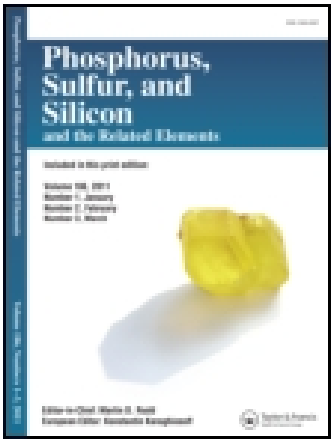

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Characterization of [1,2,4,6]Thiatriazino[2,3-a][1,3]benzimidazol-1(2H)-one and [1,3,5]Thiadiazino[3,4-a][1,3]benzimidazol-2-imine

A. Hajri [a] & R. Abderrahim [a]

[a] Laboratory of Physics of Lamellaires Materials and Hybrids Nanomaterials, Faculty of Sciences of Bizerte , University of Carthage , Bizerte, Tunisia

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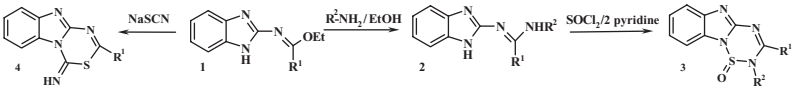
SYNTHESIS AND CHARACTERIZATION OF [1,2,4,6] THIATRIAZINO[2,3-a][1,3]BENZIMIDAZOL-1(2H)-ONE AND [1,3,5]THIADIAZINO[3,4-a][1,3]BENZIMIDAZOL-2-IMINE

A. Hajri and R. Abderrahim
Laboratory of Physics of Lamellaires Materials and Hybrids Nanomaterials, Faculty of Sciences of Bizerte, University of Carthage, Bizerte, Tunisia

GRAPHICAL ABSTRACT



Abstract *The reaction of thionyl chloride with amidines **2**, derived from N-benzimidazol-2-yl imidates 1, leads to [1,2,4,6]thiatriazino[2,3-a][1,3]benzimidazol-1(2H)-one **3** in good yields. [1,3,5]Thiadiazino[3,4-a][1,3]benzimidazol-2-imine **4** was prepared by condensation of NaSCN with benzimidazol-2-yl imidate **1**. The isolated compounds **3** and **4** were identified by spectroscopic methods including IR, ^{1}H NMR, and ^{13}C NMR as well as elemental analyses and MS of **3d** and **4b**.*

Keywords Amidines; imidates; [1,3,5]thiadiazino[3,4-a][1,3]benzimidazol-2-imine; [1,2,4,6]thiatriazino[2,3-a][1,3]benzimidazol-1 (2H)-one; thionyl chloride

INTRODUCTION

The chemistry of benzimidazole attracts much research because of its wide applications in several domains. Compounds derived from benzimidazole have diverse biocidal activities and pharmaceutical applications.[1–3] In particular, tricyclic benzimidazole derivatives have been investigated as potential inhibitors of dihydrofolate reductase in the search for anticancer and antibacterial agents[4–6] and for DNA intercalating agents.[6] As a continuation of our previous work,[7–9] we aimed, in this manuscript, to combine both nuclei, namelybenzimidazole and thiatriazine or thiadiazine, in a new series of benzimidazoles having the thiatriazine or thiadiazine ring directly linked to the benzimidazole moiety. It is important to note that substituted 1,3,5,2-thiatriazine-S-oxide derivatives are known for their useful proprieties from pharmacological and biological activities. They are used as anticoagulant,[10–12] anti-imflamatory,[13] antiviral,[14,15] antitumor,[16–19] and fungicidal agents,[20]

Received 14 May 2010; accepted 2 July 2010.
Address correspondence to R. Abderrahim, Chemistry Department, Faculty of Sciences Bizerte, Zarzouna 7021, Tunisie. E-mail: Abderrahim_raoudha@yahoo.fr

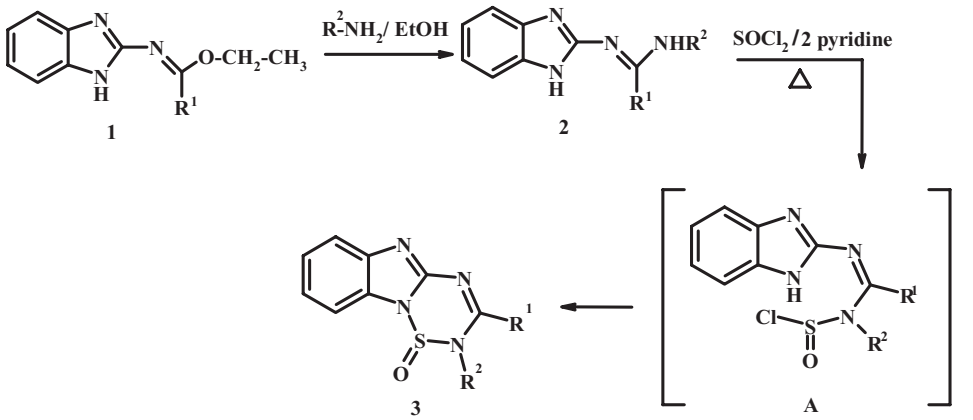
whereas 1,3,5-thiadiazine derivatives have a wide spectrum of antimicrobial activity. Several studies related to the antifungal, antiviral, antihelmintic, and tuberculostatic activity of these compounds has been extensively reported.[21,22] We report in this article a new method for the synthesis of [1,2,4,6]thiatriazino[2,3-a][1,3]benzimidazol-1(2H)-one **3** and [1,3,5]thiadiazino[3,4-a][1,3]benzimidazol-2-imine **4**.

RESULTS AND DISCUSSION

[1,2a]Benzimidazol-2-yl iminoesters **1** and [1,2a]benzimidazol-2-yl amidines **2** previously described by our group[7–9] were used as starting compounds to prepare the thiatriazine and thiadiazine benzimidazole derivatives.

Reaction of thionyl chloride with compound **2** derivatives in the presence of two equivalents of pyridine under reflux for 3 h yielded [1,2,4,6]thiatriazino [2,3-a][1,3]benzimidazol-1(2H)-one **3** in good yields. The structures of the isolated products were established on the basis of elemental analyses and the MS of **3d** and spectral data. For example, the ^{1}H NMR spectrum of compound **3a** displayed a singlet at δ 2.42 due to methyl protons, a triplet signal at δ 3.38 and quartet at δ 1.60 due to ethyl protons, in addition to aromatic multiplets in the region δ 7.50–8.10.

The formation of compounds **3** was confirmed by the IR spectra showing a strong band in the region 1080–1086 cm^{-1} assigned to the S=O group and another band in the region 1615–1622 cm^{-1} corresponding to C=N cyclic. The ^{13}C NMR spectra display the characteristic signals of all carbons. From a mechanistic viewpoint, the condensation of thionyl chloride and compound **2** under reflux gives **3**; we did not isolate intermediates **A** (Scheme 1).



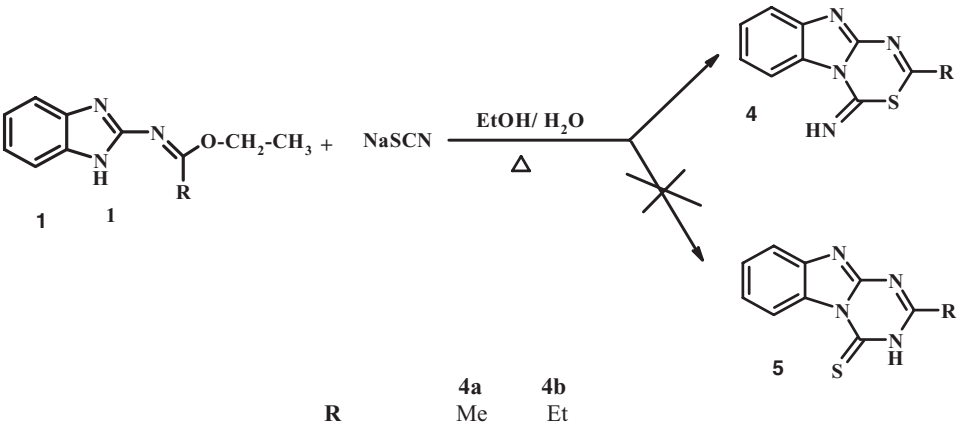
3	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
R^1	Me	Et	Me	Et	Me	Et
R^2	Et	Et	Pr	Pr	Ph-CH$_2$	Ph-CH$_2$

Pr : CH_3-CH_2CH_2 ; Ph : C_6H_5

Scheme 1

Treatment of [1,2a]benzimidazol-2-yl as iminoesters derivatives **1** with NaSCN in dioxane/H_2O under reflux gave only the product (Scheme 2). The formation of compound

4 was confirmed by ^{1}H NMR, ^{13}C NMR, IR spectrum, and elemental analyses. The isolated products were identified as [1,3,5]thiadiazino[3,4-a][1,3]benzimidazol-2-imine derivatives **4a** and **4b** (Scheme 2). The ^{1}H NMR spectrum of compound **4a**, taken as an example, revealed two singlet signals at δ 1.70 and δ 4.96 due, respectively, to methyl and NH protons, in addition to aromatic multiplets in the region δ 6.71–7.30. The ^{13}C NMR spectra recorded for compound **4a** and **4b** confirmed the formation of **4** and the total absence of compound **5**. The IR spectra showed the presence of a band in the region 1630–1638 cm^{-1} (C=N) and 3445–3460 cm^{-1} (C=NH) and total absence of absorption band corresponding to a C=S group, all of which support the formation of **4.**



Scheme 2

EXPERIMENTAL

IR spectra were recorded in $CHCl_3$ solution on a Perkin Elmer Paragon 1000 PC spectrometer. ^{1}H, ^{13}C NMR spectra were recorded with $CDCl_3$ or a mixture of $CDCl_3$ and $(CD_3)_2SO$ as the solvents containing TMS on a Bruker 300 spectrometer. The chemical shifts were reported in δ values relative to TMS (internal reference). For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet.

Melting points were obtained using a Büchi melting point apparatus. Elemental microanalysis was performed on a Perkin-Elmer CHN-2400 analyser apparatus. Mass spectra were recorded on a HP-5890 A using the impact mode (70 eV).

Synthesis of [1,2,4,6]Thiatriazino [2,3-a][1,3]benzimidazol-1(2H)-one 3

To a solution of compound **2** (1 mmol) in dioxane (10 mL) containing pyridine (2 mmol), thionyl chloride (1 mmol) was added dropwise. The reaction mixture was heated under reflux for 3 h and then left to cool. The solvent was evaporated to dryness under vacuum, and the solid obtained was filtered off and recrystallized from a mixture of chloroform and ethanol (v/v 9:1) to give **3**.

2-Ethyl-3-methyl [1,2,4,6] thiatriazino[2,3-a][1,3]benzimidazol-1(2H)-one (3a). Yield = 54%, mp = 186–188°C, IR ($CHCl_3$, ν (cm^{-1})): 1615 (C=N), 1086 (S=O). ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.38 (q, $^3J_{HH}$ = 8.8 Hz, $CH_3-\underline{CH_2}-N-$, 2H), 1.60 (t, $^3J_{HH}$ = 8.8 Hz, $\underline{CH_3}-CH_2-N-$, 3H), 7.50–8.10 (m, $4H_{arom}$). ^{13}C NMR ($CDCl_3$) δ 11.4 ($\underline{C}H_3$), 18.3 ($\underline{C}H_3-CH_2-N-$), 42.1 ($CH_3-\underline{C}H_2-N-$), 115.3 (HC−$\underline{C}$H=C−N=C−), 116.4 (−HC−$\underline{C}$H=C−NSO), 123.0 (H$\underline{C}$−CH=C−N−SO), 123.8 (H$\underline{C}$−CH=C−N=C−), 129.3 (HC−CH=$\underline{C}$−N−SO), 130.4 (HC−CH=$\underline{C}$−N=C−), 157.3 (−N=$\underline{C}$(N)−N−), 162.7 (−N=$\underline{C}$(CH_3)−N−). Calcd for $C_{11}H_{12}N_4SO$: C, 53.22; H, 4.83; N, 22.58. Found: C, 53.23; H, 4.80; N, 22.55.

2,3-Diethyl [1,2,4,6]thiatriazino [2,3-a][1,3]benzimidazol-1(2H)-one (3b). Yield = 61%, mp = 192–193°C, IR ($CHCl_3$ ν (cm^{-1})): 1618 (C=N), 1081(S=O). ^1H NMR ($CDCl_3$) δ 2.82 (q, $^3J_{HH}$ = 9.0 Hz, $CH_3-\underline{CH_2}$, 2H), 1.05 (t, $^3J_{HH}$ = 9.0 Hz, $\underline{CH_3}-CH_2$, 3H), 3.70 (q, $^3J_{HH}$ = 9.0 Hz, $CH_3-\underline{CH_2}-N$, 2H), 1.30 (t, $^3J_{HH}$ = 9 Hz, $\underline{CH_3}-CH_2-N$, 3H), 7.20–7.80 (m, $4H_{arom}$). ^{13}C NMR ($CDCl_3$) δ 10.1 ($\underline{C}H_3-CH_2$), 16.5 ($CH_3-\underline{C}H_2$), 20.5 ($\underline{C}H_3-CH_2-N-$), 43.3 ($CH_3-\underline{C}H_2-N-$), 112.6 (HC−$\underline{C}$H=C−N=C−), 112.8 (−HC−$\underline{C}$H=C−NSO), 116.0 (H$\underline{C}$−CH=C−N−SO), 117.0 (H$\underline{C}$−CH=C−N=C−), 139.4 (HC−CH=$\underline{C}$−N−SO), 140.6 (HC−CH=$\underline{C}$−N=C−), 156.1 (−N=$\underline{C}$(N)−N−), 164.0 (−N=$\underline{C}$(−CH_2-CH_3)−N−). Calcd for $C_{12}H_{14}N_4SO$: C, 54.96; H, 5.34; N, 21.37. Found: C, 54.93; H , 5.32; N, 21.35.

3-Methyl-2-propyl[1,2,4,6] thiatriazino [2,3-a][1,3]benzimidazol-1(2H)-one (3c). Yield = 66%, mp = 178–180°C, IR ($CHCl_3$, ν (cm^{-1})): 1622 (C=N), 1087 (S=O). ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.91 (t, $^3J_{HH}$ = 6.0 Hz, $CH_3-CH_2-\underline{CH_2}-N-$, 2H), 2.20 (m, 2H), 1.11 (t, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}-CH_2-CH_2-N-$, 3H), 7.54−8.60 (m, $4H_{arom}$). ^{13}C NMR ($CDCl_3$) δ 10.8 ($\underline{C}H_3$), 11.5 ($\underline{C}H_3-CH_2-CH_2-N-$), 21.9 ($CH_3-\underline{C}H_2-CH_2-N$), 45.6 ($CH_3-CH_2-\underline{C}H_2-N$), 111.3 (HC−$\underline{C}$H=C−N=C−), 112.2 (−HC−$\underline{C}$H=C−NSO), 124.8 (H$\underline{C}$−CH=C−N−SO), 125.0 (H$\underline{C}$−CH=C−N=C−), 139.8 (HC−CH=$\underline{C}$−N−SO), 144.6 (HC−CH=$\underline{C}$−N=C−), 159.1 (−N=$\underline{C}$(N)−N−), 170.7 (−N=$\underline{C}$(CH_3)−N−) Calcd for $C_{12}H_{14}N_4SO$: C, 54.96; H, 5.34, N, 21.37. Found: C, 54.93; H, 5.31; N, 21.40.

3-Ethyl-2-propyl[1,2,4,6] thiatriazino [2,3-a][1,3]benzimidazol-1(2H)-one (3d). Yield = 73%, mp = 166–168°C, IR ($CHCl_3$, ν (cm^{-1})): 1620 (C=N), 1085 (S=O). ^1H NMR ($CDCl_3$) δ 1.40 (t, , $^3J_{HH}$ = 9.0 Hz, $\underline{CH_3}-CH_2$, 3H), 2.71 (q, $^3J_{HH}$ = 6.0 Hz, $CH_3-\underline{CH_2}$, 2H), 3.47 (t, $^3J_{HH}$ = 6.0 Hz, $CH_3-CH_2-\underline{CH_2}-N$, 2H), 1.83 (m, 2H), 1.03 (t, $^3J_{HH}$ = 6.3 Hz, $\underline{CH_3}-CH_2-CH_2-N$, 3H), 8.24–9.09 (m, $4H_{arom}$). ^{13}C NMR ($CDCl_3$) δ 11.1 ($\underline{C}H_3-CH_2$), 11.2 ($\underline{C}H_3-CH_2-CH_2-N$), 20.3 ($CH_3-\underline{C}H_2$), 21.1 ($CH_3-\underline{C}H_2-CH_2-N$), 46.0 ($CH_3-CH_2-\underline{C}H_2-N$), 110.8 (HC−$\underline{C}$H=C−N=C−), 114.6 (−HC−$\underline{C}$H=C−NSO), 125.1 (H$\underline{C}$−CH=C−N−SO), 125.3 (H$\underline{C}$−CH=C−N=C−), 141.2 (HC−CH=$\underline{C}$−N−SO), 146.6 (HC−CH=$\underline{C}$−N=C−), 155.2 (−N=$\underline{C}$(N)−N−), 170.1 (−N=$\underline{C}$(−CH_2-CH_3)−N−). Calcd for $C_{13}H_{16}N_4SO$: C, 56.52; H, 5.79; N, 20.28. Found: C, 56.53; H, 5.79; N, 20.30. MS (m/z, %): 190 (33%), 145 (120%), 118 (96%), 131 (15%), 91 (25%).

2-Benzyl-3-methyl[1,2,4,6]thiatriazino[2,3-a][1,3]benzimidazol-1(2H)-one (3e). Yield = 80%, mp = 154–156°C, IR ($CHCl_3$, ν (cm^{-1})): 1620 (C=N), 1080 (S=O). ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 4.73 (s, 2H), 7.09-7.43 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 21.0($\underline{C}H_3$), 45.9 (Ph−$\underline{C}H_2$−N−), 115.0 (HC−$\underline{C}$H=C−N=C−), 115.2 (−HC−$\underline{C}$H=C−NSO), 124.1 (H$\underline{C}$−CH=C−N−SO), 124.3 (H$\underline{C}$−CH=C−N=C−), 127.1, 128.0, 131.2, 133.0 (C_{arom},$\underline{C}_6H_5$−), 136.7 (HC−CH=$\underline{C}$−N−SO), 137.0

(HC−CH=C−N=C−), 155.7 (−N=C(N)−N−), 166.9 (−N=C(CH_3)−N−). Calcd. for $C_{16}H_{14}N_4SO$: C, 61.90; H, 4.50; N, 18.00. Found: C, 62.03; H, 4.51; N, 18.03.

2-Benzyl-3-ethyl[1,2,4,6]thiatriazino[2,3-a][1,3]benzimidazol-1(2H)-one (3f). Yield = 71%, mp = 143–145°C, IR ($CHCl_3$, ν (cm^{-1})): 1620 (C=N), 1083 (S=O). ^1H NMR ($CDCl_3$) δ 1.30 (t, $^3J_{HH}$ = 9.0 Hz, CH_3−CH_2, 3H), 2.65 (q, $^3J_{HH}$ = 6.1 Hz, CH_3−CH_2, 2H), 4.65 (s, 2H), 7.15–7.50 (m, 9H). ^{13}C NMR ($CDCl_3$) δ. 11.8 (CH_3−CH_2), 26.4 (CH_3−CH_2), 40.5 (Ph−CH_2−N), 107.4 (HC−CH=C−N=C−), 110.5 (−HC−CH=C−NSO), 125.2 (HC−CH=C−N−SO), 125.8 (HC−CH=C−N=C−), 126.2, 127.9, 130.4, 134.0 (C_{arom}, C_6H_5−), 138.5 (HC−CH=C−N−SO), 139.3 (HC−CH=C−N=C−), 154.5 (−N=C(N)−N−), 167.4 (−N=C(−CH_2−CH_3)−N−).Calcd for $C_{17}H_{16}N_4SO$: C, 62.96; H, 4.93; N, 17.28. Found: C, 62.94; H, 4.90; N, 17.32.

Synthesis of [1,3,5]Thiadiazino[3,4-a][1,3]benzimidazol-2-imine 4

Equimolecular amounts (1 mmol) of **1** and NaSCN were dissolved under vigorous stirring in a mixture of ethanol (16 mL) and water (4 mL). After complete dissolution of the reagents, the solution was heated under reflux for 3 h. After cooling to room temperature, the organic solution was extracted with $CHCl_3$ (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure yielded crude compound. The product was recrystallized from methanol to give **4a**, **4b**.

6-Methyl[1,3,5]thiadiazino[3,4-a][1,3]benzimidazol-2-imine (4a). Yield = 57%, mp = 226–227°C, IR ($CHCl_3$, ν (cm^{-1})): 1630(C=N), 3445 (NH). ^1H NMR (DMSO-d_6 + $CDCl_3$) δ 1.70 (s, 3H), 4.96 (s, 1H), 6.71-7.30 (m, $4H_{arom}$). ^{13}C NMR (DMSO-d_6 + $CDCl_3$), δ: 19.1(CH_3), 111.6 (HC=C−N−C(NH−S), 114.0 (HC=C−N=C(N)−N=), 118.1 (HC−CH=C−N=C−), 120.6 (HC−CH=C−N (NH)−S−), 121.0 (HC=C−N−C(NH)−S), 136.8 (HC=C−N=C(N)−N=), 153.8 (−N=C(N)−N=), 154.2 (−N−C(S)=NH), 173.0 (−N=C(−CH_3)−S−). Calcd for $C_{10}H_8N_4S$: C, 55.55; H, 3.70; N, 26.01. Found: C, 55.57; H, 3.65; N, 26.05.

6-Ethyl[1,3,5]thiadiazino[3,4-a][1,3]benzimidazol-2-imine (4b). Yield = 61%, mp = 212–214°C, IR ($CHCl_3$, ν (cm^{-1})): 1638 (C=N), 3460 (NH). ^1H NMR (DMSO-d_6 + $CDCl_3$), δ 1.18 (t, $^3J_{HH}$ = 9.0 Hz, CH_3−CH_2, 3H), 2.70 (q, $^3J_{HH}$ = 9.0 Hz, CH_3−CH_2, 2H), 5.80 (s, 1H), 7.00–7.50 (m, $4H_{arom}$). ^{13}C NMR (DMSO-d_6 + $CDCl_3$) δ 10.2 (CH_3−CH_2), 24.7 (CH_3−CH_2), 111.5 (HC=C−N−C(NH−S), 113.4 (HC=C−N=C(N)−N=), 119.4 (HC−CH=C−N=C−), 120.4 (HC−CH=C−N (NH)−S−), 121.0 (HC=C−N−C(NH)−S), 137.7 (HC=C−N=C(N)−N=), 154.0 (−N=C(N)−N=), 154.8 (−N−C(S)=NH), 174.1 (−N=C(−CH_2−CH_3)−S−). MS (m/z, %): 170 (20), 143 (42), 133 (100); 105 (12); 90 (3); 78 (25); 57 (11). Calcd for $C_{11}H_{10}N_4S$: C, 57.39; H, 4.38; N, 24.33. Found: C, 57.40; H, 4.35; N, 24.35.

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