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

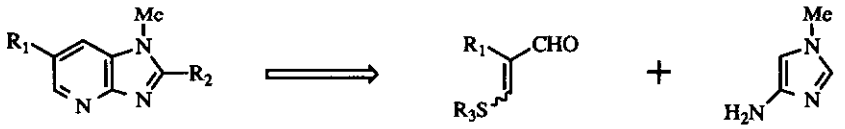
Kenichi Harada, Tominari Choshi, Eiichi Sugino, Koichi Sato,
and Satoshi Hibino*

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 A_2 receptor antagonists,[3] sequence specific DNA-binding agents[4] 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]



(**1a**) R_1=Ph, R_2=NH_2
(**1b**) R_1=Me, R_2=NH_2
(**2a**) R_1=Ph, R_2=H
(**2b**) R_1=Me, R_2=H

(**3**) (**4**)

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 retro-synthetic 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

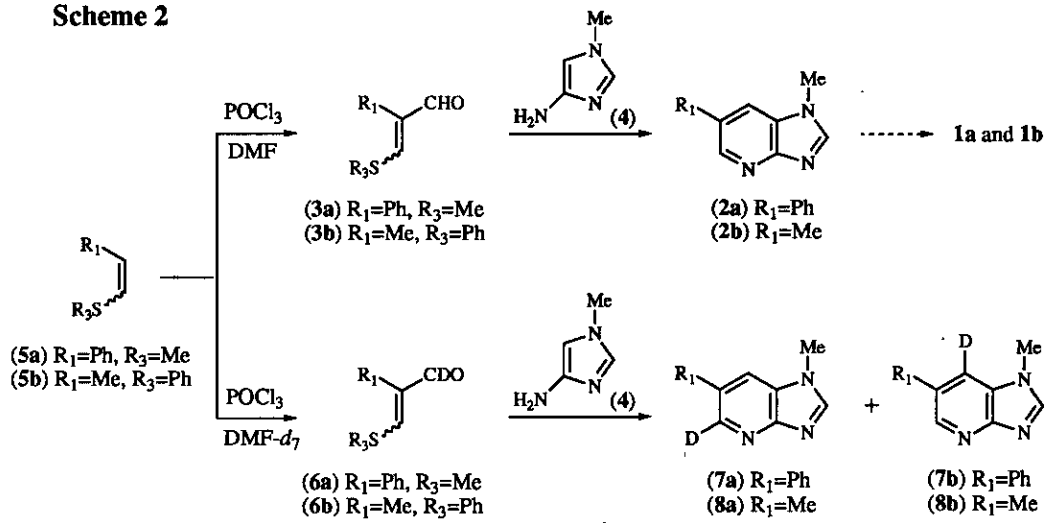


Table I. Vilsmeier reaction of alkenyl sulfides (**5**)

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-	Acid or	Yield(%)**
	R_1	R_3	imidazole(eq.*)	Lewis Acid	
1	Ph	Me	1.5	*p*-TsOH	52.5
2	Ph	Me	2.0	*p*-TsOH	54.5
3	Ph	Me	3.0	*p*-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	*p*-TsOH	65.8
8	Me	Ph	3.0	*p*-TsOH	64.3

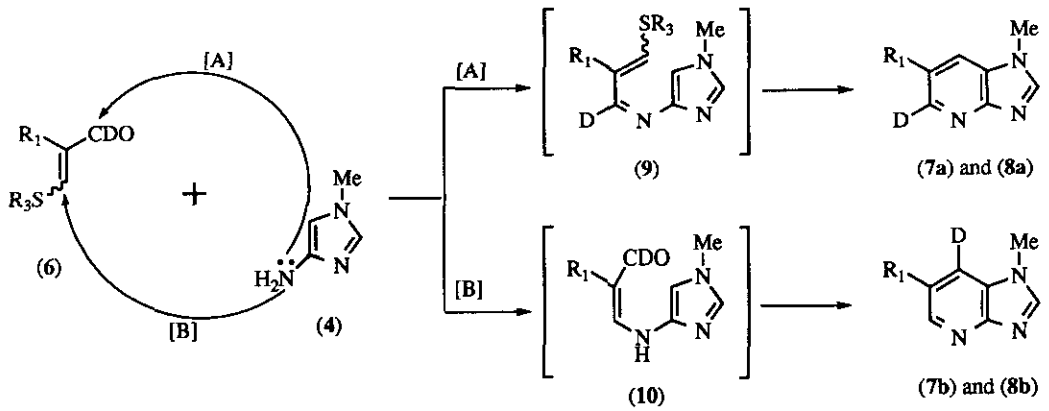
*inexact amounts ** isolated yields

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 ($POCl_3$) at different reaction temperatures. Five equimolar amounts of $POCl_3$ 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 aquired yet.

Next, the acroleins (**3**) were subjected to reaction with the 4-aminoimidazole (**4**) derived from 1-methyl-4-nitroimidazole[11] 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[7e] 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 ethoxymethylidenemalonate. 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 ^{1}H-nmr spectra of the compound (**7**), the singlet signals due to C_7-H and C_5-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-annelation might proceed through two routes, [A] and [B] as follows (**Scheme 3**). The C_5-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 C_7-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-d, 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. ^{1}H-Nmr spectra were taken by JEOL PMX60Si and JEOL JNM A400 spectrometers with $SiMe_4$ 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 $POCl_3$ (12.4 ml, 0.14 mol) was added to an ice-cooled solution of DMF (43.4 ml, 0.55 mol) under N_2 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 Na_2SO_4 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). ^{1}H-Nmr ($CDCl_3$): δ 2.45(3H, s, SC<u>H</u>$_3$), 7.28(5H, s, C$_6$<u>H</u>$_5$), 7.37(1H, s, =C<u>H</u>-), 9.37(1H, s, C<u>H</u>O). Ms: *m/z* 178 (M^+). HRms calcd for $C_{10}H_{10}OS$ 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). ^{1}H-Nmr ($CDCl_3$): δ 2.49(3H, s, SC<u>H</u>$_3$), 7.33(5H, s, C$_6$<u>H</u>$_5$), 7.42(1H, s, =C<u>H</u>-). Ms: *m/z* 179 (M^+). HRms calcd for $C_{10}H_9DOS$ 179.0515, found 179.0510.

2-Methyl-3-phenylthioacrolein(3b). A solution of $POCl_3$ (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 pheny 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). ^{1}H-Nmr ($CDCl_3$): δ 1.83 (3H, s, C<u>H</u>$_3$), 7.02-7.51(6H, m, =C<u>H</u>- and C_6<u>H</u>$_5$), 9.01(1H, s, C<u>H</u>O). 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). ^{1}H-Nmr ($CDCl_3$): δ 2.43(3H, s, SC<u>H</u>$_3$), 7.38(5H, s, C_6<u>H</u>$_5$), 7.38(1H, s, =C<u>H</u>-). 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 separater. 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-phenylthio-acrolein (**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). ^{1}H-Nmr ($CDCl_3$): δ 3.93(3H, s, NC<u>H</u>$_3$), 7.26-7.64(5H, m, C_6<u>H</u>$_5$), 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-phenyl-acroleine-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). ^{1}H-Nmr ($CDCl_3$): δ 2.50(3H, s, C<u>H</u>$_3$), 3.84(3H, s, C<u>H</u>$_3$), 7.52(0.65H, s,

C_7-H), 8.00(1H, s, C_2-H), 8.41(0.35H, s, C_5-H). Ms: *m/z* 148 (M^+). HRms calcd for $C_8H_8DN_3$ 148.0859, found 148.0862.

REFERENCES

1. P. Barraclough, J. W. Black, D. Cambridge, D. Collard, D. Firmin, V. P. Gerskowitch, R. C. Glen, H. Giles, A. P. Hill, R. A. D. Hull, R. Iyer, W. R. King, C. O. Kneen, J. C. Lindon, M. S. Nobbs, P. Randall, G. P. Shah, S. Smith, S. J. Vine, M. V. Whiting, and J. M. Williams, *J. Med. Chem.*, **1990**, *33*, 2231 and related references cited therein.
2. N. B. Mantlo, P. K. Chakravarty, D. L. Ondeyka, P. K. S. Siegal, R. S. Chang, V. J. Lotti, K. A. Faust, T.-B. Chen, T. W. Schorn, C. S. Sweet, S. E. Emmert, A. A. Patchett, and W. J. Greenlee, *J. Med. Chem.*, **1991**, *34*, 2919 and related references cited therein.
3. E. Nicolai, J. Goyard, T. Benchetrit, J.-M. Teulon, F. Caussade, A. Virone, C. Delchambre, and A. Cloarec, *J. Med. Chem.*, **1993**, *36*, 1175.
4. (a) M. P. Singh, T. Joseph, S. Kumar, Y. Bathini, and J. W. Lown, *Chem. Res. Toxicol.*, **1992**, *5*, 597. (b) M. P. Singh, Y. Bathini, and J. W. Lown, *Heterocycles*, **1993**, *36*, 971 and related references cited therein.
5. (a) J. S. Felton, M. G. Knize, N. H. Shen, P. R. Lewis, B. D. Andresen, J. Happe, and F. T. Hatch, *Carcinogenesis*, **1986**, *7*, 1081. (b) M. G. Knize and J. S. Felton, *Heterocycles*, **1986**, *24*, 1815. (c) G. Becher, M. G. Knize, and J. S. Felton, in Risk Assessment of Cooked Food Mutagens; Reports from the Second Nordic Meeting, Uppsala, Sweden, October 1988, *Vår Föda Suppl. 2*, 1989, Vol. 42, pp. 85-90. (d) S. Lindström, T. Ahmad, and S. Grivas, *Heterocycles*, **1994**, *38*, 529. (e) K. Wakabayashi, M. Nagao, H. Esumi, and T. Sugimura, *Cancer Res. (Suppl.)*, **1992**, *52*, 2092s and related references cited therein.
6. J. A. Montgomery and J. A. Secrist III, in "Comprehensive Heterocyclic Chemistry", Ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, 1984, Vol. 5, pp. 635-639.
7. (a) I. Hayakawa, K. Yamazaki, R. Dohmori, and N. Koga, *Heterocycles*, **1978**, *10*, 241. (b) A. Bernardini, P. Viallefont, and R. Zniber, *J. Heterocycl. Chem.*, **1978**, *15*, 937. (c) N. Katagiri, A. Koshihara, S. Atsuumi, and T. Kato, *J. Org. Chem.*, **1982**, *47*, 167. (d) A. Albert and W. Pendergast, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1794. (e) A. H. M. Al-Shaar, R. K. Chambers, D. W. Gilmour, D. J. Lythgoe, I. McClenaghan, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2789. (f) T. Choshi, A. Tonari, H. Yoshioka, K. Harada, E. Sugino, and S. Hibino, *J. Org. Chem.*, **1993**, *58*, 7952.
8. M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Am. Chem. Soc.*, **1966**, *88*, 5747.
9. W. E. Parham, L. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, **1964**, *29*, 2211.
10. (a) S. Kano, Y. Yuasa, S. Shibuya, and S. Hibino, *Heterocycles*, **1982**, *19*, 1079. (b) S. Hibino, K. Nomi, Y. Shintani, E. Sugino, H. Fujioka, S. Kadowaki, and M. Otagiri, *Drug Design and Delivery*, **1989**, *5*, 49. (c) K. Harada, T. Choshi, E. Sugino, K. Sato, and S. Hibino, *Heterocycles*, **1994**, *38*, 1119.
11. A. H. M. Al-Shaar, D. W. Gilmour, D. J. Lythgoe, I. McClenaghan, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2779.

Received, 21st December, 1994