Indian Journal of Chemistry
Vol. 45B, July 2006, pp. 1756-1758

Note

Studies in the synthesis of 2-mercapto-5-methoxybenzimidazole

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Received 9 May 2005; accepted (revised) 26 October 2005

The compound, 2-mercapto-5-methoxybenzimidazole, is an important intermediate required for the synthesis of omeprazole. It is a proton pump blocker or an inhibitor of the enzyme, H^+/K^+-ATPase. In the present work, synthesis of this intermediate by three different routes has been discussed and its yields from all the three routes have been compared.

Keywords: Mercapto-5-methoxybenzimidazole, omeprazole

IPC: **Int.Cl.[8]C07D**

The proton pump blockers or the inhibitors of the enzyme, H^+/K^+- ATPase, are found to be useful in the treatment of peptic ulceration, reflux esophagitis and Zollinger-Ellison Syndrome (ZES). The important proton pump blockers are omeprazole, lansoprazole, picoprazole and esumeprazole. Omeprazole is a substituted benzimidazole, which markedly inhibits basal and stimulated gastric acid secretion. It is an irreversible inhibitor of the proton pump as it binds covalently to the enzyme, H^+/K^+ ATPase, and produces a long lasting effect in a single dose a day[1]. The compound, 2-mercapto-5-methoxybenzimidazole, is an important intermediate required for the synthesis of omeprazole. Since the demand for omeprazole is increasing, there exists a tremendous scope for the development of its synthetic routes. This necessitates an easy availability of the intermediate, 2-mercapto-5-methoxybenzimidazole.

Results and Discussion

The important intermediate for omeprazole, 2-mercapto-5-methoxybenzimidazole, has been synthesized by three routes (**Scheme I**). The overall percent yields of this intermediate, from all the three routes, were calculated from the very first starting material, *p*-anisidine.

Route-I, involving 5 steps, resulted in the lower overall yield (22-23%) of 2-mercapto-5-methoxybenzimidazole **6** and the total time required for the reaction was 16-17 hr. **Route-II** involved 3 steps and resulted in 64-65 % overall yield of **6**. The reaction time was 20-21 hr. However, **Route-III** was found to be the best among the three schemes, since it was a two-step reaction and gave the highest overall yield (82-83%) of compound **6** in 20-21 hr. Thus, **Route-III** was found to be the most economical route for the synthesis of compound **6**.

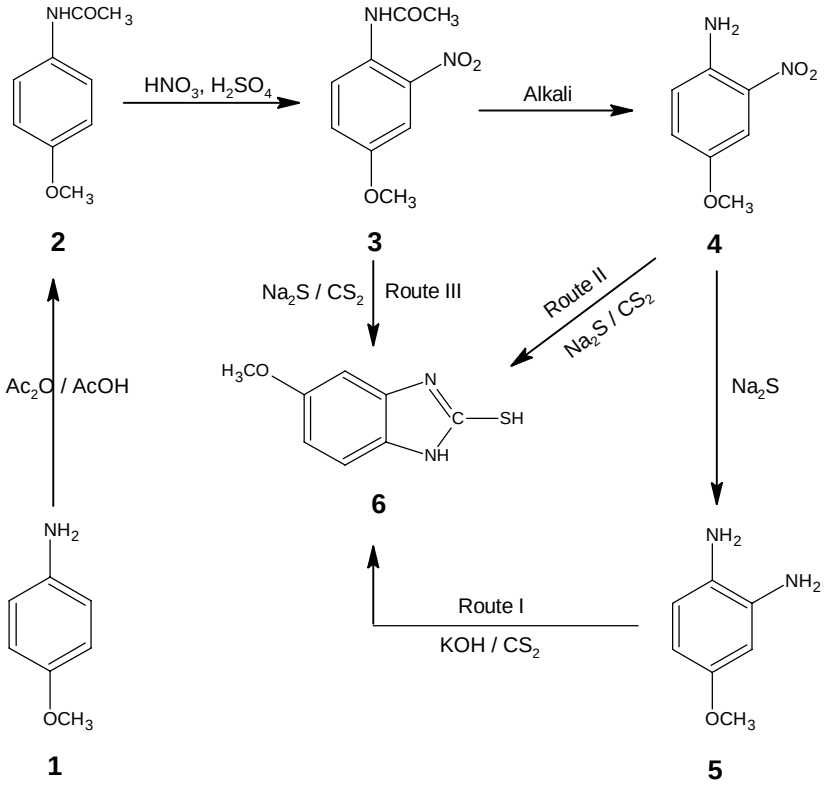
Experimental Section

Melting points of the synthesized compounds are uncorrected. IR spectra in KBr were recorded on a Jasco FTIR-5300 spectrometer; ^{1}H NMR spectra in $CDCl_3$ at 90 MHz on a Varian ^{1}H NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm); and mass spectra on a quadrupole mass spectrometer by the Electron Impact (EI) method.

Route-I

(i) **Synthesis of 4-methoxyacetanilide 2**[2]: *p*-Anisidine **1** (5.0 g, 0.04 mole) was stirred rapidly with glacial acetic acid (12.0 mL). Acetic anhydride (4.5 mL, 0.04 mole) was added to it, all at once. Acetylated product, 4-methoxyacetanilide **2,** was formed within a short time period. The crude product was recrystallized from a mixture of water-ethanol (40:60) to obtain pure compound **2** in 70% yield. This yield was increased to 85% by carrying out acetylation at reflux temperature[3], (at 110°C) for 2 hr, m.p. 130-32°C; IR (KBr): 3241 (N-H str), 1646 (C=O str), 1605 (N-H ben), 1285 (C-N str), 1245 (C-O aryl str), 1175, 1030 cm^{-1} (C-O alkyl str).

(ii) **Synthesis of 4-methoxy-2-nitroacetanilide 3**. The compound **2** was nitrated at 2-position using a mixture of conc. sulfuric acid (6.0 mL) and conc. nitric acid (2.0 mL). The nitrating mixture was cooled to 0°C and compound **2** (4.72 g, 0.03 mole) was added to it at such a rate that temperature did not exceed 5°C. After the addition, the reaction mixture was poured in ice-water. The precipitated yellow solid was washed with water and recrystallized from a mixture of water-ethanol (40:60) to get **3** in 91.0% yield, m.p.



Scheme I

116-17°C; IR (KBr): 3478 (N-H, str), 1703 (C=O str), 1627 (N-H ben), 1513, 1320 (NO_2 str), 1289 (C-N str), 1250 (C-O aryl str), 1151, 1034 cm^{-1} (C-O alkyl str).

(iii) **Synthesis of 4-methoxy-2-nitroaniline 4.** The compound **3**, (4.45 g, 0.02 mole) was hydrolysed[3] with hydrochloric acid (12.0 mL) for 30 min at 100°C. The reaction mixture was cooled and then made alkaline with NaOH solution (20%). The precipitated base was separated out and recrystallized from a mixture of water-ethanol (40:60) to get **4** in 86% yield. This yield could be increased to 93.0%, when the mixture of **3 (**4.45 g, 0.02 mole) and Claisen's alkali[2] (8.0 mL) was heated on a steam-bath for 30 min with constant shaking. When the reaction mixture was refluxed for 30 min, the yield of compound **4** increased to 99.0%, m.p. 122-23°C; IR (KBr): 3488, 3471 (N-H str, 1° amine), 1644 (N-H ben), 1573, 1376 (NO_2 str), 1279 (C-N str), 1250 (C-O aryl str), 1158, 1022 cm^{-1} (C-O alkyl str).

(iv) **Synthesis of 4-methoxy-1,2-phenylenediamine 5**. The compound **4** was reduced to compound **5**, using following four different reducing agents.

(a) *Using $SnCl_2$. $2H_2O$ and conc. HCl*. The compound **4** (4.62 g, 0.03 mole) was mixed with $SnCl_2.2H_2O$ (17.24 g, 0.08 mole) and conc. HCl (97.0 mL). The temperature rose spontaneously to 52 °C. After standing for several hours at room temperature, the solution was partly neutralized to get *p*H 5. Stannous chloride was removed by precipitating tin with H_2S as tin sulfide and then filtering it. The filtrate was concentrated to a small volume, made strongly basic and then extracted with ether. Removal of ether gave a dark coloured base, which was recrystallized from ethanol (95%) to get **5** in 39% yield**,** m.p. 45-46 °C; IR (KBr): 3347, 3402 (N-H str, 1° amine), 1624 (N-H ben), 1294 (C-N str), 1214 (C-O aryl str), and 1165, 1030 cm^{-1} (C-O alkyl str).

(b) *Using Zn dust and NaOH*. The yield of compound **5** was increased to 73% by carrying out reduction of **4** (4.62 g, 0.03 mole) with zinc dust (9.4 g), aqueous NaOH (5.0 mL, 20%) and ethanol (95%, 5.0 mL). The reaction mixture was refluxed for 6 hr.

(c) *Using Sn granules and conc. HCl*[4]. Reduction of **4** (4.62 g, 0.03 mole) with tin granules (4.65 g, 0.04 mole) and conc. HCl (10.0 mL), at reflux temperature for 20 min, resulted in 90% yield of **5**.

(d) *Using $Na_2S.9H_2O$*. The highest yield (96%) of compound **5** was obtained by refluxing compound **4** (4.62 g, 0.03 mole), with $Na_2S.9H_2O$ (30 g, 0.26 mole) in water (10.0 mL) for 6 hr.

(v) **Synthesis of 2-mercapto-5-methoxybenzimidazole 6**. The compound **5** was cyclised to compound **6**, by using KOH/CS_2. Potassium hydroxide (1.9 g, 0.03 mole) was dissolved in a mixture of ethanol (30.0 mL) and water (30.0 mL). To this, CS_2 (2.7 g, 0.03 mole) was added with stirring. This mixture was boiled and then the solution of **5** (3.45 g, 0.03 mole) in ethanol (20.0 mL) was added dropwise to it. After refluxing the reaction mixture for 6 hr, ethanol was removed. The white residue obtained was dissolved in water and the product was precipitated by the addition of dilute acetic acid (50 %). It was then recrystallized from a mixture of water-ehanol (1:1) to get compound **6** in 40.0% yield, m.p. 255-56 ^oC; IR (KBr): 3304 (N-H str), 2560 (S-H str), 1622 (N-H ben), 1265 (C-O aryl str), 1182, 1026 (C-O alkyl str), 626 cm^{-1} (C-S str); ^1H NMR ($CDCl_3$): δ 3.2 (s, 1H, -SH), 3.4 (s, 3H, -OCH_3), 6.3 (d, J = 9.8, 1H, ArH), 6.6 (d, J = 9.8, 1H, ArH), 6.7 (s, 1H, ArH), 11.3 (s, 1H, -NH). Mass: m/z (%) 180 (M^+) (100), 181 (15.2), 182 (4.4), 165 (14.2), 147 (37.7), 137 (73.0), 119 (14.1), 91 (34.2), 63 (16.2); Anal. Calcd for $C_8H_8ON_2S$: C, 53.33; H, 4.80; O, 8.88; N, 15.55; S, 17.77. Found: C, 53.83; H, 4.02; O, 8.78; N, 15.23; S, 18.14%.

Route-II

(i) **Synthesis of compound 3**. The compound **3** was synthesized from compound **1**, without separating the intermediate **2**. *p*-Anisidine **1** (5.0 g, 0.04 mole) was acetylated using glacial acetic acid (12.0 mL) and acetic anhydride (4.5 mL, 0.04 mole) to get the compound **2**. To the crude suspension of the compound **2,** a cold nitrating mixture (6.0 mL of conc. H_2SO_4 + 2.0 mL of conc. HNO_3, cooled to 0^oC) was added with rapid stirring. The temperature was maintained below 5^oC. The yellow crystals were separated out and recrystallized from the mixture of water-ethanol (40:60) to get **3** in 86.0% yield.

(ii) **Synthesis of compound 4**. Hydrolysis of the compound **3** (4.45 g, 0.02 mole) to compound **4** was carried out using Claisen′s alkali[2] (8.0 mL), as described in **Route-I (step iii)**.

(iii) **Synthesis of compound 6**. In this step, reduction and cyclisation reactions were carried out simultaneously[5]. Sodium sulphide was used as a reducing agent and CS_2 was used as a cyclising agent. The compound **4** (5.84 g, 0.03 mole) was mixed with aqueous solution of $Na_2S.9H_2O$ (35.0 mL, 0.15 mole). The mixture was refluxed and then cooled to 20 ^oC for 6 hr. To this reaction mixture, carbon disulfide (4.9 g, 0.86 mole) was added over a period of half an hour. The reaction mixture was then heated to 80 ^oC till it was free from reduced compound **5**. This required about 10 to 12 hr. In the resulting solution having *p*H 9.3 to 9.4, the compound **6** was liberated from its sodium salt by passing H_2S gas. The crude compound **6** was filtered; washed with water and recrystallized from a mixture of water-ethanol (1:1), yield 75%. In order to avoid the risk of handling inflammable CS_2, it was replaced by thiourea (4.9 g, 0.86 mole) as a cyclising agent. The reaction was carried out for 16 to 17 hr, but the yield of the compound **6** was only 52%.

Route-III

(i) **Synthesis of compound 3.** This step was exactly the same as described in **Route-II (step i)**.

(ii) **Synthesis of compound 6**. In this step, hydrolysis, reduction and cyclisation reactions were carried out simultaneously. The compound **3** (4.45 g, 0.02 mole) and $Na_2S.9H_2O$ (44.28 g, 0.1 mole) were mixed together and the reaction mixture was refluxed for 6 hr. Both, the hydrolysis and the reduction reactions, took place simultaneously. Carbon disulfide (6.1 g, 4.7 mL, 1.07 mole) was added as a cyclising agent to this reaction mixture at 30 ^oC, over a period of 30 min. The mixture was further heated for 10-12 hr at 80 ^oC till it was free from the reduced compound **5**. To the resulting solution of *p*H 9.3-9.4, H_2S gas was passed to liberate the final compound **6** from its sodium salt. The product was filtered, washed with water and recrystallized from a mixture of water-ethanol (1:1) to get **6** in 95.0% yield.

References

1 Brunton L L, In *Goodman and Gilman's: The Pharmacological Basis of Therapeutics,* 9th edn, edited by J E Hardman, L E Limbard, P B Molinoff & R W Ruddon, (McGraw Hill, New York), **1966**, 901.

2 Fanta P E & Tarbell D S, *Org Synth*, 3, **1964**, 661.

3 Kuhler T C, Fryklund J, Bergan N A, Weilitz J, Lee A & Larsson H, *J Med Chem*, 38(25), **1995**, 4906.

4 Furniss B S, Hannaford A J, Smith W G & Tatchell A R, in *Vogel's Textbook of Organic Chemistry*, 5th Edn, (ELBS, Longman Group, UK Ltd.), **1989**, 703.

5 Kacani P, Klucovsky P, Gallovic J, Sabo S & Karska S, *Chem Abstr*, 96, **1982**, 162699u.