A New Synthetic Process of Lansoprazole

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Lansoprazole is the generic name of 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole, **1** (see Scheme 1). It is a proton pump inhibitor that reduces gastric acid secretion and has successfully been used to heal and relieve symptoms of gastric or duodenal ulcers and gastro-esophagal reflux.[1]

Lansoprazole has been synthesized by an oxidation of sulfide **9** produced from a substitution reaction between 2-mercaptobenzimidazole and pyridine derivatives such as 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine, **8**.[2,3] The transformation of sulfide **9** into lansoprazole has been generally carried out with peroxyacid such as mCPBA or hydrogen peroxide in the presence of homogeneous catalyst.[3]

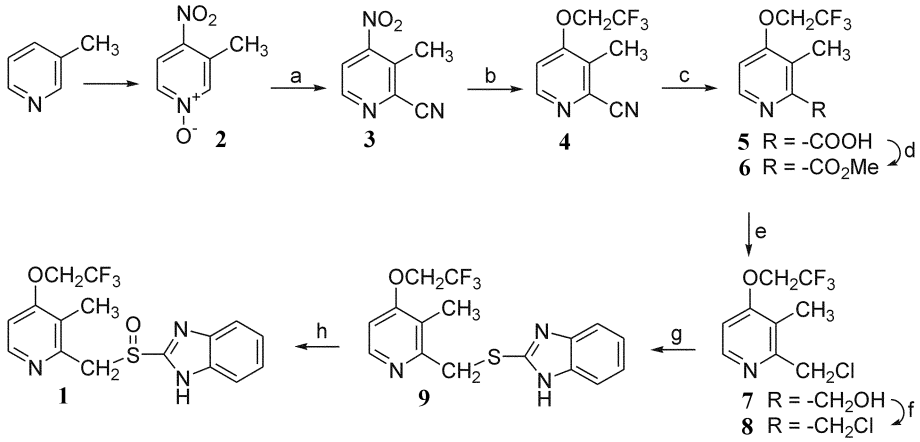
Recently, we found that trirutile type solid oxides catalyze the hydrogen peroxide oxidation of sulfides to sulfoxides very efficiently.[4] The reaction was very selective producing sulfoxide with negligible amount of sulfone. Since the reaction is performed under heterogeneous conditions, the solid catalyst can be easily recovered by a simple filtration of the final reaction mixture. Because of these advantages in purification of the product, we decided to apply the heterogeneous sulfoxidation method to the synthesis of lansoprazole.

In our approach to the synthesis of lansoprazole, we tried to devise a new process that could use 3-picoline as a starting material because it is more readily available than 2,3-lutidine, the most widely used starting material.[2,3] This strategy has become possible by adopting Matsumura's method in the synthesis of 2-cyano-3-methyl-4-nitropyridine (**3**).[5] Thus, here we report a new synthetic process for lansoprazole as shown in scheme 1.

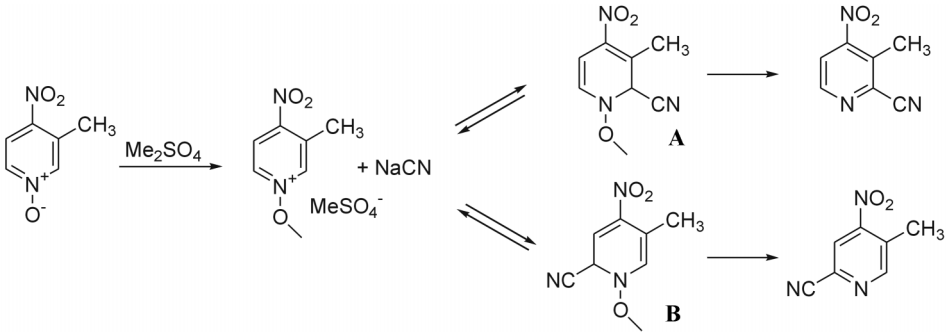
2-Cyano-3-methyl-4-nitropyridine (**3**), the key compound of the present approach for lansoprazole was prepared from **2** according to the literature method, with a yield of 81%.[5] The normal coupling constant (5 Hz) between H-5 and H-6 in ^{1}H-NMR of **3** indicates that the cyano group was selectively introduced into C2-position instead of C6. To understand the selectivity, the heat of formation of intermediates **A** and **B** (Table 1) expected in the course of substitution reaction on C2 and C6, respectively, according to the Reissert-Kaufmann type reaction mechanism (Scheme 2)[6] was calculated using semiempirical method (AM1 and PM3).[7]

As shown in Table 1, ΔH_f of intermediate **A** was ~1 kcal/mol smaller than ΔH_f of intermediate **B**. The relative stability of intermediate **A** observed from the calculation, even though small, was helpful to understand the selective substitution on C2 position.

The nitro group of **3** was replaced by 2,2,2-trifluoroethoxy group by a reaction with sodium trifluoroethoxide in 82% yield. Hydrolysis of the nitrile group of **4** with sulfuric acid and $NaNO_2$ gave **5** in 92% yield. Since zwitterion **5** was not



Scheme 1. *Reagents and conditions*: (a) Me_2SO_4, NaCN, 81% (b) $NaOCH_2CF_3$, 82% (c) H_2SO_4, $NaNO_2$, 92% (d) H_2SO_4, MeOH, 90% (e) $NaBH_4$, 97% (f) $SOCl_2$, 91% (g) 2-mercaptobenzimidazole, 96% (h) H_2O_2, $LiNbMoO_6$, 77%.



Scheme 2

Table 1. Semiempirical calculation (ΔH_f) of intermediates

Method \ Intermediate	A	B
AM1 (kcal/mol)	69.08	70.48
PM3 (kcal/mol)	52.16	53.04

soluble in ether solvent, the compound was converted to methyl ester **6**. Reduction of the ester by $NaBH_4$ followed by a reaction with thionyl chloride gave chloride **8**. Direct displacement of chloride group in **8** by 2-mercaptobenzimidazole afforded sulfide **9** in 96% yield. The reaction, performed generally in the presence of base, went successfully even without base.

The oxidation of **9** to lansoprazole has been achieved by using various oxidants such as mCPBA or hydrogen peroxide and a catalyst.[3] However, those methods normally produced a certain amount of overoxidized product, sulfone along with the desired sulfoxide, **1**. When the H_2O_2/$LiNbMoO_6$ oxidation method developed in our group was used,[4] a mixture of lansoprazole and its sulfone derivative was produced in a ratio of 48 : 1 (determined by HPLC), which is better than results obtained with other oxidation methods. After recrystallization with a mixed solution of chloroform and 2-propanol (5 : 1), pure lansoprazole was obtained in 77% yield.

In summary, we were able to synthesize lansoprazole from **2** derived from readily available 3-picoline in 8 steps. The overall yield was 36%. Our H_2O_2/$LiNbMoO_6$ sulfoxidation method was successfully applied to the oxidation of sulfide **9** to lansoprazole.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker spectrometer in $CDCl_3$ containing TMS as the internal standard. Chemical shifts are given in parts per million (ppm) downfield from TMS. Coupling constants (*J*) are given in Hz. Infrared (IR) spectra were recorded on a Jasco FT-IR-4300.

2-Cyano-3-methyl-4-nitropyridine (3). The compound was synthesized from **2** according to the literature method[5] in 81% yield: ^{1}H-NMR (CD_3OD, 200 MHz) δ 8.81 (d, J = 5.06 Hz, 1H), 8.11 (d, J = 5.18 Hz, 1H), 2.73 (3H, s).

2-Cyano-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (4). To a solution of **3** (1.35 g, 8.28 mmol) in 40 mL CF_3CH_2OH were added a solution of sodium trifluoroethoxide prepared from Na (0.243 g, 10.6 mmol) and 2,2,2-trifluoroethanol (27 mL) dropwise at 0 °C. After stirring for an hour, water was added. Product was extracted by methylene chloride. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to yield 1.47 g (82% yield) of **4** (mp 76-77 °C): IR (KBr) 2237 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.43 (d, J = 5.54 Hz, 1H), 6.89 (d, J = 5.6 Hz, 1H), 4.45 (q, J = 7.72 Hz, 2H), 2.43 (3H, s); HRMS (EI) *m/z* calcd $C_9H_7ON_2F_3$ (M^+) 216.0510, found 216.0521.

3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic acid (5). A solution of **4** (0.120 g, 0.555 mmol) in sulfuric acid (0.65 mL) was heated at 120 °C for 2 h. Into the reaction mixture, 0.134 g (1.948 mmol) of sodium nitrite in 0.2 mL of water was added dropwise with stirring at 25 °C for 30 min. The mixture was stirred for 1h at 25 °C and then for additional 1 h at 80 °C. The resulting mixture was cooled to room temperature. Cracked ice (2 g) was added to the solution. The pH of the solution was adjusted to 1.2 with Na_2CO_3. The precipitate was filtered and recrystallized from acetone to give 0.120 g (92%) of **5** (mp 199-200 °C): IR (KBr) 1611 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 8.47 (d, J = 6.34 Hz, 1H), 7.48 (d, J = 6.42 Hz, 1H), 4.92 (q, J = 9.2 Hz, 2H); HRMS (EI) *m/z* calcd $C_9H_8O_3NF_3$ (M^+) 235.0456, found 235.0450.

3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic acid methyl ester (6). A solution of **5** (0.050 g, 0.21 mmol) and sulfuric acid (catalytic amount) in MeOH (7 mL) was refluxed for 24 h. Sodium carbonate was added to remove the sulfuric acid. Evaporation of solvent afforded 0.048 g of **6** (90%, mp 209-212 °C): IR (KBr) 1639 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.46 (d, J = 5.5 Hz, 1H), 6.84 (d, J = 5.56 Hz, 1H), 4.43 (q, J = 7.78 Hz, 2H), 3.96 (3H, s), 2.42 (3H, s); HRMS (EI) *m/z* calcd $C_{10}H_{10}O_3NF_3$ (M^+) 249.0613, found 249.0651.

2-Hydroxymethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (7)[2]. To a solution of **6** (289 mg, 1.16 mmol) in MeOH (3 mL) was added sodium borohydride (439 mg, 11.6 mmol) at 0 °C. After 5 h stirring at room temperature, water was added to quench the reaction. The aqueous layer was extracted with dichloromethane and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded 250 mg of pure **7** (97%): ^{1}H-NMR

($CDCl_3$, 200 MHz) δ 8.36 (d, J = 5.7 Hz, 1H), 6.69 (d, J = 5.7 Hz, 1H), 4.68 (s, 2H), 4.41 (q, J = 7.8 Hz, 2H), 2.09 (s, 3H).

2-Chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (8). To a solution of **7** (250 mg, 1.13 mmol) in dioxane (2.5 mL) was added thionyl chloride (0.11 mL, 1.47 mmol) at room temperature. The mixture was stirred for 3 h at 50 °C and then cooled to room temperature. The reaction mixture was diluted with dichloromethane and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 245 mg (91%) of **8**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.34 (d, J = 5.6 Hz, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.68 (s, 2H), 4.38 (q, J = 7.8 Hz, 2H), 2.31 (s, 3H).

2-[[2-(3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl)methyl]-thio]-1*H*-benzimidazole (9)[2]. A suspension of **8** (10.0g, 36.2 mmol) and 2-mercaptobenzimidazole (5.71 g, 38.0 mmol) in methanol (100 mL) was refluxed for 1.5 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was triturated with a mixed solution of acetone and diisopropyl ether (1/5). A suspension of the residue in a mixture of chloroform (300 mL) and MeOH (30 mL) was washed with aqueous saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 14.8 g (96%) of **9**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.40 (d, J = 5.7 Hz, 1H), 7.53 (dd, J = 6.0 Hz, J = 3.2 Hz, 2H), 7.18 (dd, J = 6.0 Hz, J = 3.2 Hz, 2H), 6.72 (d, J =5.7 Hz, 1H), 4.41 (q, J = 7.7 Hz, 2H), 4.40 (s, 2H), 2.31 (s, 3H).

2-[[2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl]methyl]-sulfinyl]-1*H*-benzimidazole (1). To a solution of **9** (100 mg, 0.28 mmol) in MeOH (4 mL) were added $LiNbMoO_6$[8] (25 mg, 0.08 mmol) and 35% H_2O_2 (0.82 mL, 8.40 mmol) at -20 °C. After stirring for 5.5 h at -20 °C, the reaction mixture was filtered. To the filtrate was added 1% aqueous $Na_2S_2O_3$ and stirred for 5 min at 0 °C. The mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 87 mg (81% yield) of lansoprazole. The compound was recrystallized with a solution of chloroform and 2-propanol (5 : 1) to yield 81 mg (77%) of pure lansoprazole (mp 165-170 °C (dec.), lit.[2] 168-170 °C): IR (KBr) 1587, 1464, 1408, 1276, 1172, 1115, 1040, 973, 860, 756 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.34 (d, J = 5.6 Hz, 1H), 7.65 (br., 2H), 7.35 (d, J = 3.9 Hz, 1H), 7.30 (d, J = 3.9 Hz, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.74 (q, J = 13.8 Hz, 2H), 4.40 (d, J = 7.8 Hz, 1H), 4.32 (d, J = 7.8 Hz, 1H), 2.21 (s, 3H); MS (EI), m/z 369 (M^+), 353, 321, 238, 204, 149.

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