

A CONVENIENT ROUTE TO THE IMIDAZO[4,5-*b*]PYRIDINES

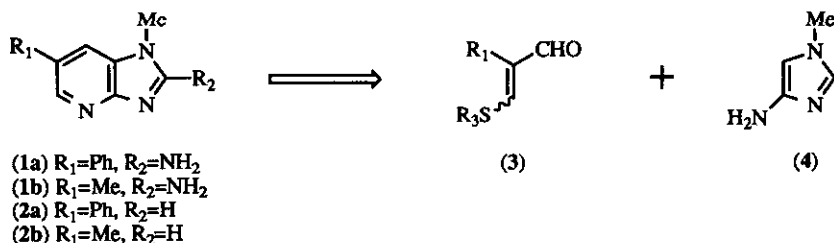
Kenichi Harada, Tominari Choshi, Eiichi Sugino, Koichi Sato,
and Satoshi Hibino*

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

Abstract---The reaction of the acroleins possessing a leaving group, derived from alkenyl sulfides by Vilsmeier reaction, with 4-amino-1-methylimidazole provided a new and convenient route to the imidazo[4,5-*b*]pyridines, the reaction mechanisms of which were examined by a deuterium labelled experiment.

Imidazo[4,5-*b*]pyridine derivatives have recently attracted much attention as agents having various biological activities, such as inotropic agents,¹ angiotensin II receptor antagonists,² thromboxane A₂ receptor antagonists,³ sequence specific DNA-binding agents⁴ and food-derived mutagens.⁵

Although many synthetic efforts in this area have been made, almost all of the procedures for the preparation of imidazo[4,5-*b*]pyridines have involved the ring closure of imidazoles using 2,3-diaminopyridines with either carboxylic acids or their equivalents.¹⁻⁶ On the other hand, there are only six reports on the preparation of the pyridine rings by imidazole derivatives including our method.⁷ Our method is based on the thermal electrocyclic reaction of 2-azahexatriene system involving the imidazole 4,5-bond for the synthesis of food-derived mutagens 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP:1a) and 2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine (DMIP:1b).^{7f}



Scheme 1

In seeking a more convenient route to the imidazo[4,5-*b*]pyridines, we envisaged that the reaction of the acrolein derivatives (3) possessing a proper leaving group with 4-amino-1-methylimidazole (4) based on the retrosynthetic analysis (Scheme 1) might give the imidazo[4,5-*b*]pyridines effectively. We describe here a new and

*This paper is dedicated to the memory of the late Professor Yoshio Ban.

Scheme 2

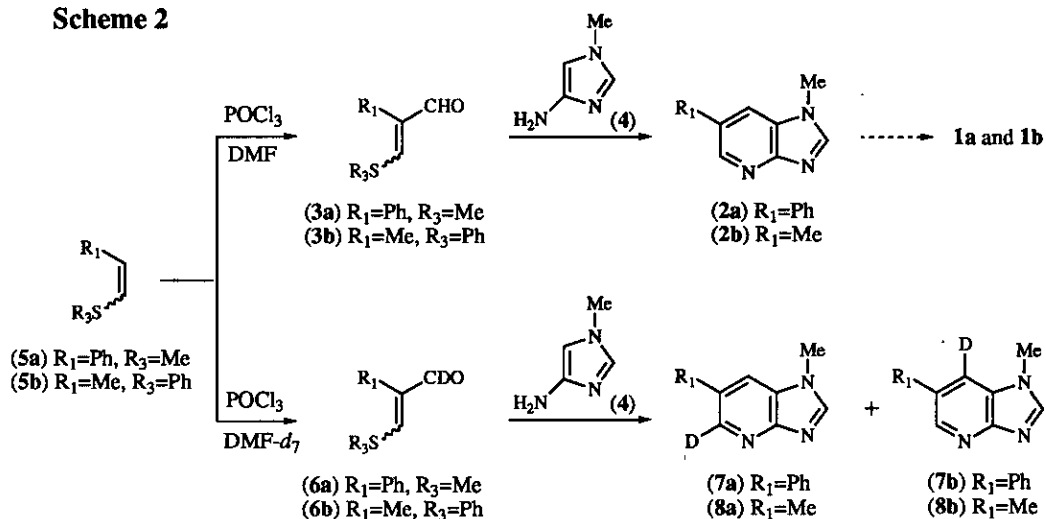


Table I. Vilsmeier reaction of alkenyl sulfides (5)

Run	R_1	R_3	$POCl_3$ (eq.)	Temp.(°C)	Time(h)	Yield(%)*
1	Ph	Me	2.0	room temp.	14	trace
2	Ph	Me	2.0	60	3	37.5
3	Ph	Me	2.0	90	3	51.1
4	Ph	Me	4.0	room temp.	14	trace
5	Ph	Me	4.0	60	3	48.1
6	Ph	Me	4.0	90	3	60.0
7	Ph	Me	5.0	room temp.	14	39.5
8	Ph	Me	5.0	60	3	70.1
9	Ph	Me	5.0	90	3	72.3
10	Me	Ph	5.0	60	3	54.9
11	Me	Ph	5.0	90	3	64.1

* isolated yields

Table II. Reactions of acroleins (3) with 4-aminoimidazole (4)

Run	Compds (3)		4-amino-1-methyl-imidazole(eq. *)	Acid or Lewis Acid	Yield(%)**
	R_1	R_3			
1	Ph	Me	1.5	<i>p</i> -TsOH	52.5
2	Ph	Me	2.0	<i>p</i> -TsOH	54.5
3	Ph	Me	3.0	<i>p</i> -TsOH	43.3
4	Ph	Me	2.0	$ZnCl_2$	17.0
5	Ph	Me	2.0	$BF_3 \cdot Et_2O$	17.0
6	Ph	Me	2.0	$TiCl_4$	16.2
7	Me	Ph	2.0	<i>p</i> -TsOH	65.8
8	Me	Ph	3.0	<i>p</i> -TsOH	64.3

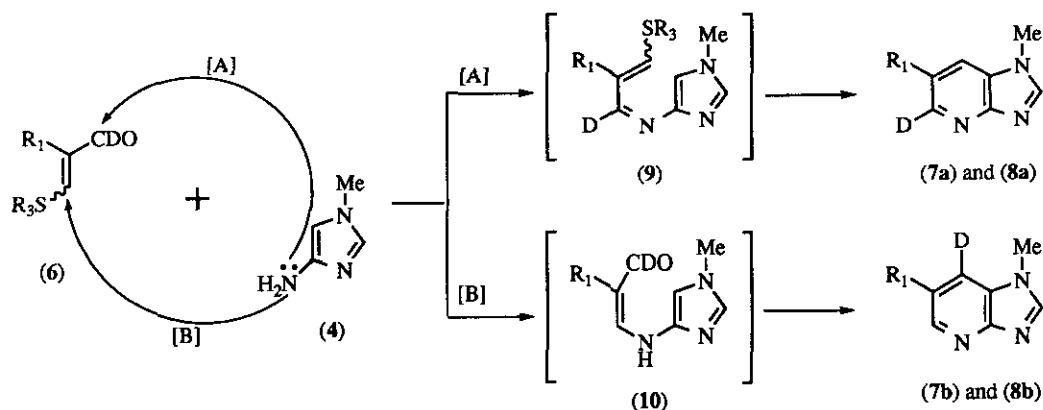
*inexact amounts ** isolated yields

convenient method of synthesis of the imidazo[4,5-*b*]pyridine ring system and its reaction mechanisms. The acrolein derivatives (3) were prepared by Vilsmeier reaction of the alkenyl sulfides (5)^{8,9} according to our reported method.¹⁰ As shown in Scheme 2 and Table I, we examined several reaction conditions concerning amounts of phosphorus oxychloride (POCl₃) at different reaction temperatures. Five equimolar amounts of POCl₃ was necessary in each case. Furthermore, the reaction temperature at 90 °C (external) provided the best results. Namely, 3a and 3b were obtained at the yield of 72.3 and 64.1%, respectively. Although the stereochemistry of 3 is presumed to be *E*-form, the detailed data have not been acquired yet.

Next, the acroleins (3) were subjected to reaction with the 4-aminoimidazole (4) derived from 1-methyl-4-nitroimidazole¹¹ by hydrogenation. After catalytic reduction of 4-nitroimidazole and the following filtration and subsequent replacement of the solvent, 4-aminoimidazole (4) was used without isolation because of its high air-sensitivity.¹¹ The reaction of the acroleins (3) with 4-aminoimidazole (4) was carried out by heating at the reflux temperature in benzene in the presence of *p*-toluenesulfonic acid (*p*-TsOH) (Table II). The addition of Lewis acids instead of *p*-TsOH was not effective and two equimolar amounts of 4-amino-1-methylimidazole was at least necessary. The yields of the imidazo[4,5-*b*]pyridines (2a) and (2b) were 54.5 and 65.8%, respectively.

In literatures, Hayakawa and co-workers^{7a} reported that the reaction of diethyl ethoxyethylidenemalonate with 5-amino-2-mercapto-1-methylimidazole involves the 1,4-addition-elimination process by the enamine group to give a *C*-addition product at the 5-position of the imidazole. On the other hand, Ramsden and co-workers^{7c} also reported that a 1,4-addition-elimination reaction product (*N*-addition) by the amino group was obtained when the catalytic reduction of 1-methyl-5-nitroimidazole was carried out in the presence of diethyl ethoxy-methylidenemalonate. However, the acceptors in both reports are α,β -unsaturated esters, whose reactivity might be different from α,β -unsaturated aldehydes (3) used in our work.

In order to elucidate our reaction mechanism, we repeated this reaction using a *d*-labelled compound (Scheme 2). The deuterated acroleins (6a) and (6b) were prepared by Vilsmeier reaction by using DMF-*d*₇ instead of DMF, which was subjected to the preparation of the deuterium incorporated imidazo[4,5-*b*]pyridines (7) and (8) in the same way. In the ¹H-nmr spectra of the compound (7), the singlet signals due to C₇-H and C₅-H appeared at δ 7.89 and δ 8.83, respectively. In the case of 8, the corresponding signals were observed at δ 7.52 and δ 8.41. As a result, a mixture of deuterated imidazo[4,5-*b*]pyridines (7a / 7b and 8a / 8b) was obtained, the ratios



Scheme 3

of which were 1 : 1 for **7a** : **7b** and 0.54 : 1 for **8a** : **8b**. In this reaction, the 1,2-addition or 1,4-addition-elimination process to the acroleins (**3**) by the enamine group of **4** might be considered to have taken place, but no C-addition products and imidazo[4,5-*b*]pyridines were obtained by the methods reported previously.^{7a,c} These results demonstrated that this pyrido-annulation might proceed through two routes, [A] and [B] as follows (Scheme 3). The C₃-deuterated imidazo[4,5-*b*]pyridines (**7a**) and (**8a**) were derived from the 1,2-addition to the acroleins (**3**) by the amino group of **4** followed by the thermal electrocyclic reaction of the 3-azahexatriene system (**9**) (Route A). By contrast, the C₇-deuterated imidazo[4,5-*b*]pyridines (**7b**) and (**8b**) were derived from the 1,4-addition-elimination reaction by the amino group followed by intramolecular condensation of an enamino-aldehyde (**10**) (Route B).

Thus, a two step synthesis of imidazo[4,5-*b*]pyridines has been established, the reaction mechanisms of which have been studied by the deuterium labelled experiment. We found that the three carbon units of an alkyl or arylthioacroleins (**3**) is an useful component for the construction of the fused pyridine ring system. This new route to the imidazo[4,5-*b*]pyridine ring system also formally provided an improved and short step route to PhIP (**1a**) and DMIP (**1b**).^{5b-4, 7f}

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. ¹H-Nmr spectra were taken by JEOL PMX60Si and JEOL JNM A400 spectrometers with SiMe₄ as an internal standard. Mass spectra (Ms) and high resolution mass spectra (HRms) were recorded on a Shimadzu GC-MS 9020DF spectrometer (EI). Silica gel (60-100 mesh, Merck Art 7734) was used for column chromatography.

3-Methylthio-2-phenylacrolein(3a). A solution of POCl₃ (12.4 ml, 0.14 mol) was added to an ice-cooled solution of DMF (43.4 ml, 0.55 mol) under N₂ atmosphere and then the solution was stirred at 70-75 °C for 30 min. After addition of methyl 2-phenylethenyl sulfide (**5a**)⁸ (4.1 g, 27.3 mmol) in DMF (5 ml), the mixture was heated at 90 °C for 3 h under stirring. The mixture was poured into ice water. The whole was neutralized with 30% NaOH solution and then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica gel, 150 g) using benzene/hexane (1/1) as an eluent to give the acrolein (**3a**) (3.5 g, 72.3%), bp 148-149 °C/2.5 torr. Ir (neat): 1668 cm⁻¹(C=O). ¹H-Nmr (CDCl₃): δ 2.45(3H, s, SCH₃), 7.28(5H, s, C₆H₅), 7.37(1H, s, =CH-), 9.37(1H, s, CHO). Ms: *m/z* 178 (M⁺). HRms calcd for C₁₀H₁₀OS 178.0452, found 178.0445.

3-Methylthio-2-phenylacrolein-*d*₁ (6a). The same procedure as above using DMF-*d*₇ instead of DMF gave the acrolein-*d*₁ (**6a**) (75.5%), bp 150-151 °C/3 torr. Ir (neat): 1670 cm⁻¹(C=O). ¹H-Nmr (CDCl₃): δ 2.49(3H, s, SCH₃), 7.33(5H, s, C₆H₅), 7.42(1H, s, =CH-). Ms: *m/z* 179 (M⁺). HRms calcd for C₁₀H₉DOS 179.0515, found 179.0510.

2-Methyl-3-phenylthioacrolein(3b). A solution of POCl₃ (15.0 ml, 0.17 mol) was added to an ice-cooled

solution of DMF (52.7 ml, 0.67 mol) under N_2 atmosphere and then the solution was stirred at 70-75 °C for 30 min. After addition of a solution of phenyl 1-propenyl sulfide (**5b**)⁹ (5 g, 33.3 mmol) in DMF (5 ml), the mixture was heated at 90 °C for 3 h under stirring. The mixture was poured into ice water. The whole was neutralized with 30% NaOH solution and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 200 g) using EtOAc/hexane (1/9) as an eluent to give the acrolein (**3b**) (3.8 g, 64.1%), bp 132-134 °C/2 torr. Ir (neat): 1670 cm^{-1} (C=O). 1H -Nmr ($CDCl_3$): δ 1.83 (3H, s, CH_3), 7.02-7.51 (6H, m, =CH- and C_6H_5), 9.01 (1H, s, CHO). Ms: m/z 178 (M^+). HRms calcd for $C_{10}H_{10}OS$ 178.0452, found 178.0440.

2-Methyl-3-phenylthioacrolein- d_1 (6b). The same procedure as above using $DMF-d_7$ instead of DMF gave the acrolein- d_1 (**6b**) (72.8%), bp 125-126 °C/1.8 torr. Ir (neat): 1670 cm^{-1} (C=O). 1H -Nmr ($CDCl_3$): δ 2.43 (3H, s, SCH_3), 7.38 (5H, s, C_6H_5), 7.38 (1H, s, =CH-). Ms: m/z 179 (M^+). HRms calcd for $C_{10}H_9DOS$ 179.0515, found 179.0523.

1-Methyl-6-phenylimidazo[4,5-*b*]pyridine (2a). A mixture of 1-methyl-4-nitroimidazole (142 mg, 1.12 mmol), 5% Pd-C (50 mg) in EtOH (5 ml) was stirred at room temperature under H_2 atmosphere. The mixture was filtered through celite and the filtrate was concentrated. The residue was immediately dissolved in benzene without isolation. The acrolein (**3a**) (100 mg, 0.56 mmol) and *p*-TsOH (70 mg, 0.29 mmol) were added to a solution of the aminoimidazole (**4**) in benzene. The mixture was refluxed at 100 °C for 14 h equipped with a water separator. After removal of solvent followed by addition of 20% $KHCO_3$ solution, the mixture was extracted with $CHCl_3$ (containing 5% MeOH). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 25 g) using MeOH/ $CHCl_3$ (0.5/99.5) to give the imidazopyridine (**2a**) (64 mg, 54.7%), mp 131-133 °C ($CHCl_3/Et_2O$) (lit.,^{7f} mp 131-133 °C).

1,6-Dimethylimidazo[4,5-*b*]pyridine (2b). The same procedure as above using 2-methyl-3-phenylthioacrolein (**3b**) instead of **3a** gave the imidazopyridine (**2b**) (65.8%), mp 120-121 °C (benzene/hexane) (lit.,^{7f} mp 120-121 °C).

A mixture of 5-deuterio-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (7a) and 7-deuterio-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (7b). The same procedure as above using 3-methylthio-2-phenylacrolein- d_1 (**6a**) instead of **3a** gave the imidazopyridine (**7a**) and (**7b**) (53.0% as a 1 : 1 mixture), mp 130-133 °C ($CHCl_3/Et_2O$). 1H -Nmr ($CDCl_3$): δ 3.93 (3H, s, NCH_3), 7.26-7.64 (5H, m, C_6H_5), 7.89 (0.5H, s, C_7 -H), 8.12 (1H, s, C_2 -H), 8.83 (0.5H, s, C_5 -H). Ms: m/z 210 (M^+). HRms calcd for $C_{13}H_{10}DN_3$ 210.1015, found 210.1009.

A mixture of 5-deuterio-1,6-dimethylimidazo[4,5-*b*]pyridine (8a) and 7-deuterio-1,6-dimethylimidazo[4,5-*b*]pyridine (8b). The same procedure as above using 3-methylthio-2-phenylacrolein- d_1 (**6b**) instead of **3b** gave the imidazopyridines (**8a**) and (**8b**) (69.6% as a 0.54 : 1 mixture), mp 119-122 °C (benzene/hexane). 1H -Nmr ($CDCl_3$): δ 2.50 (3H, s, CH_3), 3.84 (3H, s, CH_3), 7.52 (0.65H, s,

C₇-H), 8.00(1H, s, C₂-H), 8.41(0.35H, s, C₅-H). Ms: *m/z* 148 (M⁺). HRms calcd for C₈H₈DN₃, 148.0859, found 148.0862.

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