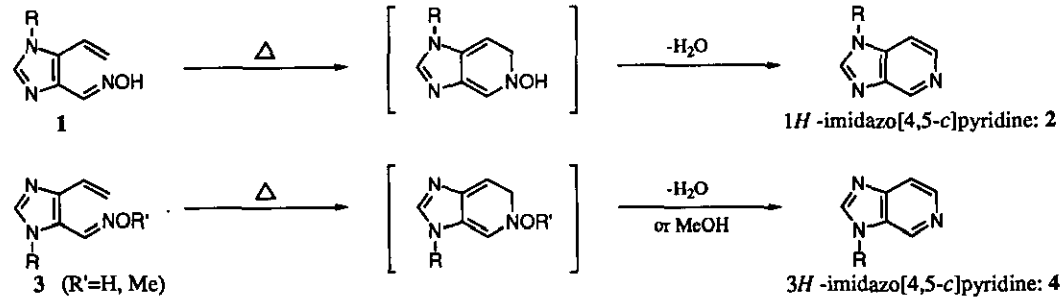
NEW SYNTHETIC ROUTE TO IMIDAZO[4,5-*c*]PYRIDINES BY THE THERMAL ELECTROCYCLIC REACTION OF 1-AZAHEXATRIENE SYSTEMS

Haruyuki Yashioka, Tominari Choshi, Eiichi Sugino, and Satoshi Hibino*

Faculty of Pharmacy and Pharmaceutical Sciences,
Fukuyama University
Fukuyama, Hiroshima 729-02, Japan

Abstract----New routes to 1*H*- and 3*H*-imidazo[4,5-*c*]pyridines have been developed by the thermal electrocyclic reaction of 1-azahexatriene systems involving the imidazole 4,5-bond.

We are currently developping the synthesis of condensed heteroaromatic compounds, especially fused pyridine ring systems, by the thermal electrocyclic reaction[1] of either 1-aza-[2,3] or 2-azahexatriene[4] systems including one double bond of the aromatic or heteroaromatic portion. Gilchrist and co-worker have recently reported the extensive use of this reaction for the synthesis of indolo[3,2,1-*ij*][1,6]naphthyridine ring.[5] We describe here the new syntheses of 1*H*- and 3*H*-imidazo[4,5-*c*]pyridine rings by an application of this methodology (**Scheme 1**).



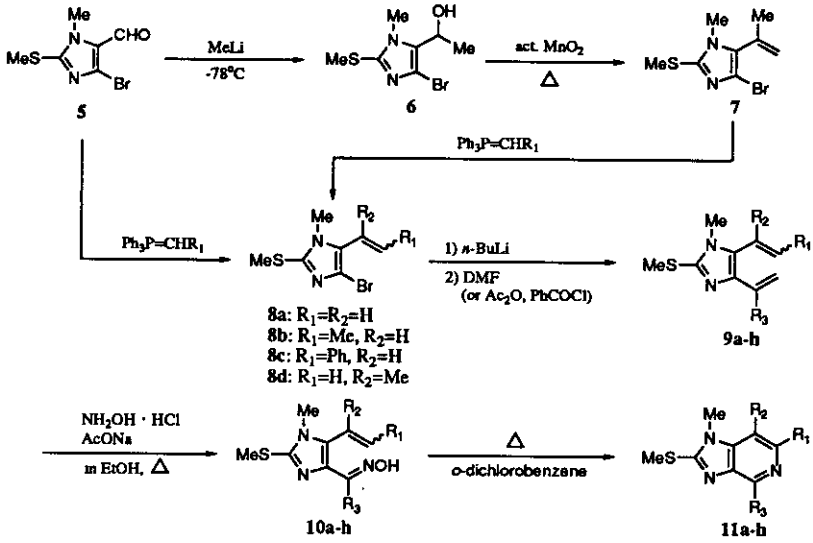
Scheme 1

Although many synthetic efforts in this area have appeared,[6] there is still need for a general and versatile method to gain access to the imidazo[4,5-*c*]pyridines because of their biological properties.[7] The present methodology is based on the thermal electrocyclic reaction of 1-azahexatriene systems (**1**) or (**3**) with loss of water or methanol to construct the corresponding imidazo[4,5-*c*]pyridines (**2**) or (**4**).

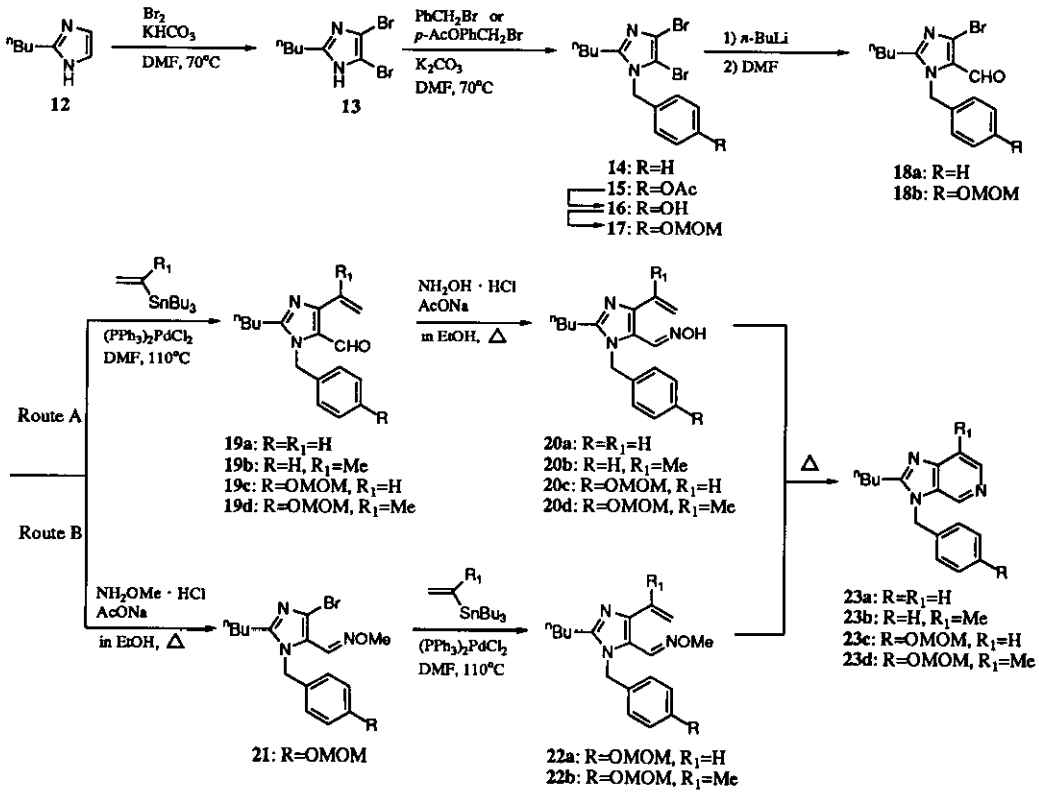
We first attempted the synthesis of 1*H*-imidazo[4,5-*c*]pyridine (**2**) (**Scheme 2**). For the synthesis of a type of 1-azahexatriene system (**1**), a readily available 4-bromo-5-formylimidazole (**5**)[4c] from 4,5-dibromo-1-methyl-2-methylthioimidazole was subjected to Wittig reaction using several alkylidenetriphenylphosphoranes (CH_2=, MeCH=, PhCH=) to provide the 5-alkenylimidazoles (**8a-c**) in good yields, respectively. 5-Isopropenylimidazole (**8d**) was prepared from **5** in a three step sequence [i; MeLi (70.7%), ii; act. MnO_2 (42.1%), iii; Ph_3P=CH_2 (98.4%)] because it was difficult to obtain **8d** directly from 4,5-dibromo-1-methyl-2-methylthioimidazole. Subsequent treatment of the 5-alkenyl-4-bromoimidazoles (**8a-d**) with *n*-BuLi at -78°C followed by quenching with several electrophiles [DMF, $(MeCO)_2O$, PhCOCl] gave the corresponding 4-acylimidazoles (**9a-h**) (31-89.8%). The acylimidazole derivatives (**9a-h**) were converted into the oximes (**10a-h**) (36.4-95.8%), that is 1-azahexatriene system (**1**), by treatment with hydroxylamine in the usual manner. The thermal electrocyclic reaction of the oximes (**10a-h**) was carried out at the reflux temperature in *o*-dichlorobenzene to yield the proposed 1*H*-imidazo[4,5-*c*] pyridines (**11a-h**) in a moderate to good yield except **11a** (17.4%). In the case of **11a**, the oxime (**10a**) has been presumed to be relatively unstable, compared with the others (**10a-h**).

Next, we examined the extension of this strategy to the preparation of a type of 3*H*-imidazo[4,5-*c*]pyridine (**4**) (**Scheme 3**). To this end, an easily available 2-*n*-butylimidazole (**12**)[8] was treated with bromine in the presence of $KHCO_3$ at 70°C in DMF to give the dibromoimidazole (**13**) (91.2%). Benzylation of **13** with benzyl bromide (or *p*-acetoxylbenzyl bromide[9]) afforded the benzylimidazoles (**14**; 98.5% and **15**; 99.8%), respectively. Halogen metal exchange reactions of **14** and **17** with *n*-BuLi at -78°C followed by quenching with DMF gave the 5-formylimidazoles (**18a**; 72.7% and **18b**; 83.9%) regioselectively by the reported procedure.[10] The acetyl group of **15** was converted into the methoxymethyl (MOM) ether *via* hydrolysis because of the failure of halogen metal exchange reaction. In order to obtain a type of 1-azahexatriene system (**3**), we examined two ways of route A and B from the 4-bromo-5-formylimidazoles (**18a** and **18b**) (**Scheme 3**). In route A, the palladium-catalyzed cross-coupling reaction[11] between the 4-bromoimidazole (**18a** and **18b**) and alkenyltributyltin (vinyl or isopropenyl[12]) in the presence of $(PPh_3)_2PdCl_2$, $Et_4N^+Cl^-$ and K_2CO_3 at 110°C in DMF afforded the alkenylimidazoles (**19a-d**) (54.3%-85.2%), respectively. Treatment of **19a-d** with hydroxylamine gave the oximes (**20a-d**) (54.3-85.2%) as the 1-azahxatriene system (**3**). By contrast (Route B), the aldehyde (**18b**) was converted into the oxime ether (**21**) (98.7%) by treatment of hydroxylamine methyl ether under the conditions similar to those above. Subsequent palladium-catalyzed cross-coupling reactions[11] of the 4-bromoimidazole (**21**) with alkenyltributyltin (vinyl or isopropenyl[12]) were carried out in the presence of $(PPh_3)_2PdCl_2$, $Et_4N^+Cl^-$ and K_2CO_3 at 110°C in DMF to provide the desired alkenyl oxime ethers (**22a**; 97.6% and **22b**; 60.8%) as the 1-azahexatriene (**3**). The oximes (**20a-d**) and the oxime ethers (**22a-b**) were subjected to the thermal electrocyclic reaction at the reflux temperature in *o*-dichlorobenzene to provide the expected 3*H*-imidazo[4,5-*c*]pyridines (**23a-d**) in good yields. There was almost no difference in the two routes (A and B) for the preparation of 3*H*-imidazo[4,5-*c*]pyridines (**23c-d**) in total yields from **18b** (Route A; 57.3% and Route B; 57.4%).

The structures of all new compounds including both imidazo[4,5-*c*]pyridines were completely confirmed by spectroscopic evidence. The OH or OMe group at nitrogen atom in each dihydropyridine intermediate worked well as a leaving group to form the imidazo[4,5-*c*]pyridine (**2** or **4**) as reported previously.[2]



Scheme 2: Compds. 9-11 (a: R_1=R_2=R_3=H; b: R_1=R_2=H, R_3=Me; c: R_1=Me, R_2=R_3=H; d: R_1=R_3=Me, R_2=H; e: R_1=Ph, R_2=R_3=H; f: R_1=R_3=H, R_2=Me; g: R_1=H, R_2=R_3=Me; h: R_1=H, R_2=Me, R_3=Ph)



Scheme 3

In conclusion, the general and alternative methods of synthesis of two types of imidazo[4,5-*c*]pyridines (**2** and **4**) could be established and these findings demonstrate that the electrocyclic reactions of 1-azahexatriene systems (**1** and **3**) are useful methods to provide the 1*H*- and/or 3*H*-imidazo[4,5-*c*]pyridine nucleus.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were recorded with a Shimadzu FTIR-8500 spectrophotometer. ^{1}H-Nmr spectra were taken by a JEOL PMX60Si spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard unless otherwise stated .Mass (Ms) spectra and high resolution mass spectra (Hrms) were recorded on a Shimadzu GC-MS 9020DF spectrometer at 70 eV chamber voltage on a direct inlet system unless otherwise noted. Silica gel (60-100 mesh, Merck Art 7734) was used for column chromatography. The commercially available vinyltributyltin (Aldrich 27,143-8) was used for the cross-coupling reaction.

4-Bromo-5-(1-hydroxyethyl)-1-methyl-2-methylthioimidazole (6). A solution of *MeLi* (1.05 M in Et_2O, 4.5 ml, 4.3 mmol) was added to a stirred solution of the 5-formylimidazole (**5**)[4c] (1.0 g, 4.3 mmol) in anhyd. THF (15 ml) at -78°C under argon atmosphere. After stirring at the same temperature for 75 min, the solution was worked up with water. The mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using EtOAc/hexane (1/4) as an eluent to give the alcohol (**6**) (764 mg, 70.7%), mp 100-101°C (EtOH). Ir(KBr): 3305 cm^{-1}(OH). ^{1}H-Nmr: δ 1.54(3H, d, *J*=7 Hz, C$\underline{H_3}$CH), 2.57(3H, s, SC$\underline{H_3}$), 3.69(3H, s, NC$\underline{H_3}$) 4.76-5.23(1H, m, $CH_3C\underline{H}OH$). Ms: *m/z* 252(M^++2), 250(M^+). *Anal.* Calcd for $C_7H_{11}N_2OBrS$: C, 33.48; H, 4.41;N, 11.15. Found: C, 33.50; H, 4.18; N, 10.98.

***5-Acetyl-4-bromo-1-methyl-2-methylthioimidazole* (7).** A mixture of the alcohol (**6**) (4 g, 15.9 mmol) and activated MnO_2 (13.8 g, 159 mmol) in toluene (30 ml) was stirred at 75°C for 1 h. The mixture was cooled to an ambient temperature and filtered off with celite. The celite was washed with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 60 g) using EtOAc/hexane (1/9) as an eluent to give the ketone (**7**) (1.67 g, 42.1%), mp 93-94°C (hexane). Ir(KBr): 1655 cm^{-1}(C=O). ^{1}H-Nmr: δ 2.59(3H, s, C$\underline{H_3}$CO), 2.64(3H, s, SC$\underline{H_3}$), 3.73(3H, s, NC$\underline{H_3}$). Ms: *m/z* 250(M^++2), 248(M^+). *Anal.* Calcd for $C_7H_9N_2OBrS$: C, 33.75; H, 3.64;N, 11.24. Found: C, 33.99; H, 3.78; N, 11.01.

General procedure for the preparation of 5-alkenyl-4-bromo-1-methyl-2-methylthio-*imidazoles* (8a-d). A solution of *n*-BuLi (1.61 M in hexane, 2.9 ml, 4.70 mmol) was added to a stirred mixture of the alkyltriphenylphosphonium bromide (4.70 mmol) in anhyd. THF (40 ml) at 0℃ (ice-water) under argon atmosphere. After being stirred at room temperature for 30 min, a solution of the carbonyl compound (**5** or **7**) (4.30 mmol) in anhyd. THF (40 ml) was added to the ylide solution at 0℃ (ice-water), which was stirred at an ambient temperature for 12 h. The mixture was quenched with water and extracted

with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc/hexane (1/9) to give the oily alkenyl compounds (**8a-d**). Known compounds **8b** and **8c** were prepared by the similar method of reference 4c.

4-Bromo-5-ethenyl-1-methyl-2-mehylthioimidazole (8a): 89.7%(oil). ^{1}H-Nmr: δ 2.55(3H, s, SC$\underline{H}_3$), 3.52(3H, s, NC$\underline{H}_3$), 5.27(1H, dd, J_{gem}=2 Hz and J_{cis} =11 Hz, CH=C$\underline{H}_2$ X 1/2), 5.67(1H, dd, J_{gem} =2 Hz and Jt_{trans}=17 Hz, CH=C$\underline{H}_2$ X 1/2), 6.37(1H, dd, J_{cis}=11 Hz and J_{trans} =17 Hz, C$\underline{H}$=CH$_2$). Ms: *m/z* 234(M^++2), 232(M^+). HRms calcd for $C_7H_9N_2BrS$ 231.9669, found 231.9681.

4-Bromo-1-methyl-2-methylthio-5-(2-propenyl)imidazole (8d): 98.4%(oil). ^{1}H-Nmr: δ 2.01 (3H, s, C$\underline{H}_3$-C=), 2.55(3H, s, SC$\underline{H}_3$), 3.41(3H, s, NC$\underline{H}_3$), 4.95-5.10(1H, m, C=C$\underline{H}_2$ X 1/2), 5.28-5.45(1H, m, C=C$\underline{H}_2$ X 1/2). Ms: *m/z* 248(M^++2), 246(M^+). HRms calcd for $C_8H_{11}N_2BrS$ 245.9826, found 245.9853.

General procedure for the preparation of 5-alkenyl-1-methyl-2-methylthioimidazole-4-carboxaldehydes (9a-h). A solution of *n*-BuLi (1.56 M in hexane, 6.2 ml, 9.6 mmol) was added to a solution of the 4-bromoimidazoles (**8a-d**) (4.36 mmol) in anhyd. Et_2O (50 ml) at -78 ℃ under argon atmosphere. After being kept at -78 ℃ for 1 h, a solution of DMF (96 mmol) [Ac_2O or PhCOCl, 9.6 mmol] was added. The reaction mixture was stirred for 12 h at an ambient temperature. The mixture was quenched with water and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc/hexane (1/9) as an eluent to give the 4-formylimidazoles (**9a-h**).

5-Ethenyl-1-methyl-2-methylthioimidazole-4-carboxaldehyde (9a): 71.6%(oil). Ir(neat): 1677 cm^{-1} (CHO). ^{1}H-Nmr: δ 2.65(3H, s, SC$\underline{H}_3$), 3.54(3H, s, NC$\underline{H}_3$), 5.59(1H, dd, J_{gem}=2 Hz and J_{cis}=11 Hz, CH=C$\underline{H}_2$ X 1/2), 5.89(1H, dd, J_{gem}=2 Hz and J_{trans}=17 Hz, CH=C$\underline{H}_2$ X 1/2), 6.76(1H, dd, J_{cis}=11 Hz and J_{trans}=17 Hz, C$\underline{H}$=CH$_2$), 9.71(1H, s, C$\underline{H}$O). Ms: *m/z* 182(M^+). HRms calcd for $C_8H_{10}N_2OS$ 182.0513, found 182.0485.

4-Acetyl-5-ethenyl-1-methyl-2-methylthioimidazole (9b): 47.1%(oil). Ir(neat): 1663 cm^{-1}(C=O). ^{1}H-Nmr: δ 2.49(3H, s, C$\underline{H}_3$CO), 2.58(3H, s, SC$\underline{H}_3$), 3.53(3H, s, NC$\underline{H}_3$), 5.42(1H, dd, J_{gem}=2 Hz and J_{cis}=12 Hz, CH=C$\underline{H}_2$ X 1/2), 5.67(1H, dd, J_{gem}=2 Hz and J_{trans}=18 Hz, CH=C$\underline{H}_2$ X 1/2), 6.98(1H, dd, J_{cis}=12 Hz and J_{trans}=18 Hz, C$\underline{H}$=CH$_2$). Ms: *m/z* 196(M^+). HRms calcd for $C_9H_{12}N_2OS$ 196.0670, found 196.0689.

1-Methyl-2-methylthio-5-(1-propenyl)imidazole-4-carboxaldehyde (9c): 72.5%. mp 73-74°C (Et_2O). Ir(KBr): 1680cm^{-1}(CHO). ^{1}H-Nmr: δ 1.95(3H, d, *J*=5 Hz, C$\underline{H}_3$CH=), 2.65(3H, s, SC$\underline{H}_3$), 3.48(3H, s, NC$\underline{H}_3$), 6.11-6.57(2H, m, C$\underline{H}$=C$\underline{H}$), 9.65(1H, s, C$\underline{H}$O). Ms: *m/z* 196(M^+). *Anal.* Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27. Found: C, 54.82; H, 6.39; N, 14.19.

4-Acetyl-1-methyl-2-methylthio-5-(1-propenyl)imidazole (9d): 39.1%. mp 87.5-89.5°C (hexane). Ir(KBr): 1653 cm^{-1}(C=O). ^{1}H-Nmr: δ 1.90(3H, d, *J*=5 Hz, C$\underline{H}_3$CH=), 2.47(3H, s, C$\underline{H}_3$CO), 2.57(3H, s, SC$\underline{H}_3$), 3.46(3H, s, NC$\underline{H}_3$), 5.79-6.76(2H, m, C$\underline{H}$=C$\underline{H}$). Ms: *m/z* 210(M^+). *Anal.* Calcd for $C_{10}H_{14}N_2OS$: C, 57.12; H, 6.71; N, 13.32. Found: C, 56.98; H, 6.85; N, 13.49.

1-Methyl-2-methylthio-5-(2-phenylethenyl)imidazole-4-carboxaldehyde (9e): 89.8%(oil) [a mixture of cis/trans (1/1)]. Ir(neat) : 1672 cm^{-1}(CHO). ^{1}H-Nmr: δ 2.57(3H, s, SC$\underline{H}_3$), 2.68(3H, s, SC$\underline{H}_3$), 3.03(3H, s, NC$\underline{H}_3$), 3.60(3H, s, NC$\underline{H}_3$), 6.56(1H, d, J_{cis}=10 Hz, C$\underline{H}$=CH), 6.77-7.69(12H, m, $C_6\underline{H}_5$ X 2 and C$\underline{H}$=C$\underline{H}$), 7.88(1H, d, J_{cis}=10 Hz CH=C$\underline{H}$), 9.70(1H, s, C$\underline{H}$O), 9.81(1H, s, C$\underline{H}$O). Ms: *m/z* 258(M^+). HRms calcd for $C_{14}H_{14}N_2OS$ 258.0826, found 258.0815.

1-Methyl-2-methylthio-5-(2-propenyl)imidazole-4-carboxaldehyde (9f): 75.3%(oil). Ir(neat): 1677 cm^{-1}(CHO). ^{1}H-Nmr: δ 2.07(3H, s, C$\underline{H}_3$-C=), 2.65(3H, s, SC$\underline{H}_3$), 3.42(3H, s, NC$\underline{H}_3$), 5.09-5.19 (1H, m, C=C$\underline{H}_2$ X 1/2), 5.43-5.61(1H, m, C=C$\underline{H}_2$ X 1/2), 9.53(1H, s, C$\underline{H}$O). Ms: *m/z* 196(M^+). HRms calcd for $C_9H_{12}N_2OS$ 196.0670, found 196.0684.

4-Acetyl-1-methyl-2-methylthio-5-(2-propenyl)imidazole (9g): 31.0%(oil). Ir(neat): 1674 cm^{-1} (C=O). ^{1}H-Nmr: δ 1.41(3H, s, C$\underline{H}_3$CO), 1.97(3H, s, C$\underline{H}_3$-C=), 2.51(3H, s, SC$\underline{H}_3$), 3.34(3H, s, NC$\underline{H}_3$), 4.86-5.13(1H, m, C=C$\underline{H}_2$ X 1/2), 5.27-5.52(1H, m, C=C$\underline{H}_2$ X 1/2). Ms: *m/z* 210(M^+). HRms calcd for $C_{10}H_{14}N_2OS$ 210.0826, found 210.0835.

4-Benzoyl-1-metyl-2-methylthio-5-(2-propenyl)imidazole (9h): 45.6%(oil). Ir(neat): 1673 cm^{-1} (C=O). ^{1}H-Nmr: δ 2.04(3H, s, C$\underline{H}_3$-C=), 2.63(3H, s, SC$\underline{H}_3$), 3.44(3H, s, NC$\underline{H}_3$), 4.89-5.07(1H, m, C=C$\underline{H}_2$ X 1/2), 5.30-5.84(1H, m, C=C$\underline{H}_2$ X 1/2), 6.90-7.57(3H, m, aromatic protons), 7.76-8.30(2H, m, aromatic protons). Ms: *m/z* 272(M^+). HRms calcd for $C_{15}H_{16}N_2OS$ 272.0983, found 272.0965.

General procedure for the preparation of the oxime derivatives (10a-h). A stirred mixture of the carbonyl compounds (**9a-h**) (1.53 mmol), $NH_2OH \cdot HCl$ (3.29 g, 47.4 mmol) and AcONa (3.89 g, 47.4 mmol) in EtOH (20 ml) was refluxed for 1.5 h. After cooling to room temperature, the mixture was worked up with water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc/hexane (1/4) as an eluent to give the oximes (**10a-h**).

5-Ethenyl-4-hydroxyiminomethyl-1-methyl-2-methylthioimidazole (10a): 73.5%(oil). Ir(neat): 3235 cm^{-1}(OH). ^{1}H-Nmr: δ 2.59(3H, s, SC$\underline{H}_3$), 3.47(3H, s, NC$\underline{H}_3$), 5.27(1H, dd, J_{gem}=2 Hz and J_{cis}=12 Hz, CH=C$\underline{H}_2$ X 1/2), 5.42(1H, dd, J_{gem}=2 Hz and J_{trans}=18 Hz, CH=C$\underline{H}_2$ X 1/2), 6.55(1H, dd, J_{cis}=12 Hz and J_{trans}=18 Hz, C$\underline{H}$=CH_2), 8.01(1H, s, N=C$\underline{H}$), 9.11(1H, br s, OH). Ms(CI): *m/z* 197(M^+). HRms calcd for $C_8H_{11}N_3OS$ 197.0622, found 197.0593.

5-Ethenyl-4-(1-hydroxyimino)ethyl-1-methyl-2-methylthioimidazole (10b): 49.5%(oil). Ir(neat): 3149 cm^{-1}(OH). ^{1}H-Nmr: δ 2.28(3H, s, C$\underline{H}_3$-C=N), 2.55(3H, s, SC$\underline{H}_3$), 3.56(3H, s, NC$\underline{H}_3$), 5.24(1H, dd, J_{gem}=2 Hz and J_{cis}=12 Hz, CH=C$\underline{H}_2$ X 1/2), 5.53(1H, dd, J_{gem}=2 Hz and J_{trans}=18 Hz, CH=C$\underline{H}_2$ X 1/2), 6.78(1H, dd, J_{cis}=12 Hz and J_{trans}=18 Hz, C$\underline{H}$=CH_2), 9.13(1H, br s, OH). Ms: *m/z* 211(M^+). HRms calcd for $C_9H_{13}N_3OS$ 211.0779, found 211.0771.

4-Hydroxyiminomethyl-1-methyl-2-methylthio-5-(1-propenyl)imidazole (10c): 64.8%. mp 152.5-155°C (EtOH). Ir(KBr): 3309 cm^{-1}(OH). ^{1}H-Nmr(MeOH-d_4/$CDCl_3$): δ 1.88(3H, d, *J*=5 Hz, C$\underline{H}_3$-CH=), 2.60(3H, s, SC$\underline{H}_3$), 3.43(3H, s, NC$\underline{H}_3$), 5.80-6.37(2H, m, C$\underline{H}$=C$\underline{H}$), 7.94(1H, s, N=C$\underline{H}$). Ms(CI): *m/z* 211(M^+). *Anal.* Calcd for $C_9H_{13}N_3OS$: C, 51.16; H, 6.20; N, 19.89. Found: C, 51.02; H, 6.38; N, 20.03.

4-(1-Hydroxyimino)ethyl-1-methyl-2-methylthio-5-(1-propenyl)imidazole (10d): 58.8%. mp 125.5-127.5°C (EtOH). Ir(KBr): 3157 cm^{-1}(OH). ^{1}H-Nmr: δ 1.86(3H, d, *J*=6 Hz, C$\underline{H}_3$-CH=), 2.26(3H, s, C$\underline{H}_3$-C=N), 2.52(3H, s, SC$\underline{H}_3$), 3.51(3H, s, NC$\underline{H}_3$), 5.54-6.65(2H, m, C$\underline{H}$=C$\underline{H}$), 8.61(1H, br s, OH). Ms: *m/z* 225(M^+). *Anal.* Calcd for $C_{10}H_{15}N_3OS$: C, 53.31; H, 6.71; N, 18.65. Found: C, 53.29; H, 6.98; N, 18.71.

4-Hydroxyiminomethyl-1-methyl-2-methylthio-5-(2-phenylethenyl)imidazole (10e): 95.8% [a mixture of cis/trans (1/1)]. mp 161.5-164°C (EtOH). Ir(KBr): 3136 cm^{-1}(OH). ^{1}H-Nmr: δ 2.61(3H, s, SC$\underline{H}_3$), 2.64(3H, s, SC$\underline{H}_3$), 3.06(3H, s, NC$\underline{H}_3$), 3.55(3H, s, NC$\underline{H}_3$), 6.29(1H, d, J_{cis}=12 Hz, C$\underline{H}$=CH), 6.73-7.66(13H, m, $C_6\underline{H}_5$ X 2, C$\underline{H}$=CH and C$\underline{H}$=C$\underline{H}$), 7.93(1H, br s, OH), 8.16(1H, br s, OH). Ms: *m/z* 273(M^+). *Anal.* Calcd for $C_{14}H_{15}N_3OS$: C, 61.52; H, 5.53; N, 15.37. Found: C, 61.62; H, 5.74; N, 15.08.

4-Hydroxyiminomethyl-1-methyl-2-methylthio-5-(2-propenyl)imidazole (10f): 53.0%. mp 142-143.5°C (EtOH). Ir(KBr): 3161 cm^{-1}(OH). ^{1}H-Nmr: δ 1.99(3H, s, C$\underline{H}_3$-C=), 2.62(3H, s, SC$\underline{H}_3$), 3.38(3H, s, NC$\underline{H}_3$), 4.89-5.10(1H, m, C=C$\underline{H}_2$ X 1/2), 5.28-5.50(1H, m, C=C$\underline{H}_2$ X 1/2), 7.88(1H, s, N=C$\underline{H}$), 8.82(1H, br s, OH). Ms(CI): *m/z* 211(M^+). *Anal.* Calcd for $C_9H_{13}N_3OS$: C, 51.16; H, 6.20; N, 19.89. Found: C, 51.38; H, 6.31; N, 20.13.

4-(1-Hydroxyimino)ethyl-1-methyl-2-methylthio-5-(2-propenyl)imidazole (10g): 36.4%. mp 121-122°C (EtOH). Ir(KBr): 3160 cm^{-1}(OH). ^{1}H-Nmr: δ 1.98(3H, s, C$\underline{H}_3$-C=), 2.26(3H, s, C$\underline{H}_3$-C=N), 2.58(3H, s, SC$\underline{H}_3$), 3.44(3H, s, NC$\underline{H}_3$), 4.87-5.60(2H, m, C=C$\underline{H}_2$), 8.64(1H, br s, OH). Ms: *m/z* 225(M^+). *Anal.* Calcd for $C_{10}H_{15}N_3OS$: C, 53.31; H, 6.71; N, 18.65. Found: C, 53.12; H, 6.88; N, 18.79.

4-(1-Hydroxyimino)beznyl-1-methyl-2-methylthio-5-(2-propenyl)imidazole (10h): 40.3%. mp 143.5-144.5°C (EtOH). Ir(KBr): 3143 cm^{-1}(OH). ^{1}H-Nmr: δ 1.64(3H, s, C$\underline{H}_3$-C=), 2.60(3H, s, SC$\underline{H}_3$), 3.42(3H, s, NC$\underline{H}_3$), 4.69-5.10(2H, m, C=C$\underline{H}_2$), 6.93-7.58(5H, m, $C_6\underline{H}_5$), 10.65(1H, br s, OH). Ms: *m/z* 287(M^+). *Anal.* Calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62. Found: C, 62.85; H, 6.02; N, 14.47.

General procedure for the preparation of 1*H*-imidazo[4,5-*c*]pyridine derivatives (11a-h). A solution of the oximes (**10a-h**) (0.43 mmol) in *o*-dichlorobenzene (5 ml) was refluxed at 190°C for 30-60 min. After the reaction solution was cooled to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 7 g) using EtOAc as an eluent to give the imidazo[4,5-*c*]pyridines (**11a-h**).

1-Methyl-2-methylthio-1*H*-imidazo[4,5-*c*]pyridine (11a): 17.5%(oil). ^{1}H-Nmr: δ 2.78(3H, s, SC$\underline{H}_3$), 3.62(3H, s, NC$\underline{H}_3$), 7.06(1H, d, *J*=5 Hz, C_7-$\underline{H}$), 8.24(1H, d, *J*=5 Hz, C_6-$\underline{H}$), 8.82(1H, br s, C_4-$\underline{H}$). Ms: *m/z* 179(M^+). HRms calcd for $C_8H_9N_3S$ 179.0517 found 179.0501.

1,4-Dimethyl-2-methylthio-1*H*-imidazo[4,5-*c*]pyridine (11b): 98%. mp 108-109°C (EtOAc). ^{1}H-Nmr: δ 2.82(6H, s, C_4-C$\underline{H}_3$ and SC$\underline{H}_3$), 3.63(3H, s, NC$\underline{H}_3$), 6.98(1H, d, *J*=6 Hz, C_7-$\underline{H}$), 8.19(1H, d, *J*=6 Hz, C_6-$\underline{H}$). Ms: *m/z* 193(M^+). *Anal.* Calcd for $C_9H_{11}N_3S$: C, 55.93; H, 5.74; N, 21.74. Found: C, 56.11; H, 5.63; N, 21.64.

1,6-Dimethyl-2-methylthio-1*H*-imidazo[4,5-*c*]pyridine (11c): 78.7%(oil). ^{1}H-Nmr: δ 2.58(3H,

s, C_6-C$\underline{H}_3$), 2.77(3H, s, SC$\underline{H}_3$), 3.52(3H, s, NC$\underline{H}_3$), 6.85(1H, br s, C_7-$\underline{H}$), 8.64(1H, br s, C_4-$\underline{H}$). Ms: *m/z* 193(M^+). HRms calcd for $C_9H_{11}N_3S$ 193.0673, found 193.0698.

2-Methylthio-1,4,6-trimethyl-1*H*-imidazo[4,5-*c*]pyridine (11d): 66.4%. mp 108.5-110°C (EtOAc). ^{1}H-Nmr: δ 2.59(3H, s, C_6-C$\underline{H}_3$), 2.78(6H, s, C_4-C$\underline{H}_3$ and SC$\underline{H}_3$), 3.55(3H, s, NC$\underline{H}_3$), 6.75(1H, br s, C_7-$\underline{H}$). Ms: *m/z* 207(M^+). *Anal.* Calcd for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.32; N, 20.27. Found: C, 58.19; H, 6.21; N, 20.46.

1-Methyl-2-methylthio-6-phenyl-1*H*-imidazo[4,5-*c*]pyridine (11e): 59.5%(oil). ^{1}H-Nmr: δ 2.83 (3H, s, SC$\underline{H}_3$), 3.69(3H, s, NC$\underline{H}_3$), 7.20-8.19(6H, m, C_7-$\underline{H}$ and $C_6\underline{H}_5$), 8.93(1H, s, C_4-$\underline{H}$). Ms: *m/z* 255(M^+). HRms calcd for $C_{14}H_{13}N_3S$ 255.0829, found 255.0806.

1,7-Dimethyl-2-methylthio-1*H*-imidazo[4,5-*c*]pyridine (11f): 82.6%. mp 126-127°C (MeOH). ^{1}H-Nmr: δ 2.55(3H, s, C_7-C$\underline{H}_3$), 2.75(3H, s, SC$\underline{H}_3$), 3.76(3H, s, NC$\underline{H}_3$), 7.91(1H, br s, C_6-$\underline{H}$), 8.65 (1H, br s, C_4-$\underline{H}$). Ms: *m/z* 193(M^+). *Anal.* Calcd for $C_9H_{11}N_3S$: C, 55.93; H, 5.74; N, 21.74. Found: C, 55.99; H, 5.91; N, 21.46.

2-Methylthio-1,4,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridine (11g): 64.7%. mp 142.5-143.5°C (EtOAc). ^{1}H-Nmr: δ 2.50(3H, s, C_7-C$\underline{H}_3$), 2.75(6H, s, C_4-C$\underline{H}_3$ and SC$\underline{H}_3$), 3.76(3H, s, NC$\underline{H}_3$), 7.79(1H, br s, C_6-$\underline{H}$). Ms: *m/z* 207(M^+). *Anal.* Calcd for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.32; N, 20.27. Found: C, 57.88; H, 6.25; N, 20.45.

1,7-Dimethyl-2-methylthio-4-phenyl-1*H*-imidazo[4,5-*c*]pyridine (11h): 71.1%. mp 187-187.5°C (MeOH). ^{1}H-Nmr: δ 2.51(3H, s, C_7-C$\underline{H}_3$), 2.76(3H, s, SC$\underline{H}_3$), 3.70(3H, s, NC$\underline{H}_3$), 7.10 -7.60(3H, m, aromatic protons), 7.94(1H, br s, C_6-$\underline{H}$), 8.40-8.71(2H, m, aromatic protons). Ms: *m/z* 269(M^+). *Anal.* Calcd for $C_{15}H_{15}N_3S$: C, 66.89; H, 5.61; N, 15.60. Found: C, 67.15; H, 5.78; N, 15.41.

2-*n*-Butyl-4,5-dibromoimidazole (13). A solution of bromine (1.04 ml, 20.1 mmol) in DMF (2 ml) was added to a stirred mixture of 2-*n*-butylimidazole (**12**)[8] (1.0 g, 8.05 mmol) and $KHCO_3$ (2.01 g, 20.1 mmol) in DMF (10 ml) at an ambient temperature. The mixture was stirred at 70°C for 3 h and then cooled to an ambient temperature. After addition of aqueous 28% NH_4OH until the disappearance of excess bromine, the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 15 g) using EtOAc/hexane (1/4) to an eluent to give the dibromoimidazole (**13**) (2.07 g, 91.2%), mp 153-155°C (EtOAc/hexane). ^{1}H-Nmr: δ 0.69-1.97(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.72(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$). Ms: *m/z* 284($M^+$+4), 282($M^+$+2), 280($M^+$). *Anal.* Calcd for $C_7H_{10}N_2Br_2$: C, 29.82; H, 3.57; N, 9.93. Found: C, 29.61; H, 3.39; N, 9.81.

1-Benzyl-2-*n*-butyl-4,5-dibromoimidazole (14). A solution of benzyl bromide (0.89 ml, 7.45 mmol) in DMF (5 ml) was added to a stirred mixture of the 2-*n*-butylimidazole (**13**) (2.0 g, 7.09 mmol) and K_2CO_3 (1.37 g, 9.93 mmol) in DMF (20 ml) at room temperature. The stirred mixture was heated at 70°C for 1.5 h and then the solvent was removed. After addition of water to the residue, the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc/hexane (1/19) as an eluent to

give the oily 1-benzylimidazole (**14**) (2.60 g, 98.5%). ^{1}H-Nmr: δ 0.68-1.91(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.58(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 5.10(2H, s, $NC\underline{H}_2Ph$), 6.79-7.44(5H, m, $C_6\underline{H}_5$). Ms: *m/z* 374(M^++4), 372(M^++2), 370(M^+). Hrms calcd for $C_{14}H_{16}N_2Br_2$ 369.9679, found 369.9969.

1-(4-Acetoxybenzyl)-4,5-dibromo-2-*n*-butylimidazole (15). The same procedure as above: 2-*n*-butylimidazole (**13**) (11.3 g, 40.1 mmol), K_2CO_3 (7.75 g, 56.1 mmol) and 4-acetoxybenzyl bromide[9] (13.5 g, 58.9 mmol) in DMF (30 ml). Column chromarography (silica gel, 150 g): The eluent solvent; EtOAc/hexane=1/4. The oily 1-(4-acetoxybenzyl)imidazole (**15**); 17.2 g, 99.8%. Ir(neat): 1771 cm^{-1}(C=O). ^{1}H-Nmr: δ 0.69-1.81(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.25(3H, s, $C\underline{H}_3CO$), 2.57(2H, t, *J*=7 Hz, CH_3CH_2-$CH_2C\underline{H}_2$), 5.07(2H, s, $NC\underline{H}_2Ph$), 6.96(4H, s, aromatic protons). Ms: *m/z* 432(M^++4), 430(M^++2), 428(M^+). HRms calcd for $C_{16}H_{18}N_2O_2Br_2$ 427.9734, found 427.9752.

4,5-Dibromo-2-*n*-butyl-1-(4-hydroxybenzyl)imidazole (16). A mixture of the 1-(4-acetoxybenzyl)imidazole (**15**) (11.8 g, 27.4 mmol) and aqueous 10% K_2CO_3 (80 ml) in EtOH (80 ml) was stirred at room temperature for 12 h. After removal of the solvent, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from EtOAc to give the 1-(4-hydroxybenzyl)imidazole (**16**) (9.52 g, 89.4%), mp 160-162°C (EtOAc). Ir(KBr): 3009 cm^{-1}(OH). ^{1}H-Nmr(MeOH-d_4/$CDCl_3$): δ 0.61-1.94(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.61(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 5.04(2H, s, $NC\underline{H}_2Ph$), 6.81(4H, s, aromatic protons). Ms: *m/z* 390(M^++4), 388(M^++2), 386(M^+). *Anal.* Calcd for $C_{14}H_{16}N_2OBr_2$: C, 43.33; H, 4.16; N, 7.22. Found: C, 43.09; H, 4.25; N, 7.44.

4,5-Dibromo-2-*n*-butyl-1-(4-methoxymethyloxybenzyl)imidazole (17). A solution of 1-(4-hydroxybenzyl)imidazole (**16**) (6.0 g, 15.5 mmol) in DMF (15 ml) was added to a stirred mixture of NaH (60% dispersion, 680 mg, 17.0 mmol) in DMF (15 ml) with ice-cooling under argon atmosphere. After stirring at the same temperature for 30 min, a solution of chloromethyl methyl ether (1.29 ml, 17.0 mmol) in DMF (5 ml) was added and then the mixture was stirred at an ambient temperature for 30 min. After removal of solvent followed by addition of water, the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100 g) using EtOAc/hexane (1/9) as an eluent to give the oily methoxymethyl ether (**17**) (6.3 g, 94.0%). ^{1}H-Nmr: δ 0.66-2.01(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.58(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.42(3H, s, $OC\underline{H}_3$), 5.02(2H, s, $OC\underline{H}_2O$), 5.08(2H, s, $NC\underline{H}_2Ph$), 6.89(4H, s, aromatic protons). Ms: *m/z* 434(M^++4), 432(M^++2), 430(M^+). HRms calcd for $C_{16}H_{20}N_2O_2Br_2$ 429.9890, found 429.9883.

1-Benzyl-4-bromo-2-*n*-butylimidazole-5-carboxaldehyde (18a). A solution of *n*-BuLi (1.66 M in hexane, 13.4 ml, 22.2 mmol) was added at -78°C to a stirred solution of the 4,5-dibromoimidazole (**14**) (6.61 g, 17.8 mmol) in anhyd. Et_2O (150 ml) under argon atmosphere. After stirring at -78°C for 30 min, a solution of DMF (13.8 ml, 177.6 mmol) was added and then the mixture was stirred at an ambient

temperature for 12 h. The mixture was worked up with water, which was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100 g) using EtOAc/hexane (1/19) as an eluent to give the oily aldehyde (**18a**) (4.15 g, 72.7%). Ir(neat): 1678 cm^{-1}(CHO). ^{1}H-Nmr: δ 0.68-1.96(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.62(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 5.51(2H, s, $NC\underline{H}_2Ph$), 6.81-7.43(5H, m, $C_6\underline{H}_5$), 9.61(1H, s, C<u>H</u>O). Ms: *m/z* 322(M^++2), 320(M^+). HRms calcd for $C_{15}H_{17}N_2OBr$ 320.0523, found 320.0496.

4-Bromo-2-*n*-butyl-1-(4-methoxymethyloxybenzyl)imidazole-5-carboxaldehyde (18b). The same procedure as above: 4,5-dibromoimidazole (**17**) (3.0 g, 6.94 mmol) in anhyd. Et_2O (70 ml), *n*-BuLi (1.71 M in hexane, 8.1 ml, 13.9 mmol) and DMF (5.4 ml, 69.4 mmol). Column chromatography (silica gel, 50 g): the eluent solvent; EtOAc/hexane=1/9. The oily aldehyde (**19**); 2.22 g, 83.9%. Ir(neat): 1667 cm^{-1}(CHO). ^{1}H-Nmr: δ 0.60-1.99(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.65(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.43(3H, s, $OC\underline{H}_3$), 5.10(2H, s, $OC\underline{H}_2O$), 5.46(2H, s, $NC\underline{H}_2Ph$), 6.93(4H, s, aromatic protons), 9.62(1H, s, C<u>H</u>O). Ms: *m/z* 382(M^++2), 380(M^+). HRms calcd for $C_{17}H_{21}N_2O_3Br$ 380.0734, found 380.0760.

1-Benzyl-2-*n*-butyl-4-ethenylimidazole-5-carboxaldehyde (19a). A solution of vinyltributyltin (241 mg, 0.76 mmol) in anhyd. DMF (2 ml) was added to a stirred suspension of the 4-bromoimidazole (**18a**) (163 mg, 0.51 mmol), $Et_4N^+Cl^-$ (85 mg, 0.51 mmol), K_2CO_3 (70 mg, 0.51 mmol), $(PPh_3)_2PdCl_2$ (9 mg, 0.013 mmol) in anhyd. DMF (5 ml) at room temperature under argon atmosphere. The mixture was heated at 110°C for 1-2 h under stirring. The mixture was quenched with aqueous 30% KF, which was filtered off with celite. After concentration of the filtrate, the residue was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromarography (silica gel, 10 g) using EtOAc/hexane (1/9) as an eluent to give the oily 4-vinylimidazole (**19a**) (95 mg, 69.8%). Ir(neat): 1661 cm^{-1}(CHO). ^{1}H-Nmr: δ 0.67-1.97(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.64(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 5.46(1H, dd, J_{gem}=2 Hz and J_{cis}=10 Hz, CH=C<u>H</u>$_2$ X 1/2), 5.52(2H, s, $NC\underline{H}_2Ph$), 6.16(1H, dd, J_{gem}=2 Hz and J_{trans}=17 Hz, CH=C<u>H</u>$_2$ X 1/2), 6.69-7.42(6H, m, $C_6\underline{H}_5$ and C<u>H</u>=CH$_2$), 9.82(1H, s, C<u>H</u>O). Ms: *m/z* 268(M^+). HRms calcd for $C_{17}H_{20}N_2O$ 268.1575, found 268.1552.

1-Benzyl-2-*n*-butyl-4-(2-propenyl)imidazole-5-carboxaldehyde (19b). The same procedure as above (isopropenyltributyltin[12] was used instead of vinyltributyltin): 67.4%(oil). Ir(neat): 1666 cm^{-1}(CHO). ^{1}H-Nmr: δ 0.66-1.97(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.22(3H, s, $C\underline{H}_3$-C=), 2.65(2H, t, *J*=7 Hz, CH_3CH_2-$CH_2C\underline{H}_2$), 5.19-5.44(2H, m, CH=C<u>H</u>$_2$), 5.57(2H, s, $NC\underline{H}_2Ph$), 6.85-7.39(5H, m, $C_6\underline{H}_5$), 9.71(1H, s, C<u>H</u>O). Ms: *m/z* 282(M^+). HRms calcd for $C_{18}H_{22}N_2O$ 282.1731, found 282.1750.

2-*n*-Butyl-4-ethenyl-1-(4-methoxymethyloxybenzyl)imidazole-5-carboxaldehyde (19c). The same procedure as above: 90.7%(oil). Ir(neat): 1663 cm^{-1}(CHO). ^{1}H-Nmr: δ 0.67-1.98(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.65(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.39(3H, s, $OC\underline{H}_3$), 5.06(2H, s, $OC\underline{H}_2O$), 5.43(2H, s, $NC\underline{H}_2Ph$), 5.43(1H, dd, J_{gem}=2 Hz and J_{cis}=10 Hz, CH=C<u>H</u>$_2$ X 1/2), 6.13(1H, dd, J_{gem}=2 Hz and J_{trans}=17 Hz, CH=C<u>H</u>$_2$ X 1/2), 6.90(4H, s, aromaric protons), 6.93(1H, dd, J_{cis}=10 Hz and J_{trans}=17 Hz, C<u>H</u>=CH$_2$), 9.81(1H, s, C<u>H</u>O). Ms: *m/z* 328(M^+). HRms calcd for $C_{19}H_{24}N_2O_3$ 328.1786, found

328.1816.

2-*n*-Butyl-4-(2-propenyl)-1-(4-methoxymethyloxybenzyl)imidazole-5-carboxaldehyde (19d). The same procedure as above (isopropenyltributyltin[12] was used instead of vinyltributyltin): 75.9%(oil). Ir(neat): 1651 cm^{-1}(CHO). ^{1}H-Nmr: δ 0.69-1.95(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.20(3H, s, $C\underline{H}_3$-C=), 2.66(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.42(3H, s, $OC\underline{H}_3$), 5.07(2H, s, $OC\underline{H}_2O$), 5.15-5.39(2H, m, C=$C\underline{H}_2$), 5.46 (2H, s, $NC\underline{H}_2Ph$), 6.90(4H, s, aromaric protons), 9.66(1H, s, CHO). Ms: *m/z* 342(M^+). HRms calcd for $C_{20}H_{26}N_2O_3$ 342.1942, found 342.1928.

General procedure for the preparation of the oximes (20a-d). A mixture of the aldehydes (**19a-d**) (2.38 mmol), $NH_2OH \cdot HCl$ (5.11 g, 73.6 mmol), AcONa (6.04 g, 73.6 mmol) in EtOH (20 ml) was heated at the reflux temperature for 30 min. The mixture was poured into water, which was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc/hexane (1/4) as an eluent to give the oximes (**20a-d**).

1-Benzyl-2-*n*-butyl-4-ethenyl-5-hydroxyiminomethylimidazole (20a): 54.3%. mp 158-160°C (EtOH). Ir(KBr): 3033 cm^{-1}(OH). ^{1}H-Nmr(MeOH-d_4/$CDCl_3$): δ 0.63-1.90(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.59 (2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 2.98-3.48(1H, m, OH), 5.20(1H, dd, J_{gem}=2 Hz and J_{cis}=10 Hz, CH=$C\underline{H}_2$ X 1/2), 5.48(2H, s, $NC\underline{H}_2Ph$), 5.87(1H, dd, J_{gem}=2 Hz and J_{trans}=17 Hz, CH=$C\underline{H}_2$ X 1/2), 6.70 (1H, dd, J_{cis}=10 Hz and J_{trans}=17 Hz, $C\underline{H}$=CH_2), 6.79-7.46(5H, m, $C_6\underline{H}_5$), 8.09(1H, s, N=C$\underline{H}$). Ms(CI): *m/z* 283(M^+). *Anal.* Calcd for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.47; N, 14.83. Found: C, 71.89; H, 7.41; N, 15.03.

1-Benzyl-2-*n*-butyl-5-hydroxyiminomethyl-4-(2-propenyl)imidazole (20b): 63.6%. mp 147-148.5°C (EtOH). Ir(KBr): 3089 cm^{-1}(OH). ^{1}H-Nmr: δ 0.52-1.81(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.07(3H, s, $C\underline{H}_3$-C=), 2.47(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 4.93-5.22(2H, m, CH=$C\underline{H}_2$), 5.45(2H, s, $NC\underline{H}_2Ph$), 6.75-7.36(5H, m, $C_6\underline{H}_5$), 8.17(1H, s, N=C$\underline{H}$). Ms(CI): *m/z* 297(M^+). *Anal.* Calcd for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.80; N, 14.13. Found: C, 72.91; H, 7.69; N, 14.05.

2-*n*-Butyl-4-ethenyl-5-hydroxyiminomethyl-1-(4-methoxymethyloxybenzyl)imidazole (20c): 80.8%. mp 140-142°C (EtOH). Ir(KBr): 3110 cm^{-1}(OH). ^{1}H-Nmr(MeOH-d_4/$CDCl_3$): δ 0.64-1.84 (7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.60(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.43(3H, s, $OC\underline{H}_3$), 5.09(2H, s, $OC\underline{H}_2O$), 5.20(1H, dd, J_{gem}=2 Hz and J_{cis}=10 Hz, CH=$C\underline{H}_2$ X 1/2), 5.37(2H, s, $NC\underline{H}_2Ph$), 5.86(1H, dd, J_{gem}=2 Hz and J_{trans}=18 Hz, CH=$C\underline{H}_2$ X 1/2), 6.70(1H, dd, J_{cis}=10 Hz and J_{trans}=18 Hz, $C\underline{H}$=CH_2), 6.88(4H, s, aromatic protons), 8.07(1H, s, N=C$\underline{H}$). Ms(CI): *m/z* 343(M^+). *Anal.* Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.18; H, 7.26; N, 12.41.

2-*n*-Butyl-5-hydroxyiminomethyl-1-(4-methoxymethyloxybenzyl)-4-(2-propenyl)imidazole (20d): 85.2%. mp 106-108°C (Et_2O). Ir(KBr): 3132 cm^{-1}(OH). ^{1}H-Nmr: δ 0.55-1.77(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.07(3H, s, $C\underline{H}_3$-C=), 2.53(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.40(3H, s, $OC\underline{H}_3$), 4.97-5.22(2H, m, C=$C\underline{H}_2$), 5.09(2H, s, $OC\underline{H}_2O$), 5.42(2H, s, $NC\underline{H}_2Ph$), 6.87(4H, s, aromatic protons), 8.16(1H, s, N=CH). Ms(CI): *m/z* 357(M^+). *Anal.* Calcd for $C_{20}H_{27}N_3O_3$: C, 67.20; H, 7.61; N, 11.76. Found: C, 67.33; H, 7.78; N, 12.85.

4-Bromo-2-*n*-butyl-5-methoxyiminomethyl-1-(4-methoxymethyloxybenzyl)imidazole (21). A mixture of the aldehyde (**18b**) (500 mg, 1.31 mmol), $NH_2OMe \cdot HCl$ (3.40 g, 40.7 mmol) and AcONa (3.33 g, 40.7 mmol) in EtOH (20 ml) was heated at the reflux temperature for 30 min. The mixture was poured into water and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 7 g) using EtOAc/hexane (1/19) as an eluent to give the oily oxime ether (**21**) (531 mg, 98.7%). ^{1}H-Nmr: δ 0.63-1.93(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.61(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.43(3H, s, $OC\underline{H}_3$), 3.79(3H, s, N-$OC\underline{H}_3$), 5.09(2H, s, $OC\underline{H}_2O$), 5.43(2H, s, $NC\underline{H}_2Ph$), 6.92(4H, s, aromatic protons), 7.95(1H, s, N=C$\underline{H}$). Ms: *m/z* 411(M^++2), 409(M^+). HRms calcd for $C_{18}H_{24}N_3O_3Br$ 409.1000, found 409.1005.

2-*n*-Butyl-4-ethenyl-5-methoxyiminomethyl-1-(4-methoxymethyloxybenzyl)imidazole (22a). A solution of vinyltributyltin (232 mg, 0.731 mmol) in anhyd. DMF (2 ml) was added to a stirred suspension of the oxime ether (**21**) (200 mg, 0.487 mmol), $Et_4N^+Cl^-$ (81 mg, 0.487 mmol), K_2CO_3 (67 mg, 0.487 mmol), $(PPh_3)_2PdCl_2$ (8 mg, 0.012 mmol) in anhyd. DMF (5 ml) under an argon atmosphere. The mixture was heated at 110°C for 30 min. The mixture was quenched with aqueous 30% KF and then filtered off with celite. The celite was washed with EtOAc and the combined organic layer was washed with brine, which was dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 7 g) using EtOAc/hexane (1/9) as an eluent to give the 4-ethenylimidazole (**22a**) as an oil (170 mg, 97.6%). ^{1}H-Nmr: δ 0.64-1.95(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.61(2H, t, *J*=7 Hz, CH_3CH_2-$CH_2C\underline{H}_2$), 3.39(3H, s, $OC\underline{H}_3$), 3.76(3H, s, N-$OC\underline{H}_3$), 5.05(2H, s, $OC\underline{H}_2O$), 5.18(1H, dd, J_{gem}=2 Hz and J_{cis}=10 Hz, CH=C$\underline{H}_2$ X 1/2), 5.34(2H, s, $NC\underline{H}_2Ph$), 5.92(1H, dd, J_{gem}=2 Hz and J_{trans}=17 Hz, CH=C$\underline{H}_2$ X 1/2), 6.67(1H, dd, J_{cis}=10 Hz and J_{trans}=17 Hz, C$\underline{H}$=CH_2), 6.88(4H, s, aromatic protons), 8.01(1H, s, N=C$\underline{H}$). Ms: *m/z* 357(M^+). HRms calcd for $C_{20}H_{27}N_3O_3$ 357.2051, found 357.2075.

2-*n*-Butyl-4-(2-propenyl)-5-methoxyiminomethyl-1-(4-methoxymethyloxybenzyl)imidazole (22b). The same procedure as above (isopropenyltributyltin[12] was used instead of vinyltributyltin): 60.8%(oil). ^{1}H-Nmr: δ 0.66-1.99(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.12(3H, s, $C\underline{H}_3$-C=), 2.62(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 3.41(3H, s, $OC\underline{H}_3$), 3.75(3H, s, N-$OC\underline{H}_3$), 4.94-5.25(2H, m, C=C$\underline{H}_2$), 5.10(2H, s, $OC\underline{H}_2O$), 5.45(2H, s, $NC\underline{H}_2Ph$), 6.91(4H, s, aromatic protons), 8.07(1H, s, N=C$\underline{H}$). Ms: *m/z* 371(M^+). HRms calcd for $C_{21}H_{29}N_3O_3$ 371.2208, found 371.2198.

General procedure for the preparation of 3*H*-imidazo[4,5-*c*]pyridine derivatives (23a-d). A stirred solution of the oximes (**20a-d**) (0.251 mmol) in *o*-dichlorobenzene (4-5 ml) was refluxed at 190°C for 1-3 h. After removal of the solvent, the residue was purified by column chromatography (silica gel, 5 g) using EtOAc as an eluent to give the 3*H*-imidazo[4,5-*c*]pyridines (**23a-d**) (Route A).

3-Benzyl-2-*n*-butyl-3*H*-imidazo[4,5-*c*]pyridine (23a): 70.7%. mp 72.5-74.5°C (Et_2O/hexane). ^{1}H-Nmr: δ 0.69-2.19(7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2$), 2.86(2H, t, *J*=7 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 5.35(2H, s, $NC\underline{H}_2Ph$), 6.85-7.43(5H, m, $C_6\underline{H}_5$), 7.57(1H, d, *J*=6 Hz, C_7-$\underline{H}$), 8.32(1H, d, *J*=6 Hz, C_6-$\underline{H}$), 8.53(1H, s, C_4-$\underline{H}$). Ms: *m/z* 265(M^+). *Anal.* Calcd for $C_{17}H_{19}N_3$: C, 76.94; H, 7.22; N, 15.84. Found: C, 76.78; H, 7.31; N, 15.91.

3-Benzyl-2-*n*-butyl-7-methyl-3*H*-imidazo[4,5-*c*]pyridine (23b): 79.1%. mp 89-90.5°C (Et_2O). ^{1}H-Nmr: δ 0.71-2.04(7H, m, $CH_3CH_2CH_2$), 2.63(3H, s, C_7-CH_3), 2.88(2H, t, *J*=7 Hz, $CH_3CH_2CH_2$-CH_2), 5.34(2H, s, NCH_2Ph), 6.87-7.40(5H, m, C_6H_5), 8.18(1H, br s, C_6-H), 8.39(1H, br s, C_4-H). Ms: *m/z* 279(M^+). *Anal.* Calcd for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.63; H, 7.49; N, 14.88.

2-*n*-Butyl-3-(4-methoxymethyloxybenzyl)-3*H*-imidazo[4,5-*c*]pyridine (23c): 78.2%. mp 65.5-67.5°C (Et_2O). ^{1}H-Nmr: δ 0.66-2.05(7H, m, $CH_3CH_2CH_2$), 2.72(2H, t, *J*=7 Hz, $CH_3CH_2CH_2CH_2$), 3.36(3H, s, OCH_3), 5.01(2H, s, OCH_2O), 5.16(2H, s, NCH_2Ph), 6.83(4H, s, aromatic protons), 7.40(1H, d, *J*=5 Hz, C_7-H), 8.19(1H, d, *J*=5 Hz, C_6-H), 8.38(1H, s, C_4-H). Ms: *m/z* 325(M^+). *Anal.* Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.21; H, 7.03; N, 13.19.

2-*n*-Butyl-3-(4-methoxymethyloxybenzyl)-7-methyl-3*H*-imidazo[4,5-*c*]pyridine (23d): 88.7%. mp 103-105°C ($CHCl_3$/hexane). ^{1}H-Nmr: δ 0.73-1.99(7H, m, $CH_3CH_2CH_2$), 2.61(3H, s, C_7-CH_3) 2.90(2H, t, *J*=7 Hz, $CH_3CH_2CH_2CH_2$), 3.41(3H, s, OCH_3), 5.08(2H, s, OCH_2O), 5.27(2H, s, NCH_2Ph), 6.92(4H, s, aromatic protons), 8.15(1H, s, C_6-H), 8.39(1H, s, C_4-H). Ms: *m/z* 339(M^+). *Anal.* Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.43; N, 12.38. Found: C, 70.54; H, 7.18; N, 12.52.

2-*n*-Butyl-3-(4-methoxymethyloxybenzyl)-3*H*-imidazo[4,5-*c*]pyridine (23c) from the oxime ether (22a) (Route B). A stirred solution of the oxime ether (**22a**) (157 mg, 0.493 mmol) in *o*-dichlorobenzene (5 ml) was heated at 190°C for 3 h. After removal of the solvent, the residue was purified by column chromatography (silica gel, 7 g) using EtOAc as an eluent to give the imidazo[4,5-*c*]pyridine (**23c**) (103 mg, 72.1%).

2-*n*-Butyl-3-(4-methoxymethyloxybenzyl)-7-methyl-3*H*-imidazo[4,5-*c*]pyridine (23d) from the oxime ether (22b) (Route B). The same procedure as above, 75.5%.

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