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Preparation of 2-[(Aryl)methyl]sulfinyl-1*H*-imidazo[4,5-*c*]pyridine, Useful as an Antiosteoporotic Agent

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Abstract:

A new process for the oxidation of 2-[(aryl)methyl]thio-1*H*-imidazo[4,5-*c*]pyridine to 2-[(aryl)methyl]sulfinyl-1*H*-imidazo-[4,5-*c*]pyridine was achieved using NCS under mild condition. The reaction selectively affords the desired sulfoxide as the only product in high yield without further oxidation to the sulfone side product.

Recently it was reported that derivatives of 2-[(aryl)-methyl]sulfinyl-1*H*-imidazo[4,5-*c*]pyridine (**1**) were potent antiosteoporotic agents, which were useful in inhibiting bone resorption in a host animal, including humans.[1,2] It was reported that **1** (Figure 1) can be produced by oxidation of 2-[(aryl)methyl]thio-1*H*-imidazo[4,5-*c*]pyridine (**5**) with selenium dioxide/hydrogen peroxide or *m*-chloroperoxybenzoic acid at low temperatures.[1] This transformation was further developed by Shaw et al. using peroxyacetic acid.[2] Following both procedures, the yields of sulfoxide **1** were low to moderate. The product was contaminated with overoxidized byproduct, sulfone **6**. Attempting to remove the sulfone **6** from the sulfoxide **1** using conventional chromatography or recrystallisation methods failed. The mixture could be separated by only HPLC. To produce pure sulfoxide **1** in large quantities, it is essential to develop a selective oxidation method to obtain the desired sulfoxide. We now report an efficient synthesis of **1** and the development of a method to selectively convert sulfide **1** to sulfoxide **5**.

2-[(Aryl)methyl]thio-1*H*-imidazo[4,5-*c*]pyridine (**5**) is generally prepared by forming the sodium salt of 2-mercaptoimidazo[4,5-*c*]pyridine (**3**), that was derived from 3,4-diaminopyridine (**2**), and then treating with a suitable substituted alkylating agent (**4**) for several hours in DMF.[1] Alternately, **5** was prepared in one pot by heating a mixture of **2** and potassium *O*-ethyl dithiocarbonate in water for 8 h, followed by alkylation at −15 °C.[2] Both methods produced the desired products in 46−78% yields.

In our laboratory, **5** was prepared in high yield under mild conditions. The alkylation of **3** with benzyl bromide (**4**) was carried out in a methanol solution of potassium hydroxide at 25 °C. The reaction was completed in less than 2 h. Product **5** was isolated by precipitation from water in >90% yield (Scheme 1).

Theoretically, oxidation of sulfide to the corresponding sulfoxide or sulfone can be controlled by the number of molar

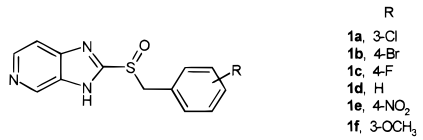
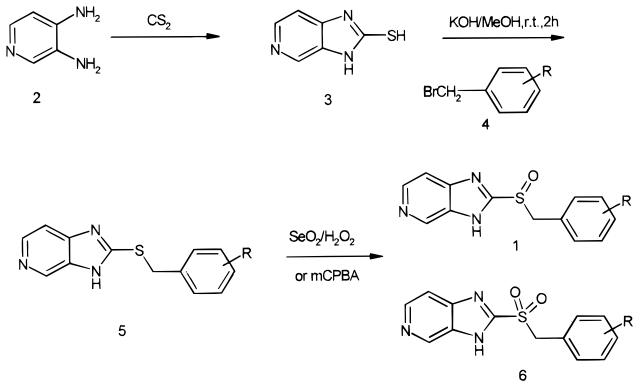
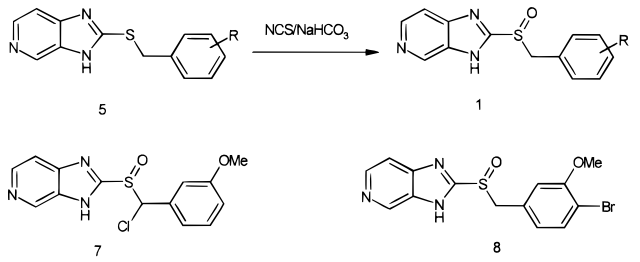


Figure 1. **Compound 1.**

Scheme 1



Scheme 2



equivalents of oxidant used.[3,4] But in practice, a mixture of sulfoxide and sulfone is often obtained. There are reports that $TiCl_3/H_2O_2$[5] or $NaIO_4$[6] would selectively oxidize sulfide to sulfoxide. These methods did not produce satisfactory results in our cases (Scheme 2). Trayanelis et al. reported that the reaction of sulfuryl chloride and sulfide at −78 °C formed a chlorine−sulfide complex.[7] This complex was hydrolysed with alcohol to afford sulfoxide selectively. The low-temperature reaction was not suitable for scale-up preparation. It was also known that a complex of *N*-

(1) Santilli, A. A.; Scotese, A. C.; Strike, D. P. EP 0 434 405 A1, Dec 19, 1990.
(2) Shaw, C.-C.; Brossard, R. N.; Gavin, G. US 5,001,238, Mar 19, 1991.
(3) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series 186; American Chemical Society: Washington, DC, 1990; p 252.
(4) Venier, C. G.; Squires, T. G.; Chen, Y.; Hussmann, G. P.; Shei, J. C.; Smith, B. F. *J. Org. Chem.* **1982**, *47*, 3773.
(5) Watanabe, Y.; Numata, T.; Oae, S. *Synthesis* **1981**, 204.
(6) Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282.
(7) Traynelis, V. J.; Yoshikawa, Y.; Tarka, S. M.; Livingston, J. R., Jr. *J. Org. Chem.* **1973**, *38*, 3986.
(8) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

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Table 1. **Oxidation of compound 5**

entry	R	temp (°C)	yield 1:6 (%)[a] NCS	NBS	$TiCl_3/H_2O_2$	mCPBA
5a	3-Cl	25	90(1:0)	89(1:0)		
5b	4-Br	25	75(1:0)	76(1:0)		
5c	4-F	25	93(1:0)	90(1:0)		
5d	H	25	92(1:0)	91(1:0)		
5e	4-NO_2	25	87(1:0)	86(1:0)		
5f	CH_3O	25	75(1:0)[b]	88(1:0)[c]	86(2:0)	60 (1:1)
5f	CH_3O	0	90(1:0)	88(1:0)[c]	70(2:0)	86(4:1)

[a] Isolated yield; ratio of **1** to **6** was determined by ^{1}H NMR. [b] Yield of compound **7**. [c] Yield of compound **8**.

chlorosuccinimide (NCS) and dimethyl sulfide was used to oxidize a primary alcohol to an aldehyde.[8] Based on these reports, we thought that hydrolysis of a complex of NCS and sulfide should lead to the desired sulfoxide. Thus, we treated sulfide **5** with NCS in water at 25 °C (Scheme 2). To our delight, the reaction produced the desired sulfoxide **1** as the only product after 1.5 h. Adding sodium bicarbonate solution increased the conversion rate. The oxidation was completed within 30 min in aqueous sodium bicarbonate solution at 25 °C. We also discovered that the reaction went equally well in most cases using *N*-bromosuccinimide (NBS). The results are summarised in Table 1.

All reactions using NCS or NBS in Table 1 produced sulfoxide **1** as the only product. The best result was achieved when we treated sulfide **5** with 2 equiv of NCS and 2 equiv of sodium bicarbonate in water at 25 °C for 30 min. The desired sulfoxide **1** precipitated out of the reaction solution. The product was isolated simply by filtration, washed with water, and dried in a vacuum. In the case of compound **5f**, NCS at 0 °C produced the desired product **1f**. At 25 °C, the reaction led to α-chlorosulfoxide **7**. When **5f** was treated with NBS at 25 °C, sulfoxide **8** was the only isolated product.

In conclusion, we have developed a highly efficient method for preparation of 2-[(aryl)methyl]sulfinyl-1*H*-imidazo[4,5-*c*]pyridine from 2-[(aryl)methyl]thio-1*H*-imidazo-[4,5-*c*]pyridine in high yield. The reaction is simple to carry out under mild condition and does not produce sulfone as a byproduct.

Experimental Section

2-[(Aryl)methyl]thio-1*H*-imidazo[4,5-*c*]pyridine (5). General Procedure. To a solution of 2-mercapto-1*H*-imidazo[4,5-*c*]pyridine (20 mmol) in methaol (100 mL) containing KOH (30 mmol) was added benzyl bromide (22 mmol) at 25 °C. After 1 h, the reaction was adjusted to pH 7 with 10% HCl. The reaction mixture was concentrated and then poured into a solution of 20 mL of saturated $NaHCO_3$ and 80 mL of water. After the solution was left

Table 2. **Compound 5 and compound 1 prepared**

product[a]	yield	mp (°C)	IR (KCl), ν (cm^{-1})	^{1}H NMR(300 MHz, DMSO-d_6/TMS)	MS(CI, NH_3), *m*/*z*
5a	92	181−183	1616, 1598, 1588, 1576, 1466, 1462	8.8 (s, 1H), 8.18 (d, *J* = 6.5Hz, 1H), 7.58 (s, 1H), 7.52 (d, *J* = 6.5 Hz, 1H), 7.45 (m, 1H), 7.32 (m, 2H), 4.61 (s, 2H)	276 (M + 1, 100%)
5b	93	193−194	1616, 1588, 1508, 1486, 1466, 1442	8.8 (s, 1H), 8.18 (d, *J* = 6.5 Hz, 1H), 7.50 (m, 5H), 4.59 (s, 2H)	320 (M + 1, 100%)
5c	91	175−176	1618, 1600, 1590, 1510	8.8 (s, 1H), 8.18 (d, *J* = 6.5 Hz, 1H), 7.45 (m, 5H), 4.59 (s, 2H)	260 (M + 1, 100%)
5d	94	175−177	1618, 1588, 1508, 1496, 1466, 1454	8.8 (s, 1H), 8.18 (d, *J* = 6.5 Hz, IH), 7.50 (m, 3H), 7.28 (m, 3H), 4.60 (s, 2H)	242 (M + 1, 100%)
5e	97	210−214	1620, 1598, 1514, 1488, 1438	8.8 (s, 1H), 8.18 (d, *J* = 6.6 Hz, 3H), 7.78 (d, *J* = 6.6 Hz, 2H), 7.51 (d, *J* = 6.6 Hz, 1H), 4.75 (s, 2H)	287 (M + 1, 100%)
5f	93	135−138	1620, 1612, 1580, 1544, 1502, 1486	8.8 (s, 1H), 8.19 (d, *J* = 6.6 Hz, 1H), 7.26 (d, *J* = 6.6 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.08 (m, 2H), 6.82 (m, 1H)	272 (M + 1, 100%)
1a	90	190 dec	1618, 1588, 1488, 1466	9.31 (s, 1H), 8.45 (d, *J* = 6.6 Hz, 1H), 7.91 (d, *J* = 6.6 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 712 (m, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 4.75 (d, *J* = 13 Hz, 1H), 4.55 (d, *J* = 13 Hz, 1H)	292 (M + 1,100%)
1b	75	198 dec	1618, 1590, 1508, 1490	9.21 (s, 1H), 8.40 (d, *J* = 6.6 Hz, 1H), 7.81 (d, *J* = 6.6 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 2H), 4.75 (d, *J* = 12.8 Hz, 1H), 4.52 (d, *J* = 12.8 Hz, 1H)	336 (M, 100%)
1c	93	177 dec	1620, 1600, 1520, 1488	9. 31 (s, 1H), 8.45 (d, *J* = 6.6 Hz, 1H), 7.81 (d, *J* = 6.6 Hz, 1H), 7.10 (m, 4H), 4.75 (d, *J* = 12.8 Hz, 1H), 4.52 (d, *J* = 12.8 Hz, 1H)	276 (M + 1, 100%)
1d	92	175 dec	1616, 1588, 1510, 1490, 1466	9.38 (s, 1H), 8.45 (d, *J* = 6.6 Hz, 1H), 7.88 (d, *J* = 6.6 Hz, 1H), 7.25 (m, 3H), 7.15 (m, 2H), 4.78 (d, *J* = 12.8 Hz, 1H), 4.52 (d, *J* = 12.8 Hz, 1H)	258 (M + 1, 100%)
1e	88	200 dec	1634, 1400, 1540, 1520, 1490,1444	9.35 (s, 1H), 8.45 (d *J* = 6.6 Hz, 1H), 8.28 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 6.6 Hz, 1H), 7.8 (d, *J* = 7.5 Hz, 2H), 4.75 (d, *J* = 12.8 Hz, 1H), 4.52 (d, *J* = 12.8 Hz, 1H)	302 (M + 1 100%)

[a] Satisfactory microanalyses obtained: C ± 0.25, H ± 0.19, N ± 0.3.

to standing overnight at room temperature, the solid was filtered and triturated with CH_2Cl_2/hexane (1/1, 40 mL) to afford **5**.

2-[(Aryl)methyl]sulfinlyl-1*H*-imidazo[4,5-*c*]pyridine (1). General Procedure. To a solution of 2-[(aryl)methyl]thio-1*H*-imidazo[4,5-*c*]pyridine (**5**) (5 mmol) in CH_2C1_2 (100 mL) at 25 °C were added $NaHCO_3$ (10 mmol), water (10 mL), and NCS (10 mmol). The reaction was stirred for 30 min. The solid was filtered, washed with water (25 mL) and ethanol (25 mL), and dried in a vacuum to afford **1**.

2-[(3-Methoxyphenyl)methyl]lsulfinyl-1*H*-imidazo[4,5-*c*]pyridine (1f). To a suspension of 2-[(4-methoxyphenyl)-methyl]thio-1*H*-imidazo[4,5-*c*]pyridine (**5f**) (10.9 g, 40 mmol) in CH_2Cl_2 (400 mL) and H_2O (80 mL) at 0 °C was added $NaHCO_3$ (8.0 g, 92 mmol), followed by NCS (12.2 g, 92 mmol). The mixture was vigorously stirred at 0 °C for 30 min. The reaction mixture was extracted with 20% NH_4-OH (2 × 50 mL). The solution was acidified with acetic acid to pH = 7 and extracted with CH_2C1_2 (3 × 250 mL). After removal of solvent, the solid was triturated with MeOH/acetone (1/10, 10 mL) and filtered to give 10.4 g of sulfoxide **1f** in 90% yield; mp 179 °C dec.

IR (KCl): ν = 1628, 1614, 1586, 1542, 1490 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 9.1 (s, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.78 (d, J = 6.6 Hz, 1H), 7.18 (dd, J = 8.8 Hz, 3 Hz), 6.83 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.70 (bs, 1H), 4.65 (d, J = 12.9 Hz, 1H), 4.45 (d, J = 12.9 Hz, 1H), 3.59 (s, 3H).

MS (*m*/*e*, CI-NH_3): *m*/*z* (intensity) = 288 (M + 1, 100%).

Anal. Calcd for $C_{14}H_{I3}N_3O_2S\cdot{}^1/_2H_2O$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.76; H, 4.46; N, 14.35.

2-[Chloro(3-methoxyphenyl)methyl]sulfinyl-1*H*-imidazo-[4,5-*c*]pyridine (7). To a suspension of 2-[(4-methoxyphenyl)methyl]thio-1*H*-imidazo[4,5-*c*]pyridine (**5f**) (1.44 g, 5 mmol) in CH_2C1_2 (100 mL) at 25 °C was added $NaHCO_3$ (10%, 10 mL), followed by NCS (1.33 g, 10 mmol). The mixture was kept at room temperature overnight. The organic layer was separated, washed with water and brine, dried, and concentrated. The crude product was recrystallised from methanol to give 7 (1.2 g) in 75% yield; mp 174 °C dec.

IR (KCl): ν = 1628, 1612, 1602, 1586, 1490 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 9.1 (s, 1H), 8.24 (d, J = 6.6 Hz, 1H), 7.80 (d, J = 6.6 Hz, 1H), 7.28 (dd, J = 8.8 Hz, 3H), 6.93 (d, J = 8.6 Hz, 1H), 6.87 (m, 1H), 6.60 (s, 1H), 3.61 (s, 3H).

MS (*m*/*e*, NH_3-CI): *m*/*z* (intensity) = 322 (M + 1,100%).

Anal. Calcd for $C_{14}H_{12}ClN_3O_2S$: C, 52.26; H, 3.76; N, 13.02. Found: C, 52.40; H, 3.46; N, 13.15.

2-[(4-Bromo-3-methoxyphenyl)methyl]sulfinyl-1*H*-imidazo[4,5-*c*]pyridine (8). To a suspension of 2-[(4-methoxyphenyl)methyl]thio-1*H*-imidazo[4,5-*c*]pyridine **(1f)** (1.15 g, 4 mmol) in CH_2C1_2 (100 mL) and water (10 mL) were added $NaHCO_3$ (0.66 g, 8 mmol) and NBS (1.4 g, 16 mmol). The mixture was stirred at room temperature for 30 min. The solid was filtered and washed with CH_2Cl_2, water, and acetone to give 1.3 g of **8** in 88% yield; mp 180 °C dec.

IR (KCl): ν = 1634, 1612, 1584, 1540, 1490 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 9.41 (s, 1H), 8.54 (d, J = 6.6 Hz, 1H), 8.13 (d, J = 6.6 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 6.93 (dd, J = 8.8 Hz, 3 Hz), 6.87 (d, J = 3 Hz, 1H), 4.85 (d, J = 12.9 Hz, 1H), 4.68 (d, J = 12.9 Hz, 1H), 3.64 (s, 3H).

MS (*m*/*e*, CI−NH_3): *m*/*z* (inteinsity) = 368(M + 1, 100%).

Anal. Calcd for $C_{14}H_{12}BrN_3SO_2$: 52.26; H, 3.76; N, 13.06. Found: C, 52.24; H, 3.88; N, 13.18.

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