MICROWAVE SYNTHESIS OF LANSOPRAZOLE DRUG INTERMEDIATE

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Abstract: The sulfide intermediate, ('2-[[[3-Methyl-4- (2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] thio]-1H-benzimidazole) (**3**), required for the industrial synthesis of the anti-ulcer drug Lansoprazole, has been prepared in excellent yields by microwave irradiation of a dry mixture of 2-chloromethyl-3-methyl-4- (2,2,2-trifluoroethoxy)pyridine hydrochloride (**1**) and 2-mercaptobenzimidazole (**2**) in the presence of Na_2CO_3.

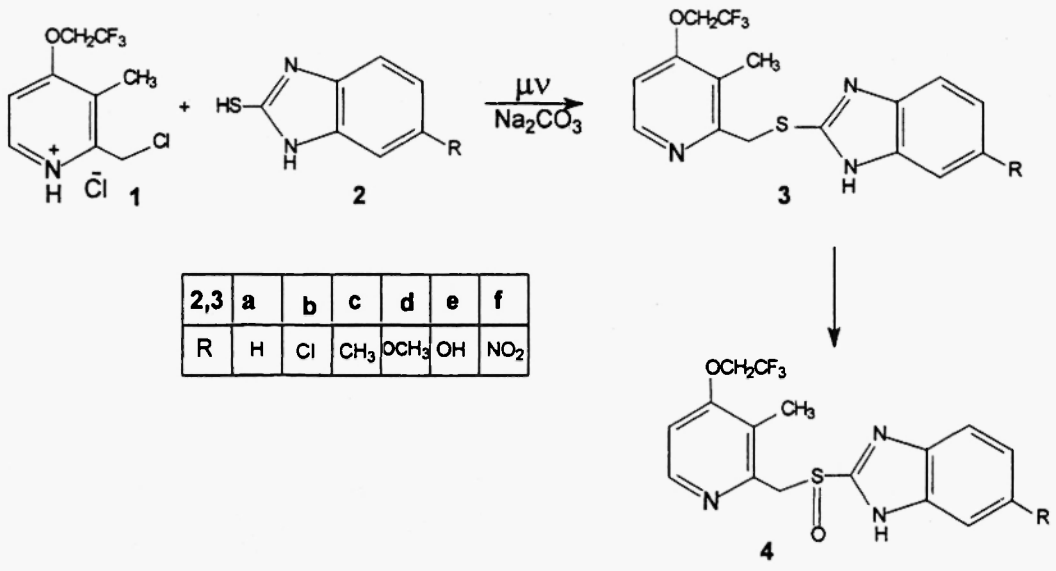
Keywords: Microwave irradiation, Lansoprazole, 2-Mercaptobenzimidazole, 2-Chloromethyl -3-methyl-4- (2,2,2-trifluoroethoxy) pyridine hydrochloride.

Introduction

Lansoprazole (**4**) is a proton pump inhibitor and has successfully been used to heal and relieve symptoms of duodenal ulcers and gastro-esophageal reflex.[1] Industrially, **4** has been synthesized by mCPBA oxidation[2] of the sulfide intermediate **3** that was obtained from 2-mercaptobenzimidazole[3] (**2**) and 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride[4] (**1**). Reaction media such as heterogeneous catalysis, p-toluenesulfonyl chloride-K_2CO_3,[5] p-toluenesulfonyl chloride-$NaHCO_3$, PBr_3–$Na_2S_2O_3$,[6] PPh_3,[7] $O(SO_2Me)_2$-Et_3N,[8] borohydride exchange resin,[9] NaOH-PCl_3[10] and $PhCONH_2$-Pd $(PPh_3)_4$[11] were used in the synthesis of **3,** The procedures are tedious and pollutes the environment. Hence, the search for a simpler, high yielding and greener synthesis of **4** continues.

Results and discussions

We report here a new and efficient synthesis of the drug intermediate **3** and its derivatives. As a representative example, the synthesis of **3a** is discussed. An equimolar mixture of 2-mercaptobenzimidazole (**2a**), 2-chloromethyl-3-methyl-4-(2,2,2,-trifluoroethoxy) pyridine hydrochloride (**1**), and anhydrous sodium carbonate was exposed to microwave radiation in a 600 watt Microwave oven for 2 -10 minutes. The melt was chromatographed over silica gel (60-120 mesh) and eluted with benzene-ethylacetate solvent mixture.The sulfide intermediate **3** was isolated in 85 per cent yield and was characterized by comparing with an authentic sample[1] and by converting it to lansoprazole **4** by a known procedure.[1] The MW synthesis of **3** was extended to five other derivatives **2(b-f).** In all cases, the corresponding sulfide intermediates **3(b-f)** were isolated in 80–85 per cent yield (Table), and characterized by spectral data. This solvent-free reaction is an important example of green synthesis.



2,3	a	b	c	d	e	f
R	H	Cl	CH_3	OCH_3	OH	NO_2

Experimental

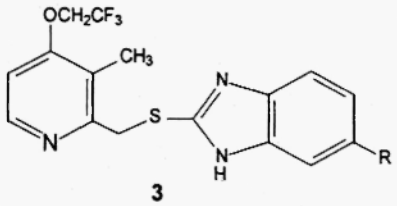
General

Melting points in ^0C were determined on Polomon melting point apparatus (Model. No. M.P-96) and are uncorrected. IR Spectra were recorded on Shimadzu-435 spectrophotometer as KBr pellets, EI-MS on a VG Micromass 7070H (70 eV) instrument and H^1-NMR Spectra were taken in DMSO-d_6 on a Varian Gemini 200 MH_Z Spectrometer using TMS as internal standard. Microwave irradiation was carried out in BPL-Sanyo, BMO and 700T domestic microwave oven at an out put of 600 watts

Experimental procedure

2-[[[3-Methyl-4- (2, 2, 2-trifluoroethoxy)-2-pyridinyl] methyl] thio]-1H-benzimidazole **3.** An equimolar solid mixture of 2-chloromethyl-3-methyl-4-(2,2,2,-trifluoroethoxy) pyridine hydrochloride (**1,** 1 g), 2-mercaptobenzimidazole (**2,** 0.697 g), and anhydrous sodium carbonate (0.445 g) was irradiated with microwave irradiation in a 600 watt Microwave oven for 2 -10 minutes in a Pyrex conical flask. After the reaction time, the melt was cooled to room temperature dissolved in methanol, adsorbed on silica gel (60-120 mesh) and chromatographed over silica gel (60-120 mesh). The column was eluted with benzene-ethyl acetate solvent mixture (7:3). The sulfide intermediate **3** was isolated from the eluant fractions in 85% yield (4.25 g) and characterized by spectral data.

Table: Reaction conditions and yields of the '2-[[[3-Methyl-4- (2, 2, 2-trifluoroethoxy)-2-pyridinyl] methyl] thio]-1H-benzimidazole (**3**)



Entry	R	Time (min.)	Yield (%)	M.P. (°C)
3a	H	2	85	126-128
3b	Cl	2.5	80	190-192
3c	CH_3	3	75	156-158
3d	OCH_3	8	60	152-154
3e	OH	6	65	110-112
3f	NO_2	10	56	220-222

IR, PMR and Mass data of 3(a-f) & 4

3a:IR (KBr) 3553, 3053, 1893, 1658, 1577, 1444, 1409, 1284, 1254, 1162, 1109, 976, 857, 745, 664, 576; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* =5.7 Hz), 7.53 (2H, dd, *J* = 6.0, 3.2 Hz), 7.18 (2H,dd, *J* = 6.0, 3.2 Hz), 6.72 (1H, d, *J* = 5.7 Hz), 4.41 (2H,q, *J* = 7.7 Hz), 4.40 (2H, s), 2.31 (3H, s); ESIMS: *m/z* 354 ($M^{+\cdot}$) (100%).

3b: IR (KBr) 3050,2951,2870, 1654, 1582, 1452, 1415, 1332, 1271, 1162, 1115, 972, 918, 864, 791, 664, 577; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* =5.7 Hz), 7.49 (2H, dd, J = 6.0, 3.2 Hz), 7.18(1H, d, J = 6.0, 3.2 Hz), 6.72 (1H, d, J = 5.7 Hz), 4.7(2H,s), 4.51(2H, q, J = 7.7 Hz), 2.31 (3H, s); ESIMS: *m/z* 388 ($M^{+\cdot}$) (100%).

3c: IR (KBr) 2942, 1654,1585, 1478,1454, 1272, 1169, 1111, 1037,975, 914, 839, 809, 756, 665, 579, 543; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* =5.7 Hz), 7.49 (2H, dd, J = 6.0, 3.2 Hz), 7.0 (1H, d, J = 6.0, 3.2 Hz), 6.72 (1H, d, J = 5.7 Hz), 4.7(2H,s), 4.5(2H, q, J = 7.7 Hz), 2.4 (3H, s), 2.31 (3H, s); ESIMS: *m/z* 368 ($M^{+\cdot}$) (100%).

3d: IR (KBr) 3154, 2951, 1624, 1582, 1495, 1425, 1341, 1284, 1255, 1156, 1112, 1030, 971, 833, 794, 665, 577; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* =5.7 Hz), 7.49 (2H, dd, J = 6.0, 3.2 Hz), 7.0 (1H, d, J = 6.0, 3.2 Hz), 6.72 (1H, d, J = 5.7 Hz), 4.7(2H,s), 4.5(2H, q, J = 7.7 Hz), 3.85 (3H,s), 2.31 (3H, s); ESIMS: *m/z* 384 ($M^{+\cdot}$) (100%).

3e: IR (KBr) 2915, 2357, 1651, 1633, 1613, 1485, 1392, 1325, 1161, 975, 810, 658, 537, 496; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* =5.7 Hz), 7.49 (2H, dd, J = 6.0, 3.2 Hz), 7.0 (1H, d, J = 6.0, 3.2 Hz), 6.72 (1H, d, J = 5.7 Hz), 5.35 (1H, br), 4.9(2H,s), 4.6(2H, q, J = 7.7 Hz), 2.31 (3H, s); ESIMS: *m/z* 370 ($M^{+\cdot}$) (100%).

3f: IR (KBr) 2530, 1628, 1578, 1537, 1414, 1343, 1254, 1179, 1112, 1063, 969, 890, 821, 731, 686, 662, 486; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* =5.7 Hz), 7.49 (2H, dd, J = 6.0, 3.2 Hz), 7.18 (1H, d, J = 6.0, 3.2 Hz), 6.72 (1H, d, J = 5.7 Hz), 4.7 (2H,s), 4.51 (2H, q, J = 7.7 Hz), 2.31 (3H, s); ESIMS: *m/z* 399 ($M^{+\cdot}$) (100%).

4: IR (KBr) 3225, 2929, 1901, 1657, 1580, 1455, 1401, 1283, 1172, 1038, 971, 857, 813, 749, 657, 527; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.34 (1H, d, *J* = 5.6 Hz), 7.65 (2H, br), 7.35 (1H, d, J = 3.9 Hz), 7.30 (1H, d, J = 3.9 Hz), 6.67 (1H,d, J = 5.6 Hz), 4.74 (2H, q, J = 13.8 Hz), 4.40 (1H, d, J = 7.8 Hz), 4.32 (1H, d, J = 7.8 Hz), 2.21 (3H, s); ESIMS: *m/z* 370 (M^{+}) (100%).

Conclusions

Microwave heating of 2-chloromethyl-3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridine hydrochloride (**1**) and 2-mercaptobenzimidazole (**2**) in the presence of Na_2CO_3 is a

simple,efficient, inexpensive and enviroment friendly synthesis of a valuable intermediate of Lansoprazole.

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