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Kinetics and Mechanism of Hydrolysis of Benzimidazolylcarbamates

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Através da carbamoilação do 2-aminobenzimidazole com diferentes cloroformatos substituídos, sintetizaram-se novos N-[1-(2-amino)benzimidazolil]carbamatos. Estudou-se a hidrólise em meio aquoso destes carbamatos numa gama de pH compreendida entre 1 e 13, a uma temperatura de 25 ºC. Os parâmetros cinéticos avaliados levaram a concluir que até pH 4 a reação se processa por mecanismo que envolve o ataque bimolecular da água ao substrato N-protonado. Esta é a primeira vez que este comportamento é observado em carbamatos, sendo muito provavelmente devido à diferença de basicidade entre um dos azotos do anel de benzimidazolilo e o oxigênio da função carbamato. Para valores mais elevados de pH, os resultados são consistentes com um mecanismo BAc2, atuando a água como nucleófilo entre pH 4 e 7 enquanto que em pH superior o íon hidróxido é o nucleófilo.

Synthesis of new 2-aminobenzimidazole-1-carbamates was accomplished by carbamoylation of 2-aminobenzimidazole using different substituted phenyl chloroformates. The aqueous hydrolysis of the new compounds was examined in the pH range 1-13 at 25 ºC. The evaluated kinetic parameters led to the conclusion that up to pH 4 reaction proceeds by a bimolecular attack of water to the N-protonated substrate. This is the first time this behavior is described for carbamates, and can be ascribed to the higher basicity of the benzimidazolyl moiety when compared with the carbonyl oxygen. For higher values of pH, the results are consistent with a BAc2 mechanism with nucleophilic catalysis, but while between pH 4 and pH 7 water acts as the nucleophile, for pH> 7 the hydroxide ion is the acting species.

Keywords: reaction mechanisms, kinetics, heterocycles, carbamates, benzimidazole

Introduction

The 2-aminobenzimidazole ring system represents the core structure of a number of biologically significant molecules and its derivatives have been found to possess a wide spectrum of biological activity. Particularly, alkyl benzimidazole-2-carbamates show potent fungicide and anti-helmintic activity, being Carbendazim® a good example of a successful market fungicide. Nevertheless, there are, to our knowledge, no studies on aryl benzimidazole-1-carbamates, either in terms of synthesis, bioactivity or chemical reactivity. So, in the sequence of our on-going work about aryl carbamates we decided to synthesize new 2-aminobenzimidazole-1-carbamates. Kinetics and mechanisms of basic hydrolysis of carbamates are well documented in literature, leading to the conclusion that tertiary carbamates hydrolyze always via a BAc2 mechanism while secondary ones decompose by a unimolecular elimination, if they have a good leaving group, or via BAc2 mechanism if they do not have it.

This paper, which presents unreported kinetic studies on tertiary carbamates, where the nitrogen atom is part of a cycle, involves the synthesis of new carbamates with potential bioactivity and the evaluation of the mechanism of hydrolysis of aryl benzimidazole-1-carbamates over the pH range 1-13.
Results and Discussion

Synthesis

A number of methods for the synthesis of alkyl benzimidazole carbamates have been reported.\(^7\) \(N\)-acylation of 2-aminobenzimidazole with alkyl chloroformates in aprotic solvents, or reaction with alkylcarbonates being the most common. The acylation of 2-aminobenzimidazole with alkyl chloroformates gives rise to benzimidazole-2-carbamates, via the formation of the \(N\) or \(N, N'\)-disubstituted benzimidazoles, which rearrange to the corresponding 1-carbamates with a base or by heat. There are, however, no reports of extending these methods to the synthesis of aryl benzimidazole carbamates. We found that aryl benzimidazole-1-carbamates can be obtained with moderate yields reacting 2-aminobenzimidazole with aryl chloroformates, even in presence of excess of base. We think that the hindrance of the exocyclic amine does not affect the stability of the endocyclic arylcarbamates, which are too stable and do not rearrange to the exocyclic ones.

Structure of compounds, including the site of carbamoylation, was elucidated both by spectroscopic and analytical data, including a single crystal X-ray diffraction, of which we show an example in Figure 1.

Reactivity

The pseudo first-order rate constants, \(k_{\text{obs}}\), for the hydrolysis of compounds 1a-e and 2 were measured at 25 ± 0.1 °C, either in aqueous HCl and NaOH or in buffer solutions (Table 1) and were found to be reproducible to within 5%. The pH rate profile obtained from the plot of \(\log k_{\text{obs}}\) vs. pH is shown in Figure 2. Under these experimental conditions, the hydrolysis was found to

| Catalyst (acid, basic or buffer) | pH | \(k_{\text{obs}}/ (10^4 \text{ s}^{-1})\) 1a | \(k_{\text{obs}}/ (10^4 \text{ s}^{-1})\) 1b | \(k_{\text{obs}}/ (10^4 \text{ s}^{-1})\) 1c | \(k_{\text{obs}}/ (10^4 \text{ s}^{-1})\) 1d | \(k_{\text{obs}}/ (10^4 \text{ s}^{-1})\) 1e | \(k_{\text{obs}}/ (10^4 \text{ s}^{-1})\) 2 |
|-------------------------------|----|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| HCl                           | 1.0| 3.16                           | 2.23                           | 2.57                           | 8.22                           | 45.2                           | 2.27                           |
| HCl                           | 2.0| 3.42                           | 1.92                           | 1.58                           | 7.64                           | 42.7                           | 2.00                           |
| Glycine                       | 2.4| —                              | —                              | —                              | 6.52                           | 42.3                           | —                              |
| Formiate                      | 3.0| —                              | 2.01                           | 2.27                           | 6.13                           | 42.1                           | —                              |
| Acetate                       | 3.8| —                              | —                              | —                              | 5.37                           | —                              | 1.31                           |
| Acetate                       | 4.0| —                              | —                              | —                              | —                              | 25.5                           | —                              |
| Acetate                       | 4.4| 2.07                           | 1.48                           | 1.52                           | —                              | —                              | —                              |
| Acetate                       | 5.0| 1.02                           | —                              | —                              | 1.20                           | 6.38                           | 0.197                          |
| Carbonate                     | 5.6| 0.46                           | 0.19                           | 0.19                           | —                              | —                              | —                              |
| Carbonate                     | 6.3| —                              | —                              | —                              | 0.197                          | 6.90                           | —                              |
| Carbonate                     | 6.4| 0.21                           | —                              | —                              | —                              | —                              | —                              |
| Carbonate                     | 6.7| —                              | —                              | —                              | 0.21                           | 8.46                           | 0.033                          |
| Phosphate                     | 7.2| 0.16                           | 0.074                          | 0.074                          | —                              | —                              | —                              |
| Phosphate                     | 7.4| —                              | —                              | —                              | —                              | 5.20                           | 0.066                          |
| Phosphate                     | 8.3| —                              | 0.97                           | 1.00                           | 3.97                           | 16.6                           | —                              |
| Borate                        | 8.8| 2.50                           | —                              | —                              | 14.5                           | 61.7                           | —                              |
| Borate                        | 9.3| 7.37                           | —                              | —                              | —                              | 96.1                           | 4.06                           |
| Borate                        | 10.0| 40.1                          | 17.9                           | 21.4                           | 119                            | 400                            | 35.2                           |
| Carbonate                     | 10.6| 24.5                          | 35.5                           | 304                            | 1320                           | 103                            | —                              |
| Carbonate                     | 10.8| 80.7                          | —                              | —                              | —                              | —                              | —                              |
| Carbonate                     | 11.0| 285                            | 28.5                           | 139                            | —                              | 2250                           | —                              |
| Carbonate                     | 11.3| —                              | —                              | —                              | —                              | 5660                           | —                              |
| Carbonate                     | 11.6| 1030                           | —                              | —                              | —                              | 7810                           | —                              |
| Carbonate                     | 11.8| 1550                           | —                              | —                              | —                              | —                              | —                              |
| Carbonate                     | 11.9| 2080                           | —                              | —                              | —                              | —                              | —                              |
| NaOH                          | 12.0| 2390                           | —                              | 2340                            | 5470                           | —                              | 1880                           |
| NaOH                          | 12.3| 6000                           | —                              | 4640                            | 11000                          | —                              | 3690                           |
| NaOH                          | 12.5| 9980                           | 3390                           | 6920                            | 15700                          | —                              | 5230                           |
| NaOH                          | 12.6| 11500                          | —                              | 9320                            | —                              | 7.760                          | —                              |
| NaOH                          | 12.7| 12800                          | 7720                           | 11400                           | —                              | —                              | 10300                          |
| NaOH                          | 12.8| —                              | 14900                          | 13800                           | —                              | —                              | —                              |
| NaOH                          | 13.0| 26300                          | 19100                          | —                              | —                              | —                              | —                              |

Table 1. Values of pH and \(k_{\text{obs}}\) for the hydrolysis of compounds 1a-e and 2 at 25 °C.

Total buffer concentration= 0.04 mol dm\(^{-3}\), \(\mu = 0.5\) mol dm\(^{-3}\) NaClO\(_4\).
follow a first order kinetics with respect to the substrate up to at least 90% completion of the reaction, being 2-aminobenzimidazole and phenol, or a substituted phenol, always the reaction products.

The pH rate profile indicates the existence of three different regions, according to different reactions of the substrate. The first region, up to pH 4 is a pH independent region with no buffer catalysis (equation 1); the second region is characterized by a decrease of $k_{obs}$ with pH up to pH 7 (equation 2 or 2'); and, finally, for pH > 7 a highly dependent pH region is observed with buffer catalysis (equation 3). All studied compounds demonstrated a similar behavior and the data for all of them fitted well to the global equation obtained from the association of equations 1 (explained by water attack to the protonated substrate), 2 or 2' (explained either by the attack of water to the neutral species or the attack of hydroxide to the protonated substrate) and 3 (related to the attack of hydroxide to the neutral substrate). $K_a$ is the acid dissociation constant for the protonated substrate obtained from kinetic parameters, $K_w$ is the ionic product of water, and $k_1$, $k_2$ or $k_3$ and $k_4$ are the second-order rate constants for reaction in solution up to pH 4, the intermediate region and the basic medium (Table 2), respectively.

$$k_{obs} = k_1 \frac{K_a[H_2O]}{[H_2O]+K_w}$$

$$k_{obs} = k_2 \frac{K_a[H_2O][OH^-]}{[OH^-]+K_w}$$

$$k_{obs} = k_3 \frac{K_a[OH^-]}{[OH^-]+K_w}$$

**Hydrolysis in acidic media**

The compounds under study are quite basic and in the pH range studied they can be protonated, being thus possible the co-existence of both species, the neutral (S) and the protonated form (SH+) of the substrate. Therefore, the pH independent region found in the pH rate profile up to pH 4, can be explained by the existence of these two species, and can be analysed as an attack of water on the protonated substrate. No buffer catalysis was observed in this region (Table 3).

Comparison of $k_1$ values obtained for compounds 1a-e (Table 2) gives rise to a Hammett plot (Figure 3) indicative of a mechanism compatible with a bimolecular attack of water as the rate determining step. This substituent effect is indicative of a pre-equilibrium

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**Table 2. Acid dissociation and rate constants for hydrolysis of carbamates 1a-e and 2**

| Compound | $k_1$ ($10^{-7}$ mol dm$^{-1}$ s$^{-1}$) | $k_2$ ($10^{-8}$ mol dm$^{-1}$ s$^{-1}$) | $k_3$ ($10^{-3}$ dm$^{-1}$ mol$^{-1}$ s$^{-1}$) | $k_4$ ($10^3$ mol dm$^{-1}$ s$^{-1}$) | $pK_a$ |
|----------|--------------------------------|-----------------|-----------------|-----------------|-------|
| 1a       | 7.40                          | 4.44            | 30.0            | 2.67            | 4.52  |
| 1b       | 4.67                          | 1.35            | 1.00            | 1.96            | 4.70  |
| 1c       | 4.85                          | 1.86            | 5.37            | 2.24            | 4.54  |
| 1d       | 16.5                          | 3.25            | 9.82            | 5.08            | 3.26  |
| 1e       | 99.7                          | 139             | 0.92            | 20.70           | 3.26  |
| 2        | 5.94                          | 0.91            | 5.37            | 1.96            | 3.52  |

**Table 3. Influence of buffer concentration on $k_{obs}$ values for the decomposition of 1a in acidic medium**

| [formate]/ [2,2'-(iminodiacetonitrile)]/ [2,2,2-trifluoroethylamine]/ | $k_{obs}$ ($10^3$ s$^{-1}$) |
|---------------------------|-----------------------------|
| pH 3.3     | 10$^{-3}$ mol dm$^{-3}$ | 10$^{-3}$ mol dm$^{-3}$ | 10$^{-3}$ mol dm$^{-3}$ |
| 4.52        | 28.7                       | 2.0                      | 18.7                  | 1.9                       | 29.5       |
| 5.44        | 29.2                       | 2.1                      | 20.0                  | 2.3                       | 28.5       |
| 6.44        | 28.8                       | 2.5                      | 19.5                  | 2.8                       | 29.5       |
| 7.52        | 29.5                       | 2.9                      | 19.5                  | 3.2                       | 28.8       |
| 10.46       | 29.5                       | 4.1                      | 19.2                  | 4.6                       | 29.8       |
protonation of the substrate followed by the rate
determining formation of the tetrahedral intermediate,
with decomposition occurring by benzimidazole acting
as a leaving group. Indeed, there are three basic sites in
the carbamate molecule, the exocyclic and endocyclic
nitrogens and the acyl oxygen, and so any of the three
tautomers can be the starting species in the hydrolysis.
Based on pKₐ calculations, we predict the site of
protonation to be the endocyclic nitrogen (pKₐ exocyclic
NH₂= -6.704; pKₐ endocyclic NH= 4.100; pKₐ oxygen=
-2.541), generating a much more stable intermediate and
a much better leaving group. Moreover, this pKₐ value is
in accordance with the one obtained by experimental
adjustment to equation 1.

Hydrolysis of compound 2 was also done in deuterated
media (Table 4) and comparison of the reaction performed
in both media gave rise to the ratio of the slopes of both
linear correlations in the two media, k₁(H₂O)/ k₁(D₂O)=
0.73. Again, this isotope effect is the one expected based
upon the contribution of two processes: pre-equilibrium
protonation of the substrate followed by the rate limiting
step of attack at the carbamate function. Therefore, in
light of the overall evidence, we propose that acid
hydrolysis of compounds 1a-e and 2 proceeds via a
bimolecular mechanism with acyl-nitrogen fission. This
conclusion is supported by theoretical studies published
for the acid hydrolysis of methyl carbamates.

### Hydrolysis in basic media

The first order rate constants for the hydrolysis of
compounds 1a-e and 2 were measured in the presence of
different NaOH concentrations and were observed to obey
equation 3. For compound 1a rate constants were also
measured in a number of aqueous buffer solutions (Table 5).

From the linear correlation of kₘₐₓ values for decomposition of 1a in basic medium.

| [TFE]/(10⁻³mol dm⁻³) | kₘₐₓ/(10⁻⁵s⁻¹) | [Pip]/(10⁻³mol dm⁻³) | kₘₐₓ/(10⁻⁵s⁻¹) | [TEA]/(10⁻³mol dm⁻³) | kₘₐₓ/(10⁻⁵s⁻¹) | [PIPE]/(10⁻³mol dm⁻³) | kₘₐₓ/(10⁻⁵s⁻¹) | [MOR]/(10⁻³mol dm⁻³) | kₘₐₓ/(10⁻⁵s⁻¹) |
|---------------------|----------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|
| pH 11.              |                | pH 10.8             |                | pH 10.3             |                | pH 10.3             |                | pH 9.4              |                |
| 1.4                 | 9.86           | 1.6                 | 1.01           | 1.8                 | 1.12           | 6.8                 | 3.94           | 8.8                 | 3.17           |
| 2.3                 | 12.60          | 2.5                 | 1.20           | 2.4                 | 1.20           | 8.8                 | 4.22           | 11.0                | 3.40           |
| 2.9                 | 17.30          | 3.0                 | 1.29           | 2.9                 | 1.23           | 9.9                 | 4.18           | 13.2                | 3.42           |
| 3.7                 | 21.40          | 3.6                 | 1.38           | 4.0                 | 1.32           | 12.1                | 4.78           | 17.5                | 3.71           |
| 6.1                 | 35.00          | 8.5                 | 2.10           | 5.0                 | 1.43           | 18.0                | 5.27           | 22.0                | 4.03           |

TFE-2,2,2-trifluorethanol, Pip-piperidline, TEA-triethylamine, PIPE-piperazine, MOR- morpholine
Buffer catalysis was observed in the region of pH > 7 and the second order rate constants obtained from the slopes of the plots of \( k_{\text{obs}} \) versus [buffer] were plotted against pKa (literature values, calculated according to Davies equation for each experimental ionic strength) giving rise to a Brönsted correlation with a \( \beta \) value of 0.98 (Figure 5). The poor correlation obtained, due to the points for triethylamine and trifluorethanol, is explained by the first buffer being a tertiary nitrogen nucleophile and the last one an oxygen nucleophile, which is frequently described as an outlier in Brönsted plots. This value may indicate a nucleophilic catalysis, since Brönsted \( \beta \) values higher than 0.8 are characteristic of nucleophilic catalysed reactions. In fact, these processes have \( \beta \) values usually higher than the ones obtained for general base catalysed reactions, for which \( \beta \) between 0.4 and 0.7 are to be expected.\(^1\)\(^2\)

As already said, the Brönsted parameter seems to point to a nucleophilic catalysed reaction in this case and so does the solvent isotope effect which is also an effective parameter to distinguish between a general base and a nucleophilic catalysed reaction. Comparison of catalysis in piperidine buffer, both in water and deuterated water for compound \( 2 \) gives, a value of 1.16 which is consistent with a rate determining step of attack of hydroxide on the neutral substrate\(^3\) (Figure 4).

Comparison of \( k_3 \) for compounds \( 1a-e \) give rise to a Hammett plot with a \( \rho \) value of 0.99 (r\(^2\)= 0.97) which is also consistent with a \( B_{\text{Ac}}^2 \) mechanism with nucleophilic catalysis,\(^8\) where the rate determining step is the hydroxide attack on the neutral substrate.

Finally, another important evidence in favor of the mechanism of hydrolysis via a nucleophilic catalysis, where the base directly attacks the substrate in the rate determining step, is the formation of \( N \)-methyl-1-(piperidin-1-ylcarbonyl)-1H-benzimidazol-2-amine (3) which must be the result of the trapping of the reactive intermediate.

**Hydrolysis in intermediate media**

Reaction occurring in the intermediate pH region can be explained by one of two possibilities, related to the co-existence of both the neutral and the protonated species in this pH range. The two possibilities are the bimolecular attack of water to the neutral species (\( k_j \)) or of hydroxide to the protonated species (\( k_j' \)). Data adjustment to equations 1 and 2 or 2’ in the Hammett plot gives rise to correlations which are better using a \( \sigma^- \) (1.27, \( R^2=0.95 \) for \( k_j \) and 1.20, \( R^2=0.61 \) for \( k_j' \)) than a \( \sigma \) value (1.82, \( R^2=0.88 \) for \( k_j \) and 1.72, \( R^2=0.57 \) for \( k_j' \)). The results obtained point to a rational use of equations 1 and 2 for the data adjustment in this pH range. Correlation with \( \sigma \) seems surprising in this case since it is commonly used when there is substantial bond cleavage and significant increase in negative charge in carbamate O atom (e.g. E1cB mechanism). One explanation may be the presence of the rather electron-withdrawing benzimidazole group which increases the electron-delocalization in the substrate. With the formation of the tetrahedral intermediate the delocalization is modified, resulting in a great change in the electron density residing in the phenol oxygen.\(^4\) A similar correlation with \( \sigma^- \), this time of \( k_3 \), gave rise to a low \( \rho \) value (0.67, \( R^2=0.98 \)) which is not easily explained by a rate limiting bimolecular process.

Thus in the intermediate region, reaction seems to occur by a much similar mechanism to the one acting in basic media, but with water acting as nucleophile. The higher \( \rho \) value, when compared with the one obtained in basic media can be explained by the much higher sensitivity of the
reaction to the substituent when water, which is a weaker nucleophile than hydroxide, is the attacking agent. The same sort of effect was observed for the hydrolysis of phenyl acetates by imidazole. As to the leaving group ability, as pH increases the amount of protonation on the benzimidazole moiety decreases significantly and this moiety is no longer a good leaving group.

The above considerations led us to propose the mechanism depicted in Scheme 1 for the hydrolysis of benzimidazolylcarbamates.

Experimental

Melting points are uncorrected. All solvents and reagents were obtained from commercial suppliers and were used without further purification except THF and pyridine, which were freshly distilled from sodium benzophenone ketyl and potassium hydroxide, respectively. IR spectra were obtained using a Hitachi 270-50 spectrophotometer on KBr pastille and only diagnostic bands are reported on a cm⁻¹ scale. ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100.4 MHz, respectively, in chloroform-δ or DMSO as solvents, and chemical shifts are reported in parts per million (ppm, δ), using as reference the appropriate signal for residual solvent protons. Coupling constants are reported to the nearest 0.1 Hz. HMOC and HMBC correlations enabled the correct peak assignment.

HR-MS were performed by EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, UK and elemental analysis was performed in Medac Ltd., Brunel Science Centre, UK. Crystal X-ray diffraction was performed by EPSRC National Mass Crystallography Service, University of Southampton. Column chromatographies were carried out using 230-400 mesh silica gel. Thin-layer chromatography were performed on pre-coated silica-gel plates and spots were visualized by UV light (254 nm)

Benzimidazolyl carbamates were prepared by one of the following methods

Method A

2-aminobenzimidazole (1.0 g; 7.5 mmol) was dissolved in anhydrous pyridine and the corresponding chloroformate (7.5 mmol) added drop wise. The reaction was carried in an ice bath for approximately 30 minutes. The reactional crude was washed with cold water (ca. 30 cm³); the white solid which precipitated was filtered off, washed with ethanol and diethyl ether and purified by column chromatography.

Method B

2-methylanobenzimidazole (1.0 g; 7.5 mmol) was dissolved in anhydrous acetonitrile and K₂CO₃ (7.5 mmol) added, followed by addition drop wise of phenyl chloroformate (7.5 mmol). The reaction was allowed to proceed at r.t. for 3 hours. The residue was poured in cold water (ca. 30 cm³); the white solid was filtered off, washed with ethanol and diethyl ether and purified by column chromatography.

Phenyl 2-amino-1H-benzimidazole-1-carboxylate (1a)

Method A

White crystals mp > 320 dec. (methanol); η = 7%; IR(KBr) νₜₘₐₓ/cm⁻¹: 3429, 1735; δₙ (400 MHz, CDCl₃) 7.79 (1H, d, J 8.0 Hz, H-7 Benzim.), 7.51 (2H, t, J 8.0 Hz, Ph), 7.39 (1H, m 4-H, H-4 Benzim.), 7.32 (1H, d, J 8.0 Hz, H-6 Benzim.), 7.26 (3H, m, Ph), 7.12 (1H, t, J 7.6 Hz, H-5 Benzim.), 6.35 (2H, s, nh₂); δ_c (100.4 MHz, CDCl₃) 153.5 (C-2 Benzim.), 149.7(C=O), 149.6 (C-1 Ph), 142.9 (C-8 Benzim.), 129.9 (C-9 Benzim), 129.7 (C-3/ C-5 Ph), 126.8 (C-4 Ph), 124.5 (C-6 Benzim.), 121.9 (C-2/ C-6 Ph), 120.1 (C-5 Benzim.), 115.6 (C-4 Benzim.), 114.0 (C-7 Benzim.); EI-MS 253 [M]+, 160, 159, 132, 105, 94, 90, 77; HR-MS (ESI) 254.0920 (254.0924 [M+H]+ for C₁₄H₁₂N₃O₂).

4-Methylphenyl 2-amino-1H-benzimidazole-1-carboxylate (1b)

Method A

White yellowish crystals mp > 320 dec. (ether/ acetonitrile); η = 31%; IR νₜₘₐₓ/cm⁻¹: 3440, 1739; δₙ (400 MHz, CDCl₃) 7.78 (1H, d, J 8.0 Hz, H-7 Benzim.), 7.38 (1H, d, J 7.4 Hz, H-4 Benzim.), 7.28 (2H, m, H-3 Ph/H-5 Ph.), 7.26 (1H, m, H-6 Benzim.), 7.19 (2H, d, J 8.4 Hz, H-2/ H-6 Ph.), 7.11 (1H, ddd, J 1.2; 7.4; 7.6 Hz, H-5 Benzim.), 6.62 (2H, s, nh₂)[H₂]; δ_c (100.4 MHz, CDCl₃) 153.6 (C-2 Benzim.), 150.9 (C=O), 147.4 (C-1 Ph), 142.4 (C-8 Benzim.), 136.9 (C-4 Ph), 130.4 (C-3/ C-5 Ph), 129.9 (C-9 Benzim), 125.1 (C-6 Benzim.), 121.2 (C-2/ C-6 Ph), 121.2 (C-5 Benzim.), 116.7 (C-4 Benzim.), 114.3 (C-7 Benzim.), 21.0 (CH₃); EI-MS [M]+ 267, 160, 159, 132, 90, 77, 65; 132; C₁₄H₁₄N₂O₂ calcd. C 74.71, H 4.90, N 15.72; found C 74.72, H 4.85, N 15.76.

4-Methoxyphenyl 2-amino-1H-benzimidazole-1-carboxylate (1c)

Method A

Column chromatography hexane/ ethyl acetate 45: 55. White crystals mp > 320 dec. (ethanol); η = 52%;
IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3462, 1735; $\delta_{H}$ (400 MHz, CDCl$_3$) 7.78 (1 H, d, $J$ 8.0 Hz, H-7 Benzim.), 7.38 (1 H, d, $J$ 7.6 Hz, H-4 Benzim.), 7.26 (1 H, ddd, $J$ 1.2, 7.4, 8.0 Hz, H-6 Benzim.), 7.23 (2 H, d, $J$ 9.0 Hz, H-3/H-5 Ph), 7.13 (1 H, ddd, $J$ 1.2; 7.4; 7.6 Hz, H-5 Benzim.); 6.99 (2 H, d, $J$ 9.0 Hz, H-2/H-6 Ph), 6.50 (2 H, s, NH$_2$), 3.85 (3 H, s, OCH$_3$); $\delta_{C}$ (100.4 MHz, d$_6$-DMSO) 153.5 (C-2 Benzim.), 151.1 (C=O), 143.1 (C-1 Ph), 142.1 (C-8 Benzim.), 158.2 (C-4 Ph), 129.9 (C-9 Benzim.), 125.1 (C-6 Benzim.), 121.2 (C-2/ C-4 Ph), 121.2 (C-5 Benzim.), 116.7 (C-4 Benzim.), 114.8 (C-3/ C-5 Ph), 114.3 (C-7 Benzim.), 55.7 (OCH$_3$). EI-MS 287 [$M^+$], 160, 159, 132, 128, 105, 90, 63; HR-MS (ESI) 288.0530 (288.0534 [M+H]$^+$ for C$_{15}$H$_{14}$N$_3$O$_3$).

4-Chlorophenyl 2-amino-1H-benzimidazole-1-carboxylate (1d)

Method A

Column chromatography dicrotomethane/ ethyl acetate 25: 75. White crystals mp > 320 dec. (ethanol/THF); $\eta$ = 10%; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3462, 1735; $\delta_{H}$ (400 MHz, CDCl$_3$) 7.75 (1 H, d, $J$ 8.0 Hz, H-7 Benzim.), 7.47 (2 H, d, $J$ 8.8 Hz, H-3/H-5 Ph), 7.39 (1 H, d, $J$ 7.6 Hz, H-4 Benzim.), 7.28 (3 H, m, H-6 Benzim., H-2/H-6 Ph), 7.12 (1 H, ddd, $J$ 1.2; 7.4; 7.6 Hz, H-5 Benzim.); $\delta_{C}$ (100.4 MHz, CDCl$_3$): 153.3 (C-2 Benzim.), 150.4(C=O), 148.0 (C-1 Ph), 142.4 (C-8 Benzim.), 132.7 (C-4 Ph), 130.0 (C-3, C-5 Ph), 129.8 (C-9 Benzim.), 125.3 (C-6 Benzim.), 122.8 (C-2/ C-6 Ph), 121.4 (C-5 Benzim.), 116.9 (C-4 Benzim.), 114.2 (C-7 Benzim.); EI-MS 287 [M]$^+$, 160, 159, 132, 128, 105, 90, 63; HR-MS (ESI) 288.0530 (288.0534 [M+H]$^+$ for C$_{15}$H$_{14}$N$_3$O$_3$Cl).

4-Nitrophenyl 2-amino-1H-benzimidazole-1-carboxylate (1e)

Method A

Yellow crystals mp > 320 dec. (ether/acetonitrile); $\eta$ = 10%; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3453, 1752; $\delta_{H}$ (400 MHz, d$_6$-DMSO) 8.41 (2 H, d, $J$ 9.2 Hz, H-3/H-5 Ph), 7.80 (2 H, d, $J$ 9.2 Hz, H-2/H-6 Ph), 7.72 (1 H, d, $J$ 8.0 Hz, H-7 Benzim.), 7.32 (2 H, s, NH$_2$), 7.25 (1 H, d, $J$ 7.6 Hz, H-4 Benzim.); 7.19 (1 H, ddd, $J$ 0.8; 7.2; 7.4 Hz, H-6 Benzim.), 7.04 (1 H, ddd, $J$ 1.2; 7.2; 7.2 Hz, H-5 Benzim.); $\delta_{C}$ (100.4 MHz, d$_6$-DMSO) 154.2 (C-1 Ph), 153.5 (C-2 Benzim.), 148.4 (C=O), 145.7 (C-4 Ph), 143.1 (C-8 Benzim.), 129.9 (C-9 Benzim.), 125.3 (C-3/C-5 Ph), 124.5 (C-6 Benzim.), 123.6 (C-2/ C-6 Ph), 120.1 (C-5 Benzim.), 115.6 (C-4 Benzim.), 114.1 (C-7 Benzim.); EI-MS 298 [M]$^+$, 160,
159, 139, 133, 105, 90, 63; HR-MS (EI) 298.06925 (298.06957 [M]+ for C₁₅H₁₃N₃O₂).

**4-Phenyl 2-(methylamino)-1H-benzimidazole-1-carboxylate, (2)**

**Method B**

Column chromatography hexane/ ethyl acetate 3:7. White crystals mp 165.5-166.6 dec. (ethanol/dichloromethane), η = 41%; IR(KBr) ν max/cm⁻¹: 3390, 1732, 1635; δ (400 MHz, d₆-DMSO) 7.72 (1 H, d, J 7.6 Benzim.), 7.53 (2H, AA'XX', H-3/H-5 Ph), 7.49 (2H, AA'XX', H-2/ H-6 Ph), 7.39 (1 H, m, H-4 Benzim.), 7.32 (1H, d, J 7.6 Hz, H-4 Benzim.), 7.19 (1H, ddd, J 1.2; 7.6, 7.6 Hz, H-6 Benzim.), 7.04 (1H, ddd, J 1.2; 7.6, 7.6 Hz, H-5 Benzim.), 3.02 (3H, d, J 4.8 Hz, NCH₃); δ (100.4 MHz, d₆-DMSO) 153.9 (C-2 Benzim.), 149.6 (C-1 Ph= C=O), 143.0 (C-8 Benzim.), 130.5 (C-9 Benzim.), 129.7 (C-3/C-5 Ph), 127.0 (C-4 Ph), 124.4 (C-6 Benzim.), 121.9 (C-2/C-6 Ph), 120.1 (C-5 Benzim.), 115.8 (C-4 Benzim.), 114.0 (C-7 Benzim.), 29.5 (N-CH₃); EL- MS 268 [M]+, 173, 146, 118, 90, 77; HR-MS (EI) 268.1083 (268.1081 [M]+ for C₁₅H₁₃N₃O₂).

**Kinetics**

Kinetic runs were carried out in thermostated quartz cells, and were triggered by injecting a small aliquot of an acetonitrile solution of substrate into the reaction mixture, and were monitored with an UV spectrophotometer Shimadzu 1603 water, 25 ºC, following either the decomposition of the substrate or the formation of the corresponding phenol and monitored with an UV spectrophotometer Shimadzu 1603 (AcOEt) and identified by HR-MS (ESI) 258.14732 (258.14752 M⁺ for C₁₅H₁₃N₃O₂).

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