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ORIGINAL ARTICLE

Hydrolysis study: Synthesis of novel styrenic Schiff bases derived from benzothiazole

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Abstract Novel styrenic Schiff base derivatives of benzothiazole are synthesized. The condensation of 4-vinylbenzaldehyde **1** with either benzothiazol-2-amine or 4-methoxy-benzothiazol-2-amine leads to a mixture of two isomers. From 4-methyl-benzothiazol-2-amine and 6-fluoro-benzothiazol-2-amine, the *N*-(4-vinylbenzylidene)-4-methyl-benzothiazol-2-amine **8** and *N*-(4-vinylbenzylidene)-6-fluoro-benzothiazol-2-amine **9** are isolated, respectively. The structures of the synthesized Schiff bases are confirmed through a combination of various spectroscopic techniques including IR, UV, ^{1}H and ^{13}C NMR. A kinetic study of the hydrolysis process of derivatives **6** and **9** in buffered aqueous medium at pH 4.4, 7.4 and 8.5 is conducted by UV spectroscopy. It is shown that the hydrolysis of these compounds is a first order reaction showing an increasing rate as the medium acidity is enhanced.

1. Introduction

Various substituted benzothiazoles are known to cover a large domain of pharmacological activities serving as antitumor (Beneteau et al., 1999), anti-microbial (Kabeer et al., 2001; Hassan et al., 1978), anthelmintic (Nadkarni et al., 2000), analgesic (Mruthyunjayasawmy and Shanthaveerappa, 2000), anti-inflammatory (Pontiki and Hadjipavoulou-Litina, 2007; Miyamatsu et al., 1974; Bhusari et al., 2001; Bhusari et al., 2000a,b) and anticonvulsive (Hays et al., 1994) agents. Moreover, it was reported that the Schiff bases (Hadjipavlou-Litina and Geronikaki, 1998) of thiazole and benzothiazole act as inhibitors of the lipoxygenase affecting inflammation and/or psoriasis. Lipoxygenase is an enzyme which catalyzes the rate-limiting step in the biosynthesis of leukotrienes from arachidonic acid (Brain and Williams, 1990; Muller, 1994). The effective role of azomethine linkage in some biological reactions was also studied (Geronikaki, 1990), and it is therefore of interest to consider the synthesis of novel styrenic Schiff bases of benzothiazole and its derivatives.

In this paper we report the preparation of four compounds and a kinetic study of the hydrolysis for two of them.

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2. Experimental

2.1. Materials and equipments

Melting points were found using Gallenkamp .7 B .9144 B apparatus. The refraction indexes were measured by a refractometer (S-WAY Digital.ABBc model). IR spectra were recorded on a JASCO FT/IR4200 spectrophotometer with samples either as 1% dispersions in KBr pellets or as liquid films. The UV–Vis spectra were carried out on Spectronic® Genesys 5 TM, spectrophotometer with 10^{-4}–10^{-5} mol/l in ethanol. The ^{1}H, ^{13}C NMR spectra were recorded on a Bruker AC instrument (300 MHz, 400 MHz, 75 MHz) with compounds in DMSO-d_6 and $CDCl_3$ solutions. ^{1}H NMR chemical shifts are expressed as δ values (ppm) relative to TMS as an internal standard. Products separations were performed by column chromatography on silica gel 66 Merck 230–400 mesh and eluted with the *n*-hexane/ethyl acetate: 6/0.50 mixture. Hydrolysis of the imines was studied at 25 °C, in homogeneous aqueous solutions, buffered at pH 4.4, 7.4 and 8.5. The acetate and phosphate buffers were prepared in aqueous medium according to the methods described by Perrin (1963) and Michaelis and Mizutani (1925). They were followed on a Shimadzu UV-2401PC, dual beam spectrophotometer, in thermostated cells at 25 °C ± 0.1 °C. pH was measured using a digital pH meter (Beckman), calibrated at 25 °C with buffer solutions at pH 4.62 (acetate) and pH 9.00 (borax) with an accuracy of 0.01 pH units. The aromatic amines used in the following preparations are commercial products. The solvents used (ethanol, methanol, benzene, toluene, chloroform, methylene chloride) were purified according to the literature procedures (Furniss et al., 1968; Lund and Bjerrum, 1931).

2.2. Synthesis of 4-vinylbenzaldehyde *1*

4-Vinylbenzaldehyde (yellow oil) was synthesised following the method of Sommelet (Ferruti, 1977) from the 4-chloromethylstyrene (CMS) with a 60% yield; IR (film on NaCl pellets) *t* (cm^{-1}): 1700.91 (C=O), 2732.64 and 2826.2 (H—C=O), 1609.5 (C=C), 1839.76 (=CH_2, overtone), 988.33 (=C—H), 917.95 (=CH_2), 3008.41 and 840.81 (Ø—H); UV (Ethanol) λ_1 max (ε max) = 281 nm (20098), λ_2 max (ε max) = 218 nm (8987), λ_3 max (ε max) = 204 nm (12426); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):10(s, H_1), 7.9 (d, H_2 and $H_{2'}$; J = 8.19 Hz), 7.71 (d, H_3 and $H_{3'}$, J = 8.15 Hz), 6.85 (dd, H_4, J = 17.64 Hz, J = 10.96 Hz), 6.06(d, H_6, J = 17.5 Hz), 5.48 (d, H_5, J = 10.96 Hz).

2.3. General procedure for preparation of compounds *6*, *7*, *8* and *9*

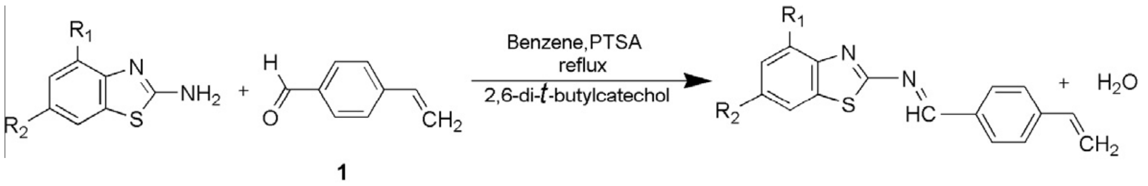
In a 100 ml flask equipped with a Dean-Stark, 77 mmol of 4-vinylbenzaldehyde and 66 mmol of aromatic amine were dissolved in 30 to 60 ml of benzene in the presence of 2 mg of 2,6-di-t-butyl catechol (antioxidant) and some traces of *para* toluene sulfonic acid (PTSA) as catalyst were reacted under reflux for 6 h. After evaporation of the solvent, the residue was recrystallized in ethanol or methanol or chromatographed on silica gel and eluted by the *n*-hexane/ethyl acetate: 6/0.50 mixture.

2.3.1. N-(4-vinylbenzylidene)-benzothiazol-2-amine (*6*)

The compound **6** was obtained using the general method of synthesis described above. After evaporation of the solvent, the residue recrystallized in ethanol gave **6** as yellow powder, with 79% yield. Two mp = 94 °C and 102 °C were detected, presumably those of the two isomers; IR (film on KBr pellets) *t* (cm^{-1}): 2825.5 and 2893 (N=C—H), 1587 (C=N, imine), 1686.4 (C=N, benzothiazole), 1524.7 (C=C, vinyl), 3238.4 and 976.7 (=C—H), 916.8 (=CH_2); UV (Ethanol) λ_1 max (ε max) = 355 nm (11531), λ_2 max (ε max) = 262 nm (34691) and λ_3 max (ε max) = 232 nm (34821); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.79 (s; H_8), 8.25 (s, H_8), 7.72 (d, H_4; J = 7.62 Hz), 7.29–7.23 (m, H_5), 7.09–7.04 (m, H_6), 7.52–7.45 (m, H_7), 7.52–7.45 (d, H_9, $H_{9'}$, J = 8.60 Hz), 7.52–7.45 (m, H_{10}, $H_{10'}$), 6.18 (d, H_{10}, $H_{10'}$, J =8.60 Hz), 6.74 (dd, H_{11}, J = 10.95 Hz, J = 17.67 Hz), 5.85 (d, $H_{12a'}$, J = 17.67 Hz), 5.27 (d, H_{12a}, J = 10.95 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ (ppm): imines carbon: 165.38 and 166.71, aromatic and vinylic carbons: 14.55, 118.45, 120.95, 121.38, 122.26, 122.48, 125.54, 125.55, 126.50, 126.75, 130.43, 135, 83, 136.12, 137.01, 138.76 and 151.79.

2.3.2. N-(4-vinylbenzylidene)-4-methoxy-benzothiazol-2-amine (*7*)

The compound **7** was obtained using the general method of synthesis described above. After evaporation of the solvent, the residue recrystallized in methanol gave **7** as yellow powder, with 64% yield. Two mp = 120 °C and 116 °C were detected, presumably those of the two isomers; IR (film on KBr pellets) *t* (cm^{-1}): 2992 (N=C—H), 1586 (C=N, imine), 1688.2 (C=N, benzothiazole), 1526.1 (C=C, vinyl), 3210.3 (=C—H), 980.4



2 R_1 = H R_2 = H
3 R_1 = OCH_3 R_2 = H
4 R_1 = CH_3 R_2 = H
5 R_1 = H R_2 = F

6 R_1 = H R_2 = H
7 R_1 = OCH_3 R_2 = H
8 R_1 = CH_3 R_2 = H
9 R_1 = H R_2 = F

Scheme 1

(=C—H), 915.4 (=CH$_2$); UV (EtOH) λ_1 max (ε max) = 353 nm (936), λ_2 max (ε max) = 261 nm (13610) and λ_3 max (ε max) = 226 nm (32503); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ (ppm): 8.79 (s, H$_8$), 8.76 (s,H$_8$),3.86 (s,OCH$_3$), 6.867 (d, H$_5$, J = 7.94 Hz), 6.868 (d, H$_5$, J = 7.94 Hz), 7.02 (t, H$_6$, J = 7.94 Hz, J = 7.98 Hz), 7.295 (d, H$_7$, J = 7.98 Hz), 7.297 (d, H$_7$, J = 7.98 Hz), 7.51–7.44 (m, H$_9$,H$_{9'}$, H$_{10}$,H$_{10'}$), 6.24 (d, H$_{10}$,H$_{10'}$, J = 8.72 Hz), 6.74 (dd, H$_{11}$, J = 11.07 Hz, J = 17.67 Hz), 5.269 (d, H$_{12a'}$, J = 17.67 Hz), 5.271 (d, H$_{12a'}$, J = 17.67 Hz), 5.841 (d, H$_{12a}$, J = 11.07 Hz), 5.844 (d, H$_{12a}$, J = 11.07 Hz).

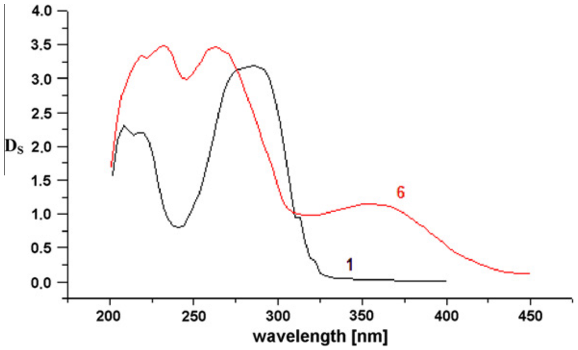


Figure 1 UV absorption spectra of 4-vinylbenzaldehyde **1** and *N*-(4-vinylbenzylidene)-benzothiazol-2-amine **6** in absolute ethanol (C = 10^{-4} M).

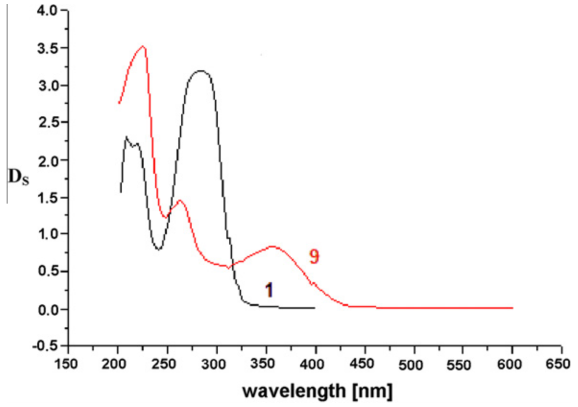


Figure 2 UV absorption spectra of 4-vinylbenzaldehyde **1** and *N*-(4-vinylbenzylidene)-6-fluoro-benzothiazol-2-amine **9** in absolute ethanol (C = 10^{-4} M).

Table 1 Optical density with respect to the initial concentration of derivative **6** at pH 4.4.

C_0 (10^{-5} mol/l)	2	4	6	8
$\mathbf{D}_S^0$	0.3659	0.7613	1.1209	1.4941

Table 2 Optical density with respect to the initial concentration of derivative **9** at pH 4.4.

C_0 (10^{-5} mol/l)	2	4	6	8
$\mathbf{D}_S^0$	0.1670	0.3401	0.4719	0.6427

*2.3.3. N-(4-vinylbenzylidene)-4-methyl-benzothiazol-2-amine (**8**)*

The compound **8** was obtained using the general method of synthesis described above. After evaporation of the solvent, the crude product was purified by column chromatography *n*-hexane/ethyl acetate: 6/0.50) to afford the desired imine as yellow oil, with 53% yield. n_D = 1.64, R_f = 0.62 *n*-hexane/ethyl acetate: 4/1; IR (film on NaCl pellets) t (cm^{-1}): 2960 (N=C—H), 1590.70 (C=N, imine), 1680 (C=N, benzothiazole), 1526 (C=C, vinyl), 3218 (=C—H), 988 ((=C—H), 917 (=CH$_2$); UV (EtOH) λ_1 max (ε max) = 357 nm (20067), λ_2 max (ε max) = 262 nm (36533) and λ_3 max (ε max) = 233 nm (38668); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 8.96 (s, H$_8$), 2.76 (s, H$_4$), 7.44–7.49 (m, H$_5$,H$_6$), 7.56–7.52 (m, H$_7$, H$_{10}$, H$_{10'}$), 8.01 (d, H$_9$, H$_{9'}$; J = 8.32 Hz), 6.77 (dd, H$_{11}$, J = 10.98 Hz, J = 17.59 Hz), 5.91 (d, H$_{12a'}$; J = 17.59 Hz), 5.41 (d, H$_{12a}$, J = 10.98 Hz); ^{13}C NMR (300 MHz, CDCl$_3$) δ (ppm): imine carbon: 165.728, aromatic

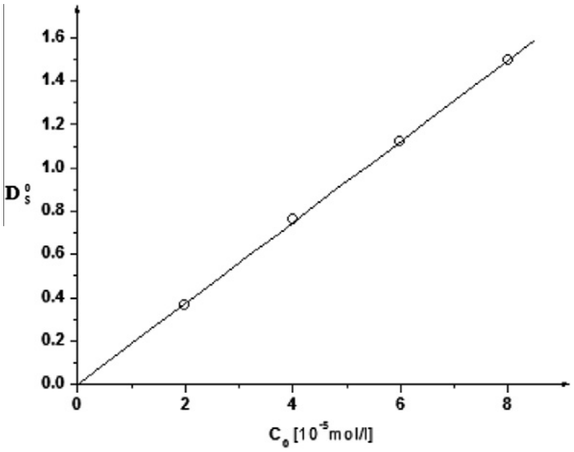


Figure 3 Optical density according to the initial concentration of derivative **6** at pH 4.4.The line is a linear fit.

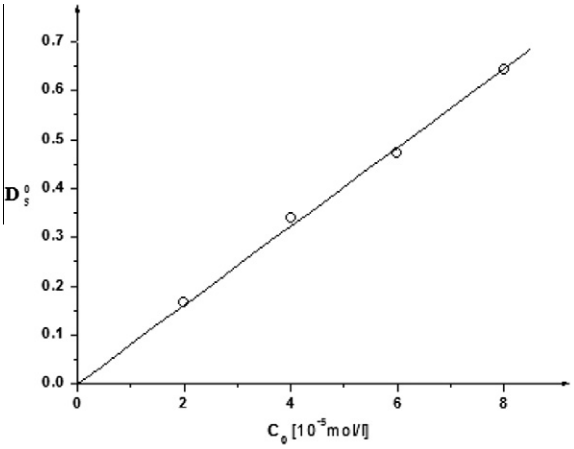


Figure 4 Optical density according to the initial concentration of derivative **9** at pH 4.4. The line is a linear fit.

and vinylic carbons: 126.34, 126.45, 126.75, 127.01, 130.07, 130.55, 136.05 and 142.25, carbon methyl group: 31.57.

*2.3.4. N-(4-vinylbenzylidene)-6-fluoro-benzothiazol-2-amine) **(9)***

The compound **9** was obtained using the general method of synthesis described above. After evaporation of the solvent, the residue obtained recrystallized in ethanol gave **9** as yellow powder, with 42% yield. mp = 96 °C; R_f = 0.64 (hexane/ethyl acetate: 4/1); IR (film on KBr pellets) t (cm^{-1}): 2970 (N=C—H), 1587 (C=N, imine), 1688.5 (C=N, benzothiazole), 1525.9 (C=C, vinyl), 3222 (=C—H);. UV (EtOH) λ_1 max (ε max) = 355 nm (8367), λ_2 max (ε max) = 261 nm (14347) and λ_3 max (ε max) = 224 nm (34951); ^{1}H NMR(300 MHz, DMSO-d_6) δ (ppm): 9.16 (s, H_8), 7.96 (dd, H_4, J = 8.95 Hz, J = 4.96 Hz), 7.39 (td, H_5, J = 8.95 Hz, J = 9.11 Hz), 8.02(dd, H_7, J = 8.78 Hz, J = 2.66 Hz), 8.07 (d, H_9,$H_{9'}$, J = 8.22 Hz),7.70 (d, H_{10}, $H_{10'}$, J =8.21 Hz), 6.85 (dd, H_{11}, J = 11.01 Hz, J = 17.67 Hz), 6.06 (d, $H_{12a'}$, J = 17.67 Hz), 5.47 (d, H_{12a}, J = 11.01 Hz);^{13}C NMR (300 MHz, DMSO-d_6) δ (ppm): imine carbon: 166.65, aromatic and vinylic carbons: 108.35, 108.35, 114.89, 114.57, 123.50, 123.62, 126.53, 130.23 and 135.58.

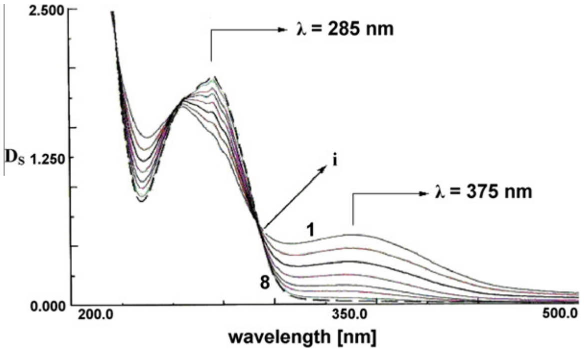


Figure 5 Temporal evolution of the *N*-(4-vinylbenzylidene)-benzothiazol-2-amine **6** UV absorption spectrum at pH 4.4; $C_0 = 0.8 \times 10^{-4}$ M.

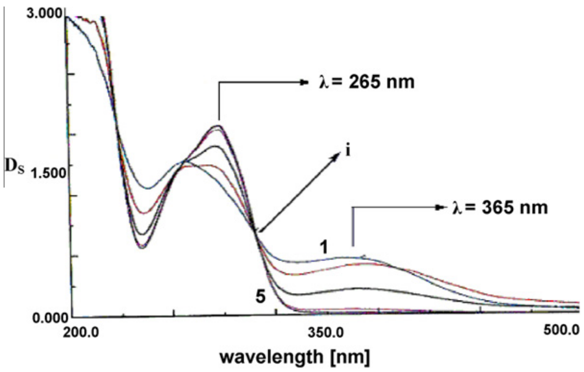


Figure 6 Temporal evolution of the *N*-(4-vinylbenzylidene)-6-fluoro-benzothiazol-2-amine **9** UV absorption spectrum at pH 4.4; $C_0 = 0.8 \times 10^{-4}$ M.

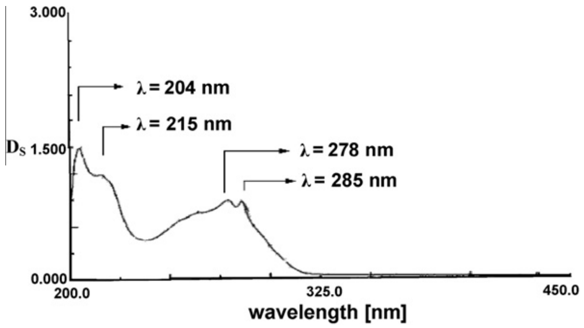


Figure 7 UV absorption spectrum of benzothiazol-2-amine and 4-vinylbenzaldehyde mixture buffered at pH 7; $C_0 = 0.8 \times 10^{-4}$ M.

3. Results and discussion

*3.1. Preparation of compounds **6**, **7**, **8** and **9***

The condensations of 4-vinylbenzaldehyde **1** on compounds **2**, **3**, **4** and **5** were performed in the presence of *para*-toluenesulfonic acid and 2,6-di-*t*-butylcatechol under reflux in benzene for 6 h according to reaction Scheme 1.

From **2** and **3**, the reaction leads to *N*-(4-vinylbenzylidene)-benzothiazol-2-amine **6** and *N*-(4-vinylbenzylidene)-4-meth-

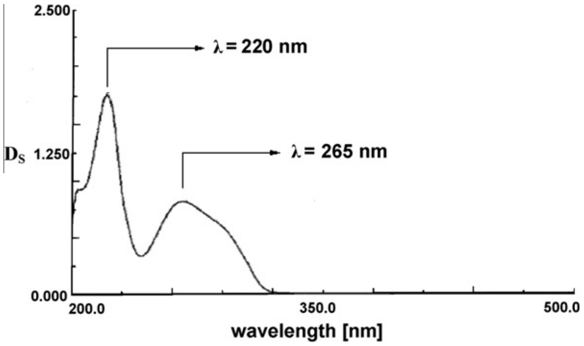


Figure 8 UV absorption spectrum of 6-fluoro-benzothiazol-2-amine and 4-vinylbenzaldehyde mixture buffered at pH 7; $C_0 = 0.8 \times 10^{-4}$ M.

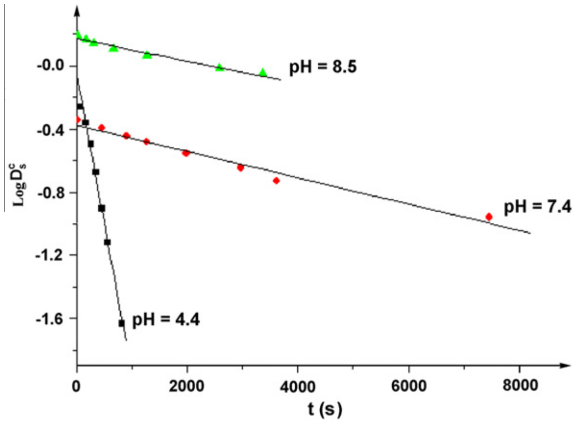


Figure 9 Log$\mathbf{D}_S^C$ variation as a function of time of compound **6** at different pH. The lines are linear fits.

oxy-benzothiazol-2-amine **7** in the form of two isomers whose proportions are, respectively, 1/0.5 and 1/0.91. However, the condensation of **1** with **4** and **5** provides *N*-(4-vinylbenzylidene)-4-methyl-benzothiazol-2-amine **8** and *N*-(4-vinylbenzylidene)-6-fluoro-benzothiazol-2-amine **9** with 42% and 53% yields, respectively.

3.2. Identification of products **6**, **7**, **8** *and* **9**

Compounds **6** and **8** show similar ^{1}H NMR spectra features, close to those of products **7** and **9,** allowing their structure to be easily deduced from ^{1}H NMR spectra. Imine protons of both isomers of products **6** and **7** appear as singlets in the range between 8.76 and 8.87 ppm, while those of **8** and **9** are located at 8.96 and 9.16 ppm, respectively. The ^{13}C NMR spectra confirm the presence of two isomers in the case of **6** and **7**, exhibiting, two peaks in between 165.38 and 166.71 ppm, while **8** and **9** ^{13}C NMR spectra show both peaks at around 166 ppm due to the imine function. The vinyl protons of compounds **6**, **7**, **8** and **9** are easily identifiable; they resonate at 6.84, 5.85 and 5.27 ppm. The IR spectra of Schiff bases **6**,**7**, **8** and **9** show an intense absorption band at 1526 cm^{-1} and two other bands located in 3210–3222 cm^{-1} and 916–988 cm^{-1} regions characteristic of the vinyl group elongation and deformation vibrations, respectively. The absorption band of the azomethine imine is located around 1587 cm^{-1}, while the imine of the thiazole nucleus absorbs around 1685 cm^{-1}. This low value (1587 cm^{-1}) could reflect a strong polarization of the imine (C═N), which follows logically from the conjugation of the remaining C═N bond with the aromatic ring. The examination of the electronic spectra of compounds **6**, **7**, **8** and **9** shows similarities among them. A strong sharp peak at 225 nm attributed to the electronic transition $\pi \rightarrow \pi^*$ is present. A second medium intensity band observed around 260 nm is due to a locally excited state of the molecule benzyliden moiety. A third low intensity band, whose maximum is located at 310 nm, is attributed to an excited state involving the whole of the molecule. Finally, these absorptions correspond to a spectral range close to that of di-substituted Schiff bases studied by several authors (Pitea et al., 1970; Ashraf El-Bayoumi et al., 1971; Belletête et al., 1977; Chafi et al., 1991).

3.3. Hydrolysis of derivatives **6** *and* **9**

Figs. 1 and 2 show the UV absorption spectra of the imines **6**, **9** in absolute ethanol, respectively, each one being associated with the 4-vinylbenzaldehyde **1** spectrum.

The analysis of these spectra shows that the low intensity band (I) which is a characteristic absorption band for each imine (λ_6 (I) = 375 nm and **9** λ_9 (I) = 365 nm) and those observed for 4-vinylbenzaldehyde **1** are well separated. Band (I) is located in a range of wavelengths where aldehyde, amine, and the buffer constituents do not absorb. This band is thus adequate to follow the hydrolysis kinetics. Hydrolysis reactions of imines **6** and **9** were studied in buffered aqueous solutions at pH 4.4, 7.4 and 8.5, and constant temperature (T = 25 °C) and ionic strength (μ = 0.01). The acetate and phosphate buffers were prepared in aqueous medium according to the methods described by Perrin (1963) and Michaelis and Mizutani (1925). Hydrolysis reactions at the different pH value being slow, complete UV spectra were then recorded over time intervals consistent with the advancement of reaction state. We also conducted several kinetic tests at the same pH values with varied initial Schiff base concentrations C_0, to verify that the optical density $\mathbf{D}_S^0$, extrapolated to time zero, is effectively proportional to C_0. The $\mathbf{D}_S^0$ data found for different C_0 values are collected in Tables 1 and 2, respectively, for **6** and **9** at pH 4.4. Figs. 3 and 4 show clearly the linear behavior of $\mathbf{D}_S^0$ with respect to C_0 of the imines.

Examples of the UV spectra evolution recorded during the hydrolysis of compounds **6** and **9** are reproduced in Figs. 5 and 6, respectively. The first spectrum is attributed to the pure Schiff base since the hydrolysis is slow. The final spectrum 8 is consistent with the mixture of 4-vinylbenzaldehyde and amine. The final state of the hydrolysis reaction for each of the derivatives **6** and **9** is established by recording the spectrum of equimolar mixture of 4-vinylbenzaldehyde and the corresponding amine at total concentration of 10^{-4} mol/l in Figs. 7 and 8, respectively. The comparison of the latter mixture spectra with the kinetic test spectra appearing in Figs. 5 and 6 shows that complete hydrolysis occurred. The experiment indicates in all cases that the chosen imine absorption band (I) disappears completely when time is long enough, suggesting that the reaction is complete in the present operating conditions.

During hydrolysis, the presence of isosbestic points (i) on the time dependent spectra corresponding to the concentration variation of our compounds show that there is no accumulation of any intermediate.

The use of band (I) optical density enables the determination of the observed apparent hydrolysis constants k_{obs}. It was verified that the reaction order is of the first kind with respect to the imine by plotting $\text{Log}\,\mathbf{D}_S^C$ as a function of time, where $\mathbf{D}_S^C$ is the optical density corrected for the always weak $\mathbf{D}_S^\infty$ value read at infinite time ($\mathbf{D}_S^C = \mathbf{D}_S - \mathbf{D}_S^\infty$). Indeed the $\mathbf{D}_S^C$ data vs t plotted in Figs. 9 and 10 for products **6** and **9**, respectively show linear behavior; they are fitted to the equation:

$$\text{Log}\,\mathbf{D}_S^C = \text{Log}\,\mathbf{D}_S^{0,C} - \frac{k_{\text{obs}}}{2,3}t$$

The linear fit provides access to the determination of the initial corrected optical density $\mathbf{D}_S^{0,C}$ by extrapolation to time t = 0 and to k_{obs} from the slope. The values of kinetic parameter k_{obs} obtained from Figs. 9 and 10 are reported in Table 3.

According to the results, the hydrolysis is first order process at any pH value. Since k_{obs} increases as pH decreases, the reac-

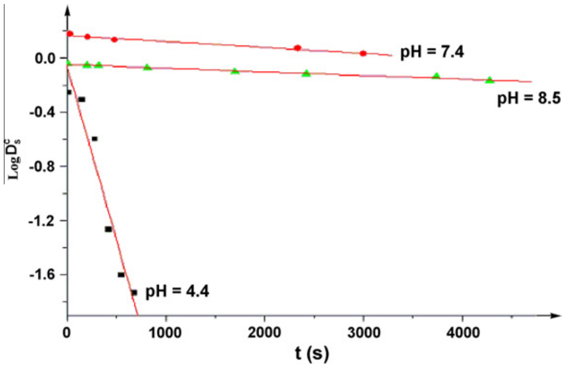


Figure 10 $\text{Log}\,\mathbf{D}_S^C$ variation as a function of time of compound **9** at different pH. The lines are linear fits.

Table 3 Experimental apparent rate constant of derivatives **6** and **9** as a function of pH.

pH	k_{obs} (10^{-5} min^{-1})	
	6	**9**
4.4	191.0 ± 0.7	257.0 ± 0.3
7.4	8.32 ± 0.51	4.36 ± 0.40
8.5	6.93 ± 0.55	2.69 ± 0.14

tion is catalyzed by the acidity. It should also be noted that at pH 4.4, the hydrolysis rate of compound **9** is greater than that of compound **6**, while an opposite effect is observed at pH 7.4 and 8.5 (see Table 3).

4. Conclusion

New Schiff bases have been synthesized by condensation of 4-vinylbenzaldehyde on benzothiazol-2-amine and its derivatives. From 4-methyl-benzothiazol-2-amine and 6-fluoro-benzothiazol-2-amine, the *N*-(4-vinylbenzylidene)-4-methyl-benzothiazol-2-amine **8** and *N*-(4- vinylbenzylidene)-6-fluoro-benzothiazol-2-amine **9,** respectively, are isolated with good yields. However, the condensations of 4-vinylbenzaldehyde with the benzothiazol-2-amine and 4-methoxy-benzothiazol-2-amine lead to mixtures of two isomers whose proportions are, respectively, 1/0.53 and 1/0.91. A hydrolysis kinetic study of products **6** and **9** in buffered aqueous medium at pH 4.4, 7.4 and 8.5 was performed and showed that hydrolysis is a first order process. For each compound, the hydrolysis rate increases with acidity.

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