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ELECTROPHILIC REACTION OF *N*-LEWIS ACID AND *N*-OXIDE LEWIS ACID COMPLEXES OF 4-METHYLPYRIDINES AND THEIR *N*-OXIDES THROUGH BASE-INDUCED DEPROTONATION

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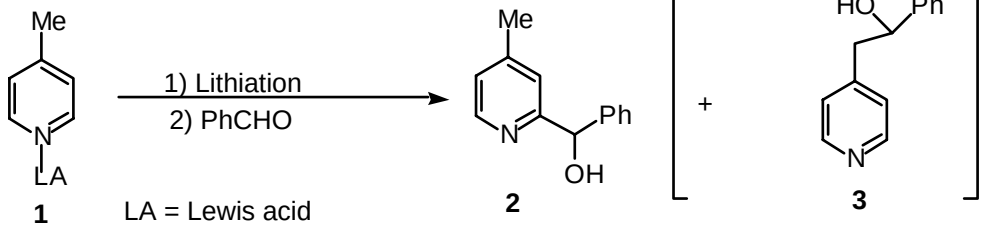
Abstract- The comparative studies were carried out on the relative reactivity of 4-methylpyridines, their *N*-oxides and their Lewis acid complexes towards electrophilic reaction. α-Deprotonation in pyridine ring rather than deprotonation of active methyl group or metal-halogen exchange occurred preferentially in the reaction of *N*- and *N*-oxides BF_3 complexes with electrophile in the presence of LTMP-TMEDA in THF to give α-substituted-4-methylpyridines and their *N*-oxides.

It has recently been reported that metalation of BF_3-pyridine complex with lithium tetramethylpiperidide(LTMP) in ether at -78 ℃, followed by reaction with carbonyl compounds, affords α-pyridyl alcohols in good yields.[1] We also showed that the reactivity order of pyridine, quinoline, isoquinoline, and their BF_3 complexes, their *N*-oxides, and their *N*-oxide-BF_3 complexes for electrophilic reaction through α-deprotonation is characterized according to the reaction substrate of pyridines, quinolines, and isoquinolines.[2] Thus, the concept of *N*- or *N*-O-Lewis acid complexes has become increasingly important in organic chemistry.[3] However, little is known about the effects of the complexes with other Lewis acids besides BF_3 for electrophilic reaction. In continuation of our work, in order to elucidate the influences of various types of other Lewis acids on lithiation, comparing with BF_3, we investigated the reaction of 4-methylpyridines and their *N*-oxide-Lewis acid complexes with electrophile in the presence of LTMP in THF at -78 ℃ to reveal the apparent difference of reactivity among Lewis acids for electrophilic reaction.

As for reaction solvent on which ethers for the reaction using Lewis acid are often employed, we chose THF as a optimal ether, judging from the result of the reaction[2] of 4-methylpyridine-BF_3 complex (**1**) with benzaldehyde in the presence of LTMP in 3 kinds of typical ethers at -78 ℃ to give only ［4-methyl(2-pyridyl)］phenylmethan-1-ol (**2**), also indicating that the addition of

N,*N*,*N*',*N*'-tetramethylethylenediamine(TMEDA) as a additive resulted in the better yield of α-pyridyl alcohol (Table 1).

Table 1 Solvent effect on the Yield of **2**



1 LA = Lewis acid **2** **3**

SM	LA	Solvent	Conditions	Yield (%) of **2**
1	BF_3	Et_2O	LTMP, -78 ℃, 1 h	15
1	BF_3	THF	LTMP, -78 ℃, 1 h	60
1	BF_3	THF	LTMP-TMEDA, -78 ℃, 1 h	78
1	BF_3	DME[a)]	LTMP, -78 ℃, 1 h	0

a) DME = 1,2-dimethoxyethane

Subsequently, using a variety of Lewis acids, the reaction of 4-methylpyridine-Lewis acid complex with benzaldehyde in Table 1 was performed in the presence of LTMP-TMEDA in THF at -78 ℃ to give **2** and 1-phenyl-2-(4-pyridyl)ethan-1-ol (**3)** (Table 2).

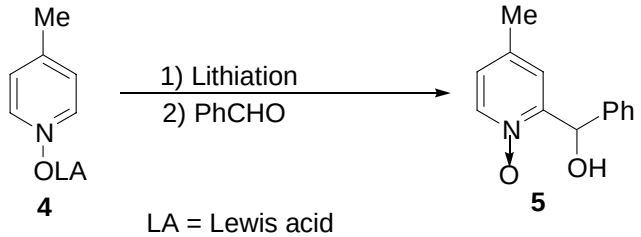
Table 2
Reaction of 4-methylpyridine *N*-LA complex **1** with PhCHO in the presence of base

SM	LA	Solvent	Conditions	Yield(%) of **2**	**3**
1	BF_3	THF	LTMP-TMEDA, -78 ℃, 1 h		0
1	$AlCl_3$	THF	LTMP-TMEDA, -78 ℃, 1 h	0	42
1	$SnCl_4$	THF	LTMP-TMEDA, -78 ℃, 1 h	0	trace
1	Ti(*i*-PrO)$_4$[a)]	THF	LTMP-TMEDA, -78 ℃, 1 h	0	34
1	TMSOTf[b)]	THF	LTMP-TMEDA, -78 ℃, 1 h	0	0
1	V(IV)O(acac)$_2$[c)]	THF	LTMP-TMEDA, -78 ℃, 1 h	0	0
1	Eu(fod)$_3$[d)]	THF	LTMP-TMEDA, -78 ℃, 1 h	0	61
1	Ti(IV)Cl_4	THF	LTMP-TMEDA, -78 ℃, 1 h	0	20

a) Ti(*i*-PrO)$_4$ = tetraisopropyl orthotitanate
b) TMSOTf = trifluoromethane sulfonic acid trimethylsilyl ester
c) V(IV)O(acac)$_2$ = vanadium(IV)oxy acetylacetonate
d) tris(heptafluorobutanoylpivaloylmethanato)europium

It is curious to note that α-deprotonation of pyridine ring occurred almost only in the case of 4-methylpyridine-BF_3 complex to give α-pyridyl alcohol (**2**) , whereas in the case of other complexes with Lewis acids besides BF_3 electrophilic reaction occurred preferentially on active methyl group to give **3**. It is also of interest to compare reactivity difference for electrophile among *N*-oxide-Lewis acid complexes. Thus, the reaction of 4-methylpyridine *N*-oxide-Lewis acid complex (**4**) with benzaldehyde gave rise to ［4-methyl-1-oxido(2-pyridyl)］phenylmethan-1-ol (**5**) (Table 3).

Table 3 Reaction of 4-methypyridine *N*-oxide-LA complex **4** with PhCHO in the presence of base



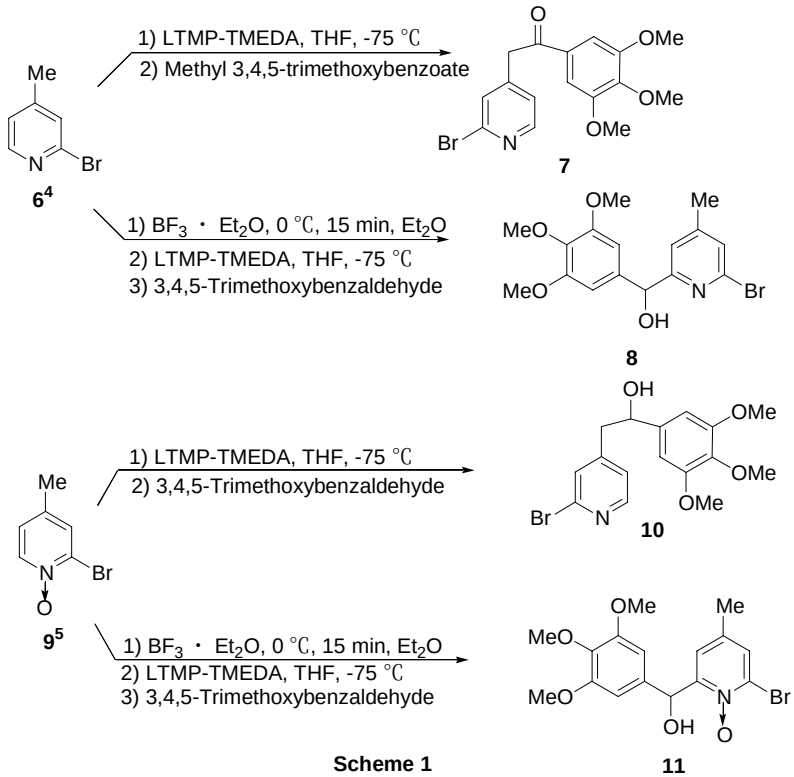
4 **5**

LA = Lewis acid

SM	LA	Solvent	Conditions	Yield (%) of **5**
4	BF_3	THF	LTMP-TMEDA, -78 ℃, 1 h	10
4	$AlCl_3$	THF	LTMP-TMEDA, -78 ℃, 1 h	20
4	Ti(*i*-PrO)$_4$	THF	LTMP-TMEDA, -78 ℃, 1 h	30
4	Eu(fod)$_3$	THF	LTMP-TMEDA, -78 ℃, 1 h	30

As can be seen from Table 3, it should be noted that in this reaction, Ti(*i*-PrO)$_4$ or Eu(fod)$_3$ as Lewis acid seem to be more appropriate than BF_3 to α-deprotonation albeit in low yields of the product on the whole.

On the basis of the results of aforementioned model reactions, in addition, to confirm the relative reactivity differences for lithiation, the electrophilic reaction of 2-bromo-4-methylpyridine (**6**), the *N*-oxide (**9**) and their BF_3 complexes which embody 3 possible reactive sites, namely, bromine atom for metal-halogen exchange reaction, methyl group and carbon atom at 2-position was carried out in the presence of LTMP-TMEDA using methyl 3,4,5-trimethoxybenzoate or more active electrophile, 3,4,5-trimethoxybenzaldehyde (Scheme 1).



6[4] **7** **8** **10** **9**[5] **11**

Scheme 1

As shown in Scheme 1, it was firmly established that electrophilic reaction for carbon atom at 2-position of pyridine ring in preference to active methyl group or bromine atom would be taken place by forming *N*- BF_3 or *N*-O-BF_3 complex, on the other hand without those complexes the deprotonation of active methyl group prevailed over other deprotonation or metal-halogen exchange reaction.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectral data were recorded in the following spectrometers: IR spectra, JASCO FT/IR-470Plus; ^{1}H-NMR spectra, JEOL GX-400 (400MHz) and JEOL A-500 (500MHz); ^{13}C-NMR spectra, JEOL GX-400 (100MHz) and JEOL A-500 (125MHz); MS spectra, Shimadzu GC-MS QP5050 for EI-MS and JMS-HX100 for FAB-MS. The H-COSY, DEPT and HMQC experiments were also used for the assignments of the structures. The chemical shifts are given in the δ scale. Elemental analyses were performed on a Yanaco CHN CORDER MT-6 instrument. Medium-pressure liquid chromatography (MPLC) was carried out with Yamazen 540 FMI-C pump and Wakogel FC-40 (20-40 μm, Wako). Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck). High-performance thin layer chromatography (HPTLC) for the yields shown Table 1 was conducted on Shimadzu high speed thin layer chromatoscanner (CS-9300PC) with the detector set at uv 254nm.

General procedure for electrophilic reaction of 4-methylpyridine-BF_3 complex with benzaldehyde at -78 ℃ in the presence of LTMP in a variety of ethers-----LMP solution was prepared by mixing of ether (15 mL), TMP (2.16 mL, 12.8 mmol) and 1.6M *n*-BuLi hexane solution (8.2 mL, 12.8 mmol) at 0 ℃ (in the case of LTMP-TMEDA, TMEDA (1.94 ml, 12.9 mmol) was further added) under nitrogen which was further stirred for 0.5 h at rt. To a solution of 4-methylpyridine (1.0 g, 10.7 mmol) and $BF_3 \cdot Et_2O$ (1.49 mL, 12.8 mmol) in ether (15 mL) which was stirred for 15 min at 0 ℃, LMP solution was added dropwise at -78 ℃ under nitrogen with stirring and after stirring for 1 h benzaldehyde (1.14 g, 10.7 mmol) was added to the reaction mixture which was further stirred for 1 h at -78 ℃. Then, the reaction was quenched at -78 ℃ with a solution of THF (10 mL) and H_2O (2 mL). The resulting solution was extracted with ether (100 mL) and after removal of the solvent the residue was purified by medium-pressure liquid chromatography (*n*-hexane:AcOEt = 5:1) to afford **2**. The yields of **2** were determined on a Shimadzu high speed thin layer chromatoscanner (CS-9300PC) with the detector set at UV 254nm.

General procedure for electrophilic reaction of 4-methylpyridine-Lewis acid complex with benzaldehyde at -78 ℃ in the presence of LTMP-TMEDA in THF-----Reaction was carried out as described in general procedure for electrophilic reaction of 4-methylpyridine-BF_3 complex with benzaldehyde at -78 ℃ in the presence of LTMP in a variety of ethers but using Lewis acid (11.8 mmol) shown in Table 2 instead of $BF_3 \cdot Et_2O$, THF as a solvent and LTMP-TMEDA instead of LTMP. The residue was purified by medium-pressure liquid chromatography to afford **2** (*n*-hexane:AcOEt = 5:1) and **3** (*n*-hexane:AcOEt = 1:1). The yields of **2** and **3** were determined on a Shimadzu high speed thin layer chromatoscanner (CS-9300PC) with the detector set at UV 254nm.

General procedure for electrophilic reaction of 4-methylpyridine *N*-oxide-Lewis acid complex with

benzaldehyde at -78 ℃ in the presence of LTMP-TMEDA in THF----- Reaction was carried out as described in general procedure for electrophilic reaction of 4-methylpyridine-Lewis acid complex with benzaldehyde at -78 ℃ in the presence of LTMP-TMEDA in THF but using 4-methylpyridine *N*-oxide (1.16 g, 10.7 mmol) instead of 4-methylpyridine and Lewis acid (11.8 mmol) shown in Table 3. The residue was purified by medium-pressure liquid chromatography ($CHCl_3$:MeOH = 3:1) to afford **5**. The yield of **5** was determined on a Shimadzu high speed thin layer chromatoscanner (CS-9300PC) with the detector set at UV 254nm.

2-［Bromo(4-pyridyl) ］-1-(3,4,5-trimethoxyphenyl)ethan-1-one (7)

Reaction was conducted as described in the previous paper.[2] The residue was purified by medium-pressure liquid chromatography (*n*-hexane:AcOEt = 3:1) to afford **7** (38% yield). mp 129-130 ℃(from Et_2O, colorless needles). IR(KBr): 1677, 1592, 1414, 1337, 1160, 1132, 1081, 893cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 3.91(6H, s, OCH_3), 3.93(3H, s, OCH_3), 4.22(2H, s, CH_2), 7.16(1H, d, H-5), 7.22(2H, s, H-2' and H-6'), 7.42(1H, s, H-3), 8.32(1H, d, H-6). ^{13}C-NMR($CDCl_3$): δ43.8(t, CH_2), 56.4(q, OCH_3), 61.0(q, OCH_3), 106.3(d, C-2'and C-6'), 124.0(d, C-5), 129.1(d, C-3), 131.1(s, C-1'), 142.5(s, C-4'), 143.5(s, C-2), 146.5(s, C-4), 150.1(d, C-6), 153.3(s, C-3'and C-5'), 193.8(s, C=O). MS(FAB^+): 336(M^++H).

2-Bromo-6-［hydroxy(3,4,5-trimethoxyphenyl)methyl］-4-methylpyridine (8)

Reaction was conducted as described in the previous paper.[2] The residue was purified by medium-pressure liquid chromatography (AcOEt) to afford **8** (19% yield). mp 132-134 ℃(from *n*-hexane-Et_2O, colorless prisms). *Anal*. Calcd for $C_{16}H_{18}NO_4Br$: C, 52.19; H, 4.93; N, 3.80. Found: C, 52.04; H, 4.96; N, 3.82. IR(KBr): 3476, 1595, 1449, 1421, 1325, 1232, 1122, 996cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 2.29(3H, s, CH_3), 3.83(3H, s, OCH_3), 3.84(6H, s, OCH_3), 4.39(1H, d, J= 4.4Hz, OH), 5.60(1H, d, J= 3.9Hz, C<u>H</u>OH), 6.61(2H, s, Ar-H), 6.93(1H, s, Ar-H), 7.23(1H, s, Ar-H). ^{13}C-NMR($CDCl_3$): δ20.8(q, CH_3), 56.2(q, OCH_3), 60.8(q, OCH_3), 75.1(d, CHOH), 104.3(s, Ar), 120.9(s, Ar), 127.5(s, Ar). MS(FAB^+): 369(M^++H).

2-Bromo-6-［hydroxy(3,4,5-trimethoxyphenyl)methyl］-4-methylpyridine 1-oxide (11)

Reaction was conducted as described in the previous paper.[2] The residue was purified by medium-pressure liquid chromatography (AcOEt) to afford **11** (28% yield). mp 172-173 ℃(from *n*-hexane-ethyl acetate, pale yellow prisms). *Anal*. Calcd for $C_{16}H_{18}NO_5Br$: C, 50.02; H, 4.72; N, 3.65. Found: C, 50.49; H, 4.50; N, 3.99. IR(KBr): 3220, 1590, 1501, 1460, 1420, 1326, 1231, 1223, 1131, 1005cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 2.28(3H, s, CH_3), 3.86(6H, s, OCH_3), 3.87(3H, s, OCH_3), 6.02(1H, s, Ar-H), 6.05(1H, d, J= 3.4Hz, Ar-H), 6.68(1H, d, J= 2.4Hz, Ar-H), 6.70(2H, s, Ar-H), 7.47(1H, d, J= 2.4Hz, Ar-H). ^{13}C-NMR($CDCl_3$): δ20.3(q, CH_3), 56.2(q, OCH_3), 60.9(q, OCH_3), 72.5(d, CHOH), 104.4(d, Ar), 124.6(d, Ar), 130.0(d, Ar), 133.0(s, Ar),133.9(s, Ar), 138.1(s, Ar), 138.5(s, Ar), 153.1(s, Ar), 153.7(s, Ar). MS(FAB^+): 386(M^++H).

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