β-(5-METHYL-4-PHENYLPYRIDIN-2-YL)ALKANOLS

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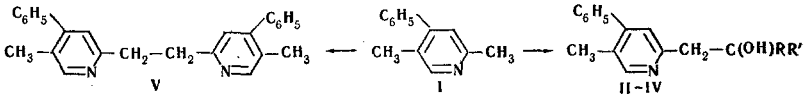
The α-lithiomethyl derivative obtained by the metallation of 2,5-dimethyl-4-phenylpyridine with methyllithium has been used in the synthesis of several alcohols of the pyridine series.

In a preceding paper [1] it was shown that the reaction of 2,5-dimethyl-4-phenylpyridine (I) with phenyllithium takes place in two directions – arylation of the free α' position of the pyridine nucleus and metallation of the α-methyl group. There is information according to which methyllithium exhibits a smaller tendency to alkylate the pyridine nucleus [2]. Consequently, we selected this compound for the metallation of the α-substituted pyridine base I. The α-lithiomethyl derivatives so obtained present great possibilities for the synthesis of many functionally substituted compounds. First of all we dealt with the synthesis in this way of a number of alcohols containing a pyridin-2-yl radical.

The treatment of I with methyllithium and then with acetone, acetaldehyde, and benzaldehyde gave, respectively, 2-methyl-1-(5-methyl-4-phenylpyridin-2-yl)propan-2-ol (II), 1-(5-methyl-4-phenylpyridin-2-yl)propan-2-ol (III), and 2-(5-methyl-4-phenylpyridin-2-yl)-1-phenylethanol (IV).



II R = R' = CH_3; III R = H, R' = CH_3; IV R = H, R' = C_6H_5

As a rule, from 32 to 65 % of the initial substituted pyridine I was recovered from the reaction mixture. Considerable difficulties were encountered in the isolation of the individual alcohols from the reaction products. Adsorption chromatography on alumina using a column 80 cm long and 1 cm in diameter with alumina of activity grade II (200 g) proved to be a preparatively convenient method for the isolation of the alcohols II and IV. Elution was performed first with petroleum ether and then with petroleum ether–ethyl acetate (10:1). The separation was monitored by thin-layer chromatography.

The IR spectra of the alcohols II, III, and IV have a broad band in the 3200-3300 cm^{-1} region due to the stretching vibrations of a hydroxy group participating in a hydrogen bond.

The metallation of I is accompanied by dimerization giving 1,2-di(5-methyl-4-phenylpyridin-2-yl)-ethane (V). It was isolated with a yield of 14 % (on the I that had reacted). The IR spectrum of V had bands at 2931 and 2840 cm^{-1} (very weak) due to the stretching vibrations (ν_{as} and ν_s) of methylene groups and a band at 1462 cm^{-1} due to the deformation vibrations of methyl and methylene groups.

EXPERIMENTAL

2-Methyl-1-(5-methyl-4-phenylpyridin-2-yl)propan-2-ol (II). At 0°C, 9.2 g (0.05 mole) of I was added to the methyllithium obtained from 0.7 g (0.1 g-at.) of lithium and 7.1 g (0.05 mole) of methyl iodide in 50 ml of ether. The mixture was stirred at room temperature for 3 hr 30 min. Then it was cooled, and 5 g (0.1 mole) of acetone in 10 ml of ether was added. After 10 hr, 25 ml of water was added to the reaction mixture. The ethereal solution yielded a residue (8.2 g) which consisted of a mixture of at least three

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substances (according to thin-layer chromatography). The separation of this mixture (8.2 g) was effected by adsorption chromatography (see above). The following were isolated successively: 3 g of the initial I – R_f 0.72 [ethyl acetate–heptane (1 :1)]; 2.83 g (33.7 % on the I that had reacted) of II – R_f 0.52 [ethyl acetate–heptane (1 :1)] and R_f 0.19 (petroleum ether). Compound II consisted of colorless crystals with mp 84-86°C (from petroleum ether). Found, %: C 79.5; H 8.0; N 6.0. Calculated for $C_{16}H_{19}NO$, %: C 79.7; H 7.9; N 5.8.

Picrate – mp 178-180°C (from ethanol). Found, %: N 11.8. Calculated for $C_{16}H_{19}NO \cdot C_6H_3N_3O_7$, %: N 11.9.

1-(5-Methyl-4-phenylpyridin-2-yl)propan-2-ol (III). In a synthesis performed similarly, 0.35 g (0.05 g-at.) of lithium, 3.5 g (0.025 mole) of methyl iodide, 30 ml of ether, 4.6 g (0.025 mole) of I, and 1.1 g (0.025 mole) of acetyldehyde were used. The residue isolated from the ethereal solution was distilled: the first fraction had bp 120-125°C (3 mm), 2.37 g, n_D^{20} 1.5831 – the initial pyridine I; the second fraction had bp 125-164°C (3 mm), 0.39 g; and the third fraction with bp 164-167°C (3 mm) consisted of 0.66 g of a viscous yellow liquid. From it was isolated 0.5 g of III (18 % of the I that had reacted) with mp 41-43°C (from petroleum ether), R_f 0.3 [ethyl acetate–petroleum ether (1 :10)]. Found, %: C 79.6; H 7.6; N 6.0. Calculated for $C_{15}H_{17}NO$, %: C 79.3; H 7.5; N 6.2.

Picrate –mp 155-156°C (from ethanol). Found, %: N 12.0. Calculated for $C_{15}H_{17}NO \cdot C_6H_3N_3O_7$, %: N 12.2.

2-(5-Methyl-4-phenylpyridin-2-yl)-1-phenylethanol (IV). The reaction was performed with 0.35 g (0.05 g-at.) of lithium, 3.5 g (0.025 mole) of methyl iodide, 50 ml of ether, 4.6 g (0.025 mole) of I, and 2.7 g (0.025 mole) of benzaldehyde. The unchanged benzaldehyde was distilled off with steam, giving 6.6 g of an oily residue from which individual substances were isolated on a chromatographic column (see above). Chromatography yielded first 3 g of the initial pyridine I – R_f 0.44 [ethyl acetate–heptane (1 : 5)] and finally 1 g (40 % on the I that had reacted) of IV with mp 80-82°C (from petroleum ether). Found, %: C 82.8; H 6.5; N 5.1. Calculated for $C_{20}H_{19}NO$, %: C 83.0; H 6.6; N 4.8.

Picrate – mp 172-173°C (from ethanol). Found, %: N 11.0. Calculated for $C_{20}H_{19}NO \cdot C_6H_3N_3O_7$, %: N 10.8.

1,2-Di(5-methyl-4-phenylpyridin-2-yl)ethane (V). Methyllithium was obtained from 0.7 g (0.1 g-at.) of lithium and 7.1 g (0.05 mole) of methyl iodide in 50 ml of ether and to this at 0°C was added 9.2 g (0.05 mole) of I. After 12 h, the mixture was treated with water. The organic bases were isolated from the ethereal solution and were distilled: the first fraction had bp 121-122°C (3.5 mm), 4 g, n_D^{20} 1.5822 – the initial pyridine I – and the second fraction had bp 230-240°C (2.5 mm), 1.08 g – a vitreous mass. From this was isolated 0.9 g (14 % on the I that reacted) of V with mp 139-140°C (from petroleum ether), R_f 0.8 [ethyl acetate–petroleum ether (1:1)]. The still residue obtained on the distillation of the reaction products (2.5 g) yielded an additional 0.5 g of V by chromatography on a column [h = 65 cm, alumina (100 g) of activity grade II, petroleum ether]. Found, %: C 86.2; H 6.9; N 7.7. Calculated for $C_{26}H_{24}N_2$, %: C 85.7; H 6.6; N 7.7. Dipicrate – mp 196-198°C (from ethanol). Found, %: N 13.5. Calculated for $C_{26}H_{24}N_2 \cdot 2C_6H_3N_3O_7$, %: N 13.6. Diperchlorate – mp 195-200°C (from ethanol). Found, %: N 4.5. Calculated for $C_{26}H_{24}N_2 \cdot 2HClO_4$, %: N 4.9.

The IR spectra given in this paper were recorded on a UR-20 spectrophotometer in the 3800-400 cm^{-1} region using LiF, NaCl, and KBr prisms. Samples II and V were prepared in the form of tablets with KBr. Samples III and IV were prepared in the form of mulls in paraffin oil.

LITERATURE CITED

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