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Efficient Synthesis of N-Oxide Derivatives: Substituted 2-(2-(Pyridyl-N-oxide)methylsulphinyl)benzimida

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Efficient Synthesis of *N*-Oxide Derivatives: Substituted 2-(2-(Pyridyl-*N*-oxide)methylsulphinyl)benzimidazoles

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Abstract: Different substituted 2-chloromethylpyridyl derivatives (**6a**–**d**) were oxidized with mCPBA to give the respective 2-chloromethylpyridine-N-oxide derivatives (**7a**–**d**) at low temperature, which on condensation with 2-mercapto-1H-benzimidazole (**8a**–**c**) in the presence of aprotic solvents give the 2-[[(pyridin-2-yl-1-oxide)methyl]-sulfanyl]-1*H*-benzimidazole (**9a**–**d**) in good yield. Finally, **9a**–**d** oxidized with mCPBA in chlorinated solvent gives a mixture of 2-[[(pyridin-2-yl-1-oxide)methyl]-sulfonyl]-*1H*-benzimidazole (**3a**–**d**, 10%) and 2-[[(pyridin-2-yl-1-oxide) methyl]sulfinyl]-*1H*-benzimidazole (**4a**–**d**, 90%) derivatives.

Keywords: lansoprazole N-oxide, mCPBA, omeprazole N-oxide, pantoprazole N-oxide, rabeprazole N-oxide

Several substituted 2-(2-pyridylmethyl)sulphinyl-1*H*-benzimidazoles derivatives such as esomeprazole, omeprazole, lansoprazole, pantoprazole, and rabeprazole are well-known proton pump inhibitors.[1] Generally, 2-(2-pyridyl methylsulphanyl)-1*H*-benzimidazoles (**1**) are oxidized to prepare 2-(2-pyridylmethylsulphinyl)-1*H*-benzimidazoles (**2**) using different oxidizing reagents such as H_2O_2, mCPBA, and NaOCl on a commercial scale.[2] Use of these oxidizing reagents results in the formation of many by-products

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such as 2-(2-(pyridyl-N-oxide)methylsulphonyl)-1*H*-benzimidazoles (**3**), 2-(2-(pyridyl-N-oxide)methylsulphinyl)-1*H*-benzimidazoles (**4**) and 2-(2-pyridylmethylsulphonyl) benzimidazoles (**5**).[2] Isolation of these by-products is very cumbersome and requires expensive techniques such as preparative high performance liquid chromatography (HPLC) and thin-layer chromatography (TLC). Compounds **3** and **5** can be prepared by oxidation of **2**, but compound **4** is difficult. Compound **4a** was isolated as a metabolite on a preparative scale.[3] Direct synthesis of **4a** is reported, but it consists of several steps and uses hazardous chemicals such as carbondisulphide, cyclohexylisocyanate, and bromine.[4] The present investigation provides a simple synthetic method to prepare different substituted N-oxides using nonhazardous reagents/solvents on a multigram scale.

RESULTS AND DISCUSSION

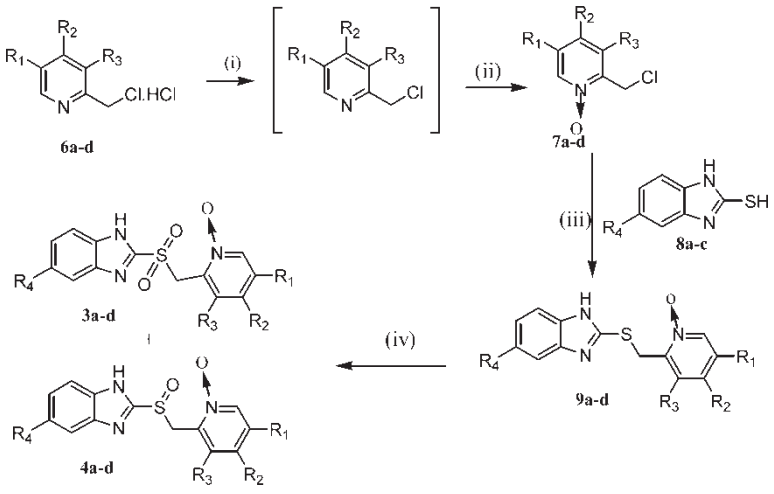
The free base of 2-chloromethyl-3,5-dimethyl-4-methoxypyridine (**6a**) was reacted with m-chloroperbenzoic acid (mCPBA) in chloroform medium at 5°C to give 2-chloromethyl-3,5-dimethyl-4-methoxypyridine-N-oxide (**7a**). The compound **7a** was condensed with 5-methoxy-2-mercapto-1*H*-benzimidazole (**8a**) in N,N-dimethylformamide containing potassium carbonate to yield a chlorine-free compound characterized as 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl-1-oxide)methyl]sulfanyl]-1*H*-benzimidazole (**9a**) [IR (KBr, cm^{-1}): 3062 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 2.26 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.69 (s, 2H, CH_2), 6.77–8.12 (m, 4H, Ar-H), 13.75 (sbr, 1H, NH), DIP MS, m/z(%)-346(M + H)].

The compound **9a** was oxidized with mCPBA in dichloromethane at 0°C. Isolated mixture of two compounds (less polar (**3a**)/more polar (**4a**) −10:90 on HPLC) was separated from column chromatography using chloroform/methanol (98:2) as eluent. The infrared spectrum of compound **3a** showed peaks at 3106 (NH), 1328, and 1153 (SO_2), and for **4a** showed peaks at 3060 (NH), 1065 (S═O). The direct insertion probe (DIP) mass spectra of **3a** and **4a** displayed molecular ion peaks at m/z 362 (M + H), 378 (M + H) respectively. In addition, in the ^{13}C NMR spectrum, shielding of the proton containing pyridine carbon (δ 137.28) indicated the presence of pyridine-*N*-oxide. The ^{1}H NMR spectra of **3a** and **4a** are similar to **9a.** Based on this spectral data, the structures of **3a** and **4a** were confirmed as 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl-1-oxide)methyl]sulfonyl]-1*H*-benzimidazole (**3a**) and 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl-1-oxide)-methyl]sulfinyl]-1*H*-benzimidazole (omeprazole N-oxide, **4a**).

This method extended to three other derivatives (i.e., lansoprazole, pantoprazole, and rabeprazole). In all these cases, the corresponding N-oxides (Table 1, Scheme 1) were obtained as final products in the ratio of ∼10%

Table 1. Preparation of substituted pyridine N-oxides (**3a–d**, **4a–d**, **7a–d**, **9a–d**)

S. no.	R_1	R_2	R_3	R_4	Mp (°C)	Yield (%)
7a	CH_3	OCH_3	CH_3	—	—	52.5
7b	H	OCH_2CF_3	CH_3	—	—	98.45
7c	H	OCH_3	OCH3	—	—	84
7d	H	$OCH_2CH_2CH_2OCH_3$	CH_3	—	—	72
9a	CH_3	OCH_3	CH_3	OCH_3	186–188	88
9b	H	OCH_2CF_3	CH_3	H	225–226	21
9c	H	OCH_3	OCH3	$OCHF_2$	120 (dec)	98.44
9d	H	$OCH_2CH_2CH_2OCH_3$	CH_3	H	153–155	96
3a	CH_3	OCH_3	CH_3	OCH_3	206–207	93.59 (mix)
3b	H	OCH_2CF_3	CH_3	H	189–190 (dec)	88.90 (mix)
3c	H	OCH3	OCH3	$OCHF_2$	170–171	96.15 (mix)
3d	H	$OCH_2CH_2CH_2OCH_3$	CH_3	H	153–156	73 (mix)
4a	CH_3	OCH_3	CH_3	OCH_3	171–173	93.59 (mix)
4b	H	OCH_2CF_3	CH_3	H	183–185	88.90 (mix)
4c	H	OCH3	OCH3	$OCHF_2$	158–159	96.15 (mix)
4d	H	$OCH_2CH_2CH_2OCH_3$	CH_3	H	153–156 (dec)	73 (mix)



Scheme 1. Solvents and reagents: (i) $CHCl_3/NaHCO_3$, (ii) mCPBA, (iii) DMF/K_2CO_3, (iv) MDC/mCPBA.

(**3**) and ~90% (**4**) on HPLC, thus providing a general method for the synthesis of the title compounds.

EXPERIMENTAL

Melting points were determineded in capillaries using a Polman digital melting-point apparatus (model no. Mp 96) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum FT-IR spectrophotometer using 1% potassium bromide pellet. ^1H and ^{13}C NMR spectra were recorded on a Bruker 300-MHz Advance NMR spectrometer at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR. Mass spectra were recorded on a LC-MSD-Trap-SL system.

The high performance liquid chromatography (Waters 2414-Alliance) is equipped with a 285 nm detector and a Develosil ODS UGS, 4.6 × 150 nm, 5 micrometers. The flow rate is about 0.8 mL per minute. The chromatogram programmed as 60 minutes run time and injuction volume 40 microliters. The mobile phase used is water and buffer (prepared a filtered and degassed mixture of acetonitrile, water and triethylamine, (160:40:1) and adjusted the pH to 7.0 with orthophosphoric acid) in the ratio of 9:1.

General Procedure for the Preparation of Substituted 2-Chloromethyl-pyridine-N-oxides (7a–d)

2-Chloromethyl-pyridine hydrochloride derivative (**6**) was dissolved in chloroform (9V). This clear solution was washed with sodium bicarbonate

solution and DM water, dried, and filtered. m-Chloroperbenzoic acid (1.1 molar ratio) was added portion wise at 5°C for 85 min and maintained for 1 h. Then, the reaction mixture was washed with sodium bicarbonate solution and DM water, dried, and concentrated in vacuo. The obtained residue of **7a** was triturated with ethyl acetate; the separated solid was filtered and dried at 40°C overnight. Remaining derivatives **7b–7d** were not isolated because of their stability and were immediately used for the next step.

Data

2-Chloromethyl-3,5-dimethyl-4-methoxypyridine-N-oxide (7a). White solid (yield 52.47%). ^{1}H NMR ($CDCl_3$) (δ ppm): 2.24 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.93 (s, 2H, CH_2), 8.06 (s, 1H, Ar-H). DIP MS: m/z (%) 202 (M + 1,60).

General Procedure for the Preparation of Substituted 2-[[(Pyridin-2-yl-1-oxide)methyl]sulfanyl]-1*H*-benzimidazoles (9a–d)

Pyridine derivative **7** (1 mol) was dissolved in dry DMF (12.22 V) and 2-mercapto-1H-benzimidazole derivative (**8.** 1.0 mol); anhydrous potassium carbonate (2.5 mol) was added subsequently. The resulting mixture was stirred at ambient temperature for 12–18 h. The reaction mixture was poured into ice-cold water, and the separated solid was extracted with chloroform. The extract was washed with DM water, dried over anhy. Sodium sulphate, and filtered. The solvent distilled out completely. The obtained solid was filtered with the help of hexane and dried at 40°C for 15 h. Characterization of the **9** was confirmed by IR, ^{1}H NMR, and mass.

Data

5-Methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl-1-oxide)methyl]sulfanyl]-1*H* benzimidazole (9a). White solid. IR (cm^{-1}): 3062 (NH). ^{1}H NMR ($CDCl_3$) (δ ppm): 2.26 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.69 (s, 2H, CH_2), 6.77–8.12 (m, 4H, Ar-H), 13.75 (sb, 1H, NH, D_2O exchangeable). DIP MS: m/z (%) 346 (M + 1,75).

2-[[(3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl-1-oxide)methyl]sulfanyl]-1*H*-benzoimidazole (9b). White solid. IR (cm^{-1}): 3108 (NH). ^{1}H NMR ($CDCl_3$) (δ ppm): 2.33 (s, 3H, CH_3), 4.81 (s, 2H, CH_2S), 4.89 (q, 2H, $J = 8.71$ Hz, OCH_2CF_3), 7.06–8.33 (m, 6H, Ar-H). DIP MS: m/z (%) 370 (M + 1,100).

5-(Difluoromethoxy)-2-[[(3,4-dimethoxypyridin-2-yl-1-oxide) methyl]sulfanyl]-1*H*-benzoimidazole (9c). White solid. IR (cm^{-1}): 3109 (NH). ^{1}H

NMR ($CDCl_3$) (δ ppm): 3.94 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.65 (s, 2H, CH_2), 6.49 (t, 1H, $J = 74.7$ Hz, $OCHF_2$), 6.83–8.17 (m, 5H, Ar-H), 14.36 (sb, 1H, NH, D_2O exchangeable). DIP MS: m/z (%) 384 (M + 1,100).

2-[[(4-(3-Methoxypropoxy)-3-methyl-pyridin-2-yl-1-oxide)methyl]sulfanyl]-1*H*-benzoimidazole (9d). White solid. IR (cm^{-1}): 3107 (NH). ^1H NMR ($CDCl_3$), (δ ppm): 2.09 (m, 2H, $OCH_2C\underline{H}_2CH_2OCH_3$), 2.34 (s, 3H, CH_3), 3.34 (s, 3H, OCH_3), 3.54 (t, 2H, $J = 5.89$ Hz, $OCH_2CH_2C\underline{H}_2OCH_3$), 4.14 (t, 2H, $J = 6.24$ Hz, $OC\underline{H}_2CH_2CH_2OCH_3$), 4.76 (s, 2H, CH_2S), 6.78–8.23 (m, 6H, Ar-H), 14.29 (sb, 1H, NH, D_2O exchangeable). DIP MS: m/z (%) 360 (M + 1,100).

General Procedure for the Preparation of Substituted 2-[[(Pyridin-2-yl-1-oxide)methyl]sulfonyl]-1*H*-benzimidazoles (3a–d) and Substituted 2-[[(Pyridin-2-yl-1-oxide)methyl]sulfinyl]-1*H*-benzimidazoles (4a–d)

The compound **9** (1 mol) was dissolved in dichloromethane (30 V) and cooled on an ice bath to 0°C. m-Chloroperbenzoic acid (1.0 mol) was added portionwise at 0°C for 145 min and maintained for 15 min. Then, the reaction mixture was washed with sodium bicarbonate solution and DM water, dried, and concentrated in vacuo. The obtained semisolid with compound is **3** is about 10% and with **4** about 90% by HPLC. The products **3** and **4** were separated by column chromatography over silica gel (60–120 mesh) using a mixture of chloroform and methanol (98:2) as eluent and confirmed by IR, NMR, and mass spectra.

Data

5-Methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl-1-oxide)methyl]sulfonyl]-1*H*-benzimidazole (3a). White solid. IR (cm^{-1}): 3106 (NH), 1328 and 1153 (SO_2). ^1H NMR (DMSO-d_6) (δ ppm): 2.17 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.33 (s, 2H, CH_2), 6.99–8.06 (m, 4H, Ar-H), 13.69 (sb, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) (δ ppm): 12.17 (CH_3), 12.81 (CH_3), 54.21 (C8), 55.51 (OCH_3), 60.27 (OCH_3), 94.38 (C4), 101.97 (C10), 114.36 (C6), 121.44 (C7), 129.66 (C12), 130.86 (3a), 135.15 (C7a), 137.48 (C13), 137.57 (C9), 147.18 (5C), 153.87 (C11), 157.92 (C2). DIP MS: m/z (%) 378 (M + 1,75).

2-[(3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl-1-oxide)methylsulfonyl]-1*H*-benzoimidazole (3b). White solid. IR (cm^{-1}): 3114 (NH), 1333 and 1169 (SO_2). ^1H NMR (DMSO-d_6), (δ ppm): 2.50 (s, 3H, CH_3), 4.94 (q, 2H, $J = 8.70$ Hz, OCH_2), 5.44 (s, 2H, CH_2SO_2), 7.20–8.32 (m, 6H, Ar-H), 13.87 (sb, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6), (δ ppm):

11.99 (CH_3), 54.05 (C8), 65.27 (q, $J = 34.4$ Hz, $O\underline{C}H_2$), 110.20 (C12), 113.08 (C7), 120.76 (C5), 123.39 (C6), 123.63 (q, $J = 276$, $\underline{C}F_3$), 125.47 (C4), 126.79 (C10), 134.24 (C3a), 136.69 (C13), 139.44 (C9), 142.31 (C7a), 148.39 (C11), 151.77 (C2). DIP MS: m/z (%) 402 (M + 1,80).

5-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl-1-oxide)methylsulfonyl]-1*H*-benzoimidazole (3c). White solid. IR (cm^{-1}): 3104 (NH), 1336 and 1131 (SO_2). ^{1}H NMR (DMSO-d_6) (δ ppm): 3.81 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 7.04–8.03 (m, 6H, Ar-5H + O$\underline{C}$HF2), 14.00 (sb, 1H, NH, D_2O exchangeable). DIP MS: m/z (%) 416 (M + 1,100).

2-[(4-(3-Methoxypropoxy)-3-methyl-pyridin-2-yl-1-oxide)methylsulfonyl]-1*H*-benzoimidazole (3d). DIP MS: m/z (%) 391 (M + 1,100).

5-Methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl-1-oxide)methyl]sulfinyl]-1*H*-benzimidazole (Omeprazole N-oxide, 4a). White solid. IR (cm^{-1}): 3060 (NH), 1065 (S═O). ^{1}H NMR (DMSO-d_6), (δ ppm): 2.01 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.81 (s, 2H, CH_2), 6.94–8.24 (m, 4H, Ar-H), 13.55 (sb, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) (δ ppm): 11.85 (CH_3), 12.83 (CH_3), 54.45 (C8), 55.48 (OCH_3), 60.24 (OCH_3), 94.53 (C4), 101.51 (C10), 113.06 (C6), 120.39 (C7), 129.29 (C12), 130.50 (C7a), 135.10 (3a), 137.58 (C13), 139.40 (C9), 152.95 (5C), 153.98 (C11), 157.01 (C2). DIP MS: m/z (%) 362 (M + 1,80).

2-[(3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl-1-oxide)methylsulfinyl]-1*H*-benzoimidazole (Lansoprazole N-oxide, 4b). White solid. IR (cm^{-1}): 3093 (NH), 1058 (S═O). ^{1}H NMR (DMSO-d_6), (δ ppm): 2.07 (s, 3H, CH_3), 4.91 (m, 4H, 2 × CH_2), 7.26–8.36 (m, 6H, Ar-H), 13.70 (sb, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) (δ ppm): 12.04 (CH_3), 54.79 (C8), 65.81 (q, $J = 34.5$ Hz, $O\underline{C}H_2$), 110.46 (C12), 112.87 (C7), 120.20 (C5), 123.25 (C6), 124.08 (q, $J = 276$ Hz, $\underline{C}F_3$), 124.41 (C4), 127.00 (C10), 135.06 (C3a), 137.28 (C13), 141.95 (C9), 143.43 (C7a), 152.47 (C11), 155.17 (C2). DIP MS: m/z (%) 386 (M + 1,100).

5-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl-1-oxide)methylsulfinyl]-1*H*-benzoimidazole (Pantoprazole N-oxide, 4c). White solid. IR (cm^{-1}): 3095 (NH), 1057 (S═O). ^{1}H NMR (DMSO-d_6) (δ ppm): 3.72 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.79 (s, 2H, CH_2), 7.01–8.21 (m, 6H, Ar-5H + O$\underline{C}$HF2), 13.85 (sb, 1H, NH, D_2O exchangeable). DIP MS: m/z (%) 400 (M + 1,100).

2-[(4-(3-Methoxypropoxy)-3-methyl-pyridin-2-yl-1-oxide)methylsulfinyl]-1*H*-benzoimidazole (Rabeprazole N-oxide, 4d). White solid. IR (cm^{-1}): 3034 (NH, br), 1060 (S═O). ^{1}H NMR (DMSO-d_6), (δ ppm): 1.96

(m, 2H, $OCH_2C\underline{H}_2CH_2OCH_3$), 2.03 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 3.45 (t, 2H, $J = 6.17$ Hz, $OCH_2CH_2C\underline{H}_2OCH_3$), 4.11 (t, 2H, $J = 6.14$ Hz, $OC\underline{H}_2$-$CH_2CH_2OCH_3$), 4.90 (AB_q, 2H, $J = 12.22$ Hz, CH_2SO), 7.11–8.24 (m, 6H, Ar-H), 13.72 (sb, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6), (δ ppm): 11.59 (CH_3), 28.56 ($OCH_2\underline{C}H_2CH_2OCH_3$), 54.28 ($CH_2SO$), 57.94 ($OCH_3$), 65.85 ($OCH_2CH_2\underline{C}H_2OCH_3$), 68.21 ($O\underline{C}H_2CH_2CH_2OCH_3$), 108.83 (C12), 112.4 5 (C7), 119.73 (C5), 122.67 (C6), 123.91 (C4), 126.10 (C10), 134.70 (C3a), 136.66 (C13), 140.83 (C9), 143.09 (C7a), 153.84 (C11), 154.81 (C2). DIP MS: m/z (%) 376 (M + 1,100).

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