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Chemistry of aryl *N*-(2-pyridyl) thionocarbamates in basic media†

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Three aryl *N*-pyridylthionocarbamates were synthesized by thioacylation of 2-aminopyridine and 2-methylaminopyridine with the respective chlorothionoformates. Their hydrolysis mechanism was studied in aqueous basic media. The aryl *N*-(2-pyridyl)thionocarbamates are considerably less reactive than their oxo analogues, the aryl *N*-(2-pyridyl) carbamates, especially the *N*-monosubstituted ones (1a-b). Absence of significant buffer catalysis, isolation of the product resulting from trapping of the unsaturated intermediate with piperidine and the entropy of activation observed for the hydrolysis of compound 1b clearly indicate an E1cB mechanism for the *N*-monosubstituted aryl *N*-(2-pyridyl)thionocarbamates. The experimental data suggest that the *N*,*N*-disubstituted substrate (2) undergoes basic hydrolysis by a general base catalysed $B_{AC}2$ mechanism. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: thionocarbamates; heterocycles; pyridyl group; kinetics; reaction mechanisms

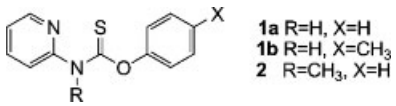
INTRODUCTION

The thionocarbamates are a class of compounds widely used as herbicides and fungicides of which Tolnaftate and Pyributicarb are two well-known examples. One important parameter in the evaluation of new thionocarbamates as biological agents is their reactivity in aqueous media and therefore the study of their kinetic behaviour is considerably interesting.

There are several examples of secondary (i.e. *N*-monosubstituted) carbamates that hydrolyse in basic media by an elimination mechanism known as E1cB, depending on structural properties such as the existence of an acidic α proton and a reasonable good leaving group.[1–4] A significant number of thionocarbamates is known to react similarly.[5–13] The E1cB mechanism is characterized by a pre-equilibrium deprotonation followed by an unimolecular rate determining step involving the formation of an unsaturated intermediate, an isocyanate for carbamates or an isothiocyanate for thionocarbamates. This intermediate is sometimes too labile to be detected directly but can be trapped through reaction with an amine.[1–7,13]

The activation parameters, namely the entropy of activation, are useful criteria to determine whether a compound reacts by a bimolecular process like the base-catalysed addition–elimination mechanism known as $B_{AC}2$ or by an unimolecular mechanism such as the E1cB. Blocking the E1cB mechanism of carbamates by introduction of *N*,*N*-disubstitutions on the substrate is a also a definitive argument in this type of discussion, since the comparison between the pH-rate profiles of both substrates, in which one is incapable of forming the conjugated anion and is a model for a $B_{AC}2$ mechanism, provides a good insight into both types of mechanistic behaviour.[1–9] Oh *et al.*[14,15] have studied the aminolysis of several secondary thionocarbamates in acetonitrile and concluded that they react by an addition–elimination mechanistic pathway.

Although there are many studies concerning the reaction mechanisms of carbamates in aqueous media, there have been very few attempts made to compare the effect of substitution of the carbonyl by a thiocarbonyl on the reactivity of this type of compounds.[8–11] With this purpose it was decided to study the reactivity of secondary aryl *N*-(2-pyridyl)thionocarbamates in order to compare them with their oxo analogues, the aryl *N*-(2-pyridyl)carbamates previously investigated in the identical reaction media.[16] This paper presents the synthesis of thionocarbamates, whose bioactivity against non-tuberculous mycobacteria was already published,[17] as well as unreported kinetic studies and the evaluation of the mechanism of hydrolysis of aryl *N*-(2-pyridyl)thionocarbamates (**1a**-**b**, **2**) over the pH range 12–13.8.



1a R=H, X=H
1b R=H, X=CH_3
2 R=CH_3, X=H

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RESULTS AND DISCUSSION

The influence of the concentration of hydroxide ion on the reaction rate was studied ranging between 0.01 and 0.5 mol·dm^{-3} for secondary thionocarbamates and between 0.1 and 0.8 mol·dm^{-3} for phenyl *N*-methyl-*N*-(2-pyridyl) thionocarbamate, using UV–Vis spectrophotometric techniques to determine the kinetic pseudo first-order rate constants, k_{obs} (Table 1). The rate of hydrolysis for compounds **1a** and **1b** is linearly proportional to [HO$^-$] being the uncatalysed hydrolysis reaction negligible as indicated in Eqn (1) (Fig. 1).

$$k_{obs} = k_{HO^-}[HO^-] \quad (1)$$

The comparison of the basic reactivity of compounds **1a** and **1b** with the one of secondary aryl *N*-(2-pyridyl)carbamates reveals that the thionocarbamates are less reactive to hydrolysis in basic media (*ca.* 5×10^3 times),[16] unlike data reported on earlier studies in which aryl *N*-(4-nitrophenyl)thionocarbamates were *ca.* 10^2 times more reactive than their oxo analogues due to the enhanced acidic character of N–H in thionocarbamates.[10,11] The secondary aryl *N*-(2-pyridyl)thionocarbamates do not present a levelling off region in their pH-rate profiles. This is unlike their oxo analogues which clearly possess such region as a consequence of a pre-equilibrium deprotonation of the nitrogen atom with the formation of an anion, typical of an E1cB mechanism.[16] The absence of such levelling off region in the pH-rate profile is not necessarily evidence that compounds **1a** and **1b** do not react by an E1cB mechanism, but only that their pK_a is higher than 14 and consequently the substrate is never completely deprotonated in aqueous solution. Although previous results indicate a considerable increase in the acidity of secondary thionocarbamates up to 3 U of pK_a compared to their oxo analogues,[10,11] this was not observed since the pK_a values of secondary aryl *N*-(2-pyridyl)carbamates are around 13.[16] This result differs considerably from the one obtained by Sartoré *et al.*[9] for phenyl *N*-phenylthionocarbamate, whose pK_a is 9.04 while the analogous phenyl *N*-phenylcarbamate studied by Hegarty *et al.* presents a value superior to 14 in aqueous media in similar conditions.[11]

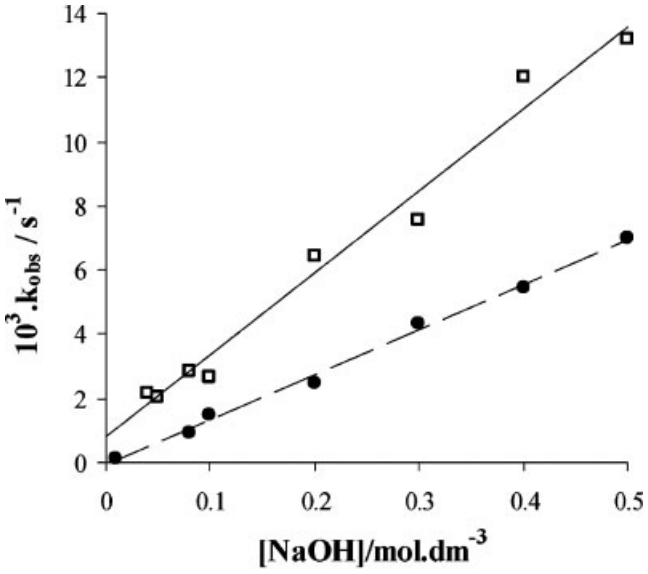


Figure 1. Effect of NaOH concentration on the rate of reaction of compounds **1a** and **1b** followed by UV–Vis spectroscopy (15% 1,4-dioxane/water (v/v), $\mu = 0.5$ mol·dm^{-3} ($NaClO_4$), at a temperature of 27.0 °C)

There is no apparent explanation for the reduced acidic character of the α proton in secondary *N*-(2-pyridyl) thionocarbamates, since the pyridine ring and thiocarbonyl adjacent to the N–H are both two powerful electron-withdrawing groups and should contribute to promote the substrate acidity.

To confirm the data obtained by UV–Vis spectrophotometric techniques HPLC kinetic studies were performed with compound **1b** because the UV–Vis spectra showed some interference. The

Table 1. Values of k_{obs} for the hydrolysis of compounds **1a-b** and **2**[a]

[NaOH] (mol·dm^{-3})	$10^3 \cdot k_{obs}$ (s^{-1}) **1a**	$10^3 \cdot k_{obs}$ (s^{-1}) **1b**	$10^5 \cdot k_{obs}$ (s^{-1}) **2**
0.01	—	0.15	—
0.04	2.19	—	—
0.05	2.04	—	—
0.08	2.85	0.93	—
0.1	2.67	1.46	0.43
0.2	6.47	2.50	0.86
0.3	7.57	4.33	1.40
0.4	12.0	5.46	1.84
0.5	13.2	6.98	2.23
0.6	—	—	2.63
0.7	—	—	3.05
0.8	—	—	3.42

[a]Solvent 15% 1,4-dioxane/water (v/v), with $\mu = 0.5$ mol·dm^{-3} ($NaClO_4$) for **1a** and **1b**, $\mu = 1.0$ mol·dm^{-3} ($NaClO_4$) for **2**, 27.0 °C.

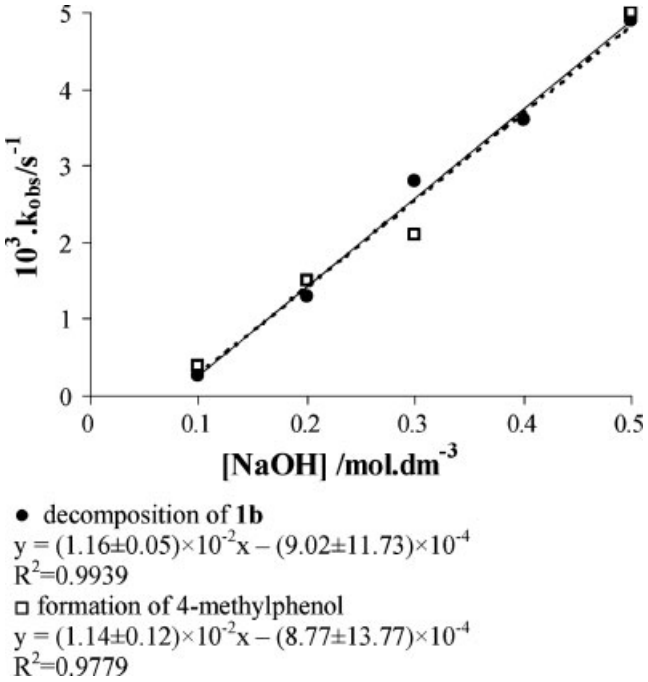


Figure 2. Effect of NaOH concentration on the rate of reaction for the decomposition of compound **1b** and the formation of 4-methylphenol followed by HPLC (15% 1,4-dioxane/water (v/v), $\mu = 0.5$ mol·dm^{-3} ($NaClO_4$), at a temperature of 27.0 °C)

hydrolysis products of **1b** were identified as being 4-methylphenol and 2-aminopyridine, and it was possible to verify that for every kinetic experiment the rate of decomposition of **1b** presents the same value as the rate of formation of 4-methylphenol (Fig. 2) confirming the existence of a reactive intermediate formed throughout the overall reaction.

The value obtained for k_{HO^-} by HPLC (1.16×10^{-3} dm^3·mol^{-1}·s^{-1}) is slightly lower than the one determined by UV–Vis spectrophotometry (1.40×10^{-3} dm^3·mol^{-1}·s^{-1}), due to experimental conditions, namely the fact that in HPLC studies the number of experimental points for each kinetic run was considerably smaller, which contributes for a greater error associated with each calculated value of k_{obs} in comparison with the ones obtained by UV–Vis techniques. The HPLC studies were also quite useful to rule out the possibility of a rearrangement of **1b** into the corresponding thiolocarbamate during the hydrolysis of the substrate in basic media, since it was not observed the peak corresponding to the formation of 4-methylthiophenol throughout the kinetic runs; such rearrangement was reported by Mindl *et al.*[12] for the hydrolysis of benzidryl *N*-phenylthionocarbamate.

Another parameter evaluated was the effect of buffer concentration on the reaction rate. The hydrolysis of **1a** was studied in several oxygen and nitrogen bases (including piperidine, *n*-butylamine, 2,2,2-trifluoroethanol), although due to spectroscopic problems, it was only possible to obtain reliable results using *tert*-butylamine buffer (pH 11.1), for which no significantly buffer effect was observed (Table 2; Fig. 3). Although there is a slight variation of k_{obs} values with the free base concentration, this clearly to small to be ascribed to buffer catalysis since there is a very poor correlation ($R^2 = 0.4624$) and the slope presents a considerably low value with quite a large error $(1.33 \pm 1.02) \times 10^{-3}$ compared to the k_{HO^-} of compound **1a**

Table 2. Hydrolysis of compound **1a** in *tert*-butylamine buffer solutions of pH 11.1[a]

10^2·[*tert*-butylamine]$_{free}$ (mol·dm^{-3})	10^4·k_{obs} (s^{-1})
6.58	1.17
5.26	1.41
4.61	0.92
3.29	0.81

[a] Solvent 15% 1,4-dioxane/water (v/v), with $\mu = 0.5$ mol·dm^{-3} ($NaClO_4$), 27.0 °C.

[$(2.56 \pm 0.15) \times 10^{-2}$], which suggests that small variations of pH in the successive dilutions of the buffer may be the probable cause of the decrease of k_{obs}.

The absence of buffer catalysis is in accordance with a rate determining unimolecular breakdown of an anionic intermediate formed in a pre-equilibrium step.[8] The decomposition of the anion is not dependent upon concentration of the buffer and an E1cB mechanism exhibits only specific base-catalysis.

The temperature effect was studied for the hydrolysis of compound **1b** in sodium hydroxide solutions, with concentrations ranging from 0.05 to 0.4 mol·dm^{-3} (Table 3) and the respective values of k_{HO^-} were calculated with Eqn (1) for each temperature (Table 4).

The activation parameters for the reactions proceeding via E1cB mechanism must include also the pre-equilibrium constant for the formation of the conjugated anion with a negative charge in the nitrogen (K_a).

The reason of such procedure can be explained by analysing the kinetic equation for an E1cB mechanism (Eqn 2):[16]

$$k_{obs} = \frac{k_1 \times K_a \times [HO^-]}{K_a \times [HO^-] + K_W} \quad (2)$$

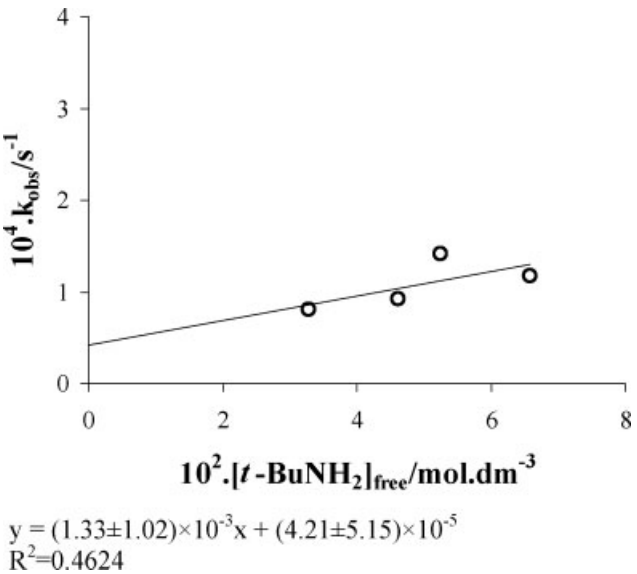


Figure 3. Hydrolysis of compound **1a** in *tert*-butylamine buffer solutions of pH 11.1 buffer in 15% 1,4-dioxane/water (v/v), with $\mu = 0.5$ mol·dm^{-3} ($NaClO_4$), at a temperature of 27.0 °C

Table 3. Values of k_{obs} for the hydrolysis of compound **1b** at different values of temperature[a] (the data for the temperature of 27.0 °C are displayed in Table 1)

[NaOH] (mol·dm^{-3})	$10^3 \cdot k_{obs}$ (s^{-1}) 20.0 °C	$10^3 \cdot k_{obs}$ (s^{-1}) 25.0 °C	$10^3 \cdot k_{obs}$ (s^{-1}) 30.0 °C	$10^3 \cdot k_{obs}$ (s^{-1}) 35.0 °C
0.05	—	—	—	1.23
0.08	—	—	—	2.15
0.1	0.62	1.11	1.74	2.93
0.2	1.29	2.17	3.72	5.84
0.3	2.02	3.49	5.71	—
0.4	2.41	4.27	7.02	—

[a] Solvent 15% 1,4-dioxane/water (v/v), with $\mu = 0.5$ mol·dm^{-3} ($NaClO_4$), 27.0 °C.

Table 4. Values of k_{HO^-} for the hydrolysis of compound **1b** at different values of temperature (with the correspondent values of R^2 for each correlation)

Temperature (°C)	$10^2 \cdot k_{HO^-}$ (dm^3·mol^{-1}·s^{-1})
20.0	0.61 ($R^2 = 0.9855$)
25.0	1.08 ($R^2 = 0.9912$)
27.0	1.40 ($R^2 = 0.9964$)
30.0	1.78 ($R^2 = 0.9915$)
35.0	3.06 ($R^2 = 0.9983$)

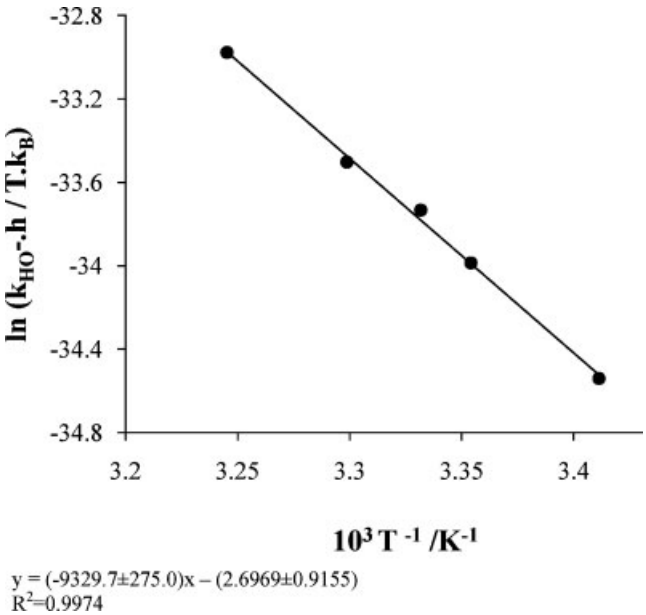


Figure 4. Eyring plot for compound **1b**

Being k_1 the kinetic constant of the rate determining step, K_a the thermodynamic acidity constant of the substrate and K_W the auto-protolysis constant for water.

In order to consider both the effect of k_1 and K_a in the calculation of activation parameters it was decided to correlate $\ln(k_{HO^-})$ with T^{-1} instead of $\ln(k_{obs})$ with T^{-1}.This procedure is valid and it can be to demonstrated by considering that the K_a of secondary *N*-(2-pyridyl)thionocarbamates is smaller than 10^{-14} and therefore assuming $K_W >> K_a \cdot [HO-]$, so when considering both Eqns (1) and (2) it is possible to admit without considerable error that

$$k_{HO^-} = \frac{k_1 \times K_a}{K_W}$$

Data adjustment to Eyring equation (Eqn 3) gives rise to a satisfactory correlation (Fig. 4) from which were determined the values for $\Delta H^{\ddagger} = 77.6$ kJ·mol^{-1} and for $\Delta S^{\ddagger} = -22$ J·mol^{-1}·K^{-1}.

$$\ln\left(\frac{^{k}HO- \times h}{k_B \times T}\right) = -\frac{\Delta H^{\ddagger}}{R} \times \frac{1}{T} + \frac{\Delta S^{\ddagger}}{R} \qquad (3)$$

The value for the entropy of activation obtained is acceptable for a unimolecular mechanism. The typical values for a $B_{AC}2$ value mechanistic pathway usually assume values between −80 and −150 J·mol^{-1}·K^{-1}, while for an E1cB mechanism it is expected a small and generally positive value for $\Delta S^{\ddagger}$.[18] The negative value for $\Delta S^{\ddagger}$ in this case can easily be explained by the solvent interactions, due to the presence of a considerable amount of 1,4-dioxane as co-solvent, whose molecules present a rearrangement in solution during the transition state, causing a decrease in the entropy of the system. This situation is not surprising, since Alborz and Douglas obtained a value for $\Delta S^{\ddagger} = -41$ J·mol^{-1}·K^{-1} for an E1cB mechanistic pathway.[19]

Another evidence of an E1cB mechanism comes from the detection of 2-pyridyl isothiocyanate as a reaction intermediate, which was trapped during hydrolysis of compound **1b** in piperidine buffer (pH 12.0), forming *N*-piperidyl-*N*′-(2-pyridyl)thiourea (**3**), whose presence was confirmed by mass spectrometry. Since the isothiocyanate is originated necessarily *via* an elimination mechanism, the presence of its derivative indicates an E1cB mechanistic pathway. The reason why piperidine was used as a trapping amine instead of *tert*-butylamine (pK_a 10.68), for which absence of buffer catalysis was verified, it is because *tert*-butylamine is too sterically hindered to provide an efficient trapping agent for 2-pyridyl isothiocyanate, while piperidine, a secondary amine with a close pK_a (11.12), is more suitable for that purpose. The possibility of aminolysis of the substrate by piperidine with formation of *N*-piperidyl-*N*′-(2-pyridyl)thiourea is quite unlikely since the E1cB mechanism is known to be quite faster than the addition–elimination mechanism and the formation of a thiourea by an

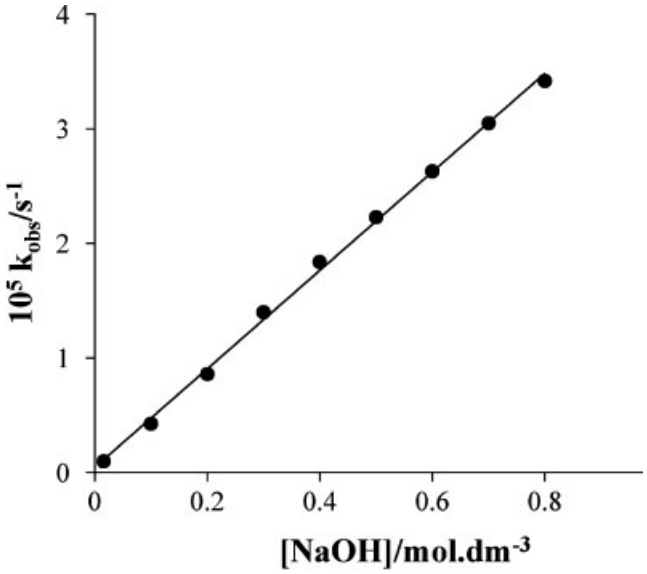
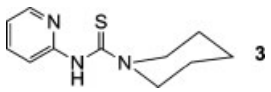


Figure 5. Effect of NaOH concentration on the rate of reaction for compound **2** (including the point obtained by graphical extrapolation for hydrolysis in piperidine buffer pH 12.2) in 15% 1,4-dioxane/water (v/v), with $\mu = 1.0\ mol{\cdot}dm^{-3}$ ($NaClO_4$), at a temperature of 27.0 °C

addition–elimination mechanism would require necessarily nucleophilic catalysis, which is difficult due to the retarding effect of thiocarbonyl group in the elimination of the leaving group (aryloxide ion) as will be later seen for compound **2**, so E1cB mechanism followed by amine trapping of isothiocyanate is definitely the pathway for the formation of compound **3**.



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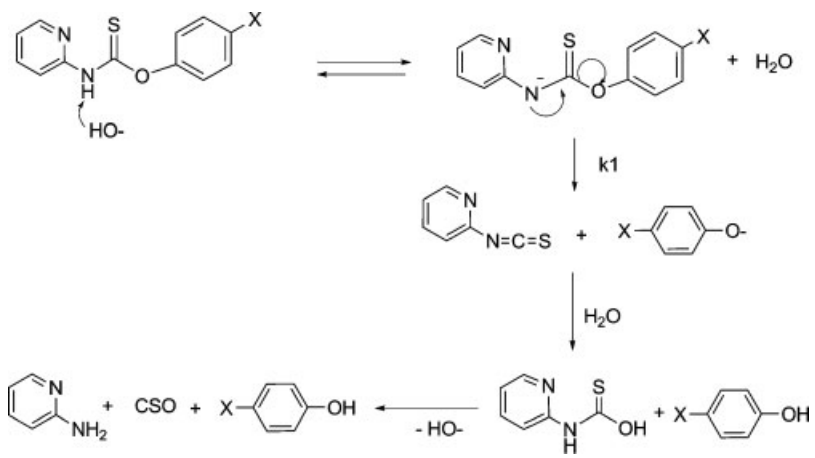
An additional evidence of an E1cB mechanism for secondary thionocarbamates comes from the comparison of the plot of k_{obs} versus hydroxide ion concentration of **1a** with the one of its *N*-methyl analogue **2**.

Hydrolysis of compound **2** in sodium hydroxide solutions gives rise to phenol and *N*-methylaminopyridine and showed also a first order dependence on the concentration of hydroxide ion (Fig. 5).

The second order rate constant (k_{HO^-}) of $4.30 \times 10^{-5}\ dm^3{\cdot}mol^{-1}{\cdot}s^{-1}$ indicates a reactivity difference of *ca.* 6×10^2 compared with the one obtained for the compound **1a**. In this case ionization is blocked converting the compound **2** into a good model of a $B_{AC}2$ mechanism, which is known to occur with much smaller reaction rates, providing a decisive argument that a faster E1cB mechanism occurs for compounds **1a** and **1b**. Based on these results we propose an E1cB mechanism for the hydrolysis of secondary aryl *N*-(2-pyridyl)thionocarbamates (Scheme 1).

The lower reactivity of secondary aryl *N*-(2- pyridyl) thionocarbamates relatively to their oxo analogues can be interpreted by considering several factors. The most relevant is the nature of the thiocarbonyl bond, which presents a remarkably more dipolar character relatively to the carbonyl bond due to the anti-bonding interactions causing a less efficient 2p–3p π-overlap in C = S compared to the 2p–2p in C = O.[5,7] The more dipolar character of thiocarbonyl contributes to retard the splitting of the aryloxide ion in the rate-determining step for an E1cB mechanism,[12] since the thiocarbonyl is a powerful electro-n-withdrawing group which can accept electrons in the sulphur atom and stabilize the anion,[13] but this will also increase the K_a of a secondary thionocarbamate relatively to its oxo analogue, so an electron-withdrawing group generally increases the product $K_a \times k_1$ and accelerates the reaction rate (*vide* Eqn 2), because the transition state in the rate-determining step bears a negative charge. So the overall effect of a thiocarbonyl group on a substrate undergoing hydrolysis by an E1cB mechanism is of a rather complex interpretation, since it can cause either an increase or a decrease in the reactivity of a substrate depending on how affects the magnitude of both k_1 and K_a. Since the aryl *N*-(2-pyridyl)thionocarbamates are considerably less acidic than the corresponding aryl *N*-(2-pyridyl)carbamates, this means that k_1 and K_a are both smaller for the secondary aryl *N*-(2-pyridyl) thionocarbamates compared to their oxo analogues, thus explaining their reduced reactivity.

On the other hand, the reactivity of *N*,*N*-disubstituted compound **2** in sodium hydroxide solutions is *ca.* 10 times smaller than phenyl *N*-methyl-*N*-(2-pyridyl)carbamate.[16] These



Scheme 1. Mechanism of hydrolysis of secondary aryl *N*-(2-pyridyl)thionocarbamates

results are analogous to the ones obtained for the hydrolysis of 4-nitrophenyl thionobenzoate and its oxo analogue in sodium hydroxide solutions, being the thionoester eight times less reactive than its analogous ester.[20] The fact that the thiocarbonyl carbon is a softer Lewis acid than its carbonylic analogue, while hydroxide ion is a hard base provides an explanation for this, since according to Pearson's Hard Soft Acid Base (HSAB) principle, a soft acid will react preferentially (thermodynamically and kinetically) with a soft base, while a hard acid will react preferentially with a hard base.[18]

The values of k_{obs} for the hydrolysis of compound **2** are linearly proportional to increasing buffer concentration according to equation 4, where k_{Buffer} is the second-order rate constant for the catalytic process in presence of buffers.

$$k_{obs} = k_{HO^-}[HO^-] + k_{Buffer}[x] \quad (4)$$

Possibility of buffer catalysis was investigated, using piperidine as buffer both in H_2O and D_2O (Table 5; Fig. 6).

The buffer independent rate of hydrolysis for piperidine in protiated solvent ($k_{HO^-}[HO^-]$) was obtained by extrapolation of the observed rate constant to zero buffer concentration in protiated solvent and found to correlate with the values of k_{obs} obtained for the of the plot of k_{obs} versus hydroxide ion concentration (Fig. 5).

The solvent isotope effect can be quantified by the ratio $k_{Pip(H_2O)}/k_{Pip(D_2O)}$, which measures the catalytic efficiency of the buffer in protiated and deuterated media. The ratio $k_{Pip(H_2O)}/k_{Pip(D_2O)} = 2.37$ indicates a proton transfer process in the rate determining step of the reaction, implying a general base-catalysed process, that is an indirect attack to the substrate by the base involving the solvent in the rate-determining step.[18]

The other alternative mechanism possible for the basic hydrolysis of compound **2** would be nucleophilic catalysis, that is a direct attack to the substrate by the base in the rate-determining step, which is kinetically distinguishable by the solvent isotope effect as observed in the hydrolysis of its oxo analogue, phenyl *N*-methyl-*N*-(2-pyridyl)carbamate, for which it was obtained a ratio for $k_{Pip(H_2O)}/k_{Pip(D_2O)} = 0.88$,[21] a value typical of a mechanism involving nucleophilic catalysis.

On the other hand, it is possible also to calculate also the values of k_{HO^-} and k_{DO^-} from graphical extrapolation for hydrolysis in piperidine buffer in protiated and deuterated media respectively, and applying Eqn (4) for null buffer concentration. In order to convert the values of pH and pD into $[HO^-]$ and $[DO^-]$, respectively, it is necessary to resort to Eqn (5):

$$pL + pOL = pK_w \quad (5)$$

Being $L = H$ and D for protiated and deuterated media, respectively. For H_2O the pK_w is 13.995 while for D_2O it presents

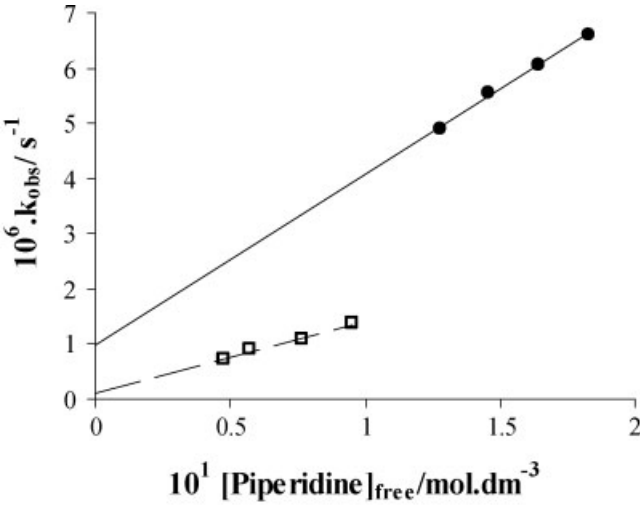


Figure 6. Isotope effect for the hydrolysis of compound **2** in piperidine buffer in 15% 1,4-dioxane/water (v/v), with $\mu = 1.0$ mol·dm^{-3} ($NaClO_4$), at a temperature of 27.0 °C

the value of 14.951 at 25 °C,[22] and these values can be used without too much error for 27 °C.

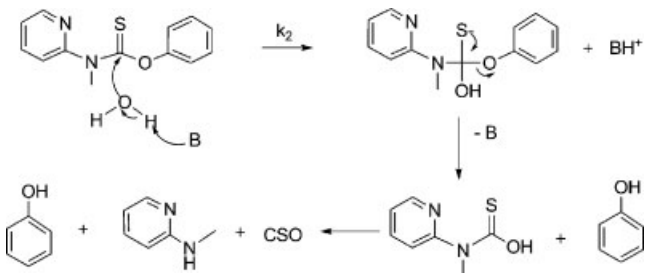
The value of k_{HO^-} determined this way is 6.18×10^{-5} dm^3·mol^{-1}·s^{-1}, which is a value quite higher than the one determined from the plot of k_{obs} versus hydroxide ion concentration of **2** (4.30×10^{-5} dm^3·mol^{-1}·s^{-1}), but the discrepancy is explainable since the associated error is quite larger for the value obtained by graphical extrapolation. The extrapolated value for k_{DO^-} is 4.31×10^{-5} dm^3·mol^{-1}·s^{-1}, and so the ratio $k_{HO^-}/k_{DO^-} = 1.43$. This value is acceptable for a general base catalysis because in the lyate ion (HO^- or DO^-) will attack directly the substrate independently of the type of catalysis, being the deuteroxide ion (pK_a 16.61) a stronger base than hydroxide (pK_a 15.74). On the other hand, there is a significant error associated with the determination of this ratio, and the validity of its interpretation is quite reduced.

The possibility of formation of a thiourea from the nucleophilic attack from piperidine to compound **2** is quite unlikely since whenever nucleophilic catalysis happens it is the predominant process, being this generally extremely faster than a general base

Table 5. Buffer catalysis for compound **2** in piperidine buffer in H_2O (pH 12.2) and in D_2O (pD 12.4)[a]

10^1·[piperidine]$_{free}$ (mol·dm^{-3}) (H_2O)	10^6·k_{obs} (s^{-1})	10^2·[piperidine]$_{free}$ (mol·dm^{-3}) (D_2O)	10^6·k_{obs} (s^{-1})
1.83	6.60	9.53	1.37
1.64	6.05	7.65	1.08
1.46	5.54	5.73	0.89
1.28	4.89	4.77	0.73

[a] Solvent 15% 1,4-dioxane/water (v/v), $\mu = 1.0$ mol·dm^{-3} ($NaClO_4$), 27.0 °C.



Scheme 2. Mechanism of hydrolysis of phenyl *N*-methyl-*N*-(2-pyridyl) thionocarbamate

catalysis process,[23] so if the experimental data points to general base catalysed mechanism the nucleophilic catalysis can be disregarded.

Another consistent parameter in favour of a general base catalysis is the absence of α effect for the hydrolysis of compound **2** in the presence of peroxymonocarbonate ion ($[HCO_4^-] = 2 \times 10^{-2}$ mol·dm^{-3} in carbonate buffer pH 9.0), since there was not observed any noticeable reaction in those conditions. The peroxymonocarbonate ion is generated from hydroperoxide solutions in carbonate buffer.[24,25] The pK_a of hydrogen peroxide is about 11.7 and at pH 9.0 the fraction of HO_2^- ion is too low to act as an effective catalyst. So in the presence of carbonate buffer the peroxymonocarbonate anion is formed (pK_a 10.6) and this particular species is highly nucleophilic. For a nucleophilic catalysis process an α nucleophile presents a considerably enhanced reactivity towards the substrate.[18] Phenyl *N*-methyl-*N*-(2-pyridyl)carbamate displays an increased reactivity in the presence of HCO_4^-, being this effect measured by the ratio of the catalytic constants of peroxymonocarbonate and hydroxide ions $k_{HCO_4^-}/k_{HO^-} = 243$.[21]

The kinetic parameters suggest a general base catalysed hydrolysis for compound **2**, in which the base assists the solvent in its attack on the carbamate carbon (Scheme 2). There are other examples of thionocarbamates undergoing hydrolysis with general base catalysis, such as the 1-(aryloxythiocarbonyl) pyridinium cations studied by Castro *et al.*[26] An explanation for the change of basic catalysis with the replacement of carbonyl by the thiocarbonyl group is that the more electrophilic carbon of thiocarbonyl group, when attacked by a nucleophile undergoes a considerably destabilized transition state for the expulsion of negatively charged phenoxide compared to a non-charged nucleophile (e.g. piperidine) expulsion. On the other hand, the stronger electron-withdrawing effect of thiocarbonyl will decrease the leaving group ability of phenoxide, thus hindering a nucleophilic attack by the catalyst. As an example, Neuvonen observed a similar change of base-catalysis for the aminolysis of 4-nitrophenyl acetates and trifluoroacetates, the latter hydrolysed via a general-base catalysed mechanistic pathway, since it possesses a much more electron-withdrawing acyl moiety.[27]

EXPERIMENTAL

Synthesis

Melting points were measured in a Stuart Scientific-melting point apparatus SMP3 and are uncorrected. IR spectra were obtained using a Hitachi 270–50 spectrophotometer on KBr pastille and only diagnostic bands are reported on a cm^{-1} scale. NMR spectra were recorded using a Bruker ARX-400 MHz spectrometer, in chloroform-*d* as solvent, and chemical shifts are reported in parts per million (ppm, d), using as reference the signal for TMS. Coupling constants are reported to the nearest 0.1 Hz. HREIMS were recorded in a Finnigan FT/MS 2001-DT. Column chromatography used silica-gel 60, 0.040–0.063 μm (Merck 9385). Thin layer chromatography (TLC) and preparative TLC (PTLC) were performed on pre-coated silica-gel 60 F254 (respectively Merck 5554 and Merck 5717). All solvents and reagents were obtained from Merck or Aldrich and used without further purification, except for acetone, which was dried with potassium carbonate for 24 h, prior to distillation.

General procedure for the preparation of pyridylthionocarbamates

To a suspension of 2-aminopyridine or 2-methylaminepyridine and potassium carbonate in dry acetone was added drop wise the corresponding aryl chlorothionoformate dissolved in acetone. The reaction was stirred for 30 min, then refluxed for 4 h, and worked up by adding water and dichloromethane; the organic layer was dried with magnesium sulphate and evaporated to dryness. The compounds were purified by column chromatography (*n*-hexane/ethyl acetate 8:2 for **1a**; *n*-hexane/dichloromethane 3:7 for **1b**; *n*-hexane/diethyl ether 1:1 for **2**) followed by recrystalization.

Phenyl N-(2-pyridyl)thionocarbamate (***1a***): (0.042 g; 2%); yellow crystals; mp 116–118 °C (from dichloromethane/*n*-hexane); IR ν_{max}(KBr)/cm^{-1}: 1591–1499, 1260; δ_H (400 MHz; $CDCl_3$; Me_4Si): 8.66 (1 H, dd, *J* 1.8, 4.5 Hz, H-6 *py*), 7.89 (1 H, dt, *J* 1.8, 7.8, H-4 *py*), 7.62 (1 H, d, *J* 8.0, H-3 *py*), 7.45 (2 H, m, C-3′, C-5′ *Ph*), 7.32 (2 H, m, CH aromatic), 7.26 (2 H, m, C-2′, C-6′ *Ph*); δ_C (100.4 MHz, $CDCl_3$; Me_4Si) 189.9 (C = S), 155.7 (C-2 *py*), 153.8 (C-1′*Ph*), 149.6 (C-6 *py*), 138.6 (C-4 *py*), 129.7 (C-3′, C-5′ *Ph*), 126.8 (C-4′ *Ph*), 123.7 (C-5 *py*), 123.5 (C-3 *py*), 121.8 (C-2′, C-6′ *Ph*); EI-MS 230 $[M^\bullet]^+$, 229, 197, 137, 136, 94, 78, 77; HREIMS: 230.050875 (230.0513885 $[M^\bullet]^+$ for $C_{12}H_{10}N_2OS$).

4-Methylphenyl N-(2-pyridyl)thionocarbamate (***1b***): (0.212 g; 8%); yellow crystals; mp 114–115 °C (dichloromethane/*n*-hexane); IR ν_{max}(KBr)/cm^{-1}: 1591–1499, 1260; δ_H (400 MHz, $CDCl_3$; Me_4Si): 8.61 (1 H, d, *J* 4.8 Hz, H-6 *py*), 7.85 (1 H, ddd, *J* 1.8, 7.5, 7.9 Hz, H-4 *py*), 7.57 (1 H, dd, *J* 0.6, 7.9 Hz, H-3 *py*), 7.34 (1 H, dd, *J* 4.8, 7.5 Hz, H-5 *py*), 7.21 (2 H, d, *J* 8.7 Hz, H-3′, H-5′ *Ph*), 7.09 (2 H, d, *J* 8.4 Hz, H-2′, H-6′ *Ph*), 2.35 (3 H, s, CH_3); δ_C (100.4 MHz, $CDCl_3$; Me_4Si) 190.2 (C = S), 155.8 (C-2 *py*), 151.7 (C-1′ *Ph*), 149.6 (C-6 *py*), 138.5 (C-4 *py*), 136.5 (C-4′ *Ph*), 130.2 (C-3′, C-5′ *Ph*), 123.6 (C-5 *py*), 123.5 (C-3 *py*), 121.4 (C-2′, C-6′ *Ph*), 21.0 (CH_3); EI-MS: 244 $[M^\bullet]^+$, 243, 211, 151, 137, 136, 123, 108, 91, 78; HREIMS: 244.067271 (244.067035 $[M^\bullet]^+$ for $C_{13}H_{12}N_2OS$).

Phenyl N-methyl-N-(2-pyridyl)thionocarbamate (***2***): (3.39 g; 75%); white crystals; mp 96–97 °C (dichloromethane/*n*-hexane); IR ν_{max}(KBr)/cm^{-1}: 1588–1432, 1215; δ_H (400 MHz, $CDCl_3$; Me_4Si): 8.54 (1 H, d, *J* 4.8 Hz, H-6 *py*), 7.76 (1 H, dt, *J* 2.0, 7.8 Hz, H-4 *py*), 7.49 (1 H, d, *J* 8.1Hz, H-3 *py*), 7.38 (2 H, t, *J* 7.8 Hz, H-3′, H-5′ *Ph*), 7.23 (2 H, m, C-H aromatic), 7.07 (2 H, m, H-2′, H-6′ *Ph*), 3.78 (3 H, s, N-CH_3). δ_C (100.4 MHz, $CDCl_3$; Me_4Si) 188.4 (C = S), 155.5 (C-2 *py*), 153.7 (C-1′ *Ph*), 149.0 (C-6 *py*), 137.9 (C-4 *py*), 129.3 (C-3′, C-5′ *Ph*, 126.1 (C-4′ *Ph*), 122.4 (C-5 *py*), 122.6 (C-2′, C-6′ *Ph*), 122.0 (C-3 *py*), 41.5 (N-CH_3). EI-MS: 244 $[M^\bullet]^+$, 151, 136, 135, 78, 77; HREIMS: 244.0674 (244.0670 $[M^\bullet]^+$ for $C_{13}H_{12}N_2OS$).

Reactivity

The kinetic studies of the aryl *N*-(2-pyridyl)thionocarbamates hydrolysis in sodium hydroxide and buffer solutions were performed in 1,4-dioxane/water 15% (v/v) with ionic strength kept constant at 0.5 mol·dm^{-3} (compounds **1a** and **1b**) or at 1.0 mol·dm^{-3} (compound **2**) with sodium perchlorate. The ionic strength was increased for compound **2** to allow to study the reactivity on higher concentrations of sodium hydroxide, since this compound was much less reactive than its secondary analogue (**1a**).

The measurements were carried out either in a UV 1603-Visible Spectrometer Shimadzu apparatus provided with thermostated cell holders, being the quartz cells kept at 27.0 ± 0.1 °C in the cell compartment of the apparatus, or in a chromatographer equipped with a Merck LichroCART 250-4 RP_8 column, manual injecting system Spectra SYSTEM P2000 with a Reodhyne loop of 20 μL and an UV–Vis detector Spectra SYSTEM UV 1000.

In the UV–Vis spectrophotometric technique, the reactions were followed by continuously monitoring the increase in absorbance at 285 nm corresponding to the formation of phenol (compound **1a**), the decrease in absorbance at 304 nm corresponding to the decomposition of the substrate (compound **1b**) and the decrease in absorbance at 260 nm corresponding to the to the decomposition of the substrate (compound **2**), and the spectra exhibited clear isosbestic points for all studied substrates.

In the HPLC technique, the reactions were followed by continuously monitoring the peak areas for both the compound **1b** and 4-methylphenol at 290 nm, thus allowing to follow simultaneously the decomposition of **1b** and the formation of 4-methylphenol for every HPLC experiment, using as eluent acetonitrile–water 75–25% (v/v) in isocratic conditions. Aliquots of 0.5 cm^3 were collected from the reaction mixture at 27.0 ± 0.1 °C and their pH adjusted to 7 with HCl 1.0 mol·dm^{-3} and cooled in an ice bath prior to be injected into the system.

The temperature effect was studied in a temperature range between 20.0 and 35.0 °C with an error less than 0.1 °C for each temperature. Absorbance-time data always fitted the first order-integrated equation $[A_t = A_\infty + (A_0 - A_\infty)e^{-k_{obs}t}]$ up to at least 90% completion of the reaction and the values of the pseudo-first-order constants (k_{obs}) were reproducible within 5%. In all cases, reactions were carried out in conditions of pseudo-first order, the thionocarbamate concentration being much lower respecting to the concentration of other reagents (between 2×10^{-5} and 3×10^{-5} mol·dm^{-3}). The peroxymonocarbonate ion solutions used in the study of basic reactivity of compound **2** were prepared by adding the corresponding amount of hydrogen peroxide in a carbonate buffer pH 9.0 ($[Buffer]_{total} = 0.2$ mol·dm^{-3}). The values of pH were measured in an Orion Research digital ionalyzer 501 potentiometer equipped with a with a KCl/AgCl electrode. All solvents and reagents were obtained from Aldrich or Merck and used without further purification, except for *tert*-butylamine and piperidine, which were distilled over potassium hydroxide pellets prior to their use.

*N-Piperidyl-N′-(2-pyridyl)thiourea (**3**)*

Compound **1b** (0.122 g; 0.5 mmol) was hydrolysed in piperidine buffer pH 12.0 ($[Buffer]_{total} = 1.0$ mol·dm^{-3}) in the same conditions of the kinetic assays. The reaction was carried out for 1 h in spite of the half live of the reaction being superior to that period of time to avoid the possibility of decomposition of the thiourea, although thioureas are less reactive than thiocarbamates in basic aqueous media. The pH of the reaction mixture was neutralized with HCl 1 mol·dm^{-3} and extracted with dichloromethane and ethyl acetate (2 × 15 cm^3 each), the combined organic phases were dried with anhydrous sodium sulphate, filtered off and evaporated to dryness. The presence of the urea was detected by TLC (*n*-hexane/diethyl ether 4:6) and identified by EI-MS. EI-MS: 221 $[M^\bullet]^+$, 137, 136, 128, 94, 78.

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