APPLICABILITY OF THE OGLIALORO CONDENSATION IN THE REACTION WITH 3-INDOLCARBALDEHYDE

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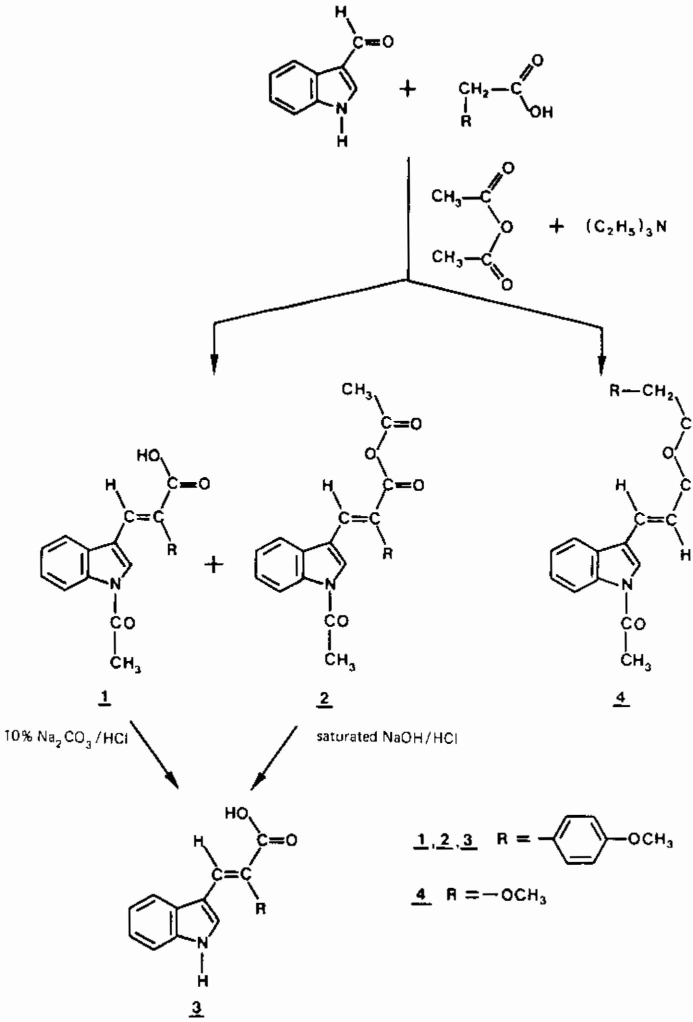
Abstract — 3-Indolcarbaldehyde exibits in Oglialoro condensation different behaviour than 2-furancarbaldehyde and 2- and 3-thiophencarbaldehydes which with substituted acetic acids give 3-(2-furyl), 3-(2-thienyl) and 3-(3-thienyl)-2-substituted acrylic acids. It is noticed that under the same reaction conditions the main product in the reaction of substituted acetic acids with 3-indolcarbaldehyde is not the corresponding 3-(3-indolyl)-2-substituted acrylic acid but the mixed anhydride 2 or 4.

As a part of our continuing interest in the synthesis and photochemistry of heterocyclic acrylic acids[1], we tried to synthesize some 3-(3-indolyl)-2-substituted acrylic acids. Only one acid synthesized from this series is E-3-(3-indolyl)-2-phenylacrylic acid synthesized from 3-indolcarbaldehyde, sodium phenylacetate and sodium acetate in the presence of acetic acid anhydride. The yield was 27%[2]. When the reaction was carried out by the Oglialoro condensation from 3-indolcarbaldehyde and 4-methoxyphenylacetic acid in the presence of triethylamine and acetic acid anhydride we obtained 3-(1-acetyl-3-indolyl)-2-(4-methoxyphenyl)acrylic acid 1 in the yield of 17%.

Hydrolysis of the acid 1 gave the acid 3 in the yield of 15%. In the ethereal extracts after trituration of the acid 1 remains the unsoluble main product 2 in the yield of 75%. The anhydride 2 was hydrolized with saturated sodium hydroxide solution by the prolonged heating and after acidification we obtained the acid 3 in the yield of 80%. When the reaction was carried out with methoxyacetic acid and 3-indolcarbaldehyde under the same conditions the only product was anhydride 4 in the yield of 80%.

The structure of the product 4 was determined by the prolonged hydrolysis with sodium hydroxide. The product of the hydrolysis was (E)-3-(3-indolyl)-acrylic acid with mp 195-196 °C.[3,4]



When 3-indolcarbaldehyde was previously acetylated with acetic acid anhydride in the presence of anhydrous sodium acetate (usually the reaction conditions for Perkin reaction) by the method described by Majima and Kotake[5] and than used in Oglialoro condensation with p-methoxyphenylacetic acid it was possible to isolate 27% of acid 1 as the only product namely 3 after hydrolysis. When the reaction of 1-acetyl-3-indolcarbaldehyde was carried out with methoxyacetic acid, after prolonged heating the only product was 3-(3-indolyl)-acrylic acid in 5% yield and no traces of anhydride structure 4 could be detected. Heating a reaction mixture of 1-acetyl-3-indolcarbaldehyde and p-nitrophenylacetic acid after short time gave only a lot of resins.

As a conclusion of our investigation we can mention that there is a difference in the behaviour between 3-indolcarbaldehyde and 1-acetyl-3-indolcarbaldehyde as expected according to the literature data[6].

1-Acetyl-3-indolcarbaldehyde is more reactive then 3-indolcarbaldehyde so that it exibits in the Oglialoro condensation the reaction of resinification markedly even when the reaction time is shortened, so the whole yield of the acid 1 is only 27%. 3-Indolcarbaldehyde reacts with mixed anhydride to give 2, so the total yield on the acid 1 is 85%.

On the other hand, reduced reactivity of 3-indolcarbaldehyde makes it possible to isolate mixed anhydrides 2 and 4 which were not noticed when 1-acetyl-3-indolcarbaldehyde was used. This was not noticed in the reaction with another heterocyclic carbaldehydes[1]. p-Methoxyphenyacetic acid and methoxyacetic acid react with acetic acid anhydride to give the mixed anhydride $CH_3O-C_6H_4-CH_2-CO-O-CO-CH_3$, namely $CH_3O-CH_2-CO-O-CO-CH_3$ which then reacts on the more reactive side in the sence of *aldol condensation*.

EXPERIMENTAL

Melting points are uncorrected. The ir *spectra were recorded* on a Perkin-Elmer Model 257 Infracord spectrophotometer in KBr discs. The uv spectra were taken on a Perkin-Elmer 124 spectrophotometer using ethanolic solution. The ^1H nmr spectra were recorded on a Varian T-60 or Joel J.M.M.-FX 100 FT spectrometer with tetramethylsilane as the internal reference. Mass spectra were obtained with Varian MAT-CH7 spectrometer operating at 70 eV by direct insertion probe.

The preparation of the acid 1 from 3-indolcarbaldehyde and 4-methoxyphenylacetic acid

4-Methoxyphenylacetic acid (1.7 g 0.01 mole) and 3-indolcarbaldehyde (1.5 g 0.01 mole) in a mixture of triethylamine (10 ml) and acetic acid anhydride (10 ml) was heated for 24 h at boiling point. After the reaction was over, the mixture was cooled, acidified with hydrochloric acid and extracted with ether. The organic layer was washed with water and acid 1 was reextracted into 10% sodium carbonate solution. The alkaline solution was acidified with acetic acid. The precipitate was filtered off and recrystallized from methanol. The yield was 17%, mp 241-243 °C; ir (KBr); 1610 cm^{-1} (C = C), 1670 (C = 0 carboxylic), 1730 (C = 0 amidic); nmr (CD_3COCD_3) δ 2.31 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.75 (s, 1H, C_2), 7.01-7.7 (m, 8H, aromatic), 8.06 (s, 1H, ethylenic).

Hydrolysis of the acid 1

Hydrolysis of the acid 1 (0.54 g 0.00017 mole) was carried out by heating it with 10% sodium carbo*nate solution and acidifying the solution. The acid* 3 was obtained in the yield of 15%, mp 182-184 °C, ir (KBr) 1600 cm^{-1} (C = C); 1650 (C = 0); nmr (CD_3COCD_3) 3.83 (s, 3H, OCH_3), 6.54 (d, 1H, C_2, J = 3 Hz; 6.94-7.47 (m, 8H, aromatic), 7.68 (d, 1H, NH, J = 3 Hz); 8.24 (s, 1H, ethylenic); 10.50 (s, 1H, COOH).

Isolation of the mixed anhydride 2

On the ethereal layer after extraction of the acid 1 remains the unsoluble main product 2 in the 75% which was recrystallized from methanol. Mp 195-197 °C; ir (KBr) 1600 cm^{-1} (C=C), 1720 (C=O amidic), 1770 (C=O anhydridic); nmr (CD_3COCD_3) 2.17 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.46 (s, 1H, C_2), 6.97-8.04 (m 10H, aromatic + ethylenic); m/e 377 (M^+), 335 (80), 293 (100), 249 (75).

Preparation of the mixed anhydride 4

When the reaction was carried out with 3-indolcarbaldehyde (1.5 g 0.01 mole) and methoxyacetic acid (1.8 g 0.02 mole) under the same reaction conditions as for the preparation of the acid 1 there was no trace of the (1-acetyl-3-indolyl)-2-methoxyacrylic acid. The only product insoluble in ether was the anhydride 4 in the yield of 80%, mp 179-180 °C, ir (KBr) 1600 cm^{-1} (C=C) 1720 (C=O amidic), 1770 (C=O anhydridic), nmr (CD_3COCD_3) δ 2.10 (s, 2H, CH_2) 2.3 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.24 (s, 1H, C_2), 7.11-8.06 (m 6H, aromatic + ethylenic). Hydrolysis of the anhydride 4 with saturated sodium hydroxide solution gave (E)-3-(3-indolyl)acrylic acid.

Preparation of the acid 1 from 1-acetyl-3-indolcarbaldehyde and 4-methoxyphenylacetic acid

A mixture of 1-acetyl-3-indolcarbaldehyde (1.45 g 0.008 mole) and 4-methoxyphenylacetic acid (1.7 g 0.01 mole) in triethylamine (10 ml) and acetic acid anhydride (10 ml) was heated for 4 h. The reaction mixture was treated as described above. The yield of the acid 1 was 26%. The intermediate product 2 was not detected.

Reaction of the 1-acetyl-3-indolcarbaldehyde with methoxyacetic acid

Methoxyacetic acid (0.9 g 0.01 mole) and 1-acetyl-3-indolcarbaldehyde (1.45 g 0.008 mole) on treatment as above during 24 h gave 3-indolylacrylic acid, mp 195 °C in the yield of 5%. There was no detected expected product 2-methoxy-3-(1-acetyl-3-indolyl)acrylic acid.

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