Acid-catalysed N–alkyl heterolysis of tertiary pyridinecarboxamides and benzamides under mild conditions

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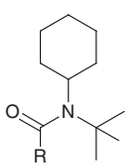
Tertiary pyridinecarboxamides **1**–**9** and related benzamides **10**–**18** bearing a *tert*-butyl substituent were found to undergo alkyl–nitrogen heterolysis under unusually mild conditions. Accordingly, the corresponding secondary amides **19**–**33** have been isolated in high yields as the sole reaction product. Through a kinetic study based on pH–rate profiles and activation parameters, we have shown that the alkyl–nitrogen fission involved an initial protonation of the amide group that would concern the oxygen atom.

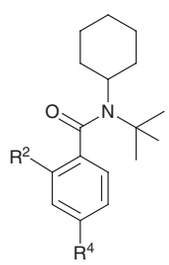
The amide bond has long attracted much attention since it is an essential building unit in proteins. The high stability of the amide linkage toward hydrolysis is of crucial importance to biological systems, since it allows the construction of peptides from relatively simple amino acid precursors. There are two plausible protonation sites of the amide in the acid-catalysed hydrolysis mechanism, *i.e.*, protonation can occur on either the oxygen or nitrogen. For many years, the protonation site of normal amides has been agreed to be oxygen. However, in the case of highly strained amides, the strong pyramidalization of the nitrogen atom thermodynamically favors N-protonation over O-protonation.[1–3] This group, for the most part, contains distorted amides which can be regarded as models for activated peptide N–C(O) units produced during enzyme-catalysed hydrolysis of peptides.[4] This is the reason why hydrolysis of such amides has been extensively documented.[5–7]

So far, little attention has been paid to the possibility of other types of amide acid-catalysed heterolysis. Of particular note is the specific behaviour of *N-tert*-alkylamides.[8–10] Examination of their heterolysis has shown fission of the alkyl–nitrogen bond to be a general reaction in strongly acidic media. The cleavage of the *N-tert*-alkylamide is supposed to arise from the unimolecular fission of the molecule in a protonated form, without intervention of other molecular species. Nevertheless, there is little mechanistic information about how this process occurs. In particular, it is not clear if steric crowding would favor N-protonation over O-protonation.[8,9]

In the course of a study devoted to the electrochemical reduction of tertiary pyridinecarboxamides[11] in aqueous acidic medium, we have shown that the presence of bulky alkyl substituents provoked the alkyl–nitrogen heterolysis of the amide function, leading to the corresponding secondary pyridinecarboxamide, under milder conditions of both temperature and acidity than those previously reported in the literature.[8,10,12,13] Consequently, we thought that an investigation of this reaction could be worthwhile to provide explanations about the factors that promote alkyl–nitrogen fission over hydrolysis.

We report herein a detailed analysis of the behaviour of pyridinecarboxamides **1**–**9** (Fig. 1). We will deal with three essential pieces of information that need to be considered in order to establish the reaction mechanism for the heterolysis of these amides. These are: (1) thorough product studies; (2) pH–rate profiles; and (3) activation parameters. Moreover, as concomitant protonation of the pyridine nucleus will complicate the analysis, we have studied the kinetics of alkyl–nitrogen heterolysis of a series of benzamide analogues **10**–**18** (Fig. 1).





1 : R = 3-pyridyl
2 : R = 4-pyridyl
3 : R = 2-pyridyl
4 : R = 3-methoxy-2-pyridyl
5 : R = 5-methoxycarbonyl-2-pyridyl
6 : R = 5-*n*-butyl-2-pyridyl
7 : R = 2-(*N*-methylpyridinium)
8 : R = 3-(*N*-methylpyridinium)
9 : R = 4-(*N*-methylpyridinium)

10 : $R^2 = R^4 = H$
11 : $R^2 = H$, $R^4 = Cl$
12 : $R^2 = H$, $R^4 = CO_2Me$
13 : $R^2 = H$, $R^4 = NO_2$
14 : $R^2 = H$, $R^4 = n$-Bu
15 : $R^2 = H$, $R^4 = OMe$
16 : $R^2 = OMe$, $R^4 = H$
17 : $R^2 = NO_2$, $R^4 = H$
18 : $R^2 = OH$, $R^4 = H$

Fig. 1 Structures of tertiary amides **1**–**18**.

Results

Reaction products

Analysis of the behaviour of pyridinecarboxamides **1**–**9**, as well as benzamide analogues **10**–**18**, required thorough product studies, which were performed under typical reaction conditions (see Experimental section). In aqueous 0.01–0.50 mol dm^{-3} sulfuric acid solutions, tertiary pyridinecarboxamides and related benzamides were observed to form, in excellent yields, the corresponding secondary amides **19**–**33** as the reaction products, according to a unimolecular N–alkyl cleavage of the protonated amide.

Kinetics

Rate constant determination and rate–pH profile for pyridinecarboxamides 1–9. Studies of the heterolysis of pyridinecarboxamides **1**–**9** were conducted in aqueous sulfuric acid (0.20–0.50 mol dm^{-3}), at 25 °C. In these media, compounds **1**–**4** and **6** were present as the predominant pyridinium conjugate form, as could be deduced from the pK_a' values of the pyridinium–pyridine equilibrium given in Table 1. The kinetics were investigated using high-field ^1H NMR spectroscopy. ^1H NMR spectra were recorded, in $CDCl_3$, from a reaction mixture containing the starting material (tertiary pyridine-

Table 1 Rate constants for N–alkyl heterolysis of compounds **1**–**9**, at 25 °C, in aqueous acidic solutions; pK_a' values of the pyridinium–pyridine equilibrium, at 25 °C. (Compound **7** was not reactive)

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**
$k_{obs}/10^{-5}$ s^{-1}	3.5[a]	0.8[a]	19.1[a]	1.5[a]	171.7[a]	10.5[a]	10.0[b]	1.5[b]
pK_a'	2.9	3.9	2.2	2.2	−0.2	2.75	—	—

[a] H_2SO_4 0.2 mol dm^{-3}. [b] H_2SO_4 0.5 mol dm^{-3}; pK_a' was measured from water–methanol (80:20) solutions, by UV-VIS absorption spectrometry following a procedure previously described for secondary pyridinecarboxamides.[22]

Table 2 Pseudo-first-order rate constants of the N–alkyl heterolysis of pyridinecarboxamides **1**–**3** and **5** in aqueous acidic solutions at different H_0' or pH values, at 25 °C

	H_0' or pH					
	0.13	0.57	0.83	1.70	2.00	3.00
Compound	$k_{obs}/10^{-5}$ s^{-1}					
1	13.7	3.5	1.5	—	—	—
2	2.3	0.83	0.5	—	—	—
3	17.5	19.1	15.8	—	12.2	3.9
5	—	—	52.8	123	85	20

carboxamide) and the product (secondary pyridinecarboxamide). This crude material was isolated after stopping the reaction for recorded times (see Experimental section). Kinetic measurements involved monitoring of the 1-H cyclohexyl signal of both the substrate and product. The 1-H cyclohexyl signal of the starting material appeared around δ 3.25, while that of the product was centred around δ 3.95. These signals in the NMR spectra were free of any overlapping signals. Reactions were followed for at least three half-lives. Excellent first-order rate constants were obtained from plots of ln $[(H_{Pd} + H_{SM})/H_{SM}]$ *vs.* time, where H_{SM} and H_{Pd} are the NMR integral heights of the starting material peak and the corresponding product peak respectively, at a fixed time. The results of these experiments are summarized in Table 1.

As can be deduced from a comparison of the rate constant values, a 5–20 fold increase in k_{obs} was observed in passing from compounds **1** and **2** to compound **3**. Moreover, the introduction of an electron-withdrawing substituent at the 5-position on the 2-pyridyl ring resulted in an increase in k_{obs} (compound **5**), while the introduction of an electron-donating substituent caused the opposite effect (compound **6**). Introduction of an electron-donating substituent at the 3-position markedly decreased the rate constant (compound **4**). A similar result was observed with the quaternary pyridine derivatives **8** and **9**. Of particular note was the specific behaviour of **7** in which *N*-methylation of the pyridine nucleus blocked the alkyl–nitrogen heterolysis.

According to the experimental results given in Table 2, the log k_{obs} *vs.* pH profiles for compounds **1**, **3** and **5**, at 25 °C, are shown in Fig. 2. The profiles for amides **2**, **8** and **9** are nearly superimposable on that for **1** and, for reasons of clarity, are not illustrated. For pH < 1, the protonating power of the medium was estimated in terms of acidity function H_0'. Each amide showed kinetics that are first order in $[H_3O^+]$, as the log k_{obs} *vs.* pH profile was a straight line whose slope was −1.0. Furthermore, **3** showed a domain for pH < pK_a' (pyridinium–pyridine equilibrium) that was pH independent. Picolinamides (pyridine-2-carboxamides) **4** and **6** gave similar results, when compared with **3**. Of the studied pyridinecarboxamides, **5** was the most reactive. So, the kinetics could only be monitored between pH 0.8 and 2.5. Although the pyridine nucleus existed predominantly in the bulk of the solution as the protonated conjugate form, the log k_{obs} *vs.* pH profile indicated that the alkyl–nitrogen cleavage involved a preequilibrium proton transfer on the amide group in the pH < pK_a' (pyridinium–pyridine equilibrium) domain, except for picolinamide derivatives. To gain a better understanding of the sole proton transfer concerning the amide group, we turned our attention towards a series of benzamide analogues.

Table 3 Rate constants for N–alkyl heterolysis of benzamides **10**–**18** in a 0.2 mol dm^{-3} water–methanol (80:20) sulfuric acid solution, at 25 °C. (Compounds **16** and **17** were not reactive)

Compound	**10**	**11**	**12**	**13**	**14**	**15**	**18**
$k_{obs}/10^{-5}$ s^{-1}	266.6	115.0	51.6	16.6	440.0	[a]	[a]

[a] Too fast to be measured at 25 °C.

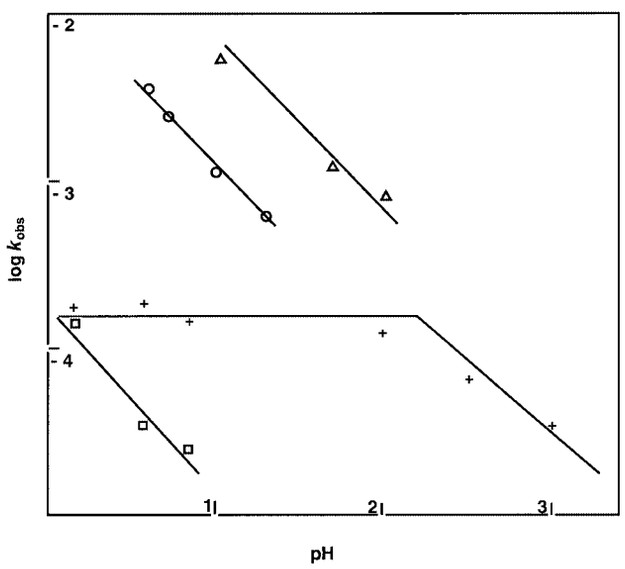


Fig. 2 pH *vs.* log k_{obs} profiles for the N–alkyl heterolysis of compounds **1**, **3**, **5** and **10**, at 25 °C, in aqueous acidic media: **1**, □; **3**, +; **5**, △; **10**, ○.

Rate constant determination and rate–pH profile for benzamides 10–18. Studies of the N–alkyl heterolysis of benzamides **10**–**18** were conducted in a water–methanol (80:20) sulfuric acid solution (0.2 mol dm^{-3}), at 25 °C, using the procedure reported above for pyridinecarboxamides **1**–**9**. Data given in Table 3 revealed that alkyl–nitrogen heterolysis was strongly dependent on structural features. Substitution at the 4-position of the phenyl ring influenced the rate constant values that decreased in the presence of electron-withdrawing substituents (compounds **12** and **13**) and conversely increased in the presence of electron-donating substituents (compounds **14** and **15**). Note that these findings were opposite to that described above in the case of substituted pyridinecarboxamides. Interesting enough, introduction of a bulky substituent at the 2-position blocked the alkyl–nitrogen heterolysis (compounds **16** and **17**), with the exception of salicylamide **18** which was remarkable in that the reaction was found to be too fast to permit the determination of k_{obs} at 25 °C.

The apparent first-order rate constant of the alkyl–nitrogen heterolysis was determined with **10** and **18**, at various acidities,

Table 4 Pseudo-first-order rate constants of the N–alkyl heterolysis of benzamides **10** and **18** in water–methanol (80:20) sulfuric acid solutions, at different pH values

	pH				
	0.60	0.70	1.00	1.30	1.60
Compound	$k_{obs}/10^{-4}$ s^{-1}				
10[a]	35.0	26.7	11.1	6.3	
18[b]	14.7	12.0	6.1	3.3	1.8

[a] 25 °C. [b] 15 °C.

Table 5 Activation parameters for the N–alkyl heterolysis of compounds **1**, **3**, **10** and **18**

Compound	θ/°C	k/mol^{-1} dm^3 s^{-1}	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/ J mol^{-1} K^{-1}
1[a]	15	6.3×10^{-5}	104.5 ± 1.0	35.5 ± 3.7
	25	2.7×10^{-4}		
3[a]	15	4.2×10^{-5}	94.9 ± 0.6	27.6 ± 2.1
	25	1.9×10^{-4}		
10[b]	15	3.63×10^{-3}	79.6 ± 0.8	−16.7 ± 2.4
	25	1.33×10^{-2}		
18[b]	5	1.85×10^{-2}	78.6 ± 0.6	−16.7 ± 2.0
	15	6.00×10^{-3}		

[a] H_2SO_4 0.5 mol dm^{-3}. [b] H_2SO_4 0.2 mol dm^{-3}.

using the method performed on pyridinecarboxamides **1**–**9**. As shown in Table 4 and Fig. 2, the log k_{obs} *vs.* pH profile for benzamide **10** was a straight line whose slope was −1.0. All benzamides **11**–**14** behaved similarly.

Activation parameters

Given in Table 5 are the activation parameters for the N–alkyl heterolysis of amides **1**, **3**, **10** and **18**. At a fixed acidity, the pseudo first-order rate constants at two temperatures were converted to second-order ones and plotted in the usual way according to the Eyring equation to yield the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values.

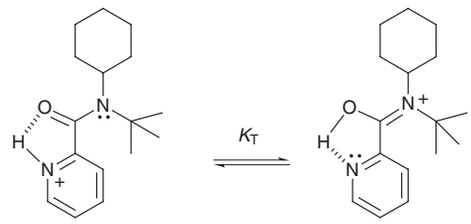
Discussion

On the basis of the results mentioned above, it appears that, in both the pyridinecarboxamide and benzamide series, N–alkyl heterolysis developed at the expense of hydrolysis under our experimental conditions. Accordingly, secondary amides **19**–**33** have been isolated in excellent yields as the sole reaction products (see Experimental section).

The appearance of the pH–rate profiles given in Fig. 2 corresponds to a kinetic law of type (i), which can be explained

$$v = k_{obs}[\text{amide}] = k\,[\text{amide}]\,[H_3O^+] \qquad \text{(i)}$$

in terms of a full protonation of the amide group, antecedent to the alkyl–nitrogen fission. However, with picolinamides, the log k_{obs} *vs.* pH profiles indicated that antecedent protonation was no longer required in the pH < pK_a' (pyridinium–pyridine equilibrium) region. Furthermore, it must be remembered that *N*-methylation of the pyridine nucleus (compound **7**) blocked the alkyl–nitrogen heterolysis. Despite the fact that steric hindrance at the 3-position of the pyridine nucleus resulted in a marked slowing (roughly one order of magnitude, compare compound **3** with **4** in Table 1), steric crowding seems to be insufficient to justify such a behaviour. All of these findings could be explained by the occurrence of an intramolecular hydrogen bond, which would initiate, in the case of picolinamide derivatives, a tautomerization implying the pyridinium hydrogen, that would be shifted towards the amidic oxygen according to eqn. (1).



(1)

3

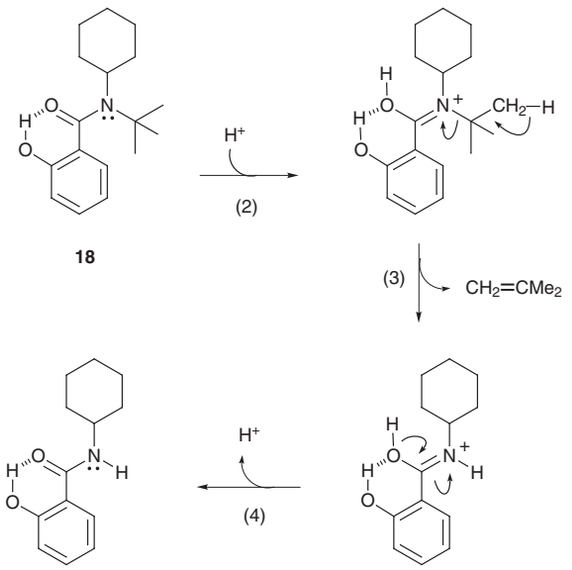
Comparison of the results obtained with pyridinecarboxamides **1**–**3** (Table 1) with those exhibited by benzamide **10** (Table 3) shows that the replacement of the pyridine nucleus by the phenyl ring led to a significant increase in the reaction rate of the alkyl–nitrogen breakdown. To explain these results, it could be noted that, under our experimental conditions, pyridinecarboxamides **1**–**3** were present as their pyridinium conjugate form, as could be deduced from the pK_a' values of the pyridinium–pyridine equilibrium (Table 1). This suggests that protonation of the pyridine nitrogen hindered the preequilibrium proton transfer at the amide group. It is indeed conventional to assume that the formation of a bicationic species is more difficult than that of a monocationic one. No doubt this is the reason why N–alkyl heterolysis proceeded more slowly with quaternary pyridine derivatives **8** and **9**. This reasoning is again supported by the observation that pyridinecarboxamide **5**, mainly present in the bulk as the neutral form (pK_a' = −0.2), was found to react at a rate approaching that found with benzamide **10**.

The dispute is whether the initial protonation of the amide group involves the oxygen or nitrogen atom or, possibly, a combination of both. The results of our investigation suggest that the most plausible protonation site in the alkyl–nitrogen fission would be the oxygen atom. A number of factors arguing in favor of this hypothesis could be listed.

a) In the benzamide series, the reaction rate was markedly dependent on the effects exerted by the substituents at the 4-position of the phenyl ring. The electron-donating substituents were more favorable than the electron-withdrawing substituents (Table 3) for the N–alkyl heterolysis. Moreover, changing the substituent from the 4-position to the 2-position totally blocked the reaction except for the hydroxy group. In the case of salicylamide (2-hydroxybenzamide) **18**, due to its high value, the rate constant k_{obs} could not be measured at 25 °C. To justify the substantial effect of the 2-hydroxy group upon N–alkyl fission, it was suggested that intramolecular hydrogen bonding maintains the planarity of the C(O)–N moiety and the aromatic ring, thus maximizing the conjugation between them, as already reported in the case of *ortho*-substituted benzamides.[14–16] The alkyl–nitrogen heterolysis required a preequilibrium proton transfer to occur, according to eqn. (2) in Scheme 1. Accordingly, the rate of alkyl–nitrogen heterolysis was found to be pH-dependent over the entire pH range studied. Obviously, the lack of reactivity observed with 2-substituted benzamides **16** and **17** must be the consequence of steric hindrance which disturbs the planarity between the phenyl ring and the carbonyl group.

b) The results obtained with the pyridinecarboxamide series corroborate the hypothesis of predominance of O-protonation over N-protonation. The intramolecular hydrogen bonding [eqn. (1)], which maintains the planarity of the C(O)–N moiety and the pyridyl ring, is probably the reason for accelerated N–alkyl heterolysis of picolinamide **3** *versus* nicotinamide **1** and isonicotinamide **2**.

c) Activation parameters also support the mechanistic interpretations. It is known that distortion of an amide causes a marked decrease in the $\Delta H^{\ddagger}$ values from 100 to 20 kJ mol^{-1},



Scheme 1

while the $\Delta S^{\ddagger}$ values are generally large and negative (about -150 J mol^{-1} K^{-1}).[2,4,7] From the data listed in Table 5, it could be deduced that: i) the $\Delta H^{\ddagger}$ values are as expected for a substrate exhibiting predominant, if not exclusive, unimolecular cleavage;[9] ii) the steric crowding exerted by both the cyclohexyl and *tert*-butyl substituents would not be sufficiently severe to provoke an appreciable distortion of the C(O)–N linkage,[17–21] that would lead to a shift from O to N protonation.

On the basis of these kinetic studies, there is little doubt left that, in both the studied tertiary amide series, the most plausible protonation site antecedent to the alkyl–nitrogen heterolysis is the oxygen atom. To further assess the validity of our arguments, we must consider some results previously obtained in our laboratory. First, they concern the electrochemical reduction of tertiary pyridinecarboxamide derivatives **1** and **3**. They afford aminomethylpyridine as the sole product, a result which is consistent with O-protonation (see scheme 5 in ref. 11), while N-protonation would lead to the C–N bond splitting reaction giving hydroxymethylpyridine and the secondary amine. Second, they deal with the relationship between pyridine nitrogen basicity and steric crowding in the N-substituted pyridinecarboxamide series. We have shown that measurement of the pK_a' value related to the pyridinium–pyridine equilibrium could be identified as a useful probe for evaluating the extent of steric crowding at the amide nitrogen position.[22] The pK_a' values found for pyridinecarboxamides **1**–**3** (Table 1) were very close to those reported in the literature for nicotinamide (3.35), isonicotinamide (3.60) and picolinamide (2.10), respectively. Therefore, it could be deduced that the attachment of both a *tert*-butyl substituent and a cyclohexyl group at the nitrogen amide position does not modify markedly the properties of the pyridine nucleus. It follows that, in the studied tertiary pyridinecarboxamide series, very probably the C(O)–N bond is not distorted. In the same way, the pK_a' values of the protonated tertiary benzamides **10** (-0.15), **11** (-0.78) and **13** (-1.07), measured by UV-VIS absorption spectrophotometry (see Experimental section) are of the same order of magnitude as those previously reported for *N*,*N*-diisopropylbenzamide (-0.55),[23] a result which corroborates the hypothesis of O-protonation rather than N-protonation. It has indeed been reported in the literature that the shift from O to N-protonation led to a large increase in the pK_a' of the protonated amide consecutively to the distortion of the C(O)–N bond.[1]

Finally, in both the studied tertiary amide series, we have shown that, thanks to its good leaving character, the *tert*-butyl substituent leads to the fission of the alkyl–nitrogen bond at the expense of hydrolysis, under unusually mild conditions of both temperature and acidity. However, the steric crowding would not be sufficiently severe to provoke appreciable distortion of the C(O)–N linkage, and consequently, to cause a change in the protonation site. At that point, it remains to establish, by varying the substituents at the amide nitrogen position, in a series of various sterically crowded tertiary benzamides, the relationship between the degree of amide distortion and susceptibility towards N–alkyl heterolysis. In this connection, further structural and kinetic investigations are currently in progress in our laboratory.

Experimental

Materials

UV-VIS spectra were recorded on a Varian Cary 13E spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300 MHz for ^{1}H observations. Chemical shifts are reported in parts per million (ppm), relative to internal tetramethylsilane. *J* values are given in Hz. The measurements were carried out using the standard pulse sequences. The carbon type (methyl, methylene, methine or quaternary) was determined by DEPT experiments. Mass spectra were recorded on a Nermag R 10-10 C spectrometer, equipped with desorption chemical ionization (DCI) mode. Samples were introduced by means of a direct insertion probe. Ammonia was used as the reagent gas. Melting points were determined on a Köfler block and were uncorrected.

Analytical TLC were performed on Merck Silica Gel 60 F 254 (lot 5714). Column chromatography was conducted on open glass columns packed with Merck Silica Gel 60 (lot 9385).

The solvents used for extractions and chromatography were obtained from S.D.S. Methanol, sulfuric acid and sodium carbonate were obtained from Prolabo (analysis purity grade). *N*-Cyclohexyl-*N*-*tert*-butylamine and nicotinoyl chloride were obtained from Aldrich. Tertiary pyridinecarboxamides **2**, **3**, **5**, **6** and tertiary benzamides **10**–**17** were synthesized as previously described for the preparation of tertiary pyridinecarboxamides **1** and **4**.[11] Tertiary salicylamide **18** was prepared following a route analogous to that reported for the synthesis of 2-hydroxy-3-methoxybenzamide.[24] Physical characteristics for compounds **2**, **3**, **5**, **6**, **10**–**18** as well as syntheses and spectroscopic data for compounds **7**–**9** are as follows.

***N*-Cyclohexyl-*N*-*tert*-butylisonicotinamide 2.** White solid, mp 101–103 °C (Found: C, 73.75; H, 9.27; N, 10.72. $C_{16}H_{24}N_2O$ requires C, 73.85; H, 9.23; N, 10.77%); δ_H (300 MHz; $CDCl_3$) 0.80 to 1.80 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.25 (1H, m, 1-H, cyclohexyl), 7.20 (2H, dd, *J* 6 and 1, 3-H and 5-H), 8.55 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 25.2, 27.0 and 33.6 (CH_2, cyclohexyl), 29.6 (Me, *tert*-butyl), 58.5 (C_Q, *tert*-butyl), 59.5 (C-1, cyclohexyl), 121.0 (C-3 and C-5), 148.8 (C-4) and 149.7 (C-2 and C-6), 172.0 (CO, amide); *m*/*z* 261 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butylpicolinamide 3.** White solid, mp 89–91 °C (Found: C, 73.71; H, 9.07; N, 10.68. $C_{16}H_{24}N_2O$ requires C, 73.85; H, 9.23; N, 10.77%); δ_H (300 MHz; $CDCl_3$) 1.00 to 2.00 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.25 (1H, m, 1-H, cyclohexyl), 7.25 (1H, m, *J* 5 and 8, 5-H), 7.40 (1H, d, *J* 8, 3-H), 7.70 (1H, m, *J* 8 and 2, 4-H), 8.55 (1H, dd, *J* 5 and 2, 6-H); δ_C (75 MHz; $CDCl_3$) 25.4, 27.1 and 32.7 (CH_2, cyclohexyl), 29.6 (Me, *tert*-butyl), 58.3 (C_Q, *tert*-butyl), 59.6 (C-1, cyclohexyl), 122.4 and 123.5 (C-3 and C-5), 136.5 (C-4), 148.1 (C-6), 158.7 (C-2), 172.1 (CO, amide); *m*/*z* 261 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-5-methoxycarbonylpicolinamide 5.** White solid, mp 124–126 °C (Found: C, 67.73; H, 8.16; N, 8.81. $C_{18}H_{26}N_2O_3$ requires C, 67.92; H, 8.18; N, 8.80%); δ_H (300

MHz; $CDCl_3$) 1.00 to 2.00 (10H, m, CH_2, cyclohexyl), 1.35 (9H, s, Me, *tert*-butyl), 3.25 (1H, m, 1-H, cyclohexyl), 3.95 (3H, s, Me, CO_2Me), 7.45 (1H, d, *J* 8, 3-H), 8.30 (1H, dd, *J* 8 and 2, 4-H), 9.10 (1H, d, *J* 2, 6-H); δ_C (75 MHz; $CDCl_3$) 25.3, 27.0 and 32.5 (CH_2, cyclohexyl), 29.7 (Me, *tert*-butyl), 52.3 (Me, CO_2Me), 58.5 (C_Q, *tert*-butyl), 59.6 (C-1, cyclohexyl), 121.9 (C-3), 125.4 (C-5), 137.6 (C-4), 149.5 (C-6), 161.9 (C-2), 165.2 (CO, ester), 170.8 (CO, amide); *m*/*z* 319 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-5-*n*-butylpicolinamide 6.** Colourless oil; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 6, Me, *n*-butyl), 1.00 to 1.95 (10H, m, CH_2, cyclohexyl), 1.30 (2H, m, *J* 6, $CH_2\gamma$, *n*-butyl), 1.40 (9H, s, Me, *tert*-butyl), 1.60 (2H, m, *J* 6, $CH_2\beta$, *n*-butyl), 2.65 (2H, t, *J* 6, $CH_2\alpha$, *n*-butyl), 3.25 (1H, m, 1-H, cyclohexyl), 7.30 (1H, d, *J* 8, 3-H), 7.50 (1H, dd, *J* 8 and 2, 4-H), 8.35 (1H, d, *J* 2, 6-H); δ_C (75 MHz; $CDCl_3$) 13.7 (Me, *n*-butyl), 22.0 ($CH_2\gamma$, *n*-butyl), 25.4, 27.0 and 32.5 (CH_2, cyclohexyl), 29.6 (Me, *tert*-butyl), 32.8 and 33.0 ($CH_2\beta$ and $CH_2\alpha$, *n*-butyl), 58.3 (C_Q, *tert*-butyl), 59.6 (C-1, cyclohexyl), 122.2 (C-3), 136.2 (C-4), 138.1 (C-5), 148.0 (C-6), 156.2 (C-2), 172.4 (CO, amide); *m*/*z* 317 (MH^+).

2-(*N*-Cyclohexyl-*N*-*tert*-butylcarbamoyl)-1-methylpyridinium iodide 7. *Method.* To a solution of compound **3** (1.0 g, 4.0 mmol) in methanol (1 cm^3) was added, at 25 °C, 22.8 g of methyl iodide (160.0 mmol). The reaction mixture was stirred and heated at reflux for 24 h, after which methyl iodide excess and methanol were removed under reduced pressure at 35 °C. Chromatography on silica gel with dichloromethane–methanol (95 : 5) as the eluent afforded compound **7** (1.3 g, 80%), mp 121–123 °C, as a yellow solid (Found: C, 49.95; H, 6.67; I, 31.37; N, 6.66. $C_{17}H_{24}IN_2O$ requires C, 50.74; H, 6.71; I, 31.59; N, 6.96%); δ_H (300 MHz; $CDCl_3$) 1.00 to 2.00 (19H, m, CH_2, cyclohexyl and Me, *tert*-butyl), 3.30 (1H, m, 1-H, cyclohexyl), 4.45 (3H, s, NMe), 7.90 (1H, dd, *J* 8 and 2, 3-H), 8.10 (1H, m, *J* 5 and 8, 5-H), 8.80 (1H, m, *J* 8 and 2, 4-H), 9.60 (1H, dd, *J* 5 and 2, 6-H); δ_C (75 MHz; $CDCl_3$) 24.8, 26.4, and 26.7 (CH_2, cyclohexyl), 29.8 (Me, *tert*-butyl), 46.7 (NMe), 60.5 (C_Q, *tert*-butyl and C-1, cyclohexyl), 125.3 and 127.7 (C-3 and C-5), 146.7 and 147.3 (C-4 and C-6), 150.7 (C-2), 162.0 (CO, amide).

3-(*N*-Cyclohexyl-*N*-*tert*-butylcarbamoyl)-1-methylpyridinium iodide 8. The same method applied to compound **1** afforded compound **8** (1.0 g, 63%), mp 119–121 °C, as a yellow solid; δ_H (300 MHz; $CDCl_3$) 0.90 to 1.90 (10H, m, CH_2, cyclohexyl), 1.40 (9H, s, Me, *tert*-butyl), 3.30 (1H, m, 1-H, cyclohexyl), 4.70 (3H, s, NMe), 8.25 (1H, m, *J* 5 and 8, 5-H), 8.35 (1H, d, *J* 8, 4-H), 9.10 (1H, s, 2-H), 9.45 (1H, d, *J* 5, 6-H); δ_C (75 MHz; $CDCl_3$) 25.0, 26.9, and 34.0 (CH_2, cyclohexyl), 29.6 (Me, *tert*-butyl), 50.0 (NMe), 59.6 (C_Q, *tert*-butyl and C-1, cyclohexyl), 128.2 (C-5), 141.1 (C-3), 142.3, 143.4 and 146.2 (C-2, C-4 and C-6), 166.8 (CO, amide).

4-(*N*-Cyclohexyl-*N*-*tert*-butylcarbamoyl)-1-methylpyridinium iodide 9. The same method applied to compound **2** afforded compound **9** (1.5 g, 94%), mp 216–218 °C, as a yellow solid; δ_H (300 MHz; $CDCl_3$) 1.00 to 1.90 (10H, m, CH_2, cyclohexyl), 1.40 (9H, s, Me, *tert*-butyl), 3.25 (1H, m, 1-H, cyclohexyl), 4.60 (3H, s, NMe), 7.85 (2H, d, *J* 6, 3-H and 5-H), 9.35 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 24.9, 26.8, and 32.9 (CH_2, cyclohexyl), 29.9 (Me, *tert*-butyl), 49.4 (NMe), 59.5 (C_Q, *tert*-butyl and C-1, cyclohexyl), 124.6 (C-3 and C-5), 146.2 (C-2 and C-6), 155.6 (C-4), 167.1 (CO, amide).

***N*-Cyclohexyl-*N*-*tert*-butylbenzamide 10.** White solid, mp <50 °C; δ_H (300 MHz; $CDCl_3$) 0.90 to 1.80 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.30 (1H, m, 1-H, cyclohexyl), 7.35 (5H, m, aromatic); δ_C (75 MHz; $CDCl_3$) 25.4, 27.2 and 34.0 (CH_2, cyclohexyl), 29.5 (Me, *tert*-butyl), 58.0 (C_Q, *tert*-butyl), 59.3 (C-1, cyclohexyl), 127.2, 127.8 and 129.2 (CH, aromatic), 141.7 (C-1), 175.5 (CO, amide); *m*/*z* 260 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-4-chlorobenzamide 11.** White solid, mp 65–67 °C; δ_H (300 MHz; $CDCl_3$) 0.90 to 1.80 (10H, m, CH_2, cyclohexyl), 1.40 (9H, s, Me, *tert*-butyl), 3.30 (1H, m, 1-H, cyclohexyl), 7.35 (4H, m, aromatic); δ_C (75 MHz; $CDCl_3$) 25.3, 27.1 and 34.1 (CH_2, cyclohexyl), 29.3 (Me, *tert*-butyl), 58.4 (C_Q, *tert*-butyl), 59.4 (C-1, cyclohexyl), 128.2 and 128.9 (CH, aromatic), 135.3 (C-4), 140.2 (C-1), 174.5 (CO, amide); *m*/*z* 294 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-4-methoxycarbonylbenzamide 12.** White solid, mp 62–64 °C (Found: C, 71.83; H, 8.54; N, 4.45. $C_{19}H_{27}NO_3$ requires C, 71.92; H, 8.52; N, 4.42%); δ_H (300 MHz; $CDCl_3$) 0.90 to 1.80 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.25 (1H, m, 1-H, cyclohexyl), 3.95 (3H, s, Me, CO_2Me), 7.45 (2H, d, *J* 6, 2-H and 6-H), 8.05 (2H, d, *J* 6, 3-H and 5-H); δ_C (75 MHz; $CDCl_3$) 25.3, 27.1 and 33.9 (CH_2, cyclohexyl), 29.5 (Me, *tert*-butyl), 52.1 (Me, CO_2Me), 58.3 (C_Q, *tert*-butyl), 59.6 (C-1, cyclohexyl), 127.0 (C-2 and C-6), 129.3 (C-3 and C-5), 130.4 (C-4), 145.8 (C-1), 166.5 (CO, ester), 174.0 (CO, amide); *m*/*z* 318 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-4-nitrobenzamide 13.** White solid, mp 91–93 °C; (Found: C, 66.97; H, 7.69; N, 9.14. $C_{17}H_{24}N_2O_3$ requires C, 67.10; H, 7.89; N, 9.21%); δ_H (300 MHz; $CDCl_3$) 0.80 to 1.80 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.30 (1H, m, 1-H, cyclohexyl), 7.50 (2H, d, *J* 8, 2-H and 6-H), 8.20 (2H, d, *J* 8, 3-H and 5-H); δ_C (75 MHz; $CDCl_3$) 25.2, 27.1 and 33.8 (CH_2, cyclohexyl), 29.5 (Me, *tert*-butyl), 58.6 (C_Q, *tert*-butyl), 59.5 (C-1, cyclohexyl), 123.3 (C-3 and C-5), 127.8 (C-2 and C-6), 147.5 and 147.8 (C-1 and C-4), 172.4 (CO, amide); *m*/*z* 305 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-4-*n*-butylbenzamide 14.** Pale yellow oil; δ_H (300 MHz; $CDCl_3$) 0.90 to 1.80 (10H, m, CH_2, cyclohexyl), 0.95 (3H, t, *J* 6, Me, *n*-butyl), 1.30 (2H, m, *J* 6, $CH_2\gamma$, *n*-butyl), 1.45 (9H, s, Me, *n*-butyl), 1.60 (2H, m, *J* 6, $CH_2\beta$, *n*-butyl), 2.65 (2H, t, *J* 6, $CH_2\alpha$, *n*-butyl), 3.30 (1H, m, 1-H, cyclohexyl), 7.15 (2H, d, *J* 6, 3-H and 5-H), 7.30 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 13.8 (Me, *n*-butyl), 22.1 ($CH_2\gamma$, *n*-butyl), 25.4, 27.2 and 34.1 (CH_2, cyclohexyl), 29.4 (Me, *tert*-butyl), 33.3 and 35.4 ($CH_2\beta$ and $CH_2\alpha$, *n*-butyl), 57.9 (C_Q, *tert*-butyl), 59.1 (C-1, cyclohexyl), 127.4 and 127.8 (CH, aromatic), 139.1 (C-4), 144.3 (C-1), 175.9 (CO, amide); *m*/*z* 316 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-4-methoxybenzamide 15.** Pale yellow oil (Found: C, 74.56; H, 9.34; N, 4.84. $C_{18}H_{27}NO_2$ requires C, 74.74; H, 9.34; N, 4.84%); δ_H (300 MHz; $CDCl_3$) 0.90 to 1.80 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.25 (1H, m, 1-H, cyclohexyl), 3.85 (3H, s, OMe), 6.85 (2H, d, *J* 6, 3-H and 5-H), 7.40 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 25.4, 27.4 and 34.5 (CH_2, cyclohexyl), 29.4 (Me, *tert*-butyl), 55.3 (OMe), 58.0 (C_Q, *tert*-butyl), 59.1 (C-1, cyclohexyl), 113.1 (C-3 and C-5), 129.6 (C-2 and C-6), 134.4 (C-1), 160.7 (C-4), 176.1 (CO, amide); *m*/*z* 290 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-2-methoxybenzamide 16.** Pale yellow oil; δ_H (300 MHz; $CDCl_3$) 0.90 to 2.00 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.35 (1H, m, 1-H, cyclohexyl), 3.85 (3H, s, OMe), 6.90, 7.10 and 7.30 (4H, m, aromatic); δ_C (75 MHz; $CDCl_3$) 25.5, 27.3 and 32.9 (CH_2, cyclohexyl), 29.8 (Me, *tert*-butyl), 55.3 (OMe), 58.2 (C_Q, *tert*-butyl), 59.1 (C-1, cyclohexyl), 110.8, 120.1 and 129.2 (*C*H, aromatic), 127.1 (C-1), 155.3 (C-2), 170.9 (CO, amide); *m*/*z* 290 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-2-nitrobenzamide 17.** White solid, mp 71–73 °C; δ_H [300 MHz; $(CD_3)_2SO$] 0.90 to 2.00 (10H, m,

CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.35 (1H, m, 1-H, cyclohexyl), 7.45 (1H, d, *J* 6, 6-H, aromatic), 7.65 and 7.80 (2H, t, *J* 6, 4-H and 5-H, aromatic), 8.15 (1H, d, *J* 6, 3-H, aromatic); δ_C [75 MHz; $(CD_3)_2SO$] 26.1, 28.0 and 34.0 (CH_2, cyclohexyl), 30.5 (Me, *tert*-butyl), 59.0 (C_Q, *tert*-butyl), 62.0 (C-1, cyclohexyl), 125.8, 130.5 and 135.5 (*C*H, aromatic), 145.8 (C-1 and C-2), 170.9 (CO, amide); *m*/*z* 305 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-2-hydroxybenzamide 18.** White solid, mp 127–129 °C; δ_H (300 MHz; $CDCl_3$) 0.90 to 1.90 (10H, m, CH_2, cyclohexyl), 1.45 (9H, s, Me, *tert*-butyl), 3.30 (1H, m, 1-H, cyclohexyl), 6.80, 6.95 and 7.35 (4H, aromatic), 9.30 (s, 1H, OH, D_2O exchanged); δ_C (75 MHz; $CDCl_3$) 25.3, 27.2 and 34.5 (CH_2, cyclohexyl), 28.9 (Me, *tert*-butyl), 58.3 (C_Q, *tert*-butyl), 59.7 (C-1, cyclohexyl), 117.0, 118.2, 129.6 and 132.6 (*C*H, aromatic), 123.7 (C-1), 158.0 (C-2), 178.7 (CO, amide); *m*/*z* 276 (MH^+).

Kinetics

Stock solutions of amides **1**–**18** (0.5 mol dm^{-3}) were prepared in methanol. The heterolysis reaction was initiated by injecting 0.5 cm^3 of the stock solution into a vessel containing 250 cm^3 of 0.2 or 0.5 mol dm^{-3} aqueous sulfuric acid (pyridinecarboxamides **1**–**9**), or a 0.2 mol dm^{-3} water–methanol (80 : 20) sulfuric acid solution (benzamides **10**–**18**), which had been previously equilibrated in a thermostated water bath for 30 min at 25 °C. All reactions were followed for at least three half-lives as follows: for recorded times, 25 cm^3 aliquots of the reaction mixture were collected and quenched with a 1 mol dm^{-3} aqueous potassium carbonate solution. Then, the resulting mixture was extracted with dichloromethane (20 cm^3). The organic phase was dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure at 40 °C. The crude material containing the starting material (tertiary amide) and the product (secondary amide) was analyzed using high-field ^1H NMR spectroscopy. Kinetic measurements involved monitoring of the 1-H cyclohexyl signal of both the substrate and product. The 1-H cyclohexyl signal of the starting material appeared around δ 3.25, while that of the product was centred around δ 3.95. These signals were free of any overlapping signals, except for products **23** and **29** where the 1-H cyclohexyl signal was obscured by the methoxycarbonyl signal. In this case, kinetic measurements necessitated monitoring aromatic signals of both the substrate and product. For pyridinecarboxamides **5** and **23**, the 3-H signal was used for all kinetic measurements, while for compounds **12** and **29**, the 2-H signal was selected. All reactions displayed excellent pseudo-first-order kinetics and pseudo-first-order constants (k_{obs}) were obtained from plots of $\ln[(H_{Pd} + H_{SM})/H_{SM}]$ *vs*. time, where H_{SM} and H_{Pd} are the NMR integral heights of the starting material peak and the corresponding product peak respectively, at a fixed time. Each determination was repeated in duplicate and had a precision of better than 5% indicating good results within the limitations of the ^1H NMR method.

For log k_{obs} *vs*. pH profiles (Fig. 2), dilute aqueous buffered sulfuric acid solutions at pH 2.0 and 3.0 were made up by adding various concentrations of sodium hydroxide.

pK_a Determinations

The pK_a' of the protonated tertiary benzamides **10**, **11** and **13** were measured by UV-VIS absorption spectrophotometry, in aqueous buffered solutions containing 20% methanol. The acidity scale used was the H_A function.[25] In the H_A range 0.0–3.0, basic strengths were measured in acidic solutions by a standard UV-VIS method, making use of increase in absorption that amides showed upon protonation, at roughly 240 nm. The pK_a' value was determined from graphs of log $[A(HB^+) - A]/[A - A(B)]$ *vs*. H_A at 240 nm, where $A(HB^+)$ and $A(B)$ are the respective absorbances of the monocationic and the neutral species, and A is the absorbance of their mixture at a fixed H_A, according to the following equation: $pH = pK_a' + \log [A(HB^+) - A]/[A - A(B)]$. For compounds **10**, **11** and **13**, the pK_a' values related to the protonation of the amide group were found to be −0.55, −0.78 and −1.07 ± 0.05 respectively, at 25 °C.

Isolation and spectroscopic data of products 19–33

***N*-Cyclohexylnicotinamide 19.** *General method.* Tertiary benzamide **1** (0.5 mmol) was dissolved in a 0.2 mol dm^{-3} water–methanol (80 : 20) sulfuric acid solution (500 cm^3). The resulting solution was stirred at 25 °C until the reaction was complete, and then adjusted to pH 7 by addition of an aqueous solution of potassium carbonate (5 mol dm^{-3}). The reaction mixture was concentrated to 200 cm^3, under reduced pressure, at 40 °C, and extracted with dichloromethane (100 cm^3). The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure at 40 °C. Flash chromatography on silica gel with toluene–acetone (90 : 10) as the eluent afforded compound **19** (97 mg, 95%), mp 140–142 °C, as a white solid.

Spectroscopic data for product **19** have been reported earlier.[11]

***N*-Cyclohexylisonicotinamide 20.** White solid, mp 133–135 °C (Found: C, 69.90; H, 7.76; N, 13.34. $C_{12}H_{16}N_2O$ requires C, 70.59; H, 7.84; N, 13.72%); δ_H (300 MHz; $CDCl_3$) 1.00 to 2.00 (10H, m, CH_2, cyclohexyl), 3.95 (1H, m, 1-H, cyclohexyl), 6.55 (1H, d, *J* 6, NH, D_2O exchanged), 7.60 (2H, dd, *J* 6 and 1, 3-H and 5-H), 8.65 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 24.8, 25.3 and 32.9 (CH_2, cyclohexyl), 49.0 (C-1, cyclohexyl), 120.9 (C-3 and C-5), 142.1 (C-4), 150.3 (C-2 and C-6), 164.6 (CO, amide); *m*/*z* 205 (MH^+).

***N*-Cyclohexylpicolinamide 21.** White solid, mp 51–53 °C (Found: C, 70.45; H, 7.84; N, 13.69. $C_{12}H_{16}N_2O$ requires C, 70.59; H, 7.84; N, 13.72%); δ_H (300 MHz; $CDCl_3$) 1.10 to 2.00 (10H, m, CH_2, cyclohexyl), 3.95 (1H, m, 1-H, cyclohexyl), 7.40 (1H, m, *J* 5 and 8, 5-H), 7.80 (1H, m, *J* 8 and 2, 4-H), 7.95 (1H, d, *J* 6, NH, D_2O exchanged), 8.20 (1H, d, *J* 8, 3-H), 8.55 (1H, dd, *J* 5 and 2, 6-H); δ_C (75 MHz; $CDCl_3$) 24.8, 25.5 and 33.0 (CH_2, cyclohexyl), 48.0 (C-1, cyclohexyl), 122.1 and 125.9 (C-3 and C-5), 137.2 (C-4), 147.8 (C-6), 150.1 (C-2), 163.1 (CO, amide); *m*/*z* 205 (MH^+).

***N*-Cyclohexyl-3-methoxypicolinamide 22.** White solid, mp 88–90 °C. Spectroscopic data for product **22** have been previously reported.[11]

***N*-Cyclohexyl-5-methoxycarbonylpicolinamide 23.** White solid, mp 119–121 °C (Found: C, 64.19; H, 6.97; N, 10.55. $C_{14}H_{18}N_2O_3$ requires C, 64.12; H, 6.87; N, 10.69%); δ_H (300 MHz; $CDCl_3$) 1.10 to 2.10 (10H, m, CH_2, cyclohexyl), 3.95 (1H, m, 1-H, cyclohexyl), 4.00 (3H, s, Me, CO_2Me), 7.95 (1H, d, *J* 6, NH, D_2O exchanged), 8.25 (1H, d, *J* 8, 3-H), 8.40 (1H, dd, *J* 8 and 2, 4-H), 9.10 (1H, d, *J* 2, 6-H); δ_C (75 MHz; $CDCl_3$) 24.7, 25.4 and 32.8 (CH_2, cyclohexyl), 48.3 (C-1, cyclohexyl), 52.5 (Me, CO_2Me), 121.7 (C-3), 127.7 (C-5), 138.4 (C-4), 149.1 (C-6), 153.1 (C-2), 162.2 (CO, amide), 165.1 (CO, ester); *m*/*z* 263 (MH^+).

***N*-Cyclohexyl-5-*n*-butylpicolinamide 24.** White solid, mp 54–56 °C; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 6, Me, *n*-butyl), 1.10 to 2.00 (10H, m, CH_2, cyclohexyl), 1.30 (2H, m, J 6, $CH_2\gamma$, *n*-butyl), 1.60 (2H, m, *J* 6, $CH_2\beta$, *n*-butyl), 2.65 (2H, t, *J* 6, $CH_2\alpha$, *n*-butyl), 3.95 (1H, m, 1-H, cyclohexyl), 7.60 (1H, dd, *J* 8 and 2, 4-H), 7.90 (1H, d, *J* 8, NH, D_2O exchanged), 8.10 (1H, d, *J* 8, 3-H), 8.30 (1H, d, *J* 2, 6-H); δ_C (75 MHz; $CDCl_3$) 13.7 (Me, *n*-butyl), 22.0 ($CH_2\gamma$, *n*-butyl), 24.8, 25.5 and 33.0 (CH_2,

cyclohexyl), 32.5 and 33.0 ($CH_2\beta$ and $CH_2\alpha$, *n*-butyl), 47.9 (C-1, cyclohexyl), 121.8 (C-3), 136.8 (C-4), 140.7 (C-5), 147.9 (C-2), 148.0 (C-6), 163.3 (CO, amide); *m*/*z* 261 (MH^+).

3-Cyclohexylcarbamoyl-1-methylpyridinium iodide 25. Yellow oil; δ_H (300 MHz; $CDCl_3$) 1.20 to 2.00 (10H, m, CH_2, cyclohexyl), 3.95 (1H, m, 1-H, cyclohexyl), 4.65 (3H, s, NMe), 8.15 (1H, m, *J* 6 and 8, 5-H), 8.25 (1H, d, *J* 8, NH, D_2O exchanged), 9.00 (1H, d, *J* 8, 4-H), 9.25 (1H, d, *J* 6, 6-H), 9.85 (1H, s, 2-H); δ_C (75 MHz; $CDCl_3$) 25.1, 25.2, and 32.5 (CH_2, cyclohexyl), 49.4 (C-1, cyclohexyl), 50.5 (NMe), 127.9 (C-5), 134.6 (C-3), 144.5, 145.0 and 146.4 (C-2, C-4 and C-6), 160.3 (CO, amide).

4-Cyclohexylcarbamoyl-1-methylpyridinium iodide 26. Yellow oil; δ_H (300 MHz; CD_3OD) 1.30 to 2.10 (10H, m, CH_2, cyclohexyl), 4.00 (1H, m, 1-H, cyclohexyl), 4.60 (3H, s, NMe), 8.50 (2H, d, *J* 6, 3-H and 5-H), 9.20 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; CD_3OD) 26.2, 26.5, and 33.4 (CH_2, cyclohexyl), 49.4 (NMe), 51.3 (C-1, cyclohexyl), 127.0 (C-3 and C-5), 147.7 (C-2 and C-6), 150.5 (C-4), 163.3 (CO, amide).

***N*-Cyclohexylbenzamide 27.** White solid, mp 152–154 °C (Found: C, 76.41; H, 8.39; N, 6.78. $C_{13}H_{17}NO$ requires C, 76.85; H, 8.37; N, 6.90%); δ_H (300 MHz; $CDCl_3$) 1.10 to 2.10 (10H, m, CH_2, cyclohexyl), 3.95 (1H, m, 1-H, cyclohexyl), 6.20 (1H, d, *J* 8, NH, D_2O exchanged), 7.40 and 7.75 (5H, m, aromatic); δ_C (75 MHz; $CDCl_3$) 24.9, 25.5, and 33.1 (CH_2, cyclohexyl), 48.6 (C-1, cyclohexyl), 126.8, 128.4 and 131.1 (*C*H, aromatic), 135.0 (C-1), 166.6 (CO, amide); *m*/*z* 204 (MH^+).

***N*-Cyclohexyl-4-chlorobenzamide 28.** White solid, mp 190–191 °C; δ_H (300 MHz; $CDCl_3$) 1.10 to 2.00 (10H, m, CH_2, cyclohexyl), 3.95 (1H, m, 1-H, cyclohexyl), 6.20 (1H, d, *J* 8, NH, D_2O exchanged), 7.35 (2H, d, *J* 6, 3-H and 5-H), 7.70 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 24.9, 25.4 and 33.1 (CH_2, cyclohexyl), 48.8 (C-1, cyclohexyl), 128.3 and 128.6 (*C*H, aromatic), 133.3 (C-4), 137.3 (C-1), 165.5 (CO, amide); *m*/*z* 238 (MH^+).

***N*-Cyclohexyl-4-methoxycarbonylbenzamide 29.** White solid, mp 62–64 °C (Found: C, 68.92; H, 7.35; N, 5.30. $C_{15}H_{19}NO_3$ requires C, 68.96; H, 7.28; N, 5.36%); δ_C (300 MHz; $CDCl_3$) 1.10 to 2.00 (10H, m, CH_2, cyclohexyl), 3.95 (4H, m, 1-H, cyclohexyl and Me, CO_2Me), 6.30 (1H, d, *J* 8, NH, D_2O exchanged), 7.80 (2H, d, *J* 6, 2-H and 6-H), 8.05 (2H, d, *J* 6, 3-H and 5-H); δ_C (75 MHz; $CDCl_3$) 24.8, 25.4 and 33.0 (CH_2, cyclohexyl), 48.9 (C-1, cyclohexyl), 52.3 (Me, CO_2Me), 126.9 (C-2 and C-6), 129.6 (C-3 and C-5), 132.3 (C-4), 139.0 (C-1), 165.7 and 166.2 (CO, ester and CO, amide); *m*/*z* 262 (MH^+).

***N*-Cyclohexyl-4-nitrobenzamide 30.** White solid, mp 204–206 °C; δ_H [300 MHz; $(CD_3)_2SO$] 1.10 to 1.90 (10H, m, CH_2, cyclohexyl), 3.80 (1H, m, 1-H, cyclohexyl), 8.05 (2H, d, *J* 8, 2-H and 6-H), 8.30 (2H, d, *J* 8, 3-H and 5-H), 8.55 (1H, d, *J* 8, NH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 26.0, 26.3 and 33.3 (CH_2, cyclohexyl), 49.8 (C-1, cyclohexyl), 124.4 (C-3 and C-5), 129.8 (C-2 and C-6), 141.6 (C-1), 149.9 (C-4), 164.8 (CO, amide); *m*/*z* 249 (MH^+).

***N*-Cyclohexyl-4-*n*-butylbenzamide 31.** White solid, mp 146–148 °C; δ_H (300 MHz; $CDCl_3$) 1.10 to 2.00 (10H, m, CH_2, cyclohexyl), 0.90 (3H, t, *J* 6, Me, *n*-butyl), 1.30 (2H, m, *J* 6, $CH_2\gamma$, *n*-butyl), 1.60 (2H, m, *J* 6, $CH_2\beta$, *n*-butyl), 2.65 (2H, t, *J* 6, $CH_2\alpha$, *n*-butyl), 3.95 (1H, m, 1-H, cyclohexyl), 6.10 (1H, d, *J* 8, NH, D_2O exchanged), 7.20 (2H, d, *J* 6, 3-H and 5-H), 7.65 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 13.8 (Me, *n*-butyl), 22.2 (CH_2^{γ}, *n*-butyl), 24.9, 25.5 and 33.1 (CH_2, cyclohexyl), 33.3 and 35.4 ($CH_2\beta$ and $CH_2\alpha$, *n*-butyl), 48.5 (C-1, cyclohexyl), 126.8 and 128.4 (*C*H, aromatic), 132.3 (C-1), 146.4 (C-4), 166.5 (CO, amide); *m*/*z* 260 (MH^+).

***N*-Cyclohexyl-4-methoxybenzamide 32.** White solid, mp 158–160 °C (Found: C, 72.41; H, 8.06; N, 6.02. $C_{14}H_{19}NO_2$ requires C, 72.10; H, 8.15; N, 6.00%); δ_H (300 MHz; $CDCl_3$) 1.10 to 2.00 (10H, m, CH_2, cyclohexyl), 3.75 (3H, s, OMe), 3.95 (1H, m, 1-H, cyclohexyl), 6.00 (1H, d, *J* 8, NH, D_2O exchanged), 6.80 (2H, d, *J* 6, 3-H and 5-H), 7.65 (2H, d, *J* 6, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 24.9, 25.5 and 33.2 (CH_2, cyclohexyl), 48.5 (C-1, cyclohexyl), 55.3 (OMe), 113.5 (C-3 and C-5), 127.2 (C-1), 128.5 (C-2 and C-6), 161.8 (C-4), 166.0 (CO, amide); *m*/*z* 234 (MH^+).

***N*-Cyclohexyl-2-hydroxybenzamide 33.** White solid, mp 78–80 °C; δ_H (300 MHz; $CDCl_3$) 1.10 to 2.00 (10H, m, CH_2, cyclohexyl), 3.95 (1H, m, 1-H, cyclohexyl), 6.35 (1H, d, *J* 8, NH, D_2O exchanged), 6.80, 6.95 and 7.35 (4H, aromatic), 12.5 (s, 1H, OH, D_2O exchanged); δ_C (75 MHz; $CDCl_3$) 24.8, 25.3 and 32.8 (CH_2, cyclohexyl), 48.6 (C-1, cyclohexyl), 114.4 (C-1), 118.3, 118.5, 125.4 and 133.9 (*C*H, aromatic), 161.4 (C-2), 169.0 (CO, amide); *m*/*z* 220 (MH^+).

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