The Efficient Synthesis of 2-Arylamino-2-imidazolines, 2-Heteroaryl-Substituted Benzimidazoles, and Their Morpholin-4-ylmethyl Derivatives

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Received 1 February 2002; revised 27 June 2002; accepted 16 July 2002.

ABSTRACT
2-Heteroaryl-substituted 1H-benzimidazoles were synthesized in good yields by heating the HSO₃, adducts of heteroaromatic aldehydes with o-phenylenediamine in DMF under reflux. This procedure is more general and shorter than earlier methods. 2-Arylamino-2-imidazolines were prepared by heating dimethyl arylthioimidocarbonates and ethylenediamine under reflux. The imine–enamine tautomerization of 2-arylamino-2-imidazolines was investigated by means of ¹H-NMR spectroscopy. Morpholin-4-ylmethyl derivatives of the benzimidazole and imidazoline products were synthesized regioselectively by treatment with morpholine and formaldehyde.

KEYWORDS
2-Substituted benzimidazoles, 2-arylamino-2-imidazolines, imine–enamine tautomerization, dimethyl arylthioimidocarbonates.

1. Introduction
The benzimidazole and imidazoline ring systems have an interesting chemistry, and they are also effective pharmacophores in medicinal chemistry. The synthesis of 2-substituted-1H-benzimidazoles and 2-substituted-1H-imidazoles as well as 2-arylamino-2-imidazoline derivatives has become of recent interest to medicinal chemists owing to the pharmacophoric properties of the heteroaromatic rings.¹–⁴ Over the past four decades, a number of methods to produce 2-arylamino-2-imidazolines derivatives from the corresponding arylamines have been reported in the literature.⁵–¹⁰ A review of the methods available for the synthesis of 2-arylamino-2-imidazolines and their derivatives was not encouraging. The reported synthetic routes are generally laborious, multi-step procedures requiring the synthesis of relatively complicated starting materials. Chapleo et al. have reported the synthesis of 2,6-dichlorophenylamino-2-imidazoline (clonidine) analogues by treating an aromatic amine with 2-methylthio-2-imidazoline in presence of pyridine.⁶ One of the most commonly used approaches entails a three-step protocol involving the conversion of an amine into the isothiocyanate, then treatment of the isothiocyanate with ethylenediamine followed by a cyclization step using mercuric oxide or acetate to form the 2-amino-2-imidazolines. Munk et al. have reported that yields in the formation of 2-amino-2-imidazolines can be moderately improved over Chapleo’s procedure by coupling an aromatic primary amine with an imidazolinesulfonic acid.⁷ There have also been reports in which a 2-chloro-2-imidazoline is coupled with an amine.⁸–¹⁰

The synthesis of 2-substituted benzimidazoles was first reported more than a century ago. Benzimidazoles can be synthesized by a number of methods, usually involving formation of the N–C–N unit as the key step.¹¹–¹⁴ One of the formerly utilized general routes to benzimidazoles involves the reaction of aldehydes and ketones with o-phenylenediamine. Although there are several routes leading to 2-substituted benzimidazoles, a typical procedure involves heating o-phenylenediamine with a substituted carboxylic acid in the presence of a mineral acid. In this method, excess carboxylic acid is used to close the ring (n_carboxylic acid / n_ophenylenediamine : 10 / 1). Reaction yields very much depend on the amount of the carboxylic acid used in this method.

This article reports the first synthesis of 2-(1H-indol-2-yl)-1H-benzimidazole 3b by this method. Also reported are syntheses of N-(morpholin-4-ylmethyl) derivatives of 2-heteroaryl substituted-1H-benzimidazoles and 2-arylamino-2-imidazolines, which have not been investigated previously.

2. Results and Discussion
In this study, a series of 2-heteroaryl-substituted 1H-benzimidazoles 3a–e was synthesized in good yield by heating the NaHSO₃, adducts of heteroaromatic and aromatic aldehydes with o-phenylenediamine in DMF at reflux (Scheme 1). This method was found to be highly advantageous over the other known methods and suitable for large scale preparations, as it is high-yielding. The yields, melting point and relevant spectroscopic data for compounds 3a–e are given in Table 1 (see Experimental section).

The chemical shift values of protons in the 2-heteroaryl benzimidazoles 3 are slightly shifted upfield compared to those of benzimidazole itself. Pyrrolyl, indolyl, furyl, thienyl and phenyl substituents have very small but similar effects on the chemical shifts of protons in the benzimidazole ring. All NH signals disappeared upon addition of D₂O to the solution, indicating that there are acidic protons in ¹H-NMR spectra.

Reaction of carbon disulfide and methyl iodide with aromatic amines in the presence of concentrated aqueous NaOH led to the formation of dimethyl arylthioimidocarbonates 5a–c which, on treatment with bis-nucleophiles such as ethylenediamine, gave 2-arylamino-2-imidazolines 6a–c (Scheme 2).
The suggested reaction mechanism for the formation of the aryl-substituted dithioimidocarbonates 5a–c is shown in Scheme 3.

Imine–enamine tautomerization of 2-arylamino-2-imidazolines 6a–c was investigated by using 1H-NMR techniques. In the 1H-NMR (200 MHz) spectra of 6a–c, singlets integrating for four hydrogens were observed at 3.78, 3.73 and 3.76 ppm, respectively. These compounds are effectively symmetrical because of imine–enamine dynamic tautomerization, which makes the CH₂ protons equivalent (Scheme 4). At the same time this effect causes lowering of the order of the spectra (Δν/ν = 0).

The imidazolidine N–H groups of these compounds are active for the Mannich reaction. 2-[1-(Morpholin-4-ylmethyl)-1H-pyrrol-2-yl]-1H-benzimidazole 7, 1-(morpholin-4-ylmethyl)-2-[1-(morpholin-4-ylmethyl)-1H-indol-2-yl]-1H-benzimidazole 8, N-(1,3-benzothiazol-2-yl)-N-[1-(morpholin-4-ylmethyl)-4,5-dihydro-1H-imidazol-2-yl]amine 9 and N-(1,3-benzothiazol-2-yl)-N-[1-(morpholin-4-ylmethyl)-4,5-dihydro-1H-imidazol-2-yl]amine 10 were synthesized from morpholine and formaldehyde (Scheme 5) for the first time in this study. The imidazolidine ring CH₂ signals of 9 and 10 compounds appeared as multiplets in the 1H-NMR spectra, which shows that the effective symmetry of their precursors has been lost.

Mannich reactions are frequently used in indole chemistry, resulting in the formation of 3-alkylaminoindoles at high temperature, although N,N-dialkylaminomethyl products can occasionally be isolated at room temperature. Under neutral conditions and at low temperature, indoles react with a mixture of formaldehyde and secondary amine by substitution at the indole nitrogen. It seems likely that this reaction involves a low equilibrium concentration of the indolyl anion. In neutral solution at higher temperature conversion into the thermodynamically more stable 3-substituted products occurs. Compounds 3a and 3b possess two different active N–H hydrogens, which can participate in Mannich reaction. The N–H hydrogens in indole and pyrrole rings (pKₐ = ~0.27 at 25°C for pyrrole) are more reactive than those in benzimidazole (pKₐ = 5.532 at 25°C). Therefore, the Mannich reaction which is conducted with one equivalent of reactant proceeds preferentially through the N–H hydrogens in the pyrrole or indole ring.

3. Experimental
Aromatic amines and hetero-aromatic aldehydes were obtained from commercial sources. Melting points (uncorrected) were determined with a Gallenkamp apparatus. IR spectra were measured on a Mattson model FT-IR spectrometer, and ¹H and ¹³C NMR spectra were measured on FX-90 Q JEOl and 200 MHz Bruker AC instruments. Chemical shift values (δ) are reported in ppm relative to TMS. Elemental analyses were performed on a LECO model 932 instrument.
Synthesis of 2-heteroaryl-substituted 1H-benzimidazoles 3a–e.

General procedure.

A solution of NaHSO₃ (0.01 mol) in water (10 ml) was added in small portions to a solution of the heteroaromatic aldehyde 1a–e (0.01 mol) in ethanol (10 ml) cooled in an ice-bath within 10 min. The precipitated bisulfite adducts 2a–e were separated by filtration and dried under reduced pressure. The bisulfite adducts were heated at reflux with o-phenylenediamine (0.011 mol) in DMF (30 ml) for 4–5 h (Scheme 1). The reaction mixture was poured into ice-water (250 ml). The precipitate formed was collected by filtration and recrystallized from ethanol. Characteristic data for the products 3a–e are listed in Table 1.

Synthesis of dimethyl aryldithioimidocarbonates 5a–c.

General procedure

To a well-stirred cold solution of aromatic amines (0.05 mol) in DMF (20 ml) were added aqueous NaOH (20 M, 4 ml), carbon disulfide (15 ml, 0.1 mol), and methyl iodide (0.1 mol) in sequence at intervals of 30 min and stirring was continued for 2–4 h. The mixture was then poured into cold water and the resulting solid was washed with water and recrystallized from ethanol (Schemes 2, 3). The following products were obtained.

Dimethyl phenyldithioimidocarbonate 5a: yield 64%; m.p. 92/6°C (ethanol); IR (KBr, cm⁻¹) 2935 (aliphatic C–H stretching), 1597 (C=N stretching); ¹H-NMR (90 MHz, CDCl₃, ppm): 2.46 (s, 6H, SC₃H₃), 7.40 (s, 5H, Ar-H). Anal. Calcd. for C₉H₁₁NS₂: C, 54.78; H, 5.62; N, 7.10; S, 32.49. Found: C, 55.42; H, 5.79; N, 7.35; S, 31.53%.

Dimethyl 1,3-benzothiazol-2-yldithioimidocarbonate 5b: yield 69%, m.p. 101/6°C (ethanol); IR (KBr, cm⁻¹) 3281 (imidazoline N–H stretching), 3220 (N–H stretching), 1611 (C=N stretching), 1528 (N–H bending); ¹H-NMR (200 MHz, CDCl₃, ppm): 2.46 (s, 6H, S–CH₃), 6.90–7.30 (m, 2H, Ar-H). Anal. Calcd. for C₁₀H₁₀N₂S₃: C, 47.21; H, 3.96; N, 11.01; S, 37.81. Found: C, 48.39; H, 4.06; N, 11.34; S, 38.79%.

Dimethyl 4-chlorophenyldithioimidocarbonate 5c: yield 71%; m.p. 112°C (ethanol); IR (KBr, cm⁻¹) 2932 (aliphatic C–H stretching), 1617 (C=N stretching), 507 (C–Cl); ¹H-NMR (200 MHz, CDCl₃, ppm): 2.46 (s, 6H, S–CH₃), 6.74–7.12 (m, 4H, Ar-H). Anal. Calcd. for C₉H₁₀ClNS₂: C, 46.64; H, 4.35; N, 6.04; S, 27.67. Found: C, 45.24; H, 4.50; N, 6.27; S, 28.65%.

In the ¹³C-NMR spectra of compounds 5a–c, S–C₃H₃ and C=N signals appeared 16.2 and 142.5 ppm, respectively.

Synthesis of 2-arylamino-2-imidazolines 6a–c.

General procedure

A solution of 5 (0.004 mol) in DMF (15 ml) was added to a solution of ethylenediamine (0.008 mol) in DMF (15 ml) with stirring at room temperature (Scheme 2). The reaction mixture was maintained at 100°C for 8 h, cooled, then added to ice-cold water. The resulting solid was washed with water, dried and recrystallized from ethanol. The following products were obtained.

N-Phenyl-N-(4,5-dihydro-1H-imidazol-2-yl)amine 6a: yield 63%, m.p. 115°C (ethanol); IR (KBr, cm⁻¹) 3277 (imidazoline N–H stretching), 3257 (N–H stretching), 1660 (C=N stretching), 1537 (N–H bending); ¹H-NMR (200 MHz, CDCl₃, ppm): 3.48 (s, 1H, NH), 3.73 (s, 4H, imidazoline C₂H), 6.30 (broad peak, 1H, imidazoline NH), 7.12–8.20 (m, 5H, Ar-H). Anal. Calcd. for C₉H₁₁N₃: C, 67.06; H, 6.88; N, 26.07. Found: C, 68.11; H, 7.24; N, 26.83%.

N-(1,3-Benzothiazol-2-yl)-N-(4,5-dihydro-1H-imidazol-2-yl)amine 6b: yield 66%, m.p. 131°C (ethanol); IR (KBr, cm⁻¹) 3277 (imidazoline N–H stretching), 3257 (N–H stretching), 1660 (C=N stretching), 1537 (N–H bending); ¹H-NMR (200 MHz, CDCl₃, ppm): 3.48 (s, 1H, NH), 3.73 (s, 4H, imidazoline C₂H), 6.30 (broad peak, 1H, imidazoline NH), 7.12–8.20 (m, 5H, Ar-H). Anal. Calcd. for C₁₀H₁₁N₄: C, 67.06; H, 6.88; N, 26.07. Found: C, 68.11; H, 7.24; N, 26.83%.

N-(1,3-Benzothiazol-2-yl)-N-(4,5-dihydro-1H-imidazol-2-yl)amine 6b: yield 66%, m.p. 131°C (ethanol); IR (KBr, cm⁻¹) 3277 (imidazoline N–H stretching), 3257 (N–H stretching), 1660 (C=N stretching), 1537 (N–H bending); ¹H-NMR (200 MHz,
The IR (KBr, cm–1) 1602 (C=N stretching), 1150 (C–N stretching), 1112 (Cyclic ether C–O–C stretching), 741 (Disubstituted benzene out-of-plane deformation vibrations); 1H-NMR (90 MHz, DMSO-d6) 2.42 (8H, t, J 7.2 Hz, morpholine NCH2), 3.50 (4H, s, NCH2N), 3.68 (8H, t, J 7.0 Hz, morpholine OCH2), 7.26–8.11 (9H, m, Ar-H). Anal. Calcd. for C21H19N5OS: C, 56.76; H, 4.50; N, 15.85%.

2-(1H-Pyrrole-2-yl)-1H-benzimidazole 3a: yield 71%; m.p. >338°C. Anal. Calcd. for C16H18N4O: C, 68.06; H, 6.43; N, 19.84. Found: C, 67.53; H, 5.86; N, 22.05%.

Furan-2-yl-1H-benzimidazole 3d: yield 49%; m.p. 215–216°C. Anal. Calcd. for C16H18N4O: C, 68.06; H, 6.43; N, 19.84. Found: C, 67.53; H, 5.86; N, 22.05%.

2-Phenyl-1H-benzimidazole 3e: yield 71%; m.p. >325°C. Anal. Calcd. for C17H15N3O: C, 77.23; H, 5.19; N, 15.72. Found: C, 76.98; H, 4.84; N, 15.85%.


A solution of 2-heteroaryl-substituted 1H-benzimidazole or 2-arylamino-2-imidazoline 3a,b or 6b (0.01 mol) in methanol (20 ml) was stirred at room temperature for 2 h with aqueous formaldehyde (35%; 0.015 or 0.03 mol) and morpholine (0.01 or 0.02 mol). The solvent was removed on a rotary evaporator. The residue was mixed with methanol, and the precipitate formed was filtered and then recrystallized from methanol (Scheme 5).

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>Molecular formula</th>
<th>Analysis</th>
<th>1H-NMR δ (CDCl3)</th>
<th>IR cm–1 (KBr)</th>
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</thead>
<tbody>
<tr>
<td>2-(1H-Pyroll-2-yl)-1H-benzimidazole 3a</td>
<td>77</td>
<td>279–280 (274–275)</td>
<td>C18H18N3</td>
<td>Calcd / Found</td>
<td>6.20–6.93 (3H, m, pyrrole), 7.10–7.51 (4H, m, benzimidazole), 11.81 (H, s, benzimidazole NH), 12.52 (H, s, pyrrole NH)</td>
<td>N-H 3100–2500 C=N 1456</td>
</tr>
<tr>
<td>2-(1H-Indol-2-yl)-1H-benzimidazole 3b</td>
<td>73</td>
<td>&gt;340</td>
<td>C18H18N3</td>
<td>Calcd / Found</td>
<td>7.13–7.35 (4H, m, benzimidazole), 7.57–8.24 (5H, m, indole), 8.02 (H, s, benzimidazole NH), 9.42 (H, s, indole NH)</td>
<td>N-H 3100–2500 C=N 1451</td>
</tr>
<tr>
<td>2-(2-Thienyl)-1H-benzimidazole 3c</td>
<td>72</td>
<td>327 (311–312)</td>
<td>C17H16N3S</td>
<td>Calcd / Found</td>
<td>7.15–7.54 (4H, m, benzimidazole), 7.21–7.84 (3H, m, thiophene), 10.28 (H, s, benzimidazole NH)</td>
<td>N-H 3100–2500 C=N 1455</td>
</tr>
<tr>
<td>Furans-2-yl-1H-benzimidazole 3d</td>
<td>86</td>
<td>295–297 (285)</td>
<td>C17H18N3S</td>
<td>Calcd / Found</td>
<td>6.70–7.92 (3H, m, furan), 7.17–7.53 (4H, m, benzimidazole), 10.60 (H, s, NH)</td>
<td>N-H 3100–2500 C=N 1433</td>
</tr>
<tr>
<td>2-Phenyl-1H-benzimidazole 3e</td>
<td>79</td>
<td>287 (292)</td>
<td>C18H18N3</td>
<td>Calcd / Found</td>
<td>7.10–8.10 (5H, m, phenyl), 7.20–7.54 (4H, m, benzimidazole), 12.89 (H, s, NH)</td>
<td>N-H 3100–2500 C=N 1441</td>
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References


