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PREPARATION OF SYNTHETICALLY USEFUL 2-ACYL-1H-IMIDAZOLES BY AN AUTOOXIDATION OF 1H-IMIDAZOLYL-2-METHANOL DERIVATIVES

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Abstract —— 1-Methyl-1H-imidazolyl-2-methanol derivatives (4) were autooxidized in a reaction medium consisting of air, sodium hydride, pyrazole and tetrahydrofuran to give the corresponding 2-acyl-1-methyl-1H-imidazoles (1) in good yields.

Although importance of 1-acylimidazoles in the organic synthesis has been introduced by Staab,[1] 2-acylimidazoles (1) have been little studied in regard to synthesis of them or their synthetic applications. We previously reported a superior leaving ability of 2-(1,3-dimethyl-1H-imidazolium) moiety and syntheses of various carbonyl compounds starting from the 2-acylimidazoles (1) by application of the property as illustrated in Chart 1.[2]

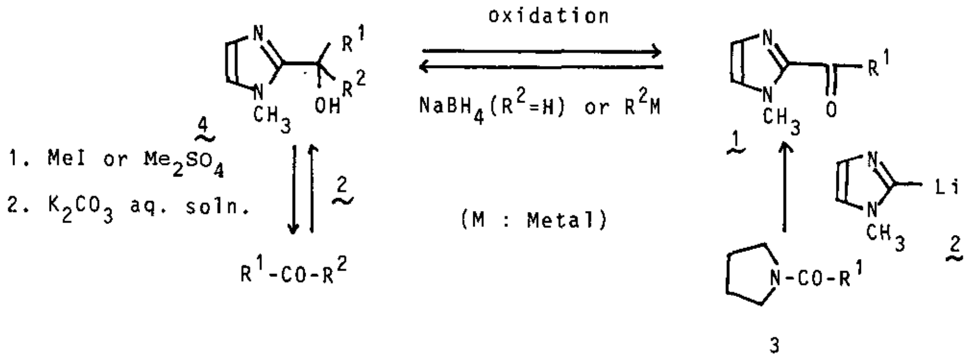
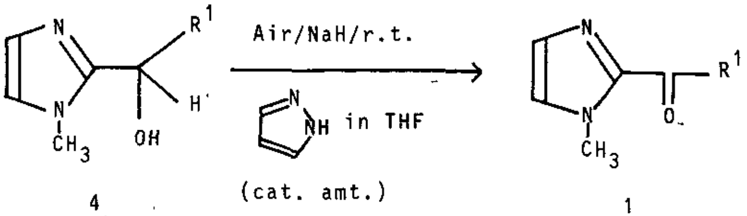


Chart 1

The 2-acylimidazoles (1) have been hitherto prepared by acylation of 2-lithio-1-methyl-1H-imidazole (2) with pyrrolidine amides (3).[3] We wish to report here an alternative procedure for synthesis of 1 based on oxidation of 2-(secondaryhydroxyalkyl)-1-methyl-1H-imidazoles (4). The alcohols (4) were easily prepared by treatment of 2 with aldehydes or by Grignard reaction of 2-formyl-1-methyl-1H-imidazole (5).[4] Of course, reduction of 1 with sodium borohydride also afforded the corresponding secondary alcohol (4) in high yield. Since the reaction of 2 with aldehydes proceeds in almost quantitative yields, the short route for the preparation of 1 including oxidation of 4 may give some benefit, especially, when aldehydes are easily available. First, pyridinium chlorochromate (PCC) oxidation[5] was examined for a conversion of 4a (R^1 = 3,4-methylenedioxyphenyl) into the corresponding ketone (1a). The ketonic product (1a) was obtained in 84% yield after repeated extractions from a gelatinous alkaline layer containing chromium hydroxide. However, the PCC oxidation resulted in poor yields in the cases of other alcohols (4). Moffatt[6] and Swern[7] oxidation procedures also gave poor results, probably because of the steric hindrance around the hydroxy group due to presence of the 1-methyl group of the imidazole ring. Recently, we reported a convenient autooxidation procedure for benzylic alcohols, which used a basic medium at room temperature consisting of air, sodium hydride, a catalytic amount of pyrazole and tetrahydrofuran (as a solvent).[8] When the autooxidation procedure was applied to 4d (R^1 = 2,6-dimethylhept-5-enyl), the reaction proceeded smoothly to give the corresponding 2-acylimidazole (1d) in an almost quantitative yield whithin 5 - 10 hours.

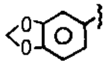
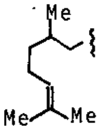


4 1

Chart 2

As shown in Table I, the present autooxidation procedure was successfully applied for preparation of various 2-acylimidazoles (1). Although we had prepared 1d starting from citronellal with a four-steps of reaction (oxidation of citronellal with Ag_2O; esterification; formation of pyrrolidine amide; acylation of 2 with the

Table I. Oxidation of 1H-Imidazolyl-2-methanol Derivatives to 2-Acyl-1H-imidazoles

Entry	R^1 of 1 and 4 (R^2 = H)	Oxidant (Reaction Time)	mp or bp[a)] of 1 (Recryst. Solv.)	Yield of 1 (Isolated)
1	a : 	PCC (1 h)	1a[b)]: mp 105-107 °C (CCl$_4$)	84.3%
2		autooxidation (1.5 h)	1a[b)]: mp 105-107 °C (CCl$_4$)	87.4%
3	b : n-hexyl	PCC (1 h)	1b[b)]: bp$_3$ 118-120 °C	trace
4	b : n-hexyl	autooxidation (15 h)	1b[b)]: bp$_3$ 118-120 °C	53.6%
5	c : indol-3-yl	autooxidation (4 h)	1c[c)]: mp 229-230 °C (ethyl acetate)	94.2%
6	d : 	PCC (1 h)	1d[b)]: bp$_1$ 119-120 °C	trace
7		autooxidation (10 h)	1d[b)]: bp$_1$ 119-122 °C	83.2%
8	e : Z-heptadec-8-enyl	autooxidation (2 h)	1e[c)]: viscous material	86.2%
9	f : cyclohexyl	autooxidation (2 h)	1f[b)]: mp 44.5-45.0 °C (-) bp$_3$ 112-116 °C	84.9%

a) Temperature of Kugel-Rohr Distillation
b) Known Compound (see reference 3c)
c) New Compound

amide), we can now prepared 1d with a two steps of reaction (citronellal → 4d → 1d). A total synthesis of perezone (6),[8] a constituent of *Peresia adnata Gr.*, starting from 1d is in progress and will be reported elswhere in the near future. When a tertiary alcohol, 2-diphenylhydroxymethyl-1-methyl-1H-imidazole, was subjected to the similar autooxidation condition, the alcohol was rapidly consumed. Benzophenone was only transitorily appeared on a TLC at the initial stage of the reaction. In that case, benzophenone might be further oxidized, and the reaction course of tertiary alcohols is now under investigation.

EXPERIMENTAL

2-(3,7-Dimethyloct-6-enoyl)-1-methyl-1H-imidazole (1d) : A mixture consisting of 2-(1-hydroxy-3,7-dimethyloct-6-enyl)-1-methyl-1H-imidazole (4d, 472 mg, 2 mmol), pyrazole (82 mg, 1 mmol), sodium hydride (240 mg, 10 mmol) and tetrahydrofuran (18 ml) was stirred for 4 h at room temperature under dry aerial atmosphere. Consumption of the starting material was checked by TLC. Water (3 ml) was added to the reaction mixture under N_2 atmosphere with ice-cooling and the whole was weakly acidified to pH 3 with 10% HCl. Ethyl acetate was added to the mixture and the aqueous layer was basified with solid K_2CO_3. The separated oily material was extracted with ethyl acetate. The organic layer was dried with sodium sulfate and evaporated under a reduced pressure to give an oily residue, which was distilled *in vacuo*. Colorless oil, bp 147 - 153 ℃ (3 mmHg) [lit. bp 119 - 122 ℃ (1 mmHg)].[2] Yield, 389 mg (83.2 %). The product was identified on the basis of comparisons of ir and TLC with those of an authentic sample.[1] Ir ($CHCl_3$) : 1680 cm^{-1}. TLC (ethyl acetate) : Rf = 0.60.

Z-2-(Octadec-9-enoyl)-1-methyl-1*H*-imidazole (1e) : A mixture consisting of Z-2-(1-hydroxyoctadec-9-enyl)-1-methyl-1*H*-imidazole (**4e**, 696 mg, 2 mmol), preparation of which is described later, pyrazole (82 mg, 1.2 mmol), sodium hydride (240 mg, 10 mmol) and tetrahydrofuran (18 ml) was treated by the similar manner as described in the preparation of **1d**. The crude oily product was purified by a preparative thin-layer chromatography on silica gel (solvent, ether : *n*-hexane = 1 : 1 in volume). Bp 220 ℃ (2 mmHg). Yield, 597 mg (86.2 %). Ir ($CHCl_3$) : 1680 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ : 0.86 (t, 3H, $C\underline{H}_3CH_2$-, *J* = 5 Hz), 1.00 ~ 2.30 (m, 26H, $CH_3(C\underline{H}_2)_7CH{=}CH(C\underline{H}_2)_6$-), 3.11 (t, 2H, -$C\underline{H}_2CO$-, *J* = 7 Hz), 3.99 (s, 3H, $C\underline{H}_3N$), 5.34 (t-like, 2H, -C$\underline{H}$=C$\underline{H}$-, *J* = 5 Hz), 7.00 - 7.11 (d each, 1H each, imidazole H, *J* ≐ 1 Hz each). High-resolution MS Calcd. for $C_{22}H_{38}N_2O$: 346.2981. Found : 346.2975. TLC (ethyl acetate) : Rf = 0.58.

2-(3-Indolylcarbonyl)-1-methyl-1*H*-imidazole (1c) : A mixture consisting of 2-[hydroxy-(3-indolylmethyl)]-1-methyl-1*H*-imidazole (**4c**, 454 mg, 2 mmol), preparation of which is described later, pyrazole (82 mg, 1 mmol), sodium hydride (240 mg, 10 mmol) and tetrahydrofuran (8 ml) was treated by the similar manner as described in the preparation of **1d**. Crude product was recrystallized from ethyl acetate to form colorless needles, mp 229 - 230 ℃. Yield, 424 mg (94.2 %). Ir (KBr) : 1680 cm^{-1}. ^{1}H-Nmr (DMSO-*d*$_6$) δ : 4.02 (s, 3H, $NC\underline{H}_3$), 8.94 (d, 1H, 2-position of indole ring), 11.90

(br, 1H, -NH), 7.10 ~ 7.60 and 8.20 ~ 8.40 (m each, 6H, other aromatic protons). *Anal*. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 68.86; H, 4.84; N, 18.18.

The 2-acylimidazoles (**1a**, **1b**, **1d** and **1f**) are known compounds[3] and also could be prepared by the similar manner as described in the synthesis of **1d**.

2-(3,4-Methylenedioxybenzoyl)-1-methyl-1*H*-imidazole (1a) : 2-[Hydroxy-(3,4-methylenedioxyphenyl)methyl]-1-methyl-1*H*-imidazole[2b] (**4a**, 464 mg, 2 mmol) was dissolved in CH_2Cl_2 (10 ml), and PCC (860 mg, 4 mmol) was added to the solution. The reaction mixture was stirred for 1 h. Ether (25 ml) was added, and then the solution was passed through a Florisil column with ether. The solvent of the eluent was evaporated under a reduced pressure to give a crystalline product. Otherwise a deposit remained in the reaction flask was dissolved in 10% NaOH and the mixture was extracted with ethyl acetate. The organic layer was dried with sodium sulfate and evaporated under a reduced pressure to give a crystalline residue, which was purified with a silica gel column chromatography. The combined product was recrystallized from carbon tetrachloride. The product was identical to the reported specimen.[3c]

Z-2-(1-Hydroxyoctadec-9-enyl)-1-methyl-1*H*-imidazole (4e) : Sodium borohydride (380 mg, 10 mmol) was added to a methanolic solution (10 ml) of **1e** (1.73 g, 5 mmol), which was prepared from stearic acid pyrrolidine amide by the reported procedure.[3] Methanol was evaporated after being stirred for 1 h at room temperature. A solution of the residue in 10% HCl (20 ml) was washed with ether and the aqueous layer was basified with solid K_2CO_3 to separate an oily material, which was extracted with ethyl acetate. The ethyl acetate layer was dried with sodium sulfate and evaporated. An analytical sample was obtained as an oil by a preparative thin-layer chromatography. Yield, 1.51 g (86.8 %). Ir ($CHCl_3$) : 3220 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ : 0.88 (t, 3H, CH_3CH_2, J=5 Hz), 1.05 ~ 1.65 (m, 24H, $CH_3(CH_2)_6CH_2CH{=}CHCH_2(CH_2)_6$-), 1.65 ~ 2.25 (m, 4H, allylic protons), 2.80 (s, 1H, -OH), 3.65 (s, 3H, NCH_3), 4.65 (t, 1H, -CH(OH)-, J = 6 Hz), 5.30 (t-like, 2H, -CH=CH-, J = 4 Hz), 6.75 and 6.90 (d each, 1H each, imidazole H, J = 1 Hz each). High Resolution MS : Calcd for $C_{22}H_{40}N_2O$

: 348.3139. Found : 348.3138.

2-[Hydroxy(3-indolyl)methyl]-1-methyl-1H-imidazole (4d) : n-Butyllithium (1.6M in n-hexane, 6.3 ml, 10 mmol) was added to a stirred solution of 1-methyl-1H-imidazole (821 mg, 10 mmol) in tetrahydrofuran (20 ml) at -78 ℃, and the mixture was stirred for 10 min. Indol-3-carboxaldehyde (1.45 g, 10 mmol) was added to the mixture and the whole was stirred for 30 min with removal of the cooling bath. Ether (20 ml) and 10% HCl were added to the mixture. The aqueous layer was washed with ether and basified with solid K_2CO_3 to precipitate a crystalline material, which was filtered, washed with water and dried. The crude product was recrystallized from ethanol to form colorless leaflets, mp 192 - 194 ℃. Yield, 1.43 g (63.2 %). Ir (KBr) : 3250 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ : 3.49 (s, 3H, NCH_3), 5.87 (d, 1H, -OH, J = 5 Hz), 6.13 (d, 1H, -CH(OH)-, J = 4 Hz), 6.65 ~ 7.40 (m, 7H, other aromatic protons), 10.93 (br, 1H, NH). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found : C, 68.61; H, 5.72; N, 18.30.

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