SYNTHESIS OF 2-ACYL-1-METHYL-1H-IMIDAZOLES AND REACTIVITY OF THE ACYL GROUP

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Abstract ——— 2-Alkanoyl- and 2-aroyl-1-methyl-1H-imidazoles (3) were prepared in good yields by treating 1-acylpyrrolidine (1) with 2-lithio-1-methyl-1H-imidazole (2) at -78°C. Although 2-benzoyl-1-methyl-1H-imidazole (3a) was stable under n-Pr-NH_2/80°C/10h; 2% K_2CO_3/aq. CH_3OH/80°C /10h; 20% H_2SO_4/80°C/10h; CF_3COOH/r.t./17h, it was hydrolysed into benzoic acid and 1-methyl-1H-imidazole by heating in 1.3N-NaOH - aq. ethanol at 80°C for 30h. The acyl group of 3 was activated by conversion to the corresponding imidazolium salt (4), which could react with various nucleophiles.

In view of chemotherapy, recently imidazole compounds have attracted many synthetic chemists and medical scientists, and especially the compounds have been important as anti-eubacterial agent[1]. For examining biological activities, many 2-aroyl-1H-imidazoles (3, R=Ar) have been synthesized by treating 1H-imidazole or 1-alkyl-1H-imidazole with aroyl chloride in the presence of organic base[2]. However, under the reaction condition 2-alkanoylimidazoles were not obtained at all probably because proton attraction by the base from an intermediate (5) occurred at α-position of the alkanoyl group rather than 2-position of the imidazole, and this may be one of the reason for the rare preparations of 2-alkanoylimidazoles in the literatures[2].

Curtis[2d] reported syntheses of 1-alkyl-2-formyl- and 2-acetyl-1-alkyl-1H-imidazole by treating 1-alkyl-2-lithio-1H-imidazole (2) with dimethylformamide and dimethylacetamide, respectively. Therefore, the authors wished to apply the procedure to higher alkanoyl homologues. Thus, various pyrrolidine amides (1) were prepared by usual manners, and they were reacted with 2 at -78°C in THF to give the

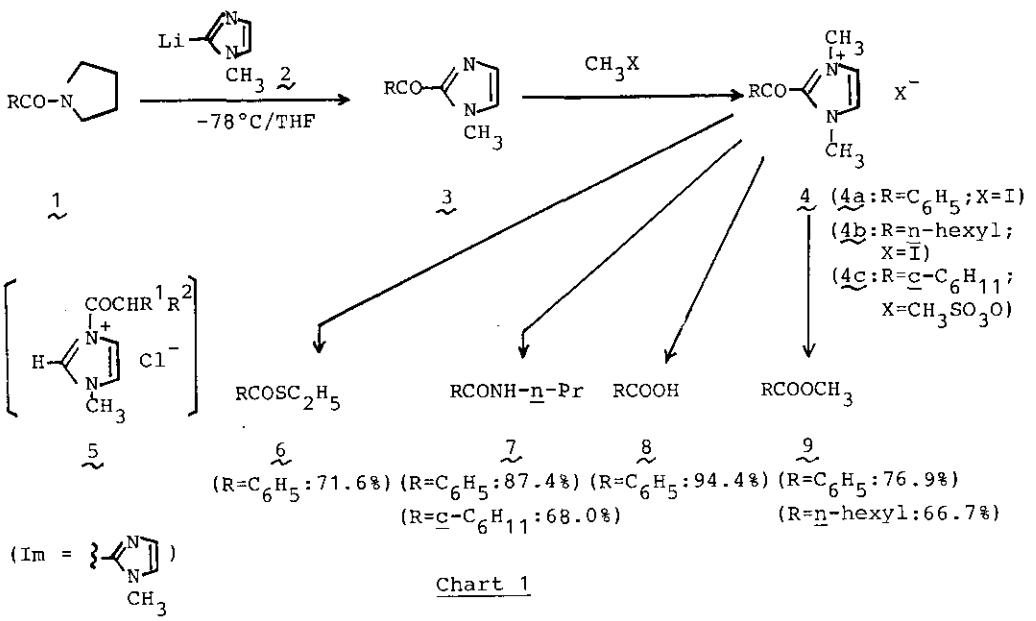
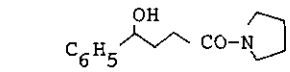
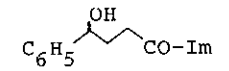
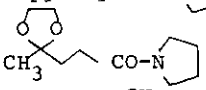
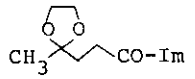
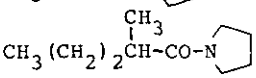
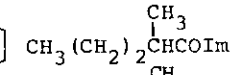
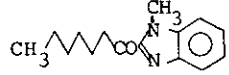
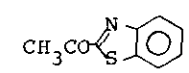


Chart 1

Table 1. Preparation of 2-Acyl-1-methyl-1H-imidazoles

t-Amide	Product		mp or bp/mmHg[a]	Yield (%)[b]
C_6H_5CO-N	C_6H_5-Im	3a	bp 140 - 145°C/3	quant.
$CH_3(CH_2)_5CO$-N	$CH_3(CH_2)_5CO$-Im	3b	bp 118 - 120°C/3	quant.
c-$C_6H_{11}CO$-N	c-$C_6H_{11}CO$-Im	3c	bp 112 - 114°C/3	quant.
$C_6H_5CH=CHCO$-N	$C_6H_5CH=CHCO$-Im	3d	mp 120 - 121°C	61.9
piperonyl-N	piperonyl-Im	3e	mp 105 - 107°C	quant.
		3f	mp 102 - 104.5°C	86.3
4-pyridyl-CO-N	4-pyridyl-CO-Im	3g	mp 66 - 68°C	83.7
		3h	bp 110 - 115°C/1	79.1
		3i	bp 125 - 128°C/3	88.6
$CH_3(CH_2)_5CO$-N		10[c]	mp 39 - 40°C	57.0
dimethylacetamide		11[d]	mp 108 - 111°	quant.

a: Kugel-Rohr distillation b: Isolated yield c: 2-Lithio-1-methylbenzimidazole was used for 2. d: 2-Lithiobenzthiazole was used for 2.

corresponding 2-acylimidazoles (3) in satisfying yields without formation of any by-product (Chart 1, Table 1).

In the previous communication[3a], the authors described the reactivity of 3 very briefly, thus we wish to report here more details. Reactivity of the acyl group of the 2-acyl-1H-imidazole (3) was examined using 3a (R=C_6H_5) as a sample. Although the compound (3a) was almost recovered under the following conditions: n-propylamine (as a solvent)/80°C/10h; 2% K_2CO_3/aq. CH_3OH/80°C/10h; 20% H_2SO_4/80°C/10h; CF_3COOH (as a solvent)/r.t./17h, in the case of heating in ethanolic 1.3N-NaOH solution at 80°C for 30h the starting material (3a) was almost consumed and from the reaction mixture benzoic acid (87.1%) was isolated accompanying the counterpart 1-methyl-1H-imidazole (89.1% by GLC analysis; 58.9% after isolation). Namely, their productions from 3a indicated that the compound was cleaved by hydrolysis, therefore the 2-acyl group revealed some property as carboxylic acid derivative as well as aromatic ketone.

Kamijo reported the activation of 1-acylimidazole by conversion to the corresponding imidazolium salt[4]. But quantitative conversion of the 2-acylimidazoles (3) to the quaternary salts by treating with methyliodide or benzyl bromide in refluxing ethyl acetate was difficult. The methiodides (4a: R=C_6H_5 and 4b: R=n-hexyl) were firstly prepared by heating respective ethyl acetate solution of 3a and 3b in a sealed tube at 100°C in the presence of excess of methyliodide. With dimethyl sulphate 3a and 3b reacted relatively easily (refluxing in ethyl acetate in open vessel), but the hindered 2-acylimidazole (3c: R=c-C_6H_{11}) remained after refluxing the ethyl acetate solution at 80°C in the presence of a slight excess of dimethyl sulphate (GLC analysis of consumption of 3c in the reaction mixture: 35.6% after 2h; 64.4% after 6h; 74.5% after 10h).

Treatment of the obtained quaternary salts (4a, 4b and 4c) with methanol[6], n-propylamine, ethylmercaptan[6] or aq. NaOH satisfactorily afforded the respective acylated compounds (6 - 9), but the reaction with active methylene compounds such as ethyl acetoacetate[6] and magnesium methyl malonate[7] did not proceed so well.

It is characteristic that the reaction of 4 with the nucleophiles includes C-C bond fission[8] whereas the common active acyl is linked to a heteroatom such as oxygen, nitrogen, sulphur, phsphorus or halogen atom[9]. However, general application of the present activation procedure seems to be difficult as long as improvement of the quaternization step is not easy. In the previous communication[3] the authors reported an improved procedure for the acyl activation of 3 and conversion of 3 to

various carbonyl compounds via 2-(1-hydroxyalkyl)-1-methyl-1H-imidazoles, so the present generally applicable procedure for the synthesis of 3 may provide some developement of the usefulness of 2-imidazolyl compounds in organic synthesis.

EXPERIMENTAL

2-n-Hepatanoyl-1-methyl-1H-imidazole (3b) (Typical Procedure for Synthesis of 3a-i, 10 and 11)

1.6M n-Butyllithium solution in hexane (25.6 ml, 40 mmol) was added to a stirred solution of 1-methyl-1H-imidazole (3.28g, 40 mmol) in THF (80 ml) at -78°C and the mixture was stirred for 10 min. 1-n-Heptanoylpyrrolidine (1b, 7.32g, 40 mmol)[10] was added to the mixture and it was stirred at ambient temperature by removing the cooling bath for 30 min. Ether (80 ml) and 10% HCl (80 ml) were added to the mixture and the aqueous phase was washed with ether, then was alkalined by addition of solid K_2CO_3 to separate an oily material, which was extracted with ethyl acetate. The organic phase was evaporated after drying over Na_2SO_4 to give an oil, which was distilled in vacuo, bp 118 - 120°C (3mmHg, Kugel-Rohr distillation). Yield, 7.76g (quantitative). IR $\nu_{max}^{CHCl_3}$: 1672 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm: 0.68 - 1.93 (m, 11H, $CH_3(CH_2)_4$-), 3.11 (t, 2H, $-CH_2CO-$, J=9 Hz), 4.00 (s, 3H, N-CH_3), 7.01 and 7.12 (d each, 1H each, imidazole H, J=1 Hz each). Anal.Calcd. for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 67.45; H, 9.81; N, 14.25.

Alkaline Hydrolysis of 2-Benzoyl-1-methyl-1H-imidazole (3a)

A mixture consisting of 3a (1.49g, 8 mmol), 4N-NaOH (7.5 ml) and ethanol (15 ml) was refluxed at 80°C under N_2 atmosphere for 30h. Diphenyl ether (200 μl) was added to it as an internal standard for GLC analysis, by which the presence of 1-methyl-1H-imidazole (89.1% of theoretical yield) was indicated. Solvent was evaporated, and water (5 ml) and ether (10 ml) were added to the residue. The aqueous layer was acidified with conc. HCl and precipitated benzoic acid was extracted with ether. The extract was evaporated to give an almost pure benzoic acid (mp 118 - 120°C, 849 mg, 87.1%). The first ethereal layer was extracted with 5 ml of 10% HCl and the aqueous layer was alkalined with KOH pellets (saturated), then the aqueous layer was extracted repeatedly with fresh ether. Evaporation of the ether layer gave an oily residue (385 mg, 58.9%), which was identified as 1-methyl-1H-imidazole by GLC and IR.

2-Benzoyl-1,3-dimethyl-1H-imidazolium Iodide (4a)

A mixture consisting of 3a (2.00g), AcOEt (10 ml) and methyl iodide (3.8 ml) was

refluxed for 5h at 95 - 100°C in a sealed tube. The resulting solution was cooled to precipitate yellow crystals, which was filtered and washed with AcOEt. Yield, 2.35g (66.7%). Recrystallization from acetone gave pale yellow leaflets, mp 227 - 228°C (decomp.). IR $\nu_{max}^{CHCl_3}$: 1675 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δppm: 3.81 (s, 6H, CH_3 x 2), 7.50 - 8.00 (m, 7H, C_6H_5- and imidazole H). Anal. Calcd. for $C_{12}H_{13}IN_2O$: C, 43.92; H, 3.99; N, 8.54. Found: C, 44.02; H, 4.28; N, 8.36.

Methiodide of 3b was prepared by using similar manner as above: 4b (R=n-hexyl; X=I), mp 130 - 133°C. Yield, 35.7%. IR $\nu_{max}^{CHCl_3}$: 1705 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 0.70 - 2.00 (m, 11H, CH_3-$(CH_2)_4$-), 3.26 (t, 2H, -CH_2CO-, J=7 Hz), 4.21 (s, 6H, 2 x N-CH_3), 7.98 (s, 2H, imidazole H). Anal. Calcd. for $C_{12}H_{21}IN_2O$: C, 42.97; H, 6.30; N, 8.30. Found: C, 42.87; H, 6.52; N, 8.08.

2-Cyclohexylcarbonyl-1,3-dimethyl-1H-imidazolium Monomethyl Sulphate (4c)

A solution consisting of 3c (1.92g, 10 mmol), dimethyl sulphate (1.50g, 12 mmol) and THF (20 ml) was refluxed under N_2 atmosphere for 10h. Removal of the solvent gave a viscous residue, which was washed with ether several times. Yield, 2.07g (65.1%). IR $\nu_{max}^{CHCl_3}$: 1703 cm^{-1} (C=O). Further purification and full characterization of the compound were difficult (viscous and unstable compd.).

Reaction of 4a with Methanol

A methanolic solution (3 ml) of 4a (164 mg, 0.5 mmol) was stirred in the presence of Et_3N (100 mg, 1 mmol) at r.t. for 10 min. Naphthalene (20 mg) was dissolved in the resulting mixture. GLC analysis of the solution indicated the quantitative formation of methyl benzoate. (Isolated yield, 76.9%)

Methyl n-heptanoate was isolated from 3b in 66.7% yield by the similar manner as above.

Reaction of 4a with n-Propylamine

A mixture consisting of 4a (100 mg), CH_2Cl_2 (4 ml) and n-propylamine (1 ml) was stirred for 2h at r.t. and then AcOEt (20 ml) was added. The mixture was washed with 5% Na_2CO_3, H_2O, 10% HCl and H_2O, and dried over Na_2SO_4. Removal of the solvent gave a crystalline residue (43 mg) of an almost pure n-propylbenzamide. n-Propylcyclohexanecarboxamide (bp_2 135 - 140°C, Kugel-Rohr distillation; crystallized after distillation) was obtained from 4c in 68% yield by the similar manner as above.

Reaction of 4a with Ethylmercaptan

A mixture consisting of 4a (939 mg, 2.9 mmol), CH_2Cl_2 (10 ml), EtSH (558 mg, 9 mmol) and Et_3N (404 mg, 4 mmol) was stirred. Work-up procedure was similar as above

(reaction of 4a with n-propylamine). The oily residue (357 mg, 71.6%) was obtained and it was identified as ethylbenzoylmercaptan[11] by comparison of IR and GLC with its authentic sample.

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5) We did not use dimethyl sulphate as possible because of allergy.

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