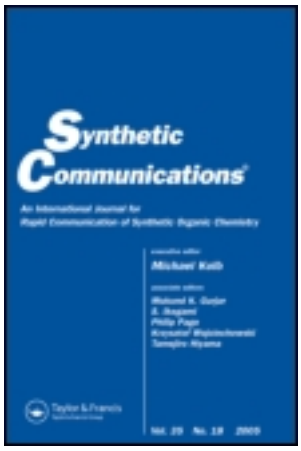

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A PRACTICAL ONE POT SYNTHESIS OF 2-[2-(PYRIDYLMETHYL)-THIO]-*1H*-BENZIMIDAZOLES

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ABSTRACT

A combination of Et_3N and *p*TSCl was found to be far superior than *p*TSCl or benzene sulfonyl chloride alone in converting substituted 2-picoline-*N*-oxides to the corresponding 2-chloromethylpyridines and has been exploited for the synthesis of a variety of 2-[2-(pyridylmethyl)-thio]-*1H*-benzimidazoles, key intermediates in the manufacture of H^+/K^+-ATPase inhibitors in a single pot.

Key Words: Omeprazole; Lansoprazole; Benzimidazole; 2-Halomethylpyridines; Pyridylmethylthiobenzimidazoles

The search for a practical yet efficient synthesis of bioactive molecules has always been the focus of our interest.[1] In this direction, synthesis of H^+/K^+-ATPase irreversible inhibitors such as omeprazole, lansoprazole

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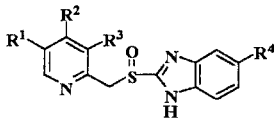


1

1a R^1= R^3= Me; R^2= OMe, R^4 = OCH_3 (Omeprazole)

1b R^1= R^4= H; R^2= OCH_2CF_3; R^3 = Me (Lansoprazole)

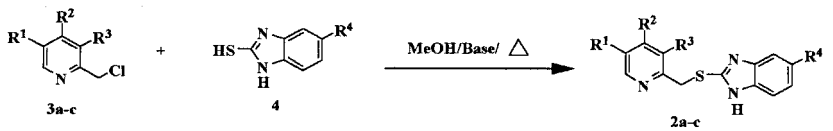
1c R^1= H; R^2= R^3= OMe; R^4 = H (Analog of **1d**)

1d R^1= H; R^2= R^3= OMe; R^4 = $OCHF_2$ (Pantoprazole)

and pantoprazole (**1a**,**1b**,**1d**), which have regained their position as leading candidates in ulcer chemotherapy, were chosen as target molecules.

The reported synthesis[2] of the prazoles **1a–c** involves the condensation of 2-halomethylpyridines (**3a–c**) with 2-mercaptobenzimidazoles (**4**) and the subsequent oxidation of the resulted sulfides (**2a–c**). The synthesis of 2-halomethylpyridines[2e,3] in turn is performed by subjecting 2-methylpyridine-*N*-oxides to Bockethide rearrangement in the presence of acetic anhydride, followed by saponification and transformation of the resulting 2-hydroxymethylpyridines to the corresponding halo derivatives (**3a–c**) by reacting with halogenating agents such as $SOCl_2$, $POCl_3$, PBr_3 etc. This method, however, suffers from drawbacks such as poor material efficiency, involvement of multisteps and formation of ring acetoxy products.

Quite a few single-step conversions of 2-picoline-*N*-oxide to give 2-chloromethylpyridine in the presence of reagents such as *p*-toluenesulfonyl chloride,[4] benzenesulfonyl chloride[5] and phosphoryl chloride[6] are also reported in the literature; however, the extension of this methodology to substituted pyridines proved to be futile in our hands. The present report describes a mild, general and convenient single-step synthesis of various 2-chloromethylpyridines and their in-situ condensation with 2-mercaptobenzimidazoles to get the desired sulfides in reasonably good yields (Scheme 1).



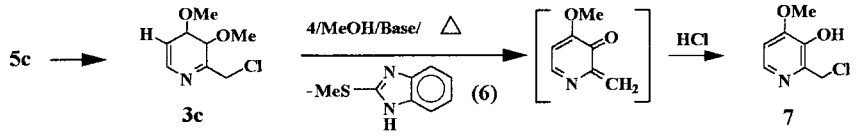
3a-c 4 2a-c

Scheme 1.

The new conditions discovered involve condensation of *p*-TSCl with various substituted 2-methylpyridine-*N*-oxides in the presence of an organic base such as triethylamine at moderate temperature (40–65°C) to give the corresponding 2-chloromethylpyridines, **3**, in high yield. The isolation of the latter is practically possible and was successfully achieved in a

few cases; however, since 2-halomethylpyridines are known to be very unstable,[7] the isolations of these intermediates was found to be unnecessary and therefore in-situ reactions with 2-mercaptobenzimidazoles to give **2** were preferred. The consumption of 2-mercaptobenzimidazoles in the condensation step was also found to be a good measure for the strength of **3** in the reaction mixture.[8] The synthesis of 2-chloromethylpyridines (**3**) can be performed under different conditions (see table); however, since the formation of 1 : 1 adduct of pyridine *N*-oxides with *p*TSCl (as analysed by ^{1}H NMR[9]) appears to be the initial step, addition of triethylamine to the substrate: *p*TSCl complex (Method A) was found to give better results.

The formation of 2-methylthiobenzimidazole (**6**) in the reaction of 2-mercaptobenzimidazole with **5c** under the conditions disclosed herewith is worth highlighting.[10b] Although all attempts to isolate 3-hydroxy-4-methoxy-2-chloromethylpyridine (**7**) or the corresponding 2-[{3-(hydroxy-4-methoxy)-2-pyridylmethyl}-thio]-*1H*-benzimidazole (**8**) from the reaction mixture were unsuccessful, the formation of **6**, however, can be rationalized based on the mechanism where thiolate anion of **4** attacks the activated 3-methoxy group of **3c**, as depicted in the Scheme 2. Cleavage of arylalkyl ethers by thiolates and thiophenolate anions is very well documented in the literature.[11,12]

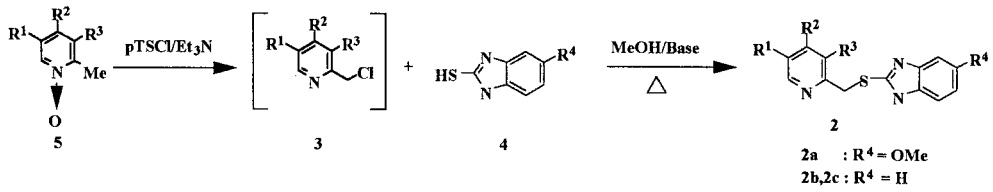


Scheme 2.

The attempted generalization of the reaction using mesyl chloride (MsCl) in the place of *p*TSCl under the reaction conditions led to quick deoxygenations of the pyridine-*N*-oxides to give the corresponding substituted pyridines in high yields. Similar *N*-deoxygenations are reported[13] to take place in the presence of large amounts of MsCl (9 mol. Eq.) and Et_3N (12 mol. Eq.).

In conclusion, the work compiled in this communication has been able to exemplify the potential of the new conditions in the synthesis of the title compounds (**2**), key intermediates in the manufacture of H^+/K^+-ATPase inhibitors such as omeprazole and lansoprazole.

Table. Preparation of 2-Methylthiobenzimidazoles (**2**) from Pyridine *N*-Oxides



				Reaction Conditions					Results		
Entry	**5**[a]	$R^1/R^2/R^3$	Method	Mol. Ratio **5**/*p*TSCl/TEA	Solvent	Et_3N Addition Temp°C/ Duration	Reaction Temp°C/ Duration	Mol. Equi. of **4** Used	Product (**2**)	Yield[b] (%)	M.P. (°C)
1.	**5a**	$CH_3/OCH_3/CH_3$	A	1 : 1.5 : 1.5	DCM	40/2 h	40/3 h	0.8	**2a** $\{C_{17}H_{19}N_3O_2S\}$	63	155
2.			A	1 :1.1 : 1.1	Toluene	0/1 h	50/3 h	0.72		52.9	
3.			A	1 : 1.5 : 1.5	Toluene	40/1 h	50/3 h	0.8		57.9	
4.	**5b**	$H/OCH_2CF_3/CH_3$	B	1 : 0.85 : 1.2	DCM	40/1 h	40/3 h	0.65	**2b** $\{C_{16}H_{16}F_3N_3O_2S\}$	44.3	144
5.			B	1 : 0.8 : 1.2	DCE	50/1 h	70/3 h	0.67		45.1	
6.			C	1 : 0.8 : 1.2	Toluene	0/0.5 h	40/1 h	0.67		51.2	
7.			A	1 : 0.95 : 1.15	Toluene	50/0.5 h	65/1.5 h	0.73		59.4	
8.			A	1 : 1.1 : 1.15	Toluene	50/1 h	55/1 h	0.73		51.9	
9.	**5c**	$H/OCH_3/OCH_3$	A	1 : 1.5 : 1.5	DCM	20/1 h	RT/2 h	0.80	**2c** $\{C_{15}H_{15}N_3O_2S\}$	55.2	121
10.			A	1 : 1.5 : 1.5	Toluene	RT/1 h	RT/2 h	0.80		51.1	

Method A: Et_3N was added after making *p*TSCl adduct with **5a–c** in solvent; Method B: Simultaneous addition of *p*TSCl and triethylamine to the substrate was made; Method **C**: *p*TSCl was added to the mixture of substrate and Et_3N in solvent. All products exhibited IR, ^1H NMR spectra in agreement with the reported values and gave satisfactory (C, H, N, S) combustion analysis within ± 0.4% of calculated values; [a]Scale of operation = 10 mmol; [b]Isolated yields of pure column chromatographed products.

EXPERIMENTAL SECTION

Melting points are uncorrected. The elemental analysis of C, H, N was performed by a Carlo Erba 1106 elemental analyser. ^{1}H NMR spectra were recorded on a Brucker 200 MHz in $CDCl_3$ with TMS as an internal indicator. Column chromatography was done with Labochemie SiO_2 (60–120 mesh). The CH_2Cl_2 was distilled from calcium hydride and toluene was dried over sodium before used. All experiments were carried out with exclusion of moisture.

Typical Procedure

Preparation of a sulfide derivative (2a) (Table, Entry 2): A mixture of 2,3,5-trimethyl-4-methoxypyridine-*N*-oxide[14] (**5a**, 1.67 g, 10 mmol) and *p*-toluenesulfonyl chloride 2.85 g (15 mmol) was stirred in CH_2Cl_2 (1 ml) at 40°C for 2 h under nitrogen atmosphere. To the resulting mixture was added dropwise, a solution of 2.1 ml (15 mmol) Et_3N in 10 ml of CH_2Cl_2 at 40°C. The reaction mixture was kept under stirring for another 3 h, neutralized with $NaHCO_3$ (1 g), and was concentrated under reduced pressure. To the methanol (20 ml) solution of the residue thus obtained was added a suspension of 1.44 g (8 mmol) of 5-methoxy-2-mercapto-*1H*-benzimidazole (**4**) in MeOH (10 ml). The reaction mixture was heated under reflux for 4 h and MeOH was distilled off to give a residue which was dissolved in EtOAc (60 ml). The organic layer was washed with 5% NaOH solution (20 ml) and then with water followed by removal of EtOAc to yield 2.4 g of 2-[{3-(5-dimethyl-4-methoxy)-2-pyridymethyl}-thio]-*1H*-5-methoxybenzimidazole, **2a**, as oily liquid. The crude product was subjected to silica gel column chromatography using $CHCl_3$/MeOH as eluent and crystallized from methanol/isopropyl ether to give 2.1 g (63%) of the title compound; assay by HPLC $\geq$ 98%; m.p. 155°C (lit.[16] m.p. 155–156°C).

2b (Table, Entry 7): Prepared in 59.4% isolated yield starting from 2,3-dimethyl-4-(2,2,2-trifluoroethoxy) pyridine *N*-oxide[14] (**5b**); m.p. 144°C (lit.[15] m.p. 144–145°C).

2c (Table, Entry 9): Prepared in 55% isolated yield starting from 2-methyl-3,4-dimethoxypyridine-*N*-oxide[15] (**5c**) followed by crystallization from chloroform/diethylether to give a white solid, m.p. 121°C,[17,18] assay by HPLC[8] $\geq$ 98%.

2-Methylthiobenzimidazole (6): Isolated by column chromatography as a white solid, m.p. 201°C (lit.[11] 201°C).

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8. HPLC Conditions = Column : Novapak C_{18}(reverse phase); Mobile Phase 0.01 M Na_2HPO_4; H_2O CH_3CN (70 : 30) Adjusted to pH 7 using H_3PO_4; Flow rate: 1.5 ml/min; detector: UV λ220 nm (Shimadzu SPD-10A).
9. **5a** : *p*TSCl (1 : 1 adduct) = ^{1}H NMR(200 MHz, $CDCl_3$) δ: 2.05 (3H, s, Me), 2.22 (6H, s, Me), 2.58 (3H, s, Me), 3.84 (3H, s, OMe), 7.06 (2H, d, $J = 8$ Hz), 7.6 (2H, d, $J = 8$ Hz), 9.35 (9H, s, ArH); **5a**: ^{1}H NMR ($CDCl_3$) δ: 2.1 (3H, s, Me), 2.19 (3H, s, Me), 2.4 (3H, s, Me), 4.7 (3H, s, OMe), 7.95 (1H, s, ArH).
10. **6**. ^{1}H NMR (DMSO-d_6) δ: 2.7 (3H, s, CH_3), 7.15 (2H, m, 5, 6-H), 7.38 (2H, m, 4, 7-H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 151.4, 139.9, 121.5, 113.9, 14.

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