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The α position of the pyridine ring is arylated by reaction of 2,5-dimethyl-4-phenylpyridine with phenyllithium and p-tolyllithium. Destructive oxidation of the diaryl-substituted pyridines primarily affects the pyridine ring.

Arylation of the pyridine ring with organometallic compounds has been previously realized primarily for pyridine itself and the simplest alkyl-substituted pyridines [1, 2]. We addressed ourselves to the arylation of γ -phenyl-substituted pyridine with alkyl substituents in the α and β positions of the ring using phenyllithium and p-tolyllithium. The readily accessible 2,5-dimethyl-4-phenylpyridine (I) [3] was used as the object of our investigations. 3,6-Dimethyl-2,4-diphenylpyridine (II) was obtained in 43% yield by treatment of I with phenyllithium. 3,6-Dimethyl-4-phenyl-2-(p-tolyl)pyridine (III) was similarly obtained in 73% yield.*



The literature contains comparatively little data on the oxidation of aryl-substituted pyridines. A comparison of the oxidation of aryl-substituted benzenes and alkyl-substituted pyridines established that the pyridine ring is more resistant to oxidation than the benzene ring.

However, depending on the conditions, either the aryl or pyridine rings can undergo destructive oxidation. Chichibabin [4] has shown that α -phenylpyridine can be converted by oxidation either to picolinic or benzoic acid. Destruction of the benzene ring with the formation of isocinchomeronic acid [5] occurs during oxidation of 5-methyl-2-phenylpyridine with potassium permanganate.

We have examined the oxidation of diaryl-substituted pyridines II and III under various conditions. 2,4-Diphenylpyridine-3,6-dicarboxylic acid (IV) is isolated in low yield (17%) on oxidation of II in an almost neutral medium. Oxidation of II with chromic anhydride in acetic acid is accompanied by destruction of the pyridine ring and formation of benzoic acid, which was isolated in approximately 38% yield.



Destructive oxidation, which accompanies oxidation of the pyridine ring of diaryl-substituted pyridine III, proceeds particularly readily. In this case, terephthalic acid was obtained in about 100% yield. It may be assumed that the presence in the pyridine ring in the α and γ positions of aromatic radicals which, together with the pyridine ring, create a single conjugated system, promotes destruction of the pyridine ring during oxidation. One must apparently also consider the effect on the oxidation process of two electron-donating methyl groups in the pyridine ring.

*Both yields are based on the amount of I entering into reaction.

Patrice Lumumba University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1359-1361, October, 1970. Original article submitted September 2, 1968.

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A peculiarity of the pyridine systems studied by us is the fact that one of the α positions of the pyridine ring is occupied by a methyl group. It is well known that α -methyl-substituted pyridines undergo metallation on reaction with organolithium compounds; this is used in the synthesis of several α -substituted pyridines [6-8].

We also considered the possibility of metallation of the α -methyl group of I and II under the conditions of our experiments. The fact that two processes – arylation in the α ' position and metallation of the α -methyl group of I – occur during reaction of I with phenyllithium is shown by the following transformations. A mixture of substances, in which the presence of 2-methyl-1-(5-methyl-4-phenyl-2-pyridyl)-2propanol (V) was established by IR spectral data, was isolated on treatment of the products of the reaction of I with phenyllithium and acetone. Subsequent dehydration of V gave 2-methyl-1-(5-methyl-4-phenyl-2pyridyl)-1-propene (VI), which was then converted to 1,2-dibromo-2-methyl-1-(5-methyl-4-phenyl-2pyridyl)propane (VII). Arylation product II was also isolated from the indicated mixture of substances, along with alcohol V.

$$I \longrightarrow CH_3 - CH_2LI \longrightarrow CH_3 - CH_2LI \longrightarrow CH_3 - CH_2 - C(CH_3)_2 \longrightarrow CH_3 - C$$

Both reaction directions – arylation and metallation of the α -methyl group – proceed quantitatively to an equal degree. As for the metallation of the α -methyl group of II, it apparently does not occur under the conditions of our experiments. It was established that 3,6-dimethyl-2,4-diphenylpyridine is recovered quantitatively after treatment of II with phenyllithium and acetone.

EXPERIMENTAL

3,6-Dimethyl-2,4-diphenylpyridine (II). Compound I [36.6 g (0.2 mole)] was added in the course of 1.5 h to phenyllithium obtained from 2.8 g (0.4 g-atom) of lithium and 31.4 g (0.2 mole) of bromobenzene in 250 ml of ether. The mixture was allowed to stand at room temperature for 12 h. The reaction mass was then treated successively with 50 ml of water and 18% hydrochloric acid with Congo red as the indicator. The aqueous layer was saturated with sodium hydroxide. The organic bases were extracted with ether and distilled to give 20 g of starting I and 10.2 g (43%) of II with bp 167-169° (2 mm) and mp 62-63° (from petroleum ether): $n_D^{49.4}$ 1.6045, $d_4^{49.4}$ 1.0696, MR_D 83.31, calc. 83.03. Found %: C 87.9; H 6.6; N 5.3. $C_{19}H_{17}N$. Calculated %: C 88.00; H 6.5; N 5.4. The picrate of II had mp 185° (from alcohol). Found %: N 11.7. $C_{19}H_{17}N \cdot C_{6}H_{3}N_{3}O_{7}$. Calculated %: N 11.5.

 $\frac{3,6-\text{Dimethyl-4-phenyl-2-(p-tolyl)pyridine (III).}}{\text{II and p-tolyllithium and had bp 186° (2 mm) and mp 80-81° (from petroleum ether). Found %: C 87.8; H 7.1; N 5.1. C₂₀H₁₉N. Calculated %: C 87.9; H 7.0; N 5.1. The picrate of III had mp 175-176° (from alcohol). Found %: N 10.9. C₂₀H₁₉N · C₆H₃N₃O₇. Calculated %: N 11.1.$

Oxidation of 3,6-Dimethyl-2,4-diphenylpyridine. A. A mixture of 3 g (0.01 mole) of II and 15 g (0.095 mole) of potassium permanganate in 250 ml of water was heated at 100° for 12 h. The resulting manganese dioxide was removed by filtration and washed three times with hot water. The aqueous solution was evaporated to 100 ml and then treated with sulfuric acid (1:1) with Congo red as the indicator. The resulting crystals were isolated and washed with water to give 0.62 g (20%) of IV with mp 199-200° [from ethyl acetate - heptane (1:10)]. Found %: C 71.2; H 4.9; N 4.2. $C_{19}H_{13}NO_4$. Calculated %: C 71.5; H 4.1; N 4.4.

B. A solution of 15 g (0.15 mole) of chromic anhydride in 50 ml of acetic acid was added gradually with constant stirring and refluxing of the solution to a solution of 6 g (0.023 mole) of II in 150 ml of acetic acid. Benzoic acid (0.5 g) and 3.2 g of starting pyridine II were isolated from the reaction products.

Oxidation of 3,6-Dimethyl-4-phenyl-2-(p-tolyl)pyridine. A. Terephthalic acid (mp 275°, decomp.) was obtained in 65% yield by oxidation of III with potassium permanganate in water.

B. Compound III [1.7 g (0.006 mole)] was oxidized with chromic anhydride in acetic acid. The residue obtained after removal of the acetic acid was dried at 120°. Absolute methanol (50 ml) was then added to the residue, and the mixture was heated for 8 h under a constant stream of dry hydrogen chloride. The methanol was removed and the residue was treated with ether to give 0.48 g (40%) of terephthalic acid dimethyl ester with mp 137-139°. Treatment of the aqueous solution with sodium carbonate and extraction with ether yielded 0.2 g of a substance with mp 106-107° (from alcohol), the structure of which has not yet been established (found %: C 81.6; H 5.4; N 4.0).

2-Methyl-1-(5-methyl-4-phenyl-2-pyridyl)-2-propanol Hydrochloride (V). A mixture of 18.3 g (0.1 mole) of I and phenyllithium (0.1 mole) was stirred for 2 h at room temperature. Acetone [14.8 ml (0.2 mole)] was then added in the course of 40 min. After 12 h the mixture was treated successively with 50 ml of water and 18% hydrochloric acid with Congo red as the indicator. The aqueous layer was saturated with potassium hydroxide, and the organic bases were extracted with ether. Distillation of the ether solution yielded 7.51 g of starting I and 5.5 g of a fraction with bp 180° (2 mm) in the form of a viscous liquid. A crystalline hydrochloride with mp 195-197° (from alcohol) was obtained from this fraction which, from the analytical data, corresponds to the hydrochloride of V. Found %: Cl 12.8. C₁₆H₁₉NO · HCl. Calculated %: Cl 12.8.

<u>2-Methyl-1-(5-methyl-4-phenyl-2-pyridyl)-1-propene (VI)</u>. A mixture of 6.86 g of the fraction with bp 180° (2 mm) and 0.5 g of powdered potassium hydroxide was heated in a Claisen flask in vacuo to give 1.23 g (25%) of VI in the form of a liquid with bp 123.5° (2.5 mm), n_D^{20} 1.5845, d_4^{20} 1.037, MR_D 72.01, calc. 72.35. The picrate of VI had mp 169-170° (from alcohol). Found %: N 12.1. C₁₆H₁₇N · C₆H₃N₃O₇. Calculated %: N 12.4. In addition to VI, 1.5 g of II with mp 62° (from petroleum ether) was isolated. The picrate of II had mp 185°.

<u>1,2-Dibromo-2-methyl-1-(5-methyl-4-phenyl-2-pyridyl)propane (VII)</u>. A mixture of 1.23 g (0.0055 mole) of VI and 0.26 ml (0.0055 mole) of bromine in 2 ml of benzene was illuminated with a UV lamp for 40 min. Benzene was removed under a slight vacuum. The precipitated crystals were separated and washed three times with benzene to give 0.76 g (37%) of VII in the form of white crystals with mp 193-195° [from alcohol-benzene (1:10)] which rapidly turned yellow in air. Found %: N 4.4. $C_{16}H_{17}Br_2N$. Calculated %: N 3.7.

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