Heteroatom Chemistry
Volume 21, Number 5, 2010

Synthesis of [1,2-*a*] Benzimidazolo-1,3,5-triazin-2-thione, [1,2-*a*] Benzimidazolo-1,3,5-thiadiazin-2-thione, [1,2-*a*] Benzimidazolo-1,3,5-triazin-2-amine, and [1,2-*a*] Benzimidazol-2-yl Amidrazone

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Received 19 May 2009; revised 21 December 2009

ABSTRACT: *N-benzimidazol-2-yl imidate type* **1** *reacts with thiourea, carbon disulfide, cyanamide, and hydrazide to give, respectively, [1,2-a] benzimidazolo-1,3,5-triazin-2-thione* **2**, *[1,2-a] benzimidazolo-1,3,5-thiadiazin-2-thione* **3**, *[1,2-a] benzimidazolo-1,3,5-triazin-2-amine* **4**, *and [1,2-a] benzimidazol-2-yl amidrazone* **5** *with good yields. Structures elucidation of all newly synthesized heterocyclic compounds was based on the data of IR, ^1H NMR, ^{13}C NMR, elemental analysis, and MS of some products.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:279–283, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20618

INTRODUCTION

Benzimidazoles and their polycyclic derivatives have been found to be of pharmacological [1] and biological activities such as anti-inflammatory agents [2], antidiabetics [3], antirheumatics [2], antihypertensives [3], antimicrobial [4,5], and as antibiotics against *Staphylococcus* [6]. They also have herbicidal activities [7,8] and antidepressant effects [9]; they act as bactericides [10], fungicides [10], and as diuretics [10]. In the literature, we noticed that [1,2-*a*] benzimidazolo-1,3,5-triazin-2-thione derivatives were prepared mainly by condensation of *N*-benzimidazoyl imidate or *N*-benzimidazol-2-yl amidine with thioisocyanate [11,12]. On the other hand, to date only a limited number of studies on the synthesis of [1,2-*a*] benzimidazolo-1,3,5-triazin-2-amine derivatives have been reported [13–15]. Whereas the synthesis of [1,2-*a*] benzimidazolo-1,3,5-thiadiazin-2-thione and [1,2-*a*] benzimidazol-2-yl amidrazone was not reported in the literature.

For all these reasons, we continue our laboratory work on the synthesis of fused benzimidazoles [11,12, 16–18]. So herein we report the synthesis of [1,2-*a*] benzimidazolo-1,3,5-triazin-2-thione, [1,2-*a*] benzimidazolo-1,3,5-thiadiazin-2-thione, [1,2-*a*] benzimidazolo-1,3,5-triazin-2-amine, and [1,2-*a*] benzimidazol-2-yl amidrazone.

RESULTS AND DISCUSSION

In extension of our previous studies of the reactivity of *N*-benzimidazol-2-yl iminoester **1**, we describe here an efficient and operationally simple method for the synthesis of fused benzimidazoles (benzimidazole thiadiazine benzimidazole triazine derivatives and benzimidazol-2-yl amidrazone).

N-benzimidazol-2-yl imidate derivatives **1** were obtained as described previously [16]. Treatment

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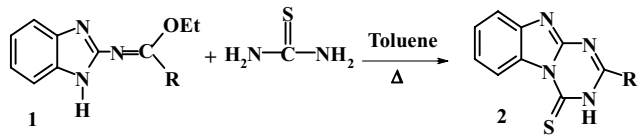


2a R = Me

2b R = Et

SCHEME 1

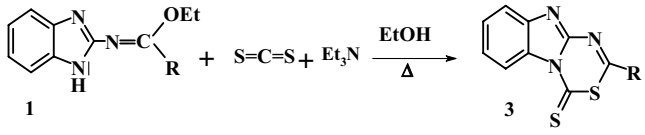
of compound **1** with thiourea in dry toluene under reflux for 48 h afforded 1,3,5-triazino [1,2-*a*] benzimidazolo-2-thione (Scheme 1). The structure of compounds **2** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and MS spectral data.

IR spectra of compounds **2** showed absorption bands at 1635, 1240, 3350, and 1570–1590 cm^{-1} related to C=N, C=S, NH, and C=C, respectively.

The ^{1}H NMR spectra showed the peaks of all hydrogen set of the expected compounds and the disappearance of the ethoxy group. The ^{13}C NMR confirmed the ^{1}H NMR spectroscopy by the appearing of signal at 184 ppm corresponding to the C=S group present in compound **2** and the absence of two signals at δ_C = 13 and 62 ppm corresponding to the ethoxy group. The spectroscopic properties and MS spectra were found to be in good agreement with the assigned structure of **2**.

The chemical reactivity of iminoester **1** was further investigated through its reaction with carbon disulfide in the presence of triethylamine and under reflux of ethanol afforded thiadiazine thione **3** (Scheme 2).

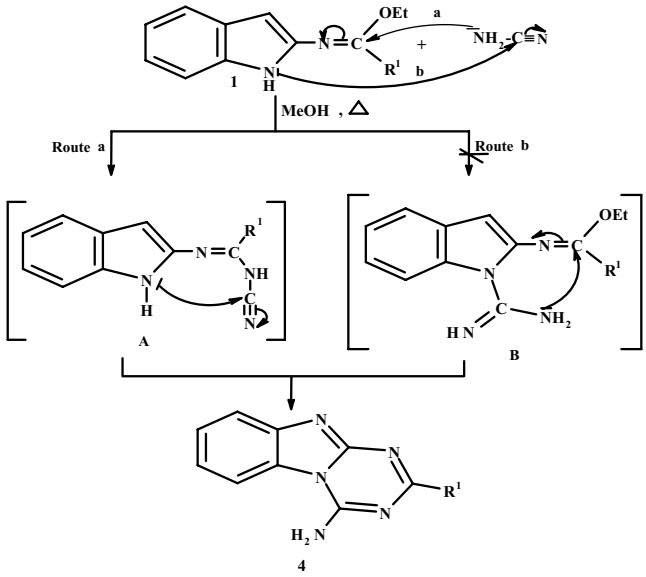
A reasonable mechanism of the reaction of **1** with carbon disulfide involves an initial elimination of the proton of NH by triethyl amine. The second step is the nucleophilic attack of the nitrogen atom of iminoester **1** (acted as nucleophilic reagents) onto the C=S group. Finally, intramolecular cyclization afforded the thiadiazine thione **3**. The structure of the latter products **3** was established with help of the spectral data. The IR spectra of compounds **3** revealed the absorption bands corresponding to C=S and C=N at 1250 and 1620 cm^{-1}, respectively, and



3a R = Me

3b R = Et

SCHEME 2



4a R^1= Me **4b** R^1 = Et **4c** R^1 = Ph

SCHEME 3

revealed the absence of the absorption band of the NH group. The ^{1}H NMR spectrum of compound **3** revealed the disappearance of the signals of NH and the ethoxy group.

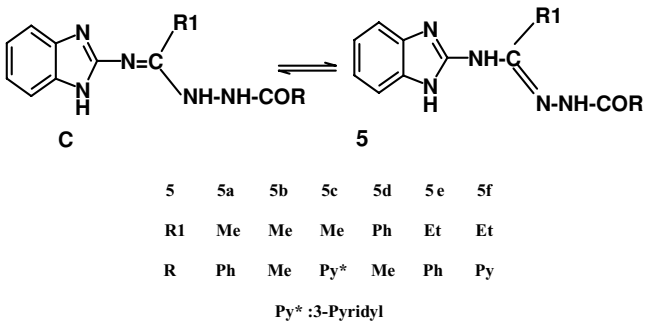
^{13}C NMR spectra of compound **3** exhibit a signal at 168.9 ppm (**3a**), and at 171.8 ppm (**3b**) attributed to the carbon of thiocarbonyl group (C=S) and displayed the characteristic signals of all carbons.

On the other hand, the reaction of *N*-benzimidazol-2-yl imidate **1** with cyanamide under reflux of methanol gave benzimidazolo triazine amine **4** (Scheme 3).

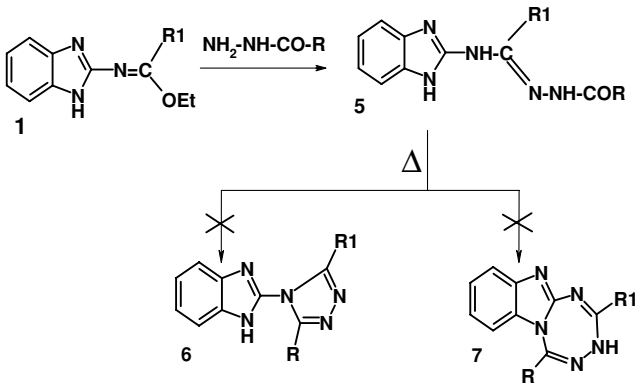
The formation of product **4**, proceeded via the nonisolable product **A** or **B**, which was followed by two separate routes for heterocyclic ring closure furnishing products **4** (Scheme 3). **A** was obtained by the attack of the carbon of imidate **1** by the nitrogen atom of cyanamide. **B** was obtained by the attack of the central atom of cyanamide by the nitrogen atom of **1**. The latter undergoes intramolecular cyclization to give the benzimidazolo triazine amine **4**.

The IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis of the reaction product **4** were found to be in a good agreement with the assigned structures (cf. the section Experimental).

The IR spectrum of compounds **4** exhibited absorption bands for NH_2 at 3120–3210 cm^{-1}, for C=N at 1620 cm^{-1}, and for C=C at 1600 cm^{-1}. The ^{1}H NMR spectrum of **4** showed signals for aryl protons at δ = 7–7.8 ppm and signals for two aryl protons



SCHEME 4



SCHEME 5

each one of which gives a multiplet at $\delta = 7.6$ ppm (**4c**). The presence of the amino group in the structure was supported by D_2O exchangeable signals at $\delta = 7.5$ ppm (**4a**), 6.0 ppm (**4b**), 7.0 ppm (**4c**), and the disappearance of ethoxy peaks and the NH peak.

Analogously, compound **1** was proved to be a key of other subsequent conversions. Thus, when it allowed to react with hydrazide, the reaction performed to produce benzimidazol-2-yl amidrazone derivatives **5**. The structure of compounds **5a–f** was deduced from their ^{1}H NMR and IR spectra and elemental analysis of **5f** and mass spectra of compounds **5a–e**.

The absorption band for the C=N group showed that the structure of compound **5** is an hydrazine-amine (amidrazone), which tautomerized to the less stable form of imine hydrazine (**C**). This result conforms to the literature [19] (Scheme 4). The IR spectroscopy of **5** showed absorption bands at 3120–3470, 1690, and 1610–1630 cm^{-1} related to the NH, carbonyl group (C=O), and C=N group, respectively. The ^{1}H NMR spectra showed disappearance of the signals of the ethoxy group and appearance of the signals of protons of the **R** introduced by hydrazide and the signal of the protons NH.

A mixture of compound **1** and hydrazide was kept at room temperature until a solid precipitated. The solid was and separated was identified as the amidrazone **5**. Whereas the intracyclization of **5** failed to give compounds **6** or **7** (Scheme 5). The intracyclization to give **6** is possible, but we can explain that the cyclization was failed because the doublet of the NH was conjugated with two aromatic systems. Then, it explains the lower nucleophilicity of this nitrogen atom.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Paragon 1000 PC spectrometer as potassium bromide pellets or in $CHCl_3$ solution.

^{1}H and ^{13}C NMR spectra were recorded with $(CD_3)_2SO$ or $CDCl_3$ solvent containing TMS (tetramethylsilane) on a Brüker 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75.47 MHz). The chemical shifts ($\delta\delta$ are reported in ppm 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, and m: multiplet.

Melting points were obtained using a Büchi melting point apparatus and are uncorrected. Elemental microanalysis was performed on a Perkin-Elmer CHN-2400 analyzer apparatus.

Mass spectra were recorded on a HP-5890 A using the impact mode (70 eV).

Synthesis of [1,2-a]Benzimidazolo-1,3,5-triazin-2-thione **2**

To a solution of imidate **1** (2 mmol), in anhydrous toluene (30 mL), thiourea (2 mmol) was added. The reaction mixture was stirred and heated under reflux for 48 h. The solvent was removed under vacuum, and the resulting solid was filtered off, dried, and crystallized from ethanol.

2a: Yield: 55%. mp: 176°C. IR (KBr, ν (cm^{-1})): 1635 (C=N), 1240(C=S). ^{1}H NMR (DMSO-d_6) δ: 1.90 (s, 3H, CH_3), 6.90–7.30 (m, 5H, NH deuterium exchangeable, $4H_{arom}$). ^{13}C NMR (DMSO d_6) δ: 18.07, 113.69, 120.62, 137.74, 154.86, 167.56, 183.75. MS (*m/z*, %): 202 (18), 158 (32), 133 (100), 90 (13), 78 (20), 59 (33).

2b: Yield: 48%. mp: 172°C. IR (KBr, ν (cm^{-1})): 1630 (C=N), 1240 (C=S). ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, 3H, CH_3), 2.61 (q, 2H, CH_2), 7.05–7.40 (m, 5H, NH deuterium exchangeable, $4H_{arom}$). ^{13}C NMR (DMSO d_6) δ: 10.58, 24.96, 113.51, 120.73, 137.89, 155.04, 171.01, 184.05. MS (*m/z*, %): 189 (20), 160 (42), 133 (100); 105 (12); 90 (3); 78 (25); 57 (4).

Synthesis of [1,2a]Benzimidazolo-1,3,5-thiadiazin-2-thione **3**

A mixture of **1** (2 mmol) and carbon disulfide (2.2 mmol) in ethanol (10 mL) containing triethylamine (2.2 mmol) was refluxed for 24 h. After cooling, the solvent was evaporated in vacuum and the resulting solid was collected by filtration, washed with ether, and crystallized from methanol.

3a: Yield: 70%. mp: 158°C. IR ($CHCl_3$, ν (cm^{-1})): 1620 (C=N), 1251 (C=S). ^{1}H NMR (DMSO-d_6) δ: 1.94 (s, 3H, CH_3), 7.05–7.30 (m, 4H, H_{arom}). ^{13}C NMR (DMSO-d_6) δ: 13.96, 25.60, 113.99, 121.47, 137.99, 154.52, 168.69. Calcd for $C_{10}H_7N_3S_2$ C 51.50, H 3.00, N 18.02; Found: C 51.39; H 3.10, N 17.95.

3b: Yield: 75%. mp: 165°C. IR ($CHCl_3$, ν (cm^{-1})): 1620 (C=N), 1251 (C=S). ^{1}H NMR (DMSO-d_6) δ: 1.18 (t, 3H, CH_3), 2.55 (q, 2H, CH_2), 7.05–7.30 (m, 4H, H_{arom}). ^{13}C NMR (DMSO-d_6) δ: 10.54, 25.21, 113.95, 121.30, 123.96, 136.36, 149.42, 171.80. Calcd for $C_{11}H_9N_3S_2$: C 53.44, H 4.45, N 17.00; Found: C 53.39, H 4.20, N 16.95.

Synthesis of [1,2-a]Benzimidazolo-1,3,5-triazin-2-amine **4**

To a solution of **1** (3 mmol) in methanol (10 mL), cyanamide (3 mmol) dissolved in methanol (5 mL) was added in dropwise. The reaction mixture was heated under reflux for 24 h. The solvent was removed under vacuum, and the formed solid product was collected by filtration and crystallized from ethanol.

4a: Yield: 75%. mp: 295°C. IR (KBr, ν (cm^{-1})): 3120–3210 (NH_2), 3030 (CH_{arom}), 1615 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6) δ: 1.90 (s, 3H, CH_3), 7.00–7.30 (mu, 4H, H_{arom}), 7.50 (broad s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 20.30, 113.10, 117.10, 119.00, 125.30, 126.00, 144.50, 149.20, 150.00, 169.00. Anal. Calcd for $C_{10}H_9N_5$: C 60.30, H 4.52, N 35.18; Found: C 60.22, H 4.44, N 35.30.

4b: Yield: 70%. mp: 265°C. IR (KBr, ν (cm^{-1})): 3120–3210 (NH_2), 3030 (CH_{arom}), 1615 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6) δ: 1.3 (t, 3H, CH_2—CH_3), 2.30 (q, 2H, CH_3—CH_2), 6.00 (broad s, 2H, NH_2 deuterium exchangeable), 7.00–7.30 (mu, 4H, H_{arom}). ^{13}C NMR (DMSO-d_6) δ: 11.00, 29.00, 113.20, 116.10, 121.10, 126.00, 126.20, 137.10, 144.00, 148.00, 169.10. Anal. Calcd for $C_{11}H_{11}N_5$: C 61.97, H 5.16, N 32.86; Found: C 61.82, H 5.14, N 32.72.

4c: Yield: 70%. mp: 265°C. IR (KBr, ν (cm^{-1})): 3120–3220 (NH_2), 3030 (CH_{arom}), 1615 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6:) δ: 7.00 (broad s, 2H, NH_2 deuterium exchangeable), 7.80 (mu, 9H, H_{arom}). ^{13}C NMR (DMSO-d_6) δ: 113.10, 117.00, 122.00, 125.00, 126.00, 128.00, 128.80, 130.10, 131.00, 145.10, 148.00, 153.10, 171.00. Anal. Calcd for $C_{15}H_{11}N_5$: C 68.96, H 4.21, N 26.83; Found: C 68.82, H 4.14, N 27.01.

Synthesis of Benzimidazol-2-yl Amidrazone **5**

To a solution of imidate (10 mmol) **1** dissolved in methanol, hydrazide (10 mmol) was added. The mixture was left at room temperature until a solid precipitated (7–10 days); the solid product was filtered and purified by recrystallization from CCl_4.

5a: Yield: 75%. mp: 145°C. IR ($CHCl_3$, ν (cm^{-1})): 3320–3470 (NH), 1690 (C=O), 1630 (C=N). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 1.80 (s, 3H, CH_3), 7.80 (broad s, 3H, NH), 7.00 (m, 9H, H_{arom}). MS (*m*/*z*, %): 293 (18), 173 (45), 158 (35), 132 (56), 120 (31), 77 (45).

5b: Yield: 70%. mp: 140°C. IR ($CHCl_3$, (ν cm^{-1})): 3220-3330–3400 (NH), 1690 (C=O), 1620 (C=N). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 2.00 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 5.90 (broad s, 3H, NH), 7.20 (m, 4H, H_{arom}). MS (*m*/*z*, %): 231(9), 173 (45), 77 (20), 58 (33).

5c: Yield: 72%. mp: 155°C. IR (KBr) ν (cm^{-1})): 3100–3230 (NH), 1690 (C=O), 1630 (C=N). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 1.90 (s, 3H, CH_3), 7.60 (broad s, 3H, NH), 7.10 (m, 8H, H_{arom}). MS (*m*/*z*, %): 294 (10), 173 (25), 135(33), 121 (37), 92 (40), 77 (15).

5d: Yield: 65%. mp: 170°C. IR ($CHCl_3$, ν (cm^{-1})): 3100–3230 (NH), 1690 (C=O); 1620 (C=N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 2.00 (s, 3H, CH_3); 8.00 (broad s, 3H, NH); 7.10 (m, 9H, H_{arom}). MS (*m*/*z*, %): 293 (5), 235 (43), 132 (35), 135(23), 77 (40), 58 (65).

5e: Yield: 70%. mp: 201°C. IR (KBr, ν (cm^{-1})): 3110–3220 (NH), 1690 (C=O), 1620 (C=N). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 1.30 (t, 3H, CH_3); 2.20 (q, 2H, CH_2), 8.00 (broad s, 3H, NH); 7.10 (m, 9H, H_{arom}). MS (*m*/*z*, %): 307 (8), 287 (43), 132 (25), 120(45), 77 (32).

5f: Yield: 65%. mp: 170°C. IR ($CHCl_3$, ν (cm^{-1})): 3100–3230 (NH), 1690 (C=O), 1610 (C=N). ^{1}H NMR ($CDCl_3$ + DMSO-d_6), δ: 1.30 (t, 3H, CH_3), 2.20 (q, 2H, CH_2), 7.80 (broad s, 3H, NH), 7.10 (m, 8H, H_{arom}). Anal. Calcd for $C_{16}H_{16}N_6O$: C 62.33, H 5.19, N 27.27; Found: C 62.22, H 5.06, N 27.21.

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