Synthesis of 1-(n-hexyl-5-one)-2-chlorobenzimidazole

P K Dubey*, A Naidu, V Anandam & G Hemasunder
Dept of Chemistry, College of Engg, J N T University, Kukatpally, Hyderabad, 500 072, India
E-mail: pkdubeyjntu@tatanova.com
Received 29 December 2003; accepted (revised) 27 December 2004

α-Phenylenediamine on condensation with urea gives the known benzimidazolin-2-one, which on reaction with phosphoryl chloride in the presence of catalytic amount of phenol yields the already reported 2-chlorobenzimidazole. The latter on alkylation with 6-chloro-2-hexanone in the presence of K2CO3 in DMF medium, gives the title compound.

IPC: Int.Cl.7 C 07 D 233/54

Pentoxyfyllin is a well-known vasodilator1 used in the treatment of several cardiac disorders. Its molecule is made up of two crucial structural entities, namely chlorohexanone and theobromine (3,7-dimethylxanthine), both of which are believed to be responsible for its biological activity. A structural variant of this drug may be conceived of as possessing a chlorohexanone moiety and a heterocyclic ring (in place of theobromine). Thus, a potentially useful molecule and a substitute of pentoxyfyllin may be prepared by hooking a chlorohexanone on to a new/other heterocyclic ring. Several derivatives of benzimidazoles are also known2 to possess diverse types of biological activities. In continuation of our earlier work3,4 on benzimidazoles, it was considered worthwhile to prepare new benzimidazoles derived from chlorohexanones and benzimidazoles substituted in 1, 2, 3 positions. The results of these studies are presented in this paper.

α-Phenylenediamine 1 was heated with urea in DMF at 135-40°C for 12 hr, followed by simple processing to obtain the known benzimidazolin-2-one 2 in 94% yield. The reported procedure5 for the preparation of 2 involves dry fusion of 1 with urea at 150°C followed by simple processing to obtain the product 2 in 88% yield. The later method of condensation gave a lower yield of the product and the product was found to be inferior in quality in m.p. and TLC. In the present work, compound 2 was prepared by using first method only. The product 2 is known in literature. However, in the present work, 2 was characterized by spectral methods also.

Thus, its IR showed peaks at ~3000 (very broad, strongly bonded-NH-stretching vibration) and at 1747 cm⁻¹ (very strong, sharp,-C=O stretching vibration) as diagnostic absorptions. Its ¹H NMR spectrum in DMSO-d₆ showed peaks at δ 6.92 (s, 4H, aryl protons) and at 10.60 (s, 2H, -NH-protons). Its mass spectrum showed the molecular ion peak at m/z 135 in Q+1 mode.

N-Alkylation of 2 with 6-chloro-2-hexanone 3 in 1:1 molar ratio in the presence of K₂CO₃ in DMF at 135-40°C for 9 hr followed by simple processing and column chromatographic separation gave mixture of two products as seen in TLC. The two products were 1:1 (4) and 1:2 (5) derivatives, respectively. Their structures were determined by spectral methods as follows: The compound 4 showed in its IR spectrum peaks at 3200 (-NH-stretching) and at 1710 cm⁻¹ (-CO-stretching). Its ¹H NMR spectra in CDCl₃ showed peaks at δ 1.55-1.90 (m, 4H (-CH₂-CH₂-CH₂-CHO), 2.10 (sharp, s, 3H, -CH₃), 2.30 (t, 3H,-N-CH₂), 6.90-7.20 (m, 4H, aryl protons). Its mass spectrum showed the molecular ion peak at m/z 233 in Q+1 mode.

Similarly, 5 was also characterized by its spectral data. Thus, its IR showed the peaks at 1715 and 1695 cm⁻¹ (strong, sharp doublet due to -NHCO, and -C=O stretching). ¹H NMR spectra in CDCl₃ showed peaks at δ 1.55-1.85 (m, 8H, (CH₂-CH₂-CH₂-CHO) × 2), 2.10 (sharp s, 6H, CH₃ × 2), 2.50 (t, 4H, -CH₂CO × 2), 3.85 (t, 4H, -NCH₂ × 2), 6.85-7.15 (m, 4H, aryl protons). Its mass spectrum showed the molecular ion peak at m/z 331 when recorded in Q+1 mode.

When the reaction was carried out by using 1:2 molar ratio of 2 and 3 under similar conditions, 5 was obtained exclusively as the product in the reaction. Attempted chlorination of compound 4 with phosphoryl chloride (POCl₃) in the presence of catalytic amount of phenol at 110°C for 12 hr, did not
give the expected compound 7. But it gave only tarry material. In view of the above, an alternative approach, involving conversion of benzimidazolin-2-one 2 to the corresponding chloro compound with POCl₃ followed by its alkylation to obtain the title compound was adopted. Thus, compound 2 was reacted with phosphoryl chloride in the presence of catalytic amount of phenol at 110°C for 12 hr, to obtain 2-chlorobenzimidazole 6 in 90% yield. The compound 6 is also known in literature⁶, however it was characterized by spectral data. IR showed peaks at 3061 (very broad, strong-NH-bonded stretching) and other absorptions at 1525, 1436, 1270, 1232 cm⁻¹ etc as series of sharp absorptions.¹H NMR spectrum in CDCl₃ showed peaks at δ 6.50-7.90 (m, 4H, aryl protons), and at 12.25 (s, 1H, -NH-).

N-Alkylation of compound 6 with 6-chloro-2-hexanone 3 in 1:1 molar ratio in the presence of an acid scavenger like K₂CO₃ in DMF medium at 140-45°C for 14 hr followed by simple processing gave the title compound 7 as crude syrupy residue. This residue was further purified by column chromatography (ethyl acetate:n-hexane 1:3) to obtain white colourless crystals of 7 in 54% yield. The compound 7 was characterized by spectral data. Thus, its IR spectrum showed the peak at 1715 (very strong, -C=O stretching vibration) and other peaks at 1470, 1378, 1280 cm⁻¹ etc as series of sharp absorptions. Its ¹H NMR spectrum in CDCl₃ showed peaks at δ 1.50-1.90 (m, 4H, -CH₂-CH₂, -CH₂-CO), 2.15 (s, 3H, -CO-CH₃), 2.30-2.60 (t, 2H, -CH₂-CO), 4.10-4.30 (t, 2H, -N-CH₂), 7.10-7.80 (m, 4H, aryl protons). Its mass spectrum showed the molecular ion peak at m/z 250 (22.5%) and 252 (2%) corresponding to the twin peaks of ³⁵Cl and ³⁷Cl respectively.

The reagent which is used as alkylation agent namely, 6-chloro-2-hexanone 3 was prepared by simple method as follows: Condensation of the active methylene compound, methyl acetoacetate 8, with 3-chloro-1-bromopropane in the presence of K₂CO₃ gave a cyclic pyran ester 9 in 90% yield. The reaction of 9 with conc HCl at 50°C followed by treatment with 5% aq NaHCO₃ solution gave the compound 3 in yield of 93%. The compound 3, although known in literature was further characterized in the present work. Thus, its IR spectrum showed peaks at 1720 cm⁻¹ as the only diagnostic absorption. Its ¹H NMR spectrum in CDCl₃ showed peaks at δ 1.60-1.80 (m, 4H, -CH₂-CH₂-CH₂-CO), 2.10 (sharp s, 3H, -CH₃), 2.40-2.60 (t, 2H, -CH₂-10), 3.45-3.60 (t, 4H, 4-CH₂). Its mass spectrum showed the molecular ion peak at m/z 137 and 135 when recorded in Q+1 mode corresponding to chlorines of masses 37 and 35 respectively.

All the above reactions are briefly summarized in Schemes I and II. Characterization data for some of the compounds have been given in Table I.
Experimental Section

All melting points are uncorrected and were obtained by using open capillary tubes in sulphuric acid-bath. TLC checking was done on glass plates coated with silica gel G and spotting was done using Iodine/UV lamp. IR spectra were recorded using Perkin-Elmer model 446 instrument in KBr phase. 1H NMR were recorded on a Bruker instrument operating at 250 MHz. Mass spectra have been recorded on a CEC-21-110 under electron impact or under chemical ionization conditions.

Preparation of 1,3-dihydro-benzimidazol-2-one 2. To a solution of o-phenylenediamine 1 (5 g, 0.046 mole) in DMF was added urea (5.52 g, 0.092 mole) and the mixture heated to 135-40°C for 12 hr. When the reaction was complete, DMF was removed in vacuo, the separated solid was washed with water, and then dissolved in 10% NaOH solution. The aqueous alkaline solution was filtered and neutralised with aq HCl (35%). The separated product was filtered, washed and dried to obtain pure 2, yield 5.8 g (94%).

Preparation of (5-oxo-hexyl)-1,3-dihydrobenzimidazol-2-one 4 and 1,3-bis-(5-oxo-hexyl)-1,3-dihydrobenzimidazolin-2-one 5. To a solution of 2 (1.0 g, 0.007 mole) in DMF was added 3 (1.0 g, 0.007 mole) and K2CO3 (1.53 g, 0.011 mole). The reaction mixture was heated in an oil-bath at 135-40°C for 9 hr. At end of this period, DMF was removed in vacuo, the residue was cooled and diluted with water. The reaction mixture was then extracted with ethyl acetate and evaporated to obtain a crude residue. Purification of the latter by column chromatography on silica gel (n-hexane:ethyl acetate 3:1) gave two compounds as colourless crystals which on recrystallization with (ether:hexane) gave 4 (1:1) and 5 (1:2) as pure products in the yields 0.8 g (46%) and 0.69 g (30%), respectively.

Preparation of 1,3-bis-(5-oxo-hexyl)-1,3-dihydrobenzimidazolin-2-one 5. To a solution of 2 (0.5 g,
0.0037 mole) in DMF was added 3 (1 g, 0.007 mole) and K₂CO₃ (1.02 g, 0.007 mole). The reaction mixture was heated in oil-bath at 135-40°C for 9 hr. At the end of this period, DMF was removed in vacuo, the mixture was diluted with water and extracted with ethyl acetate, dried over Na₂SO₄ and concentrated to yield a crude residue. The latter was purified by column chromatography on silica gel (n-hexane:ethyl acetate 2:1) to obtain a colourless syrup, which was recrystallized (ether:n-hexane 1:3) to obtain pure 5, yield 0.8 g (65%).

Preparation of 6-(2-chloro-2-benzimidazol-1-yl)-hexane-2-one 7. A mixture of 4 (10 g, 0.043 mole), phosphoryl chloride (22.88 g, 0.149 mole) and catalytic amount of phenol was heated to 100-10°C for 12 hr. After completion of the reaction, the mixture was treated with xylene and then distilled under reduced pressure (to remove excess POCl₃). The hot reaction mixture was filtered. To the filtrate was added crushed ice, neutralized with 40% NaOH solution to pH 10.0 leading to separation of black tarry material.

Preparation of 2-chloro-1H-benzimidazole 6: A mixture of 2 (10.0 g, 0.07 mole), POCl₃ (22.88 g, 0.14 mole) and catalytic amount of phenol was heated to 103-07°C for 12 hr. After completion of reaction the mixture was cooled in ice, and neutralized with 40% NaOH to pH ~10.0, the crude material was recrystallized to obtain pure product 6, yield 11.0 g (97%).

Preparation of 6-(2-chloro-2-benzimidazol-1-yl)-hexan-2-one 7. To a solution of 6 (10 g, 0.065 mole) in DMF (10 mL) was added 3 (0.92 g, 0.0068 mole) and K₂CO₃ (1.81 g, 0.0131 mole), and the mixture heated in oil-bath at 140-45°C. After completion of the reaction, DMF was removed in vacuo, the residue was cooled to rt and diluted with water. The mixture was then extracted with ethyl acetate, the organic extract dried over Na₂SO₄ and then evaporated to obtain a crude residue. The latter on separation by column chromatography (n-hexane-ethyl acetate 2:1) gave pure compound 7, yield 9 g (54%).

References