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REGIOSPECIFIC FUNCTIONALISATION OF CARBON ATOMS α TO HETEROCYCLIC NITROGEN[1]

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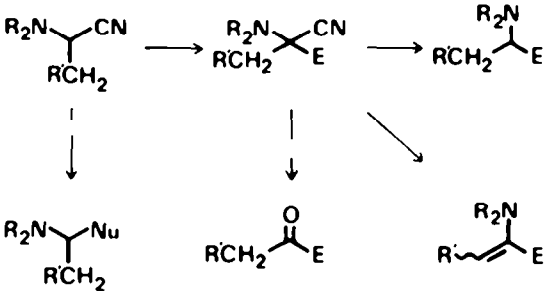
Abstract—Previously, methods have been devised to functionalise the two endocyclic C atoms α to the piperidine N. In the present study we show that a nitrile substituent can be introduced also to the exocyclic α-C, making the centre either nucleo- or electrophilic in subsequent transformations. NMR studies have been used to gain knowledge of the mechanistic aspects leading to the observed regiospecificity. The generality of the method, along with the ease of operation, high yields and regiospecificity, make it highly versatile for synthetic purposes.

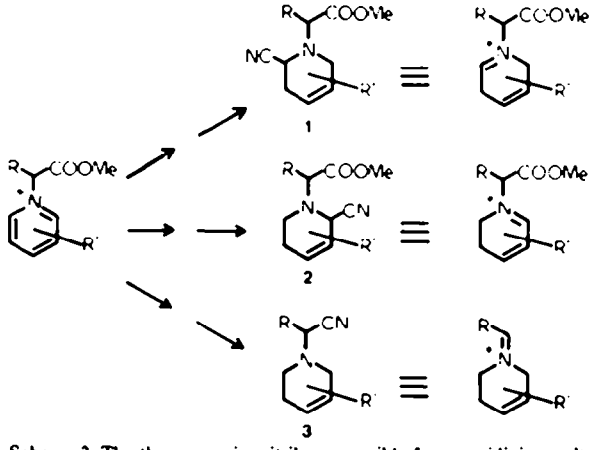
α-Amino nitriles have proven to be extremely versatile synthetic reagents: the C atom α to the N can be made nucleophilic or electrophilic at will, providing, in the former case, a masked carbonyl anion equivalent[2] and, in the latter case, an iminium salt through loss of cyanide ion.[3] The functionality can also be dehydrocyanated to the corresponding enamine[4] or decyanated reductively to the amine[5] (Scheme 1).

The α-amino nitriles derived from piperidine derivatives have gained much attention due to their general utility in indole alkaloid synthesis. Some time ago Husson *et al.*[6] reported the synthesis of 2-cyano-1,2,5,6-tetrahydropyridines **2** from the corresponding 1,2,5,6-tetrahydropyridines *via* the so-called modified Polonovski (Polonovski–Potier) reaction[7,8] and applications of these 5,6-dihydropyridinium salt synthons in alkaloid synthesis have appeared frequently[9–13]. On the other hand, the 2-cyano-1,2,3,6-tetrahydropyridines **1**, easily accessible from the corresponding pyridinium salts by way of sodium borohydride assisted cyanation[14,15], have proven to be useful synthons for 2,5-dihydropyridinium salts[16]. Both these methods provide a convenient framework for the synthesis of various substituted piperidine derivatives. The synthons **1** and **2** thus prepared are, however, synthetic equivalents of endocyclic iminium salts and the question of the possible functionalisation of the exocyclic α-position has thus remained open.



Scheme 1. α-Aminonitriles as synthons.

In a recent preliminary communication[17] we reported the synthesis of the exocyclic α-amino nitrile **9a** from the corresponding α-amino ester **6a** *via* a method based on the application of the modified Polonovski reaction.[7,8] The method has now been extended to make the whole range of both exo- and endocyclic α-amino nitriles **1**, **2** and **3** accessible from the same starting compounds. With these three complementary methods presented in short form in Scheme 2 it is possible to prepare selectively any of the desired iminium salt equivalents in the presence of other functionalities. In effect, the exocyclic methoxycarbonyl group is used as an activating group which can selectively be called upon when needed.



Scheme 2. The three α-aminonitriles accessible from pyridinium salts.

RESULTS AND DISCUSSION

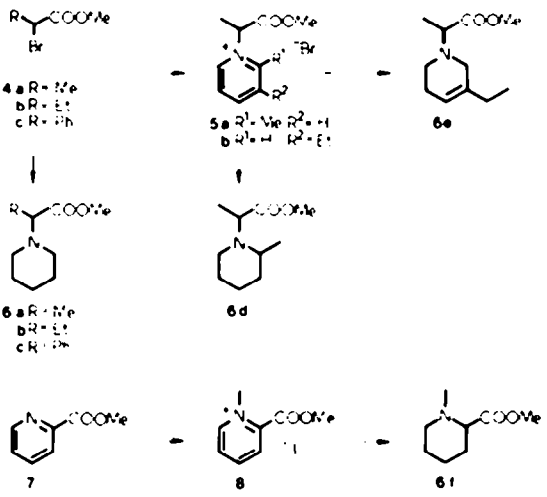
The preparation of the starting piperidines **6a** to **6f** is presented in Scheme 3. The piperidines **6** were then subjected to either of two experimental procedures to provide the α-amino nitriles:

(a) method A in which the aminoester is oxidised with H_2O_2 and the isolated N-oxide then subjected to the modified Polonovski reaction conditions (trifluoroacetic anhydride) followed by cyano trapping[6] of the iminium salt to give the decarboxymethylated aminonitriles **9**.

(b) method B in which the oxidation is performed *in situ* using *m*-chloroperbenzoic acid (mCPBA) as oxidizing reagents and the N-oxide carried through the same operations as in method A to furnish the α-amino nitriles **10**.

Scheme 4 summarises the reaction courses for the two complementary methods A and B described above for various starting piperidines. Note that the **e** series (**6e**, **9e** and **10e**) represent an example of the "missing link" in Scheme 2 giving either **2** or **3**.

The results for these two methods for various starting materials are presented in the Table 1. The yields cited are those for purified products† but for synthetic purposes the crude products were pure enough to be used in subsequent reactions.



Scheme 3. Preparation of the aminoesters **6**.

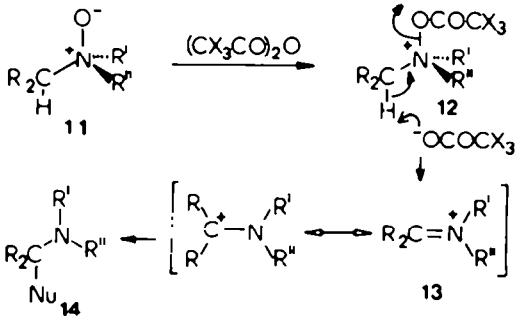
†Due to the instability of the product α-amino nitriles, losses of up to 40% during purification procedure were consistently encountered. The crude products were, however, about 95% pure as judged on TLC.

Table 1. α-Aminonitriles **9** and **10** from α-aminoesters **6**

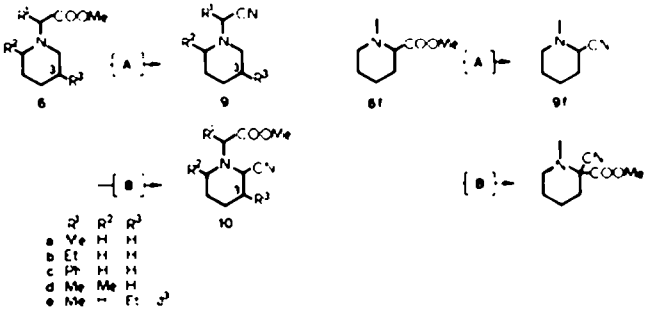
Starting mat.	Method	Product	Yield %
6a	A	9a	55
	B	10a	50
6b	A	9b	48
	B	10b	42
6c	A	9c	31
	B	10c	43
6d	A	9d	57
	B	10d	67
6e	A	9e	48
	B	10e	61
6f	A	9f	53
	B	10f	50

Preparation of exocyclic iminium salt equivalents

Although the mechanism of the modified Polonovski reaction has not been studied in detail, it is generally accepted that the reaction proceeds analogously to the conventional Polonovski reaction[18] (acetic anhydride in place of trifluoroacetic anhydride). Furthermore, of the several possible mechanisms proposed for the Polonovski reaction[19–21], that of Huisgen[20] proceeding *via* the acetoxyammonium species **12** followed by base catalysed elimination has generally been utilised for the interpretation of the reaction course (Scheme 5). In this case,



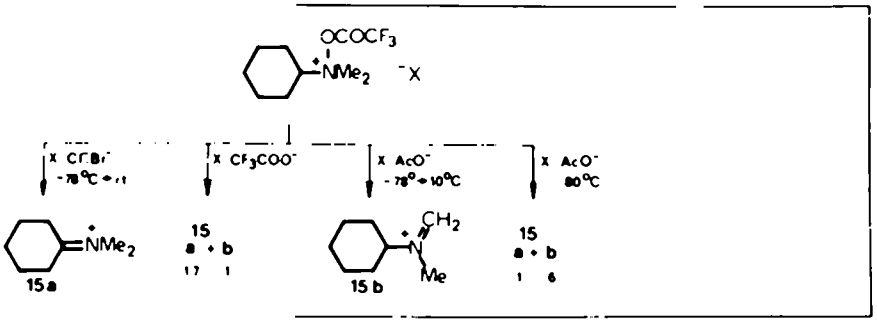
Scheme 5. Mechanism of the modified Polonovski reaction according to the Huisgen mechanism[20].



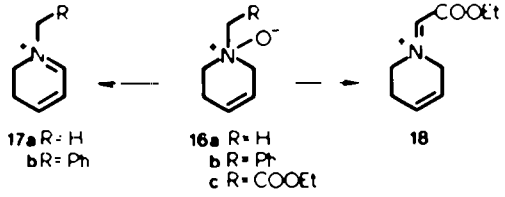
Scheme 4. α-Aminonitriles **9** and **10** from α-aminoesters **6**.

the base induced elimination (E_2) should abstract the H whereby the thermodynamically most stable iminium species would be generated in accordance with the Saytzeff rule. Gartner[22] has recently studied the mechanism of the Polonovski reaction and observed also that the elimination is first order in base concentration. In addition, stronger bases give faster reactions, as noticed for the cases where the bases were chloride and bromide ions ($Cl^- > Br^-$).

Gartner also pointed out that the low nucleophilicity of trifluoroacetate disfavours the formation of the α-trifluoroacetoxy amine **14** and the iminium salts **13** have indeed been amenable to isolation and spectrometric characterisation[22,23]. It was also noted[22] that in the case of dimethyl cyclohexyl amine N-oxide, weakly basic nucleophiles, such as Cl^-, tend to give the thermodynamic product **15a** while stronger ones, such as AcO^-, favour kinetic deprotonation **15b**.



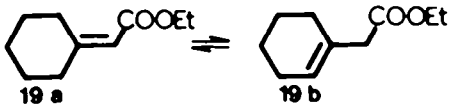
Similar reasoning was adopted by Chevolot *et al.*[24] in explaining the rather anomalous formation of exocyclic iminium species **18** during trifluoroacetic anhydride treatment of the piperidine acetate N-oxide **16c**.



In the other two cases studied (R = H and R = Ph), the endocyclic iminiums **17a** and **17b** were formed in conformity with the expected acidities of the eliminated protons:

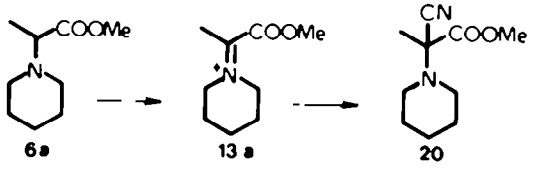
$$R_1\dot{N}-CH_2-COOR' > R_1\dot{N}-CH_2-C=C > R_1\dot{N}-CH_2-Ph.$$

The observations of Chevolot *et al.*[24] were based merely on ^{1}H NMR spectroscopic data and the lack of suitable trapping methods at that time excluded the possibility of forming derivatives to substantiate the reasoning. It must, however, be mentioned that no correction for the pronounced stability of the endocyclic double bond over the exocyclic double bond was taken into account. In fact, 1-methylcyclohexene was shown to be 3.1 kcal/mol more stable than the corresponding exocyclic methylenecyclohexene[25]. Moreover, Lindstead[26,27] has studied equilibria between α,β- and β,γ-unsaturated carbonyl compounds possessing exocyclic (cyclohexylidene) and endocyclic (cyclohexenyl) double bonds and observed that the unconjugated, endocyclic forms prevail to such an extent that, under equilibrium conditions, the cyclohexylidene ester **19a** was present in only 5% concentration.



Because the modified Polonovski reaction is assumed to proceed under essentially equilibrium deprotonation conditions, the results of Chevolot *et al.* would seem to be confusing.

Isolation of the intermediate N-*oxide.* At the time we started our work on the subject, the cyano trapping method had been developed by Husson *et al.*[6] to a stage suitable for application to this problem. It thus became reasonable to assume that on the modified Polonovski reaction of the aminoester **6a** we might trap the proposed exocyclic iminium ion **13a** as the cyanide **20**.



To our astonishment, however, the only isolable product exhibited no signal attributable to the methoxycarbonyl protons in ^{1}H NMR spectrum. Moreover, the terminal Me signal was a beautiful doublet at δ 1.45 coupling to a one-proton quartet centered at δ 3.63 with a coupling constant of 7.3 Hz. Hence, it was evident that the methoxycarbonyl group had been cleaved during the two-step reaction sequence and replaced by cyanide group.

When the reaction was performed using only deuterium oxide, no D incorporation in the product **9a** was observed, thus excluding the possibility of the formation of the malononitrile derivative **20** as an intermediate. Therefore, it became necessary to fully characterise the N-oxide produced by H_2O_2-oxidation (*vide infra*).

II. *Preparation of endocyclic iminium equivalents–the other* N-*oxide*

Modifying the oxidation method of the aminoester **6a** to an *in situ* mCPBA oxidation drastically changed the reaction course. In this case, the product isolated did contain the methoxycarbonyl group intact, as judged by ^{1}H NMR. Furthermore, the signal attributable to the terminal Me group was a doublet centered at δ 1.34. The introduction of the cyano group (IR: 2220 cm^{-1} w) must therefore have occurred endocyclically, which was indeed corroborated by the observation that the symmetry of the signals of the ring protons in ^{1}H NMR had been

destroyed. Further confirmation of this conclusion was obtained from ^{13}C NMR data[29] which clearly showed signals attributable to the proposed structure **10a**. In addition, the two diastereomers could be distinguished in the ^{13}C NMR spectrum, exhibiting the *cis* and *trans* forms **10a** and **10a'** in a ratio approx. 1:1.

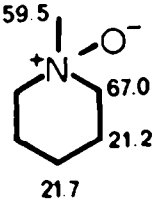
The course of the reaction was similar in all cases **6a** to **6e**, and the pipecolate ester **6f** gave the malononitrile **10f** in a similar experiment. These results were therefore in complete agreement with the above discussion of the mechanism for the modified Polonovski reaction giving the thermodynamically more stable (endocyclic) iminium ion. Steric considerations must be taken into consideration in the case of **6d** where deprotonation gave the kinetic product (*vide supra*) **10d**.

However, the method of oxidation must have a profound effect on the course of the reaction and therefore also on the reaction intermediates. We assumed that a careful study of the oxidation products (the two N-oxides) would shed light on the problem and indeed the oxidation products from the hydrogen peroxide and *m*CPBA oxidation did differ from each other, as deduced from TLC and spectroscopic data.

III. *The two N-oxides compared—mechanistic implications*

On thin layer chromatography (alumina, 10% MeOH in $CHCl_3$) the product from H_2O_2-oxidation had $R_f = 0.27$ while the product from *m*CPBA oxidation had $R_f = 0.61$. Also, on Dragendorff–Munier reagent[30], the colours developed were distinguishably different, the former being rather brownish while the latter was clearly red.

On ^1H NMR the N-oxides differed only in that the H_2O_2-oxidation product seemed to exhibit no signal attributable to a methyl ester. ^{13}C NMR data finally gave the most conclusive evidence for the structures of the N-oxides. The C resonances for N-methylpiperidine N-oxide **22** have been recorded[22] and could be used to predict the resonances in our case.



22

The products **21a** and **21b** from H_2O_2 and *m*CPBA mediated oxidations, respectively, both exhibited ^{13}C NMR spectra in which the symmetry had been destroyed and a total of 8 and 9 resonance peaks could be distinguished. Moreover, the H_2O_2-oxidation product **21a** was quantitatively converted to material identical to **21b** (TLC, ^1H NMR and ^{13}C NMR) on treatment with diazomethane. Hydrolysis of the ester moiety during H_2O_2 oxidation must therefore be a concomitant reaction and is probably faster than N-oxidation, since no **21b** was noted on TLC-monitoring of the reaction.†

†The intermediate **21b** was, in fact, postulated[1,11] as an intermediate in the H_2O_2 oxidation, too, but that notion must now be considered premature.

From the dissymmetry of the ^{13}C NMR spectra, one can deduce that the rotation around the exocyclic N–C bond is restricted. The molecule must thus exist in one preferred conformation. It has been shown[31,32] that the O tends to occupy the axial position in N-oxides. Of the possible conformations A to F (Fig. 1) one can exclude the eclipsed ones (D, E and F) on energetic grounds. Three staggered conformations A, B and C, therefore remain to be considered. In conformations A and B, there is one gauche interaction between the methyl group and the equatorial C-2 hydrogen, whereas, in conformation C, the Me group is involved in two gauche interactions with the axial C-2 and C-6 hydrogens. Therefore one should expect the conformation C to exhibit a symmetrical shielding effect at C-2 and C-6 of about 5.5 ppm caused by the Me group, whereas in conformations A and B the shielding due to the Me should be non-symmetric, equaling *ca* 6.2 ppm for the C-2 and leaving the C-6 unshielded. The Me group itself would experience a shielding effect of *ca* 2 ppm in conformations A and B and *ca* 7 ppm in conformation C. Thus, the conformation C can be ruled out of consideration. Of the remaining two conformations, A and B, one would expect the conformation A to predominate on the following grounds: in the free acid N-oxide **21a** it is reasonable to assume the carboxyl group to be H-bonded to the N-oxide oxygen (^1H NMR: resonance at δ 11.1). Esterification of the acid leaves the resonances of the ring carbons practically unchanged and thus the molecule **21b** is expected to adopt the same conformation as the acid **21a**. In conformation B, where the carboxyl group is antiperiplanar with the oxygen, such H-bonding is impossible.

The concise explanation for the two observed reaction pathways can thus be summarised (Scheme 6).

In H_2O_2 oxidation, the ester function is hydrolysed simultaneously to generate the α amino *acid* N-oxide **21a** whose treatment with trifluoroacetic anhydride generates the exocyclic iminium species **23a** in accordance with the Huisgen mechanism for the Polonovski reaction. Treatment of the α-amino acid *ester* N-oxide **21b**, generated by means of *m*CPBA-mediated oxidation of **6a**, with trifluoroacetic anhydride leads to an unexceptional modified Polonovski reaction generating the thermodynamically favoured endocyclic iminium species **23b**.

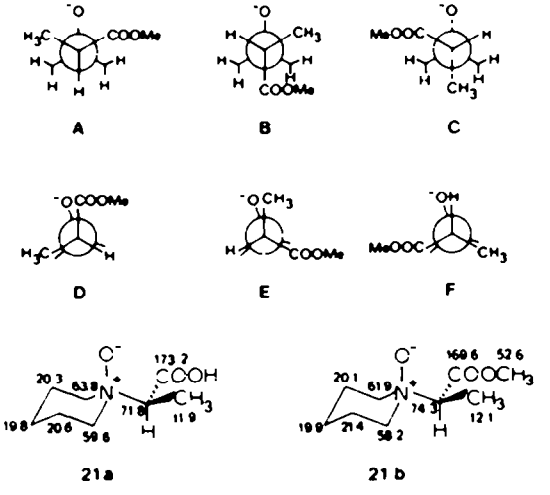
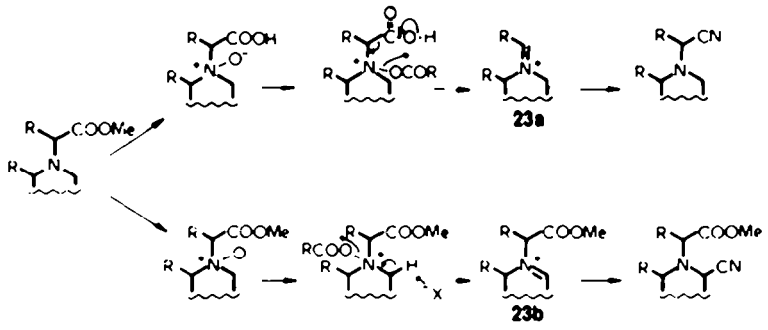


Fig. 1.



Scheme 6. Mechanisms for the two pathways.

These two complementary routes thus provide a highly efficient methodology to be used in selective functionalisation of the C atoms α to the piperidine N.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 700 Spectrophotometer using KBr for solid samples and liquid film between NaCl crystals for liquids. IR absorption bands are expressed in reciprocal centimeters (cm^{-1}) using polystyrene calibration. Bands yielding structural information are reported. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS as internal standard $\delta = 0$) on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS where s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet, respectively. Coupling constants J are given in Hz. Mass spectrometry was performed on a Jeol JMS-D-100.

For column chromatography, Silica Woelm TSC (act. III) or Alumina Woelm TSC (act. III) was used. TLC plates were coated with either Silica gel 60 $PF_{254-366}$ or Aluminium oxide $PF_{254-366}$, both from Merck. Dragendorff–Munier reagent[36] was used to locate reaction components.

1-(1-Methoxycarbonyl ethyl)-2-methyl pyridinium bromide **5a**. According to an established procedure,[11] **5a** was prepared from methyl 2-bromopropionate and 2-picoline, yield 89%. IR: 1740 cm^{-1} (s) (COOMe).

1-(1-Methoxycarbonyl ethyl)-3-methyl pyridinium bromide **5b**. Methyl 2-bromopropionate was reacted with 3-ethyl pyridine to give **5b** as highly hygroscopic solid, yield 98%, IR: 1745 cm^{-1} (s) (COOMe).

Preparation of 1-(1-methoxycarbonylalkyl) piperidines (**6a–c**). These (**6a–c**) were prepared by reacting the methyl 2-bromoalkanoate with excess piperidine in dry Et_2O under N_2 for 48 hr at r.t. The mixture was then basified to pH 9 by the addition of 10% Na_2CO_3. Extraction with CH_2Cl_2, washing of the combined extracts with water, drying and evaporation gave the crude products, which were purified by flash column chromatography[34] over silica using 2% MeOH in CH_2Cl_2.

1-(1-Methoxycarbonyl ethyl) piperidine **6a**. From methyl 2-bromopropionate (33.4 g, 20 mmol) and piperidine (17.0 g, 100 mmol) in 50 ml dry Et_2O, yield 89%, oil, IR: 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.27 (d, 7.1 Hz, 3H), 1.2–1.6 (m, 6H), 2.35–2.60 (m, 4H), 3.26 (q, 7.1 Hz, 1H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 14.15 (q), 23.96 (t), 25.78 (t, 2C), 50.06 (t, 2C), 50.45 (q), 62.59 (d), 172.84 (s). MS *m/z* (rel. int.): 171 (M^+, 5%), 112 (100%).

1-(1-Methoxycarbonyl propyl piperidine **6b**. From methyl 2-bromobutanoate (36.2 g, 20 mmol) and piperidine (17.0 g, 100 mmol) in 50 ml dry Et_2O, yield 87%, oil, IR: 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, 7 Hz, 3H), 1.15–2.00 (m, 8H), 2.35–2.60 (m, 4H), 3.05 (q, 7 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 10.71 (q), 22.47 (t), 24.54 (t), 26.36 (t, 2C), 50.71 (t, 2C), 50.73 (q), 70.00 (d), 172.78 (s). MS *m/z* (rel. int.) 185 (M^+, 5%), 156 (4%), 126 (100%).

1(1-Methoxycarbonyl benzyl) piperidine **6c**. From methyl 2-bromophenylacetate (11.5 g, 50 mmol) and piperidine (17.0 g, 100 mmol) in 50 ml dry Et_2O, yield 78%, oil, IR: 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.2–1.6 (m, 6H), 2.35–2.60 (m, 4H), 3.65 (s, 3H) 3.99 (s, 1H), 7.33 (br s, 5H) ^{13}C NMR ($CDCl_3$) δ 24.02 (t), 25.45 (t, 2C), 51.36 (q), 51.94 (t, 2C), 74.48 (d), 127.72 (d), 127.98 (d, 2C), 128.37 (d, 2C), 135.84 (s), 171.80 (s). MS *m/z* (rel. int.): 233 (M^+, 4%), 174 (95%), 91 (100%).

1-(1-Methoxycarbonyl ethyl)-2-methyl piperidine **6d**. **5a** (3.30 g, 12.7 mmol) was dissolved in 20 ml MeOH and hydrogenated at r.t. over PtO_2 (150 mg) under atmospheric pressure for 6 hr. The catalyst was filtered off and MeOH evaporated *in vacuo*. The yellow solid residue of **6d**·HBr was dissolved in 8% $NaHCO_3$, pH adjusted to 10 and the aqueous layer extracted several times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated to give crude **6d** which was purified column chromatographically (Silica, 5% MeOH–$CHCl_3$) to give pure **6d** 2.01 g (85%) as a pale yellow oil. IR: 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.05 (d, 7 Hz, 3H), 1.15 (d, 7 Hz, 3H), 1.25–1.85 (m, 6H), 2.35–2.80 (m, 3H), 3.70 (s, 3H), 3.78 (q, 7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 8.44 (q), 17.53 (q), 23.05 (t), 25.39 (t), 33.89 (t), 46.36 (t), 50.65 (q), 52.33 (d), 56.88 (d), 173.36 (s). MS *m/z* (rel. int.): 185 (M^+, 4%), 170 (10%), 126 (100%).

1-(1-Methoxycarbonylethyl)-3-ethyl-1,2,5,6-tetrahydropyridine **6e**. $NaBH_4$ (2.64 g, 69.5 mmol) was added portionwise over a 30 min period to a stirred soln of **5b** (13.50 g, 49.2 mmol) in 30 ml MeOH kept at 0°. Stirring was continued for another 1 hr at 0° and 40 min at r.t. After dilution with water (120 ml), the soln was extracted with CH_2Cl_2 (5 × 40 ml). The combined extracts were washed with water, dried (Na_2SO_4) and evaporated to give 8.26 g pale yellow oil. Chromatography over silica (5% MeOH–$CHCl_3$ as eluant) gave 7.85 g (81%) pure **6e** as faintly yellow oil. IR: 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 0.99 (t, 7 Hz, 3H), 1.32 (d, 7 Hz, 3H), 1.94 (q, 7 Hz, 2H), 2.12 (br s, 2H), 2.63 (m, 2H), 3.03 (br s, 2H), 3.40 (q, 7 Hz, 1H), 3.67 (s, 3H), 5.39 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 11.17 (q), 13.89 (q), 25.45 (t), 26.88 (t), 45.32 (t), 50.00 (q), 50.78 (t), 61.03 (d), 116.62 (d), 136.87 (s), 172.20 (s). MS *m/z* (rel. int.): 197 (M^+, 22%), 182 (8%), 168 (14%), 138 (100%).

1-Methyl-2-methoxycarbonylpyridinium iodide **8**. **7**[14] (6.40 g, 46.7 mmol) and MeI (8.0 g, 56.5 mmol) were refluxed in 25 ml dry Et_2O under N_2 for 25 hr during which time the ether was allowed to evaporate and MeI (4.0 g, 28.3 mmol) was added. The solid was crushed under dry ether, filtered and washed several times to give 10.7 g (82%) salt **8** with m.p. 94–96°. IR: 1740 (s) (COOMe).

1-Methyl-2-methoxycarbonylpiperidine **6f**. **8** (2.86 g, 10 mmol) was dissolved in 15 ml MeOH and hydrogenated over PtO_2 at r.t. and under atmospheric pressure for 12 hr. Usual work-up and column chromatographic purification (silica, 5% MeOH–$CHCl_3$) gave 1.50 g (95%) **6f** as a pale yellow oil. IR: 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.25–2.00 (m, 6H), 2.25 (s, 3H), 2.60–3.08 (m, 3H), 3.65–3.80 (m, 1H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 22.66 (t), 25.00 (t), 29.48 (t), 44.09 (q), 51.49 (q), 54.74 (t), 67.53 (d), 173.68 (s). MS *m/z* (rel. int.): 157 (M^+, 3%), 98 (100%).

Preparation of exocyclic aminonitriles **9a–f**

The desired compounds (**9a–f**) were prepared according to the following procedure, which is typically exemplified by the preparation of **9e** outlined below.

1-(1-Cyanoethyl)-3-ethyl-1,2,5,6-tetrahydropyridine **9e**. Excess 30% H_2O_2 (3.5 ml) was added to a soln of **6e** (4.05 g, 20.5 mmol) in 20 ml 1:1 CH_2Cl_2–EtOH and the resulting soln was stirred at 62° for 28 hr (disappearence of starting material as judged by TLC on aluminium oxide with 10% MeOH in $CHCl_3$ as eluant). Excess peroxide was destroyed by the addition of 300 mg 10% Pd/C and stirring at 60° for 7 hr. The mixture was filtered and concentrated under diminished pressure (water bath temp 35°). The residue was dissolved in 20 ml CH_2Cl_2 and shaken vigorously with Na_2SO_4. Filtration, evaporation and final drying in vacuum pump for 5 hr gave the N oxide of **6e** as a semi-solid yellow oil (3.50 g, 86%), which was immediately used in the following step. The N-oxide (3.50 g, 17.4 mmol) was dissolved in 40 ml dry $CHCl_3$ (dried by distillation from P_2O_5), cooled to −10° and stirred under an atmosphere of argon. Trifluoroacetic anhydride (4.60 ml, 2 eq) was added *via* syringe over a period of 15 min. Stirring was continued at 0° for 1 hr and at r.t. for 15 min. Then, an aqueous soln of KCN (1.70 g, 1.5 eq) in 10 ml H_2O was added and the pH of the aqueous layer adjusted to pH 5 by the addition of solid NaOAc. The mixture was stirred at r.t. for 30 min, basified to pH 10 with 10% $Na_2CO_3^{aq}$ and extracted several times with CH_2Cl_2. The combined extracts were washed with water (2 × 20 ml), dried (Na_2SO_4) and concentrated to give 2.10 g (78%) faintly brown oil (homogeneous on TLC), which was purified by flushing through a short column of alumina (1:1 CH_2Cl_2–hexane as eluant). Pure **9e** (1.35 g, 48%) was obtained as a nearly colourless liquid which soon began to darken. IR: 2240 cm^{-1} (w) (CN). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.02 (t, 7.4 Hz, 3H), 1.48 (d, 7.2 Hz, 3H), 1.99 (q, 7.4 Hz, 2H), 2.20 (br s, 2H), 2.45–2.86 (m, 2H), 2.97 (br s, 2H), 3.77 (q, 7.2 Hz, 1H), 5.45 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 11.56 (q), 16.62 (q), 25.32 (t), 27.14 (t), 46.23 (t), 51.16 (t), 51.81 (d), 117.00 (d), 117.13 (s), 136.22 (s). MS *m/z* (rel. int.): 164 (M^+, 55%), 149 (56%), 135 (100%).

1-(1-Cyanoethyl) piperidine **9a**. Compound **9a** was prepared as described in 55% yield. IR: 2220 (w) (CN) ^1H NMR ($CDCl_3$, 60 MHz) δ 1.45 (d, 7.3 Hz, 3H), 1.40–1.95 (m, 6H), 2.51 (m, 4H), 3.63 (q, 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 17.01 (q), 23.89 (t), 25.52 (t, 2C), 50.45 (t, 2C), 52.78 (d), 117.39 (s). MS *m/z* (rel. int.): 138 (M^+, 19%), 123 (100%), 112 (38%), 111 (62%), 110 (50%), 96 (66%), 82 (30%), 69 (40%), 55 (80%).

1-(1-Cyanopropyl) piperidine **9b**. As described, compound **9b** was prepared in 48% yield from **6b**. IR: 2260 cm^{-1} (w) (CN). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.05 (t, 7 Hz, 3H), 1.40–1.95 (m, 8H), 2.53 (m, 4H), 3.37 (t, 7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 10.39 (q), 23.76 (t), 24.22 (t), 25.45 (t, 2C), 50.65 (t, 2C), 60.12 (d), 116.94 (s), MS *m/z* (rel. int.): 152 (M^+, 10%), 123 (100%), 110 (10%), 96 (7%).

1-(1-Cyanobenzyl) piperidine **9c**. As described, compound **9c** was prepared in 31% yield from **6c**. IR: 2260 cm^{-1} (w) (CN). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.10–1.95 (m, 6H), 2.20–2.65 (m, 4H), 4.82 (s, 1H), 7.10–8.00 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 23.83 (t), 25.71 (t, 2C), 50.78 (t, 2C), 62.85 (d), 115.45 (s), 127.65 (d, 2C), 128.50 (d, 2C), 128.88 (d, 1H), 134.47 (s). MS *m/z* (rel. int.): 200 (M^+, 45%), 199 (40%), 116 (80%), 84 (100%).

1-(1-Cyanoethyl)-2-methylpiperidine **9d**. As described, **9d** was prepared in 57% yield from **6d**. IR: 2250 cm^{-1} (w) (CN) ^1H NMR ($CDCl_3$, 60 MHz) δ 1.16 (d, 7 Hz, 3H), 1.46 (d, 7 Hz, 3H), 1.05–2.00 (m, 6H), 2.05–3.05 (m, 3H), 3.50 (q, 7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 9.87 (q), 18.83 (q), 23.96 (t), 24.67 (t), 32.53 (t), 42.85 (t), 52.17 (d), 55.13 (d), 118.89 (s). MS *m/z* (rel. int.): 152 (M^+, 5%), 137 (100%), 126 (45%), 110 (40%).

1-Methyl-2-cyanopiperidine **9f**. As described, **9f** was prepared in 53% yield from **6f**. IR: 2280 cm^{-1} (w) (CN). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40–1.85 (m, 6H), 2.36 (s, 3H), 2.35–2.85 (m, 2H), 3.75 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.54 (t), 24.54 (t), 28.44 (t), 44.02 (q), 50.78 (t), 54.41 (d), 116.10 (s). MS *m/z* (rel. int.): 124 (M^+, 35%), 123 (32%), 98 (15%), 96 (35%), 84 (70%), 70 (50%), 42 (100%).

Preparation of endocyclic aminonitriles **10a–f**. These (**10a–f**) were prepared according to the following procedure, which is typically exemplified by the preparation of **10e** outlined below.

1(1-Methoxycarbonylmethyl)-2-cyano-3-ethyl-1,2,5,6-tetrahydropyridine **10e**. *m*-Chloroperbenzoic acid (90% 1.085 g, 6.2 mmol) in 12 ml dry CH_2Cl_2 was added to a cooled (0°) stirred soln of **6e** (1.036 g, 5.3 mmol) in 8 ml dry CH_2Cl_2 under argon. Stirring was continued at 0° for 1.5 hr, the soln was then cooled to −15° and trifluoroacetic anhydride (1.82 ml, 13.1 mmol) was added *via* syringe over a period of 15 min. During the addition, a white milky ppt formed, which redissolved on further addition of TFAA. The clear pale yellow soln was stirred for 1.5 hr, during which time the temp was allowed to reach 0°. KCN (0.65 g, 10 mmol) in 3 ml water was then added and the pH adjusted to 5 by the addition of solid NaOAc. The two-phase mixture was stirred vigorously under a stream of N_2 for 20 min, basified with 10% $NaCO_3^{aq}$ and extracted with CH_2Cl_2 (5 × 30 ml). The combined extracts were washed with 10% $Na_2CO_3^{aq}$ (30 ml) and water (2 × 50 ml), dried over Na_2SO_4 and concentrated to give 1.03 g (88%) essentially pure **10e** as a pale brown oil. Purification was effected by filtration through a short column of alumina eluting with CH_2Cl_2–hexane 1:1, yield: 708 mg (61%) IR: 2270 cm^{-1} (w) (CN), 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.08 (t, 7 Hz, 3H), 1.39 (d, 7 Hz, 3H), 2.12 (q, 7 Hz, 2H), 2.05–2.30 (m, 2H), 2.45–2.90 (m, 2H), 3.42 (q, 7 Hz, 1H), 3.71 (s, 3H), 4.19 (br s, 1H), 5.66 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.78 (q), 13.77 and 15.19 (q), 24.61 (t), 25.58 (t), 40.97 and 42.72 (t), 50.71 (q), 51.56 and 52.20 (d), 59.02 and 60.19 (d), 115.38 and 116.55 (s), 121.55 (d), 132.33 (s), 171.60 and 172.26 (s). MS *m/z* (rel. int.): 222 (M^+, 10%), 207 (5%), 153 (100%).

1-(1-Methoxycarbonylethyl)2-cyanopiperidine **10a**. Compound **10a** was prepared as described for **10e** in 50% yield. IR: 2280 cm^{-1} (w) (CN), 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.34 (d, 7 Hz, 3H), 1.30–2.10 (m, 6H), 2.40–3.05 (m, 2H), 3.48 and 3.54 (q, 7 Hz, 1H), 3.73 (s, 3H), 3.90 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.22 and 14.87 (q), 20.00 and 20.32 (t), 24.67 (t), 28.83 and 29.41 (t), 45.52 and 46.04 (t), 49.80 and 50.19 (d), 50.97 (q), 60.64 and 61.49 (d), 116.16 and 117.07 (s), 171.86 and 172.32 (s). MS *m/z* (rel. int.): 196 M^+ (2%), 181 (100%), 166 (25%), 113 (50%).

1 - (1 - Methoxycarbonyl propyl)2 - cyanopiperidine **10b**. Compound **10b** was prepared as described for **10e** in 42% yield. IR: 2280 cm^{-1} (w) (CN), 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, 7 Hz, 3H), 1.40–2.05 (m, 8H), 2.76 (m, 2H), 3.19 (q, 7 Hz, 1H), 3.74 (s, 3H), 3.91 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 9.54 and 9.67 (q), 20.19 and 20.58 (t), 21.43 and 22.27 (t), 24.80 (t), 29.35 and 29.74 (t), 44.22 and 46.88 (t), 49.35 and 50.45 (d), 51.66 (q), 66.94 and 68.05 (d), 116.42 and 117.01 (s), 170.90 and 171.28 (s). MS *m/z* (rel. int.): 210 (M^+, 7%), 183 (10%), 181 (5%), 151 (100%), 124 (65%).

1 - (1 - Methoxycarbonyl benzyl)2 - cyanopiperidine **10c**. Compound **10c** was prepared as described for **10e** in 43% yield. IR: 2290 cm^{-1} (w) (CN), 1760 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.25–2.00 (m, 6H), 2.25–2.85 (m, 2H), 3.66 (s, 3H), 3.91 (s, 1H), 4.18 (m, 1H), 7.05–7.70 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.92 (t), 24.80 (t, 2C), 50.84 (q), 55.71 and 56.49 (t), 71.03 and 71.55 (d), 81.42 (d), 115.12 and 115.64 (s), 126.88 (d, 2C), 127.72 (d, 2C), 127.98 (d), 134.99 (s), 171.02 (s). MS *m/z* (rel. int.): 258 (M^+, 1%), 231 (2%), 199 (30%), 172 (10%), 150 (10%), 100 (65%), 56 (100%).

1 - (1 - Methoxycarbonylethyl)2 - cyano - 6 - methylpiperidine **10d**. Compound **10d** was prepared as described for **10e** in 67% yield. IR: 2280 cm^{-1} (w) (CN), 1745 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.26 (d, 7 Hz, 3H), 1.36 (d, 7 Hz, 3H), 1.30–2.05 (m, 6H), 2.45–3.20 (m, 1H), 3.69 (s, 3H), 3.72 (q, 7 Hz, 1H), 3.89 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 11.17 and 15.97 (q), 20.39 and 21.49 (t), 19.54 and 24.74 (q), 25.19 and 29.28 (t), 39.09 and 39.67 (t), 49.80 and 50.13 (d), 51.10 and 51.36 (q), 55.65 and 56.16 (d), 67.66 and 67.92 (d), 118.56 and 119.02 (s), 170.64 and 172.98 (s). MS *m/z* (rel. int.): 210 M^+ (7%), 195 (5%), 183 (10%), 151 (100%), 124 (100%).

1 - Methyl - 2 - cyano - 2 - methoxycarbonylpiperidine **10f**. Compound **10f** was prepared as described for **10e** in 50% yield. IR: 2260 cm^{-1} (w) (CN), 1745 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.35–1.90 (m, 6H), 1.91–2.16 (m, 1H), 2.29 (s, 3H), 2.60–3.05 (m, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 19.67 (t), 23.96 (t), 34.02 (t), 41.42 (q), 51.23 (t), 53.37 (q), 68.57 (s), 113.43 (s), 168.10 (s). MS *m/z* (rel. int.): 182 (M^+, 1%), 155 (5%), 123 (100%).

1-(1-Carboxyethyl) piperidine N-oxide **21a**. Aminoester **6a** (856 mg, 5 mmol) was dissolved in 60 ml 1:1 EtOH–$CHCl_3$ and

30% H_2O_2 (3.5 ml, excess) was added; the homogeneous mixture was stirred at 60° for 13 hr, 200 mg Pd/C (10%) was added and stirring continued for 2 hr. After the usual work-up, 860 mg (99%) acid N-oxide **21a** was obtained as a highly hygroscopic white solid, IR: 950 cm^{-1} (m) (N→0). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.66 (d, 7 Hz, 3H), 1.50–2.35 (m, 6H), 3.00–3.95 (m, 4H), 4.20 (q, 7 Hz, 1H), 11.09 (br s). ^{13}C NMR ($CDCl_3$) δ 11.88 (q), 19.80 (t), 20.26 (t), 20.58 (t), 59.61 (t), 63.76 (t), 71.74 (d), 173.24 (s).

1-(1-*Methoxycarbonylethyl*) *piperideine N-oxide* **21b**

(a) From **6a**. To a cooled, stirred soln of **6a** (856 mg, 5 mmol) in 10 ml dry CH_2Cl_2 under N_2, *m*CPBA (1.06 g, 1.1 eq) in 10 ml CH_2Cl_2 was slowly added. The resulting soln was stirred for 3 hr during which time the starting material had completely disappeared. The soln was then passed through a short column of alumina (35 g) using 20% MeOH:$CHCl_3$ as eluant. Evaporation of fractions containing only the desired product gave 710 mg (76%) **21b** as a pale yellow oil which could not be induced to crystallise. IR: 1740 cm^{-1} (s) (COOMe), 970 (m) (N→0). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.64 (d, 7 Hz, 3H), 1.15–1.90 (m, 4H), 2.00–2.60 (m, 2H), 2.95–3.50 (m, 4H), 3.80 (s, 3H), 4.15 (q, 7 Hz, 1H), 6.22 (br s). ^{13}C NMR ($CDCl_3$) δ 12.08 (q), 19.87 (t), 20.13 (t), 21.43 (t), 52.59 (q), 58.18 (t), 61.94 (t), 74.28 (d), 169.60 (s).

(b) From **21a**. Acid N-oxide **21a** (100 mg) was dissolved in 3 ml CH_2Cl_2 and ethereal diazomethane soln was added until the liquid remained faintly yellow. Purification of the product was effected as in method (a) and 106 mg (97%) pale yellow oil was obtained identical (TLC, IR, ^1H NMR, ^{13}C NMR) with **21b**.

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