Indian Journal of Chemistry
Vol. 47B, September 2008, pp. 1443-1446

Note

Studies on synthesis of unsymmetrical 2,2′-bisbenzimidazole sulphides of pharmacological interest

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Received 28 September 2007; accepted (revised) 10 June 2008

Condensation of 2-(α-chloroethyl)benzimidazole **1** with benzimidazole-2-thiol **2** gives 2-(α-thioethyl-2′-benzimidazolyl)-benzimidazole **3**. The latter can also be prepared by the reaction of 2-(α-thioethyl)benzimidazole **4** with 2-chlorobenzimidazole **5**. Alternatively, **3** can also be synthesized by the independent condensation of *o*-phenylenediamine **7** respectively with 2-(*s*-α-ethyl-*o*-ethyldithio- carbonate)benzimidazole **6** and with 2-(α-thiopropionic acid) benzimidazole **8**. The structures of all the compounds synthesized have been established on the basis of their spectroscopic data.

Keywords: Benzimidazole, sulphides, TEA, TBAB, *o*-ethyl dithiocarbonate, TFA, deoxy prazole

Benzimidazoles are very important compounds due to their wide spectrum of biological activity behaving as anti-hypertensive, anti-viral, anti-fungal, anti-tumor and anti-helminthic agents in veterinary medicine[1]. In addition to this, substituted benzimidazoles are potent inhibitors of the parietal cell proton pump, the H^+/K^+ ATPase[2]. And these substituted benzimidazoles are capable of blocking gastric acid secretion in response to known stimuli. The structure-activity relationship of anti-ulcer agents have been studied in detail and it is believed that the sulfoxide grouping, benzimidazole ring, adjoining methylene group along with a heteryl moiety is essential for the anti-ulcer properties of these compounds[3]. It is also reported that, benzimidazole sulphide is capable of inhibiting gastric acid secretion *in vivo*[4]. So in this connection, herein is reported the synthesis of sulphur containing benzimidazoles, more specifically those of chiral, unsymmetrical 2,2′-bisbenzimidazole sulphides *i.e.*, 2-(α-thioethyl-2′-benzimidazolyl)benzimidazole **3**, which are the heterocyclic deoxy analogues of the well-known anti-ulcer agent and the proton pump inhibitor - Omeprazole[5].

Results and Discussion

Condensation of *o*-phenylenediamine **7** with lactic acid in 4N HCl under reflux conditions gave the known 2-(α-hydroxyethyl)benzimidazole[6]. The latter on treatment with thionyl chloride in CCl_4 under reflux yielded 2-(α-chloroethyl)benzimidazole **1** in 88% yield, which was found to be identical in m.p., mixed m.p., TLC and co-TLC with the product already reported in literature[7]. **1**, on reaction with 5-substituted-benzimidazole-2-thiol **2a-e** (Ref 8) in acetone and triethylamine as base at RT gave a product, which has been characterized as 2-(α-thioethyl-2′-benzimidazolyl)-5-subsituted-benzimidazole **3a-e** on the basis of its spectral data (**Table I**). The IR (KBr) spectrum of **3**, showed absorption around 3100-2700 cm^{-1} as a medium but very broad band assignable to the tautomeric -NH- grouping of the imidazoles and benzimidazoles[9].

In an alternative approach, the reaction of **1** with thiourea led to the formation of 2-(α-thioethyl)-benzimidazole **4** in 80% yield by the basic hydrolysis of the salt formed initially. The product obtained in this reaction has shown the same m.p., mixed m.p., TLC and co-TLC with that of **4** prepared by the literature method[10]. The latter on reaction with 5-substituted-2-chlorobenzimidazole **5a-e** (Ref 11) in DMF, K_2CO_3 and TBAB (*tetra*-butyl ammonium bromide) as phase transfer catalyst gave the corresponding **3a-e**. The structures of **3** obtained were confirmed by their identity *i.e.*, m.p., mixed m.p., TLC and co-TLC with those of the same products obtained by the earlier route, **1+2→3**.

In another alternative approach, **3a-e** could also be prepared by the condensation of 2-(*s*-α-ethyl-*o*-ethyldithiocarbonate)benzimidazole **6** with **7a-e** under reflux in acidic conditions. The former, *i.e.*, **6** in turn, synthesized by the reaction of **1** with potassium *o*-ethyl dithiocarbonate in ethanol at RT in 78% yield. The compound **3a-e** has shown same m.p., mixed m.p., TLC and co-TLC with that of the same products obtained earlier by the above two routes *i.e.*, **1+2→3** and **4+5→3**.

In another approach, *i.e.*, the fourth approach, reaction of **2a-e** with α-chloropropionic acid in alc. KOH under refluxing conditions gave **8a-e** that have been previously characterized on the basis of

Table I — Spectral characterization data of compounds **3a-e, 6** and **8a-e**

Compd	^{1}H NMR (δ, ppm)	M^+ (Q+1)
3a	δ 1.87 (d, 3H, *J*=8 Hz, -CH-CH_3), 5.39 (q, 1H, *J*=8Hz, -CH-S-), 7.10-7.60 (complex m, 8H, aryl protons), 12.50 (br, s, 2H, D_2O exch., 2×–NH-)	295
3b	δ 1.84 (d, 3H, -CH-CH_3), 2.54 (s, 3H, Ar–CH_3), 5.35 (q, 1H, -CH-), 6.96-7.57 (complex m, 7H, aryl protons), 12.60 (br, s, 2H, D_2O exch., 2× –NH-)	309
3c	1.86 (d, 3H, -CH-CH_3), 3.74 (s, 3H, Ar–OCH_3), 5.33 (q, 1H, -CH-), 6.76-7.57 (complex m, 7H, aryl protons)	325
3d	1.86 (d, 3H, -CH-CH_3), 5.38 (q, 1H, -CH-), 6.85-7.67 (complex m, 7H, aryl protons), 12.47 (br, s, 2H, D_2O exch., 2× –NH-)	340
3e	1.84 (d, 3H, -CH-CH_3), 5.36 (q, 1H, -CH-), 6.95-7.47 (complex m, 7H, aryl protons), 12.58 (br, s, 2H, D_2O exch., 2× –NH-)	329
6	1.22 (t, 3H, -CH-CH_3), 1.92 (d, 3H, -CH_3), 4.57(q, 3H, -CH_2-) 5.48 (q, 1H, -CH-), 7.16-7.56 (complex m, 4H, aryl protons), 12.73 (br, s, 12H, D_2O exch., –NH-)	267
8a	δ 1.56 (d, 3H, -CH-CH_3), 4.53 (q, 1H, -CH-S-), 7.00-7.50 (complex m, 4H, aryl protons), 12.80 (br, s, 2H, D_2O exch., –NH- and –COOH protons).	223
8b	1.53 (d, 3H, -CH-CH_3), 2.37 (s, 3H, Ar–CH_3), 4.75 (q, 1H, -CH-S-), 6.93-7.34 (complex m, 3H, aryl protons), 12.85 (br, s, 2H, D_2O exch., -NH- and –COOH)	237
8c	1.49 (d, 3H, -CH-CH_3), 3.67 (s, 3H, Ar-OCH_3), 4.65 (q, 1H, -CH-S-), 7.15-7.64 (complex m, 3H, aryl protons), 12.75 (br, s, 2H, D_2O exch., -NH- and –COOH)	253
8d	1.58 (d, 3H, -CH-CH_3), 4.69 (q, 1H, -CH-S-), 6.93-7.20 (complex m, 3H, aryl protons), 12.79 (br, s, 2H, D_2O exch., -NH- and –COOH)	268
8e	1.55 (d, 3H, -CH-CH_3), 4.53 (q, 1H, -CH-S-), 7.09-7.50 (complex m, 3H, aryl protons), 12.68 (br, s, 2H, D_2O exch., -NH- and –COOH)	257

analytical data[12]. In the present work, their structures have been further confirmed on the basis of spectral data (**Table I**). Condensation of **8a-e** with that of **7a** under Phillip's conditions[13] gave the respective products **3a-e**. The products obtained by this route have been found to be identical in m.p., mixed m.p., TLC and co-TLC, with those of the corresponding compounds obtained from the earlier three routes. All the above reactions are briefly summarized in **Scheme I**.

Experimental Section

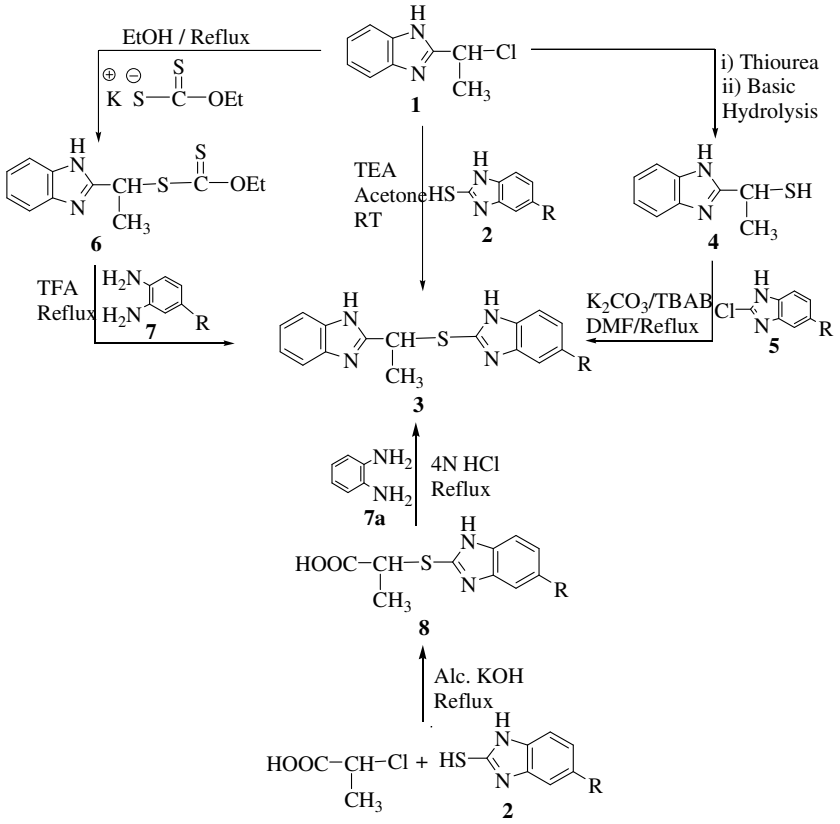
Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. TLC analyses were carried out on glass plates coated with silica gel GF-254 and visualized using Iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer model 446 instrument in KBr phase. ^{1}H NMR were recorded in $CDCl_3$/DMSO-d_6 using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on a LCMS spectrometer, model HP-5989A.

Synthesis of 1: A mixture of 2-(α-hydroxyethyl) benzimidazole[5] (1.62 g, 10 mmol), CCl_4 (50 mL) and thionyl chloride (2.2 mL, 30 mmol) was refluxed for 4 hr. Then, the reaction mixture was cooled to RT and the separated solid was extracted with water and treated with sat. $NaHCO_3$ solution. The separated solid was filtered, washed with water, dried and purified by recrystallization from ethyl acetate to obtain pure **1**. m.p. 134-36°C (Lit. m.p. 135-37°C, Ref.6).

General procedure for the synthesis of 3 from 1 and 2: A mixture of **1** (0.9 g, 5 mmol), **2** (5 mmol), TEA (0.8 mL, 6 mmol) and acetone (25 mL) was stirred at RT for 3-4 hr. After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water. The separated product was filtered, washed with water, dried and purified by recrystallization from ethanol to obtain **3** (**Table II**).

Synthesis of 4: A mixture of **1** (1.8 g, 10 mmol), thiourea (0.85 g, 11 mmol) and acetone (25 mL) was refluxed for 3 hr. The insoluble solid was treated with ethanol (10 mL) followed by NaOH (1 g) and refluxed for further 2 hr. At the end of this period, the reaction mass was diluted with water and *p*H of the mixture adjusted to ≤ 6.0 by acetic acid. The separated solid was filtered, washed with water, dried and purified by recrystallization from ethanol to obtain pure **4** m.p. 202°C.

General procedure for the synthesis of 3 from 4 and 5: A mixture of **4** (0.89 g, 5 mmol), **5** (5 mmol), K_2CO_3 (1.38 g, 10 mmol), TBAB (0.05 g) and DMF



Scheme I

Table II — Characterization data of compounds **3a-e** and **8a-e**

Starting material used		R	Product obtained	Yield (%)	m.p. (°C)
1	**2a**	H	**3a**	88	230-32
1	**2b**	CH_3	**3b**	85	218-20
1	**2c**	OCH_3	**3c**	83	204-06
1	**2d**	NO_2	**3d**	81	224-27
1	**2e**	Cl	**3e**	85	203-05
4	**5a**	H	**3a**	79	231-33
4	**5b**	CH_3	**3b**	78	218-21
4	**5c**	OCH_3	**3c**	75	204-06
4	**5d**	NO_2	**3d**	70	225-28
4	**5e**	Cl	**3e**	73	203-05
6	**7a**	H	**3a**	66	230-33
6	**7b**	CH_3	**3b**	61	218-19
6	**7c**	OCH_3	**3c**	64	204-05
6	**7d**	NO_2	**3d**	66	225-27
6	**7e**	Cl	**3e**	59	203-05
2a	**Acid**	H	**8a**	91	181-83
2b	**Acid**	CH_3	**8b**	88	162-64
2c	**Acid**	OCH_3	**8c**	90	150-52
2d	**Acid**	NO_2	**8d**	89	188-90
2e	**Acid**	Cl	**8e**	89	166-68
8a	**7a**	H	**3a**	64	230-32
8b	**7a**	CH_3	**3b**	62	218-20
8c	**7a**	OCH_3	**3c**	61	203-05
8d	**7a**	NO_2	**3d**	60	225-28
8e	**7a**	Cl	**3e**	61	203-05

Acid: α-chloropropionic acid.

(10 mL) was heated in an oil-bath at 135-40°C for 12-16 hr. At the end of this period, the reaction mass was poured into ice-cold water. The separated solid was filtered, washed with water, dried and purified by recrystallization from ethanol to obtain **3** (**Table II**).

Synthesis of 6: A mixture of **1** (1.8 g, 10 mmol), ethanol (25 mL) and potassium *o*-ethyl dithiocarbonate (1.92 g, 12 mmol) was stirred at RT for 4 hr. At the end of this period the reaction mixture was filtered to remove separated potassium chloride and the ethanolic filtrate concentrated under reduced pressure to obtain a crude residue. The latter was poured into ice-cold water. The separated solid was filtered, washed with water, dried and purified by recrystallization from ethanol to obtain **6**. m.p. 120°C.

General procedure for the synthesis of 3 from 6 and 7: A mixture of **6** (1.25 g, 5 mmol), **7** (5 mmol), trifluoroacetic acid (0.6 mL, 5 mmol) and toluene (30 mL) were refluxed at 110°C in an oil-bath for 6-8 hr, until the reaction is completed. At the end of this period, toluene was distilled off, and the residue treated with aq. NaOH solution. The separated solid was filtered, washed with water, dried and purified by recrystallization from ethanol to give **3** (**Table II**).

General procedure for the synthesis of 8 from 2 and α-chloropropionic acid: A mixture of **2** (10 mmol), alc KOH (25 mL) and α-chloropropionic acid (1.08 g, 10 mmol) was refluxed for 6 hr. On completion of the reaction, as monitored by TLC, the alcohol was distilled off and the crude residue diluted with water. The *p*H of the solution was adjusted to ≤ 6.0 with acetic acid. The separated solid was filtered, washed with water, dried and purified by recrystallization from ethyl acetate to obtain **8** (**Table II**).

General procedure for the synthesis of 3 from 8 and 7a: A mixture of **8** (5 mmol) and **7a** (0.54 g, 5 mmol) was refluxed in 6N HCl (50 mL) (Phillip's condition) for 12-14 hr. At the end of this period, the reaction mass was diluted with water and *p*H was adjusted to ≥ 7.0 with aqueous NH_3. The separated solid was filtered, washed with water, dried and purified by recrystallization from ethanol to obtain **3** (**Table II**).

Conclusion

The target molecule 2-(α-thioethyl-2′-benzimidazolyl)benzimidazole **3** has been synthesized by four different routes. Of all the methodologies discussed, the condensation of 2-(α-chloroethyl)-benzimidazole **1** with various substituted benzi-midazole-2-thilos **2** using triethylamine as base, appears to be the better and efficient route in terms of yields and also in terms of the quality of products obtained, compared to the other three routes, which also involve multi-step syntheses.

The compound synthesized is a heterocyclic deoxy analogue of the well-known anti-ulcer agent and the proton pump inhibitor - Omeprazole. The oxidation studies of **3** into its corresponding sulfoxide and sulfone derivatives are in progress. Once the final compounds are synthesized they will be screened for their anti-ulcer activities and the complete details will be published in the future.

Acknowledgement

The authors are highly indebted to the University Grants Commission, Govt. of India, New Delhi, for financial assistance. They are also thankful to the authorities of Jawaharlal Nehru Technological University for providing laboratory facilities.

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