PREPARATION OF STERICALLY MORE CROWDED 1,5-DISUBSTITUTED IMIDAZOLES BY THE REGIOSELECTIVE *N*-ALKYLATION†

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Abstract——4-Substituted 1-acetylimidazoles (**6**), which were derived from 4(5)-substituted imidazoles (**1**), were *N*-alkylated by the treatment with alkyl halides. During the work-up, the resulting *N*-alkylated products were easily hydrolyzed into 1,5-disubstituted imidazoles (**3**). These reactions were regarded to be the general method for the preparation of sterically more crowded 1,5-disubstituted imidazoles (**3**).

We have previously reported on products and reaction mechanisms of the ozonolysis of azoles,[1] such as pyrroles,[2] oxazoles[3] and imidazoles.[4] In the course of investigations, we required disubstituted imidazoles in order to clarify the reaction mechanisms of the ozonolysis of imidazoles.

Since 4(5)-substituted imidazoles (**1**) possess two possible nucleophilic sites in the molecule and isomerize from N-1 to N-3 by the rapid proton transfer, the direct alkylation of **1** with alkyl halides gives the mixture of 1,4- (**2**) and 1,5-disubstituted imidazoles (**3**) and 1,3,4-trisubstituted imidazolium salts (**4**). In order to depress

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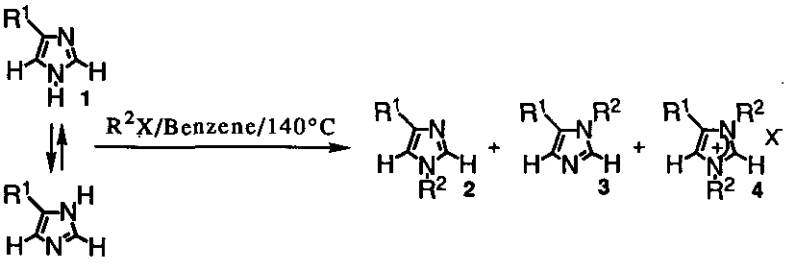
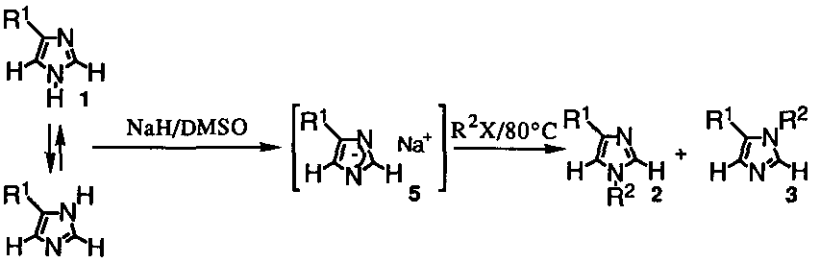
† This paper is dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday for his brilliant achievement in the field of heterocyclic chemistry.

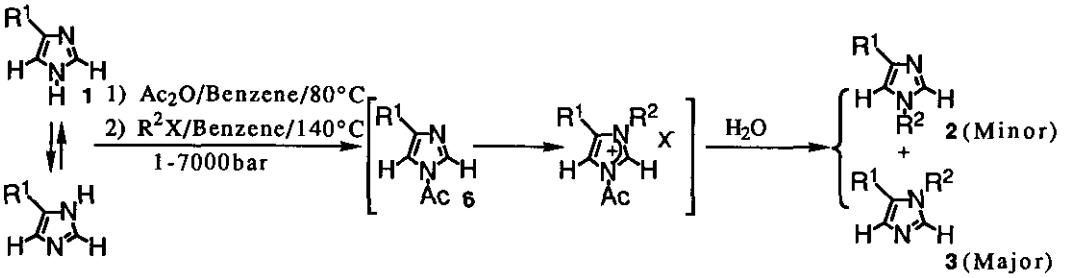
Method A (Direct Alkylation)



Method B (Alkylation under Basic Condition)



Method C



1	R^1
a	H
b	Me
c	Ph

2 - 3	R^1	R^2	2 - 3	R^1	R^2
a a	H	Me	b b	Me	Bu
a b	H	Bu	b c	Me	Bn
a c	H	Bn	c a	Ph	Me
b a	Me	Me	c b	Ph	Bu

the formation of **4**, the reaction of **1** with alkyl halides was performed under the strongly basic conditions. By the treatment with sodium hydride, **1** was deprotonated to give sodium salt (**5**), which was much reactive to electrophiles. As the results, the total yield of **2** and **3** was increased and the formation of **4** was successfully suppressed. For example, 1,4-dimethyl- (**2ba**) and 1,5-dimethylimidazole (**3ba**) were obtained in roughly 1:1 ratio by the treatment of 4-methylimidazole (**1b**) with methyl iodide using sodium hydride, summarized in Table. However, any effective method of the regioselective *N*-alkylation of 4(5)-substituted imidazoles (**1**) has never been reported in the literature.

Table Total Yield and Product Ratio of 1,4- (**2**) and 1,5-Disubstituted Imidazoles (**3**)

Substrate		Halide	Method A		Method B		Method C		Method D	
	R^1	R^2X	Yield[a] (%)	Ratio[b] (**2** : **3**)	Yield[a] (%)	Ratio[b] (**2** : **3**)	Yield[a] (%)	Ratio[b] (**2** : **3**)	Yield[a] (%)	Ratio[b] (**2** : **3**)
1a	H	MeI	21	—:—	51	—:—	64	—:—		
1a	H	BuBr	37	—:—	55	—:—	42	—:—		
1a	H	BnBr	33	—:—	56	—:—	63	—:—		
1b	Me	MeI	28	52:48	31	55:45	52	14:86	50	10:90
1b	Me	BuBr	30	76:24	62	52:48	41	18:82		
1b	Me	BnBr	34	76:24	38	58:42	33	22:78		
1c	Ph	MeI	46	89:11	75	93:7	86	7:93	76	1:99
1c	Ph	BuBr	52	78:22	97	99:1			31	0:100

a Isolated yield by distillation or column chromatography.

b The isomer ratio was determined by nmr or glc.

It has been extensively reported that imidazole is acylated with various acylating agents to 1-acylimidazole, which reacts easily with various nucleophiles such as water, alcohols and amines to afford the corresponding carboxylic derivatives as well as the original imidazole.[5] Moreover, the *N*-alkylation of 1-acylimidazole was reported to increase their reactivity toward the nucleophiles.[6] These facts gave us a hint that the acyl group would act as a protecting group in the alkylation of imidazoles.

When **1b** was treated with acetic anhydride in the presence of triethylamine, 1-acetyl-4-methylimidazole (**6b**) was exclusively obtained without any contamination of 1-acetyl-5-methylimidazole (**7b**). Similarly, 1-pivaloyl-4-methylimidazole (**8b**) was obtained regioselectively by the reaction of **1b** with pivaloyl chloride. These facts suggested that the less hindered nitrogen atom on imidazole ring was regioselectively acylated and resultantly protected forward alkylation.

The isomerically pure 1-acetylimidazoles (**6**) were directly alkylated by the treatment with alkyl halides. By the usual work-up, the acyl group was subsequently hydrolyzed to afford 1,5-dialkylimidazoles (**3**) in good yields. Actually, by the methylation of 1-acetyl-4-methylimidazole (**6b**) with methyl iodide and the subsequent hydrolysis as the usual work-up, 1,5-dimethylimidazole (**3ba**) was obtained with a small contamination of 1,4-dimethylimidazole (**2ba**). Even under the forced conditions of high pressure over 7 kbar, the alkylation in the presence of acetic anhydride proceeded without any formation of 1,3-dialkylimidazolium salt (**4**). Similarly, 1,5-disubstituted imidazoles (**3**) were prepared by the treatment of various 4(5)-substituted imidazoles (**1**) with some alkyl halides summarized in Table.

After all, the regioselective *N*-protection of 4(5)-substituted imidazoles (**1**) using acetyl chloride or acetic anhydride followed by *N'*-alkylation with alkyl halides was concluded to be the general method for the preparation of sterically more crowded 1,5-disubstituted imidazoles (**3**).

EXPERIMENTAL

Melting points were measured on Yanagimoto MicroMelting Point Apparatus, and uncorrected. Ir spectra were measured on a Shimadzu IR-460 spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were recorded by JEOL JNM-PMX 60SI (60 MHz) and JEOL JNM-EX270 (270 MHz) spectrometers using TMS as an internal standard. Gas chromatography was performed on a Shimadzu GC-4CM Gas Chromatograph using SE-30 column (2 m). Mass spectra were recorded on a Shimadzu QP-2000 spectrometer ionizing by electron beam.

General Procedure:

Method A. A mixture of **1** (10 mmol) and alkyl halide (10 mmol) in benzene (5 ml) was placed in a sealed tube, and heated overnight at 140°C. After the reaction mixture was quenched with water, the aqueous solution was extracted with dichloromethane under basic conditions. The extract was dried over anhydrous magnesium sulfate and concentrated. The crude product was purified by distillation under reduced pressure by Kugelrohr to yield the isomeric mixture of *N*-substituted imidazoles (**2** and **3**). (In the case of **1b**, the separation between **2** and **3** was failed by chromatography or distillation) The isomer ratio (**2**:**3**) was evaluated by the nmr peak intensities of imidazole ring protons at C-4 and C-5. In the reaction of **1c**, the products (**2** and **3**) were isolated by column chromatography on silica gel with $CHCl_3$-acetone-MeOH mixture and the isomer ratio was evaluated by glc.

Method B. A mixture of sodium hydride (300 mg, 12 mmol) and **1** (13 mmol) in DMSO (6 ml) was stirred at 80°C for 2 h. To this mixture was added alkyl halide (10 mmol), and the resulting solution was allowed to heat overnight at 80°C. The reaction mixture was worked up as described above.

Method C. The mixture of acetic anhydride (1 g, 10 mmol) and **1** (4 mmol) in benzene (3 ml) was heated for 1.5 h at 80°C. After addition of alkyl halides (10 mmol) in benzene (3 ml), heating was continued overnight at 140°C in sealed tube. The reaction mixture was worked up as described above.

Method D. The mixture of acetic anhydride (1.3 g, 13 mmol), **1** (10 mmol), and alkyl halides (15 mmol) in acetonitrile (2 ml) was heated in the high pressure reactor for 18 h at 80°C under 7000 bar.

1,4-Dimethylimidazole (2ba) and 1,5-dimethylimidazole (3ba): bp 130°C/5 mmHg.

1,4-Dimethylimidazole (**2ba**): ^{1}H-Nmr ($CDCl_3$): δ= 7.26 (s, 1H, CH), 6.57 (d, 1H, J=0.7 Hz, CH), 3.57 (s, 3H, CH_3), 2.17 (q, 3H, J=0.7 Hz, CH_3); ms: m/z= 96 (M^+, 100), 81 (12), 68 (28), 54 (25), 42 (70).

1,5-Dimethylimidazole (**3ba**): ^{1}H-Nmr ($CDCl_3$): δ= 7.32 (s, 1H, CH), 6.72 (d, 1H, J=1.0 Hz, CH), 3.49 (s, 3H, CH_3), 2.17 (q, 3H, J=1.0 Hz, CH_3); ms: m/z= 96 (M^+, 100), 81 (12), 68 (28), 56 (28), 54 (30), 42 (59).

1-Butyl-4-methylimidazole (2bb) and 1-butyl-5-methylimidazole (3bb): bp 135°C/6 mmHg.

1-Butyl-4-methylimidazole (**2bb**): ^{1}H-Nmr ($CDCl_3$): δ= 7.22 (s, 1H, CH), 6.50 (s, 1H, CH), 3.77 (t, 2H, J=8 Hz, CH_2), 2.17 (s, 3H, CH_3), 2.00-1.10 (m, 4H, CH_2), 0.97 (t, 3H, J=8 Hz, CH_3); ms: m/z= 138 (M^+, 40), 97 (78), 95 (68), 69 (100), 54 (36).

1-Butyl-5-methylimidazole (**3bb**): ^{1}H-nmr ($CDCl_3$): δ= 7.22 (s, 1H, CH), 6.63 (s, 1H, CH), 3.77 (t, 2H, J=8 Hz, CH_2), 2.17 (s, 3H, CH_3), 2.00-1.10 (m, 4H, CH_2), 0.97 (t, 3H, J=8 Hz, CH_3); ms: m/z= 138 (M^+, 51), 104 (21), 96 (100), 95 (93), 69 (75).

1-Benzyl-4-methylimidazole (2bc) and 1-benzyl-5-methylimidazole (3bc): bp 200°C/4 mmHg.

1-Benzyl-4-methylimidazole (**2bc**): ^{1}H-Nmr ($CDCl_3$): δ= 6.80-7.43 (m, 6H, Ph and CH), 6.47 (s, 1H, CH), 4.95 (s, 2H, CH_2), 2.17 (s, 3H, CH_3).

1-Benzyl-5-methylimidazole (**3bc**): ^{1}H-nmr ($CDCl_3$): δ= 6.80-7.43 (m, 6H, Ph and CH), 6.74 (s, 1H, CH), 4.95 (s, 2H, CH_2), 2.07 (s, 3H, CH_3).

1-Methyl-4-phenylimidazole (2ca):

mp 109-110°C (from hexane-benzene mixture); ^{1}H-nmr ($CDCl_3$): δ=7.60-7.80 (m, 2H, Ph), 7.10-7.50 (m, 4H, CH and Ph), 7.08 (d, 1H, J=1.5 Hz, CH), 3.58 (s, 3H, CH_3); ^{13}C-nmr ($CDCl_3$): δ= 142.2 (C), 137.9 (CH), 134.3 (C), 128.5 (CH), 126.6 (CH), 124.7 (CH),

115.9 (CH), 33.3 (CH_3); ms: m/z= 158 (M^+, 100), 130 (13), 117 (20), 116 (45), 89 (30), 63 (16), 51 (11), 42 (18). Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.92; H, 6.44; N, 17.66.

1-Methyl-5-phenylimidazole (3ca):

mp 96-97°C (from hexane-benzene mixture); ^{1}H-nmr ($CDCl_3$): δ=7.50 (, 1H, CH), 7.39 (s, 5H, Ph), 7.09 (d, 1H, J=1.0 Hz, CH), 3.65 (s, 3H, CH_3); ^{13}C-nmr ($CDCl_3$): δ= 128.7 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 32.5 (CH_3); ms: m/z= 158 (M^+, 100), 130 (21), 118 (12), 117 (14), 116 (18), 103 (22), 90 (15), 89 (24), 77 (22), 63 (14), 55 (21), 51 (14), 42 (14). Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.94; H, 6.40; N, 17.58.

1-Butyl-4-phenylimidazole (2cb):

bp 265-270°C/5 mmHg ; ^{1}H-nmr ($CDCl_3$): δ=7.77 (d, 2H, J=8.2 Hz, Ph), 7.46 (d, 1H, J=1.0 Hz, CH), 7.15-7.35 (m, 3H, Ph), 7.17 (d, 1H, J=1.3 Hz, CH), 3.89 (t, 2H, J=7.0 Hz, CH_2), 1.75 (quint, 2H, J=7.3 Hz, CH_2), 1.33 (sex, 2H, J=7.6 Hz, CH_2), 0.93 (t, 3H, J=7.3 Hz, CH_3); ^{13}C-nmr ($CDCl_3$): δ= 142.0 (C), 137.1 (CH), 134.2 (C), 128.4 (CH), 126.5 (CH), 124.6 (CH), 114.5 (CH), 46.8 (CH_2), 32.9 (CH_2), 19.6 (CH_2), 13.4 (CH_3); ms: m/z=201 (M^+, 17), 200 (100), 158 (41), 157 (37), 131 (24), 130 (33), 117 (21), 103 (43), 97 (44), 90 (20), 89 (36), 82 (28), 77 (20), 63 (20), 51 (15), 42 (22), 41 (59). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.72; H, 8.16; N, 13.96.

1-Butyl-5-phenylimidazole (3cb):

bp 250-260°C/8 mmHg ; ^{1}H-nmr ($CDCl_3$): δ=7.55 (d, 1H, J=1.0 Hz, CH), 7.20-7.50 (m, 5H, Ph), 7.05 (d, 1H, J=1.3 Hz, CH), 3.96 (t, 2H, J=7.2 Hz, CH_2), 1.61 (quint, 2H, J=7.3 Hz, CH_2), 1.23 (sex, 2H, J=7.6 Hz, CH_2), 0.83 (t, 3H, J=7.2 Hz, CH_3); ^{13}C-nmr ($CDCl_3$): δ=138.1 (CH), 133.0 (C), 130.3 (C), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 45.1 (CH_2), 32.9 (CH_2), 19.7 (CH_2), 13.4 (CH_3); ms: m/z=201 (M^+, 16), 200 (100), 158 (48), 157 (82), 144 (21), 131 (17), 130 (18), 117 (19), 104 (19), 103 (47), 90 (15), 89 (30), 77 (19), 63 (15), 51 (13), 41 (45). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.87; H, 8.09; N, 14.02.

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