FORMYLATION OF 2,5-UNSUBSTITUTED OXAZOLE: PREPARATION AND CHARACTERIZATION OF 2- AND 5-FORMYL-4-METHYLOXAZOLES

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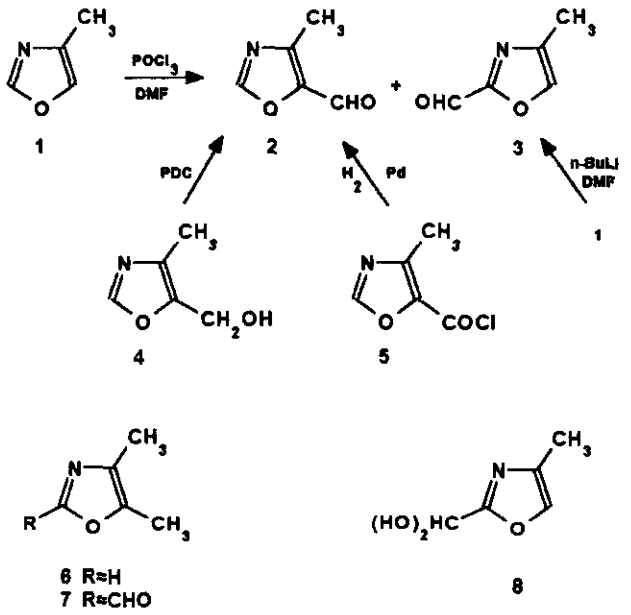
Abstract - Vilsmeier formylation of 4-methyloxazole (**1**) gave a mixture of 4-methyl-5-oxazolecarboxaldehyde (**2**) and 4-methyl-2-oxazolecarboxaldehyde (**3**) in 1:1 ratio. Both aldehydes were prepared unambiguously: aldehyde (**2**) by oxidation of 5-hydroxymethyl-4-methyloxazole (**4**) and reduction of chloride of 4-methyl-5-oxazolecarboxylic acid (**5**) and aldehyde (**3**) by n-butyllithium/DMF procedure. Aldehyde (**2**) sublimes in a refrigerator while aldehyde (**3**) forms hydrate, 5-dihydroxymethyl-4-methyloxazole (**8**).

In connection with our interest in the synthesis of intermediates of vitamin B_6[1] it became essential to consider the synthesis of certain oxazoles containing the formyl group at the 2- or 5-position of the heterocyclic nucleus. Although numerous oxazoles[2] have been reported, surprisingly, formyloxazoles have not been extensively studied. 4-Formyloxazoles[3-10] are the best known of these species whereas 2-formyl-[10-13] and 5-formyloxazoles[14-15] are sparse mentioned. Some of them have been seen in gc[16] or only stated[17] on the way with some other reactions.

Herein we report the first example of the electrophilic substitution reaction of 2,5-unsubstituted oxazole leading



to new 2- and 5-functionalized oxazoles. Contrary to our expectation, Vilsmeier-Haack formylation of 4-methyloxazole (**1**) with DMF-phosphoryl chloride complex gave a mixture of two aldehydes, 4-methyl-5-oxazolecarboxaldehyde (**2**) and 4-methyl-2-oxazolecarboxaldehyde (**3**) in 10% of isolated yield, respectively. The presence of the pyridine-type nitrogen of the oxazole ring deactivates this system to a great extent and therefore the electrophilic substitution is expected to be difficult specially at C-2. On the other hand, the presence of a methyl group at C-4 in oxazole (**1**) should activate position C-5 toward electrophilic substitution, thus stimulating formation of aldehyde (**2**). In our case it seems that the degree of ring activation by the methyl group at C-4 combined with steric effects is insufficient for the reaction to occur regioselectively at C-5. The structure of these two isomers was determined by their independent syntheses. If the Vilsmeier formylation is applied to 4,5-dimethyloxazole (**6**) with only one free position, 2-formyl derivative (**7**) was obtained (approximately 10%), thus showing the same possibility for substitution at C-2 as **1**.

Much better method for the preparation of aldehyde (**7**) as well as (**3**) is the metallation[10,18-22] of corresponding oxazole (**6** and **1**, resp.) with n-butyllithium and subsequent reaction with DMF (*ca.* 50% yield). Deprotonation of 4-methyloxazole (**1**) is regioselective and it occurs at the C-2 position giving the anion which after treatment with DMF gave the desired product (**3**).

It is interesting to note that nice needle-like crystals of this aldehyde (**3**), which was completely characterized by ^{1}H and ^{13}C nmr in $CDCl_3$, standing in the refrigerator easily transform into powder-like material insoluble in $CDCl_3$. By melting this powder and subsequent cooling, the material is again soluble in $CDCl_3$ and its nmr spectrum is equal to starting aldehyde (**3**). ^{1}H Nmr spectrum of powder taken in DMSO-d_6 showed it to be a mixture of aldehyde (**3**) and hydrate (**8**). The spectrum showed besides three signals of aldehyde (**3**) four new signals of **8**: one proton quartet at 7.70 (J=1 Hz), two proton doublet at 6.78 (J= 7 Hz), one proton triplet at 5.70 (J=7 Hz) and three proton doublet at 2.22 ppm (J=1 Hz). By adding D_2O to DMSO-d_6 solution the doublet of hydroxy protons disappeared and the triplet became singlet, thus confirming the structure (**8**). In the ^{13}C nmr spectrum of the mixture the most characteristic signal (doublet) at 84.7 ppm was assigned to carbon bearing two hydroxy groups (**8**). The methyl carbons appeared at the same position, 11.2 ppm, aldehyde carbon at 178.6 and the doublets of C-5 at 139.4 (**3**) and 134.4 (**8**). Small signals (singlets) at 163.4 (**8**), 157.6 (**3**) and 139.2 (**3**), 135.2 (**8**) were assigned to C-2 and C-4 carbons. It was observed that **3** and **8** are in DMSO-d_6 in mobile equilibrium depending on water content of solvent and the temperature. After standing in the refrigerator the equilibrium moved to hydrate (**8**). Warming up the nmr sample to 60-90 °C for 15 minutes the equilibrium moved completely to aldehyde (**3**). Existence of such equilibrium in solid state was confirmed by taking ir spectrum of hydrate (**8**) in KBr which showed characteristic strong broad band with maximum at 3140 cm^{-1} as well as week sharp band at 1700 cm^{-1}. After heating the KBr-disc to 100 °C the strong band above 3000 cm^{-1} disappeared while the band at 1700 cm^{-1} beccame the most intensiv one. Water, necessary for the formation of the hydrate, most probably came of isolation procedure.

The straightforward synthesis of 4-methyl-5-oxazolecarboxaldehyde (**2**) was performed either by oxidation of 5-hydroxymethyl-4-methyloxazole (**4**) or by hydrogenation of chloride of 4-methyl-5-oxazolecarboxylic acid (**5**) by Rosenmund method. The hydrogenation reaction is very useful for the large-scale preparation because of high yield. The spectroscopic properties of this compound were equal to those of aldehyde (**2**) obtained by Vilsmeier reaction of oxazole (**1**).

Aldehydes (**2**) and (**3**) may be isolated from their mixture after standing in cold for several weeks. Namely, the aldehyde (**2**) sublimes in nice long needles on the top of the bottle and **3** remains on the bottom as a white powder (**8**).

EXPERIMENTAL SECTION

^1H and ^{13}C Nmr spectra were taken on JEOL FX 90Q and Varian GEMINI 300 spectrometers. Ir spectra were recorded with Perkin-Elmer 297 spectrophotometer. Mass spectra were recorded on EXTREL FTMS 2001. Melting points are determined in a Thiele apparatus and are uncorrected.

Vilsmeier formylation of 4-methyloxazole (1). To the prepared $POCl_3$-DMF complex by adding 6.4 g (40 mmol) of $POCl_3$ into 3 g (40 mmol) of DMF under stirring and cooling 3.3 g (40 mmol) of oxazole derivative (**1**) was slowly added. After standing at room temperature overnight the reaction mixture was poured on ice, neutralized with 15% sodium hydroxide solution and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel with petroleum ether-ether (9:1) as the eluent to give in the first fractions 4-methyl-2-oxazolecarboxaldehyde (**3**), 0.44 g (10% yield) and later 4-methyl-5-oxazolecarboxaldehyde (**2**), 0.44 g (10% yield).

2: mp 38 °C; ms m/z 111 (M^+); hrms: calcd for $C_5H_5NO_2$ 111.031480 found 111.032160; ir (KBr)ν 3120, 1685, 1595 cm^{-1}; ^1H nmr ($CDCl_3$) δ 9.90 (s, 1H), 8.02 (s, 1H), 2.55 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 176.92 (d), 152.93 (d), 147.12 (s), 144.87 (s), 12.18 (q).

3: mp 50-52 °C; ms m/z 111 (M^+); hrms: calcd for $C_5H_5NO_2$ 111.031480 found 111.031511; ir (KBr) ν 1700, 1580, 1520 cm^{-1}; ^1H nmr ($CDCl_3$) δ 9.73 (d, 1H, J=0.6 Hz), 7.62 (m, 1H), 2.30 (d, 3H, J=1 Hz); ^{13}C nmr ($CDCl_3$) δ 177.21 (d), 157.54 (s), 139.73 (s), 138.21 (d), 10.97 (q).

Oxidation of 5-hydroxymethyl-4-methyloxazole (4). To a solution of 1.1 g (10.5 mmol) of **4**[23] in 4 ml of dichloromethane was added 1.5 g of PDC.[24] The reaction mixture was stirred at room temperature overnight, filtered over silica gel and washed with ether. The solvents were combined and evaporated. The residue was chromatographed over silica gel with petroleum ether-ether (9:1) as eluent to give 664 mg (57% yield[25]) of 4-methyl-5-oxazolecarboxaldehyde (**2**) as colourless crystals.

Hydrogenation of chloride of 4-methyl-5-oxazolecarboxylic acid (5). To a solution of 20 g (0.137 mol) of **5** (obtained from the acid and $SOCl_2$ catalized by DMF) in 100 ml of benzene was added 16 g of Pd (5%)/barium sulfate. The reaction mixture was refluxed and hydrogenated for 26 h at atmospheric pressure. The catalyst was

filtered off and washed with benzene. The filtrates were combined and kept over sodium hydroxide. After filtration and evaporation of benzene at atmospheric pressure the residue was distilled in vacuum (bp 72-74 °C /12 mm Hg) to give 11.7 g (76%) of **2**. Redisilled product solidified immediatelly, mp 38 °C.

4-Methyl-2-oxazolecarboxaldehyde (3). To a stirred solution of 3.3 g (40 mmol) of **1** in 20 ml of dry THF at -75 °C under a nitrogen atmosphere was added 1.10 equiv. of n-butyllithium in hexane and stirred for 45 min. To this mixture is added 2.92 g (40 mmol) of dry DMF and left to warm up to room temperature. After standing overnight the reaction mixture was neutralized with 2N HCl and extracted with ether. The organic extracts were combined and dried over magnesium sulfate. The solvent was evaporated and the residue was distilled in vacuum (bp 60-70 °C /20 mm Hg) to give 2.13 g (48% yield) of **3** which solidifies, mp 50-52°C.

4,5-Dimethyl-2-oxazolecarboxaldehyde (7). Prepared by Vilsmeier formylation of **6**[26] (10% yield) as described for the preparation of **2** and **3** and by n-butyllithium/DMF procedure (50% yield) as the preparation of **3**.

7: mp 32-33 °C; ms m/z 125 (M^+); hrms: calcd for $C_6H_7NO_2$ 125.047130 found 125.046786; ir (KBr) ν 1695, 1605, 1515 cm^{-1}; ^1H nmr ($CDCl_3$) δ 9.61 (s, 1H), 2.37 (s, 3H), 2.21 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 176.58 (d), 155.87 (s), 148.61 (s), 134.82 (s), 10.85 (q), 10.04 (q).

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