 H, d, 3-H), 7.66 (1 H, td, 4-H), 8.59 (1 H, dd, 6-H) and 10.74 (1 H, br s, CO_2H); *m*/*z* (CI, NH_3) 222 (MH^+, 100%).

Alkylation of 2-(α,α-dialkyl)pyridines (6–8)

In a dried, argon-flushed 50 cm³ flask was placed potassium *tert*-butoxide (χ mmol), anhydrous THF (5 cm³) and diisopropylamine (χ mmol). The mixture was cooled to the temperature given below and BuLi (χ mmol) was slowly added. The reaction mixture was then warmed to the second temperature given below over 15 min before adding the 2-alkylpyridine (2 mmol). After 1 h of metallation, the mixture was cooled to −75 °C and a cooled (−75 °C) solution of 4-bromobutene (χ mmol) in THF (1 cm³) was added all at once. The cooling bath was removed to allow vigorous stirring for 1.5–2 min, after which 5 cm³ of water were added. After extraction with dichloromethane (3 × 10 cm³) and drying ($MgSO_4$), the solvent was removed and the residue chromatographed over silica gel using petroleum ether–ethyl acetate, 9.5:0.5 as eluent.

5-Methyl-5-(2-pyridyl)hex-1-ene (18) and 5-methyl-5-(2-pyridyl)hex-2-ene (21). 2-Alkylpyridine: 2-isopropylpyridine. Amount of metallating agent and electrophile: χ = 2.6 mmol; reaction temperature: −70 °C then warmed to −50 °C; yield: 309 mg, 88% (96:4 mixture of terminal:branched alkene) as a colourless oil (Found: C, 81.9; H, 9.5; N, 7.7. Calc. for $C_{12}H_{17}N$: C, 82.2; H, 9.8; N, 8.0%).

*Isomer **18***. ν_{max}(film)/cm^{-1} 3075 (=CH_2), 2963, 1640 (C=C), 1588, 1570, 1475, 1430, 1384, 1361, 992 and 909 (=C−H), 790 and 747; δ_H(200 MHz; $CDCl_3$) 1.35 (6 H, s, 2 × CH_3), 1.79 (4 H, m, CH_2–CH_2–CH=), 4.84 (1 H, d, *J* 9.6, H_{cis}), 4.90 (1 H, d, *J* 16.6, H_{trans}), 5.70 (1 H, m, H_{vinyl}), 7.06 (1 H, dd, 5-H), 7.27 (1 H, d, 3-H), 7.58 (1 H, td, 4-H) and 8.53 (1 H, dd, 6-H).

*Isomer **21***. The isomerized alkene **21** was characterized by its allylic and vinylic proton signals: δ_H(200 MHz; $CDCl_3$) 1.55 (3 H, d, *J* 6.2, =C–CH_3), 2.37 (2 H, d, *J* 7.0, CH_2), 5.26 (2 H, m, $CH_2C{=}CH$ + $CH_3C{=}CH$).

5-Methyl-5-(2-pyridyl)hept-1-ene (19). 2-Alkylpyridine: 2-(2-butyl)pyridine **15**. Amount of metallating agent and electrophile: χ = 2.6 mmol; reaction temperature: −50 °C then warmed to −30 °C; yield: 303 mg, 80% as a colourless oil (Found: C, 82.2; H, 10.4; N, 7.1. Calc. for $C_{13}H_{19}N$: C, 82.5; H, 10.1; N, 7.4%); ν_{max}(film)/cm^{-1} 3077 (=CH_2), 2966, 1640 (C=C), 1588, 1570, 1470, 1431, 1381, 992 and 909 (=C−H), 796 and 747; δ_H(200 MHz; $CDCl_3$) 0.67 (3 H, t, *J* 7.4, CH_2CH_3), 1.34 (3 H, s, CH_3), 1.60–2.06 (6 H, m, CH_2 + =C–CH_2 + =C–CH_2CH_2), 4.87 (1 H, d, *J* 10.0, H_{cis}), 4.94 (1 H, d, *J* 15.6, H_{trans}), 5.76 (1 H, m, H_{vinyl}), 7.09 (1 H, dd, 5-H), 7.26 (1 H, d, 3-H), 7.61 (1 H, td, 4-H) and 8.60 (1 H, dd, 6-H).

5-Ethyl-5-(2-pyridyl)hept-1-ene (20) and 5-ethyl-5-(2-pyridyl)-hept-2-ene (22). 2-Alkylpyridine: 2-(3-pentyl)pyridine. Amount of metallating agent and electrophile: χ = 3.6 mmol; reaction temperature: −50 °C then warmed to −30 °C; yield: 321 mg, 79% (95:5 mixture of terminal:branched alkene) as a colourless oil (Found: C, 82.4; H, 10.7; N, 6.6. Calc. for $C_{14}H_{21}N$: C, 82.7; H, 10.4; N, 6.9%).

*Isomer **20***. ν_{max}(film)/cm^{-1} 3077 (=CH_2), 2965, 1640 (C=C), 1588, 1571, 1469, 1431, 1378, 993 and 909 (=C−H), 796 and 747; δ_H(200 MHz; $CDCl_3$) 0.67 (6 H, t, *J* 7.4, 2 × CH_3), 1.80 (8 H, m, 2 × CH_2 + =C–CH_2 + =C–CH_2CH_2), 4.87 (1 H, d, *J* 10.1, H_{cis}), 4.94 (1 H, d, *J* 17.0, H_{trans}), 5.76 (1 H, ddt, H_{vinyl}), 7.06 (1 H, dd, 5-H), 7.23 (1 H, d, 3-H), 7.59 (1 H, td, 4-H) and 8.60 (1 H, dd, 6-H).

*Isomer **22***. The isomerized alkene **22** was characterized by its allylic and vinylic proton signals: δ_H(200 MHz; $CDCl_3$) 1.55 (3 H, d, *J* 6.2, =C–CH_3), 2.44 (2 H, d, *J* 7.1, CH_2), 5.21 (2 H, m, $CH_2C{=}CH$ + $CH_3C{=}CH$).

Oxidative cleavage of double bonds

In a 50 cm³ flask was placed the mixture of the alkenylpyridine isomers (1.5 mmol, containing mainly the desired terminal alkene). A cooled solution of potassium permanganate (877 mg, 5.55 mmol) in water (13 cm³) was added in one portion, and immediately afterwards acetic acid (1.5 cm³) was added. After 30 min of stirring at room temperature, sodium sulfite was added (1 g) and the mixture filtered through a plug of Celite. The plug was copiously washed with MeOH–AcOH, 9:1 and the filtrate concentrated and adjusted to pH 5 if necessary. After extraction with dichloromethane (3 × 10 cm³) and drying ($MgSO_4$), the solvent was removed and the residue chromatographed over silica gel using CH_2Cl_2–MeOH–AcOH, 97:3:0.5 as eluent.

4-Methyl-4-(2-pyridyl)hexanoic acid (2). Yield: 193 mg, 62%. See above for characterizing data.

4-Ethyl-4-(2-pyridyl)hexanoic acid (3). Yield: 186 mg, 56%. See above for characterizing data.

4-Methyl-4-(2-pyridyl)pentanoic acid (1). Yield: 220 mg, 76% as a white solid, mp 99 °C (Found: C, 68.5; H, 8.1; N, 7.0. Calc. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.25%); ν_{max}(KBr)/cm^{-1} 2972, 2934, 2508, 1701 (CO), 1597, 1575, 1303, 1228, 797 and 761; δ_H(200 MHz; $CDCl_3$) 1.36 (6 H, s, 2 × CH_3), 2.13 (4 H, m, CH_2 + CH_2CO_2H), 7.14 (1 H, dd, 5-H), 7.34 (1 H, d, 3-H), 7.66 (1 H, td, 4-H), 8.59 (1 H, dd, 6-H) and 11.21 (1 H, br s, CO_2H).

Acknowledgements

We thank the Ministère de l'Education Nationale, de la Recherche et de la Technologie (Allocation de recherche no. 9625) for financial support.

References

1 G. Quéguiner, F. Marsais, V. Snieckus and J. Epsztajn, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Academic Press, San Diego, 1991, vol. 52, pp. 187–304.
2 S. J. Gould and S. M. Weinreb, *Fortschr. Chem. Org. Naturst.*, 1982, **41**, 77; D. M. Balitz, J. A. Bush, W. T. Bradner, F. A. O'Herron and D. E. Nettleton, *J. Antibiot.*, 1982, **25**, 259; M. E. Wall and M. C. Wani, in *Anticancer Agents Based on Natural Product Models*, ed. J. M. Cassady and J. D. Douros, Academic Press, New York, 1980, pp. 417–436.
3 A. R. Katritzky and C. W. Rees, in *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 1984, vol. 2, p. 333; C. Mathis and T. E. Hogen-Esch, *J. Am. Chem. Soc.*, 1982, **104**, 634; T. A. Crabb and A. Fallah, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1335; O. F. Beumel, Jr. W. N. Smith and B. Rybalka, *Synthesis*, 1974, 43.
4 E. Pasquinet, P. Rocca, A. Godard, F. Marsais and G. Quéguiner, *Tetrahedron*, 1998, **54**, 8771 and references cited therein.

5 H. Beyer, W. Lässig and G. Schudy, *Chem. Ber.*, 1957, **90**, 592.
6 R. P. Cassity, L. T. Taylor and J. F. Wolfe, *J. Org. Chem.*, 1978, **43**, 2286.
7 J. A. Adamcik and E. J. Miklasiewicz, *J. Org. Chem.*, 1963, **28**, 336.
8 J. Plesek and S. Hermanek, *Sodium Hydride*, *Its Use in the Laboratory and in Technology*, Iliffe Books, London, 1968.
9 Huang-Minlon, *J. Am. Chem. Soc.*, 1946, **68**, 2487.
10 G. W. Kabalka and S. T. Summers, *J. Org. Chem.*, 1981, **46**, 1217; R. O. Hutchins and N. R. Natale, *J. Org. Chem.*, 1978, **43**, 2299; R. O. Hutchins, C. A. Milewski and B. E. Maryanoff, *J. Am. Chem. Soc.*, 1973, **95**, 3662; R. O. Hutchins and B. E. Maryanoff, *J. Am. Chem. Soc.*, 1971, **93**, 1793.
11 L. Caglioti, P. Grasselli and A. Selva, *Gazz. Chim. Ital.*, 1964, 537.
12 D. Desmaële, K. Mekouar and J. d'Angelo, *J. Org. Chem.*, 1997, **62**, 3890. See also Experimental section.
13 P. Lamour, PhD Thesis, University of Rouen, 1993.
14 Alkylpyridines **6**–**8** were prepared by the lithiation–alkylation sequence using BuLi and alkyl iodides as described by our team in a previous paper, see ref. 5.
15 For compound **6**: see ref. 5. For compounds **7** and **8** see: H. Pines and B. Notari, *J. Am. Chem. Soc.*, 1960, **82**, 2209; F. J. Villani, USP 3 188 315/1965 (*Chem. Abstr.*, 1965, **63**, 16311).
16 A. P. Krapcho, J. R. Larson and J. M. Eldridge, *J. Org. Chem.*, 1977, **42**, 3749.
17 J.-C. Ortuno, N. Langlois and Y. Langlois, *Tetrahedron Lett.*, 1989, **30**, 4957; A. Padwa and M. Semones, *Tetrahedron Lett.*, 1996, **37**, 335; A. G. Schultz and L. Pettus, *J. Org. Chem.*, 1997, **62**, 6855.
18 D. J. Abraham, R. D. Rosenstein, R. L. Lyon and H. H. Fong, *Tetrahedron Lett.*, 1972, **10**, 909. K. T. DeSilva, A. H. Ratcliffe, G. F. Smith and G. N. Smith, *Tetrahedron Lett.*, 1972, **10**, 913. This work is a collaboration with the team of F. Guéritte-Voëgelein of the Institut de Chimie des Substances Naturelles (ICSN Gif/Yvette, France).
19 C. Pascal, F. Guéritte-Voëgelein, C. Thal and D. Guénard, *Synth. Commun.*, 1997, **27**, 1501; C. Pascal, PhD. Thesis, University of Paris Sud, 1997.
20 J. Bizot, *Bull. Soc. Chim. Fr.*, 1967, **1**, 151.
21 J. V. Greenhill, H. Loghmani-Khouzani and D. Maitland, *Tetrahedron*, 1988, **44**, 3319; R. Mondelli and L. Merlini, *Tetrahedron*, 1966, **22**, 3253; J. B. Paine III, *J. Heterocycl. Chem.*, 1991, **28**, 1463.

Paper 8/05778H