Studies on syntheses of 1-alkyl-2-substitutedthiazolylbenzimidazoles

P K Dubey* , A Naidu & C Ravi Kumar
Dept. of Chemistry, College of Engg., J. N. T. University,
Kukatpally, Hyderabad 500 072, India

Received 4 July 2000; accepted (revised) 1 May 2002

Studies on syntheses of 1-alkyl-2-substitutedthiazolylbenzimidazoles have been reported. Alkylation of 1 leads to 1-alkyl-2-acetylbenezimidazoles, which on bromination yield the known 1-alkyl-2-(α-bromoacetyl)benzimidazoles. The latter on treatment with thioureas yield 4.

Benzimidazoles are an important group of heterocyclic compounds possessing a variety of biological activities. In continuation of our earlier work on benzimidazoles, we wish to report herein syntheses of 1-alkyl-2-substitutedthiazolylbenzimidazoles.

Alkylation of 2-acetylbenzimidazole under phase-transfer catalysed conditions yields 1-alkyl-2-acetylbenezimidazoles, which on bromination results in the formation of the known 1-alkyl-2-(α-bromoacetyl)benzimidazoles. Treatment of 3a (i.e., 3, R=Me) with p-methylphenylthiourea in DMF at RT for 2 hr gave a product, which has been characterized as 1-methyl-2-(2'-p-methylphenylamino-1,3-thiazolyl)benzimidazole 4a, on the basis of analytical and spectral data. The yield of the product was found to be 75%, m.p. 234°C. Thus, its IR (KBr) spectrum showed peaks at 3242 (-NH-), 3117 (-CH-), 1610 (-C=N-), 1527 (-C=C-) with a shoulder at 1530 (s), 1460 (vw), 1380 (vs) cm⁻¹ etc (series of absorptions due to various C-C stretching and bending vibrations). Its ¹H NMR (CDCl₃/TMS) showed signals at δ 2.35 (s, 3H, -C₆H₄ CH₃(p)), 4.2 (s, 3H, -N-CH₃), 7.1-7.4 (complex m, 8H, Ar-H), 7.55 (s, 1H, -S-CH=), 7.75 (br s, 1H, -NH-). Its electron impact mass spectrum showed peaks at m/z (mol %): 320 (100, M⁺), 319 (6, M⁺-1), 287 (9), 214 (54), 183 (31), 187 (19), 156 (41), 107 (9), 77 (11).

The reaction of 2a (i.e., 2, R=Me) with p-methylphenylthiourea in iso-propanol in the presence of iodine under reflux for 2 hr and subsequent processing gave a product, which was found to be identical in m.p., m.m.p. and co-TLC with 4a obtained above.

Compound 4a could also be prepared by another route. Thus, reaction of 1 with p-methylphenylthiourea and iodine in iso-propanol under reflux for 2.5 hr followed by simple processing gave a product, which was characterized as 2-(2'-p-methylphenylamino-1,3-thiazolyl)benzimidazole 5a [i.e., 5, Ar = C₆H₄ CH₃(p)]. Its IR (KBr) showed peaks at 3308 and 3260 (due to -NH- of imidazole and aminothiazole), and absence of absorption at 1665 cm⁻¹ which was present in the starting material.

Compound 5a was alkylated under phase-transfer catalysed conditions using DMS in acetonitrile to obtain 4a [i.e., 4, R=Me, R'=C₆H₄ CH₃(p)]. The m.p., m.m.p., co-TLC and superimposable IR of 4a were found to be identical with those of the products obtained above using the two routes 2→3→4 and 3→4.

Furthermore, it has been found that 4a obtained in the route 2→3→4 gave the best product in terms of m.p. and TLC. Therefore, the above reaction of 3a in DMF has been extended to 3b (i.e., 3, R=Et) and 3c (i.e., 3, R=-CH₂Ph) with various substituted thioureas and the products obtained have all been assigned structure 4 on the basis of analytical and spectral data (Tables I and II).

All the above reactions have been described in Scheme I.

Experimental Section

Melting points are uncorrected and have been determined in open capillary tubes in sulfuric acid bath. TLC analyses were done on glass plates coated with silica-G and spotting was done using iodine or UV light. IR spectra were recorded on JASCO FT-IR 5300 spectrometer, ¹H NMR spectra on VARIAN 200 MH z spectrometer and mass spectra on Hewlett Packard Mass spectrometer operating at 70eV.

Preparation of 4 from 3 (General procedure). To a solution of 3 (10 m mole) in DMF (10 mL) was added the respective thiourea (10 m mole) in DMF (10 mL). The reaction mixture was stirred at RT for 2 hr and poured into ice-cold water. The separated solid was filtered, washed with water, suspended in water and neutralized with aq. NaHCO₃. The product was

Note
Scheme I

Table I—Characterization data for compound 4

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Reagent used</th>
<th>Product obtained</th>
<th>Yield (%)</th>
<th>m.p. °C</th>
<th>Mol. formula</th>
<th>%N Found (Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a H₂NCSNH-PhCH₃ (p)</td>
<td>4a₁ (R=Me, Ar=p-MePh)</td>
<td>75</td>
<td>234</td>
<td>C₁₇H₁₃N₄S₂</td>
<td>17.46 (17.48)</td>
<td></td>
</tr>
<tr>
<td>3a H₂NCSNH₂</td>
<td>4a₂ (R=Me, Ar=H)</td>
<td>73</td>
<td>235</td>
<td>C₁₇H₁₃N₄S₂</td>
<td>24.31 (24.34)</td>
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</tr>
<tr>
<td>3a H₂NCSNHPh</td>
<td>4a₃ (R=Me, Ar=C₆H₅)</td>
<td>74</td>
<td>220</td>
<td>C₁₇H₁₃N₄S₂</td>
<td>18.28 (18.28)</td>
<td></td>
</tr>
<tr>
<td>3a H₂NCSNHPh</td>
<td>4a₄ (R=Me, Ar=p-ClPh)</td>
<td>75</td>
<td>30</td>
<td>C₁₇H₁₃N₄SCl</td>
<td>16.42 (16.43)</td>
<td></td>
</tr>
<tr>
<td>3a H₂NCSNHPhBr (p)</td>
<td>4a₅ (R=Me, Ar=p-BrPh)</td>
<td>68</td>
<td>241</td>
<td>C₁₇H₁₃N₄SBr</td>
<td>14.53 (14.54)</td>
<td></td>
</tr>
<tr>
<td>3b H₂NCSNH-PhCH₃ (p)</td>
<td>4b₁ (R=Et, Ar=p-MePh)</td>
<td>78</td>
<td>190</td>
<td>C₁₉H₁₄N₄S</td>
<td>16.73 (16.75)</td>
<td></td>
</tr>
<tr>
<td>3b H₂NCSNH₂</td>
<td>4b₂ (R=Et, Ar=H)</td>
<td>78</td>
<td>170</td>
<td>C₁₉H₁₄N₄S</td>
<td>22.90 (22.92)</td>
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<tr>
<td>3b H₂NCSNHPh</td>
<td>4b₃ (R=Et, Ar=C₆H₅)</td>
<td>75</td>
<td>160</td>
<td>C₁₉H₁₄N₄S</td>
<td>17.40 (17.42)</td>
<td></td>
</tr>
<tr>
<td>3b H₂NCSNHPh</td>
<td>4b₄ (R=Et, Ar=p-ClPh)</td>
<td>73</td>
<td>250</td>
<td>C₁₉H₁₄N₄SCl</td>
<td>15.74 (15.78)</td>
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<tr>
<td>3c H₂NCSNH-PhCH₃ (p)</td>
<td>4c₁ (R=CH₃, Ar=p-MePh)</td>
<td>76</td>
<td>155</td>
<td>C₂₀H₁₈N₄S</td>
<td>14.00 (14.03)</td>
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<tr>
<td>3c H₂NCSNH₂</td>
<td>4c₂ (R=CH₃, Ar=H)</td>
<td>62</td>
<td>210</td>
<td>C₂₀H₁₈N₄S</td>
<td>19.91 (19.94)</td>
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<tr>
<td>3c H₂NCSNHPh</td>
<td>4c₃ (R=CH₃, Ar=C₆H₅)</td>
<td>65</td>
<td>125</td>
<td>C₂₀H₁₈N₄S</td>
<td>15.12 (15.15)</td>
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<tr>
<td>3c H₂NCSNHPh</td>
<td>4c₄ (R=CH₃, Ar=p-ClPh)</td>
<td>61</td>
<td>132</td>
<td>C₂₀H₁₈N₄S</td>
<td>13.82 (13.86)</td>
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</table>
Product & I R (KBr) cm⁻¹ & ¹H NMR (CDCl₃) (8, ppm) & M S m/z (%) \\
4a₁ & 3150, 3297 (unequal doublet, m), 1614 (s, -C=O-), 1528 (vs) with a shoulder at 1530 (s), 1455 (vw), 1381 (s) etc. & — & — \\
4a₂ & 3242 (vs, -NH-str), 3115 (sharp, s, -CH-str), 1608 (m, -C=O-), 1524 (vs, with a shoulder at 1528), 1458 (vw), 1380 (vs) etc. & 4.2 (t, 3H, NCH₃), 7.2-7.5 (complex m, 9H, four phenyl and four aryl protons), 7.35 (s, 1H, =CH-S), 7.75 (broad s, 1H, -NH-). & — \\
4a₂ & 3242 (vs, -NH-str), 3105 (sharp, s, -CH-str), 1605 (m, -C=O-), 1523 (vs, with a shoulder at 1527), 1455 (vw), 1380 (vs) etc. & 4.22 (t, 3H, NCH₃), 7.2-7.5 (complex m, 8H, four p-chlorophenyl and four aryl protons), 7.57 (s, 1H, =CH-S), 7.79 (broad s, 1H, -NH-). & — \\
4b₁ & 3230 (vs, -NH-str), 3110 (sharp, s, -CH-str), 1608 (m, -C=O-), 1520 (vs, with a shoulder at 1525), 1458 (vw), 1380 (vs) etc. & 1.55 (t, 3H, NCH₂CH₃), 2.35 (s, 3H, -CH₃), 4.7-4.9 (q, 2H, -N-CH₂CH₃), 7.1-7.8 (complex m for 10H, four p-methylphenyl and four aryl protons one -NH & one -CH-proton). & — \\
4b₂ & 3240 (vs, -NH-str), 3118 (sharp, s, -CH-str), 1605 (m, -C=O-), 1527 (vs) with a shoulder at 1528 (s), 1449 (vw), 1378 (vs) etc. & 1.55 (t, 3H, NCH₂CH₃), 2.37 (s, 3H, -CH₃), 4.75-4.92 (q, 2H, -N-CH₂CH₃), 7.15-7.82 (complex m for 10H, four p-chlorophenyl and four aryl protons, one -NH & one -CH-proton). & — \\
4c₁ & 3242 (vs, -NH-str), 3115 (sharp, s, -CH-str), 1608 (m, -C=O-), 1524 (vs) with a shoulder at 1528 (s), 1458 (vw), 1380 (vs) etc. & 2.35 (s, 3H, -CH₃), 6.1 (s, 2H, -N-CH₂CH₃), 7.0-7.8 (complex m for 15H, four p-methylphenyl, four aryl protons and five phenyl one -NH- and one -CH-proton). & — \\
4c₁ & 3244 (vs, -NH-str), 3120 (sharp, s, -CH-str), 1610 (m, -C=O-), 1527 (vs) with a shoulder at 1529 (s), 1458 (vw), 1380 (vs) etc. & 2.35 (s, 3H, -CH₃), 6.1 (s, 2H, -N-CH₂CH₃), 7.0-7.8 (complex m, for 15H, four p-chlorophenyl, four aryl protons and five phenyl one -NH- and one -CH-proton) & — \\

Preparation of 5a/4a₁ from 1/2a (General procedure). To a solution of 1/2a (10 m mole) in isopropanol (20 mL) was added the p-methylphenylthioure (1.66 g, 10 m mole) and iodine (2.53 g, 12 m mole) in isopropanol (20 mL). The reaction mixture was refluxed for ~3.5 hr. The contents were reduced to half the volume and separated solid (which is the HI salt of 5a/4a₁) was filtered, washed with iso-propanol and dried. The solid thus obtained was suspended in water (50 mL) and neutralized with NaHCO₃ to obtain the free base. The separated compound, which is crude 5a/4a₁, was recrystallized from ethanol to obtain pure 5a/4a₁ (yield of 5a = 51%, m.p. 170°C, yield of 4a₁ = 45%, m.p. 234°C).

Preparation of 4a₁, from 5a₅. To a solution of triethylbenzylammonium chloride (TEBAC) in CH₃CN (15 mL) was added K₂CO₃ (0.7 g, 5 m mole) and the mixture stirred at RT. To this, a solution of 5a (1.53 g, 5 m mole) in CH₃CN (10 mL) was added with stirring followed by the alkylation agent (DMS) (5 m mole) at RT. The mixture was stirred at RT for 3 hr and then filtered. The CH₃CN filtrate was evaporated to dryness yielding a residue. The latter was treated with chloroform (20 mL), washed with water and evaporated to dryness yielding a second residue. The latter on trituration with hexane and recrystallization from a suitable solvent gave pure 4a₁ (yield 45%, m.p. 233°C).

Acknowledgement

The authors are highly indebted to UGC (Govt. of India), New Delhi for financial support.

References
